Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Migden MR, Rischin D, Schmults CD, et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. N Engl J Med 2018;379:341-51. DOI: 10.1056/NEJMoa1805131

Supplementary Appendix: PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous Cell Carcinoma. Migden & Rischin et al.

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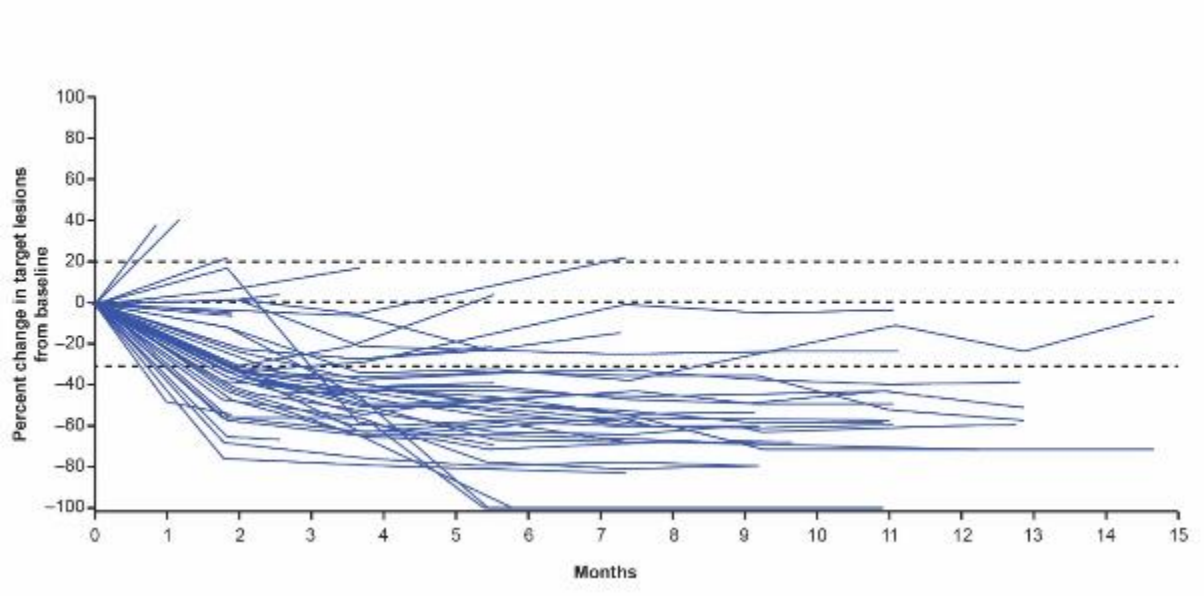
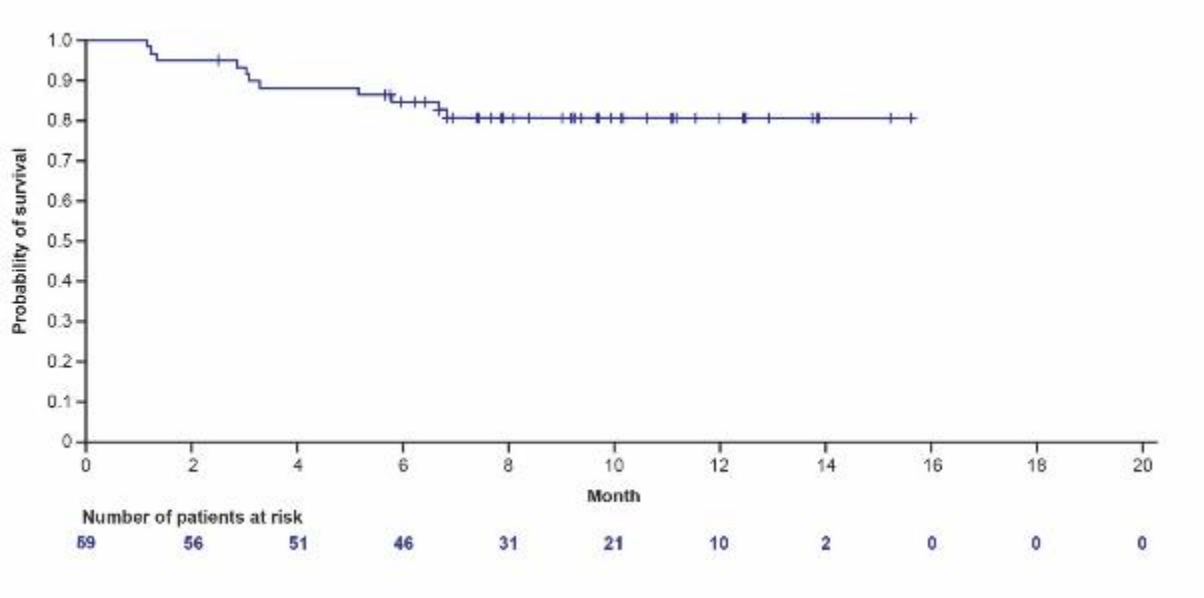
Figure S1. Kinetics of Change in Target Lesion Diameters Over Time in Patients with Metastatic CSCC from the Phase 2 Study



Rapid, deep and durable target lesion reductions were observed in most patients who had at least one tumor assessment on treatment. Patients shown on this panel are the same as those on Panel A of Figure 2.

CSCC, cutaneous squamous cell carcinoma.

