

Protocol

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This supplement contains the following items:

Phase I Trial: Study of Cemiplimab (REGN2810, an Anti-PD-1) in Patients with Advanced Malignancies (NCT02383212)

1. Original protocol, final protocol, summary of changes
2. Original SAP (no changes)

Phase II Trial: Study of Cemiplimab (REGN2810, an Anti-PD-1) in Patients with Advanced Cutaneous Squamous Cell Carcinoma (NCT02760498)

1. Original protocol, final protocol, summary of changes
2. Original SAP, final SAP, summary of changes

Clinical Study Protocol

A FIRST-IN-HUMAN STUDY OF REPEAT DOSING WITH REGN2810, A MONOCLONAL, FULLY HUMAN ANTIBODY TO PROGRAMMED DEATH – 1 (PD-1), AS SINGLE THERAPY AND IN COMBINATION WITH OTHER ANTI-CANCER THERAPIES, IN PATIENTS WITH ADVANCED MALIGNANCIES

Compound: REGN2810 (anti-PD-1 mAb)

Clinical Phase: 1

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Scientific/Medical Monitor:

Elizabeth Stankevich, BS
Director, Clinical Sciences, Oncology

Israel Lowy, MD, PhD
VP Translational Sciences and Oncology

Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A First-in-Human Study of Repeat Dosing with REGN2810, a Monoclonal, Fully Human Antibody to Programmed Death – 1 (PD-1), as Single Therapy and in Combination with Other Anti-Cancer Therapies in Patients with Advanced Malignancies
Site Locations	Up to 10 sites in the United States
Objectives	<p>The primary objective of the study is to characterize the safety, tolerability, and dose limiting toxicities (DLTs) of REGN2810 administered intravenously (IV) as monotherapy, or in combination with targeted radiation (with the intent to have this serve as an immuno-stimulatory, rather than primarily tumor-ablative therapy), low-dose cyclophosphamide (a therapy shown to inhibit regulatory T-cell responses), or both in patients with advanced malignancies.</p> <p>The secondary objectives of the study are:</p> <ul style="list-style-type: none">• To determine a recommended phase 2 dose (RP2D) of REGN2810 as monotherapy and in combination with other anti-cancer therapies (targeted radiation, low-dose cyclophosphamide, or both)• To describe preliminary antitumor activity of REGN2810, alone and with each combination partner• To characterize the pharmacokinetics (PK) of REGN2810 as monotherapy and in combination with other anti-cancer therapies (targeted radiation, low-dose cyclophosphamide, or both).• To assess immunogenicity of REGN2810
Study Design	<p>This is a phase 1, open-label, multicenter, dose-escalation study of REGN2810 alone or in combination with radiation therapy, cyclophosphamide, or both in patients with advanced malignancies. Safety will be assessed in separate, standard 3 + 3 dose escalation cohorts (in monotherapy, combination with radiation therapy, combination with cyclophosphamide, and combination with radiation therapy plus cyclophosphamide).</p> <p>The choice of combination therapy with radiation, cyclophosphamide, or both will be based on investigator assessment of the best choice of therapy for an individual patient in consultation with the sponsor. To be enrolled in a radiotherapy cohort, a patient must have a lesion that can be safely irradiated and for which radiation at the limited, palliative doses contemplated would be considered medically appropriate, and at least one other lesion suitable for response</p>

evaluation. A patient will be allowed to enroll only if a slot is available in the cohort for the chosen treatment.

Patients will undergo screening procedures to determine eligibility within 28 days prior to the initial administration of REGN2810. Following enrollment of patients into a REGN2810 monotherapy cohort, enrollment of subsequent cohorts will be determined by occurrence of DLTs in prior cohorts (ie, no DLT in a cohort of 3 patients, or no more than 1 DLT in an expanded cohort of 6 patients), and the availability of patient slots. The planned monotherapy dose levels are 1, 3, or 10 mg/kg administered IV every 14 days (2 weeks).

Once one or both of the 1 mg/kg or 3 mg/kg REGN2810 monotherapy cohort DLT observation periods are completed without a DLT in a cohort of 3 patients or with no more than 1 DLT in an expanded cohort of 6 patients, patients can be enrolled into a cohort combining cyclophosphamide or radiotherapy with REGN2810 at that monotherapy dose level. Patients can be enrolled into a combination REGN2810 + cyclophosphamide/radiotherapy cohort once the DLT observation periods for both the cohort for that REGN2810 dose level + cyclophosphamide and the cohort for that REGN2810 dose level + the same radiotherapy regimen are completed with no DLT in a cohort of 3 patients, or no more than 1 DLT in an expanded cohort of 6 patients. Once the 3 mg/kg REGN2810 monotherapy cohort DLT observation period is completed with no DLT in a cohort of 3 patients, or no more than 1 DLT in an expanded cohort of 6 patients, a 10 mg/kg REGN2810 monotherapy cohort may also enroll.

Study Duration

Patients will receive up to 48 weeks of treatment, after which there will be a 24 week follow-up period. A patient will receive treatment until the 48 week treatment period is complete, or until disease progression, unacceptable toxicity, withdrawal of consent, or meeting of another study withdrawal criterion. After a minimum of 24 weeks of treatment, patients with confirmed complete responses (CR) may elect to discontinue treatment and continue with all relevant study assessments (eg, efficacy assessments) as scheduled per protocol. After a minimum of 24 weeks of treatment and after consultation with the investigator and the Sponsor, patients with tumor burden assessments of stable disease (SD) or partial response (PR) that have been unchanged for 3 successive tumor evaluations may also elect to discontinue treatment and continue with all relevant study assessments (eg, efficacy assessments) as scheduled per protocol.

Population**Sample Size:**

Up to 60 adult patients are expected to be enrolled. The total number

of patients enrolled will depend upon observed DLTs.

Target Population:

Patients with advanced malignancies that are incurable and have failed to respond to or showed tumor progression despite standard therapy, or patients who are not candidates for standard therapy, unwilling to undergo standard therapy, or for whom no available therapy is expected to convey clinical benefit.

Treatments

Study Drug

Dose/Route/Schedule:

- REGN2810 at 1 or 3 mg/kg administered IV over 30 minutes every 14 days for 48 weeks, alone or in combination with:
 - Radiotherapy (30 Gy administered as 5 doses of 6 Gy over 1 week) given 1 week after the first dose of REGN2810 **OR**
 - Radiotherapy (27 Gy administered as 3 doses of 9 Gy over 1 week) given 1 week after the first dose of REGN2810 **OR**
 - Low-dose cyclophosphamide (200 mg/m² IV) approximately once every 14 days for 4 doses, starting day –1, and given 1 day prior to each of the first 4 REGN2810 doses, **OR**
 - Radiotherapy (30 Gy administered as 5 doses of 6 Gy over 1 week) given 1 week after the first dose of REGN2810 plus low-dose cyclophosphamide (200 mg/m² IV) approximately once every 14 days for 4 doses, starting day –1, and given 1 day prior to each of the first 4 REGN2810 doses, **OR**
 - Radiotherapy (27 Gy administered as 3 doses of 9 Gy over 1 week) given 1 week after the first dose of REGN2810 plus low-dose cyclophosphamide (200 mg/m² IV) approximately once every 14 days for 4 doses, starting day –1, and given 1 day prior to each of the first 4 REGN2810 doses,
- REGN2810 10 mg/kg administered IV over 30 minutes every 14 days for 48 weeks.

REGN2810 3 mg/kg and 10 mg/kg monotherapy cohorts will enroll only after the requisite number of patients in the prior monotherapy dose cohort (ie, 1 mg/kg and 3 mg/kg, respectively) have cleared the 28 day DLT observation period without a maximum tolerated dose (MTD) being demonstrated for that dose level. A REGN2810 1 mg/kg combination treatment cohort will enroll only after completion of the DLT observation period for the 1 mg/kg

monotherapy cohort. Combination cohorts receiving 3 mg/kg REGN2810 will enroll only when the requisite number of patients in the respective 1 mg/kg REGN2810 combination cohorts have cleared the DLT observation period without demonstrating a MTD. Triple combination cohorts combining REGN2810 with cyclophosphamide and a radiation regimen will enroll only when the requisite number of patients in both corresponding double combination cohorts at that dosage level have cleared the DLT observation period without a MTD being demonstrated.

Assignment of a patient to a treatment cohort will be determined by occurrence of DLTs/establishment of a MTD in prior cohorts, the investigator's assessment of the appropriateness of therapies for the patient, and the availability of patient slots.

Variables**Primary:**

Primary safety variables include incidence of DLTs, incidence and severity of treatment-emergent adverse events (TEAEs), and abnormal laboratory findings through 48 weeks of treatment

Secondary:

Key secondary variables include the following:

- Serum concentration and pharmacokinetics (PK) of REGN2810
- Antitumor activities assessed using the appropriate criteria for the indication:
 - Response Evaluation Criteria in Solid Tumors (RECIST) criteria measured by computed tomography (CT) or magnetic resonance imaging (MRI)
 - Other assessment criteria should also be used for specific tumors in which RECIST measurements are not the standard.
 - Immune-Related Response Criteria (irRC) applied to RECIST measurements.

In all cases, irRC will be the governing tool to determine progression of disease (PD), SD, CR, or PR. Standard RECIST data will also be collected for information purposes.

- Anti-REGN2810 antibodies
-

Procedures and Assessments	<p>Tumor imaging (CT or MRI) will be performed to measure tumor burden and to characterize the efficacy profile of study treatments using irRC.</p> <p>Physical examination, laboratory tests, vital signs, electrocardiogram (ECG), pregnancy test for women of childbearing potential, and recording of AEs and concomitant medications will be performed to ensure patient safety and to characterize the safety profiles of study treatments.</p> <p>Other assessments will include:</p> <ul style="list-style-type: none">• PK/pharmacodynamic samples• Optional tumor biopsies• Biomarkers (cellular and molecular) as well as tumor and genomic genetic markers related to REGN2810 treatment exposure, clinical activity, or underlying disease
Statistical Plan	<p>The study dose escalation is based on a traditional 3 + 3 design with 3 to 6 patients assigned per dose level. The exact number of patients enrolled in the study will depend on the number of protocol-defined DLTs observed, and the need to expand currently defined dose levels, or open additional cohorts at lower dose levels. After the required initial enrollment to the next cohort in the dose escalation has occurred, enrollment to each of the previous cohorts below the MTD for that treatment will be expanded (if not previously expanded during escalation) to a total of 6 patients.</p> <p>Data will be summarized using descriptive statistics only. In general, data will be summarized by dose levels and combinations. The safety summaries and analyses will be performed on the safety analysis set (SAF). The primary analysis of safety will be based on treatment-emergent AEs (TEAEs).</p>

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADL	Activities of Daily Living
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ARISg	Pharmacovigilance and clinical safety software system
AST	Aspartate aminotransferase
AUC	Area under the concentration–time curve
BAL	Bronchoalveolar lavage
BUN	Blood urea nitrogen
CPA	Cyclophosphamide
CR	Complete response
CRF; eCRF	Case report form (electronic or paper); electronic case report form
CRO	Contract research organization
CRP	C-reactive protein
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte antigen 4
CTV	Clinical target volume
(NCI-) CTCAE	(National Cancer Institute) Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
Dmax	Maximum radiation dose
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic data capture
FACS	Fluorescence-activated cell sorting
FDG-PET	¹⁸ F-fluorodeoxyglucose positron emission tomography
FFPE	Formalin-fixed, paraffin-embedded
FNA	Fine-needle aspirate
fx	Fraction(s)
GCP	Good clinical practice
GBM	Glioblastoma multiforme

GTV	Gross target volume
HLA	Human leukocyte antigen
ICF	Informed consent form
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry
INR	International Normalized Ratio
irRC	Immune-related response criteria
IRB	Institutional Review Board
irAE	Immune-related adverse event
ITV.	Internal target volume
IUD	Intrauterine device
IV	Intravenous
LC	Local control
LD	Longest diameter
LE	Local enlargement
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LLOQ	Lower limit of quantification
mAb	Monoclonal antibody
Max Vol	Maximum (tissue) volume
MedDRA	Medical Dictionary for Regulatory Activities
monoRX	Monotherapy
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NOAEL	No-observed-adverse-effect level
NSCLC	Non-small-cell lung cancer
PBMC	Peripheral blood mononucleated cell
PD-1	Programmed death-1 (receptor)
PD-L1, PD-L2	Programmed death ligand 1, programmed death ligand 2
PET	Positron-emission tomography
PK	Pharmacokinetic
PR	Partial response
PT	Preferred term
PTV	Planning target volume
RBC	Red blood cell

RCC	Renal cell cancer
RECIST	Response Evaluation Criteria in Solid Tumors
Regeneron	Regeneron Pharmaceuticals, Inc.
RF	Rheumatoid factor
RILD	Radiation-induced liver disease
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Systems (software)
SCHNC	squamous-cell head and neck cancer
SOC	System organ class
SSA	Sjögren's syndrome A antigen
SSB	Sjögren's syndrome B antigen
$t_{1/2}$	Beta-phase terminal half life
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
WBC	White blood cell
XRT	Radiotherapy

1. INTRODUCTION AND RATIONALE

1.1. Introduction

Enhancement of the anti-tumor immune response with cancer immunotherapy agents has emerged as a highly effective and complementary approach to the therapeutic mainstays of surgery, cytotoxic drugs, targeted therapeutics, and radiation. Moreover, induction of durable and extensive tumor regressions suggest that immunotherapy may convert previously fatal diseases into chronic, manageable ones for some patients.

Under chronic stimulation, T cells lose proliferative and effector function capacity, often due to signal down-modulation via the increased expression of proteins such as PD-1, an inhibitory checkpoint receptor of the CD28 receptor family. The ligand for the PD-1 receptor, PD-L1, is expressed in a variety of human malignancies ([Zou 2008](#)), and its high level of expression has been previously correlated with poor patient prognosis and resistance to treatment in non-small-cell lung cancer (NSCLC; [Creelan 2014](#)), glioblastoma multiforme (GBM; [Wei 2014](#)), and squamous-cell carcinoma of head and neck (SCCHN; [Zandberg 2014](#)). Binding of ligand (PD-L1 or PD-L2), often expressed on tumor cells, to PD-1 imparts an inhibitory signal to the T cell, thus down-modulating the anti-tumor T-cell response ([Francisco 2010](#)).

Blockade of the PD-1/PD-L1 T-cell checkpoint pathway is an effective and well tolerated approach to stimulating the immune response, and has achieved significant objective responses in advanced, melanoma, renal cell cancer (RCC), and NSCLC ([Topalian 2010](#)). However, optimal therapy will likely require combining anti-PD-1 monoclonal antibody (mAb) treatment with conventional therapies and novel immunotherapy approaches. Combinatorial approaches to stimulate convergent aspects of host immunity by employing complementary immunomodulators as well as immune-stimulatory aspects of conventional modalities such as radiation and chemotherapy may result in the development of more effective cancer therapies. Combination blockade of PD-1 and the cytotoxic T-lymphocyte antigen 4 (CTLA-4) is effective in controlling growth of syngeneic mouse tumors of ID8-VEGF ovarian carcinoma and CT26 colon carcinoma cell lines in immune-competent mice, providing support to this notion ([Duraishwamy 2013](#)). Furthermore, adding blockade of CTLA-4 to PD-1 blockade in melanoma patients achieves response rates twice of that achieved with anti-PD-1 alone (ie, >50%; [Wolchok 2013](#)). In a subset of patients with PD-L1+ tumors, preliminary results demonstrated an enhanced systemic response when treatment with an anti-PD-L1 antibody (MPDL3280A) coincided with palliative local irradiation ([Sagiv-Barfi, 2014](#)).

REGN2810 is a high-affinity, fully human, hinge-stabilized IgG4P antibody directed to the PD-1 receptor that potently blocks the interaction of PD-1 with its ligands, PD-L1 and PD-L2. In syngeneic tumor models in immunocompetent mice humanized for PD-1, the antitumor activity of REGN2810 delivered as a monotherapy against a mouse colon adenocarcinoma tumor line is similar to that observed with antibodies generated in house based on the publically available genetic sequences of pembrolizumab and nivolumab, anti-PD-1 antibodies approved for the treatment of melanoma, and in late-stage development for use against several other malignancies. (See the Investigator's Brochure for further details of nonclinical pharmacology and antitumor activity of REGN2810).

This first-in-human protocol is designed to assess the safety of REGN2810, as monotherapy at different dose levels and in combination with selected other anti-tumor agents that may augment the potency and durability of anti-tumor immune response. Based on the premise that select combination therapies may be more active than PD-1 blockade monotherapy, therapies initially combining REGN2810 with cyclophosphamide, radiation therapy, or both will be tested in patients with advanced malignancies for whom a standard curative therapy does not exist.

Additional background information on the study drug and development program can be found in the Investigator's Brochure.

1.2. Rationale

1.2.1. Rationale for Study Design

The 3 + 3 model for the dose-escalation phase of this first-in-human study is designed to permit evaluation of the safety of REGN2810, both as monotherapy at different dose levels, and in combination with immune-enhancing treatments: cyclophosphamide; limited, targeted radiation delivered in 1 of 2 dosing regimens; or combined radiation and cyclophosphamide.

The initial planned treatment with REGN2810 will be every 14 days for up to 48 weeks, with 24 weeks of follow-up observation. Radiation will be administered a week after the first dose of REGN2810. Low-dose cyclophosphamide will be administered to patients assigned to cyclophosphamide 1 day before each of the first 4 doses of REGN2810. After a minimum of 24 weeks of treatment, a patient with a confirmed complete response (CR) may elect to discontinue treatment and continue with all relevant study assessments (eg, efficacy assessments) as scheduled per protocol. After consultation with the investigator and the Sponsor and after a minimum of 24 weeks of treatment, a patient with a tumor burden assessment of stable disease (SD) or partial response (PR) that has been unchanged for 3 successive tumor evaluations also may elect to discontinue treatment and continue with all relevant study assessments (eg, efficacy assessments) as scheduled per protocol.

Combination with Cyclophosphamide

Cyclophosphamide, particularly when administered in relatively low doses, has been shown to augment both the immunologic and clinical responses of anticancer vaccines. This immune enhancement may be achieved by increased expression of class I human leukocyte antigen (HLA) in the tumor microenvironment or on cancer cells themselves, as well as by selectively depleting T regulatory (Treg) cells ([Ghiringhelli 2004](#)). By reducing Treg cells, the likely mediators of tumor tolerance, anti-tumor CD8+ cytotoxic effector T cells can be activated and expanded ([Le 2012](#), [Emens 2012](#), [Hermans 2003](#)).

Low-dose cyclophosphamide has been shown to improve antitumor immune responses in various animal tumor models and in patients with metastatic melanoma ([Cerullo 2011](#)). In PROb tumor-bearing rats, a single administration of cyclophosphamide depletes CD4+CD25+ T cells, delaying PROb tumor growth, and curing rats with established PROb tumors when followed by an immunotherapy that is ineffective as monotherapy ([Ghiringhelli 2004](#)). Low-dose cyclophosphamide also decreases Tregs in patients treated with an oncolytic adenovirus without compromising induction of antitumor or antiviral T-cell responses ([Cerullo 2011](#)).

Combination with Radiotherapy

Nonclinical studies suggest that radiotherapy may sensitize tumor cells to immune-mediated attack (McFarland 2012) by prompting release of soluble tumor antigens from killed cells as well as by increasing tumor cell surface expression of antigens and receptors mediating T-cell recognition and/or killing and enhanced efficiency of professional antigen-presenting cells (Ferrara 2009, Kershaw 2013). Together with the observation that radiation may induce expression of chemokines needed for T-cell trafficking (Kershaw 2013, Hellevik 2014), these data suggest that radiation can function as an immune adjuvant to help reverse the suppression of tumor immune responses.

As a crucial tumor immune-evasion mechanism, however, Treg-mediated immunosuppression may be a key obstacle for successful tumor immunotherapy in general, and following radiation in particular. Following sublethal irradiation of antigen-primed mice, antigen-specific immune suppression mediated primarily by CD4⁺ CD25⁺ Tregs develops over several weeks. The proportion of Treg to T effector populations is skewed, with higher numbers of Tregs (McFarland 2012). The influx of Treg cells into an irradiated tumor microenvironment therefore may counteract any benefit obtained from increased antigen release, enhanced antigen presentation, or influx of T effector cells.

Data from mice also suggest that tumor cells may counterbalance this effect by upregulating PD-L1 in response to radiation (Deng 2014). Importantly, administration of an anti-PD-L1 antibody was able to greatly enhance radiation-induced tumor regression and survival in this study, providing strong support to the notion that PD-1/PD-L1 blockade may overcome immunosuppression mediated by radiation-induced PD-L1 upregulation.

Combination with Radiotherapy and Cyclophosphamide

In a syngeneic TSA cell line breast cancer model in BALB/c mice, the combination of low-dose cyclophosphamide and fractionated radiation was able to elicit regression of tumors significantly better than either modality alone (Dewan 2012). By counterbalancing radiotherapy-induced increases in Tregs, combining cyclophosphamide with radiation therapy and REGN2810 may improve tumor responses relative to those obtained with any agent alone.

1.2.2. Rationale for Dose Selection

REGN2810:

The starting dose chosen for this first-in-human study is based on the similar in vitro and in vivo potency of REGN2810 compared to antibodies generated based on publically available sequences of 2 approved anti-PD-1 antibodies, nivolumab and pembrolizumab. When compared to REGN1672 (primary sequence identical to nivolumab) and REGN2626 (primary sequence identical to pembrolizumab) in both in vitro and cell-based assays, REGN2810 demonstrated similar in vitro PD-1 binding affinity, blocking efficiency for PD-1/PD-L1 and PD-L2 interactions in vitro, and ability to antagonize PD-1-induced T-cell inhibitory signaling in a cell-based bioassay. Additionally, REGN2810 demonstrated similar in vivo anti-tumor efficacy to REGN1672 and REGN2626 in humanized-PD-1 mouse tumor model bioassays. Furthermore, the pharmacokinetic (PK) profile for REGN2810 in monkeys is similar to that of nivolumab (Wang 2014). These results suggest that clinical activity of REGN2810 will be similar to those of pembrolizumab and nivolumab at equivalent doses.

In pharmacokinetic studies in cynomolgus monkeys administered 1, 5, and 15 mg/kg REGN2810, estimates of the beta-phase terminal half life ($t_{1/2}$) of REGN2810 were comparable across dose groups: 9.84, 10.9 and 12.4 days, respectively. Accordingly, REGN2810 will be administered every 14 days in this study to maintain targeted serum concentrations over the dosing interval.

In a 4 week toxicology study in monkeys at the no-observed-adverse-effect level (NOAEL) of 50 mg/kg per week, the area under the concentration–time curve (AUC) over the last dosing interval was estimated at 6170 day•mg/mL, a greater than 12-fold higher exposure than steady-state exposures predicted with 1 mg/kg, and a 14% higher exposure than that anticipated with 10 mg/kg administered to human patients every 14 days. Based on preclinical activity and toxicology data and greater than 10-fold exposure margin over 1 mg/kg REGN2810, in addition to the clinical efficacy and safety data from other anti-PD-1 mAbs at similar doses/dosing intervals, a dosage of 1 mg/kg REGN2810 every 14 days is expected to be both safe and active, and was therefore chosen as a starting dosage, with plans to de-escalate if necessary. If safety of 1 mg/kg REGN2810 is confirmed in the first cohort, the dosage may be successively escalated to 3 mg/kg and then to 10 mg/kg.

Experience with other anti-PD-1 antibodies suggests that REGN2810 dosage can be escalated safely. In an open-label expansion cohort of a phase 1 trial of intravenous (IV) pembrolizumab in patients with advanced melanoma previously treated with ipilimumab, treatment at 2 mg/kg or 10 mg/kg every 3 weeks was well tolerated, with similar safety profiles across dose groups, and no drug-related death ([Robert 2014](#)). In a 3 + 3 dose-escalation study of nivolumab in patients with advanced melanoma, NSCLC, RCC, castration-resistant prostate cancer, or colorectal cancer, a maximum tolerated dose (MTD) was not reached with dose levels of 1, 3, or 10 mg/kg. A limited dose–response exploration for REGN2810 monotherapy is planned to examine the potential for dose-dependence of anti-tumor activity, and also to rule out potential for toxicity as a consequence of any unexpected differentiating features of REGN2810. Three dosages are planned for this first-in-human study of REGN2810: 1, 3, and 10 mg/kg, administered every 14 days.

In patients with advanced melanoma receiving nivolumab, the majority of responses emerged before 24 weeks, and were noted to be durable in those patients who required discontinuation of treatment due to toxicity ([Topalian 2014](#)). Responses with the combination of ipilimumab and nivolumab appeared to occur faster, more frequently, to a greater depth, and with greater durability as compared to historical response data with either agent as monotherapy for melanoma ([Wolchok 2013](#)). Therefore, 48 weeks was chosen as the planned duration of treatment for this study. The study includes an option to hold treatment after evidence of “consolidated response” (unchanging SD or PR), or confirmed CR, after a minimum of 24 weeks of treatment. Dosing to consolidated response may better preserve utility of retreatment at later times of progression, reduce chances for toxicity due to unnecessary chronic treatment, and permit assessment of the utility of this approach. Opportunities for retreatment/reinduction with REGN2810-based therapies for patients who progressed or relapsed after their first treatment may be made available through future protocols.

Radiotherapy:

In a series of mouse tumor models treated with an anti-CTLA-4 antibody combined with 3 different radiation regimens, enhanced tumor responses were observed when treated with

fractionated radiation regimens of 8 Gy \times 3 or 6 Gy \times 5 administered on consecutive days, but not with 20 Gy \times 1 (unfractionated; [Dewan 2009](#)).

The fractionated regimens, but not the single radiation dose, also resulted in abscopal effects, defined as a significant inhibition of tumor growth outside the radiation field. Other nonclinical studies have suggested that a single, unfractionated treatment can produce abscopal effects as well, particularly in combination with PD-1 pathway blockade ([Deng 2014](#)) or other immunomodulatory treatment.

An abscopal effect is seen very rarely when patients receive radiation to a single site, usually for palliative purposes, as the only anti-tumor therapy. Anecdotal reports describe striking and durable abscopal effects in patients who received palliative doses of radiation during treatment with immunomodulatory therapies such as anti-CTLA-4 or PD-1/PD-L1 pathway blockade ([Sagiv-Barfi 2014](#), [Postow 2012](#)).

The optimal fractionated regimen for augmenting immunogenicity of tumors in human patients is unknown; therefore 2 fractionated regimens will be tested in this study initially. Targeted focal radiation is currently planned as 6 Gy administered 5 times a week for a total of 30 Gy or 9 Gy administered 3 times a week for a total of 27 Gy. While both treatment regimens are within the range of regimens used for palliative radiation treatment and the difference of 3 Gy may appear small, these regimens differ significantly in the biologically effective dose (BED) of absorbed radiation ([Guerrero 2004](#)), and therefore may also appreciably differ in immunopotentiating effects. Radiation will be administered starting 1 week after initial administration of REGN2810. A single course of radiation is planned, as the objective is to provide this treatment as the equivalent of a potent, autologous tumor vaccine to augment the response achieved by PD-1 blockade.

Cyclophosphamide:

Cyclophosphamide will be administered as a 200 mg/m² infusion 1 day before each of the first 4 REGN2810 infusions (ie, approximately once every 14 days). This dosage delivered as monotherapy would not be expected to be curative for advanced malignancies, but has been shown to augment both the immunologic and clinical responses of therapeutic vaccines by selectively depleting Treg cells without resulting in profound systemic lymphopenia, and has been employed routinely in many ongoing therapeutic vaccination studies ([Le 2012](#), [Emens 2012](#)). Because cyclophosphamide is rapidly cleared, potentially permitting reappearance of Treg cells after initial treatment, co-administration of cyclophosphamide (4 doses) initially is planned throughout the first cycle of treatment with REGN2810. The choice to administer cyclophosphamide every 14 days, rather than daily, is supported by data suggesting that this approach may avoid the ablation of responding antitumor immune cells, thereby maximizing immune responses ([Chen 2014](#)).

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to characterize the safety, tolerability, DLTs of REGN2810 administered IV as monotherapy, or in combination with targeted radiation (with the intent to have this serve as an immuno-stimulatory, rather than primarily tumor-ablative therapy), low-dose cyclophosphamide (a therapy shown to inhibit regulatory T-cell responses), or both in patients with advanced malignancies.

2.2. Secondary Objective(s)

The secondary objectives of the study are:

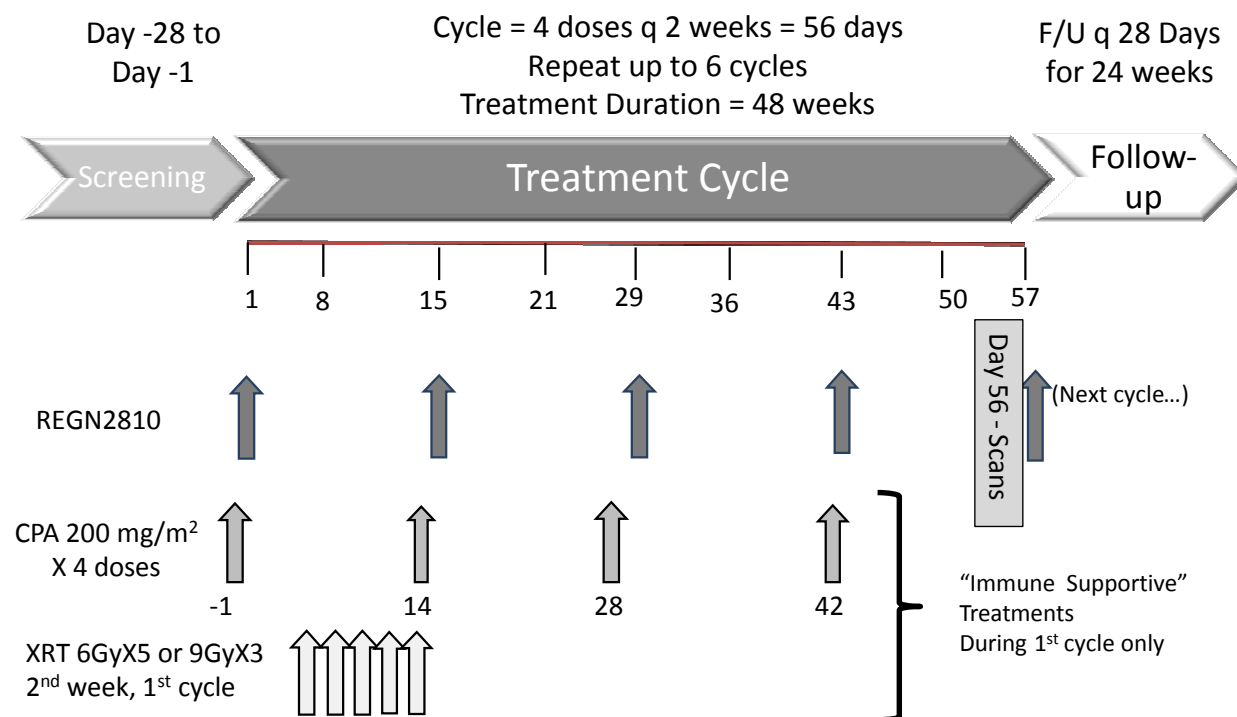
- To determine a recommended phase 2 dose (RP2D) of REGN2810 as monotherapy and in combination with other anti-cancer therapies (targeted radiation, low-dose cyclophosphamide, or both).
- To describe preliminary antitumor activity of REGN2810, alone and with each combination partner (s).
- To characterize the PK of REGN2810 as monotherapy and in combination with other anti-cancer therapies (targeted radiation, low-dose cyclophosphamide, or both).
- To assess immunogenicity of REGN2810

3. STUDY DESIGN

3.1. Study Description and Duration

This is a phase 1, open-label, multicenter, ascending-dose escalation study of REGN2810, alone and in combination with radiation therapy, cyclophosphamide, or radiation therapy plus cyclophosphamide in patients with advanced malignancies. Safety will be assessed in separate, standard 3 + 3 dose escalation cohorts (in monotherapy, combination with radiation therapy, combination with cyclophosphamide, and combination with radiation therapy plus cyclophosphamide).

After a screening period of up to 28 days, patients will receive up to six 56 day treatment cycles for a total of up to 48 weeks of treatment, followed by a 24 week follow-up period ([Figure 1](#)). Each patient will be administered REGN2810 on days 1, 15±3, 29±3, and 43±3 during each treatment cycle. Patients enrolled to combination therapy cohorts may also receive one of two radiation therapy regimens, cyclophosphamide, or both cyclophosphamide and one of two radiotherapy regimens (see [section 3.1.1](#)). Tumor assessments will be made at the end of each treatment cycle. Extensive safety evaluations made at baseline/cycle 1, day 1 of dosing will be repeated on day 1 of each treatment cycle throughout the study, with routine safety evaluations to be conducted at each REGN2810 dosing visit.

Figure 1: Overall Patient Treatment and Follow-Up Timeline

CPA=cyclophosphamide; F/U=follow-up; XRT=radiotherapy.

A patient will receive treatment until the 48 week treatment period is complete, or until complete response (CR), disease progression, unacceptable toxicity, withdrawal of consent, or meeting of another study withdrawal criterion. After a minimum of 24 weeks of treatment, patients with confirmed CR may elect to discontinue treatment and continue with all relevant study assessments (eg, efficacy assessments) per [Table 4](#) and [Table 5](#). After a minimum of 24 weeks of treatment and after consultation with the investigator and the Sponsor, patients with tumor burden assessments of SD or PR that have been maintained for 3 successive tumor evaluations may also elect to discontinue treatment and continue with all relevant study assessments (eg, efficacy assessments) as scheduled per [Table 4](#) and [Table 5](#). Any patient who develops progressive disease (PD) after at least 2 consecutive assessments of SD, or CR or PR, will be eligible to receive retreatment with REGN2810 and the same or additional combination therapies under the auspices of a companion protocol.

As part of an optional genomics substudy, blood may be collected for DNA extraction. Biomarkers (cellular and molecular) related to REGN2810 treatment exposure, clinical activity, or underlying disease will also be assessed, and results will be presented separately from the main study report.

3.1.1. Study Cohorts

A patient may be assigned to receive 1 of 11 possible treatments (monotherapy, combination with radiation therapy, combination with cyclophosphamide, or combination with radiation therapy and cyclophosphamide; [Table 1](#)); up to 10 treatment cohorts will be enrolled. A patient may be assigned to a specific treatment cohort based on the investigator's assessment of the

appropriateness of a therapy regimen for that patient, completion of the safety observation periods for the requisite prior treatment cohorts without exceeding a MTD, and the availability of patient slots in the preferred treatment cohort. The first cohort to be enrolled will receive REGN2810 monotherapy at 1 mg/kg. Subsequent enrollment of each additional cohort may also be limited by the number of DLTs observed in prior cohorts (see section 3.1.2).

Table 1: Possible Dose Escalation Cohorts

n	Possible Assigned Treatment Cohort
3–6	0.3 mg/kg REGN2810 monotherapy (<i>to be enrolled only if MTD < 1 mg/kg REGN2810</i>)
3–6	1 mg/kg REGN2810 monotherapy
3–6	3 mg/kg REGN2810 monotherapy ^a
3–6	10 mg/kg REGN2810 monotherapy ^b
3–6	1 mg/kg ^a REGN2810 + radiotherapy (6 Gy × 5)
3–6	1 mg/kg ^a REGN2810 + radiotherapy (9 Gy × 3)
3–6	3 mg/kg ^b (or MTD) REGN2810 + cyclophosphamide
3–6	3 mg/kg ^b (or MTD) REGN2810 + radiotherapy (6 Gy × 5)
3–6	3 mg/kg ^b (or MTD) REGN2810 + radiotherapy (9 Gy × 3)
3–6	3 mg/kg ^b (or MTD) REGN2810 + radiotherapy (6 Gy × 5) + cyclophosphamide
3–6	3 mg/kg ^b (or MTD) REGN2810 + radiotherapy (9 Gy × 3) + cyclophosphamide

^a Assuming MTD > 1 mg/kg

^b Assuming MTD > 3 mg/kg

3.1.2. Dose Escalation Rules

Dose escalation rules for the study will follow a traditional 3 + 3 dose-escalation design, enrolling a total of 3 (or, in the case of 1 DLT observed in the initial 3 patients, an expanded total of 6 patients) per cohort until either all cohorts have fully enrolled or a MTD is established according to the rules in this section. At any point, the Safety Monitoring Team may decide to expand a cohort to 6 patients even in the absence of a DLT.

After the required initial enrollment to the next cohort(s) in the dose escalation has occurred, enrollment to each of the previous cohorts below the MTD for that treatment will be expanded (if not previously expanded due to DLT) to a total of 6 patients.

No inpatient dose escalation is permitted in the study. The DLT observation period is defined as the first 28 days after receiving the first dose of REGN2810. Escalation to the next cohort will occur once all of the initial patients enrolled in a cohort (although screening for the next dose cohort may begin prior to confirmation that the current dose is safe) have completed day 28 safety assessments and the data have been reviewed at a Dose Escalation Review meeting. This meeting will be led by a designated member of the Regeneron clinical team (generally either the medical monitor or the clinical trial manager) and at a minimum will be attended by the Regeneron Medical Monitor and the Risk Management Lead; other individuals, including the investigator, may be included. Details on patient cohort assessment through the dose-escalation portion of the study will be provided in the study reference manuals.

The first REGN 2810 cohort to be enrolled will be 1 mg/kg. A 48 hour waiting period between initial study drug administrations will be required for the first 3 patients enrolled at REGN2810

1 mg/kg. Provided that no unexpected toxicity is observed in this first cohort, each subsequent cohort can enroll patients without implementing a waiting period.

The treatment cohort enrollment sequence is described in sections 3.1.2.1, 3.1.2.2, 3.1.2.3, and 3.1.2.4.

3.1.2.1. General Escalation Rules

If 1 of the first 3 patients enrolled in a cohort exhibits a DLT (defined in [section 3.1.3](#)) in the first cycle of therapy, 3 additional patients will be enrolled, expanding the cohort to a total of 6 patients.

If 2 or more patients in the cohort experience DLTs in the first cycle of monotherapy:

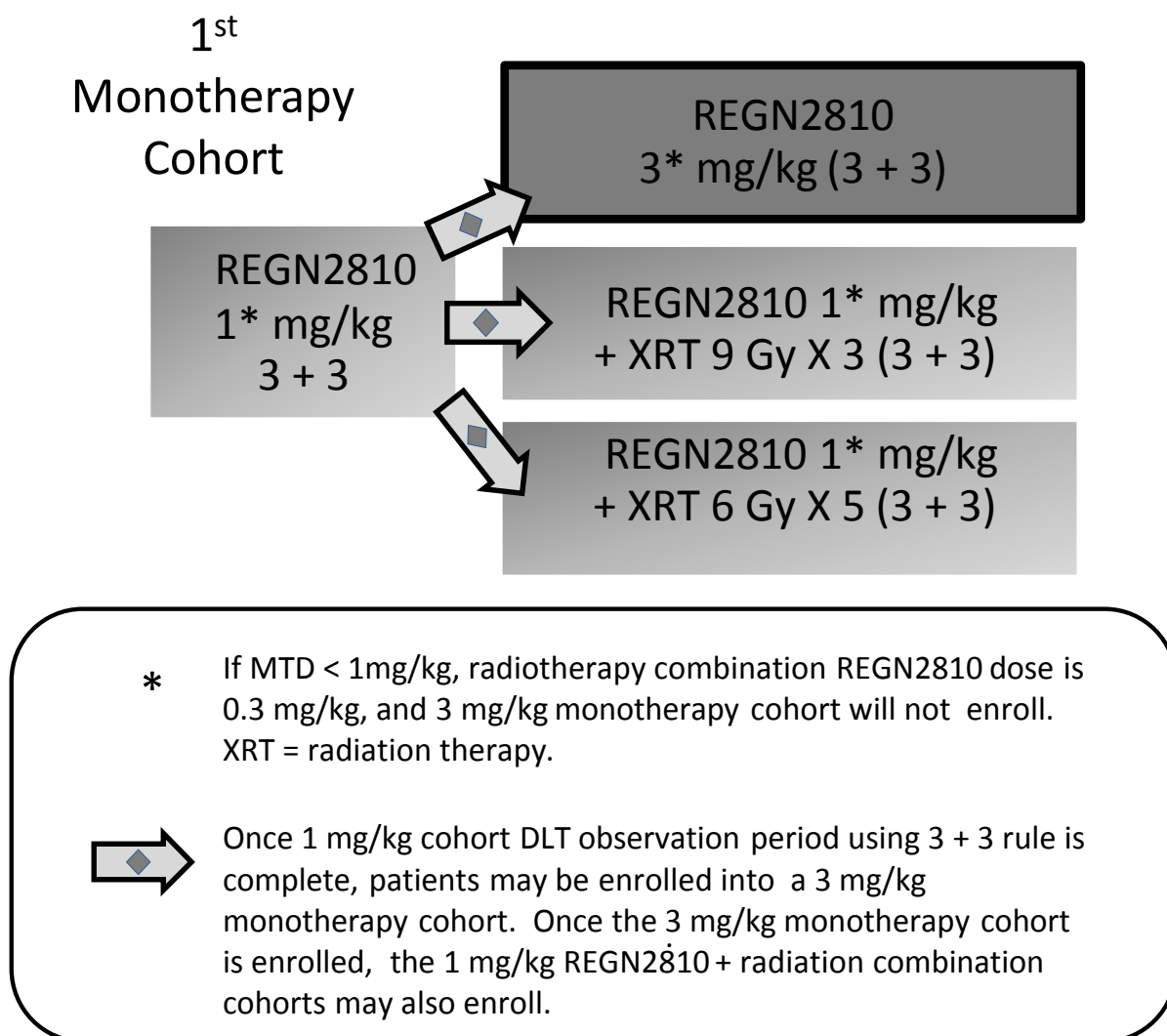
1. Dose escalation will be stopped, and that REGN2810 dose level will be considered to have exceeded the MTD for monotherapy or for the specific combination.
2. If the MTD is exceeded at 1 mg/kg (the lowest planned dose level), a cohort may be enrolled at 0.3 mg/kg, as defined in [Table 1](#).
3. If the REGN2810 MTD is exceeded at 3 mg/kg, REGN2810 dosages for remaining patients will be reduced to the previous tested dose level (ie, 1 mg/kg).
4. Unless already expanded to 6 patients, the lower REGN2810 dose level (as described in item 2 or 3) will be expanded to 6 patients.

3.1.2.2. Monotherapy Escalation Rules

Each successive REGN2810 monotherapy dose level ([Table 1](#)) may be enrolled after the monotherapy group at the previous REGN2810 dose level has completed the 28 day observation period without a DLT (defined in [section 3.1.3](#)) in 3 patients, or with no more than 1 DLT in an expanded cohort of 6 patients.

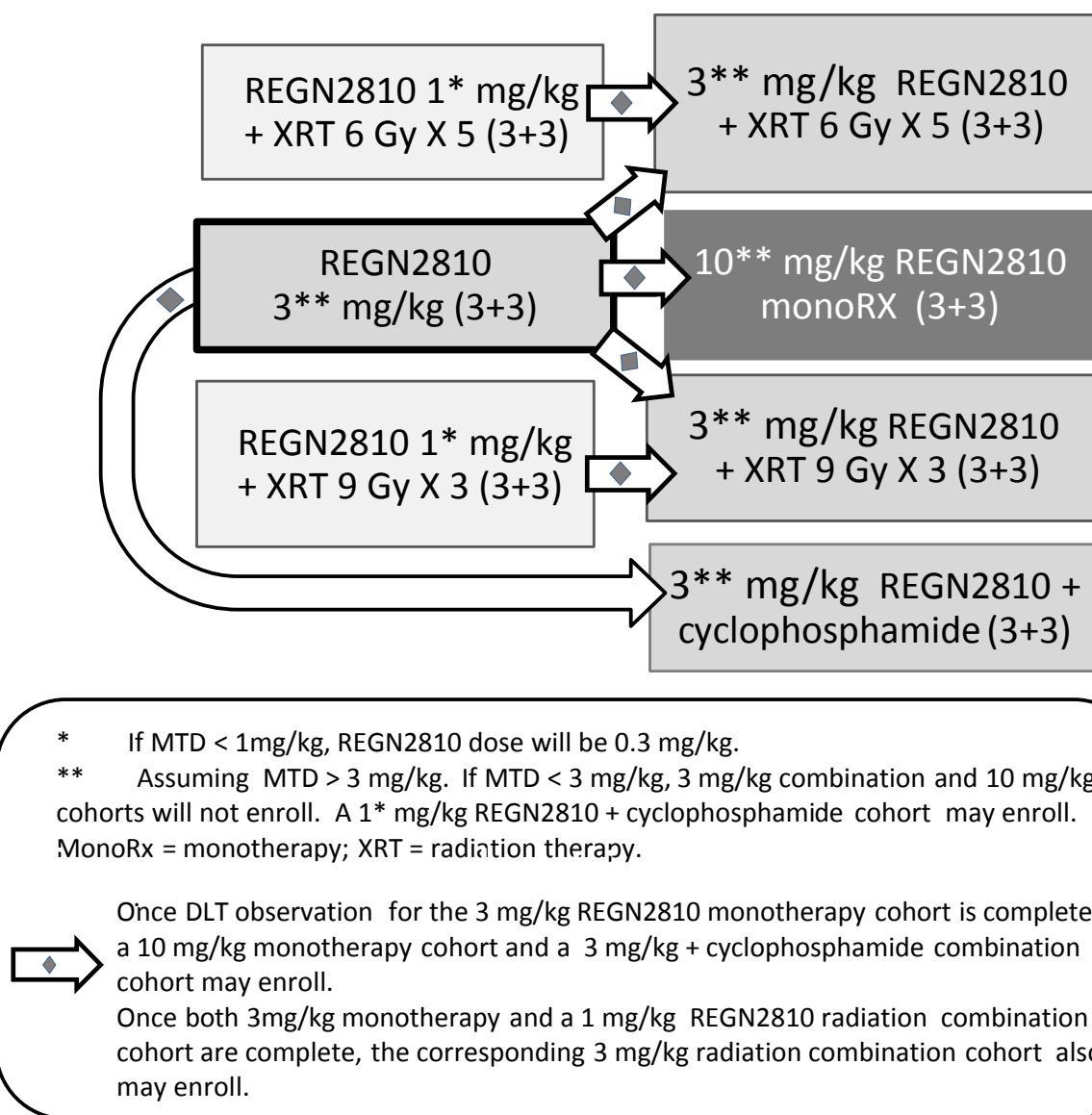
If the MTD is not established with completion of the 1 mg/kg monotherapy cohort, the dose may be escalated to 3 mg/kg monotherapy ([Figure 2](#)). If the maximum tolerated dose (MTD) is established in the first cohort according to the rules described in [section 3.1.4](#), the sponsor may choose to enroll a cohort at 0.3 mg/kg REGN2810.

Figure 2: Planned Treatment Cohort Enrollment, First Progression Set: 3 mg/kg Monotherapy and 1 mg/kg Radiotherapy Combination Cohorts



If a MTD is not established with completion of the 3 mg/kg monotherapy cohort, the dose may be escalated to 10 mg/kg monotherapy ([Figure 3](#)).

Figure 3: Planned Treatment Cohort Enrollment, Second Progression Set: 10 mg/kg Monotherapy, 3 mg/kg plus Radiotherapy Combination, and 3 mg/kg plus Cyclophosphamide Combination Cohorts



Dose escalation will stop once the MTD (defined in [section 3.1.4](#)) has been reached, or after the highest planned dose level (10 mg/kg) has been evaluated.

3.1.2.3. Dual Combination Therapy Escalation Rules

Two different radiation regimens will be evaluated independently with respect to MTD and dose escalation. Enrollment in cohorts to receive a combination of 1 mg/kg REGN2810 with each radiation regimen may proceed once all patients in the 1 mg/kg monotherapy cohort have been observed for at least 28 days with no DLT in 3 patients, or no more than 1 DLT in an expanded cohort of 6 patients (Figure 3).

Enrollment of a cohort receiving a combination of REGN2810 3 mg/kg and a particular radiotherapy regimen may take place once all patients in the 3 mg/kg monotherapy cohort and the cohort combining 1 mg/kg with that radiotherapy regimen have completed the 28 day observation period without a DLT in a cohort of 3 patients, or with no more than 1 DLT in an expanded cohort of 6 patients (Figure 3).

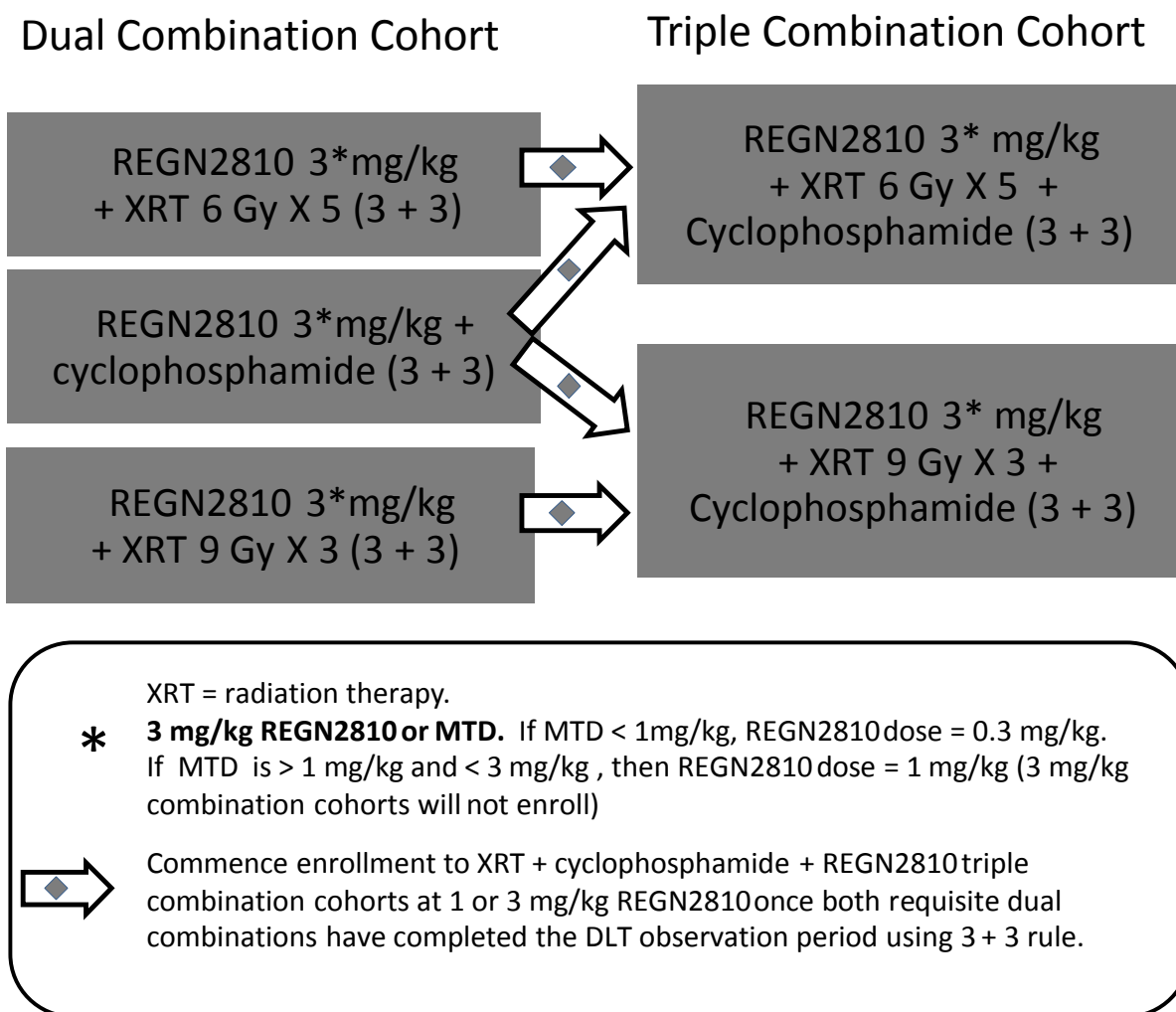
The cohort to receive 3 mg/kg REGN2810 combined with cyclophosphamide may be enrolled only once the 28 day observation period for the 3 mg/kg monotherapy cohort has completed with no DLT in a cohort of 3 patients, or no more than 1 DLT in an expanded cohort of 6 patients (Figure 3).

If the MTD for REGN2810 monotherapy is determined to be <3 mg/kg, then a cohort will be enrolled to receive a combination of cyclophosphamide with REGN2810 at the MTD. The combination therapy assigned to each patient will be determined by the appropriateness of the treatment for the patient as judged by the investigator, in consultation with the sponsor.

3.1.2.4. Triple Combination Therapy Escalation Rules

Combination of a radiation regimen plus cyclophosphamide with REGN2810 at 3 mg/kg (or MTD if <3 mg/kg) can proceed only if the cohorts for combination therapy of that REGN2810 dose level with the radiation regimen, and combination therapy of the REGN2810 dose level with cyclophosphamide have each completed the 28 day observation period with no DLT in 3 patients, or no more than 1 DLT in an expanded cohort of 6 patients per cohort (Figure 4).

Figure 4: Planned Treatment Cohort Progression, Third Set: Triple Combination Therapy Cohorts



3.1.3. Dose-Limiting Toxicities

The DLT observation period for determination of safety for dose escalation or initiation of new combination therapy is defined as 28 days starting with cycle 1, day 1, with the intent to monitor safety and tolerability of the first 2 doses of REGN2810. To be evaluable for a DLT, an individual patient must have received at least the first 2 administrations of REGN2810 (ie, day 1 and day 15±3) and be monitored for at least 28 days following the first administration, and at least 14 days from the second administration. Patients with a delayed second dose will thus have an extended duration of the DLT observation period, as will patients experiencing an AE whose time course of resolution must be assessed to determine if the event was a DLT. An exception for the requirement of 2 doses of REGN2810 would be made in the event that emergence of a DLT after the first dose precluded the second dose.

Any of the below outlined events occurring during the DLT observation period and considered to be at least possibly related to REGN2810 will qualify as a DLT.

A DLT is defined as any of the following:

Non-Hematologic Toxicity

1. Grade ≥ 2 uveitis (considered as a potential immune-related adverse event [irAE]).
2. Any Grade ≥ 3 non-hematologic toxicity; with the exception of:
 - a. Grade 3 nausea, vomiting or diarrhea unless persistent (>7 days duration) despite maximal supportive care measures as prescribed by the treating physician.
 - b. Grade ≥ 3 laboratory abnormalities that are considered clinically insignificant and do not meet criteria for an AE.
 - c. Grade 3 infusion-related reactions that respond to medical management.
 - d. Grade 3 immune-related AE (as defined by experience with other immunomodulatory drugs – see [Appendix 2](#) describing common irAEs) other than uveitis that improves within 7 to 14 days to Grade 2 or lower with medical management (including treatment with steroids).

Hematologic Toxicity

1. Grade 4 neutropenia lasting more than 7 days
2. Grade 4 thrombocytopenia
3. Grade 3 thrombocytopenia with bleeding
4. Grade ≥ 3 febrile neutropenia (fever $\geq 38.5^{\circ}\text{C}$ with absolute neutrophil count [ANC] $< 1.0 \times 10^9/\text{L}$), or Grade ≥ 3 neutropenia with documented infection

The frequency, time to onset, and severity of toxicities, as well as the success of standard medical management and dosing interruptions/delays ([section 5.3](#)), will be analyzed to determine if a given toxicity should be considered a DLT for dose escalation purposes.

In general, as there is as yet no clinical experience for the new biologic molecule REGN2810, alone or in combination with other therapies, any AE that has been clearly described for other agents that block the PD-1/PD-L1 pathway or that is expected with a therapy included as a component of combination therapy in this study initially will be treated as unexpected. Such treatment-emergent adverse events (TEAEs) will be monitored and especially considered on an ongoing basis to assess possible differences in event frequency or severity from that observed with other PD-/PD-L1 blockers or combination therapy components.

Treatment-emergent adverse events that appear to meet the DLT definition will be discussed between the sponsor and the investigator. The final decision of whether or not the AE meets the DLT definition will be based on a careful review of all relevant data and consensus between the medical monitor and the designated Risk Management lead from the Pharmacovigilance & Risk Management department. The investigator may also be consulted.

Regardless of whether a patient remains on study treatment and/or continues to participate in study procedures, such an event will count as a DLT for the involved cohort if the event occurs during the DLT observation period.

3.1.4. Maximum Tolerated Dose

The MTD will be identified separately for the monotherapy group and each combination group; up to 4 MTDs may be identified. The MTD for either combination therapy group will not exceed the monotherapy MTD dose level, as the occurrence of 2 DLTs for that monotherapy dose level and the resulting determination of the MTD preclude further dose escalation (see dose escalation rules, [section 3.1.2](#)).

The MTD for a group is defined as the highest dose at which fewer than a third of an expanded cohort of 6 patients experience a DLT during the first cycle of treatment. Thus, the MTD is defined as the dose level immediately below the level at which dosing is stopped due to the occurrence of 2 or more DLTs in an expanded cohort of 6 patients. If dose escalation is not stopped due to the occurrence of DLTs, it will be considered that the MTD has not been determined.

Based on data with other anti-PD-1 investigational compounds, it is possible that an MTD may not be defined in this study, either for a monotherapy group or for individual combination groups. Additionally, it is possible that REGN2810 MTDs may differ between monotherapy and each combination treatment regimen.

3.2. Planned Interim Analysis

No interim analysis is planned.

4. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

4.1. Number of Patients Planned

Up to 60 adult patients are expected to be enrolled at approximately 10 sites in the United States. The total number of patients enrolled will depend upon observed DLTs during the monotherapy and combination therapy cycles.

4.2. Study Population

The target population for this study comprises patients with advanced malignancies who are not candidates for standard therapy, unwilling to undergo standard therapy, or for whom no available therapy is expected to convey clinical benefit; and patients with malignancies that are incurable and have failed to respond to or showed tumor progression despite standard therapy.

4.2.1. Inclusion Criteria

A patient must meet the following criteria to be eligible for inclusion in the study:

1. Demonstrated progression of a solid tumor with no alternative standard-of-care therapeutic option available.
2. At least 1 lesion for response assessment. Patients assigned to radiotherapy require at least 1 additional lesion that can be safely irradiated while sparing the index lesion(s),

and for which radiation at the limited, palliative doses contemplated would be considered medically appropriate.

3. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1
4. ≥ 18 years old
5. Hepatic function:
 - a. Total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN; if liver metastases $\leq 3 \times$ ULN)
 - b. Transaminases $\leq 3 \times$ ULN (or $\leq 5.0 \times$ ULN, if liver metastases)
 - c. Alkaline phosphatase (ALP) $\leq 2.5 \times$ ULN (or $\leq 5.0 \times$ ULN, if liver metastases)
6. Renal function: Serum creatinine $\leq 1.5 \times$ ULN
7. Bone marrow function:
 - a. Hemoglobin ≥ 9.0 g/dL
 - b. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$
 - c. Platelet count $\geq 75 \times 10^9/L$
8. Ability to provide signed informed consent
9. Ability and willingness to comply with scheduled visits, treatment plans, laboratory tests, and other study-related procedures

4.2.2. Exclusion Criteria

A patient who meets any of the following criteria will be excluded from the study:

1. Ongoing or recent (within 5 years) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest risk for irAEs
2. Prior treatment with an agent that blocks the PD-1/PD-L1 pathway
3. Prior treatment with other immune modulating agents within fewer than 4 weeks or 4 half-lives, whichever is greater, prior to the first dose of REGN2810. Examples of immune modulating agents include blockers of CTLA-4, 4-1BB (CD137), OX-40, therapeutic vaccines, or cytokine treatments.
4. Untreated brain metastasis (es) that may be considered active. Patients with previously treated brain metastases may participate provided they are stable (ie, without evidence of progression by imaging for at least 4 weeks prior to the first dose of study treatment, and any neurologic symptoms have returned to baseline), and there is no evidence of new or enlarging brain metastases.
5. Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of REGN2810
6. Deep vein thrombosis, pulmonary embolism (including asymptomatic pulmonary embolism identified on imaging), or other thromboembolic event within the 6 months preceding the first dose of REGN2810.

7. Active infection requiring therapy, including known infection with human immunodeficiency virus, or active infection with hepatitis B or hepatitis C virus.
8. History of pneumonitis within the last 5 years.
9. Any investigational or antitumor treatment within 30 days prior to the initial administration of REGN2810.
10. History of documented allergic reactions or acute hypersensitivity reaction attributed to treatment with antibody therapies in general, or to agents specifically used in the study.
11. Known allergy to doxycycline or tetracycline.
(precaution due to presence of trace components in REGN2810)
12. Breast-feeding
13. Positive serum pregnancy test
14. History within the last 5 years of an invasive malignancy other than the one treated in this study, with the exception of resected/ablated basal or squamous-cell carcinoma of the skin or carcinoma in situ of the cervix, or other local tumors considered cured by local treatment.
15. Acute or chronic psychiatric problems that, under the evaluation of the investigator, make the patient ineligible for participation
16. Continued sexual activity in men* or women of childbearing potential** who are unwilling to practice adequate contraception during the study (adequate contraceptive measures include stable use of oral contraceptives or other prescription pharmaceutical contraceptives for 2 or more menstrual cycles prior to screening; intrauterine device [IUD]; bilateral tubal ligation; vasectomy; condom plus contraceptive sponge, foam, or jelly, or diaphragm plus contraceptive sponge, foam, or jelly)
*Contraception is not required for men with documented vasectomy.
Postmenopausal women must be amenorrheic for at least 12 months in order **not to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

4.3. Premature Withdrawal from the Study or from Study Treatment

4.3.1. Reasons for Premature Withdrawal or Discontinuation of Study Treatment

A patient has the right to voluntarily discontinue study treatment or withdraw from the study at any time, for any reason, and without repercussion.

The investigator and sponsor have the right to discontinue a patient from study treatment or withdraw a patient from the study at any time.

Reasons for discontinuation of study treatment or withdrawal from the study may include, but are not limited to:

- Patient withdrawal of consent at any time

- Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety if he or she continues in the study or continues treatment with study drug
- The investigator or sponsor determines it is in the best interest of the patient
- Patient noncompliance (eg, not complying with protocol required visits, assessments, and dosing instructions)
- Pregnancy

4.3.2. Discontinuation of Study Treatment

A patient who permanently discontinues study treatment and who does not withdraw from study participation will be asked to return to the clinic for all remaining study visits per the visit schedule, and will be expected to continue with relevant study assessments. After a minimum of 24 weeks of treatment, patients with confirmed CR may elect to discontinue treatment and continue with all relevant study assessments (eg, efficacy assessments) per [Table 4](#) and [Table 5](#). Patients with tumor burden assessments of SD or PR that have been maintained for 3 successive tumor evaluations may also elect to discontinue treatment after a minimum of 24 weeks of treatment and after consultation with the investigator and the Sponsor, and should continue with all relevant study assessments (eg, efficacy assessments) as scheduled per [Table 4](#) and [Table 5](#).

A patient who discontinues study treatment prematurely during the treatment period due to PD, toxicity, or another reason besides confirmed CR, PR, or SD should return to the clinic 14 to 30 days after the last study treatment to complete follow-up visit 1, and should continue with all relevant study assessments (eg, efficacy assessments) for follow-up visits 2 through 6 as scheduled per [Table 5](#).

4.3.3. Withdrawal from Study Participation

During the treatment period and follow-up period, a patient who withdraws consent to continue participation in the study will not be followed for any reason after consent has been withdrawn. Every effort should be made to obtain information on patients who withdraw from the study.

An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

4.4. Replacement of Patients

Any patient who discontinues treatment or withdraws from the study prior to completing the DLT observation period (days 1 through 28) for any reason other than the occurrence of a protocol-defined DLT or other AE leading to study treatment discontinuation will be replaced. Each replacement patient will be assigned a unique patient number, and will be treated at the same dose level as the replaced, prematurely withdrawn patient. Any patient who discontinues after the DLT observation period will not be replaced.

5. STUDY TREATMENTS

5.1. Investigational Treatment

REGN2810 will be supplied as a liquid in sterile, single-use vials. [REDACTED]

Instructions on dose preparation are provided in the study reference manuals.

REGN2810 will be administered in an outpatient setting as a 30 minute IV infusion. Each patient's dose will depend on individual body weight. The dose of REGN2810 must be adjusted each cycle for changes in body weight of $\geq 10\%$. Dose adjustments for changes in body weight of $< 10\%$ will be at the discretion of the investigator.

REGN2810 will be administered alone (section 5.1.1) and in combination with radiation (section 5.1.2.1) and or cyclophosphamide (section 5.1.2.2).

5.1.1. Monotherapy

REGN2810 will be administered in an outpatient setting by IV infusion over 30 minutes every 14 days for 48 weeks (ie, Days 1, 15 \pm 3, 29 \pm 3, and 43 \pm 3 of a 56 day cycle). Planned monotherapy regimens to be assigned may include:

- 1 mg/kg IV infusion over 30 minutes every 14 days for 48 weeks
- 3 mg/kg infusion over 30 minutes every 14 days for 48 weeks
- 10 mg/kg infusion over 30 minutes every 14 days for 48 weeks
- 0.3 mg/kg infusion over 30 minutes every 14 days for 48 weeks (if MTD is determined to be below 1 mg/kg)

5.1.2. Combination Therapy

Concomitant radiation therapy and cyclophosphamide will not be provided by the sponsor, and will be supplied through a prescription by the treating investigator. Their usage, dose, dose modifications, reductions, or delays, as well as any potential AEs resulting from their use, will be tracked along with that of REGN2810.

5.1.2.1. REGN2810 plus Radiation

5.1.2.1.1. REGN2810 plus Radiation Combination Cohorts

REGN2810 will be administered by IV infusion over 30 minutes every 14 days for 48 weeks in combination with radiation treatment from day 8 to day 12.

Planned combination REGN2810 and radiation therapy regimens may include:

- 1 mg/kg REGN2810 infusion over 30 minutes every 14 days for 48 weeks plus 30 Gy radiotherapy (6 Gy \times 5 times/week; given 1 week after the first dose of REGN2810, preferably on consecutive days)

- 1 mg/kg REGN2810 infusion over 30 minutes every 14 days for 48 weeks plus 27 Gy radiotherapy (9 Gy \times 3 times/week; given 1 week after the first dose of REGN2810, preferably **not** on consecutive days)
- 3 mg/kg REGN2810 infusion over 30 minutes every 14 days for 48 weeks plus 30 Gy radiotherapy (6 Gy \times 5 times/week; given 1 week after the first dose of REGN2810, preferably on consecutive days)
- 3 mg/kg REGN2810 infusion over 30 minutes every 14 days for 48 weeks plus 27 Gy radiotherapy (9 Gy \times 3 times/week; given 1 week after the first dose of REGN2810, preferably **not** on consecutive days)

5.1.2.1.2. Specifications for Radiation Therapy

Patients will receive either 30 Gy given as 5 fractions of 6 Gy administered daily starting 1 week after the first dose of REGN2810, or 27 Gy given as 3 fractions of 9 Gy administered every other day starting 1 week after the first dose of REGN2810.

The lesion selected for radiation should be a lesion that can be safely irradiated with focal irradiation while sparing the index lesion(s), and for which radiation at the limited, palliative doses contemplated would be considered medically appropriate.

The target dose for a patient will be based on cohort assignment and should conform to the normal tissue requirements described in [Appendix 1](#), in accord with standard radiation oncology practice. Treatment at the protocol-specified dosing regimen is permitted only if the normal tissue criteria are met. If the normal tissue criteria cannot be met at either of the radiation therapy regimens specified in the protocol, the patient is not eligible for enrollment in a combination radiation treatment cohort in this study.

5.1.2.2. REGN2810 plus Cyclophosphamide

REGN2810 will be administered by IV infusion over 30 minutes every 14 days (2 weeks) for 48 weeks in combination with cyclophosphamide 200 mg/m² every 14 days for 4 doses. Each of the 4 cyclophosphamide doses will be administered 1 day before each of the first 4 REGN2810 doses (days -1, 14, 28, and 42 of the first 56 day cycle).

Notes:

Though cyclophosphamide has been used successfully concurrently with other drugs, the rate of metabolism and the leukopenic activity of cyclophosphamide reportedly are increased by chronic administration of high doses of phenobarbital.

Cyclophosphamide treatment causes a marked and persistent inhibition of cholinesterase activity, thus potentiating the effect of succinylcholine chloride. If a patient has been treated with cyclophosphamide within 10 days of general anesthesia, the anesthesiologist should be alerted.

The planned combination REGN2910 and cyclophosphamide regimen to be assigned is:

- Cyclophosphamide 200 mg/m² every 14 days (days -1, 14, 28, and 42 of the first 56 day cycle) for a total of 4 doses plus

- 3 mg/kg REGN2810 infusion over 30 minutes every 14 days for 48 weeks (provided monotherapy dose of 3 mg/kg < MTD; if 3 mg/kg > MTD, dose will be 1 mg/kg)

5.1.2.3. REGN2810 plus Radiation and Cyclophosphamide

The planned combination REGN2810, radiation, and cyclophosphamide regimen includes:

- Cyclophosphamide 200 mg/m² every 14 days (days –1, 14, 28, and 42 of the first 56 day cycle) for a total of 4 doses
plus
- 27 Gy radiotherapy (9 Gy × 3 times/week; given 1 week after the first dose of REGN2810, preferably **not** on consecutive days) OR
30 Gy radiotherapy (6 Gy × 5 times/week; given 1 week after the first dose of REGN2810, preferably on consecutive days)
plus
- 3 mg/kg REGN2810 infusion over 30 minutes every 14 days for 48 weeks (provided monotherapy dose of 3 mg/kg < MTD; if 3 mg/kg > MTD, dose will be 1 mg/kg)

5.2. Pretreatments

Appropriate premedication for study treatments may be administered at the investigator's discretion as per usual clinical practice and in accordance with institutional guidelines.

5.3. Dose Modification and Study Treatment Discontinuation Rules

5.3.1. Dose Modification

Inpatient dose escalation is not permitted in this study. Patients will generally remain on the assigned dosage of REGN2810 throughout the course of study treatment. Dose reduction of REGN2810 may be allowed, based on the guidelines below, and only after discussion and agreement between the investigator and Sponsor.

5.3.2. Study Treatment Hold or Discontinuation

Patients who experience protocol-defined DLTs (either during or outside the DLT observation period), or Grade ≥3 treatment-related toxicity (excluding exceptions outlined in [section 3.1.3](#) and laboratory abnormalities that are considered clinically insignificant, and do not meet criteria for an AE) that is not otherwise specified in the protocol will be required to temporarily discontinue treatment with REGN2810. Such patients may be considered for resumption of treatment once the toxicity resolves to Grade 1 or baseline, or when the toxicity is stable and manageable through supportive/medical therapy (eg, Grade 3 hypertension that can be controlled with addition of a second anti-hypertensive agent).

Upon occurrence of a DLT or other study treatment-related event at any dose level and at any time on the study, resumption of treatment after resolution or stabilization of the condition is allowed at the discretion of the investigator and sponsor if resuming treatment is thought to be in the best interest of the patient, with the exception of the following categories requiring permanent discontinuation of REGN2810:

- Patients with events that require REGN2810 to be discontinued for more than 42 days (or 3 missed doses)
- Patients with DLTs of Grade ≥ 2 uveitis
- Patients with DLTs of hepatic abnormalities consistent with Hy's Law

Resumption of treatment may be at the initial dose level or one dose level reduced, based upon the discretion of the investigator and the sponsor. A repeat occurrence of the same DLT after resumption of treatment will require permanent discontinuation of study treatment.

If REGN2810 is discontinued (either permanently or temporarily) for an AE, if the patient is in a combination therapy cohort, the patient will generally discontinue the combination therapy treatment as well. If, however, a patient experiences an AE that in the opinion of the investigator is SOLELY related to the combination partner, REGN2810 may be continued, and the combination partner therapy may be discontinued as per [section 5.3](#). Conversely, if a patient experiences an AE that in the opinion of the investigator is SOLELY related to REGN2810, then the combination therapy may be continued while REGN2810 may be discontinued or reduced in dosage as per [section 5.3](#).

Guidelines for study treatment temporary discontinuations, including delays and interruptions, and permanent discontinuations for toxicity are outlined in [Table 2](#).

Table 2: Study Treatment Dose Modifications or Discontinuations

Toxicity	Grade	Hold Treatment?	Restarting Criteria	Restarting Dose/Schedule	Discontinuation Criteria
Hematological Toxicity	1, 2, 3	No	N/A	N/A	N/A
	4	Yes	Toxicity resolves to Grade ≤ 1 or baseline	May decrease REGN2810 dosage to the next lower dosing level (see Table 1)	Toxicity does not resolve within 12 weeks of last infusion <i>Permanent discontinuation should be considered for any severe or life-threatening event</i>
Nonhematological Toxicity Note: Exceptions to be treated as for Grade 1 toxicity: <ul style="list-style-type: none">• Grade 2 alopecia• Grade 2 fatigue• Clinically insignificant lab abnormality not meeting AE criteria	1	No	N/A	N/A	N/A
	2	Consider withholding for persistent symptoms	Toxicity resolves to Grade 0–1 or baseline	<i>Clinical AE resolves within 4 weeks:</i> Same dose and schedule <i>Clinical AE does not resolve within 4 weeks:</i> May decrease REGN2810 dosage to the next lower dosing level (see Table 1)	Toxicity does not resolve within 12 weeks of last infusion
	3	Yes	Toxicity resolves to Grade 0–1 or baseline	May decrease REGN2810 dosage to the next lower dosing level (see Table 1)	Toxicity does not resolve within 12 weeks of last infusion
	4	Yes	N/A	N/A	Patient must be discontinued

For additional information regarding AEs with a potential immune etiology (irAEs), reference [Table 3](#) and [Appendix 2](#).

[Appendix 2](#) includes recommendations on the management of specific treatment-related AEs and when to delay and/or discontinue REGN2810. These guidelines are intended to be applied when the investigator determines the events to be treatment related.

5.3.2.1. Immune-Related Adverse Events (irAEs)

Special attention should be paid to AEs that may be suggestive of a potential immune-mediated pathophysiology (irAEs), defined as AEs of unknown etiology associated with drug exposure and consistent with an immune phenomenon, which may be predicted based on the nature of the REGN2810 compound, its mechanism of action, and reported experience with immunotherapies with a similar mechanism of action. [Table 3](#) includes guidelines for managing irAEs not listed in [Appendix 2](#).

Table 3: General Treatment Hold Guidelines for Immune-Related Adverse Events

Severity	Withhold/Discontinue Treatment?	Supportive Care
Grade 1	No action	Provide symptomatic treatment
Grade 2	May withhold treatment	Consider systemic corticosteroids in addition to appropriate symptomatic treatment
Grade 3 Grade 4	Withhold treatment Discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisone equivalent within 12 weeks of toxicity	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks.

Note: These recommendations should be seen as guidelines, and the treating physician should exercise clinical judgment based on the symptoms and condition of the individual patient.

5.3.2.2. Hold of Radiation Therapy

Radiation therapy will be held for Grade 3 or higher radiation therapy-related, nonhematologic toxicity with exception of Grade 3 liver enzyme elevation (see recommendations for management of hepatic injury in [section 5.5.2](#)). Radiation therapy will resume at the discretion of the investigator at full dose when toxicity returns to Grade 1 or 0. In addition, though development of symptomatic pneumonitis during the actual period of radiation treatment is unlikely, radiation therapy for any patient experiencing pneumonitis prior to completing the treatment should be put on hold until symptoms resolve and the case is clinically evaluated. See [section 5.5](#) for detailed instructions regarding management of radiation therapy-related toxicities.

5.3.2.3. Permanent Discontinuation of Study Treatment

In the event of an infusion reaction of Grade ≥ 3 severity during or directly following REGN2810 infusion, dosing should be stopped and the patient must permanently discontinue REGN2810 treatment.

Study treatment will be permanently stopped in the event of evidence of pregnancy.

In addition, study treatment for any patient may be discontinued for other safety reasons or compliance issues at the discretion of the investigator or sponsor. A patient may choose to discontinue study treatment or study participation at any time for any reason.

A patient who permanently discontinues REGN2810 treatment may continue follow-up in the study without additional treatment until progression of disease or closure of the study ([section 4.3](#)). A patient who permanently discontinues study treatment and who does not withdraw from study participation will be asked to return to the clinic for all remaining study visits per the visit schedule.

5.4. Management of Infusion/Allergic/Hypersensitivity Reactions

Acute infusion reactions are defined as any AE that occurs during the infusion or within 2 hours after the infusion is completed. Emergency equipment and medication for the treatment of these potential adverse effects (eg, antihistamines, bronchodilators, IV saline, corticosteroids,

acetaminophen, and/or epinephrine) must be available for immediate use. Infusion reactions must be reported as AEs ([section 7.2.1](#)) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 grading scale ([section 7.3.1](#)).

Note: In the event of an infusion reaction of Grade 3 or greater severity during or directly following REGN2810 infusion, dosing should be stopped and the patient must be permanently discontinued from REGN2810 treatment.

Acute infusion reactions can include cytokine release syndrome, angioedema, or anaphylaxis, and differ from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Signs/symptoms may include: allergic reaction/hypersensitivity (including drug fever); arthralgia (joint pain); bronchospasm; cough; dizziness; dyspnea (shortness of breath); fatigue (asthenia, lethargy, malaise); headache; hypertension; hypotension; myalgia (muscle pain); nausea; pruritis/itching; rash/desquamation; rigors/chills; sweating (diaphoresis); tachycardia; tumor pain (onset or exacerbation of tumor pain due to treatment); urticaria (hives, welts, wheals); and vomiting.

5.4.1. Interruption of the Infusion

The infusion should be interrupted if any of the following AEs are observed:

- cough
- rigors/chills
- rash, pruritus (itching)
- urticaria (hives, welts, wheals)
- diaphoresis (sweating)
- hypotension
- dyspnea (shortness of breath)
- vomiting
- flushing

The reaction(s) should be treated symptomatically, and the infusion may be restarted at 50% of the original rate.

If investigators feel there is a medical need for treatment or discontinuation of the infusion other than described above, they should use clinical judgment to provide the appropriate response according to typical clinical practice.

5.4.2. Termination of the Infusion

The infusion should be terminated and NOT restarted if any of the following AEs occur:

- anaphylaxis

- laryngeal/pharyngeal edema
- severe bronchospasm
- chest pain
- seizure
- severe hypotension

5.5. Management of Radiation Toxicity

5.5.1. Radiation Pneumonitis

Radiation pneumonitis is a subacute (weeks to months from treatment) inflammation of the end bronchioles and alveoli. Any patient suspected of having radiation pneumonitis will be assessed by a medical oncologist and radiation oncologist, as the clinical picture may resemble that of acute bacterial pneumonia, with fatigue, fever, shortness of breath, nonproductive cough, and a pulmonary infiltrate on chest x-ray. An effort also must be made to distinguish symptoms of radiation pneumonitis from those of an immune-related event possibly related to study drug (Table 3 and Appendix 2). Pneumonitis has been observed as a toxicity associated with multiple agents blocking the PD-1/PD-L1 pathway, occurring at a frequency between 1% and 5%, and generally low grade when caught early and treated with either withholding of the agent and/or a course of steroid immunosuppression (Topalian 2012, Inoue 2001). As noted above, such events will generally be attributed to the combination therapy unless there is clear data to implicate one or the other. Given that delayed radiation toxicities may be at least in part immunologically mediated, it is possible that adding REGN2810 to radiation may exacerbate the severity and/or the frequency of these events. It may therefore not be straightforward to attribute such events exclusively to REGN2810 or to radiation, and such events may need to be attributed to the combination.

The infiltrate on chest x-ray should include the area treated to high dose, but may extend outside of these regions. The infiltrates may be characteristically “geometric” corresponding to the radiation portal, but may also be ill defined.

Patients reporting symptoms as above will be promptly evaluated and treated. Mild radiation pneumonitis may be treated with nonsteroidal anti-inflammatory agents. More significant pneumonitis will be treated with systemic steroids, bronchodilators, and pulmonary toilet after discussion with the biotherapy physician. Infections should be treated with antibiotics. Consideration of prophylaxis of opportunistic infections should be considered in immunocompromised patients.

Though development of symptomatic pneumonitis during the actual period of radiation treatment is unlikely, radiation therapy for any patient experiencing pneumonitis prior to completing the treatment should be put on hold until symptoms resolve. At that point, a clinical decision will be made for the patient as to whether the course of therapy should be completed.

5.5.2. Hepatic Injury

Although hepatic injury is not anticipated with the radiation regimens in this protocol, radiation therapy should be held for a Grade 4 hepatic AE. It is expected that a proportion of patients

treated for right lower lobe lung or liver lesions will have transient elevation of liver enzymes following treatment. If up to Grade 3 elevation of liver enzymes is observed, more frequent measurements (at least twice weekly) of the liver enzymes are recommended until the enzymes stabilize or return to baseline levels. Repeat of blood work for all Grade 4 elevations is required at least 5 days following the first abnormal lab value to determine if the Grade 4 levels are transient (defined as lasting <5 days) or persistent.

Radiation-induced liver disease (RILD) is a clinical syndrome of anicteric ascites, hepatomegaly and elevation of ALP relative to other transaminases that may occur 2 weeks to 3 months following radiation to the liver. An increase in ALP must be at least 2-fold above the baseline ALP.

If ascites develops within 3 months following treatment, an abdominal CT and paracentesis with pathological evaluation of the ascitic fluid is required to aid in distinguishing RILD from disease progression. A Grade 3 or higher elevation of ALP ($\geq 5 \times \text{ULN}$) in the absence of disease progression and presence of ascites lacking evidence of malignancy will be reported as RILD.

Treatment of RILD with repeat paracenteses, diuretics, and close follow-up is recommended. In patients with liver enzyme elevations approaching Grade 4 levels and/or early nonspecific signs or symptoms of liver injury, close follow-up with repeat blood work is required. If no tumor progression is documented in these patients, liver injury will be presumed related to treatment.

5.5.3. Gastrointestinal Radiation Toxicity

Radiation dose constraints for normal stomach and small intestine should limit gastrointestinal toxicity, and pretreatment to reduce risk of late gastrointestinal bleeding is required when these sites are irradiated ([section 5.2](#)); therefore gastrointestinal toxicity is not expected to be dose limiting. However, patients will be followed for gastrointestinal toxicity at each follow-up visit.

5.6. Method of Treatment Assignment

Each patient who signs the informed consent form (ICF) will be assigned a patient number and tracked centrally as described in the study reference manuals.

The sponsor will conduct regular calls with the sites to facilitate coordination of enrollment. Eligible patients will be enrolled sequentially as confirmed and tracked by the sponsor, until each cohort is filled per protocol criteria. Details on treatment assignment can be found in the study reference manuals.

5.6.1. Blinding

This is an open-label study; no blinding will be employed.

5.7. Treatment Logistics and Accountability

5.7.1. Packaging, Labeling, and Storage

Open-label REGN2810 will be supplied as a liquid in sterile, single-use vials that will display the product lot number on the label. [REDACTED]

[REDACTED] Further storage instructions will be provided in the study reference manuals.

A pharmacist or other qualified individual will be identified at each site to prepare REGN2810 for administration. [REDACTED]

[REDACTED] Detailed preparation and administration instructions will be provided to the sites in the study reference manuals.

Packaging, labeling, stability, and storage information for cyclophosphamide is specified in the manufacturer's package insert.

5.7.2. Supply and Disposition of Treatments

Study drug will be shipped [REDACTED] to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed -or- returned to the sponsor or designee.

5.7.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication dispensed to each patient, returned from each patient (if applicable), and disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

5.7.4. Treatment Compliance

REGN2810, cyclophosphamide, and radiation treatments will be administered at the study site and recorded on the electronic case report form (eCRF). All dosing records for each patient will be kept by the site. All drug compliance records must be kept current and must be made available for inspection by the sponsor and regulatory agency inspectors.

5.8. Concomitant Medications and Procedures

5.8.1. Concomitant Medications

Any treatment administered from the time of informed consent until 30 days after the last study treatment will be considered concomitant treatment. This includes medications and other therapies for which administration started before the study and will continue during the study, as well as any therapies started in the 5 month follow-up period to treat a study-drug-related AE. All concomitant treatments must be recorded in the study CRF with the generic name, dose, dose unit, frequency, indication, and start/stop date, as appropriate.

5.8.2. Prohibited Medications

While participating in this study, a patient may not receive any standard or investigational agent for treatment of a tumor other than REGN2810 as monotherapy or in combination with radiation therapy or cyclophosphamide. Any other medication which is considered necessary for the patient's welfare, and which is not expected to interfere with the evaluation of the study drug, may be given at the discretion of the investigator.

Patients using immunosuppressive doses (>10 mg per day of prednisone or equivalent) of systemic corticosteroids other than for corticosteroid replacement will not be eligible for the study. It is recommended that patients do not receive systemic corticosteroids such as hydrocortisone, prednisone, prednisolone (Solu-Medrol®) or dexamethasone (Decadron®) at any time throughout the study except in the case of a life-threatening emergency and/or to treat an irAE. Physiologic replacement doses of systemic corticosteroids are permitted, even if >10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

6. STUDY SCHEDULE AND VISIT DESCRIPTIONS

6.1. Study Schedule

Study assessments and procedures are presented by study period and visit in [Table 4](#) and [Table 5](#).

Table 4: Study Schedule (Screening and Treatment)

Study Procedure	Screening	Treatment																		Cycle 1					Treatment Cycles 2–6 ^a				
Visit Days	–28 to –1	–1 ^b	1	2	3	4	8	9	10	11	12	14	15±3	28	29±3	42	43±3	56±3 ^c	1 ^d	15±3	29±3	43±3	56±3 ^e						
Baseline assessments																													
Informed Consent ^e	X																												
Genomics Informed Consent (optional)	X																												
Medical/Oncology History	X																												
Demographics	X																												
Physical Examination, Complete ^f	X																		X										
Physical Examination, Limited ^g		X	X										X		X		X	X		X	X	X							
12-Lead ECG ^h	X		X																X										
ECOG Status	X																		X										
Vital Signs ⁱ	X	X	X				X						X		X		X	X	X	X	X	X							
Height	X																												
Weight	X	X	X				X						X		X		X	X	X	X	X	X							
Brain MRI ^j	X																												
Chest X-Ray ^k	X																												
Inclusion/Exclusion Criteria/Study Enrollment	X																												
Laboratory Tests																													
Hematology ^l	X	X	X	X			X	X						X		X		X		X	X	X	X						
Blood Chemistry ^m	X		X	X			X	X						X		X		X		X	X	X	X						
Serum HCG ≤ 72 Hour Predose ⁿ	X																												
Urine Pregnancy Test														X		X		X		X	X	X	X						
Urinalysis ^o	X		X				X	X						X		X		X		X									
Serum IgG, IgM, IgE			X																X										
aPTT; INR			X																X										
Immune Safety Assays																													
Rheumatoid Factor (RF)			X																X										
Antinuclear Antibody (ANA)			X																X										
Thyroid-Stimulating Hormone (TSH)			X																X										
C-Reactive Protein (CRP)			X																X										

Study Procedure	Screening	Treatment Cycle 1																	Treatment Cycles 2–6 ^a				
Visit Days	–28 to –1	–1 ^b	1	2	3	4	8	9	10	11	12	14	15±3	28	29±3	42	43±3	56±3 ^c	1 ^d	15±3	29±3	43±3	56±3 ^e
PK Drug Conc./ADA sample																							
REGN2810 PK/Drug Conc. Sample ^p			X	X	X	X	X						X		X		X		X	X	X	X	
Anti-Drug Antibody (ADA)Sample ^q			X																X				
Research samples																							
Serum/plasma cytokine samples			X	X			X												X				
PBMC			X																X				
Tumor-specific markers ^r	X		X																X				
Optional genomic DNA sample			X																				
Obtain archived tumor material ^s	X																						
Optional tumor biopsy ^t	X														X								
Study Treatment																							
1, 3, or 10 mg/kg REGN2810 IV			X										X		X		X		X	X	X	X	
Cyclophosphamide 200 mg/m ² IV		X										X		X		X							
Radiotherapy: 6 Gy × 5 (30 Gy total) ^u							X	X	X	X	X												
Radiotherapy: 9 Gy × 3 (27 Gy total) ^v							X		X		X												
Tumor assessments																							
CT/MRI (chest/abdomen/pelvis) ^w	X																	X					X
Other clinical assessments																							
Adverse Events (AEs) ^x	←=====→																						
Concomitant Medication/Treatment ^y	←=====→																						

ADA=anti-drug antibody; AE=adverse event; ANA=antinuclear antibody; aPTT=activated partial thromboplastin time; CRP=C-reactive protein; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; HCG=human chorionic gonadotropin; INR=International Normalized Ratio; MRI=magnetic resonance imaging; PMBC=peripheral blood mononuclear cells; RF= rheumatoid factor; TSH=thyroid-stimulating hormone.

^a The maximum number of treatment cycles is 6. The decision to continue treatment will be based on tumor response evaluations completed prior to the first dose in the next cycle. Patients will continue to receive REGN2810 until confirmed progressive disease (PD), toxicity, or completion of 48 weeks of treatment. After a minimum of 24 weeks of treatment, patients with confirmed complete responses (CR) or with tumor burden assessments of stable disease (SD) or partial response (PR) that are maintained for 3 successive tumor evaluations may elect to discontinue treatment and continue with all relevant study procedures (eg, efficacy assessments) per [Table 4](#) and [Table 5](#).

^b Visit only for patients enrolled in a cohort assigned to cyclophosphamide treatment.

^c Visit for radiological assessment and evaluation of results for response assessment using RECIST criteria and immune-related response criteria (irRC) prior to start of next treatment cycle.

^d Should occur at least 56 days from day 1 of previous cycle, and no sooner than 14 days after the previous dose.

^e Informed consent may be obtained more than 28 days before the start of screening procedures. Assessments performed as part of standard of care that fall within the screening window but before informed consent is obtained may be used for screening, and need not be repeated for enrollment eligibility.

^f Complete physical examination includes skin, head, eyes, nose, throat, neck, joints, lungs, heart, pulse, abdomen (including liver and spleen), lymph nodes, and extremities. A brief neurologic examination should also be performed.

^g Limited physical exam includes lungs, heart abdomen, and skin.

^h A 12-lead electrocardiogram should be recorded at screening, and 30 minutes after end of infusion at day 1 visits during cycle 1 and cycle 3.

ⁱ Vital signs include temperature, resting blood pressure, pulse, and respiration. When scheduled at the same visit as other procedures, vital signs should be measured prior to clinical laboratory assessments, PK, or exploratory sample collection. Vital signs will be collected on treatment days during cycle 1 prior to treatment, at the end of the infusion, every 30 minutes for the first 4 hours postinfusion, and at 6 and 8 hours after study drug administration. Vital signs on treatment days for subsequent cycles will be assessed and documented prior to the infusion, every 30 minutes for the first 2 hours, and then hourly until 4 hours following study drug administration.

^j Brain MRI required at screening if not performed in the prior 60 days. Brain scans during the treatment and follow-up periods are required if there is a prior history of lesions present at screening or as clinically indicated.

^k Chest x-ray required at screening if not performed in the prior 60 days. Chest x-rays during the treatment and follow-up periods are required as clinically indicated.

^l Hematology includes: white blood cell (WBC) count, 3-cell differential (absolute neutrophil count [ANC], monocyte count, lymphocyte count), hemoglobin, and platelet count. Samples may be collected ≤ 72 hours prior to dosing on the day 1 visit of each cycle.

^m Chemistry includes: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), uric acid, a alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, indirect bilirubin, alkaline phosphatase (ALP), and lactate dehydrogenase (LDH). Samples may be collected ≤ 72 hours prior to dosing on the day 1 visit of each cycle.

^{e n} Predose β -HCG (serum) at screening up to 72 hours prior to first administration. Subsequent pregnancy tests may be urine β -HCG.

^o Urinalysis: glucose, blood, pH, specific gravity, ketones, and spot urine protein. Samples may be collected ≤ 72 hours prior to dosing on the day 1 visit of each cycle.

^p During cycle 1, blood samples for PK analysis will be collected preinfusion, at end of infusion, and 1, 4, and 8 hours (± 10 minutes) after end of infusion on day 1; at 24 ± 1 hours after end of infusion on day 2; at 48 ± 3 hours after end of infusion on day 3; at 72 ± 3 hours after end of infusion on day 4; at any time during visit on day 8; and preinfusion and end of infusion on days 15 ± 3 , 29 ± 3 , and 43 ± 3 . During cycles 2 through 6, blood samples will be collected preinfusion and end of infusion on days 1, 15 ± 3 , 29 ± 3 , and 43 ± 3 .

^q Anti-REGN2810 antibody samples will be collected preinfusion on day 1 of cycles 1 through 6.

^r Protein expression of a prespecified set of markers of immune cell infiltration and activity may be analyzed by immunohistochemistry (IHC) on evaluable archival samples taken at baseline and (samples permitting) biopsies on study.

^s Formalin-fixed, paraffin-embedded (FFPE) tissue from excisional or incisional resection and, when possible, fine-needle aspirates (FNAs) will be collected for biomarker analyses.

^t Study biopsies may be obtained if, in the opinion of the investigator, the lesion is accessible and samples can be obtained without significant risk to the patient.

^u If possible, fractions should be delivered on 5 consecutive days.

^v If possible, fractions should be administered on nonconsecutive days (ie, spaced by at least 1 day between fractions)

^w The same method (CT or MRI) used at baseline should be used throughout the study.

^x Adverse event recording will be ongoing throughout the course of the study. Nonserious AE and SAE data will be collected from the first dose of study medication until 30 days after the last dose of REGN2810. Any AE assessed as related to a study treatment or procedure, including events occurring after 30 days post last dose, should be reported. Any SAE should be reported until resolution or stabilization. Additionally, any SAE after obtaining informed consent should be reported.

^y Concomitant medication recording will be ongoing throughout the course of the study. Record concomitant medications from the date of signing the ICF through 30 days after the last dose of study treatment.

Table 5: Study Schedule (Follow-Up)

Study Procedure	Visit	Follow-up 1	Follow-up 2	Follow-up 3	Follow-up 4	Follow-up 5	Follow-up 6	Follow-up 7
Time point (Day)	Last cycle visit + 1 to 7 days ^a	Follow-up 1 + 28 ± 7 days	Follow-up 2 + 28 ± 7 days	Follow-up 3 + 28 ± 7 days	Follow-up 4 + 28 ± 7 days	Follow-up 5 + 28 ± 7 days	Follow-up 6 + 28 ± 7 days	Follow-up 7 + 28 ± 7 days
Physical examination (complete) ^b	X	X	X	X	X	X	X	X
ECOG Status	X	X	X	X	X	X	X	X
Vital Signs ^c	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X
Laboratory Tests								
Hematology ^d	X	X	X	X	X	X	X	X
Blood Chemistry ^e	X	X	X	X	X	X	X	X
Urine Pregnancy Test	X							
Urinalysis ^f	X	X	X	X	X	X	X	X
Serum IgG, IgM, IgE	X							
Immune Safety Assays								
Rheumatoid Factor (RF)	X							
Antinuclear Antibody (ANA)	X							
Thyroid-Stimulating Hormone (TSH)	X							
C-Reactive Protein (CRP)	X							
PK Drug Conc/ADA Sample								
Anti-Drug Antibody (ADA) sample	X			X				X
Research Samples								
Serum/plasma cytokine ^g	X							
PBMC	X							
Tumor-Specific Markers ^h	X							
Tumor Assessments								
CT/MRI (chest/abdomen/pelvis) ⁱ			X		X			X
Other Clinical Assessments								
AEs ^j	X	X	X	X	X	X	X	X
Concomitant medications and treatments ^k	←=====→							

ADA=anti-drug antibody; AE=adverse event; ANA=antinuclear antibody; CRP=C-reactive protein; CT=computed tomography; ECOG=Eastern Cooperative Oncology Group; MRI=magnetic resonance imaging; PMBC=peripheral blood mononuclear cells; RF= rheumatoid factor; TSH=thyroid-stimulating hormone.

^a Follow-up Visit 1 should be scheduled 14 to 30 days after the last study treatment for a patient who discontinues treatment during the treatment period due to PD; toxicity; or another reason besides confirmed CR, SD, or PR, but who does not withdraw consent to participate in the study. If a scan within the preceding 8 weeks is available, it is not necessary to obtain a repeat scan. The patient should also continue with all relevant study assessments (eg, efficacy assessments) for follow-up visits 2 through 7.

^b Complete physical examination: including examination of skin, head, eyes, nose, throat, neck, joints, lungs, heart, pulse, abdomen (including liver and spleen), lymph nodes, and extremities. A brief neurologic examination should also be performed.

^c Vital signs include temperature, resting blood pressure, pulse and respiration. Blood pressure should be measured after the patient has been resting quietly for at least 5 minutes.

^d Hematology includes: white blood cell (WBC) count, 3-cell differential (absolute neutrophil count [ANC], monocyte count, lymphocyte count), hemoglobin, and platelet count.

^e Chemistry includes: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), uric acid, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, indirect bilirubin, alkaline phosphatase (ALP), and lactate dehydrogenase (LDH).

^f Urinalysis: glucose, blood, pH, specific gravity, ketones, and spot urine protein.

^g At follow-up visit 1, collect 3 mL serum and 3 mL plasma for measurement of cytokines. .

^h Protein expression of a set of prespecified markers of immune cell infiltration and activity may be analyzed by immunohistochemistry (IHC) on evaluable archival samples taken at baseline and (samples permitting) biopsies on study..

ⁱ The same method (CT/MRI) used at baseline should be used throughout the study. Scans are required only if PD has not been confirmed previously while on study.

^s Nonserious AE and SAE data will be collected from the day of informed consent until 30 days after the administration of the last dose of REGN2810. Any AE assessed as related to study treatment, including events occurring after 30 days post last dose, also should be reported. Any SAE should be reported until resolution or stabilization.

^k Record concomitant medications from date of ICF through 30 days after last dose of study drug. Also record any drug started in the 5 month follow-up to treat a study-drug-related AE. In addition, any cancer treatments should be recorded.

6.2. Study Follow-Up and Treatment Discontinuation

6.2.1. Unscheduled Visits

All attempts should be made to keep patients on the study schedule as specified in [Table 4](#) and [Table 5](#). Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted.

6.2.2. Early Treatment Discontinuation

After a minimum of 24 weeks of treatment, a patient with confirmed CR may elect to discontinue treatment and continue with all relevant study assessments (eg, efficacy assessments) as scheduled per [Table 4](#) and [Table 5](#).

After a minimum of 24 weeks of treatment and after consultation with the investigator and the Sponsor, a patient with a tumor burden assessment of SD or PR maintained for 3 successive tumor evaluations also may elect to discontinue treatment, and continue with all relevant study assessments (eg, efficacy assessments) as scheduled per [Table 4](#) and [Table 5](#).

A patient who discontinues study treatment prematurely during the treatment period due to PD; toxicity; or other reason besides confirmed CR, SD, or PR should return to the clinic 14 to 30 days after the last study treatment to complete follow-up visit 1, and should continue with all relevant study assessments (eg, efficacy assessments) at subsequent follow-up visits per [Table 5](#) unless eligible for retreatment, or unable to come in to the clinic.

6.2.3. Follow-up

Patients who complete the maximum number of 6 cycles of treatment and those who discontinued treatment early for CR or for SD or PR maintained for 3 successive evaluations should return to the clinic for follow-up visit 1 scheduled 1 to 7 days after the last cycle visit and subsequent follow-up visits 2 through 6, per [Table 5](#). Patients who discontinued treatment early for CR, SD, or PR should continue with all relevant study assessments (eg, efficacy assessments) as scheduled per [Table 5](#).

A patient who discontinues study treatment prematurely during the treatment period due to PD; toxicity; or another reason besides confirmed CR, SD, or PR should return to the clinic 14 to 30 days after the last study treatment to complete follow-up visit 1, and should continue with all relevant study assessments (eg, efficacy assessments) as scheduled per [Table 5](#).

After completion of the follow-up period, a patient may be eligible to enter a roll-over protocol affording retreatment and/or collection of survival information.

6.3. Study Procedures

6.3.1. Procedures Required Only at the Screening/Baseline Visit

The following procedures will be performed at screening for the purpose of determining study eligibility or characterizing the baseline population:

- Serum β -HCG (result must be ≤ 72 hours before first dose).

- Collection of archived tumor material: After a patient has given informed consent, the patient will be asked to arrange to provide any available previously collected tumor samples.
- Brain MRI: Brain MRI is required at screening if not performed in the prior 60 days.
- Chest x-ray: Chest x-ray is required at screening if not performed in the prior 60 days.

6.3.2. Efficacy Procedures

A CT or MRI for tumor assessment will be performed at the screening visit (within 28 days prior to infusion) and during every cycle (approximately every 8 weeks) on day 56±3, and when disease progression is suspected. Additionally, for patients who have not progressed on study, tumor assessment will be performed for follow-up visits 3, 5, and 7. Note: after PD has been confirmed while on study, additional scans are not required as scheduled follow-up visit procedures.

The choice of whether the imaging is by CT or MRI is an investigator decision. Once the choice has been made to use CT scan or MRI, subsequent assessments will be made using the same modality.

Tumor response evaluation will be performed according to immune-related response criteria (irRC; [Appendix 3](#); [Nishino 2013](#)). Assessments according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 ([Eisenhauer 2009](#)) will also be performed as a supportive exploration; however, the primary determination of disease progression for an individual patient will be made according to irRC. Measurable lesions selected as target lesions for RECIST assessments will also be included as index lesions for irRC assessments.

Copies of scans may be requested by the Sponsor.

6.3.3. Safety Procedures

6.3.3.1. Vital Signs

Vital signs, including temperature, resting blood pressure, pulse, and respiration, will be collected at time points according to [Table 4](#) and [Table 5](#).

Note: blood pressure should be measured after the patient has been resting quietly for at least 5 minutes.

When scheduled at the same visit as other procedures, vital signs should be measured prior to clinical laboratory assessments, PK, or exploratory sample collection. During cycle 1, vital signs will be recorded on treatment days prior to treatment, at the end of the infusion, every 30 minutes for the first 4 hours postinfusion, and at 6 and 8 hours post study drug administration. On subsequent cycles, vital signs on treatment days will be assessed and documented prior to the infusion, every 30 minutes for the first 2 hours, and then hourly until 4 hours following study drug administration.

6.3.3.2. Physical Examination

A thorough complete or limited physical examination will be performed at visits specified in [Table 4](#) and [Table 5](#). Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

Complete physical examination will include examination of skin, head, eyes, nose, throat, neck, joints, lungs, heart, pulse, abdomen (including liver and spleen), lymph nodes, and extremities, as well as a brief neurologic examination.

Limited physical examination will include lungs, heart, abdomen, and skin.

6.3.3.3. Electrocardiogram

A standard 12-lead ECG will be performed at time points according to [Table 4](#) and [Table 5](#).

The patient should be relaxed and in a recumbent or semi-recumbent position at least 5 minutes before recording an ECG. The ECG is to be recorded in triplicate. The ECG strips or reports will be retained with the source. The ECG will be reviewed by the investigator (paper or electronic tracing) and will be available for comparison with subsequent ECGs by the investigator. The following will be recorded on the CRF:

- PR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- Heart Rate (BPM; recorded from the ventricular rate).

Any ECG finding that is judged by the investigator as a clinically significant change (worsening) compared to the baseline value will be considered an AE, recorded, and monitored.

6.3.3.4. Immune Safety Assays

Immune safety assays consist of rheumatoid factor (RF), thyroid stimulating hormone (TSH), C-reactive protein (CRP), and antinuclear antibody (ANA) titer and pattern.

If, during the course of the study, a 4-fold or greater increase from baseline in RF or ANA or abnormal levels of TSH or CRP are observed, the following tests may also be performed: anti-DNA antibody, anti-Sjögren's syndrome A antigen (SSA) antibody (Ro), anti-Sjögren's syndrome B antigen (SSB) antibody (La), antithyroglobulin antibody, anti-LKM antibody, antiphospholipid antibody, anti-islet cell antibody, antineutrophil cytoplasm antibody, C3, C4, CH50.

6.3.3.5. Coagulation Tests

Activated partial thromboplastin time (aPTT) and International Normalized Ratio (INR) will be analyzed by the site's local laboratory.

6.3.3.6. Laboratory Testing

Hematology, chemistry, urinalysis, and pregnancy testing samples will be analyzed by the site's local laboratory.

Detailed instructions for blood sample collection are in the study reference manuals provided to study sites.

Samples for laboratory testing will be collected at time points according to [Table 4](#) and [Table 5](#). Tests will include:

Blood Chemistry

Sodium	Phosphorus	Alanine aminotransferase (ALT)
Potassium	Glucose	Aspartate aminotransferase (AST)
Chloride	Albumin	Total and indirect bilirubin
Bicarbonate	Creatinine	Alkaline phosphatase (ALP)
Calcium	Blood urea nitrogen (BUN)	Lactate dehydrogenase (LDH)
Magnesium	Uric acid	

Hematology

Hemoglobin	Differential:
White blood cells (WBCs)	Neutrophils
Platelet count	Lymphocytes
	Monocytes

Urinalysis

Glucose	pH	Ketones
Blood	Specific gravity	Spot urine protein

Abnormal Laboratory Values and Laboratory Adverse Events

- All laboratory values must be reviewed by the investigator or authorized designee.
- Significantly abnormal tests must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the medical monitor must be consulted.
- The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in [section 7.2.5](#).

6.3.4. Pharmacokinetic and Antibody Procedures

6.3.4.1. Drug Concentration Measurements and Samples

REGN2810 PK parameters will be determined by measuring REGN2810 concentrations in serum samples using a validated assay at visits and time points indicated in [Table 4](#) and [Table 5](#), and listed in [Appendix 4](#). Actual time of each blood draw must be recorded. “Predose” is defined as immediately before the start of the first REGN2810 infusion; subsequent PK sampling times will be based on time of administration of the previous REGN2810 dose. “0 hour” is defined as immediately after the end of the REGN2810 infusion. On days when study drug is

not administered, all PK sampling times will be based on time of last administered study drug dose.

Any unused samples collected for drug concentration measurements may be used for exploratory biomarker research or to investigate unexpected AEs.

6.3.4.2. Anti-drug Antibody Measurements and Samples

Samples for ADA assessment will be collected at time points listed in [Table 4](#) and [Table 5](#).

Anti-REGN2810 antibodies will be assessed using an appropriate assay in predose serum samples and at multiple time points during the dose escalation and safety expansion portions of the study.

6.3.5. Exploratory Biomarker and Cytokine Procedures

Exploratory [REDACTED] pharmacodynamic biomarkers related to REGN2810 treatment exposure, clinical activity, or underlying disease will be investigated from collected DNA, tumor tissue, and biopsy samples. Exploratory biomarker and/or cytokine results will be reported separately from the clinical study report. [REDACTED]

6.3.5.1. Exploratory Biomarker Procedures

[REDACTED] During the screening period, after patients have given informed consent, they will be requested to arrange to provide any available tumor samples archived from previous treatments. Samples will be collected according to directions in the study reference manuals.

Additionally, optional tumor biopsies will be collected, if, in the opinion of the investigator, a lesion is accessible and the sample may be obtained without significant risk to the patient. If the patient only has 1 lesion that can be safely biopsied, and can only be sampled once, a sample at progression of disease is preferred over the cycle 1 sample. Samples will be collected and prepared according to directions in the study reference manuals.

The following markers may be assayed in archived and/or biopsy tumor tissue samples using IHC:

CD3, CD4, CD8, FoxP3, CD274 (PD-L1), CD279 (PD-1), TIM-3, LAG-3, IDO, and GZMB. Additional immune cell markers and/or tumor markers specific to any of the tumor types may be included.

6.3.5.2. Exploratory Circulating Cytokine Procedures

Circulating cytokine levels that may relate to REGN2810 treatment exposure, clinical activity, or underlying disease will be assessed at time points according to [Table 4](#) and [Table 5](#). Serum and plasma samples (3 mL each) will be collected for measurement of cytokines. Cytokines to be analyzed may include but are not limited to: IL-1 β , IL-2, IL-6, IL-8, IL-10, IL-12p70, GM-CSF, IFN γ , TNF α .

Use and Storage of Research Samples (Serum/Plasma)

Research serum and plasma samples will be collected to study the effects of the study drug on modulation of the target as well as on disease processes. Remaining samples may be stored for future use in experiments related to the chosen indication for the study. If necessary, the samples may also be used to identify markers associated with toxicity.

Any unused serum samples collected for drug concentration measurements may be used for exploratory biomarker research or to investigate unexpected AEs.

6.3.5.3. Peripheral Blood Mononucleated Cell Assay

Four 10 mL tubes of whole blood should be collected for peripheral blood mononucleated cell (PMBC) assay.

6.3.5.4. Genomics Sub-study - Optional

Patients who agree to participate in the genomics sub-study will be required to sign a separate genomics sub-study ICF before collection of the samples. Blood for DNA extraction should be collected on day 1/baseline (predose), but may be collected at any study visit. Optional RNA samples will be collected from tumor biopsies during screening. Patients are not required to participate in the genomics sub-study in order to enroll in the primary study.

DNA and RNA samples for the genomics sub-study will be double-coded as defined by the ICH guideline E15. Sub study samples may be stored for up to 10 years after the final date of the clinical study report and may be used for research purposes.

Blood samples for DNA analysis will be collected from each consenting patient immediately before the first dose of study drug. Tumor DNA will be isolated from archived tumor biopsies and from fresh tumor biopsies, as available.

7. SAFETY DEFINITIONS, REPORTING, AND MONITORING

7.1. Definitions

7.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug.

An AE also includes any worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug.

Progression of underlying malignancy will not be considered an AE if it is clearly consistent with the typical progression pattern of the underlying cancer (including time course, affected organs, etc.). Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

If there is any uncertainty about an AE being due only to progression of the underlying malignancy, it should be reported as an AE or SAE as outlined in [section 7.2](#).

7.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent 1 of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm;

blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Hospitalization or death due solely to manifestations consistent with typical progression of underlying malignancy will not be considered a SAE.

SAEs must be reported as directed in section 7.2.

7.2. Recording and Reporting Adverse Events

7.2.1. Adverse Events

The investigator (or designee) will seek information on AEs at each patient contact, and record all AEs that occur from the time the informed consent is signed until 30 days after the end of study treatment. Prior to initiation of study treatment, only the following categories of AEs should be reported on the AE eCRF:

- SAEs
- Nonserious AEs associated with a protocol-mandated intervention (eg, AEs related to an invasive procedure such as a biopsy)

(Other AEs that occur prior to first treatment should be reported on the medical history CRF.)

All AEs after initiation of study treatment and until 30 days after the last study treatment, regardless of relationship to study treatment, will be reported on the AE eCRF. Additionally, any SAE or other AE of concern that the investigator believes may be related to study treatment and that occurs later than 30 days after last study treatment should be reported.

Study treatment includes REGN2810, radiation therapy, and cyclophosphamide.

Information on follow-up for AEs is provided in [section 7.2.6](#). Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs as outlined in [section 7.2.5](#).

7.2.2. Serious Adverse Events

All SAEs, regardless of assessment of causal relationship to study treatment must be reported to the sponsor (or designee) within 24 hours. Refer to the study reference manuals for the procedure to be followed.

Information not available at the time of the initial report must be documented in a follow-up report. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested.

The investigator must promptly report to the Institutional Review Board (IRB) all unanticipated problems involving risks to patients. This includes death from any cause and all SAEs related to the use of the study drug or treatment. It is recommended that all SAEs be reported to the IRB, regardless of assessed causality.

In the event the investigator is informed of an SAE that occurs after 30 days after the last dose of study treatment, only those SAEs or other AEs of concern deemed by the investigator to be related to study treatment will be reported to the sponsor. The investigator should make every

effort to obtain follow-up information on the outcome of a treatment-related SAE until the event is considered chronic and/or stable.

7.2.3. Other Events that Require Accelerated Reporting

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

Symptomatic Overdose of Study Drug:

Accidental or intentional overdose of at least 2 times the intended dose of study drug within the intended therapeutic window, if associated with an AE.

Pregnancy:

Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), by telephone within 24 hours of identification, any pregnancy occurring in a female patient or female partner of a male patient, during the study or within 90 days of the last dose of study drug. Any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn must be reported as an SAE.

Adverse Events of Special Interest:

An AE of special interest (AESI) must be reported within 24 hours of identification. AEs of special interest for this study include:

- Any AE that meets DLT criteria
- Grade 2 or greater infusion-related reactions
- Grade 2 or greater allergic/hypersensitivity reactions
- Grade 3 immune-related toxicities (irAE).

Note: An irAE can occur shortly after the first dose or several months after the last dose of treatment. All AEs of unknown etiology associated with drug exposure should be evaluated to determine possible immune etiology. If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an AE as an irAE.

Refer to the study reference manuals for the reporting procedures to be followed.

If any SAE or unusual AE is judged related to study treatment, and as possible and practical, obtain a blood sample from the patient to permit measurement of plasma drug levels.

7.2.4. Reporting Adverse Events Leading to Withdrawal from the Study

All AEs that lead to a patient's withdrawal from study treatment or from the study must be reported to the sponsor's medical monitor within 30 days.

Refer to the study reference manuals for the procedures to be followed.

7.2.5. Abnormal Laboratory, Vital Signs, or Electrocardiogram Results

The criteria for determining whether an abnormal objective test finding should be reported as an AE include:

- the test result is associated with accompanying symptoms, and/or
- the test result requires additional diagnostic testing or medical/surgical intervention, and/or
- the test result leads to a change in dosing (outside of protocol-stipulated dose adjustments)
- the test result leads to discontinuation from the study, significant additional concomitant medication, or other therapy

Contact the medical monitor in the event the investigator feels that an abnormal test finding should be reported as an AE, although it does not meet any of the above criteria.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Evaluation of severity of laboratory abnormalities will be assessed according to the scale outlined in section 7.3.1.

7.2.6. Follow-up

Information for any nonserious AE that starts during the treatment period or within 30 days after last treatment will be collected from the time of the event until resolution of the event, or until the patient's last study visit, whichever comes first.

Serious adverse event information will be collected until the event is considered chronic and/or stable.

7.3. Evaluation of Severity and Causality

7.3.1. Evaluation of Severity

The severity of AEs (including test findings classified as AEs) will be graded using the current version of the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grading system. Adverse events not listed in the NCI-CTCAE, will be graded according to the following scale:

- | | |
|------------------------------|--|
| 1 (Mild): | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. |
| 2 (Moderate): | Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*. |
| 3 (Severe): | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**. |
| 4 (Life-threatening): | Life-threatening consequences; urgent intervention indicated. |
| 5 (Death): | Death related to AE |

*Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

7.3.2. Evaluation of Causality

Relationship of AEs to Study Drug:

The relationship of AEs to study drug will be assessed by the investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by the study drug?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by the study drug

Related: There is a reasonable possibility that the event may have been caused by the study drug

The sponsor will request information to justify the causality assessment of SAEs, as needed.

[Appendix 5](#) lists factors to consider in assessing the relationship of AEs to REGN2810 or infusion procedures, study procedures, or background treatment.

7.4. Safety Monitoring

The investigator will monitor the safety of study patients at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The medical monitor will have primary responsibility for the emerging safety profile of the compound. The study monitor will be supported by other departments (eg, Pharmacovigilance and Risk Management; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

7.5. Investigator Alert Notification

Regeneron (or designee) will inform all investigators participating in this clinical trial, as well as in any other clinical trial using the same investigational drug, of any SAE that meets the relevant requirements for expedited reporting (an AE that is serious, unexpected based on the Investigator's Brochure, and has a reasonable suspected causal relationship to the medicinal/study drug).

8. STUDY VARIABLES

8.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height), disease characteristics including medical history, and medication history for each patient.

8.2. Primary and Secondary Variables

The primary variables in the study are DLT incidence and the incidence and severity of TEAEs and abnormal laboratory findings through 48 weeks of treatment.