Figure S2. Kaplan–Meier Curve Showing Probability of Overall Survival in the Phase 2 Study

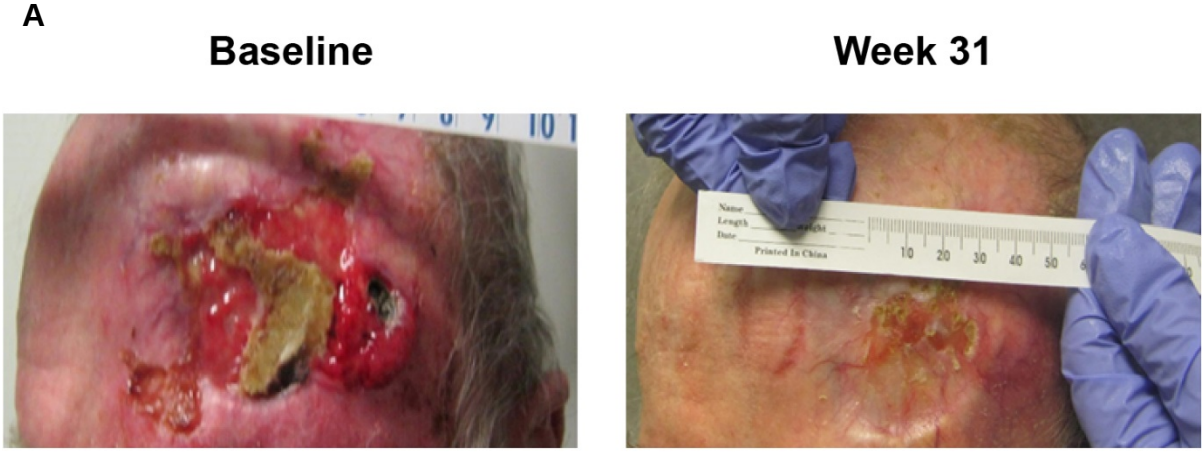


Median overall survival had not been reached at the time of data cut-off. The estimated probability of survival at 12 months was 80.6% (95% CI, 67.7 to 88.8).

CI, confidence interval.

Figure S3. Additional Examples of Changes in Externally Visible CSCC Lesions on Cemiplimab Treatment

A



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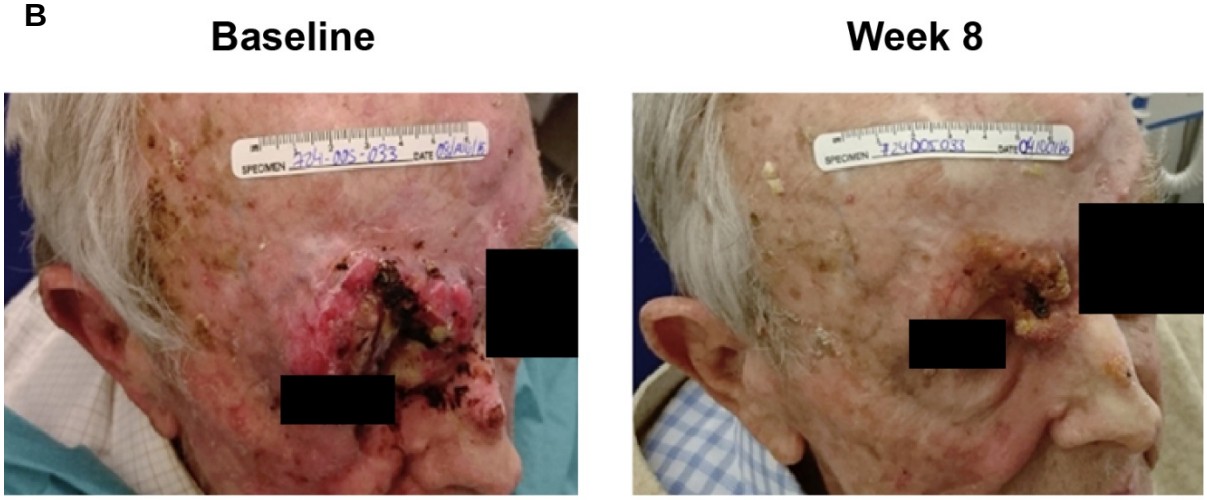

C

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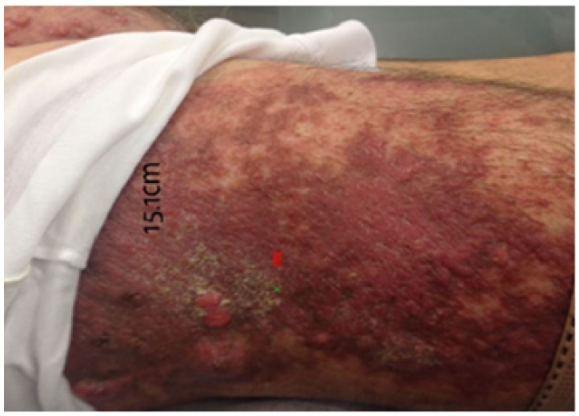
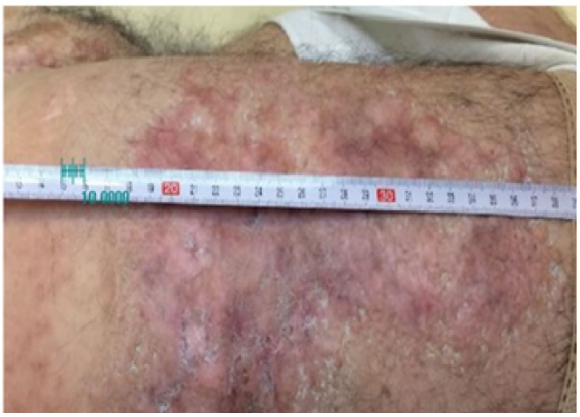
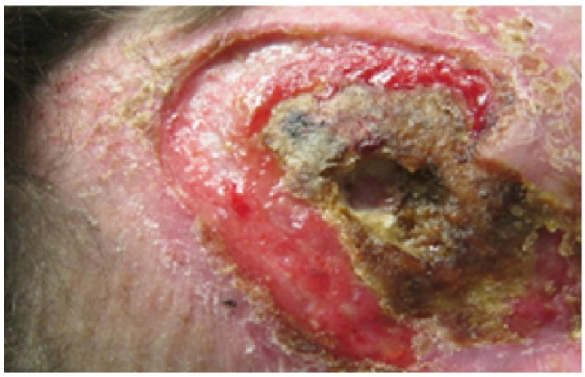