The secondary variables are:

- Antitumor activities assessed using the appropriate criteria for the indication ([Appendix 3](#)):
 - Response Evaluation Criteria in Solid Tumors (RECIST; [Eisenhauer 2009](#)) criteria measured by CT or MRI
 - Other assessment criteria should also be used for specific tumors in which RECIST measurements are not the standard.
 - Immune-Related Response Criteria (irRC; [Nishino 2013](#)) applied to RECIST measurements.
In all cases, irRC will be the governing tool to determine PD, SD, CR, or PR. Standard RECIST data will also be collected for information purposes.
- Incidence of development of anti-REGN2810 antibodies

8.3. Pharmacokinetic Variables

Serum concentration of REGN2810 will be assessed at multiple time points throughout the study treatment and follow-up periods, and the PK will be analyzed

Pharmacokinetic variables may include, but are not limited to, the following:

- AUC_{all} - area under the curve (AUC) computed from time zero to the time of the last concentration
- $AUC_{all}/Dose$ - AUC_{all} -to-dose ratio
- AUC_{inf} - AUC from time zero extrapolated to infinity
- $AUC_{inf}/dose$ - AUC_{inf} -to-dose ratio
- AUC_{last} - AUC computed from time zero to the time of the last positive concentration
- $AUC_{last}/Dose$ - AUC_{last} -to-dose ratio
- CL - clearance
- C_{max} - the peak concentration
- $C_{max}/Dose$ - C_{max} -to-dose ratio
- C_{last} - last positive (quantifiable) concentration
- MRT_{inf} - mean residence time extrapolated to infinity
- MRT_{last} - mean residence time when the drug concentration profile is based on values up to and including the last positive concentration
- $t_{1/2}$ - observed terminal half-life
- $t_{1/2}$ beta

- t_{last} - time of the last positive (quantifiable) concentration
- t_{max} - time to C_{max}
- V_{ss} - volume of distribution at steady state
- V_z – volume of distribution of the terminal phase

8.4. Anti-drug Antibody Variables

Regeneron plans to evaluate the impact of the immunogenicity of REGN2810.

Anti-drug antibody variables include status (positive or negative) and titer as follows:

- Total ADA negative at any time
- Total assay positivity at any time
- Pre-existing immunoreactivity – defined either as a positive ADA assay response at baseline with all post-treatment ADA results negative, or a positive assay response at baseline with all post-treatment ADA assay responses less than 4-fold over baseline titer levels.
- Treatment emergent - defined as either any positive response post-treatment when baseline results are negative, or if any post treatment ADA response is greater than or equal to 4-fold over baseline titer levels. Treatment emergent responses will be further characterized into persistent and transient.
- Persistent response – treatment-emergent ADA positive response with 2 or more ADA-positive sampling time points during the treatment period (and follow-up phase, if any) such that the first and last ADA-positive sample (with no intervening ADA-negative sample) is separated by at least a 12 week period, or only the last collected sample is ADA-positive
- Transient response – any treatment-emergent ADA-positive response that is not considered persistent
- Titer values (Titer value category):
 - Low (titer < 1,000)
 - Moderate ($1,000 \leq \text{titer} \leq 10,000$)
 - High (titer > 10,000)

9. STATISTICAL PLAN

This section provides the basis for the statistical analysis plan (SAP) for the study. The SAP may be revised during the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the database is locked.

Analysis variables are listed in [section 8](#).

9.1. Justification of Sample Size

This is a 3 + 3 study design adapted to evaluate DLTs in monotherapy and combination therapy groups independently within a cohort. Planned sample sizes are consistent with widely accepted standards for phase 1 safety studies in cancer patients.

9.2. Analysis Sets

9.2.1. Safety Analysis Set

The safety analysis set (SAF) includes all enrolled patients who received any study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety and efficacy variables will be analyzed or summarized using the SAF.

The safety and efficacy summaries and analyses will be performed on the SAF.

9.2.2. Pharmacokinetic Analysis Set

The PK analysis set will include all patients who have a predose sample and at least 1 post REGN2810 treatment study drug concentration value above the lower limit of quantification (LLOQ) of the assay.

9.2.3. Anti-Drug Antibody Set

The ADA population includes all treated patients who had at least 1 nonbaseline ADA result.

9.3. Patient Disposition

The following will be provided:

- The number of screened patients
- The number of patients included in the SAF
- The number of patients who discontinued study participation, and the reasons for discontinuation from the study
- The number of patients who discontinued treatment, and the reasons for treatment discontinuation

9.4. Statistical Methods

The analysis of this study will be descriptive and exploratory in nature. In general, data collected during the monotherapy and combination therapy periods will be summarized separately and in combination. Data will be summarized by dose cohorts, and by diagnosis if necessary, using descriptive statistics only.

Continuous variables will be summarized with mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized with frequency and percentage.

9.4.1. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by dose cohorts and by monotherapy and combination therapy that patients received.

9.4.2. Efficacy Analyses

No formal statistical analysis will be performed on efficacy. Objective tumor response determined by immune-related response criteria (irRC; [Nishino 2013](#)) and RECIST version 1.1 ([Eisenhauer 2009](#)) will be summarized by dose cohort and/or diagnosis ([Appendix 3](#)).

9.4.3. Safety Analysis

Safety observations and measurements including drug exposure, AEs, laboratory data, vital signs, and ECOG performance status will be summarized and presented in tables and listings.

9.4.3.1. Adverse Events

Definitions

For safety variables, 3 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment period is defined as the day from first dose of study drug to follow-up visit 1
- The posttreatment period is defined as the time after follow-up visit 1.

Treatment-emergent adverse events (TEAEs) are defined as those not present at baseline or represent the exacerbation during the on-treatment period of a condition present at baseline.

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA[®]). Coding will be to lowest level terms. The verbatim text, the preferred term (PT), and the primary system organ class (SOC) will be listed.

Summaries of all TEAEs by treatment group will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (CTCAE, version 4.03 grade), presented by SOC and PT
- TEAEs by outcome
- TEAEs by relationship to experimental treatment (related, not related), presented by SOC and PT

Deaths and other SAEs will be listed and summarized by treatment group.

Events of CTCAE Grade 3 and Grade 4 severity will be summarized by cohort and by monotherapy or combination treatment period.

TEAEs leading to permanent treatment discontinuation will be listed and summarized by treatment group.

9.4.3.2. Other Safety

Vital Signs

Vital signs (temperature, pulse, blood pressure, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Laboratory Tests

Laboratory test results will be listed.

9.4.3.3. Treatment Exposure

Dose intensity and number of cycles administered will be summarized by dose cohort. Dose intensity will be calculated by dividing actual dose by body weight for REGN2810 and by body surface area for cyclophosphamide at the time of visit.

9.4.3.4. Treatment Compliance

Patients will be administered IV study drug and cyclophosphamide in a clinic under supervision of appropriate study personnel. Compliance will not be evaluated for radiation therapy, to be supplied commercially through a prescription.

9.4.4. Analysis of Drug Concentration Data

9.4.4.1. Descriptive Analysis of Drug Concentrations

Summaries of study drug concentrations will be presented by nominal time point (ie, the time points specified in the protocol) and dose group.

Dose proportionality will be evaluated.

9.4.4.2. Noncompartmental Analysis

The observed elimination rate constant will be calculated as the negative of the slope of the terminal portion of the concentration–time curve. The specific range of times will be determined using the default options of WinNonlin and confirmed by visual inspection of the semilogarithmic plots. If there are 2 or more elimination phases, then each phase may be explored separately. A “linear trapezoidal” or “log-linear trapezoidal” rule will be used to calculate AUC_{inf} as appropriate. Uniform weights will be used. For calculation of mean concentrations of REGN2810, values below the LLOQ will be set to zero, and imputed as LLOQ/2 when plot in semi-log format. Observed noncompartmental estimates will be reported. Selected PK parameters will be plotted versus dose.

9.4.4.3. Compartmental Analysis

If conducted, the compartmental analysis will be exploratory.

9.4.5. Analysis of Anti-Drug Antibody Data

Formation of ADA will be assessed in individual patients and per dose level/dose cohort as follows:

- Possible correlation between changes in PK profile and the presence/absence of anti-REGN2810 antibodies will be evaluated to identify a potential impact of anti-REGN2810 antibodies on drug exposure.
- Possible correlation between AEs and the presence/absence of anti-REGN2810 antibodies will be evaluated to identify a potential impact of anti-REGN2810 antibodies on the incidence of Grade 3 and 4 AEs, atypical AEs, and SAEs.

Cases of ADA positivity will be listed and summarized as appropriate.

9.4.6. Analysis of Pharmacodynamic Data

Circulating tumor cells will be summarized by cohort and by monotherapy or combination treatment period. Data will be analyzed using standard scientific and statistical methods, and will be described in a separate report.

9.4.7. Analysis of Biomarker Data

Data will be analyzed using standard scientific and statistical methods, and will be described in a separate report.

9.5. Recommended Phase 2 Doses

Recommended phase 2 doses will be determined based on the MTD in each of the combination therapies; up to 4 RP2Ds may be identified. It is possible that an RP2Ds for REGN2810 in combination with radiation therapy may differ from that determined for REGN2810 in combination with cyclophosphamide or for REGN2810 in combination with radiation plus cyclophosphamide.

If no MTD is defined between the 3 and 10 mg/kg dose levels, an RP2D will be determined using a combination of the following: safety, tolerability, PK, pharmacodynamic evidence of target and pathway engagement, and preliminary antitumor activity.

9.6. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed:

Definition of baseline:

- Unless otherwise specified, the last assessment before the initial administration of REGN2810 will be considered the baseline evaluation

General rules for handling missing data:

- Unless otherwise specified, there will be no imputations for the missing data
- If the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the intake of study medication except if an incomplete date (eg, month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the intake of study medication date, then the start date by the study medication intake date will be imputed, otherwise, the missing day or month by the first day or the first month will be imputed.

Visit windows:

- Assessments taken outside of protocol allowable windows will be displayed according to the case report form (CRF) assessment recorded by the investigator.

9.7. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in [section 15.1](#).

10. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

10.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation, cleaning, correcting, releasing) will be maintained and stored at Regeneron.

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, medical /surgical history) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with electronic data capture (EDC) tool. User training must be documented before the user is granted access to the EDC system.

10.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- EDC system – data capture
- Statistical Analysis Systems (SAS) Software – statistical review and analysis
- ARISg – a pharmacovigilance and clinical safety software system

11. STUDY MONITORING

11.1. Monitoring of Study Sites

The study monitor and/or designee (eg, contract research organization [CRO] monitor) will visit each site prior to enrollment of the first patient, and periodically during the study. In accordance with International Conference on Harmonisation (ICH) guidelines, the monitor will compare the CRF entries with the appropriate source documents. Additional review may include, but is not limited to, patient ICFs, documentation of patient recruitment and follow-up, AEs, SAEs, and concomitant therapy; as well as records of study drug dispensing, compliance, and accountability. A copy of the drug dispensing log must be provided to the sponsor upon request.

11.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents).

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

11.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic CRFs by trained site personnel. A CRF must be completed for each and every patient enrolled in the study. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each CRF page is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the system. For corrections made via data queries, a reason for any alteration must be provided.

12. AUDITS AND INSPECTIONS

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

13.2. Informed Consent

The principles of informed consent are described in ICH Guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB. A copy of the IRB-approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, the ICF must be reviewed and updated appropriately. All study patients must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient.

13.3. Patient Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by their initials and a patient identification number, only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The patient's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

13.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/EC, as described in ICH Guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design or operation of the protocol or ICF without an IRB-approved amendment.

15. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

15.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

15.2. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of patients required for the study are enrolled earlier than expected

In all cases, the appropriate IRB and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

16. STUDY DOCUMENTATION**16.1. Certification of Accuracy of Data**

A declaration assuring the accuracy and content of the data recorded on the CRFs must be signed by the investigator. This certification form accompanies each set of CRFs. The signed form will be provided to the sponsor with the final set of CRFs for each patient.

16.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer if a longer period is required by relevant regulatory authorities. The investigator must consult with the sponsor before discarding or destroying any essential study documents following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor and the relevant records will be transferred to a mutually agreed-upon destination.

17. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

18. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

19. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

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21. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A First-in-Human Study of Repeat Dosing with REGN2810, a Monoclonal, Fully Human Antibody to Programmed Death – 1 (PD-1), as Single Therapy and in Combination with Other Anti-Cancer Therapies in Patients with Advanced Malignancies, dated 12 Dec 2014, and agree to abide by all provisions set forth therein.

I agree to comply with the current International Conference on Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

(Signature of Investigator)

(Date)

(Printed Name)

APPENDIX 1. TECHNICAL SPECIFICATIONS AND STRUCTURAL CONSIDERATIONS FOR PLANNING RADIOTHERAPY

Physical Specifications: Conventional linear accelerators and specialized linear accelerators with image guidance are allowed sources. Treatment will be delivered with 4–25 MV photons, with selection of appropriate energies to optimize the dose distribution within the target volume and minimize dose to normal tissue.

Dose verification may be obtained through the use of personal dosimeters (eg, diode, thermoluminescence dosimeter) as per physician and institutional preference, but is not required per protocol.

Localization, Simulation, and Immobilization: Patient positioning will be based on clinical judgment to best achieve the ideal dose distribution. Patients should be positioned in a stable position that allows accurate reproduction of the target position between planning and each treatment. Immobilization systems should be used for planning and treatment when there is expected movement of the target volume with respiration. An abdominal compression device may be used for planning and treatment. A 4D-CT should be used to aid in definition of an internal target volume (ITV).

Localization – Isocenter port localization films (anterior/posterior and lateral or cone-beam CT) should be obtained at each treatment on the treatment unit immediately before treatment to ensure proper alignment of the simulated fields.

Treatment Planning/Target Volumes: CT-based treatment planning will be used for all patients. Axial scan will be required with a maximum of 5 mm spacing between slices.

The target lesion will be outlined by an appropriately trained physician and designated gross tumor volume (GTV). For 4D-CT planning, an ITV will be defined that accounts for respiratory motion. No margin will be given for presumed microscopic extension (thus GTV, ITV, and clinical target volume [CTV] are identical). The planning target volume (PTV) will be determined by the immobilization device used and the individual patient breathing motion. The minimal and maximal PTV margins permitted are 0 mm (if tumor is in contact with stomach or bowel) and 10 mm, respectively, dependent on the immobilization method used and breathing motion. Typical expansion of the GTV will be 5 mm and of the ITV will be 3 mm. Expansion should be limited to prevent expansion into stomach or bowel.

It is recommended that IMRT treatment planning be used for all patients. Typically, ≥ 9 nonopposing, noncoplanar beams should be used; this can be up to the radiologist's discretion.

Critical Organ Dose-Volume Limits: The absolute limits for maximum dose to a point or volume within critical organs are summarized in the following table. **These are absolute limits, and treatment delivery that exceeds these limits will constitute a major protocol violation.** These limits are from the American Association of Physicists in Medicine Task Group 101 report on stereotactic body radiation therapy ([Benedict 2010](#)). To verify each of these limits, the organs must be contoured such that appropriate dose volume histograms can be generated.

Critical Organ Dose-Volume Limits for One Dose

Serial Tissue	Max Vol Above Threshold	1fx Threshold	1fx Dmax	3fx Threshold	3 fx Dmax	5fx Threshold	5fx Dmax	End Point (Grade ≥ 3)
Bladder wall	< 15 cc	11.4 Gy	18.4 Gy	16.8 Gy	28.2 Gy	18.3 Gy	38 Gy	Cystitis/fistula
Brachial plexus	< 3 cc	14 Gy	17.5 Gy	20.4 Gy	24 Gy	27 Gy	30.5 Gy	Neuropathy
Brainstem (not medulla)	< 0.5 cc	10 Gy	15 Gy	18 Gy	23.1 Gy	23 Gy	31 Gy	Cranial neuropathy
Bronchi/small airways	<0.5 cc	12.4 Gy	13.3 Gy	18.9 Gy	23.1 Gy	21 Gy	33 Gy	Stenosis/atelectasis
Cauda equina	< 5 cc	14 Gy	16 Gy	21.9 Gy	24 Gy	30 Gy	32 Gy	Neuritis
Cochlea	N/A	N/A	9 Gy	N/A	17.1 Gy	N/A	25 Gy	Hearing Loss
Colon	< 20 cc	14.3 Gy	18.4 Gy	24 Gy	28.2 Gy	25 Gy	38 Gy	Colitis/fistula
Cord & medulla	< 0.35 cc	10 Gy	14 Gy	18 Gy	21.9 Gy	23 Gy	30 Gy	Myelitis
Cord & medulla	< 1.2 cc	7 Gy	14 Gy	12.3 Gy	21.9 Gy	14.5. Gy	30 Gy	Myelitis
Cord Subvolume (5–6 mm above and below target)	10% of subvolume	10 Gy	14 Gy	18 Gy	21.9 Gy	23 Gy	30 Gy	Myelitis
Duodenum	< 10 cc	9 Gy	12.4 Gy	11.4 Gy	22.2 Gy	12.5 Gy	32 Gy	Ulceration
Duodenum	< 5 cc	11.2 Gy	12.4 Gy	16.5 Gy	22.2 Gy	18 Gy	32 Gy	Ulceration
Esophagus	< 5 cc	11.9 Gy	15.4 Gy	17.7 Gy	25.2 Gy	19.5 Gy	35 Gy	Stenosis/fistula
Femoral heads (each)	< 10 cc	14 Gy	N/A	21.9 Gy	N/A	30 Gy	N/A	Necrosis
Great vessels	< 10 cc	31 Gy	37 Gy	39 Gy	45 Gy	47 Gy	53 Gy	Aneurysm
Heart/pericardium	< 15 cc	16 Gy	22 Gy	24 Gy	30 Gy	32 Gy	38 Gy	Pericarditis
Jejunum/ileum	< 5 cc	11.9 Gy	15.4 Gy	17.7 Gy	25.2 Gy	19.5 Gy	35 Gy	Enteritis/obstruction
Optic pathway	0.2 cc	8 Gy	10 Gy	15.3 Gy	17.4 Gy	23 Gy	25 Gy	Neuritis
Penile bulb	< 3 cc	14 Gy	34 Gy	21.9 Gy	42 Gy	30 Gy	50 Gy	Erectile Dysfunction
Rectum	< 20 cc	14.3 Gy	18.4 Gy	24 Gy	28.2 Gy	25 Gy	38 Gy	Colitis/fistula
Renal hilum (each)	< 2/3rds	10.6 Gy	18.6 Gy	N/A	N/A	23 Gy	N/A	Malignant hypertension
Ribs/chest Wall	< 1 cc	22 Gy	30 Gy	28.8 Gy	36.9 Gy	35 Gy	43 Gy	Pain/fracture

Serial Tissue	Max Vol Above Threshold	1fx Threshold	1fx Dmax	3fx Threshold	3 fx Dmax	5fx Threshold	5fx Dmax	End Point (Grade ≥ 3)
Ribs/chest Wall	< 30 cc	N/A	N/A	30 Gy	36.9 Gy	N/A	N/A	Pain/fracture
Sacral plexus	< 5 cc	14.4 Gy	16 Gy	22.5 Gy	24 Gy	30 Gy	32 Gy	Neuropathy
Skin	< 10 cc	23 Gy	26 Gy	30 Gy	33 Gy	36.5 Gy	39.5 Gy	Ulceration
Stomach	< 10 cc	11.2 Gy	12.4 Gy	16.5 Gy	22.2 Gy	18 Gy	32 Gy	Ulceration
Trachea & large bronchi	< 4 cc	10.5 Gy	20.2 Gy	15 Gy	30 Gy	16.5 Gy	40 Gy	Stenosis/fistula

Dmax=maximum dose; fx=fraction(s); Max Vol=maximum volume.

APPENDIX 2. RECOMMENDED DOSE MODIFICATION OR DISCONTINUATION AND SUPPORTIVE CARE GUIDELINES FOR SPECIFIC DRUG-RELATED ADVERSE EVENTS

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Colitis events <ul style="list-style-type: none"> • Bowel obstruction • Colitis • Colitis microscopic 	≤ Grade 1	No change in dose	<ul style="list-style-type: none"> • For diarrhea, treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet). Endoscopy is recommended if symptoms persist. • Grade 1 diarrhea that persist for >1 week should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily. 	Symptoms may include (but are not limited to): <ul style="list-style-type: none"> • Abdominal pain, cramping and/or bloating • Blood and/or mucus in stool with or without fever • Constipation • Diarrhea • Ileus • Nausea and/or vomiting • Peritoneal signs consistent with bowel perforation • Rectal bleeding • With or without fever Patients with diarrhea should be	All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, and a <i>Clostridium difficile</i> titer.
	Grade 2	Hold until ≤Grade 1. Resume at same dose level. May increase dosing interval by 1 week if it takes more than 4 weeks for toxicities to resolve.	<ul style="list-style-type: none"> • GI consultation and endoscopy is recommended to confirm or rule out colitis for grade 2 diarrhea that persists >1 week or grade 1-2 diarrhea with rectal bleeding (additional guidelines for the treatment of persistent colitis are provided below). • Grade 2 diarrhea should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily. • Grade 2 diarrhea with diffuse ulceration and bleeding seen on endoscopy may require oral steroids with prolonged taper and represent an increased risk for the development of bowel perforation. Consider prophylactic antibiotics for opportunistic infections. • When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • In patients with Grade 2 enterocolitis, REGN2810 should be withheld and antidiarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (eg, 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. 		

Diarrhea: All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Colitis events (continued)	Grade 3–4	<p>Withhold REGN2810</p> <p>Discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisone equivalent within 12 weeks of toxicity</p>	<ul style="list-style-type: none"> In patients with Grade 3 enterocolitis, REGN2810 will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1–2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. Consider prophylactic antibiotics for opportunistic infections. <p>For Grade 3–4 diarrhea (or Grade 2 diarrhea that persists after initial steroid treatment),</p> <ul style="list-style-type: none"> Rule out bowel perforation. Imaging with plain films or computed tomography (CT) can be useful. Consider consultation with gastroenterologist and confirmation biopsy with endoscopy. Treat with intravenous (IV) steroids (methylprednisolone 125 mg) followed by high-dose oral steroids (prednisone 1–2 mg/kg once per day or dexamethasone 4 mg every 4 hours). When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Taper over 6–8 weeks in patients with diffuse and severe ulceration and/or bleeding. If IV steroids followed by high-dose oral steroids does not reduce initial symptoms within 48–72 hours, consider treatment with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45–60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab. CAUTION: infliximab is contraindicated in patients with bowel perforation or sepsis^b. If symptoms persist despite the above treatment a surgical consult should be obtained. 	carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.	

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Endocrine events <ul style="list-style-type: none"> • Hyperthyroidism • Hypophysitis • Hypopituitarism 	Grade 1-2	No change in dose	<ul style="list-style-type: none"> • Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values. 	Symptoms may include (but not limited to): <ul style="list-style-type: none"> • Abdominal pain • Abnormal thyroid function tests and/or serum chemistries (Thyroid-stimulating hormone increased [decreased], Free thyroxine increased, Tri-iodothyronine increased.) • Arrhythmias^c • Cold or heat intolerance • Fatigue • Fever • Headache • Hypotension^c • Loss of appetite • Mental status and/or behavior changes • Nausea and/or vomiting • Unusual bowel habits • Vision disturbances • Weakness 	All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection. An endocrinology consultation is recommended.
Endocrine events <ul style="list-style-type: none"> • Hypothyroidism • Thyroid disorder • Thyroiditis 	Grade 3-4	Hold until on stable replacement dose	<ul style="list-style-type: none"> • Consider endocrine consultation. • Rule out infection and sepsis with appropriate cultures and imaging. • Replacement of appropriate hormones as required. 		
Endocrine events <ul style="list-style-type: none"> • Adrenal insufficiency • Hypophysitis • Pan-hypopituitarism 	Grade 1-4	Hold until on stable replacement dose	<ul style="list-style-type: none"> • Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency. • If Grade 1–2 hypophysitis is considered, pituitary gland imaging should be considered (magnetic resonance imaging [MRIs] with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis). • Grade 3–4 hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis. Hospitalization and IV methylprednisolone should be initiated. 		

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Eye event: Uveitis (iritis, iridocyclitis)	Grade 1	Discontinue REGN2810 if symptoms persist despite treatment with topical immunosuppressive therapy	<ul style="list-style-type: none"> Evaluation by an ophthalmologist is strongly recommended. Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics. 	Symptoms may include (but are not limited to): <ul style="list-style-type: none"> Blurred vision Diffuse erythema and a prominent blush on the sclerae Dryness of the eyes Pain Photophobia 	All attempts should be made to rule out other causes such as metastatic disease, infection, or other ocular disease (e.g., glaucoma or cataracts).
	Grade 2	Discontinue REGN2810 if symptoms persist despite treatment with topical immunosuppressive therapy and do not improve to Grade 1 within the retreatment period OR requires systemic treatment.	<ul style="list-style-type: none"> Evaluation by an ophthalmologist is strongly recommended. Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics. 		
	Grade 3–4	Discontinue REGN2810.	<ul style="list-style-type: none"> Treat with systemic corticosteroids such as prednisone at a dose of 1–2 mg/kg per day. When symptoms improve to ≤Grade 1, steroid taper should be started and continued over no less than 4 weeks. 		
Hepatic events <ul style="list-style-type: none"> Hepatitis Hepatitis, Autoimmune 	Grade 1–2	No change in dose	<ul style="list-style-type: none"> Monitor liver function tests more frequently until returned to baseline values. 	Symptoms may include (but are not limited to): <ul style="list-style-type: none"> Elevations in: <ul style="list-style-type: none"> AST >2.5 × ULN ALT >2.5 × ULN Total bilirubin > 1.5 × ULN Fever Malaise Upper quadrant abdominal pain 	All attempts should be made to rule out other causes such as metastatic disease, progressive liver disease, viral hepatitis, alternative drug toxicity, infectious causes and/or myositis.
	Grade 3–4	Discontinue REGN2810 when AST or ALT >5.0 times ULN and/or total bilirubin >3.0 times ULN.	<ul style="list-style-type: none"> Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury, if necessary. Treat with high-dose IV glucocorticosteroids for 24–48 hours. When symptoms improve to grade 1 or less, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1–2 mg/kg should be started and continued over no less than 4 weeks. If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity^b. Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased 		

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Nausea	≤Grade 1	No change in dose	<ul style="list-style-type: none"> Nausea should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake. 		
	Grade 2	Hold until ≤Grade 1. Resume at same dose level. May increase dosing interval by 1 week if it takes more than 4 weeks for toxicities to resolve.			
	Grade 3	Hold until <Grade 2. May increase dosing interval by 1 week for each occurrence. Discontinue if toxicities do not resolve within 12 weeks.			
	Grade 4	Off protocol therapy			
Neutropenia	≤Grade 1	No change in dose			
	Grade 2	No change in dose			
	Grade 3	No change in dose			
	Grade 4	Hold until resolves to ≤Grade 1. May increase the dosing interval by 1 week. Discontinue if toxicities do not resolve within 12 weeks.			

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Pneumonitis events <ul style="list-style-type: none"> • Pneumonitis • Interstitial lung disease • Acute interstitial pneumonitis 	Grade 1	Consider hold of therapy. REGN2810 may be continued with close monitoring.	<ul style="list-style-type: none"> • Radiologic findings should be followed on serial imaging studies at least every 3 weeks. • Monitor for symptoms every 2–3 days. • Consider pulmonary consultation and/or bronchoscopy if clinically indicated. 	Symptoms may include (but are not limited to): <ul style="list-style-type: none"> • Abnormal breath sounds • Chest pain and/or tightness^c • Dyspnea^c • Dry cough • Fatigue • Fever • Hemoptysis 	All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection.
	Grade 2	Hold REGN2810	<p>To rule out other causes such as infection:</p> <ul style="list-style-type: none"> • Consider pulmonary consultation with bronchoscopy and biopsy/bronchoalveolar lavage (BAL). • Consider pulmonary function tests. • Follow radiologic findings on serial imaging studies every 1–3 days <p>If the patient is determined to have study drug associated pneumonitis:</p> <ul style="list-style-type: none"> • Monitor symptoms daily; consider hospitalization. • Treat with systemic corticosteroids at a dose of 1–2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • Treatment with REGN2810 may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of methylprednisolone 10 mg by mouth daily or less. Repeat chest imaging monthly as clinically indicated. <p>For Grade 2 pneumonitis that improves to ≤ Grade 1 within 12 weeks, the following rules should apply:</p> <ul style="list-style-type: none"> • <u>First episode of pneumonitis</u>: May increase dosing interval by one week in subsequent cycles. • <u>Second episode of pneumonitis</u>: Discontinue REGN2810 if upon rechallenge the patient develops a second episode of ≥ Grade 2 pneumonitis. 		
	Grade 3–4	Discontinue REGN2810.	<ul style="list-style-type: none"> • Consider pulmonary function tests with pulmonary consult. • Bronchoscopy with biopsy and/or BAL is recommended. • Treat with IV steroids (2–4 mg/kg per day prednisone or equivalent). When symptoms improve to grade 1 or less, a high-dose oral steroid (1–2 mg/kg prednisone once per day or 4 mg dexamethasone every 4 hours) taper should be started and continued over no less than 4 weeks. • Add prophylactic antibiotics for opportunistic infections. • If IV steroids followed by high-dose oral steroids does not reduce initial symptoms within 48–72 hours, treat with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45–60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab. 		

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Renal events <ul style="list-style-type: none"> • Nephritis • Nephritis autoimmune • Renal failure • Renal failure, Acute 	Grade 1	Consider withholding REGN2810 if event does not improve with symptomatic treatment	<ul style="list-style-type: none"> • Provide symptomatic treatment. • Monitor creatinine weekly; when it returns to baseline, resume routine creatinine monitoring per protocol. 	Symptoms may include (but not limited to): <ul style="list-style-type: none"> • Fatigue • High blood pressure • Increased serum creatinine • Swelling 	All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury to other chemotherapy agents. A renal consultation is recommended.
	Grade 2	Consider withholding REGN2810.	<ul style="list-style-type: none"> • Systemic corticosteroids at a dose of 1–2 mg/kg/day of prednisone or equivalent may be indicated. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. • Consider prophylactic antibiotics for opportunistic infections. • Consider renal biopsy. • If elevations persist >7 days or worsen, treat as Grade 4. 		
	Grade 3-4	Discontinue REGN2810.	<ul style="list-style-type: none"> • Renal consultation with consideration of ultrasound and/or biopsy as appropriate. • Monitor creatinine daily. • Treat with systemic corticosteroids at a dose of 1–2 mg/kg prednisone or equivalent once per day. • When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • Discontinue REGN2810 if unable to reduce corticosteroid dose for irAEs to ≤10 mg. • REGN2810 treatment may be restarted and the dose modified as specified in the protocol. 		

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Skin events <ul style="list-style-type: none"> • Dermatitis exfoliative • Erythema multiforme • Stevens-Johnson syndrome • Toxic epidermal necrolysis If considered to be immune related, \geq Grade 3 or result in dose modification or discontinuation: <ul style="list-style-type: none"> • Pruritus • Rash • Rash generalized • Rash maculo-papular • Vitiligo 	Grade 1–2	No change in dose	<ul style="list-style-type: none"> • Symptomatic treatment should be given such as topical glucocorticosteroids (eg, betamethasone 0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral antipruritics (eg, diphenhydramine HCl or hydroxyzine HCl). • Treatment with oral steroids is at investigator discretion for Grade 2 events. 		All attempts should be made to rule out other causes such as metastatic disease, infection, or allergic dermatitis.
	Grade 3	Hold REGN2810.	<ul style="list-style-type: none"> • Consider dermatology consultation and biopsy for confirmation of diagnosis. • Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg four times orally daily. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. 		
	Grade 4	Permanently discontinue REGN2810.	<ul style="list-style-type: none"> • Dermatology consultation and consideration of biopsy and clinical dermatology photograph. • Initiate steroids at 1–2 mg/kg prednisone or equivalent. When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. 		
Thrombocytopenia	\leq Grade 1	No change in dose			
	Grade 2	No change in dose			
	Grade 3	No change in dose	<ul style="list-style-type: none"> • Grade 3 drug-related thrombocytopenia >7 days or associated with bleeding requires discontinuation. 		
	Grade 4	Hold REGN2810 until resolves to \leq Grade 1. May increase the dosing interval by 1 week.	<ul style="list-style-type: none"> • Grade 4 drug-related thrombocytopenia >7 days or associated with bleeding requires discontinuation. 		

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Vomiting	≤ Grade 1	No change in dose	<ul style="list-style-type: none"> Vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake. 		
	Grade 2	Hold until ≤Grade 1. Resume at same dose level. May increase dosing interval by 1 week if it takes more than 4 weeks for toxicities to resolve.			
	Grade 3	Hold until <Grade 2. May increase dosing interval by 1 week for each occurrence. Discontinue if toxicities do not resolve within 12 weeks.			
	Grade 4	Off protocol therapy			

^a The signs and symptoms may be associated with any of the diagnoses in the associated “Event(s)” column.

^b REMICADE (Infliximab) prescribing information

^c If symptoms indicate possible new or worsening cardiac abnormalities, additional testing and/or a cardiology consultation should be considered.

APPENDIX 3. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS: RECIST GUIDELINE (VERSION 1.1)

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. Confirmatory scans should also be obtained 4 weeks following initial documentation of objective response or progressive disease.

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1; [Eisenhauer 2009](#)). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Selection of Lesions

- **Measurable disease:** Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm (≥ 2 cm) by chest x-ray or as ≥ 10 mm (≥ 1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).
Note: Refer to [Appendix 6](#) for evaluation of radiated target lesions.
- **Malignant lymph nodes:** To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm (≥ 1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.
- **Non-measurable disease:** All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm [< 1 cm] or pathological lymph nodes with ≥ 10 to < 15 mm [≥ 1 to < 1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

- **Target lesions:** All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest

lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

- **Non-target lesions:** All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- **Clinical lesions.** Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules and palpable lymph nodes) and ≥ 10 mm (≥ 1 cm) diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- **Chest x-ray.** Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Conventional CT and MRI.** This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situation.
- **PET-CT.** At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.
- **Ultrasound.** Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in

their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

- **Endoscopy, Laparoscopy.** The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.
- **Tumor markers.** Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- **Cytology, Histology.** These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (eg, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease

- **FDG-PET.** While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
 - a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
 - b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
 - b. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Response Criteria

Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).
- **Partial Response (PR):** At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

- **Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).
Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease (PD):** Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Immune-Related Response Criteria

Immune-related response criteria differ from RECIST (Version 1.1) in that the sum of the longest diameters of all target lesions AND new lesions if any are used to determine response. The presence of new lesions per se does not determine progression; the total tumor burden is considered.

Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).
- **Partial Response (PR):** At least a 30% decrease in the sum of the diameters of target lesions, including new lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** At least a 20% increase in the sum of the diameters of target lesions, including new lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm).
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study and including the measurements of new lesions.

Evaluation of Non-Target Lesions

- **Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).
- **Note:** If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Overall Response Criteria

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. Revised Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 ([Eisenhauer 2009](#)) and immune-related response criteria (irRC; [Nishino 2013](#)) are summarized in tables within this section.

Response According to Revised Response Evaluation Criteria in Solid Tumors (Version 1.1)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required ^a
CR	CR	No	CR	≥4 weeks confirmation
CR	Non-CR/Non-PD	No	PR	≥4 weeks confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 weeks from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease.

^a In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as PD.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “*symptomatic deterioration*.” Every effort should be made to document the objective progression even after discontinuation of treatment.

Immune-Related Response Criteria Evaluation

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required
CR	CR	No	CR	≥4 weeks Confirmation
CR	Non-CR/Non-PD	No	PR	≥4 weeks. Confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	Yes or No ^a	PR	
SD	Non-CR/Non-PD/not evaluated	Yes or No	SD	Documented at least once ≥4 weeks from baseline
PD	Any	Yes or No ^b	PD	no prior SD, PR or CR
Any	PD ^c	Yes or No	PD	

CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease.

^a Considered to be PR if measurements of target lesions and new lesions ≤ 30% of baseline.

^b Considered to be PD if measurements of target lesions and new lesions ≥ 20% from the lowest measurements.

^c In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as PD.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “*symptomatic deterioration*.” Every effort should be made to document the objective progression even after discontinuation of treatment.

APPENDIX 4. REGN2810 PHARMACOKINETIC SAMPLING AND ASSESSMENT SCHEDULE

Study Visit	PK Sampling Time
cycle 1, day 1	<ul style="list-style-type: none"> • preinfusion • within 10 minutes after end of infusion • 1 hour (\pm 10 minutes) after end of infusion • 4 hours (\pm 10 minutes) after end of infusion • 8 hours (\pm 10 minutes) after end of infusion
cycle 1, day2	24 \pm 1 hours after end of infusion
cycle 1, day 3	48 \pm 3 hours after end of infusion
cycle 1, day 4	72 \pm 3 hours after end of infusion
cycle 1, day 8	any time during visit
cycle 1, days 15 \pm 3, 29 \pm 3, 43 \pm 3	<ul style="list-style-type: none"> • preinfusion • end of infusion
cycles 2–6, day 1	<ul style="list-style-type: none"> • preinfusion • end of infusion
cycles 2–6, day 15 \pm 3	<ul style="list-style-type: none"> • preinfusion • end of infusion
cycles 2–6, day 29 \pm 3	<ul style="list-style-type: none"> • preinfusion • end of infusion
cycles 2–6, day 43 \pm 3	<ul style="list-style-type: none"> • preinfusion • end of infusion

APPENDIX 5. FACTORS TO CONSIDER IN ASSESSING THE RELATIONSHIP OF AES TO REGN2810 OR INFUSION PROCEDURE, STUDY PROCEDURE, OR COMBINATION TREATMENT.

Is there a reasonable possibility that the event may have been caused by the study drugs or infusion procedure, study procedure, or concomitant treatment?

No:

- due to external causes such as environmental factors or other treatment/s being administered
- due to the patient's/subject's disease state or clinical condition
- do not follow a reasonable temporal sequence following the time of administration of the dose of REGN2810, study procedure, or combination treatment
- do not reappear or worsen when dosing with REGN2810, study procedure, or combination treatment is resumed
- are not a known response to REGN2810 or infusion procedure, study procedure, or combination treatment based upon pre-clinical data or prior clinical data

Yes:

- could not be explained by environmental factors or other treatment/s being administered
- could not be explained by the patient's disease state or clinical condition
- follow a reasonable temporal sequence following the time of administration of the dose of REGN2810
- resolve or improve after discontinuation of REGN2810, study procedure, or combination treatment
- reappear or worsen when dosing with REGN2810, study procedure, or combination treatment is resumed
- are known to be a response to REGN2810 or the infusion procedure, study procedure, or combination treatment based upon pre-clinical data or prior clinical data

NOTE: This list is not exhaustive.

APPENDIX 6. EVALUATION OF RADIATED TARGET LESIONS

Radiated target lesions will be evaluated with a modified version of the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1. Additional definitions beyond the RECIST 1.1 guidelines specific to this protocol are incorporated to define local control.

Response Criteria for Radiated Lesions

Local Enlargement (LE)	At least a 20% increase in the LD of target lesion, taking as reference the smallest LD recorded since the treatment started. Ideally, this determination will be made based on CT image evaluation.
Local Failure (LF)	Refers to the primary treated tumor after protocol therapy and corresponds to meeting both of the following two criteria: <ol style="list-style-type: none"> 1. Increase in tumor dimension of 20% as defined above for local enlargement (LE); 2. The measurable tumor with criteria meeting LE should be avid on Positron Emission Tomography (PET) imaging with uptake of a similar intensity as the pretreatment staging PET, OR the measurable tumor should be biopsied confirming viable carcinoma. <p>The EORTC criteria for post-treatment PET evaluation will be used as a basis for evaluation in cases more difficult to assign as to whether the uptake is pathological for cancer recurrence vs inflammation.</p>
Local Control (LC)	The absence of Local Failure.

The longest diameter (LD) for the radiated target lesion calculated from the treatment-planning CT scan, using appropriate tissue-specific windowing, will be reported as the baseline LD. The baseline LD will be used as the reference by which to characterize the objective tumor. For follow-up assessment, diagnostic CT scans performed using a 5 mm contiguous reconstruction algorithm using pulmonary windowing taken as part of scheduled protocol follow-up are preferred as the method of evaluation for response. When CT scans are not available, MRI or x-ray determination will be allowed, as long as the target lesion is clearly visible.

Local treatment effects in the vicinity of the tumor target may make determination of tumor dimensions difficult. For example, bronchial or bronchiolar damage may cause patchy consolidation around the tumor that, over time, may coalesce with the residual tumor. In cases in which it is indeterminate whether consolidation represents residual tumor or treatment effect, it should be assumed that abnormalities are residual tumor.

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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A FIRST-IN-HUMAN STUDY OF REPEAT DOSING WITH REGN2810, A MONOCLONAL, FULLY HUMAN ANTIBODY TO PROGRAMMED DEATH – 1 (PD-1), AS SINGLE THERAPY AND IN COMBINATION WITH OTHER ANTI-CANCER THERAPIES, IN PATIENTS WITH ADVANCED MALIGNANCIES

Compound:	REGN2810 (anti-PD-1 mAb)
Clinical Phase:	1
Protocol Number:	R2810-ONC-1423
Protocol Version:	R2810-ONC-1423 Amendment 7
Amendment 7 Date of Issue	<i>See appended electronic signature page</i>
Amendment 6 Date of Issue:	17 JUL 2017
Amendment 5 Date of Issue:	28 JUN 2016
Amendment 4 Date of Issue:	30 SEP 2015
Amendment 3 Date of Issue:	7 AUG 2015
Amendment 2 Date of Issue:	15 MAY 2015
Amendment 1 Date of Issue:	4 FEB 2015
Original Date of Issue:	12 DEC 2014
Scientific/Medical Monitor:	Elizabeth Stankevich, BS Director, Clinical Sciences, Oncology Matthew Fury, MD, PhD Senior Director, Clinical Sciences, Oncology Petra Rietschel, MD, PhD Director, Clinical Sciences, Oncology Glenn Kroog, MD Senior Director, Clinical Sciences, Oncology Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591

Confidential: This document contains confidential information that is the property of Regeneron Pharmaceuticals, Inc., [REDACTED]

[REDACTED] This information must not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Regeneron Pharmaceuticals, Inc.

AMENDMENT HISTORY

Amendment 7 Global

The following table outlines the changes made to the protocol and the affected sections:

Change	Sections Changed
The protocol is amended to extend the dosing in the retreatment setting for 96 weeks. The rationale for extension is as follows: because the optimal duration of therapy of cemiplimab in patients experiencing clinical benefit is unknown, the duration of retreatment has been extended up to 96 weeks (previously up to 48 weeks).	Synopsis Section 3.1 Study Description and Duration Section 6.2.3 Follow-up

Amendment 6 Global

The following table outlines the changes made to the protocol and the affected sections:

Change	Sections Changed
An exclusion criterion has been added for the following reason: Patients who have previously been treated with idelalisib will be excluded from treatment with REGN2810 as a result of the safety findings for 3 patients with indolent lymphoma previously treated with idelalisib, a phosphatidylinositol 3-kinase (PI 3-K) inhibitor, in study R1979-ONC-1504. Following a single dose of REGN2810 monotherapy in each case, 2 patients experienced severe stomatitis and/or skin reactions. The third patient experienced myositis and myasthenia gravis after 2 doses of REGN2810.	Section 4.2.2 Exclusion Criteria #30
Additional safety guidance language added for the management of patients developing stomatitis or mucositis	Section 5.3.2 Study Treatment Hold or Discontinuation
An adverse event of special interest (AESI) has been added to the list of AESIs: An irAE of any grade in a patient previously treated with a PI 3-K inhibitor.	Section 7.2.3 Other Events that Require Accelerated Reporting

Amendment 5

The purpose of this amendment is to incorporate the following changes:

- Addition of Expansion Cohorts 21 through 26
- Reduction in size of expansion cohorts for tumor types that are not accruing well (MSI) or have been split up into smaller cohorts (NSCLC)
- Reduction in frequency of post treatment follow up scans from q 8 weeks to q 12 weeks
- Reduction in intensity of PK collection schedule, except for cohorts that are testing combinations that are still new for REGN2810 ([Appendix 4](#)).
- Glioblastoma (GBM) radiation therapy (RT) plan revision ([Appendix 7](#))
- Language in Statistics section has been simplified because early stopping rules for futility not needed for some cohorts that have been reduced in sample size (Expansion Cohorts 9,10,11,12, and 13).
- Additional Medical Monitor added to the current list of Scientific/Medical Monitors

These and other changes are outlined below:

<p>Added Expansion Cohorts 21, 22, 23, 24, 25, and 26:</p> <ul style="list-style-type: none"> • Cohort 21: for advanced NSCLC, previously untreated • Cohort 22: for advanced non-squamous NSCLC, previously untreated • Cohort 23: for cervical cancer, recurrent or metastatic (RT not planned) • Cohort 24: for cervical cancer, recurrent or metastatic (palliative RT planned) • Cohort 25: for basal cell carcinoma, refractory or recurring after hedgehog pathway inhibition • Cohort 26: advanced solid tumor 	<p>Section 1.2.1 Rationale for Study Design</p> <p>Section 1.2.3 Rationale for Selected Indications for the Expansion Cohorts</p>
<p>Updated the safety and tolerability objectives for Cohorts 9 through 12, and 14, 15, and 17.</p>	<p>Section 2.1 Primary Objectives</p> <p>Section 2.2 Secondary Objectives</p>
<p>Clarified the Dose Escalation Rules and DLT Monitoring Plan to ensure a cohort will not be expanded beyond 6 patients in the event more than 1 DLT in the first 6 patients.</p>	<p>Section 3.1 Study Description and Duration</p> <p>Section 3.1.2 Dose Escalation Rules</p> <p>Section 3.1.1.2 Expansion Cohorts</p> <p>Section 3.1.2.5 Expansion Cohorts – 6-Patient Run-in Design</p> <p>Section 3.1.3 Dose-Limiting Toxicities</p> <p>Figure 1 Overall Patient Treatment and Follow-Up Timeline (Figure 1D)</p> <p>Table 2 Expansion Cohorts</p>

<p>Updated aspects to the inclusion/exclusion criteria.</p> <ul style="list-style-type: none"> • Amended the number of patients expecting to enroll in the study • Amended the number of sites used in the study • Minor update to inclusion #1 to add criteria for new cohorts and provide clarification for some of the other cohorts • Corrected spelling of aspartate aminotransferase (inclusion #5) • Added platelet count requirement for Expansion Cohort 13 (inclusion #7) • Corrected spelling of antiretroviral (inclusion #13) • (exclusion #5) to clarify corticosteroid use in GBM patients and as a pre-medication for combination therapies • Updated text for invasive malignancy (exclusion #15) 	<p>Clinical Study Protocol Synopsis: Site Locations, Population</p> <p>Section 4.1 Number of Patients Planned</p> <p>Section 4.2.1 Inclusion Criteria #1, #5, #7, #13</p> <p>Section 4.2.2 Exclusion Criteria #5, #15</p>
Updated the timing of the planned Gy radiotherapy.	Section 5.1.2.3 REGN2810 plus Radiation and Cyclophosphamide
Updated timing for administering GM-CSF.	<p>Section 5.1.2.4 REGN2810 plus Radiation and GM-CSF</p> <p>Section 5.1.2.5 REGN2810 plus Radiation, GM-CSF, and Cyclophosphamide</p> <p>Section 5.1.2.6 REGN2810 plus Docetaxel with or without Carboplatin</p> <p>Section 5.1.2.8 Advanced NSCLC, Previously Untreated (Cohort 21, 22, and 23 Full Dose of Chemotherapy)</p>
Pretreatments	Section 5.2 Pretreatments
Clarified the approach to be taken for missed doses.	<p>Section 5.3.2 Study Treatment Hold or Discontinuation</p> <p>Section 5.3.2.1 Guidance for Hematologic Toxicity Management in Cohorts Containing Platinum and/or Taxane-Based Chemotherapy</p> <p>Section 5.3.2.2 Guidance for Non-Hematologic Toxicity Management in Cohorts Containing Platinum and/or Taxane-Based Chemotherapy</p> <p>Section 5.3.2.3 General Rule for All Dose Reductions</p>
Added note for suggested infusion times.	<p>Section 5.7.1 Packaging, Labeling, and Storage</p> <p>Section 5.7.4 Treatment Compliance</p>
Concomitant Medications and Procedures	Section 5.8.2 Prohibited Medications

Updated the schedule of events and footnotes in Table 6 to provide clarification on timing of PK, cytokine samples, and PBMC isolation.	Section 6.2.3 Follow Up criteria for patients who complete 6 cycles of treatment without disease progression and subsequently experience progression of disease without any intervening systemic anticancer therapy, Section 6.3.3.1 Vital signs assessments for paclitaxel plus carboplatin and pemetrexed plus carboplatin updated. Table 6 Study Schedule (Screening and Treatment) Section 6.3.2 Efficacy Procedures
Updates CT/MRI (chest/abdomen/pelvis), PK/ADA sample collection, and added survival test for the follow-up visit.	Table 8 Study Schedule (Follow-Up) Section 6.3.2 Efficacy Procedures
Added “and/or mRNA” to the list of analyzed exploratory biomarker procedures and that DNA/RNA samples will be double-coded.	Section 6.3.5.1 Exploratory Biomarker Procedures
Adverse Events recording and reporting for carboplatin added	Section 7.2.1 Adverse Events
Pharmacokinetic variable descriptions updated.	Section 8.3 Pharmacokinetic Variables
Anti-drug antibodies variable descriptions updated.	Section 8.4 Anti-drug Antibody Variables
Updated definition for patient included in the PK analysis set.	Section 9.1 Justification of Sample Size Section 9.2.2 Pharmacokinetic Analysis Set
Updated definition for patients in the ADA population.	Section 9.2.3 Anti-Drug Antibody Set
Updated the efficacy analyses and clarified hypothesis testing will only be performed on Expansion Cohorts 2, 3, 4, and 6.	Section 9.4.2 Efficacy Analyses
Clarified that compartmental analysis data will be collected and presented in a separate report.	Section 9.4.4.3 Compartmental Analysis Section 9.6 Interim Analysis
New references added.	Section 20 References
Critical Organ Dose-Volume Limits for One Dose Table updated.	Appendix 1 Technical Specifications and Structural Considerations for Planning Radiotherapy (Non-GBM) Appendix 4 REGN2810 Pharmacokinetic Sampling and Assessment Schedule
Treatment planning /Target volumes section updated	Appendix 7 Technical Specifications and Structural Considerations for Planning Radiotherapy for Glioblastoma Patients

Amendment 4

The purpose of this amendment is to incorporate the following changes:

- To reduce the number of patients enrolled in the expansion cohorts for cutaneous squamous cell cancer (CSCC) as a dedicated CSCC study will be conducted.
- To revise the permitted methods of contraception to only those considered highly effective according to the 2014 recommendations of the Clinical Trial Facilitation Group.

Amendment 3

The purpose of this amendment is to add expansion cohorts to explore PD-1 blockade in patient populations with the following advanced cancers: 1) cutaneous squamous cell cancer (CSCC); 2) colorectal cancer with microsatellite instability (MSI); 3) endometrial cancer with MSI; 4) prostate cancer with MSI; 5) other advanced solid tumors with MSI; 6) hepatocellular carcinoma (HCC); 7) advanced solid tumors, refractory to first-line therapy, in which treatment with carboplatin and/or docetaxel is clinically appropriate; 8) advanced non-small cell lung cancer (NSCLC), previously untreated; 9) newly diagnosed or recurrent glioblastoma multiforme (GBM); 10) Human immunodeficiency virus (HIV) infection and advanced solid tumors.

In the following new expansion cohorts, patients will receive REGN2810 3 mg/kg monotherapy every 14 days (cohorts are grouped by treatment plan):

- Expansion Cohort 7 – Metastatic (M1) CSCC
- Expansion Cohort 8 – Locally and/or regionally advanced CSCC (M0) that is unresectable
- Expansion Cohorts 9 and 16 – Metastatic colorectal cancer with MSI, with progression of disease after 2 lines of systemic therapy for recurrent and/or metastatic disease (Cohort 9), or previously untreated for metastatic disease (Cohort 16)
- Expansion Cohort 10 – Metastatic endometrial cancer with MSI, with progression of disease after first line systemic therapy for recurrent and/or metastatic disease
- Expansion Cohort 11 - Castrate recurrent prostate cancer with MSI, with progression of disease after docetaxel
- Expansion Cohort 12 – Any other (non-colorectal, endometrial, or prostate) advanced solid tumor with MSI, with progression of disease after standard therapy
- Expansion Cohort 13 – Advanced or metastatic HCC
- Expansion Cohort 20 - Advanced solid tumors in patients infected with HIV

In the following new expansion cohorts, patients will receive REGN2810 in combination with low-dose chemotherapy in cycle 1:

- Expansion Cohort 14 - Advanced solid tumors that are refractory to first line chemotherapy for recurrent/metastatic disease, in which treatment with carboplatin and docetaxel is clinically appropriate
- Expansion Cohort 15 - Advanced solid tumors that are refractory to first line chemotherapy for recurrent/metastatic disease, in which treatment with docetaxel is clinically appropriate
- Expansion Cohort 17 - Advanced NSCLC, previously untreated, in which treatment with carboplatin and docetaxel is clinically appropriate.

In the following expansion cohorts, GBM patients will receive REGN2810 in combination with radiation therapy (6 Gy x 5 days):

- Expansion Cohort 18 - Newly diagnosed GBM, unmethylated at the MGMT promoter
- Expansion Cohort 19 - Recurrent GBM

Amendment 2

The purpose of this amendment is to add expansion cohorts to: 1) Explore PD-1 blockade in combination with radiation treatment, radiation treatment and cyclophosphamide, and radiation treatment plus cyclophosphamide and GM-CSF; 2) Evaluate the flat dosing of REGN2810; and 3) Treat patients who have progressed on another anti-PD-1/PD-L1 antibodies with REGN2810. The following expansion cohorts have been added:

- Expansion Cohort 1 - NSCLC: REGN2810 at a flat dose of 200 mg.
- Expansion Cohort 2 - NSCLC: 3 mg/kg REGN2810 + radiotherapy (9 Gy × 3)
- Expansion Cohort 3 - H&N: 3 mg/kg REGN2810 + radiotherapy (9 Gy × 3) + cyclophosphamide + GM-CSF
- Expansion Cohort 4 - BC: 3 mg/kg REGN2810 + radiotherapy (9 Gy × 3) + cyclophosphamide
- Expansion Cohort 5 - Advanced solid tumors in patients previously treated with another anti-PD-1/PD-L1 antibody; patients have progressed after achieving disease control (CR, PR, SD for at least 8 weeks): 3 mg/kg REGN2810+ radiotherapy (9 Gy x 3)+ cyclophosphamide + GM-CSF.
- Expansion Cohort 6 - Advanced solid tumors, excluding NSCLC, H&N, and BC; 3 mg/kg REGN2810+ radiotherapy (9 Gy × 3) + cyclophosphamide + GM-CSF

Amendment 1

The purpose of this amendment is to incorporate the following changes and clarifications requested by the FDA:

- Clarification that the planned route of administration of cyclophosphamide is intravenous (IV).
- Added criteria specifying that the absolute neutrophil count (ANC) must be greater than 1000/ μ L before administering cyclophosphamide on days 14, 28, and 42.
- Clarification that patients are required to have confirmed histological or cytological evidence of malignancies at study entry.
- Details added to inclusion criterion 2 specifying the response criteria to be used (RECIST 1.1), as well as a more detailed definition for 'medically appropriate'.
- Deletion of the statement that patients who are unwilling to undergo standard therapy are the target population for this study, as it was inconsistent with the inclusion criteria.
- Added sub-bullet to the hepatic function inclusion criterion excluding patients with hepatic lesions who have high aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) and high bilirubin simultaneously.
- Added exclusion criterion to exclude those patients with known hypersensitivity to cyclophosphamide from enrolling in cohorts receiving cyclophosphamide.
- Clarification that patients should continue contraception practice until 6 months after the last dose of study drug.
- Clarification that no premedication are to be administered for the first dose of REGN2810.
- Clarification that patients with confirmed and increasing progressive disease (PD) per RECIST (2 radiologic assessments of PD at least 4 weeks apart), or patients who are rapidly progressing and/or experiencing significant clinical deterioration, should discontinue study treatment.
- Clarification that REGN2810 will be withheld if there is a treatment-emergent concurrent elevation of ALT and bilirubin that corresponds to an upward shift of 2 or more grades in both parameters.

Other modifications include:

- Deletion of physical examination, vital signs, and weight assessments from the cycle 1 day 56 study visit, as it is a scanning visit only.
- The tumor-specific markers assessment has been removed from Tables 4 and 5 as the content is covered in the text for research serum samples. Footnotes for archived tumor material and optional tumor biopsy have been corrected in Table 4.
- Vital sign collection time points have been reduced following the cycle 1 day 1 visit.
- Typographical corrections.

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A First-in-Human Study of Repeat Dosing with REGN2810, a Monoclonal, Fully Human Antibody to Programmed Death – 1 (PD-1), as Single Therapy and in Combination with Other Anti-Cancer Therapies, in Patients with Advanced Malignancies
Site Locations	Up to 50 sites in North America, the EU, and Asia-Pacific
Objectives	<p>The co-primary objectives of the study are:</p> <ul style="list-style-type: none"> For Dose Escalation and Expansion Cohorts: to characterize the safety, tolerability, DLTs of REGN2810 administered IV as monotherapy, or in combination with targeted radiation (with the intent to have this serve as an immuno-stimulatory, rather than primarily tumor-ablative therapy), low dose cyclophosphamide (a therapy shown to inhibit regulatory T-cell responses) administered IV, or both radiation and cyclophosphamide with or without GM-CSF, or in combination with low dose carboplatin plus docetaxel, or in combination with low dose docetaxel, or in combination with full dose carboplatin plus paclitaxel, or carboplatin plus pemetrexed in patients with advanced malignancies. For selected expansion cohorts (Expansion Cohorts 2 through 4): to evaluate the efficacy of REGN2810, alone or in combination therapy, by measuring overall response rate. <p>The secondary objectives of the study are:</p> <ul style="list-style-type: none"> To determine a recommended phase 2 dose (RP2D) of REGN2810 as monotherapy and in combination with other anti-cancer therapies (targeted radiation, low-dose cyclophosphamide, targeted radiation plus low dose cyclophosphamide with or without GM-CSF, low dose carboplatin plus docetaxel or in combination with low dose docetaxel, or in combination with full dose carboplatin plus paclitaxel, or carboplatin plus pemetrexed) To describe antitumor activity of REGN2810, alone and with each combination partner(s) <p>In the expansion cohorts, activity measurements will include quantitative analysis of time to response, as well as depth of response (area under the concentration time curve [AUC] of tumor burden), in addition to standard overall response assessments:</p> <ul style="list-style-type: none"> Expansion Cohort 1 – non-small-cell lung cancer (NSCLC): REGN2810 at a flat dose of 200 mg Expansion Cohort 2 - NSCLC: 3 mg/kg REGN2810 + radiotherapy (9 Gy × 3) Expansion Cohort 3 – head & neck squamous cell carcinoma (HNSCC): 3 mg/kg REGN2810 + radiotherapy (9 Gy × 3) + cyclophosphamide + GM-CSF

-
- Expansion Cohort 4 – breast cancer (BC): 3 mg/kg REGN2810 + radiotherapy (9 Gy × 3) + cyclophosphamide
 - Expansion Cohort 5 - Patients who have progressed after achieving disease control (complete response [CR], partial response [PR], SD for at least 8 weeks) with another programmed death-1 (PD-1)/ programmed death ligand 1 (PD-L1) antibody: 3 mg/kg REGN2810 + radiotherapy (9 Gy × 3) + cyclophosphamide + (GM-CSF)
 - Expansion Cohort 6 - Advanced solid tumors, excluding NSCLC, HNSCC, and BC: 3 mg/kg REGN2810 + radiotherapy (9 Gy × 3) + cyclophosphamide + GM-CSF
 - To describe the safety and tolerability of the following treatment regimens:
 - Expansion Cohorts 7 and 8 – CSCC, metastatic, M1 (Cohort 7) or locally and/or regionally advanced, unresectable, M0 (Cohort 8): 3 mg/kg REGN2810
 - Expansion Cohorts 9 through 12 – Advanced solid tumors with MSI arising in the colon (Cohort 9), endometrium (Cohort 10), prostate (Cohort 11), or other primary MSI solid tumor not eligible for other MSI cohorts (Cohort 12): 3 mg/kg REGN2810
 - Expansion Cohort 13 – advanced or metastatic HCC: 3 mg/kg REGN2810
 - Expansion Cohorts 14 and 15 - Advanced solid tumors: 3 mg/kg REGN2810 + carboplatin + docetaxel (Cohort 14), or 3 mg/kg REN2810 + docetaxel (Cohort 15)
 - Expansion Cohort 16 - Metastatic colorectal cancer with MSI, previously untreated (prior adjuvant chemotherapy is allowed): 3 mg/kg REGN2810
 - Expansion Cohort 17: Advanced NSCLC, previously untreated: 3 mg/kg REGN2810 + low dose carboplatin + low dose docetaxel
 - Expansion Cohorts 18 and 19 - Newly diagnosed glioblastoma multiforme (GBM), unmethylated at the MGMT promoter: REGN2810 (1 or 3 mg/kg) + radiotherapy (6 Gy x 5 days) (Cohort 18), or recurrent GBM: REGN2810 (1 or 3 mg/kg) + radiotherapy (6 Gy x 5 days) (Cohort 19)
 - Expansion Cohort 20 – Human immunodeficiency virus (HIV) and advanced solid tumors: 3 mg/kg REGN2810
 - Expansion Cohorts 21 and 22 - advanced NSCLC, previously untreated: 3 mg/kg REGN2810 + full dose platinum doublet
 - Expansion Cohort 23 and 24: Recurrent or metastatic cervical cancer, resistant to or intolerant of platinum + taxane doublet chemotherapy : 3 mg/kg REGN2810 monotherapy (Cohort 23) or with hypofractionated RT (9 Gy X 3; Cohort 24)
-

-
- Expansion Cohort 25: cutaneous basal cell carcinoma (BCC), unresectable locally advanced and/or metastatic, resistant to or intolerant of a hedgehog pathway inhibitor (vismodegib or sonidegib)
 - Expansion Cohort 26 ([REDACTED]): Any advanced solid tumors.
- To characterize the pharmacokinetics (PK) of REGN2810 as monotherapy and in combination with other anti-cancer therapies
 - To assess immunogenicity of REGN2810
 - For all expansion cohorts, to summarize PFS and overall survival
-

Study Design

This is a phase 1, open-label, multicenter, ascending-dose escalation study of REGN2810, alone and in combination with radiation therapy, cyclophosphamide, or radiation therapy plus cyclophosphamide, or GM-CSF, or in combination with low dose carboplatin plus docetaxel, or in combination with low dose docetaxel, or in combination with full dose carboplatin plus paclitaxel, or carboplatin plus pemetrexed in patients with advanced malignancies.

In the dose-escalation phase, safety will be assessed in separate, standard 3 + 3 dose escalation cohorts (in monotherapy, combination with radiation therapy, combination with cyclophosphamide, and combination with radiation therapy plus cyclophosphamide).

Following dose escalation, multiple expansion cohorts will be explored in select indications.

After a screening period of up to 28 days, patients will receive up to six 56 day treatment cycles for a total of up to 48 weeks of treatment, followed by a 24 week follow-up period. Each patient will be administered REGN2810 on days 1, 15±3, 29±3, and 43±3 during each treatment cycle. Patients enrolled to combination therapy cohorts may also receive 1 of 2 radiation therapy regimens, cyclophosphamide, or both cyclophosphamide and 1 of 2 radiotherapy regimens. Tumor assessments will be made at the end of each treatment cycle. Extensive safety evaluations made at baseline/cycle 1, day 1 of dosing will be repeated on day 1 of each treatment cycle throughout the study, with routine safety evaluations to be conducted at each REGN2810 dosing visit.

In the expansion cohorts, patients may also receive REGN2810 in combination with GM-CSF and radiotherapy, or in combination with GM-CSF, radiotherapy, and cyclophosphamide, or in combination with low dose carboplatin plus docetaxel, or in combination with low dose docetaxel, or in combination with full dose carboplatin plus paclitaxel, or carboplatin plus pemetrexed. In cohorts featuring full dose chemotherapy, REGN2810 will be administered as 3 mg/kg every 3 weeks. Several expansion cohorts feature REGN2810 monotherapy.

Patients whose tumors progress during post-treatment follow up (after

	completion of planned treatment) may be eligible for retreatment for up to 96 weeks.
Study Duration	Patients will receive up to 48 weeks of treatment, after which there will be a 24 week follow-up period. A patient will receive treatment until the 48 week treatment period is complete, or until disease progression, unacceptable toxicity, withdrawal of consent, or meeting of another study withdrawal criterion. After a minimum of 24 weeks of treatment, patients with confirmed complete responses (CR) may elect to discontinue treatment and continue with all relevant study assessments (eg, efficacy assessments) as scheduled per protocol. After a minimum of 24 weeks of treatment and after consultation with the investigator and the Sponsor, patients with tumor burden assessments of stable disease (SD) or partial response (PR) that have been unchanged for 3 successive tumor evaluations may also elect to discontinue treatment and continue with all relevant study assessments (eg, efficacy assessments) as scheduled per protocol.
Population	
Sample Size:	Up to 560 adult patients are expected to be enrolled. The total number of patients enrolled will depend upon observed DLTs.
Target Population:	Patients with advanced malignancies that are incurable and have failed to respond to or showed tumor progression despite standard therapy, or patients who are not candidates for standard therapy, or for whom no available therapy is expected to convey clinical benefit, or for whom PD-1 blockade has been shown to be at least equivalent to standard of care.
Treatments	
Study Drug Dose/Route/Schedule:	<ul style="list-style-type: none"> • REGN2810 at 1 or 3 mg/kg administered IV over 30 minutes every 14 days for 48 weeks, alone or in combination with: <ul style="list-style-type: none"> – Radiotherapy (30 Gy administered as 5 doses of 6 Gy over 1 week) given 1 week after the first dose of REGN2810 OR – Radiotherapy (27 Gy administered as 3 doses of 9 Gy over 1 week) given 1 week after the first dose of REGN2810 OR – Low-dose cyclophosphamide (200 mg/m² IV) approximately once every 14 days for 4 doses, starting day –1, and given 1 day prior to each of the first 4 REGN2810 doses, OR – Radiotherapy (30 Gy administered as 5 doses of 6 Gy over 1 week) given 1 week after the first dose of REGN2810 plus low-dose cyclophosphamide (200 mg/m² IV) approximately once every 14 days for 4 doses, starting day –1, and given 1 day prior to each of the first 4 REGN2810 doses, OR – Radiotherapy (27 Gy administered as 3 doses of 9 Gy over 1 week) given 1 week after the first dose of REGN2810 plus low-dose cyclophosphamide (200 mg/m² IV) approximately once every 14 days for 4 doses, starting day –1, and given 1 day prior to each of the first 4 REGN2810 doses, • REGN2810 10 mg/ administered IV over 30 minutes every 14 days for

48 weeks.

The REGN2810 plus radiation, and GM-CSF regimen includes:

- GM-CSF 250 mcg subcutaneous (SC) daily for 7 days, for four 7-day cycles (days 1 through 7, 15 through 21, 29 through 35, and 43 through 49 of the first 56-day cycle).
- plus
- 27 Gy radiotherapy (9 Gy \times 3 times/week; starting 6 or 8 days after the first dose of REGN2810, preferably not on consecutive days)
- plus
- 3 mg/kg REGN2810 infusion over 30 minutes every 14 days for 48 weeks (provided monotherapy dose of 3 mg/kg < maximum tolerated dose (MTD); if 3 mg/kg > MTD, dose will be 1 mg/kg)

The REGN2810 plus radiation, GM-CSF, and cyclophosphamide regimen includes:

- GM-CSF 250 mcg SC daily for 7 days, for four 7-day cycles (days 1 through 7, 15 through 21, 29 through 35, and 43 through 49 of the first 56-day cycle).
- plus
- 27 Gy radiotherapy (9 Gy \times 3 times/week; starting 6 or 8 days after the first dose of REGN2810, preferably not on consecutive days)
- plus
- Cyclophosphamide 200 mg/m² IV every 14 days (days - 1, 14, 28, and 42 of the first 56 day cycle) for a total of 4 doses
- plus
- 3 mg/kg REGN2810 infusion over 30 minutes every 14 days for 48 weeks (provided monotherapy dose of 3 mg/kg < MTD; if 3 mg/kg > MTD, dose will be 1 mg/kg)

For cohorts receiving carboplatin and docetaxel, or docetaxel, the suggested sequence of drug administration is docetaxel followed by carboplatin (if enrolled in a carboplatin-containing cohort), followed by REGN2810:

- Docetaxel 30 mg/m² IV over approximately 1 hour on days 1, 8, 29, and 36 of the first 56-day cycle. Dexamethasone 8 mg IV will be administered prior to the first dose of docetaxel. For subsequent docetaxel treatments, the dose of dexamethasone premedication may be 8 mg or 4 mg, per investigator discretion
 - Carboplatin AUC 2 IV over approximately 30 minutes on days 1, 8, 29, and 36 of the first 56-day cycle.
 - 3 mg/kg REGN2810 infusion over approximately 30 minutes every
-

14 days for 48 weeks

For cohorts receiving carboplatin plus paclitaxel, the suggested sequence of drug administration is

- 3 mg/kg REGN2810 infusion over approximately 30 minutes every 21 days for 48 weeks (16 planned treatments of REGN2810).
- Paclitaxel 200 mg/m² is administered IV over approximately 3 hours on day 1 of each of the 4 planned 21-day paclitaxel treatment intervals.
- Carboplatin AUC 6 is administered IV over approximately 30 minutes on day 1 of each of the 4 planned 21-day carboplatin treatment intervals.

For cohorts receiving carboplatin plus pemetrexed regimen, the suggested sequence of drug administration is

- 3 mg/kg REGN2810 infusion over approximately 30 minutes every 21 days for 48 weeks (16 planned treatments of REGN2810).
- Pemetrexed 500 mg/m² is administered IV over approximately 10 minutes on day 1 of each of the 4 planned 21-day pemetrexed treatment intervals.
- It is the intent of the study that pemetrexed and carboplatin will be discontinued at the end of 4 treatments. If the investigator wishes to continue maintenance pemetrexed after the initial 4 planned treatments, this may be allowed after communication with and approval from medical monitor.
- Carboplatin is administered IV over approximately 30 minutes on day 1 of each of each of the 4 planned 21-day carboplatin treatment intervals.

Assignment of a patient to a treatment cohort will be determined by occurrence of DLTs/establishment of a MTD in prior cohorts, the investigator's assessment of the appropriateness of therapies for the patient, and the availability of patient slots.

Variables**Primary:**

Primary safety variables include incidence of DLTs, incidence and severity of treatment-emergent adverse events (TEAEs), and abnormal laboratory findings through 48 weeks of treatment

Secondary:	<p>Key secondary variables include the following:</p> <ul style="list-style-type: none">• Serum concentration and PK of REGN2810• Antitumor activities assessed using the appropriate criteria for the indication:<ul style="list-style-type: none">– Response Evaluation Criteria in Solid Tumors (RECIST) criteria measured by computed tomography (CT) or magnetic resonance imaging (MRI)– Other assessment criteria should also be used for specific tumors in which RECIST measurements are not the standard.– Immune-Related Response Criteria (irRC) applied to RECIST measurements. <p>In all cases, RECIST (or other tumor-specific criteria) will be the governing tool to determine progression of disease (PD), SD, CR, or PR. The irRC will be collected for clinical decisions and information purposes.</p> <ul style="list-style-type: none">• Anti-REGN2810 antibodies• Antitumor activity measured by PFS and overall survival
Procedures and Assessments	<p>Tumor imaging (CT or MRI) will be performed to measure tumor burden and to characterize the efficacy profile of study treatments using RECIST (or other tumor-specific criteria).</p> <p>Physical examination, laboratory tests, vital signs, electrocardiogram (ECG), pregnancy test for women of childbearing potential, and recording of AEs and concomitant medications will be performed to ensure patient safety and to characterize the safety profiles of study treatments.</p> <p>Other assessments will include:</p> <ul style="list-style-type: none">• Pharmacokinetic/Pharmacodynamic samples• Tumor biopsies (optional during the dose escalation portion of the study, but should be obtained for all patients in the expansion cohorts)• Biomarkers (cellular and molecular) as well as tumor and genomic genetic markers related to REGN2810 treatment exposure, clinical activity, or underlying disease

Statistical Plan

The dose escalation portion of the study is based on a traditional 3 + 3 design with 3 to 6 patients assigned per dose level. The exact number of patients enrolled in the study will depend on the number of protocol-defined DLTs observed, and the need to expand currently defined dose levels, or open additional cohorts at lower dose levels. After the required initial enrollment to the next cohort in the dose escalation has occurred, enrollment to each of the previous cohorts below the MTD for that treatment will be expanded (if not previously expanded during escalation) to a total of 6 patients.

Data will be summarized using descriptive statistics only. In general, data will be summarized by dose levels and combinations. The safety summaries and analyses will be performed on the safety analysis set (SAF). The primary analysis of safety will be based on treatment-emergent AEs (TEAEs).

For the expansion cohorts, data will be summarized using descriptive statistics, along with 2-sided 95% confidence interval, by dose cohort and/or diagnosis.

Continuous variables will be summarized with mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized with frequency and percentage. Time-to-event variables will be summarized with Kaplan-Meier curves and estimates.

The exact binomial test and Kaplan-Meier estimates may be performed for expansion cohorts with formal hypotheses, per the statistical design.

The objective of the interim analysis in this study is to stop enrollment in a cohort if the treatment is not efficacious, ie, a futility stopping rule rather than an efficacy stopping rule. Interim analyses for futility will be performed within each cohort, if applicable. The futility stopping rule is determined by utilizing stage I stopping criteria from the Optimal Simon 2-stage design with 1-sided type I error rate of 5%, power of 90% for respective null hypotheses in each cohort. The interim analysis for futility will be performed once Stage I patients have enrolled into each cohort and completed 2 tumor assessments. The stopping rule will be based on the number of responders observed at the time of the interim analysis.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations	Definition of Term
ADL	Activities of Daily Living
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ARGUS	Pharmacovigilance and clinical safety software system
AST	Aspartate aminotransferase
AUC	Area under the concentration–time curve
BAL	Bronchoalveolar lavage
BC	Breast cancer
BCC	Basal cell carcinoma
BUN	Blood urea nitrogen
CPA	Cyclophosphamide
CR	Complete response
CRF; eCRF	Case report form (electronic or paper); electronic case report form
CRO	Contract research organization
CRP	C-reactive protein
CSCC	Cutaneous squamous cell cancer
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte antigen 4
CTV	Clinical target volume
(NCI-) CTCAE	(National Cancer Institute) Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
Dmax	Maximum radiation dose
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic data capture
FDG-PET	¹⁸ F-fluorodeoxyglucose positron emission tomography
FFPE	Formalin-fixed, paraffin-embedded
FNA	Fine-needle aspirate
fx	Fraction(s)

Abbreviations	Definition of Term
GCP	Good clinical practice
GBM	Glioblastoma multiforme
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GnRH	Gonadotropin-releasing hormone
GTV	Gross tumor volume
HCC	Hepatocellular carcinoma
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papillomavirus
ICF	Informed consent form
ICH	International Council for Harmonisation
IHC	Immunohistochemistry
INR	International Normalized Ratio
irRC	Immune-related response criteria
IRB	Institutional Review Board
irAE	Immune-related adverse event
ITV	Internal target volume
IUD	Intrauterine device
IV	Intravenous
LC	Local control
LD	Longest diameter
LE	Local enlargement
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LLOQ	Lower limit of quantification
mAb	Monoclonal antibody
Max Vol	Maximum (tissue) volume
MedDRA	Medical Dictionary for Regulatory Activities
monoRX	Monotherapy
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MTD	Maximum tolerated dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NOAEL	No-observed-adverse-effect level

Abbreviations	Definition of Term
NSCLC	Non-small-cell lung cancer
PBMC	Peripheral blood mononucleated cell
PD-1	Programmed death-1 (receptor)
PD-L1, PD-L2	Programmed death ligand 1, programmed death ligand 2
PET	Positron-emission tomography
PFS	Progression-free survival
PI 3-K	Phosphatidylinositol 3-kinase
PK	Pharmacokinetic
PR	Partial response
PT	Preferred term
PTV	Planning target volume
RANO	Response Assessment in Neuro-Oncology
RBC	Red blood cell
RCC	Renal cell cancer
RECIST	Response Evaluation Criteria in Solid Tumors
Regeneron	Regeneron Pharmaceuticals, Inc.
RF	Rheumatoid factor
RILD	Radiation-induced liver disease
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Systems (software)
SC	Subcutaneous
SCHNC	Squamous-cell head and neck cancer
SOC	System organ class
SSA	Sjögren's syndrome A antigen
SSB	Sjögren's syndrome B antigen
$t_{1/2}$	Beta-phase terminal half life
TEAE	Treatment-emergent adverse event
TSA	A mouse mammary adenocarcinoma cell line
TSH	Thyroid-stimulating hormone
US	United States
WBC	White blood cell
XRT	Radiotherapy

1. INTRODUCTION AND RATIONALE

1.1. Introduction

Enhancement of the anti-tumor immune response with cancer immunotherapy agents has emerged as a highly effective and complementary approach to the therapeutic mainstays of surgery, cytotoxic drugs, targeted therapeutics, and radiation. Moreover, induction of durable and extensive tumor regressions suggest that immunotherapy may convert previously fatal diseases into chronic, manageable ones for some patients.

Under chronic stimulation, T cells lose proliferative and effector function capacity, often due to signal down-modulation via the increased expression of proteins such as PD-1, an inhibitory checkpoint receptor of the CD28 receptor family. The ligand for the PD-1 receptor, PD-L1, is expressed in a variety of human malignancies ([Zou 2008](#)), and its high level of expression has been previously correlated with poor patient prognosis and resistance to treatment in non-small-cell lung cancer (NSCLC; [Creelan 2014](#)), glioblastoma multiforme (GBM; [Wei 2014](#)), and squamous-cell carcinoma of head and neck (SCCHN; [Zandberg 2014](#)). Binding of ligand (PD-L1 or PD-L2), often expressed on tumor cells, to PD-1 imparts an inhibitory signal to the T cell, thus down-modulating the anti-tumor T-cell response ([Francisco 2010](#)).

Blockade of the PD-1/PD-L1 T-cell checkpoint pathway is an effective and well tolerated approach to stimulating the immune response, and has achieved significant objective responses in advanced, melanoma, renal cell cancer (RCC), and NSCLC ([Topalian 2012](#)). However, optimal therapy will likely require combining anti-PD-1 monoclonal antibody (mAb) treatment with conventional therapies and novel immunotherapy approaches. Combinatorial approaches to stimulate convergent aspects of host immunity by employing complementary immunomodulators as well as immune-stimulatory aspects of conventional modalities such as radiation and chemotherapy may result in the development of more effective cancer therapies. Combination blockade of PD-1 and the cytotoxic T-lymphocyte antigen 4 (CTLA-4) is effective in controlling growth of syngeneic mouse tumors of ID8-VEGF ovarian carcinoma and CT26 colon carcinoma cell lines in immune-competent mice, providing support to this notion ([Duraismamy 2013](#)). Furthermore, adding blockade of CTLA-4 to PD-1 blockade in melanoma patients achieves response rates twice of that achieved with anti-PD-1 alone (ie, >50%; [Wolchok 2013](#)). In a subset of patients with PD-L1+ tumors, preliminary results demonstrated an enhanced systemic response when treatment with an anti-PD-L1 antibody (MPDL3280A) coincided with palliative local irradiation ([Sagiv-Barfi 2014](#)).

REGN2810 is a high-affinity, fully human, hinge-stabilized IgG4P antibody directed to the PD-1 receptor that potently blocks the interaction of PD-1 with its ligands, PD-L1 and PD-L2. In syngeneic tumor models in immunocompetent mice humanized for PD-1, the antitumor activity of REGN2810 delivered as a monotherapy against a mouse colon adenocarcinoma tumor line is similar to that observed with antibodies generated in house based on the publically available genetic sequences of pembrolizumab and nivolumab, anti-PD-1 antibodies approved for the treatment of melanoma, and in late-stage development for use against several other malignancies. (See the Investigator's Brochure for further details of nonclinical pharmacology and antitumor activity of REGN2810).

This first-in-human protocol is designed to assess the safety of REGN2810, as monotherapy at different dose levels and in combination with selected other anti-tumor agents that may augment the potency and durability of anti-tumor immune response. Based on the premise that select combination therapies may be more active than PD-1 blockade monotherapy, therapies initially combining REGN2810 with cyclophosphamide, radiation therapy, or both will be tested in patients with advanced malignancies for whom a standard curative therapy does not exist.

Additional expansion cohorts to assess the safety and activity of REGN2810 either alone or in combination with other therapies in NSCLC, head and neck squamous cell cancer (HNSCC), breast cancer (BC), cutaneous squamous cell carcinoma (CSCC), tumors with microsatellite instability (MSI); colorectal, endometrial, prostate, and other tumor types, hepatocellular carcinoma (HCC), and GBM patients, as well as in patients with other advanced solid tumors, including patients infected with human immunodeficiency virus (HIV), will be added once the dose escalation cohorts have enrolled and completed the dose-limiting toxicity (DLT) observation period. In addition, flat dosing of REGN2810 and treatment with REGN2810 in patients who have progressed after showing clinical benefit to treatment with other anti-PD-1/PD-L1 antibodies will be explored.

Additional background information on the study drug and development program can be found in the Investigator's Brochure.

1.2. Rationale

1.2.1. Rationale for Study Design

The 3 + 3 model for the dose-escalation phase of this first-in-human study is designed to permit evaluation of the safety of REGN2810, both as monotherapy at different dose levels, and in combination with immune-enhancing treatments: cyclophosphamide; limited, targeted radiation delivered in 1 of 2 dosing regimens; or combined radiation and cyclophosphamide.

Once the tolerability of REGN2810 has been established alone and in combination with radiation and/or cyclophosphamide, multiple expansion cohorts using various combinations or monotherapy in select indications (NSCLC, BC, HNSCC, CSCC, basal cell carcinoma [BCC], cervical cancer, tumors with MSI [colorectal, endometrial, prostate, or other tumor types], HCC, and other advanced solid tumors) will be added in order to further confirm the safety and evaluate the augmentation of antitumor activity. Expansion cohorts with combinations including granulocyte-macrophage colony-stimulating factor (GM-CSF), low dose carboplatin plus docetaxel, low dose docetaxel, full dose carboplatin plus paclitaxel, or carboplatin plus pemetrexed will be added. Expansion cohorts that have GM-CSF, carboplatin, and/or docetaxel or other new chemotherapies added will have a 6-patient, 28-day DLT observation period, in order to allow for observation of both acute and non-acute toxicity prior to enrollment of the full cohort of patients. The indications for expansion were chosen on the basis of their suitability to these types of combinations.

Patients with GBM will be evaluated in disease-specific dose escalation cohorts in which REGN2810 is given with hypofractionated radiotherapy. Human immunodeficiency virus patients with advanced solid tumors may enroll in an exploratory cohort of REGN2810 monotherapy.

The initial planned treatment with REGN2810 will be every 14 days for up to 48 weeks, with 24 weeks of follow-up observation. In cohorts featuring full dose chemotherapy, REGN2810 will be administered as 3 mg/kg every 3 weeks. Radiation will be administered a week after the first dose of REGN2810. Low-dose cyclophosphamide will be administered to patients assigned to cyclophosphamide 1 day before each of the first 4 doses of REGN2810. After a minimum of 24 weeks of treatment, a patient with a confirmed complete response (CR) may elect to discontinue treatment and continue with all relevant study assessments (eg, efficacy assessments) as scheduled per protocol. After consultation with the investigator and the Sponsor and after a minimum of 24 weeks of treatment, a patient with a tumor burden assessment of stable disease (SD) or partial response (PR) that has been unchanged for 3 successive tumor evaluations also may elect to discontinue treatment and continue with all relevant study assessments (eg, efficacy assessments) as scheduled per protocol.

Combination with Cyclophosphamide

Cyclophosphamide, particularly when administered in relatively low doses, has been shown to augment both the immunologic and clinical responses of anticancer vaccines. This immune enhancement may be achieved by increased expression of class I human leukocyte antigen (HLA) in the tumor microenvironment or on cancer cells themselves, as well as by selectively depleting T regulatory (Treg) cells ([Ghiringhelli 2004](#)). By reducing Treg cells, the likely mediators of tumor tolerance, anti-tumor CD8+ cytotoxic effector T cells can be activated and expanded ([Le 2012](#), [Emens 2012](#), [Hermans 2003](#)).

Low-dose cyclophosphamide has been shown to improve antitumor immune responses in various animal tumor models and in patients with metastatic melanoma ([Cerullo 2011](#)). In PROb tumor-bearing rats, a single administration of cyclophosphamide depletes CD4+CD25+ T cells, delaying PROb tumor growth, and curing rats with established PROb tumors when followed by an immunotherapy that is ineffective as monotherapy ([Ghiringhelli 2004](#)). Low-dose cyclophosphamide also decreases Tregs in patients treated with an oncolytic adenovirus without compromising induction of antitumor or antiviral T-cell responses ([Cerullo 2011](#)).

Combination with Radiotherapy

Nonclinical studies suggest that radiotherapy may sensitize tumor cells to immune-mediated attack ([McFarland 2012](#)) by prompting release of soluble tumor antigens from killed cells as well as by increasing tumor cell surface expression of antigens and receptors mediating T-cell recognition and/or killing and enhanced efficiency of professional antigen-presenting cells ([Ferrara 2009](#), [Kershaw 2013](#)). Together with the observation that radiation may induce expression of chemokines needed for T-cell trafficking ([Kershaw 2013](#), [Hellevik 2014](#)), these data suggest that radiation can function as an immune adjuvant to help reverse the suppression of tumor immune responses.

As a crucial tumor immune-evasion mechanism, however, Treg-mediated immunosuppression may be a key obstacle for successful tumor immunotherapy in general, and following radiation in particular. Following sub-lethal irradiation of antigen-primed mice, antigen-specific immune suppression mediated primarily by CD4+ CD25+ Tregs develops over several weeks. The proportion of Treg to T effector populations is skewed, with higher numbers of Tregs ([McFarland 2012](#)). The influx of Treg cells into an irradiated tumor microenvironment therefore

may counteract any benefit obtained from increased antigen release, enhanced antigen presentation, or influx of T effector cells.

Data from mice also suggest that tumor cells may counterbalance this effect by upregulating PD-L1 in response to radiation (Deng 2014). Importantly, administration of an anti-PD-L1 antibody was able to greatly enhance radiation-induced tumor regression and survival in this study, providing strong support to the notion that PD-1/PD-L1 blockade may overcome immunosuppression mediated by radiation-induced PD-L1 upregulation.

Combination with Radiotherapy and Cyclophosphamide

In a syngeneic mouse mammary adenocarcinoma cell line (TSA) breast cancer model in BALB/c mice, the combination of low-dose cyclophosphamide and fractionated radiation was able to elicit regression of tumors significantly better than either modality alone (Dewan 2012). By counterbalancing radiotherapy-induced increases in Tregs, combining cyclophosphamide with radiation therapy and REGN2810 may improve tumor responses relative to those obtained with any agent alone.

Combination with GM-CSF

Granulocyte-macrophage colony-stimulating factor plays a critical role in development and maturation of dendritic cells and proliferation and activation of T-cells, linking the innate and acquired immune response (Hercus 2009). Granulocyte-macrophage colony-stimulating factor has been shown to increase the percentage of dendritic cells and promote their maturation; facilitating cross-presentation of newly released antigens after cancer cell death is achieved within the irradiated tumor (Vatner 2014). Studies in mice with established tumors have shown that combining PD-1 blockade with GM-CSF-secreting tumor cell immunotherapy resulted in increased tumor-specific T-cell responses, which correlated with prolonged survival of the mice compared with animals treated with either therapy alone (Li 2009). A study was conducted enrolling 41 patients who had stable or progressive metastatic cancer during systemic chemotherapy with at least 3 measurable lesions. Systemic therapy was maintained and radiation therapy was added to 1 lesion, 3.5 Gy X 10, over 2 weeks. After a week of radiation, GM-CSF 125 micrograms/m² was given subcutaneously (SC) daily for 14 consecutive days. The combination of radiation therapy and GM-CSF resulted in a systemic effect outside the radiation field in 27.6% of patients who either had not responded or had progressed during chemotherapy. Median survival of responders (20.98 months [95% confidence interval: 11.05 months – 30.96]) was significantly superior to nonresponders (8.3 months [95% confidence interval: 5.03 to 13.29 months]) (Golden 2015). These data indicate that GM-CSF may have the potential to increase the efficacy of combinations of REGN2810 with radiation and/or cyclophosphamide.

1.2.2. Rationale for Dose Selection

REGN2810:

The starting dose chosen for this first-in-human study is based on the similar in vitro and in vivo potency of REGN2810 compared to antibodies generated based on publically available sequences of 2 approved anti-PD-1 antibodies, nivolumab and pembrolizumab. When compared to REGN1672 (primary sequence identical to nivolumab) and REGN2626 (primary sequence identical to pembrolizumab) in both in vitro and cell-based assays, REGN2810 demonstrated similar in vitro PD-1 binding affinity, blocking efficiency for PD-1/PD-L1 and PD-L2 interactions in vitro, and ability to antagonize PD-1-induced T-cell inhibitory signaling in a cell-based bioassay. Additionally, REGN2810 demonstrated similar in vivo anti-tumor efficacy to REGN1672 and REGN2626 in humanized-PD-1 mouse tumor model bioassays. Furthermore, the pharmacokinetic (PK) profile for REGN2810 in monkeys is similar to that of nivolumab ([Wang 2014](#)). These results suggest that clinical activity of REGN2810 will be similar to those of pembrolizumab and nivolumab at equivalent doses.

In pharmacokinetic studies in cynomolgus monkeys administered 1, 5, and 15 mg/kg REGN2810, estimates of the beta-phase terminal half-life ($t_{1/2}$) of REGN2810 were comparable across dose groups: 9.84, 10.9 and 12.4 days, respectively. Accordingly, REGN2810 will be administered every 14 days in this study to maintain targeted serum concentrations over the dosing interval.

In a 4 week toxicology study in monkeys at the no-observed-adverse-effect level (NOAEL) of 50 mg/kg per week, the area under the concentration-time curve (AUC) over the last dosing interval was estimated at 6170 day•mg/mL, a greater than 12-fold higher exposure than steady-state exposures predicted with 1 mg/kg, and a 14% higher exposure than that anticipated with 10 mg/kg administered to human patients every 14 days. Based on preclinical activity and toxicology data and greater than 10-fold exposure margin over 1 mg/kg REGN2810, in addition to the clinical efficacy and safety data from other anti-PD-1 mAbs at similar doses/dosing intervals, a dosage of 1 mg/kg REGN2810 every 14 days is expected to be both safe and active, and was therefore chosen as a starting dosage, with plans to de-escalate if necessary. If safety of 1 mg/kg REGN2810 is confirmed in the first cohort, the dosage may be successively escalated to 3 mg/kg and then to 10 mg/kg.

Experience with other anti-PD-1 antibodies suggests that REGN2810 dosage can be escalated safely. In an open-label expansion cohort of a phase 1 trial of intravenous (IV) pembrolizumab in patients with advanced melanoma previously treated with ipilimumab, treatment at 2 mg/kg or 10 mg/kg every 3 weeks was well tolerated, with similar safety profiles across dose groups, and no drug-related death ([Robert 2014](#)). In a 3 + 3 dose-escalation study of nivolumab in patients with advanced melanoma, NSCLC, RCC, castration-resistant prostate cancer, or colorectal cancer, a maximum tolerated dose (MTD) was not reached with dose levels of 1, 3, or 10 mg/kg. A limited dose-response exploration for REGN2810 monotherapy is planned to examine the potential for dose-dependence of anti-tumor activity, and also to rule out potential for toxicity as a consequence of any unexpected differentiating features of REGN2810. Three dosages are planned for this first-in-human study of REGN2810: 1, 3, and 10 mg/kg, administered every 14 days.

In patients with advanced melanoma receiving nivolumab, the majority of responses emerged before 24 weeks, and were noted to be durable in those patients who required discontinuation of treatment due to toxicity (Topalian 2014). Responses with the combination of ipilimumab and nivolumab appeared to occur faster, more frequently, to a greater depth, and with greater durability as compared to historical response data with either agent as monotherapy for melanoma (Wolchok 2013). Therefore, 48 weeks was chosen as the planned duration of treatment for this study. The study includes an option to hold treatment after evidence of “consolidated response” (unchanging SD or PR), or confirmed CR, after a minimum of 24 weeks of treatment. Dosing to consolidated response may better preserve utility of retreatment at later times of progression, reduce chances for toxicity due to unnecessary chronic treatment, and permit assessment of the utility of this approach. Opportunities for retreatment/reinduction with REGN2810-based therapies for patients who progressed or relapsed after their first treatment may be made available through future protocols.

Radiotherapy:

In a series of mouse tumor models treated with an anti-CTLA-4 antibody combined with 3 different radiation regimens, enhanced tumor responses were observed when treated with fractionated radiation regimens of 8 Gy \times 3 or 6 Gy \times 5 administered on consecutive days, but not with 20 Gy \times 1 (unfractionated; Dewan 2009).

The fractionated regimens, but not the single radiation dose, also resulted in abscopal effects, defined as a significant inhibition of tumor growth outside the radiation field. Other nonclinical studies have suggested that a single, unfractionated treatment can produce abscopal effects as well, particularly in combination with PD-1 pathway blockade (Deng 2014) or other immunomodulatory treatment.

An abscopal effect is seen very rarely when patients receive radiation to a single site, usually for palliative purposes, as the only anti-tumor therapy. Anecdotal reports describe striking and durable abscopal effects in patients who received palliative doses of radiation during treatment with immunomodulatory therapies such as anti-CTLA-4 or PD-1/PD-L1 pathway blockade (Sagiv-Barfi 2014, Postow 2012).

The optimal fractionated regimen for augmenting immunogenicity of tumors in human patients is unknown; therefore 2 fractionated regimens will be tested in this study initially. Targeted focal radiation is currently planned as 6 Gy administered 5 times a week for a total of 30 Gy or 9 Gy administered 3 times a week for a total of 27 Gy. While both treatment regimens are within the range of regimens used for palliative radiation treatment and the difference of 3 Gy may appear small, these regimens differ significantly in the biologically effective dose (BED) of absorbed radiation (Guerrero 2004), and therefore may also appreciably differ in immunopotentiating effects. Radiation will be administered starting 1 week after initial administration of REGN2810. A single course of radiation is planned, as the objective is to provide this treatment as the equivalent of a potent, autologous tumor vaccine to augment the response achieved by PD-1 blockade.

Cyclophosphamide:

Cyclophosphamide will be administered as a 200 mg/m² IV infusion 1 day before each of the first 4 REGN2810 infusions (ie, approximately once every 14 days). This dosage delivered as monotherapy would not be expected to be curative for advanced malignancies, but has been shown to augment both the immunologic and clinical responses of therapeutic vaccines by selectively depleting Treg cells without resulting in profound systemic lymphopenia, and has been employed routinely in many ongoing therapeutic vaccination studies ([Le 2012](#), [Emens 2012](#)). Because cyclophosphamide is rapidly cleared, potentially permitting reappearance of Treg cells after initial treatment, co-administration of cyclophosphamide (4 doses) initially is planned throughout the first cycle of treatment with REGN2810. The choice to administer cyclophosphamide every 14 days, rather than daily, is supported by data suggesting that this approach may avoid the ablation of responding antitumor immune cells, thereby maximizing immune responses ([Chen 2014](#)).

GM-CSF:

Patients will receive LEUKINE[®] (sargramostim) ([Leukine Package Insert](#)), a recombinant human GM-CSF (rhu GM-CSF), administered as a 250 mcg SC daily dose for 7 days, for four 7-day cycles (days 1 through 7, 15 through 21, 29 through 35, and 43 through 49 of the first 56-day cycle). There is evidence from numerous preclinical and clinical studies that GM-CSF can induce antitumor immunity when administered by a variety of different routes and regimens ([Kaufman 2014](#)). This dosage is less than the recommended treatment dose of 250 mcg/m²/day; thus, reducing the potential of rapid increase in blood counts. Should excessive blood counts occur, discontinuation of therapy should decrease the levels to normal within 3 to 7 days ([Leukine Package Insert](#)). Therefore, a 7-day on, 7-day off schedule should afford the patients an opportunity for recovery.

Since GM-CSF dosing in this study is less than the usual recommended dose, cyclophosphamide is given at a low dose, and the radiation therapy is hypofractionated, there will be no requirement for a 24-hour interval between GM-CSF administration and dosing of cyclophosphamide or radiation therapy.

1.2.3. Rationale for Selected Indications for the Expansion Cohorts**Non-Small Cell Lung Cancer (Expansion Cohorts 1 and 2)**

Anti-PD-1 antibodies have demonstrated activity in the treatment of lung cancer. Opdivo[®] (nivolumab) was approved in February 2015 by the Food and Drug Administration for patients with metastatic squamous NSCLC with progression on or after platinum-based therapy ([OPDIVO Package Insert](#)). In an open-label study, patients randomized to receive OPDIVO (n=135), administered IV at 3 mg/kg every 2 weeks, had a median survival of 9.2 months (95% confidence interval 7.3, 13.3), compared to 6.0 months (95% confidence interval 5.1, 7.3) in patients administered docetaxel (n=137) IV at 75 mg/m² every 3 weeks. This was a statistically significant improvement in overall survival (p-value=0.00025, hazard ratio 0.59 [95% confidence interval 0.44, 0.79]) [Table 2](#) ([OPDIVO Package Insert](#)).

As part of a dose-range finding, flat dosing with 200 mg IV will also be explored in patients with NSCLC. For a bodyweight range of 45 kg (100 lbs) to 113 kg (250 lbs), this dose corresponds to a dose range of 4.4 mg/kg to 1.77 mg/kg.

Breast Cancer (Expansion Cohort 4)

Breast cancer has not been traditionally regarded as a typical immunogenic tumor. Studies in animal models have shown that radiation therapy can convert poorly immunogenic tumors resistant to antibodies into susceptible ones. A study conducted using BALB/c mice inoculated with the syngeneic poorly immunogenic TSA BC cells showed that TSA tumors were resistant to PD-1 blockade, but when radiation therapy was combined with an anti-PD-1 mAb, all of the mice completely rejected tumors by day 25 ([Pilonis 2014](#)). Recent phase 1 trials of PD-1 and PD-L1 inhibitors in BC have demonstrated responses. Of the 27 advanced triple-negative BC patients in the Keynote-012 trial who could be evaluated, 5 patients (18.5%) had an overall response, including 1 CR (3.7%) to pembrolizumab. Three of the 5 responders remained on therapy for at least 48 weeks, and the other 2 patients who had discontinued treatment at the time of analysis received therapy for 40 weeks ([Nanda 2014](#)). Of the 9 patients that could be evaluated in a phase 1 study of MPDL3280A, a mAb against PD-L1, 3 patients had a response, including 1 CR ([Emens 2014](#)) [[Table 2](#)].

Head and Neck Squamous Cell Carcinoma (Expansion Cohort 3)

Head and neck squamous cell carcinoma is another tumor that is a candidate for PD-1 and PD-L1 blockade. PD-L1 expression has been demonstrated in human papillomavirus (HPV)-associated HNSCC, and the PD-1:PD-L1 pathway has been shown to play a role in HPV-HNSCC immune resistance ([Lyford-Pike 2013](#)). Preliminary data on the antitumor activity of pembrolizumab from the HNSCC dose expansion cohort of the phase 1b KEYNOTE-012 trial was presented at ASCO 2014 ([Seiwert 2014](#)). Sixty eligible patients with at least 1% PD-L1 expression in their tumor were treated with pembrolizumab. At the time of data cutoff in May 2014, the best overall response rate was 19.6% (95% confidence interval, 10.2-32.4). Both HPV-positive and HPV-negative patients responded in equal percentages. One patient had pseudoprogression followed by PR on treatment ([Kim 2014](#)) [[Table 2](#)].

Other Advanced Solid Tumors for which Radiation Therapy is Planned (Expansion Cohort 6)

Patients with advanced solid tumors (excluding NSCLC, HNSCC, BC, CSCC, any advanced solid tumor with MSI, or HCC) for which radiation therapy is planned, will be eligible to enroll into Expansion Cohort 6, if all other eligibility criteria are met [[Table 2](#)].

There is evidence that treatment with an anti-PD-1 antibody may benefit patients with many different tumor types, immunogenic as well as nonimmunogenic ([Dolan 2014](#)). The purpose of this cohort will be to gain exploratory information regarding the safety and antitumor activity of REGN2810 in combination with radiotherapy, cyclophosphamide, and GM-CSF in various tumor types.

**Retreatment after Previous Treatment with Other PD-1/PD-L1 Antibodies
(Expansion Cohort 5)**

Patients with advanced solid tumors who progressed after initially achieving disease control (CR, PR, SD for at least 8 weeks) when receiving other PD-1/PD-L1 antibodies will be eligible to enroll in this cohort [Table 2].

There is clinical evidence that retreatment with an immune-modulating agent can provide clinical benefit. Patients who initially achieved clinical benefit when treated with ipilimumab (inhibiting CTLA-4) and then progressed, had objective tumor responses and/or disease stabilization when re-treated with ipilimumab (Robert 2013). In addition, a patient with melanoma who achieved a PR that was stable for 16 months off therapy and then experienced recurrence was successfully re-induced with anti-PD-1 therapy with a sustained PR documented 16 months following initiation of re-induction therapy (Lipson 2013). There is data suggesting that tumor-specific T-cells that mediate the initial responses achieved with ipilimumab may no longer control the tumor because of its changing antigen repertoire as a result of the attack by the initially relevant T cells. It has been hypothesized that (i) PD-1 blockade, similar to CTLA-4 inhibition, has the potential to establish a favorable equilibrium between adequate T-cell response against the tumor and immune evasion by the tumor; (ii) tumor recurrence after successful treatment with PD-1 blockade indicates disruption of this equilibrium; and (iii) retreatment with PD-1 inhibition after recurrence can reset this balance (Ott 2013). It is also becoming increasingly apparent that combination therapies will be needed to make the immune checkpoint modulation therapeutic approach applicable to a larger number of patients, and a broader spectrum of tumor types (Zamarin 2015); therefore, patients who progressed on other PD-1/PD-L1 antibodies will be treated with REGN2810 in combination with other therapies.

Cutaneous Squamous Cell Cancer (Expansion Cohorts 7 and 8)

Cutaneous squamous cell cancer is the second most common malignancy in the United States (US) (Karia 2013). Risk factors include ultraviolet exposure, advanced age, and immunosuppression (Pfister 2007). Most tumors are cured with surgical-based management, but approximately 2% of patients die due to recurrent or metastatic disease (Schmults 2013). Cutaneous squamous cell cancer is not tracked in the Surveillance, Epidemiology, and End Results (SEER) database. Best estimates indicate that there are approximately 3,900 to 8,800 deaths annually in the US due to this disease (Karia 2013). The incidence of CSCC has been steadily increasing in recent decades (Rogers 2010). In central and southern regions of the US with high sun exposure, the annual mortality is comparable to that of melanoma (Karia 2013). There have been single-arm studies of several systemic therapies, but there is no standard of care for systemic therapy in this disease (Maubec 2011, Nakamura 2013). There is no systemic therapy with known survival benefit for CSCC. The unmet need for patients with unresectable locally/regionally recurrent or metastatic CSCC is unambiguous [Table 2].

Cutaneous SCC has several clinical and biological factors that suggest that it is appropriate for the clinical study of immune checkpoint inhibition (Mavropoulos 2014). For example, CSCC harbors a mutational burden far greater than that of other solid tumors (eg, melanoma, NSCLC) for which checkpoint inhibition has demonstrated clinical efficacy (Pickering 2014, Rizvi 2015). In the first cohort of REGN2810 monotherapy (1 mg/kg), a confirmed partial response has been

observed in a 52 year-old man with unresectable recurrent CSCC who has an extensive prior history of surgery, systemic therapy, and radiation therapy for recurrent disease.

Metastatic (M1) CSCC is associated with worse overall survival than locally advanced disease without distant metastases (M0) CSCC ([Brunner 2013](#)). Patients with M1 CSCC have not been well represented in trials of systemic therapy. In a recent literature review for systemic therapy trials for CSCC, only 14% (36/249) of patients in 10 clinical trials had M1 disease ([Nakamura 2013](#)). For these reasons, the optimal strategy to assess the clinical efficacy of REGN2810 requires separate cohorts for patients with M1 disease and for patients with unresectable locally and/or regionally recurrent M0 disease, which would be consistent with the drug development paradigm for non-melanoma skin cancer that was established with another agent for basal cell carcinoma (BCC) ([Sekulic 2012](#)).

Solid Tumors with Microsatellite Instability (Expansion Cohorts 9 through 12, and Expansion Cohort 16)

Tumors with DNA mismatch repair deficiency are characterized by a high number of non-synonymous mutations and increased lymphocytic infiltrate ([Dolcetti 1999](#), [TCGA-Network 2012](#)). Non-synonymous mutations can give rise to unique peptides in cancer cells that are presented in the context of MHC for recognition by T cells ([Segal 2008](#)). Tumors with mismatch repair deficiency harbor regions of DNA MSI that can be detected with a commercially available test (MSI Analysis System, Promega) [[Table 2](#)].

MSI has been identified in a wide range of solid tumor types, including colorectal cancer, endometrial cancer, and prostate cancer. To investigate the hypothesis that tumors with MSI may be sensitive to therapeutic blockade of the PD-1 checkpoint, Le and colleagues conducted a phase 2 study of pembrolizumab (10 mg/kg every 2 weeks) with cohorts for patients with colorectal cancer with MSI, colorectal cancer without MSI, and other advanced solid tumors with MSI ([Le 2015](#)). As \geq third line therapy for metastatic colorectal cancer, pembrolizumab yielded an immune-related response rate of 40% (4/10) among patients with MSI, versus 0% (0/18) for cancer patients without MSI. In the cohort for patients with other solid tumors harboring MSI, the response rate was 71% (5/7) ([Le 2015](#)). These robust efficacy findings motivate further clinical development of the PD-1 inhibition strategy in patients with MSI.

The current study includes cohorts to explore the activity of REGN2810 for patients with advanced colorectal cancer with MSI (Cohort 9), advanced endometrial cancer with MSI (Cohort 10), advanced prostate cancer with MSI (Cohort 11), and other advanced solid tumors with MSI (Cohort 12). For patients with metastatic colorectal cancer who have progressed through all standard therapies, regorafenib is associated with a response rate of 1%, median progression-free survival (PFS) of 1.9 months, and median overall survival of 6.4 months ([Grothey 2013](#)). For women with metastatic endometrial cancer, the efficacy of conventional systemic therapies is low and there is not a widely accepted standard of care ([McMeekin 2015](#)). For men with castration recurrent prostate cancer that has progressed after docetaxel chemotherapy, there is no consensus for best additional therapy ([Mohler 2015](#)). For patients in these clinical settings with tumors that harbor MSI, blockade of the PD-1 checkpoint with REGN2810 is an appropriate clinical trial option. In view of the anticipated high efficacy of REGN2810 against tumors with MSI, Cohort 16 will explore REGN2810 monotherapy for patients with metastatic colorectal cancer with MSI that is previously untreated ([Vanderbosch 2014](#)).

Hepatocellular Carcinoma (Expansion Cohort 13)

For patients with unresectable HCC, sorafenib monotherapy as first line therapy has yielded median overall survival times of 6.5 to 10.7 months in phase 3 studies ([Cheng 2009](#), [Llovet 2008](#)). After progression on sorafenib, there is no established therapy to significantly improve median overall survival beyond the duration of approximately 7 to 8 months that is achievable with best supportive care ([Llovet 2013](#), [Zhu 2014](#)) [Table 2].

With preclinical data identifying inhibition of the PD-1 checkpoint as an appropriate research strategy for this disease ([Hato 2014b](#)), a phase 1/2 trial of nivolumab was launched for patients with unresectable HCC with 3 cohorts: patients without viral infection, patients with hepatitis B on antiviral therapy, and patients with hepatitis C (CA209-040) ([El-Khoueiry 2015](#)). Sixty-eight percent of patients had received prior sorafenib. Dose levels explored were between 0.1 mg/kg to 10 mg/kg. There was one DLT among 47 patients evaluable for safety, which was a hepatic decompensation in a patient in the 10 mg/kg cohort. Treatment was generally well tolerated in all cohorts, and an MTD was not reached. For the uninfected cohort and the HCV cohort, the recommended dose is 3 mg/kg. Dose escalation is ongoing in the HBV cohort at 3 mg/kg at the time of the analysis of the presented data. Preliminary efficacy observations among patients evaluable for response (N= 42) were response rate of 19% and 1 year overall survival of 62% (95% CI, 42076) ([El-Khoueiry 2015](#)). These findings suggest that clinical study of REGN2810 is clinically appropriate for this patient population.

Advanced Solid Tumors in Combination with Carboplatin plus Docetaxel, or Docetaxel (Expansion Cohorts 14, 15, and 17)

Although the notion of combining conventional cytotoxic chemotherapy with immune checkpoint blockade may initially seem counter-intuitive, cytotoxic chemotherapy can have immune-supportive effects ([Zitvogel 2013](#)). Platinum agents may facilitate immune responses by a variety of mechanisms, including sensitizing tumor cells to cytotoxic T cell killing ([Hato 2014a](#)). Taxanes, such as docetaxel, also have a variety of potential immune supportive effects, including depletion of myeloid-derived suppressor cells ([Kodamundi 2010](#)) [Table 2].

In an ongoing phase 1b trial, the anti-PD-L1 monoclonal antibody MPDL3280A is combined with various chemotherapy regimens (NCT01633970). In cohorts C, D, and E, chemo-naïve patients with advanced NSCLC receive MPDL3280A and carboplatin in combination with paclitaxel, pemetrexed, or nab-paclitaxel, respectively ([Liu 2015](#)). MPDL3280A is combined with the cytotoxic chemotherapy agents at full dose for 4 to 6 cycles, followed by maintenance MPDL3280A. Among the first 30 patients evaluable for response, preliminary efficacy results demonstrate objective radiologic response rates of 60%, 75%, and 62%, respectively, on cohorts C, D, and E. Patients experienced the anticipated side effects of high dose cytotoxic chemotherapy in each cohort ([Liu 2015](#)). In phase 1b explorations of nivolumab plus platinum-based doublets given at full dose for patients with treatment-naïve advanced NSCLC patients, response rates ranged between 33% to 47% across 4 cohorts, and grade 3-4 toxicities occurred in 45% of patients ([Antonia 2014](#)). The optimal dose and schedule strategy for combining blockade of the PD-1/PD-L1 axis with cytotoxic chemotherapy is not known. Expansion cohorts in this study will explore lower dose chemotherapy (carboplatin, docetaxel) given over a short period of time ([Kushner 2007](#), [Rein 2002](#), [Weissman 2006](#)), combined with blockade of the PD-1 checkpoint by REGN2810, in advanced solid tumor patients who are not

chemotherapy naïve. Expansion Cohort 17 will address this question specifically in patients with advanced NSCLC who were not previously treated.

Glioblastoma (Expansion Cohorts 18 and 19)

Glioblastoma is the most common primary brain tumor in adults, and is characterized by short survival and poor quality of life. Glioblastoma may prevent an effective immune response by creating an immunosuppressive environment, including high expression of immunosuppressive cytokines, enrichment of Tregs, PD-1 expression on T cells, and PD-L1 expression on tumor cells and tumor-associated macrophages (Bloch 2013, Jackson 2011, Wintterle 2003). These factors suggest that PD-1 blockade should be studied in clinical trials for GBM, and preliminary activity has been observed with the anti-PD-1 antibody nivolumab (Sampson 2015) [Table 2].

Preclinical and early clinical data provide proof-of-principal for the therapeutic potential of strategies to enhance the immune response against GBM. In a murine model of intracranial implantation of a glioma cell line, combined intracranial radiation therapy and systemic administration of an anti-PD-1 monoclonal antibody resulted in doubling of median overall survival, compared to either intervention alone. After combination therapy, re-challenge of the long-term survivors with the same tumor cells resulted in tumor clearance in 100% of the animals (Zeng 2013).

Newly diagnosed GBM: The current standard of care for newly diagnosed patients is maximal surgical resection, followed by radiotherapy (60 Gy over 6 weeks) with concurrent temozolamide (TMZ) and maintenance TMZ (Stupp 2005). Subgroup analysis demonstrates that the therapeutic advantage of TMZ in this regimen is restricted to patients with tumors that are methylated at the MGMT promoter (Hegi 2005). Randomized trial data indicates that the benefit of standard radiation therapy for GBM patients >60 years of age is unclear (Malmstrom 2012). As such, this expansion cohort will explore the safety and tolerability of a regimen of REGN2810 + hypofractionated radiation therapy in individuals ≥60 years of age with newly diagnosed GBM that is unmethylated at the MGMT promoter.

Recurrent GBM: For patients with recurrent GBM, management depends upon extent of disease and patient condition. If performance status is favorable, systemic agents that may be considered include bevacizumab, lomustine, and irinotecan (Nabors 2015). Re-irradiation (≥30 Gy total dose) may be considered for patients if prior radiation achieved durable disease control (Combs 2007). Bevacizumab was granted accelerated approval in the US for recurrent GBM based on improvement in objective response rate, but was rejected by the European Medicines Agency due to lack of control groups without bevacizumab (Friedman 2009, Kreisl 2009, Vredenburgh 2007). The BELOB trial was a randomized phase 2 comparisons of lomustine monotherapy, bevacizumab monotherapy, and the combination of bevacizumab plus lomustine. Nine month overall survival in each arm was 43%, 38%, and 59%, respectively (Taal 2014). Recognizing the possibility that the tolerability of PD-1 inhibition plus hypofractionated radiation therapy may differ in recurrent GBM, a separate safety evaluation in this patient population is warranted.

HIV and Advanced Solid Tumor (Expansion Cohort 20)

Cancer patients with HIV are often excluded from phase 1 studies, but several lines of evidence suggest that immune checkpoint inhibition is likely to be a safe and well tolerated intervention in this patient population. Immune checkpoint regulators such as PD-1 and CTLA-4 are preferentially upregulated on HIV-infected T cells, and in vitro blockade of PD-1 restores HIV-specific T-cell responses (Khaitan 2011). From an oncologic standpoint, case reports indicate that blockade of the CTLA-4 immune checkpoint can be associated with clinical benefit in patients with HIV and advanced cancers (Burke 2011, Ruzevick 2013). Patients infected with HIV who are on an active regimen of anti-retroviral therapy with stable viral suppression and evidence of significant immune reconstitution with CD4 counts above 200 mm³, may well benefit from treatment for their tumors with PD-1 blockade. A REGN2810 monotherapy exploratory expansion cohort will explore the safety and tolerability of REGN2810 in this patient population [Table 2].

Advanced NSCLC, First Line, Full Dose Chemotherapy (Expansion Cohorts 21 and 22)

For patients with advanced NSCLC, several platinum-based doublet regimens have shown similar efficacy as first line therapy (Schiller 2002). First line therapy with carboplatin + paclitaxel is associated with median overall survival of approximately 10 to 12 months (Ohe 2007, Sandler 2006). Cisplatin + pemetrexed achieves median overall survival of approximately 10 months, and is less toxic to bone-marrow than cisplatin + gemcitabine (Scagliotti 2008). However, in NSCLC patients with squamous histology, cisplatin + gemcitabine achieves superior overall survival, compared with cisplatin + pemetrexed (Scagliotti 2008). The addition of nivolumab to full dose platinum doublets has been described in expansion cohorts in phase 1 studies. Among 14 NSCLC patients treated with 5 mg/kg nivolumab + full dose carboplatin + paclitaxel, 1 year overall survival rate was 85% (Antonia 2014). The addition of 10 mg/kg nivolumab to cisplatin + pemetrexed (N=15 patients) or to cisplatin + gemcitabine (N=12 patients) achieved 1 year overall survival rates of 87% and 50%, respectively (Antonia 2014). Although these findings are preliminary, they suggest that treatment efficacy for some patients may be improved by the addition of PD-1 blockade to full dose platinum doublet chemotherapy when given as first line therapy for advanced NSCLC. Cohort 17 of this trial evaluates REGN2810 + low dose chemotherapy given in cycle 1 only as first line therapy for advanced NSCLC. Cohorts 21 and 22 will provide preliminary experience for REGN2810 + full dose platinum doublet chemotherapy as first line therapy in advanced NSCLC.