Week 52



D

Baseline



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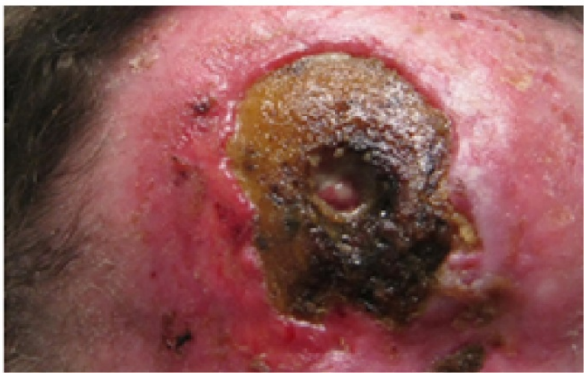

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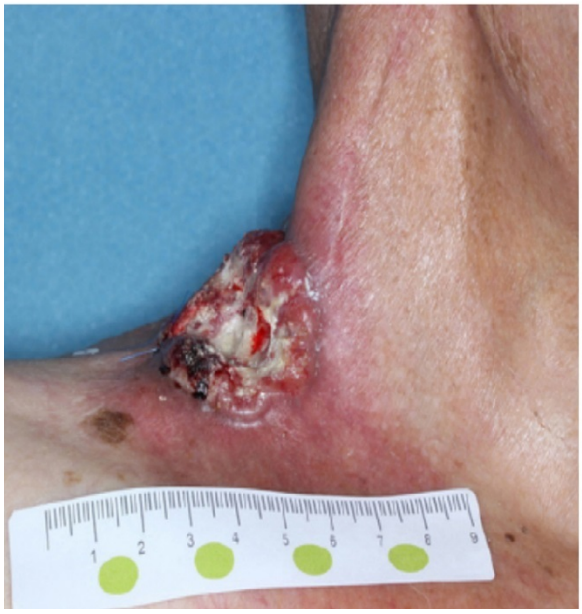

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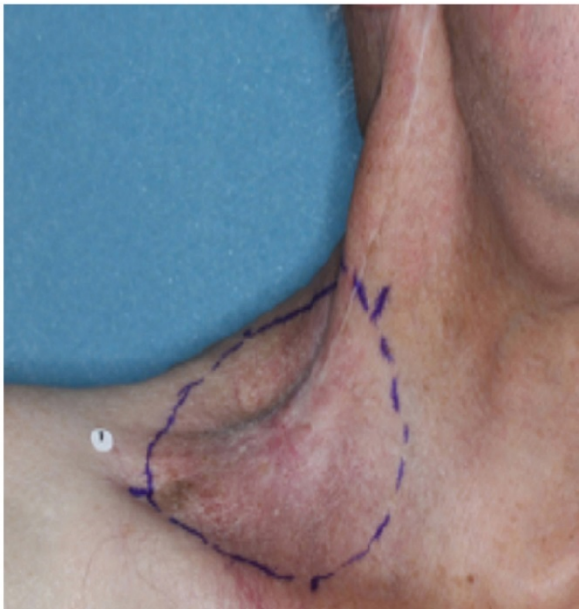

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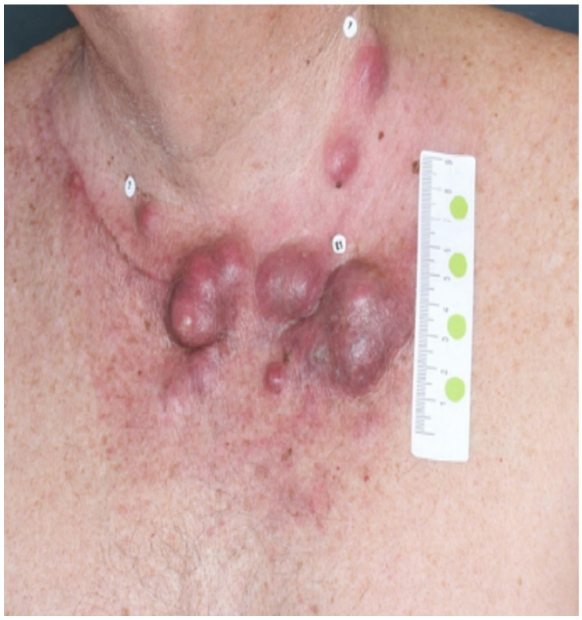
Baseline



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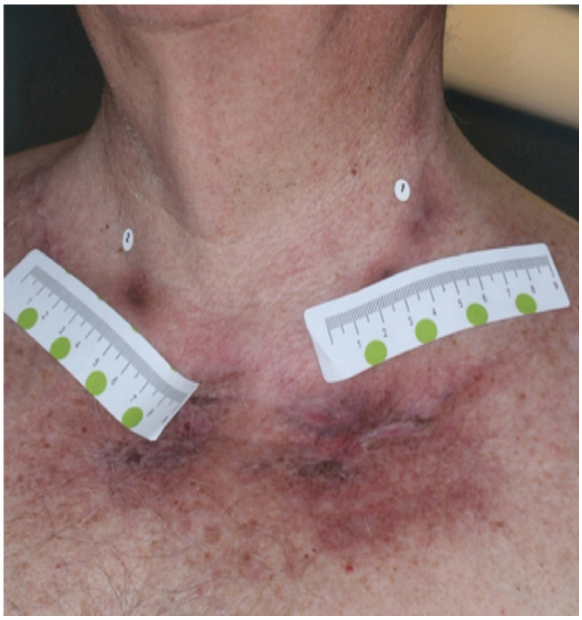

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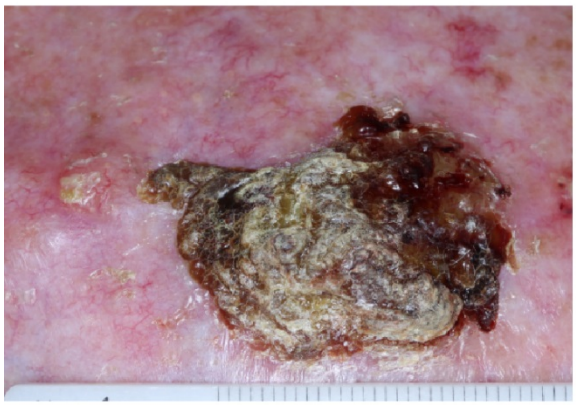
Baseline