Recurrent or Metastatic Cervical Cancer, s/p Platinum + Taxane Doublet Chemotherapy (Expansion Cohorts 23 and 24)

There are more than 500,000 new cases of cervical cancer globally each year, with an estimated annual mortality of approximately 275,000 globally (Eskander 2014). Infection with high risk-HPV strains is the most important risk factor for cervical cancer. For patients with locally advanced disease, combined modality therapy with radiation therapy and concurrent cisplatin is a widely accepted standard of care. For patients with recurrent or metastatic disease, first line therapy with the triplet regimen of bevacizumab + carboplatin + paclitaxel yields an objective response rate of 48% and a median overall survival of 17 months (Tewari 2014). After first line therapy, several cytotoxic agents have modest palliative activity and clinical trials are needed for

these patients (Eskander 2014). Characteristics of cervical cancer that are supportive of clinical exploration of REGN2810 treatment include the presence of viral antigen and expression of PD-L1 (Howitt 2016, Eskander 2015). In the dose escalation portion of this phase 1 study, 2 responses (1 PR, 1 CR) have been observed among 3 patients assigned to receive REGN2810 + hypo fractionated Radiation Therapy (Papadopoulos 2016). After initiation of treatment, 1 cervical cancer response occurred at the end of cycle 1 and the other at the end of cycle 2 [Table 2].

Unresectable Locally Advanced or Metastatic BCC, s/p Vismodegib or Sonidegib (Expansion Cohort 25)

Cutaneous BCC is the most common malignancy in the United States. Risk factors are advanced age, ultraviolet exposure, and immunosuppression (Rubin 2005). Although BCC can almost always be cured by surgical or other local methods, a small percentage of patients develop unresectable locally advanced or metastatic disease. Aberrant activation of the hedgehog signaling pathway, usually due to mutations in smoothened homologue, is present in almost all basal cell cancers. For patients with unresectable locally advanced or metastatic disease, the smoothened homologue inhibitor vismodegib achieves major responses in 43% of unresectable locally advanced tumors and 30% of metastatic tumors (Sekulic 2012). Sonidegib, another smoothened homologue inhibitor, achieves response rates of 43% of unresectable locally advanced tumors (Migden 2015). However, acquired resistance emerges after initial responses to vismodegib or sonidegib, and there is no standard of care for subsequent therapy. Several lines of evidence, including high mutation burden and increased risk of BCC in immunosuppressed individuals, suggest that blockade of the PD-1 checkpoint is an appropriate clinical trial option for these patients (Jayaraman 2014, Euvrard 2003).

Expansion Cohort 26:

Cohorts 1 through 25 are all initiated with REGN2810 produced from a cell line called C1. Cohort 26 will open [REDACTED] aailable. This cohort would be open to patients with any advanced solid tumor. [REDACTED]

2. STUDY OBJECTIVES

2.1. Primary Objectives

The co-primary objectives of the study are:

- **For Dose Escalation and Expansion Cohorts:** to characterize the safety, tolerability, DLTs of REGN2810 administered IV as monotherapy, or in combination with targeted radiation (with the intent to have this serve as an immuno-stimulatory, rather than primarily tumor-ablative therapy), low-dose cyclophosphamide (a therapy shown to inhibit regulatory T-cell responses) administered IV, or both radiation and cyclophosphamide with or without GM-CSF, or in combination with low dose carboplatin plus docetaxel, or in combination with low dose docetaxel, or in combination with full dose carboplatin plus paclitaxel, or carboplatin plus pemetrexed in patients with advanced malignancies.
- **For selected expansion cohorts (Expansion Cohorts 2 through 4):** to evaluate the efficacy of REGN2810, alone or in combination therapy, by measuring overall response rate.

2.2. Secondary Objectives

The secondary objectives of the study are:

- To determine a recommended phase 2 dose (RP2D) of REGN2810 as monotherapy and in combination with other anti-cancer therapies (targeted radiation, low-dose cyclophosphamide, targeted radiation plus low dose cyclophosphamide with or without GM-CSF, low dose carboplatin plus docetaxel, or in combination with low dose docetaxel, or in combination with full dose carboplatin plus paclitaxel, carboplatin plus pemetrexed).
- To describe antitumor activity of REGN2810, alone and with each combination partner(s).
 - In the expansion cohorts, activity measurements will include quantitative analysis of time to response, as well as depth of response (AUC of tumor burden), in addition to standard overall response assessments:
 - Expansion Cohort 1 - NSCLC: REGN2810 at a flat dose of 200 mg
 - Expansion Cohort 2 - NSCLC: 3 mg/kg REGN2810 + radiotherapy (9 Gy × 3)
 - Expansion Cohort 3 - HNSCC: 3 mg/kg REGN2810 + radiotherapy (9 Gy × 3) + cyclophosphamide + GM-CSF
 - Expansion Cohort 4 - BC: 3 mg/kg REGN2810 + radiotherapy (9 Gy × 3) + cyclophosphamide

- Expansion Cohort 5 - Patients who have progressed after achieving disease control (CR, PR, SD for at least 8 weeks) with another PD-1/PD-L1 antibody: 3 mg/kg REGN2810 + radiotherapy (9 Gy × 3) + cyclophosphamide + GM-CSF
- Expansion Cohort 6 - Advanced solid tumors, excluding NSCLC, HNSCC, and BC: 3 mg/kg REGN2810 + radiotherapy (9 Gy × 3) + cyclophosphamide + GM-CSF
- To describe the safety and tolerability of the following treatment regimens:
 - Expansion Cohorts 7 and 8 – CSCC, metastatic, M1 (Cohort 7) or locally and/or regionally advanced, unresectable, M0 (Cohort 8): 3 mg/kg REGN2810
 - Expansion Cohorts 9 through 12 – Advanced solid tumors with MSI arising in the colon (Cohort 9), endometrium (Cohort 10), prostate (Cohort 11), or other primary MSI solid tumor not eligible for other MSI cohorts (Cohort 12): 3 mg/kg REGN2810
 - Expansion Cohort 13 – Advanced or metastatic HCC: 3 mg/kg REGN2810
 - Expansion Cohorts 14 and 15 - Advanced solid tumors: 3 mg/kg REGN2810 + carboplatin + docetaxel (Cohort 14), or 3 mg/kg REGN2810 + docetaxel (Cohort 15)
 - Expansion Cohort 16 - Metastatic colorectal cancer with MSI, previously untreated (prior adjuvant chemotherapy is allowed): 3 mg/kg REGN2810
 - Expansion Cohort 17: Advanced NSCLC, previously untreated: 3 mg/kg REGN2810 + low dose carboplatin + low dose docetaxel.
 - Expansion Cohorts 18 and 19 - Newly diagnosed GBM, unmethylated at the MGMT promoter: REGN2810 (1 or 3 mg/kg) + radiotherapy (6 Gy x 5 days) (Cohort 18), or recurrent GBM: REGN2810 (1 or 3 mg/kg) + radiotherapy (6 Gy x 5 days) (Cohort 19)
 - Expansion Cohort 20 - HIV and advanced solid tumors: 3 mg/kg REGN2810
 - Expansion Cohorts 21 and 22: - advanced NSCLC, previously untreated: 3 mg/kg REGN2810 + full dose platinum doublets
 - Expansion Cohorts 23 and 24: Recurrent or metastatic cervical cancer, resistant to or intolerant of platinum + taxane doublet chemotherapy: 3 mg/kg REGN2810 3 mg/kg REGN2810 monotherapy (Cohort 23) or with hypofractionated RT (9 Gy X 3; Cohort 24)
 - Expansion Cohort 25: cutaneous BCC, unresectable locally advanced and/or metastatic, resistant to or intolerant of a hedgehog pathway inhibitor (vismodegib or sonidegib)
 - Expansion Cohort 26 ([REDACTED]): Any advanced solid tumors.

- To characterize the PK of REGN2810 as monotherapy and in combination with other anti-cancer therapies
- To assess immunogenicity of REGN2810
- For all expansion cohorts, to summarize PFS and overall survival

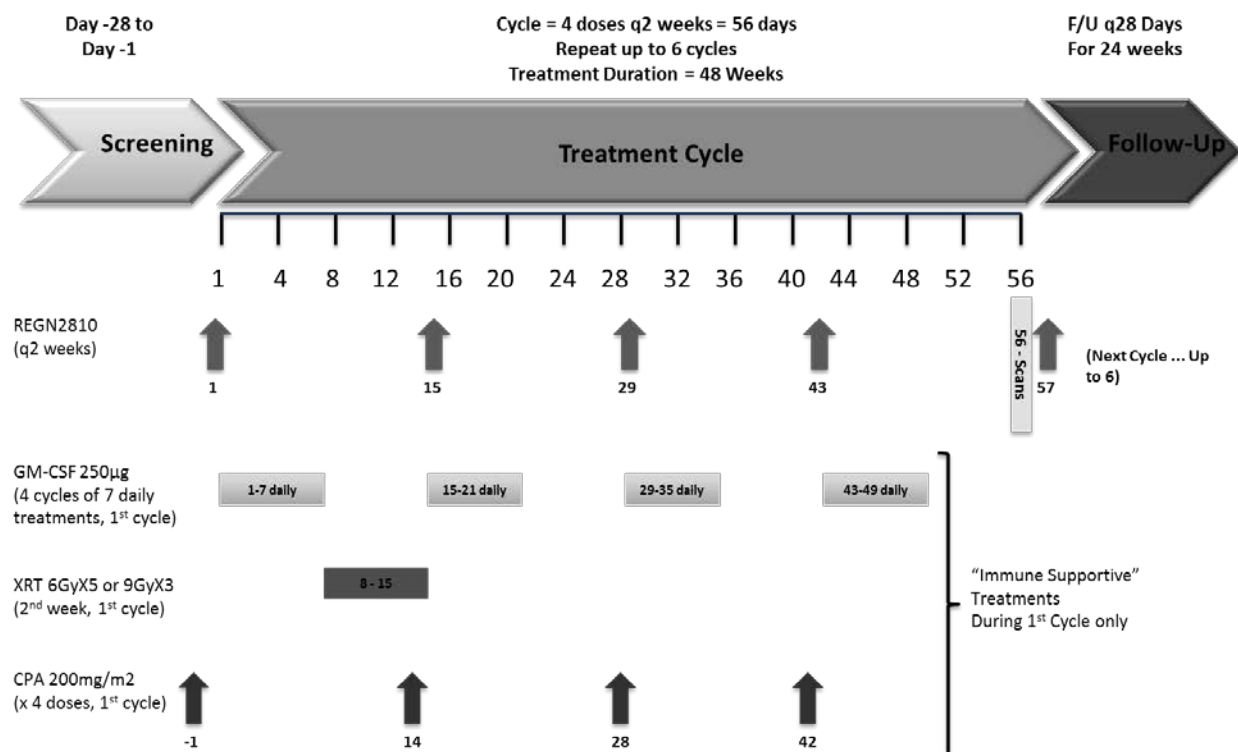
3. STUDY DESIGN

3.1. Study Description and Duration

This is a phase 1, open-label, multicenter, ascending-dose escalation study of REGN2810, alone and in combination with radiation therapy, cyclophosphamide, or radiation therapy plus cyclophosphamide, or GM-CSF, or in combination with low dose carboplatin plus docetaxel, or in combination with low dose docetaxel, or in combination with full dose carboplatin plus paclitaxel, or carboplatin plus pemetrexed in patients with advanced malignancies. In the dose-escalation phase, safety will be assessed in separate, standard 3 + 3 dose escalation cohorts (in monotherapy, combination with radiation therapy, combination with cyclophosphamide, and combination with radiation therapy plus cyclophosphamide). Following dose escalation, multiple expansion cohorts will be explored in select indications (see Section 3.1.1.2).

After a screening period of up to 28 days, patients will receive up to six 56 day treatment cycles for a total of up to 48 weeks of treatment, followed by a 24 week follow-up period (Figure 1). Each patient will be administered REGN2810 on days 1, 15±3, 29±3, and 43±3 during each treatment cycle. Patients enrolled to combination therapy cohorts may also receive one of two radiation therapy regimens, cyclophosphamide, or both cyclophosphamide and one of two radiotherapy regimens (see Section 3.1.1.1). Tumor assessments will be made at the end of each treatment cycle. Extensive safety evaluations made at baseline/cycle 1, day 1 of dosing will be repeated on day 1 of each treatment cycle throughout the study, with routine safety evaluations to be conducted at each REGN2810 dosing visit.

In the expansion cohorts, patients may also receive REGN2810 in combination with GM-CSF and radiotherapy, or in combination with GM-CSF, radiotherapy, and cyclophosphamide, or in combination with low dose carboplatin plus docetaxel, or in combination with low dose docetaxel, or in combination with full dose carboplatin plus paclitaxel, or carboplatin plus pemetrexed. Several expansion cohorts feature REGN2810 monotherapy (see Section 3.1.1.2).

Figure 1: Overall Patient Treatment and Follow-Up Timeline**1A: Timeline for Cohorts with REGN2810, GM-CSF, Radiation Therapy, and Cyclophosphamide**

CPA=cyclophosphamide; F/U=follow-up; XRT=radiotherapy.

1B: Timeline for Cohorts with REGN2810, Carboplatin, and Docetaxel (Low Dose)

Figure 1B

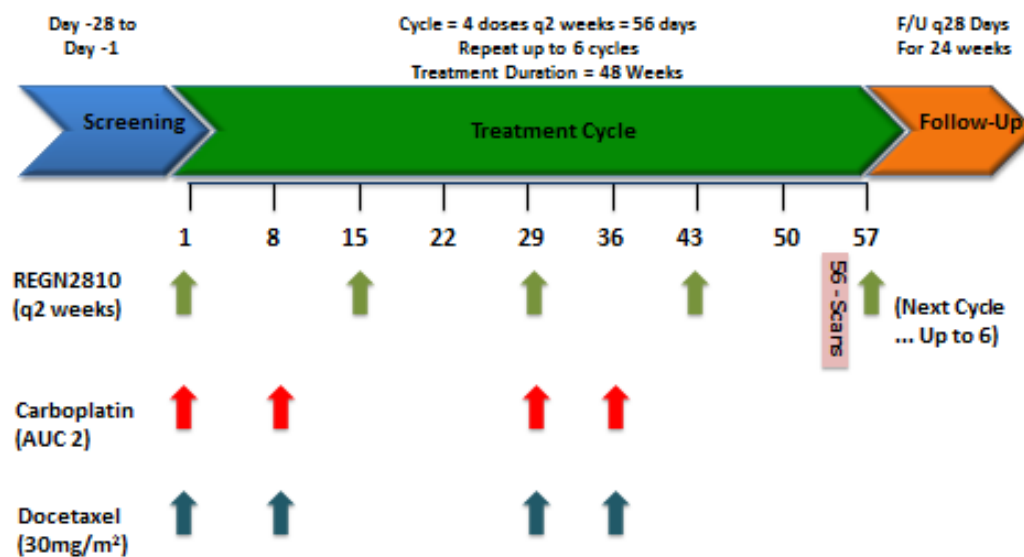


Figure 1C: Timeline for Glioblastoma Cohorts

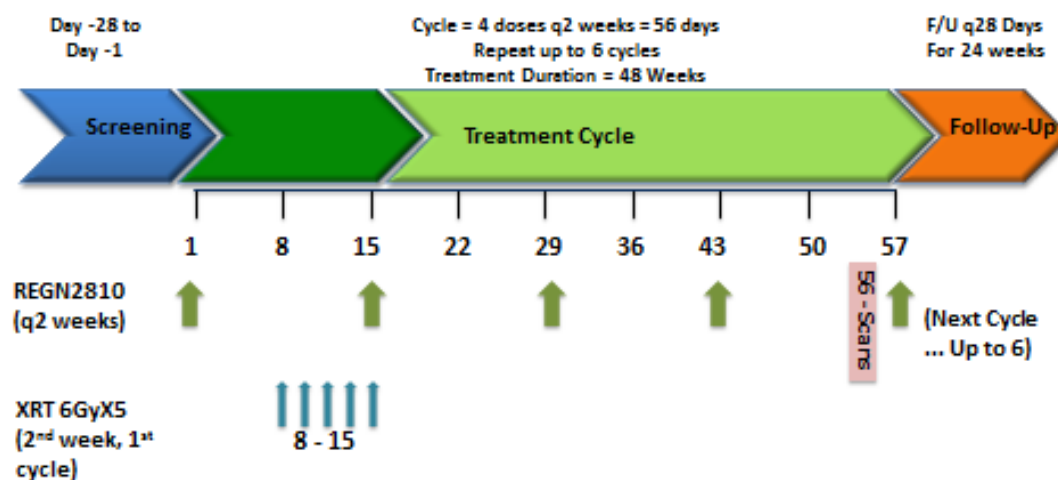
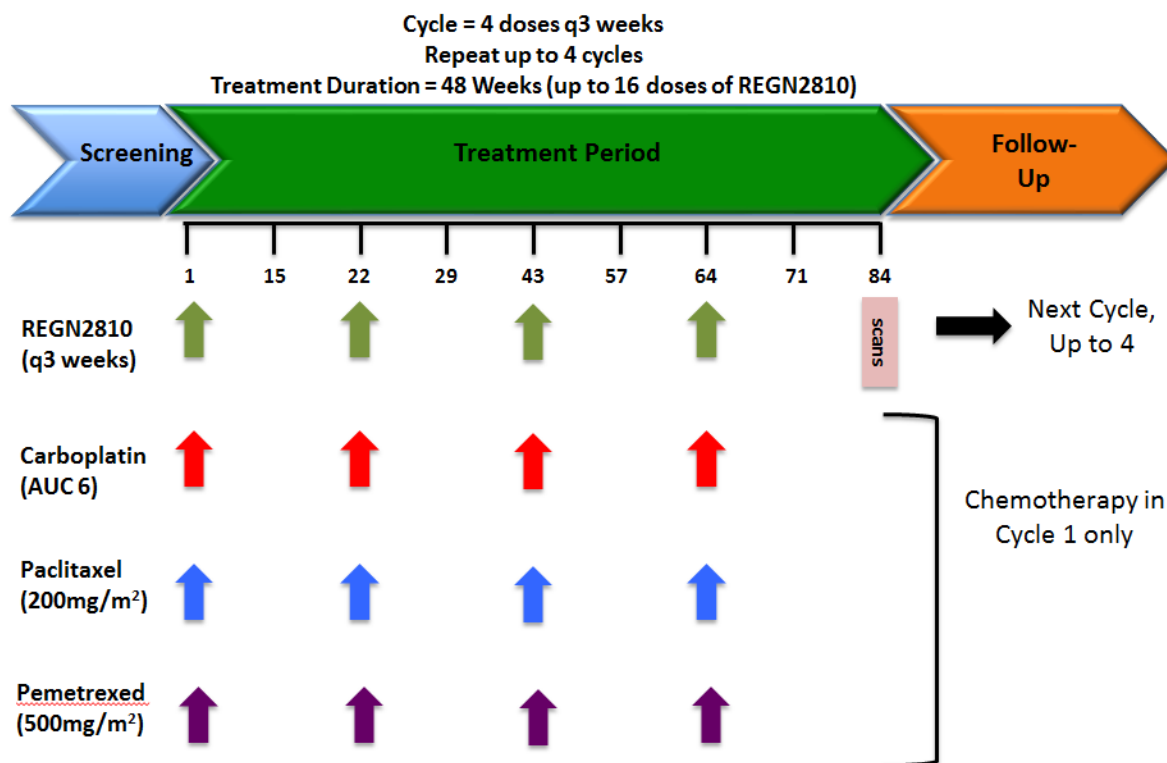


Figure 1D: Timeline for Cohorts 21 and 22 with REGN2810 + Full Dose Platinum Doublet in NSCLC

Cohort 21, carboplatin + paclitaxel, Cohort 22, carboplatin + pemetrexed

A patient will receive treatment until the 48 week treatment period is complete, or until complete response (CR), disease progression, unacceptable toxicity, withdrawal of consent, or meeting of another study withdrawal criterion. After a minimum of 24 weeks of treatment, patients with confirmed CR may elect to discontinue treatment and continue with all relevant study assessments (eg, efficacy assessments) per [Table 6](#) and [Table 8](#). After a minimum of 24 weeks of treatment and after consultation with the investigator and the Sponsor, patients with tumor burden assessments of SD or PR that have been maintained for 3 successive tumor evaluations may also elect to discontinue treatment and continue with all relevant study assessments (eg, efficacy assessments) as scheduled per [Table 6](#) and [Table 8](#). Patients whose tumors progress during post-treatment follow up (after completion of planned treatment) may be eligible for retreatment for up to 96 weeks (See Section [6.2.3](#)).

Cellular and molecular biomarkers (including, but not limited to, tumor DNA and RNA biomarkers) related to REGN2810 treatment exposure, clinical activity, or underlying disease, will also be assessed, and results will be presented separately from the main study report.

As part of an optional genomics sub-study, blood will be collected for DNA extraction and genetic biomarkers analysis.

3.1.1. Study Cohorts

3.1.1.1. Dose Escalation Cohorts

A patient may be assigned to receive 1 of 11 possible treatments (monotherapy, combination with radiation therapy, combination with cyclophosphamide, or combination with radiation therapy and cyclophosphamide; [Table 1](#)); up to 10 treatment cohorts will be enrolled. A patient may be assigned to a specific treatment cohort based on the investigator's assessment of the appropriateness of a therapy regimen for that patient, completion of the safety observation periods for the requisite prior treatment cohorts without exceeding a MTD, and the availability of patient slots in the preferred treatment cohort. The first cohort to be enrolled will receive REGN2810 monotherapy at 1 mg/kg. Subsequent enrollment of each additional cohort may also be limited by the number of DLTs observed in prior cohorts (see [Section 3.1.2](#)).

Table 1: Possible Dose Escalation Cohorts

n	Possible Assigned Treatment Cohort
3–6	0.3 mg/kg REGN2810 monotherapy (<i>to be enrolled only if MTD < 1 mg/kg REGN2810</i>)
3–6	1 mg/kg REGN2810 monotherapy
3–6	3 mg/kg REGN2810 monotherapy ^a
3–6	10 mg/kg REGN2810 monotherapy ^b
3–6	1 mg/kg ^a REGN2810 + radiotherapy (6 Gy × 5)
3–6	1 mg/kg ^a REGN2810 + radiotherapy (9 Gy × 3)
3–6	3 mg/kg ^b (or MTD) REGN2810 + cyclophosphamide
3–6	3 mg/kg ^b (or MTD) REGN2810 + radiotherapy (6 Gy × 5)
3–6	3 mg/kg ^b (or MTD) REGN2810 + radiotherapy (9 Gy × 3)
3–6	3 mg/kg ^b (or MTD) REGN2810 + radiotherapy (6 Gy × 5) + cyclophosphamide
3–6	3 mg/kg ^b (or MTD) REGN2810 + radiotherapy (9 Gy × 3) + cyclophosphamide

^a Assuming MTD > 1 mg/kg

^b Assuming MTD > 3 mg/kg

3.1.1.2. Expansion Cohorts

Up to an additional 26 expansion cohorts will be enrolled ([Table 2](#)). A patient will be assigned to a specific treatment cohort based on the patient's tumor type, the investigator's assessment of the appropriateness of a therapy regimen for that patient, completion of the safety observation periods, and the availability of the patient slots in the assigned treatment cohort. Enrollment of each additional cohort may be limited by the number of DLTs observed in the 28-day DLT period (21 day DLT period for Cohorts 21 and 22) (see [Section 3.1.2](#)).

Table 2: Expansion Cohorts

Expansion Cohort*	n	Indication**	Treatment
1	20	NSCLC	Flat dose – 200 mg REGN2810
2	60	NSCLC	3 mg/kg REGN2810 + radiotherapy (9 Gy × 3)
3	60	HNSCC	3 mg/kg REGN2810 + radiotherapy (9 Gy × 3) + cyclophosphamide + GM-CSF*
4	60	BC	3 mg/kg REGN2810 + radiotherapy (9 Gy × 3) + cyclophosphamide
5	20	Advanced solid tumors –Previous treatment with an anti PD-1/PD-L1 antibody	3 mg/kg REGN2810+ radiotherapy (9 Gy × 3) + cyclophosphamide + GM-CSF*
6	30	Advanced solid tumors (excluding NSCLC, HNSCC, and BC)	3 mg/kg REGN2810+ radiotherapy (9 Gy × 3) + cyclophosphamide + GM-CSF*
7	10	Metastatic (M1) CSCC	3 mg/kg REGN2810
8	20	Locally and/or regionally advanced CSCC (M0) that is unresectable	3 mg/kg REGN2810
9	10	Metastatic colorectal cancer with MSI	3 mg/kg REGN2810
10	1***	Metastatic endometrial cancer with MSI	3 mg/kg REGN2810: closed due to insufficient accrual
11	0***	Castrate recurrent prostate cancer with MSI	3 mg/kg REGN2810 : closed due to insufficient accrual
12	10	Any other advanced solid tumor with MSI	3 mg/kg REGN2810
13	20	Advanced or metastatic HCC	3 mg/kg REGN2810
14	20	Advanced solid tumor refractory to first line chemotherapy	3 mg/kg REGN2810 + carboplatin + docetaxel (low dose)
15	20	Advanced solid tumor refractory to first line chemotherapy	3 mg/kg REGN2810 + docetaxel (low dose)
16	0***	Metastatic colorectal cancer with MSI, previously untreated	3 mg/kg REGN2810: closed due to insufficient accrual
17	10	Advanced NSCLC previously untreated	3 mg/kg REGN2810 + carboplatin + docetaxel (low dose)
18	22	Newly diagnosed GBM	REGN2810 (1 or 3 mg/kg) + radiotherapy (6 Gy x 5 days)
19	22	Recurrent GBM	REGN2810 (1 or 3 mg/kg) + radiotherapy (6 Gy x 5 days)
20	10	HIV and solid tumors	3 mg/kg REGN2810
21	10	Advanced NSCLC, previously untreated	3 mg/kg REGN2810 + Carboplatin + Paclitaxel (Full Dose)*
22	10	Advanced Non-Squamous NSCLC, previously untreated	3 mg/kg REGN2810 + Carboplatin + Pemetrexed*
23	10	Cervical Cancer, recurrent or metastatic	3 mg/kg REGN2810
24	10	Cervical Cancer, recurrent or metastatic	3 mg/kg REGN2810 + radiotherapy (9 Gy X 3)
25	15	BCC, refractory to hedgehog pathway inhibition	3 mg/kg REGN2810
26	20	Advanced Solid Tumor	3 mg/kg REGN2810 ()

* There will be a 6-patient, 28-day DLT observation period for patients enrolled in several of the expansion cohorts (see Section 3.1.2.5). Cohorts 21 and 22 have a 21-day DLT observation period for the first 6 patients.

** See Section 4.2.1 for detailed description of indication, REGN2810 every 2 weeks, except in Cohorts 21 and 22, where every 3 weeks.

*** Patient numbers for cohorts 10, 11, and 16 reflect actual numbers when sponsor administratively put these cohorts on hold due to lack of accrual in June 2016.

3.1.2. Dose Escalation Rules

Dose escalation rules for the study will follow a traditional 3 + 3 dose-escalation design, enrolling a total of 3 (or, in the case of 1 DLT observed in the initial 3 patients, an expanded total of 6 patients) per cohort until either all cohorts have fully enrolled or a MTD is established according to the rules in this section. At any point, the Safety Monitoring Team may decide to expand a cohort to 6 patients even in the absence of a DLT.

After the required initial enrollment to the next cohort(s) in the dose escalation has occurred, enrollment to each of the previous cohorts below the MTD for that treatment will be expanded (if not previously expanded due to DLT) to a total of 6 patients.

No inpatient dose escalation is permitted in the study. The DLT observation period is defined as the first 28 days after receiving the first dose of REGN2810, except for Expansion Cohorts 21 and 22 where the DLT observation period is defined as the first 21 days after receiving the first dose of REGN2810. Escalation to the next cohort will occur once all of the initial patients enrolled in a cohort (although screening for the next dose cohort may begin prior to confirmation that the current dose is safe) have completed day 28 safety assessments and the data have been reviewed at a Dose Escalation Review meeting. This meeting will be led by a designated member of the Regeneron clinical team (generally either the medical monitor or the clinical trial manager) and at a minimum will be attended by the Regeneron Medical Monitor and the Risk Management Lead; other individuals, including the investigator, may be included. Details on patient cohort assessment through the dose-escalation portion of the study will be provided in the study reference manuals.

The first REGN2810 cohort to be enrolled will be 1 mg/kg. A 48 hour waiting period between initial study drug administrations will be required for the first 3 patients enrolled at REGN2810 1 mg/kg. Provided that no unexpected toxicity is observed in this first cohort, each subsequent cohort can enroll patients without implementing a waiting period.

The treatment cohort enrollment sequence is described in Sections [3.1.2.1](#), [3.1.2.2](#), [3.1.2.3](#), and [3.1.2.4](#).

Note: The intent of the Dose Escalation Rules and DLT Monitoring Plan (Section [3.1.2](#), Section [3.1.3](#), and Section [3.1.4](#)) is to ensure that a cohort will not be expanded beyond 6 patients in the event of more than 1 DLT in the first 6 patients. If 5 of 6 patients have received 2 doses and completed the DLT monitoring period without DLT, the cohort may be expanded.

3.1.2.1. General Escalation Rules

If 1 of the first 3 patients enrolled in a cohort exhibits a DLT (defined in Section [3.1.3](#)) in the first cycle of therapy, 3 additional patients will be enrolled, expanding the cohort to a total of 6 patients.

If 2 or more patients in the cohort experience DLTs in the first cycle of monotherapy:

1. Dose escalation will be stopped, and that REGN2810 dose level will be considered to have exceeded the MTD for monotherapy or for the specific combination.
2. If the MTD is exceeded at 1 mg/kg (the lowest planned dose level), a cohort may be enrolled at 0.3 mg/kg, as defined in [Table 1](#).

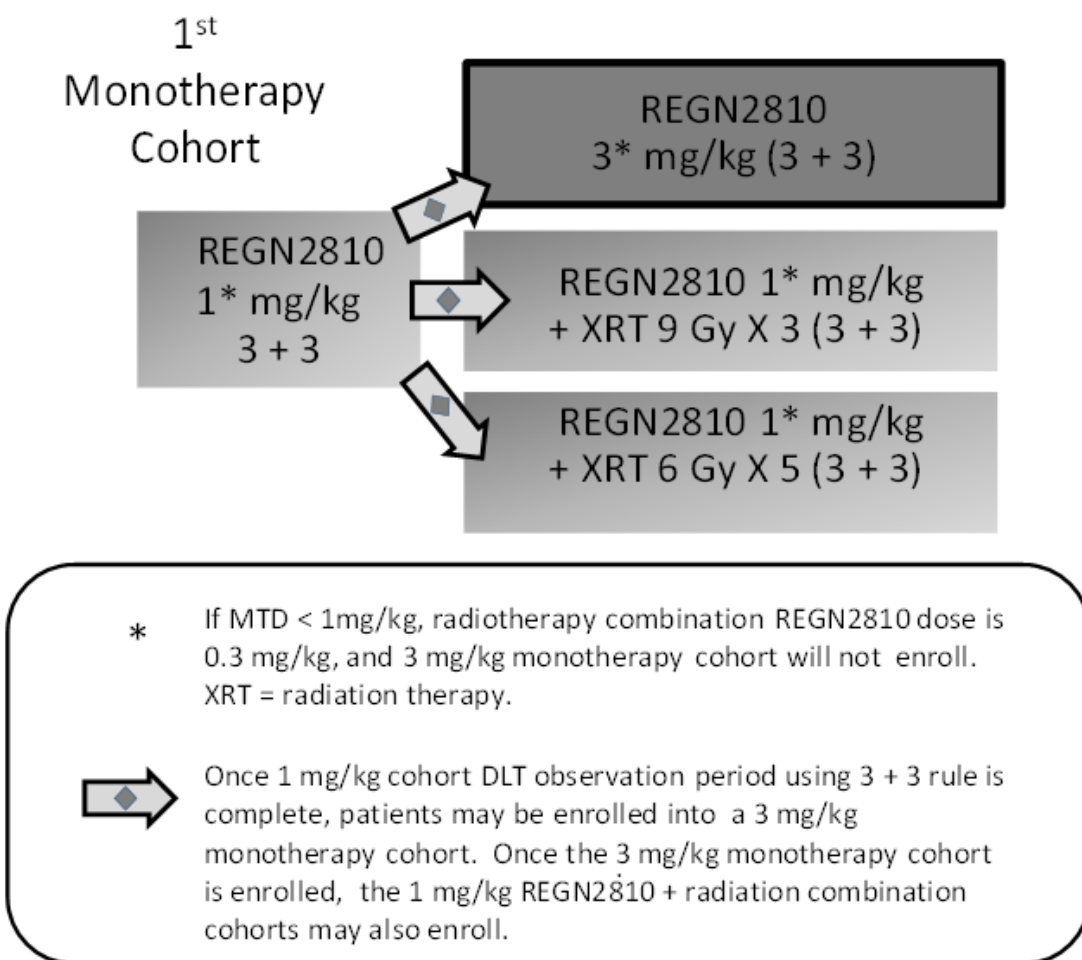
3. If the REGN2810 MTD is exceeded at 3 mg/kg, REGN2810 dosages for remaining patients will be reduced to the previous tested dose level (ie, 1 mg/kg).
4. Unless already expanded to 6 patients, the lower REGN2810 dose level (as described in item 2 or 3) will be expanded to 6 patients.

3.1.2.2. Monotherapy Escalation Rules

Each successive REGN2810 monotherapy dose level (Table 1) may be enrolled after the monotherapy group at the previous REGN2810 dose level has completed the 28 day observation period without a DLT (defined in Section 3.1.3) in 3 patients, or with no more than 1 DLT in an expanded cohort of 6 patients.

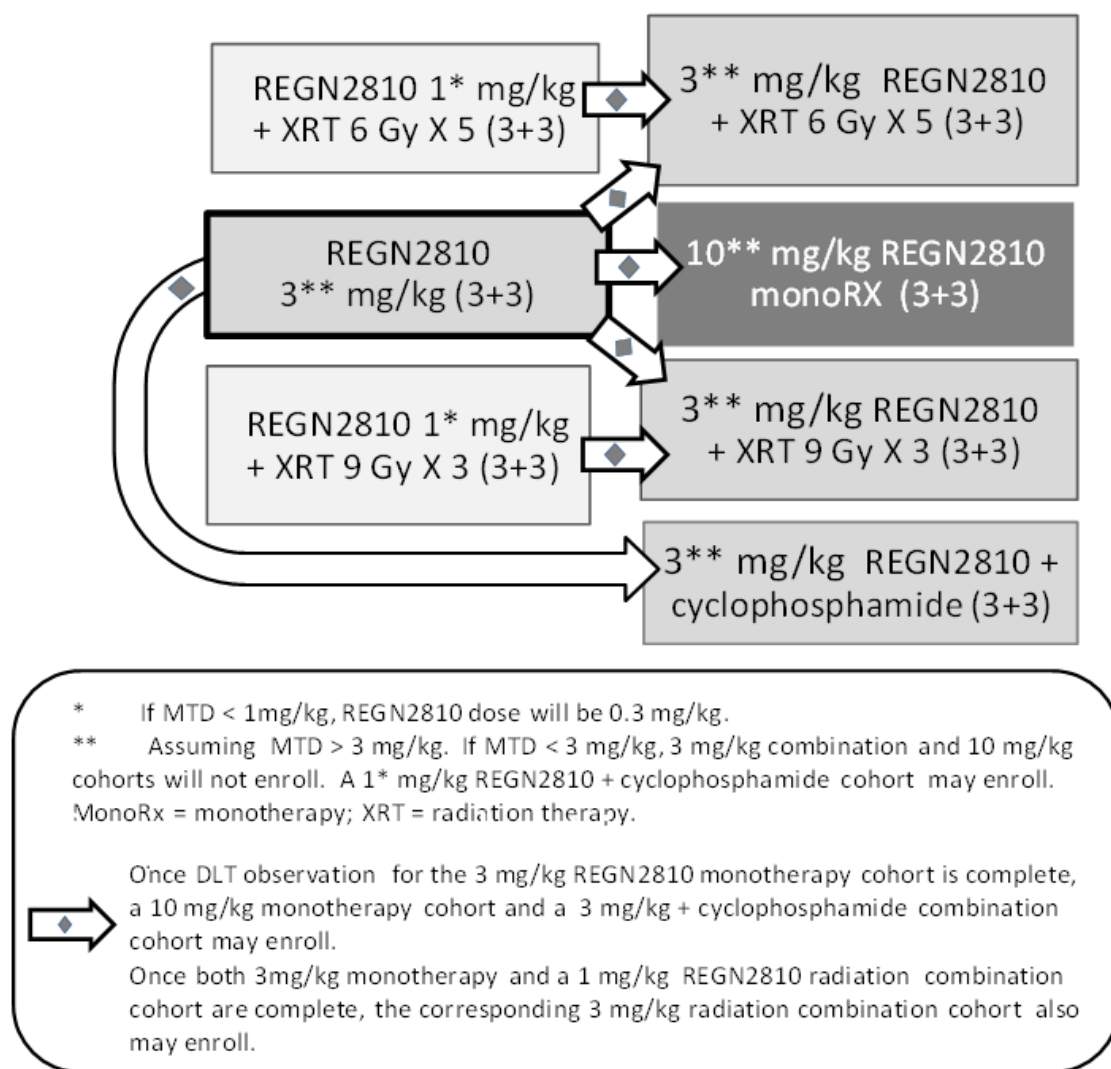
If the MTD is not established with completion of the 1 mg/kg monotherapy cohort, the dose may be escalated to 3 mg/kg monotherapy (Figure 2). If the MTD is established in the first cohort according to the rules described in Section 3.1.4, the sponsor may choose to enroll a cohort at 0.3 mg/kg REGN2810.

Figure 2: Planned Treatment Cohort Enrollment, First Progression Set: 3 mg/kg Monotherapy and 1 mg/kg Radiotherapy Combination Cohorts



If a MTD is not established with completion of the 3 mg/kg monotherapy cohort, the dose may be escalated to 10 mg/kg monotherapy (Figure 3).

Figure 3: Planned Treatment Cohort Enrollment, Second Progression Set: 10 mg/kg Monotherapy, 3 mg/kg plus Radiotherapy Combination, and 3 mg/kg plus Cyclophosphamide Combination Cohorts



Dose escalation will stop once the MTD (defined in Section 3.1.4) has been reached, or after the highest planned dose level (10 mg/kg) has been evaluated.

3.1.2.3. Dual Combination Therapy Escalation Rules

Two different radiation regimens will be evaluated independently with respect to MTD and dose escalation. Enrollment in cohorts to receive a combination of 1 mg/kg REGN2810 with each radiation regimen may proceed once all patients in the 1 mg/kg monotherapy cohort have been observed for at least 28 days with no DLT in 3 patients, or no more than 1 DLT in an expanded cohort of 6 patients (Figure 3).

Enrollment of a cohort receiving a combination of REGN2810 3 mg/kg and a particular radiotherapy regimen may take place once all patients in the 3 mg/kg monotherapy cohort and the cohort combining 1 mg/kg with that radiotherapy regimen have completed the 28 day observation period without a DLT in a cohort of 3 patients, or with no more than 1 DLT in an expanded cohort of 6 patients (Figure 3).

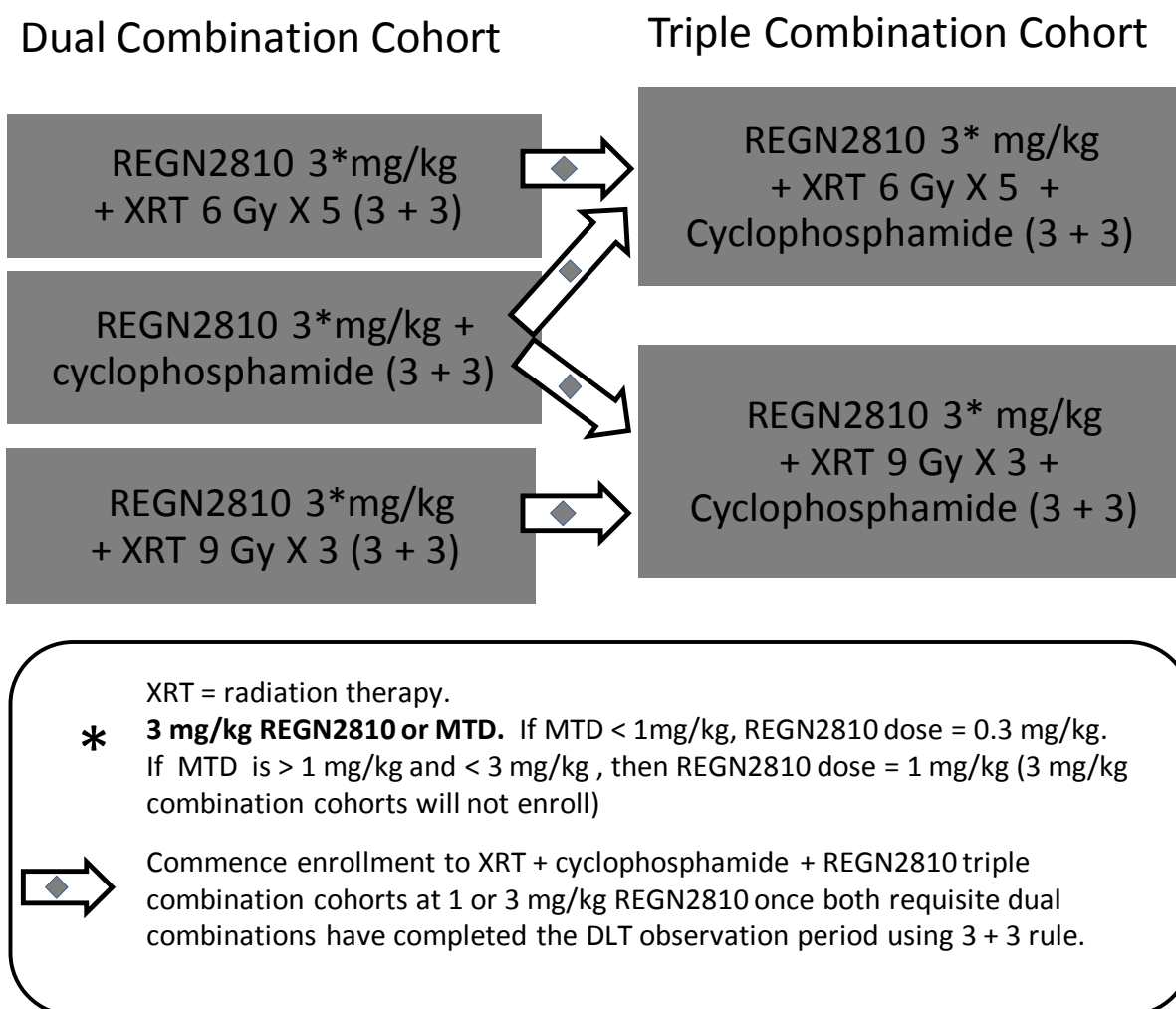
The cohort to receive 3 mg/kg REGN2810 combined with cyclophosphamide may be enrolled only once the 28 day observation period for the 3 mg/kg monotherapy cohort has completed with no DLT in a cohort of 3 patients, or no more than 1 DLT in an expanded cohort of 6 patients (Figure 3).

If the MTD for REGN2810 monotherapy is determined to be <3 mg/kg, then a cohort will be enrolled to receive a combination of cyclophosphamide with REGN2810 at the MTD. The combination therapy assigned to each patient will be determined by the appropriateness of the treatment for the patient as judged by the investigator, in consultation with the sponsor.

3.1.2.4. Triple Combination Therapy Escalation Rules

Combination of a radiation regimen plus cyclophosphamide with REGN2810 at 3 mg/kg (or MTD if <3 mg/kg) can proceed only if the cohorts for combination therapy of that REGN2810 dose level with the radiation regimen, and combination therapy of the REGN2810 dose level with cyclophosphamide have each completed the 28 day observation period with no DLT in 3 patients, or no more than 1 DLT in an expanded cohort of 6 patients per cohort (Figure 4).

Figure 4: Planned Treatment Cohort Progression, Third Set: Triple Combination Therapy Cohorts



3.1.2.5. Expansion Cohorts – 6-Patient Run-in Design

There will be a 6-patient, 28-day DLT observation period for patients enrolled in expansion cohorts that have GM-CSF added, low dose carboplatin plus docetaxel added, low dose docetaxel added, full dose carboplatin plus paclitaxel added, or carboplatin plus pemetrexed added, in order to allow for observation of both acute and non-acute toxicity prior to enrollment of the full cohorts. Similarly, there will be a 6-patient, 28-day DLT observation period for patients with HIV and advanced solid tumors in Expansion Cohort 20. (Expansion Cohorts 18 and 19 will not have a 6-patient run-in design, but rather a standard 3+3 design, due to a potential for different safety and tolerability profile of the regimen in GBM patients).

There will be a 6-patient run-in for each of Expansion Cohorts 3, 5, and 6; once a total of 6 patients are enrolled into each of these cohorts, enrollment will stop and patients will be observed for 28 days (the DLT observation period for each patient will be the first 28 days on

treatment). If there is no more than 1 DLT observed in these 6 patients at the end of the 28-day period (see Section 3.1.3), the remaining patients will be enrolled into that cohort.

Expansion Cohorts 14 (carboplatin plus docetaxel), 15 (docetaxel), and 17 (carboplatin plus docetaxel) will each have a separate 6 patient run-in. In each cohort, enrollment will stop after 6 patients have been enrolled and the patients will be observed for the 28-day DLT observation period. For each cohort, if there is no more than 1 DLT observed among the 6 patients at the end of the 28-day period (see Section 3.1.3), the remaining patients will be enrolled into the cohort. DLT determinations for Expansion Cohorts 14 and 15 will be mutually independent.

Expansion Cohort 18 (newly diagnosed GBM) and Expansion Cohort 19 (recurrent GBM) will each have separate dose escalations: REGN 2810 1 mg/kg and 3 mg/kg every 14 days. Dose escalation rules will be as described in Section 3.1.2, and DLT definitions are as described in Section 3.1.3. DLT determinations for Expansion Cohorts 18 and 19 will be mutually independent. After the RP2D is established for Cohort 18, 10 additional patients will be enrolled into the cohort to further describe the safety of the regimen. After the RP2D is established for Cohort 19, 10 additional patients will be enrolled to that cohort as well, to further describe the safety of the regimen.

Expansion Cohort 20 (patients with HIV and advanced solid tumors): Enrollment will stop after 6 patients have been enrolled; the patients will be observed for the 28-day DLT observation period. If there is no more than 1 DLT observed among 6 patients at the end of the 28-day period (see Section 3.1.3), the remaining patients will be enrolled into the cohort.

Expansion Cohorts 21 and 22 (advanced NSCLC, previously untreated): Enrollment will stop after 6 patients have been enrolled in any of these cohorts. The patients will be observed for the 21-day DLT observation period. If there is no more than 1 DLT observed among 6 patients at the end of the 21-day period (see Section 3.1.3), the remaining patients will be enrolled into the cohort. If there are more than 2 DLTs among the first 6 patients enrolled in Expansion Cohort 21 or Expansion Cohort 22, the MTD will be deemed to have been exceeded and enrollment would stop in this cohort only. For Expansion Cohorts 17, 21 and 22, if there is not more than 1 DLT among the first 6 patients in the cohort, the sponsor may expand that particular cohort to 10 patients.

3.1.3. Dose-Limiting Toxicities

The DLT observation period for determination of safety for dose escalation or initiation of new combination therapy is defined as 28 days starting with cycle 1, day 1, with the intent to monitor safety and tolerability of the first 2 doses of REGN2810. To be evaluable for a DLT, an individual patient must have received at least the first 2 administrations of REGN2810 (ie day 1 and day 15 \pm 3) and be monitored for at least 28 days following the first administration, and at least 14 days (7 days for patients in Cohorts 21 and 22, DLT observation period for Cohorts 21 and 22 is only 21 days,) from the second administration. Patients with a delayed second dose will thus have an extended duration of the DLT observation period, as will patients experiencing an AE whose time course of resolution must be assessed to determine if the event was a DLT. An exception for the requirement of 2 doses of REGN2810 would be made in the event that emergence of a DLT after the first dose precluded the second dose.

Any of the below outlined events occurring during the DLT observation period and considered to be at least possibly related to REGN2810 will qualify as a DLT.

A DLT is defined as any of the following:

Non-Hematologic Toxicity

1. Grade ≥ 2 uveitis (considered as a potential immune-related adverse event [irAE]).
2. Any Grade ≥ 3 non-hematologic toxicity; with the exception of:
 - a. Grade 3 nausea, vomiting or diarrhea unless persistent (>7 days duration) despite maximal supportive care measures as prescribed by the treating physician.
 - b. Grade ≥ 3 laboratory abnormalities that are considered clinically insignificant and do not meet criteria for an AE.
 - c. Grade 3 infusion-related reactions that respond to medical management.
 - d. Grade 3 irAE (as defined by experience with other immunomodulatory drugs – see [Appendix 2](#) describing common irAEs) other than uveitis that improves within 14 days to Grade 2 or lower with medical management (including treatment with steroids).

Hematologic Toxicity

1. Grade 4 neutropenia lasting more than 7 days
2. Grade 4 thrombocytopenia
3. Grade 3 thrombocytopenia with bleeding
4. Grade ≥ 3 febrile neutropenia (fever $\geq 38.5^{\circ}\text{C}$ with absolute neutrophil count [ANC] $< 1.0 \times 10^9/\text{L}$), or Grade ≥ 3 neutropenia with documented infection

The frequency, time to onset, and severity of toxicities, as well as the success of standard medical management and dosing interruptions/delays (Section 5.3), will be analyzed to determine if a given toxicity should be considered a DLT for dose escalation purposes.

In general, as there is as yet no clinical experience for the new biologic molecule REGN2810, alone or in combination with other therapies, any AE that has been clearly described for other agents that block the PD-1/PD-L1 pathway or that is expected with a therapy included as a component of combination therapy in this study initially will be treated as unexpected. Such treatment-emergent adverse events (TEAEs) will be monitored and especially considered on an ongoing basis to assess possible differences in event frequency or severity from that observed with other PD-/PD-L1 blockers or combination therapy components.

Treatment-emergent adverse events that appear to meet the DLT definition will be discussed between the sponsor and the investigator. The final decision of whether or not the AE meets the DLT definition will be based on a careful review of all relevant data and consensus between the medical monitor and the designated Risk Management lead from the Pharmacovigilance & Risk Management department. The investigator may also be consulted.

Regardless of whether a patient remains on study treatment and/or continues to participate in study procedures, such an event will count as a DLT for the involved cohort if the event occurs during the DLT observation period.

3.1.4. Maximum Tolerated Dose

The MTD will be identified separately for the monotherapy group and each combination group; up to 4 MTDs may be identified in the dose escalation cohorts described in [Table 1](#). Expansion Cohort 18 and Expansion Cohort 19 will each have independent MTD determinations. The MTD for either combination therapy group will not exceed the monotherapy MTD dose level, as the occurrence of 2 DLTs for that monotherapy dose level and the resulting determination of the MTD preclude further dose escalation (see dose escalation rules, Section [3.1.2](#)).

The MTD for a group is defined as the highest dose at which fewer than a third of an expanded cohort of 6 patients experience a DLT during the DLT monitoring period. Thus, the MTD is defined as the dose level immediately below the level at which dosing is stopped due to the occurrence of 2 or more DLTs in an expanded cohort of 6 patients. If dose escalation is not stopped due to the occurrence of DLTs, it will be considered that the MTD has not been determined.

Based on data with other anti-PD-1 investigational compounds, it is possible that an MTD may not be defined in this study, either for a monotherapy group or for individual combination groups. Additionally, it is possible that REGN2810 MTDs may differ between monotherapy and each combination treatment regimen.

3.2. Planned Interim Analysis

See Section [9.6](#).

4. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

4.1. Number of Patients Planned

Up to 560 adult patients are expected to be enrolled at up to 50 sites in North America, the EU, and Asia-Pacific. The total number of patients enrolled will depend upon observed DLTs during the monotherapy and combination therapy cycles.

4.2. Study Population

The target population for this study comprises patients with advanced malignancies who are not candidates for standard therapy, or for whom no available therapy is expected to convey clinical benefit or for whom PD-1 blockade has been shown to be at least equivalent to standard of care; and patients with malignancies that are incurable and have failed to respond to or showed tumor progression despite standard therapy.

If a patient is a candidate for a disease-specific cohort in this study, the patient should be enrolled into that disease-specific cohort, rather than into a cohort that allows patients with any advanced solid tumor to enroll.

4.2.1. Inclusion Criteria

A patient must meet the following criteria to be eligible for inclusion in the study:

1. Histologically or cytologically confirmed diagnosis of malignancy with demonstrated progression of a solid tumor (non-lymphoma) with no alternative standard-of-care therapeutic option. (Exceptions are Expansion Cohorts 16 [Colorectal cancer with MSI] and 17 [NSCLC], 18 [newly diagnosed GBM] and 21 and 22 [NSCLC] which are for patients who have not received prior chemotherapy for recurrent/metastatic disease. Expansion Cohorts 1 and 2 allow NSCLC patients who have received 1 or more lines of therapy for recurrent or metastatic disease. Expansion Cohort 13 allows HCC patients who refuse first-line therapy. Expansion Cohort 11 allows prostate cancer patients who have not received cabazitaxel).
 - a. **Expansion Cohorts 1 and 2:** Patients in the NSCLC expansion cohorts must have relapsed after, or be refractory to at least first line therapy in the recurrent or metastatic disease setting. (Note: NSCLC patients with activating EGFR mutations or ALK rearrangements must have previously received an appropriate EGFR or ALK-targeted therapy with subsequent disease progression or intolerability prior to enrolling. NSCLC patients in Expansion Cohort 2 must have disease for which palliative radiation therapy is clinically indicated). Patients enrolled in Expansion Cohort 1 must weigh between 45 kg (100 lbs) and 113 kg (250 lbs).
 - b. **Expansion Cohort 3:** Patients in the HNSCC expansion cohort must be refractory to at least first line therapy in the recurrent or metastatic disease setting and must have disease for which palliative radiation therapy is clinically indicated. Patients in this cohort will have primary tumor sites of oral cavity, oropharynx, larynx, or hypopharynx.
 - c. **Expansion Cohort 4:** Patients in the BC expansion cohort (if hormone receptor negative and HER2 negative) must have relapsed after, or be refractory to at least 2 prior chemotherapy regimens in the recurrent or metastatic disease setting, and must have disease for which palliative radiation therapy is clinically indicated. Selected hormone receptor positive or HER2+ patients with BC may enroll without prior cytotoxic chemotherapy:
 - I. Patients who are hormone receptor positive + and are hormone refractory, defined as disease progression within 6 months from starting the most recent hormonal therapy
 - II. Patients who are HER2+ and have demonstrated progression of disease while on treatment with trastuzumab
 - d. **Expansion Cohort 5:** Patients with advanced solid tumors who previously received other PD-1/PD-L1 antibodies must have progressed after initially achieving disease control (CR, PR, SD for at least 8 weeks, according to RECIST 1.1 criteria) while being treated with other PD-1/PD-L1 antibodies, and must have disease for which palliative radiotherapy is clinically indicated.

- e. **Expansion Cohort 6:** Patients with an advanced solid tumor (other than NSCLC, HNSCC, or BC) who have relapsed after, or become refractory to at least first line therapy in the recurrent or metastatic disease setting, and for whom palliative radiotherapy is clinically indicated
- f. **Expansion Cohort 7:** Patients with metastatic (M1) CSCC. (Note: This cohort does not include patients with primary tumors of the lip or eyelid).
- g. **Expansion Cohort 8:** Patients with unresectable locally and/or regionally advanced CSCC without distant metastases (M0). Acceptable reasons for surgery to be considered inappropriate are 1 or both of the following: 1) recurrence of CSCC after 2 or more surgical procedures and an expectation that curative resection would be unlikely, and/or 2) substantial morbidity or deformity anticipated from surgery. (**Note:** This cohort does not include patients with primary tumors of the lip or eyelid).
- h. **Expansion Cohort 9:** Metastatic colorectal cancer with MSI*, refractory to 2 prior lines of therapy for recurrent disease
- i. **Expansion Cohort 10:** Metastatic endometrial cancer with MSI*, refractory to at least first line therapy for recurrent disease
- j. **Expansion Cohort 11:** Castration recurrent prostate cancer with MSI*, refractory to docetaxel (see [Scher 2008](#) for guidelines)
- k. **Expansion Cohort 12:** Other advanced or metastatic solid tumors with MSI*. (Note: Patients with metastatic CRC with MSI*, refractory to first line therapy for recurrent disease, are eligible for this cohort).
- l. **Expansion Cohort 13:** HCC not amenable to curative resection, and with Child-Pugh Score ≤ 7 . Patients with HCC may be eligible if they have progressed through first-line systemic therapy for advanced disease, were intolerant of first-line therapy, or refused first-line therapy. Patients with hepatitis B must be on antiviral therapy.
- m. **Expansion Cohort 14:** Advanced solid tumor, in which treatment with carboplatin and docetaxel is clinically appropriate. Patients must not be a candidate for any other disease-specific cohort in this study.
- n. **Expansion Cohort 15:** Advanced solid tumor, in which treatment with docetaxel is clinically appropriate. Patients must not be a candidate for any other disease-specific cohort in this study.
- o. **Expansion Cohort 16:** Metastatic colorectal cancer with MSI*, previously untreated (prior adjuvant chemotherapy is allowed)
- p. **Expansion Cohort 17:** Stage IIIB or IV NSCLC, previously untreated (prior neoadjuvant/adjuvant chemotherapy is allowed), and without activating EGFR mutation or ALK rearrangement.
- q. **Expansion Cohort 18:** Newly diagnosed GBM, ≤ 5 cm in maximum diameter, on post-operative imaging, unmethylated at the MGMT promoter*, for patients ≥ 60 years of age.
- r. **Expansion Cohort 19:** Recurrent GBM, ≤ 4 cm in maximum diameter, by diagnostic biopsy or contrast-enhanced MRI within 28 days prior to day 1 per modified RANO criteria ([Wen 2010](#)). Note: Recurrence is defined as progression following therapy (eg, chemotherapy, radiation).

- s. **Expansion Cohort 20:** Advanced solid tumors and HIV infection, as documented by any federally approved, licensed HIV rapid test performed in conjunction with screening (or enzyme linked immunosorbent assay [ELISA] test kit, and confirmed by Western blot or other approved test); alternatively, the documentation may include a record demonstrating that another physician has documented the patient's HIV status based on either: 1) approved diagnostic tests, or 2) the referring physician's written record that HIV infection was documented, with supporting information on the participant's relevant medical history and/or current management of HIV infection.
 - t. **Expansion Cohort 21:** Stage IIIB or IV NSCLC, previously untreated (prior neoadjuvant/adjuvant chemotherapy is allowed), and without activating EGFR mutation or ALK rearrangement.
 - u. **Expansion Cohort 22:** Stage IIIB or IV non-squamous NSCLC, previously untreated (prior neoadjuvant/adjuvant chemotherapy is allowed), and without activating EGFR mutation or ALK rearrangement.
 - v. **Expansion Cohort 23:** Recurrent or metastatic cervical carcinoma, resistant to or intolerant of prior platinum + taxane doublet chemotherapy, for which palliative radiotherapy is **not** planned
 - w. **Expansion Cohort 24:** Recurrent or metastatic cervical carcinoma, resistant to or intolerant of prior platinum + taxane doublet chemotherapy, for which palliative radiotherapy is planned
 - x. **Expansion Cohort 25:** Unresectable locally advanced or metastatic cutaneous basal cell carcinoma, resistant to or intolerant of prior treatment with hedgehog pathway inhibitor (vismodegib or sonidegib).
 - y. **Expansion Cohort 26:** Any advanced solid tumor
 - * MSI status (Expansion Cohorts 9 through 12 and Expansion Cohort 16) and methylation status of MGMT promoter in GBM (Expansion Cohort 18) will be established with CLIA-approved assays or equivalent, and may be subsequently confirmed centrally.
2. At least 1 measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria for response assessment (excluding GBM cohorts; GBM patients may have measureable or non-measurable disease). Patients (other than GBM patients) assigned to radiotherapy require at least 1 additional lesion that can be safely irradiated while sparing the index lesion(s), and for which radiation at the limited, palliative doses contemplated would be considered medically appropriate. The lesion should be causing some signs or symptoms (eg, tumor-related pain or obstruction-associated decrease in the function of an organ), for which radiation is indicated per the physician's standard clinical practice (does not apply to GBM cohorts).
- Note:** C5CC patients without radiographically measurable disease are not excluded if there is at least 1 lesion ≥ 10 mm in at least 1 dimension documented by color photography
3. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 (ECOG PS 1 definition: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work).
- Note:** Patients with ECOG PS >1 are ineligible.

4. ≥ 18 years old
5. Hepatic function:
 - a. Total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN; if liver metastases $\leq 3 \times$ ULN, or HCC $\leq 3 \times$ ULN in non-docetaxel containing cohorts-only). Patients with Gilbert's Disease and total bilirubin up to $3 \times$ ULN may be eligible after communication with and approval from medical monitor.
 - b. Transaminases $\leq 3 \times$ ULN (or $\leq 5.0 \times$ ULN, if liver metastases or HCC)
 - c. Alkaline phosphatase (ALP) $\leq 2.5 \times$ ULN (or $\leq 5.0 \times$ ULN, if liver or bone metastases, or HCC)
 - d. For patients with hepatic metastases or hepatic malignancies, exclude patients with concomitant $3 \times$ ULN \leq aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) $\leq 5 \times$ ULN **AND** $1.5 \times$ ULN \leq total bilirubin $\leq 3 \times$ ULN
6. Renal function: Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance (CrCl) > 50 ml/min
7. Bone marrow function:
 - a. Hemoglobin ≥ 9.0 g/dL
 - b. ANC $\geq 1.5 \times 10^9$ /L
 - c. Platelet count $\geq 75 \times 10^9$ /L

Note: For Expansion Cohort 13 (hepatocellular cancer), the platelet count requirement is $\geq 60 \times 10^9$ /L.
8. Ability to provide signed informed consent
9. Ability and willingness to comply with scheduled visits, treatment plans, laboratory tests, and other study-related procedures
10. **Expansion Cohort 19:** At least 12 weeks from prior radiation therapy on day 1 of the study (unless progressive disease outside of the radiation field)
11. **Expansion Cohort 20:** HIV plasma HIV-1 ribonucleic acid (RNA) below detected limit obtained by Food and Drug Administration (FDA)-approved assays (limit of detection: 75) within 4 weeks prior to first dose of REGN2810
12. **Expansion Cohort 20:** CD4+ cell count greater than 200 cells/mm³ obtained within 14 days prior to enrollment at any US laboratory that has clinical laboratory improvement amendments (CLIA) certification or its equivalent
13. **Expansion Cohort 20:** Patients must receive appropriate care and treatment for HIV infection, including antiretroviral medications when clinically indicated, and should be under the care of a physician experienced with HIV management. Participants will be eligible regardless of antiretroviral medication (including no antiretroviral medication), provided there is no intention to initiate therapy or the regimen has been stable for at least 4 weeks with no intention to change the regimen within 8 weeks following enrollment.

4.2.2. Exclusion Criteria

A patient who meets any of the following criteria will be excluded from the study:

1. Ongoing or recent (within 5 years) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest risk for irAEs. The following are not exclusionary: vitiligo, childhood asthma that has resolved, residual hypothyroidism that required only hormone replacement, or psoriasis that does not require systemic treatment.
2. Prior treatment with an agent that blocks the PD-1/PD-L1 pathway, except for patients who are to be enrolled into Expansion Cohort 5.
3. Prior treatment with other immune modulating agents within fewer than 4 weeks prior to the first dose of REGN2810.
Examples of immune modulating agents include blockers of CTLA-4, 4-1BB (CD137), OX-40, therapeutic vaccines, or cytokine treatments.
4. Untreated brain metastasis(es) that may be considered active. Patients with previously treated brain metastases may participate provided they are stable (ie, without evidence of progression by imaging for at least 6 weeks prior to the first dose of study treatment, and any neurologic symptoms have returned to baseline), and there is no evidence of new or enlarging brain metastases, and the patient does not require any systemic corticosteroids for management of brain metastases within 4 weeks prior to the first dose of REGN2810. (GBM patients may enroll into Cohorts 18 and 19, but primary tumors in spinal cord or brainstem are excluded).
5. Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of REGN2810. Patients with previously treated brain metastases must not have been on systemic corticosteroids for 4 weeks prior to first dose of REGN2810, as per Exclusion 4.
Note: In addition, GBM patients must not be on systemic corticosteroids at the time of first dose of REGN2810.
Note: corticosteroids given within 24 hours of an imaging study for purposes of pre-medication in patients with hypersensitivity to radiologic contrast agents or as pre-medication for the combination agents in the protocol are allowed.
6. [placeholder for deleted exclusion criterion]
7. Active infection requiring therapy, including known infection with human immunodeficiency virus, or active infection with hepatitis B or hepatitis C virus, except for designated cohorts that allow hepatitis or HIV (Patients with hepatitis B on antiviral therapy or patients with hepatitis C may be eligible for the HCC expansion cohort (Cohort 13), but HCC patients with co-infection of hepatitis B and C are excluded. Patients with HIV may enroll only into Expansion Cohort 20. Patients with HIV and hepatitis B on antiviral therapy and patients with HIV and hepatitis C may enroll into Cohort 20 if all other criteria are met).
8. History of pneumonitis within the last 5 years.

9. Any investigational or antitumor systemic treatment within 4 weeks prior to the initial administration of REGN2810. Patients on gonadotropin-releasing hormone (GnRH) agonists (eg, for prostate cancer) are not excluded. Patients receiving bisphosphonates or denosumab are not excluded.
10. History of documented allergic reactions or acute hypersensitivity reaction attributed to treatment with antibody therapies in general, or to agents specifically used in the study.
11. Known allergy to doxycycline or tetracycline
(precaution due to presence of trace components in REGN2810)
12. Known hypersensitivity to cyclophosphamide for patients enrolled in cohorts receiving cyclophosphamide.
13. Breast-feeding
14. Positive serum pregnancy test. (A false positive pregnancy test, if demonstrated by serial measurements and negative ultrasound, will not be exclusionary, upon communication with and approval from the medical monitor).
15. History within the last 5 years of an invasive malignancy other than the one treated in this study and/or any leukemia or lymphoma, with the exception of resected/ablated basal or squamous-cell carcinoma of the skin or carcinoma in situ of the cervix, or ductal carcinoma in situ of the breast, or history of prostate adenocarcinoma treated with curative intent at least 3 years ago, and with undetectable prostate-specific antigen for at least 3 years prior to enrollment or other local tumors considered cured by local treatment, upon communication with and approval from the medical monitor.

Note: regarding Expansion Cohorts 7, 8, and 25: CSCC and BCC patients with clinically stable chronic lymphocytic leukemia that has not required treatment (chemotherapy, targeted systemic therapy, or radiation) within the last 6 months may be eligible, after discussion with and approval from the medical monitor.

16. Acute or chronic psychiatric problems that, under the evaluation of the investigator, make the patient ineligible for participation
17. Continued sexual activity in men^{**} or women of childbearing potential^{***} who are unwilling to practice highly effective contraception during the study and until 6 months after the last dose of study drug (highly effective contraceptive measures include stable use of oral contraceptives such as combined estrogen and progestogen and progestogen only hormonal contraception or other prescription pharmaceutical contraceptives for 2 or more menstrual cycles prior to screening; intrauterine device [IUD]; intrauterine hormone-releasing system (IUS); bilateral tubal ligation; vasectomy and sexual abstinence.
^{**} Contraception is not required for men with documented vasectomy.
^{***} Postmenopausal women must be amenorrheic for at least 12 months in order **not** to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.
18. For patients enrolled in cohorts receiving GM-CSF, known hypersensitivity to GM-CSF, yeast-derived products, or any component of the product.

19. For patients enrolled in the cohort containing carboplatin, history of hypersensitivity reaction to carboplatin (Grade ≥ 2 allergic reaction)
20. For patients enrolled in a cohort containing docetaxel, history of hypersensitivity reaction to docetaxel (Grade ≥ 2 allergic reaction)
21. Patients with a history of solid organ transplant (patients with prior corneal transplant may be allowed to enroll following discussion and approval from the medical monitor)
22. **Expansion Cohorts 7 and 8:** Prior treatment with BRAF inhibitor
23. **Expansion Cohorts 18 and 19:** Patients with extensive CNS edema (will be determined by judgment of the investigator in consultation with the medical monitor)
24. **Expansion Cohorts 18 and 19:** Known contra-indication to gadolinium MRI
25. **Expansion Cohort 18:** Any prior anti-cancer therapy for GBM (other than prior surgery)
26. **Expansion Cohort 19:** Prior re-irradiation or stereotactic radiosurgery for recurrent disease at the same tumor location
27. **Expansion Cohort 19:** Prior treatment with Gliadel, unless administered ≥ 3 months prior to study treatment
28. **Expansion Cohorts 18 and 19:** Diffuse leptomeningeal disease or extracranial disease
29. **Expansion Cohort 20:** Opportunistic infection within the last 3 months
30. Prior treatment with idelalisib

4.3. Premature Withdrawal from the Study or from Study Treatment

4.3.1. Reasons for Premature Withdrawal or Discontinuation of Study Treatment

A patient has the right to voluntarily discontinue study treatment or withdraw from the study at any time, for any reason, and without repercussion.

The investigator and sponsor have the right to discontinue a patient from study treatment or withdraw a patient from the study at any time.

Reasons for discontinuation of study treatment or withdrawal from the study may include, but are not limited to:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety if he or she continues in the study or continues treatment with study drug
- The investigator or sponsor determines it is in the best interest of the patient
- Patient noncompliance (eg, not complying with protocol required visits, assessments, and dosing instructions)
- Pregnancy

4.3.2. Discontinuation of Study Treatment

A patient who permanently discontinues study treatment and who does not withdraw from study participation will be asked to return to the clinic for all remaining study visits per the visit schedule, and will be expected to continue with relevant study assessments. After a minimum of 24 weeks of treatment, patients with confirmed CR may elect to discontinue treatment and continue with all relevant study assessments (eg, efficacy assessments) per Table 6 and Table 8. Patients with tumor burden assessments of SD or PR that have been maintained for 3 successive tumor evaluations may also elect to discontinue treatment after a minimum of 24 weeks of treatment and after consultation with the investigator and the Sponsor, and should continue with all relevant study assessments (eg, efficacy assessments) as scheduled per Table 6 and Table 8.

Patients with confirmed and increasing PD per RECIST (2 radiologic assessments of PD at least 4 weeks apart), or patients who are rapidly progressing and/or experiencing significant clinical deterioration, should discontinue study treatment.

A patient who discontinues study treatment prematurely during the treatment period due to PD, toxicity, or another reason besides confirmed CR, PR, or SD should return to the clinic 14 to 30 days after the last study treatment to complete follow-up visit 1. Patients who maintain active follow-up should continue with all relevant study assessments for follow-up visits 2 through 6 as scheduled per Table 8.

4.3.3. Withdrawal from Study Participation

During the treatment period and follow-up period, a patient who withdraws consent to continue participation in the study will not be followed for any reason after consent has been withdrawn. Every effort should be made to obtain information on patients who withdraw from the study.

An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

4.4. Replacement of Patients

Any patient who discontinues treatment or withdraws from the study prior to completing the DLT observation period (days 1 through 28) for any reason other than the occurrence of a protocol-defined DLT or other AE leading to study treatment discontinuation will be replaced. Each replacement patient will be assigned a unique patient number, and will be treated at the same dose level as the replaced, prematurely withdrawn patient. Any patient who discontinues after the DLT observation period will not be replaced.

5. STUDY TREATMENTS

5.1. Investigational Treatment

REGN2810 will be supplied as a liquid in sterile, single-use vials. For all treatment cohorts (except Expansion Cohort 26), [REDACTED]

[REDACTED] Instructions on dose preparation are provided in the study reference manuals.

REGN2810 will be administered in an outpatient setting as a 30 minute IV infusion. Each patient's dose will depend on individual body weight. The dose of REGN2810 must be adjusted each cycle for changes in body weight of $\geq 10\%$. Dose adjustments for changes in body weight of $< 10\%$ will be at the discretion of the investigator.

REGN2810 will be administered alone (Section 5.1.1), in combination with radiation (Section 5.1.2.1), in combination with cyclophosphamide (Section 5.1.2.2), in combination with radiation and cyclophosphamide (Section 5.1.2.3), in combination with radiation and GM-CSF (Section 5.1.2.4), and in combination with radiation, GM-CSF, and cyclophosphamide (Section 5.1.2.5), or with carboplatin plus docetaxel, or docetaxel (Section 5.1.2.6) in combination with carboplatin plus paclitaxel, or in combination with carboplatin plus pemetrexed (Section 5.1.2.8).

In Expansion Cohort 26, [REDACTED] REGN2810 is given as monotherapy at 3 mg/kg IV every 2 weeks.

5.1.1. Monotherapy

REGN2810 will be administered in an outpatient setting by IV infusion over 30 minutes every 14 days for 48 weeks (ie, Days 1, 15 ± 3 , 29 ± 3 , and 43 ± 3 of a 56 day cycle). Planned monotherapy regimens to be assigned may include:

- 1 mg/kg IV infusion over 30 minutes every 14 days for 48 weeks
- 3 mg/kg infusion over 30 minutes every 14 days for 48 weeks
- 10 mg/kg infusion over 30 minutes every 14 days for 48 weeks
- 0.3 mg/kg infusion over 30 minutes every 14 days for 48 weeks (if MTD is determined to be below 1 mg/kg)
- 200 mg flat dose IV infusion over 30 minutes every 14 days for 48 weeks (Expansion Cohort 1)
- 3 mg/kg infusion of [REDACTED] of REGN2810, administered over 30 minutes every 14 days for 48 weeks (Expansion Cohort 26)

5.1.2. Combination Therapy

Concomitant radiation therapy, GM-CSF, cyclophosphamide, carboplatin, docetaxel, paclitaxel, and pemetrexed generally will not be provided by the sponsor, and will be supplied through a prescription by the treating investigator, unless not permitted per local regulations. Their usage, dose, dose modifications, reductions, or delays, as well as any potential AEs resulting from their use, will be tracked along with that of REGN2810.

Patients will record their GM-CSF use (date, time of day, location of injection, and volume of injection) in a patient diary, and will submit it to the site during their treatment visits.

5.1.2.1. REGN2810 plus Radiation

5.1.2.1.1. REGN2810 plus Radiation Combination Cohorts

REGN2810 will be administered by IV infusion over 30 minutes every 14 days for 48 weeks in combination with radiation treatment from day 8 to day 12.

Planned combination REGN2810 and radiation therapy regimens may include:

- 1 mg/kg REGN2810 infusion over 30 minutes every 14 days for 48 weeks plus
- 30 Gy radiotherapy (6 Gy \times 5 times/week; given 1 week after the first dose of REGN2810, preferably on consecutive days)
- 1 mg/kg REGN2810 infusion over 30 minutes every 14 days for 48 weeks plus
- 27 Gy radiotherapy (9 Gy \times 3 times/week; given 1 week after the first dose of REGN2810, preferably **not** on consecutive days)
- 3 mg/kg REGN2810 infusion over 30 minutes every 14 days for 48 weeks plus
- 30 Gy radiotherapy (6 Gy \times 5 times/week; given 1 week after the first dose of REGN2810, preferably on consecutive days)
- 3 mg/kg REGN2810 infusion over 30 minutes every 14 days for 48 weeks plus
- 27 Gy radiotherapy (9 Gy \times 3 times/week; given 1 week after the first dose of REGN2810, preferably **not** on consecutive days)

5.1.2.1.2. Specifications for Radiation Therapy (non-GBM Patients)

Patients will receive either 30 Gy given as 5 fractions of 6 Gy administered daily starting 1 week after the first dose of REGN2810, or 27 Gy given as 3 fractions of 9 Gy administered every other day starting 1 week after the first dose of REGN2810.

The lesion selected for radiation should be a lesion that can be safely irradiated with focal irradiation while sparing the index lesion(s), and for which radiation at the limited, palliative doses contemplated would be considered medically appropriate.

The target dose for a patient will be based on cohort assignment and should conform to the normal tissue requirements described in [Appendix 1](#), in accord with standard radiation oncology practice. Treatment at the protocol-specified dosing regimen is permitted only if the normal tissue criteria are met. If the normal tissue criteria cannot be met at either of the radiation therapy regimens specified in the protocol, the patient is not eligible for enrollment in a combination radiation treatment cohort in this study. Final radiation treatment records, including final dosimetric calculations, may be reviewed centrally.

For specifications for radiation therapy for GBM patients, see [Appendix 7](#).

5.1.2.2. REGN2810 plus Cyclophosphamide

REGN2810 will be administered by IV infusion over 30 minutes every 14 days (2 weeks) for 48 weeks in combination with cyclophosphamide 200 mg/m² IV infusion every 14 days for 4 doses. Each of the 4 cyclophosphamide doses will be administered 1 day before each of the first 4 REGN2810 doses (days –1, 14, 28, and 42 of the first 56 day cycle).

Notes:

The ANC must be greater than 1000/μL before administering cyclophosphamide on days 1, 14, 28, and 42.

Though cyclophosphamide has been used successfully concurrently with other drugs, the rate of metabolism and the leukopenic activity of cyclophosphamide reportedly are increased by chronic administration of high doses of phenobarbital.

Cyclophosphamide treatment causes a marked and persistent inhibition of cholinesterase activity, thus potentiating the effect of succinylcholine chloride. If a patient has been treated with cyclophosphamide within 10 days of general anesthesia, the anesthesiologist should be alerted.

The planned combination REGN2810 and cyclophosphamide regimen to be assigned is:

- Cyclophosphamide 200 mg/m² IV every 14 days (days –1, 14, 28, and 42 of the first 56 day cycle) for a total of 4 doses plus
- 3 mg/kg REGN2810 infusion over 30 minutes every 14 days for 48 weeks (provided monotherapy dose of 3 mg/kg < MTD; if 3 mg/kg > MTD, dose will be 1 mg/kg)

5.1.2.3. REGN2810 plus Radiation and Cyclophosphamide

The planned combination REGN2810, radiation, and cyclophosphamide regimen includes:

- Cyclophosphamide 200 mg/m² IV every 14 days (days –1, 14, 28, and 42 of the first 56 day cycle) for a total of 4 doses
plus
- 27 Gy radiotherapy (9 Gy × 3 times/week; starting 6 or 8 days after the first dose of REGN2810, preferably **not** on consecutive days) OR
30 Gy radiotherapy (6 Gy × 5 times/week; starting 6 or 8 days after the first dose of REGN2810, preferably on consecutive days)
plus
- 3 mg/kg REGN2810 infusion over 30 minutes every 14 days for 48 weeks (provided monotherapy dose of 3 mg/kg < MTD; if 3 mg/kg > MTD, dose will be 1 mg/kg)

5.1.2.4. REGN2810 plus Radiation and GM-CSF

The planned combination REGN2810, radiation, and GM-CSF regimen includes:

- GM-CSF 250 mcg SC daily for 7 days, for four 7-day intervals (days 1 through 7, 15 through 21, 29 through 35, and 43 through 49 of the first 56-day cycle). GM-CSF should be administered at approximately the same time each day, if possible.
plus
- 27 Gy radiotherapy (9 Gy \times 3 times/week; starting 6 or 8 days after the first dose of REGN2810, preferably **not** on consecutive days)
plus
- 3 mg/kg REGN2810 infusion over 30 minutes every 14 days for 48 weeks (provided monotherapy dose of 3 mg/kg < MTD; if 3 mg/kg > MTD, dose will be 1 mg/kg). It is recommended that REGN2810 infusion start at least 30 minutes after GM-CSF, if possible. The timing of GM-CSF with regard to REGN2810 is at the discretion of the investigator.

Notes: Complete blood count (CBC) with differential should be monitored during treatment with GM-CSF (suggest 3 or 4 days into each 7 day cycle and prior to the start of each 7 day cycle). The dose of GM-CSF should be reduced by half for documented white blood cell (WBC) greater than 50,000/mm³, and discontinued for any significant toxicity the investigator believes to be related to GM-CSF administration.

5.1.2.5. REGN2810 plus Radiation, GM-CSF, and Cyclophosphamide

The planned combination REGN2810, radiation, GM-CSF, and cyclophosphamide regimen includes:

- GM-CSF 250 mcg SC daily for 7 days, for four 7-day intervals (days 1 through 7, 15 through 21, 29 through 35, and 43 through 49 of the first 56-day cycle). GM-CSF should be administered at approximately the same time each day, if possible.
plus
- 27 Gy radiotherapy (9 Gy \times 3 times/week; starting 6 or 8 days after the first dose of REGN2810, preferably **not** on consecutive days)
plus
- Cyclophosphamide 200 mg/m² IV every 14 days (days -1, 14, 28, and 42 of the first 56 day cycle) for a total of 4 doses
plus
- 3 mg/kg REGN2810 infusion over 30 minutes every 14 days for 48 weeks (provided monotherapy dose of 3 mg/kg < MTD; if 3 mg/kg > MTD, dose will be 1 mg/kg). It is recommended that REGN2810 infusion start at least 30 minutes after GM-CSF, if possible. The timing of GM-CSF with regard to REGN2810 is at the discretion of the investigator.

5.1.2.6. REGN2810 plus Docetaxel with or without Carboplatin

The suggested sequence of drug administration is docetaxel followed by carboplatin (if enrolled in a carboplatin-containing cohort), followed by REGN2810:

- Docetaxel 30 mg/m² IV over approximately 1 hour on days 1, 8, 29, and 36 of the first 56-day cycle. Dexamethasone 8 mg IV will be administered prior to the first dose of docetaxel. For subsequent docetaxel treatments, the dose of dexamethasone premedication may be 8 mg or 4 mg, per investigator discretion ([Hainsworth 2004](#)).
- Carboplatin AUC 2 IV over approximately 30 minutes on days 1, 8, 29, and 36 of the first 56-day cycle. Carboplatin dosing should use the Calvert formula on the carboplatin label. Creatinine clearance should be calculated using the Cockcroft-Gault equation.
- 3 mg/kg REGN2810 infusion over approximately 30 minutes every 14 days for 48 weeks

Carboplatin dosing for patients with high glomerular filtration (GFR) rate should be capped in accordance with FDA guidance (<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm228974.htm>)

Based on the Calvert formula described in the carboplatin label, the maximum doses can be calculated as:

Total Carboplatin Dose (mg) = (target AUC) x (GFR +25) [Calvert formula]

Maximum Carboplatin Dose (mg) = target AUC (mg·min/mL) x (150 mL/min)

The maximum dose is based on a GFR estimate that is capped at 125 mL/min for patients with normal renal function. No higher estimated GFR values should be used.

For a target AUC = 2, the maximum dose is 2 X 150 = 300 mg.

The investigator may use the creatinine and weight values obtained on cycle 1 day 1 to calculate the carboplatin starting dose, or may use the values from the most recent measurements obtained within 14 days prior to cycle 1 day 1. For days 8, 29, and 36, the investigator may administer carboplatin with flat dosing of the dose used on cycle 1 day 1, or may recalculate the carboplatin dose based on weight and creatinine values obtained within 1 week of the treatment day, per investigator discretion.

Anti-emetics for low-dose carboplatin are per investigator discretion. Metoclopramide PO (oral) or IV is recommended as needed. Ondansetron or other anti-emetics per institutional guidelines are allowed, but dexamethasone (other than the IV dose on each docetaxel treatment day) should be avoided, if possible.

5.1.2.7. Glioblastoma Expansion Cohorts

The treatment regimen will be REGN2810 (either 1 mg/kg or 3 mg/kg, per dose escalation scheme) over 30 minutes every 14 days for 48 weeks, plus 30 Gy radiotherapy (6 Gy X 5 times/week, given 1 week after the first dose of REGN2810, preferably on consecutive days). For patients who develop symptomatic intracranial edema at any time during the study, REGN2810 will be held. VEGF inhibition is preferred for management of intracranial edema/inflammation rather than high dose steroids, due to concerns that the latter may suppress immune response against the tumor. The VEGF inhibition strategy will be bevacizumab (at a maximum dose of 10 mg/kg IV, every 14 days, administered for a minimum of 3 doses to treat symptomatic intracranial edema. REGN2810 may resume when symptoms related to intracranial edema have resolved. If VEGF inhibition does not resolve the intracranial edema, the investigator may institute systemic corticosteroids, in addition to or as replacement for VEGF inhibition, at the lowest dose that is appropriate for symptom management.

5.1.2.8. Advanced NSCLC, Previously Untreated (Cohorts 21 and 22, Full Dose of Chemotherapy)

For Expansion Cohorts 21 and 22, a cycle is defined as 12 weeks of treatment. Imaging is obtained at the completion of each 12-week cycle. REGN2810 dosing is maintained at every 3 weeks after the completion of the 4 planned treatments with platinum doublet chemotherapy. The total number of planned every 3 week REGN2810 treatments in cohorts 21 and 22 is 16 (4 treatments in combination with chemotherapy, 12 treatments as monotherapy). The study schedule for Cohorts 21 and 22 is different than that for the other cohorts, and is provided in [Table 7](#) and [Table 8](#).

Carboplatin + Paclitaxel + REGN2810, Expansion Cohort 21:

Anti-emetics to be given as per local institutional standards; this may include oral or IV 5HT3 antagonists.

The suggested sequence of drug administration is REGN2810, followed by paclitaxel, followed by carboplatin.

- 3 mg/kg REGN2810 infusion over approximately 30 minutes every 21 days for 48 weeks (16 planned treatments of REGN2810).
- Paclitaxel 200 mg/m² is administered IV over approximately 3 hours on day 1 of each of the 4 planned paclitaxel treatments. The interval between paclitaxel treatments is 21 days. All patients should be premedicated with corticosteroids, diphenhydramine, and H₂ antagonists prior to paclitaxel administration in order to prevent severe hypersensitivity reactions, and the details of the premedication regimen will be at investigator discretion. The recommended steroid premedication regimen for IV paclitaxel is dexamethasone 20 mg oral approximately 12 and 6 hours prior to paclitaxel or 20 mg IV just prior to IV therapy.
- Carboplatin AUC 6 is administered IV over approximately 30 minutes on day 1 of each of the 4 planned carboplatin treatments. The interval between carboplatin treatments is 21 days. Dosing should use the Calvert formula on the carboplatin label. Creatinine clearance should be calculated using the Cockcroft Gault equation.

Carboplatin dosing for patients with high GFR should be capped in accordance with FDA guidance, as described in Section 5.1.2.6.

For a target AUC = 6, the maximum dose is $6 \times 150 = 900$ mg.

The investigator may use the creatinine and weight values obtained on cycle 1 day 1 to calculate the carboplatin starting dose, or may use the values from the most recent measurements obtained within 14 days prior to cycle 1 day 1. For day 1 of subsequent carboplatin treatments, the investigator may administer carboplatin with flat dosing of the dose used on cycle 1 day 1, or may recalculate the carboplatin dose based on weight and creatinine values obtained within 1 week of the treatment day, per investigator discretion.

Carboplatin + Pemetrexed + REGN2810, Expansion Cohort 22:

Before pemetrexed administration, patients should receive oral corticosteroid, folic acid (350 - 1000 µg orally, once daily), and vitamin B12 supplementation, according to the pemetrexed label. Anti-emetics to be given as per local institutional standards; this may include oral or IV 5HT3 antagonists.

The suggested sequence of drug administration is REGN2810, followed by pemetrexed, followed by carboplatin:

- 3 mg/kg REGN2810 infusion over approximately 30 minutes every 21 days for 48 weeks (16 planned treatments of REGN2810).
- Pemetrexed 500 mg/m² is administered IV over approximately 10 minutes on day 1 of each of the 4 planned pemetrexed treatments. Folic acid prophylaxis and vitamin B12 prophylaxis will follow standard supportive measures. The interval between pemetrexed treatments is 21 days.
- It is the intent of the study that pemetrexed and carboplatin will be discontinued at the end of 4 treatments. If the investigator wishes to continue maintenance pemetrexed after the initial 4 planned treatments, this may be allowed after communication with and approval from medical monitor.
- Carboplatin is administered IV over approximately 30 minutes on day 1 of each of the 4 planned carboplatin treatments. The interval between carboplatin treatments is 21 days. Dosing should use the Calvert formula on the carboplatin label. Creatinine clearance should be calculated using the Cockcroft Gault equation (see instruction for Carboplatin + Paclitaxel + REGN2810).

5.2. Pretreatments

Appropriate premedication for study treatments may be administered at the investigator's discretion as per usual clinical practice and in accordance with institutional guidelines. No premedications are to be administered for the first dose of REGN2810.

Pretreatments for Expansion Cohort 21 and 22 are addressed in Section 5.1.2.8.

5.3. Dose Modification and Study Treatment Discontinuation Rules

5.3.1. Dose Modification

Inpatient dose escalation is not permitted in this study. Patients will generally remain on the assigned dosage of REGN2810 throughout the course of study treatment. Dose reduction of REGN2810 may be allowed, based on the guidelines below, and only after discussion and agreement between the investigator and Sponsor.

5.3.2. Study Treatment Hold or Discontinuation

Patients who experience protocol-defined DLTs (either during or outside the DLT observation period), or Grade ≥ 3 treatment-related toxicity (excluding exceptions outlined in Section 3.1.3 and laboratory abnormalities that are considered clinically insignificant, and do not meet criteria for an AE) that is not otherwise specified in the protocol will be required to temporarily discontinue treatment with REGN2810. Such patients may be considered for resumption of treatment once the toxicity resolves to Grade 1 or baseline, or when the toxicity is stable and manageable through supportive/medical therapy (eg, Grade 3 hypertension that can be controlled with addition of a second anti-hypertensive agent).

Upon occurrence of a DLT or other study treatment-related event at any dose level and at any time on the study, resumption of treatment after resolution or stabilization of the condition is allowed at the discretion of the investigator and sponsor if resuming treatment is thought to be in the best interest of the patient, with the exception of the following categories requiring permanent discontinuation of REGN2810:

- Patients with events that require REGN2810 to be discontinued for more than 84 days (after consultation with the sponsor, permanent discontinuation of REGN2810 may be required if treatment cannot be resumed after 84 days)
- Patients with DLTs of Grade ≥ 2 uveitis
- Patients with DLTs of hepatic abnormalities consistent with Hy's Law

Resumption of treatment may be at the initial dose level or one dose level reduced, based upon the discretion of the investigator and the sponsor. A repeat occurrence of the same DLT after resumption of treatment will require permanent discontinuation of study treatment.

If REGN2810 is discontinued (either permanently or temporarily) for an AE, if the patient is in a combination therapy cohort, the patient will generally discontinue the combination therapy treatment as well. If, however, a patient experiences an AE that in the opinion of the investigator is SOLELY related to the combination partner, REGN2810 may be continued, and the combination partner therapy may be discontinued as per Section 5.3. Conversely, if a patient experiences an AE that in the opinion of the investigator is SOLELY related to REGN2810, then the combination therapy may be continued while REGN2810 may be discontinued or reduced in dosage as per Section 5.3.

Guidelines for study treatment temporary discontinuations, including delays and interruptions, and permanent discontinuations for toxicity are outlined in Table 3.

The general approach regarding missed doses, other than those in the DLT monitoring period, of systemic therapy (eg, due to AEs) is "time marches on." Missed doses of systemic therapy will not be made up, unless ≤ 3 business days from the scheduled date (or unless in the DLT monitoring period). If an investigator deems that re-scheduling a missed dose of systemic therapy outside of the 3 day window is in the best interest of the patient, this should be discussed with the medical monitor.

Table 3: Study Treatment Dose Modifications or Discontinuations

Toxicity	Grade	Hold Treatment?	Restarting Criteria	Restarting Dose/Schedule	Discontinuation Criteria
Hematological Toxicity	1, 2, 3	No	N/A	N/A	N/A
	4	Yes	Toxicity resolves to Grade ≤ 1 or baseline	May decrease REGN2810 dosage to the next lower dosing level (see Table 1)	Toxicity does not resolve within 12 weeks of last infusion <i>Permanent discontinuation should be considered for any severe or life-threatening event</i>
Nonhematological Toxicity Note: Exceptions to be treated as for Grade 1 toxicity: <ul style="list-style-type: none">• Grade 2 alopecia• Grade 2 fatigue• Clinically insignificant lab abnormality not meeting AE criteria	1	No	N/A	N/A	N/A
	2	Consider withholding for persistent symptoms	Toxicity resolves to Grade 0–1 or baseline	<i>Clinical AE resolves within 4 weeks:</i> Same dose and schedule <i>Clinical AE does not resolve within 4 weeks:</i> May decrease REGN2810 dosage to the next lower dosing level (see Table 1)	Toxicity does not resolve within 12 weeks of last infusion
	3	Yes	Toxicity resolves to Grade 0–1 or baseline	May decrease REGN2810 dosage to the next lower dosing level (see Table 1)	Toxicity does not resolve within 12 weeks of last infusion
	4	Yes	N/A	N/A	Patient must be discontinued

For additional information regarding AEs with a potential immune etiology (irAEs), reference [Table 5](#) and [Appendix 2](#).

Any patient currently receiving REGN2810 who was previously treated with a phosphatidylinositol 3-kinase (PI 3-K) inhibitor and who develops stomatitis or mucositis should temporarily suspend study treatment. If this or any other immune-related AE occurs among these patients, the sponsor should be informed as soon as possible to discuss further management of the patient. An irAE of any grade in a patient previously treated with a PI 3-K inhibitor should be reported as an adverse event of special interest (AESI).

[Appendix 2](#) includes recommendations on the management of specific treatment-related AEs and when to delay and/or discontinue REGN2810. These guidelines are intended to be applied when the investigator determines the events to be treatment related.

For patients in cohorts containing GM-CSF (Leukine)

GM-CSF treatment should be interrupted or the dose reduced by half if the ANC exceeds 20,000 cells/mm³.

For patients in cohorts containing cyclophosphamide

Uncomplicated neutropenia:

If ANC <1000/μL without Grade ≥3 febrile neutropenia, cyclophosphamide should be held, but other protocol treatments may continue. Upon recovery of ANC to ≥1000/μL, cyclophosphamide treatment may be resumed as scheduled without dose reduction, but missed treatments will not be made up.

Febrile neutropenia:

In the event of Grade ≥3 neutropenia, cyclophosphamide and REGN2810 should be held. Radiation therapy may be held or continued, at the discretion of the investigator. Once the Grade 3 febrile neutropenia resolves, cyclophosphamide (dose reduced to 150 mg/m²) and REGN2810 (no dose reduction) may resume as scheduled, but missed treatments will not be made up.

In the event of febrile neutropenia, the use of growth factors (eg, GM-CSF, filgrastim, or pegfilgrastim) will be at investigator's discretion.

If a patient requires a subsequent dose reduction of cyclophosphamide after an initial dose reduction to 150 mg/m², the patient will not receive any further cyclophosphamide, but may continue on study for other treatments.

5.3.2.1. Guidance for Hematologic Toxicity Management in Cohorts Containing Platinum and/or Taxane-Based Chemotherapy

These hematologic toxicity guidelines are for patients in cohorts containing carboplatin and docetaxel, or docetaxel, or carboplatin plus paclitaxel, or carboplatin plus pemetrexed (referred to as “cytotoxic chemotherapy”) (Table 4).

Uncomplicated neutropenia:

If ANC <1000/μL without Grade ≥3 febrile neutropenia, cytotoxic chemotherapy (carboplatin and/or docetaxel; carboplatin plus paclitaxel; carboplatin plus pemetrexed) should be held.

Upon recovery of ANC to ≥1000/μL, cytotoxic chemotherapy may be resumed at the next scheduled chemotherapy date, but missed treatments will not be made up. The general approach outside of the DLT monitoring period, is that “time marches on” and missed doses are not re-scheduled.

Febrile neutropenia:

In the event of Grade ≥3 febrile neutropenia, cytotoxic chemotherapy and REGN2810 should be held. Once the Grade 3 febrile neutropenia resolves, cytotoxic chemotherapy and REGN2810 may resume as scheduled with the following dose modifications:

Thrombocytopenia:

In the event of Grade ≥ 3 thrombocytopenia, cytotoxic chemotherapy and REGN2810 should be held. Once the Grade 3 neutropenia resolves to grade 1 or better, cytotoxic chemotherapy and REGN2810 may resume as scheduled with the following dose modifications (see [Table 4](#)):

For patients receiving low dose carboplatin and/or docetaxel:

Carboplatin dose reduced to AUC 1.5; docetaxel dose reduced to 20 mg/m²; and REGN2810 without dose reduction. Missed treatments will not be made up. If a patient requires a subsequent dose reduction of low dose carboplatin and/or docetaxel after an initial dose reduction of either drug, the patient will not receive any further carboplatin and/or docetaxel, but may continue on study for other treatments.

For patients receiving full dose carboplatin and paclitaxel:

For first dose reduction, carboplatin dose reduced to AUC 5, paclitaxel dose reduced to 175 mg/m², and REGN2810 without dose reduction. Missed treatments will not be made up (other than in the DLT monitoring period). If a patient requires a subsequent dose reduction, carboplatin will be reduced to AUC 4 and paclitaxel to 135 mg/m²; REGN2810 dose will not be reduced. If a patient requires a third dose reduction in either drug, the patient will not receive any further carboplatin or paclitaxel, but may continue on study for other treatments.

For patients receiving carboplatin and pemetrexed:

For first dose reduction, carboplatin dose reduced to AUC 5, pemetrexed dose reduced to 375 mg/m², and REGN2810 without dose reduction. Missed treatments will not be made up (other than in the DLT monitoring period). If a patient requires a subsequent dose reduction, carboplatin will be reduced to AUC 4 and pemetrexed will be dose reduced to 250 mg/m²; REGN2810 will not be dose reduced. If a patient requires a third dose reduction in either drug, the patient will not receive any further carboplatin and pemetrexed, but may continue on study for other treatments.

Table 4: Dose Reductions for Hematological Toxicity in Cohorts 21 and 22

	Carboplatin	Paclitaxel	Pemetrexed
Starting Dose	AUC6	200 mg/m ²	500 mg/m ²
Dose level -1	AUC5	175 mg/m ²	375 mg/m ²
Dose level -2	AUC4	135 mg/m ²	250 mg/m ²

5.3.2.2. Guidance for Non-Hematologic Toxicity Management in Cohorts Containing Platinum and/or Taxane-Based Chemotherapy

These non-hematologic toxicity guidelines are for patients in cohorts containing carboplatin and docetaxel, or docetaxel, or carboplatin plus paclitaxel, or carboplatin plus pemetrexed, (referred to as “cytotoxic chemotherapy”). The first and second dose reductions are as described in [Section 5.3.2.1](#).

For nonhematologic toxicities of Grade ≥ 3 , treatment must be delayed until resolution of the event to Grade ≤ 2 or baseline. Treatment will be resumed with a dose reduction of one level if deemed appropriate by the investigator.

Renal Toxicity (Paclitaxel and Carboplatin):

In any case where serum creatinine is $>1.2 \times \text{ULN}$ or calculated creatinine clearance is $<50 \text{ mL/minute}$, all treatment must be held until serum creatinine is $\leq 1.2 \times \text{ULN}$ or calculated creatinine clearance is $\geq 50 \text{ mL/minute}$. Upon resumption of treatment, carboplatin must be reduced by 1 dose level as per Table 4.

Mucositis (Pemetrexed):

Patients who experience Grade 0-2 mucositis may continue to receive treatment with no change to the dose. In the event of Grade 3-4 mucositis for a patient on pemetrexed, delay treatment with pemetrexed until resolution of the event. Then, treatment will be resumed with a pemetrexed dose reduction of 2 levels.

Neurologic Toxicity (Paclitaxel):

Patients who experience Grade 0-1 neurologic toxicity may continue to receive treatment with no change to the dose. For Grade 2 peripheral sensory neuropathy, paclitaxel will be reduced by 2 dose levels.

In the event of Grade 3 neurologic toxicity due to paclitaxel, hold paclitaxel until resolution to Grade 1 or better. Upon resolution to toxicity to Grade 1 or better, retreatment with paclitaxel can only be given with reduction by 2 dose levels. Permanently discontinue paclitaxel for Grade 4 peripheral sensory neuropathy.

Hypersensitivity Reaction (Paclitaxel)

Patients who experience mild hypersensitivity reactions to paclitaxel may repeat the premedication and be rechallenged with a dilute solution and slow infusion, at the discretion of the investigator. Patients who experience severe hypersensitivity reactions to paclitaxel will not be re-challenged.

If paclitaxel (200 mg/m^2 or 135 mg/m^2) is discontinued due to hypersensitivity reaction, docetaxel (75 mg/m^2) may be substituted at the discretion of the investigator.

Hepatic Toxicity (Paclitaxel):

Because paclitaxel has significant hepatic metabolism, in the event of \geq Grade 2 toxicity, hold paclitaxel until resolution to Grade 1 or less. After resolution, retreatment requires dose reduction in paclitaxel by 1 dose level.

5.3.2.3. General Rule for All Dose Reductions

After any dose reduction for GM-CSF, REGN2810, cyclophosphamide, docetaxel, and/or carboplatin, or carboplatin and paclitaxel, or carboplatin and pemetrexed, subsequent re-escalation of the dose is not allowed.

For nonhematologic toxicity not specifically covered in the protocol, dose reduction/discontinuation may be warranted for events of Grade ≥ 3 if clinically appropriate in the opinion of the investigator. No treatment modifications are required for alopecia.

In the event of multiple AEs in a particular patient, in which the guidance for toxicity management may be discordant, the investigator should select the larger dose reduction or the longer treatment hold, such that the more conservative toxicity management plan is chosen to optimize patient safety.

If the investigator feels that the patient requires a dose modification other than that which is specified in the protocol, the medical monitor should be consulted.

5.3.2.4. Immune-Related Adverse Events (irAEs)

Special attention should be paid to AEs that may be suggestive of a potential immune-mediated pathophysiology (irAEs), defined as AEs of unknown etiology associated with drug exposure and consistent with an immune phenomenon. Table 5 includes guidelines for managing irAEs not listed in Appendix 2.

Table 5: General Treatment Hold Guidelines for Immune-Related Adverse Events

Severity	Withhold/Discontinue Treatment?	Supportive Care
Grade 1	No action	Provide symptomatic treatment
Grade 2	May withhold treatment	Consider systemic corticosteroids in addition to appropriate symptomatic treatment
Grade 3 Grade 4	Withhold treatment Discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisone equivalent within 12 weeks of toxicity	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks.

Note: These recommendations should be seen as guidelines, and the treating physician should exercise clinical judgment based on the symptoms and condition of the individual patient.

Note regarding irAEs: For any AE that is of a type known to be potentially immune-related (eg, rash, colitis, transaminitis, endocrine), but is deemed not to be an irAE by the investigator, the sponsor may request additional information.

5.3.2.5. Hold of Radiation Therapy

Radiation therapy will be held for Grade 3 or higher radiation therapy-related, nonhematologic toxicity with exception of Grade 3 liver enzyme elevation (see recommendations for management of hepatic injury in Section 5.5.2). Radiation therapy will resume at the discretion of the investigator at full dose when toxicity returns to Grade 1 or 0. In addition, though development of symptomatic pneumonitis during the actual period of radiation treatment is unlikely, radiation therapy for any patient experiencing pneumonitis prior to completing the treatment should be put on hold until symptoms resolve and the case is clinically evaluated. See Section 5.5 for detailed instructions regarding management of radiation therapy-related toxicities.

5.3.2.6. Permanent Discontinuation of Study Treatment

In the event of an infusion reaction of Grade ≥ 3 severity during or directly following REGN2810 infusion, dosing should be stopped and the patient must permanently discontinue REGN2810 treatment.

Study treatment will be permanently stopped in the event of evidence of pregnancy.

In addition, study treatment for any patient may be discontinued for other safety reasons or compliance issues at the discretion of the investigator or sponsor. A patient may choose to discontinue study treatment or study participation at any time for any reason.

A patient who permanently discontinues REGN2810 treatment may continue follow-up in the study without additional treatment until progression of disease or closure of the study (Section 4.3). A patient who permanently discontinues study treatment and who does not withdraw from study participation will be asked to return to the clinic for all remaining study visits per the visit schedule.

5.4. Management of Infusion/Allergic/Hypersensitivity Reactions

Acute infusion reactions are defined as any AE that occurs during the infusion or within 2 hours after the infusion is completed. Emergency equipment and medication for the treatment of these potential adverse effects (eg, antihistamines, bronchodilators, IV saline, corticosteroids, acetaminophen, and/or epinephrine) must be available for immediate use. Infusion reactions must be reported as AEs (Section 7.2.1) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 grading scale (Section 7.3.1).

Note: In the event of an infusion reaction of Grade 3 or greater severity during or directly following REGN2810 infusion, dosing should be stopped and the patient must be permanently discontinued from REGN2810 treatment.

Acute infusion reactions can include cytokine release syndrome, angioedema, or anaphylaxis, and differ from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Signs/symptoms may include: allergic reaction/hypersensitivity (including drug fever); arthralgia (joint pain); bronchospasm; cough; dizziness; dyspnea (shortness of breath); fatigue (asthenia, lethargy, malaise); headache; hypertension; hypotension; myalgia (muscle pain); nausea; pruritus/itching; rash/desquamation; rigors/chills; sweating (diaphoresis); tachycardia; tumor pain (onset or exacerbation of tumor pain due to treatment); urticaria (hives, welts, wheals); and vomiting.

5.4.1. Interruption of the Infusion

The infusion should be interrupted if any of the following AEs are observed:

- cough
- rigors/chills
- rash, pruritus (itching)
- urticaria (hives, welts, wheals)
- diaphoresis (sweating)
- hypotension
- dyspnea (shortness of breath)

- vomiting
- flushing

The reaction(s) should be treated symptomatically, and the infusion may be restarted at 50% of the original rate.

If investigators feel there is a medical need for treatment or discontinuation of the infusion other than described above, they should use clinical judgment to provide the appropriate response according to typical clinical practice.

5.4.2. Termination of the Infusion

The infusion should be terminated and NOT restarted if any of the following AEs occur:

- anaphylaxis
- laryngeal/pharyngeal edema
- severe bronchospasm
- chest pain
- seizure
- severe hypotension

5.5. Management of Radiation Toxicity

5.5.1. Radiation Pneumonitis

Radiation pneumonitis is a subacute (weeks to months from treatment) inflammation of the end bronchioles and alveoli. Any patient suspected of having radiation pneumonitis will be assessed by a medical oncologist and radiation oncologist, as the clinical picture may resemble that of acute bacterial pneumonia, with fatigue, fever, shortness of breath, nonproductive cough, and a pulmonary infiltrate on chest X-ray. An effort also must be made to distinguish symptoms of radiation pneumonitis from those of an immune-related event possibly related to study drug (Table 5 and Appendix 2). Pneumonitis has been observed as toxicity associated with multiple agents blocking the PD-1/PD-L1 pathway, occurring at a frequency between 1% and 5%, and generally low grade when caught early and treated with either withholding of the agent and/or a course of steroid immunosuppression (Topalian 2012, Inoue 2001). As noted above, such events will generally be attributed to the combination therapy unless there is clear data to implicate one or the other. Given that delayed radiation toxicities may be at least in part immunologically mediated, it is possible that adding REGN2810 to radiation may exacerbate the severity and/or the frequency of these events. It may therefore not be straightforward to attribute such events exclusively to REGN2810 or to radiation, and such events may need to be attributed to the combination.

The infiltrate on chest X-ray should include the area treated to high dose, but may extend outside of these regions. The infiltrates may be characteristically “geometric” corresponding to the radiation portal, but may also be ill defined.

Patients reporting symptoms as above will be promptly evaluated and treated. Mild radiation pneumonitis may be treated with nonsteroidal anti-inflammatory agents. More significant pneumonitis will be treated with systemic steroids, bronchodilators, and pulmonary toilet after discussion with the biotherapy physician. Infections should be treated with antibiotics. Consideration of prophylaxis of opportunistic infections should be considered in immunocompromised patients.

Though development of symptomatic pneumonitis during the actual period of radiation treatment is unlikely, radiation therapy for any patient experiencing pneumonitis prior to completing the treatment should be put on hold until symptoms resolve. At that point, a clinical decision will be made for the patient as to whether the course of therapy should be completed.

5.5.2. Hepatic Injury

Although hepatic injury is not anticipated with the radiation regimens in this protocol, radiation therapy should be held for a Grade 4 hepatic AE. It is expected that a proportion of patients treated for right lower lobe lung or liver lesions will have transient elevation of liver enzymes following treatment. If up to Grade 3 elevation of liver enzymes is observed, more frequent measurements (at least twice weekly) of the liver enzymes are recommended until the enzymes stabilize or return to baseline levels. Repeat of blood work for all Grade 4 elevations is required at least 5 days following the first abnormal lab value to determine if the Grade 4 levels are transient (defined as lasting <5 days) or persistent.

Radiation-induced liver disease (RILD) is a clinical syndrome of anicteric ascites, hepatomegaly and elevation of ALP relative to other transaminases that may occur 2 weeks to 3 months following radiation to the liver. An increase in ALP must be at least 2-fold above the baseline ALP.

If ascites develops within 3 months following treatment, an abdominal CT and paracentesis with pathological evaluation of the ascitic fluid is required to aid in distinguishing RILD from disease progression. A Grade 3 or higher elevation of ALP ($\geq 5 \times \text{ULN}$) in the absence of disease progression and presence of ascites lacking evidence of malignancy will be reported as RILD.

Treatment of RILD with repeat paracenteses, diuretics, and close follow-up is recommended. In patients with liver enzyme elevations approaching Grade 4 levels and/or early nonspecific signs or symptoms of liver injury, close follow-up with repeat blood work is required. If no tumor progression is documented in these patients, liver injury will be presumed related to treatment.

5.5.3. Gastrointestinal Radiation Toxicity

Radiation dose constraints for normal stomach and small intestine should limit gastrointestinal toxicity, and pretreatment to reduce risk of late gastrointestinal bleeding is required when these sites are irradiated (Section 5.2); therefore gastrointestinal toxicity is not expected to be dose limiting. However, patients will be followed for gastrointestinal toxicity at each follow-up visit.

5.6. Method of Treatment Assignment

Each patient who signs the informed consent form (ICF) will be assigned a patient number and tracked centrally as described in the study reference manuals.

The sponsor will conduct regular calls with the sites to facilitate coordination of enrollment. Eligible patients will be enrolled sequentially as confirmed and tracked by the sponsor, until each cohort is filled per protocol criteria. Details on treatment assignment can be found in the study reference manuals.

5.6.1. Blinding

This is an open-label study; no blinding will be employed.

5.7. Treatment Logistics and Accountability

5.7.1. Packaging, Labeling, and Storage

Open-label REGN2810 will be supplied as a liquid in sterile, single-use vials that will display the product lot number on the label. [REDACTED]

[REDACTED] Further storage instructions will be provided in the study reference manuals.

A pharmacist or other qualified individual will be identified at each site to prepare REGN2810 for administration. [REDACTED]

[REDACTED] Detailed preparation and administration instructions will be provided to the sites in the study reference manuals.

Packaging, labeling, stability, and storage information for cyclophosphamide and GM-CSF is specified in the manufacturer's package insert.

5.7.2. Supply and Disposition of Treatments

Study drug will be shipped [REDACTED] to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed -or- returned to the sponsor or designee.

5.7.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication dispensed to each patient, returned from each patient (if applicable), and disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

5.7.4. Treatment Compliance

REGN2810, cyclophosphamide, carboplatin, docetaxel, paclitaxel, pemetrexed, and radiation treatments will be administered at the study site and recorded on the electronic case report form (eCRF). Granulocyte-macrophage colony-stimulating factor may be administered at the study

site or by the patient. All dosing records for each patient will be kept by the site. All drug compliance records must be kept current and must be made available for inspection by the sponsor and regulatory agency inspectors.

Note: Suggested infusion times for chemotherapy in this protocol are given as approximate infusion times, to infusion times of chemotherapy drugs according to local institutional guidelines.

5.8. Concomitant Medications and Procedures

5.8.1. Concomitant Medications

Any treatment administered from the time of informed consent until 30 days after the last study treatment will be considered concomitant treatment. This includes medications and other therapies for which administration started before the study and will continue during the study, as well as any therapies started in the 5 month follow-up period to treat a study-drug-related AE. All concomitant treatments must be recorded in the study CRF with the generic name, dose, dose unit, frequency, indication, and start/stop date, as appropriate.

5.8.2. Prohibited Medications

While participating in this study, a patient may not receive any standard or investigational agent for treatment of a tumor other than REGN2810 as monotherapy or in combination with radiation therapy, GM-CSF, cyclophosphamide, low dose carboplatin, and/or docetaxel, or full dose carboplatin and paclitaxel, or carboplatin and pemetrexed, per the study's specified dosing regimens. After communication with the sponsor, focal palliative treatment (eg, radiation) would be allowed for local control of a tumor once a patient has completed 8 weeks of study treatment. Any other medication which is considered necessary for the patient's welfare, and which is not expected to interfere with the evaluation of the study drug, may be given at the discretion of the investigator.

Patients using immunosuppressive doses (>10 mg per day of prednisone or equivalent) of systemic corticosteroids other than for corticosteroid replacement will not be eligible for the study. It is recommended that patients do not receive systemic corticosteroids such as hydrocortisone, prednisone, prednisolone (Solu-Medrol®) or dexamethasone (Decadron®) at any time throughout the study except in the case of a life-threatening emergency and/or to treat an irAE. Physiologic replacement doses of systemic corticosteroids are permitted, even if >10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

Note regarding other anti-cancer treatments: GnRH agonist therapy (eg, for prostate cancer) may be continued and is not prohibited.

Note: Treatments for bone metastases (bisphosphonates, denosumab) are not prohibited.

6. STUDY SCHEDULE AND VISIT DESCRIPTIONS

6.1. Study Schedule

Study assessments and procedures are presented by study period and visit in [Table 6](#), [Table 7](#), and [Table 8](#).

Study visits can be scheduled so as not to fall on weekends or holidays, after discussion and approval by the Sponsor.