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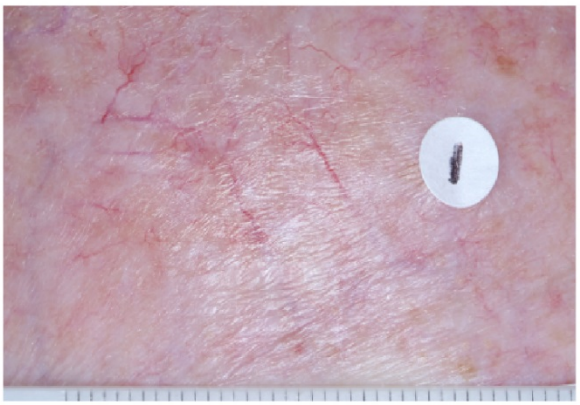
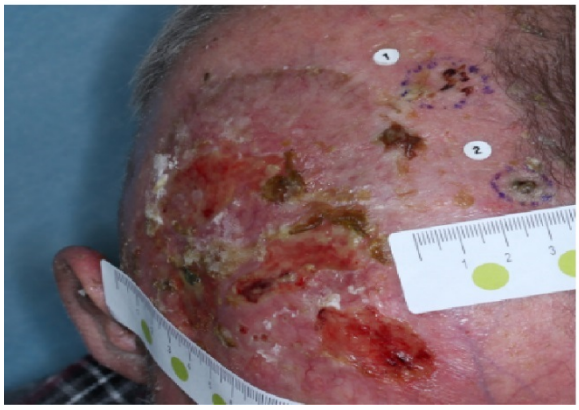
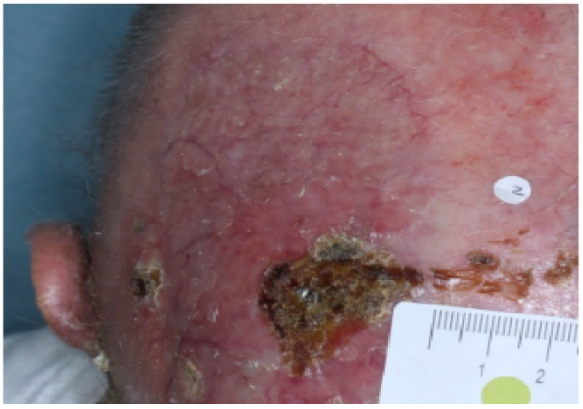


H

Baseline

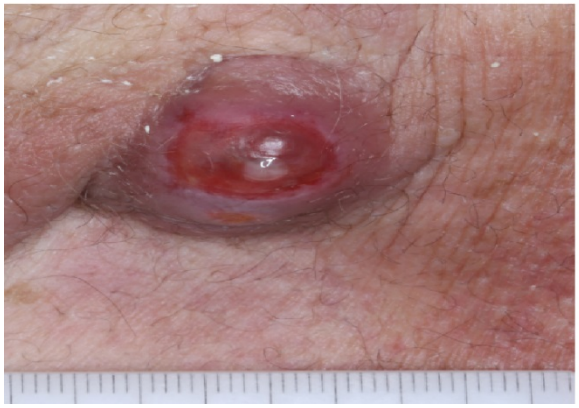


Week 16



I

Baseline



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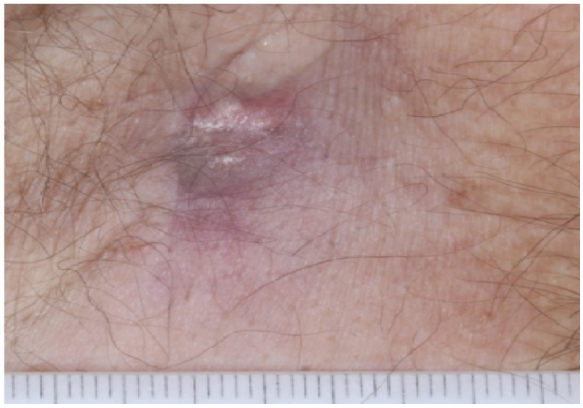