Table 6: Study Schedule (Screening and Treatment for Cohorts 1-20, and 23-26)

Study Procedure	Screening	Treatment Cycle 1																	Treatment Cycles 2–6 ^a						
Visit Days	–28 to –1	–1	1 ^b	2	3	4	8	9	10	11	12	14	15±3	28	29±3	36±3	42	43±3	56±3 ^c	1 ^d	15±3	29±3	43±3	56±3	
Baseline assessments																									
Informed Consent ^e	X																								
Genomics Informed Consent (optional)	X																								
Medical/Oncology History	X																								
Demographics	X																								
Physical Examination, Complete ^f	X																			X					
Physical Examination, Limited ^g		X	X										X		X			X			X	X	X		
12-Lead ECG ^h	X		X																	X					
ECOG Status	X																			X					
Vital Signs ⁱ	X	X	X				X						X		X			X		X	X	X	X		
Height	X																								
Weight	X	X	X				X						X		X			X		X	X	X	X		
Brain MRI ^j	X																								
Chest X-Ray ^k	X																								
Inclusion/Exclusion Criteria/Study Enrollment	X																								
Laboratory Tests																									
Hematology ^l	X	X	X	X		X	X					X ^b	X	X ^b	X	X	X ^b	X		X	X	X	X		
Blood Chemistry ^m	X		X	X		X	X						X		X	X		X		X	X	X	X		
Serum HCG ≤ 72 Hour Predose ⁿ	X																								
Urine Pregnancy Test													X		X			X		X	X	X	X		
Urinalysis ^o	X		X			X	X						X		X			X		X					
Serum IgG, IgM, IgE			X																	X					
aPTT; INR			X																	X					

Study Procedure	Screening	Treatment Cycle 1																	Treatment Cycles 2–6 ^a						
Visit Days	–28 to –1	–1	1 ^b	2	3	4	8	9	10	11	12	14	15±3	28	29±3	36±3	42	43±3	56±3 ^c	1 ^d	15±3	29±3	43±3	56± 3	
Immune Safety Assays																									
Rheumatoid Factor (RF)			X																	X					
Antinuclear Antibody (ANA)			X																	X					
Thyroid-Stimulating Hormone (TSH)			X																	X					
C-Reactive Protein (CRP)			X																	X					
PK Drug Conc./ADA sample																									
REGN2810 PK/Drug Conc. Sample ^p			PK Collection Schedule Varies by Cohort. See Appendix 4																						
Anti-Drug Antibody (ADA)Sample ^q			X																	X					
Research samples																									
Serum/plasma cytokine samples		X ^r	X	X			X					X								X ^s					
PBMC		X ^t	X									X								X ^u					
Optional genomic DNA sample			X																						
Obtain archived tumor material	X																								
Tumor biopsy ^v	X												X		X										
Study Treatment																									
1, 3, 10 mg/kg, or 200 mg flat dose REGN2810 IV			X										X		X			X		X	X	X	X		
Cyclophosphamide 200 mg/m ² IV		X										X		X			X								
GM-CSF (on Days 1-7, 15-21, 29-35, 43-49) ^w			X	X	X	X							X		X			X							
Radiotherapy: 6 Gy × 5 (30 Gy total) ^x							X	X	X	X	X														
Radiotherapy: 9 Gy × 3 (27 Gy total) ^y							X		X		X														
Carboplatin plus docetaxel (Cohorts 14 and 17) or docetaxel alone (Cohort 15) ^z			X				X								X	X									
Tumor assessments																									
CT/MRI (chest/abdomen/pelvis) ^{aa}	X																		X					X	

Study Procedure	Screening	Treatment Cycle 1																	Treatment Cycles 2–6 ^a						
Visit Days	–28 to –1	–1	1 ^b	2	3	4	8	9	10	11	12	14	15±3	28	29±3	36±3	42	43±3	56±3 ^c	1 ^d	15±3	29±3	43±3	56±3	
Other clinical assessments																									
Adverse Events (AEs) ^{bb}	←===== : =====→																								
Concomitant Medication/Treatment ^{cc}	←===== : =====→																								

- The maximum number of treatment cycles is 6. The decision to continue treatment will be based on tumor response evaluations completed prior to the first dose in the next cycle. Patients will continue to receive REGN2810 until progressive disease (PD), toxicity, or completion of 48 weeks of treatment. After a minimum of 24 weeks of treatment, patients with confirmed complete responses (CR) or with tumor burden assessments of stable disease (SD) or partial response (PR) that are maintained for 3 successive tumor evaluations may elect to discontinue treatment and continue with all relevant study procedures (eg, efficacy assessments) per [Table 6](#) and [Table 8](#). Cumulative maximum number of treatment cycles is not applicable to patients who are being re-treated.
- Visit only for patients enrolled in a cohort assigned to cyclophosphamide treatment. The ANC must be $\geq 1000/\mu\text{L}$ before administering cyclophosphamide on days 1, 14, 28, and 42. The peripheral blood mononucleated cell (PBMC) sample should be collected prior to cyclophosphamide infusion.
- Visit for radiological assessment and evaluation of results for response assessment using RECIST criteria and immune-related response criteria (irRC) prior to start of next treatment cycle.
- Should occur at least 56 days from day 1 of previous cycle, and no sooner than 14 days after the previous dose.
- Informed consent may be obtained more than 28 days before the start of screening procedures. Assessments performed as part of standard of care that fall within the screening window but before informed consent is obtained may be used for screening, and need not be repeated for enrollment eligibility.
- Complete physical examination includes skin, head, eyes, nose, throat, neck, joints, lungs, heart, pulse, abdomen (including liver and spleen), lymph nodes, and extremities. A brief neurologic examination should also be performed. The exam may be performed ≤ 72 hours prior to dosing on the day 1 visit of each cycle.
- Limited physical exam includes lungs, heart abdomen, and skin.
- A 12-lead electrocardiogram should be recorded at screening, and 30 minutes after end of infusion at day 1 visits during cycle 1 and cycle 3.
- Vital signs include temperature, resting blood pressure, pulse, and respiration. At cycle 1 day 1, vital signs will be collected prior to treatment, at the end of the infusion, every 30 minutes for the first 4 hours postinfusion, and at 6 and 8 hours after study drug administration. Vital signs on subsequent treatment days of cycle 1 and all subsequent cycles will be assessed and documented prior to the infusion, and then approximately 30 minutes after the completion of the infusion. See also [Section 6.3.3.1](#) for vital signs with carboplatin and/or docetaxel administration.
- Brain MRI required at screening if not performed in the prior 60 days. Brain scans during the treatment and follow-up periods are required if there is a prior history of lesions present at screening or as clinically indicated. A brain CT may be performed if an MRI is contraindicated in a non-GBM patient. All GBM patients require MRI with gadolinium during the screening period.
- Chest X-ray required at screening if not performed in the prior 60 days. Chest X-rays during the treatment and follow-up periods are required as clinically indicated.
- Hematology includes: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, and platelet count. Samples may be collected ≤ 72 hours prior to study treatment. See also footnote y for ANC values before administering carboplatin and/or docetaxel.
- Chemistry includes: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), uric acid, ALT, AST, total bilirubin, direct and/or indirect bilirubin, alkaline phosphatase (ALP), and lactate dehydrogenase (LDH). Samples may be collected ≤ 72 hours prior to study treatment.
- Predose β -HCG (serum) at screening up to 72 hours prior to first administration. Subsequent pregnancy tests may be urine β -HCG.

- o. Urinalysis: glucose, blood, pH, specific gravity, ketones, and spot urine protein. Samples may be collected ≤ 72 hours prior to dosing on the day 1 visit of each cycle.
- p. See Appendix 4. PK collection schedule is determined by Cohort.
- q. Anti-REGN2810 antibody samples will be collected preinfusion on day 1 of cycles 1, 2, 4, and 6.
- r. Serum/plasma cytokine samples will be collected on day -1 only in patients receiving cyclophosphamide. This sample should be collected prior to cyclophosphamide infusion.
- s. Serum/plasma cytokine samples should be collected only on day 1 of Cycle 2. No collection should be performed for the subsequent cycles.
- t. Blood samples for PBMC isolation will be collected on day -1 only in patients receiving cyclophosphamide. This sample should be collected prior to cyclophosphamide infusion.
- u. Samples for PBMC isolation should be collected only on day 1 of Cycle 2. No collection should be performed for the subsequent cycles.
- v. Tumor biopsies are optional during the dose escalation portion of the study, but should be obtained for all patients in the expansion cohorts. Study biopsies may be obtained if, in the opinion of the investigator, the lesion is accessible and samples can be obtained without significant risk to the patient. A tumor biopsy should also be collected at progression. The requirements for research tumor biopsies do not pertain to GBM and HCC patients. Prior to study entry in the expansion cohorts, the investigator must contact the sponsor for patients that the investigator feels cannot provide screening, on treatment and subsequent post treatment tumor biopsies. These patients will be evaluated for study eligibility.
- w. Complete blood counts need to be checked twice weekly in Expansion Cohorts 3, 5, and 6 while GM-CSF is being administered.
- x. If possible, fractions should be delivered on 5 consecutive days.
- y. If possible, fractions should be administered on nonconsecutive days (ie, spaced by at least 1 day between fractions).
- z. Carboplatin and docetaxel (Cohorts 14 and 17) on days 1, 8, 29, and 36 of cycle 1, or docetaxel (Cohort 15) on days 1, 8, 29, and 36 of cycle 1. The ANC must be $\geq 1000/\mu\text{L}$ before administering carboplatin and/or docetaxel on days 1, 8, 29, and 36. See Section 5.3.2 for further information.
- aa. The same method (CT or MRI) used at baseline should be used throughout the study. The requirement for imaging of chest/abdomen/pelvis does not pertain to GBM cohorts (Expansion Cohorts 18 and 19). See Section 6.3.2 for further details.
- bb. Adverse event recording will be ongoing throughout the course of the study. Non-SAE and SAE data will be collected from the first dose of study medication until 30 days after the last dose of REGN2810. Any AE assessed as related to a study treatment or procedure, including events occurring after 30 days post last dose, should be reported. Any SAE should be reported until resolution or stabilization. Additionally, any SAE after obtaining informed consent should be reported.
- cc. Concomitant medication recording will be ongoing throughout the course of the study. Record concomitant medications from the date of signing the ICF through 30 days after the last dose of study treatment.

Table 7: Study Schedule (Screening and Treatment for Expansion Cohorts 21 and 22)

Study Procedure	Screening	Treatment Cycle 1										Treatment Cycles 2–4 ^a				
Visit Days	–28 to –1	1	2	3	4	8	22±3	43±3	64±3	85±3	1 ^{b, c}	22±3	43±3	64± 3	85±3	
Baseline assessments																
Informed Consent ^d	X															
Genomics Informed Consent (optional)	X															
Medical/Oncology History	X															
Demographics	X															
Physical Examination, Complete ^e	X										X					
Physical Examination, Limited ^f		X					X	X	X			X	X	X		
12-Lead ECG ^g	X	X									X					
ECOG Status	X										X					
Vital Signs ^h	X	X				X	X	X	X		X	X	X	X		
Height	X															
Weight	X	X				X	X	X	X		X	X	X	X		
Brain MRI ⁱ	X															
Chest X-Ray ^j	X															
Inclusion/Exclusion Criteria/Study Enrollment	X															
Laboratory Assessments																
Hematology ^k	X	X	X		X	X	X	X	X		X	X	X	X		
Blood Chemistry ^l	X	X	X		X	X	X	X	X		X	X	X	X		
Serum HCG ≤ 72 Hour Predose ^m	X															
Urine Pregnancy Test							X	X	X		X	X	X	X		
Urinalysis ⁿ	X	X			X	X	X	X	X		X					
Serum IgG, IgM, IgE		X									X					
aPTT; INR		X									X					

ADA=anti-drug antibody; AE=adverse event; ANA=antinuclear antibody; aPTT=activated partial thromboplastin time; CRP=C-reactive protein; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; HCG=human chorionic gonadotropin; INR=International Normalized Ratio; MRI=magnetic resonance imaging; PMBC=peripheral blood mononuclear cells; RF= rheumatoid factor; TSH=thyroid-stimulating hormone.

- a. The maximum number of treatment cycles is 4. Cycle length is 12 weeks for Cohorts 21, 22, and 23. The decision to continue treatment will be based on tumor response evaluations completed prior to the first dose in the next cycle. Patients will continue to receive REGN2810 until PD, toxicity, or completion of 48 weeks of treatment. After a minimum of 24 weeks of treatment, patients with confirmed complete responses (CR) or with tumor burden assessments of SD or PR that are maintained for 3 successive tumor evaluations may elect to discontinue treatment and continue with all relevant study procedures (eg, efficacy assessments) in [Table 7](#) and [Table 8](#).
- b. Visit for radiological assessment and evaluation of results for response assessment using RECIST criteria and immune-related response criteria (irRC) prior to start of next treatment cycle.
- c. Should occur at least 85 days from day 1 of previous cycle, and no sooner than 14 days after the previous dose.
- d. Informed consent may be obtained more than 28 days before the start of screening procedures. Assessments performed as part of standard of care that fall within the screening window but before informed consent is obtained may be used for screening, and need not be repeated for enrollment eligibility.
- e. Complete physical examination includes skin, head, eyes, nose, throat, neck, joints, lungs, heart, pulse, abdomen (including liver and spleen), lymph nodes, and extremities. A brief neurologic examination should also be performed. The exam may be performed ≤ 72 hours prior to dosing on the day 1 visit of each cycle.
- f. Limited physical exam includes lungs, heart abdomen, and skin.
- g. A 12-lead ECG should be recorded at screening, and 30 minutes after end of infusion at day 1 visits during cycle 1 and cycle 3.
- h. Vital signs include temperature, resting blood pressure, pulse, and respiration. At cycle 1 day 1, vital signs will be collected prior to treatment, at the end of the infusion, every 30 minutes for the first 4 hours post infusion, and at 6 and 8 hours after study drug administration. Vital signs on subsequent treatment days of cycle 1 and all subsequent cycles will be assessed and documented prior to the infusion, and then approximately 30 minutes after the completion of the infusion. See also Section [6.3.3.1](#) for vital signs with carboplatin, paclitaxel or pemetrexed infusion.
- i. Brain MRI required at screening if not performed in the prior 60 days. Brain scans during the treatment and follow-up periods are required if there is a prior history of lesions present at screening or as clinically indicated. A brain CT may be performed if an MRI is contraindicated in a non-GBM patient. All GBM patients require MRI with gadolinium during the screening period.
- j. Chest X-ray required at screening if not performed in the prior 60 days. Chest X-rays during the treatment and follow-up periods are required as clinically indicated.
- k. Hematology includes: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, and platelet count. Samples may be collected ≤ 72 hours prior to study treatment. See also Section [5.3.2.1](#) for hematologic toxicity management.
- l. Chemistry includes: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), uric acid, ALT, AST, total bilirubin, direct and/or indirect bilirubin, alkaline phosphatase (ALP), and lactate dehydrogenase (LDH). Samples may be collected ≤ 72 hours prior to study treatment.
- m. Predose β -HCG (serum) at screening up to 72 hours prior to first administration. Subsequent pregnancy tests may be urine β -HCG.
- n. Urinalysis: glucose, blood, pH, specific gravity, ketones, and spot urine protein. Samples may be collected ≤ 72 hours prior to study treatment.
- o. See [Appendix 4](#) for PK collection schedule.
- p. Anti-REGN2810 antibody samples will be collected preinfusion on day 1 of cycles 1, 2, and 4.
- q. Serum/plasma cytokine samples should be collected only on day 1 of Cycle 2. No collection should be performed for the subsequent cycles.
- r. Samples for PBMC isolation should be collected only on day 1 of Cycle 2. No collection should be performed for the subsequent cycles.
- s. Tumor biopsies are optional during the dose escalation portion of the study, but should be obtained for all patients in the expansion cohorts. Study biopsies may be obtained if, in the opinion of the investigator, the lesion is accessible and samples can be obtained without significant risk to the patient. A tumor biopsy should also be collected at progression.
- t. The ANC must be $\geq 1000/\mu\text{L}$ before administering carboplatin, paclitaxel, pemetrexed. See Section [5.3.2](#) for further information regarding when to hold treatment and/or reduce dose.

- u. The same method (CT or MRI) used at baseline should be used throughout the study.
- v. Adverse event recording will be ongoing throughout the course of the study. Non serious AE and SAE data will be collected from the first dose of study medication until 30 days after the last dose of REGN2810. Any AE assessed as related to a study treatment or procedure, including events occurring after 30 days post last dose, should be reported. Any SAE should be reported until resolution or stabilization. Additionally, any SAE after obtaining informed consent should be reported.
- w. Concomitant medication recording will be ongoing throughout the course of the study. Record concomitant medications from the date of signing the ICF through 30 days after the last dose of study treatment.

Table 8: Study Schedule (Follow-Up)

Study Procedure Visit	Follow-up 1 ^a	Follow-up 2	Follow-up 3	Follow-up 4	Follow-up 5	Follow-up 6	Follow-up 7 ^k	
Time point (Day)	Last cycle visit + 1 to 7 days	Follow-up 1 + 28 ± 7 days	Follow-up 2 + 28 ± 7 days	Follow-up 3 + 28 ± 7 days	Follow-up 4 + 28 ± 7 days	Follow-up 5 + 28 ± 7 days	Follow-up 6 + 28 ± 7 days	Survival visit
Physical examination (complete) ^b	X	X	X	X	X	X	X	
ECOG Status	X	X	X	X	X	X	X	
Vital Signs ^c	X	X	X	X	X	X	X	
Weight	X	X	X	X	X	X	X	
Laboratory Tests								
Hematology ^d	X	X	X	X	X	X	X	
Blood Chemistry ^e	X	X	X	X	X	X	X	
Urine Pregnancy Test	X							
Urinalysis ^f	X	X	X	X	X	X	X	
Serum IgG, IgM, IgE	X							
Immune Safety Assays								
Rheumatoid Factor (RF)	X							
Antinuclear Antibody (ANA)	X							
Thyroid-Stimulating Hormone (TSH)	X							
C-Reactive Protein (CRP)	X							
PK Drug Conc/ADA Sample								
REGN2810 PK/Drug Conc. Sample	X						X	
Anti-Drug Antibody (ADA) sample	X						X	
Research Samples								
Serum/plasma cytokine ^g	X							
PBMC ^g	X							
Tumor biopsy ^g	X							
Tumor Assessments								
CT/MRI (chest/abdomen/pelvis) ^h			X			X		
Other Clinical Assessments								
AEs ⁱ	X	X	X	X	X	X	X	
Concomitant medications and treatments ^j	←=====							→
Collect survival Information ^k								X

ADA=anti-drug antibody; AE=adverse event; ANA=antinuclear antibody; CRP=C-reactive protein; CT=computed tomography; ECOG=Eastern Cooperative Oncology Group; MRI=magnetic resonance imaging; PMBC=peripheral blood mononuclear cells; RF= rheumatoid factor; TSH=thyroid-stimulating hormone.

- a Follow-up Visit 1 should be scheduled 14 to 30 days after the last study treatment for a patient who discontinues treatment during the treatment period due to PD; toxicity; or another reason besides confirmed CR, SD, or PR, but who does not withdraw consent to participate in the study. If a scan within the preceding 8 weeks is available, it is not necessary to obtain a repeat scan. Patients who maintain active follow-up should continue with all relevant study assessments (eg, efficacy assessments) for follow-up visits 2 through 7.

- b Complete physical examination: including examination of skin, head, eyes, nose, throat, neck, joints, lungs, heart, pulse, abdomen (including liver and spleen), lymph nodes, and extremities. A brief neurologic examination should also be performed.
- c Vital signs include temperature, resting blood pressure, pulse and respiration. Blood pressure should be measured after the patient has been resting quietly for at least 5 minutes.
- d Hematology includes: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, and platelet count.
- e Chemistry includes: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), uric acid, ALT, AST, total bilirubin, direct and/or indirect bilirubin, alkaline phosphatase (ALP), and lactate dehydrogenase (LDH).
- f Urinalysis: glucose, blood, pH, specific gravity, ketones, and spot urine protein.
- g Tumor biopsies and blood draws for PBMC and serum/plasma cytokines should also be collected at progression.
- h The same method (CT/MRI) used at baseline should be used throughout the study. Scans are required only if PD has not been confirmed previously while on study. Scans may be done every 8 to 12 weeks during follow-up.
- i Nonserious AE and SAE data will be collected from the day of informed consent until 30 days after the administration of the last dose of REGN2810. Any AE assessed as related to study treatment, including events occurring after 30 days post last dose, also should be reported. Any SAE should be reported until resolution or stabilization.
- j Record concomitant medications from date of ICF through 30 days after last dose of study drug. Also record any drug started in the 5 month follow-up to treat a study-drug-related AE. In addition, any cancer treatments should be recorded.
- k After treatment and follow-up are completed or if patients prematurely discontinue from treatment and follow-up, patients will be followed quarterly for survival and tumor treatment status, if available, until death.

6.2. Study Follow-Up and Treatment Discontinuation

6.2.1. Unscheduled Visits

All attempts should be made to keep patients on the study schedule as specified in [Table 6](#), [Table 7](#), and [Table 8](#). Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted.

6.2.2. Early Treatment Discontinuation

After a minimum of 24 weeks of treatment, a patient with confirmed CR may elect to discontinue treatment and continue with all relevant study assessments (eg, efficacy assessments) as scheduled per [Table 6](#), [Table 7](#), and [Table 8](#).

After a minimum of 24 weeks of treatment and after consultation with the investigator and the Sponsor, a patient with a tumor burden assessment of SD or PR maintained for 3 successive tumor evaluations also may elect to discontinue treatment, and continue with all relevant study assessments (eg, efficacy assessments) as scheduled per [Table 6](#), [Table 7](#), and [Table 8](#).

A patient who discontinues study treatment prematurely during the treatment period due to PD; toxicity; or other reason besides confirmed CR, SD, or PR should return to the clinic 14 to 30 days after the last study treatment to complete follow-up visit 1, and should continue with all relevant study assessments (eg, efficacy assessments) at subsequent follow-up visits per [Table 8](#) unless eligible for retreatment, or unable to come in to the clinic.

6.2.3. Follow-up

Patients who complete the maximum number of 6 cycles of treatment and those who discontinued treatment early for CR or for SD or PR maintained for 3 successive evaluations should return to the clinic for follow-up visit 1 scheduled 1 to 7 days after the last cycle visit and subsequent follow-up visits 2 through 6, per [Table 8](#). Patients who discontinued treatment early for CR, SD, or PR should continue with all relevant study assessments (eg, efficacy assessments) as scheduled per [Table 8](#). Every effort should be made to ensure completion of these follow-up visits. If a patient is unable to complete follow-up visits due to withdrawal of consent, clinical decline, or loss to follow-up, the reason will be communicated to the sponsor and may not be considered a protocol violation.

A patient who discontinues study treatment prematurely during the treatment period due to PD; toxicity; or another reason besides confirmed CR, SD, or PR should return to the clinic 14 to 30 days after the last study treatment to complete follow-up visit 1, and should continue with all relevant study assessments (eg, efficacy assessments) as scheduled per [Table 8](#).

For patients who complete 6 cycles of treatment without disease progression and subsequently experience progression of disease without any intervening systemic anticancer therapy, resumption of treatment with 3 mg/kg REGN2810 every 2 weeks by vein will be allowed, after discussion with medical monitor. Prior to resumption of treatment, patients must repeat all screening activities (with the exception of providing new archived pathology material, or research biopsies), and the investigator must confirm that the patient still meets all eligibility criteria (other than exclusion regarding prior treatment with anti-PD-1). Such patients will resume 3 mg/kg REGN2810 monotherapy treatment IV every 2 weeks for 96 weeks.

(maximum 12 retreatment cycles). The retreatment visit schedule will follow the schedule of events and assessments in Table 6, and the patient can complete this schedule of events up to 2 times during retreatment. However, screening MRI, 12-Lead ECG, and chest X-ray, PK assessments, research biopsies, and other research sample collections are not required for these patients during retreatment. The tests listed under the subheading of “research samples” in Table 6 are not required in the context of retreatment. All of the other blood samples in Table 6, except those mentioned above related to safety (Immune Safety Assays, Laboratory Tests, and ADA) should be obtained as per Table 6. The following tests listed in Table 6 do not need to be performed:

Cycle 1 Day 2 – hematology, blood chemistry,

Cycle 1 Day 4 - hematology, biochemistry, urinalysis,

Cycle 1 Day 8 – vital signs, weight, hematology, blood chemistry, urinalysis,

After treatment and follow-up are completed or if patients prematurely discontinue from treatment and follow-up, patients will be followed quarterly for survival and tumor treatment status, if available, until death.

6.3. Study Procedures

6.3.1. Procedures Required Only at the Screening/Baseline Visit

The following procedures will be performed at screening for the purpose of determining study eligibility or characterizing the baseline population:

- Serum β -HCG (result must be ≤ 72 hours before first dose).
- Collection of archived tumor material: After a patient has given informed consent, the patient will be asked to arrange to provide any available previously collected tumor samples.
- Brain MRI: Brain MRI is required at screening if not performed in the prior 60 days. Brain scans during the treatment and follow-up periods are required if there is a prior history of lesions present at screening or as clinically indicated. A brain CT may be performed if an MRI is contraindicated in a non-GBM patient. All GBM patients require MRI with gadolinium during the screening period.
- Chest X-ray: Chest X-ray is required at screening if not performed in the prior 60 days.

Note: Baseline chest X-ray is required as this may assist in subsequent clinical assessments that may occur during the study. For example, in a circumstance in which a patient presents to a provider with signs and symptoms that may be related to a pulmonary process, standard clinical practice often is to obtain a chest X-ray. In order to interpret a chest X-ray in this situation, it is clinically helpful to have a recent baseline chest X-ray on file. Hence, a baseline chest X-ray is required if not performed in the prior 60 days. In the absence of a baseline chest X-ray, the most recent chest imaging would be a CT scan of the chest, which could lead to the clinical

decision to obtain another CT scan of the chest in clinical circumstances in which a chest X-ray would have been sufficient.

6.3.2. Efficacy Procedures

A CT or MRI for tumor assessment will be performed at the screening visit (within 28 days prior to infusion) and during every cycle (approximately every 8 weeks), on day 56±3, and when disease progression is suspected. Additionally, for patients who have not progressed on study and who maintain active follow-up, tumor assessment will be performed for follow-up visits 3, 5, and 7 (note that it is acceptable for scans to be done every 8 to 12 weeks during follow-up).

Note: after PD has been confirmed while on study, additional scans are not required as scheduled follow-up visit procedures.

The choice of whether the imaging is by CT or MRI is an investigator decision. Once the choice has been made to use CT scan or MRI, subsequent assessments should be made using the same modality whenever possible.

Tumor response assessments will be performed according to RECIST version 1.1 ([Eisenhauer 2009](#)). Measurable lesions selected as target lesions for RECIST measurements will also be included as index lesions for immune-related response criteria (irRC; [Appendix 3](#); [Nishino 2013](#)). RECIST response will be prioritized as statistical assessment of response rate. For an individual patient, irRC can inform the decision regarding whether to continue treatment at the discretion of the investigator due to the possibility of unconventional responses.

For CSCC lesions that are not measurable radiographically, the approach that was used for basal cell carcinoma (BCC) in the study that led to the approval of vismodegib will be used ([Sekulic 2012](#)). Response is defined as a decrease of 30% or more in externally visible or radiographic dimension (if applicable), or complete resolution of ulceration (if present at baseline). Residual scarring is to be included when measuring the externally visible dimension. Responses must be confirmed at least 4 weeks after the initial determination of response. Progressive disease is defined as an increase in 20% or more in the externally visible or radiographic dimension (if applicable), new ulceration, or new lesion. Central review of photographs in addition to radiologic images may be performed.

For the GBM cohorts, response assessments will be performed according to RANO criteria ([Appendix 8](#)). Imaging of chest/abdomen/pelvis is not required at baseline or during study for Cohorts 18 and 19 (the GBM Expansion Cohorts), but may be obtained if clinically indicated in the opinion of the investigator.

Copies of scans will be requested to be sent to a central repository.

6.3.3. Safety Procedures

6.3.3.1. Vital Signs

Vital signs, including temperature, resting blood pressure, pulse, and respiration, will be collected at time points according to [Table 6](#), [Table 7](#), and [Table 8](#).

Note: blood pressure should be measured after the patient has been resting quietly for at least 5 minutes.

When scheduled at the same visit as other procedures, vital signs should be measured prior to clinical laboratory assessments, PK, or exploratory sample collection. At cycle 1 day 1, vital signs will be collected prior to treatment, at the end of the infusion, every 30 minutes for the first 4 hours post infusion, and at 6 and 8 hours after study drug administration. Vital signs on subsequent treatment days of cycle 1 and all subsequent cycles will be assessed and documented prior to the infusion, and then approximately 30 minutes after the completion of the infusion.

For cohorts receiving docetaxel: Vital signs will also be assessed and documented prior to docetaxel infusion, and after the completion of docetaxel infusion.

For cohorts receiving docetaxel and carboplatin: Vital signs will also be assessed and documented prior to the docetaxel infusion, prior to the carboplatin infusion, and after the completion of the carboplatin infusion.

For cohorts receiving paclitaxel and carboplatin: Vital signs will also be assessed and documented prior to the paclitaxel infusion, prior to the carboplatin infusion, and after the completion of the carboplatin infusion.

For cohorts receiving pemetrexed and carboplatin: Vital signs will also be assessed and documented prior to the pemetrexed infusion, prior to the carboplatin infusion, and after the completion of the carboplatin infusion.

6.3.3.2. Physical Examination

A thorough complete or limited physical examination will be performed at visits specified in [Table 6](#), [Table 7](#), and [Table 8](#). Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

Complete physical examination will include examination of skin, head, eyes, nose, throat, neck, joints, lungs, heart, pulse, abdomen (including liver and spleen), lymph nodes, and extremities, as well as a brief neurologic examination.

Limited physical examination will include lungs, heart, abdomen, and skin.

6.3.3.3. Electrocardiogram

A standard 12-lead ECG will be performed at time points according to [Table 6](#), [Table 7](#), and [Table 8](#).

The patient should be relaxed and in a recumbent or semi-recumbent position at least 5 minutes before recording an ECG. The ECG is to be recorded in triplicate. The ECG strips or reports will be retained with the source. The ECG will be reviewed by the investigator (paper or electronic tracing) and will be available for comparison with subsequent ECGs by the investigator. The following will be recorded on the CRF:

- PR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- Heart Rate (BPM; recorded from the ventricular rate).

Any ECG finding that is judged by the investigator as a clinically significant change (worsening) compared to the baseline value will be considered an AE, recorded, and monitored.

6.3.3.4. Immune Safety Assays

Immune safety assays consist of rheumatoid factor (RF), thyroid stimulating hormone (TSH), C-reactive protein (CRP), and antinuclear antibody (ANA) titer and pattern.

If, during the course of the study, a 4-fold or greater increase from baseline in RF or ANA or abnormal levels of TSH or CRP are observed, the following tests may also be performed: anti-DNA antibody, anti-Sjögren's syndrome A antigen (SSA) antibody (Ro), anti-Sjögren's syndrome B antigen (SSB) antibody (La), antithyroglobulin antibody, anti-LKM antibody, antiphospholipid antibody, anti-islet cell antibody, antineutrophil cytoplasm antibody, C3, C4, CH50.

6.3.3.5. Coagulation Tests

Activated partial thromboplastin time (aPTT) and International Normalized Ratio (INR) will be analyzed by the site's local laboratory.

6.3.3.6. Laboratory Testing

Hematology, chemistry, urinalysis, and pregnancy testing samples will be analyzed by the site's local laboratory.

Detailed instructions for blood sample collection are in the study reference manuals provided to study sites.

Samples for laboratory testing will be collected at time points according to [Table 6](#) and [Table 7](#). Tests will include:

Blood Chemistry

Sodium	Phosphorus	ALT
Potassium	Glucose	AST
Chloride	Albumin	Total and direct and/or indirect bilirubin
Bicarbonate	Creatinine	Alkaline phosphatase (ALP)
Calcium	Blood urea nitrogen (BUN)	Lactate dehydrogenase (LDH)
Magnesium	Uric acid	

Hematology

Hemoglobin	Differential:
WBCs	Neutrophils
Platelet count	Lymphocytes
	Monocytes

Urinalysis

Glucose	pH	Ketones
Blood	Specific gravity	Spot urine protein

Abnormal Laboratory Values and Laboratory Adverse Events

- All laboratory values must be reviewed by the investigator or authorized designee.
- Significantly abnormal tests must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the medical monitor must be consulted.
- The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section [7.2.5](#).

6.3.4. Pharmacokinetic and Antibody Procedures**6.3.4.1. Drug Concentration Measurements and Samples**

REGN2810 PK parameters will be determined by measuring REGN2810 concentrations in serum samples using a validated assay at visits and time points indicated in [Table 6](#), [Table 7](#), and [Table 8](#), and listed in [Appendix 4](#). Actual time of each blood draw must be recorded. “Predose” is defined as before the start of the first REGN2810 infusion; subsequent PK sampling times will be based on the REGN2810 dosing time that precedes the PK sampling. Predose samples may be collected ≤ 72 hours prior to day 1 dosing. “0 hour” is defined as immediately after the end of the REGN2810 infusion. On days when study drug is not administered, all PK sampling times will be based on time of last administered study drug dose.

Any unused samples collected for drug concentration measurements may be used for exploratory biomarker research or investigation.

6.3.4.2. Anti-drug Antibody Measurements and Samples

Samples for ADA assessment will be collected at time points listed in [Table 6](#), [Table 7](#), and [Table 8](#).

Anti-REGN2810 antibodies will be assessed in predose serum samples and at multiple time points during the dose escalation and safety expansion portions of the study. Any unused samples collected for ADA assessment may be used for exploratory biomarker research or investigation.

6.3.5. Exploratory Biomarker and Cytokine Procedures

Exploratory [REDACTED] pharmacodynamic biomarkers related to REGN2810 treatment exposure, clinical activity, or underlying disease will be investigated from collected serum, plasma, peripheral blood mononuclear cell (PBMC), archived tumor tissue, on-study tumor biopsy tissue, tumor DNA (including circulating tumor DNA) and tumor RNA samples. [REDACTED]

[REDACTED] All unused biomarker samples will be stored for 15 years.

6.3.5.1. Exploratory Biomarker Procedures

[REDACTED]

During the screening period, after patients have given informed consent, they will be requested to arrange to provide any available tumor samples archived from previous treatments. Archived biopsy samples will be collected according to directions in the study reference manuals.

Additionally, on-study tumor biopsies will be collected, if, in the opinion of the investigator, a lesion is accessible and the sample may be obtained without significant risk to the patient (tumor biopsies are optional during the dose-escalation portion of the study, but should be obtained for all patients in the expansion cohorts). If the patient only has 1 lesion that can be safely biopsied, and can only be sampled once, a sample at progression of disease is preferred over the cycle 1 sample. Samples will be collected and prepared according to directions in the study reference manuals.

The following markers may be assayed in archived and/or biopsy tumor tissue samples:

CD3, CD4, CD8, FoxP3, CD274 (PD-L1), CD279 (PD-1), TIM-3, LAG-3, IDO, and GZMB. Additional immune cell markers and/or tumor markers specific to any of the tumor types may be included.

Tumor tissue samples (archived and on-study) may be used for extraction of tumor DNA and RNA and subsequent analyses of putative genetic biomarkers relevant to study treatment and disease. All tumor DNA and tumor RNA samples will be double-coded as defined by the ICH guideline E15.

Research biopsy requirements do not pertain to GBM and HCC patients.

6.3.5.2. Exploratory Circulating Cytokine Procedures

Circulating cytokine levels that may relate to REGN2810 treatment exposure, clinical activity, or underlying disease will be assessed at time points according to [Table 6](#), [Table 7](#), and [Table 8](#).

Serum and plasma samples will be collected for measurement of cytokines and other circulating biomarkers. Cytokines to be analyzed may include but are not limited to: IL-1 β , IL-2, IL-6, IL-8, IL-10, IL-12p70, GM-CSF, IFN γ , TNF α .

6.3.5.3. Peripheral Blood Mononuclear Cell Assay

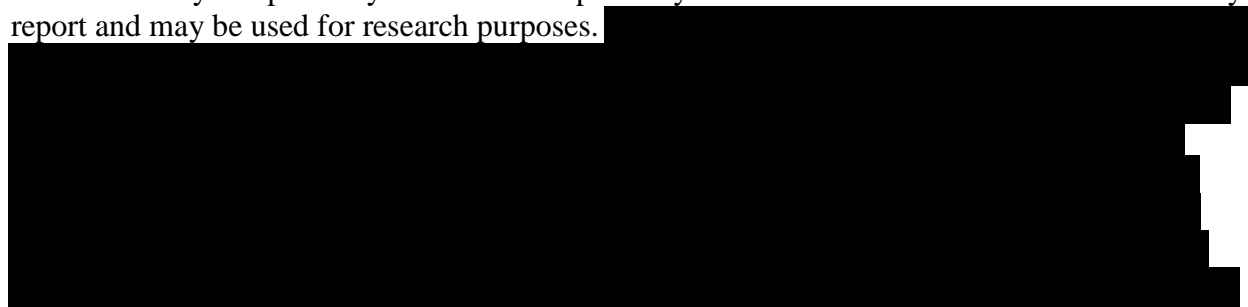
Analysis of circulating lymphocyte populations at selected time points per [Table 6](#), [Table 7](#), and [Table 8](#) will be conducted. Peripheral blood mononuclear cells will be assessed by fluorescence-activated cell sorting for changes in cell subsets including, but not limited to, naive and memory CD8 and CD4 T cells, MDSCs, NK, and B cells.

Any unused serum samples collected for drug concentration measurements may be used for exploratory biomarker research.

6.3.5.4. Genomics Sub-study - Optional

Patients who agree to participate in the genomics sub-study will be required to sign a separate genomics sub-study ICF before collection of the samples. Blood for genomic DNA extraction should be collected on day 1/baseline (predose), but may be collected at any study visit. Patients are not required to participate in the genomics sub-study in order to enroll in the primary study.

DNA samples for the genomics sub-study will be double-coded as defined by the ICH guideline E15. Sub-study samples may be stored for up to 15 years after the final date of the clinical study report and may be used for research purposes.



7. SAFETY DEFINITIONS, REPORTING, AND MONITORING

7.1. Definitions

7.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug.

An AE also includes any worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug.

Progression of underlying malignancy will not be considered an AE if it is clearly consistent with the typical progression pattern of the underlying cancer (including time course, affected organs, etc.). Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

If there is any uncertainty about an AE being due only to progression of the underlying malignancy, it should be reported as an AE or SAE as outlined in Section 7.2.

CTCAE version 4.03 terms should be used.

7.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger), with the exception of death due to the progression of underlying malignancy, if it is clearly consistent with the typical progression pattern of the underlying cancer.
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician. Hospitalization or prolongation of existing hospitalization due to the progression of underlying malignancy will not be considered an SAE, if it is clearly consistent with the typical progression pattern of the underlying cancer.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**

- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent 1 of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Hospitalization or death due solely to manifestations consistent with typical progression of underlying malignancy will not be considered a SAE.

SAEs must be reported as directed in Section 7.2.

7.2. Recording and Reporting Adverse Events

7.2.1. Adverse Events

The investigator (or designee) will seek information on AEs at each patient contact, and record all AEs that occur from the time the informed consent is signed until 30 days after the end of study treatment. CTCAE version 4.03 terms should be used. Prior to initiation of study treatment, only the following categories of AEs should be reported on the AE eCRF:

- SAEs
- Non-SAEs associated with a protocol-mandated intervention (eg, AEs related to an invasive procedure such as a biopsy)

(Other AEs that occur prior to first treatment should be reported on the medical history CRF.)

All AEs after initiation of study treatment and until 30 days after the last study treatment, regardless of relationship to study treatment, will be reported on the AE eCRF. Additionally, any SAE or other AE of concern that the investigator believes may be related to study treatment and that occurs later than 30 days after last study treatment should be reported.

Study treatment includes REGN2810, radiation therapy, GM-CSF, and cyclophosphamide, low dose carboplatin, low dose docetaxel, full dose carboplatin, full dose paclitaxel, and full dose pemetrexed in selected cohorts.

Information on follow-up for AEs is provided in Section 7.2.6. Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs as outlined in Section 7.2.5.

7.2.2. Serious Adverse Events

All SAEs, regardless of assessment of causal relationship to study treatment must be reported to the sponsor (or designee) within 24 hours. Refer to the study reference manuals for the procedure to be followed.

Information not available at the time of the initial report must be documented in a follow-up report. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested.

The investigator must promptly report to the Institutional Review Board (IRB) all unanticipated problems involving risks to patients. This includes death from any cause and all SAEs related to

the use of the study drug or treatment. It is recommended that all SAEs be reported to the IRB, regardless of assessed causality.

In the event the investigator is informed of an SAE that occurs after 30 days after the last dose of study treatment, only those SAEs or other AEs of concern deemed by the investigator to be related to study treatment will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome of a treatment-related SAE until the event is considered chronic and/or stable.

7.2.3. Other Events that Require Accelerated Reporting

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

Symptomatic Overdose of Study Drug:

Accidental or intentional overdose of at least 2 times the intended dose of study drug within the intended therapeutic window, if associated with an AE.

Pregnancy:

Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), by telephone within 24 hours of identification, any pregnancy occurring in a female patient or female partner of a male patient, during the study or within 90 days of the last dose of study drug. Any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn must be reported as an SAE. All pregnancy outcomes will be followed.

Adverse Events of Special Interest:

An AESI must be reported within 24 hours of identification. AEs of special interest for this study include:

- Any AE that meets DLT criteria
- Grade 2 or greater infusion-related reactions
- Grade 2 or greater allergic/hypersensitivity reactions
- Grade 3 immune-related toxicities (irAE)
- An irAE of any grade in a patient previously treated with a PI 3-K inhibitor

Note: An irAE can occur shortly after the first dose or several months after the last dose of treatment. All AEs of unknown etiology associated with drug exposure should be evaluated to determine possible immune etiology. If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an AE as an irAE.

Refer to the study reference manuals for the reporting procedures to be followed.

If any SAE or unusual AE is judged related to study treatment, and as possible and practical, obtain a blood sample from the patient to permit measurement of plasma drug levels.

7.2.4. Reporting Adverse Events Leading to Withdrawal from the Study

All AEs that lead to a patient's withdrawal from study treatment or from the study must be reported to the sponsor's medical monitor within 30 days.

Refer to the study reference manuals for the procedures to be followed.

7.2.5. Abnormal Laboratory, Vital Signs, or Electrocardiogram Results

The criteria for determining whether an abnormal objective test finding should be reported as an AE include:

- the test result is associated with accompanying symptoms, and/or
- the test result requires additional diagnostic testing or medical/surgical intervention, and/or
- the test result leads to a change in dosing (outside of protocol-stipulated dose adjustments)
- the test result leads to discontinuation from the study, significant additional concomitant medication, or other therapy

Contact the medical monitor in the event the investigator feels that an abnormal test finding should be reported as an AE, although it does not meet any of the above criteria.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Evaluation of severity of laboratory abnormalities will be assessed according to the scale outlined in Section 7.3.1.

7.2.6. Follow-up

Information for any non-SAE that starts during the treatment period or within 30 days after last treatment will be collected from the time of the event until resolution of the event, or until the patient's last study visit, whichever comes first.

Serious adverse event information will be collected until the event is considered chronic and/or stable.

7.3. Evaluation of Severity and Causality

7.3.1. Evaluation of Severity

The severity of AEs (including test findings classified as AEs) will be graded using the current version of the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grading system. Adverse events not listed in the NCI-CTCAE, will be graded according to the following scale:

1 (Mild): Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- 2 (Moderate):** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- 3 (Severe):** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- 4 (Life-threatening):** Life-threatening consequences; urgent intervention indicated.
- 5 (Death):** Death related to AE

* Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

7.3.2. Evaluation of Causality

Relationship of AEs to Study Drug:

The relationship of AEs to study drug will be assessed by the investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by the study drug?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by the study drug

Related: There is a reasonable possibility that the event may have been caused by the study drug

The sponsor will request information to justify the causality assessment of SAEs, as needed.

[Appendix 5](#) lists factors to consider in assessing the relationship of AEs to REGN2810 or infusion procedures, study procedures, or background treatment.

If an event is deemed “expected” for the chemotherapy, the occurrence of such an AE would be deemed expected in a cohort that combines REGN2810 with chemotherapy.

7.4. Safety Monitoring

The investigator will monitor the safety of study patients at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The medical monitor will have primary responsibility for the emerging safety profile of the compound. The study monitor will be supported by other departments (eg, Pharmacovigilance and Risk Management; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

7.5. Investigator Alert Notification

Regeneron (or designee) will inform all investigators participating in this clinical trial, as well as in any other clinical trial using the same investigational drug, of any SAE that meets the relevant requirements for expedited reporting (an AE that is serious, unexpected based on the Investigator's Brochure, and has a reasonable suspected causal relationship to the medicinal/study drug).

7.6. Obligations of Sponsor

During the course of the study, the sponsor will report in an expedited manner all SAEs that are both unexpected and at least reasonably related to the study drug (suspected unexpected serious adverse reaction [SUSAR]), to the health authorities, according to local regulations, IECs/IRBs as appropriate, and to the investigators. At the completion of the study, the sponsor will report all safety observations made during the conduct of the trial in the clinical study report to health authorities and IECs/IRB as appropriate.

8. STUDY VARIABLES

8.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height), disease characteristics including medical history, and medication history for each patient.

8.2. Primary and Secondary Variables

The primary variables in the study are DLT incidence and the incidence and severity of TEAEs and abnormal laboratory findings through 48 weeks of treatment.

The secondary variables are:

- Antitumor activities assessed using the appropriate criteria for the indication ([Appendix 3](#)):
 - Response Evaluation Criteria in Solid Tumors (RECIST; [Eisenhauer 2009](#)) criteria measured by CT or MRI
 - Other assessment criteria should also be used for specific tumors in which RECIST measurements are not the standard.
 - Immune-Related Response Criteria (irRC; [Nishino 2013](#)) applied to RECIST measurements.
In all cases, RECIST (or other tumor-specific criteria) will be the governing tool to determine PD, SD, CR, or PR. The irRC will be collected for clinical decisions and information purposes.
- Incidence of development of anti-REGN2810 antibodies
- Antitumor activity measured by PFS and overall survival

8.3. Pharmacokinetic Variables

Serum concentration of REGN2810 will be assessed at multiple time points throughout the study treatment and follow-up periods, and the PK will be analyzed.

Pharmacokinetic variables may include, but are not limited to, the following:

- AUC_{all} - area under the curve (AUC) computed from time zero to the time of the last concentration
- $AUC_{all}/Dose$ - AUC_{all} -to-dose ratio
- AUC_{last} - AUC computed from time zero to the time of the last positive concentration
- $AUC_{last}/Dose$ - AUC_{last} -to-dose ratio
- CL - clearance
- C_{max} - the peak concentration
- $C_{max}/Dose$ - C_{max} -to-dose ratio
- C_{last} - last positive (quantifiable) concentration
- MRT_{last} - mean residence time when the drug concentration profile is based on values up to and including the last positive concentration
- $t_{1/2}$ - observed terminal half-life
- t_{last} - time of the last positive (quantifiable) concentration
- t_{max} - time to C_{max}
- V_{ss} - volume of distribution at steady state
- V_z - volume of distribution of the terminal phase

8.4. Anti-drug Antibody Variables

Regeneron plans to evaluate the impact of the immunogenicity of REGN2810.

Anti-drug antibody variables include status (positive or negative) and titer as follows:

- Total ADA negative at any time
- Total ADA positivity at any time
- Pre-existing immunoreactivity – defined either as a positive ADA assay response at baseline with all post-treatment ADA results negative, or a positive assay response at baseline with all post-treatment ADA assay responses less than 9-fold over baseline titer levels.
- Treatment emergent - defined as any positive response post-treatment when baseline results are negative.
- Treatment boosted - defined as any post treatment ADA response is greater than or equal to 9-fold over baseline titer levels when baseline ADA results are positive.

- Titer values (Titer value category):
 - Low (titer < 1,000)
 - Moderate ($1,000 \leq \text{titer} \leq 10,000$)
 - High (titer > 10,000)

9. STATISTICAL PLAN

This section provides the basis for the statistical analysis plan (SAP) for the study. The SAP may be revised during the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the database is locked.

Analysis variables are listed in Section 8.

9.1. Justification of Sample Size

The dose escalation portion of the study will use a 3 + 3 design adapted to evaluate DLTs in monotherapy and combination therapy groups independently within a cohort. With standard 6-patient cohorts in the phase 1 dose escalation portion, a total of 60 patients are planned in 10 cohorts.

Sample sizes for each of the 26 expansion cohorts in the expansion portion of the study have been determined separately.

For the flat-dose cohort (Expansion Cohort 1) and the advanced solid tumor cohort for patients who have been previously treated with a PD-1/PD-L1 antibody (Expansion Cohort 5), [REDACTED] (Expansion Cohort 26), a cohort size of 20 patients was selected based on clinical consideration to evaluate the safety profile of study REGN2810 treatment in the selected patient population.

For Expansion Cohorts 2, 3, and 4 (NSCLC, HN, and BC, respectively), the sample size of 60 patients was selected based on a 95% confidence interval approach. With standard treatment, a response rate of ~ 5% to 10% is reported in literature, and a response rate around 15% is reported with treatment associated with PD-1/PD-L1 antibody. With 60 patients, if there are at least 9 (15.0%), 13 (21.7%), or 16 (26.7%) responders observed in a cohort, the 2-sided 95% confidence interval determined by normal approximation will exclude a response rate of 5%, 10% or 15%, respectively (Table 9). For Expansion Cohort 6 (other advanced solid tumors), a cohort size of 30 patients was selected based on clinical consideration to evaluate the safety profile of study REGN2810 in this combination regimen in various advanced solid tumors.

Table 9: Response Rates and Corresponding Two Sided 95% Confidence Intervals with 60 Patients

Number of Responders	Percentage of response	Two sided 95%CI	Half length of 95% CI
24	40.0%	(27.6, 52.4)	0.124
21	35.0%	(22.9, 47.1)	0.121

Number of Responders	Percentage of response	Two sided 95%CI	Half length of 95% CI
18	30.0%	(18.4, 41.6)	0.116
16	26.7%	(15.2, 37.9)	0.112
15	25.0%	(13.9, 36.1)	0.111
13	21.7%	(11.3, 32.1)	0.104
9	15.0%	(6.0, 24.0)	0.090

For Expansion Cohort 7, 10 patients will be enrolled to evaluate the safety and tolerability of REGN2810 monotherapy in the metastatic (M1) CSCC population. For Expansion Cohort 8, 20 patients will be enrolled to evaluate the safety and tolerability of REGN2810 monotherapy in the locally and/or regionally advanced (M0) CSCC that is unresectable.

For Expansion Cohorts 9 through 12, as per Amendment 5, no patients will be enrolled to evaluate the safety and tolerability of REGN2810 monotherapy in each selected solid tumor types harboring MSI. The overall response rates with standard treatments for these cancer patient populations were approximately 15% ([Cunningham 2004](#), [de Bono 2010](#), [Fracasso 2006](#), [Grothey 2013](#), [Martin-Martorell 2008](#), [Muggia 2002](#), [Sutton 1996](#)), but the individual cohorts 9 through 12 are not intended for formal efficacy comparisons.

For Expansion Cohort 13, a sample size of 20 patients was selected based on clinical considerations to provide sufficient data for safety and feasibility.

For Expansion Cohorts 14 and 15, a sample size of 20 patients (with a 6 patient safety run-in in each cohort) was selected based on clinical considerations to provide sufficient data for safety and feasibility.

For Expansion Cohort 16, as per Amendment 5, no patients will be enrolled to describe the safety and tolerability of REGN2810 monotherapy as first line therapy for colorectal cancer patients with MSI.

For Expansion Cohorts 18 and 19, the dose escalation plan for determination of R2PDs will be as described in Section 9.5, requiring at most 12 patients for exploring 2 dose levels. After the R2PD is established in each cohort, 10 additional patients will be enrolled into each cohort to evaluate the safety and tolerability of the treatment regimen.

For Expansion Cohort 20, 10 patients will be enrolled to evaluate the safety and tolerability of REGN2810 monotherapy in the HIV patient population.

For Expansion Cohorts 17, 21, and 22, a sample size of 10 patients (with a 6 patient safety run-in) was selected based on clinical considerations to provide sufficient data for safety and feasibility of REGN2810 with platinum chemotherapy doublets as first line therapy for patients with advanced NSCLC.

For Expansion Cohorts 23 and 24, 10 patients will be enrolled to evaluate the safety and tolerability of REGN2810 in patients with recurrent or metastatic cervical cancer that is refractory to platinum/taxane doublet chemotherapy, either as monotherapy (Cohort 23) or in combination with hypofractionated RT (Cohort 24).

For Expansion Cohort 25, 15 patients will be enrolled to evaluate the safety and tolerability of REGN2810 monotherapy in patients with locally advanced (unresectable) or metastatic BCC that is refractory to hedgehog pathway inhibition.

For expansion Cohort 26, 20 patients with any solid tumors will be enrolled to evaluate the safety and tolerability of REGN2810 monotherapy [REDACTED]

9.2. Analysis Sets

9.2.1. Safety Analysis Set

The safety analysis set (SAF) includes all enrolled patients who received any study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety and efficacy variables will be analyzed or summarized using the SAF.

The safety and efficacy summaries and analyses will be performed on the SAF.

9.2.2. Pharmacokinetic Analysis Set

The PK analysis set will include all patients who have at least 1 post REGN2810 treatment study drug concentration value above the lower limit of quantification (LLOQ) of the assay.

9.2.3. Anti-Drug Antibody Set

The ADA population includes all treated patients who had at least 1 nonbaseline post-dose ADA result.

9.3. Patient Disposition

The following will be provided:

- The number of screened patients
- The number of patients included in the SAF
- The number of patients who discontinued study participation, and the reasons for discontinuation from the study
- The number of patients who discontinued treatment, and the reasons for treatment discontinuation

9.4. Statistical Methods

The analysis of this study will be mostly descriptive and exploratory in nature, except for cohorts designed with formal hypothesis tests. In general, data collected during the monotherapy and combination therapy periods will be summarized separately and in combination. Data will be summarized by dose cohorts, and by diagnosis if necessary, using descriptive statistics and 2-sided 95% confidence interval, if applicable.

Continuous variables will be summarized with mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized with frequency and percentage.

Time-to-event variables will be summarized with Kaplan-Meier curves and estimates and survival rate at the key landmark time point with 95% confidence interval.

9.4.1. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by dose cohorts and by monotherapy and combination therapy that patients received.

9.4.2. Efficacy Analyses

Objective tumor response determined by RECIST version 1.1 ([Eisenhauer 2009](#)) (or appropriate disease-specific tumor response assessment guidelines) and immune-related response criteria (irRC; [Nishino 2013](#)) will be summarized using descriptive statistics, along with 2-sided 95% confidence interval, by dose cohort and/or diagnosis ([Appendix 3](#)).

Objective response rate measured by RECIST version 1.1 (or appropriate disease-specific tumor response assessment guidelines) will be the primary endpoint for efficacy analyses.

For Expansion Cohorts, no formal hypothesis testing will be performed on efficacy (except for Expansion Cohorts 2, 3, and 4). Objective tumor response will be summarized descriptively, along with 2-sided 95% confidence interval.

9.4.3. Safety Analysis

Safety observations and measurements including drug exposure, AEs, laboratory data, vital signs, and ECOG performance status will be summarized and presented in tables and listings.

9.4.3.1. Adverse Events

Definitions

For safety variables, 3 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment period is defined as the day from first dose of study drug to follow-up visit 1
- The posttreatment period is defined as the time after follow-up visit 1.

Treatment-emergent adverse events (TEAEs) are defined as those not present at baseline or represent the exacerbation during the on treatment period of a condition present at baseline.

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA[®]). Coding will be to lowest level terms. The verbatim text, the preferred term (PT), and the primary system organ class (SOC) will be listed.

Summaries of all TEAEs by treatment group will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (CTCAE, version 4.03 grade), presented by SOC and PT
- TEAEs by outcome

- TEAEs by relationship to experimental treatment (related, not related), presented by SOC and PT

Deaths and other SAEs will be listed and summarized by treatment group.

Events of CTCAE Grade 3 and Grade 4 severity will be summarized by cohort and by monotherapy or combination treatment period.

TEAEs leading to permanent treatment discontinuation will be listed and summarized by treatment group.

9.4.3.2. Other Safety

Vital Signs

Vital signs (temperature, pulse, blood pressure, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Laboratory Tests

Laboratory test results will be listed.

9.4.3.3. Treatment Exposure

Dose intensity and number of cycles administered will be summarized by dose cohort. Dose intensity will be calculated by dividing actual dose by body weight for REGN2810 and by body surface area for cyclophosphamide at the time of visit.

9.4.3.4. Treatment Compliance

Patients will be administered IV study drug and cyclophosphamide in a clinic under supervision of appropriate study personnel. Compliance will not be evaluated for radiation therapy, to be supplied commercially through a prescription.

9.4.4. Analysis of Drug Concentration Data

9.4.4.1. Descriptive Analysis of Drug Concentrations

Summaries of study drug concentrations will be presented by nominal time point (ie, the time points specified in the protocol) and dose group.

Dose proportionality will be evaluated.

9.4.4.2. Noncompartmental Analysis

The observed elimination rate constant will be calculated as the negative of the slope of the terminal portion of the concentration-time curve. The specific range of times will be determined using the default options of WinNonlin and confirmed by visual inspection of the semilogarithmic plots. If there are 2 or more elimination phases, then each phase may be explored separately. A “linear trapezoidal” or “log-linear trapezoidal” rule will be used to calculate AUC_{inf} as appropriate. Uniform weights will be used. For calculation of mean concentrations of REGN2810, values below the LLOQ will be set to zero, and imputed as LLOQ/2 when plot in semi-log format. Observed noncompartmental estimates will be reported. Selected PK parameters will be plotted versus dose.

9.4.4.3. Compartmental Analysis

The data collected in this study may be included in a population PK analysis, as appropriate, and will be presented in a separate report.

9.4.5. Analysis of Anti-Drug Antibody Data

Formation of ADA will be assessed in individual patients and per dose level/dose cohort as follows:

- Possible correlation between changes in PK profile and the presence/absence of anti-REGN2810 antibodies will be evaluated to identify a potential impact of anti-REGN2810 antibodies on drug exposure.
- Possible correlation between AEs and the presence/absence of anti-REGN2810 antibodies will be evaluated to identify a potential impact of anti-REGN2810 antibodies on the incidence of Grade 3 and 4 AEs, atypical AEs, and SAEs.

Cases of ADA positivity will be listed and summarized as appropriate.

9.4.6. Analysis of Pharmacodynamic Data

Circulating tumor cells will be summarized by cohort and by monotherapy or combination treatment period. Data will be analyzed using standard scientific and statistical methods, and will be described in a separate report.

9.4.7. Analysis of Biomarker Data

Data will be analyzed using standard scientific and statistical methods, and will be described in a separate report.

9.5. Recommended Phase 2 Doses

Recommended phase 2 doses will be determined based on the MTD in each of the combination therapies; up to 4 RP2Ds may be identified in the dose escalation cohorts in [Table 1](#). For Cohorts 18 and 19, the RP2Ds will be determined independently for newly diagnosed and recurrent GBM. It is possible that an RP2Ds for REGN2810 in combination with radiation therapy may differ from that determined for REGN2810 in combination with cyclophosphamide or for REGN2810 in combination with radiation plus cyclophosphamide.

If no MTD is defined between the 3 and 10 mg/kg dose levels, an RP2D will be determined using a combination of the following: safety, tolerability, PK, pharmacodynamic evidence of target and pathway engagement, and preliminary antitumor activity.

9.6. Interim Analysis

The objective of the interim analysis in this study is to stop enrollment in a cohort if the treatment is not efficacious, ie, a futility stopping rule rather than an efficacy stopping rule. Interim analyses for futility will be performed within each cohort, if applicable. The futility stopping rule is determined by utilizing stage I stopping criteria from the Optimal Simon 2-stage design with 1-sided type I error rate of 5%, power of 90% for respective null hypotheses in each cohort. The interim analysis for futility will be performed once Stage I patients have enrolled

into each cohort and completed 2 tumor assessments. The stopping rule will be based on the number of responders observed at the time of the interim analysis. Of note, there may be heterogeneity in terms of response for different tumor types in patients enrolled in some expansion cohorts. As the heterogeneity affects the estimation of efficacy mainly if the treatment is efficacious, the stopping rule defined above is still a good measurement for futility.

For Expansion Cohorts 1 and Cohorts 5 through 26, an interim analysis for futility is not planned due to the small sample size and the descriptive nature.

For Expansion Cohorts 2, 3, and 4 (planned enrollment of 60 patients per cohort), if the number of responders observed is less than or equal to 2 out of first 37 patients, then the treatment effect in terms of response rate will be deemed no better than 5%, and the enrollment into that cohort will be stopped.

9.7. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed:

Definition of baseline:

- Unless otherwise specified, the last assessment before the initial administration of REGN2810 will be considered the baseline evaluation

General rules for handling missing data:

- Unless otherwise specified, there will be no imputations for the missing data
- If the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the intake of study medication except if an incomplete date (eg, month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the intake of study medication date, then the start date by the study medication intake date will be imputed, otherwise, the missing day or month by the first day or the first month will be imputed.

Visit windows:

- Assessments taken outside of protocol allowable windows will be displayed according to the case report form (CRF) assessment recorded by the investigator.

9.8. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 15.1.

10. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

10.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation, cleaning, correcting, releasing) will be maintained and stored at Regeneron.

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, medical /surgical history) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with electronic data capture (EDC) tool. User training must be documented before the user is granted access to the EDC system.

10.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- EDC system – data capture
- Statistical Analysis Systems (SAS) Software – statistical review and analysis
- ARGUS – a pharmacovigilance and clinical safety software system

11. STUDY MONITORING

11.1. Monitoring of Study Sites

The study monitor and/or designee (eg, contract research organization [CRO] monitor) will visit each site prior to enrollment of the first patient, and periodically during the study. In accordance with International Council for Harmonisation (ICH) guidelines, the monitor will compare the CRF entries with the appropriate source documents. Additional review may include, but is not limited to, patient ICFs, documentation of patient recruitment and follow-up, AEs, SAEs, and concomitant therapy; as well as records of study drug dispensing, compliance, and accountability. A copy of the drug dispensing log must be provided to the sponsor upon request.

11.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents).

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

11.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic CRFs by trained site personnel. A CRF must be completed for each and every patient enrolled in the study. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each CRF page is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the system. For corrections made via data queries, a reason for any alteration must be provided.

12. AUDITS AND INSPECTIONS

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

13.2. Informed Consent

The principles of informed consent are described in ICH Guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB. A copy of the IRB-approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, the ICF must be reviewed and updated appropriately. All study patients must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient.

13.3. Patient Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by their initials and a patient identification number, only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The patient's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

13.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/EC, as described in ICH Guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study

- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design or operation of the protocol or ICF without an IRB-approved amendment.

15. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

15.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

15.2. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments),

breach of the applicable laws and regulations, or breach of any applicable ICH guidelines

- The total number of patients required for the study are enrolled earlier than expected

In all cases, the appropriate IRB and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

16. STUDY DOCUMENTATION

16.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the CRFs must be signed by the investigator. This certification form accompanies each set of CRFs. The signed form will be provided to the sponsor with the final set of CRFs for each patient.

16.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer if a longer period is required by relevant regulatory authorities. The investigator must consult with the sponsor before discarding or destroying any essential study documents following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor and the relevant records will be transferred to a mutually agreed-upon destination.

17. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

18. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

19. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

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21. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A First-in-Human Study of Repeat Dosing with REGN2810, a Monoclonal, Fully Human Antibody to Programmed Death – 1 (PD-1), as Single Therapy and in Combination with Other Anti-Cancer Therapies, in Patients with Advanced Malignancies, and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

(Signature of Investigator)

(Date)

(Printed Name)

APPENDIX 1. TECHNICAL SPECIFICATIONS AND STRUCTURAL CONSIDERATIONS FOR PLANNING RADIOTHERAPY (NON-GBM)

Physical Specifications: Conventional linear accelerators and specialized linear accelerators with image guidance are allowed sources. Treatment will be delivered with 4–25 MV photons, with selection of appropriate energies to optimize the dose distribution within the target volume and minimize dose to normal tissue.

Dose verification may be obtained through the use of personal dosimeters (eg, diode, thermoluminescence dosimeter) as per physician and institutional preference, but is not required per protocol.

Localization, Simulation, and Immobilization: Patient positioning will be based on clinical judgment to best achieve the ideal dose distribution. Patients should be positioned in a stable position that allows accurate reproduction of the target position between planning and each treatment. Immobilization systems should be used for planning and treatment when there is expected movement of the target volume with respiration. An abdominal compression device may be used for planning and treatment. A 4D-CT should be used to aid in definition of an internal target volume (ITV).

Localization – Isocenter port localization films (anterior/posterior and lateral or cone-beam CT) should be obtained at each treatment on the treatment unit immediately before treatment to ensure proper alignment of the simulated fields.

Treatment Planning/Target Volumes: CT-based treatment planning will be used for all patients. Axial scan will be required with a maximum of 5 mm spacing between slices.

The target lesion will be outlined by an appropriately trained physician and designated gross tumor volume (GTV). For 4D-CT planning, an ITV will be defined that accounts for respiratory motion. No margin will be given for presumed microscopic extension (thus GTV, ITV, and clinical target volume [CTV] are identical). The planning target volume (PTV) will be determined by the immobilization device used and the individual patient breathing motion. The minimal and maximal PTV margins permitted are 0 mm (if tumor is in contact with stomach or bowel) and 10 mm, respectively, dependent on the immobilization method used and breathing motion. Typical expansion of the GTV will be 5 mm and of the ITV will be 3 mm. Expansion should be limited to prevent expansion into stomach or bowel.

It is recommended that IMRT treatment planning be used for all patients. Typically, ≥ 9 nonopposing, noncoplanar beams should be used; this can be up to the radiologist's discretion.

Critical Organ Dose-Volume Limits: The absolute limits for maximum dose to a point or volume within critical organs are summarized in the following table. **These are absolute limits, and treatment delivery that exceeds these limits will constitute a major protocol violation.** These limits are from the American Association of Physicists in Medicine Task Group 101 report on stereotactic body radiation therapy ([Benedict 2010](#)). To verify each of these limits, the organs must be contoured such that appropriate dose volume histograms can be generated.

Critical Organ Dose-Volume Limits for One Dose

Serial Tissue	Max Vol Above Threshold	1fx Threshold	1fx Dmax	3fx Threshold	3 fx Dmax	5fx Threshold	5fx Dmax ^a	End Point (Grade ≥3)
Bladder wall	< 15 cc	11.4 Gy	18.4 Gy	16.8 Gy	28.2 Gy	18.3 Gy	38 Gy	Cystitis/fistula
Brachial plexus	< 3 cc	14 Gy	17.5 Gy	20.4 Gy	24 Gy	27 Gy	30.5 Gy	Neuropathy
Brainstem (not medulla)	< 0.5 cc	10 Gy	15 Gy	18 Gy	23.1 Gy	23 Gy	31 Gy	Cranial neuropathy
Bronchi/small airways	<0.5 cc	12.4 Gy	13.3 Gy	18.9 Gy	23.1 Gy	21 Gy	33 Gy	Stenosis/atelectasis
Cauda equina	< 5 cc	14 Gy	16 Gy	21.9 Gy	24 Gy	30 Gy	32 Gy	Neuritis
Cochlea	N/A	N/A	9 Gy	N/A	17.1 Gy	N/A	25 Gy	Hearing Loss
Colon	< 20 cc	14.3 Gy	18.4 Gy	24 Gy	28.2 Gy	25 Gy	38 Gy	Colitis/fistula
Cord & medulla	< 0.35 cc	10 Gy	14 Gy	18 Gy	21.9 Gy	23 Gy	30 Gy	Myelitis
Cord & medulla	< 1.2 cc	7 Gy	14 Gy	12.3 Gy	21.9 Gy	14.5. Gy	30 Gy	Myelitis
Cord Subvolume (5–6 mm above and below target)	10% of subvolume	10 Gy	14 Gy	18 Gy	21.9 Gy	23 Gy	30 Gy	Myelitis
Duodenum	< 10 cc	9 Gy	12.4 Gy	11.4 Gy	22.2 Gy	12.5 Gy	32 Gy	Ulceration
Duodenum	< 5 cc	11.2 Gy	12.4 Gy	16.5 Gy	22.2 Gy	18 Gy	32 Gy	Ulceration
Esophagus ^b	< 5 cc	11.9 Gy	15.4 Gy	17.7 Gy	25.2 Gy	19.5 Gy	35 Gy	Stenosis/fistula
Femoral heads (each)	< 10 cc	14 Gy	N/A	21.9 Gy	N/A	30 Gy	N/A	Necrosis
Great vessels	< 10 cc	31 Gy	37 Gy	39 Gy	45 Gy	47 Gy	53 Gy	Aneurysm
Heart/pericardium	< 15 cc	16 Gy	22 Gy	24 Gy	30 Gy	32 Gy	38 Gy	Pericarditis
Jejunum/ileum	< 5 cc	11.9 Gy	15.4 Gy	17.7 Gy	25.2 Gy	19.5 Gy	35 Gy	Enteritis/obstruction
Optic pathway	0.2 cc	8 Gy	10 Gy	15.3 Gy	17.4 Gy	23 Gy	25 Gy	Neuritis
Penile bulb	< 3 cc	14 Gy	34 Gy	21.9 Gy	42 Gy	30 Gy	50 Gy	Erectile Dysfunction
Rectum	< 20 cc	14.3 Gy	18.4 Gy	24 Gy	28.2 Gy	25 Gy	38 Gy	Colitis/fistula
Renal hilum (each)	< 2/3rds	10.6 Gy	18.6 Gy	N/A	N/A	23 Gy	N/A	Malignant hypertension

Serial Tissue	Max Vol Above Threshold	1fx Threshold	1fx Dmax	3fx Threshold	3 fx Dmax	5fx Threshold	5fx Dmax^a	End Point (Grade ≥3)
Ribs/chest Wall	< 1 cc	22 Gy	30 Gy	28.8 Gy	36.9 Gy	35 Gy	43 Gy	Pain/fracture
Ribs/chest Wall	< 30 cc	N/A	N/A	30 Gy	36.9 Gy	N/A	N/A	Pain/fracture
Sacral plexus	< 5 cc	14.4 Gy	16 Gy	22.5 Gy	24 Gy	30 Gy	32 Gy	Neuropathy
Skin	< 10 cc	23 Gy	26 Gy	30 Gy	33 Gy	36.5 Gy	39.5 Gy	Ulceration
Stomach	< 10 cc	11.2 Gy	12.4 Gy	16.5 Gy	22.2 Gy	18 Gy	32 Gy	Ulceration
Trachea & large bronchi	< 4 cc	10.5 Gy	20.2 Gy	15 Gy	30 Gy	16.5 Gy	40 Gy	Stenosis/fistula
Parallel Tissue	Max Vol Above Threshold	1fx Threshold	1fx Dmax	3fx Threshold	3 fx Dmax	5fx Threshold	5fx Dmax	End Point (Grade ≥3)
Lung (right and left)	1500 cc	7	NA-Parallel tissue	11.6 (2.9 Gy/fx)	NA-Parallel tissue	12.5 (2.5 Gy/fx)	NA-Parallel tissue	Basic lung function
Lung (right and left)	1000 cc	7.4	NA-Parallel tissue	12.4 (3.1 Gy/fx)	NA-Parallel tissue	13.5 (2.7 Gy/fx)	NA-Parallel tissue	Pneumonitis
Liver	700 cc	9.1	NA-Parallel tissue	19.2 (4.8 Gy/fx)	NA-Parallel tissue	21 (4.2 Gy/fx)	NA-Parallel tissue	Basic liver function
Renal cortex (right and left)	200 cc	8.4	NA-Parallel tissue	16 (4 Gy/fx)	NA-Parallel tissue	17.5 (3.5 Gy/fx)	NA-Parallel tissue	Basic renal function

^a “Point” defined as 0.035 cc or less.

^b Avoid circumferential irradiation

Dmax=maximum dose; fx=fraction(s); Max Vol=maximum volume.

APPENDIX 2. RECOMMENDED DOSE MODIFICATION OR DISCONTINUATION AND SUPPORTIVE CARE GUIDELINES FOR SPECIFIC DRUG-RELATED ADVERSE EVENTS

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Colitis events <ul style="list-style-type: none"> Bowel obstruction Colitis Colitis microscopic 	≤ Grade 1	No change in dose	<ul style="list-style-type: none"> For diarrhea, treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet). Endoscopy is recommended if symptoms persist. Grade 1 diarrhea that persist for >1 week should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily. 	Symptoms may include (but are not limited to): <ul style="list-style-type: none"> Abdominal pain, cramping and/or bloating 	All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, and a <i>Clostridium difficile</i> titer.
<ul style="list-style-type: none"> Enterocolitis hemorrhagic Gastrointestinal (GI) perforation Necrotizing colitis Diarrhea: <i>All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.</i>	Grade 2	Hold until ≤Grade 1. Resume at same dose level. May increase dosing interval by 1 week if it takes more than 4 weeks for toxicities to resolve.	<ul style="list-style-type: none"> GI consultation and endoscopy is recommended to confirm or rule out colitis for grade 2 diarrhea that persists >1 week or grade 1-2 diarrhea with rectal bleeding (additional guidelines for the treatment of persistent colitis are provided below). Grade 2 diarrhea should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily. Grade 2 diarrhea with diffuse ulceration and bleeding seen on endoscopy may require oral steroids with prolonged taper and represent an increased risk for the development of bowel perforation. Consider prophylactic antibiotics for opportunistic infections. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. In patients with Grade 2 enterocolitis, REGN2810 should be withheld and antidiarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (eg, 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. 	<ul style="list-style-type: none"> Blood and/or mucus in stool with or without fever Constipation Diarrhea Ileus Nausea and/or vomiting Peritoneal signs consistent with bowel perforation Rectal bleeding With or without fever Patients with diarrhea should be	

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Colitis events (continued)	Grade 3–4	<p>Withhold REGN2810</p> <p>Discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisone equivalent within 12 weeks of toxicity</p>	<ul style="list-style-type: none"> In patients with Grade 3 enterocolitis, REGN2810 will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1–2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. Consider prophylactic antibiotics for opportunistic infections. <p>For Grade 3–4 diarrhea (or Grade 2 diarrhea that persists after initial steroid treatment),</p> <ul style="list-style-type: none"> Rule out bowel perforation. Imaging with plain films or computed tomography (CT) can be useful. Consider consultation with gastroenterologist and confirmation biopsy with endoscopy. Treat with intravenous (IV) steroids (methylprednisolone 125 mg) followed by high-dose oral steroids (prednisone 1–2 mg/kg once per day or dexamethasone 4 mg every 4 hours). When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Taper over 6–8 weeks in patients with diffuse and severe ulceration and/or bleeding. If IV steroids followed by high-dose oral steroids does not reduce initial symptoms within 48–72 hours, consider treatment with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45–60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab. CAUTION: infliximab is contraindicated in patients with bowel perforation or sepsis^b. If symptoms persist despite the above treatment a surgical consult should be obtained. 	carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.	

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Endocrine events <ul style="list-style-type: none"> • Hyperthyroidism • Hypophysitis • Hypopituitarism 	Grade 1-2	No change in dose	<ul style="list-style-type: none"> • Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values. 	Symptoms may include (but not limited to): <ul style="list-style-type: none"> • Abdominal pain • Abnormal thyroid function tests and/or serum chemistries (Thyroid-stimulating hormone increased [decreased], Free thyroxine increased, Tri-iodothyronine increased.) • Arrhythmias^c • Cold or heat intolerance • Fatigue • Fever • Headache • Hypotension^c • Loss of appetite • Mental status and/or behavior changes • Nausea and/or vomiting • Unusual bowel habits • Vision disturbances • Weakness 	All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection. An endocrinology consultation is recommended.
Endocrine events <ul style="list-style-type: none"> • Hypothyroidism • Thyroid disorder • Thyroiditis 	Grade 3-4	Hold until on stable replacement dose	<ul style="list-style-type: none"> • Consider endocrine consultation. • Rule out infection and sepsis with appropriate cultures and imaging. • Replacement of appropriate hormones as required. 		
Endocrine events <ul style="list-style-type: none"> • Adrenal insufficiency • Hypophysitis • Pan-hypopituitarism 	Grade 1-4	Hold until on stable replacement dose	<ul style="list-style-type: none"> • Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency. • If Grade 1–2 hypophysitis is considered, pituitary gland imaging should be considered (magnetic resonance imaging [MRIs] with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis). • Grade 3–4 hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis. Hospitalization and IV methylprednisolone should be initiated. 		

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Eye event: Uveitis (iritis, iridocyclitis)	Grade 1	Discontinue REGN2810 if symptoms persist despite treatment with topical immunosuppressive therapy	<ul style="list-style-type: none"> • Evaluation by an ophthalmologist is strongly recommended. • Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics. 	Symptoms may include (but are not limited to): <ul style="list-style-type: none"> • Blurred vision • Diffuse erythema and a prominent blush on the sclerae • Dryness of the eyes • Pain • Photophobia 	All attempts should be made to rule out other causes such as metastatic disease, infection, or other ocular disease (<i>e.g.</i> , glaucoma or cataracts).
	Grade 2	Discontinue REGN2810 if symptoms persist despite treatment with topical immunosuppressive therapy and do not improve to Grade 1 within the retreatment period OR requires systemic treatment.	<ul style="list-style-type: none"> • Evaluation by an ophthalmologist is strongly recommended. • Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics. 		
	Grade 3–4	Discontinue REGN2810.	<ul style="list-style-type: none"> • Treat with systemic corticosteroids such as prednisone at a dose of 1-2 mg/kg per day. When symptoms improve to ≤Grade 1, steroid taper should be started and continued over no less than 4 weeks. 		

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Hepatic events <ul style="list-style-type: none"> Hepatitis Hepatitis, Autoimmune 	Grade 1–2	Withhold REGN2810 if there is a treatment-emergent concurrent elevation of ALT and bilirubin that corresponds to an upward shift of 2 or more grades in both parameters.	<ul style="list-style-type: none"> Monitor liver function tests more frequently until returned to baseline values. 	Symptoms may include (but are not limited to): <ul style="list-style-type: none"> Elevations in: <ul style="list-style-type: none"> AST >2.5 × ULN ALT >2.5 × ULN Total bilirubin >1.5 × ULN Fever Malaise Upper quadrant abdominal pain 	All attempts should be made to rule out other causes such as metastatic disease, progressive liver disease, viral hepatitis, alternative drug toxicity, infectious causes and/or myositis.
	Grade 3–4	Discontinue REGN2810 when AST or ALT >5.0 times ULN and/or total bilirubin >3.0 times ULN.	<ul style="list-style-type: none"> Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury, if necessary. Treat with high-dose IV glucocorticosteroids for 24–48 hours. When symptoms improve to grade 1 or less, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1–2 mg/kg should be started and continued over no less than 4 weeks. If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity^b. Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. 		
Nausea	≤Grade 1	No change in dose	<ul style="list-style-type: none"> Nausea should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake. 		
	Grade 2	Hold until ≤Grade 1. Resume at same dose level. May increase dosing interval by 1 week if it takes more than 4 weeks for toxicities to resolve.			
	Grade 3	Hold until <Grade 2. May increase dosing interval by 1 week for each occurrence. Discontinue if toxicities do not resolve within 12 weeks.			
	Grade 4	Off protocol therapy			

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Neutropenia	≤Grade 1	No change in dose			
	Grade 2	No change in dose			
	Grade 3	No change in dose			
	Grade 4	Hold until resolves to ≤Grade 1. May increase the dosing interval by 1 week. Discontinue if toxicities do not resolve within 12 weeks.			

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Pneumonitis events <ul style="list-style-type: none"> • Pneumonitis • Interstitial lung disease • Acute interstitial pneumonitis 	Grade 1	Consider hold of therapy. REGN2810 may be continued with close monitoring.	<ul style="list-style-type: none"> • Radiologic findings should be followed on serial imaging studies at least every 3 weeks. • Monitor for symptoms every 2–3 days. • Consider pulmonary consultation and/or bronchoscopy if clinically indicated. 	Symptoms may include (but are not limited to): <ul style="list-style-type: none"> • Abnormal breath sounds • Chest pain and/or tightness^c • Dyspnea^c • Dry cough • Fatigue • Fever • Hemoptysis 	All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection.
	Grade 2	Hold REGN2810	<p>To rule out other causes such as infection:</p> <ul style="list-style-type: none"> • Consider pulmonary consultation with bronchoscopy and biopsy/bronchoalveolar lavage (BAL). • Consider pulmonary function tests. • Follow radiologic findings on serial imaging studies every 1–3 days <p>If the patient is determined to have study drug associated pneumonitis:</p> <ul style="list-style-type: none"> • Monitor symptoms daily; consider hospitalization. • Treat with systemic corticosteroids at a dose of 1–2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • Treatment with REGN2810 may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of methylprednisolone 10 mg by mouth daily or less. Repeat chest imaging monthly as clinically indicated. <p>For Grade 2 pneumonitis that improves to ≤ Grade 1 within 12 weeks, the following rules should apply:</p> <ul style="list-style-type: none"> • <u>First episode of pneumonitis</u>: May increase dosing interval by one week in subsequent cycles. • <u>Second episode of pneumonitis</u>: Discontinue REGN2810 if upon rechallenge the patient develops a second episode of ≥ Grade 2 pneumonitis. 		
	Grade 3–4	Discontinue REGN2810.	<ul style="list-style-type: none"> • Consider pulmonary function tests with pulmonary consult. • Bronchoscopy with biopsy and/or BAL is recommended. • Treat with IV steroids (2–4 mg/kg per day prednisone or equivalent). When symptoms improve to grade 1 or less, a high-dose oral steroid (1–2 mg/kg prednisone once per day or 4 mg dexamethasone every 4 hours) taper should be started and continued over no less than 4 weeks. • Add prophylactic antibiotics for opportunistic infections. • If IV steroids followed by high-dose oral steroids does not reduce initial symptoms within 48–72 hours, treat with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45–60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab. 		

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Renal events <ul style="list-style-type: none"> • Nephritis • Nephritis autoimmune • Renal failure • Renal failure, Acute 	Grade 1	Consider withholding REGN2810 if event does not improve with symptomatic treatment	<ul style="list-style-type: none"> • Provide symptomatic treatment. • Monitor creatinine weekly; when it returns to baseline, resume routine creatinine monitoring per protocol. 	Symptoms may include (but not limited to): <ul style="list-style-type: none"> • Fatigue • High blood pressure • Increased serum creatinine • Swelling 	All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury to other chemotherapy agents. A renal consultation is recommended.
	Grade 2	Consider withholding REGN2810.	<ul style="list-style-type: none"> • Systemic corticosteroids at a dose of 1–2 mg/kg/day of prednisone or equivalent may be indicated. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. • Consider prophylactic antibiotics for opportunistic infections. • Consider renal biopsy. • If elevations persist >7 days or worsen, treat as Grade 4. 		
	Grade 3-4	Discontinue REGN2810.	<ul style="list-style-type: none"> • Renal consultation with consideration of ultrasound and/or biopsy as appropriate. • Monitor creatinine daily. • Treat with systemic corticosteroids at a dose of 1–2 mg/kg prednisone or equivalent once per day. • When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • Discontinue REGN2810 if unable to reduce corticosteroid dose for irAEs to ≤10 mg. • REGN2810 treatment may be restarted and the dose modified as specified in the protocol. 		

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Skin events <ul style="list-style-type: none"> • Dermatitis exfoliative • Erythema multiforme • Stevens-Johnson syndrome • Toxic epidermal necrolysis If considered to be immune related, \geq Grade 3 or result in dose modification or discontinuation: <ul style="list-style-type: none"> • Pruritus • Rash • Rash generalized • Rash maculo-papular • Vitiligo 	Grade 1–2	No change in dose	<ul style="list-style-type: none"> • Symptomatic treatment should be given such as topical glucocorticosteroids (eg, betamethasone 0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral antipruritics (eg, diphenhydramine HCl or hydroxyzine HCl). • Treatment with oral steroids is at investigator discretion for Grade 2 events. 		All attempts should be made to rule out other causes such as metastatic disease, infection, or allergic dermatitis.
	Grade 3	Hold REGN2810.	<ul style="list-style-type: none"> • Consider dermatology consultation and biopsy for confirmation of diagnosis. • Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg four times orally daily. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. 		
	Grade 4	Permanently discontinue REGN2810.	<ul style="list-style-type: none"> • Dermatology consultation and consideration of biopsy and clinical dermatology photograph. • Initiate steroids at 1–2 mg/kg prednisone or equivalent. When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. 		
Thrombocytopenia	\leq Grade 1	No change in dose			
	Grade 2	No change in dose			
	Grade 3	No change in dose	<ul style="list-style-type: none"> • Grade 3 drug-related thrombocytopenia >7 days or associated with bleeding requires discontinuation. 		
	Grade 4	Hold REGN2810 until resolves to \leq Grade 1. May increase the dosing interval by 1 week.	<ul style="list-style-type: none"> • Grade 4 drug-related thrombocytopenia >7 days or associated with bleeding requires discontinuation. 		

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Vomiting	≤ Grade 1	No change in dose	<ul style="list-style-type: none"> Vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake. 		
	Grade 2	Hold until ≤Grade 1. Resume at same dose level. May increase dosing interval by 1 week if it takes more than 4 weeks for toxicities to resolve.			
	Grade 3	Hold until <Grade 2. May increase dosing interval by 1 week for each occurrence. Discontinue if toxicities do not resolve within 12 weeks.			
	Grade 4	Off protocol therapy			

^a The signs and symptoms may be associated with any of the diagnoses in the associated “Event(s)” column.

^b REMICADE (Infliximab) prescribing information

^c If symptoms indicate possible new or worsening cardiac abnormalities, additional testing and/or a cardiology consultation should be considered.

APPENDIX 3. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS: RECIST GUIDELINE (VERSION 1.1)

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. Confirmatory scans should also be obtained 4 weeks following initial documentation of objective response or progressive disease.

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1; [Eisenhauer 2009](#)). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Selection of Lesions

- **Measurable disease:** Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm (≥ 2 cm) by chest X-ray or as ≥ 10 mm (≥ 1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).
Note: Refer to [Appendix 6](#) for evaluation of radiated target lesions.
- **Malignant lymph nodes:** To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm (≥ 1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.
- **Non-measurable disease:** All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm [< 1 cm] or pathological lymph nodes with ≥ 10 to < 15 mm [≥ 1 to < 1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

- **Target lesions:** All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for

non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

- **Non-target lesions:** All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- **Clinical lesions.** Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules and palpable lymph nodes) and ≥ 10 mm (≥ 1 cm) diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- **Chest X-ray.** Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Conventional CT and MRI.** This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situation.
- **PET-CT.** At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

- **Ultrasound.** Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- **Endoscopy, Laparoscopy.** The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.
- **Tumor markers.** Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- **Cytology, Histology.** These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (eg, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease

- **FDG-PET.** While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
 - a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
 - b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
 - c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Response Criteria

Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).
- **Partial Response (PR):** At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

- **Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).
Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease (PD):** Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Immune-Related Response Criteria

Immune-related response criteria differ from RECIST (Version 1.1) in that the sum of the longest diameters of all target lesions AND new lesions if any are used to determine response. The presence of new lesions per se does not determine progression; the total tumor burden is considered.

Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).
- **Partial Response (PR):** At least a 30% decrease in the sum of the diameters of target lesions, including new lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** At least a 20% increase in the sum of the diameters of target lesions, including new lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm).
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study and including the measurements of new lesions.

Evaluation of Non-Target Lesions

- **Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).
- **Note:** If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Overall Response Criteria

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. Revised Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 ([Eisenhauer 2009](#)) and immune-related response criteria (irRC; [Nishino 2013](#)) are summarized in tables within this section.

Response According to Revised Response Evaluation Criteria in Solid Tumors (Version 1.1)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required ^a
CR	CR	No	CR	≥4 weeks confirmation
CR	Non-CR/Non-PD	No	PR	≥4 weeks confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 weeks from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease.

^a In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as PD.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “*symptomatic deterioration*.” Every effort should be made to document the objective progression even after discontinuation of treatment.

Additional guidance for response assessment in CSCC patients: In some patients with unresectable locoregionally advanced basal cell carcinoma (BCC) or CSCC, it may not be possible to measure disease radiographically. For CSCC lesions that are not measurable radiographically, the approach from the phase II study of vismodegib in BCC will be used (Sekulic 2012). Response is defined at a decrease of 30% or more in externally visible or radiographic dimension (if applicable) or complete resolution of ulceration (if present at baseline). Residual scarring is to be included when measuring the externally visible dimension. Responses must be confirmed at least 4 weeks after the initial determination of response. Progressive disease is defined as an increase in 20% or more in the externally visible or radiographic dimension (if applicable), new ulceration, or new lesion (Sekulic 2012). These criteria will be applied to CSCC lesions that are not measurable radiographically in the current study. Central review of photographic images may be performed.

Immune-Related Response Criteria Evaluation

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required
CR	CR	No	CR	≥4 weeks Confirmation
CR	Non-CR/Non-PD	No	PR	≥4 weeks. Confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	Yes or No ^a	PR	
SD	Non-CR/Non-PD/not evaluated	Yes or No	SD	Documented at least once ≥4 weeks from baseline
PD	Any	Yes or No ^b	PD	no prior SD, PR or CR
Any	PD ^c	Yes or No	PD	

CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease.

^a Considered to be PR if measurements of target lesions and new lesions ≤ 30% of baseline.

^b Considered to be PD if measurements of target lesions and new lesions ≥ 20% from the lowest measurements.

^c In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as PD.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “symptomatic deterioration.” Every effort should be made to document the objective progression even after discontinuation of treatment.

Additional guidance for response assessment in CSCC patients: In some patients with unresectable locoregionally advanced basal cell carcinoma (BCC) or CSCC, it may not be possible to measure disease radiographically. For CSCC lesions that are not measurable radiographically, the approach from the phase II study of vismodegib in BCC will be used ([Sekulic 2012](#)). Response is defined at a decrease of 30% or more in externally visible or radiographic dimension (if applicable) or complete resolution of ulceration (if present at baseline). Residual scarring is to be included when measuring the externally visible dimension. Responses must be confirmed at least 4 weeks after the initial determination of response. Progressive disease is defined as an increase in 20% or more in the externally visible or radiographic dimension (if applicable), new ulceration, or new lesion ([Sekulic 2012](#)). These criteria will be applied to CSCC lesions that are not measurable radiographically in the current study. Central review of photographic images may be performed.

APPENDIX 4. REGN2810 PHARMACOKINETIC SAMPLING AND ASSESSMENT SCHEDULE

Table 1: REGN2810 Pharmacokinetic Sampling and Assessment Schedule for Cohorts 1, 14, 15, 17, 18, 19, 20, and 26 (every 2 week dosing; Q2W)

Study Visit	PK Sampling Time
cycle 1, day 1	<ul style="list-style-type: none"> • preinfusion • within 10 minutes after end of infusion • 1 hour (\pm 10 minutes) after end of infusion • 4 hours (\pm 10 minutes) after end of infusion • 8 hours (\pm 10 minutes) after end of infusion
cycle 1, day2	24 \pm 1 hours after end of infusion
cycle 1, day 3	48 \pm 3 hours after end of infusion
cycle 1, day 4	72 \pm 3 hours after end of infusion
cycle 1, day 8	any time during visit
cycle 1, days 15 \pm 3, 29 \pm 3, 43 \pm 3	<ul style="list-style-type: none"> • preinfusion • end of infusion
cycles 2–6, day 1	<ul style="list-style-type: none"> • preinfusion • end of infusion
cycles 2–6, day 15 \pm 3	<ul style="list-style-type: none"> • preinfusion • end of infusion
cycles 2–6, day 29 \pm 3	<ul style="list-style-type: none"> • preinfusion • end of infusion
cycles 2–6, day 43 \pm 3	<ul style="list-style-type: none"> • preinfusion • end of infusion

Table 2: REGN2810 Pharmacokinetic Sampling and Assessment Schedule for Cohorts 2 through 13, 16, 23, 24, and 25 (every 2 week dosing; Q2W)

Study Visit	PK Sampling Time
cycle 1, day 1	<ul style="list-style-type: none">• Preinfusion• Within 10 minutes after end of infusion
cycle 1: day 15 \pm 3, day 29 \pm 3, day 43 \pm 3	<ul style="list-style-type: none">• Preinfusion• Within 10 min after end of infusion
cycles 2–6: day 1	<ul style="list-style-type: none">• Preinfusion• Within 10 min after end of infusion
End of study (if progression during cycles 1-6) or Follow-up Visit 1	Anytime during the visit
Follow-up Visit 7 (for patients who maintain active follow-up)	Anytime during the visit

Table 3: REGN2810 Pharmacokinetic Sampling and Assessment Schedule for Expansion Cohorts 21 and 22 (every 3 week dosing, Q3W)

Study Visit	PK Sampling Time
cycle 1, day 1	<ul style="list-style-type: none"> • preinfusion • within 10 minutes after end of infusion • 1 hour (\pm 10 minutes) after end of infusion • 4 hours (\pm 10 minutes) after end of infusion • 8 hours (\pm 10 minutes) after end of infusion
cycle 1, day 2	24 \pm 1 hours after end of infusion
cycle 1, day 3	48 \pm 3 hours after end of infusion
cycle 1, day 4	72 \pm 3 hours after end of infusion
cycle 1, day 8	any time during visit
cycle 1, days 22 \pm 3, 43 \pm 3	<ul style="list-style-type: none"> • preinfusion • end of infusion
cycles 2–4, day 1	<ul style="list-style-type: none"> • preinfusion • end of infusion
cycles 2–4, day 22 \pm 3	<ul style="list-style-type: none"> • preinfusion • end of infusion
cycles 2–4, day 43 \pm 3	<ul style="list-style-type: none"> • preinfusion • end of infusion

APPENDIX 5. FACTORS TO CONSIDER IN ASSESSING THE RELATIONSHIP OF AES TO REGN2810 OR INFUSION PROCEDURE, STUDY PROCEDURE, OR COMBINATION TREATMENT.

Is there a reasonable possibility that the event may have been caused by the study drugs or infusion procedure, study procedure, or concomitant treatment?

No:

- due to external causes such as environmental factors or other treatment/s being administered
- due to the patient's/subject's disease state or clinical condition
- do not follow a reasonable temporal sequence following the time of administration of the dose of REGN2810, study procedure, or combination treatment
- do not reappear or worsen when dosing with REGN2810, study procedure, or combination treatment is resumed
- are not a known response to REGN2810 or infusion procedure, study procedure, or combination treatment based upon pre-clinical data or prior clinical data

Yes:

- could not be explained by environmental factors or other treatment/s being administered
- could not be explained by the patient's disease state or clinical condition
- follow a reasonable temporal sequence following the time of administration of the dose of REGN2810
- resolve or improve after discontinuation of REGN2810, study procedure, or combination treatment
- reappear or worsen when dosing with REGN2810, study procedure, or combination treatment is resumed
- are known to be a response to REGN2810 or the infusion procedure, study procedure, or combination treatment based upon pre-clinical data or prior clinical data

NOTE: This list is not exhaustive.

APPENDIX 6. EVALUATION OF RADIATED TARGET LESIONS

Radiated target lesions will be evaluated with a modified version of the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1. Additional definitions beyond the RECIST 1.1 guidelines specific to this protocol are incorporated to define local control.

Response Criteria for Radiated Lesions

Local Enlargement (LE)	At least a 20% increase in the LD of target lesion, taking as reference the smallest LD recorded since the treatment started. Ideally, this determination will be made based on CT image evaluation.
Local Failure (LF)	<p>Refers to the primary treated tumor after protocol therapy and corresponds to meeting both of the following two criteria:</p> <ol style="list-style-type: none">1. Increase in tumor dimension of 20% as defined above for local enlargement (LE);2. The measurable tumor with criteria meeting LE should be avid on Positron Emission Tomography (PET) imaging with uptake of a similar intensity as the pretreatment staging PET, OR the measurable tumor should be biopsied confirming viable carcinoma. <p>The EORTC criteria for post-treatment PET evaluation will be used as a basis for evaluation in cases more difficult to assign as to whether the uptake is pathological for cancer recurrence vs inflammation.</p>
Local Control (LC)	The absence of Local Failure.

The longest diameter (LD) for the radiated target lesion calculated from the treatment-planning CT scan, using appropriate tissue-specific windowing, will be reported as the baseline LD. The baseline LD will be used as the reference by which to characterize the objective tumor. For follow-up assessment, diagnostic CT scans performed using a 5 mm contiguous reconstruction algorithm using pulmonary windowing taken as part of scheduled protocol follow-up are preferred as the method of evaluation for response. When CT scans are not available, MRI or X-ray determination will be allowed, as long as the target lesion is clearly visible.

Local treatment effects in the vicinity of the tumor target may make determination of tumor dimensions difficult. For example, bronchial or bronchiolar damage may cause patchy consolidation around the tumor that, over time, may coalesce with the residual tumor. In cases in which it is indeterminate whether consolidation represents residual tumor or treatment effect, it should be assumed that abnormalities are residual tumor.

APPENDIX 7. TECHNICAL SPECIFICATIONS AND STRUCTURAL CONSIDERATIONS FOR PLANNING RADIOTHERAPY FOR GLIOBLASTOMA PATIENTS

Technique:

Intensity modulated radiotherapy (IMRT) via any method (eg, VMAT, static field IMRT) or Stereotactic Radiosurgery (SRS) is required. 3D planning is not allowed.

Dose Specifications

Treatment shall consist of 30 Gy delivered in 5 fractions delivered over 5 consecutive treatment days. The treatments may extend over the weekend (eg, 5 treatment days over 8 calendar days.) Target coverage and homogeneity limits and deviations are listed in Table 1.

Table 1: Target Coverage and Dose Limits

Dose Metric	Per Protocol	Variation Acceptable	Deviation Unacceptable
Volume of PTV covered by the prescription dose of 30 Gy	Greater than or equal to 95% of the PTV should receive greater than or equal to 30 Gy	Greater than or equal to 90% of the PTV receiving greater than or equal to 30 Gy	Less than 90% of the PTV receiving greater than or equal to 30 Gy. Coverage less than 90% is acceptable in areas of OAR/PTV overlap.
Minimum dose to the PTV (0.03 cc)	Greater than or equal to 25.5 Gy (85% of the prescription dose)	Greater than or equal to 24 Gy (80% of the prescription dose); Minimum doses of less than 24 Gy are acceptable if they occur due to OAR/PTV overlap	Less than 24 Gy (80% of the prescription dose); Minimum doses of less than 24 Gy are unacceptable unless they occur in regions of OAR/PTV overlap
Maximum dose to the PTV (0.03 cc)	Less than or equal to 36 Gy (120% Rx Dose. For SRS, this represents a plan prescribed to the 84% or greater Isodose line)	Less than or equal to 37.5 Gy (125% Rx Dose. For SRS, this represents a plan prescribed to the 80% isodose line)	Greater than 37.5 Gy (125% Rx Dose or an isodose line less than 80% for a radiosurgical plan)

Technical Factors (Equipment, Energies)

Intensity modulated radiotherapy (IMRT) via any method (eg, VMAT, static field IMRT) or Stereotactic Radiosurgery (SRS) is required. 3D planning is not allowed.

If utilizing non-stereotactic equipment, then image guided radiotherapy (IGRT) is required. Daily, pretreatment kv/kv imaging is sufficient. Daily cone-beam CT (CBCT) is preferred.

Imaging for treatment planning will be obtained with the patient in the same position and immobilization device as for treatment. All patients will be positioned via a combination of rigid immobilization and daily image guidance to ensure positioning accuracy of 3 mm or better, and of a magnitude that justifies the PTV margin applied (the participating institutions must document the immobilization and localization methods applied).

Localization, Simulation, and Immobilization

MRI fusion with CT, with injected contrast, are required for treatment planning. At least 1 of these scans must be of the patient immobilized in treatment position, and with image resolution of no worse than 1.5 mm x 1.5 mm x 3 mm. MRI sequences should include axial T1 post-contrast stereotactic image (such as MP-RAGE or FSPGR BRAVO). Contrast may be omitted if medically indicated. Additionally, a T2 sequence (eg, FLAIR or T2, preferably stereotactic, thin slice, contiguous) is helpful to identify any non-enhancing tumor.

Immobilization must be rigid (eg, thermoplastic masks). For daily treatment, localization will include the steps of a) immobilization with the same device used for simulation, and b) daily image guidance using at a minimum orthogonal pairs of radiographs aligned to DRRs as a computer-assisted process (CT-CBCT alignment is permitted as well).

Treatment Planning/Target Volumes

A GTV will be defined using the CT and MRI images.

The GTV includes the post-operative resection cavity if no residual enhancing tumor is noted. The GTV also includes any non-enhancing tumor as identified on T2/FLAIR. T2/FLAIR signal consistent with edema is not included in the GTV. Therefore a distinction is made between T2 edema (typically without mass effect, sparing the cortical ribbon, obeying the grey/white junction, etc) with T2 tumor (mass effect with sulcal effacement, involvement of the grey/white junction, obliteration of the cortical ribbon). Care is made to not include any enhancement or T2 signal on the post-operative scan that is due to post-surgical infarct. Fusion of the pre-operative MRI to determine initial extent of the tumor is helpful.

For newly diagnosed GBM patients, the GTV is expanded by 5 mm to make the CTV. The CTV should be trimmed at anatomic boundaries to rational tumor spread, such as the tentorium, falx if not near the corpus callosum, and skull. For recurrent GBM, do not add a 5 mm CTV margin, just a PTV margin.

A PTV expansion that is justified based on image guidance and immobilization will be applied. Regardless of immobilization and localization methods, the PTV expansion should be no larger than 3 mm. Therefore, for stereotactic treatment, the PTV is typically 1 mm. For non-stereotactic treatment with IGRT, then the PTV is typically 3mm.

Critical Structures

Normal tissues to be contoured will include the brain, brainstem, optic nerves and chiasm. Planning risk volume (PRV) expansions the same size as the PTV expansion (eg. If the PTV is 3 mm, then the PRV is 3 mm. For stereotactic machines, a PTV of 0mm is acceptable; therefore the PTV = CTV = GTV + 5 mm in this instance) should be utilized for optic nerves and chiasm.

Special consideration should be given to avoid doses greater than the prescription dose within the scalp as well as limiting the exit dose through the oral cavity and mucosa.

The treatment parameters should be modified to optimize the conformity of the prescription isodose volume to the target volume while minimizing dose to critical structures. Target delineation and OAR limits are given in Table 2.

Table 2: Normal Dose Limits for newly diagnosed GBM (5 Fractions)

For NEWLY diagnosed GBM		
GTV includes: <ol style="list-style-type: none"> 1. The post-operative resection cavity 2. Any residual enhancing tumor 3. Any nodular non-enhancing tumor. <u>Edema per T2 or FLAIR imaging is NOT included.</u> <p>CTV is a 5 mm margin on GTV, shaved at anatomic boundaries to tumor spread</p> <p>PTV is a machine specific 0-3 mm margin on the CTV</p>		
Dose Metric	Per Protocol	Deviation Unacceptable
Maximum Dose (0.03 cc) to PRV for Optic Nerves, Chiasm	Less than or equal to 25 Gy	Greater than 25 Gy
Maximum Dose (0.03 cc) to PRV for Brainstem	Less than or equal to 27.5 Gy	Greater than 27.5 Gy
For RECURRENT GBM		
GTV includes: <ol style="list-style-type: none"> 1. The recurrent enhancing tumor. <u>Edema per T2 or FLAIR imaging is NOT included.</u> <p>CTV is a 0 mm margin on GTV.</p> <p>PTV is a machine specific 0-3 mm margin on the CTV</p>		
Dose Metric(see note below)	Per Protocol	Deviation Unacceptable
Maximum Dose (0.03 cc) to PRV for Optic Nerves, Chiasm	Less than or equal to 17.5 Gy	Greater than 17.5 Gy
Maximum Dose (0.03 cc) to PRV for Brainstem	Less than or equal to 20 Gy	Greater than 20 Gy

Coverage of the PTV will be decreased in order to fulfill these limits.

Note: for recurrent GBM, if the chiasm, optic nerves and brainstem received <20 Gy maximum dose from the initial radiotherapy course of 60 Gy in 30 fractions, then the Newly Diagnosed GBM OAR limits may be used instead of the Recurrent GBM limits.

APPENDIX 8. RANO RESPONSE CRITERIA

Table 4. Summary of the Proposed RANO Response Criteria				
Criterion	CR	PR	SD	PD
T1 gadolinium enhancing disease	None	≥ 50% ↓	< 50% ↓ but < 25% ↑	≥ 25% ↑*
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑*
New lesion	None	None	None	Present*
Corticosteroids	None	Stable or ↓	Stable or ↓	NA†
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	↓*
Requirement for response	All	All	All	Any*

Abbreviations: RANO, Response Assessment in Neuro-Oncology; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; FLAIR, fluid-attenuated inversion recovery; NA, not applicable.

*Progression occurs when this criterion is present.

†Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

Source: [Wen 2010](#)

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Medical/Study Director, Regulatory Representative, Clinical Study Team Lead, and Biostatistician)

To the best of my knowledge, this report accurately describes the conduct of the study.

Study Title: A First-in-Human Study of Repeat Dosing with REGN2810, a Monoclonal, Fully Human Antibody to Programmed Death – 1 (PD-1), as Single Therapy and in Combination with Other Anti-Cancer Therapies, in Patients with Advanced Malignancies

Protocol Number: R2810-ONC-1423

Protocol Version: R2810-ONC-1423 Amendment 7

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Team Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

IND: 127100
EudraCT: TBD

Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

**A PHASE 2 STUDY OF REGN2810, A FULLY HUMAN MONOCLONAL
ANTIBODY TO PROGRAMMED DEATH – 1 (PD-1), IN PATIENTS WITH
ADVANCED CUTANEOUS SQUAMOUS CELL CARCINOMA**

Compound: REGN2810 (anti-PD-1 mAb)

Clinical Phase: 2

Protocol Number: R2810-ONC-1540

Date of Issue: 23 NOV 2015

Scientific/Medical Monitor:

Elizabeth Stankevich, BS
Director, Clinical Sciences, Oncology

Matthew Fury, MD, PhD
Senior Director, Clinical Sciences, Oncology

Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591

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[REDACTED] This information must not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Regeneron Pharmaceuticals, Inc.

CLINICAL STUDY PROTOCOL SYNOPSIS

Title

A Phase 2 Study of REGN2810, a Fully Human Monoclonal Antibody to Programmed Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma (CSCC)

Site Locations

Up to 30 sites globally

Objectives

The primary objective of this study is to estimate the clinical benefit of REGN2810 monotherapy for patients with metastatic (nodal or distant) cutaneous squamous cell carcinoma (CSCC) (Group 1) or with unresectable locally advanced CSCC (Group 2), as measured by overall response rate (ORR), according to central review.

The secondary objectives of the study are:

- To estimate ORR according to investigator review
- To estimate the duration of response, progression-free survival (PFS), and overall survival (OS) by central and investigator review
- To estimate the complete response (CR) rate by central review
- To assess the safety and tolerability of REGN2810
- To assess the pharmacokinetics (PK) of REGN2810 (at select sites only)
- To assess the immunogenicity of REGN2810
- To assess the impact of REGN2810 on quality of life using EORTC QLQ-C30.

Exploratory Objectives (Group 2 only)

- To explore the pharmacodynamic effects of REGN2810 in tumor biopsies obtained at baseline, during treatment, and at progression in CSCC patients treated with REGN2810 [REDACTED]
[REDACTED]
 - [REDACTED]
 - [REDACTED]
[REDACTED]
[REDACTED]
 - [REDACTED]
[REDACTED]
[REDACTED]
 - [REDACTED]
 - [REDACTED]

Study Design	<p>This is a phase 2, non-randomized, 2-group, multicenter study of REGN2810 at a dose of 3 mg/kg administered intravenously (IV) every 2 weeks for patients with advanced CSCC. The study will have 2 groups. Group 1 is for patients with metastatic CSCC. Group 2 is for patients with unresectable locally advanced CSCC. All patients will undergo screening procedures to determine eligibility within 28 days prior to the initial administration of REGN2810. There is no randomization or placebo control.</p> <p>After a screening period of up to 28 days, patients will receive up to twelve 56-day (8-week) treatment cycles for up to 96 weeks of treatment. Each patient will receive 3 mg/kg REGN2810 IV on days 1, 15±3, 29±3, and 43±3 during each treatment cycle. Tumor assessments will be made at the end of each treatment cycle. Extensive safety evaluations will occur on day 1 of each cycle, with routine safety evaluations to be conducted at each REGN2810 dosing visit.</p> <p>A patient will receive treatment until the 96-week treatment period is complete, or until disease progression, unacceptable toxicity, withdrawal of consent, or confirmed CR. Patients with confirmed CR after a minimum of 48 weeks of treatment may elect to discontinue treatment and continue with all relevant study assessments (eg, efficacy assessments). Patients who discontinue study treatment due to PD should return to the clinic 30 days (range: 28 to 42 days) after the last study treatment to complete the EOS assessments indicated in Table 4. After the EOS visit, patients should be followed for survival status until death, loss to follow-up, or study termination by the sponsor.</p>
Study Duration	Screening (up to 4 weeks), up to 96 weeks of treatment, and up to 6 months of follow-up.
Population	
Sample Size:	Up to 129 adult patients (Group 1, 53 patients; Group 2, 76 patients) are planned to enroll.
Target Population:	Patients with metastatic CSCC or with unresectable locally advanced CSCC.
Treatments	
Study Drug	REGN2810 3 mg/kg administered IV over 30 minutes every 14 days for 96 weeks.
Dose/Route/Schedule:	
Variables	
Primary:	<p>The primary efficacy endpoint for this study is ORR during the 12 treatment cycles. Overall response rate will be assessed separately for patients with metastatic CSCC or unresectable locally advanced CSCC:</p> <ul style="list-style-type: none">For patients in Group 1, Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 will be used to determine ORR.For patients in Group 2, composite response criteria will be used to determine ORR. In patients achieving a CR, tumor biopsies will be used in the final determination of complete versus partial response (PR).
Secondary:	The secondary efficacy outcome measures are:

- Duration of response
- Duration of disease control
- PFS
- OS
- CR rate
- Change in scores of patient-reported outcomes on EORTC QLQ-C30
- Adverse events (AEs)
- Concentrations of REGN2810 in serum (at select sites)
- Anti-REGN2810 antibodies

Exploratory Endpoint

- The following exploratory analyses are planned:
 - Fold-change in mRNA expression of genes expressed in tumor tissue
 - Percent change in number of TILs (CD8+ T cells, CD4+ T cells, T regulatory cells, and tissue permitting, other subtypes such as B cells, myeloid-derived cells, NK cells, etc) and descriptive change in distribution of TILs in respect to tumor tissue and stroma
 - Percent change in expression levels (mRNA and/or protein) of PD-L1, GITR, and LAG-3, and possibly other check-point modulators
 - Change in number and type of genetic mutations in known oncogenes and potential tumor neoantigens
 - Change in tumor mutation burden

Procedures and Assessments

Tumor imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) and digital medical photography (for externally visible lesions) will be performed to measure tumor burden and to characterize the efficacy profile of study treatments using response criteria.

Physical examination, laboratory tests, vital signs, electrocardiogram (ECG), pregnancy test for women of childbearing potential, and recording of AEs and concomitant medications will be performed to ensure patient safety and to characterize the safety profiles of study treatments.

Other assessments will include:

- Peripheral blood samples for PK
- Peripheral blood samples to assess anti-REGN2810 antibodies
- Tumor biopsies
- Quality of life assessments

Statistical Plan

The sample sizes for both Group 1 and Group 2 were selected such that the lower limit of the 95% confidence interval of the estimated overall response rate will be clinically meaningful. The non-clinically meaningful ORR of 15% for Group 1 will be excluded using the lower limit of 95% CI if the observed ORR is 28.0% or more. For Group 1, 50 patients will be required to provide at least 85% power to reject a null hypothesis. The non-clinically meaningful ORR of 25% for Group 2 will be excluded using the lower limit of 95% CI if the observed ORR is 36.1% or more. For Group 2, 72 patients will be required to provide at least 90% power to reject a null hypothesis. The sample sizes will be further increased by 5% to account for patients who withdraw prematurely from the study. Hence, the total sample sizes will be 53 patients for Group 1, and 76 patients for Group 2, for a total of 129 patients.

Demographic and baseline characteristics will be summarized descriptively by group and extent of prior therapy.

The primary endpoint for efficacy analyses is the ORR as determined by RECIST version 1.1 or by the composite response criteria. The ORR assessment for the primary analysis will be performed by an independent central review committee. The investigator-assessed ORR will be considered as a secondary analysis. Patients who are deemed as not evaluable according to RECIST 1.1 or inevaluable by the composite efficacy criteria will be considered as not reaching PR/CR for ORR.

The primary analyses of efficacy are based on the exact binomial confidence interval approach, ie, whether the lower limit of 95% confidence interval will exclude an historical control ORR that is not deemed clinically meaningful for each group, respectively. The secondary analyses of efficacy as measured by duration of response, duration of disease control, PFS, and OS will be summarized by median and its 95% confidence interval using the Kaplan-Meier method.

The quality of life of patients will be repeatedly measured by the EORTC QLQ-C30 at the day 1 of each treatment cycle. The change in scores of QLQ-C30 will be summarized descriptively at each post-baseline time point. The summary scores of QLQ-C30 will also be graphically depicted by longitudinal plots.

Safety observations and measurements including drug exposure, AEs, laboratory data, vital signs, and Eastern Cooperative Oncology Group (ECOG) performance status will be summarized and presented in tables and listings.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-drug antibody
ADL	Activities of Daily Living
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the concentration–time curve
BAL	Bronchoalveolar lavage
BCC	Basal cell carcinoma
BUN	Blood urea nitrogen
CR	Complete response
CRF; eCRF	Case report form (electronic or paper); electronic case report form
CRO	Contract research organization
CRP	C-reactive protein
CSCC	Cutaneous squamous cell carcinoma
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte antigen 4
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EOS	End of study
FAS	Full analysis set
FDG-PET	¹⁸ F-fluorodeoxyglucose positron emission tomography
FFPE	Formalin-fixed, paraffin-embedded
GCP	Good clinical practice
GITR	Glucocorticoid-induced TNFR family related gene

GnRH	Gonadotropin-releasing hormone
HIV	Human immunodeficiency virus
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papillomavirus
ICF	Informed consent form
ICH	International Conference on Harmonisation
INR	International Normalized Ratio
irAE	Immune-related adverse event
IRB	Institutional Review Board
irRC	Immune-related response criteria
IUD	Intrauterine device
IV	Intravenous
IWRS	Interactive Web Response System
LAG-3	Lymphocyte activation gene-3
LD	Longest diameter
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LLOQ	Lower limit of quantification
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCCN	The National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NSCLC	Non-small-cell lung cancer
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed death-1 (receptor)
PD-L1, PD-L2	Programmed death ligand 1, programmed death ligand 2
PET	Positron-emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
PT	Preferred term
RCC	Renal cell cancer
RECIST	Response Evaluation Criteria in Solid Tumors
Regeneron	Regeneron Pharmaceuticals, Inc.

RF	Rheumatoid factor
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Systems (software)
SOC	System organ class
TEAE	Treatment-emergent adverse event
TIL	Tumor-infiltrating lymphocytes
TSH	Thyroid-stimulating hormone
US	United States
WBC	White blood cell

1. INTRODUCTION AND RATIONALE

1.1. Introduction

Cutaneous squamous cell carcinoma (CSCC) is the second most common malignancy in the United States (US), with approximately 186,000 to 420,000 individuals diagnosed with CSCC each year ([Karia 2013](#)). Precise incidence and mortality measurements are not available because these cancers are not included in the Surveillance, Epidemiology, and End Results (SEER) database. A review of other national databases indicates that incidence of non-melanoma skin cancers, mostly basal cell carcinoma (BCC) and CSCC, approximately doubled between 1994 and 2006 in the context of an aging population ([Rogers 2010](#)). Most CSCC patients have a favorable prognosis, but annual mortality is approximately 3,900 to 8,800 deaths in the US ([Karia 2013](#)). Risk factors for CSCC include UV exposure, advanced age, and immunosuppression ([Alam 2001](#), [Madan 2010](#)). Although the vast majority of individuals with diagnosis of CSCC or BCC have a very favorable prognosis, CSCC has a greater propensity for aggressive recurrences than BCC. Individuals diagnosed with CSCC, unlike those diagnosed with BCC, have an increased mortality compared with age-matched controls ([Rees 2015](#)).

In the American Joint Committee on Cancer 7th Edition Staging System, tumor size less than or greater than 2 cm is a key distinction between stage 1 and 2, and selected risk factors are also incorporated in the staging ([Farasat 2011](#)). Stage 3 designates CSCC with involvement of a single lymph node ≤ 3 cm, and stage 4 includes patients with a broad range of locally invasive tumors and/or distant metastatic disease ([Farasat 2011](#)). Limitations of this staging system include heterogeneity of outcomes in stage I and II tumors; alternative risk-adapted staging has been proposed but not externally validated ([Karia 2014](#)).

Surgical resection is the centerpiece of clinical management of CSCC. The primary goal is complete resection of cancer, and acceptable cosmetic outcome is a secondary goal ([Madan 2010](#)). The choice of surgical intervention is influenced by a number of factors, including size and histology of the tumor, expertise of the local clinical team, and comorbidities of the patient. Factors associated with poor prognosis in CSCC include tumor size >2 cm, tumor

depth >2mm, perineural invasion, host immunosuppression, and recurrent lesions (Madan 2010, Schmults 2013).

Efficacy for radiation therapy for CSCC has been described in the adjuvant setting in a large retrospective study of 167 patients with nodal involvement who underwent surgical resection. Patients undergoing post-operative radiation therapy had a lower rate of locoregional recurrence compared to those who underwent surgery only (20 vs. 43%), and superior 5-year overall survival (OS) (73% vs. 54%) of CSCC (Veness 2005). In a small prospective phase 1 study of 15 CSCC patients who received post-operative radiation (60 to 66 Gy for 6 weeks) with concurrent erlotinib, the 2 year OS was 65% (Heath 2013).

For the small percentage of patients who develop unresectable locally recurrent or metastatic disease, treatment options are limited. A phase 2 prospective study of 14 patients with unresectable or inoperable CSCC treated with platinum based-chemoradiation, reported in abstract form only, found that OS at 3 years was 54% (Nottage 2012). In a single institution retrospective case series of 12 patients with unresectable CSCC that were treated with radiation therapy (median dose 60 Gy in 30 fractions) and concurrent cetuximab, median OS was 8 months (Samstein 2014). Durable disease control was achieved in some patients, and this retrospective study also reviewed other reports of CSCC treated with chemoradiotherapy (case reports, case series) in the literature, in which some patients experienced long term disease control (Samstein 2014). These results underscore that for patients with unresectable advanced CSCC, the malignancy is a life-threatening condition but some patients may achieve durable disease control with radiation-based therapy. As such, radiation-based therapy is appropriately considered for some patients with unresectable CSCC.

Regarding systemic therapies, there have been single-arm studies that often contained heterogeneous groups of CSCC patients with different stages of disease, but none of these studies clearly demonstrated therapeutic advantage (Maubec 2011, Nakamura 2013). As a result, there is a dearth of data to guide clinical decision-making for oncologists who take care of patients with advanced CSCC. The National Comprehensive Cancer Network (NCCN) guidelines do not provide firm recommendations. Cisplatin monotherapy, cisplatin plus 5-fluorouracil (5-FU), and cetuximab are discussed only as “possible options,” and participation in clinical trials is recommended with the caveat that such trials are scarce (Bichakjian 2015). One factor that has prevented the adoption of a standard-of-care for advanced CSCC is the lack of an adequate demonstration of safety of any regimen for this patient population. Two frequently-cited studies of cisplatin + 5-FU-based chemotherapy enrolled 14 and 7 advanced CSCC patients, respectively, and therefore were unable to provide a meaningful safety assessment (Sadek 1990, Khansur 1991). A more comprehensive description of the safety profile of cisplatin + 5-FU was obtained in a large randomized clinical trial for a different patient population, head and neck squamous cell carcinoma (HNSCC). Among 215 patients with a median age of 57 years who were treated with cisplatin + 5-FU for advanced HNSCC, 76% experienced Grade 3 or 4 toxicities. Given that CSCC occurs in an older patient population (Gray 1997, Diffey 2005, Karia 2014), the lack of optimization of dose and schedule of cisplatin and 5-FU for older individuals is a practical limitation to the clinical use of these regimens in CSCC. Advanced age increases the probability of requirement for dose reduction in the first cycle of chemotherapy among patients with advanced solid tumors (Gajra 2015). As such, platinum and/or 5-FU-based chemotherapy is not an attractive option for many CSCC patients due to safety and tolerability concerns associated with advanced age.

Targeting of the epidermal growth factor receptor (EGFR) in CSCC has been explored by several groups. In a phase 2 study of cetuximab monotherapy for patients with unresectable squamous cell carcinoma of the skin, median age was 79 years (Maubec 2011). The observed response rate was 28% (10/36 patients), median progression-free survival (PFS) was 4.1 months, and median OS was 8.1 months (Maubec 2011). A phase 2 study of panitumumab enrolled 16 patients with advanced CSCC that was deemed incurable; 2 patients had metastatic disease (Foote 2014). Overall response rate (ORR) was 31% (95% CI: 11-59%). These studies of EGFR-targeting monoclonal antibodies share some of the same limitations of the studies of cytotoxic chemotherapy that were noted above, including small sample size and lack of demonstration of benefit in quality of life.

1.1.1. Blockade of the PD-1 Checkpoint with REGN2810

Under chronic stimulation, T cells lose proliferative and effector function capacity, often due to signal down-modulation via the increased expression of proteins such as programmed cell death-1 (PD-1), an inhibitory checkpoint receptor of the CD28 receptor family. Blockade of the PD-1/PD-L1 T-cell checkpoint pathway is an effective and well tolerated approach to stimulating the immune response, and has achieved significant objective responses in advanced melanoma, renal cell cancer (RCC), non-small-cell lung cancer (NSCLC), and other solid tumors (Postow 2015).

REGN2810 is a high-affinity, fully human, hinge-stabilized IgG4P antibody directed to the PD-1 receptor that potently blocks the interaction of PD-1 with its ligands, PD-L1 and PD-L2 (See the Investigator's Brochure for further details of nonclinical pharmacology and antitumor activity of REGN2810). REGN2810 is currently undergoing evaluation in the first in human study R2810-ONC-1423 (NCT02383212). It is a phase 1, open-label, multicenter repeat-dosing study of REGN2810, alone and in combination with other anti-cancer therapies in patients with advanced malignancies, and contains both dose escalation and expansion cohorts.

1.2. Rationale

1.2.1. Rationale for Dose Selection

As of 12 September 2015, 53 patients have been enrolled in study R2810-ONC-1423 in 8 dose escalation cohorts, including 3 monotherapy cohorts (1 mg/kg, 3 mg/kg, 10 mg/kg REGN 2810 administered intravenously [IV] every 2 weeks) and 5 combination therapy cohorts (3 mg/kg REGN2810 administered IV every 2 weeks in combination with various combinations of hypofractionated radiation therapy or cyclophosphamide). No dose-limiting toxicities have been observed. The dose escalation portion of the study established that 3 mg/kg REGN2810 administered IV over 30 minutes every 2 weeks is the recommended monotherapy dosing regimen for the agent in further studies for advanced cancer patients.

1.2.2. Rationale for Study of REGN2810 in CSCC

The central role of sun exposure in the pathogenesis of CSCC is evident at the molecular and cellular level. Most somatic mutations in CSCC tumors are C > T transitions, consistent with UV damage (Durinck 2011, Pickering 2014, Li 2015). The total mutation burden of CSCC is approximately 30 to 60 per megabase, compared with approximately 13 per megabase in malignant melanoma, which is the tumor type with the highest mutation burden in The Cancer

Genome Atlas ([Durinck 2011](#), [Pickering 2014](#), [Li 2015](#)). Pre-clinical studies suggest that UV light may also be carcinogenic due to incompletely understood immunosuppressive effects ([Fisher 1982](#), [Moodycliffe 2000](#)), in addition to mutagenicity.

Cutaneous squamous cell carcinoma has several clinical and biological factors that suggest that it is appropriate for the clinical study of inhibition of the PD-1 immune checkpoint: high mutation burden ([Pickering 2014](#)), presence of tumor-infiltrating lymphocytes (TILs) ([Muhleisen 2009](#), [Freeman 2014](#)), association with immunosuppression as a risk factor ([Euvrard 2003](#)), evidence of direct immunosuppressive effects of UV radiation ([Yu 2014](#)), and some clinical efficacy with interferon α 2a-based treatment ([Lippman 1992](#)).

The presence of high mutation burden appears to be a shared characteristic of other solid tumors for which inhibition of the PD-1/PD-L1 axis has been associated with therapeutic efficacy, including melanoma, NSCLC, and bladder cancer ([Alexandrov 2013](#)). Among NSCLC patients treated with pembrolizumab, emerging clinical data suggest a direct correlation between mutation burden and clinical efficacy of PD-1 inhibition ([Rizvi 2015](#)). Preliminary clinical results from a phase 2 study of pembrolizumab for patients with advanced solid tumors that are hypermutated due to mismatch repair deficiency demonstrates that overall radiographic response rates are approximately 60% ([Le 2015](#)).

Taken together, these observations suggest that PD-1 inhibition may also achieve robust efficacy against CSCC. In the ongoing phase 1 study of REGN2810 for patients with advanced solid tumors (NCT02383212), evidence of biologic activity has been seen in the first cohort of REGN2810 monotherapy (1 mg/kg, administered IV every 2 weeks). A partial response (PR) was observed in a 52-year-old man with unresectable recurrent CSCC at the first tumor assessment after his first 4 doses of REGN2810, and was confirmed after 8 doses (the patient is still receiving treatment and PR has been maintained for 20+ weeks as of 18 Sep 2015). This patient has an extensive prior history of surgery, systemic therapy, and radiation therapy for recurrent disease for over 13 years. Additionally, a recent case report described a dramatic response to pembrolizumab (off-label use) in a male with recurrent unresectable CSCC ([Chang 2015](#)).

2. STUDY OBJECTIVES

2.1. Primary Objectives

The primary objective of this study is to estimate the clinical benefit of REGN2810 monotherapy for patients with metastatic (nodal or distant) CSCC (Group 1) or with unresectable locally advanced CSCC (Group 2), as measured by ORR (see [Appendix 2](#) and [Appendix 3](#)), according to central review.

2.2. Secondary Objectives

The secondary objectives for both Group 1 and Group 2 are:

- To estimate ORR (see [Appendix 2](#) and [Appendix 3](#)) according to investigator review
- To estimate the duration of response, PFS, and OS by central and investigator review

- To estimate the complete response (CR) rate by central review
- To assess the safety and tolerability of REGN2810
- To assess the pharmacokinetics (PK) of REGN2810 (at select sites only)
- To assess the immunogenicity of REGN2810
- To assess the impact of REGN2810 on quality of life using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) ([Appendix 1](#))

2.3. Exploratory Objective (Group 2 only)

To explore the pharmacodynamic effects of REGN2810 in tumor biopsies obtained at baseline, during treatment, and at progression in CSCC patients treated with REGN2810 [REDACTED]

- [REDACTED]

- [REDACTED]

- [REDACTED]

- [REDACTED]

- [REDACTED]

3. STUDY DESIGN

3.1. Study Description and Duration

This is a phase 2, non-randomized, 2-group, multicenter pivotal trial evaluating the efficacy and safety of REGN2810 in patients with advanced CSCC. After a screening period of up to 28 days, patients will receive up to twelve 56-day (8-week) treatment cycles for a total of up to 96 weeks of treatment. Each patient will receive 3 mg/kg REGN2810 IV on days 1, 15±3, 29±3, and 43±3 during each treatment cycle. Tumor assessments will be made at the end of each treatment cycle. Extensive safety evaluations will occur on day 1 of each cycle; routine safety evaluations will be conducted at each REGN2810 dosing visit.

A patient will receive treatment until the 96-week treatment period is complete, or until disease progression, unacceptable toxicity, withdrawal of consent, or confirmed CR. Patients with confirmed CR after a minimum of 48 weeks of treatment may elect to discontinue treatment and continue with all relevant study assessments (eg, efficacy assessments). After completion of the current study, patients may be eligible for enrollment into the companion protocol (R2810-ONC-1425).

Group 2 patients: Biopsies are obtained at baseline and cycle 1 day 29. Biopsies at progression are strongly encouraged. Additional biopsies may be obtained at baseline and at response assessments to clarify malignant versus benign status of indeterminate-appearing tissue, at the discretion of the investigator ([Appendix 6](#)).

3.1.1. Study Groups

There will be 2 study groups:

- Group 1: Patients with metastatic CSCC. These patients are required to have histologic confirmation of distant CSCC metastases (eg, lung, liver, bone, or lymph node). Group 1 includes patients with both nodal metastatic and distant metastatic disease.
- Group 2: Patients with unresectable locally advanced CSCC. These patients are required to have disease that is considered inoperable or to have medical contraindication to surgery or radiation, or have not achieved disease control with these treatments (see section 4.2.1).

The study populations in Group 1 and Group 2 include patients with both unresectable and metastatic CSCC, which is conceptually similar to the enrollment of patients with unresectable or metastatic melanoma in immunotherapy trials ([Larkin 2015](#)). The decision to analyze separate cohorts for patients with locally advanced (Group 2) and metastatic (Group 1) disease is based on a literature review of the reported experiences with other systemic therapies in CSCC, which demonstrates that response rates for various chemotherapy regimens generally are higher against advanced primary tumors that are locally advanced than against tumors that have metastasized to lymph nodes or distant visceral organs ([Nakamura 2013](#)). This observation of higher response rates in locally advanced versus metastatic patients is also seen in data from studies of Smoothed inhibitors against basal cell carcinoma, the most common non-melanoma skin cancer ([Sekulic 2012](#), [Migden 2015](#)).

3.2. Planned Interim Analysis

No interim analysis is planned.

4. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

4.1. Number of Patients Planned

Up to 129 adult patients (Group 1, 53 patients; Group 2, 76 patients) are expected to be enrolled at approximately 30 sites globally.

4.2. Study Population

Eligible patients with metastatic CSCC (Group 1) and unresectable locally advanced CSCC (Group 2).

4.2.1. Inclusion Criteria

A patient must meet the following criteria to be eligible for inclusion in the study:

1. Histologically confirmed diagnosis of invasive CSCC.

Notes on tumor primary site: Patients for whom the primary site of squamous cell carcinoma was the dry red lip (vermillion) are not eligible. Patients with tumors arising on the cutaneous hairbearing (non-glabrous) lip with extension onto dry red lip (vermillion) may be eligible after communication with and approval from medical monitor. Patients for whom the primary site of squamous cell carcinoma was the anogenital area (penis, scrotum, and perianal region) are not eligible. Patients for whom the primary site is nose are only eligible if the investigator is able to establish unambiguously that the primary site was skin, not nasal mucosa with outward extension to skin.

Notes on tumor histology: Patients with mixed histologies (eg, sarcomatoid, adenosquamous) generally will not be eligible. Patients with mixed histology in which the predominant histology is invasive CSCC (with only a minimal component of mixed histology) may be eligible, after communication with and approval from medical monitor.

2. At least 1 lesion that is measurable by study criteria.

If a previously radiated lesion is to be followed as a target lesion, progression must be confirmed by biopsy after radiation therapy. Previously radiated lesions may be followed as non-target lesions if there is at least 1 other measurable target lesion.

Group 1: There must be at least 1 baseline measurable lesion ≥ 10 mm in maximal diameter (1.5 cm for lymph nodes) according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria ([Appendix 2](#); [Eisenhauer 2009](#))

Group 2: There must be at least 1 measureable baseline lesion in which the longest diameter (LD) and the perpendicular diameter are both ≥ 10 mm on digital medical photography (see [Appendix 3](#)). Non-measurable disease for Group 2 is defined as either unidimensionally measurable lesions, tumors with margins that are not clearly defined, or lesions with maximum perpendicular diameters less than 10 mm. Patients without measureable disease at baseline are not eligible for the study.

Note: In the case of a Group 1 patient with metastatic disease that does not meet target lesion criteria by RECIST 1.1 criteria (eg, bone only lesions, perineural disease; [Appendix 2](#)) and with externally visible CSCC target lesions, [Appendix 3](#) may be used, in which bi-dimensional measurements are required (at baseline, perpendicular diameters must both be ≥ 10 mm), after communication with and approval from medical monitor. The patient would then be enrolled in Group 1 with the plan to follow externally visible disease as target lesion(s), and metastatic lesions that are not measurable by RECIST 1.1 criteria may be followed as non-target lesions.

3. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 (ECOG PS 1 definition: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work; [Appendix 8](#)).
Note: Patients with ECOG PS > 1 are ineligible.

4. ≥ 18 years old

5. Hepatic function:

- a. Total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN; if liver metastases $\leq 3 \times$ ULN). Patients with Gilbert's Disease and total bilirubin up to $3 \times$ ULN may be eligible after communication with and approval from the medical monitor.
 - b. Transaminases $\leq 3 \times$ ULN (or $\leq 5.0 \times$ ULN, if liver metastases)
 - c. Alkaline phosphatase (ALP) $\leq 2.5 \times$ ULN (or $\leq 5.0 \times$ ULN, if liver or bone metastases)
- Note:** For patients with hepatic metastases or hepatic malignancies, exclude patients with concomitant $3 \times$ ULN \leq aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) $\leq 5 \times$ ULN AND $1.5 \times$ ULN \leq total bilirubin $\leq 3 \times$ ULN
6. Renal function: Serum creatinine $\leq 1.5 \times$ ULN or estimated creatinine clearance (CrCl) > 50 mL/min
 7. Bone marrow function:
 - a. Hemoglobin ≥ 9.0 g/dL
 - b. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$
 - c. Platelet count $\geq 75 \times 10^9/L$
 8. Ability to provide signed informed consent
 9. Ability and willingness to comply with scheduled visits, treatment plans, laboratory tests, and other study-related procedures
 10. Anticipated life expectancy > 12 weeks
 11. **Group 2 only:** Surgery must be deemed contraindicated in the opinion of a Mohs dermatologic surgeon, a head and neck surgeon, or plastic surgeon. A copy of the surgeon's consultation note from a clinical visit within 60 days of enrollment must be submitted.

Acceptable contraindications in the surgeon's note include:

- CSCC that has recurred in the same location after 2 or more surgical procedures and curative resection is deemed unlikely
 - CSCCs with significant local invasion that precludes complete resection
 - CSCCs in anatomically challenging locations for which surgery may result in severe disfigurement or dysfunction (eg, removal of all or part of a facial structure, such as nose, ear, or eye; or requirement for limb amputation)
 - Other conditions deemed to be contraindicating for surgery must be discussed with the medical monitor before enrolling the patient.
12. **Group 2 only:** Patients must be deemed as not appropriate for radiation therapy. Specifically, patients must meet at least 1 of the following criteria:
 - a. A patient previously received radiation therapy for CSCC, such that further radiation therapy would exceed the threshold of acceptable cumulative dose, per the radiation oncologist. A copy of the radiation oncologist's consultation note, from a clinical visit within 60 days of enrollment, must be submitted.

- b. Judgment of radiation oncologist that such tumor is unlikely to respond to therapy. A copy of the radiation oncologist's consultation note, from a clinical visit within 60 days of enrollment, must be submitted.
- c. A clinic note from the investigator indicating that an individualized benefit:risk assessment was performed by a multidisciplinary team (consisting of, at minimum, a radiation oncologist AND EITHER a medical oncologist with expertise in cutaneous malignancies OR a dermatologist, OR a head and neck surgeon) within 60 days prior to enrollment in the proposed study, and the radiation therapy was deemed to be contraindicated.

Acceptable contraindications to radiation therapy in the investigator's note for patients who have not received any prior radiation include:

- CSCCs in anatomically challenging locations for which radiation therapy would be associated with unacceptable toxicity risk in the context of the patient's overall medical condition in the opinion of the multidisciplinary team (eg, a neck tumor for which radiation therapy would result in potential need for a percutaneous gastrostomy tube). A copy of the investigator's consultation note documenting the multidisciplinary assessment must be submitted.
 - Other conditions deemed to be contraindicating for radiation therapy must be discussed with the medical monitor before enrolling the patient.
13. All patients in either group must consent to provide archived or newly obtained tumor material (either formalin-fixed, paraffin-embedded [FFPE] block or 10 unstained slides) for central pathology review for confirmation of diagnosis of CSCC. This material must be received by the sponsor prior to enrollment.
 14. **Group 2 only:** Patients must consent to undergo biopsies of externally visible CSCC lesions at baseline, cycle 1 day 29 (± 3 business days), at time of tumor progression, and at other time points that may be clinically indicated in the opinion of the investigator.
 15. **Group 2 only:** An investigator note which states that the natural history of the patient's advanced CSCC would likely be life-threatening within 3 years with currently available management options outside of a clinical trial.

4.2.2. Exclusion Criteria

A patient who meets any of the following criteria will be excluded from the study:

1. Ongoing or recent (within 5 years) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest risk for immune-related adverse events (irAEs). The following are not exclusionary: vitiligo, childhood asthma that has resolved, residual hypothyroidism that required only hormone replacement, or psoriasis that does not require systemic treatment.
2. Prior treatment with an agent that blocks the PD-1/PD-L1 pathway.
3. Prior treatment with other immune modulating agents within fewer than 4 weeks prior to the first dose of REGN2810. Examples of immune modulating include therapeutic

vaccines, cytokine treatments, or agents that target cytotoxic T-lymphocyte antigen 4 (CTLA-4), 4-1BB (CD137), or OX-40.

4. Untreated brain metastasis(es) that may be considered active. (Note: patients with brain involvement of CSCC due to direct extension of invading tumor, rather than metastasis, may be allowed to enroll if they do not require greater than 10 mg prednisone daily, after discussion and approval of the medical monitor). Patients with previously treated brain metastases may participate provided that the lesion(s) is (are) stable (without evidence of progression for at least 6 weeks on imaging obtained in the screening period), and there is no evidence of new or enlarging brain metastases, and the patient does not require any immunosuppressive doses of systemic corticosteroids for management of brain metastasis(es) within 4 weeks of first dose of REGN2810.
5. Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of REGN2810.

Note: Patients who require brief course of steroids (eg, as prophylaxis for imaging studies due to hypersensitivity to contrast agents) are not excluded.

6. Active infection requiring therapy, including known infection with human immunodeficiency virus, or active infection with hepatitis B virus or hepatitis C virus.
7. History of pneumonitis within the last 5 years
8. Grade ≥ 3 hypercalcemia at time of enrollment
9. Any anticancer treatment (chemotherapy, targeted systemic therapy, radiation therapy, photodynamic therapy), investigational or standard of care, within 30 days of the initial administration of REGN2810 or planned to occur during the study period (Patients receiving bisphosphonates or denosumab are not excluded).

Notes: For patients with multiple CSCCs at baseline that are not designated by the investigator as target lesions, treatment of these non-target CSCCs with surgery may be permitted but must be discussed with the medical monitor prior to any surgical procedure.

10. History of documented allergic reactions or acute hypersensitivity reaction attributed to antibody treatments.
11. Known allergy to doxycycline or tetracycline (precaution due to presence of trace components in REGN2810).
12. Breast feeding
13. Positive serum pregnancy test (a false positive pregnancy test, if demonstrated by serial measurements and negative ultrasound, will not be exclusionary, upon communication with and approval from the medical monitor).
14. Concurrent malignancy other than CSCC and/or history of malignancy other than CSCC within 3 years of date of first planned dose of REGN2810, except for tumors with negligible risk of metastasis or death, such as adequately treated BCC of the skin, carcinoma in situ of the cervix, or ductal carcinoma in situ of the breast, or history of prostate adenocarcinoma treated with curative intent at least 3 years ago, and with undetectable prostate-specific antigen (PSA) for at least 3 years prior to enrollment.

Patients with hematologic malignancies (eg, chronic lymphocytic leukemia, CLL) are excluded.

15. Any acute or chronic psychiatric problems that, in the opinion of the investigator, make the patient ineligible for participation.
16. Continued sexual activity in men** or women of childbearing potential*** who are unwilling to practice adequate contraception during the study and until 6 months after the last dose of study drug (adequate contraceptive measures include stable use of oral contraceptives such as combined estrogen and progestogen and progestogen only hormonal contraception or other prescription pharmaceutical contraceptives for 2 or more menstrual cycles prior to screening; intrauterine device [IUD]; intrauterine hormone-releasing system (IUS); bilateral tubal ligation; vasectomy, and sexual abstinence).

**Contraception is not required for men with documented vasectomy.

***Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.
17. Patients with a history of solid organ transplant (patients with prior corneal transplant(s) may be allowed to enroll after discussion with and approval from the medical monitor).
18. Prior treatment with a BRAF inhibitor
19. Any medical co-morbidity, physical examination finding, or metabolic dysfunction, or clinical laboratory abnormality that, in the opinion of the investigator, renders the patient unsuitable for participation in a clinical trial due to high safety risks and/or potential to affect interpretation of results of the study.
20. Inability to undergo any contrast-enhanced radiologic response assessment.

Notes regarding imaging options: A patient who is unable to undergo computed tomography (CT) with iodinated contrast (eg, due to contrast allergy) would not be excluded if his/her disease can be measured by magnetic resonance imaging (MRI) with gadolinium. A patient who is unable to undergo MRI with gadolinium would not be excluded if his/her disease can be measured by CT scan with contrast.

Note regarding Group 2 patients: In selected cases, a patient in Group 2 who is unable to undergo any contrast enhanced radiographic imaging (neither CT with iodinated contrast nor MRI with gadolinium) may be eligible if the patient's disease can be comprehensively assessed with digital medical photography, after communication with and approval from medical monitor.

4.3. Premature Withdrawal from the Study or from Study Treatment

4.3.1. Reasons for Premature Withdrawal or Discontinuation of Study Treatment

A patient has the right to voluntarily discontinue study treatment or withdraw from the study at any time, for any reason, and without repercussion.

The investigator and sponsor have the right to discontinue a patient from study treatment or withdraw a patient from the study at any time.

Reasons for discontinuation of study treatment or withdrawal from the study may include, but are not limited to:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety if he or she continues in the study or continues treatment with study drug
- The investigator or sponsor determines it is in the best interest of the patient
- Patient noncompliance (eg, not complying with protocol required visits, assessments, and dosing instructions)
- Pregnancy

4.3.2. Discontinuation of Study Treatment

A patient who permanently discontinues study treatment will be followed as detailed in [section 6.2.2](#).

4.3.3. Withdrawal from Study Participation

During the treatment period and follow-up period, a patient who withdraws consent to continue participation in the study will not be followed for any reason after consent has been withdrawn.

An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

4.4. Replacement of Patients

Patients prematurely discontinued from the study who had received at least 1 treatment with REGN2810 will not be replaced.

5. STUDY TREATMENTS

5.1. Investigational Treatment

REGN2810 will be supplied as a liquid in sterile, single-use vials. [REDACTED]

Instructions on dose preparation are provided in the pharmacy manual.

REGN2810 will be administered in an outpatient setting as a 30 minute IV infusion. Each patient's dose will depend on individual body weight. The dose of REGN2810 must be adjusted each cycle for changes in body weight of $\geq 10\%$. Dose adjustments for changes in body weight of $< 10\%$ will be at the discretion of the investigator.

5.2. Pretreatments

Appropriate premedication for study treatments may be administered at the investigator's discretion as per usual clinical practice and in accordance with institutional guidelines. No premedications are to be administered for the first dose of REGN2810.

5.3. Dose Modification and Study Drug Discontinuation Rules

5.3.1. Dose Modification

The planned dose and schedule is 3 mg/kg REGN2810 IV over 30 minutes every 14 days. Patients will generally remain on the assigned dosage of REGN2810 throughout the course of study treatment. Dose reduction of REGN2810 may be allowed, based on the guidelines below, and only after discussion and agreement between the investigator and sponsor.

5.3.2. Study Treatment Hold or Discontinuation

Adverse events (AEs) are to be reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. Patients who experience grade ≥ 3 treatment-related toxicity (excluding laboratory abnormalities that are considered clinically insignificant) that is not otherwise specified in the protocol will be required to temporarily discontinue treatment with REGN2810. Such patients may be considered for resumption of treatment once the toxicity resolves to grade 1 or baseline, or when the toxicity is stable and manageable through supportive/medical therapy (eg, grade 3 hypertension that can be controlled with addition of a second anti-hypertensive agent).

Upon occurrence of a study treatment-related event at any time on the study, resumption of treatment after resolution or stabilization of the condition is allowed at the discretion of the investigator and sponsor if resuming treatment is thought to be in the best interest of the patient, with the exception of the following categories:

- Patients with events that require REGN2810 to be discontinued for more than 84 days from last scheduled dose.
- Patients with grade ≥ 2 uveitis. Patients with grade 2 uveitis will generally be discontinued from study treatment, unless there is resolution to grade ≤ 1 as outlined in [Appendix 5](#) AND discussion with and approval by the medical monitor. All patients with grade ≥ 3 uveitis will be permanently discontinued from study treatment.

After other AEs, resumption of treatment may be at the initial dose level, or at 1 dose level reduced based upon the discretion of the investigator and the sponsor (Table 1).

Table 1: Dose Reductions

Dose Level	Reduction Order	Dose
Dose Level -1	First dose reduction	1 mg/kg REGN2810 every 14 days
Dose Level -2	Second dose reduction	0.3 mg/kg REGN2810 every 14 days

A patient who requires dose reduction below dose level -2 will be removed from the study.

Guidelines for study treatment temporary discontinuations, including delays and interruptions, and permanent discontinuations for toxicity are outlined in Table 2.

Table 2: Study Treatment Dose Modifications or Discontinuations

Toxicity	Grade	Hold Treatment?	Restarting Criteria	Restarting Dose/Schedule	Discontinuation Criteria
Hematological Toxicity	1, 2, 3	No	N/A	N/A	N/A
	4	Yes	Toxicity resolves to Grade ≤ 1 or baseline	May decrease REGN2810 dosage to the next lower dosing level (see Table 1)	Toxicity does not resolve within 84 days of last infusion <i>Permanent discontinuation should be considered for any severe or life-threatening event</i>
Nonhematological Toxicity Note: Exceptions to be treated as for Grade 1 toxicity: <ul style="list-style-type: none">• Grade 2 alopecia• Grade 2 fatigue• Clinically insignificant lab abnormality not meeting AE criteria	1	No	N/A	N/A	N/A
	2	Consider withholding for persistent symptoms	Toxicity resolves to Grade 0–1 or baseline	<i>Clinical AE resolves within 4 weeks:</i> Same dose and schedule <i>Clinical AE does not resolve within 4 weeks:</i> May decrease REGN2810 dosage to the next lower dosing level (see Table 1)	Toxicity does not resolve within 84 days of last infusion
	3	Yes	Toxicity resolves to Grade 0–1 or baseline	May decrease REGN2810 dosage to the next lower dosing level (see Table 1)	Toxicity does not resolve within 84 days of last infusion
	4	Yes	N/A	N/A	Patient must be discontinued

For additional information regarding AEs with a potential for irAEs, reference [Table 3](#) and [Appendix 5](#).

5.3.2.1. Immune-Related Adverse Events

Case report forms (CRFs) for this study are designed to capture AEs that may be suggestive of potential irAEs. Attribution of AEs in the CRFs will require not only the investigator's assessment regarding whether the AE was related to REGN2810, but also whether the AE was an irAE. Please see the CRF completion guidelines for information about attribution of irAEs.

Investigators must be extremely vigilant and be ready to intervene early in the management of irAEs, as the onset of symptoms of irAEs (eg, pneumonitis) may be subtle. Detailed guidance of management of irAEs is provided in [Appendix 5](#). In the event of irAEs that are not addressed in [Appendix 5](#), general guidance is provided in [Table 3](#). The recommendations in [Table 3](#) and [Appendix 5](#) should be seen as guidelines, and the treating physician should exercise clinical judgment based on the symptoms and condition of the individual patient.

Table 3: General Treatment Hold Guidelines for Immune-Related Adverse Events

Severity	Withhold/Discontinue Treatment?	Supportive Care
Grade 1	No action	Provide symptomatic treatment
Grade 2	May withhold treatment	Consider systemic corticosteroids in addition to appropriate symptomatic treatment
Grade 3 Grade 4	Withhold treatment Discontinue if unable to reduce corticosteroid dose to <10 mg per day prednisone equivalent within 12 weeks of toxicity	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks.

Note: These recommendations should be seen as guidelines, and the treating physician should exercise clinical judgment based on the symptoms and condition of the individual patient.

Note regarding irAEs: For any AE that is of a type known to be potentially immune-related (eg, rash, colitis, elevated transaminases, endocrine), but is deemed not to be an irAE by the investigator, the sponsor may request additional information.

5.3.2.2. Permanent Discontinuation of Study Treatment

In the event of an infusion reaction of grade ≥ 3 severity during or directly following REGN2810 infusion, dosing should be stopped and the patient must permanently discontinue REGN2810 treatment.

Study treatment will be permanently stopped in the event of evidence of pregnancy.

In addition, study treatment for any patient may be discontinued for other safety reasons or compliance issues at the discretion of the investigator or sponsor. A patient may choose to discontinue study treatment or study participation at any time for any reason.

A patient who permanently discontinues REGN2810 treatment should continue follow-up in the study without additional treatment until progression of disease, completion of all study assessments, or closure of the study ([section 4.3](#)).

5.4. Management of Infusion/Allergic/Hypersensitivity Reactions

Acute infusion reactions are defined as any AE that occurs during the infusion or within 2 hours after the infusion is completed. Emergency equipment and medication for the treatment of these potential adverse effects (eg, antihistamines, bronchodilators, IV saline, corticosteroids, acetaminophen, and/or epinephrine) must be available for immediate use. Infusion reactions must be reported as AEs ([section 7.2.1](#)) and graded according to the NCI-CTCAE version 4.03 grading scale ([section 7.3.1](#)).

In the event of an infusion reaction of Grade 3 or greater severity during or directly following REGN2810 infusion, dosing should be stopped and the patient must be permanently discontinued from REGN2810 treatment.

5.4.1. Interruption of the Infusion

The infusion should be interrupted if any of the following AEs are observed:

- cough
- rigors/chills
- rash, pruritus (itching)
- urticaria (hives, welts, wheals)
- diaphoresis (sweating)
- hypotension
- dyspnea (shortness of breath)
- vomiting
- flushing

The reaction(s) should be treated symptomatically, and the infusion may be restarted at 50% of the original rate.

If investigators feel there is a medical need for treatment or discontinuation of the infusion other than described above, they should use clinical judgment to provide the appropriate response according to typical clinical practice.

5.4.2. Termination of the Infusion

The infusion should be terminated and NOT restarted if any of the following AEs occur:

- anaphylaxis
- laryngeal/pharyngeal edema
- severe bronchospasm
- chest pain
- seizure
- severe hypotension

5.5. Method of Treatment Assignment

Each patient who signs the informed consent form (ICF) will be assigned a patient number and tracked centrally as described in the Interactive Web Response System (IWRS) manual.

Eligible patients will be enrolled sequentially as confirmed and tracked by the sponsor, until each group is filled per protocol criteria. Details on treatment assignment can be found in the IWRS manual.

5.5.1. Blinding

This is an open-label study; no blinding will be employed.

5.6. Treatment Logistics and Accountability

5.6.1. Packaging, Labeling, and Storage

Open-label REGN2810 will be supplied as a liquid in sterile, single-use vials that will display the product lot number on the label. [REDACTED]

[REDACTED]. Further storage instructions will be provided in the pharmacy manual.

A pharmacist or other qualified individual will be identified at each site to prepare REGN2810 for administration. [REDACTED]

[REDACTED] Detailed preparation and administration instructions will be provided to the sites in the pharmacy manual.

5.6.2. Supply and Disposition of Treatments

Study drug will be shipped [REDACTED] to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed -or- returned to the sponsor or designee.

5.6.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication dispensed to each patient, returned from each patient (if applicable), and disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

5.6.4. Treatment Compliance

REGN2810 will be administered at the study site and recorded on the electronic case report form (eCRF). All dosing records for each patient will be kept by the site. All drug compliance records must be kept current and must be made available for inspection by the sponsor and regulatory agency inspectors.

5.7. Concomitant Medications and Procedures

5.7.1. Concomitant Medications

Any treatment administered from the time of informed consent until 30 days after the last study treatment will be considered concomitant treatment. This includes medications and other therapies for which administration started before the study and will continue during the study, as well as any therapies started in the 5 month follow-up period to treat a study-drug-related AE. All concomitant treatments must be recorded in the study CRF with the generic name, dose, dose unit, frequency, indication, and start/stop date, as appropriate.

5.7.2. Prohibited Medications and Concomitant Treatments

While participating in this study, a patient may not receive any standard or investigational agent for treatment of a tumor other than REGN2810 as monotherapy. **After communication with the sponsor, focal palliative treatment (eg, radiation) would be allowed for local control of a tumor once a patient has completed 24 weeks of study treatment.** Any other medication which is considered necessary for the patient's welfare, and which is not expected to interfere with the evaluation of the study drug, may be given at the discretion of the investigator.

Patients using immunosuppressive doses (>10 mg per day of prednisone or equivalent) of systemic corticosteroids other than for corticosteroid replacement will not be eligible for the study. It is recommended that patients do not receive systemic corticosteroids such as hydrocortisone, prednisone, prednisolone (Solu-Medrol®) or dexamethasone (Decadron®) at any time throughout the study except in the case of a life-threatening emergency and/or to treat an irAE. Physiologic replacement doses of systemic corticosteroids are permitted, even if >10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

Note: Bisphosphonates and denosumab are not prohibited.

5.7.3. Surgery

For patients with locally advanced target lesions that are considered unresectable at baseline, but are subsequently deemed resectable during the course of the study due to tumor response to REGN2810, curative intent surgery may be allowed but must be discussed with the medical monitor prior to any surgical procedure. (This statement does not apply to patients in emergency life-threatening situations that require immediate surgery). Patients with inoperable CSCC at baseline who are rendered operable with clear margins will be deemed to have experienced PR.

If during the course of the study a patient develops new cutaneous lesions that are suspected to be a non-melanoma skin cancer other than CSCC (eg, BCC), removal of the lesion and continued treatment on study may be allowed after discussion with the medical monitor.

5.7.4. Radiation Therapy

Radiation therapy is not part of the study regimen. Patients for whom radiation therapy is planned are not eligible. If during the course of the study, a patient develops a symptomatic lesion for which palliative radiation therapy is deemed appropriate by the investigator, this will be deemed PD and generally the patient would be removed from study. Palliative radiation therapy may be allowed in certain circumstances in patients who have been on study for at least 24 weeks (see section 5.7.2). Such cases must be discussed with the medical monitor prior to any radiation therapy if the investigator feels that restarting REGN2810 after radiation is in the best interest of the patient. The patient will be deemed to have experienced disease progression if radiation therapy is instituted, but will be followed for OS.

6. STUDY SCHEDULE AND VISIT DESCRIPTIONS

6.1. Study Schedule

Study assessments and procedures are presented by study period and visit in [Table 4](#) and [Table 5](#).

Study visits can be scheduled so as not to fall on weekends or holidays, after discussion and approval by the Sponsor.

Table 4: Study Schedule (Screening and Treatment)

Study Procedure	Screening	Cycle 1					Cycles 2 - 12 ^a					End of Study
Visit Days	-28 to -1	1	15±3	29±3	43±3	56±3	1 ^b	15±3	29±3	43±3	56±3	30 days after last dose of REGN2810 ⁱ
Clinical Assessments and Study Treatment												
Informed Consent ^c	X											
Genomics Substudy Informed Consent (optional)	X											
Medical/Oncology History	X											
Complete Physical Examination and ECOG PS ^d	X	X					X					X
Physical Examination, Limited ^e		-	X	X	X			X	X	X		
12-Lead ECG ^f	X	X					X					X
Vital Signs and Weight ^g	X	X	X	X	X		X	X	X	X		X
Height	X											
Brain MRI ^h	X											
3 mg/kg REGN2810 IV		X	X	X	X		X	X	X	X		
Laboratory Tests												
Hematology ^j and Blood Chemistry ^j	X	X	X	X	X		X	X	X	X		X
Serum HCG ≤72 Hour Predose ^k	X											
Urine Pregnancy Test							X					X
Urinalysis ^l	X	X					X					X
Serum IgG, IgM, IgE		X					X					X
aPTT; INR		X					X					
Immune Safety and PK Blood Samples												
RF and ANA		X					X					X
TSH and CRP		X					X					X
ADA ^m		X					X					X
REGN2810 PK/Drug Conc. Sample ⁿ		X	X	X	X		X					X

Study Procedure	Screening	Cycle 1					Cycles 2 - 12 ^a					End of Study
Visit Days	−28 to −1	1	15±3	29±3	43±3	56±3	1 ^b	15±3	29±3	43±3	56±3	30 days after last dose of REGN2810
Pathology and Research Samples												
Archived tissue for histological confirmation of CSCC ^c	X											
Optional blood DNA for genomics substudy		X										
Tumor biopsies for Group 2 ^p	X			X	As needed to clarify response status							
Response Imaging and other assessments												
CT/MRI and/or digital photography ^q	X					X					X	X
EORTC QLQ-C30		X					X					X
Concomitant medications ^r		X					X					X
Adverse Events ^s	← continuous monitoring→											

ADA=anti-drug antibody; AE=adverse event; ANA=antinuclear antibody; aPTT=activated partial thromboplastin time; CRP=C-reactive protein; CT=computed tomography; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOS=end of study; HCG=human chorionic gonadotropin; INR=International Normalized Ratio; MRI=magnetic resonance imaging; PMBC=peripheral blood mononuclear cells; RF= rheumatoid factor; TSH=thyroid-stimulating hormone

a The maximum number of treatment cycles is 12 (planned 96 weeks total). See [section 6.2](#) regarding treatment discontinuation.

b Should occur at least 53 days from day 1 of previous cycle, and no sooner than 11 days after the previous dose.

c Informed consent may be obtained more than 28 days before the start of screening procedures. Assessments performed as part of standard of care that fall within the screening window but before informed consent is obtained may be used for screening, and need not be repeated for enrollment eligibility.

d Complete physical examination includes head and neck, lungs, heart, abdomen, lymph nodes, extremities, and skin. A brief neurologic examination should also be performed. The exam may be performed ≤72 hours prior to dosing on the day 1 visit of each cycle. Complete physical exam must be accompanied by assessment and documentation of ECOG Performance Status ([Appendix 8](#)).

e Limited physical exam includes lungs, heart, abdomen, and skin.

f A 12-lead electrocardiogram should be recorded at screening, and 30 minutes after end of infusion at day 1 visits during cycle 1 and cycle 3.

g Vital signs include temperature, resting blood pressure, pulse, and respiration. Vital signs will be assessed and documented prior to the REGN2810 infusion, and then approximately 15 minutes after the completion of the REGN2810 infusion.

h brain MRI with gadolinium is required at screening if not performed in the prior 60 days. Brain scans during the treatment and follow-up periods are required if there is a prior history of lesions present at screening or as clinically indicated. A brain CT with iodinated contrast may be performed if an MRI with gadolinium is contraindicated.

i Hematology includes: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, and platelet count. Samples may be collected ≤72 hours prior to dosing on the day 1 visit of each cycle.

J Chemistry includes: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), ALT, AST, total bilirubin, alkaline phosphatase (ALP), uric acid, and LDH. Samples may be collected ≤72 hours prior to dosing on the day 1 visit of each cycle.

- k Predose β -HCG (serum) at screening up to 72 hours prior to first administration. Subsequent pregnancy tests may be urine β -HCG. Serum pregnancy test and urine pregnancy test are requirements for women of child bearing potential only.
- l Urinalysis: glucose, blood, pH, specific gravity, ketones, and spot urine protein. Samples may be collected ≤ 72 hours prior to dosing on the day 1 visit of each cycle.
- m ADA samples are collected prior to treatment on day 1 of cycles 1, 3, 5, 7, 9, 11, and at the EOS visit.
- n Blood samples for PK will be collected (at select sites) at pre-infusion and end of infusion on days 1, 15, 29, and 43 of cycle 1, on day 1 of cycles 2 through 6, 7, 9, and 11, at 30 days after last dose of study drug, and at follow-up visit 4. See [Appendix 4](#) for details on PK collection schedule.
- o See [section 6.3.1](#) regarding requirements for documentation of histologic confirmation of diagnosis of CSCC.
- P For Group 2 patients only: Tumor biopsies are required at baseline and on cycle 1 day 29 (± 3 business days). Tumor biopsies should be performed at any response assessment in which there is indeterminate-appearing skin regarding malignant versus benign status. Tumor biopsies should also be collected for histologic confirmation of complete response in any patient for whom the clinical impression is complete response, as well as at progression. Biopsies must be annotated and photographed. Guidelines for tumor biopsies are provided in [Appendix 6](#).
- q The same method (CT with iodinated contrast or MRI with gadolinium) and/or digital medical photography used at baseline should be used throughout the study. For patients with locally advanced CSCC, guidelines for digital photography are provided in [Appendix 7](#). Imaging requirements differ for patients in Group 1 and Group 2; see [sections 6.3.1](#) and [6.3.2](#) for further details.
- r Concomitant medication recording will be done at the start of each cycle, at a minimum. Concomitant medications should be recorded from the date of signing the ICF through follow-up visit 1 (post-treatment; [Table 5](#)).
- S Adverse event recording will be ongoing throughout the course of the study, using NCI-CTCAE v4. See [section 7.2](#).
- t (1) The EOS visit is for patients who experience PD or toxicity requiring study discontinuation in cycles 1 through 12. This visit should occur 30 days (allowed window: 21 to 42 days) after the last dose of REGN2810. The only post-treatment assessment that can occur outside of this timeframe is the post-treatment biopsy (required in Group 2) that can be obtained at any time within 28 days of last dose of REGN2810. (2) Patients who complete the required events in [Table 4](#) (excluding the EOS visit) with any status other than PD (eg, CR, PR, or SD) will go on to complete the assessments in [Table 5](#). These patients do not need to complete the EOS visit at end of cycle 12 as they will be assessed per [Table 5](#). Patients not enrolled into the roll-over protocol (REGN2810-ONC-1425) will be followed quarterly for survival and tumor treatment status, if available.

Table 5: Study Schedule (Follow-Up after Cycle 12)

Study Procedure Visit	Follow-up 1	Follow-up 2	Follow-up 3	Follow-up 4	Follow-up 5	Follow-up 6	Follow-up 7 ^k
Time point (Day)	Cycle 12 visit + 28 ± 7 days	Follow-up 1 + 28 ± 7 days	Follow-up 2 + 28 ± 7 days	Follow-up 3 + 28 ± 7 days	Follow-up 4 + 28 ± 7 days	Follow-up 5 + 28 ± 7 days	Follow-up 6 + 28 ± 7 days
Physical examination (complete) ^a	X	X	X	X	X	X	X
ECOG Status	X	X	X	X	X	X	X
Vital Signs ^b	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X
Laboratory Tests							
Hematology ^{c, g}	X						
Blood Chemistry ^{c, d, g}	X						
Urine Pregnancy Test ^{c, g}	X						
Urinalysis ^{l, g}	X						
Serum IgG, IgM, IgE ^g	X						
Immune Safety Assays							
RF ^g	X						
ANA ^g	X						
TSH ^g	X						
CRP ^g	X						
PK Drug Conc/ADA Sample							
REGN2810 PK/Drug Conc. Sample	X			X			
ADA sample	X						
Pathology Samples							
Tumor biopsy ^e	←===== At Time of Progression =====→						
Tumor Assessments							
CT/MRI (chest/abdomen/pelvis) And/or digital photography ^h		X		X			X
Other Clinical Assessments							
Concomitant medications ⁱ	X						
Adverse events ^j	←=====						→

ADA=anti-drug antibody; AE=adverse event; ANA=antinuclear antibody; CRP=C-reactive protein; CT=computed tomography; ECOG=Eastern Cooperative Oncology Group; MRI=magnetic resonance imaging; PMBC=peripheral blood mononuclear cells; RF= rheumatoid factor; TSH=thyroid-stimulating hormone.

- a Complete physical examination includes head and neck, lungs, heart, abdomen, lymph nodes, extremities, and skin. A brief neurologic examination should also be performed. Complete physical exam must be accompanied by assessment and documentation of ECOG Performance Status ([Appendix 8](#)).
- b Vital signs include temperature, resting blood pressure, pulse, and respiration.
- c Hematology includes: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, and platelet count.
- d Chemistry includes: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), ALT, AST, total bilirubin, alkaline phosphatase (ALP), uric acid, and LDH

- e Pregnancy tests may be urine β -HCG.
- f Urinalysis: glucose, blood, pH, specific gravity, ketones, and spot urine protein.
- g At time of progression, the EOS tumor biopsy should be obtained for all patients in Group 2 (see [section 6.2.2](#) and [Appendix 6](#)). Blood samples for laboratory tests (hematology, blood chemistry, urine pregnancy test, urinalysis, serum Ig) and immune safety (RF, ANA, TSH, CRP) are also obtained at time of progression (within 28 days of the imaging study that documented progression) according to the EOS assessment schedule in [Table 4](#). ADA is not required at the EOS visit if it was collected at follow-up visit 1. PK is not required at the EOS visit if it was collected at follow-up visit 1 and follow-up visit 4.
- h The same method (CT/MRI) and/or digital medical photography used at baseline should be used throughout the study. Scans linked to follow-up visits are required only if PD has not been confirmed previously while on study. CT/MRI imaging will be obtained within 14 days prior to the follow-up visit (per [Table 5](#)), so that the disease status is known at the time of the visit. Digital medical photography may be obtained within 14 days prior to visit, or on the day of the visit, and response status (CR, PR, SD, PR) will guide whether the visit is to be treated as a follow-up visit or as the EOS visit.
- i Concomitant medications should be recorded from the date of informed consent through 30 days after last dose of study drug. Any drug started to treat a study drug-related AE during the 5 month follow-up will also be recorded. In addition, any cancer treatments should be recorded from the day of informed consent until 30 days after the administration of the last dose of REGN2810. Any AE assessed as related to study treatment and persisting after 30 days post-last dose should be reported until resolution to baseline or grade ≤ 1 .
- j Nonserious AE and SAE data will be collected from the day of informed consent until 30 days after the last dose of REGN2810. Any AE assessed as related to study treatment and persisting after 30 days post-last dose should be reported until resolution to baseline or grade ≤ 1 .
- k Patients not transitioning into the roll-over protocol (REGN2810-ONC-1425) will be followed quarterly for survival and tumor treatment status, if available. See [section 6.2.2](#).

6.2. Study Follow-Up and Treatment Discontinuation

6.2.1. Unscheduled Visits

All attempts should be made to keep patients on the study schedule as specified in [Table 4](#) and [Table 5](#). Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted.

6.2.2. Follow-up

Patients who discontinue study treatment due to PD should return to the clinic 30 days (range: 28 to 42 days) after the last study treatment to complete the EOS assessments indicated in [Table 4](#). After the EOS visit, patients should be followed for survival status until death, loss to follow-up, or study termination by the sponsor.

For all patients in Group 2, tumor biopsies ([Appendix 6](#)) should be obtained at time of progression, whether progression occurs in cycles 1 through 12 or during follow-up (after cycle 12).

Patients who discontinue study treatment due to reasons other than PD (eg, toxicity, confirmed CR after 48 weeks) should continue follow-up to complete all assessments in [Table 4](#) and [Table 5](#) until PD or completion of follow-up visit 7. If patients experience PD during the follow-up period detailed in [Table 5](#), they should complete the EOS visit. After follow-up visit 7 (or sooner if the patient experiences PD during the follow up period), patients should be followed for survival status until death, loss to follow-up, or study termination by the sponsor.

Follow up status may be determined at clinic visits or via telephone contact with the patient, a family member of the patient, or the physician.

After patients complete the EOS visit (or follow-up visit 7 for patients who do not experience PD), they should be followed for survival (and possible re-treatment) in the roll-over protocol (R2810-ONC-1425).

6.3. Study Procedures

6.3.1. Procedures Required Only at the Screening/Baseline Visit

The following procedures will be performed at screening for the purpose of determining study eligibility or characterizing the baseline population:

- Serum β -HCG (result must be ≤ 72 hours before first dose).
- Documentation of pathologic confirmation of CSCC by a pathologist at the study site (see [section 4.2.1](#), Inclusion 1). The pathology report that documents the diagnosis of CSCC should be from the most recent biopsy that documented CSCC. Pathology material (FFPE block or 10 unstained slides from the sample in the submitted pathology report) must be provided to the sponsor prior to enrollment.
- **Group 2 only:** Baseline/screening research biopsy is required (see [Appendix 6](#) for guidelines). This baseline biopsy is intended for exploratory assessments, but will only be used for this purpose after central pathology confirmation of diagnosis of

CSCC is obtained on archived material. If the archived material is not sufficient for confirmation of diagnosis of CSCC by central review, baseline biopsy material will be used for central pathologic confirmation; remaining baseline tumor material can only be used for exploratory assessments after central pathology confirmation of diagnosis of CSCC has been established.

- **Brain MRI:** Brain MRI is required at screening if not performed in the prior 60 days. Brain scans during the treatment and follow-up periods are required if there is a prior history of lesions present at screening or as clinically indicated. A brain CT may be performed if an MRI is contraindicated.
- **Group 1** – Baseline imaging should include all known target lesions. Baseline scans must evaluate extent of disease, including imaging of chest, abdomen, and pelvis. This may be accomplished with CT chest, abdomen, and pelvis with contrast, or CT chest with contrast and MRI abdomen/pelvis with gadolinium. The imaging modality for metastatic lesions may be either CT with iodinated contrast or MRI with gadolinium, per investigator discretion. Magnetic resonance imaging with gadolinium is generally preferred for bone lesions, perineural lesions, abdomen, pelvis, extremity, and head and neck. Computed tomography with contrast is generally preferred for chest. For Group 1 patients who also have externally visible lesions, digital medical photography will be used, and these lesions generally will be followed as non-target lesions. **Note:** In the case of a Group 1 patient with metastatic disease that is not measurable by RECIST criteria (eg, bone only lesions, perineural disease) and with externally visible CSCC target lesions, digital medical photography may be used to follow the externally visible lesions as target lesions.
- **Group 2** – Externally visible lesions will be followed by digital medical photography. Baseline assessments will include radiologic imaging of all target lesions (preferably MRI with gadolinium for all anatomic sites except lung, but CT with iodinated contrast allowed at any anatomic site, per investigator discretion) to assess for deep invasion. Baseline radiologic assessment will also include CT chest, preferably with contrast (If CT chest identifies a metastatic lesion, the patient should be assigned to Group 1).

6.3.2. Efficacy Procedures

For patients with disease that can be measured radiologically according to RECIST 1.1 criteria ([Appendix 2](#); [Eisenhauer 2009](#)), a CT or MRI for tumor assessment will be performed as detailed in [Table 4](#) and [Table 5](#). The choice of whether the imaging is by CT or MRI is an investigator decision, but preferred imaging choices are provided in [section 6.3.1](#). Once the choice of CT scan or MRI has been made, subsequent assessments should be made using the same modality whenever possible. For patients whose CSCC lesions are evaluable on the skin, composite response criteria ([Appendix 3](#)) should be used on the same schedule (every 8 weeks), in combination with radiologic imaging if appropriate.

- **Group 1:** Whole-body imaging – as performed at the baseline assessment – is strongly recommended at each response assessment. At a minimum, all radiologically measureable target lesions (RECIST 1.1) should be imaged at each response assessment. The same radiologic imaging modality should be used at each response assessment.

Additionally, radiologic imaging of anatomic area of externally visible target lesions should be performed at each response assessment (MRI with gadolinium is preferred for all anatomic sites except lung). Externally visible CSCC lesions noted at baseline should be photographed at each response assessment ([Appendix 7](#)), and will generally be deemed non-target. New externally visible lesions that are clinically suspicious for malignancy should be photographed ([Appendix 7](#)) and biopsied. **Note:** In the case of a Group 1 patient with metastatic disease that is not measurable by RECIST criteria (eg, bone only lesions, perineural disease) and with externally visible CSCC target lesions, digital medical photography may be used to follow the externally visible lesions as target lesions.

- **Group 2:** All externally visible CSCC lesions should be photographed in a consistent manner at each response assessment as described in [Appendix 7](#). Radiologic imaging (MRI with gadolinium preferred) of anatomic area of externally visible target lesions should be performed at each response assessment. In cases in which it is the opinion of the investigator that no significant added information was provided by baseline radiologic imaging of the lesion (beyond the information that was provided by baseline digital medical photography), it is allowed to use digital medical photography only (without radiologic imaging) at subsequent response assessments of that lesion, at the discretion of the investigator.

To account for the possibility of unconventional immune responses, immune-related response criteria (irRC) ([Nishino 2013](#)) can inform the decision regarding whether to continue treatment for an individual patient if the investigator believes it is in the best clinical interest of the patient, **after discussion and approval from the medical monitor**. Reasons for any such decision to treat beyond the protocol definitions of progression **must be documented in the CRFs**. However, irRC are currently deemed a surrogate endpoint ([Postow 2015](#)), and irRC data are not included in the primary endpoint of this study. Any patient who experiences best response (PR or CR) after initial progression (per [Appendix 2](#) or [Appendix 3](#), as appropriate) in the context of continued treatment (according to principles of irRC in after sponsor approval) will not have that best response (partial or complete) counted towards the primary endpoint of this study.

In Group 1, patients will generally be followed by RECIST 1.1 criteria ([Appendix 2](#)). It is possible that some patients in Group 1 may also have externally visible lesions that are measurable by digital medical photography. Generally, it will be clinically appropriate to follow these externally visible lesions as non-targets. However, for Group 1 patients with externally visible lesions that are deemed clinically significant by the investigator, the clinical and composite response criteria in [Appendix 3](#) may be used in selected cases. However, it is anticipated that most patients in Group 1 will be followed by RECIST 1.1 only.

For Group 2, response assessment is according to the clinical and composite response criteria in [Appendix 3](#).

For externally visible lesions that are indeterminate-appearing regarding presence of CSCC, see [Appendix 6](#) for guidelines on tumor biopsies.

All radiology, photography and biopsy results will be independently reviewed. A blinded central review committee will be formed to determine overall response for each patient based on the integration of these modalities.

6.3.3. Safety Procedures

6.3.3.1. Vital Signs

Vital signs, including temperature, resting blood pressure, pulse, and respiration, will be collected at time points according to [Table 4](#) and [Table 5](#).

Note: blood pressure should be measured after the patient has been resting quietly for at least 5 minutes.

At cycle 1 day 1 and on all subsequent treatment days, vital signs will be collected prior to infusion, and approximately 15 minutes after the completion of the infusion.

6.3.3.2. Physical Examination

A thorough complete or limited physical examination will be performed at visits specified in [Table 4](#) and [Table 5](#). Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

Complete physical examination will include examination of head and neck, lungs, heart, abdomen, lymph nodes, extremities, and skin. A brief neurologic examination also should be performed. Complete physical exam must be accompanied by assessment and documentation of ECOG Performance Status ([Appendix 8](#)).

Limited physical examination will include lungs, heart, abdomen, and skin.

6.3.3.3. Electrocardiogram

A standard 12-lead ECG will be performed at time points according to [Table 4](#) and [Table 5](#).

The patient should be relaxed and in a recumbent or semi-recumbent position at least 5 minutes before recording an ECG. The ECG is to be recorded in triplicate. The ECG strips or reports will be retained with the source. The ECG will be reviewed by the investigator (paper or electronic tracing) and will be available for comparison with subsequent ECGs by the investigator. The following will be recorded on the CRF:

- PR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- Heart Rate (BPM; recorded from the ventricular rate).

Any ECG finding that is judged by the investigator as a clinically significant change (worsening) compared to the baseline value will be considered an AE, recorded, and monitored.

6.3.3.4. Immune Safety Assays

Immune safety assays consist of rheumatoid factor (RF), thyroid-stimulating hormone (TSH), C-reactive protein (CRP), and antinuclear antibody (ANA) titer and pattern.

If, during the course of the study, a 4-fold or greater increase from baseline in RF or ANA or abnormal levels of TSH or CRP are observed, the following tests may also be performed: anti-DNA antibody, anti-Sjögren's syndrome A antigen (SSA) antibody (Ro), anti-Sjögren's

syndrome B antigen (SSB) antibody (La), antithyroglobulin antibody, anti-LKM antibody, antiphospholipid antibody, anti-islet cell antibody, antineutrophil cytoplasm antibody, C3, C4, CH50.

6.3.3.5. Immunoglobulin Levels

Serum IgG, IgM, and IgE will be measured at timepoints according to [Table 4](#) and [Table 5](#).

6.3.3.6. Coagulation Tests

Activated partial thromboplastin time (aPTT) and International Normalized Ratio (INR) will be analyzed by the site's local laboratory.

6.3.3.7. Laboratory Testing

Hematology, chemistry, urinalysis, and pregnancy testing samples will be analyzed by the site's local laboratory.

Detailed instructions for blood sample collection are in the laboratory manual provided to study sites.

Samples for laboratory testing will be collected at time points according to [Table 4](#) and [Table 5](#). Tests will include:

Blood Chemistry

Sodium	Phosphorus	ALT
Potassium	Glucose	AST
Chloride	Albumin	Total bilirubin
Bicarbonate	Creatinine	Alkaline phosphatase (ALP)
Calcium	Blood urea nitrogen (BUN)	Lactate dehydrogenase (LDH)
Magnesium	Uric acid	

Hematology

Hemoglobin	Differential:
WBCs	Neutrophils
Platelet count	Lymphocytes
	Monocytes

Urinalysis

Glucose	pH	Ketones
Blood	Specific gravity	Spot urine protein

Abnormal Laboratory Values and Laboratory Adverse Events

- All laboratory values must be reviewed by the investigator or authorized designee.
- Significantly abnormal tests must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions

unrelated to the study medication or its administration, the medical monitor must be consulted.

- The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in [section 7.2.5](#).

6.3.4. Pharmacokinetic and Antibody Procedures

6.3.4.1. Drug Concentration Measurements and Samples

REGN2810 PK parameters will be determined by measuring REGN2810 concentrations in serum samples using a validated assay at visits and time points indicated in [Table 4](#) and [Table 5](#), and listed in [Appendix 4](#). Actual time of each blood draw must be recorded. “Predose” is defined as before the start of the first REGN2810 infusion. Predose samples may be collected ≤ 72 hours prior to day 1 dosing. Subsequent PK sampling times will be based on the REGN2810 dosing time that precedes the PK sampling. Pre-infusion is defined as before the start of the REGN2810 infusion and “0 hour” is defined as immediately after the end of the REGN2810 infusion.

Any unused samples collected for drug concentration measurements may be used for exploratory biomarker research or to investigate unexpected AEs.

6.3.4.2. Anti-drug Antibody Measurements and Samples

Samples for ADA assessment will be collected prior to dosing at time points listed in [Table 4](#) and [Table 5](#).

Any unused samples collected for ADA assessment may be used for exploratory biomarker research or to investigate unexpected AEs.

6.3.5. Biomarker Measurements and Samples

Speculated pharmacodynamic, [REDACTED] biomarkers related to REGN2810 treatment exposure, clinical activity, or underlying disease will be investigated in tumor biopsy tissue collected at baseline, after treatment with REGN2810, and at progression, if available.

[REDACTED] Biomarker results will be reported separately from the clinical study report.

6.3.5.1. Tumor Biomarker Procedures

For patients with locally advanced CSCC (Group 2), tumor biopsies will be collected per the timepoints and methodology in [Appendix 6](#).

Expression levels (mRNA and/or protein) of PD-L1, GITR, and LAG-3, as well as the number and distribution of TILs (defined by lineage markers CD4, CD8, CD25, FoxP3) will be assessed in tumor biopsy samples. Additional biomarkers may be measured tissue permitting. [REDACTED]

Tumor tissue, as well as RNA and DNA isolated from tumor tissue, will be used to assess changes in potential pharmacodynamic biomarkers induced by REGN2810 treatment from baseline.

Main exploratory potential biomarkers of interest include, but are not limited to:

- Tumor RNA expression
- Number and distribution of TILs (CD8+ T cells, CD4+ T cells, T regulatory cells, and tissue permitting, other subtypes such as B cells, myeloid-derived cells, NK cells, etc.)
- Expression levels (mRNA and/or protein) of PD-L1, GITR, and LAG-3, and possibly other check-point modulators
- Mutations in known oncogenes and potential tumor neoantigens
- Tumor mutation burden

Additional biomarkers may be measured (for example, exome sequencing, single cell RNA analysis, microsatellite instability, T cell clonality) tissue permitting. [REDACTED]

6.3.5.2. Genomics Sub-Study – Optional

Patients who agree to participate in the genomics sub-study will be required to sign a separate genomics sub-study ICF before collection of the samples. Blood for genomic DNA extraction should be collected on day 1/baseline (predose), but may be collected at any study visit. Patients are not required to participate in the genomics sub-study in order to enroll in the primary study.

DNA samples for the genomics sub-study will be double-coded as defined by the ICH guideline E15. Sub-study samples may be stored for up to 15 years after the final date of the clinical study report and may be used for research purposes. The purpose of the genomic analyses is to identify genomic associations with clinical or biomarker response to target modulation, disease prognosis and progression, or other clinical outcome measures. [REDACTED]

7. SAFETY DEFINITIONS, REPORTING, AND MONITORING

7.1. Definitions

7.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug.

An AE also includes any worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug.

Progression of underlying malignancy will not be considered an AE if it is clearly consistent with the typical progression pattern of the underlying cancer (including time course, affected organs, etc.). Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

If there is any uncertainty about an AE being due only to progression of the underlying malignancy, it should be reported as an AE or SAE as outlined in [section 7.2](#).

NCI-CTCAE version 4.03 terms should be used.

7.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger), within 30 days of last dose of REGN2810.
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician. Hospitalization or prolongation of existing hospitalization due to the progression of underlying malignancy will not be considered an SAE, if it is clearly consistent with the typical progression pattern of the underlying cancer.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**

- Is an **important medical event** – Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent 1 of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Hospitalization or death occurring greater than 30 days after last dose of REGN2810 and due solely to manifestations consistent with typical progression of underlying malignancy will not be considered an SAE in this study.

Serious adverse events must be reported as directed in section 7.2.

7.1.3. Adverse Events of Special Interest

An adverse event of special interest (AESI) (serious or non-serious) is one of scientific and medical interest specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (eg, regulators) might also be warranted ([section 7.2.3](#))

7.2. Recording and Reporting Adverse Events

7.2.1. Adverse Events

The investigator (or designee) will seek information on AEs at each patient contact, and record all AEs that occur from the time the informed consent is signed until 30 days after the end of study treatment. NCI-CTCAE version 4.03 terms should be used. Prior to initiation of study treatment, only the following categories of AEs should be reported on the AE eCRF:

- SAEs
- Nonserious AEs associated with a protocol-mandated intervention (eg, AEs related to an invasive procedure such as a biopsy)

(Other AEs that occur prior to first treatment should be reported on the medical history CRF.)

All AEs after initiation of study treatment and until 30 days after the last study treatment, regardless of relationship to study treatment, will be reported on the AE eCRF. Additionally, any SAE or other AE of concern that the investigator believes may be related to study treatment and that occurs later than 30 days after last study treatment should be reported.

Information on follow-up for AEs is provided in [section 7.2.6](#). Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs as outlined in [section 7.2.5](#).

7.2.2. Serious Adverse Events

All SAEs, regardless of assessment of causal relationship to study treatment must be reported to the sponsor (or designee) within 24 hours. Refer to the safety reporting guidelines for the procedure to be followed.

Information not available at the time of the initial report must be documented in a follow-up report. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested.

In the event the investigator is informed of an SAE that occurs after 30 days after the last dose of study treatment, only those SAEs or other AEs of concern deemed by the investigator to be related to study treatment will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome of a treatment-related SAE until the event is considered chronic and/or stable.

7.2.3. Other Events that Require Accelerated Reporting to the Sponsor

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

Symptomatic Overdose of Study Drug:

Accidental or intentional overdose of at least 2 times the intended dose of study drug within the intended therapeutic window, if associated with an AE.

Pregnancy:

Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female patient or female partner of a male patient, during the study or within 90 days of the last dose of study drug. Any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn must be reported as an SAE. Outcomes for all pregnancies should be reported to the sponsor.

Adverse Events of Special Interest:

An AESI must be reported within 24 hours of identification. Adverse events of special interest for this study include:

- Grade 2 or greater infusion-related reactions
- Grade 2 or greater allergic/hypersensitivity reactions
- Grade 3 irAEs.

Note: An irAE can occur shortly after the first dose or several months after the last dose of treatment. All AEs of unknown etiology associated with drug exposure should be evaluated to determine possible immune etiology. If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an AE as an irAE.

Refer to the safety reporting guidelines for the reporting procedures to be followed.

If any SAE or unusual AE is judged related to study treatment, and as possible and practical, obtain a blood sample from the patient to permit measurement of plasma drug levels.

7.2.4. Reporting Adverse Events Leading to Withdrawal from the Study

All AEs that lead to a patient's withdrawal from study treatment or from the study must be reported to the sponsor's medical monitor within 30 days.

Refer to the safety reporting guidelines for the procedures to be followed.

7.2.5. Abnormal Laboratory, Vital Signs, or Electrocardiogram Results

The criteria for determining whether an abnormal objective test finding should be reported as an AE include:

- the test result is associated with accompanying symptoms, and/or
- the test result requires additional diagnostic testing or medical/surgical intervention, and/or
- the test result leads to a change in dosing (outside of protocol-stipulated dose adjustments), and/or
- the test result leads to discontinuation from the study, significant additional concomitant medication, or other therapy

Contact the medical monitor in the event the investigator feels that an abnormal test finding should be reported as an AE, although it does not meet any of the above criteria.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Evaluation of severity of laboratory abnormalities will be assessed according to the scale outlined in section 7.3.1.

7.2.6. Follow-up

Information for any nonserious AE that starts during the treatment period or within 30 days after last treatment will be collected from the time of the event until resolution of the event, or until the patient's last study visit, whichever comes first.

Serious adverse event information will be collected until the event is considered chronic and/or stable.

7.3. Evaluation of Severity and Causality

7.3.1. Evaluation of Severity

The severity of AEs (including test findings classified as AEs) will be graded using the current version of the NCI-CTCAE grading system. Adverse events not listed in the NCI-CTCAE will be graded according to the following scale:

- | | |
|----------------------|--|
| 1 (Mild): | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. |
| 2 (Moderate): | Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*. |
| 3 (Severe): | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**. |

4 (Life-threatening): Life-threatening consequences; urgent intervention indicated.

5 (Death): Death related to AE

*Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

7.3.2. Evaluation of Causality

Relationship of AEs to Study Drug:

The relationship of AEs to study drug will be assessed by the investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by the study drug?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by the study drug

Related: There is a reasonable possibility that the event may have been caused by the study drug

The investigator should justify the causality assessment of each reported SAE.

[Appendix 9](#) lists factors to consider in assessing the relationship of AEs to REGN2810 or infusion procedures, study procedures, or background treatment.

7.4. Safety Monitoring

The investigator will monitor the safety of study patients at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The medical monitor will have primary responsibility for the emerging safety profile of the compound. The study monitor will be supported by other departments (eg, Pharmacovigilance and Risk Management; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

7.5. Investigator Alert Notification

Regeneron (or designee) will inform all investigators participating in this clinical trial, as well as in any other clinical trial using the same investigational drug, of any SAE that meets the relevant requirements for expedited reporting (an AE that is serious, unexpected based on the Investigator's Brochure or this protocol, and has a reasonable suspected causal relationship to the medicinal/study drug).

8. STUDY VARIABLES

8.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height), disease characteristics including medical history, and medication history for each patient.

8.2. Primary and Secondary Variables

8.2.1. Primary Efficacy Outcome Measure

The primary efficacy endpoint for this study is overall response rate (ORR) during the 12 treatment cycles. Overall response rate will be assessed separately for patients with metastatic C5CC or unresectable locally advanced C5CC:

- For patients in Group 1, RECIST version 1.1 will be used to determine ORR ([Eisenhauer 2009](#)) ([Appendix 2](#)).
- For patients in Group 2, composite response criteria will be used to determine ORR ([Appendix 3](#)). In patients achieving a CR, tumor biopsies will be used in the final determination of complete versus PR.

Patients who are deemed not evaluable (NE) by RECIST version 1.1 (Group 1; [Appendix 2](#)) or inevaluable by the composite response criteria (Group 2; [Appendix 3](#)) will be considered as not reaching PR/CR for ORR.

8.2.2. Secondary Outcome Measures

The secondary efficacy outcome measures are:

- Duration of response
- Duration of disease control
- PFS
- OS
- CR rate
- Change in scores of patient-reported outcomes on EORTC QLQ-C30 ([Appendix 1](#))
- AEs
- REGN2810 concentrations in serum ([Appendix 4](#); at select sites)
- Anti-REGN2810 antibodies

8.2.3. Exploratory Outcome Measures

The following exploratory analyses are planned:

- [REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

8.3. Pharmacokinetic Variables

Serum concentration of REGN2810 will be assessed at multiple time points throughout the study treatment and follow-up periods, and the PK will be analyzed.

Pharmacokinetic variables may include, but are not limited to, the following:

- AUC_{all} – area under the curve (AUC) computed from time zero to the time of the last concentration
- $AUC_{all}/Dose$ – AUC_{all} -to-dose ratio
- CL – clearance
- C_{eoi} – concentration at end-of-infusion
- $C_{eoi}/Dose$ – C_{eoi} -to-dose ratio
- C_{last} – last positive (quantifiable) concentration
- C_{trough} – pre-infusion concentration
- t_{last} – time of the last positive (quantifiable) concentration
- t_{eoi} – time of end-of-infusion
- V_{ss} – volume of distribution at steady state
- V_z – volume of distribution of the terminal phase

8.4. Anti-drug Antibody Variables

Regeneron plans to evaluate the impact of the immunogenicity of REGN2810.

Anti-drug antibody variables include status (positive or negative) and titer as follows:

- Total number of patients whose ADA response is negative
- Total number of patients whose ADA response is positivity at any time
- Pre-existing immunoreactivity – defined either as a positive ADA assay response at baseline with all post-treatment ADA results negative, or a positive assay response at baseline with all post-treatment ADA assay responses less than 4-fold over baseline titer levels.

- Treatment emergent – defined as either any positive response post-treatment when baseline results are negative, or if any post treatment ADA response is greater than or equal to 4-fold over baseline titer levels. Treatment emergent responses will be further characterized into persistent and transient.
- Persistent response – treatment-emergent ADA positive response with 2 or more ADA-positive sampling time points during the treatment period (and follow-up phase, if any) such that the first and last ADA-positive sample (with no intervening ADA-negative sample) is separated by at least a 16 week period
- Transient response – any treatment-emergent ADA-positive response that is not considered persistent
- Titer values (Titer value category):
 - Low (titer < 1,000)
 - Moderate ($1,000 \leq \text{titer} \leq 10,000$)
 - High (titer > 10,000)

9. STATISTICAL PLAN

This section provides the basis for the statistical analysis plan (SAP) for the study. The SAP may be revised during the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the database is locked.

Analysis variables are listed in [section 8](#).

9.1. Statistical Hypothesis

For the primary endpoint of ORR, the following null hypothesis and alternative will be tested for Group 1 and Group 2, respectively.

Group 1: H_0 : ORR = 15% vs. H_1 : ORR \neq 15%

Group 2: H_0 : ORR = 25% vs. H_1 : ORR \neq 25%

9.2. Justification of Sample Size

Patients will be enrolled into 2 separate groups according to the stage of disease: metastatic CSCC (Group 1) or locally advanced CSCC (Group 2). A single-stage exact binomial design is adopted for each group, respectively, for the primary endpoint of ORR.

Published clinical studies for CSCC patients have had relatively small sample sizes and often include a wide range of disease stages ([Nakamura 2013](#)). Clinical studies of CSCC patients have been predominantly comprised of patients locally advanced disease (primary site). In the NCCN guidelines for CSCC, cisplatin monotherapy, cisplatin plus 5-FU, and cetuximab are described as “possible options” ([Bichakjian 2015](#)). In the only study of cisplatin-based therapy for advanced CSCC reported in the last 15 years, the ORR was 34% ([Shin 2002](#)). Cetuximab yielded a response rate of 28% in a phase 2 study for patients with advanced CSCC ([Maubec 2011](#)). Most

patients in these studies had locoregionally advanced disease. There hasn't been a publication of a clinical study specifically for patients with metastatic CSCC. The aggregate experience of patients enrolled in trials of systemic therapy indicates that a clinically meaningful ORR for an investigational agent would be >15% for patients with metastatic disease or >25% for patients with unresectable locally/regionally advanced CSCC (Khansur 1991, Lippman 1992, Nakamura 2013, Shin 2002).

Hence, the sample sizes for both Group 1 and Group 2 were selected such that the lower limit of the 95% confidence interval of the estimated overall response rate will be clinically meaningful. The non-clinically meaningful ORR of 15% for Group 1 will be excluded using the lower limit of 95% CI if the observed ORR is 28.0% or more; ie, the ORR for Group 1 is significantly different from 15%. The non-clinically meaningful ORR of 25% for Group 2 will be excluded using the lower limit of 95% CI if the observed ORR is 36.1% or more; ie, the ORR for Group 2 is significantly different from 25% (see Table 6 and Table 7).

Table 6: The 95% Binomial Exact Confidence Intervals for Observed ORR in Group 1 Given a Sample Size of 50 Patients (Based on 85% Power)

Number of Responders	Observed ORR	95% CI – lower	95% CI – upper
7	0.14	0.058	0.267
8	0.16	0.072	0.291
9	0.18	0.086	0.314
10	0.20	0.100	0.337
11	0.22	0.115	0.360
12	0.24	0.131	0.382
13	0.26	0.146	0.403
14	0.28	0.162	0.425
15	0.30	0.179	0.446
16	0.32	0.195	0.467
17	0.34	0.212	0.488

Table 7: The 95% Binomial Exact Confidence Intervals for Observed ORR in Group 2 Given a Sample Size of 72 Patients (Based on 90% Power)

Number of Responders	Observed ORR	95% CI – lower	95% CI – upper
18	0.250	0.155	0.366
19	0.264	0.167	0.381
20	0.278	0.179	0.396
21	0.292	0.190	0.411
22	0.306	0.202	0.425
23	0.319	0.214	0.440
24	0.333	0.227	0.454

Number of Responders	Observed ORR	95% CI – lower	95% CI – upper
25	0.347	0.239	0.469
26	0.361	0.251	0.483
27	0.375	0.264	0.497
28	0.389	0.276	0.511
29	0.403	0.289	0.525
30	0.417	0.302	0.539
31	0.431	0.314	0.553
32	0.444	0.327	0.566

For Group 1, 50 patients will be required to provide at least 85% power to reject a null hypothesis of an ORR of 15% at a 2-sided significance level of no more than 5% if the true ORR is 34%. For Group 2, 72 patients will be required to provide at least 90% power to reject a null hypothesis of an ORR of 25% at a 2-sided significance level of no more than 5% if the true ORR is 44%. The sample sizes will be further increased by 5% to account for patients who withdraw prematurely from the study. Hence, the total sample sizes will be 53 patients for Group 1, and 76 patients for Group 2, for a total of 129 patients.

9.3. Analysis Sets

9.3.1. Full Analysis Set

The full analysis set (FAS) includes all patients who have passed screening and deemed to be eligible for this study.

9.3.2. Per Protocol Set

The per protocol set (PPS) includes all enrolled patients in the FAS, except for those who prematurely withdraw from the study before receiving at least 1 dose of study drug.

The PPS is the primary analysis set for the efficacy endpoints.

9.3.3. Safety Analysis Set

The safety analysis set (SAF) includes all enrolled patients who received any study drug for each group. Treatment compliance/administration and all clinical safety variables will be analyzed or summarized using the SAF.

9.3.4. Pharmacokinetic Analysis Set

The PK analysis set will include all patients who had received REGN2810 and had at least 1 qualified (non-missing) post-baseline measurement of REGN2810 concentration in serum..

9.3.5. Anti-drug Antibody Set

The ADA population includes all treated patients who had at least 1 post-dose ADA result.

9.3.6. Biomarker Analysis Set

The biomarker analysis set (BAS) includes all treated patients who had at least 1 sample assayed.

9.4. Patient Disposition

The following will be provided by group and overall:

- The number of screened patients
- The number of patients included in the FAS and the SAF
- The number of patients who discontinued study participation, and the reasons for discontinuation from the study
- The number of patients who discontinued treatment, and the reasons for treatment discontinuation

9.5. Statistical Methods

In general, the descriptive summary for continuous data will include the number of observations (n), mean, standard deviation (SD), median, minimum and maximum. In addition, 25% percentile and 75%-percentile will also be provided.

The descriptive summary for categorical data will include counts (n) and percentages calculated in each group. The denominator will be determined by the analysis population used for the summary. Non-evaluable outcome or missing data will be handled based on the data handling strategy.

The descriptive summary for time-to-event data will include the median time-to-event and its 95% confidence intervals using the Kaplan-Meier method.

9.5.1. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively for each group by extent of prior therapy (no prior systemic therapy versus having received any prior systemic therapy).

9.5.2. Efficacy Analyses

The primary endpoint for efficacy analyses is the ORR as determined by RECIST version 1.1 (Eisenhauer 2009) or by the composite response criteria (see [section 6.3.2](#)). The ORR assessment for the primary analysis will be performed by an independent central review committee. The investigator-assessed ORR will be considered as a secondary analysis.

The irRC (Nishino 2013) will also be used to assess tumor response to REGN2810 as an immunotherapy. The ORR determined by irRC will only be used for sensitivity analysis.

The primary analyses of efficacy are based on the binomial exact confidence interval approach, ie, whether the lower limit of 95% confidence interval will exclude an historical control ORR that is not deemed clinically meaningful. The 95% binomial exact confidence intervals using Clopper-Pearson method (Clopper 1934) for observed ORRs are listed for Group 1 and Group 2, respectively (see [Table 6](#) and [Table 7](#)).

The secondary analyses of efficacy as measured by duration of response, duration of disease control, PFS, and OS will be summarized by median and its 95% confidence interval by the Kaplan-Meier method.

The CR rate will be summarized descriptively with 95% confidence interval. Absence of residual CSCC in patients with locally advanced CSCC achieving a clinical response to REGN2810, as measured by central review, will be summarized descriptively.

9.5.3. Exploratory Analyses

Subgroup analyses: Subgroup efficacy analyses will be performed based on the number of prior systemic therapy regimens, the degree of differentiation of the tumor (well, moderate, or poor), the presence or absence of human papillomavirus (HPV) in the tumor, and the presence or absence of use of immune suppressive medications (eg, high dose steroids) to manage irAEs that may arise during the study. However, such analyses may not have enough power for hypothesis tests, and in that case will serve only for hypothesis-generating purpose.

Quality of life analysis: The quality of life of patients will be repeatedly measured by the EORTC QLQ-C30 at the day 1 of each treatment cycle. The change scores of QLQ-C30 will be summarized descriptively at each post-baseline time point. The summary scores of QLQ-C30 will also be graphically depicted by longitudinal plots.

9.5.4. Safety Analysis

Safety observations and measurements including drug exposure, AEs, laboratory data, vital signs, and ECOG performance status will be summarized and presented in tables and listings.

9.5.4.1. Adverse Events

Definitions

For safety variables, 3 observation periods are defined:

- The pre-treatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment period is defined as the day from first dose of study drug to follow-up visit 1
- The post-treatment period is defined as the time after follow-up visit 1.

Treatment-emergent adverse events (TEAEs) are defined as those not present at baseline or represent the exacerbation during the on-treatment period of a condition present at baseline.

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Coding will be to lowest level terms. The verbatim text, the preferred term (PT), and the primary system organ class (SOC) will be listed.

Summaries of all TEAEs by group will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (NCI-CTCAE, version 4.03 grade), presented by SOC and PT

- TEAEs by outcome
- TEAEs by relationship to experimental treatment (related, not related), presented by SOC and PT

Deaths and other SAEs will be listed and summarized by group.

Events of NCI-CTCAE Grade 3 and Grade 4 severity will be summarized by group.

Treatment-emergent adverse events leading to permanent treatment discontinuation will be listed and summarized by group.

9.5.4.2. Other Safety

Vital Signs

Vital signs (temperature, pulse, blood pressure, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Laboratory Tests

Laboratory test results will be listed, and number and percentage of patients with NCI-CTCAE Grade 3 or Grade 4 lab values will be summarized by lab test and by group.

9.5.4.3. Treatment Exposure

Duration of exposure, number of dose administered and dose intensity will be summarized by group. Dose intensity will be calculated by dividing actual dose by body weight for REGN2810.

9.5.4.4. Treatment Compliance

Patients will be administered IV study drug and treatment compliance will be defined in detail in the SAP and summarized by group.

9.5.5. Analysis of Drug Concentration Data

9.5.5.1. Descriptive Analysis of Drug Concentrations

Summaries of study drug concentrations will be presented by nominal time point (ie, the time points specified in the protocol) and group.

9.5.6. Analysis of Anti-Drug Antibody Data

Formation of ADA will be assessed in individual patients and per treatment group as follows:

- Possible correlation between changes in PK profile and the presence/absence of anti-REGN2810 antibodies will be evaluated to identify a potential impact of anti-REGN2810 antibodies on drug exposure.
- Possible correlation between AEs and the presence/absence of anti-REGN2810 antibodies will be evaluated to identify a potential impact of anti-REGN2810 antibodies on the incidence of Grade 3 and 4 AEs, atypical AEs, and SAEs.

Cases of ADA positivity will be listed and summarized as appropriate.

9.5.7. Analysis of Biomarker Data

Biomarker data will be analyzed using standard scientific methods and summarized by descriptive statistics and plot. Comparative analysis of biomarker data with parent study may be performed using paired t-test or nonparametric Wilcoxon signed rank test or Chi-square test. Correlative analysis with clinical response may be performed using correlation coefficient, box plot and scatter plot, and basic regression models. Both comparative analysis and correlative analysis will be exploratory in nature and will be described in a separate report.

9.5.7.1. Sample Size Justification for Biomarker Measurements in Tumor Tissue Biopsies

Although many biomarkers may be assayed in tumor biopsy tissues, CD274 (PD-L1) was selected to illustrate the power analysis as an example. PD-L1 expression level was reported to be associated with clinical activity of Nivolumab ([Borghaei 2015](#)). The prevalence of PD-L1 expression levels $\geq 1\%$, $\geq 5\%$, $\geq 10\%$ were 53%, 41%, and 37%, respectively, and the ORRs were reported as 9% vs. 31%, 10% vs. 36%, 11% vs. 37% for each categorization of PD-L1 expression level, respectively. In the following power analysis, the following variations are considered (Table 8):

1. Actual number of tumor biopsy obtained and deemed evaluable are 60, 50, or 40.
2. The PD-L1 expression level categorization results in PD-L1 negative / positive ratio as 1:1 or 3:2.
3. Objective response rates of 10% (PD-L1 negative) vs. 30% (PD-L1 positive) results an odds ratio of 3.857 and 10% (PD-L1 negative) vs. 25% (PD-L1 positive) results an odds ratio of 3.0

The power analysis was based on the one-sided Chi-square test with type I error of 20% due to the exploratory nature of biomarker analysis, performed in nQuery Advisor 7.0 ([Elashoff 2007](#)). The power may be overestimated for some configurations as the large sample approximation may not be adequate for a Chi-square test with small sample sizes.

In summary, requiring each patient enrolled in this study to provide tumor biopsy provides moderate power for exploratory biomarker analysis.

Table 8: Power Analysis for PD-L1 Biomarkers from Tumor Biopsies

Number of Tumor Biopsies	PD-L1 Neg/Pos	Tumor Response	Power (%)
		Odds Ratio	
60	1:1	3.857	87
		3.0	75
50	1:1	3.857	83
		3.0	71
40	1:1	3.857	77
		3.0	66
60	3:2	3.857	86
		3.0	75

Number of Tumor Biopsies	PD-L1 Neg/Pos	Tumor Response Odds Ratio	Power (%)
50	3:2	3.857	82
		3.0	70
40	3:2	3.857	76
		3.0	65

9.6. Multiplicity Considerations

Adjustments to the significance level for the purposes of multiple testing are not applicable for this study. Statistical analyses for Group 1 and Group 2 will be conducted and reported separately; ie, efficacy results and clinical conclusions from Group 1 will not affect those of Group 2, and vice versa. Therefore, statistical control of overall type I error for the whole study is not planned.

9.7. Interim Analysis

No interim analysis is planned.

9.8. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed:

Definition of baseline:

- Unless otherwise specified, the last assessment before the initial administration of REGN2810 will be considered the baseline evaluation

General rules for handling missing data:

- Unless otherwise specified, there will be no imputations for the missing data
- If the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the intake of study medication except if an incomplete date (eg, month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the intake of study medication date, then the start date by the study medication intake date will be imputed, otherwise, the missing day or month by the first day or the first month will be imputed.
- Patients who are deemed NE by RECIST version 1.1 (Group 1; [Appendix 2](#)) or inevaluable by the composite response criteria (Group 2; [Appendix 3](#)) will be considered as not reaching PR/CR for ORR. Their disease progression will be censored at the date of baseline tumor assessment + 1 day. Duration of response and PFS will be censored at the last tumor assessment date for patients without disease progression.
- Missing data in quality of life analysis will be presented as missing in changes scores.

Visit windows:

- Assessments taken outside of protocol allowable windows will be displayed according to the case report form (CRF) assessment recorded by the investigator.

9.9. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in [section 15.1](#).

10. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

10.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation, cleaning, correcting, releasing) will be maintained and stored at Regeneron.

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, medical /surgical history) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with electronic data capture (EDC) tool. User training must be documented before the user is granted access to the EDC system.

10.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- EDC system – data capture
- Statistical Analysis Systems (SAS) (Software)– statistical review, analysis and reporting
- Pharmacovigilance safety database
- IWRS

11. STUDY MONITORING

11.1. Monitoring of Study Sites

The study monitor and/or designee (eg, contract research organization [CRO] monitor) will visit each site prior to enrollment of the first patient, and periodically during the study. In accordance with International Conference on Harmonisation (ICH) guidelines, the monitor will compare the CRF entries with the appropriate source documents. Additional review may include, but is not limited to, patient ICFs, documentation of patient recruitment and follow-up, AEs, SAEs, and

concomitant therapy; as well as records of study drug dispensing, compliance, and accountability. A copy of the drug dispensing log must be provided to the sponsor upon request.

11.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents).

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an eCRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

11.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic CRFs by trained site personnel. A CRF must be completed for each and every patient enrolled in the study. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each CRF page is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the system. For corrections made via data queries, a reason for any alteration must be provided.

12. AUDITS AND INSPECTIONS

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, Institutional Review Board (IRB) files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may

observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

13.2. Informed Consent

The principles of informed consent are described in ICH Guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB. A copy of the IRB-approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, the ICF must be reviewed and updated appropriately. All study patients must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient.

13.3. Patient Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by their initials and a patient identification number, only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The patient's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

13.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/Ethics Committee (EC), as described in ICH Guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design or operation of the protocol or ICF without an IRB-approved amendment.

15. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

15.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

15.2. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of patients required for the study are enrolled earlier than expected

In all cases, the appropriate IRB/EC and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

16. STUDY DOCUMENTATION**16.1. Certification of Accuracy of Data**

A declaration assuring the accuracy and content of the data recorded on the CRFs must be signed by the investigator. This certification form accompanies each set of CRFs. The signed form will be provided to the sponsor with the final set of CRFs for each patient.

16.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer if a longer period is required by relevant regulatory authorities. The investigator must consult with the sponsor before discarding or destroying any essential study documents following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor and the relevant records will be transferred to a mutually agreed-upon destination.

17. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

18. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

19. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

20. REFERENCES

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21. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A Phase 2 Study of REGN2810, a Fully Human Monoclonal Antibody to Programmed Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma (CSCC), dated 23 Nov 2015, and agree to abide by all provisions set forth therein.

I agree to comply with the current International Conference on Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

(Signature of Investigator)

(Date)

(Printed Name)

APPENDIX 1. EORTC-QLQ-C30**To be completed by study team:**

Study Patient Number:

Today's date:

Cycle: Day:

To be completed by study participant:

We are interested in some things about you and your health. Please answer all of the questions by yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will be strictly confidential.

	No	Yes
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2
2. Do you have any trouble taking a <u>long</u> walk?	1	2
3. Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2
4. Do you have to stay in a bed or a chair for most of the day?	1	2
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2
6. Are you limited in any way in doing either your work or doing household jobs?	1	2
7. Are you completely unable to work at a job or to do household jobs?	1	2

DURING THE PAST WEEK:

	Not at All	A Little	Quite a Bit	Very Much
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had diffi- culty in concentrating on things, like reading a newspaper or watch- ing television?	1	2	3	4

- | | | | | |
|---|---|---|---|---|
| 21. Did you feel tense? | 1 | 2 | 3 | 4 |
| 22. Did you worry? | 1 | 2 | 3 | 4 |
| 23. Did you feel irritable? | 1 | 2 | 3 | 4 |
| 24. Did you feel depressed? | 1 | 2 | 3 | 4 |
| 25. Have you had difficulty remembering things? | 1 | 2 | 3 | 4 |
| 26. Has your physical condition or medical treatment interfered with your <u>family</u> life? | 1 | 2 | 3 | 4 |
| 27. Has your physical condition or medical treatment interfered with your <u>social</u> activities? | 1 | 2 | 3 | 4 |
| 28. Has your physical condition or medical treatment caused you financial difficulties? | 1 | 2 | 3 | 4 |

FOR THE FOLLOWING QUESTIONS PLEASE CIRCLE THE NUMBER BETWEEN 1 AND 7 THAT BEST APPLIES TO YOU

29. How would you rate your overall physical condition during the past week?

1 2 3 4 5 6 7

Very poor

Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor

Excellent

APPENDIX 2. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS: RECIST GUIDELINE (VERSION 1.1)

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. Confirmatory scans should also be obtained 4 weeks following initial documentation of objective response or progressive disease.

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1; [Eisenhauer 2009](#)). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Selection of Lesions

- **Measurable disease:** Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm (≥ 2 cm) by chest x-ray or as ≥ 10 mm (≥ 1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note:

- **Malignant lymph nodes:** To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm (≥ 1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.
- **Non-measurable disease:** All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm [< 1 cm] or pathological lymph nodes with ≥ 10 to < 15 mm [≥ 1 to < 1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

- **Target lesions:** All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can

be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

- **Non-target lesions:** All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- **Clinical lesions.** Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules and palpable lymph nodes) and ≥ 10 mm (≥ 1 cm) diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- **Chest x-ray.** Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Conventional CT and MRI.** This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situation.
- **PET-CT.** At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

- **Ultrasound.** Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- **Endoscopy, Laparoscopy.** The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.
- **Tumor markers.** Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- **Cytology, Histology.** These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (eg, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease

- **FDG-PET.** While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible ‘new’ disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
 - a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
 - b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
 - c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it

must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Response Criteria

Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).
- **Partial Response (PR):** At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

- **Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).
Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease (PD):** Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Overall Response Criteria

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient’s best response assignment will depend on the achievement of both measurement and confirmation criteria. Revised Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 ([Eisenhauer 2009](#)) are summarized in the table:

Response According to Revised Response Evaluation Criteria in Solid Tumors (Version 1.1)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required ^a
CR	CR	No	CR	≥4 weeks confirmation
CR	Non-CR/Non-PD	No	PR	≥4 weeks confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 weeks from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease.

^a In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as PD.

APPENDIX 3. COMPOSITE RESPONSE CRITERIA FOR PATIENTS WITH LOCALLY ADVANCED CSCC

These criteria are designed primarily for patients in Group 2. This appendix describes clinical response criteria for externally visible lesions that can be measured bi-dimensionally using digital medical photography. This appendix also provides composite response criteria for disease that is measurable by both clinical response criteria and RECIST 1.1.

Group 2 patients will be followed by digital medical photography. Group 2 patients will also undergo radiologic imaging (typically, MRI with gadolinium) at baseline, and this will also be performed serially at each response assessment unless the investigator deems that baseline radiologic imaging was uninformative. Radiologic imaging (preferably, MRI with gadolinium) will be essential in the evaluation of tumors that have subdermal components that cannot be adequately assessed by digital medical photography. See protocol [Section 6.3.1](#) and [6.3.2](#) for further information on imaging requirements for Group 2 patients.

Response assessments occur every 8 weeks. Standardized digital photographs of the externally visible component of all target lesions must be obtained at baseline and at the time of each subsequent tumor assessment. Guidelines for digital medical photography are provided in [Appendix 7](#). Investigators will also provide a clinical description of the externally visible target lesion(s) at baseline and at each tumor assessment, as well as comments on any changes in the lesion(s) since the previous assessment.

SPECIAL ISSUES FOR EXTERNALLY VISIBLE TUMORS:

B) Anatomic Defects

Regarding tumor around a surgical cavity/anatomic defect (eg, rhinectomy), such lesions should be considered non-measurable unless there is a nodular lesion measuring ≥ 10 mm in maximal bi-dimensional perpendicular diameters. The surgical cavity or anatomic defect should not be considered in measuring the lesion.

2) Indeterminate-Appearing Tissue

If there is uncertainty about whether a given lesion or area of a lesion represents malignancy versus benign process (eg, scarring, fibrosis), biopsies should be obtained. Indeterminate-appearing areas (eg, scarring, fibrosis) are included in the tumor measurements unless biopsies are obtained to establish benign status.

To reduce risk of sample error, biopsy of only a single area on the tumor is not allowed. Biopsy of at least two separate areas of the lesion are required when biopsy is indicated. Each biopsy will be performed in a pairwise manner (approximately adjacent) so that there will be one sample for local review and one for central review for each biopsy, as per [Appendix 6](#).

As such, when the decision is made to perform biopsy, at least 4 biopsy samples are obtained (biopsy of two separate areas, with two biopsies in each area: one for central, one for local from each area). Biopsy samples will not be bisected or split in half for local and central review; rather, separate adjacent samples will be obtained. See [Appendix 6](#) for biopsy details.

Note on timeline for finalization of measurement/response assessment: Generally, baseline disease measurements and response assessments should be completed on the day of the visit at which digital medical photography was performed. However, for visits in which tumor biopsies are performed, it is understood that the local pathology report may not be available for up to 5 business days after the biopsy.

When biopsies are performed to distinguish between benign versus malignant tissue, the annotated photograph for that visit should clearly indicate the region of the tumor that was biopsied to distinguish benign versus malignant tissue. Within one week of the date of biopsies, the investigator should finalize the tumor measurements for that visit with the benefit of the local pathology report.

For circumstances in which the intent of the biopsy is to distinguish between disease stability and response, it is not necessary to hold study treatment while the local pathology report is pending. For circumstances in which the biopsy, if positive, would result in discontinuation of study treatment due to progression, treatment should be held until biopsy results are finalized and progression has been ruled out.

3) Local Versus Central Review

An independent central review committee, with access to de-identified digital medical photography results and biopsy results, will provide response assessments as required by the sponsor to address study objectives ([Section 2](#)). Central reviews will be scheduled by the sponsor, but will not be continuous or “real-time.” Clinical management decisions generally will be as per investigator response assessments and local pathology review. In the unlikely event that central review yields major differences with the local response assessment that could have implications for the ongoing management of an active patient on study, the situation will be discussed between the sponsor and the investigator in order to determine patient management.

4) Confirmation of Responses

After any objective response, confirmatory digital photography (and radiologic imaging, if performed as part of the initial response assessment) will be obtained at least 4 weeks following initial documentation of objective response. Confirmatory biopsies are not required for partial response.

5) Patients in Group 1 with Externally Visible Tumors

Regarding Group 1 (metastatic CSCC), these patients will generally be followed by RECIST 1.1 criteria ([Appendix 2](#)). It is possible that some patients in Group 1 may also have externally visible lesions that are measurable by digital medical photography. In such circumstances, the externally visible lesions generally will be followed as non-target lesions. The exception to this rule would be a patient with externally visible lesions in whom the only M1 lesions are not measurable by RECIST (eg, a patient with bone-only metastases), in which case the externally visible lesions (lesion size ≥ 10 mm in baseline dimensional perpendicular axes) would be target lesions and followed as per clinical response criteria in this appendix, and the non-measurable metastatic lesions (eg, bone metastases) would be followed as non-target lesions.

Clinical Response Criteria for Externally Visible Tumors (for all patients with locally advanced CSCC)

B. Externally Visible Tumor Dimension

The externally visible component of target lesion(s) will be measured using bi-dimensional WHO criteria as the sum of the products (of individual target lesions) in the longest dimension and perpendicular second longest dimension – at each tumor assessment and will be documented using standardized digital photography ([Appendix 7](#)). In the absence of substantial change in lesion geometry, subsequent visit measurements should be performed in the same axes and the investigator should refer to the previous visit's annotated photographs as a starting point to identify axis for measurement when making subsequent assessments.

Clinical response criteria for externally visible tumor(s) require bidimensional measurements according to WHO criteria (reference), and are as follows:

- Complete response of externally visible disease (vCR): all target lesion(s) no longer visible, maintained for at least 4 weeks. Documentation of vCR requires confirmation by biopsies of site(s) of externally visible target lesion(s) with histologic confirmation of no residual malignancy, per central pathology review ([Appendix 6](#)). In the absence of such histologic confirmation, a patient cannot be deemed to have experienced vCR and the best response would be partial response.
- Partial response of externally visible disease (vPR): decrease of 50% (WHO criteria) or greater in the sum the products of perpendicular longest dimensions of target lesion(s), maintained for at least 4 weeks
- Stable externally visible disease (vSD): not meeting criteria for vCR, vPR, or progressive disease
- Progression of visible disease (vPD): increase of $\geq 25\%$ (WHO criteria) in the sum of the products of perpendicular longest dimensions of target lesion(s)

B. New Lesions

A new cutaneous lesion consistent with CSCC will be considered as cPD if the lesion is ≥ 10 mm in both maximal perpendicular diameters, and can be clearly documented as not being previously present, unless it is confirmed on biopsy not to be consistent with CSCC. If a new cutaneous lesion is not biopsied or if the histology is inconclusive, it should be considered CSCC and deemed cPD.

**Overall Clinical Responses For All Possible Combinations of Clinical Tumor Responses
For Locally Advanced CSCC**

Externally Visible Tumor Dimension^a	New Lesions^a	Clinical Response
vCR	No	cCR ^b
vPR	No	cPR ^c
vSD	No	cSD ^d
vPD	Yes or No	cPD ^e
Any	Yes	cPD

^aSee above for definitions

^bClinical Complete Response

^cClinical Partial Response

^dClinical Stable Disease

^eClinical Progression of Disease

Composite Response Criteria: For patients who have disease that is measurable by BOTH clinical response criteria by digital medical photography and RECIST 1.1 using radiologic imaging.

Clinical Response (Digital Medical Photography)	RECIST 1.1 Response (Radiology)	Composite (Overall): Clinical + RECIST Response
cCR	CR	CR
cCR	PR or SD	PR
cPR	CR, PR, or SD	PR
cSD	CR or PR	PR
SD	SD	SD
PD	Any	PD
Any	PD	PD

In addition, if all previously inoperable target lesions are rendered operable with clear margins obtained at the time of surgery, this will be considered a PR. If the investigator deems a previously unresectable lesion to be potentially resectable due to response to REGN2810, the Medical Monitor should be consulted prior to any surgical procedure being performed. A decision will be rendered by the sponsor as to whether the planned surgical intervention is compatible with study requirements. (This statement does not apply to patients in emergency life-threatening situations that require immediate surgery).

APPENDIX 4. REGN2810 PHARMACOKINETIC SAMPLING AND ASSESSMENT SCHEDULE

Study Visit	PK Sampling Time
Cycle 1, day 1	<ul style="list-style-type: none">• Preinfusion• Within 10 minutes after end of infusion
Cycle 1: day 15 \pm 3, day 29 \pm 3, day 43 \pm 3	<ul style="list-style-type: none">• Preinfusion• Within 10 min after end of infusion
Cycles 2–6: day 1	<ul style="list-style-type: none">• Preinfusion• Within 10 min after end of infusion
Cycles 7, 9, 11: day 1	<ul style="list-style-type: none">• Preinfusion• Within 10 min after end of infusion
End of study (if progression during cycles 1-12) or Follow-up Visit 1	Anytime during the visit
Follow-up Visit 4 (for patients who maintain active follow-up)	Anytime during the visit

APPENDIX 5. RECOMMENDED DOSE MODIFICATION OR DISCONTINUATION AND SUPPORTIVE CARE GUIDELINES FOR SPECIFIC STUDY DRUG-RELATED ADVERSE EVENTS

Section 5.3.2 provides the dose level reductions.

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Colitis events <ul style="list-style-type: none"> Bowel obstruction Colitis Colitis microscopic 	≤ Grade 1	No change in dose	<ul style="list-style-type: none"> For diarrhea, treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet). Endoscopy is recommended if symptoms persist. Grade 1 diarrhea that persist for >1 week should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily. 	Symptoms may include (but are not limited to): <ul style="list-style-type: none"> Abdominal pain, cramping and/or bloating Blood and/or mucus in stool with or without fever Constipation Diarrhea Ileus Nausea and/or vomiting Peritoneal signs consistent with bowel perforation Rectal bleeding With or without fever Patients with diarrhea should be	All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, and a <i>Clostridium difficile</i> titer.
	Grade 2	Hold until ≤Grade 1. Resume at same dose level. May increase dosing interval by 1 week if it takes more than 4 weeks for toxicities to resolve.	<ul style="list-style-type: none"> GI consultation and endoscopy is recommended to confirm or rule out colitis for grade 2 diarrhea that persists >1 week or grade 1-2 diarrhea with rectal bleeding (additional guidelines for the treatment of persistent colitis are provided below). Grade 2 diarrhea should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily. Grade 2 diarrhea with diffuse ulceration and bleeding seen on endoscopy may require oral steroids with prolonged taper and represent an increased risk for the development of bowel perforation. Consider prophylactic antibiotics for opportunistic infections. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. In patients with Grade 2 enterocolitis, REGN2810 should be withheld and antidiarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (eg, 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. 		

All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Colitis events (continued)	Grade 3–4	<p>Withhold REGN2810</p> <p>Discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisone equivalent within 12 weeks of toxicity</p>	<ul style="list-style-type: none"> In patients with Grade 3 enterocolitis, REGN2810 will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1–2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. Consider prophylactic antibiotics for opportunistic infections. <p>For Grade 3–4 diarrhea (or Grade 2 diarrhea that persists after initial steroid treatment),</p> <ul style="list-style-type: none"> Rule out bowel perforation. Imaging with plain films or computed tomography (CT) can be useful. Consider consultation with gastroenterologist and confirmation biopsy with endoscopy. Treat with intravenous (IV) steroids (methylprednisolone 125 mg) followed by high-dose oral steroids (prednisone 1–2 mg/kg once per day or dexamethasone 4 mg every 4 hours). When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Taper over 6–8 weeks in patients with diffuse and severe ulceration and/or bleeding. If IV steroids followed by high-dose oral steroids does not reduce initial symptoms within 48–72 hours, consider treatment with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45–60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab. CAUTION: infliximab is contraindicated in patients with bowel perforation or sepsis^b. If symptoms persist despite the above treatment a surgical consult should be obtained. 	carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.	

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Endocrine events <ul style="list-style-type: none"> • Hyperthyroidism • Hypophysitis • Hypopituitarism 	Grade 1-2	No change in dose	<ul style="list-style-type: none"> • Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values. 	Symptoms may include (but not limited to): <ul style="list-style-type: none"> • Abdominal pain • Abnormal thyroid function tests and/or serum chemistries (Thyroid-stimulating hormone increased [decreased], Free thyroxine increased, Tri-iodothyronine increased.) • Arrhythmias^c • Cold or heat intolerance • Fatigue • Fever • Headache • Hypotension^c • Loss of appetite • Mental status and/or behavior changes • Nausea and/or vomiting • Unusual bowel habits • Vision disturbances • Weakness 	All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection. An endocrinology consultation is recommended.
Endocrine events <ul style="list-style-type: none"> • Hypothyroidism • Thyroid disorder • Thyroiditis 	Grade 3-4	Hold until on stable replacement dose	<ul style="list-style-type: none"> • Consider endocrine consultation. • Rule out infection and sepsis with appropriate cultures and imaging. • Replacement of appropriate hormones as required. 		
Endocrine events <ul style="list-style-type: none"> • Adrenal insufficiency • Hypophysitis • Pan-hypopituitarism 	Grade 1-4	Hold until on stable replacement dose	<ul style="list-style-type: none"> • Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency. • If Grade 1–2 hypophysitis is considered, pituitary gland imaging should be considered (magnetic resonance imaging [MRIs] with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis). • Grade 3–4 hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis. Hospitalization and IV methylprednisolone should be initiated. 		

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Eye event: Uveitis (iritis, iridocyclitis)	Grade 1	Discontinue REGN2810 if symptoms persist despite treatment with topical immunosuppressive therapy	<ul style="list-style-type: none"> • Evaluation by an ophthalmologist is strongly recommended. • Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics. 	Symptoms may include (but are not limited to): <ul style="list-style-type: none"> • Blurred vision • Diffuse erythema and a prominent blush on the sclerae • Dryness of the eyes • Pain • Photophobia 	All attempts should be made to rule out other causes such as metastatic disease, infection, or other ocular disease (e.g., glaucoma or cataracts).
	Grade 2	Discontinue REGN2810 if symptoms persist despite treatment with topical immunosuppressive therapy and do not improve to Grade 1 within the retreatment period OR requires systemic treatment.	<ul style="list-style-type: none"> • Evaluation by an ophthalmologist is strongly recommended. • Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics. 		
	Grade 3–4	Discontinue REGN2810.	<ul style="list-style-type: none"> • Treat with systemic corticosteroids such as prednisone at a dose of 1-2 mg/kg per day. When symptoms improve to ≤Grade 1, steroid taper should be started and continued over no less than 4 weeks. 		

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Hepatic events <ul style="list-style-type: none"> Hepatitis Hepatitis, Autoimmune 	Grade 1–2	Withhold REGN2810 if there is a treatment-emergent concurrent elevation of ALT and bilirubin that corresponds to an upward shift of 2 or more grades in both parameters.	<ul style="list-style-type: none"> Monitor liver function tests more frequently until returned to baseline values. 	Symptoms may include (but are not limited to): <ul style="list-style-type: none"> Elevations in: <ul style="list-style-type: none"> AST >2.5 × ULN ALT >2.5 × ULN Total bilirubin >1.5 × ULN Fever Malaise Upper quadrant abdominal pain 	All attempts should be made to rule out other causes such as metastatic disease, progressive liver disease, viral hepatitis, alternative drug toxicity, infectious causes and/or myositis.
	Grade 3–4	Discontinue REGN2810 when AST or ALT >5.0 times ULN and/or total bilirubin >3.0 times ULN.	<ul style="list-style-type: none"> Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury, if necessary. Treat with high-dose IV glucocorticosteroids for 24–48 hours. When symptoms improve to grade 1 or less, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1–2 mg/kg should be started and continued over no less than 4 weeks. If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity^b. Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. 		
Nausea	≤Grade 1	No change in dose	<ul style="list-style-type: none"> Nausea should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake. 		
	Grade 2	Hold until ≤Grade 1. Resume at same dose level. May increase dosing interval by 1 week if it takes more than 4 weeks for toxicities to resolve.			
	Grade 3	Hold until <Grade 2. May increase dosing interval by 1 week for each occurrence. Discontinue if toxicities do not resolve within 12 weeks.			
	Grade 4	Off protocol therapy			

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Neutropenia	≤Grade 1	No change in dose			
	Grade 2	No change in dose			
	Grade 3	No change in dose			
	Grade 4	Hold until resolves to ≤Grade 1. May increase the dosing interval by 1 week. Discontinue if toxicities do not resolve within 12 weeks.			

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Pneumonitis events <ul style="list-style-type: none"> • Pneumonitis • Interstitial lung disease • Acute interstitial pneumonitis 	Grade 1	Consider hold of therapy. REGN2810 may be continued with close monitoring.	<ul style="list-style-type: none"> • Radiologic findings should be followed on serial imaging studies at least every 3 weeks. • Monitor for symptoms every 2–3 days. • Consider pulmonary consultation and/or bronchoscopy if clinically indicated. 	Symptoms may include (but are not limited to): <ul style="list-style-type: none"> • Abnormal breath sounds • Chest pain and/or tightness^c • Dyspnea^c • Dry cough • Fatigue • Fever • Hemoptysis 	All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection.
	Grade 2	Hold REGN2810	<p>To rule out other causes such as infection:</p> <ul style="list-style-type: none"> • Consider pulmonary consultation with bronchoscopy and biopsy/bronchoalveolar lavage (BAL). • Consider pulmonary function tests. • Follow radiologic findings on serial imaging studies every 1–3 days <p>If the patient is determined to have study drug associated pneumonitis:</p> <ul style="list-style-type: none"> • Monitor symptoms daily; consider hospitalization. • Treat with systemic corticosteroids at a dose of 1–2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • Treatment with REGN2810 may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of methylprednisolone 10 mg by mouth daily or less. Repeat chest imaging monthly as clinically indicated. <p>For Grade 2 pneumonitis that improves to ≤ Grade 1 within 12 weeks, the following rules should apply:</p> <ul style="list-style-type: none"> • <u>First episode of pneumonitis</u>: May increase dosing interval by one week in subsequent cycles. • <u>Second episode of pneumonitis</u>: Discontinue REGN2810 if upon rechallenge the patient develops a second episode of ≥ Grade 2 pneumonitis. 		
	Grade 3–4	Discontinue REGN2810.	<ul style="list-style-type: none"> • Consider pulmonary function tests with pulmonary consult. • Bronchoscopy with biopsy and/or BAL is recommended. • Treat with IV steroids (2–4 mg/kg per day prednisone or equivalent). When symptoms improve to grade 1 or less, a high-dose oral steroid (1–2 mg/kg prednisone once per day or 4 mg dexamethasone every 4 hours) taper should be started and continued over no less than 4 weeks. • Add prophylactic antibiotics for opportunistic infections. • If IV steroids followed by high-dose oral steroids does not reduce initial symptoms within 48–72 hours, treat with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45–60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab. 		

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Renal events <ul style="list-style-type: none"> • Nephritis • Nephritis autoimmune • Renal failure • Renal failure, Acute 	Grade 1	Consider withholding REGN2810 if event does not improve with symptomatic treatment	<ul style="list-style-type: none"> • Provide symptomatic treatment. • Monitor creatinine weekly; when it returns to baseline, resume routine creatinine monitoring per protocol. 	Symptoms may include (but not limited to): <ul style="list-style-type: none"> • Fatigue • High blood pressure • Increased serum creatinine • Swelling 	All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury to other chemotherapy agents. A renal consultation is recommended.
	Grade 2	Consider withholding REGN2810.	<ul style="list-style-type: none"> • Systemic corticosteroids at a dose of 1–2 mg/kg/day of prednisone or equivalent may be indicated. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. • Consider prophylactic antibiotics for opportunistic infections. • Consider renal biopsy. • If elevations persist >7 days or worsen, treat as Grade 4. 		
	Grade 3-4	Discontinue REGN2810.	<ul style="list-style-type: none"> • Renal consultation with consideration of ultrasound and/or biopsy as appropriate. • Monitor creatinine daily. • Treat with systemic corticosteroids at a dose of 1–2 mg/kg prednisone or equivalent once per day. • When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • Discontinue REGN2810 if unable to reduce corticosteroid dose for irAEs to ≤10 mg. • REGN2810 treatment may be restarted and the dose modified as specified in the protocol. 		

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Skin events <ul style="list-style-type: none"> • Dermatitis exfoliative • Erythema multiforme • Stevens-Johnson syndrome • Toxic epidermal necrolysis If considered to be immune related, \geq Grade 3 or result in dose modification or discontinuation: <ul style="list-style-type: none"> • Pruritus • Rash • Rash generalized • Rash maculo-papular • Vitiligo 	Grade 1–2	No change in dose	<ul style="list-style-type: none"> • Symptomatic treatment should be given such as topical glucocorticosteroids (eg, betamethasone 0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral antipruritics (eg, diphenhydramine HCl or hydroxyzine HCl). • Treatment with oral steroids is at investigator discretion for Grade 2 events. 		All attempts should be made to rule out other causes such as metastatic disease, infection, or allergic dermatitis.
	Grade 3	Hold REGN2810.	<ul style="list-style-type: none"> • Consider dermatology consultation and biopsy for confirmation of diagnosis. • Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg four times orally daily. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. 		
	Grade 4	Permanently discontinue REGN2810.	<ul style="list-style-type: none"> • Dermatology consultation and consideration of biopsy and clinical dermatology photograph. • Initiate steroids at 1–2 mg/kg prednisone or equivalent. When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. 		
Thrombocytopenia	\leq Grade 1	No change in dose			
	Grade 2	No change in dose			
	Grade 3	No change in dose	<ul style="list-style-type: none"> • Grade 3 drug-related thrombocytopenia >7 days or associated with bleeding requires discontinuation. 		
	Grade 4	Hold REGN2810 until resolves to \leq Grade 1. May increase the dosing interval by 1 week.	<ul style="list-style-type: none"> • Grade 4 drug-related thrombocytopenia >7 days or associated with bleeding requires discontinuation. 		