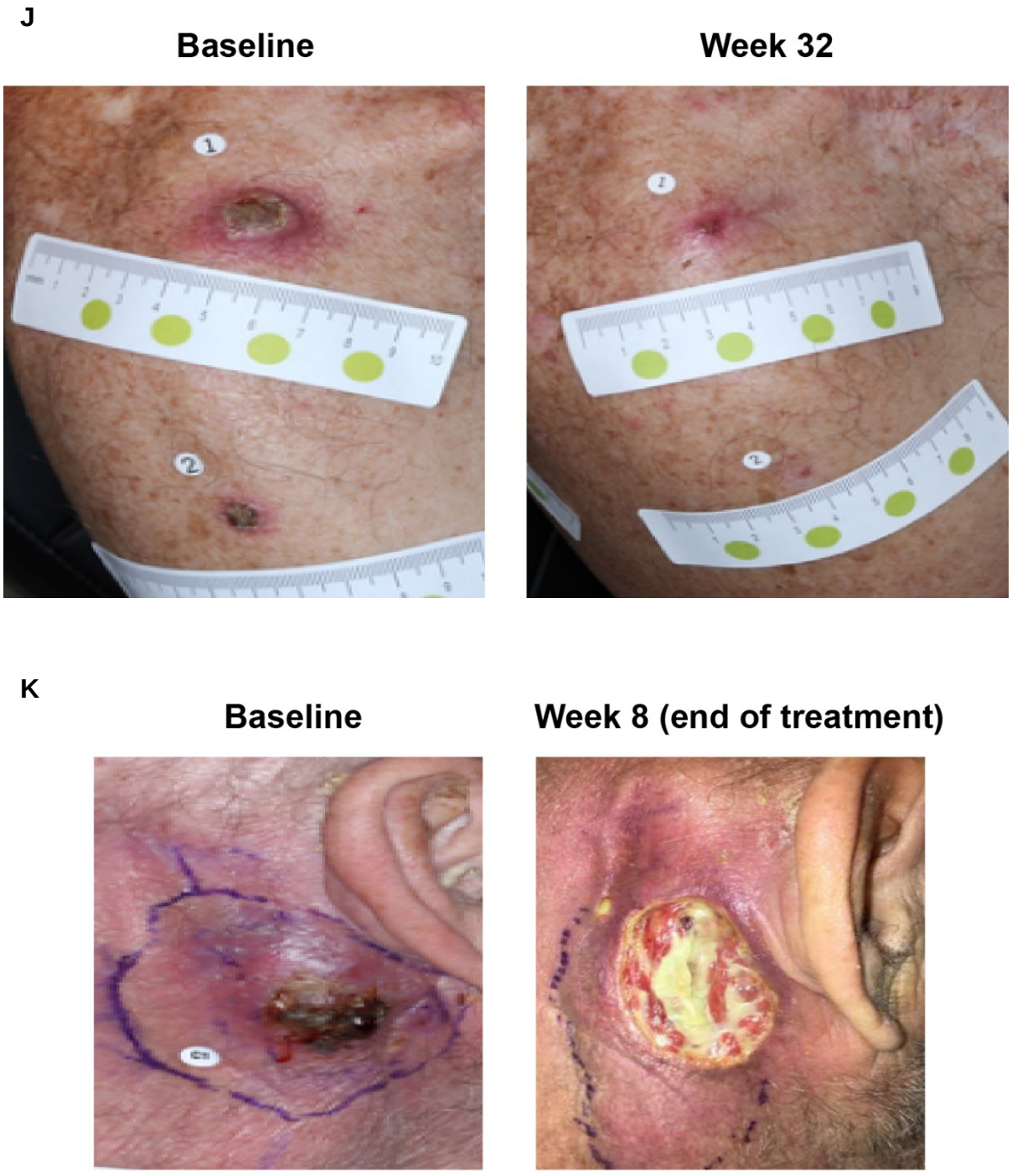

The patients in panels A–D are from the phase 1 study. Panel A shows an 80-year-old man with locally advanced CSCC forehead lesion. Panel B shows an 88-year-old man with periorbital CSCC. Panel C shows a 78-year-old man with CSCC of lower extremity who was deemed not evaluable for response by independent central review due to inadequate imaging. Panel D shows a 56-year-old man with forehead lesion who experienced stable disease. The patients in panels E–K are from the phase 2 study of patients with metastatic CSCC and externally visible lesions. Panel E shows an 85-year-old man with a supraclavicular lesion. Panel F shows a 66-year-old man with anterior chest wall CSCC lesions. Panel G shows a 61-year-old man with scalp

lesion. Panel H shows a 74 year-old man with scalp CSCC. Panel I shows a 75-year-old man with axillary squamous cell carcinoma. Panel J shows a 56-year-old man with anterior shoulder lesions. Panel K shows an 81-year-old man with regional nodal lesion that did not respond to cemiplimab.

CSCC, cutaneous squamous cell carcinoma.

Table S1. Disposition and Follow-Up of Patients in the Phase 1 CSCC Expansion Cohorts

	Total (N = 26)
On treatment, no. (%)	1 (3.8)
Off treatment, no. (%)	25 (96.2)
Treatment completed	11 (42.3)
Treatment discontinued	14 (53.8)
Primary reason for treatment discontinuation	
Disease progression	7 (26.9)
Adverse events	2 (7.7)
Death	2 (7.7)
Patient decision	1 (3.8)
Investigator decision	1 (3.8)
Withdrawal of consent	1 (3.8)
Median duration of follow-up (range), months	11.0 (1.1–17.0)

The data cut-off point was October 2, 2017.

CSCC, cutaneous squamous cell carcinoma; no., number.

Table S2. Cemiplimab Exposure in the Phase 1 CSCC Expansion Cohorts

	Total (N = 26)
Median duration of exposure (range), weeks	36.0 (4.0–71.0*)
Duration of exposure, no. (%)	
≥0 week	26 (100)
≥6 weeks	22 (84.6)
≥12 weeks	18 (69.2)
≥24 weeks	15 (57.7)
≥36 weeks	13 (50.0)
≥48 weeks	9 (34.6)
Median number of doses administered (range)	16 (2–36)

*One patient was allowed to continue treatment without interruption because extended treatment beyond the 48-week treatment duration was considered to be in the best interest of the patient; hence the upper limit of 71.0 weeks shown here.

CSCC, cutaneous squamous cell carcinoma; no., number.

Table S3. Adverse Events, Regardless of Attribution, in the Phase 1 CSCC Expansion Cohorts

Adverse events*	Total (N = 26)	
	Any grade	Grade ≥3
	Number of patients (percent)	
Any	26 (100.0)	12 (46.2)
Serious	7 (26.9)	6 (23.1)
Led to discontinuation	2 (7.7)	0
With an outcome of death†	1 (3.8)	1 (3.8)
Fatigue	7 (26.9)	0
Constipation	4 (15.4)	0
Decreased appetite	4 (15.4)	0
Diarrhea	4 (15.4)	0
Hypercalcemia	4 (15.4)	2 (7.7)
Hypophosphatemia	4 (15.4)	0
Nausea	4 (15.4)	0
Urinary tract infection	4 (15.4)	1 (3.8)
Anemia	3 (11.5)	0
Arthralgia	3 (11.5)	1 (3.8)
Dry mouth	3 (11.5)	0
Fall	3 (11.5)	0
Hypertension	3 (11.5)	0
Muscular weakness	3 (11.5)	0
Myalgia	3 (11.5)	1 (3.8)
Peripheral edema	3 (11.5)	0
Pruritus	3 (11.5)	0
Pyrexia	3 (11.5)	0
Skin infection	3 (11.5)	2 (7.7)

Acute kidney injury	2 (7.7)	1 (3.8)
Anxiety	2 (7.7)	0
Asthenia	2 (7.7)	1 (3.8)
Cough	2 (7.7)	0
Decreased weight	2 (7.7)	1 (3.8)
Diplopia	2 (7.7)	0
Dizziness	2 (7.7)	0
Erythema	2 (7.7)	0
Failure to thrive	2 (7.7)	2 (7.7)
Headache	2 (7.7)	0
Hypokalemia	2 (7.7)	0
Hyponatremia	2 (7.7)	1 (3.8)
Hypotension	2 (7.7)	0
Hypothyroidism	2 (7.7)	0
Increased weight	2 (7.7)	0
Infusion related reaction	2 (7.7)	0
Insomnia	2 (7.7)	0
Maculo-papular rash	2 (7.7)	1 (3.8)
Muscle spasms	2 (7.7)	0
Pain in extremity	2 (7.7)	1 (3.8)
Rash	2 (7.7)	0
Acne	1 (3.8)	0
Adrenal insufficiency	1 (3.8)	1 (3.8)
Amnesia	1 (3.8)	0
Atrial fibrillation	1 (3.8)	1 (3.8)
Back pain	1 (3.8)	0
Blurred vision	1 (3.8)	0
Bradyphrenia	1 (3.8)	0
Brain edema	1 (3.8)	0

Chronic inflammatory demyelinating polyradiculoneuropathy	1 (3.8)	0
Conjunctivitis	1 (3.8)	0
Craniocerebral injury	1 (3.8)	0
Unilateral deafness	1 (3.8)	0
Deep vein thrombosis	1 (3.8)	0
Decreased neutrophil count	1 (3.8)	0
Decreased white blood cell count	1 (3.8)	0
Dehydration	1 (3.8)	0
Delirium	1 (3.8)	1 (3.8)
Dental caries	1 (3.8)	0
Depressed mood	1 (3.8)	0
Dermal cyst	1 (3.8)	0
Diverticulitis	1 (3.8)	0
Dry skin	1 (3.8)	0
Dysgeusia	1 (3.8)	0
Dyspnea	1 (3.8)	0
Encephalopathy	1 (3.8)	0
Eye pain	1 (3.8)	0
Flatulence	1 (3.8)	0
Flushing	1 (3.8)	0
Folliculitis	1 (3.8)	0
Furuncle	1 (3.8)	0
Groin pain	1 (3.8)	0
Herpes zoster	1 (3.8)	0
Hyperuricemia	1 (3.8)	0
Hypoalbuminemia	1 (3.8)	0
Hypochloremia	1 (3.8)	0
Hypomagnesemia	1 (3.8)	0
Increased alanine aminotransferase	1 (3.8)	1 (3.8)

Increased aspartate aminotransferase	1 (3.8)	1 (3.8)
Increased blood creatine	1 (3.8)	0
Increased blood creatinine	1 (3.8)	0
Increased blood phosphorus	1 (3.8)	0
Increased blood urea	1 (3.8)	0
Immune thrombocytopenic purpura	1 (3.8)	0
Influenza like illness	1 (3.8)	0
Intervertebral disc degeneration	1 (3.8)	1 (3.8)
Laceration	1 (3.8)	0
Lip swelling	1 (3.8)	0
Localised infection	1 (3.8)	0
Malnutrition	1 (3.8)	0
Metabolic acidosis	1 (3.8)	0
Musculoskeletal chest pain	1 (3.8)	0
Nasal congestion	1 (3.8)	0
Neck pain	1 (3.8)	0
Neurotrophic keratopathy	1 (3.8)	0
Night sweats	1 (3.8)	0
Non-cardiac chest pain	1 (3.8)	1 (3.8)
Ocular myasthenia	1 (3.8)	0
Oral candidiasis	1 (3.8)	0
Oral disorder	1 (3.8)	0
Osteoarthritis	1 (3.8)	1 (3.8)
Pain	1 (3.8)	0
Paronychia	1 (3.8)	0
Periorbital oedema	1 (3.8)	0
Peripheral neuropathy	1 (3.8)	0
Photophobia	1 (3.8)	0
Postoperative wound infection	1 (3.8)	0

Proteinuria	1 (3.8)	0
Pruritic rash	1 (3.8)	0
Respiratory tract infection	1 (3.8)	0
Sepsis	1 (3.8)	1 (3.8)
Sinusitis	1 (3.8)	0
Sjogren's syndrome	1 (3.8)	0
Skin induration	1 (3.8)	0
Skin lesion	1 (3.8)	0
Stomatitis	1 (3.8)	0
Superinfection	1 (3.8)	0
Tooth infection	1 (3.8)	0
Tumour hemorrhage	1 (3.8)	0
Upper respiratory tract infection	1 (3.8)	0
Upper-airway cough syndrome	1 (3.8)	0
Urinary retention	1 (3.8)	0
Viral upper respiratory tract infection	1 (3.8)	0
Xerophthalmia	1 (3.8)	0

*Events were coded according to Preferred Terms (MedDRA version 20.0), NCI grades were coded using CTCAE version 4.03. Although rash and maculopapular rash may reflect the same condition, they were listed as two distinct events in the safety report. Adverse events are listed in decreasing order of frequency. [†]The fatal adverse event occurred in an 80-year-old man with baseline congestive heart failure and renal insufficiency. He was hospitalized on study day 30 with urinary tract infection and became anuric; the fatal renal failure was considered unrelated to study treatment.

CSCC, cutaneous squamous cell carcinoma; CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute.