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Vomiting	≤ Grade 1	No change in dose	<ul style="list-style-type: none"> Vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake. 		
	Grade 2	Hold until ≤Grade 1. Resume at same dose level. May increase dosing interval by 1 week if it takes more than 4 weeks for toxicities to resolve.			
	Grade 3	Hold until <Grade 2. May increase dosing interval by 1 week for each occurrence. Discontinue if toxicities do not resolve within 12 weeks.			
	Grade 4	Off protocol therapy			

^a The signs and symptoms may be associated with any of the diagnoses in the associated “Event(s)” column.

^b REMICADE (Infliximab) prescribing information

^c If symptoms indicate possible new or worsening cardiac abnormalities, additional testing and/or a cardiology consultation should be considered.

APPENDIX 6. GUIDELINES FOR BIOPSIES FOR LOCALLY ADVANCED CSCC

This appendix provides timepoints and research procedures for biopsies in patients with locally advanced CSCC. Because of the potential for sampling error with any single biopsy, two separate sites (preferably on the same target lesion) should be biopsied for any biopsy assessment.

Timepoints:

1. Baseline (required):

The study inclusion criteria require that the sponsor be provided with archived pathology material that will be used for the purpose of confirmation of the diagnosis of CSCC by central pathology review for all study patients. This baseline biopsy is intended for exploratory assessments, but only used for this purpose after central pathology confirmation of diagnosis of CSCC is obtained on archived material. If the archived material is not sufficient for confirmation of diagnosis of CSCC by central review, baseline biopsy material will be used for central pathologic confirmation; remaining baseline tumor material can only be used for exploratory assessments after central pathology confirmation of diagnosis of CSCC has been established.

2. Baseline or at any scheduled response assessment (If needed to differentiate benign versus malignant area of skin):

Areas of indeterminate-appearing tissue should be biopsied to distinguish malignant tissue versus benign process (eg, scarring, fibrosis). In circumstances in which biopsies are planned, it is preferred that these be performed on the day of a regularly-scheduled response assessment.

3. On cycle 1 day 29 (± 3 business days) for exploratory assessments 5 mm each) should be obtained, preferably from the same externally visible lesion from which the baseline biopsies were taken. Both samples will be provided to the sponsor for exploratory assessments. The cycle 1 day 29 samples are not intended for local pathology review.

4. At clinical complete response (required): Complete response status for externally visible lesions requires biopsies of 2 sites on the same lesion which are histologically negative for malignancy (see secondary objectives).

5. At progression (strongly encouraged): Two sites of externally visible progressing tumor should be biopsied.

Research procedures for ALL biopsies:

1. Where and How:

The technique and sites of biopsies will be selected by the investigator based on the sizes and locations of lesions. Generally, biopsies will be 3 to 5 mm punches. Biopsies should not be taken at the perimeter of a lesion because this could interfere with measurement of bi-dimensional perpendicular diameters for response assessments. Whenever possible, biopsy sites should be ≥ 5 mm from the edge of baseline lesional area.

2. How many:

For exploratory assessments: 2 biopsies of externally visible CSCC will be obtained at baseline and again at cycle 1 day 29 (± 3 business days). Two biopsies at time of progression should also be obtained. In the event that an investigator determines that clinical circumstances interfere with the ability to obtain the recommended number of minimal biopsies at baseline or cycle 1 day 29 (± 3 business days), the monitor will be contacted to discuss the number of biopsies that can be reasonably obtained and this will not be deemed a protocol violation.

For indeterminate-appearing tissue: In addition to these biopsies for exploratory assessments, biopsies should be taken at baseline and at any response assessment if there is tissue that is indeterminate-appearing regarding presence of benign versus malignant tissue. When the decision is made to biopsy a lesion (or an area of a lesion) to clarify benign versus malignant status, 4 biopsies should be taken. This approach will mitigate the possibility for sample error or misleading results with any 1 biopsy, because 2 sites in the “indeterminate appearing” tissue will be selected. At each of the selected sites, 2 biopsies should be performed that are approximately adjacent (1 for central review, 1 for local pathology review). As such, 4 biopsies would be performed (2 sites, with paired biopsies at each site: 1 for local pathology, and 1 for central = 4 total biopsies).

3. Annotation and Photography

The punch biopsies should be labeled (annotated) on the patient and photographed, such that on review of the photograph the following information is clear for each biopsy site: the study week and day of the biopsy (eg, Baseline, Cycle 1, Day 29, etc), the identifying number of the biopsy (because at least 2 sites would be biopsied), and which samples are for central review and which samples are for local review. The tumor will also be annotated with a skin pen to indicate the tumor perimeter and delimiters of the longest bi-dimensional perpendicular axes. All biopsies will be photographed and annotated, including the cycle 1 day 29 biopsies that are for exploratory assessments.

Annotated photographs must be uploaded into Canfield secure website (see [Appendix 7](#)).

4. Disposition of Samples

Biopsy samples required for exploratory assessments (baseline, cycle 1 day 29) will be provided to the sponsor. It is also strongly encouraged that biopsy samples at time of progression be obtained for exploratory assessments, and these should also be provided to the sponsor.

For each site that is biopsied to clarify indeterminate tissue, the entire block for one biopsy sample (designated for central) must be submitted to the vendor as per the Central Laboratory Manual. Because each biopsy site is sampled twice (closely adjacent samples) when there is indeterminate-appearing tissue, the second sample may be used for local pathology review. If only 1 adequate (eg, interpretable by pathologist) sample is obtained at a biopsy site, it will be provided to the sponsor for central review to address the study objectives ([Section 2](#)).

5. Classification of Pathology Samples

For response assessments in which biopsies were performed, pathology results guide the determination of the area of invasive CSCC versus benign tissue. Residual squamous carcinoma in situ will not be deemed to be invasive cancer. A minute focus of residual CSCC in an otherwise benign responding biopsy sample will not automatically supersede a determination of

partial response. However, the best response that can be recorded if the pathology report demonstrates any residual CSCC is partial response (not complete response).

APPENDIX 7. DIGITAL PHOTOGRAPHIC PROCEDURES

Image Capture

- Close-up view with millimeter scale of the target area of the CSCC
- Global view of the target CSCC area

Equipment

- Camera: Canon SL1 with Ranging Lights
- Lens: 60mm Canon Lens
- Flash: Canfield TwinFlash RL
- Millimeter scale attachment
- Dedicated laptop with Canfield Capture Application (software includes capturing, viewing and transferring images)
- Canfield Tracing and Analysis application
- Standardized background material

The supplied equipment is to be used exclusively for this study. No modification, adjustments, or repairs of the camera equipment are to be undertaken without the expressed instruction of Canfield Scientific, Inc.

Canfield will provide each study site with the necessary hardware as well as technical support as needed. All supplied photographic equipment remains the property of the Sponsor.

Proper Patient Preparation and Positioning:

In these clinical photographs for the duration of the study, the only variable allowed to change is the skin condition itself. Therefore, anything extraneous to the condition (furniture, etc.) is to be eliminated from the photographic field, starting at the entry visit through the final visit. The necessity of good end-of-study photographs should be stressed to patients to ensure their cooperation. Lighting, framing, exposure, and reproduction ratios must be held constant. In the end, the images should read like a time-lapse movie.

In the close up view, the area of interest is the individual target lesion itself. In the global view, the area of interest includes the target lesion as well as relevant anatomical landmarks, e.g. side of face, side of neck, upper torso, full view of shoulder, etc. Photographs should be taken with the camera positioned at the same vertical height as the center of area of interest. Further, all shots should be made with the axis of the camera lens perpendicular to the surface of area of interest when possible. Glancing shots where the camera lens is not perpendicular to the patient's area of interest are to be avoided as these photographic angles may distort the image perspective yielding inaccuracies when measurement of lesions is performed on photos by central review.

The supplied standardized background material is to be used. Do not use wrinkled or crimped material.

The Canfield Capture software controls the setting of the camera specific to the protocol. The lens is set for auto focusing. The **close-up view** is accomplished using the attached standardized mm scale. The **global view** is accomplished when the ranging lights converge on the target area. Any doubt as to the correctness of the photographic technique should result in an immediate re-shoot.

For each global view and each close up view, an unannotated photograph must be taken followed by a manually annotated photograph.

For response assessments, Canfield imaging software should be used to assure that the photograph is taken at the same position and angle as the Baseline photograph. The annotated image from the prior visit should be referenced on the laptop screen prior to making annotations on the new image.

Photographic Procedures:

1. Prior to capturing the patient images using the camera system, the photographer launches the Canfield Scientific Canfield Capture Application by selecting the icon from the desktop.
2. The photographer either creates a New Patient for an initial visit or, for a return subject, highlights the appropriate existing Patient ID listed in the Canfield Capture database. The visit name (as per study schedule) is selected by the photographer and the image date is captured by the software.
3. With the patient's target area positioned correctly in front of the camera system, the Photographer adjusts the camera distance for accurate system focus. The first capture is a Close-up view of patient's target CSCC area(s) using the attached mm scale, consisting of one individual CSCC lesion. The second capture is Global view of patient's target CSCC area(s), consisting of up to two individual CSCC lesions. For the global view the camera is moved closer to or further away from the target until the two green ranging lights converge to become one dot.
4. The Photographer captures the image and is then prompted to review image acceptability. The Photographer either accepts the image and moves on to the next capture or does not accept and recaptures the image.
5. After capturing the series of non-annotated lesion(s), the Investigator will annotate the circumference and axes delimiters of lesion with supplied skin pen. **If any biopsies are taken at this visit (eg, baseline, cycle 1 day 29, at any regularly scheduled visit, or at time of progression), each biopsy will also be annotated as per [Appendix 6](#).** Following the same procedure as the non-annotated image capture the site will capture the series of annotated lesion(s) images
6. Following the session, the Photographer submits the images to Canfield. Upon exiting, the software automatically reads, checksums, encrypts, packages, and duplicates the data to submit to Canfield via internet or removable media submission.
 - a. Internet: A secure, validated, compliant web server set up at Canfield is used for secure transfer of study images by study sites. Images are to be transferred the day they are recorded. Only approved individuals by the Sponsor have access to the website.

The application logs a record of this action to a local database and prompts the Photographer when completed.

1. Upon completion of photography session, the Investigator will log in to the Canfield tracing application to annotate the lesion and the software will provide measurements (surface area, longest diameter, perpendicular diameter) of the lesion.
2. Trained Canfield staff review the data files for technical quality and acceptability and communicate any comments to the site.
3. At the end of the study, a copy of site specific patient images will be provided to each site. This is in addition to the Photography Result Reports available for printing from the Clinical Services Website after each session. Remote access to all images by the Sponsor is also provided.

Any questions or problems regarding the photographic portion of this study are to be forwarded to the assigned Project Manager at Canfield Scientific.

Canfield Scientific, Inc.

253 Passaic Avenue

Fairfield, NJ 07004 United States

Toll-free telephone number: (800) 815-4375

Telephone number: (973) 276-0300

Facsimile number: (973) 276-0333

**APPENDIX 8. EASTERN COOPERATIVE ONCOLOGY GROUP
PERFORMANCE STATUS**

Grade	Description
0	Fully active; able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; Up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair 50% or more of waking hours
4	Completed disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

Source: [Oken 1982](#)

APPENDIX 9. FACTORS TO CONSIDER IN ASSESSING THE RELATIONSHIP OF AES TO REGN2810 OR INFUSION PROCEDURE, STUDY PROCEDURE, OR COMBINATION TREATMENT.

Is there a reasonable possibility that the event may have been caused by the study drugs or infusion procedure, study procedure, or concomitant treatment?

No:

- due to external causes such as environmental factors or other treatment/s being administered
- due to the patient's disease state or clinical condition
- do not follow a reasonable temporal sequence following the time of administration of the dose of REGN2810, study procedure, or combination treatment
- do not reappear or worsen when dosing with REGN2810, study procedure, or combination treatment is resumed
- are not a known response to REGN2810 or infusion procedure, study procedure, or combination treatment based upon pre-clinical data or prior clinical data

Yes:

- could not be explained by environmental factors or other treatment/s being administered
- could not be explained by the patient's disease state or clinical condition
- follow a reasonable temporal sequence following the time of administration of the dose of REGN2810
- resolve or improve after discontinuation of REGN2810, study procedure, or combination treatment
- reappear or worsen when dosing with REGN2810, study procedure, or combination treatment is resumed
- are known to be a response to REGN2810 or the infusion procedure, study procedure, or combination treatment based upon pre-clinical data or prior clinical data

NOTE: This list is not exhaustive.

IND: 127100

Regeneron Pharmaceuticals, Inc.

EudraCT: 2016-000105-36

Clinical Study Protocol**A PHASE 2 STUDY OF REGN2810, A FULLY HUMAN MONOCLONAL ANTIBODY TO PROGRAMMED DEATH – 1 (PD-1), IN PATIENTS WITH ADVANCED CUTANEOUS SQUAMOUS CELL CARCINOMA**

Compound:	REGN2810 (anti-PD-1 mAb)
Clinical Phase:	2
Protocol Number:	R2810-ONC-1540
Protocol Version:	R2810-ONC-1540 Amendment 5 Global
Amendment 5 Global Date of Issue:	<i>See appended signature page</i>
Amendment 4 Global Date of Issue:	22 JUN 2017
Amendment 3 Global Date of Issue:	18 May 2017
Amendment 2 Global Date of Issue:	12 DEC 2016
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Scientific/Medical Monitor:	Elizabeth Stankevich, BS Director, Clinical Sciences, Oncology Matthew Fury, MD, PhD Senior Director, Clinical Sciences, Oncology Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591

Confidential: This document contains confidential information that is the property of Regeneron Pharmaceuticals, Inc., [REDACTED]

[REDACTED] This information must not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Regeneron Pharmaceuticals, Inc.

Amendment History

Amendment 5 Global

The following table outlines the changes made to the protocol and the affected sections

Change	Sections Changed
In response to health authority guidance, added an interim analysis for Group 2 and revised the statistical considerations (ie, secondary efficacy outcome measures, analysis sets, definition of the observation period for treatment-emergent adverse events).	Synopsis – Secondary Variables Section 3.2 Planned Interim Analysis Section 8.2.2 Secondary Outcome Measures Section 9.3.1 Full Analysis Set Section 9.3.2 . Per Protocol Set (<i>deleted</i>) Section 9.5.2 Efficacy Analyses Section 9.5.4.1 Adverse Events Section 9.7 Interim Analysis
Revised footnote “t” in Table 5 and footnote “s” in Table 6 for clarity to emphasize that all patients who discontinue study treatment should enter the follow-up schedule of events, unless there was a progression of disease or other factors (eg, withdrawal of consent)	Table 5 Study Schedule (Screening and Treatment) for Groups 1 and 2 Table 6 Study Schedule (Screening and Treatment) for Group 3
Specified that tumor staging (according to AJCC cancer staging manual, 7th edition) will be collected as part of baseline characteristics	Section 8.1 Demographic and Baseline Characteristics Section 20 References
Clarified that use of the Canfield tracing application is optional	Appendix 6 Digital Photographic Procedures
Made editorial changes for clarity and consistency	Table 6 Study Schedule (Screening and Treatment) for Group 3 Section 8.2.1 Primary Efficacy Outcome Measure Section 8.2.2 Secondary Outcome Measures Section 9.5.3 Exploratory Analyses Appendix 8 Factors to Consider in Assessing the Relationship of AEs to REGN2810 or Study Conduct

Amendment 4 Global

The following table outlines the changes made to the protocol and the affected sections

Change	Sections Changed
An exclusion criterion has been added for the following reason: Patients who have previously been treated with idelalisib will be excluded from treatment with REGN2810 as a result of the safety findings for 3 patients with indolent lymphoma previously treated with idelalisib, a phosphatidylinositol 3-kinase (PI 3-K) inhibitor, in study R1979-ONC-1504. Following a single dose of REGN2810 monotherapy in each case, 2 patients experienced severe stomatitis and/or skin reactions. The third patient experienced myositis and myasthenia gravis after 2 doses of REGN2810.	Section 4.2.2 Exclusion Criteria #21
Additional safety guidance language added for the management of patients developing stomatitis or mucositis	Section 5.3.2 Study Treatment Hold or Discontinuation
An adverse event of special interest (AESI) has been added to the list of AESIs: An irAE of any grade in a patient previously treated with a PI 3-K inhibitor.	Section 7.2.3 Other Events that Require Accelerated Reporting to the Sponsor

Amendment 3 Global

Changes to the protocol are summarized in the table below.

Change	Section Affected
The primary purpose of this amendment is to enroll metastatic (nodal or distant) cutaneous squamous cell carcinoma (CSCC) patients who are dosed at 350 mg flat dose every 3 weeks (Q3W) as Group 3. This cohort opens after the completion of enrollment to Group 1 and provides data in support of Q3W dosing in CSCC patients. Updated number of patients to up to 182 adult patients (Group 3: 53 patients). Primary objective, study description, schedule	Clinical Study Protocol Synopsis: Objectives, Study Design, Study Duration, Population, Treatments, Endpoints, Statistical Plan Section 1.2.1 Rationale For Dose Selection Section 2.1 Primary Objectives Section 3.1 Study Description and Duration Section 3.1.1 Study Groups Section 4.1 Number of Patients Planned Section 4.2 Patient Population

<p>of events, duration, treatment assignment, primary and secondary variables, secondary outcomes measure, follow-up, and statistical plan of the study are revised to include the additional group.</p> <p>Additionally, the amendment contains clarifications and minor revisions suggested at the external Steering Committee Meeting of 7 April.</p>	<p>Section 4.2.1 Inclusion Criteria, #2, #5</p> <p>Section 5.1 Investigational Treatment</p> <p>Section 5.3.1 Dose Modification</p> <p>Table 2 Dose Reductions</p> <p>Section 5.5 Method of Treatment Assignment</p> <p>Table 6 Study Schedule (Screening and Treatment) for Group 3</p> <p>Table 7 Study Schedule: Follow-Up (After Cycle 12 for Group 1 and Group 2 Patients, or after Cycle 6 for Group 3 Patients)</p> <p>Section 6.2.1 Unscheduled Visits</p> <p>Section 6.2.2 Follow-up</p> <p>Section 6.3.1 Procedures Required Only at the Screening/Baseline Visit</p> <p>Section 6.3.2 Efficacy Procedures</p> <p>Section 6.3.6 Group 3 Only: Guidance Regarding Patients who Wish to Continue Treatment Beyond 54 Weeks</p> <p>Section 8.2.1 Primary Efficacy Outcome Measure</p> <p>Section 8.2.2 Secondary Outcomes Measure</p> <p>Section 9.1 Statistical hypothesis</p> <p>Section 9.2 Justification of Sample Size</p> <p>Table 8 The 95% Binomial Exact Confidence Intervals for Observed ORR in Group 1 and Group 3 Given a Sample Size of 50 Patients (Based on 85% Power)</p> <p>Section 9.5.2 Efficacy Analyses</p> <p>Section 9.6 Multiplicity Considerations</p> <p>Appendix 1 Response Evaluation Criteria in Solid Tumors: RECIST Guideline (Version 1.1)</p> <p>Appendix 2 Composite Response Criteria for Patients with Locally Advanced CSCC</p> <p>Appendix 3 REGN2810 Pharmacokinetic Sampling and Assessment Schedule</p>
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Added clarification regarding the 3 independent central imaging review committees.	Section 3.3.3 Independent Review Committees
Added clarification for procedures if visits are missed.	Section 5.3.2 Study Treatment Hold or Discontinuation
Removed ADA sample at the end of study visit. Clarify when PK samples will be collected. End of study definition added.	Table 5 Study Schedule (Screening and Treatment) for Groups 1 and 2, footnotes m, n, t
Updated HBV, HCV, and HIV screening at the screening/baseline visit.	Section 6.3.1 Procedures Required Only at the Screening/Baseline Visit
Removed language “in triplicate” for ECG recordings.	Table 5 Study Schedule (Screening and Treatment) for Groups 1 and 2, footnote f Section 6.3.3.3 Electrocardiogram
Clarified SAEs in event of hospitalization or death.	Section 7.1.2 Serious Adverse Event
Removed the NCI-CTCAE v4.03 and clarified when AEs should be reported.	Section 7.2.1 Adverse Events
Clarified timing in the event an SAE occurs after last dose of study treatment.	Section 7.2.2 Serious Adverse Events
Clarified when to report pregnancy.	Section 7.2.3 Other events that Require Accelerated Reporting to the Sponsor
Added text about relationship of AEs to study conduct.	Section 7.3.2 Evaluation of Causality
Updated ADA variables definitions.	Section 8.4 Anti-drug Antibody Variables
Updated title of appendix.	Appendix 8 Factors to Consider in Assessing the Relationship of AEs to REGN2810 or Study Procedure
Minor editorial/grammatical updates	Throughout document
Appendix 1 EORTC-QLQ-C30 (VERSION 3) deleted. The study teams are expected to complete QOL data per Schedules of Events.	

Amendment 2 Global

The primary purpose of this amendment is to revise the text for toxicity management.

In addition, there have been several other changes:

- To integrate comments raised by regulatory authorities to provide a common global protocol
- A new section that outlines the role of study committees has been added
- Some inclusion/exclusion criteria have been clarified
- Some footnotes to the Study Schedule Tables have been modified
- Description of the follow-up period has been revised
- Clarified time points and research procedures for biopsies
- Minor edits

Amendment 2DE

The purpose of this amendment was to incorporate the following changes and clarifications requested by the Paul Ehrlich Institute in Germany:

- Add baseline testing for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV)
- Clarify exclusion criteria for active infection requiring therapy, and for known allergy to doxycycline or tetracycline
- Extend post treatment follow up to 5 half-lives (105 days) after the last dose of REGN2810

Amendment 1

The purpose of this amendment was to incorporate the following changes and clarifications requested by the FDA:

- Provide further justification for including patients with regional nodal metastases in Group 1 rather than Group 2
- Clarification of the note for patients with hepatic metastases who wish to enroll in Group 1 (Inclusion 5, Hepatic Function)
- Revise Table 3 to require dose reduction for grade 3 nonhematological toxicities, grade 4 hematological toxicities, and grade 3 thrombocytopenia lasting greater than seven days or associated with bleeding
- Additional guidelines for administration of premedication with subsequent treatments for patients who experience infusion-related hypersensitivity reactions that are less than grade 3 and who plan to continue treatment
- Language added to Appendix 3 to clarify the approach to response assessments of externally visible tumors; a section on criteria for assessing response in extensively ulcerated lesions has been added.
- New language added to Appendix 7 on profile view to be obtained at baseline, and at subsequent visits as appropriate

Other minor modifications include:

- Clarification that patients who do not experience progressive disease will be followed for an additional non-treatment period of up to approximately 6 months with scans performed every 8 weeks
- Clarification regarding concomitant medications
- Time window added for vital signs collection
- Follow-up visit 4 will not require PK sample collection; the list of PK variables has been updated.

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Phase 2 Study of REGN2810, a Fully Human Monoclonal Antibody to Programmed Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma
Site Locations	Up to 45 sites globally
Objectives	<p>The primary objective of this study is to estimate the clinical benefit of REGN2810 monotherapy for patients with: metastatic (nodal or distant) CSCC, treated every 2 weeks (Group 1); or with unresectable locally advanced CSCC, treated every 2 weeks (Group 2); or with metastatic (nodal or distant) CSCC, treated every 3 weeks (Group 3); as measured by ORR according to central review in each Group.</p> <p>The secondary objectives of the study are:</p> <ul style="list-style-type: none">• To estimate ORR according to investigator review• To estimate the duration of response, progression-free survival (PFS), and overall survival (OS) by central and investigator review• To estimate the complete response (CR) rate by central review• To assess the safety and tolerability of REGN2810• To assess the pharmacokinetics (PK) of REGN2810 (at select sites only)• To assess the immunogenicity of REGN2810<ul style="list-style-type: none">– To assess the impact of REGN2810 on quality of life using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) <p>Exploratory Objectives (Group 2 only)</p> <ul style="list-style-type: none">• To explore the pharmacodynamic effects of REGN2810 in tumor biopsies obtained at baseline, during treatment, and at progression in CSCC patients treated with REGN2810

Study Design

This is a phase 2, non-randomized, 3-group, multicenter study of REGN2810 at a dose of 3 mg/kg administered intravenously (IV) every 2 weeks (Groups 1 and 2) or 350 mg administered IV every 3 weeks (Group 3) for patients with advanced CSCC. The study will have 3 groups. Groups 1 and 3 are for patients with metastatic CSCC. Group 2 is for patients with unresectable locally advanced CSCC. All patients will undergo screening procedures to determine eligibility within 28 days prior to the initial administration of REGN2810. There is no randomization or placebo control. After Group 1 enrollment is completed, Group 3 opens to enroll patients who will receive 350 mg REGN2810 flat dose every 3 weeks).

After a screening period of up to 28 days, Group 1 and Group 2 patients will receive up to twelve 56-day (8-week) treatment cycles for up to 96 weeks of treatment. Each patient will receive 3 mg/kg REGN2810 IV on days 1, 15 \pm 3, 29 \pm 3, and 43 \pm 3 during each treatment cycle. Tumor assessments will be made at the end of each treatment cycle. Extensive safety evaluations will occur on day 1 of each cycle, with routine safety evaluations to be conducted at each REGN2810 dosing visit.

Group 3 patients will receive up to six 63-day (9-week) treatment cycles for up to 54 weeks of treatment. Each patient will receive 350 mg REGN2810 IV on days 1, 22 \pm 3, and 43 \pm 3 during each treatment cycle. Tumor assessments will be made at the end of each treatment cycle. Extensive safety evaluations will occur on day 1 of each cycle, with routine safety evaluations to be conducted at each REGN2810 dosing visit.

A patient will receive treatment until the treatment period (96 weeks in Groups 1 and 2; 54 weeks in Group 3) is complete, or until disease progression, unacceptable toxicity, withdrawal of consent, or confirmed CR. Group 1 and 2 patients with confirmed CR after a minimum of 48 weeks of treatment may elect to discontinue treatment and continue with all relevant study assessments (eg, efficacy assessments). Patients in all groups who do not experience progressive disease (PD) will be followed for an additional nontreatment period of up to approximately 6 months with scans performed every 8 weeks.

Study Duration

Screening (up to 4 weeks), up to 96 weeks of treatment in Groups 1 and 2 (up to 54 weeks of treatment in Group 3), and up to 6 months of follow-up.

Population**Sample Size:**

Up to 182 adult patients (Group 1, 53 patients; Group 2, 76 patients; Group 3, up to 53 patients) are planned to enroll.

Target Population:

Patients with metastatic CSCC or with unresectable locally advanced CSCC.

Treatments**Study Drug**

Groups 1 and 2: REGN2810 3 mg/kg administered IV over 30 minutes every 14 days for up to 96 weeks.

Dose/Route/Schedule:

Group 3: REGN2810 350 mg IV over 30 minutes every 21 days for up to 54 weeks.

Variables**Primary:**

The primary efficacy endpoint for this study is ORR according to central review during the 12 treatment cycles (Groups 1 and 2) or 6 treatment cycles (Group 3). Overall response rate will be assessed separately for patients with metastatic CSCC or unresectable locally advanced CSCC:

- For patients in Group 1 and Group 3, RECIST version 1.1 will be used to determine ORR. For Group 1 and Group 3, patients in which all response assessments are performed on radiologic scans according to RECIST 1.1, the determination of the independent radiologic response assessment committee will serve as the central response assessment. Clinical or composite response criteria may be used for patients with externally visible target lesions, if all metastatic lesions are not measureable by RECIST (such as may occur in patients with bone-only metastases).
- For patients in Group 2, clinical response criteria will be used to determine ORR, for externally visible tumor(s) require bidimensional measurements according to World Health Organization (WHO) criteria. Composite response criteria will be used for patients who have both target lesions measurable by clinical response criteria and by RECIST 1.1 to determine ORR. In patients achieving a CR, tumor biopsies will be used in the final determination of complete versus PR.

Secondary:

The secondary efficacy outcome measures are:

- ORR for Group 1, Group 2, and Group 3 by investigator review
- Duration of response
- PFS
- OS
- CR rate
- Change in scores of patient-reported outcomes on EORTC QLQ-C30
- Adverse events (AEs)
- REGN2810 concentrations in serum (at select sites)
- Anti-REGN2810 antibodies

Exploratory Endpoint

The following exploratory analyses are planned:

- Fold-change in mRNA expression of genes expressed in tumor tissue
- Percent change in number of TILs (CD8+ T cells, CD4+ T cells, T regulatory cells, and tissue permitting, other subtypes such as B cells, myeloid-derived cells, NK cells, etc) and descriptive change in distribution of TILs in respect to tumor tissue and stroma
- Percent change in expression levels (mRNA and/or protein) of PD-L1, GITR, and LAG-3, and possibly other check-point modulators
- Change in number and type of genetic mutations in known oncogenes and potential tumor neoantigens
- Change in tumor mutation burden

Procedures and Assessments

Tumor imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) and digital medical photography (for externally visible lesions) will be performed to measure tumor burden and to characterize the efficacy profile of study treatments using response criteria.

Physical examination, laboratory tests, vital signs, electrocardiogram (ECG), pregnancy test for women of childbearing potential, and recording of AEs and concomitant medications will be performed to ensure patient safety and to characterize the safety profiles of study treatments.

Other assessments will include:

- Peripheral blood samples for PK
- Peripheral blood samples to assess anti-REGN2810 antibodies
- Tumor biopsies
- Quality of life assessments

Statistical Plan

The sample sizes for each group were selected such that the lower limit of the 95% confidence intervals of the estimated ORRs will be clinically meaningful. The non-clinically meaningful ORR of 15% for Group 1 and Group 3 will be excluded using the lower limit of 95% CI if the observed ORR is 28.0% or more. For Group 1 and for Group 3, 50 patients (in each group) will be required to provide at least 85% power to reject a null hypothesis. Although Group 1 and 3 have same statistical assumptions, efficacy in each group is analyzed independently. For Group 2, 72 patients will be required to provide at least 90% power to reject a null hypothesis. The non-clinically meaningful ORR of 25% for Group 2 will be excluded using the lower limit of 95% CI if the observed ORR is 36.1% or more. The sample sizes will be further increased by 5% to account for patients who withdraw prematurely from the study. Hence, the total sample sizes will be 53 patients for Group 1, 76 patients for Group 2, and 53 patients for Group 3, for up to 182 patients.

Demographic and baseline characteristics will be summarized descriptively by group and extent of prior therapy.

The primary endpoint for efficacy analyses is the ORR, by central review. For Group 1 and Group 3 patients in which all response assessments are done by RECIST 1.1 analysis of radiologic scans, the independent radiology review is the central review. For Group 2 patients (and some Group 1 and Group 3 patients), response assessments include photos and radiologic scans, and the independent composite review committee will serve as the central review. The investigator-assessed ORR will be considered as a secondary analysis. Patients who are deemed as not evaluable according to RECIST 1.1 or inevaluable by the composite efficacy criteria will be considered as not reaching PR/CR for ORR.

The primary analyses of efficacy are based on the exact binomial confidence interval approach, ie, whether the lower limit of 95% confidence interval will exclude a historical control ORR that is not deemed clinically meaningful for each group, respectively. The secondary analyses of efficacy as measured by duration of

response, duration of disease control, PFS, and OS will be summarized by median and its 95% confidence interval using the Kaplan-Meier method.

The quality of life of patients will be repeatedly measured by the EORTC QLQ-C30 at the day 1 of each treatment cycle. The change in scores of QLQ-C30 will be summarized descriptively at each post-baseline time point. The summary scores of QLQ-C30 will also be graphically depicted by longitudinal plots.

Safety observations and measurements including drug exposure, AEs, laboratory data, vital signs, and Eastern Cooperative Oncology Group (ECOG) performance status will be summarized and presented in tables and listings.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-drug antibody
ADL	Activities of Daily Living
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the concentration–time curve
BAL	Bronchoalveolar lavage
BCC	Basal cell carcinoma
BUN	Blood urea nitrogen
CR	Complete response
CRC	Central Review Committee
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CRP	C-reactive protein
CSCC	Cutaneous squamous cell carcinoma
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte antigen 4
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EOS	End of study
FAS	Full analysis set
FDG-PET	¹⁸ F-fluorodeoxyglucose positron emission tomography
FIH	First-in-human
FFPE	Formalin-fixed, paraffin-embedded
GCP	Good clinical practice

GITR	Glucocorticoid-induced TNFR family related gene
GnRH	Gonadotropin-releasing hormone
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papillomavirus
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
INR	International Normalized Ratio
irAE	Immune-related adverse event
IRB	Institutional Review Board
irRC	Immune-related response criteria
IUD	Intrauterine device
IV	Intravenous
IWRS	Interactive Web Response System
LAG-3	Lymphocyte activation gene-3
LD	Longest diameter
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LLOQ	Lower limit of quantification
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCCN	The National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NSCLC	Non-small-cell lung cancer
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed death-1 (receptor)
PD-L1, PD-L2	Programmed death ligand 1, programmed death ligand 2
PET	Positron-emission tomography
PFS	Progression-free survival
PI 3-K	phosphatidylinositol 3-kinase
PK	Pharmacokinetic

PR	Partial response
PT	Preferred term
Q2W	Every 2 weeks
Q3W	Every 3 weeks
RCC	Renal cell cancer
RECIST	Response Evaluation Criteria in Solid Tumors
Regeneron	Regeneron Pharmaceuticals, Inc.
RF	Rheumatoid factor
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Systems (software)
SOC	System organ class
SSC	Study Steering Committee
TEAE	Treatment-emergent adverse event
TIL	Tumor-infiltrating lymphocytes
TSH	Thyroid-stimulating hormone
US	United States
WBC	White blood cell

1. INTRODUCTION AND RATIONALE

1.1. Introduction

Cutaneous squamous cell carcinoma (CSCC) is the second most common malignancy in the United States (US), with approximately 186,000 to 420,000 individuals diagnosed with CSCC each year ([Karia 2013](#)). Precise incidence and mortality measurements are not available because these cancers are not included in the Surveillance, Epidemiology, and End Results (SEER) database. A review of other national databases indicates that incidence of non-melanoma skin cancers, mostly basal cell carcinoma (BCC) and CSCC, approximately doubled between 1994 and 2006 in the context of an aging population ([Rogers 2010](#)). Most CSCC patients have a favorable prognosis, but annual mortality is approximately 3,900 to 8,800 deaths in the US ([Karia 2013](#)). Risk factors for CSCC include UV exposure, advanced age, and immunosuppression ([Alam 2001](#), [Madan 2010](#)). Although the vast majority of individuals with diagnosis of CSCC or BCC have a very favorable prognosis, CSCC has a greater propensity for aggressive recurrences than BCC. Individuals diagnosed with CSCC, unlike those diagnosed with BCC, have an increased mortality compared with age-matched controls ([Rees 2015](#)).

In the American Joint Committee on Cancer 7th Edition Staging System, tumor size less than or greater than 2 cm is a key distinction between stage 1 and 2, and selected risk factors are also incorporated in the staging ([Farasat 2011](#)). Stage 3 designates CSCC with involvement of a single lymph node ≤ 3 cm, and stage 4 includes patients with a broad range of locally invasive tumors and/or distant metastatic disease ([Farasat 2011](#)). Limitations of this staging system include heterogeneity of outcomes in stage I and II tumors; alternative risk-adapted staging has been proposed but not externally validated ([Karia 2014](#)).

Surgical resection is the centerpiece of clinical management of CSCC. The primary goal is complete resection of cancer, and acceptable cosmetic outcome is a secondary goal ([Madan 2010](#)). The choice of surgical intervention is influenced by a number of factors, including size and histology of the tumor, expertise of the local clinical team, and comorbidities of the patient. Factors associated with poor prognosis in CSCC include tumor size >2 cm, tumor depth >2 mm, perineural invasion, host immunosuppression, and recurrent lesions ([Madan 2010](#), [Schmults 2013](#)).

Efficacy for radiation therapy for CSCC has been described in the adjuvant setting in a large retrospective study of 167 patients with nodal involvement who underwent surgical resection. Patients undergoing post-operative radiation therapy had a lower rate of locoregional recurrence compared to those who underwent surgery only (20 vs. 43%), and superior 5-year overall survival (OS) (73% vs. 54%) of CSCC ([Veness 2005](#)). In a small prospective phase 1 study of 15 CSCC patients who received post-operative radiation (60 to 66 Gy for 6 weeks) with concurrent erlotinib, the 2 year OS was 65% ([Heath 2013](#)).

For the small percentage of patients who develop unresectable locally recurrent or metastatic disease, treatment options are limited. A phase 2 prospective study of 14 patients with unresectable or inoperable CSCC treated with platinum based-chemoradiation, reported in abstract form only, found that OS at 3 years was 54% (Nottage 2012). In a single institution retrospective case series of 12 patients with unresectable CSCC that were treated with radiation therapy (median dose 60 Gy in 30 fractions) and concurrent cetuximab, median OS was 8 months (Samstein 2014). Durable disease control was achieved in some patients, and this retrospective study also reviewed other reports of CSCC treated with chemoradiotherapy (case reports, case series) in the literature, in which some patients experienced long term disease control (Samstein 2014). These results underscore that for patients with unresectable advanced CSCC, the malignancy is a life-threatening condition but some patients may achieve durable disease control with radiation-based therapy. As such, radiation-based therapy is appropriately considered for some patients with unresectable CSCC.

Regarding systemic therapies, there have been single-arm studies that often contained heterogeneous groups of CSCC patients with different stages of disease, but none of these studies clearly demonstrated therapeutic advantage (Maubec 2011, Nakamura 2013). As a result, there is a dearth of data to guide clinical decision-making for oncologists who take care of patients with advanced CSCC. The National Comprehensive Cancer Network (NCCN) guidelines do not provide firm recommendations. Cisplatin monotherapy, cisplatin plus 5-fluorouracil (5-FU), and cetuximab are discussed only as “possible options,” and participation in clinical trials is recommended with the caveat that such trials are scarce (Bichakjian 2015). One factor that has prevented the adoption of a standard-of-care for advanced CSCC is the lack of an adequate demonstration of safety of any regimen for this patient population. Two frequently-cited studies of cisplatin + 5-FU-based chemotherapy enrolled 14 and 7 advanced CSCC patients, respectively, and therefore were unable to provide a meaningful safety assessment (Sadek 1990, Khansur 1991). A more comprehensive description of the safety profile of cisplatin + 5-FU was obtained in a large randomized clinical trial for a different patient population, head and neck squamous cell carcinoma (HNSCC). Among 215 patients with a median age of 57 years who were treated with cisplatin + 5-FU for advanced HNSCC, 76% experienced Grade 3 or 4 toxicities. Given that CSCC occurs in an older patient population (Gray 1997, Diffey 2005, Karia 2014), the lack of optimization of dose and schedule of cisplatin and 5-FU for older individuals is a practical limitation to the clinical use of these regimens in CSCC. Advanced age increases the probability of requirement for dose reduction in the first cycle of chemotherapy among patients with advanced solid tumors (Gajra 2015). As such, platinum and/or 5-FU-based chemotherapy is not an attractive option for many CSCC patients due to safety and tolerability concerns associated with advanced age.

Targeting of the epidermal growth factor receptor (EGFR) in CSCC has been explored by several groups. In a phase 2 study of cetuximab monotherapy for patients with unresectable squamous cell carcinoma of the skin, median age was 79 years (Maubec 2011). The observed response rate was 28% (10/36 patients), median progression-free survival (PFS) was 4.1 months, and median OS was 8.1 months (Maubec 2011). A phase 2 study of panitumumab enrolled 16 patients with advanced CSCC that was deemed incurable; 2 patients had metastatic disease (Foote 2014). Overall response rate (ORR) was 31% (95% CI: 11-59%). These studies of EGFR-targeting monoclonal antibodies share some of the same limitations of the studies of cytotoxic

chemotherapy that were noted above, including small sample size and lack of demonstration of benefit in quality of life.

A review of the published literature for systemic therapy for CSCC demonstrates that response rates appear to be associated with extent of disease. [Table 1](#) includes only studies with a least 20 evaluable patients with advanced CSCC. Response rates for locally advanced (primary site) tumors are generally higher than response rates for tumors that have metastasized to regional lymph nodes or distant visceral sites. As such, in prospective clinical research for patients with advanced CSCC, it is appropriate to evaluate patients with locally advanced CSCC as a distinct group, and combine patients with nodal or distant visceral metastatic disease as another distinct group, such as has been done in pivotal trials in basal cell carcinoma ([Sekulic 2012](#), [Migden 2015](#)). Caveats regarding the response rates in [Table 1](#) are that the response assessment criteria for externally visible lesions were not described in the rigorous manner of contemporary studies in non-melanoma skin cancer ([Sekulic 2012](#), [Migden 2015](#)), and central review was only applied in the cetuximab study ([Maubec 2011](#)). With these caveats, a key observation from these studies is that patients with disease that has metastasized to lymph nodes or distant sites have response rates that are lower than those achieved in patients with disease that has remained localized at the primary site.

Table 1: Systemic Therapy for Advanced Cutaneous Squamous Cell Carcinoma

Study	Regimen	N	Response Rate, percent (number of responses/total evaluable lesions)		
			Overall	Primary	Metastatic, Nodal and Distant
1	Peplomycin (Ikeda 1986)	86	62 (53/86) ^a	68 (50/73) ^a	19 (5/26) ^a
2	Cis-retinoic acid+ interferon α + cisplatin (Shin 2002)	35	34 (12/35)	67 (8/12)	17 (4/23)
3	Irinotecan (Ikeda 1993)	34	41 (14/34)	38 (10/26)	50 (4/8)
4	Cis-retinoic acid + interferon α (Lippman 1992)	28	68 (19/28)	93 (13/14)	43 (6/14)
5	Cetuximab (Maubec 2011)	36	28 (10/36)	35 (6/17)	21 (4/19)
All	Total (all patients in Studies 1–5)	219	49 (108/219)	61 (87/142)	26 (23/90)

^a Response was assessed for each individual lesion on the peplomycin study. Some patients had more than 1 lesion assessed. Therefore, the number of response assessments is greater than the number of patients in the peplomycin study.

Adapted from [Nakumura 2013](#)

1.1.1. Blockade of the PD-1 Checkpoint with REGN2810

Under chronic stimulation, T cells lose proliferative and effector function capacity, often due to signal down-modulation via the increased expression of proteins such as programmed cell death-1 (PD-1), an inhibitory checkpoint receptor of the CD28 receptor family. Blockade of the PD-1/PD-L1 T-cell checkpoint pathway is an effective and well tolerated approach to stimulating the immune response, and has achieved significant objective responses in advanced melanoma, renal cell cancer (RCC), non-small-cell lung cancer (NSCLC), and other solid tumors ([Postow 2015](#)).

REGN2810 is a high-affinity, fully human, hinge-stabilized IgG4P antibody directed to the PD-1 receptor that potently blocks the interaction of PD-1 with its ligands, PD-L1 and PD-L2 (See the Investigator's Brochure for further details of nonclinical pharmacology and antitumor activity of REGN2810). REGN2810 is currently undergoing evaluation in the first-in-human (FIH) study R2810-ONC-1423 (NCT02383212). It is a phase 1, open-label, multicenter repeat-dosing study of REGN2810, alone and in combination with other anti-cancer therapies in patients with advanced malignancies, and contains both dose escalation and expansion cohorts.

1.2. Rationale

1.2.1. Rationale for Dose Selection

For Groups 1 and 2: As of 12 September 2015, 53 patients have been enrolled in study R2810-ONC-1423 in 8 dose escalation cohorts, including 3 monotherapy cohorts (1 mg/kg, 3 mg/kg, 10 mg/kg REGN2810 administered intravenously [IV] every 2 weeks [Q2W]) and 5 combination therapy cohorts (3 mg/kg REGN2810 administered IV Q2W in combination with various combinations of hypofractionated radiation therapy or cyclophosphamide). No dose-limiting toxicities have been observed. The dose escalation portion of the study established that 3 mg/kg REGN2810 administered IV over 30 minutes Q2W is the recommended monotherapy dosing regimen for the agent in further studies for advanced cancer patients.

For Group 3: This REGN2810 dose of 350 mg every 3 weeks (Q3W) was chosen for Group 3 based on the safety and preliminary anti-tumor activity observed in the ongoing FIH study R2810-ONC-1423 (NCT02383212), and was supported by modeling of REGN2810 exposure in serum based on data collected in the FIH study. Simulations of REGN2810 exposure in 1000 patients using population pharmacokinetic (PK) analyses indicated that: 1) the variability in REGN2810 exposure (CV%) was similar with body weight adjusted as compared to fixed doses; therefore, supporting the fixed dose selection, and 2) that a 350 mg Q3W dose resulted in similar ($\leq 20\%$ difference) C_{trough} , AUC_{12W} and C_{max} as compared to a 3 mg/kg Q2W dose used in the FIH study. These REGN2810 concentrations exceed those observed at the 1 mg/kg Q2W dose, and demonstrated clinical efficacy in the FIH study. At the 350 mg Q3W dose, C_{trough} values at steady state generally exceed concentrations of approximately 5 mg/L to 20 mg/L, above which (based on animal data) saturation of PD-1 target occupancy is expected to occur. Therefore, the 350 mg Q3W dose of REGN2810 is being proposed in Group 3 and in new phase 2 and phase 3 studies across the REGN2810 program.

1.2.2. Rationale for Study of REGN2810 in CSCC

The central role of sun exposure in the pathogenesis of CSCC is evident at the molecular and cellular level. Most somatic mutations in CSCC tumors are C > T transitions, consistent with UV damage (Durinck 2011, Pickering 2014, Li 2015). The total mutation burden of CSCC is approximately 30 to 60 per megabase, compared with approximately 13 per megabase in malignant melanoma, which is the tumor type with the highest mutation burden in The Cancer Genome Atlas (Durinck 2011, Pickering 2014, Li 2015). Pre-clinical studies suggest that UV light may also be carcinogenic due to incompletely understood immunosuppressive effects (Fisher 1982, Moodycliffe 2000), in addition to mutagenicity.

Cutaneous squamous cell carcinoma has several clinical and biological factors that suggest that it is appropriate for the clinical study of inhibition of the PD-1 immune checkpoint: high mutation burden ([Pickering 2014](#)), presence of tumor-infiltrating lymphocytes (TILs) ([Muhleisen 2009](#), [Freeman 2014](#)), association with immunosuppression as a risk factor ([Euvrard 2003](#)), evidence of direct immunosuppressive effects of UV radiation ([Yu 2014](#)), and some clinical efficacy with interferon α 2a-based treatment ([Lippman 1992](#)).

The presence of high mutation burden appears to be a shared characteristic of other solid tumors for which inhibition of the PD-1/PD-L1 axis has been associated with therapeutic efficacy, including melanoma, NSCLC, and bladder cancer ([Alexandrov 2013](#)). Among NSCLC patients treated with pembrolizumab, emerging clinical data suggest a direct correlation between mutation burden and clinical efficacy of PD-1 inhibition ([Rizvi 2015](#)). Preliminary clinical results from a phase 2 study of pembrolizumab for patients with advanced solid tumors that are hypermutated due to mismatch repair deficiency demonstrates that overall radiographic response rates are approximately 60% ([Le 2015](#)).

Taken together, these observations suggest that PD-1 inhibition may also achieve robust efficacy against CSCC. In the ongoing phase 1 study of REGN2810 for patients with advanced solid tumors (NCT02383212), evidence of biologic activity has been seen in the first cohort of REGN2810 monotherapy (1 mg/kg, administered IV every 2 weeks). A partial response (PR) was observed in a 52-year-old man with unresectable recurrent CSCC at the first tumor assessment after his first 4 doses of REGN2810, and was confirmed after 8 doses (the patient is still receiving treatment and PR has been maintained for 20+ weeks as of 18 Sep 2015). This patient has an extensive prior history of surgery, systemic therapy, and radiation therapy for recurrent disease for over 13 years. Additionally, a recent case report described a dramatic response to pembrolizumab (off-label use) in a male with recurrent unresectable CSCC ([Chang 2015](#)).

2. STUDY OBJECTIVES

2.1. Primary Objectives

The primary objective of this study is to estimate the clinical benefit of REGN2810 monotherapy for patients with: metastatic (nodal or distant) CSCC, treated Q2W (Group 1); or with unresectable locally advanced CSCC, treated Q2W (Group 2); or with metastatic (nodal or distant) CSCC, treated Q3W (Group 3); as measured by ORR (see [Appendix 1](#) and [Appendix 2](#)) according to central review in each Group.

2.2. Secondary Objectives

The secondary objectives for Group 1, Group 2, and Group 3 are:

- To estimate ORR (see [Appendix 1](#) and [Appendix 2](#)) according to investigator review
- To estimate the duration of response, PFS, and OS by central and investigator review
- To estimate the complete response (CR) rate by central review
- To assess the safety and tolerability of REGN2810

- To assess the PK of REGN2810 (at select sites only)
- To assess the immunogenicity of REGN2810
- To assess the impact of REGN2810 on quality of life using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)

2.3. Exploratory Objective (Group 2 only)

To explore the pharmacodynamic effects of REGN2810 in tumor biopsies obtained at baseline, during treatment, and at progression in CSCC patients treated with REGN2810 [REDACTED]

3. STUDY DESIGN

3.1. Study Description and Duration

This is a phase 2, non-randomized, 3-group, multicenter pivotal trial evaluating the efficacy and safety of REGN2810 in patients with advanced CSCC. After a screening period of up to 28 days, patients in Groups 1 and 2 will receive up to twelve 56-day (8-week) treatment cycles for a total of up to 96 weeks of treatment. Each patient will receive 3 mg/kg REGN2810 IV on days 1, 15±3, 29±3, and 43±3 during each treatment cycle. Tumor assessments will be made at the end of each treatment cycle. Extensive safety evaluations will occur on day 1 of each cycle; routine safety evaluations will be conducted at each REGN2810 dosing visit.

Group 1 and Group 2 patients will receive treatment until the 96-week treatment period is complete, or until disease progression, unacceptable toxicity, withdrawal of consent, or confirmed CR. Patients with confirmed CR after a minimum of 48 weeks of treatment may elect to discontinue treatment and continue with all relevant study assessments (eg, efficacy assessments). Patients who do not experience progressive disease (PD) will be followed for an additional nontreatment period of up to approximately 6 months (see [Table 7](#)) with scans performed every 8 weeks.

Group 2 patients: Biopsies are obtained at baseline and cycle 1 day 29. Biopsies at progression are strongly encouraged. Additional biopsies may be obtained at baseline and at response assessments to clarify malignant versus benign status of indeterminate-appearing tissue, at the discretion of the investigator ([Appendix 5](#)).

Group 3 patients: This cohort enrolls patients with metastatic CSCC. Group 3 only begins enrollment after completion of enrollment to Group 1. The regimen is a 350 mg flat dose Q3W for up to 54 weeks. Patients will receive treatment until the 54-week treatment period is complete, or until disease progression, unacceptable toxicity or withdrawal of consent. Patients who do not experience PD will be followed for an additional nontreatment period of up to approximately 6 months (see [Table 6](#)), with scans performed every 8 weeks. No research biopsies are required.

3.1.1. Study Groups

There will be 3 study groups:

- Group 1: Patients with metastatic CSCC. These patients are required to have CSCC metastases. Group 1 includes patients with both nodal metastatic and distant metastatic disease.
- Group 2: Patients with unresectable locally advanced CSCC. These patients are required to have disease that is considered inoperable or to have medical contraindication to surgery or radiation, or have not achieved disease control with these treatments (see [Section 4.2.1](#)).

The study populations in Group 1 and Group 2 include patients with both unresectable and metastatic CSCC, which is conceptually similar to the enrollment of patients with unresectable or metastatic melanoma in immunotherapy trials ([Larkin 2015](#)). The decision to analyze separate cohorts for patients with locally advanced (Group 2) and metastatic (Group 1) disease is based on a literature review of the reported experiences with other systemic therapies in CSCC, which demonstrates that response rates for various chemotherapy regimens generally are higher against advanced primary tumors that are locally advanced than against tumors that have metastasized to lymph nodes or distant visceral organs ([Nakamura 2013](#)). This observation of higher response rates in locally advanced versus metastatic patients is also seen in data from studies of Smoothed inhibitors against basal cell carcinoma, the most common non-melanoma skin cancer ([Sekulic 2012](#), [Migden 2015](#)).

Note in clarification: For patients with in-transit metastases ([Carucci 2004](#)), if the baseline comprehensive work-up confirms that there are no nodal metastases or distant metastases, the patient will be deemed to have locally advanced disease and would be enrolled in Group 2. Patients with in-transit metastases are typically managed by a multidisciplinary team ([Carucci 2004](#)), and, therefore, the multidisciplinary review regarding potential surgery or radiation therapy options that is required prior to study enrolment for all Group 2 patients is appropriate for patients with in-transit metastases.

- Group 3: This cohort opens after the completion of enrollment to Group 1, and is for patients with metastatic CSCC. As was the case for Group 1 patients, Group 3 patients are required to have metastatic disease). As in Group 1, Group 3 includes patients with both nodal metastatic and distant metastatic disease. Group 3 patients receive 350 mg REGN2810 Q3W for up to 54 weeks (whereas patients in Groups 1 and 2 received 3 mg/kg REGN2810 Q2W for up to 96 weeks).

Histologic confirmation of CSCC is required for all patients (Groups 1, 2, and 3), as per inclusion criterion 13 in [Section 4.2.1](#).

3.1.2. End of Study Definition

The end of study for Group 1 and 2 patients is approximately 6 months from the completion of 96 week treatment period. The end of study for Group 3 patients is approximately 6 months from the completion of 54 week treatment period.

3.2. Planned Interim Analysis

At the time of the planned efficacy analysis for Group 1 (6 months after last patient, first dose), an interim analysis of Group 2 patients will be performed in order to assess the risks and benefits of REGN2810 in unresectable locally advanced CSCC. This analysis will be restricted to Group 2 patients with potential for adequate follow-up, defined as patients who have the opportunity to receive approximately 9 months of study treatment at the time of the interim analysis. This analysis will provide an ORR (with 95% confidence interval) for Group 2 patients with adequate follow-up.

3.3. Study Committees

3.3.1. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) composed of members who are independent from the sponsor and the study sites will be established to monitor patient safety by conducting formal reviews of accumulated safety data.

The IDMC will provide the sponsor with appropriate recommendations on the conduct of the clinical study to ensure the protection and safety of the patients enrolled in the study, per IDMC charter.

3.3.2. Study Steering Committee

A Study Steering Committee (SSC) will be appointed by Regeneron Pharmaceuticals, Inc. (Regeneron), comprising approximately 3 to 7 investigators participating in the trial and Regeneron representatives from the study team. The SSC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SSC will review protocol amendments as appropriate. Together with the study team, the SSC will also develop recommendations for publications of study results including authorship rules. The details of the role of the steering committee will be defined in a steering committee charter.

3.3.3. Independent Review Committees

Three Independent Review Committees will be established to assess the primary endpoint of response rate by central review: independent radiologic response assessment committee, independent photographic response assessment committee, and independent composite response assessment committee. Committee members will follow charters that are established for each of these committees.

4. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

4.1. Number of Patients Planned

Up to 182 adult patients (Group 1, 53 patients; Group 2, 76 patients; Group 3, 53 patients) are expected to be enrolled at approximately 45 sites globally.

4.2. Study Population

The study will include eligible patients with metastatic (nodal and/or distant) CSCC (Group 1 and Group 3) and unresectable locally advanced CSCC (Group 2). Group 3 for metastatic CSCC opens only after enrollment to Group 1 is complete.

4.2.1. Inclusion Criteria

A patient must meet the following criteria to be eligible for inclusion in the study:

1. Histologically confirmed diagnosis of invasive CSCC.

Notes on tumor primary site: Patients for whom the primary site of squamous cell carcinoma was the dry red lip (vermillion) are not eligible. Patients with tumors arising on the cutaneous hairbearing (non-glabrous) lip with extension onto dry red lip (vermillion) may be eligible after communication with and approval from medical monitor. Patients for whom the primary site of squamous cell carcinoma was the anogenital area (penis, scrotum, and perianal region) are not eligible. Patients for whom the primary site is nose are only eligible if the investigator is able to establish unambiguously that the primary site was skin, not nasal mucosa with outward extension to skin.

Notes on tumor histology: Patients with mixed histologies (eg, sarcomatoid, adenosquamous) generally will not be eligible. Patients with mixed histology in which the predominant histology is invasive CSCC (with only a minimal component of mixed histology) may be eligible, after communication with and approval from medical monitor.

2. At least 1 lesion that is measurable by study criteria.

If a previously radiated lesion is to be followed as a target lesion, progression must be confirmed by biopsy after radiation therapy. Previously radiated lesions may be followed as non-target lesions if there is at least 1 other measurable target lesion.

Group 1 and Group 3: There must be at least 1 baseline measurable lesion ≥ 10 mm in maximal diameter (1.5 cm for lymph nodes) according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria ([Appendix 1](#); [Eisenhauer 2009](#))

Group 2: There must be at least 1 measurable baseline lesion in which the longest diameter (LD) and the perpendicular diameter are both ≥ 10 mm if followed by digital medical photography (see [Appendix 2](#)). Non-measurable disease for Group 2 is defined as either unidimensionally measurable lesions, tumors with margins that are not clearly

defined, or lesions with maximum perpendicular diameters less than 10 mm. Patients without measurable disease at baseline are not eligible for the study.

Note: In the case of a Group 1 or Group 3 patient with metastatic disease that does not meet target lesion criteria by RECIST 1.1 (eg, bone only lesions, perineural disease; [Appendix 1](#)) and with externally visible CSCC target lesion(s), [Appendix 2](#) may be used, in which bi-dimensional measurements are required (at baseline, perpendicular diameters must both be ≥ 10 mm). The patient would then be enrolled in Group 1 with the plan to measure externally visible target lesion(s) by photography with bi-dimensional measurements; the metastatic lesions that are not measurable by RECIST 1.1 criteria would be followed as non-target lesions on scans.

In the case of a Group 2 patient with a deeply invasive lesion that the investigator deems is best measured by magnetic resonance imaging (MRI) or computed tomography (CT), measurement for that target lesion will be done according to RECIST 1.1 criteria ([Appendix 1](#)). The requirement for a lesion to be measurable by RECIST 1.1 is that it must be ≥ 10 mm in longest dimension.

3. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 (ECOG PS 1 definition: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work; [Appendix 7](#)).
Note: Patients with ECOG PS > 1 are ineligible.

4. ≥ 18 years old

5. Hepatic function:

- a. Total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN; if liver metastases $\leq 3 \times$ ULN). Patients with Gilbert's Disease and total bilirubin up to $3 \times$ ULN may be eligible after communication with and approval from the medical monitor.
- b. Transaminases $\leq 3 \times$ ULN (or $\leq 5.0 \times$ ULN, if liver metastases)
- c. Alkaline phosphatase (ALP) $\leq 2.5 \times$ ULN (or $\leq 5.0 \times$ ULN, if liver or bone metastases)

Note for patients with hepatic metastases who wish to enroll in Group 1 or Group 3: If transaminase levels (AST and/or ALT) are $> 3 \times$ but $\leq 5 \times$ ULN, total bilirubin must be $\leq 1.5 \times$ ULN. If total bilirubin is $> 1.5 \times$ but $\leq 3 \times$ ULN, both transaminases (AST and ALT) must be $\leq 3 \times$ ULN.

6. Renal function: Serum creatinine $\leq 1.5 \times$ ULN or estimated creatinine clearance (CrCl) > 30 mL/min
7. Bone marrow function:
 - a. Hemoglobin ≥ 9.0 g/dL
 - b. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$
 - c. Platelet count $\geq 75 \times 10^9/L$
8. Ability to provide signed informed consent
9. Ability and willingness to comply with scheduled visits, treatment plans, laboratory tests, and other study-related procedures

10. Anticipated life expectancy >12 weeks

11. **Group 2 only:** Surgery must be deemed contraindicated in the opinion of a Mohs dermatologic surgeon, a head and neck surgeon, or plastic surgeon. A copy of the surgeon's consultation note from a clinical visit within 60 days of enrollment must be submitted.

Acceptable contraindications in the surgeon's note include:

- CSCC that has recurred in the same location after 2 or more surgical procedures and curative resection is deemed unlikely
- CSCCs with significant local invasion that precludes complete resection
- CSCCs in anatomically challenging locations for which surgery may result in severe disfigurement or dysfunction (eg, removal of all or part of a facial structure, such as nose, ear, or eye; or requirement for limb amputation)
- Other conditions deemed to be contraindicating for surgery must be discussed with the medical monitor before enrolling the patient.

12. **Group 2 only:** Patients must be deemed as not appropriate for radiation therapy.

Specifically, patients must meet at least 1 of the following criteria:

- a. A patient previously received radiation therapy for CSCC, such that further radiation therapy would exceed the threshold of acceptable cumulative dose, per the radiation oncologist. A copy of the radiation oncologist's consultation note, from a clinical visit within 60 days of enrollment, must be submitted.
- b. Judgment of radiation oncologist that such tumor is unlikely to respond to therapy. A copy of the radiation oncologist's consultation note, from a clinical visit within 60 days of enrollment, must be submitted.
- c. A clinic note from the investigator indicating that an individualized benefit:risk assessment was performed by a multidisciplinary team (consisting of, at minimum, a radiation oncologist AND EITHER a medical oncologist with expertise in cutaneous malignancies OR a dermato-oncologist, OR a head and neck surgeon) within 60 days prior to enrollment in the proposed study, and the radiation therapy was deemed to be contraindicated.

Acceptable contraindications to radiation therapy in the investigator's note for patients who have not received any prior radiation include:

- CSCCs in anatomically challenging locations for which radiation therapy would be associated with unacceptable toxicity risk in the context of the patient's overall medical condition in the opinion of the multidisciplinary team (eg, a neck tumor for which radiation therapy would result in potential need for a percutaneous gastrostomy tube). A copy of the investigator's consultation note documenting the multidisciplinary assessment must be submitted.
- Other conditions deemed to be contraindicating for radiation therapy must be discussed with the medical monitor before enrolling the patient.

13. All patients in either group must consent to provide archived or newly obtained tumor material (either formalin-fixed, paraffin-embedded [FFPE] block or 10 unstained or stained slides) for central pathology review for confirmation of diagnosis of CSCC. This material must be confirmed as received by the central lab prior to enrollment.
14. **Group 2 only:** Patients must consent to undergo biopsies of externally visible CSCC lesions at baseline, cycle 1 day 29 (± 3 business days), at time of tumor progression, and at other time points that may be clinically indicated in the opinion of the investigator.
15. **Group 2 only:** An investigator note which states that the natural history of the patient's advanced CSCC would likely be life-threatening within 3 years with currently available management options outside of a clinical trial.

4.2.2. Exclusion Criteria

A patient who meets any of the following criteria will be excluded from the study:

1. Ongoing or recent (within 5 years) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest risk for immune-related adverse events (irAEs). The following are not exclusionary: vitiligo, childhood asthma that has resolved, type 1 diabetes, residual hypothyroidism that required only hormone replacement, or psoriasis that does not require systemic treatment.
2. Prior treatment with an agent that blocks the PD-1/PD-L1 pathway.
3. Prior treatment with other immune modulating agents that was (a) within fewer than 4 weeks (28 days) prior to the first dose of REGN2810, or (b) associated with immune-mediated adverse events that were \geq grade 1 within 90 days prior to the first dose of REGN2810, or (c) associated with toxicity that resulted in discontinuation of the immune-modulating agent. Examples of immune modulating agents include therapeutic anti-cancer vaccines, cytokine treatments (other than G-CSF or erythropoietin), or agents that target cytotoxic T-lymphocyte antigen 4 (CTLA-4), 4-1BB (CD137), PI 3-K-delta, or OX-40.
4. Untreated brain metastasis(es) that may be considered active. (Note: patients with brain involvement of CSCC due to direct extension of invading tumor, rather than metastasis, may be allowed to enroll if they do not require greater than 10 mg prednisone daily, after discussion and approval of the medical monitor). Patients with previously treated brain metastases may participate provided that the lesion(s) is (are) stable (without evidence of progression for at least 6 weeks on imaging obtained in the screening period), and there is no evidence of new or enlarging brain metastases, and the patient does not require any immunosuppressive doses of systemic corticosteroids for management of brain metastasis(es) within 4 weeks of first dose of REGN2810.
5. Immunosuppressive corticosteroid doses (> 10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of REGN2810.

Note: Patients who require brief course of steroids (eg, as prophylaxis for imaging studies due to hypersensitivity to contrast agents) are not excluded.

6. Active infection requiring therapy, including infection with human immunodeficiency virus, or active infection with hepatitis B virus (HBV) or hepatitis C virus (HCV).
7. History of pneumonitis within the last 5 years
8. Grade ≥ 3 hypercalcemia at time of enrollment
9. Any systemic anticancer treatment (chemotherapy, targeted systemic therapy, photodynamic therapy), investigational or standard of care, within 30 days of the initial administration of REGN2810 or planned to occur during the study period (Patients receiving bisphosphonates or denosumab are not excluded), radiation therapy within 14 days of initial administration of REGN2810 or planned to occur during the study period.

Note: For patients with multiple CSCCs at baseline that are not designated by the investigator as target lesions, treatment of these non-target CSCCs with surgery may be permitted but must be discussed with the medical monitor prior to any surgical procedure.

10. History of documented allergic reactions or acute hypersensitivity reaction attributed to antibody treatments.
11. Patients with allergy or hypersensitivity to REGN2810 or to any of the excipients must be excluded. Specifically, because of the presence of trace components in REGN2810, patients with allergy or hypersensitivity to doxycycline or tetracycline are excluded.
12. Breast feeding
13. Positive serum pregnancy test (a false positive pregnancy test, if demonstrated by serial measurements and negative ultrasound, will not be exclusionary, upon communication with and approval from the medical monitor).
14. Concurrent malignancy other than CSCC and/or history of malignancy other than CSCC within 3 years of date of first planned dose of REGN2810, except for tumors with negligible risk of metastasis or death, such as adequately treated BCC of the skin, carcinoma in situ of the cervix, or ductal carcinoma in situ of the breast, or low-risk early stage prostate adenocarcinoma (T1-T2_aN0M0 and Gleason score ≤ 6 and PSA ≤ 10 ng/mL) for which the management plan is active surveillance, or prostate adenocarcinoma with biochemical-only recurrence with documented PSA doubling time of > 12 months for which the management plan is active surveillance ([D'Amico 2005](#), [Pham 2016](#)). Patients with hematologic malignancies (eg, chronic lymphocytic leukemia, CLL) are excluded.
15. Any acute or chronic psychiatric problems that, in the opinion of the investigator, make the patient ineligible for participation.

16. Continued sexual activity in men** or women of childbearing potential*** who are unwilling to practice highly effective contraception during the study and until 6 months after the last dose of study drug (highly effective contraceptive measures include stable use of oral contraceptives such as combined estrogen and progestogen and progestogen only hormonal contraception or other prescription pharmaceutical contraceptives for 2 or more menstrual cycles prior to screening; intrauterine device [IUD]; intrauterine hormone-releasing system (IUS); bilateral tubal ligation; vasectomy, and sexual abstinence).

** Contraception is not required for men with documented vasectomy.

*** Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

17. Patients with a history of solid organ transplant (patients with prior corneal transplant(s) may be allowed to enroll after discussion with and approval from the medical monitor).
18. Prior treatment with a BRAF inhibitor
19. Any medical co-morbidity, physical examination finding, or metabolic dysfunction, or clinical laboratory abnormality that, in the opinion of the investigator, renders the patient unsuitable for participation in a clinical trial due to high safety risks and/or potential to affect interpretation of results of the study.

Note in clarification: For Group 2 patients, the investigator must contact the sponsor's medical monitor regarding any patients that the investigator feels cannot provide the required baseline tumor biopsies.

20. Inability to undergo any contrast-enhanced radiologic response assessment.

Notes regarding imaging options: A patient who is unable to undergo CT with iodinated contrast (eg, due to contrast allergy) would not be excluded if his/her disease can be measured by MRI with gadolinium. A patient who is unable to undergo MRI with gadolinium would not be excluded if his/her disease can be measured by CT scan with contrast.

Note regarding Group 2 patients: In selected cases, a patient in Group 2 who is unable to undergo any contrast enhanced radiographic imaging (neither CT with iodinated contrast nor MRI with gadolinium) may be eligible if the patient's disease can be comprehensively assessed with digital medical photography, after communication with and approval from medical monitor.

21. Prior treatment with idelalisib

4.3. Premature Withdrawal from the Study or from Study Treatment

4.3.1. Reasons for Premature Withdrawal or Discontinuation of Study Treatment

A patient has the right to voluntarily discontinue study treatment or withdraw from the study at any time, for any reason, and without repercussion.

The investigator and sponsor have the right to discontinue a patient from study treatment or withdraw a patient from the study at any time.

Reasons for discontinuation of study treatment or withdrawal from the study may include, but are not limited to:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety if he or she continues in the study or continues treatment with study drug
- The investigator or sponsor determines it is in the best interest of the patient
- Patient noncompliance (eg, not complying with protocol required visits, assessments, and dosing instructions)
- Pregnancy

4.3.2. Discontinuation of Study Treatment

A patient who permanently discontinues study treatment will be followed as detailed in Section 6.2.2.

4.3.3. Withdrawal from Study Participation

During the treatment period and follow-up period, a patient who withdraws consent to continue participation in the study will not be followed for any reason after consent has been withdrawn.

An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

4.4. Replacement of Patients

Patients prematurely discontinued from the study who had received at least 1 treatment with REGN2810 will not be replaced.

5. STUDY TREATMENTS

5.1. Investigational Treatment

REGN2810 will be supplied as a liquid in sterile, single-use vials. [REDACTED]

[REDACTED] Instructions on dose preparation are provided in the pharmacy manual.

REGN2810 will be administered in an outpatient setting as an approximately 30 minute (± 10 minutes) IV infusion. Each patient's dose will depend on individual body weight, with the exception of Group 3 patients who will receive a flat dose. The dose of REGN2810 must be adjusted each cycle for changes in body weight of $\geq 10\%$. Dose adjustments for changes in body weight of $< 10\%$ will be at the discretion of the investigator.

5.2. Pretreatments

Appropriate premedication for study treatments may be administered at the investigator's discretion as per usual clinical practice and in accordance with institutional guidelines. No premedications are to be administered for the first dose of REGN2810.

5.3. Dose Modification and Study Drug Discontinuation Rules

5.3.1. Dose Modification

For Groups 1 and 2, the planned dose and schedule is 3 mg/kg REGN2810 IV over approximately 30 minutes every 14 days. For Group 3, the planned dose and schedule is 350 mg REGN2810 IV over approximately 30 minutes every 21 days. Patients will generally remain on the assigned dosage of REGN2810 throughout the course of study treatment. Dose reduction of REGN2810 may be allowed, based on the guidelines below, and only after discussion and agreement between the investigator and sponsor.

5.3.2. Study Treatment Hold or Discontinuation

Adverse events (AEs) are to be reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. Patients who experience grade ≥ 3 treatment-related toxicity (excluding laboratory abnormalities that are considered clinically insignificant) that is not otherwise specified in the protocol will be required to temporarily discontinue treatment with REGN2810. Such patients may be considered for resumption of treatment once the toxicity resolves to grade 1 or baseline, or when the toxicity is stable and manageable through supportive/medical therapy (eg, grade 3 hypertension that can be controlled with addition of a second anti-hypertensive agent).

Note in clarification on scheduling after missed visits/assessments: The general approach regarding missed treatments of REGN2810 (eg, due to AEs or other reasons) is "time marches on." Missed doses of REGN2810 will not be made up, unless missed doses occur ≤ 3 calendar days from the scheduled date.

Study visits cannot be performed outside of the scheduled visit. As such, if a patient misses a dose by more than 3 days for any reason, the next dose would be at the subsequent every 2 week dose (which could be given 3 days early if need be). If an investigator deems that re-scheduling a missed dose of REGN2810 outside of the 3 day window is in the best interest of the patient, this should be discussed with the medical monitor.

Holding of treatment due to an AE or a missed visit if a patient is hospitalized is not a violation. If a patient is able to come in for a study visit according to the visit schedule, but does not receive REGN2810, the visit should be entered into the database. The protocol assessments required at the visit (ie, labs, physical exam) should still be completed as far as possible and the

data entered at the appropriate visit in the electronic case report form (CRF). If the patient is not able to come in for a study visit, according to the study schedule, the visit should be skipped.

Upon occurrence of a study treatment-related event at any time on the study, resumption of treatment after resolution or stabilization of the condition is allowed at the discretion of the investigator and sponsor if resuming treatment is thought to be in the best interest of the patient, with the exception of the following categories:

- Patients with events that require REGN2810 to be discontinued for more than 84 days from last scheduled dose.
- Patients with grade ≥ 2 uveitis. Patients with grade 2 uveitis will generally be discontinued from study treatment, unless there is resolution to grade ≤ 1 as outlined in [Appendix 4](#) AND discussion with and approval by the medical monitor. All patients with grade ≥ 3 uveitis will be permanently discontinued from study treatment.

After other AEs, resumption of treatment may be at the initial dose level, or at 1 dose level reduced based upon the discretion of the investigator and the sponsor ([Table 2](#)).

Table 2: Dose Reductions

For Groups 1 and 2:

Dose Level	Reduction Order	Dose
Dose Level -1	First dose reduction	1 mg/kg REGN2810 every 14 days
Dose Level -2	Second dose reduction	0.3 mg/kg REGN2810 every 14 days

For Group 3:

Dose Level	Reduction Order	Dose
Dose Level -1	First dose reduction	120 mg REGN2810 Q3W
Dose Level -2	Second dose reduction	60 mg REGN2810 Q3W

A patient who requires dose reduction below dose level -2 will be removed from the study.

Guidelines for study treatment temporary discontinuations, including delays and interruptions, and permanent discontinuations for toxicity are outlined in [Table 3](#).

Table 3: Study Treatment Dose Modifications or Discontinuations

Toxicity	Grade	Hold Treatment?	Restarting Criteria	Restarting Dose/Schedule	Discontinuation Criteria
Hematological Toxicity (other than grade 3 thrombocytopenia greater than 7 days or associated with bleeding)	1, 2, 3	No	N/A	N/A	N/A
	4	Yes	Toxicity resolves to Grade \leq 1 or baseline	Decrease REGN2810 dosage to the next lower dosing level (see Table 2)	Toxicity does not resolve within 84 days of last infusion <i>Permanent discontinuation should be considered for any severe or life-threatening event</i>
Grade 3 thrombocytopenia greater than 7 days or associated with bleeding	3	Yes	Toxicity resolves to Grade \leq 1 or baseline	Decrease REGN2810 dosage to the next lower dosing level (see Table 2)	Toxicity does not resolve within 84 days of last infusion <i>Permanent discontinuation should be considered for any severe or life-threatening event</i>
Nonhematological Toxicity Note: Exceptions to be treated as for Grade 1 toxicity: <ul style="list-style-type: none"> Grade 2 alopecia Grade 2 fatigue Clinically insignificant lab abnormality not meeting AE criteria 	1	No	N/A	N/A	N/A
	2	Consider withholding for persistent symptoms	Toxicity resolves to Grade 0–1 or baseline	<i>Clinical AE resolves within 4 weeks:</i> Same dose and schedule <i>Clinical AE does not resolve within 4 weeks:</i> May decrease REGN2810 dosage to the next lower dosing level (see Table 2)	Toxicity does not resolve within 84 days of last infusion
	3	Yes	Toxicity resolves to Grade 0–1 or baseline	Decrease REGN2810 dosage to the next lower dosing level (see Table 2)	Toxicity does not resolve within 84 days of last infusion
	4	Yes	N/A	N/A	Patient must be discontinued

For additional information regarding AEs with a potential for irAEs, reference [Table 4](#) and [Appendix 4](#).

Any patient currently receiving REGN2810 who was previously treated with a phosphatidylinositol 3-kinase (PI 3-K) inhibitor and who develops stomatitis or mucositis should temporarily suspend study treatment. If this or any other immune-related AE occurs among these patients, the sponsor should be informed as soon as possible to discuss further management of the patient. An irAE of any grade in a patient previously treated with a PI 3-K inhibitor should be reported as an adverse event of special interest (AESI).

5.3.2.1. Immune-Related Adverse Events

Case report forms (CRFs) for this study are designed to capture AEs that may be suggestive of potential irAEs. Attribution of AEs in the CRFs will require not only the investigator's assessment regarding whether the AE was related to REGN2810, but also whether the AE was an irAE. Please see the CRF completion guidelines for information about attribution of irAEs.

Investigators must be extremely vigilant and be ready to intervene early in the management of irAEs, as the onset of symptoms of irAEs (eg, pneumonitis) may be subtle. Detailed guidance of management of irAEs is provided in [Appendix 4](#). In the event of irAEs that are not addressed in [Appendix 4](#), general guidance is provided in [Table 4](#). The recommendations in [Table 4](#) and [Appendix 4](#) should be seen as guidelines, and the treating physician should exercise clinical judgment based on the symptoms and condition of the individual patient.

Table 4: General Treatment Hold Guidelines for Immune-Related Adverse Events

Severity	Withhold/Discontinue Treatment?	Supportive Care
Grade 1	No action	Provide symptomatic treatment
Grade 2	May withhold treatment	Consider systemic corticosteroids in addition to appropriate symptomatic treatment
Grade 3 Grade 4	Withhold treatment Discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisone equivalent within 12 weeks of toxicity	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks. For any severe (Grade 3-4) irAE, if symptoms worsen or do not improve on adequate corticosteroids within 48 to 72 hours, consider adding additional immunosuppressive agents (to be selected from agents such as infliximab, cyclophosphamide, cyclosporine, mycophenolate-mofetil). Referral of the patient to a specialized unit for assessment and treatment should be considered.

Note: These recommendations should be seen as guidelines, and the treating physician should exercise clinical judgment based on the symptoms and condition of the individual patient.

Note regarding irAEs: For any AE that is of a type known to be potentially immune-related (eg, rash, colitis, elevated transaminases, endocrine), but is deemed not to be an irAE by the investigator, the sponsor may request additional information.

5.3.2.2. Permanent Discontinuation of Study Treatment

In the event of an infusion reaction of grade ≥ 3 severity during or directly following REGN2810 infusion, dosing should be stopped and the patient must permanently discontinue REGN2810 treatment.

Study treatment will be permanently stopped in the event of evidence of pregnancy.

In addition, study treatment for any patient may be discontinued for other safety reasons or compliance issues at the discretion of the investigator or sponsor. A patient may choose to discontinue study treatment or study participation at any time for any reason.

A patient who permanently discontinues REGN2810 treatment should continue follow-up in the study without additional treatment until progression of disease, completion of all study assessments, or closure of the study (Section 4.3).

5.4. Management of Infusion/Allergic/Hypersensitivity Reactions

Acute infusion reactions are defined as any AE that occurs during the infusion or within 2 hours after the infusion is completed. Emergency equipment and medication for the treatment of these potential adverse effects (eg, antihistamines, bronchodilators, IV saline, corticosteroids, acetaminophen, and/or epinephrine) must be available for immediate use. Infusion reactions must be reported as AEs (Section 7.2.1) and graded according to the NCI-CTCAE version 4.03 grading scale (Section 7.3.1).

In the event of an infusion reaction of Grade 3 or greater severity during or directly following REGN2810 infusion, dosing should be stopped and the patient must be permanently discontinued from REGN2810 treatment.

5.4.1. Interruption of the Infusion

The infusion should be interrupted if any of the following AEs are observed:

- cough
- rigors/chills
- rash, pruritus (itching)
- urticaria (hives, welts, wheals)
- diaphoresis (sweating)
- hypotension
- dyspnea (shortness of breath)
- vomiting
- flushing

The reaction(s) should be treated symptomatically, and the infusion may be restarted at 50% of the original rate.

If investigators feel there is a medical need for treatment or discontinuation of the infusion other than described above, they should use clinical judgment to provide the appropriate response according to typical clinical practice.

For patients who experience infusion-related hypersensitivity reactions that are less than grade 3 and who plan to continue treatment, premedication will be required for re-treatment.

For grade 1 symptoms (mild reaction; infusion interruption not indicated; intervention not indicated), the following prophylactic medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 mg to 1000 mg at least 30 minutes prior to subsequent REGN2810 infusions.

For grade 2 symptoms (moderate reaction that requires therapy or infusion interruption, but for which symptoms resolve promptly with appropriate treatment such as antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, and/or IV fluids; prophylactic medications indicated ≤ 24 hours), the following prophylactic medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 mg to 1000 mg at least 30 minutes prior to subsequent REGN2810 infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

5.4.2. Termination of the Infusion

The infusion should be terminated and NOT restarted if any of the following AEs occur:

- anaphylaxis
- laryngeal/pharyngeal edema
- severe bronchospasm
- chest pain
- seizure
- severe hypotension

5.5. Method of Treatment Assignment

Each patient who signs the informed consent form (ICF) will be assigned a patient number and tracked centrally as described in the Interactive Web Response System (IWRS) manual.

Eligible patients will be enrolled sequentially as confirmed and tracked by the sponsor, until each group is filled per protocol criteria. Details on treatment assignment can be found in the IWRS manual.

Patients can only be enrolled in Group 3 after enrollment in Group 1 is complete.

5.5.1. Blinding

This is an open-label study; no blinding will be employed.

5.6. Treatment Logistics and Accountability

5.6.1. Packaging, Labeling, and Storage

Open-label REGN2810 will be supplied as a liquid in sterile, single-use vials that will display the product lot number on the label. [REDACTED]

[REDACTED] Further storage instructions will be provided in the pharmacy manual.

A pharmacist or other qualified individual will be identified at each site to prepare REGN2810 for administration. [REDACTED]

[REDACTED] Detailed preparation and administration instructions will be provided to the sites in the pharmacy manual.

5.6.2. Supply and Disposition of Treatments

Study drug will be shipped [REDACTED] to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed -or- returned to the sponsor or designee.

5.6.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication dispensed to each patient, returned from each patient (if applicable), and disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

5.6.4. Treatment Compliance

REGN2810 will be administered at the study site and recorded on the electronic CRF. All dosing records for each patient will be kept by the site. All drug compliance records must be kept current and must be made available for inspection by the sponsor and regulatory agency inspectors.

5.7. Concomitant Medications and Procedures

5.7.1. Concomitant Medications

Any treatment administered from the time of informed consent until 30 days after the last study treatment will be considered concomitant treatment. This includes medications and other therapies for which administration started before the study and will continue during the study, as well as any therapies started in the follow-up period (approximately 6 months [Table 7]) to treat a study-drug-related AE. All concomitant treatments must be recorded in the study CRF with the generic name, dose, dose unit, frequency, indication, and start/stop date, as appropriate.

5.7.2. Prohibited Medications and Concomitant Treatments

While participating in this study, a patient may not receive any standard or investigational agent for treatment of a tumor other than REGN2810 as monotherapy. **After communication with the sponsor, focal palliative treatment (eg, radiation) would be allowed for local control of a tumor once a patient has completed 24 weeks of study treatment.** Any other medication which is considered necessary for the patient's welfare, and which is not expected to interfere with the evaluation of the study drug, may be given at the discretion of the investigator.

Patients using immunosuppressive doses (> 10 mg per day of prednisone or equivalent) of systemic corticosteroids other than for corticosteroid replacement will not be eligible for the study. It is recommended that patients do not receive systemic corticosteroids such as hydrocortisone, prednisone, prednisolone (Solu-Medrol[®]) or dexamethasone (Decadron[®]) at any time throughout the study except in the case of a life-threatening emergency and/or to treat an irAE. Physiologic replacement doses of systemic corticosteroids are permitted, even if >10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

Note: Bisphosphonates and denosumab are not prohibited.

5.7.3. Surgery

For patients with locally advanced target lesions that are considered unresectable at baseline, but are subsequently deemed resectable during the course of the study due to tumor response to REGN2810, curative intent surgery may be allowed but must be discussed with the medical monitor prior to any surgical procedure. (This statement does not apply to patients in emergency life-threatening situations that require immediate surgery). Patients with inoperable CSCC at baseline who are rendered operable with clear margins will be deemed to have experienced PR.

If during the course of the study a patient develops new cutaneous lesions that are suspected to be a non-melanoma skin cancer other than CSCC (eg, BCC), removal of the lesion and continued treatment on study may be allowed after discussion with the medical monitor.

5.7.4. Radiation Therapy

Radiation therapy is not part of the study regimen. Patients for whom radiation therapy is planned are not eligible. If during the course of the study, a patient develops a symptomatic lesion for which palliative radiation therapy is deemed appropriate by the investigator, this will be deemed PD and generally the patient would be removed from study. Palliative radiation therapy may be allowed in certain circumstances in patients who have been on study for at least 24 weeks (see Section 5.7.2). Such cases must be discussed with the medical monitor prior to any radiation therapy if the investigator feels that restarting REGN2810 after radiation is in the best interest of the patient. The patient will be deemed to have experienced disease progression if radiation therapy is instituted, but will be followed for OS.

6. STUDY SCHEDULE AND VISIT DESCRIPTIONS

6.1. Study Schedule

Study assessments and procedures are presented by study period and visit in [Table 5](#) for Groups 1 and 2, and [Table 6](#) for patients in Group 3; [Table 7](#) presents study assessments and procedures for all groups during the follow-up period. Study visits can be scheduled so as not to fall on weekends or holidays, after discussion and approval by the Sponsor.

Table 5: Study Schedule (Screening and Treatment) for Groups 1 and 2

Study Procedure	Screening	Cycle 1					Cycles 2 - 12 ^a					End of Study
Visit Days	-28 to -1	1	15±3	29±3	43±3	56±3	1 ^b	15±3	29±3	43±3	56±3	30 days after last dose of REGN2810 ^t
Clinical Assessments and Study Treatment												
Informed Consent ^c	X											
Genomics Substudy Informed Consent (optional)	X											
Medical/Oncology History	X											
Complete Physical Examination and ECOG PS ^d	X	X					X					X
Physical Examination, Limited ^e		-	X	X	X			X	X	X		
12-Lead ECG ^f	X	X					X					X
Vital Signs and Weight ^g	X	X	X	X	X		X	X	X	X		X
Height	X											
Brain MRI ^h	X											
3 mg/kg REGN2810 IV		X	X	X	X		X	X	X	X		
Laboratory Tests												
Hematology ⁱ and Blood Chemistry ^j	X	X	X	X	X		X	X	X	X		X
Serum HCG ≤72 Hour Predose ^k	X											
Urine Pregnancy Test							X					X
Urinalysis ^l	X	X					X					X
Serum IgG, IgM, IgE		X					X					X
aPTT; INR		X					X					
HBV, HCV, HIV	X											
Immune Safety and PK Blood Samples												
RF and ANA		X					X					X
TSH and CRP		X					X					X
ADA ^m		X					X					
REGN2810 PK/Drug Conc. Sample ⁿ		X	X	X	X		X					X

Study Procedure	Screening	Cycle 1					Cycles 2 - 12 ^a					End of Study
Visit Days	-28 to -1	1	15±3	29±3	43±3	56±3	1 ^b	15±3	29±3	43±3	56±3	30 days after last dose of REGN2810 ^t
Pathology and Research Samples												
Archived tissue for histological confirmation of CSCC ^o	X											
Optional blood DNA for genomics substudy		X										
Tumor biopsies for Group 2 ^p	X			X	As needed to clarify response status							
Response Imaging and other assessments												
CT/MRI and/or digital photography ^q	X			X (only photography for Group 2 patients)		X					X	X
EORTC QLQ-C30		X					X					X
Concomitant medications ^r		X					X					X
Adverse Events ^s	← continuous monitoring→											

ADA=anti-drug antibody; AE=adverse event; ANA=antinuclear antibody; aPTT=activated partial thromboplastin time; CRP=C-reactive protein; CT=computed tomography; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOS=end of study; HCG=human chorionic gonadotropin; INR=International Normalized Ratio; MRI=magnetic resonance imaging; RF= rheumatoid factor; TSH=thyroid-stimulating hormone; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus

^a The maximum number of treatment cycles is 12 (planned 96 weeks total). See Section 6.2 regarding treatment discontinuation.

^b Should occur at least 53 days from day 1 of previous cycle, and no sooner than 11 days after the previous dose.

^c Informed consent must be provided before the initiation of screening procedures and must be obtained within 45 days prior to cycle1/day1. All screening assessments must be performed within 28 days prior to cycle 1/day 1 (with the exception of brain MRI according to footnote h). Assessments performed as part of standard of care that fall within the screening window but before informed consent is obtained may be used for screening, and need not be repeated for enrollment eligibility.

^d Complete physical examination includes head and neck, lungs, heart, abdomen, lymph nodes, extremities, and skin. A brief neurologic examination should also be performed. The exam may be performed ≤72 hours prior to study treatment. Complete physical exam must be accompanied by assessment and documentation of ECOG Performance Status (Appendix 7).

^e Limited physical exam includes lungs, heart, abdomen, and skin.

^f A 12-lead electrocardiogram should be recorded at screening, and 30±10 minutes after end of infusion at day 1 visits during cycle 1 and cycle 3.

^g Vital signs include temperature, resting blood pressure, pulse, and respiration. Vital signs will be assessed and documented prior to the REGN2810 infusion, and then approximately 15 minutes after the completion of the REGN2810 infusion. The allowable window for each specified time point is ±10 minutes.

^h Brain MRI with gadolinium is required at screening if not performed in the prior 60 days. Brain scans during the treatment and follow-up periods are required if there is a prior history of lesions present at screening or as clinically indicated. A brain CT with iodinated contrast may be performed if an MRI with gadolinium is contraindicated.

- ⁱ Hematology includes: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, and platelet count. Samples may be collected ≤72 hours prior to study treatment.
- ^j Chemistry includes: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), ALT, AST, total bilirubin, alkaline phosphatase (ALP), uric acid, and LDH. Samples may be collected ≤72 hours prior to study treatment.
- ^k Predose β-HCG (serum) at screening up to 72 hours prior to first administration. Subsequent pregnancy tests may be urine β-HCG. Serum pregnancy test and urine pregnancy test are requirements for women of child bearing potential only.
- ^l Urinalysis: glucose, blood, pH, specific gravity, ketones, and spot urine protein. Samples may be collected ≤72 hours prior to study treatment.
- ^m ADA samples are collected prior to treatment on day 1 of cycles 1, 3, 5, 7, and 11.
- ⁿ Blood samples for PK will be collected (at select sites) at pre-infusion and end of infusion on days 1, 15, 29, and 43 of cycle 1, on day 1 of cycles 2 through 6, 7, 9, and 11. The final PK sample will be collected either at the EOS visit (for patients who discontinue treatment due to progression or toxicity during cycles 1 through 12) or at the follow-up visit 1 in [Table 7](#) (for patients who complete cycles 1 through 12). See [Appendix 3](#) for details on PK collection schedule.
- ^o See Section [6.3.1](#) regarding requirements for documentation of histologic confirmation of diagnosis of CSCC.
- ^p For Group 2 patients only: Tumor biopsies are required at baseline and on cycle 1 day 29 (±3 business days). Tumor biopsies should be performed at any response assessment in which there is indeterminate-appearing skin regarding malignant versus benign status. Tumor biopsies should also be collected for histologic confirmation of complete response in any patient for whom the clinical impression is complete response, as well as at progression. Biopsies must be annotated and photographed. Guidelines for tumor biopsies are provided in [Appendix 5](#).
- ^q The same method (CT with iodinated contrast or MRI with gadolinium) and/or digital medical photography used at baseline should be used throughout the study. For patients with locally advanced CSCC, guidelines for digital photography are provided in [Appendix 6](#). Imaging requirements differ for patients in Group 1 and Group 2; see Sections [6.3.1](#) and [6.3.2](#) for further details. For day 29 photos for Group 2 patients, the intent of the photography is to show locations of the biopsies; formal response assessments are not planned for day 29 photos.
- ^r Concomitant medication recording will be done at the start of each cycle, at a minimum. Concomitant medications should be recorded from the date of signing the ICF through follow-up visit 1 (post-treatment; [Table 7](#)).
- ^s Adverse event recording will be ongoing throughout the course of the study, using NCI-CTCAE v4. See Section [7.2](#).
- ^t (1) The EOS visit is for patients who experience PD requiring study discontinuation in cycles 1 through 12. This visit should occur 30 days (allowed window: 21 to 42 days) after the last dose of REGN2810. The only post-treatment assessment that can occur outside of this timeframe is the post-treatment biopsy (required in Group 2) that can be obtained at any time within 28 days of last dose of REGN2810. (2) Patients who complete the required events in [Table 5](#) (excluding the EOS visit) with any status other than PD (eg, CR, PR, or SD), or who discontinue treatment during cycles 1- 12 for any reason other than PD, should go on to complete the assessments in [Table 7](#) (unless not possible, due to factors such as clinical decline or withdrawal of consent). These patients do not need to complete the EOS visit at end of cycle 12 as they will be assessed per [Table 7](#). After treatment and follow-up are completed or patients prematurely discontinue treatment and follow-up, patients will be followed quarterly for survival and tumor treatment status, if available.

Table 6: Study Schedule (Screening and Treatment) for Group 3

Study Procedure	Screening	Cycle 1				Cycles 2 – 6 ^a				End Of study
Visit Days	-28 to -1	1	22±3	43±3	63±3	1 ^b	22±3	43±3	63±3	30 days after last dose of REGN2810 ^s
Clinical Assessments and Study Treatment										
Informed Consent ^c	X									
Genomics Substudy Informed Consent (optional)	X									
Medical/Oncology History	X									
Complete Physical Examination and ECOG PS ^d	X	X				X				X
Physical Examination, Limited ^e		-	X	X			X	X		
12-Lead ECG ^f	X	X				X				X
Vital Signs and Weight ^g	X	X	X	X		X	X	X		X
Height	X									
Brain MRI ^h	X									
350 mg REGN2810 IV		X	X	X		X	X	X		
Laboratory Tests										
Hematology ⁱ and Blood Chemistry ^j	X	X	X	X		X	X	X		X
Serum HCG ≤72 Hour Predose ^k	X									
Urine Pregnancy Test						X				X
Urinalysis ^l	X	X				X				X
Serum IgG, IgM, IgE		X				X				X
aPTT; INR		X				X				
HBV, HCV, HIV	X									
Immune Safety and PK Blood Samples										
RF and ANA		X				X				X
TSH and CRP		X				X				X
ADA ^m		X				X				

Study Procedure	Screening	Cycle 1				Cycles 2 – 6 ^a				End Of study
Visit Days	-28 to -1	1	22±3	43±3	63±3	1 ^b	22±3	43±3	63±3	30 days after last dose of REGN2810 ^s
REGN2810 PK/Drug Conc. Sample ⁿ		X	X	X		X				X
Pathology and Research Samples										
Archived tissue for histological confirmation of CSCC ^o	X									
Optional blood DNA for genomics substudy		X								
Response Imaging and other assessments										
CT/MRI and/or digital photography ^p	X				X				X	X
EORTC QLQ-C30		X				X				X
Concomitant medications ^q		X				X				X
Adverse Events ^r	← continuous monitoring →									

ADA=anti-drug antibody; AE=adverse event; ANA=antinuclear antibody; aPTT=activated partial thromboplastin time; CRP=C-reactive protein; CT=computed tomography; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOS=end of study; HCG=human chorionic gonadotropin; INR=International Normalized Ratio; MRI=magnetic resonance imaging; RF= rheumatoid factor; TSH=thyroid-stimulating hormone; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus

^a The maximum number of treatment cycles is 6 (planned 54 weeks total). See Section 6.2 regarding treatment discontinuation.

^b Should occur at least 60 days from day 1 of previous cycle, and no sooner than 18 days after the previous dose.

^c Informed consent must be provided before the initiation of screening procedures and must be obtained within 45 days prior to cycle1/day1. All screening assessments must be performed within 28 days prior to cycle 1/day 1 (with the exception of brain MRI according to footnote h). Assessments performed as part of standard of care that fall within the screening window but before informed consent is obtained may be used for screening, and need not be repeated for enrollment eligibility.

^d Complete physical examination includes head and neck, lungs, heart, abdomen, lymph nodes, extremities, and skin. A brief neurologic examination should also be performed. The exam may be performed ≤72 hours prior to study treatment. Complete physical exam must be accompanied by assessment and documentation of ECOG Performance Status (Appendix 7).

^e Limited physical exam includes lungs, heart, abdomen, and skin.

^f A 12-lead electrocardiogram should be recorded at screening, and 30±10 minutes after end of infusion at day 1 visits during cycle 1 and cycle 3.

^g Vital signs include temperature, resting blood pressure, pulse, and respiration. Vital signs will be assessed and documented prior to the REGN2810 infusion, and then approximately 15 minutes after the completion of the REGN2810 infusion. The allowable window for each specified time point is ±10 minutes.

^h Brain MRI with gadolinium is required at screening if not performed in the prior 60 days. Brain scans during the treatment and follow-up periods are required if there is a prior history of lesions present at screening or as clinically indicated. A brain CT with iodinated contrast may be performed if an MRI with gadolinium is contraindicated.

ⁱ Hematology includes: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, and platelet count. Samples may be collected ≤72 hours prior to study treatment.

- ^j Chemistry includes: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), ALT, AST, total bilirubin, alkaline phosphatase (ALP), uric acid, and LDH. Samples may be collected ≤72 hours prior to study treatment.
- ^k Predose β-HCG (serum) at screening up to 72 hours prior to first administration. Subsequent pregnancy tests may be urine β-HCG. Serum pregnancy test and urine pregnancy test are requirements for women of child bearing potential only.
- ^l Urinalysis: glucose, blood, pH, specific gravity, ketones, and spot urine protein. Samples may be collected ≤72 hours prior to study treatment.
- ^m ADA samples are collected prior to treatment on day 1 of cycles 1, 3, and 5.
- ⁿ Blood samples for PK will be collected (at select sites) at pre-infusion and end of infusion on days 1, 22, and 43 of cycle 1, and on day 1 of cycles 2 through 6. The final PK sample will be collected either at the EOS visit (for patients who discontinue treatment due to progression or toxicity during cycles 1 through 6) or at the follow-up visit 1 in [Table 7](#) (for patients who complete cycles 1 through 6). See [Appendix 3](#) for details on PK collection schedule.
- ^o See Section [6.3.1](#) regarding requirements for documentation of histologic confirmation of diagnosis of CSCC.
- ^p The same method (CT with iodinated contrast or MRI with gadolinium) and/or digital medical photography used at baseline should be used throughout the study. See Sections [6.3.1](#) and [6.3.2](#) for further details regarding imaging requirements for Group 3.
- ^q Concomitant medication recording will be done at the start of each cycle, at a minimum. Concomitant medications should be recorded from the date of signing the ICF through follow-up visit 1 (post-treatment; [Table 7](#)).
- ^r Adverse event recording will be ongoing throughout the course of the study, using NCI-CTCAE v4. See Section [7.2](#).
- ^s (1) The EOS visit is for patients who experience PD requiring study discontinuation in cycles 1 through 6. This visit should occur 30 days (allowed window: 21 to 42 days) after the last dose of REGN2810. (2) Patients who complete the required events in [Table 6](#) (excluding the EOS visit) with any status other than PD (eg, CR, PR, or SD), or who discontinue treatment during cycles 1-6 for any reason other than PD, should go on to complete the assessments in [Table 7](#) (unless not possible, due to factors such as clinical decline or withdrawal of consent). These patients do not need to complete the EOS visit at end of cycle 6 as they will be assessed per [Table 7](#). After treatment and follow-up are completed or patients prematurely discontinue treatment and follow-up, patients will be followed quarterly for survival and tumor treatment status, if available.

Table 7: Study Schedule: Follow-Up (After Cycle 12 for Group 1 and 2 Patients, or after Cycle 6 for Group 3 Patients)

Study Procedure Visit	Follow-up 1	Follow-up 2	Follow-up 3	Follow-up 4	Follow-up 5	Follow-up 6	Follow-up 7 ^k
Time point (Day)	Cycle 12 (Gp1 and 2) or Cycle 6 (Gp 3) visit + 28 ± 7 days	Follow-up 1 + 28 ± 7 days	Follow-up 2 + 28 ± 7 days	Follow-up 3 + 28 ± 7 days	Follow-up 4 + 28 ± 7 days	Follow-up 5 + 28 ± 7 days	Follow-up 6 + 28 ± 7 days
Physical examination (complete) ^a	X	X	X	X	X	X	X
ECOG Status	X	X	X	X	X	X	X
Vital Signs ^b	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X
Laboratory Tests							
Hematology ^{c, g}	X						
Blood Chemistry ^{d, g}	X						
Urine Pregnancy Test ^{e, g}	X						
Urinalysis ^{f, g}	X						
Serum IgG, IgM, IgE ^g	X						
Immune Safety Assays							
RF ^g	X						
ANA ^g	X						
TSH ^g	X						
CRP ^g	X						
PK Drug Conc/ADA Sample							
REGN2810 PK/Drug Conc. Sample	X						
ADA sample	X						X

Study Procedure Visit	Follow-up 1	Follow-up 2	Follow-up 3	Follow-up 4	Follow-up 5	Follow-up 6	Follow-up 7 ^k
Time point (Day)	Cycle 12 (Gp1 and 2) or Cycle 6 (Gp 3) visit + 28 ± 7 days	Follow-up 1 + 28 ± 7 days	Follow-up 2 + 28 ± 7 days	Follow-up 3 + 28 ± 7 days	Follow-up 4 + 28 ± 7 days	Follow-up 5 + 28 ± 7 days	Follow-up 6 + 28 ± 7 days
Pathology Samples							
Tumor biopsy ^g	←===== At Time of Progression =====>						
Tumor Assessments							
CT/MRI (chest/abdomen/pelvis) And/or digital photography ^h		X		X			X
Other Clinical Assessments							
Concomitant medications ⁱ	X						
Adverse events ^j	←===== >						

ADA=anti-drug antibody; AE=adverse event; ANA=antinuclear antibody; CRP=C-reactive protein; CT=computed tomography; ECOG=Eastern Cooperative Oncology Group; MRI=magnetic resonance imaging; RF= rheumatoid factor; TSH=thyroid-stimulating hormone.

^a Complete physical examination includes head and neck, lungs, heart, abdomen, lymph nodes, extremities, and skin. A brief neurologic examination should also be performed. Complete physical exam must be accompanied by assessment and documentation of ECOG Performance Status ([Appendix 7](#)).

^b Vital signs include temperature, resting blood pressure, pulse, and respiration.

^c Hematology includes: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, and platelet count.

^d Chemistry includes: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), ALT, AST, total bilirubin, alkaline phosphatase (ALP), uric acid, and LDH.

^e Pregnancy tests may be urine β-HCG.

^f Urinalysis: glucose, blood, pH, specific gravity, ketones, and spot urine protein.

^g At time of progression, the EOS tumor biopsy should be obtained for all patients in Group 2 (see Section 6.2.2 and [Appendix 5](#)). Blood samples for laboratory tests (hematology, blood chemistry, urine pregnancy test, urinalysis, serum IgG, IgM, and IgE) and immune safety (RF, ANA, TSH, CRP) are also obtained at time of progression (within 28 days of the imaging study that documented progression) according to the EOS assessment schedule in [Table 5](#) and [Table 6](#).

^h The same method (CT/MRI) and/or digital medical photography used at baseline should be used throughout the study. Scans linked to follow-up visits are required only if PD has not been confirmed previously while on study. CT/MRI imaging will be obtained within 14 days prior to the follow-up visit (per [Table 7](#)), so that the disease status is known at the time of the visit. Digital medical photography may be obtained within 14 days prior to visit, or on the day of the visit, and response status (CR, PR, SD, PR) will guide whether the visit is to be treated as a follow-up visit or as the EOS visit.

ⁱ Concomitant medications should be recorded from the date of informed consent through 30 days after last dose of study drug. Any drug started to treat a study drug-related AE during the follow-up will also be recorded. In addition, any cancer treatments should be recorded from the day of informed consent until 105 days (5 half-lives) after the administration of the last dose of REGN2810. Any AE assessed as related to study treatment and persisting after 105 days (5 half-lives) post-last dose should be reported until resolution to baseline or grade ≤1.

^j Nonserious AE and SAE data will be collected from the day of informed consent until 105 days (5 half-lives) after the last dose of REGN2810. Any AE assessed as related to study treatment and persisting after 105 days (5 half-lives) post-last dose should be reported until resolution to baseline or grade ≤1.

^k After treatment and follow-up are completed or patients prematurely discontinue treatment and follow-up, patients will be followed quarterly for survival and tumor treatment status, if available. See Section 6.2.2.

6.2. Study Follow-Up and Treatment Discontinuation

6.2.1. Unscheduled Visits

All attempts should be made to keep patients on the study schedule as specified in [Table 5](#) and [Table 6](#). Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted.

6.2.2. Follow-up

Patients who discontinue study treatment due to PD should return to the clinic 30 days (range: 28 to 42 days) after the last study treatment to complete the EOS assessments indicated in [Table 5](#), [Table 6](#). After the EOS visit, patients should be followed for survival status until death, loss to follow-up, or study termination by the sponsor.

For all patients in Group 2, tumor biopsies ([Appendix 5](#)) should be obtained at time of progression, whether progression occurs in cycles 1 through 12 or during follow-up (after cycle 12).

Patients who discontinue study treatment due to reasons other than PD (eg, toxicity, confirmed CR after 48 weeks) should continue follow-up to complete all assessments in [Table 5](#) and [Table 6](#) until PD or completion of follow-up visit 7.

For patients in Group 1 or Group 2 who complete 12 cycles of treatment or for patients in Group 3 who complete 6 cycles of treatment without disease progression and subsequently experience disease progression without any intervening systemic anticancer therapy, resumption of treatment with 3 mg/kg REGN2810 IV every 2 weeks will be allowed (with 350 mg IV every 3 weeks, for Group 3). Prior to resumption of REGN2810 treatment, patients must be re-consented and repeat all screening activities (with the exception of providing new archived pathology material, or research biopsies), and the investigator must confirm that the patient still meets all eligibility criteria (other than the exclusion regarding prior treatment with anti-PD-1). Such patients will resume 3 mg/kg REGN2810 monotherapy treatment every 2 weeks for up to 96 weeks if originally enrolled in Group 1 or 2 (maximum 12 re-treatment cycles), or 350 mg REGN2810 monotherapy treatment every 3 weeks for up to 54 weeks if enrolled in Group 3 (maximum 6 re-treatment cycles). The re-treatment visit schedule will follow the study schedule in [Table 5](#) (Group 1 and Group 2) or [Table 6](#) (Group 3). However, PK, research blood samples, and research tumor biopsies (exploratory “Tumor Biopsies for Group 2) are not required for these patients during re-treatment.

After treatment and follow-up are completed or if patients prematurely discontinue from treatment and follow-up, patients will be followed quarterly for survival and tumor treatment status, if available, until death. Follow-up status may be determined at clinic visits or via telephone contact with the patient, a family member of the patient, or the physician.

6.3. Study Procedures

6.3.1. Procedures Required Only at the Screening/Baseline Visit

The following procedures will be performed at screening for the purpose of determining study eligibility or characterizing the baseline population:

- Serum β -HCG (result must be ≤ 72 hours before first dose).
- HBV, HCV, and HIV screening. The required serologies are: hepatitis B surface antigen, hepatitis C antibody test (if positive, obtain hepatitis C RNA PCR to rule out active infection), HIV-1 and HIV-2 serum antibody
- Documentation of pathologic confirmation of CSCC by a pathologist at the study site (see Section 4.2.1, Inclusion 1). The pathology report that documents the diagnosis of CSCC should be from the most recent biopsy that documented CSCC. Pathology material (FFPE block or 10 unstained slides from the sample in the submitted pathology report) must be provided to the sponsor prior to enrollment.
- **Group 2 only:** Baseline/screening research biopsy is required (see Appendix 5 for guidelines). This baseline biopsy is intended for exploratory assessments, but will only be used for this purpose after central pathology confirmation of diagnosis of CSCC is obtained on archived material. If the archived material is not sufficient for confirmation of diagnosis of CSCC by central review, baseline biopsy material will be used for central pathologic confirmation; remaining baseline tumor material can only be used for exploratory assessments after central pathology confirmation of diagnosis of CSCC has been established.
- **Brain MRI:** Brain MRI is required at screening if not performed in the prior 60 days. Brain scans during the treatment and follow-up periods are required if there is a prior history of lesions present at screening or as clinically indicated. A brain CT may be performed if an MRI is contraindicated.
- **Group 1 and Group 3 –** Baseline imaging should include all known target lesions. Baseline scans must evaluate extent of disease, including imaging of chest, abdomen, and pelvis. This may be accomplished with CT chest, abdomen, and pelvis with contrast, or CT chest with contrast and MRI abdomen/pelvis with gadolinium. The imaging modality for metastatic lesions may be either CT with iodinated contrast or MRI with gadolinium, per investigator discretion. Magnetic resonance imaging with gadolinium is generally preferred for bone lesions, perineural lesions, abdomen, pelvis, extremity, and head and neck. Computed tomography with contrast is generally preferred for chest. For Group 1 patients who also have externally visible lesions, digital medical photography will be used, and these lesions generally will be followed as non-target lesions. **Note:** In the case of a Group 1 or Group 3 patient with metastatic disease that is not measurable by RECIST criteria (eg, bone only lesions, perineural disease) and with externally visible CSCC target lesions, digital medical photography may be used to follow the externally visible lesions as target lesions.

- **Group 2** – Externally visible lesions will be followed by digital medical photography. Baseline assessments will include radiologic imaging of all target lesions (preferably MRI with gadolinium for all anatomic sites except lung, but CT with iodinated contrast allowed at any anatomic site, per investigator discretion) to assess for deep invasion. Baseline radiologic assessment will also include CT chest, preferably with contrast (If CT chest identifies a metastatic lesion, the patient should be assigned to Group 1 if open for enrollment, or Group 3, if open for enrollment).

6.3.2. Efficacy Procedures

For patients with disease that can be measured radiologically according to RECIST 1.1 criteria ([Appendix 1](#); [Eisenhauer 2009](#)), a CT or MRI for tumor assessment will be performed as detailed in [Table 5](#) and [Table 6](#). The choice of whether the imaging is by CT or MRI is an investigator decision, but preferred imaging choices are provided in Section 6.3.1. Once the choice of CT scan or MRI has been made, subsequent assessments should be made using the same modality whenever possible. For patients whose CSCC lesions are evaluable on the skin, composite response criteria ([Appendix 2](#)) should be used on the same schedule (every 8 weeks for Groups 1 and 2, every 9 weeks for Group 3), in combination with radiologic imaging if appropriate.

- **Group 1 and Group 3:** Whole-body imaging – as performed at the baseline assessment – is strongly recommended at each response assessment. At a minimum, all radiologically measureable target lesions (RECIST 1.1) should be imaged at each response assessment. The same radiologic imaging modality should be used at each response assessment. Additionally, radiologic imaging of anatomic area of externally visible target lesions should be performed at each response assessment (MRI with gadolinium is preferred for all anatomic sites except lung). Externally visible CSCC lesions noted at baseline should be photographed at each response assessment ([Appendix 6](#)), and will generally be deemed non-target. New externally visible lesions that are clinically suspicious for malignancy should be photographed ([Appendix 6](#)) and biopsied. **Note:** In the case of a Group 1 or Group 3 patient with metastatic disease that is not measurable by RECIST criteria (eg, bone only lesions, perineural disease) and with externally visible CSCC target lesions, digital medical photography may be used to follow the externally visible lesions as target lesions.
- **Group 2:** All externally visible CSCC lesions should be photographed in a consistent manner at each response assessment as described in [Appendix 6](#). Radiologic imaging (MRI with gadolinium preferred) of anatomic area of externally visible target lesions should be performed at each response assessment. In cases in which it is the opinion of the investigator that no significant added information was provided by baseline radiologic imaging of the lesion (beyond the information that was provided by baseline digital medical photography), it is allowed to use digital medical photography only (without radiologic imaging) at subsequent response assessments of that lesion, at the discretion of the investigator.

To account for the possibility of unconventional immune responses, immune-related response criteria (irRC) ([Nishino 2013](#)) can inform the decision regarding whether to continue treatment for an individual patient if the investigator believes it is in the best clinical interest of the patient, **after discussion and approval from the medical monitor**. Reasons for any such decision to

treat beyond the protocol definitions of progression **must be documented in the CRFs**. However, irRC are currently deemed a surrogate endpoint ([Postow 2015](#)), and irRC data are not included in the primary endpoint of this study. Any patient who experiences best response (PR or CR) after initial progression (per [Appendix 1](#) or [Appendix 2](#), as appropriate) in the context of continued treatment (according to principles of irRC in after sponsor approval) will not have that best response (partial or complete) counted towards the primary endpoint of this study.

In Group 1 and Group 3, patients will generally be followed by RECIST 1.1 criteria ([Appendix 1](#)). It is possible that some patients in Group 1 and Group 3 may also have externally visible lesions that are measurable by digital medical photography. Generally, it will be clinically appropriate to follow these externally visible lesions as non-targets. However, for Group 1 and Group 3 patients with externally visible lesions that are deemed clinically significant by the investigator, the clinical and composite response criteria in [Appendix 2](#) may be used in selected cases. However, it is anticipated that most patients in Group 1 and Group 3 will be followed by RECIST 1.1 only.

For Group 2, response assessment is according to the clinical and composite response criteria in [Appendix 2](#).

For externally visible lesions that are indeterminate-appearing regarding presence of CSCC, see [Appendix 5](#) for guidelines on tumor biopsies. Annotation of tumor measurements and biopsies should adhere to the guidelines in [Appendix 5](#). If annotation of the full perimeter of a lesion is deemed not clinically appropriate by the investigator (eg, an ulcerated lesion), the priority annotation will be the axes delimiters. The perimeter of the lesion should be annotated as fully as possible without causing undue discomfort to the patient.

All radiology, photography and biopsy results will be independently reviewed. A blinded central review committee will be formed to determine overall response for each patient based on the integration of these modalities.

6.3.3. Safety Procedures

6.3.3.1. Vital Signs

Vital signs, including temperature, resting blood pressure, pulse, and respiration, will be collected at time points according to [Table 5](#), [Table 6](#) and, [Table 7](#).

Note: blood pressure should be measured after the patient has been resting quietly for at least 5 minutes.

At cycle 1 day 1 and on all subsequent treatment days, vital signs will be collected prior to infusion, and approximately 15 minutes after the completion of the infusion. The allowable window for each specified time point is ± 10 minutes.

6.3.3.2. Physical Examination

A thorough complete or limited physical examination will be performed at visits specified in [Table 5](#), [Table 6](#) and, [Table 7](#). Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

Complete physical examination will include examination of head and neck, lungs, heart, abdomen, lymph nodes, extremities, and skin. A brief neurologic examination also should be performed. Complete physical exam must be accompanied by assessment and documentation of ECOG Performance Status ([Appendix 7](#)).

Limited physical examination will include lungs, heart, abdomen, and skin.

6.3.3.3. Electrocardiogram

A standard 12-lead ECG will be performed at time points according to [Table 5](#), [Table 6](#) and [Table 7](#).

The patient should be relaxed and in a recumbent or semi-recumbent position at least 5 minutes before recording an ECG. The ECG strips or reports will be retained with the source. The ECG will be reviewed by the investigator (paper or electronic tracing) and will be available for comparison with subsequent ECGs by the investigator. The following will be recorded on the CRF:

- PR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- Heart Rate (BPM; recorded from the ventricular rate).

Any ECG finding that is judged by the investigator as a clinically significant change (worsening) compared to the baseline value will be considered an AE, recorded, and monitored.

6.3.3.4. Immune Safety Assays

Immune safety assays consist of rheumatoid factor (RF), thyroid-stimulating hormone (TSH), C-reactive protein (CRP), and antinuclear antibody (ANA) titer and pattern.

If, during the course of the study, a 4-fold or greater increase from baseline in RF or ANA or abnormal levels of TSH or CRP are observed, the following tests may also be performed: anti-DNA antibody, anti-Sjögren's syndrome A antigen (SSA) antibody (Ro), anti-Sjögren's syndrome B antigen (SSB) antibody (La), antithyroglobulin antibody, anti-LKM antibody, antiphospholipid antibody, anti-islet cell antibody, antineutrophil cytoplasm antibody, C3, C4, CH50.

6.3.3.5. Immunoglobulin Levels

Serum IgG, IgM, and IgE will be measured at timepoints according to [Table 5](#), [Table 6](#), and [Table 7](#).

6.3.3.6. Coagulation Tests

Activated partial thromboplastin time (aPTT) and International Normalized Ratio (INR) will be analyzed by the site's local laboratory.

6.3.3.7. Laboratory Testing

Hematology, chemistry, urinalysis, and pregnancy testing samples will be analyzed by the site's local laboratory.

Detailed instructions for blood sample collection are in the laboratory manual provided to study sites.

Samples for laboratory testing will be collected at time points according to [Table 5](#), [Table 6](#), and [Table 7](#).

Tests will include:

Blood Chemistry

Sodium	Phosphorus	ALT
Potassium	Glucose	AST
Chloride	Albumin	Total bilirubin
Bicarbonate*	Creatinine	Alkaline phosphatase (ALP)
Calcium	Blood urea nitrogen (BUN)**	Lactate dehydrogenase (LDH)
Magnesium	Uric acid	

Hematology

Hemoglobin	Differential (absolute, percent if absolute not performed):
WBCs	Neutrophils
Platelet count	Lymphocytes
	Monocytes

Urinalysis

Glucose	pH	Ketones
Blood	Specific gravity	Spot urine protein

* At ex-US centers where the bicarbonate test is not performed as part of the routine chemistry panel, it may be omitted.

** At ex-US centers where Urea assay is performed instead of Blood Urea Nitrogen (Urea), the Urea assay will be acceptable.

Abnormal Laboratory Values and Laboratory Adverse Events

- All laboratory values must be reviewed by the investigator or authorized designee.
- Significantly abnormal tests must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the medical monitor must be consulted.
- The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section [7.2.5](#).

6.3.4. Pharmacokinetic and Antibody Procedures

6.3.4.1. Drug Concentration Measurements and Samples

REGN2810 PK parameters will be determined by measuring REGN2810 concentrations in serum samples using a validated assay at visits and time points indicated in [Table 5](#), [Table 6](#), and [Table 7](#), and listed in [Appendix 3](#). Actual time of each blood draw must be recorded. “Predose” is defined as before the start of the first REGN2810 infusion. Predose samples may be collected ≤ 72 hours prior to day 1 dosing. Subsequent PK sampling times will be based on the REGN2810 dosing time that precedes the PK sampling. Pre-infusion is defined as before the start of the REGN2810 infusion and “0 hour” is defined as immediately after the end of the REGN2810 infusion.

Any unused samples collected for drug concentration measurements may be used for exploratory biomarker research or to investigate unexpected AEs.

6.3.4.2. Anti-drug Antibody Measurements and Samples

Samples for ADA assessment will be collected prior to dosing at time points listed in [Table 5](#), [Table 6](#) and, [Table 7](#).

Any unused samples collected for ADA assessment may be used for exploratory biomarker research or to investigate unexpected AEs.

6.3.5. Biomarker Measurements and Samples

Speculated pharmacodynamic, [REDACTED] biomarkers related to REGN2810 treatment exposure, clinical activity, or underlying disease will be investigated in tumor biopsy tissue collected at baseline, after treatment with REGN2810, and at progression, if available. [REDACTED]

[REDACTED] Biomarker results will be reported separately from the clinical study report.

6.3.5.1. Tumor Biomarker Procedures

For patients with locally advanced CSCC (Group 2), tumor biopsies will be collected per the timepoints and methodology in [Appendix 5](#).

Expression levels (mRNA and/or protein) of PD-L1, GITR, and LAG-3, as well as the number and distribution of TILs (defined by lineage markers CD4, CD8, CD25, FoxP3) will be assessed in tumor biopsy samples. Additional biomarkers may be measured tissue permitting. [REDACTED]

Tumor tissue, as well as RNA and DNA isolated from tumor tissue, will be used to assess changes in potential pharmacodynamic biomarkers induced by REGN2810 treatment from baseline.

Main exploratory potential biomarkers of interest include, but are not limited to:

- Tumor RNA expression
- Number and distribution of TILs (CD8+ T cells, CD4+ T cells, T regulatory cells, and tissue permitting, other subtypes such as B cells, myeloid-derived cells, NK cells, etc.)
- Expression levels (mRNA and/or protein) of PD-L1, GITR, and LAG-3, and possibly other check-point modulators
- Mutations in known oncogenes and potential tumor neoantigens
- Tumor mutation burden

Additional biomarkers may be measured (for example, exome sequencing, single cell RNA analysis, microsatellite instability, T cell clonality) tissue permitting. [REDACTED]

6.3.5.2. Genomics Sub-Study – Optional

Patients who agree to participate in the genomics sub-study will be required to sign a separate genomics sub-study ICF before collection of the samples. Blood for genomic DNA extraction should be collected on day 1/baseline (predose), but may be collected at any study visit. Patients are not required to participate in the genomics sub-study in order to enroll in the primary study.

DNA samples for the genomics sub-study will be double-coded as defined by the International Council for Harmonisation (ICH) guideline E15. Sub-study samples may be stored for up to 15 years after the final date of the clinical study report and may be used for research purposes. The purpose of the genomic analyses is to identify genomic associations with clinical or biomarker response to target modulation, disease prognosis and progression, or other clinical outcome measures. [REDACTED]

6.3.6. Group 3 Only: Guidance Regarding Patients who Wish to Continue Treatment Beyond 54 Weeks

The intent of Group 3 is that patients who have completed 54 weeks of treatment without PD will enter post-treatment follow-up. The potential risks and benefits of continued treatment beyond 54 weeks are not known, but risks may include cumulative toxicities with cytotoxic chemotherapy and late immune-related toxicities with PD-1 inhibition. The Group 3 design of up to 54 weeks of planned treatment, with an option for re-treatment as set forth in Section 6.2.2, must be discussed with Group 3 patients during the informed consent process.

Some patients who are experiencing clinical benefit may be hesitant to stop treatment at 54 weeks. It is important that study teams remind patients of the treatment duration as they

approach the completion of 54 weeks. Patients who are experiencing durable responses or stable disease (>6 months) should be reminded that study treatment ends at 54 weeks, with a plan for follow-up and potential re-treatment in the event of PD.

Patients are strongly encouraged to adhere to the study plan. However, it is anticipated that some Group 3 patients who have experienced clinical benefit may be unwilling to discontinue treatment at 54 weeks. In such cases, the investigator will contact the medical monitor. Patients who have not experienced PD and who are unwilling to stop study treatment will be allowed to continue study treatment if the investigator deems that there are not unacceptable safety risks with continued treatment, after notification of medical monitor. After 54 weeks, such patients may continue on the same dose and schedule of study treatment (350 mg REGN2810 every 3 weeks, unless there has been dose reduction) that they have been receiving. The schedule of events will follow [Table 6](#), but cycles will be counted as 7 - 12 (instead of 1 – 6). The patient will not repeat screening assessments before beginning cycle 7.

7. SAFETY DEFINITIONS, REPORTING, AND MONITORING

7.1. Definitions

7.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug.

An AE also includes any worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug.

Progression of underlying malignancy will not be considered an AE if it is clearly consistent with the typical progression pattern of the underlying cancer (including time course, affected organs, etc.). Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

If there is any uncertainty about an AE being due only to progression of the underlying malignancy, it should be reported as an AE or SAE as outlined in [Section 7.2](#).

NCI-CTCAE version 4.03 terms should be used.

7.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger), within 30 days of last dose of REGN2810.
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician. Hospitalization or prolongation of existing hospitalization due to the progression of underlying malignancy will not be considered an SAE, if it is clearly consistent with the typical progression pattern of the underlying cancer.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** – Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent 1 of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Hospitalization or death due solely to manifestations consistent with typical progression of underlying malignancy will not be considered an SAE in this study.

Serious adverse events must be reported as directed in Section 7.2.

7.1.3. Adverse Events of Special Interest

An AESI (serious or non-serious) is one of scientific and medical interest specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (eg, regulators) might also be warranted (Section 7.2.3).

7.2. Recording and Reporting Adverse Events

7.2.1. Adverse Events

The investigator (or designee) will seek information on AEs at each patient contact, and record all AEs that occur from the time the informed consent is signed until 105 days (5 half-lives) after the end of study treatment. After informed consent has been obtained but prior to initiation of study treatment, only the following categories of AEs should be reported on the AE electronic CRF:

- SAEs
- Nonserious AEs associated with a protocol-mandated intervention (eg, AEs related to an invasive procedure such as a biopsy)

(Other AEs that occur prior to first treatment should be reported on the medical history CRF.)

All AEs after initiation of study treatment and until 105 days (5 half-lives) after the last study treatment, regardless of relationship to study treatment, will be reported on the AE electronic CRF. Additionally, any SAE or other AE of concern that the investigator believes may be related to study treatment and that occurs later than 105 days (5 half-lives) after last study treatment should be reported.

Information on follow-up for AEs is provided in Section 7.2.6. Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs as outlined in Section 7.2.5.

7.2.2. Serious Adverse Events

All SAEs, regardless of assessment of causal relationship to study treatment must be reported to the sponsor (or designee) within 24 hours. Refer to the safety reporting guidelines for the procedure to be followed.

Information not available at the time of the initial report must be documented in a follow-up report. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested.

In the event the investigator is informed of an SAE that occurs more than 105 days (5 half-lives) after the last dose of study treatment, only those SAEs or other AEs of concern deemed by the investigator to be related to study treatment will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome of a treatment-related SAE until the event is considered chronic and/or stable.

7.2.3. Other Events that Require Accelerated Reporting to the Sponsor

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

Symptomatic Overdose of Study Drug:

Accidental or intentional overdose of at least 2 times the intended dose of study drug within the intended therapeutic window, if associated with an AE.

Pregnancy:

Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female patient or female partner of a male patient, during the study or within 105 days of the last dose of study drug. Any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn must be reported as an SAE. Outcomes for all pregnancies should be reported to the sponsor.

Adverse Events of Special Interest:

An AESI must be reported within 24 hours of identification. Adverse events of special interest for this study include:

- Grade 2 or greater infusion-related reactions
- Grade 2 or greater allergic/hypersensitivity reactions
- Grade 3 or higher irAEs.
- An irAE of any grade in a patient previously treated with a PI 3-K inhibitor

Note: An irAE can occur shortly after the first dose or several months after the last dose of treatment. All AEs of unknown etiology associated with drug exposure should be evaluated to determine possible immune etiology. If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an AE as an irAE.

Refer to the safety reporting guidelines for the reporting procedures to be followed.

If any SAE or unusual AE is judged related to study treatment, and as possible and practical, obtain a blood sample from the patient to permit measurement of plasma drug levels.

7.2.4. Reporting Adverse Events Leading to Withdrawal from the Study

All AEs that lead to a patient's withdrawal from study treatment or from the study must be reported to the sponsor's medical monitor within 30 days.

Refer to the safety reporting guidelines for the procedures to be followed.

7.2.5. Abnormal Laboratory, Vital Signs, or Electrocardiogram Results

The criteria for determining whether an abnormal objective test finding should be reported as an AE include:

- the test result is associated with accompanying symptoms, and/or
- the test result requires additional diagnostic testing or medical/surgical intervention, and/or
- the test result leads to a change in dosing (outside of protocol-stipulated dose adjustments), and/or
- the test result leads to discontinuation from the study, significant additional concomitant medication, or other therapy

Contact the medical monitor in the event the investigator feels that an abnormal test finding should be reported as an AE, although it does not meet any of the above criteria.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Evaluation of severity of laboratory abnormalities will be assessed according to the scale outlined in Section 7.3.1.

7.2.6. Follow-up

Information for any nonserious AE that starts during the treatment period or within 105 days (5 half-lives) after last treatment will be collected from the time of the event until resolution of the event, or until the patient's last study visit, whichever comes first.

Serious adverse event information will be collected until the event is considered chronic and/or stable.

7.3. Evaluation of Severity and Causality

7.3.1. Evaluation of Severity

The severity of AEs (including test findings classified as AEs) will be graded using the current version of the NCI-CTCAE grading system. Adverse events not listed in the NCI-CTCAE will be graded according to the following scale:

- | | |
|------------------------------|--|
| 1 (Mild): | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. |
| 2 (Moderate): | Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*. |
| 3 (Severe): | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**. |
| 4 (Life-threatening): | Life-threatening consequences; urgent intervention indicated. |
| 5 (Death): | Death related to AE |

* Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

7.3.2. Evaluation of Causality

Relationship of AEs to Study Drug:

The relationship of AEs to study drug will be assessed by the investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by the study drug?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by the study drug

Related: There is a reasonable possibility that the event may have been caused by the study drug

The investigator should justify the causality assessment of each reported SAE.

[Appendix 8](#) lists factors to consider in assessing the relationship of AEs to REGN2810.

Relationship of Adverse Events to Study Conduct:

The relationship of AEs or SAEs to study conduct will be assessed by the investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE or SAE may have been caused by study conduct?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by study conduct

Related: There is a reasonable possibility that the event may have been caused by study conduct.

A list of factors to consider when assessing the relationship of AEs or SAEs to study conduct is provided in [Appendix 8](#).

The investigator should justify the causality assessment of each SAE.

7.4. Safety Monitoring

The investigator will monitor the safety of study patients at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The medical monitor will have primary responsibility for the emerging safety profile of the compound. The study monitor will be supported by other departments (eg, Pharmacovigilance and Risk Management; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

7.5. Investigator Alert Notification

Regeneron (or designee) will inform all investigators participating in this clinical trial, as well as in any other clinical trial using the same investigational drug, of any SAE that meets the relevant requirements for expedited reporting (an AE that is serious, unexpected based on the Investigator's Brochure, and has a reasonable suspected causal relationship to the medicinal/study drug).

8. STUDY VARIABLES

8.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height), disease characteristics including medical history, cancer stage ([Edge 2010](#)), and medication history for each patient.

8.2. Primary and Secondary Variables

8.2.1. Primary Efficacy Outcome Measure

The primary efficacy endpoint for this study is ORR according to central review during the 12 treatment cycles (Groups 1 and 2) or 6 treatment cycles (Group 3). Overall response rate will be assessed separately for patients with metastatic CSCC or unresectable locally advanced CSCC:

- For patients in Group 1 and Group 3, RECIST version 1.1 will be used to determine ORR ([Eisenhauer 2009](#)) ([Appendix 1](#)). For Group 1 and Group 3, patients in which all response assessments are performed on radiologic scans according to RECIST 1.1, the determination of the independent radiologic response assessment committee will serve as the central response assessment. Clinical or composite response criteria ([Appendix 2](#)) may be used for patients with externally visible target lesions, if all metastatic lesions are not measureable by RECIST (such as may occur in patients with bone-only metastases).
- For patients in Group 2, clinical response criteria ([Appendix 1](#)) will be used to determine ORR, for externally visible tumor(s) require bidimensional measurements according to World Health Organization (WHO) criteria. Composite response criteria will be used for patients who have both target lesions measurable by clinical response criteria and by RECIST 1.1 to determine ORR ([Appendix 2](#)). In patients achieving a CR, tumor biopsies will be used in the final determination of complete versus PR.

Patients who are deemed not evaluable (NE) by RECIST version 1.1 (Group 1 and Group 3; [Appendix 1](#)) or inevaluable by the clinical or composite response criteria (Group 2; [Appendix 2](#)) will be considered as not reaching PR/CR for ORR.

8.2.2. Secondary Outcome Measures

The secondary efficacy outcome measures are:

- ORR for Group 1, Group 2, and Group 3 by investigator assessments
 - For Group 1 and Group 3 patients in which all response assessments are performed on radiologic scans according to RECIST 1.1, the term “composite response assessment” is not applicable. The investigator’s response assessment for such patients will be RECIST 1.1 assessment.
 - For Group 2 patients in which all response assessments are performed on photographs according to Clinical Response Criteria for Externally Visible Tumors (in [Appendix 2](#)), the term “composite response assessment” is not

applicable. The investigator's response assessment for such patients will be according to Clinical Response Criteria for Externally Visible Tumors.

- For patients in which target lesion response assessments are performed with both scans (according to RECIST 1.1) and photographs (according to Clinical Response Criteria for Externally Visible Tumors), the investigator's response assessment will be according to Composite Response Criteria (in [Appendix 3](#)).
- Duration of response
- PFS
- OS
- CR rate
- Change in scores of patient-reported outcomes on EORTC QLQ-C30
- AEs
- REGN2810 concentrations in serum ([Appendix 3](#); at select sites)
- Anti-REGN2810 antibodies

8.2.3. Exploratory Outcome Measures

The following exploratory analyses are planned:

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

8.3. Pharmacokinetic Variables

Serum concentration of REGN2810 will be assessed at multiple time points throughout the study treatment and follow-up periods, and the PK will be analyzed.

Pharmacokinetic variables may include, but are not limited to, the following:

- C_{eoi} – concentration at end-of-infusion
- C_{trough} – pre-infusion concentration
- t_{eoi} – time of end-of-infusion

8.4. Anti-drug Antibody Variables

Regeneron plans to evaluate the impact of the immunogenicity of REGN2810.

Anti-drug antibody variables include status (positive or negative) and titer as follows:

- Treatment emergent – defined as any positive post-dose ADA assay response when baseline results are negative
- Treatment boosted – defined as any post-dose ADA response that is at least 4-fold over baseline titer levels
- Titer values (Titer value category):
 - Low (titer < 1,000)
 - Moderate ($1,000 \leq \text{titer} \leq 10,000$)
 - High (titer > 10,000)

9. STATISTICAL PLAN

This section provides the basis for the statistical analysis plan (SAP) for the study. The SAP may be revised during the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the database is locked.

Analysis variables are listed in Section 8.

9.1. Statistical Hypothesis

For the primary endpoint of ORR, the following null hypothesis and alternative will be tested for Group 1, 3 and Group 2, respectively.

Group 1: H_0 : ORR = 15% vs. H_1 : ORR \neq 15%

Group 2: H_0 : ORR = 25% vs. H_1 : ORR \neq 25%

Group 3: H_0 : ORR = 15% vs. H_1 : ORR \neq 15%

9.2. Justification of Sample Size

Patients will be enrolled into 3 separate groups according to the stage of disease: metastatic CSCC (Group 1 and Group 3) or locally advanced CSCC (Group 2). A single-stage exact binomial design is adopted for each group, respectively, for the primary endpoint of ORR. After completion of enrollment in Group 1, up to 53 additional patients with metastatic CSCC will be enrolled in Group 3.

Published clinical studies for CSCC patients have had relatively small sample sizes and often include a wide range of disease stages (Nakamura 2013). Clinical studies of CSCC patients have been predominantly composed of patients with locally advanced disease (primary site). The NCCN guidelines for CSCC, cisplatin monotherapy, cisplatin plus 5-FU, and cetuximab are described as “possible options” (Bichakjian 2015). In the only study of cisplatin-based therapy for advanced CSCC reported in the last 15 years, the ORR was 34% (Shin 2002). Cetuximab yielded a response rate of 28% in a phase 2 study for patients with advanced CSCC

(Maubec 2011). Most patients in these studies had locoregionally advanced disease. There hasn't been a publication of a clinical study specifically for patients with metastatic CSCC. The aggregate experience of patients enrolled in trials of systemic therapy indicates that a clinically meaningful ORR for an investigational agent would be >15% for patients with metastatic disease or >25% for patients with unresectable locally/regionally advanced CSCC (Khansur 1991, Lippman 1992, Nakamura 2013, Shin 2002).

Hence, the sample sizes for Group 1, Group 2, and Group 3 were selected such that the lower limit of the 95% confidence intervals of the estimated ORRs will be clinically meaningful. The non-clinically meaningful ORR of 15% for Group 1 and Group 3 (evaluated independently) will be excluded using the lower limit of 95% CI if the observed ORR is 28.0% or more; ie, the ORR for Group 1 and/or Group 3 (evaluated independently) is significantly different from 15%. The non-clinically meaningful ORR of 25% for Group 2 will be excluded using the lower limit of 95% CI if the observed ORR is 36.1% or more; ie, the ORR for Group 2 is significantly different from 25% (see Table 8 and Table 9).

Table 8: The 95% Binomial Exact Confidence Intervals for Observed ORR in Group 1 and Group 3 Given a Sample Size of 50 Patients (Based on 85% Power)

Number of Responders	Observed ORR	95%CI – lower	95% CI – upper
7	0.14	0.058	0.267
8	0.16	0.072	0.291
9	0.18	0.086	0.314
10	0.20	0.100	0.337
11	0.22	0.115	0.360
12	0.24	0.131	0.382
13	0.26	0.146	0.403
14	0.28	0.162	0.425
15	0.30	0.179	0.446
16	0.32	0.195	0.467
17	0.34	0.212	0.488

Table 9: The 95% Binomial Exact Confidence Intervals for Observed ORR in Group 2 Given a Sample Size of 72 Patients (Based on 90% Power)

Number of Responders	Observed ORR	95%CI – lower	95% CI – upper
18	0.250	0.155	0.366
19	0.264	0.167	0.381
20	0.278	0.179	0.396
21	0.292	0.190	0.411
22	0.306	0.202	0.425
23	0.319	0.214	0.440
24	0.333	0.227	0.454
25	0.347	0.239	0.469
26	0.361	0.251	0.483
27	0.375	0.264	0.497
28	0.389	0.276	0.511
29	0.403	0.289	0.525
30	0.417	0.302	0.539
31	0.431	0.314	0.553
32	0.444	0.327	0.566

For Group 1 and Group 3, 50 patients (in each group) will be required to provide at least 85% power to reject a null hypothesis of an ORR of 15% at a 2-sided significance level of no more than 5% if the true ORR is 34%. For Group 2, 72 patients will be required to provide at least 90% power to reject a null hypothesis of an ORR of 25% at a 2-sided significance level of no more than 5% if the true ORR is 44%. The sample sizes will be further increased by 5% to account for patients who withdraw prematurely from the study. Hence, the total sample sizes will be 53 patients for Group 1, 76 patients for Group 2, and 53 patients in Group 3, for a total of 182 patients.

9.3. Analysis Sets

9.3.1. Full Analysis Set

The full analysis set (FAS) includes all patients who have passed screening and deemed to be eligible for this study. All efficacy endpoints will be analyzed using FAS.

9.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all enrolled patients who received any study drug for each group. Treatment compliance/administration and all clinical safety variables will be analyzed or summarized using the SAF.

9.3.3. Pharmacokinetic Analysis Set

The PK analysis set will include all patients who had received REGN2810 and had at least 1 qualified (non-missing) post-baseline measurement of REGN2810 concentration in serum.

9.3.4. Anti-drug Antibody Set

The ADA population includes all treated patients who had at least 1 post-dose ADA result.

9.3.5. Biomarker Analysis Set

The biomarker analysis set (BAS) includes all treated patients who had at least 1 sample assayed.

9.4. Patient Disposition

The following will be provided by group and overall:

- The number of screened patients
- The number of patients included in the FAS and the SAF
- The number of patients who discontinued study participation, and the reasons for discontinuation from the study
- The number of patients who discontinued treatment, and the reasons for treatment discontinuation

9.5. Statistical Methods

In general, the descriptive summary for continuous data will include the number of observations (n), mean, standard deviation (SD), median, minimum and maximum. In addition, 25% percentile and 75%-percentile will also be provided.

The descriptive summary for categorical data will include counts (n) and percentages calculated in each group. The denominator will be determined by the analysis population used for the summary. Non-evaluable outcome or missing data will be handled based on the data handling strategy.

The descriptive summary for time-to-event data will include the median time-to-event and its 95% confidence intervals using the Kaplan-Meier method.

9.5.1. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively for each group by extent of prior therapy (no prior systemic therapy versus having received any prior systemic therapy).

9.5.2. Efficacy Analyses

The primary endpoint for efficacy analyses is the ORR, by central review. For Group 1 and Group 3 patients in which all response assessments are done by RECIST 1.1 ([Eisenhauer 2009](#)) analysis of radiologic scans, the independent radiology review is the central review. For Group 2 patients (and some Group 1 and Group 3 patients), response assessments include photos and radiologic scans, and the independent composite review committee will serve as the central

review. The investigator-assessed ORR will be considered as a secondary analysis. Patients who are deemed as not evaluable according to RECIST 1.1 or inevaluable by the composite efficacy criteria will be considered as not reaching PR/CR for ORR (see Section 6.3.2).

The primary analyses of efficacy are based on the binomial exact confidence interval approach, ie, whether the lower limit of 95% confidence interval will exclude a historical control ORR that is not deemed clinically meaningful. The 95% binomial exact confidence intervals using Clopper-Pearson method (Clopper 1934) for observed ORRs are listed for Group 1 (Table 8) and Group 2 (Table 9) and Group 3 (Table 8).

The secondary analyses of efficacy as measured by duration of response, PFS, and OS will be summarized by median and its 95% confidence interval by the Kaplan-Meier method.

The CR rate will be summarized descriptively with 95% confidence interval. Absence of residual CSCC in patients with locally advanced CSCC achieving a clinical response to REGN2810, as measured by central review, will be summarized descriptively.

9.5.3. Exploratory Analyses

Subgroup analyses: Subgroup efficacy analyses may be performed based on the number of prior systemic therapy regimens, the degree of differentiation of the tumor (well, moderate, or poor), the presence or absence of human papillomavirus (HPV) in the tumor, and the presence or absence of use of immune suppressive medications (eg, high dose steroids) to manage irAEs that may arise during the study. However, such analyses may not have enough power for hypothesis tests, and in that case will serve only for hypothesis-generating purpose.

Quality of life analysis: The quality of life of patients will be repeatedly measured by the EORTC QLQ-C30 at the day 1 of each treatment cycle. The change scores of QLQ-C30 will be summarized descriptively at each post-baseline time point. The summary scores of QLQ-C30 will also be graphically depicted by longitudinal plots.

9.5.4. Safety Analysis

Safety observations and measurements including drug exposure, AEs, laboratory data, vital signs, and ECOG performance status will be summarized and presented in tables and listings.

9.5.4.1. Adverse Events

Definitions

For safety variables, 3 observation periods are defined:

- The pre-treatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment period is defined as the day from first dose of study drug to follow-up visit 1
- The post-treatment period is defined as the time after follow-up visit 1.

Treatment-emergent adverse events (TEAEs) are defined as those not present at baseline or represent the exacerbation of a condition present at baseline during the on-treatment period or within 105 days after the last study dose.

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA[®]). Coding will be to lowest level terms. The verbatim text, the preferred term (PT), and the primary system organ class (SOC) will be listed.

Summaries of all TEAEs by group will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (NCI-CTCAE, version 4.03 grade), presented by SOC and PT
- TEAEs by outcome
- TEAEs by relationship to experimental treatment (related, not related), presented by SOC and PT

Deaths and other SAEs will be listed and summarized by group.

Events of NCI-CTCAE Grade 3 and Grade 4 severity will be summarized by group.

Treatment-emergent adverse events leading to permanent treatment discontinuation will be listed and summarized by group.

9.5.4.2. Other Safety

Vital Signs

Vital signs (temperature, pulse, blood pressure, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Laboratory Tests

Laboratory test results will be listed, and number and percentage of patients with NCI-CTCAE Grade 3 or Grade 4 lab values will be summarized by lab test and by group.

9.5.4.3. Treatment Exposure

Duration of exposure, number of dose administered and dose intensity will be summarized by group. Dose intensity will be calculated by dividing actual dose by body weight for REGN2810.

9.5.4.4. Treatment Compliance

Patients will be administered IV study drug and treatment compliance will be defined in detail in the SAP and summarized by group.

9.5.5. Analysis of Drug Concentration Data

9.5.5.1. Descriptive Analysis of Drug Concentrations

Summaries of study drug concentrations will be presented by nominal time point (ie, the time points specified in the protocol) and group.

9.5.6. Analysis of Anti-Drug Antibody Data

Formation of ADA will be assessed in individual patients and per treatment group as follows:

- Possible correlation between changes in PK profile and the presence/absence of anti-REGN2810 antibodies will be evaluated to identify a potential impact of anti-REGN2810 antibodies on drug exposure.
- Possible correlation between AEs and the presence/absence of anti-REGN2810 antibodies may be evaluated to identify a potential impact of anti-REGN2810 antibodies on the incidence of Grade 3 and 4 AEs, atypical AEs, and SAEs.

Cases of ADA positivity will be listed and summarized as appropriate.

9.5.7. Analysis of Biomarker Data

Biomarker data will be analyzed using standard scientific methods and summarized by descriptive statistics and plot. Comparative analysis of biomarker data with parent study may be performed using paired t-test or nonparametric Wilcoxon signed rank test or Chi-square test. Correlative analysis with clinical response may be performed using correlation coefficient, box plot and scatter plot, and basic regression models. Both comparative analysis and correlative analysis will be exploratory in nature and will be described in a separate report.

9.5.7.1. Sample Size Justification for Biomarker Measurements in Tumor Tissue Biopsies

Although many biomarkers may be assayed in tumor biopsy tissues, CD274 (PD-L1) was selected to illustrate the power analysis as an example. PD-L1 expression level, as defined by percent tumor cells with membranous staining by immunohistochemistry, was reported to be associated with clinical activity of Nivolumab ([Borghaei 2015](#)). The prevalence of PD-L1 expression levels $\geq 1\%$, $\geq 5\%$, $\geq 10\%$ were 53%, 41%, and 37%, respectively, and the ORRs were reported as 9% vs. 31%, 10% vs. 36%, 11% vs. 37% for each categorization of PD-L1 expression level, respectively. In the following power analysis, the following variations are considered ([Table 10](#)):

1. Actual number of tumor biopsy obtained and deemed evaluable are 60, 50, or 40.
2. The PD-L1 expression level categorization results in PD-L1 negative / positive ratio as 1:1 or 3:2.
3. Objective response rates of 10% (PD-L1 negative) vs. 30% (PD-L1 positive) results an odds ratio of 3.857 and 10% (PD-L1 negative) vs. 25% (PD-L1 positive) results an odds ratio of 3.0

The power analysis was based on the one-sided Chi-square test with type I error of 20% due to the exploratory nature of biomarker analysis, performed in nQuery Advisor 7.0 ([Elashoff 2007](#)). The power may be overestimated for some configurations as the large sample approximation may not be adequate for a Chi-square test with small sample sizes.

In summary, requiring each patient enrolled in this study to provide tumor biopsy provides moderate power for exploratory biomarker analysis.

Table 10 Power Analysis for PD-L1 Biomarkers from Tumor Biopsies

Number of Tumor Biopsies	PD-L1 Neg/Pos	Tumor Response Odds Ratio	Power (%)
60	1:1	3.857	87
		3.0	75
50	1:1	3.857	83
		3.0	71
40	1:1	3.857	77
		3.0	66
60	3:2	3.857	86
		3.0	75
50	3:2	3.857	82
		3.0	70
40	3:2	3.857	76
		3.0	65

9.6. Multiplicity Considerations

Adjustments to the significance level for the purposes of multiple testing are not applicable for this study. Statistical analyses for Group 1 and Group 2 will be conducted and reported separately; ie, efficacy results and clinical conclusions from Group 1 will not affect those of Group 2, and vice versa. Therefore, statistical control of overall type I error for the whole study is not planned.

Group 3 is a 53 patient cohort that opens after Group 1 completes enrollment. Efficacy results and clinical conclusions from Group 3 will not affect those of Group 1 or Group 2. Efficacy results and clinical conclusions from Group 1 or Group 2 will not affect those of Group 3.

9.7. Interim Analysis

For regions where alpha spending is not required: For this planned interim analysis, the ORR and associated 95% confidence interval will be summarized. As the primary objective of this the interim analysis is point estimation on ORR and characterizing the precision of point estimation, there is no hypothesis testing associated with this interim analysis. Also, no decisions will be made regarding study conduct associated with the interim analysis. Therefore, Type I error adjustment is not applicable for this planned interim analysis.

For regions where alpha spending is required: For this interim analysis on Group 2 patients, 2-sided alpha of 0.0001 will be allocated for interim analysis, and 2-sided alpha of 0.0499 will be preserved for the final analysis. Correspondingly, for the interim analysis of the primary endpoint of ORR in Group 2 patients, the precision of ORR will be estimated by adjusted and 2-sided 99.99% exact confidence interval. The un-adjusted and 2-sided 95% exact confidence interval will also be reported at the time of interim analysis. At the time of the final analysis for Group 2 patients, both adjusted 95.01% and un-adjusted 95% exact confidence interval will be reported.

For other efficacy endpoints in Group 2 patients, only 2-sided 95% exact confidence interval will be presented both at the interim and at the final analysis.

9.8. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed:

Definition of baseline:

- Unless otherwise specified, the last assessment before the initial administration of REGN2810 will be considered the baseline evaluation

General rules for handling missing data:

- Unless otherwise specified, there will be no imputations for the missing data
- If the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the intake of study medication except if an incomplete date (eg, month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the intake of study medication date, then the start date by the study medication intake date will be imputed, otherwise, the missing day or month by the first day or the first month will be imputed.
- Patients who are deemed NE by RECIST version 1.1 (Group 1; [Appendix 1](#)) or inevaluable by the composite response criteria (Group 2; [Appendix 2](#)) will be considered as not reaching PR/CR for ORR. Their disease progression will be censored at the date of baseline tumor assessment + 1 day. Duration of response and PFS will be censored at the last tumor assessment date for patients without disease progression.
- Missing data in quality of life analysis will be presented as missing in changes scores.

Visit windows:

- Assessments taken outside of protocol allowable windows will be displayed according to the case report form (CRF) assessment recorded by the investigator.

9.9. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in [Section 15.1](#).

10. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

10.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation, cleaning, correcting, releasing) will be maintained and stored at Regeneron.

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, medical /surgical history) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with electronic data capture (EDC) tool. User training must be documented before the user is granted access to the EDC system.

10.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- EDC system – data capture
- Statistical Analysis Systems (SAS) (Software)– statistical review, analysis and reporting
- Pharmacovigilance safety database
- IWRS

11. STUDY MONITORING

11.1. Monitoring of Study Sites

The study monitor and/or designee (eg, contract research organization [CRO] monitor) will visit each site prior to enrollment of the first patient, and periodically during the study. In accordance with ICH guidelines, the monitor will compare the CRF entries with the appropriate source documents. Additional review may include, but is not limited to, patient ICFs, documentation of patient recruitment and follow-up, AEs, SAEs, and concomitant therapy; as well as records of study drug dispensing, compliance, and accountability. A copy of the drug dispensing log must be provided to the sponsor upon request.

11.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents).

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an eCRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

11.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic CRFs by trained site personnel. A CRF must be completed for each and every patient enrolled in the study. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each CRF page is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the system. For corrections made via data queries, a reason for any alteration must be provided.

12. AUDITS AND INSPECTIONS

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, Institutional Review Board (IRB) files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

13.2. Informed Consent

The principles of informed consent are described in ICH Guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB. A copy of the IRB-approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, the ICF must be reviewed and updated appropriately. All study patients must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient.

13.3. Patient Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by a patient identification number, only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The patient's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

13.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/Ethics Committee (EC), as described in ICH Guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design or operation of the protocol or ICF without an IRB/EC-approved amendment.

15. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

15.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

15.2. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of patients required for the study are enrolled earlier than expected

In all cases, the appropriate IRB/EC and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

16. STUDY DOCUMENTATION**16.1. Certification of Accuracy of Data**

A declaration assuring the accuracy and content of the data recorded on the CRFs must be signed by the investigator. This certification form accompanies each set of CRFs. The signed form will be provided to the sponsor with the final set of CRFs for each patient.

16.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer if a longer period is required by relevant regulatory authorities. The investigator must consult with the sponsor before discarding or destroying any essential study documents following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor and the relevant records will be transferred to a mutually agreed-upon destination.

17. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

18. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

19. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

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21. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A Phase 2 Study of REGN2810, a Fully Human Monoclonal Antibody to Programmed Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma, and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

(Signature of Investigator)

(Date)

(Printed Name)

APPENDIX 1. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS: RECIST GUIDELINE (VERSION 1.1)

For the purposes of this study, patients should be re-evaluated for response every 8 weeks (Group 1 and Group 2) or every 9 weeks (Group 3). Confirmatory scans should also be obtained 4 weeks following initial documentation of objective response or progressive disease.

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1; [Eisenhauer 2009](#)). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Selection of Lesions

- **Measurable disease:** Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm (≥ 2 cm) by chest x-ray or as ≥ 10 mm (≥ 1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note:

- **Malignant lymph nodes:** To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm (≥ 1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.
- **Non-measurable disease:** All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm [< 1 cm] or pathological lymph nodes with ≥ 10 to < 15 mm [≥ 1 to < 1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

- **Target lesions:** All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the

diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

- **Non-target lesions:** All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- **Clinical lesions.** Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules and palpable lymph nodes) and ≥ 10 mm (≥ 1 cm) diameter as assessed using calipers (eg, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- **Chest x-ray.** Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Conventional CT and MRI.** This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situation.
- **PET-CT.** At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.
- **Ultrasound.** Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator

dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

- **Endoscopy, Laparoscopy.** The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.
- **Tumor markers.** Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- **Cytology, Histology.** These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (eg, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease

- **FDG-PET.** While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible ‘new’ disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
 - a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
 - b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
 - c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Response Criteria

Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).
- **Partial Response (PR):** At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

- **Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).
Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease (PD):** Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Overall Response Criteria

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient’s best response assignment will depend on the achievement of both measurement and confirmation criteria. Revised Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 ([Eisenhauer 2009](#)) are summarized in the table:

**Response According to Revised Response Evaluation Criteria in Solid Tumors
(Version 1.1)**

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required^a
CR	CR	No	CR	≥4 weeks confirmation
CR	Non-CR/Non-PD	No	PR	≥4 weeks confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 weeks from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease.

^a In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as PD.

APPENDIX 2. COMPOSITE RESPONSE CRITERIA FOR PATIENTS WITH LOCALLY ADVANCED CSCC

These criteria are designed primarily for patients in Group 2. This appendix describes clinical response criteria for externally visible lesions that can be measured bi-dimensionally using digital medical photography. This appendix also provides composite response criteria for disease that is measurable by both clinical response criteria and RECIST 1.1.

Group 2 patients will be followed by digital medical photography. Group 2 patients will also undergo radiologic imaging (typically, MRI with gadolinium) at baseline, and this will also be performed serially at each response assessment unless the investigator deems that baseline radiologic imaging was uninformative. Radiologic imaging (preferably, MRI with gadolinium) will be essential in the evaluation of tumors that have subdermal components that cannot be adequately assessed by digital medical photography. See protocol Section 6.3.1 and 6.3.2 for further information on imaging requirements for Group 2 patients.

Response assessments occur every 8 weeks (except for Group 3, in which response assessments occur every 9 weeks). Standardized digital photographs of the externally visible component of all target lesions must be obtained at baseline and at the time of each subsequent tumor assessment. Guidelines for digital medical photography are provided in [Appendix 6](#). Investigators will also provide a clinical description of the externally visible target lesion(s) at baseline and at each tumor assessment, as well as comments on any changes in the lesion(s) since the previous assessment.

SPECIAL ISSUES FOR EXTERNALLY VISIBLE TUMORS:

1) Anatomic Defects

Regarding tumor around a surgical cavity/anatomic defect (eg, rhinectomy), such lesions should be considered non-measurable unless there is a nodular lesion measuring ≥ 10 mm in maximal bi-dimensional perpendicular diameters. The surgical cavity or anatomic defect should not be considered in measuring the lesion.

2) Indeterminate-Appearing Tissue

If there is uncertainty about whether a given lesion or area of a lesion represents malignancy versus benign process (eg, scarring, fibrosis), biopsies should be obtained. Indeterminate-appearing areas (eg, scarring, fibrosis) are included in the tumor measurements unless biopsies are obtained to establish benign status.

To reduce risk of sample error, biopsy of only a single area on the tumor is not allowed. Biopsy of at least two separate areas of the lesion are required when biopsy is indicated. Each biopsy will be performed in a pairwise manner (approximately adjacent) so that there will be one sample for local review and one for central review for each biopsy, as per [Appendix 5](#).

As such, when the decision is made to perform biopsy, at least 4 biopsy samples are obtained (biopsy of two separate areas, with two biopsies in each area: one for central, one for local from each area). Biopsy samples will not be bisected or split in half for local and central review; rather, separate adjacent samples will be obtained. See [Appendix 5](#) for biopsy details.

Note on timeline for finalization of measurement/response assessment: Generally, baseline disease measurements and response assessments should be completed on the day of the visit at which digital medical photography was performed. However, for visits in which tumor biopsies are performed, it is understood that the local pathology report may not be available for up to 5 business days after the biopsy.

When biopsies are performed to distinguish between benign versus malignant tissue, the annotated photograph for that visit should clearly indicate the region of the tumor that was biopsied to distinguish benign versus malignant tissue. Within one week of the date of biopsies, the investigator should finalize the tumor measurements for that visit with the benefit of the local pathology report.

For circumstances in which the intent of the biopsy is to distinguish between disease stability and response, it is not necessary to hold study treatment while the local pathology report is pending. For circumstances in which the biopsy, if positive, would result in discontinuation of study treatment due to progression, treatment should be held until biopsy results are finalized and progression has been ruled out.

3) Local Versus Central Review

An independent photographic review committee, with access to de-identified digital medical photography results and biopsy results, will provide response assessments as required by the sponsor to address study objectives (Section 2). Independent photographic reviews will be scheduled by the sponsor in coordination with vendor, but will not be “real-time.” Clinical management decisions generally will be as per investigator response assessments and local pathology review. In the unlikely event that independent review yields major differences with the local response assessment that could have implications for the ongoing management of an active patient on study, the situation will be discussed between the sponsor and the investigator in order to determine patient management.

4) Confirmation of Responses

After any objective response, confirmatory digital photography (and radiologic imaging, if performed as part of the initial response assessment) will be obtained at least 4 weeks following initial documentation of objective response.

For any complete responses observed in digital medical photography of externally visible target lesions, confirmatory biopsies are required to establish status of complete response.

5) Patients in Group 1 and Group 3 with Externally Visible Tumors

Regarding Group 1 and Group 3 (metastatic CSCC), these patients will generally be followed by RECIST 1.1 criteria ([Appendix 1](#)). It is possible that some patients in Group 1 or Group 3 may also have externally visible lesions that are measurable by digital medical photography. In such circumstances, the externally visible lesions generally will be followed as non-target lesions. The exception to this rule would be a patient with externally visible lesions in whom the only M1 lesions are not measurable by RECIST (eg, a patient with bone-only metastases), in which case the externally visible lesions (lesion size ≥ 10 mm in baseline dimensional perpendicular axes) would be target lesions and followed as per clinical response criteria in this appendix, and the non-measurable metastatic lesions (eg, bone metastases) would be followed as non-target

lesions. For any target lesions in Group 2 or Group 1 or Group 3 that are measured by digital medical photography, measurements will be bi-dimensional.

6) Patients in Group 2 with Deeply Invasive Tumors

Regarding Group 2 (unresectable locally advanced CSCC), tumor measurements for these patients will generally be performed with digital medical photography (bi-dimensional measurements). However, some patients in Group 2 may have deeply invasive target lesions in which tumor measurements can better be obtained with cross-sectional imaging (eg, MRI with gadolinium or CT with contrast). For any target lesions in Group 2 (as in Group 1 or Group 3) that are measured by cross-sectional imaging (MRI gadolinium or CT with contrast), measurements will be unidimensional according to RECIST 1.1.

Clinical Response Criteria for Externally Visible Tumors (for Group 2 patients with locally advanced CSCC, and selected Group 1 and Group 3 patients in which target lesions are followed by digital medical photography)

A. Externally Visible Tumor Dimension

The externally visible component of target lesion(s) will be measured using bi-dimensional WHO criteria as the sum of the products (of individual target lesions) in the longest dimension and perpendicular second longest dimension at each tumor assessment and will be documented using standardized digital photography ([Appendix 6](#)). In the absence of substantial change in lesion geometry, subsequent visit measurements should be performed in the same axes and the investigator should refer to the previous visit's annotated photographs as a starting point to identify axis for measurement when making subsequent assessments.

Clinical response criteria for externally visible tumor(s) require bidimensional measurements according to WHO criteria (reference), and are as follows:

- Complete response of externally visible disease (vCR): all target lesion(s) and non-target lesion(s) no longer visible, maintained for at least 4 weeks. Documentation of vCR requires confirmation by biopsies of site(s) of externally visible target lesion(s) with histologic confirmation of no residual malignancy, per central pathology review ([Appendix 5](#)). In the absence of such histologic confirmation, a patient cannot be deemed to have experienced vCR and the best response would be partial response.
- Partial response of externally visible disease (vPR): decrease of 50% (WHO criteria) or greater in the sum of the products of perpendicular longest dimensions of target lesion(s), maintained for at least 4 weeks
- Stable externally visible disease (vSD): not meeting criteria for vCR, vPR, or progressive disease
- Progression of visible disease (vPD): increase of $\geq 25\%$ (WHO criteria) in the sum of the products of perpendicular longest dimensions of target lesion(s). In rare cases, unequivocal progression of a non-target lesion may be accepted as vPD.

B. New Lesions

A new cutaneous lesion consistent with CSCC will be considered as cPD if the lesion is ≥ 10 mm in both maximal perpendicular diameters, and can be clearly documented as not being previously present, unless it is confirmed on biopsy not to be consistent with CSCC. If a new cutaneous lesion is not biopsied or if the histology is inconclusive, it should be considered CSCC and deemed cPD.

Overall Clinical Responses For Locally Advanced CSCC Lesions that are Measured by Digital Medical Photography

Externally Visible Tumor Dimension ^a	New Lesions ^a	Clinical Response
vCR	No	cCR ^{b,c}
vPR	No	cPR ^d
vSD	No	cSD ^e
vPD	Yes or No	cPD ^f
Any	Yes	cPD ^f

^a See above for definitions

^b Clinical Complete Response

^c Negative biopsy showing no residual malignant cells is required for any lesion be deemed cCR

^d Clinical Partial Response

^e Clinical Stable Disease

^f Clinical Progression of Disease

Composite Response Criteria

These criteria are for patients who have locally advanced or metastatic CSCC (any Group) that is measurable by BOTH clinical response criteria by digital medical photography and RECIST 1.1 using radiologic imaging. **The “Clinical Response” column in this table will be based on the results of the “Clinical Response” (far-right) column of the table above. RECIST 1.1 response is according to Appendix 1. The determinations of the Independent Composite Response Committee will serve as the central reviews for these patients.**

Clinical Response (Digital Medical Photography)	RECIST 1.1 Response (Radiology)	Composite (Overall): Clinical + RECIST Response
cCR	CR or NA ^a	CR
NA	CR	CR
cCR	PR or SD	PR
cPR	CR, PR, or SD, or NA	PR
NA	PR	PR
cSD	CR or PR	PR

Clinical Response (Digital Medical Photography)	RECIST 1.1 Response (Radiology)	Composite (Overall): Clinical + RECIST Response
cSD	SD or NA	SD
NA	SD	SD
cPD	Any	PD
Any	PD	PD

^a NA indicates “Not applicable” (eg, because the assessment was not done)

In addition, if all previously inoperable target lesions are rendered operable with clear margins obtained at the time of surgery, this will be considered a PR. If the investigator deems a previously unresectable lesion to be potentially resectable due to response to REGN2810, the Medical Monitor should be consulted prior to any surgical procedure being performed. A decision will be rendered by the sponsor as to whether the planned surgical intervention is compatible with study requirements. (This statement does not apply to patients in emergency life-threatening situations that require immediate surgery).

C. Ulcerated Lesions

This section only pertains to target lesions that have extensive ulceration at baseline that prevents measurement by the above methods in this appendix. Response criteria are as follows:

- Complete response: re-epithelialization of the entire baseline area of ulceration of target lesion(s), maintained over at least 4 weeks.
- Partial response: there are no criteria for partial response
- Stable disease: not meeting criteria for complete response or progressive disease
- Progressive disease: new ulceration of target lesion(s) not related to (ie, in a location separate from) tissue biopsy or other known trauma, persistent without evidence of healing for at least 2 weeks

APPENDIX 3. REGN2810 PHARMACOKINETIC SAMPLING AND ASSESSMENT SCHEDULE

For Groups 1 and 2:

Study Visit	PK Sampling Time
Cycle 1, day 1	<ul style="list-style-type: none"> • Preinfusion • Within 10 minutes after end of infusion
Cycle 1: day 15 \pm 3, day 29 \pm 3, day 43 \pm 3	<ul style="list-style-type: none"> • Preinfusion • Within 10 min after end of infusion
Cycles 2–6: day 1	<ul style="list-style-type: none"> • Preinfusion • Within 10 min after end of infusion
Cycles 7, 9, 11: day 1	<ul style="list-style-type: none"> • Preinfusion • Within 10 min after end of infusion
End of study (if progression during cycles 1-12) or Follow-up Visit 1	Anytime during the visit

For Group 3:

Study Visit	PK Sampling Time
Cycle 1, day 1	<ul style="list-style-type: none"> • Preinfusion • Within 10 minutes after end of infusion
Cycle 1: day 22 \pm 3, day 43 \pm 3	<ul style="list-style-type: none"> • Preinfusion • Within 10 min after end of infusion
Cycles 2-6: day 1	<ul style="list-style-type: none"> • Preinfusion • Within 10 min after end of infusion
End of study (if progression during cycles 1-6) or Follow-up Visit 1	Anytime during the visit

APPENDIX 4. RECOMMENDED DOSE MODIFICATION OR DISCONTINUATION AND SUPPORTIVE CARE GUIDELINES FOR SPECIFIC STUDY DRUG-RELATED ADVERSE EVENTS

Section 5.3.2 provides the dose level reductions.

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Colitis events <ul style="list-style-type: none"> • Bowel obstruction • Colitis • Colitis microscopic 	≤ Grade 1	No change in dose	<ul style="list-style-type: none"> • For diarrhea, treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet). Endoscopy is recommended if symptoms persist. • Grade 1 diarrhea that persist for >1 week should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily. 	Symptoms may include (but are not limited to): <ul style="list-style-type: none"> • Abdominal pain, cramping and/or bloating • Blood and/or mucus in stool with or without fever • Constipation • Diarrhea • Ileus • Nausea and/or vomiting • Peritoneal signs consistent with bowel perforation • Rectal bleeding • With or without fever Patients with diarrhea should be	All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, and a <i>Clostridium difficile</i> titer.
	Grade 2	Hold until ≤Grade 1. Resume at same dose level. May increase dosing interval by 1 week if it takes more than 4 weeks for toxicities to resolve.	<ul style="list-style-type: none"> • GI consultation and endoscopy is recommended to confirm or rule out colitis for grade 2 diarrhea that persists >1 week or grade 1-2 diarrhea with rectal bleeding (additional guidelines for the treatment of persistent colitis are provided below). • Grade 2 diarrhea should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily. • Grade 2 diarrhea with diffuse ulceration and bleeding seen on endoscopy may require oral steroids with prolonged taper and represent an increased risk for the development of bowel perforation. Consider prophylactic antibiotics for opportunistic infections. • When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • In patients with Grade 2 enterocolitis, REGN2810 should be withheld and antidiarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (eg, 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. 		

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Colitis events (continued)	Grade 3–4	<p>Withhold REGN2810</p> <p>Discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisone equivalent within 12 weeks of toxicity</p>	<ul style="list-style-type: none"> In patients with Grade 3 enterocolitis, REGN2810 will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1–2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. Consider prophylactic antibiotics for opportunistic infections. <p>For Grade 3–4 diarrhea (or Grade 2 diarrhea that persists after initial steroid treatment),</p> <ul style="list-style-type: none"> Rule out bowel perforation. Imaging with plain films or computed tomography (CT) can be useful. Consider consultation with gastroenterologist and confirmation biopsy with endoscopy. Treat with intravenous (IV) steroids (methylprednisolone 125 mg) followed by high-dose oral steroids (prednisone 1–2 mg/kg once per day or dexamethasone 4 mg every 4 hours). When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Taper over 6–8 weeks in patients with diffuse and severe ulceration and/or bleeding. If IV steroids followed by high-dose oral steroids does not reduce initial symptoms within 48–72 hours, consider treatment with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45–60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab. CAUTION: infliximab is contraindicated in patients with bowel perforation or sepsis^b. If symptoms persist despite the above treatment a surgical consult should be obtained. 	carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.	

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Endocrine events <ul style="list-style-type: none"> • Hyperthyroidism • Hypophysitis • Hypopituitarism 	Grade 1-2	No change in dose	<ul style="list-style-type: none"> • Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values. 	Symptoms may include (but not limited to): <ul style="list-style-type: none"> • Abdominal pain • Abnormal thyroid function tests and/or serum chemistries (Thyroid-stimulating hormone increased [decreased], Free thyroxine increased, Tri-iodothyronine increased.) • Arrhythmias^c • Cold or heat intolerance • Fatigue • Fever • Headache • Hypotension^c • Loss of appetite • Mental status and/or behavior changes • Nausea and/or vomiting • Unusual bowel habits • Vision disturbances • Weakness 	All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection. An endocrinology consultation is recommended.
Endocrine events <ul style="list-style-type: none"> • Hypothyroidism • Thyroid disorder • Thyroiditis 	Grade 3-4	Hold until on stable replacement dose	<ul style="list-style-type: none"> • Consider endocrine consultation. • Rule out infection and sepsis with appropriate cultures and imaging. • Replacement of appropriate hormones as required. 		
Endocrine events <ul style="list-style-type: none"> • Adrenal insufficiency • Hypophysitis • Pan-hypopituitarism 	Grade 1-4	Hold until on stable replacement dose	<ul style="list-style-type: none"> • Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency. • If Grade 1–2 hypophysitis is considered, pituitary gland imaging should be considered (magnetic resonance imaging [MRIs] with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis). • Grade 3–4 hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis. Hospitalization and IV methylprednisolone should be initiated. 		

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Eye event: Uveitis (iritis, iridocyclitis)	Grade 1	Discontinue REGN2810 if symptoms persist despite treatment with topical immunosuppressive therapy	<ul style="list-style-type: none"> • Evaluation by an ophthalmologist is strongly recommended. • Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics. 	Symptoms may include (but are not limited to): <ul style="list-style-type: none"> • Blurred vision • Diffuse erythema and a prominent blush on the sclerae • Dryness of the eyes • Pain • Photophobia 	All attempts should be made to rule out other causes such as metastatic disease, infection, or other ocular disease (e.g., glaucoma or cataracts).
	Grade 2	Discontinue REGN2810 if symptoms persist despite treatment with topical immunosuppressive therapy and do not improve to Grade 1 within the retreatment period OR requires systemic treatment.	<ul style="list-style-type: none"> • Evaluation by an ophthalmologist is strongly recommended. • Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics. 		
	Grade 3–4	Discontinue REGN2810.	<ul style="list-style-type: none"> • Treat with systemic corticosteroids such as prednisone at a dose of 1-2 mg/kg per day. When symptoms improve to ≤Grade 1, steroid taper should be started and continued over no less than 4 weeks. 		

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Hepatic events <ul style="list-style-type: none"> Hepatitis Hepatitis, Autoimmune 	Grade 1–2	Withhold REGN2810 if there is a treatment-emergent concurrent elevation of ALT and bilirubin that corresponds to an upward shift of 2 or more grades in both parameters.	<ul style="list-style-type: none"> Monitor liver function tests more frequently until returned to baseline values. 	Symptoms may include (but are not limited to): <ul style="list-style-type: none"> Elevations in: <ul style="list-style-type: none"> AST >2.5 × ULN ALT >2.5 × ULN Total bilirubin >1.5 × ULN Fever Malaise Upper quadrant abdominal pain 	All attempts should be made to rule out other causes such as metastatic disease, progressive liver disease, viral hepatitis, alternative drug toxicity, infectious causes and/or myositis.
	Grade 3–4	Withhold (and consider Discontinuation of) REGN2810 when AST or ALT >5.0 times ULN and/or total bilirubin >3.0 times ULN.	<ul style="list-style-type: none"> Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury, if necessary. Treat with high-dose IV glucocorticosteroids for 24–48 hours. When symptoms improve to grade 1 or less, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1–2 mg/kg should be started and continued over no less than 4 weeks. If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity^b. Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. 		
Nausea	≤Grade 1	No change in dose	<ul style="list-style-type: none"> Nausea should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake. 		
	Grade 2	Hold until ≤Grade 1. Resume at same dose level. May increase dosing interval by 1 week if it takes more than 4 weeks for toxicities to resolve.			
	Grade 3	Hold until <Grade 2. May increase dosing interval by 1 week for each occurrence. Discontinue if toxicities do not resolve within 12 weeks.			
	Grade 4	Off protocol therapy			

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Neutropenia	≤Grade 1	No change in dose	For neutropenia, see general guidelines on hematologic toxicity in Table 3		
	Grade 2	No change in dose			
	Grade 3	No change in dose			
	Grade 4	See Table 3			

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Pneumonitis events <ul style="list-style-type: none"> • Pneumonitis • Interstitial lung disease • Acute interstitial pneumonitis 	Grade 1	Consider hold of therapy. REGN2810 may be continued with close monitoring.	<ul style="list-style-type: none"> • Radiologic findings should be followed on serial imaging studies at least every 3 weeks. • Monitor for symptoms every 2–3 days. • Consider pulmonary consultation and/or bronchoscopy if clinically indicated. 	Symptoms may include (but are not limited to): <ul style="list-style-type: none"> • Abnormal breath sounds • Chest pain and/or tightness^c • Dyspnea^c • Dry cough • Fatigue • Fever • Hemoptysis 	All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection.
	Grade 2	Hold REGN2810	<p>To rule out other causes such as infection:</p> <ul style="list-style-type: none"> • Consider pulmonary consultation with bronchoscopy and biopsy/bronchoalveolar lavage (BAL). • Consider pulmonary function tests. • Follow radiologic findings on serial imaging studies every 1–3 days <p>If the patient is determined to have study drug associated pneumonitis:</p> <ul style="list-style-type: none"> • Monitor symptoms daily; consider hospitalization. • Treat with systemic corticosteroids at a dose of 1–2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • Treatment with REGN2810 may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of methylprednisolone 10 mg by mouth daily or less. Repeat chest imaging monthly as clinically indicated. <p>For Grade 2 pneumonitis that improves to ≤ Grade 1 within 12 weeks, the following rules should apply:</p> <ul style="list-style-type: none"> • <u>First episode of pneumonitis</u>: May increase dosing interval by one week in subsequent cycles. • <u>Second episode of pneumonitis</u>: Discontinue REGN2810 if upon rechallenge the patient develops a second episode of ≥ Grade 2 pneumonitis. 		
	Grade 3–4	Discontinue REGN2810.	<ul style="list-style-type: none"> • Consider pulmonary function tests with pulmonary consult. • Bronchoscopy with biopsy and/or BAL is recommended. • Treat with IV steroids (2–4 mg/kg per day prednisone or equivalent). When symptoms improve to grade 1 or less, a high-dose oral steroid (1–2 mg/kg prednisone once per day or 4 mg dexamethasone every 4 hours) taper should be started and continued over no less than 4 weeks. • Add prophylactic antibiotics for opportunistic infections. • If IV steroids followed by high-dose oral steroids does not reduce initial symptoms within 48–72 hours, treat with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45–60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab. 		

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Renal events <ul style="list-style-type: none"> • Nephritis • Nephritis autoimmune • Renal failure • Renal failure, Acute 	Grade 1	Consider withholding REGN2810 if event does not improve with symptomatic treatment	<ul style="list-style-type: none"> • Provide symptomatic treatment. • Monitor creatinine weekly; when it returns to baseline, resume routine creatinine monitoring per protocol. 	Symptoms may include (but not limited to): <ul style="list-style-type: none"> • Fatigue • High blood pressure • Increased serum creatinine • Swelling 	All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury to other chemotherapy agents. A renal consultation is recommended.
	Grade 2	Consider withholding REGN2810.	<ul style="list-style-type: none"> • Systemic corticosteroids at a dose of 1–2 mg/kg/day of prednisone or equivalent may be indicated. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. • Consider prophylactic antibiotics for opportunistic infections. • Consider renal biopsy. • If elevations persist >7 days or worsen, treat as Grade 4. 		
	Grade 3-4	Discontinue REGN2810.	<ul style="list-style-type: none"> • Renal consultation with consideration of ultrasound and/or biopsy as appropriate. • Monitor creatinine daily. • Treat with systemic corticosteroids at a dose of 1–2 mg/kg prednisone or equivalent once per day. • When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • Discontinue REGN2810 if unable to reduce corticosteroid dose for irAEs to ≤10 mg. • REGN2810 treatment may be restarted and the dose modified as specified in the protocol. 		

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Skin events <ul style="list-style-type: none"> • Dermatitis exfoliative • Erythema multiforme • Stevens-Johnson syndrome • Toxic epidermal necrolysis If considered to be immune related, ≥ Grade 3 or result in dose modification or discontinuation: <ul style="list-style-type: none"> • Pruritus • Rash • Rash generalized • Rash maculo-papular • Vitiligo 	Grade 1–2	No change in dose	<ul style="list-style-type: none"> • Symptomatic treatment should be given such as topical glucocorticosteroids (eg, betamethasone 0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral antipruritics (eg, diphenhydramine HCl or hydroxyzine HCl). • Treatment with oral steroids is at investigator discretion for Grade 2 events. 		All attempts should be made to rule out other causes such as metastatic disease, infection, or allergic dermatitis.
	Grade 3	Hold REGN2810.	<ul style="list-style-type: none"> • Consider dermatology consultation and biopsy for confirmation of diagnosis. • Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg four times orally daily. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. 		
	Grade 4	Permanently discontinue REGN2810.	<ul style="list-style-type: none"> • Dermatology consultation and consideration of biopsy and clinical dermatology photograph. • Initiate steroids at 1–2 mg/kg prednisones or equivalent. When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. 		
Thrombocytopenia	≤ Grade 1	No change in dose			
	Grade 2	No change in dose			
	Grade 3	See Table 3			
	Grade 4	See Table 3			

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms ^a	Differential Diagnosis
Vomiting	≤ Grade 1	No change in dose	<ul style="list-style-type: none"> Vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake. 		
	Grade 2	Hold until ≤Grade 1. Resume at same dose level. May increase dosing interval by 1 week if it takes more than 4 weeks for toxicities to resolve.			
	Grade 3	Hold until <Grade 2. May increase dosing interval by 1 week for each occurrence. Discontinue if toxicities do not resolve within 12 weeks.			
	Grade 4	Off protocol therapy			

^a The signs and symptoms may be associated with any of the diagnoses in the associated “Event(s)” column.

^b REMICADE (Infliximab) prescribing information

^c If symptoms indicate possible new or worsening cardiac abnormalities, additional testing and/or a cardiology consultation should be considered.

APPENDIX 5. GUIDELINES FOR BIOPSIES FOR LOCALLY ADVANCED CSCC

This appendix provides timepoints and research procedures for biopsies in patients with locally advanced CSCC. Because of the potential for sampling error with any single biopsy, two separate sites (preferably on the same target lesion) should be biopsied for any biopsy assessment. Regarding the required exploratory biopsies, if the investigator feels the biopsy would create an unacceptable safety risk for the patient or cannot be performed without interfering with the measurements of the target lesions, the biopsy requirement may be waived for an individual patient after communication with the medical monitor.

Time points:

1. Baseline (required):

The study inclusion criteria require that the sponsor be provided with archived pathology material that will be used for the purpose of confirmation of the diagnosis of CSCC by central pathology review for all study patients. If the archived material is not sufficient for confirmation of diagnosis of CSCC by central review, baseline “exploratory” biopsy material (required for only Group 2 patients) may be used for central pathologic confirmation only if it is determined that no other archived pathology material is available for confirmation of diagnosis of CSCC by central pathology review. Remaining baseline tumor material can only be used for exploratory assessments after central pathology confirmation of diagnosis of CSCC has been established.

2. Baseline or at any scheduled response assessment (If needed to differentiate benign versus malignant area of skin):

Areas of indeterminate-appearing tissue should be biopsied to distinguish malignant tissue versus benign process (eg, scarring, fibrosis). In circumstances in which biopsies are planned, it is preferred that these be performed on the day of a regularly-scheduled response assessment.

3. On cycle 1 day 29 (± 3 business days) for exploratory assessments, 2 biopsies (punch biopsies, 3 to 5 mm each) should be obtained, preferably from the same externally visible lesion from which the baseline biopsies were taken. Both samples will be provided to the sponsor for exploratory assessments. The cycle 1 day 29 samples are not intended for local pathology review.

4. At clinical complete response (required): Complete response status for externally visible lesions requires biopsies of 2 sites on the same lesion which are histologically negative for malignancy (see secondary objectives).

5. At progression (strongly encouraged): Two sites of externally visible progressing tumor should be biopsied.

Research procedures for ALL biopsies:

1. Where and How:

The technique and sites of biopsies will be selected by the investigator based on the sizes and locations of lesions. Generally, biopsies will be 3 to 5 mm punches. Biopsies should not be taken at the perimeter of a lesion because this could interfere with measurement of bi-dimensional perpendicular diameters for response assessments. Whenever possible, biopsy sites should be ≥ 5 mm from the edge of baseline lesional area.

2. How many:

For exploratory assessments: 2 biopsies of externally visible CSCC will be obtained at baseline and again at cycle 1 day 29 (± 3 business days). These required biopsies for Group 2 patients are called “Exploratory Biopsies” for the purposes of this study. Two biopsies at time of progression should also be obtained. In the event that an investigator determines that clinical circumstances interfere with the ability to obtain the recommended number of minimal biopsies at baseline or cycle 1 day 29 (± 3 business days), the monitor will be contacted to discuss the number of biopsies that can be reasonably obtained and this will not be deemed a protocol violation.

For indeterminate-appearing tissue: In addition to these biopsies for exploratory assessments, biopsies should be taken at baseline and at any response assessment if there is tissue that is indeterminate-appearing regarding presence of benign versus malignant tissue. These optional biopsies are referred to as “Response biopsies” (eg, in response to a clinical question), to distinguish from the required “Exploratory Biopsies” described above. When the decision is made to perform a “Response biopsy” of a lesion (or an area of a lesion) to clarify benign versus malignant status, 4 biopsies should be taken. This approach will mitigate the possibility for sample error or misleading results with any 1 biopsy, because 2 sites in the “indeterminate appearing” tissue will be selected. At each of the selected sites, 2 biopsies should be performed that are approximately adjacent (1 for central review, 1 for local pathology review). As such, 4 biopsies would be performed (2 sites, with paired biopsies at each site: 1 for local pathology, and 1 for central = 4 total biopsies).

3. Annotation and Photography

The punch biopsies should be labeled (annotated) on the patient and photographed, such that on review of the photograph the following information is clear for each biopsy site: the study week and day of the biopsy (eg, Baseline, Cycle 1, Day 29, etc), the identifying number of the biopsy (because at least 2 sites would be biopsied), and which samples are for central review and which samples are for local review. The tumor will also be annotated with a skin pen to indicate the tumor perimeter and delimiters of the longest bi-dimensional perpendicular axes. All biopsies will be photographed and annotated, including the cycle 1 day 29 biopsies that are for exploratory assessments.

Annotated photographs must be uploaded into Canfield secure website (see [Appendix 6](#)).

4. Disposition of Samples

Biopsy samples required for exploratory assessments (baseline, cycle 1 day 29) will be provided to the sponsor. It is also strongly encouraged that biopsy samples at time of

progression be obtained for exploratory assessments, and these should also be provided to the sponsor.

For each site that is biopsied to clarify indeterminate tissue, the entire block for one biopsy sample (designated for central) must be submitted to the vendor as per the Central Laboratory Manual. Because each biopsy site is sampled twice (closely adjacent samples) when there is indeterminate-appearing tissue, the second sample may be used for local pathology review. If only 1 adequate (eg, interpretable by pathologist) sample is obtained at a biopsy site, it will be provided to the sponsor for central review to address the study objectives (Section 2).

5. Classification of Pathology Samples

For response assessments in which biopsies were performed, pathology results guide the determination of the area of invasive CSCC versus benign tissue. Residual squamous carcinoma in situ will not be deemed to be invasive cancer. A minute focus of residual CSCC in an otherwise benign responding biopsy sample will not automatically supersede a determination of partial response. However, the best response that can be recorded if the pathology report demonstrates any residual CSCC is partial response (not complete response).

APPENDIX 6. DIGITAL PHOTOGRAPHIC PROCEDURES

Image Capture

- Close-up view with millimeter scale of the target area of the CSCC
- Global view of the target CSCC area

Equipment

- Camera: Canon SL1 with Ranging Lights
- Lens: 60mm Canon Lens
- Flash: Canfield TwinFlash RL
- Millimeter scale attachment
- Dedicated laptop with Canfield Capture Application (software includes capturing, viewing and transferring images)
- Canfield Tracing and Analysis application
- Standardized background material

The supplied equipment is to be used exclusively for this study. No modification, adjustments, or repairs of the camera equipment are to be undertaken without the expressed instruction of Canfield Scientific, Inc.

Canfield will provide each study site with the necessary hardware as well as technical support as needed. All supplied photographic equipment remains the property of the Sponsor.

Proper Patient Preparation and Positioning:

In these clinical photographs for the duration of the study, the only variable allowed to change is the skin condition itself. Therefore, anything extraneous to the condition (furniture, etc.) is to be eliminated from the photographic field, starting at the entry visit through the final visit. The necessity of good end-of-study photographs should be stressed to patients to ensure their cooperation. Lighting, framing, exposure, and reproduction ratios must be held constant. In the end, the images should read like a time-lapse movie.

In the close up view, the area of interest is the individual target lesion itself. In the global view, the area of interest includes the target lesion as well as relevant anatomical landmarks, e.g. side of face, side of neck, upper torso, full view of shoulder, etc. Photographs should be taken with the camera positioned at the same vertical height as the center of area of interest. Further, all shots should be made with the axis of the camera lens perpendicular to the surface of area of interest when possible. Glancing shots where the camera lens is not perpendicular to the patient's area of interest are to be avoided as these photographic angles may distort the image perspective yielding inaccuracies when measurement of lesions is performed on photos by central review.

The supplied standardized background material is to be used. Do not use wrinkled or crimped material.

The Canfield Capture software controls the setting of the camera specific to the protocol. The lens is set for auto focusing. The **close-up view** is accomplished using the attached standardized

mm scale. The **global view** is accomplished when the ranging lights converge on the target area. Any doubt as to the correctness of the photographic technique should result in an immediate re-shoot. At the baseline visit, a **profile view** (perpendicular to the skin's plane) will also be obtained of each lesion to capture any projection above the skin. For all lesions in which the baseline profile view demonstrates significant projection above the skin, defined as $\geq 15\text{mm}$, the profile view will also be obtained at subsequent scheduled clinical assessments of response.

For each global view and each close up view, an unannotated photograph must be taken followed by a manually annotated photograph.

For response assessments, Canfield imaging software should be used to assure that the photograph is taken at the same position and angle as the Baseline photograph. The annotated image from the prior visit should be referenced on the laptop screen prior to making annotations on the new image.

Photographic Procedures:

1. Prior to capturing the patient images using the camera system, the photographer launches the Canfield Scientific Canfield Capture Application by selecting the icon from the desktop.
2. The photographer either creates a New Patient for an initial visit or, for a return subject, highlights the appropriate existing Patient ID listed in the Canfield Capture database. The visit name (as per study schedule) is selected by the photographer and the image date is captured by the software.
3. With the patient's target area positioned correctly in front of the camera system, the Photographer adjusts the camera distance for accurate system focus. The first capture is a Close-up view of patient's target CSCC area(s) using the attached mm scale, consisting of one individual CSCC lesion. The second capture is Global view of patient's target CSCC area(s), consisting of up to two individual CSCC lesions. For the global view the camera is moved closer to or further away from the target until the two green ranging lights converge to become one dot.
4. The Photographer captures the image and is then prompted to review image acceptability. The Photographer either accepts the image and moves on to the next capture or does not accept and recaptures the image.
5. After capturing the series of non-annotated lesion(s), the Investigator will annotate the circumference and axes delimiters of lesion with supplied skin pen. **If any biopsies are taken at this visit (eg, baseline, cycle 1 day 29, at any regularly scheduled visit, or at time of progression), each biopsy will also be annotated as per [Appendix 5](#). The annotated photo will include the largest area, including both palpable and visible components of the lesion, as outlined by the investigator.** Following the same procedure as the non-annotated image capture the site will capture the series of annotated lesion(s) images

6. Following the session, the Photographer submits the images to Canfield. Upon exiting, the software automatically reads, checksums, encrypts, packages, and duplicates the data to submit to Canfield via internet or removable media submission.
 - a. Internet: A secure, validated, compliant web server set up at Canfield is used for secure transfer of study images by study sites. Images are to be transferred the day they are recorded. Only approved individuals by the Sponsor have access to the website.

The application logs a record of this action to a local database and prompts the Photographer when completed.

1. Upon completion of photography session, the Investigator will log in to the Canfield tracing application may (optional) annotate the lesion and the software will provide measurements (surface area, longest diameter, perpendicular diameter) of the lesion.
2. Trained Canfield staff review the data files for technical quality and acceptability and communicate any comments to the site.
3. At the end of the study, a copy of site specific patient images will be provided to each site. This is in addition to the Photography Result Reports available for printing from the Clinical Services Website after each session. Remote access to all images by the Sponsor is also provided.

Any questions or problems regarding the photographic portion of this study are to be forwarded to the assigned Project Manager at Canfield Scientific.

Canfield Scientific, Inc.

253 Passaic Avenue

Fairfield, NJ 07004 United States

Toll-free telephone number: (800) 815-4375

Telephone number: (973) 276-0300

Facsimile number: (973) 276-0333

**APPENDIX 7. EASTERN COOPERATIVE ONCOLOGY GROUP
PERFORMANCE STATUS**

Grade	Description
0	Fully active; able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; Up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair 50% or more of waking hours
4	Completed disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

Source: [Oken 1982](#)

APPENDIX 8. FACTORS TO CONSIDER IN ASSESSING THE RELATIONSHIP OF AES TO REGN2810 OR STUDY CONDUCT.

Is there a reasonable possibility that the event may have been caused by the study drugs or infusion procedure, study procedure, or concomitant treatment?

No:

- due to external causes such as environmental factors or other treatment/s being administered
- due to the patient's disease state or clinical condition
- do not follow a reasonable temporal sequence following the time of administration of the dose of REGN2810, study procedure, or combination treatment
- do not reappear or worsen when dosing with REGN2810, study procedure, or combination treatment is resumed

Yes:

- could not be explained by environmental factors or other treatment/s being administered
- could not be explained by the patient's disease state or clinical condition
- follow a reasonable temporal sequence following the time of administration of the dose of REGN2810
- resolve or improve after discontinuation of REGN2810, study procedure, or combination treatment
- reappear or worsen when dosing with REGN2810, study procedure, or combination treatment is resumed
- are known to be a response to REGN2810 or the infusion procedure, study procedure, or combination treatment based upon pre-clinical data or prior clinical data

NOTE: This list is not exhaustive.

Signature of Sponsor's Responsible Officers

(Medical/Study Director, Regulatory Representative, Clinical Study Team Lead, and Biostatistician)

To the best of my knowledge, this protocol accurately describes the conduct of the study.

Study Title: A Phase 2 Study of REGN2810, a Fully Human Monoclonal Antibody to Programmed Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma

Protocol Number: R2810-ONC-1540

Protocol Version: R2810-ONC-1540 Amendment 5 Global

See appended electronic signature page

Sponsor's Responsible Medical/Study Director:

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison:

See appended electronic signature page

Sponsor's Responsible Clinical Study Team Lead:

See appended electronic signature page

Sponsor's Responsible Biostatistician:

STATISTICAL ANALYSIS PLAN

Title: A First-in-Human Study of Repeat Dosing with REGN2810, A Monoclonal, Fully Human Antibody to Programmed Death-1 (PD-1), as Single Therapy and in Combination with Other Anti-Cancer Therapies, in Patients with Advanced Malignancies

Protocol: R2810-ONC-1423

Investigational product: REGN2810 (anti-PD-1 mAb)

Sponsor: Regeneron Pharmaceuticals, Inc.

Study Biostatistician: Jingjin Li, PhD

Clinical Trial Manager: Katharine Nunnink

Study Medical Director: Elizabeth Stankevich, BS
Matthew Fury, MD, PhD

Version: 1.0

Date: 25Oct2017

The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

See appended electronic signature page

Jingjin Li, PhD
Study Biostatistician

See appended electronic signature page

Bo Gao, PhD
Director, Biostatistics

See appended electronic signature page

Matthew Fury, MD, PhD
Senior Director, Clinical Sciences Oncology

See appended electronic signature page

Yuhwen Soo, PhD
Vice President, Biostatistics and Data Management

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ABBREVIATIONS AND DEFINITIONS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the concentration–time curve
BAL	Bronchoalveolar lavage
BC	Breast cancer
BCC	Basal cell carcinoma
BLA	Biologic License Application
BMI	Body mass index
BUN	Blood urea nitrogen
CL	Clearance
CPA	Cyclophosphamide
CR	Complete response
CRF	Case report form (electronic or paper)
CSCC	Cutaneous Squamous Cell Carcinoma
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DDCR	Durable disease control rate
DEP	Depth of response
DLT	Dose-limiting toxicity
DODC	Duration of disease control
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

FAS	Full analysis set
FDA	Food and drug administration
GBM	Glioblastoma multiforme
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HCC	Hepatocellular carcinoma
HIV	Human immunodeficiency virus
H&N	Head and neck
HNSCC	Head and neck squamous cell carcinoma
ICF	Informed consent form
ICH	International Council for Harmonisation
IHC	Immunohistochemistry
INR	International Normalized Ratio
irRC	Immune-related response criteria
irAE	Immune-related adverse event
IRR	Infusion related reaction
IV	Intravenous
laCSCC	Locally advanced CSCC
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
MAA	Marketing Authorisation Application
mAb	Monoclonal antibody
mCSCC	Metastatic CSCC
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MRT	Mean residence time
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non-small-cell lung cancer
ORR	Objective response rate

OS	Overall survival
PBMC	Peripheral blood mononucleated cell
PDDD	Protocol deviation definition document
PD-1	Programmed death-1 (receptor)
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PET	Positron-emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
PT	Preferred term
PTV	Planning target volume
RBC	Red blood cell
RCC	Renal cell cancer
RECIST	Response Evaluation Criteria in Solid Tumors
RILD	Radiation-induced liver disease
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Systems (software)
SCHNC	squamous-cell head and neck cancer
SD	Stable disease
SOC	System organ class
$t_{1/2}$	Beta-phase terminal half life
TEAE	Treatment-emergent adverse event
TOR	Time to response
TSH	Thyroid-stimulating hormone
WBC	White blood cell
WHODD	WHO Drug Dictionary
XRT	Radiotherapy

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study prior to the database lock. The SAP is intended to be a comprehensive and detailed description of strategy and statistical technique to be used in the analysis for the study objectives and variables defined in the R2810-ONC-1423 study protocol.

This plan may be revised during the study to accommodate protocol amendments and/or to make changes to adapt to unexpected issues in study execution and/or data that affect planned analyses. These revisions will be based on review of the study and data, and a final plan will be issued prior to data lock.

An interim analysis is included in this analysis plan to support initial US BLA (Biologic License Application) and EU MAA (Marketing Authorisation Application) submission for the CSCC (Cutaneous Squamous Cell Carcinoma) indication. The details for this interim analysis are described in Section 7.

1.1. Background and Rationale

1.1.1. Background

Enhancement of the anti-tumor immune response with cancer immunotherapy agents has emerged as a highly effective and complementary approach to the therapeutic mainstays of surgery, cytotoxic drugs, targeted therapeutics, and radiation. Blockade of the PD-1/PD-L1 T-cell checkpoint pathway is an effective and well tolerated approach to stimulating the immune response, and has achieved significant objective responses in advanced melanoma, renal cell cancer (RCC), non-small-cell lung cancer (NSCLC) and other tumors. Combinatorial approaches to stimulate convergent aspects of host immunity by employing complementary immunomodulators as well as immune-stimulatory aspects of conventional modalities such as radiation and chemotherapy may result in the development of more effective cancer therapies. REGN2810 is a high-affinity, fully human, hinge-stabilized IgG4P antibody directed to the PD-1 receptor that potently blocks the interaction of PD-1 with its ligands, PD-L1 and PD-L2.

This first-in-human protocol is designed to assess the safety of REGN2810, as monotherapy at different dose levels and in combination with selected other anti-tumor agents that may augment the potency and durability of anti-tumor immune response. Based on the premise that select combination therapies may be more active than PD-1 blockade monotherapy, therapies initially combining REGN2810 with cyclophosphamide, radiation therapy, or both will be tested in patients with advanced malignancies for whom a standard curative therapy does not exist. Additional expansion cohorts to assess the safety and activity of REGN2810 either alone or in combination with other therapies will be added once the dose escalation cohorts have enrolled and completed the dose limiting toxicity (DLT) observation period.

1.1.2. Rationale

The 3 + 3 design for the dose-escalation phase of this first-in-human study is designed to permit evaluation of the safety of REGN2810, both as monotherapy at different dose levels, and in

combination with immune-enhancing treatments: cyclophosphamide; limited, targeted radiation delivered in 1 of 2 dosing regimens; or combined radiation and cyclophosphamide. Once the tolerability of REGN2810 has been established alone and in combination with radiation and/or cyclophosphamide, multiple expansion cohorts using various combinations in select indications will be added in order to further confirm the safety and evaluate the augmentation of antitumor activity. Granulocyte-macrophage colony-stimulating factor (GM-CSF) will be added to some of these combinations. A few expansion cohorts will have a 6-patient, 28-day DLT observation period, in order to allow for observation of both acute and non-acute toxicity prior to enrollment of the full cohort of patients. The indications for expansion cohorts were chosen on the basis of their biological or clinical suitability to these types of combinations.

The starting dose chosen for this first-in-human study is based on the similar *in vitro* and *in vivo* potency of REGN2810 compared to antibodies generated based on publically available sequences of two approved anti-PD-1 antibodies, nivolumab and pembrolizumab. Experience with other anti-PD-1 antibodies suggests that REGN2810 dosage can be escalated safely.

1.2. Study Objectives

1.2.1. Primary Objectives

The co-primary objectives of the study are:

For Dose Escalation and Expansion Cohorts: to characterize the safety, tolerability, DLTs of REGN2810 administered IV as monotherapy, or in combination with targeted radiation (with the intent to have this serve as an immuno-stimulatory, rather than primarily tumor-ablative therapy), low dose cyclophosphamide (a therapy shown to inhibit regulatory T-cell responses) administered IV, or both radiation and cyclophosphamide with or without GM-CSF, or in combination with low dose carboplatin plus docetaxel, or in combination with low dose docetaxel, or in combination with full dose carboplatin plus paclitaxel, or carboplatin plus pemetrexed in patients with advanced malignancies.

For selected expansion cohorts (Expansion Cohorts 2 through 4): to evaluate the efficacy of REGN2810, alone or in combination therapy, by measuring overall response rate.

1.2.2. Secondary Objectives

The secondary objectives of the study are:

- To determine a recommended phase 2 dose (RP2D) of REGN2810 as monotherapy and in combination with other anti-cancer therapies (targeted radiation, low-dose cyclophosphamide, targeted radiation plus low dose cyclophosphamide with or without GM-CSF, low dose carboplatin plus docetaxel, or in combination with low dose docetaxel, or in combination with full dose carboplatin plus paclitaxel, carboplatin plus pemetrexed).
- To describe preliminary antitumor activity of REGN2810, alone and with each combination partner(s). In the expansion cohorts, activity measurements will include quantitative analysis of time to response, as well as depth of response, in addition to standard overall response assessments.

- Expansion Cohort 1 - NSCLC: REGN2810 at a flat dose of 200 mg
- Expansion Cohort 2 - NSCLC: 3 mg/kg REGN2810 + radiotherapy (9 Gy × 3)
- Expansion Cohort 3 - HNSCC: 3 mg/kg REGN2810 + radiotherapy (9 Gy × 3) + cyclophosphamide + GM-CSF
- Expansion Cohort 4 - BC: 3 mg/kg REGN2810 + radiotherapy (9 Gy × 3) + cyclophosphamide
- Expansion Cohort 5 - Patients who have progressed after achieving disease control (CR, PR, SD for at least 8 weeks) with another PD-1/PD-L1 antibody: 3 mg/kg REGN2810 + radiotherapy (9 Gy × 3) + cyclophosphamide + GM-CSF
- Expansion Cohort 6 - Advanced solid tumors, excluding NSCLC, HNSCC, and BC: 3 mg/kg REGN2810 + radiotherapy (9 Gy × 3) + cyclophosphamide + GM-CSF
- Expansion Cohorts 7 and 8 – CSCC, metastatic, M1 (Cohort 7) or locally and/or regionally advanced, unresectable, M0 (Cohort 8): 3 mg/kg REGN2810
- To describe the safety and tolerability of the following treatment regimens:
 - Expansion Cohorts 7 and 8 – CSCC, metastatic, M1 (Cohort 7) or locally and/or regionally advanced, unresectable, M0 (Cohort 8): 3 mg/kg REGN2810
 - Expansion Cohorts 9 through 12 –Advanced solid tumors with MSI arising in the colon (Cohort 9), endometrium (Cohort 10), prostate (Cohort 11), or other primary MSI solid tumor not eligible for other MSI cohorts (Cohort 12): 3 mg/kg REGN2810
 - Expansion Cohort 13 – Advanced HCC: 3 mg/kg REGN2810
 - Expansion Cohorts 14 and 15 - Advanced solid tumors: 3 mg/kg REGN2810 + carboplatin + docetaxel (Cohort 14), or 3 mg/kg REGN2810 + docetaxel (Cohort 15)
 - Expansion Cohort 16 - Metastatic colorectal cancer with MSI, previously untreated (prior adjuvant chemotherapy is allowed): 3 mg/kg REGN2810
 - Expansion Cohort 17: Advanced NSCLC, previously untreated: 3 mg/kg REGN2810 + low dose carboplatin + low dose docetaxel
 - Expansion Cohorts 18 and 19 - Newly diagnosed GBM, unmethylated at the MGMT promoter: REGN2810 (1 or 3 mg/kg) + radiotherapy (6 Gy x 5 days) (Cohort 18), or recurrent GBM: REGN2810 (1 or 3 mg/kg) + radiotherapy (6 Gy x 5 days) (Cohort 19)
 - Expansion Cohort 20 - HIV and advanced solid tumors: 3 mg/kg REGN2810
 - Expansion Cohorts 21 and 22: Advanced NSCLC, previously untreated: 3 mg/kg REGN2810 + full dose platinum doublets

- Expansion Cohorts 23 and 24: Recurrent or metastatic cervical cancer, resistant to or intolerant of platinum + taxane doublet chemotherapy: 3 mg/kg REGN2810
- Expansion Cohort 25: cutaneous BCC, unresectable locally advanced and/or metastatic, resistant to or intolerant of a hedgehog pathway inhibitor (vismodegib or sonidegib)
- Expansion Cohort 26 ([REDACTED]): Any advanced solid tumors
- To characterize the PK of REGN2810 as monotherapy and in combination with other anti-cancer therapies.
- To assess immunogenicity of REGN2810.
- To summarize progression-free survival (PFS) and overall survival (OS).

1.2.3. Modifications from the Statistical Section in the Final Protocol

The following modifications from the statistical section in the protocol were made:

- Added a secondary objective to describe preliminary antitumor activity of REGN2810 for cohorts 7 and 8.
- Added ORR and DOR assessed by independent central review and investigators as efficacy measurement for cohort 7, cohort 8 and any other cohort if clinical meaningful benefit is observed by investigator assessment.
- An interim analysis was added to support US BLA and EU MAA submission for CSCC indication.
- Full Analysis Set (FAS) was added for analyses of baseline and efficacy variables. The definition for FAS is the same as that for Safety Set in the protocol.
- Dose Limiting Toxicity Set was added for analysis of dose limiting toxicities.

1.2.4. Modifications from the Approved Statistical Analysis Plan

This first version of SAP that is based on the protocol amendment 6.

2. INVESTIGATION PLAN

2.1. Study Design

This is a phase 1, open-label, multicenter, dose-escalation study of REGN2810 alone or in combination with radiation therapy, cyclophosphamide, or radiation plus cyclophosphamide, or GM-CSF, or in combination with low dose carboplatin plus docetaxel, or in combination with low dose docetaxel, or in combination with full dose carboplatin plus paclitaxel, or carboplatin plus pemetrexed in patients with advanced malignancies. Safety will be assessed in separate, standard 3 + 3 dose escalation cohorts in the dose escalation phase (in monotherapy, combination with radiation therapy, combination with cyclophosphamide, and combination with radiation therapy plus cyclophosphamide).

In the dose escalation phase, a patient may be assigned to receive 1 of 11 possible treatments (monotherapy, combination with radiation therapy, combination with cyclophosphamide, or combination with radiation and cyclophosphamide). The choice of combination therapy will be based on investigator assessment of the best choice of therapy for an individual patient in consultation with the sponsor. To be enrolled in a radiotherapy cohort, a patient must have a lesion that can be safely irradiated and for which radiation at the limited, palliative doses contemplated would be considered medically appropriate, and at least one other lesion suitable for response evaluation. Following enrollment of patients into a REGN2810 monotherapy cohort, enrollment of subsequent cohorts will be determined by occurrence of DLTs in prior cohorts (i.e., no DLT in a cohort of 3 patients, or no more than 1 DLT in an expanded cohort of 6 patients), and the availability of patient slots. The planned monotherapy dose levels are 1, 3, or 10 mg/kg administered IV every 14 days (q2w).

In the dose expansion phase, patients will be assigned to specific treatment cohorts based on their tumor type, investigator assessment of appropriateness of the therapy regimen, safety considerations and slot availability. Up to 26 expansion cohorts will be enrolled. Enrollment of each additional cohort may be limited by the number of DLTs observed during the DLT period.

After a screening period of up to 28 days, patients will receive up to six 56 day treatment cycles for a total of up to 48 weeks of treatment, followed by a 24 week follow-up period. Each patient will be administered REGN2810 every 2 weeks on days 1, 15 \pm 3, 29 \pm 3, and 43 \pm 3 during each treatment cycle. Patients enrolled to combination therapy cohorts may also receive 1 of 2 radiation therapy regimens, cyclophosphamide, or both cyclophosphamide and 1 of 2 radiotherapy regimens. Tumor assessments will be made at the end of each treatment cycle. Extensive safety evaluations made at baseline/cycle 1, day 1 of dosing will be repeated on day 1 of each treatment cycle throughout the study, with routine safety evaluations to be conducted at each REGN2810 dosing visit. In the expansion cohorts, patients may also receive REGN2810 in combination with GM-CSF and radiotherapy, or in combination with GM-CSF, radiotherapy, and cyclophosphamide, or in combination with low dose carboplatin plus docetaxel, or in combination with low dose docetaxel, or in combination with full dose carboplatin plus paclitaxel, or carboplatin plus pemetrexed. In cohorts featuring full dose chemotherapy, REGN2810 will be administered as 3 mg/kg every 3 weeks. Several expansion cohorts feature REGN2810 monotherapy.

2.2. Sample Size and Power Considerations

The actual sample size of the study will vary depending on number of patients with observed DLTs and resultant cohort sizes and number of dose cohorts actually enrolled. For this dose-escalation study in which patients with a wide variety tumor types are likely to be enrolled, a formal power analysis of efficacy measures is not suitable. Given the 3+3 design and total 10 dose levels (monotherapy and combination therapy) to explore, we estimate the maximum sample size for dose escalation to be 60 patients (6 patients per dose level).

The sample size for the expansion cohorts are determined by either clinical considerations or interval estimation. Hence, there is no formal power analysis and sample size calculation based on hypothesis tests. Sample sizes for each of the 26 expansion cohorts in the expansion portion of the study have been determined separately.

- For the flat-dose cohort (Expansion Cohort 1) and the advanced solid tumor cohort for patients who have been previously treated with a PD-1/PD-L1 antibody (Expansion Cohort 5), and [REDACTED] (Expansion Cohort 26), a cohort size of 20 patients was selected based on clinical consideration to evaluate the safety profile of study REGN2810 treatment in the selected patient population.
- For Expansion Cohorts 2, 3, and 4 (NSCLC, HN, and BC, respectively), the sample size of 60 patients was selected based on a 95% confidence interval approach. With standard treatment, a response rate of ~ 5% to 10% is reported in literature, and a response rate around 15% is reported with treatment associated with PD-1/PD-L1 antibody. With 60 patients, if there are at least 9 (15.0%), 13 (21.7%), or 16 (26.7%) responders observed in a cohort, the 2-sided 95% confidence interval determined by normal approximation will exclude a response rate of 5%, 10% or 15%, respectively (Table 9 of protocol).
- For Expansion Cohort 6 (other advanced solid tumors), a cohort size of 30 patients was selected based on clinical consideration to evaluate the safety profile of study REGN2810 in this combination regimen in various advanced solid tumors.
- For Expansion Cohort 7, 10 patients will be enrolled to evaluate the safety and tolerability of REGN2810 monotherapy in the metastatic (M1) CSCC population.
- For Expansion Cohort 8, 20 patients will be enrolled to evaluate the safety and tolerability of REGN2810 monotherapy in the locally and/or regionally advanced (M0) CSCC that is unresectable.
- For Expansion Cohorts 9 through 12, per Amendment 5, no patients will be enrolled to evaluate the safety and tolerability of REGN2810 monotherapy in each selected solid tumor types harboring MSI. Cohorts 10 and 11 were closed to accrual after 1 patient enrolled in Cohort 10 and no patients enrolled in Cohort 11. The overall response rates with standard treatments for these cancer patient populations were approximately 15%, but the individual cohorts 9 through 12 are not intended for formal efficacy comparisons.
- For Expansion Cohort 13, a sample size of 20 patients was selected based on clinical considerations to provide sufficient data for safety and feasibility.

- For Expansion Cohorts 14 and 15, a sample size of 20 patients (with a 6 patient safety run-in in each cohort) was selected based on clinical considerations to provide sufficient data for safety and feasibility.
- Expansion Cohort 16 was closed for accrual prior to the enrollment of any patients per Amendment 5.
- For Expansion Cohorts 18 and 19, the dose escalation for RP2D requires at most 12 patients for exploring 2 dose levels. After the RP2D is established in each cohort, 10 additional patients will be enrolled into each cohort to evaluate the safety and tolerability of the treatment regimen.
- For Expansion Cohort 20, 10 patients will be enrolled to evaluate the safety and tolerability of REGN2810 monotherapy in the HIV patient population.
- For Expansion Cohorts 17, 21, and 22, a sample size of 10 patients (with a 6 patient safety run-in) was selected based on clinical considerations to provide sufficient data for safety and feasibility of REGN2810 with platinum chemotherapy doublets as first-line therapy for patients with advanced NSCLC.
- For Expansion Cohorts 23 and 24, 10 patients will be enrolled to evaluate the safety and tolerability of REGN2810 in patients with recurrent or metastatic cervical cancer that is refractory to platinum/taxane doublet chemotherapy, either as monotherapy (Cohort 23) or in combination with hypofractionated RT (Cohort 24).
- For Expansion Cohort 25, 15 patients will be enrolled to evaluate the safety and tolerability of REGN2810 monotherapy in patients with locally advanced (unresectable) or metastatic BCC that is refractory to hedgehog pathway inhibition.
- For expansion Cohort 26, 20 patients with any solid tumors will be enrolled to evaluate the safety and tolerability of REGN2810 monotherapy [REDACTED]

In total, up to 500 patients are expected to be recruited from up to 50 sites, but the exact total number of patients enrolled may depend upon observed DLTs.

2.3. Study Plan

2.3.1. Treatment and Enrollment

REGN2810 at 1 or 3 mg/kg administered IV over 30 minutes every 14 days (q2w) for 48 weeks, alone or in combination with:

- Radiotherapy (30 Gy administered as 5 doses of 6 Gy over 1 week) given 1 week after the first dose of REGN2810 OR
- Radiotherapy (27 Gy administered as 3 doses of 9 Gy over 1 week) given 1 week after the first dose of REGN2810 OR
- Low-dose cyclophosphamide (200 mg/m² IV) approximately once every 14 days for 4 doses, starting day -1, and given 1 day prior to each of the first 4 REGN2810 doses, OR

- Radiotherapy (30 Gy administered as 5 doses of 6 Gy over 1 week) given 1 week after the first dose of REGN2810 plus low-dose cyclophosphamide (200 mg/m² IV) approximately once every 14 days for 4 doses, starting day –1, and given 1 day prior to each of the first 4 REGN2810 doses, OR
- Radiotherapy (27 Gy administered as 3 doses of 9 Gy over 1 week) given 1 week after the first dose of REGN2810 plus low-dose cyclophosphamide (200 mg/m² IV) approximately once every 14 days for 4 doses, starting day –1, and given 1 day prior to each of the first 4 REGN2810 doses.

REGN2810 10 mg/kg administered IV over 30 minutes every 14 days (q2w) for 48 weeks. The REGN2810 plus radiation, and GM-CSF regimen includes:

- GM-CSF 250 mcg subcutaneous daily for 7 days, for four 7-day cycles (days 1 through 7, 15 through 21, 29 through 35, and 43 through 49 of the first 56-day cycle), plus
- 27 Gy radiotherapy (9 Gy × 3 times/week; given 1 week after the first dose of REGN2810, preferably not on consecutive days), plus
- 3 mg/kg REGN2810 infusion over 30 minutes every 14 days for 48 weeks (provided monotherapy dose of 3 mg/kg < maximum tolerated dose (MTD); if 3 mg/kg > MTD, dose will be 1 mg/kg).

The REGN2810 plus radiation, GM-CSF, and cyclophosphamide regimen includes:

- GM-CSF 250 mcg subcutaneous daily for 7 days, for four 7-day cycles (days 1 through 7, 15 through 21, 29 through 35, and 43 through 49 of the first 56-day cycle), plus
- 27 Gy radiotherapy (9 Gy × 3 times/week; given 1 week after the first dose of REGN2810, preferably not on consecutive days), plus
- Cyclophosphamide 200 mg/m² IV every 14 days (days – 1, 14, 28, and 42 of the first 56 day cycle) for a total of 4 doses, plus
- 3 mg/kg REGN2810 infusion over 30 minutes every 14 days for 48 weeks (provided monotherapy dose of 3 mg/kg < MTD; if 3 mg/kg > MTD, dose will be 1 mg/kg).

For cohorts receiving carboplatin and docetaxel, or docetaxel, the suggested sequence of drug administration is docetaxel followed by carboplatin (if enrolled in a carboplatin-containing cohort), followed by REGN2810:

- Docetaxel 30 mg/m² IV over approximately 1 hour on days 1, 8, 29, and 36 of the first 56-day cycle. Dexamethasone 8 mg IV will be administered prior to the first dose of docetaxel. For subsequent docetaxel treatments, the dose of dexamethasone premedication may be 8 mg or 4 mg, per investigator discretion
- Carboplatin AUC 2 IV over approximately 30 minutes on days 1, 8, 29, and 36 of the first 56-day cycle.
- 3 mg/kg REGN2810 infusion over approximately 30 minutes every 14 days for 48 weeks.

For cohorts receiving carboplatin plus paclitaxel, the suggested sequence of drug administration is

- 3 mg/kg REGN2810 infusion over approximately 30 minutes every 21 days (q3w) for 48 weeks (16 planned treatments of REGN2810).
- Paclitaxel 200 mg/m² is administered IV over approximately 3 hours on day 1 of each of the 4 planned 21-day paclitaxel treatment intervals.
- Carboplatin AUC 6 is administered IV over approximately 30 minutes on day 1 of each of the 4 planned 21-day carboplatin treatment intervals.

For cohorts receiving carboplatin plus pemetrexed regimen, the suggested sequence of drug administration is

- 3 mg/kg REGN2810 infusion over approximately 30 minutes every 21 days (q3w) for 48 weeks (16 planned treatments of REGN2810).
- Pemetrexed 500 mg/m² is administered IV over approximately 10 minutes on day 1 of each of the 4 planned 21-day pemetrexed treatment intervals.
- It is the intent of the study that pemetrexed and carboplatin will be discontinued at the end of 4 treatments. If the investigator wishes to continue maintenance pemetrexed after the initial 4 planned treatments, this may be allowed after communication with and approval from medical monitor.
- Carboplatin is administered IV over approximately 30 minutes on day 1 of each of the 4 planned 21-day carboplatin treatment intervals.

Assignment of a patient to a treatment cohort will be determined by occurrence of DLTs/establishment of a MTD in prior cohorts, the investigator's assessment of the appropriateness of therapies for the patient, and the availability of patient slots.

2.3.2. Early Treatment Discontinuation

A patient will receive treatment until the 48 week treatment period is complete, or until disease progression, unacceptable toxicity, withdrawal of consent, or meeting of another study withdrawal criterion. After a minimum of 24 weeks of treatment, patients with confirmed complete responses (CR) may elect to discontinue treatment and continue with all relevant study assessments (e.g., efficacy assessments) as scheduled per protocol. After a minimum of 24 weeks of treatment and after consultation with the investigator and the Sponsor, patients with tumor burden assessments of stable disease (SD) or partial response (PR) that have been maintained for 3 successive tumor evaluations may also elect to discontinue treatment and continue with all relevant study assessments (e.g., efficacy assessments) as scheduled per protocol.

2.3.3. Follow-up

Patients who complete the maximum number of 6 cycles of treatment and those who discontinued treatment early for CR or for SD or PR maintained for 3 successive evaluations are encouraged to return to the clinic for follow-up visit 1 scheduled 1 to 7 days after the last cycle visit and subsequent follow-up visits 2 through 7. Patients who discontinued treatment early for CR, SD, or PR should continue with all relevant study assessments (e.g., efficacy assessments)

as scheduled per Table 8 of protocol. Every effort should be made to ensure completion of these follow-up visits. If a patient is unable to complete follow-up visits due to withdrawal of consent, clinical decline, or loss to follow-up, the reason will be communicated to the sponsor and may not be considered a protocol violation.

A patient who discontinues study treatment prematurely during the treatment period due to PD, toxicity, or another reason besides confirmed CR, SD, or PR should return to the clinic 14 to 30 days after the last study treatment to complete follow-up visit 1, and should continue with all relevant study assessments (e.g., efficacy assessments) as scheduled per Table 8 of protocol.

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline [ICH E9 Statistical Principles for Clinical Trials \(1998\)](#), the following analysis populations will be used for the statistical analysis as specified:

3.1. The Full Analysis Set (FAS)

The full analysis set (FAS) includes all enrolled patients who received any study drug. Efficacy and baseline variables will be analyzed or summarized using the FAS.

3.2. The Safety Set (SAF)

The safety analysis set (SAF) includes all enrolled patients who received any study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed or summarized using the SAF.

3.3. The Dose Limiting Toxicity Set

For each dose escalation cohort and run-in period (first six patients) of selected expansion cohort, all patients who complete the 28 days of the monotherapy or the first cycle of the combination therapy or withdraw early with a reason due to safety will be evaluated for DLT and the determination of MTD.

3.4. The PK Analysis Set

The PK analysis set will include all patients who have at least 1 post REGN2810 treatment study drug concentration value above the lower limit of quantification (LLOQ) of the assay.

3.5. The Anti-Drug Antibody Set

The ADA population includes all treated patients who had at least 1 non-baseline post-dose ADA result.

4. ANALYSIS VARIABLES

Because REGN2810 is the primary focus in this study, study drug refers to REGN2810 in this document, unless specified otherwise (e.g., duration of exposure to treatment component). Therefore the definitions for baseline, study periods (e.g., on-treatment period) and analysis variables (e.g., AEs related to study drug or treatment-related AEs) are based on REGN2810.

4.1. Disposition of Patients

The following summaries will be provided to assess the patient disposition:

- Summary of analysis populations, patients screened.
- Number of patients who discontinued treatment and the reasons for treatment discontinuation
- Number of patients who discontinued study participation and the reasons for study discontinuation.

4.2. Demographic and Baseline Characteristics

The following demographic variables will be summarized:

- Age at screening (year)
- Age category (<65, ≥65)
- Sex (Male, Female)
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White and Other)
- Ethnicity (Hispanic/Latino)
- Baseline weight (kg)
- Baseline height (m)
- Body mass index (BMI) calculated from weight and height: $\text{weight (kg)} / [\text{height (m)}]^2$
- ECOG performance status

4.3. Disease Characteristics

The following variables will be summarized to characterize the extent of disease in the study for all patients:

- Primary site of cancer
- Histological grade (Well differentiated, Moderately differentiated, poorly differentiated, Undifferentiated, Unknown)
- Stage at initial diagnosis

- Time since most recent relapse/recurrence
- Time since initial diagnosis of metastatic disease

The TNM stage at initial diagnosis and at screening may be summarized for relevant indications or cohorts, if applicable.

4.4. Medical History

Medical history will be coded to a Preferred Term (PT), High Level Term (HLT), High Level Group Term (HLGT) and primary System Organ Class (SOC) according to the latest available version of MedDRA.

4.5. Prior-Treatment / Concomitant Medication

Medications/Procedures will be recorded from the day of informed consent until the end of study (EOS) visit. Medications will be coded to the ATC level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of WHO Drug Dictionary (WHODD). Patients will be counted once in all ATC categories linked to the medication.

Prior-treatment medications/procedures: medications taken or procedures performed prior to the first administration of REGN 2810. Particularly, prior cancer related surgery, prior cancer related systemic therapy: chemotherapy, targeted therapy, immunotherapy, others and prior cancer related radiotherapy. Premedications for planned combination therapies given on day -1 will not be counted as prior medication.

Concomitant medications/procedures: Any treatment administered from the time of informed consent until 30 days after the last study treatment will be considered concomitant treatment. This includes medications and other therapies for which administration started before the study and will continue during the study, as well as any therapies started in the 5 month follow-up period to treat a study-drug-related AE.

4.6. Efficacy Variable

All efficacy analyses will be based on FAS.

Objective response rate (ORR) measured by RECIST version 1.1 ([Eisenhauer 2009](#)) (or appropriate disease-specific tumor response assessment guidelines) is used to assess the preliminary anti-tumor activity of REGN2810 alone and in combination with specified regimen. It is determined by the proportion of patients with best overall response of CR or PR among patients in the FAS by each expansion cohort. Patients with best overall response of NE will be considered as not reaching an objective response of CR or PR.

Overall response is assessed at each time point.

Best overall response is determined once all the data for the patient is known. The best overall response is the best response recorded from the start of the study treatment until the end of the follow up period, using responses assessed prior to the start of any new antineoplastic therapies and taking into account any requirement for confirmation.

- Best overall response of CR or PR needs to be confirmed by subsequent evaluations of overall response of CR or PR at time points at least 4 weeks apart.
- Best overall response of SD must have met the response SD criteria at least once ≥ 39 days after start of study treatment.
- Best overall response of early PD does not require confirmation using RECIST 1.1.
- Best overall response for patients who do not have any post-baseline tumor assessment will not be evaluable (NE).

Disease control rate (DCR) is determined by the proportion of patients with best overall response of CR, PR and SD among patients in the FAS by each expansion cohort.

Durable disease control rate (DDCR) is defined as the proportion of patients with best overall response of CR, PR and SD without progression for at least 16 weeks (allowing tumor assessment made 1 week earlier than Week 16).

Depth of response (DEP) is determined by the percentage change or best percent change from baseline in sum of longest diameters of target lesions.

Time to response (TOR) is determined for patients with best overall response of CR or PR. Time to response is measured from the start of treatment until the time measurement criteria are first met for CR/PR (whichever is first recorded).

Duration of response (DOR) is defined for responders (patients with a best overall response of CR or PR) and is defined as the time from the date of the first documented confirmed response (CR or PR) until the date of the first documented progression (radiographic) or death due to any cause, whichever occurs first. If a patient has not progressed or died at the cutoff date of the analysis, DOR will be censored at the time of the last adequate tumor assessment on or before the cutoff date.

Duration of disease control (DODC) is determined for patients with best overall response of SD, CR or PR. Duration of disease control is measured from the start of treatment until the first date of recurrent or progressive disease (radiographic), or death due to any cause. Patient who never progress while being followed will be censored at the last valid tumor measurement.

Progression-free survival (PFS) is determined for all patients in FAS. Progression-free survival is measured from the start of treatment until the first date of recurrent or progressive disease (radiographic), or death due to any cause. If a patient has not progressed or died at the date of the analysis cut-off, PFS will be censored at the time of the last adequate tumor assessment before the cutoff date. If a patient has no post-baseline evaluation, PFS will be censored at the treatment start date.

Overall survival (OS) is measured from the start of treatment until death due to any cause. If a patient is not known to have died at the date of the analysis cut-off, OS will be censored at the last date that patient is documented to be alive.

4.7. Safety Variables

For safety variables, the observation period will be divided into three segments: pre-treatment, on-treatment and post-treatment.

- The pre-treatment period is defined as the time between when the subjects give informed consent and before the start of REGN2810 treatment.
- The on-treatment period
 - For patients who did not receive REGN2810 as re-treatment: it is defined as the time from the first dose of REGN2810 up to 30 days after the last dose of REGN2810;
 - For patients who started REGN2810 as re-treatment more than 30 days of last dose of regular REGN2810 treatment: it is defined as the time from the first dose of REGN2810 up to 30 days after the last dose of REGN2810;
 - For patients who started REGN2810 re-treatment within 30 days of their last regular REGN2810 treatment: it is defined as the time from the first dose of REGN2810 up to the 30 days after the last dose of REGN2810 re-treatment. That is, the re-treatment is considered as a part of the regular treatment in this case.
- The post-treatment period is defined as the time starting 1 days after the on-treatment period.

Day 1 is the first day of patient receiving REGN2810 treatment, Day –1 is the day before, and there is no Day 0.

4.7.1. Adverse Events and Serious Adverse Events

AEs after initiation of study treatment and until 30 days after the last study treatment, will be reported on the AE eCRF. Prior to initiation of study treatment, only the SAE and Non-SAEs associated with a protocol-mandated intervention (eg, AEs related to an invasive procedure such as a biopsy) will be reported on the AE eCRF. Additionally, any SAE or other AE of concern that the investigator believes may be related to study treatment and that occurs later than 30 days after last study treatment will be reported.

An **Adverse Event** is any untoward medical occurrence in a patient administered a study drug and which does not necessarily have to have a causal relationship with the study drug.

A **Serious Adverse Event** is an AE that is classified as serious according to the criteria specified in the protocol.

An **Infusion Related Reaction (IRR)** is any AE that occurs during or within 2 hours after the infusion of REGN2810 is completed.

An **Immune Related Adverse Event (irAEs)** is any AE with unknown etiology associated with drug exposure and consistent with an immune phenomenon. irAEs are identified for REGN2810 by investigator assessment.

Pre-treatment AEs are defined as AEs that developed during the pre-treatment period and are not the treatment-emergent AEs defined below.

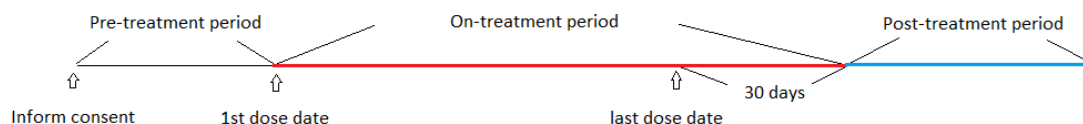
Treatment-emergent AEs (TEAEs) (Figure 1)

- For patients who did not receive REGN2810 as re-treatment: it is defined as AEs that developed or worsened during the on-treatment period and any treatment-related AEs that occurs during the post-treatment period;
- For patients who started REGN2810 as re-treatment more than 30 days of last dose of regular REGN2810 treatment: it is defined as AEs that developed or worsened during the on-treatment period and any treatment-related AEs that occurs during the post-treatment period but prior to start of re-treatment.
- For patients who started REGN2810 re-treatment within 30 days of their last regular REGN2810 treatment: it is defined as AEs that developed or worsened during the on-treatment period and any treatment-related AEs that occurs during the post-treatment period.

Figure 1: Treatment-emergent Adverse Events (TEAEs)

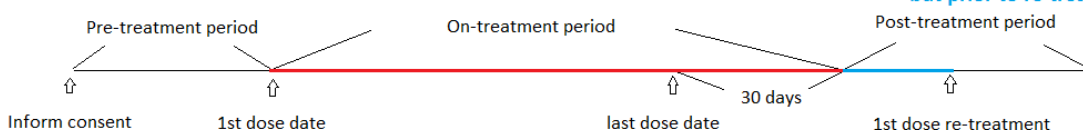
A: No re-treatment

TEAEs = All AEs started or worsened during on-treatment period + Treatment-related AEs during post-treatment period



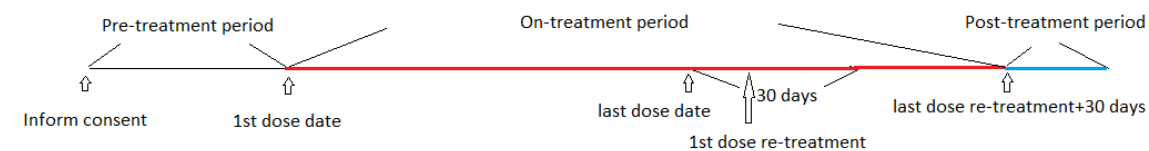
B: Re-treatment started more than 30 days of last dose of regular REGN2810

TEAEs = All AEs started or worsened during on-treatment period + Treatment-related AEs during post-treatment period but prior to re-treatment



C: Re-treatment started within 30 days of last dose of regular REGN2810

TEAEs = All AEs started or worsened during on-treatment period + Treatment-related AEs during post-treatment period



Post-treatment AEs are defined as AEs that developed or worsened during the post-treatment period and are not considered drug related by the investigator.

The relationship of AEs to study drug will be assessed by the investigator and be determined based on protocol specified criteria.

Laboratory results, vital signs, or ECG abnormalities are to be recorded as AEs if they are medically relevant: symptomatic, requiring corrective therapy, leading to treatment discontinuation and/or fulfilling a seriousness criterion.

All AEs are to be coded to a Preferred Term ("PT") and associated primary System Organ Class ("SOC") according to the MedDRA[®] (the latest current available version). AEs will be assessed

according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist for an adverse event, grades 1 – 4 corresponding to the severity of mild, moderate, severe and life-threatening will be used.

4.7.2. Special Safety Variables of Interest

4.7.2.1. Adverse Events of Special Interest

An AE of special interest (AESI) must be reported within 24 hours of identification. AEs of special interest for this study include:

- Any AE that meets DLT criteria
- Grade 2 or greater infusion-related reactions
- Grade 2 or greater allergic/hypersensitivity reactions
- Grade 3 or greater immune-related toxicities (irAE) (as indicated on the eCRF).

Note: An irAE can occur shortly after the first dose or several months after the last dose of treatment. All AEs of unknown etiology associated with drug exposure should be evaluated to determine possible immune etiology. If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an AE as an irAE.

4.7.2.2. Dose Limiting Toxicity

Dose-limiting toxicities (DLTs) are generally defined as any of the following study drug related toxicities observed during the DLT evaluation period (only for cohorts that include a DLT evaluation period):

Non-Hematologic Toxicity:

1. Grade ≥ 2 uveitis (considered as a potential immune-related adverse event [irAE]).
2. Any Grade ≥ 3 non-hematologic toxicity; with the exception of:
 - a. Grade 3 nausea, vomiting or diarrhea unless persistent (>7 days duration) despite maximal supportive care measures as prescribed by the treating physician.
 - b. Grade ≥ 3 laboratory abnormalities that are considered clinically insignificant and do not meet criteria for an AE.
 - c. Grade 3 infusion-related reactions that respond to medical management.
 - d. Grade 3 immune-related AE (as defined by experience with other immunomodulatory drugs – see Appendix 2 of protocol describing common irAEs) other than uveitis that improves within 7 to 14 days to Grade 2 or lower with medical management (including treatment with steroids).

Hematologic Toxicity:

1. Grade 4 neutropenia lasting more than 7 days
2. Grade 4 thrombocytopenia
3. Grade 3 thrombocytopenia with bleeding

4. Grade ≥ 3 febrile neutropenia (fever $\geq 38.5^{\circ}\text{C}$ with absolute neutrophil count [ANC] $< 1.0 \times 10^9/\text{L}$), or Grade ≥ 3 neutropenia with documented infection

The frequency, time to onset, and severity of toxicities, as well as the success of standard medical management and dosing interruptions/delays, will be analyzed to determine if a given toxicity should be considered a DLT for dose escalation purposes.