Table S4. Investigator-Assessed Treatment-Related Adverse Events in the Phase 1 CSCC Expansion Cohorts

Treatment-related adverse events*	Total (N = 26)	
	Any grade	Grade ≥3
	Number of patients (percent)	
Any	15 (57.7)	5 (19.2)
Serious	2 (7.7)	2 (7.7)
Led to discontinuation	2 (7.7)	0
Led to death	0	0
Fatigue	7 (26.9)	0
Arthralgia	2 (7.7)	0
Diarrhea	2 (7.7)	0
Hypothyroidism	2 (7.7)	0
Muscle weakness	2 (7.7)	0
Maculo-papular rash	2 (7.7)	1 (3.8)
Acne	1 (3.8)	0
Adrenal insufficiency	1 (3.8)	1 (3.8)
Asthenia	1 (3.8)	1 (3.8)
Chronic inflammatory demyelinating polyradiculoneuropathy	1 (3.8)	0
Constipation	1 (3.8)	0
Cough	1 (3.8)	0
Decreased appetite	1 (3.8)	0
Dry mouth	1 (3.8)	0
Dry skin	1 (3.8)	0
Dysgeusia	1 (3.8)	0
Erythema	1 (3.8)	0
Flushing	1 (3.8)	0

Hypertension	1 (3.8)	0
Increased alanine aminotransferase	1 (3.8)	1 (3.8)
Increase aspartate aminotransferase	1 (3.8)	1 (3.8)
Increased blood creatinine	1 (3.8)	0
Increased blood urea	1 (3.8)	0
Immune thrombocytopenic purpura	1 (3.8)	0
Infusion related reaction	1 (3.8)	0
Myalgia	1 (3.8)	1 (3.8)
Nausea	1 (3.8)	0
Paronychia	1 (3.8)	0
Pruritus	1 (3.8)	0
Pyrexia	1 (3.8)	0
Rash	1 (3.8)	0
Sjogren's syndrome	1 (3.8)	0
Skin induration	1 (3.8)	0
Upper-airway cough syndrome	1 (3.8)	0
Urinary tract infection	1 (3.8)	0

*Events were coded according to Preferred Terms (MedDRA version 20.0), NCI grades were coded using CTCAE version 4.03. Events are listed in decreasing order of frequency by any grade.

CSCC, cutaneous squamous cell carcinoma; CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute.

Table S5. Disposition and Follow-Up in the Phase 2 Study

	Metastatic CSCC* (N = 59)
On treatment, no. (%)	35 (59.3)
Off treatment, no. (%)	24 (40.7)
Treatment completed	0
Treatment discontinued	24 (40.7)
Primary reason for treatment discontinuation	
Disease progression	14 (23.7)
Adverse events	4 (6.8)
Death	2 (3.4)
Patient decision	2 (3.4)
Investigator decision	1 (1.7)
Withdrawal of consent	0
Other	1 (1.7)
Median duration of follow-up (range), months	7.9 (1.1–15.6)

*In the phase 2 study, metastatic CSCC included patients with distant and/or nodal metastatic disease. The data cut-off point was October 27, 2017.

CSCC, cutaneous squamous cell carcinoma; no., number.

Table S6. Cemiplimab Exposure in the Phase 2 Study

	Metastatic CSCC* (N = 59)
Median duration of exposure (range), weeks	32.7 (2.0–69.3)
Duration of exposure, no. (%)	
≥0 week	59 (100.0)
≥6 weeks	54 (91.5)
≥12 weeks	42 (71.2)
≥24 weeks	40 (67.8)
≥36 weeks	26 (44.1)
≥48 weeks	16 (27.1)
Median number of doses administered (range)	17 (1–35)

*In the phase 2 study, metastatic CSCC included patients with distant and/or nodal metastatic disease.

CSCC, cutaneous squamous cell carcinoma; no., number.

Table S7. Adverse Events, Regardless of Attribution, in the Phase 2 Study

Adverse events*	Metastatic CSCC (N = 59)	
	Any grade	Grade ≥3
	number of patients (percent)	
Any	59 (100.0)	25 (42.4)
Serious	21 (35.6)	17 (28.8)
Led to discontinuation	4 (6.8)	3 (5.1)
With an outcome of death	3 (5.1)	3 (5.1)
Diarrhea	16 (27.1)	1 (1.7)
Fatigue	14 (23.7)	1 (1.7)
Nausea	10 (16.9)	0
Constipation	9 (15.3)	1 (1.7)
Rash	9 (15.3)	0
Cough	8 (13.6)	0
Decreased appetite	8 (13.6)	0
Pruritus	8 (13.6)	0
Headache	8 (13.6)	0
Dry skin	6 (10.2)	0
Maculo-papular rash	6 (10.2)	0
Vomiting	6 (10.2)	0
Anemia	5 (8.5)	1 (1.7)
Hypothyroidism	5 (8.5)	0
Increased alanine aminotransferase	5 (8.5)	0
Pneumonitis	5 (8.5)	2 (3.4)
Arthralgia	4 (6.8)	0
Cellulitis	4 (6.8)	4 (6.8)
Depression	4 (6.8)	1 (1.7)
Dizziness	4 (6.8)	0

Dry mouth	4 (6.8)	0
Oropharyngeal pain	4 (6.8)	0
Abdominal pain	3 (5.1)	0
Dysgeusia	3 (5.1)	0
Dyspnea	3 (5.1)	1 (1.7)
Epistaxis	3 (5.1)	0
Fall	3 (5.1)	0
Gastrooesophageal reflux disease	3 (5.1)	0
Hypercalcemia	3 (5.1)	2 (3.4)
Hypertension	3 (5.1)	1 (1.7)
Hypokalemia	3 (5.1)	1 (1.7)
Increased blood creatinine	3 (5.1)	0
Myalgia	3 (5.1)	0
Nasal congestion	3 (5.1)	0
Oral candidiasis	3 (5.1)	0
Pain in extremity	3 (5.1)	0
Peripheral edema	3 (5.1)	0
Renal failure	3 (5.1)	0
Skin infection	3 (5.1)	1 (1.7)
Tumour pain	3 (5.1)	1 (1.7)
Upper respiratory tract infection	3 (5.1)	0
Wound infection	3 (5.1)	1 (1.7)
Acne	2 (3.4)	0
Actinic keratosis	2 (3.4)	0
Asthenia	2 (3.4)	0
Chills	2 (3.4)	0
Death[†]	2 (3.4)	2 (3.4)
Dehydration	2 (3.4)	1 (1.7)
Dry eye	2 (3.4)	0