4.7.3. Laboratory Safety Variables

The clinical laboratory data consists of serum chemistry, hematology, and other. Clinical laboratory values will be converted to standard international (SI) units and grouped by function in summary tables. Conventional unit may be provided. Functions are defined as follows:

- **Blood Chemistry** including sodium, phosphorus, AST, ALT, ALP, Phosphorus, Pottasium, Glucose, Chloride, Albumin, Total direct and/or indirect bilirubin, bicarbonate, creatinine, blood urea nitrogen, lactate dehydrogenase, magnesium, uric acid.
- **Hematology** including Hemoglobin, white blood cells, platelet count, differentials (neutrophils, lymphocytes, monocytes).
- **Urinalysis** including glucose, pH, ketones, blood, specific gravity, spot urine protein.

4.7.4. Vital Signs

Vital signs will be collected according to the study schedule of protocol:

- Body temperature ($^{\circ}\text{C}$)
- Resting systolic blood pressure and diastolic blood pressure (mmHg)
- Pulse (beats/minute)
- Respiratory rate (breaths/minute)

4.7.5. 12-Lead Electrocardiography (ECG)

A standard 12-lead ECG will be performed at time points according to Tables 6 and 7 of protocol. The 12-lead ECG parameters include :

- PR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- Heart Rate (BPM; recorded from the ventricular rate)

Corrected QT (QTc) will be calculated from the QT interval and RR by two methods:

- Bazett's correction = $\text{QT}/[\text{RR}]^{1/2}$
- Fridericia's Correction = $\text{QT}/[\text{RR}]^{1/3}$

Any ECG finding that is judged by the investigator as a clinically significant change (worsening) compared to the baseline value will be considered an AE, recorded, and monitored.

4.7.6. Physical Examination Variables

A thorough complete or limited physical examination will be performed at visits specified in Tables 6, 7 and 8 of protocol. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

Complete physical examination will include examination of skin, head, eyes, nose, throat, neck, joints, lungs, heart, pulse, abdomen (including liver and spleen), lymph nodes, and extremities, as well as a brief neurologic examination. Limited physical examination will include lungs, heart, abdomen, and skin. The result for each body system is an outcome of Normal, Abnormal, clinically significant, and Abnormal, Not clinically significant.

4.8. Pharmacokinetic Variables and Anti-Drug Antibody Variables (ADA)

Concentration of REGN2810 in serum will be assessed at multiple time points throughout the study treatment and follow-up periods, and the PK will be analyzed.

Pharmacokinetic variables may include, but are not limited to, the following:

- AUC_{τ} - area under the curve (AUC) computed from time zero to the time of the last concentration over the dosing interval
- $AUC_{\tau}/Dose$ - AUC_{τ} -to-dose ratio
- AUC_{last} - AUC computed from time zero to the time of the last positive concentration
- $AUC_{last}/Dose$ - AUC_{last} -to-dose ratio
- CL - clearance
- C_{max} - the peak concentration
- $C_{max}/Dose$ - C_{max} -to-dose ratio
- C_{last} - last positive (quantifiable) concentration
- MRT_{last} - mean residence time when the drug concentration profile is based on values up to and including the last positive concentration
- $t_{1/2}$ - observed terminal half-life
- t_{last} - time of the last positive (quantifiable) concentration
- t_{max} - time to C_{max}
- V_{ss} - volume of distribution at steady state

Anti-drug antibody variables include ADA response status and titer as follows:

- Total number of patients negative in the ADA assay at all time points analyzed
- Pre-existing immunoreactivity – defined either as a positive ADA assay response at baseline with all post-treatment ADA assay results negative, or a positive assay response at baseline with all post-treatment ADA assay responses less than 9-fold over baseline titer levels.

- Treatment emergent response - defined as any post-treatment positive response in the ADA assay, when the baseline result is negative.
- Treatment boosted - defined as any post treatment positive ADA assay response that is at least 9-fold over baseline titer levels when baseline ADA results are positive.
- Treatment emergent responses will be further characterized into persistent, transient and indeterminate ADA responses.
 - Persistent response - defined as 2 consecutive treatment emergent positive responses in the ADA assay that span at least a 16-week period during the treatment period and follow-up phase, if any.
 - Indeterminate response - a treatment emergent positive response in the ADA assay only at the last ADA sampling time point analyzed.
 - Transient response - any treatment emergent positive response in the ADA assay that is not considered persistent or indeterminate.
- Treatment boosted - defined as any post treatment positive ADA assay response that is at least 9-fold over baseline titer levels when baseline ADA results are positive.
- Titer values (Titer value category):
 - Low (titer < 1,000)
 - Moderate ($1,000 \leq \text{titer} \leq 10,000$)
 - High (titer > 10,000)
- Total number of patients positive in the NAb assay at any time point analyzed.

4.9. Exploratory Biomarker Procedures

The following markers may be assayed in archived and/or biopsy tumor tissue samples using IHC: CD3, CD4, CD8, FoxP3, CD274 (PD-L1), CD279 (PD-1), TIM-3, LAG-3, IDO, and GZMB. Additional immune cell markers and/or tumor markers specific to any of the tumor types may be included.

Cytokines to be analyzed may include but are not limited to: IL-1 β , IL-2, IL-6, IL-8, IL-10, IL-12p70, GM-CSF, IFN γ , TNF α .

Peripheral blood mononucleated cells will be assessed by fluorescence-activated cell sorting for changes in cell subsets including but not limited to, naïve and memory CD8 and CD4 T cells, MDSCs, NK, and B cells.

Additional biomarkers may be assessed if sufficient sample quantities are available.

5. STATISTICAL METHODS

For continuous variables, descriptive statistics will include the following: the number of patients reflected in the calculation (n), mean, median, standard deviation, minimum, and maximum. In addition, 25th percentile and 75th percentile will be provided.

For categorical or ordinal data, frequencies and percentages will be displayed for each category. The denominator will be determined by the analysis population used for the summary.

For time-to-event variables, median time-to-event (and the survival rate at a fixed time point) and its 95% confidence intervals will be summarized by the Kaplan-Meier method.

Summary analyses will be presented by group (e.g., cohort, dose level, cancer type) and overall if deemed clinically meaningful.

5.1. Subject Disposition

For subject disposition, the following summaries by table will be provided:

- The total number of screened patients
- The total number of patients in each analysis set
- The total number of patients who discontinued the study treatment and the reasons for the treatment discontinuation
- The total number of patients who discontinued the study, and the reasons for the study discontinuation

Listing of patient disposition will include dates of the first and the last REGN2810 administration, date of the end of treatment and end of study visits, and reasons for treatment and study discontinuation.

5.2. Demographics and Baseline Characteristics

Patient demographics and baseline characteristics will be summarized based on the FAS population.

Assessments made before the first dose of REGN2810 will be used as baseline measurements for the purposes of statistical analysis and reporting unless otherwise specified.

5.3. Protocol Deviations

Protocol deviations will be defined in a separate protocol deviation definition document (PDDD). Listing of all patients with protocol deviations and the description of deviation will be provided. The major protocol deviation, such as violation of inclusion/exclusion criteria; post-enrollment deviations which may impact assessment of efficacy or safety endpoints, will be determined before database lock and be summarized.

5.4. Medical History

Medical history will be summarized and listed based on the FAS population. The summaries will be presented by primary system organ class and preferred term in descending of frequency of SOC followed by preferred term.

5.5. Diagnosis and Extent of Cancer

Summary statistics will be tabulated for diagnosis and extent of cancer. The number and percentage of patients for each variable listed in Section 4.3 will be presented. Time since initial diagnosis, time since most recent recurrence/relapse will be summarized in months.

5.6. Prior Anti-Cancer Therapy

Prior anti-cancer therapy will be listed in three separate listings: medications, radiotherapy and surgery based on the FAS.

The number and percentage of patients using any prior anti-cancer therapies will be summarized.

Prior anti-cancer medications will be summarized by therapy type, ATC Level 2 and ATC Level 4.

5.7. Prior and concomitant Medications

Prior and concomitant medications will be summarized and listed based on the FAS and SAF, respectively.

Listing of prior and concomitant medications will include generic name and ATC Levels 2 and 4, indication, study day onset (for medications started before treatment, the study day onset is defined as date of medication start - date of the first dose; for medications started on or after treatment, the study day onset is defined as date of medication start - date of the first dose+1), the study end date (defined similarly as for study onset day), ongoing status, dose, frequency, and route.

The number and proportion of patients taking concomitant medications will be summarized, sorted by decreasing frequency of ATC Level 2 and ATC Level 4.

5.8. Extent of Study Treatment Exposure and Compliance

5.8.1. Measurement of Compliance

Compliance with protocol-defined investigational product will be analyzed separately for each study treatment component based on the SAF and will be calculated as follows:

$$\text{Treatment Compliance} = (\text{Number of investigational product taken during treatment period}) / (\text{Number of investigational product planned to be taken during period}) \times 100\%$$

where temporary dose discontinuation is ignored.

The number and percentage of subjects who have <60%, 60-80%, 80-100%, and >100% compliance will be summarized for each treatment component, if applicable..

5.8.2. Exposure to Investigational product

Duration of study treatment exposure, number of doses administered, cumulative dose and dose intensity will be summarized separately for each study treatment component, if applicable. In addition, duration of exposure to study treatment will be categorized into time intervals; frequency counts and percentages will be presented for the number of patients in each interval.

The duration of exposure to REGN2810 Q2W, Cyclophosphamide (200mg/m² IV), in weeks will be summarized as:

$$\{ \min(\text{last dose date}+14, \text{datacutoff date}+1, \text{death date}+1) - \text{first dose date} \} / 7$$

The duration of exposure to REGN2810 Q3W (cohorts 20, 21), Paclitaxel 200mg/m², Carboplatin AUC 6 IV and Pemetrexed 500mg/m² in weeks will be summarized as:

$$\{ \min(\text{last dose date}+21, \text{datacutoff date}+1, \text{death date}+1) - \text{first dose date} \} / 7$$

The duration of exposure to Docetaxel 30mg/m² IV, GM-CSF 250 mcg and Carboplatin AUC 2 IV in weeks will be summarized as:

$$\{ \min(\text{last dose date}+7, \text{datacutoff date}+1, \text{death date}+1) - \text{first dose date} \} / 7$$

Duration of exposure is not calculated for the radiotherapy combination treatments.

In addition, the extent of exposure will be summarized for REGN2810 using the following parameters:

- Cumulative dose : defined as the total dose given during the study treatment exposure period.

- The cumulative dose to REGN2810 (mg/kg), will be given as:

Cumulative dose =

$$\text{Cumulative dose} = \sum_{k=1}^K \text{Actual dose in cycle } [k],$$

where K is the overall total number of treatment cycles received by the patient.

- Actual dose intensity (units/week) is defined as:

$$\text{Actual dose intensity} = \text{Cumulative dose} / \text{Duration of exposure (weeks)}$$

- Relative dose intensity is defined as:

$$\text{Relative dose intensity} = \text{Actual dose intensity} / \text{Planned dose intensity},$$

where Planned dose intensity is defined as:

Planned dose intensity (mg/kg/week) = planned dose (mg/kg) / 2 for weight based dose and Q2W schedule;

Planned dose intensity (mg/kg/week) = planned dose (mg/kg) / 3 for weight based dose and Q3W schedule;

Planned dose intensity (mg /week) = planned dose (mg) / 2 for flat dose and Q2W schedule.

For patients who also receive REGN2810 as re-treatment which starts more than 30 days after their last regular REGN2810 treatment, the re-treatment dose will not be included in summary of on-treatment exposure, instead, they will be listed and summarized if necessary.

5.9. Analyses of Efficacy Variables

The analyses for efficacy variables will be conducted by group (e.g., cohort, dose level, cancer type) if deemed clinically meaningful. All efficacy analyses will be based on FAS. There is no formal hypothesis test for this study due to the aim of dose-finding and exploratory nature of expansion cohorts.

Tumor measurement and response of target lesions and non-target lesion, presence of new lesions, and overall response will be listed.

Tumor measurement and response of irradiated lesions will be listed.

Objective Response Rate (ORR) will be summarized, along with two-sided 95% exact binomial confidence intervals using the Clopper-Pearson method (Clopper 1934). Patients with a best overall response of unknown or 'NE' will be treated as non-responders in the calculation of ORR. In addition, waterfall graphs will be used to depict the anti-tumor activity. These graphs will display the percentage change from baseline in the sum of diameter of all target lesions for each patient per RECIST 1.1.

Other efficacy variables are disease control rate, durable disease control rate, duration of response, duration of disease control, progression-free survival, overall survival and depth of response as defined in Section 4.

Disease Control Rate (DCR) and Durable Disease Control Rate (DDCR) will be summarized, along with two-sided 95% exact binomial confidence intervals using the Clopper-Pearson method (Clopper 1934). Patients with a best overall response of unknown or 'NE' will be treated as non-responders.

For the time-to-event variables, the time to event (day) is the date of event/censor – the date of start + 1. That is,

For duration of response, event/censor time = date of event/censor - date of the first documented response (CR or PR)+1;

For duration of disease control, progression-free survival and overall survival, event/censor time = date of event/censor - start date of study drug+1.

Duration of response (DOR) will be summarized using Kaplan-Meier methodology based on the FAS. The median duration of response will be presented along with 95% confidence intervals. Kaplan-Meier estimates along with 95% confidence intervals at specific time points will be presented.

Duration of disease control (DODC) will be summarized using Kaplan-Meier methodology based on the FAS. The median duration of disease control will be presented along with 95% confidence intervals. Kaplan-Meier estimates along with 95% confidence intervals at specific time points will be presented.

Depth of response (DEP) will be displayed using waterfall plot and spider plot and summarized

by descriptive statistics.

Time to response (TOR) will be summarized by descriptive statistics for patients who have best overall response CR or PR.

PFS and OS will be listed and summarized descriptively using Kaplan-Meier methodology if applicable.

5.9.1. Adjustment for Multiple Comparisons

Not applicable.

5.10. Analysis of Safety Data

The analysis of safety and tolerance will be performed on the SAF, as defined in Section 3.2. The safety analysis will be based on the reported AEs and other safety information (clinical laboratory evaluations, vital signs and 12-lead ECG). The analysis will comprise the basis upon which conclusions will be drawn regarding the REGN2810. For patients who received cyclophosphamide, the AEs started or worsened on Day -1 will be summarized.

The safety analysis will be concentrated on events occur during on-treatment period. Events occur during post-treatment period, or during REGN2810 re-treatment will be listed and summarized if necessary.

5.10.1. Adverse Events

The verbatim text, the preferred term, and the primary system organ class (SOC) will be listed in subject listings. Summaries that include frequencies and proportions of patients reporting AEs will include the preferred terms and the SOC.

The focus of adverse event reporting in the CSR will be on TEAEs. For details on handling missing data and partial dates, see Section 6.

Summaries of adverse events will include: TEAEs, Treatment related TEAEs, Serious TEAEs, Treatment-related Serious TEAEs, AESI, immune-related AEs (irAE), and infusion related reaction (IRR). For AEs (TEAEs, AESIs, irAEs and IRRs), the following will be summarized:

- The number and proportions of patients reporting at least 1 AE, presented by SOC and PT
- AEs by severity (CTCAE, version 4.03 grade), presented by SOC and PT
- AEs by relationship to treatment (related, not related), presented by SOC and PT
- AEs occurring in > x% patients, presented by PT
- AEs leading to permanent treatment discontinuation, presented by SOC and PT
- AEs leading to death, presented by SOC and PT

For each AE summary presented by SOC and PT, the summary table will be sorted by decreasing frequency of SOC and PT. For AE summary presented by PT, the summary table will be sorted by decreasing frequency of PT.

The irAEs reported by investigator will be summarized. Additionally, irAEs identified by the sponsor will be summarized. The sponsor-defined irAEs are listed in a separate document. The list may be updated to include all possible irAEs. All irAEs occurred during the on-treatment period will be included.

For AE listings, the following variables will be displayed:

- Age/gender/race
- Verbatim Term
- PT
- SOC
- AE start date and end date/ongoing (and corresponding study day)
- AE duration
- Relationship to study drug: unrelated or related
- Seriousness (Serious AE or not)
- National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade: mild, moderate, severe, life-threatening or death
- Action taken: none, dose decreased, dose temporarily stopped or discontinued
- Treatment for AE: none, medication, surgery or others
- Outcome: recovered/resolved, recovered/resolved with residual effects, recovering/resolving, not recovered/not resolved, fatal, or unknown

Counts will be provided for each PT within each SOC. Percentages will be calculated using the number of patients from the safety set.

Number and proportion of patients with DLTs will be summarized using the Dose Limiting Toxicity Set.

5.10.2. Clinical Laboratory Measurements and Vital Signs

Listings of laboratory values, normal ranges, grade, date, and visit/cycle will be provided. For numeric lab variables, values and change from baseline to each visit/cycle will be summarized. Listings of abnormal lab values and clinical significant (Yes/No) ECG, physical exam and urinalysis by patient and visit/cycle will also be constructed.

Summary tables for new or worsened laboratory values with all grade and NCI CTCAE v4.03 grade ≥ 3 will be generated.

Summary of Shift tables from baseline to post-treatment worst NCI CTCAE v4.03 grade will be generated.

The shift tables include:

- Overall and individual Hematologic Test (Hemoglobin, Platelet counts, WBCs, and differential of Neutrophils, Lymphocytes and Monocytes).

- Overall and individual Liver Function Test: (AST, ALT, ALP, Total Bilirubin and Albumin).
- Overall and individual Electrolytes (Sodium, Potassium, Magnesium, Calcium, Chloride, Bicarbonate, Phosphorus).

Baseline clinical laboratory analytes and change from baseline in selected clinical laboratory analytes to each scheduled assessment time will be summarized with descriptive statistics. Summary statistics will include the number of patients, mean, median, standard deviation, quartiles, minimum, and maximum.

5.10.3. Analysis of Vital Signs

Vital signs (pulse, sitting blood pressures, and temperature) will be summarized by values and change from Baseline to each scheduled assessment time with descriptive statistics.

5.10.4. Analysis of 12-Lead ECG

ECG parameters (P-R interval, QT interval, QTc interval, QRS interval, Ventricular rate and Heart rate) will be summarized by values and change from Baseline to each scheduled and collected assessment time.

ECG status (i.e. normal, abnormal) will be reported. Shift tables will be provided to present the post-baseline status according to the baseline status (normal or missing / abnormal) by treatment group.

5.10.5. Physical Exams

The number (n) and percentage (%) of subjects with new or worsened physical exams will be summarized. Physical examination findings by body system and status (normal, abnormal, not done) will be listed.

5.11. Analysis of Pharmacokinetic and Antibody Data

5.11.1. Analysis of Pharmacokinetic Data

Summaries of study drug concentrations will be presented by nominal time point (i.e., the time points specified in the protocol) and group. Analysis of pharmacokinetic data will be provided in a separate report.

5.11.2. Analysis of Anti-drug Antibody Data

Listings of treatment-emergent ADA and titers presented by subject, time point, and dose cohort will be provided. Incidence of treatment-emergent and treatment boosted ADA responses will be assessed as absolute occurrence (N) and percent of subjects (%), grouped by study cohorts and ADA titer level.

Assessment of association of treatment-emergent, persistent and treatment-boostered ADA responses with impact on PK, safety and efficacy may be evaluated.

5.11.3. Analysis of Exploratory Biomarker Data

Biomarker data will be analyzed using standard scientific methods and summarized by descriptive statistics and plots, if applicable. Baseline PD-L1 levels will be summarized and the relationship to best overall response and other measures of clinical efficacy will be evaluated. Any comparative analysis and correlative analysis will be exploratory in nature and may be provided either as an appendix to CSR or in a separate report.

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline for Efficacy / Safety Variables

Unless otherwise specified, the Baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of investigational product.

6.2. Data Handling Convention for Efficacy Variables

Patients who are deemed NE according to RECIST version 1.1. or inevaluable by the other response criteria will be considered as not reaching PR/CR in calculating ORR, i.e. they are not considered as responders in the numerator of ORR, but they are counted in the denominator of ORR.

6.3. Data Handling Convention for Missing Data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

Medication missing/partial dates

To determine whether a medication is prior, concomitant or post-treatment medication, the missing medication start date is estimated as early as possible up to date of the first study treatment, and the missing medication end date is estimated as late as possible. If the medication start date is missing, the onset day will not be imputed in medication listings.
Adverse event Severity

If the intensity of a TEAE is missing, it will be classified as “severe” in the frequency tables by intensity of TEAEs. If the assessment of relationship of a TEAE to the investigational product is missing, it will be classified as related to the investigational product.

Missing AE and Concomitant Medication dates

Imputation of AE and Concomitant Missing and Partial start dates:

Every effort will be made to collect the start dates of all AEs and concomitant medications. However, in the case the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the first dose of study medication, except if an incomplete date (e.g., month and year) clearly indicates that the event started prior to treatment.

If the partial date indicates the same month or year of the first dose of study medication date, then the start date of the first dose will be imputed, otherwise, the missing day or month by the first day or the first month will be imputed. However if the imputed start date is after the non-missing end date, the start date will be imputed to the end date.

Imputation of Partial AE and concomitant Medication Partial end dates:

When only year is present, missing AE/concomitant medication end day and month will be imputed to the earlier of (study end date, 31DECYYYY).

When both month and year present, missing AE/concomitant medication end day will imputed to the last day of the month.

There will be no attempt to impute completely missing AE or concomitant medication end dates.

This represents the most conservative approach in the handling of missing or partial AE/concomitant medication start and end dates as well as missing AE severity.

Incomplete date of death in OS analysis

- If the day of death is missing, it will be imputed to the first day of the month except if the date of patient's last contact is the same month as the death date. In this case, the death date will be imputed to the date of the last contact + 1 day.
- If the day and month of death are missing, date of death will be imputed to the 1st of January of the year, except if date of patients' last contact is the same year as death date. In this case, the death date will be imputed to the date of the last contact + 1 day.

Last contact date:

Last contact date will be used for censoring patients in the OS analysis. The last contact date will be derived for patients alive at the analysis cut off using the latest complete date among the following:

- 'Last known date alive' recorded on the 'Survival status' eCRF page.
- Assessments with non-missing values corresponding to actual patient contact (including: retreatment screening, vital signs assessments, performance status assessments, physical examinations, tumor imaging, brain MRI, chest X-ray, scans, laboratory, ECG, pregnancy test, immunoglobulin, HIV testing, sample collection dates, AE start date, AE resolution date and other dates on AE CRF, concomitant medication, procedures, post treatment anti-cancer procedure, study drug administration, cyclophosphamide administration, chemotherapy administration, radiation therapy administration, GM-CSF administration, inform consent tracking.

Date of first / last injection

The date of first administration of study drug is derived as the first date when a non-zero dose of any component of study treatment was administered on the eCRF. The date of last administration of study treatment is derived as the last date when a non-zero dose of any component of study drug was administered and recorded on the eCRF. If a patient's date of the last dose is totally missing or unknown, his/her last visit date will be substituted.

6.4. **Unscheduled Assessments**

Unscheduled visit measurements may be used to provide a measurement for a baseline or endpoint value if appropriate according to their definition. The measurements may also be used to determine abnormal laboratory or ECG values.

The determination of baselines and values at the end of treatment for both efficacy and safety variables will be based on scheduled available assessments and unscheduled available assessments.

Extra assessments (laboratory data or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing adverse events) will be included in listings, but not summaries except for the endpoint determination. If more than one laboratory value is available for a given visit, the first observation will be used in summaries and all observations will be presented in listings.

7. **INTERIM ANALYSIS**

An interim analysis will be performed to support the US BLA and EU MAA submission (and any other submissions based on the BLA/MAA interim analysis) in patients with CSCC and treated with REGN2810 as monotherapy. The cut-off date for efficacy and safety data of those CSCC patients will be October 2, 2017. In addition, the safety data from other patients enrolled in the study will also be analyzed to assess overall safety profile of REGN2810. The data cutoff date for those safety data will be September 1, 2017.

Definition for analysis variables and statistical methodology are defined in Section 4 and Section 5. In the following sections, details are included to describe the grouping for interim summary analysis and the analysis variables to be reported.

7.1. **Grouping for interim analysis**

For interim analysis of efficacy and safety for CSCC patients:

In Study 1540, patients with anogenital SCC were explicitly excluded because this is felt to be clinically different entity than UV-induced CSCC.

UV-induced CSCC, when metastatic to nodes (regional or distant) or other distant sites, is defined as mCSCC (metastatic CSCC). UV-induced CSCC that has not metastasized to nodes (regional or distant) or other distant sites is defined as laCSCC (locally advanced CSCC). These definitions of mCSCC and laCSCC are different than the enrollment criteria for Expansion Cohorts 7 and 8 in Study 1423. Cohort 7 enrolled patients with distantly metastatic CSCC. Cohort 8 enrolled CSCC patients with regional nodal involvement and patients without nodal involvement. Expansion Cohorts 7 and 8 did not exclude patients with anogenital CSCC, but such patients are not included in the definitions of mCSCC or laCSCC.

Therefore, the safety and efficacy for CSCC patients will be presented in two ways: (1) according the definitions of mCSCC and laCSCC, and (2) according to enrollment in dose escalation cohort, Expansion Cohort 7, or Expansion Cohort 8 in Study 1423. That is,

- All CSCC patients, excluding the patients with anogenital SCC, treated with REGN2810 as monotherapy recategorized as having Metastatic (mCSCC) or Locally Advanced (laCSCC) disease using the definitions from Study 1540;
- All CSCC patients treated with REGN2810 as monotherapy by enrollment cohort.

For interim analysis of safety for patients in dose escalation cohorts:

Safety for patients in dose escalation cohorts will be summarized by REGN2810 Dose Level (1 mg/kg, 3 mg/kg, 10 mg/kg).

For interim analysis of safety for all patients:

The safety of all patients in the study will also be assessed and will be analyzed by

- Patients who received REGN280 as monotherapy excluding patients with HCC;
- Patients who received REGN280 as monotherapy including patients with HCC;
- Patients who received REGN2810 as combination therapy.

In addition, the supportive safety analysis will also be performed in the following subgroups of patients:

- Patients who received REGN2810 as monotherapy (excluding HCC patients) summarized by REGN2810 Dose Level (1 mg/kg, 3 mg/kg, 10 mg/kg, 200 mg)
- Patients who received REGN2810 as combination treatment summarized by type of combination regimen (REGN2810 + Chemo therapy only, REGN2810 + Radio therapy only, REGN2810 + Chemo therapy + Radio therapy)
- All patients summarized by REGN2810 Dose Level (1 mg/kg Q2W, 3 mg/kg Q2W, 3 mg/kg Q3W, 10 mg/kg Q2W, 200 mg)

7.2. Disposition of Patients

The following variables will be reported based on the grouping for safety analysis specified in Section 7.1 and using the methodologies described in Section 5.1.

- Analysis populations, patients screened.
- Number of patients who discontinued treatment and the reasons for treatment discontinuation
- Number of patients who discontinued study participation and the reasons for study discontinuation.

7.3. Demographic and Baseline Characteristics

The following demographic variables will be reported based on the grouping for safety analysis specified in Section 7.1.

- Age at screening (year)
- Age category (<65, ≥65)

- Sex (Male, Female)
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White and Other)
- Ethnicity (Hispanic/Latino)
- Baseline weight (kg)
- Baseline height (m)
- Body mass index (BMI) calculated from weight and height: $\text{weight (kg)} / [\text{height (m)}]^2$
- ECOG performance status

7.4. Protocol Deviations

Protocol deviations will be reported based on the grouping for safety analysis specified in Section 7.1 and using the methodologies described in Section 5.3.

7.5. Disease Characteristics

The following variables will be reported based on the grouping for safety analysis specified in Section 7.1.

- Primary site of cancer
- Histological grade (Well differentiated, Moderately differentiated, poorly differentiated, Undifferentiated, Unknown)
- Stage at initial diagnosis
- Time since most recent relapse/recurrence
- Time since initial diagnosis of metastatic disease

In addition, the TNM stage at initial diagnosis and at screening will be summarized for CSCC patients.

7.6. Medical History

Medical history will be reported based on the grouping for safety analysis specified in Section 7.1 and using the methodologies described in Section 5.4.

7.7. Prior Anti-Cancer Therapy

Prior anti-cancer therapy will be reported based on the grouping for safety analysis specified in Section 7.1 and using the methodologies described in Section 5.6.

7.8. Prior and Concomitant Medication

Prior and concomitant medications will be reported based on the grouping for safety analysis specified in Section 7.1 and using the methodologies described in Section 5.7.

7.9. Extent of Study Treatment Exposure and Compliance

Treatment compliance and exposure (duration, number of doses administered, cumulative dose, actual dose intensity, relative dose intensity) will be summarized for REGN2810. Duration of exposure (except for radiotherapy) and number of doses administered will also be summarized for other treatment components.

The analysis will be performed based on the grouping for safety analysis specified in Section 7.1 and using the methodologies described in Section 5.8.

7.10. Efficacy

Interim analysis of efficacy will be performed for patients with CSCC and treated with REGN2810 as monotherapy based on the grouping for efficacy specified in Section 7.1 and using the methodologies described in Section 5.9.

The following efficacy variables will be reported.

- Overall Response Rate (ORR) by independent central review and by investigator review per RECIST 1.1 criteria
- Disease Control Rate (DCR) by independent central review and by investigator review per RECIST 1.1 criteria
- Durable Disease Control Rate (DDCR) by independent central review and by investigator review per RECIST 1.1 criteria
- Duration of response (DOR) by independent central review and by investigator review per RECIST 1.1 criteria
- Progression Free Survival (PFS) by independent central review and by investigator review per RECIST 1.1 criteria
- Overall survival (OS)

7.11. Safety

The following variables will be reported based on the grouping for safety analysis described in Section 7.1 and using the methodologies described in Section 5.10.

- Treatment-emergent adverse events (TEAEs)
- Serious adverse events (SAEs)
- Immune Related Adverse Events (irAEs)
- Infusion related reaction (IRR)
- Adverse events of interest (AESI)
- Dose limiting toxicities (DLTs)

The following variables will be reported based on the grouping for safety analysis (except for dose escalation patients) described in Section 7.1 and using the methodologies described in Section 5.10.

- Blood chemistry
- Hematology
- Urinalysis
- Vital signs
- ECG parameters
- Physical examination

7.12. Pharmacokinetic and Anti-Drug Antibody (ADA)

Analysis for pharmacokinetic data will be provided in a separate report.

ADA will be reported for all patients using the methodologies described in Section [5.11.2](#).

8. SOFTWARE

All statistical analyses will be done using SAS Version 9.2 or above.

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STATISTICAL ANALYSIS PLAN

Title: A Phase II Study of REGN2810, A Fully Human Monoclonal Antibody to Programmed Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma

Protocol: R2810-ONC-1540

Investigational product: REGN2810 (anti-PD-1 mAb)

Sponsor: Regeneron Pharmaceuticals, Inc.

Study Biostatistician: Rui Qin, PhD

Clinical Trial Manager: Karen Knice

Study Medical Director: Matthew Fury, MD, PhD

Version: 1.0

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The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

Study Biostatistician Riu Qin (Author)

Study Medical Director Matthew Fury

Head of BDM or designee Yuhwen Soo

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ABBREVIATIONS AND DEFINITIONS

ADA	Anti-drug antibody
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the concentration–time curve
BAS	Biomarker analysis set
BCC	Basal cell carcinoma
BLA	Biologic license application
BSA	Body surface area
BUN	Blood urea nitrogen
CI	Confidence interval
CSR	Clinical study summary
CR	Complete response
CRF	Case report form
CSCC	Cutaneous squamous cell carcinoma
CT	Computed tomography
ECG	Electrocardiogram
ECOG	East Cooperative Oncology Group
EOS	End of study
FAS	Full analysis set
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry
irAE	Immune-related adverse event

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irRC	Immune-related response criteria
IV	Intravenous
LLOQ	Lower limit of quantification
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
mAb	Monoclonal antibody
MAA	Marketing authorization application
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCCN	National comprehensive cancer network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NE	Not evaluable
NSCLC	Non-small cell lung cancer
PBMC	Peripheral blood mononucleated cell
PD	Progression
PD-1	Programmed death-1 (receptor)
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PET	Positron-emission tomography
PK	Pharmacokinetic
PPS	Per protocol set
PR	Partial response
PT	Preferred term
PTV	Planning target volume
RBC	Red blood cell
RCC	Renal cell cancer
RECIST	Response Evaluation Criteria in Solid Tumors
Regeneron	Regeneron Pharmaceuticals, Inc.
RNA	Ribonucleic acid
SAE	Serious adverse event

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SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Systems (software)
SD	Stable disease
SI	Standard international
SOC	System organ class
$t_{1/2}$	Beta-phase terminal half life
TEAE	Treatment-emergent adverse event
TIL	Tumor-infiltrating lymphocytes
UV	Ultraviolet
WHODD	World Health Organization drug dictionary
WBC	White blood cell

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1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study prior to the database lock. The SAP is intended to be a comprehensive and detailed description of strategy and statistical technique to be used to realize the analysis of data for R2810-ONC-1540 study.

This plan may be revised during the study to accommodate protocol amendments and/or to make changes to adapt to unexpected issues in study execution and/or data that affect planned analyses. The final plan, if revised, will document all changes and be issued prior to data lock.

1.1. Background/Rationale

1.1.1. Background

Cutaneous squamous cell carcinoma (CSCC) is the second most common malignancy in the United States. A review of national databases indicates that incidence of non-melanoma skin cancers, mostly basal cell carcinoma (BCC) and CSCC, approximately doubled between 1994 and 2006 in the context of an aging population. Most CSCC patients have a favorable prognosis, but annual mortality is approximately 3,900 to 8,800 deaths in the United States.

Surgical resection is the centerpiece of clinical management of CSCC. Radiation therapy for CSCC has also been used in the adjuvant setting. For the small percentage of patients who develop unresectable locally recurrent or metastatic disease, treatment options are limited. Regarding systemic therapies, there is a dearth of data to guide clinical decision-making for oncologists who take care of patients with advanced CSCC. National Comprehensive Cancer Network (NCCN) guidelines do not provide firm recommendations.

Blockade of the PD-1/PD-L1 T-cell checkpoint pathway is an effective and well tolerated approach to stimulating the immune response, and has achieved significant objective responses in advanced melanoma, renal cell cancer (RCC), non-small cell lung cancer (NSCLC), and other solid tumors. REGN2810 is a high-affinity, fully human, hinge-stabilized IgG4P antibody directed to the PD-1 receptor that potently blocks the interaction of PD-1 with its ligands, PD-L1 and PD-L2.

R2810-ONC-1423 is an ongoing first-in-human study of REGN2810 (NCT02383212). It is a phase 1, open label, multicenter repeat-dosing study of REGN2810, alone and in combination with other anti-cancer therapies in patients with advanced malignancies, and contains both dose escalation and expansion cohorts. As of 12 September 2015, 50 patients have been enrolled in 8 dose escalation cohorts, including 3 monotherapy cohorts (1 mg/kg, 3 mg/kg, 10 mg/kg REGN2810 administered IV every 14 days) and 5 combination therapy cohorts (3 mg/kg REGN2810 administered intravenously every two weeks in combination with various combinations of hypofractionated radiation therapy or cyclophosphamide). No dose limiting

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toxicities have been observed. The dose escalation portion of the study established that 3 mg/kg REGN2810 administered intravenously over 30 minutes every 2 weeks is the recommended monotherapy dosing regimen for the agent in further studies for advanced cancer patients.

1.1.2. Rationale

CSCC has several clinical and biological factors that suggest that it is appropriate for the clinical study of inhibition of the PD-1 immune checkpoint: high mutation burden, presence of tumor infiltrating lymphocytes (TILs), association with immunosuppression as a risk factor, evidence of direct immunosuppressive effects of ultraviolet (UV) radiation, and some clinical efficacy with interferon α 2a-based treatment.

In the ongoing phase 1 study of REGN2810 for patients with advanced solid tumors (NCT02383212), evidence of biologic activity has been seen in the first cohort of REGN2810 monotherapy (1 mg/kg, administered intravenously every 2 weeks). A partial response (PR) was observed in a 52 year old man with unresectable recurrent CSCC at the first tumor assessment after his first 4 doses of REGN2810, and this is ongoing after 12 doses at this time. This patient has an extensive prior history of surgery, systemic therapy, and radiation therapy for recurrent disease for over 13 years. In a recently published case report, a major response was observed in a patient with recurrent CSCC who received treatment with the anti-PD1- antibody pembrolizumab off label.

1.2. Study Objectives

1.2.1. Primary Objective

To estimate the clinical benefit of REGN2810 monotherapy for patients with metastatic (nodal or distant) CSCC (Group 1) or with unresectable locally advanced CSCC (Group 2), **respectively**, as measured by objective response rate (ORR) according to central review.

1.2.2. Secondary Objectives

- To estimate the ORR according to investigator review
- To estimate the duration of response, progression-free survival (PFS), and overall survival (OS) by central and investigator review
- To estimate the complete response (CR) rate by central review
- To assess the safety and tolerability of REGN2810
- To assess the pharmacokinetics of REGN2810 (at selective sites only)
- To assess the immunogenicity of REGN2810
- To assess the impact of REGN2810 on quality of life using EORTC QLQ-C30

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1.2.3. Exploratory Objective (Group 2 only)

To explore the pharmacodynamic effects of REGN2810 in tumor biopsies obtained at baseline, during treatment, and at progression in CSCC patients treated with REGN2810 [REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

1.2.4. Modifications from the Statistical Section in the Final Protocol

This study is expected to be a pivotal trial and will be part of the core of the BLA/MAA submission. Accordingly, revision to this plan may be made if deemed necessary to the furtherance of the trial objectives. Such revision, if necessary, will be completed prior to the final data base lock.

1.2.5. Modifications from the Approved Statistical Analysis Plan

This is the first version of SAP based on the study protocol.

2. INVESTIGATION PLAN

2.1. Study Design

There are two study groups for this study, which will be analyzed separately. For each group, this is a phase II, non-randomized, multicenter pivotal trial evaluating the efficacy and safety of REGN2810.

- Group 1: Patients with metastatic CSCC. These patients are required to have histologic confirmation of distant CSCC metastases (eg, lung, liver, bone, or lymph node). Group 1 includes patients with both nodal metastatic and distant metastatic disease.
- Group 2: Patients with unresectable locally advanced CSCC. These patients are required to have disease that is considered inoperable or to have medical contraindication to surgery or radiation, or have not achieved disease control with these treatments.

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2.2. Sample Size and Power Considerations

The sample sizes for both Group 1 and Group 2 were selected such that the lower limit of the two-sided 95% confidence interval (CI) of the estimated ORR will be clinically meaningful. The non-clinically meaningful ORR of 15% for Group 1 will be excluded using the lower limit of 95% CI if the observed ORR is around 28.0% or more; ie, the ORR for Group 1 is significantly different from 15%. The non-clinically meaningful ORR of 25% for Group 2 will be excluded using the lower limit of 95% CI if the observed ORR is around 36.1% or more; ie, the ORR for Group 2 is significantly different from 25% (see Table 6 and Table 7 of the protocol).

For Group 1, 50 patients will be required to provide at least 85% power to reject a null hypothesis of an ORR of 15% at a 2-sided significance level of no more than 5% if the true ORR is 34%. For Group 2, 72 patients will be required to provide at least 90% power to reject a null hypothesis of an ORR of 25% at a 2-sided significance level of no more than 5% if the true ORR is 44%. The sample sizes will be further increased by 5% to account for patients who withdraw prematurely from the study. Hence, the total sample sizes will be 53 patients for Group 1, and 76 patients for Group 2, for a total of 129 patients. The sample size calculation was based on the exact binomial test using nQuery Advisor v. 7.0 ([Elashoff 2007](#)).

2.3. Study Plan

After a screening period of up to 28 days, patients will receive up to twelve 56-day (8-week) treatment cycles for a total of up to 96 weeks of treatment. Each patient will receive 3 mg/kg REGN2810 intravenously on days 1, 15±3, 29±3, and 43±3 during each treatment cycle. Tumor assessments will be made at the end of each treatment cycle. Extensive safety evaluations will occur on day 1 of each cycle; routine safety evaluations will be conducted at each REGN2810 dosing visit.

A patient will receive treatment until the 96 week treatment period is complete, or until disease progression, unacceptable toxicity, withdrawal of consent, or confirmed complete response (CR). Patients with confirmed CR after a minimum of 48 weeks of treatment may elect to discontinue treatment and continue with all relevant study assessments (eg, efficacy assessments). Patients who discontinue study treatment will be followed for survival approximately every 3 months until death, lost to follow-up, or study termination by the sponsor.

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials ([ICH 1998](#)), the following populations of analysis will be used for statistical analysis:

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3.1. Full Analysis Set (FAS)

The full analysis set (FAS) includes all patients who have passed screening and deemed to be eligible for this study.

3.2. Per Protocol Set (PPS)

The per protocol set (PPS) includes all enrolled patients in the FAS except for those who prematurely withdraw from the study before receiving at least 1 dose of the study drug. The PPS is the primary analysis set for the efficacy endpoints.

3.3. Safety Analysis Set (SAF)

The safety analysis set (SAF) includes all enrolled patients who have received any REGN2810. Treatment compliance/administration and all clinical safety variables will be analyzed or summarized using the SAF.

3.4. PK Analysis Set (PKA)

The pharmacokinetic analysis set (PKA) will include all patients who have at least 1 post REGN2810 treatment study drug concentration value above the lower limit of quantification (LLOQ) of the assay.

3.5. Anti-Drug Antibody Set (ADA)

The anti-drug antibody (ADA) set includes all treated patients who had at least 1 post-dose ADA result.

3.6. Biomarker Analysis Set (BAS)

The biomarker analysis set (BAS) includes all treated patients who had at least 1 sample assayed.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic variables will be summarized:

- Age at screening (year), and range if needed
- Sex (Male, Female)
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White and Other)
- Ethnicity (Hispanic/Latino)

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- Baseline Weight
- Baseline Height
- Baseline Body mass index (BMI) calculated from weight and height
- Body Surface Area (BSA)
- ECOG performance status

4.2. Medical History

Medical history will be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) according to the latest available version of MedDRA.

Oncology history:

- Primary diagnosis
- Primary tumor site
- Time from initial diagnosis
- Histologic type
- Baseline cancer stage

4.3. Pre-Treatment/Concomitant Medication

Medications/Procedures will be recorded from the day of informed consent until the end of study (EOS) visit. Medications will be coded to the anatomical therapeutic chemical (ATC) level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of WHO Drug Dictionary (WHODD). Patients will be counted once in all ATC categories linked to the medication.

Pre-treatment medications/procedures: medications taken or procedures performed prior to administration of the study drug. Particularly, prior cancer related surgery, prior cancer related radiotherapy, and prior cancer related systemic therapy: chemotherapy, targeted therapy, immunotherapy and others.

Concomitant medications/procedures: Any treatment administered from the time of informed consent until 30 days after the last study treatment will be considered concomitant treatment. This includes medications and other therapies for which administration started before the study and will continue during the study, as well as any therapies started in the 5 month follow-up period to treat a study-drug-related AE. All concomitant treatments must be recorded in the study case report form (CRF) with the generic name, dose, dose unit, frequency, indication, and start/stop date, as appropriate.

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4.4. Rescue Medication/or Prohibited Medication

While participating in this study, a patient may not receive any standard or investigational agent for treatment of a tumor other than REGN2810 as monotherapy. Any other medication which is considered necessary for the patient's welfare, and which is not expected to interfere with the evaluation of the study drug, may be given at the discretion of the investigator.

Patients using immunosuppressive doses (>10 mg per day of prednisone or equivalent) of systemic corticosteroids other than for corticosteroid replacement will not be eligible for the study. It is recommended that patients do not receive systemic corticosteroids such as hydrocortisone, prednisone, prednisolone (Solu-Medrol[®]) or dexamethasone (Decadron[®]) at any time throughout the study except in the case of a life-threatening emergency and/or to treat an immune-related adverse event (irAE). Physiologic replacement doses of systemic corticosteroids are permitted, even if >10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

4.5. Efficacy Variable

4.5.1. Primary Efficacy Variable

Overall response is based on **central-reviewed evaluation** at each time point at which a response assessment occurs using the RECIST version 1.1 ([Appendix 2 of the protocol](#)) or composite response criteria ([Appendix 3 of the protocol](#)).

Best overall response is determined once all the data for the patient is known. The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. Best overall response of CR or PR must be confirmed by consecutive evaluations of overall response of CR or PR at time points at least 4 weeks apart. Best overall response of SD must have met the response SD criteria at least once ≥ 6 weeks after start of study treatment. Best overall response of early PD does not require confirmation using RECIST or composite response criteria. The best overall response for patients who do not have any post-baseline tumor assessments will be not evaluable (NE).

Objective response rate (ORR) is determined by the proportion of patients with best overall response of CR or PR. Patients with best overall response of NE will be considered as not reaching an objective response of CR or PR.

4.5.2. Secondary Efficacy Variable(s)

ORR is also derived from the overall response that is based on **investigator-reviewed evaluation** at each time point at which a response assessment occurs using the RECIST version 1.1 ([Appendix 2 of the protocol](#)) or composite response criteria ([Appendix 3 of the protocol](#)). This is considered as a secondary efficacy variable.

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Duration of response is determined for patients with best overall response of CR or PR. Duration of response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date of recurrent or progressive disease (radiographic), or death due to any cause. Patients who never progress while being followed will be censored at the last valid tumor measurement.

Duration of disease control is determined for patients with best overall response of SD, CR or PR. Duration of disease control is measured from the start of treatment until the first date of recurrent or progressive disease (radiographic), or death due to any cause. Patient who never progress while being followed will be censored at the last valid tumor measurement.

Progression-free survival (PFS) is measured from the start of treatment until the first date of recurrent or progressive disease (radiographic), or death due to any cause. Patient who never progress while being followed will be censored at the last valid tumor measurement. If a patient has no post-baseline evaluation, the patient will be censored at first treatment date.

Overall survival (OS) is measured from the start of treatment until death due to any cause. Patients who do not have a survival event will be censored at the last date that patient is alive.

Depth of tumor response is the percentage change in tumor size from baseline for target lesions which will be summarized in terms of time-adjusted area under the curve (AUC) for all patients.

In addition, to account for the possibility of unconventional immune responses, immune-related response criteria (irRC) will also be applied to assess tumor response, mostly to inform the decision regarding whether to continue treatment for an individual patient rather than as primary efficacy variables. Best overall response of early PD must be confirmed using irRC.

Patient-reported outcomes quality of life are measured by the EORTC QLQ-C30 on day 1 of every cycle. Change scores are defined as change of summary score of EORTC QLQ-C30 from day 1 of first treatment cycle.

4.5.3. Exploratory Biomarker Variables

Biomarker variables for exploratory analyses may include

- Fold-change in mRNA expression of genes expressed in tumor tissue
- Percent change in number of TILs (CD8+ T cells, CD4+ T cells, T regulatory cells, and tissue permitting, other subtypes such as B cells, myeloid-derived cells, NK cells, etc.) and descriptive change in distribution of TILs in respect to tumor tissue and stroma
- Percent change in expression levels (mRNA and/or protein) of PD-L1, GITR, and LAG-3, and possibly other check-point modulators
- Change in number and type of genetic mutations in known oncogenes and potential tumor neoantigens

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- Change in tumor mutation burden

4.6. Safety Variables

4.6.1. Adverse Events and Serious Adverse Events

Adverse events and serious adverse events will be collected from the time of informed consent signature and then at each visit until the end of the study. All adverse events are to be coded to a Preferred Term and associated primary System Organ Class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA).

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. A Serious Adverse Event (SAE) is an AE that is classified as serious according to the criteria specified in the protocol.

The severity of AEs (including test findings classified as AEs) will be graded using the current version of the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grading system. Adverse events not listed in the NCI-CTCAE, will be graded according to the following scale:

- | | |
|-----------------------|--|
| 1 (Mild): | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. |
| 2 (Moderate): | Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*. |
| 3 (Severe): | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**. |
| 4 (Life-threatening): | Life-threatening consequences; urgent intervention indicated. |
| 5 (Death): | Death related to AE. |

* Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The relationship of AEs to study drug will be assessed by the investigator and be determined based on protocol specified criteria.

Laboratory results, vital signs, or ECG abnormalities are to be recorded as AEs if they are medically relevant: symptomatic, requiring corrective therapy, leading to treatment discontinuation and/or fulfilling a seriousness criterion.

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4.6.2. Special Safety Variables of Interest

Adverse Events of Special Interest

An AE of special interest (AESI) must be reported within 24 hours of identification. AEs of special interest for this study include:

- Grade 2 or greater infusion-related reactions
- Grade 2 or greater allergic/hypersensitivity reactions
- Grade 3 immune-related toxicities (irAE)

Note: An irAE can occur shortly after the first dose or several months after the last dose of treatment. All AEs of unknown etiology associated with drug exposure should be evaluated to determine possible immune etiology. If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an AE as an irAE.

4.6.3. Laboratory Safety Variables

The clinical laboratory data consists of serum chemistry, hematology, and other. Clinical laboratory values will be converted to standard international (SI) units and grouped by function in summary tables. Conventional unit may be provided. Functions are defined as follows:

Blood Chemistry

- Sodium
- Phosphorus
- ALT
- Potassium
- Glucose
- AST
- Chloride
- Albumin
- Total bilirubin
- Bicarbonate
- Creatinine
- Alkaline phosphatase (ALP)
- Calcium
- Blood urea nitrogen (BUN)

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- Lactate dehydrogenase (LDH)
- Magnesium
- Uric acid

Hematology

- Hemoglobin
- WBCs
- Platelet count
- Differential: Neutrophils, Lymphocytes, Monocytes

Urinalysis

- Glucose
- pH
- Ketones
- Blood
- Specific gravity
- Spot urine protein

4.6.4. Vital Signs

Vital signs will be collected according to Table 3 and Table 4 Study Schedule of protocol:

- Body temperature (oC)
- Resting systolic blood pressure and diastolic blood pressure (mmHg)
- Pulse (beats/minute)
- Respiratory rate (breaths/minute)

4.6.5. 12-Lead Electrocardiography (ECG)

A standard 12-lead ECG will be performed at time points according to Table 4 and Table 5 of the protocol. The patient should be relaxed and in a recumbent or semi-recumbent position at least 5 minutes before recording an ECG. The ECG is to be recorded in triplicate. The ECG strips or reports will be retained with the source. The ECG will be reviewed by the investigator (paper or electronic tracing) and will be available for comparison with subsequent ECGs by the investigator. The following will be recorded on the CRF:

- PR Interval (msec)
- QRS Interval (msec)

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- QT Interval (msec)
- Heart Rate (BPM; recorded from the ventricular rate)

Any ECG finding that is judged by the investigator as a clinically significant change (worsening) compared to the baseline value will be considered an AE, recorded, and monitored.

4.6.6. Physical Examination Variables

A thorough complete or limited physical examination will be performed at visits specified in Table 4 and Table 5 of the protocol. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

Complete physical examination will include examination of skin, head, eyes, nose, throat, neck, joints, lungs, heart, pulse, abdomen (including liver and spleen), lymph nodes, and extremities, as well as a brief neurologic examination. Limited physical examination will include lungs, heart, abdomen, and skin.

4.7. Pharmacokinetic Variables and Anti-Drug Antibody Variables (ADA)

Serum concentration of REGN2810 will be assessed at multiple time points throughout the study treatment and follow-up periods, and the PK will be analyzed.

Pharmacokinetic variables may include, but are not limited to, the following:

- AUC_{all} - area under the curve (AUC) computed from time zero to the time of the last concentration
- $AUC_{all}/Dose$ - AUC_{all} -to-dose ratio
- CL - clearance
- C_{eoi} – concentration at end-of-infusion
- $C_{eoi}/Dose$ – C_{eoi} -to-dose ratio
- C_{last} - last positive (quantifiable) concentration
- t_{last} - time of the last positive (quantifiable) concentration
- t_{eoi} - time of end-of-infusion
- V_{ss} - volume of distribution at steady state
- V_z – volume of distribution of the terminal phase

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Anti-drug antibody variables include status (positive or negative) and titer as follows:

- Total number of patients whose ADA response is negative at any time
- Total number of patients whose ADA response is positive at any time
- Pre-existing immunoreactivity – defined either as a positive ADA assay response at baseline with all post-treatment ADA results negative, or a positive assay response at baseline with all post-treatment ADA assay responses less than 4-fold over baseline titer levels.
- Treatment emergent - defined as either any positive response post-treatment when
- baseline results are negative, or if any post treatment ADA response is greater than or equal to 4-fold over baseline titer levels. Treatment emergent responses will be further characterized into persistent and transient.
- Persistent response – treatment-emergent ADA positive response with 2 or more
- ADA-positive sampling time points during the treatment period (and follow-up phase, if any) such that the first and last ADA-positive sample (with no intervening ADA-negative sample) is separated by at least a 16 week period, or only the last collected sample is ADA-positive
- Transient response – any treatment-emergent ADA-positive response that is not
- considered persistent
- Titer values (Titer value category):
 - Low (titer < 1,000)
 - Moderate ($1,000 \leq \text{titer} \leq 10,000$)
 - High (titer > 10,000)

5. STATISTICAL METHODS

For continuous variables, descriptive statistics will include the following: the number of patients reflected in the calculation (n), mean, median, standard deviation, minimum, and maximum. In addition, 25%-percentile and 75%-percentile may be provided if needed.

For categorical or ordinal data, frequencies and percentages will be displayed for each category. The denominator will be determined by the analysis population used for the summary. Non-evaluable outcome or missing data will be handled based on the data handling strategy.

For time-to-event variables, median time-to-event and its 95% confidence intervals will be summarized by the Kaplan-Meier method.

Statistical analysis for Group 1 and Group 2 will be conducted separately.

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5.1. Demographics and Baseline Characteristics

Patient demographics and baseline characteristics will be summarized by group based on the FAS population.

Assessments made before the first dose of REGN2810 will be used as baseline measurements for the purposes of statistical analysis and reporting unless otherwise specified.

5.2. Medical History

Medical history will be listed and summarized which includes SOC, PT, investigator verbatim and start and end dates and summarized by SOC and PT. Cancer diagnosis will be listed and summarized by primary tumor site, primary cancer diagnosis, histological site, stage and grade of disease. Prior cancer related surgery will be listed and summarized including type of procedure and date of surgery. Prior cancer related systemic therapy will be listed and summarized which contains systemic therapy type, name of drug and start and end dates. Prior cancer related radiotherapy will be listed and summarized by site, total dose and start and end dates.

5.3. Prior/concomitant Medications

Prior/concomitant medications patient takes before the first dose of REGN2810 will be listed, the medication taken between the first dose of REGN2810 and thirty days after the last dose of REGN2810 will be summarized by group based on the SAF population.

5.4. Subject Disposition

Subject disposition will be summarized by the total of screened subjects, the number of subjects in FAS by group, the number of discontinuations from study treatment and from study by reasons.

5.5. Extent of Study Treatment Exposure and Compliance

5.5.1. Measurement of Compliance

Compliance with REGN2810 treatment will be calculated as follows:

$$\text{Treatment Compliance} = \frac{(\text{Number of investigational product taken during treatment period})}{(\text{Number of REGN2810 planned to be taken during period})} \times 100\%$$

where temporary dose discontinuation is ignored.

The percentage of subjects who have <60%, 60-80%, 80-100%, and >100% compliance will be summarized for each group.

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5.5.2. Exposure to Investigational Product

Exposure to investigational product will be examined for each subject. The following variables will be summarized:

- The total number of study doses administered
- The total dosage of REGN2810 administered
- Duration of treatment calculated as: [last dose day] – [first dose day] + 14

The number of subjects exposed to REGN2810 will be presented by specific time point periods for each group. The time periods of interest are as follows:

- \geq Days 28, 56, 84, 112, 168 and 224

5.6. Analyses of Efficacy Variables

5.6.1. Analysis of Primary Efficacy Variable(s)

The primary analysis of efficacy is based on the exact binomial confidence interval approach, i.e., whether the lower limit of 95% confidence interval will exclude an historical control ORR that is not deemed clinically meaningful. The two-sided 95% exact binomial confidence intervals are derived using Clopper-Pearson method ([Clopper 1934](#)). If the lower limit of 95% confidence interval of observed ORRs excluding 15% for group 1 and 25% for group 2, respectively, the study treatment is deemed effective for that group. The p-values from the exact binomial test of 15% for group 1 and 25% for group 2 will also be reported.

Best overall response: CR/PR/SD/PD/NE will be summarized by group:

- Not evaluated response includes the missing and unknown response (NE).
- CR/PR must be confirmed by repeated assessments no less than 4 weeks apart.
- SD criteria must be met at least once for a minimum duration of 39 days (7 days/week * 6 weeks – 3 days) after first dose date.
- Early PD must be confirmed by repeated assessments no less than 4 weeks apart using irRC (NOT required for RECIST 1.1 or composite response criteria).

For the primary efficacy analysis, patients with the best overall response of NE will not be considered as responder (CR/PR).

The ORR determined by irRC criteria will be analyzed similarly as primary efficacy variable, as a sensitivity efficacy analysis.

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5.6.2. Analysis of Secondary Efficacy Variables

ORR derived from the overall response that is based on **investigator-reviewed evaluation** will be analyzed similarly as primary efficacy variable, as a secondary efficacy analysis.

For the following time-to-event variables, the time to event (day) is the date of event/censor – the date of start + 1, which will be summarized and displayed using Kaplan-Meier approach.

- Duration of response will be summarized and displayed by Kaplan-Meier approach, this is considered as the key secondary analysis.
- Duration of disease control will be summarized and displayed by Kaplan-Meier approach.
- PFS will be summarized and displayed by Kaplan-Meier approach.
- OS will be summarized and displayed by Kaplan-Meier approach.

The complete response (CR) rate by central review will be summarized descriptively with 95% confidence interval using Clopper-Pearson method. Absence of residual CSCC in biopsy samples from patients with locally advanced CSCC achieving a clinical response to REGN2810, as measured by independent central pathological review, will be summarized descriptively as complete response (CR).

Depth of tumor response will be depicted by spaghetti plot and summarized by time-adjusted AUC.

5.6.3. Analysis of Quality of Life Variables

The quality of life of patients will be repeatedly measured by the EORTC QLQ-C30 at the day 1 of each treatment cycle. The change scores of QLQ-C30 will be summarized descriptively at each post-baseline time point. The summary scores of QLQ-C30 will also be graphically depicted by longitudinal plots.

5.6.4. Subgroup Analysis

Subgroup efficacy analyses will be performed based on the number of prior systemic therapy regimens, the degree of differentiation of the tumor (well, moderate, or poor), the presence or absence of HPV in the tumor, and the presence or absence of use of immune suppressive medications (eg, high dose steroids) to manage irAEs that may arise during the study. However, such analyses may not have enough power for hypothesis tests, the analysis is exploratory in nature.

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5.7. Analysis of Safety Data

The analysis of safety and tolerance will be performed on the SAF, as defined in [Section 3.3](#). The safety analysis will be based on the reported AEs and other safety information (clinical laboratory evaluations, vital signs and 12-lead ECG). The analysis will comprise the basis upon which conclusions will be drawn regarding the REGN2810. The AE of special interest will be determined by the list provided by medical monitors.

The summary of safety results will be presented for each group and by overall total is deemed appropriate.

5.7.1. Adverse Events

The verbatim text, the preferred term, and the primary system organ class (SOC) will be listed in subject listings. Summaries that include frequencies and proportions of patients reporting AEs will include the preferred terms and the SOC.

Period of observation: The observation period will be divided into three segments: pre-treatment, on-treatment and post-treatment. The pre-treatment period is defined as the time between when the subjects give informed consent and before the start of REGN2810 treatment. The on-treatment period is defined as the time from first dose of REGN2810 up to 30 days after the last dose of REGN2810. The post-treatment period is defined as the time starting 30+1 days after last dose of REGN2810 (after the on-treatment period).

Day 1 is the first day of patient receiving REGN2810 treatment, Day -1 is the day before, and there is no Day 0.

Pre-treatment AEs are defined as AEs that developed during the pre-treatment period.

Treatment-emergent AEs (TEAEs) are defined as AEs that developed or worsened during the on-treatment period.

Post-treatment AEs are defined as AEs that developed or worsened during the post-treatment period and are not considered drug related by the investigator.

The focus of adverse event reporting in the CSR will be on TEAEs. For details on handling missing data and partial dates, see [Section 6](#). Summaries of TEAEs will include: TEAEs, TEAEs/related, TEAEs/Serious, TEAEs/treatment-related Serious TEAEs. For TEAEs, the following will be summarized:

- The number and proportions of patients reporting at least 1 TEAE
- TEAEs by severity (CTCAE, version 4.03 grade), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT
- TEAEs occurring in > 5% patients

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- TEAEs leading to permanent treatment discontinuation
- TEAEs leading to death

For AE listings, the following variables will be displayed:

- Verbatim Term
- PT
- SOC
- AE start date and end date/ongoing (and corresponding study day)
- AE duration
- Relationship to study drug: unrelated or related
- Seriousness (Serious AE or not)
- National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade: mild, moderate, severe, life-threatening or death
- Action taken: none, dose decreased, dose temporarily stopped or discontinued
- Treatment: none, medication, surgery or others
- Outcome: recovered/resolved, recovered/resolved with residual effects, recovering/resolving, not recovered/not resolved, fatal, or unknown

Counts will be provided for each patient within each SOC. Percentages will be calculated using the number of patients from the safety population in each group.

Primary SOC's will be sorted according to the order described in the Guideline on summary of product characteristics (December 1999, European commission), with the total overall classes coming first and labeled "Any class". Within each primary SOC, patients will be sorted by decreasing frequency of investigational product.

The description of common TEAEs will also be performed for demographic factors including: gender, age (<65, ≥65), and race if appropriate.

5.7.2. Clinical Laboratory Measurements and Vital Signs

Listings of laboratory values, normal ranges, grade, by dose cohort, date, and cycle will be provided. For numeric lab variables and change from baseline to each cycle and overall will be summarized. Listings of abnormal lab values and clinical significant (Yes/No) by patient and cycle will also be constructed.

Summary tables for laboratory values with all grade and NCI CTCAE v4.03 grade ≥ 3 will be generated.

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Summary of Shift tables from baseline to post-treatment worst NCI CTCAE v4.03 grade will be generated.

The shift tables include:

- Overall and individual Hematologic Test (Hemoglobin, Platelets, WBC, ANC).
- Overall and individual Liver Function Test: (AST, ALT, ALK, PHOS, TBILI, Albumin),
- Overall and individual Electrolytes (Sodium, Potassium, Magnesium, Calcium, Phosphorus).

5.7.3. Analysis of Vital Signs

Vital signs (pulse, sitting blood pressures, and temperature) will be summarized by Baseline and change from Baseline to each scheduled assessment time with descriptive statistics.

5.7.4. Analysis of 12-Lead ECG

ECG parameters (*P-R interval*, *QT interval*, *QTc interval*, *QRS interval*, *Ventricular rate and Heart rate*) will be summarized by Baseline and change from Baseline to each scheduled and collected assessment time.

ECG status (ie normal, abnormal) will be reported. Shift tables will be provided to present the post-baseline status according to the baseline status (normal or missing / abnormal) by group.

5.7.5. Physical Exams

Physical examination findings at baseline as well as post-treatment abnormal findings by body system and status (normal, abnormal and not done) will be provided with Listing.

5.8. Analysis of Pharmacokinetic and Antibody Data

5.8.1. Analysis of Pharmacokinetic Data

Analysis of pharmacokinetic data will be provided in a separate report.

5.8.2. Analysis of Anti-drug Antibody Data

Analysis of anti-drug antibody data will be provided in a separate report.

5.8.3. Analysis of Exploratory Biomarker Data

Analysis of exploratory biomarker data will be provided in a separate report.

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6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the Baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of investigational product.

6.2. Data Handling Convention for Efficacy Variables

Patients who are deemed NE according to RECIST version 1.1. or inevaluable by the composite response criteria will be considered as not reaching PR/CR in calculating ORR, i.e. they are not considered as responders in the numerator of ORR, but they are counted in the denominator of ORR.

6.3. Data Handling Convention for Missing Data

No missing data imputation is planned in this study unless specified otherwise.

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

Medication missing/partial dates

To determine whether a medication is prior, concomitant or post-treatment medication, the missing medication start date is estimated as early as possible up to randomization date, and the missing medication end date is estimated as late as possible. If the medication start date is missing, the onset day will not be imputed in medication listings.

Date of first / last study treatment

Date of first injection is the first non-missing start date of dosing filled in the CRF “Investigational Product” module.

If a patient’s date of the last dose is totally missing or unknown, his/her last visit date will be substituted.

6.4. Unscheduled Assessments

Unscheduled visit measurements may be used to provide a measurement for a baseline or endpoint value if appropriate according to their definition. The measurements may also be used to determine abnormal laboratory or ECG values.

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The determination of baselines and values at the end of treatment for both efficacy and safety variables will be based on scheduled available assessments and unscheduled available assessments.

Extra assessments (laboratory data or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing adverse events) will be included in listings, but not by visit summaries except for the endpoint determination. If more than one laboratory value is available for a given visit, the first observation will be used in summaries and all observations will be presented in listings.

7. MULTIPLICITY CONSIDERATIONS

Adjustments to the significance level for the purposes of multiple testing are not applicable for this study. Statistical analyses for Group 1 and Group 2 will be conducted and reported separately; ie, efficacy results and clinical conclusions from Group 1 will not affect those of Group 2, and vice versa. Therefore, statistical control of overall type I error for the whole study is not planned.

8. INTERIM ANALYSIS

No formal interim analysis is planned.

9. SOFTWARE

All statistical analyses will be done using SAS Version 9.

10. REFERENCES

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11. APPENDIX

11.1. Summary of Statistical Analyses

Efficacy Analysis:

Endpoint	Analysis Populations	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Primary Endpoint						
ORR	PPS	Overall response rate (central review)	95% exact binomial confidence interval using Clopper-Pearson method	Exact binomial test p-value	Yes	ORR based on irRC
Secondary Endpoints						
ORR	PPS	Overall response rate (investigator review)	95% exact binomial confidence interval using Clopper-Pearson method	Exact binomial test p-value	No	No
Duration of response	Patients with best overall response of CR/PR in PPS	From the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date of recurrent or progressive disease (radiographic), or death due to any cause	Kaplan-Meier method	No	Yes	No
Progression-free survival	PPS	From the start of treatment until the first date of recurrent or progressive disease (radiographic), or death due to any cause.	Kaplan-Meier method	No	Yes	No

Endpoint	Analysis Populations	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Overall survival	PPS	From the start of treatment until death due to any cause.	Kaplan-Meier method	No	Yes	No
Quality of life	PPS	Changes scores from day 1 of EORTC-QLQ-C30	Descriptive statistics and longitudinal plots	No	Yes	No

Safety Analyses:

Endpoint	Analysis Populations	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Adverse Events	SAF	Percent of patients by system organ class	Descriptive Statistics	No	Yes for subgroups: age, gender, etc.	% Change from baseline, Δ in % predicted

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VERSION 3.0

Title: A Phase II Study of REGN2810, A Fully Human Monoclonal Antibody to Programmed Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma

Protocol: R2810-ONC-1540

Investigational product: REGN2810 (anti-PD-1 mAb)

Sponsor: Regeneron Pharmaceuticals, Inc.

Study Biostatistician: Bo Gao, PhD

Clinical Study Team Leader: Christina Perry

Study Medical Directors: Matthew Fury, MD, PhD
Elizabeth Stankevich

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The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

Study Biostatistician:

See appended electronic signature page

Bo Gao, PhD
Director, Biostatistics

Study Medical Director:

See appended electronic signature page

Matthew Fury, MD, PhD
Senior Director, Clinical Sciences Oncology

Head of Biostatistics and Data Management:

See appended electronic signature page

Yuhwen Soo, PhD
Vice President, Biostatistics and Data Management

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ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition of Term
ADA	Anti-drug antibody
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BAS	Biomarker analysis set
BCC	Basal cell carcinoma
BLA	Biologics license application
BMI	Body mass index
BOR	Best overall response
BUN	Blood urea nitrogen
CI	Confidence interval
CSR	Clinical study summary
CR	Complete response
CRF	Case report form
CSCC	Cutaneous squamous cell carcinoma
CT	Computed tomography
EAS	Efficacy analysis set
ECG	Electrocardiogram
ECOG	East Cooperative Oncology Group
EOS	End of study
FAS	Full analysis set
ICH	International Council for Harmonisation
irAE	Immune-related adverse event
irRC	Immune-related response criteria

Abbreviation	Definition of Term
IWRS	Interactive web response system
LLOQ	Lower limit of quantification
LDH	Lactate dehydrogenase
MAA	Marketing authorization application
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NE	Not evaluable
NSCLC	Non-small cell lung cancer
PBMC	Peripheral blood mononuclear cell
ORR	Objective response rate
OS	Overall survival
PD	Progression
PD-1	Programmed death-1 (receptor)
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PET	Positron-emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
PT	Preferred term
RCC	Renal cell cancer
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Systems (software)

Abbreviation	Definition of Term
SD	Stable disease
SI	Standard international
SOC	System organ class
t _{1/2}	Beta-phase terminal half life
TEAE	Treatment-emergent adverse event
TILs	Tumor-infiltrating lymphocytes
UV	Ultraviolet
WHODD	World Health Organization drug dictionary
WBC	White blood cell

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study prior to the database lock. The SAP is intended to be a comprehensive and detailed description of strategy and statistical technique to be used to realize the analysis of data for R2810-ONC-1540 study.

This plan may be revised during the study to accommodate protocol amendments and/or to make changes to adapt to unexpected issues in study execution and/or data that affect planned analyses. The final plan, if revised, will document all changes and be issued prior to database lock.

There are three groups in R2810-ONC-1540, Group 1 of patients with metastatic CSCC treated every 2 weeks [Q2W] with REGN2810 3 mg/kg, Group 2 of patients with unresectable locally advanced CSCC treated Q2W with REGN2810 3 mg/kg, and Group 3 of patients with metastatic CSCC treated Q3W with REGN2810 350 mg flat dose. Although living in the same clinical trial, the statistical analyses of the three groups will be conducted independently and summarized separately, except for safety data analyses may be combined at a later stage when deemed appropriate.

1.1. Background/Rationale

1.1.1. Background

Cutaneous squamous cell carcinoma (CSCC) is the second most common malignancy in the United States. A review of national databases indicates that incidence of non-melanoma skin cancers, mostly basal cell carcinoma (BCC) and CSCC, approximately doubled between 1994 and 2006 in the context of an aging population. Most CSCC patients have a favorable prognosis, but annual mortality is approximately 3,900 to 8,800 deaths in the United States.

Surgical resection is the centerpiece of clinical management of CSCC. Radiation therapy for CSCC has also been used in the adjuvant setting. For the small percentage of patients who develop unresectable locally recurrent or metastatic disease, treatment options are limited. Regarding systemic therapies, there is a dearth of data to guide clinical decision-making for oncologists who take care of patients with advanced CSCC. National Comprehensive Cancer Network (NCCN) guidelines do not provide firm recommendations.

Blockade of the PD-1/PD-L1 immune checkpoint pathway is an effective and well tolerated approach to stimulate the immune response, and has achieved significant objective responses in advanced melanoma, renal cell cancer (RCC), non-small cell lung cancer (NSCLC), and other solid tumors. REGN2810 is a high-affinity, fully human, hinge-stabilized IgG4P antibody directed to the PD-1 receptor that potently blocks the interaction of PD-1 with its ligands, PD-L1 and PD-L2.

1.1.2. Rationale

CSCC has several clinical and biological factors that suggest that it is appropriate for the clinical study of inhibition of the PD-1 immune checkpoint: high mutation burden, presence of tumor infiltrating lymphocytes (TILs), association with immunosuppression as a risk factor, evidence of direct immunosuppressive effects of ultraviolet radiation (UV) which predisposes to CSSC, and some clinical efficacy with interferon α 2a-based treatment.

1.2. Study Objectives

1.2.1. Primary Objective

To estimate the clinical benefit of REGN2810 monotherapy for patients with metastatic (nodal or distant) CSCC treated Q2W (Group 1), with unresectable locally advanced CSCC treated Q2W (Group 2), or with metastatic (nodal or distant) CSCC treated Q3W, **respectively**, as measured by objective response rate (ORR) according to central review.

1.2.2. Secondary Objectives

- To estimate the ORR according to investigator review
- To estimate the duration of response (DOR) and progression-free survival (PFS) by central and investigator review, and overall survival (OS)
- To estimate the complete response (CR) rate by central review
- To assess the safety and tolerability of REGN2810
- To assess the pharmacokinetics of REGN2810 (at selective sites only)
- To assess the immunogenicity of REGN2810
- To assess the impact of REGN2810 on quality of life using EORTC QLQ-C30

1.2.3. Exploratory Objective (Group 2 only)

To explore the pharmacodynamic effects of REGN2810 in tumor biopsies obtained at baseline, during treatment, and at progression in CSCC patients treated with REGN2810

- [REDACTED]
- [REDACTED]
- [REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]

1.2.4. Modifications from the Statistical Section in the Final Protocol

This study is expected to be a pivotal trial and will be part of the core of the BLA/MAA submission. Accordingly, revision to this plan will only be made if deemed necessary to the furtherance of the trial objectives. Such revision, if necessary, will be completed prior to the final database lock.

Modifications from the Statistical Section in the protocols are listed below:

- Added some clarifications on the observation period in determining BOR for analysis of primary efficacy endpoint (Section 5)
- Added some clarifications on the extended observation period in reporting duration of response evaluation

1.2.5. Modifications from the Approved Statistical Analysis Plan

This is the third version of the SAP, based on the study protocol R2810-ONC-1540.05 Global Amendment.

The main changes include

1. Adding a cohort (group 3) per protocol amendment 4,
2. Extending TEAE observation period to up to 105 days after the last dose per protocol amendment 2.
3. Adding an interim analysis for patients in group 2 per amendment 5.

2. INVESTIGATION PLAN

2.1. Study Design

There are three study groups for this clinical trial, which will be analyzed independently. For each group, this is a phase II, non-randomized, multi-center pivotal trial evaluating the efficacy and safety of REGN2810.

- Group 1: Patients with metastatic CSCC, treated with REGN2810 3 mg/kg Q2W. These patients are required to have histologic confirmation of distant CSCC metastases (e.g. lung, liver, bone, or lymph node). Group 1 includes patients with both nodal metastatic and distant metastatic disease.
- Group 2: Patients with unresectable locally advanced CSCC, treated with REGN2810 3 mg/kg Q2W. These patients are required to have disease that is considered inoperable or to have medical contraindication to surgery or radiation, or have not achieved disease control with these treatments.
- Group 3: Patients with metastatic CSCC, treated with REGN2810 350 mg Q3W.

2.2. Sample Size and Power Considerations

For Group 1 and Group 3, 50 patients (in each group) are required to provide at least 85% power to reject a null hypothesis of an ORR of 15% at a 2-sided significance level of no more than 5% if the true ORR is 34%. For Group 2, 72 patients are required to provide at least 90% power to reject a null hypothesis of an ORR of 25% at a 2-sided significance level of no more than 5% if the true ORR is 44%.

The sample sizes for each group were selected such that the lower limit of the two-sided 95% confidence interval (CI) of the estimated ORR will be clinically meaningful. The non-clinically meaningful ORR of 15% for Group 1 and Group 3 will be excluded using the lower limit of 95% CI if the observed ORR is around 28.0% or more; ie, the ORR for Group 1 and/or Group 3 is significantly different from 15%. The non-clinically meaningful ORR of 25% for Group 2 will be excluded using the lower limit of 95% CI if the observed ORR is around 36.1% or more; ie, the ORR for Group 2 is significantly different from 25% (see [Table 8](#) and [Table 9 of the protocol](#)).

The sample sizes are further increased by 5% to account for patients who withdraw prematurely from the study. Hence, the total sample sizes will be 53 patients for Group 1, 76 patients for Group 2, and 53 patients for Group 3, for a total of 182 patients. The sample size calculation was based on the exact binomial test using nQuery Advisor version 7.0 ([Elashoff 2007](#)).

2.3. Study Plan

After a screening period of up to 28 days, Group 1 and Group 2 patients will receive up to twelve 56-day (8-week) treatment cycles for a total of up to 96 weeks of treatment. Each patient will receive 3 mg/kg REGN2810 intravenously on days 1, 15±3, 29±3, and 43±3 during each treatment cycle. Tumor assessments will be made at the end of each treatment cycle. Extensive safety evaluations will occur on day 1 of each cycle; routine safety evaluations will be conducted at each REGN2810 dosing visit.

Group 3 patients will receive up to six 63-day (9-week) treatment cycles for up to 54 weeks of treatment. Each patient will receive 350 mg REGN2810 intravenously on days 1, 22±3, and 43±3 during each treatment cycle. Tumor assessments will be made at the end of each treatment cycle. Extensive safety evaluations will occur on day 1 of each cycle, with routine safety evaluations to be conducted at each REGN2810 dosing visit.

A patient will receive treatment until the treatment period (96 weeks in Group 1 and Group 2; 54 weeks in Group 3) is complete, or until disease progression, unacceptable toxicity, withdrawal of consent, or confirmed complete response (CR). Group 1 and Group 2 patients with confirmed CR after a minimum of 48 weeks of treatment may elect to discontinue treatment and continue with all relevant study assessments (eg, efficacy assessments). Patients in all groups who do not experience progressive disease (PD) will be followed for an additional nontreatment period of up to approximately 6 months with scans performed every 8-12 weeks.

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials ([ICH 1998](#)), the following population sets will be used for statistical analysis. A patient is deemed eligible and enrolled after the patient completes the screening process and the investigator deems that the subject is eligible, and the investigator orders study drug in interactive web response system (IWRS). At that point, the patient's status in IWRS changes from "in screening" to "enrolled." A patient is not deemed eligible until he/ she is enrolled in IWRS.

3.1. Full Analysis Set (FAS)

The full analysis set (FAS) includes all enrolled patients who have passed screening and are deemed to be eligible for this study. The FAS by group is the primary analysis population for the efficacy endpoints.

3.2. Safety Analysis Set (SAF)

The safety analysis set (SAF) includes all enrolled patients who have received at least one dose of REGN2810. Treatment compliance/administration and all clinical safety variables will be analyzed or summarized using the SAF.

3.3. PK Analysis Set (PKA)

The pharmacokinetic analysis set (PKA) includes all patients who have received any REGN2810 and who have at least one non-missing drug concentration after the first dose of study drug.

3.4. Anti-Drug Antibody Set (ADA)

The anti-drug antibody (ADA) set includes all patients who have received any REGN2810 and who have at least one post-dose ADA result.

3.5. Biomarker Analysis Set (BAS)

The biomarker analysis set (BAS) includes all patients who have received any REGN2810 and who have at least one sample assayed.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic and baseline characteristics variables will be summarized:

- Age at screening in years (quantitative and qualitative variable: <65 , ≥ 65 years)
- Sex (Male, Female)
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White and Other)
- Ethnicity (Hispanic/Latino or not)
- Weight (kg)
- Height (cm)
- Body mass index (BMI) calculated from weight and height: $\text{weight (kg)} / [\text{height (m)}]^2$
- ECOG performance status (0, 1) For group 1 and group 3, Type metastatic disease (Distant or Nodal only).

4.2. Medical History

Medical history will be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) according to the latest available version of MedDRA.

Oncology history:

- Primary diagnosis
- Time from initial diagnosis to study entry

- Histologic gradeCancer stages at initial diagnosis and at screening
- Prior anticancer systemic therapy
- Prior radiotherapy
- Duration of latest anticancer systemic therapy

4.3. Pre-Treatment/Concomitant Medication

Medications/Procedures will be recorded from the day of informed consent until the end of study (EOS) visit. Medications will be coded to the anatomical therapeutic chemical (ATC) level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of WHO Drug Dictionary (WHODD). Patients will be counted once in all ATC categories linked to the medication.

Pre-treatment medications/procedures: medications taken or procedures performed prior to administration of the study drug, particularly, prior cancer related surgery, prior cancer related radiotherapy, and prior cancer related systemic therapy: chemotherapy, targeted therapy, immunotherapy and others.

Concomitant medications/procedures: any treatment administered from the time of informed consent until 30 days after the last study treatment will be considered concomitant treatment. This includes medications and other therapies for which administration started before the study and will continue during the study, as well as any therapies started in the 6 month follow-up period to treat a study drug related AE. All concomitant treatments must be recorded in the study case report form (CRF) with the generic name, dose, dose unit, frequency, indication, and start/stop date, as appropriate.

4.4. Rescue Medication/Prohibited Medication

While participating in this study, a patient may not receive any standard or investigational agent for treatment of a tumor other than REGN2810 as monotherapy. Any other medication which is considered necessary for the patient's welfare, and which is not expected to interfere with the evaluation of the study drug, may be given at the discretion of the investigator.

Patients using immunosuppressive doses (>10 mg per day of prednisone or equivalent) of systemic corticosteroids other than for corticosteroid replacement will not be eligible for the study. It is recommended that patients do not receive systemic corticosteroids such as hydrocortisone, prednisone, prednisolone (Solu-Medrol®) or dexamethasone (Decadron®) at any time throughout the study except in the case of a life-threatening emergency and/or to treat an immune-related adverse event (irAE). Physiologic replacement doses of systemic corticosteroids are permitted, even if >10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

4.5. Efficacy Variable

4.5.1. Primary Efficacy Variable

Overall response is based on **central-reviewed evaluation** at each time point at which a response assessment occurs using the RECIST version 1.1 ([Appendix 1](#) of the protocol) or the composite response criteria ([Appendix 2](#) of the protocol).

Best overall response (BOR) is determined once all the data for the patient are known. The best overall response is the best response recorded during the study. Best overall response of CR or PR must be confirmed by consecutive evaluations of overall response of CR or PR at time points at least 4 weeks apart. Best overall response of SD must have met the response SD criteria at least once ≥ 39 days (6 weeks*7 days/week -3 days) after start of study treatment. Best overall response of (early) PD does not require confirmation using the RECIST or the composite response criteria. The best overall response for patients who do not have any post-baseline tumor assessment will be not evaluable (NE).

Objective response rate (ORR) is determined by the proportion of patients with best overall response of CR or PR in the FAS by group. Patients with best overall response of NE will be considered as not reaching an objective response of CR or PR.

4.5.2. Secondary Efficacy Variables

ORR based on investigator-assessed evaluation is also derived from the overall response that is based on **investigator-assessed evaluation** at each time point at which a response assessment occurs using the RECIST version 1.1 ([Appendix 1](#) of the protocol) or the composite response criteria ([Appendix 2](#) of the protocol).

Duration of response is determined for patients with best overall response of CR or PR. Duration of response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date of recurrent or progressive disease (radiographic), or death due to any cause. Patients who never progress while being followed will be censored at the last valid tumor measurement. DOR by **central-reviewed evaluation** is the key secondary endpoint.

Progression-free survival (PFS) is measured from the start of treatment until the first date of recurrent or progressive disease (radiographic), or death due to any cause. Patients who never progress while being followed will be censored at the last valid tumor measurement. If a patient has no post-baseline evaluation, the patient will be censored at first treatment date.

Overall survival (OS) is measured from the start of treatment until death due to any cause. Patients who do not have a survival event will be censored at the last date that patient is documented to be alive. As many patients may receive subsequent therapy after disease progression, a variant of OS will also be defined as censoring patients who do not have a survival event at the first date of a subsequent therapy is taken.

For all of the above time-to-event variables, the time to event (day) is the date of event/censor - the date of first study treatment+ 1.

CR rate is determined by the proportion of patients with best overall response of CR after tumor biopsy confirmation. Patients with best overall response of NE will be considered as not reaching an objective response of CR.

Patient-reported quality of life is measured by the EORTC QLQ-C30 ([Appendix 1](#) of protocol) on day 1 of every cycle ([Aronson 1993](#)). The global health status/QoL, five functional scales (physical, role, cognitive, emotional and social), and three symptom scales (fatigue, pain, nausea and vomiting) and a number of single items assessing additional symptom commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease will be computed using the QLQ-C30 scoring procedures ([Fayers 2001](#)). Change scores are defined as change of summary score of EORTC QLQ-C30 from day 1 of first treatment cycle.

4.5.3. Exploratory Biomarker Variables

Biomarker variables for exploratory analyses may include:

- Baseline PD-L1 expression by IHC on tumor cells and immune cells(as determined by PD-L1 IHC 22C3 pharmDx assay)
- Fold-change in mRNA expression of genes expressed in tumor tissue
- Percent change in number of TILs (CD8+ T cells, CD4+ T cells, T regulatory cells, and tissue permitting, other subtypes such as B cells, myeloid-derived cells, NK cells, etc.) and descriptive change in distribution of TILs in respect to tumor tissue and stroma
- Percent change in expression levels (mRNA and/or protein) of PD-L1, GITR, and LAG-3, and possibly other check-point modulators
- Change in number and type of genetic mutations in known oncogenes and potential tumor neoantigens
- Change in tumor mutation burden

4.6. Safety Variables

Patient safety will be assessed through the collection of reported adverse events (AEs), clinical laboratory data, vital signs, ECG and physical exam. Unless otherwise noted, the baseline value is defined as the last available value before the first dose of study treatment.

4.6.1. Adverse Events and Serious Adverse Events

Adverse events and serious adverse events will be collected from the time of informed consent signature and then at each visit until the end of the study. All adverse events are to be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) according to the latest available version of Medical Dictionary for Regulatory Activities (MedDRA).

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. A Serious Adverse Event (SAE) is an AE that is classified as serious according to the criteria specified in the protocol.

The severity of AEs (including test findings classified as AEs) will be graded using the current version of the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grading system. Adverse events not listed in the NCI-CTCAE will be graded according to the following scale:

1. (Mild): Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2. (Moderate): Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
3. (Severe): Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
4. (Life-threatening): Life-threatening consequences; urgent intervention indicated.
5. (Death): Death related to AE.

* Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The relationship of AEs to study drug will be assessed by the investigator and be determined based on protocol specified criteria.

Laboratory results, vital signs, or ECG abnormalities are to be recorded as AEs if they are medically relevant: symptomatic, requiring corrective therapy, leading to treatment discontinuation and/or fulfilling a seriousness criterion.

4.6.2. Adverse Events of Special Interest

An AE of special interest (AESI) must be reported within 24 hours of identification. AEs of special interest for this study include:

- Grade 2 or greater infusion-related reactions
- Grade 2 or greater allergic/hypersensitivity reactions
- Grade 3 immune-related toxicities (irAE)
- An irAE of any grade in a patient previously treated with a PI 3-K inhibitor

Note: An irAE can occur shortly after the first dose, several months after the last dose of treatment, or any time in-between. All AEs of unknown etiology associated with drug exposure should be evaluated to determine possible immune etiology. If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an AE as an irAE.

4.6.3. Laboratory Safety Variables

The clinical laboratory data consists of serum chemistry, hematology, and urinalysis. Clinical laboratory values will be converted to standard international (SI) units and grouped by function in summary tables. Conventional unit may be provided. Functions are defined as follows:

Blood Chemistry

- Sodium
- Phosphorus
- Alanine aminotransferase (ALT)
- Potassium
- Glucose
- Aspartate aminotransferase (AST)
- Chloride
- Albumin
- Total bilirubin
- Bicarbonate
- Creatinine
- Alkaline phosphatase (ALP)
- Calcium
- Blood urea nitrogen (BUN)
- Lactate dehydrogenase (LDH)
- Magnesium
- Uric acid

Hematology

- Hemoglobin
- White blood cells (WBCs)
- Platelet count
- Differential: Neutrophils, Lymphocytes, Monocytes

Urinalysis

- Glucose
- pH
- Ketones
- Blood
- Specific gravity
- Spot urine protein

Immune safety tests rheumatoid factor (RF), thyroid-stimulating hormone (TSH), C-reactive protein (CRP), and antinuclear antibody (ANA) will also be summarized

4.6.4. Vital Signs

Vital signs will be collected according to [Table 5](#), [Table 6](#) and [Table 7 Study Schedule of the protocol](#):

- Body temperature (°C)
- Resting systolic blood pressure and diastolic blood pressure (mmHg)
- Pulse (beats/minute)
- Respiratory rate (breaths/minute)

4.6.5. 12-Lead Electrocardiography (ECG)

A standard 12-lead ECG will be performed at time points according to [Table 5](#), [Table 6](#) and [Table 7 of the protocol](#). The ECG is to be recorded in triplicate. The ECG strips or reports will be retained with the source. The ECG will be reviewed by the investigator (paper or electronic tracing) and will be available for comparison with subsequent ECGs by the investigator:

- PR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- Heart Rate (BPM; recorded from the ventricular rate)

Corrected QT (QTc) will be calculated from the QT interval and RR by two methods:

- Bazett's correction = $QT/[RR^{1/2}]$
- Fredericia's Correction = $QT/[RR^{1/3}]$

Any ECG finding that is judged by the investigator as a clinically significant change (worsening) compared to the baseline value will be considered an AE, recorded, and monitored.

4.6.6. Physical Examination Variables

A thorough complete or limited physical examination will be performed at visits specified in Table 5, Table 6 and Table 7 of the protocol. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

Complete physical examination will include examination of skin, head, eyes, nose, throat, neck, joints, lungs, heart, pulse, abdomen (including liver and spleen), lymph nodes, and extremities, as well as a brief neurologic examination. Limited physical examination will include lungs, heart, abdomen, and skin.

4.7. Pharmacokinetic Variables and Anti-Drug Antibody Variables (ADA)

Serum concentration of REGN2810 will be assessed at multiple time points throughout the study treatment and follow-up periods, and descriptive PK variables will include:

- C_{trough} – pre-infusion concentration
- C_{eoi} – concentration at end-of-infusion
- t_{eoi} – time of end-of-infusion

Anti-drug antibody variables include status (positive or negative) and titer as follows:

- Total number of patients whose response in the ADA assay is negative at all times
- Total number of patients whose response in the ADA assay is positive at any time
- Pre-existing immunoreactivity – defined either as a positive ADA assay response at baseline with all post-treatment ADA assay results negative, or a positive assay response at baseline with all post-treatment ADA assay responses less than 4-fold over baseline titer levels
- Treatment emergent – defined as any post-treatment positive ADA assay response when the baseline is ADA negative. Treatment emergent responses will be further characterized into persistent, transient and indeterminate in patients with ADA assay results for over at least a one year period.
 - Persistent response – 2 consecutive treatment-emergent positive responses in the ADA assay that span at least a 16 week period during the treatment period and follow-up phase, if any.
 - Indeterminate response – a treatment-emergent positive response in the ADA assay only at the last ADA sampling timepoint analyzed.
 - Transient response – any treatment-emergent positive response in the ADA assay that is not considered persistent or indeterminate.

- Treatment boosted – defined as any post treatment positive ADA assay response that is greater than 4-fold over the baseline titer level when baseline is positive in the ADA assay.
- Titer values (Titer value category):
 - Low (titer < 1,000)
 - Moderate (1,000 ≤ titer ≤ 10,000)
 - High (titer > 10,000)

5. STATISTICAL METHODS

For continuous variables, descriptive statistics will include the following: the number of patients reflected in the calculation (n), mean, median, standard deviation, minimum, and maximum. In addition, 25th percentile and 75th percentile will be provided.

For categorical or ordinal data, frequencies and percentages will be displayed for each category. The denominator will be determined by the analysis population used for the summary.

For time-to-event variables, median time-to-event (and the survival rate at a fixed time point) and its 95% confidence intervals will be summarized by the Kaplan-Meier method.

Statistical analysis for efficacy will be conducted independently for each group.

The data cut-off for primary efficacy analysis will be six months after the last patient starts the treatment, plus at most three additional months if a tumor response of CR or PR occurring at six months need be confirmed. The study will continue for data collection of tumor response, duration of response and safety after primary efficacy analysis. The statistical analysis of duration of response will be updated after four additional months to allow for sufficient data maturation.

5.1. Demographics and Baseline Characteristics

Patient demographics and baseline characteristics will be summarized by group based on the FAS population.

Assessments made before the first dose of REGN2810 will be used as baseline measurements for the purposes of statistical analysis and reporting unless otherwise specified.

5.2. Medical History

Medical history will be listed which includes SOC, PT, investigator verbatim and start and end dates and summarized by SOC and PT. Tables will be sorted by decreasing frequency of SOC followed by PT.

Cancer diagnosis will be listed and summarized by primary cancer diagnosis, histological grade and stages.

Prior cancer related surgery will be listed including type of procedure and date of surgery and summarized by prior surgery status. Prior cancer related systemic therapy will be listed including systemic therapy type, name of drug and start and end dates and summarized by systemic therapy type. Prior cancer related radiotherapy will be listed by site, total dose and start and end dates and summarized by prior radiotherapy status.

5.3. Prior/Concomitant Medications

Prior/concomitant medications will be listed including generic name and ATC levels 2 and 4, indication, study day onset (for medications started before treatment, the study day onset is defined as date of medication start - date of the first dose; for medications started on or after treatment, the study day onset is defined as date of medication start - date of the first dose+1), the study end date (defined similarly as for study onset day), ongoing status, dose, frequency, and route. Number and proportion of subjects taking concomitant medications sorted by decreasing frequency of ATC Level 2 and ATC level 4.

5.4. Subject Disposition

For subject disposition, the following summaries by table will be provided:

- The total number of screened patients
- The total number of patients in each analysis set
- The total number of patients who discontinued the study treatment and the reasons for the treatment discontinuation
- The total number of patients who discontinued the study, and the reasons for the study discontinuation

Listing of patient disposition will include dates of the first and the last REGN2810 administration, date of the end of treatment and end of study visits, and reasons for treatment and study discontinuation.

5.5. Protocol Deviations

Protocol deviations will be defined in separate protocol deviation definition document. Listing of all patients with protocol deviations and the reason of deviation will be provided. The major protocol deviation, such as violation of inclusion/exclusion criteria; post-enrollment deviations which will impact assessment of efficacy or safety endpoints, will be determined before database lock and be summarized by group.

5.6. Measurement of Compliance

Compliance with REGN2810 treatment will be calculated as follows:

$$\text{Treatment Compliance} = \frac{(\text{Number of doses of REGN2810 administered during treatment period})}{(\text{Number of doses of REGN2810 planned to be administered during period})} \times 100\%$$

where temporary dose discontinuation is ignored.

The percentage of subjects who have <60%, 60-80%, 80-100%, and >100% compliance will be summarized for each group.

5.7. Exposure to Investigational Product

Exposure to REGN2810 will be examined for each subject and the following variables will be summarized:

- The total number of study doses administered
- The total dosage of REGN2810 administered
- Duration of treatment exposure (in weeks) calculated as the minimum of
 1. [date of last dose – date of first dose + 14 days based on Q2 weekly dosing schedule] / 7 for Group 1 and Group 2;
[date of last dose – date of first dose + 21 days based on Q3 weekly dosing schedule] / 7 for Group 3
or
 2. [date of clinical data cut-off or date of death – date of first dose + 1] / 7
- The number of subjects exposed to REGN2810 will be presented by specific time point periods for each group. The time periods of interest are weeks 4, 8, 12, 16, 24, 48, 72
- The actual dose intensity (mg/kg/week) = total dose received per kg (mg/kg) / duration of treatment exposure (week) for Group 1 and Group 2;
The actual dose intensity (mg /week) = total dose received (mg) / duration of treatment exposure (week) for Group 3
- The relative dose intensity = actual dose intensity / planned dose intensity,
 - Planned dose intensity (mg/kg/week) = planned dose (mg/kg) / 2 for Group 1 and Group 2;
 - Planned dose intensity (mg /week) = planned dose (mg) / 3 for Group 3

For patients who also receive REGN2810 as re-treatment which starts more than 30 days after their last regular REGN2810 treatment, the retreatment dose will not be included in summary of on-treatment exposure, instead, they will be listed and summarized if necessary.

5.8. Analyses of Efficacy Variables

5.8.1. Analysis of Primary Efficacy Variable

Best overall response: CR/PR/SD/PD/NE will be summarized by group:

- Not evaluated response includes the missing and unknown response
- CR/PR must be confirmed by repeated assessments no less than 4 weeks apart
- SD criteria must be met at least once for a minimum duration of 39 days (7 days/week * 6 weeks – 3 days) after first dose date

Patients with the best overall response of NE will be considered as non-responder (CR/PR).

The primary analysis of efficacy is based on the exact binomial confidence interval approach of ORR. The two-sided 95% exact binomial confidence intervals will be derived using the Clopper-Pearson method (Clopper 1934). If the lower limit of 95% confidence interval of observed ORRs excludes 15% for Group 1 and Group 3, or excludes 25% for Group 2, the study treatment is deemed effective for that group, respectively.

In addition, ORR along with two-sided 95% exact binomial confidence intervals for all patients treated with REGN2810 3 mg/kg will be presented. ORR in patients whose CSCC disease has been confirmed by central pathology review will also be summarized.

The primary endpoint of ORR will also be summarized by pooling the objective response observed in CSCC patients in this study with object response data of CSCC patients in Regeneron study R2810-ONC-1423 to satisfy regulatory requirements from certain regions. Details will be provided in separate SAP for integrated efficacy analysis.

5.8.2. Analysis of Secondary Efficacy Variables

ORR derived from the overall response that is based on **investigator-reviewed evaluation** will be analyzed similarly as primary efficacy variable.

Duration of response will be summarized by median and range, and displayed by Kaplan-Meier approach.

PFS will be summarized by median (if observed) and PFS rate at milestone time points (12, 24, 36 and 48 weeks, etc), and displayed by Kaplan-Meier approach.

OS will be summarized by median (if observed) and OS rate at milestone time points (weeks 24, 48, and 96 weeks, etc), and displayed by Kaplan-Meier approach. A variant of OS defined by censoring patients at the start date of subsequent therapy will be summarized and displayed by Kaplan-Meier approach as a sensitivity analysis.

Depth of tumor response will be displayed using waterfall plot and spider plot and summarized by descriptive statistics.

CR rate with 95% confidence interval will be estimated using the Clopper-Pearson method. Absence of residual CSCC in biopsy samples from patients with locally advanced CSCC achieving a clinical response to REGN2810, as measured by independent central pathological review, will be summarized descriptively.

5.8.3. Analysis of Quality of Life Variables

The quality of life of patients will be repeatedly measured by the EORTC QLQ-C30 at the day 1 of each treatment cycle. The change scores of each component of QLQ-C30 will be summarized descriptively at each post-baseline time point. The summary scores of each component of QLQ-C30 will also be graphically depicted by longitudinal plots. Partial missing data in QLQ-C30 will be taken care by the scoring algorithm, no additional imputations will be conducted for missing data.

5.8.4. Subgroup Efficacy Analysis

Subgroup efficacy analyses will be performed based on the following factors, respectively:

- gender (Male, Female)
- age group (<65, ≥65)
- race (White, Non-white)
- geographical region (North American, Europe and Rest of World)
- the number of prior systemic therapies
- ECOG (0, 1)
- Prior systemic anticancer therapy (Yes, No)
- Prior radiotherapy (Yes, No)
- For Group 1 and Group 3 only: Metastatic status (Distant or Nodal only)

However, as such analyses may not have enough power for hypothesis tests, the analysis will be exploratory in nature.

5.9. Analysis of Safety Data

The analysis of safety and tolerance will be performed on the SAF, as defined in Section 3.2. The safety analysis will be based on the reported AEs and other safety information (clinical laboratory evaluations, vital signs and 12-lead ECG). The analysis will comprise the basis upon which conclusions will be drawn regarding the REGN2810. The AE of special interest will be determined by the list provided by medical monitors.

Period of observation: The observation period will be divided into three segments: pre-treatment, on-treatment and post-treatment.

- The pre-treatment period is defined as the time between when the subjects give informed consent and before the start of REGN2810 treatment.
- The on-treatment period is defined as the time from first dose of REGN2810 up to 105 days after the last dose of REGN2810. For patients who also receive REGN2810 as re-treatment which starts more than 30 days after their last regular REGN2810 treatment, the on-treatment period ends at the earlier day of 105 days after the last regular REGN2810 dose and the day before their first REGN2810 re-treatment dose.
- The post-treatment period is defined as the time starting 1 days after the on-treatment period.

Day 1 is the first day of patient receiving REGN2810 treatment, Day –1 is the day before, and there is no Day 0.

The safety analysis will be concentrated on events occur during on-treatment period. Events occur during post-treatment period, or during REGN2810 re-treatment will be listed and summarized if necessary.

The summary of safety results will be presented by group and in overall total.

5.9.1. Adverse Events

The verbatim text, the preferred term (PT), and the primary system organ class (SOC) will be displayed in subject listings. Summaries that include frequencies and proportions of patients reporting AEs will include the PTs and the SOC.

- Pre-treatment AEs are defined as AEs that developed during the pre-treatment period.
- Treatment-emergent AEs (TEAEs) are defined as AEs that developed or worsened during the on-treatment period and any immune-related AEs that occurs anytime after the first R2810 dose.
- Post-treatment AEs are defined as AEs that developed or worsened during the post-treatment period and are not considered drug related by the investigator.

The focus of adverse event reporting in the CSR will be on TEAEs. For details on handling missing data and partial dates, see Section 6.

Summaries of adverse events will include: TEAEs, Treatment related TEAEs, Serious TEAEs, Treatment-related Serious TEAEs, AESI (grade 2 or greater infusion-related reactions, grade 2 or greater allergic/hypersensitivity reactions, and grade 3 irAEs), immune-related AEs, and infusion related AEs. For TEAEs, the following will be summarized:

- The number and proportions of patients reporting at least 1 TEAE, presented by SOC and PT
- TEAEs by severity (CTCAE, version 4.03 grade), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT
- TEAEs occurring in > 5% patients, presented by PT
- TEAEs leading to permanent treatment discontinuation, presented by SOC and PT
- TEAEs leading to death, presented by SOC and PT

For each TEAE summary presented by SOC and PT, the summary table will be sorted by decreasing frequency of SOC and PT. For TEAE summary presented by PT, the summary table will be sorted by decreasing frequency of PT.

The irAEs reported by investigator will be summarized. Additionally, irAEs identified by the sponsor will be summarized. The sponsor-defined irAEs are listed in [Appendix 2](#). The list may be updated to include all possible irAEs. All irAEs occurred during the on-treatment and post-treatment period will be included.

For AE listings, the following variables will be displayed:

- Age/gender/race
- Verbatim Term
- PT
- SOC
- AE start date and end date/ongoing (and corresponding study day)
- AE duration
- Relationship to study drug: unrelated or related
- Seriousness (Serious AE or not)
- National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade: mild, moderate, severe, life-threatening or death

- Action taken: none, dose decreased, dose temporarily stopped or discontinued

Treatment: none, medication, surgery or others

- Outcome: recovered/resolved, recovered/resolved with residual effects, recovering/resolving, not recovered/not resolved, fatal, or unknown

Counts will be provided for each patient within each SOC and PT. Percentages will be calculated using the number of patients from the SAF in each group.

5.9.2. Clinical Laboratory Measurements and Vital Signs

Listings of laboratory values, normal ranges, grade, by group, date, and visit/cycle will be provided. For numeric lab variables and change from baseline to each visit/cycle and overall will be summarized. Listings of abnormal lab values and clinical significant (Yes/No) by patient and visit/cycle will also be constructed.

Summary tables for worst laboratory values with NCI CTCAE v4.03 all grade and grade ≥ 3 observed during on-treatment period will be generated.

Summary of Shift tables from baseline to worst NCI CTCAE v4.03 grade observed during on-treatment period will be generated.

The shift tables include:

- Overall and individual Hematologic Test (Hemoglobin, Platelets, WBC)
- Overall and individual Liver Function Test: (AST, ALT, ALP, Total Bilirubin and Albumin)
- Overall and individual Electrolytes (Sodium, Potassium, Magnesium, Calcium, Chloride, Bicarbonate, Phosphorus)

5.9.3. Analysis of Vital Signs

Vital signs (pulse, sitting blood pressures, and temperature) will be listed and summarized by Baseline and change from Baseline to each scheduled assessment time with descriptive statistics.

5.9.4. Analysis of 12-Lead ECG

ECG parameters (P-R interval, QT interval, QTc interval, QRS interval, Ventricular rate and Heart rate) will be listed and summarized by Baseline and change from Baseline to each scheduled assessment time with descriptive statistics.

ECG status (i.e. normal, abnormal) will be reported. Shift tables will be provided to present the post-baseline status according to the baseline status (normal or missing / abnormal) by group.

5.9.5. Physical Exams

Physical examination findings at baseline as well as post-treatment abnormal findings by body system and status (normal, abnormal and not done) will be provided with Listing.

5.10. Analysis of Pharmacokinetic and Antibody Data

5.10.1. Analysis of Pharmacokinetic Data

Serum concentration of REGN2810 will be assessed at multiple time points throughout the study treatment and follow-up periods, and the PK variables will be determined.

Summaries of study drug concentrations will be presented by nominal time point (ie, the time points specified in the protocol) and group. Pharmacokinetic variables, including C_{eoi} , C_{trough} , and t_{eoi} , will be presented as individual values with descriptive statistics.

5.10.2. Analysis of Anti-Drug Antibody Data

Formation of ADA will be assessed in individual patients and per group as follows:

- Possible relationship between changes in PK profile and treatment-emergent positive responses in the ADA assay will be assessed to evaluate a potential impact of anti-REGN2810 antibodies on drug exposure.
- Possible relationship between AEs and treatment-emergent positive responses in the ADA assay will be assessed to evaluate a potential impact of anti-REGN2810 antibodies on the incidence of Grade 3 and 4 AEs, atypical AEs, and SAEs.

Cases of ADA positivity will be listed and summarized as appropriate. Analysis of ADA data will be provided in a separate report.

5.10.3. Analysis of Exploratory Biomarker Data

Biomarker data will be analyzed using standard scientific methods and summarized by descriptive statistics and plots. Comparative analysis of biomarker data with parent study (R2810-ONC-1423) may be performed using paired t -test or nonparametric Wilcoxon signed-rank test or Chi-square test. Correlative analysis with clinical response may be performed using correlation coefficient, box plot and scatter plot, and basic regression models. Both comparative analysis and correlative analysis will be exploratory in nature and may be provided either as an appendix to CSR or in a separate report.

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the Baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of investigational product.

6.2. Data Handling Convention for Efficacy Variables

Patients who are deemed NE according to RECIST version 1.1. or inevaluable by the composite response criteria will be considered as not reaching PR/CR in calculating ORR, i.e. they are not considered as responders in the numerator of ORR, but they are counted in the denominator of ORR.

6.3. Data Handling Convention for Missing Data

No missing data imputation is planned in this study unless specified otherwise.

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

Medication missing/partial dates

To determine whether a medication is prior, concomitant or post-treatment medication, the missing medication start date is estimated as early as possible up to date of the first study treatment, and the missing medication end date is estimated as late as possible. If the medication start date is missing, the onset day will not be imputed in medication listings.

Date of first / last study treatment

Date of first infusion is the first non-missing start date of dosing filled in the CRF “Investigational Product” module.

If a patient’s date of the last dose is totally missing or unknown, his/her last visit date will be substituted.

6.4. Unscheduled Assessments

Unscheduled visit measurements may be used to provide a measurement for a baseline or endpoint value if appropriate according to their definition. The measurements may also be used to determine abnormal laboratory or ECG values.

The determination of baselines and values at the end of treatment for both efficacy and safety variables will be based on scheduled available assessments and unscheduled available assessments.

Extra assessments (laboratory data or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing adverse events) will be included in listings, but not by visit summaries except for the endpoint determination. If more than one laboratory value is available for a given visit, the first observation will be used in summaries and all observations will be presented in listings.

7. MULTIPLICITY CONSIDERATIONS

Adjustments to the significance level for the purposes of multiple testing are not applicable for this study. Statistical analyses of efficacy for each group will be conducted and reported separately; ie, efficacy results and clinical conclusions from one Group will not affect those of other Groups, and vice versa. Therefore, statistical control of overall type I error for the whole study is not planned. There is no multiplicity adjustment for secondary endpoint.

8. INTERIM ANALYSIS

At the time of the planned efficacy analysis for Group 1 (6 months after last patient, first dose), an interim analysis of efficacy for Group 2 patients will be performed in order to better assess the risks and benefits of REGN2810 in CSCC. This analysis will be restricted to Group 2 patients with potential for adequate follow up, defined as patients who have opportunity to receive approximately 9 months of study treatment at the time of the interim analysis.

For regions where alpha spending is not required: For this planned interim analysis, the overall response rate and associated 95% confidence interval will be summarized. As the primary objective of this the interim analysis is point estimation on ORR and characterizing the precision of point estimation, there is no hypothesis testing associated with this interim analysis. Also, no decisions will be made regarding study conduct associated with the interim analysis. Therefore, Type I error adjustment is not applicable for this planned interim analysis.

For regions where alpha spending is required: fFr this interim analysis on group 2 patients, two-sided alpha of 0.0001 will be allocated for interim analysis and two-sided alpha of 0.0499 will be preserved for the final analysis. Correspondingly, for the interim analysis of primary endpoint of ORR in group 2 patients, the precision of ORR will be estimated by adjusted and two-sided 99.99% exact confidence interval. The un-adjusted and two-sided 95% exact confidence interval will also be reported at the time of interim analysis. At the time of the final analysis for group 2 patients, both adjusted 95.01% and un-adjusted 95% exact confidence interval will be reported.

For other efficacy endpoints in group 2 patients, only two-sided 95% exact confidence interval will be presented both at the interm and at the final analysis.

9. SOFTWARE

All statistical analyses will be done using SAS Version 9.2 or above.

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APPENDIX 1. SUMMARY OF STATISTICAL ANALYSES

Efficacy Analysis:

<i>Endpoint</i>	<i>Analysis Populations</i>	<i>Primary Analysis</i>	<i>Statistical Method</i>	<i>Supportive Analysis</i>	<i>Subgroup Analysis</i>	<i>Other Analyses</i>
<i>Primary Endpoint</i>						
<i>ORR</i>	<i>FAS</i>	<i>Overall response rate (central review)</i>	<i>95% exact binomial confidence interval using Clopper-Pearson method</i>	<i>Exact binomial test p-value</i>	<i>Yes</i>	<i>No</i>
<i>Secondary Endpoints</i>						
<i>ORR</i>	<i>FAS</i>	<i>Overall response rate (investigator review)</i>	<i>95% exact binomial confidence interval using Clopper-Pearson method</i>	<i>Exact binomial test p-value</i>	<i>No</i>	<i>No</i>
<i>Duration of response</i>	<i>Patients with best overall response of CR/PR in FAS</i>	<i>From the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date of recurrent or progressive disease (radiographic), or death due to any cause</i>	<i>Kaplan-Meier method</i>	<i>No</i>	<i>Yes</i>	<i>No</i>
<i>Progression-free survival</i>	<i>FAS</i>	<i>From the start of treatment until the first date of recurrent or progressive disease (radiographic), or death due to any cause.</i>	<i>Kaplan-Meier method</i>	<i>No</i>	<i>No</i>	<i>No</i>
<i>Overall survival</i>	<i>FAS</i>	<i>From the start of treatment until death due to any cause.</i>	<i>Kaplan-Meier method</i>	<i>No</i>	<i>No</i>	<i>No</i>
<i>Quality of life</i>	<i>FAS</i>	<i>Changes scores from day 1 of EORTC-QLQ-C30</i>	<i>Descriptive statistics and longitudinal plots</i>	<i>No</i>	<i>No</i>	<i>No</i>

Safety Analyses:

<i>Endpoint</i>	<i>Analysis Populations</i>	<i>Primary Analysis</i>	<i>Statistical Method</i>	<i>Supportive Analysis</i>	<i>Subgroup Analysis</i>	<i>Other Analyses</i>
<i>Adverse Events</i>	<i>SAF</i>	<i>Percent of patients by system organ class</i>	<i>Descriptive Statistics</i>	<i>No</i>	<i>No</i>	<i>No</i>

APPENDIX 2. DEFINITION OF ADVERSE EVENTS OF SPECIAL INTEREST AND OTHER SIGNIFICANT ADVERSE EVENTS

AEs of special interest (AESI) for this study include:

- Grade 2 or greater infusion-related reactions
- Grade 2 or greater allergic/hypersensitivity reactions
- Grade 3 immune-related toxicities (irAE) (as indicated on the eCRF)
- An irAE of any grade in a patient previously treated with a PI 3-K inhibitor

Infusion Related Reaction is any AE that occurs during or within 2 hours after the infusion is completed.

Immune Related Adverse Event (irAEs) is any AE with unknown etiology associated with drug exposure and consistent with an immune phenomenon. All irAEs occurred during the on-treatment period and post-treatment period will be included. In addition to the investigator-identified irAEs, a sponsor-defined list of irAEs search criteria will be used to identify cases of irAEs. The list is presented in below.

Organ disorder	MedDRA PTs	Composite Term
Gastrointestinal disorders	Enterocolitis haemorrhagic	Colitis
	Autoimmune colitis	
	Enterocolitis	
	Colitis	
	Colitis microscopic	
	Diarrhoea	
	Duodenitis	
	Gastrointestinal perforation	
	Pancreatitis	
	Stomatitis	
Respiratory disorders	Acute interstitial pneumonitis	Pneumonitis
	Pneumonitis	

Organ disorder	MedDRA PTs	Composite Term
Hepatobiliary disorders	Hepatic failure	Hepatic failure
	Acute hepatic failure	
	Alanine aminotransferase increased	
	Aspartate aminotransferase increased	
	Blood alkaline phosphatase increased	
	Blood bilirubin increased	
	Autoimmune hepatitis	Hepatitis
	Hepatitis	
	Hepatitis acute	
	Hyperbilirubinaemia	
	Jaundice	
	Transaminases increased	
Eye disorders	Iridocyclitis	
	Iritis	
	Uveitis	
Renal disorders	Autoimmune nephritis	Nephritis
	Nephritis	
	Tubulointerstitial nephritis	
	Acute kidney injury	Renal failure
	Renal failure	
Endocrine disorders	Adrenal insufficiency	
	Autoimmune thyroiditis	
	Blood thyroid stimulating hormone increased	
	Diabetic ketoacidosis	
	Hyperthyroidism	

Organ disorder	MedDRA PTs	Composite Term
	Hypophysitis	
	Hypopituitarism	
	Hypothyroidism	
	Thyroid disorder	
	Thyroiditis	
	Diabetes mellitus	Diabetes mellitus
	Type 1 diabetes mellitus	
Nervous System disorders	Autoimmune neuropathy	
	Central nervous system inflammation	
	Demyelination	
	Encephalitis	
	Guillain-Barre Syndrome	
	Meningitis	Meningitis
	Meningitis aseptic	
	Myasthenia gravis	
	Myasthenic syndrome	
	Motor Dysfunction	
	Paraneoplastic encephalomyelitis	
	Polyneuropathy	
Skin disorders	Acute generalised exanthematous pustulosis	
	Cutaneous vasculitis	
	Dermatitis	Dermatitis
	Dermatitis acneiform	
	Dermatitis bullous	
	Dermatitis exfoliative	

Organ disorder	MedDRA PTs	Composite Term
	Dermatitis exfoliative generalised	
	Drug reaction with eosinophilia and systemic symptoms	
	Erythema multiforme	
	Oculomucocutaneous syndrome	
	Pruritus	Pruritus
	Pruritus generalised	
	Exfoliative rash	Rash
	Rash	
	Rash erythematous	
	Rash generalized	
	Rash macular	
	Rash maculo-papular	
	Rash maculovesicular	
	Rash morbilliform	
	Rash popular	
	Rash pruritic	
	Rash rubelliform	
	Rash scarlatiniform	
	Rash vesicular	
	Epidermal necrosis	Skin necrosis
	Skin necrosis	
	Stevens-Johnson syndrome	
	Toxic epidermal necrolysis	
	Toxic skin eruption	
	Vitiligo	

Organ disorder	MedDRA PTs	Composite Term
Cardiac disorders	Myocarditis	
Musculoskeletal disorders	Arthralgia	
	Myositis	
	Polymyalgia rheumatica	
Vascular disorders	Vasculitis	
General disorders	Systemic inflammatory response syndrome	

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Approval	Yuhwen Soo yuhwen.soo@regeneron.com Biostatistics / Data Management 22-Sep-2017 16:39:43 GMT+0000
Approval	Bo Gao Bo.Gao@regeneron.com Biostatistics / Data Management 22-Sep-2017 16:40:30 GMT+0000
Approval	Matthew Fury matthew.fury@regeneron.com Clinical 22-Sep-2017 17:37:36 GMT+0000

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