Eczema	2 (3.4)	0
Face edema	2 (3.4)	0
Hyperkalemia	2 (3.4)	0
Hyperuricemia	2 (3.4)	1 (1.7)
Hypoacusis	2 (3.4)	0
Hypomagnesemia	2 (3.4)	0
Hypotension	2 (3.4)	0
Increased aspartate aminotransferase	2 (3.4)	0
Increased blood alkaline phosphatase	2 (3.4)	0
Increased blood immunoglobulin E	2 (3.4)	0
Infusion related reaction	2 (3.4)	0
Irritability	2 (3.4)	0
Lower respiratory tract infection	2 (3.4)	0
Lymphadenopathy	2 (3.4)	0
Lymphoedema	2 (3.4)	0
Memory impairment	2 (3.4)	0
Muscle spasms	2 (3.4)	0
Musculoskeletal pain	2 (3.4)	0
Non-cardiac chest pain	2 (3.4)	0
Pleural effusion	2 (3.4)	2 (3.4)
Pyrexia	2 (3.4)	0
Tumour hemorrhage	2 (3.4)	0
Urinary tract infection	2 (3.4)	0
Viral upper respiratory tract infection	2 (3.4)	0
Abdominal discomfort	1 (1.7)	0
Abdominal distension	1 (1.7)	0
Abdominal pain lower	1 (1.7)	0
Abscess limb	1 (1.7)	1 (1.7)
Acute kidney injury	1 (1.7)	1 (1.7)

Acute pulmonary edema	1 (1.7)	0
Acute respiratory distress syndrome	1 (1.7)	1 (1.7)
Akathisia	1 (1.7)	0
Altered mood	1 (1.7)	0
Angina pectoris	1 (1.7)	1 (1.7)
Arthritis infective	1 (1.7)	0
Asymptomatic bacteriuria	1 (1.7)	0
Atrial fibrillation	1 (1.7)	0
Back pain	1 (1.7)	0
Benign prostatic hyperplasia	1 (1.7)	0
Bronchitis	1 (1.7)	0
Bursitis	1 (1.7)	0
C-reactive protein increased	1 (1.7)	0
Cancer pain	1 (1.7)	0
Cardiac failure	1 (1.7)	0
Cataract	1 (1.7)	0
Catheter site infection	1 (1.7)	1 (1.7)
Cerebral infarction	1 (1.7)	1 (1.7)
Colitis	1 (1.7)	1 (1.7)
Complete atrioventricular block	1 (1.7)	1 (1.7)
Complex regional pain syndrome	1 (1.7)	0
Confusional state	1 (1.7)	1 (1.7)
Conjunctival ulcer	1 (1.7)	0
Contusion	1 (1.7)	0
Cystitis	1 (1.7)	0
Delirium	1 (1.7)	0
Dermatitis	1 (1.7)	0
Dermatitis bullous	1 (1.7)	0
Dysphagia	1 (1.7)	0

Decreased platelet count	1 (1.7)	0
Decreased weight	1 (1.7)	0
Deep vein thrombosis	1 (1.7)	1 (1.7)
Depressed mood	1 (1.7)	0
Diabetes mellitus	1 (1.7)	0
Drug eruption	1 (1.7)	0
Duodenal ulcer	1 (1.7)	1 (1.7)
Ear infection	1 (1.7)	0
Ear pain	1 (1.7)	0
Eczema nummular	1 (1.7)	0
Embolism	1 (1.7)	0
Excoriation	1 (1.7)	0
Eye infection	1 (1.7)	0
Eye injury	1 (1.7)	0
Facial nerve disorder	1 (1.7)	0
Facial pain	1 (1.7)	0
Flank pain	1 (1.7)	0
Focal dyscognitive seizures	1 (1.7)	0
First degree atrioventricular block	1 (1.7)	0
Generalised rash	1 (1.7)	0
Gout	1 (1.7)	0
Groin infection	1 (1.7)	1 (1.7)
Hemoptysis	1 (1.7)	0
Hypercholesterolemia	1 (1.7)	0
Hyperphosphatemia	1 (1.7)	0
Hypertensive crisis	1 (1.7)	1 (1.7)
Hyperthyroidism	1 (1.7)	0
Hypoglycemia	1 (1.7)	0
Hyponatremia	1 (1.7)	1 (1.7)

Hypophysitis	1 (1.7)	1 (1.7)
Increased antinuclear antibody	1 (1.7)	0
Increased blood lactate dehydrogenase	1 (1.7)	0
Increased lacrimation	1 (1.7)	0
Increased weight	1 (1.7)	0
Influenza like illness	1 (1.7)	0
Ingrowing nail	1 (1.7)	0
Insomnia	1 (1.7)	0
Joint swelling	1 (1.7)	0
Lactose intolerance	1 (1.7)	0
Lung infection	1 (1.7)	1 (1.7)
Meningitis aseptic	1 (1.7)	1 (1.7)
Mouth ulceration	1 (1.7)	0
Musculoskeletal stiffness	1 (1.7)	0
Myocardial infarction	1 (1.7)	1 (1.7)
Nail disorder	1 (1.7)	0
Neck pain	1 (1.7)	1 (1.7)
Nephrolithiasis	1 (1.7)	0
Neuralgia	1 (1.7)	0
Neuritis	1 (1.7)	0
Neutropenia	1 (1.7)	0
Night sweats	1 (1.7)	0
Noninfective cystitis	1 (1.7)	0
Oesophagitis	1 (1.7)	1 (1.7)
Optic atrophy	1 (1.7)	1 (1.7)
Oral pain	1 (1.7)	0
Osteoarthritis	1 (1.7)	0
Pelvic discomfort	1 (1.7)	0
Peripheral swelling	1 (1.7)	0

Pharyngitis	1 (1.7)	0
Pneumonia	1 (1.7)	1 (1.7)
Pneumothorax	1 (1.7)	0
Pollakiuria	1 (1.7)	0
Polyarthritis	1 (1.7)	1 (1.7)
Prostatic disorder	1 (1.7)	0
Pulmonary edema	1 (1.7)	1 (1.7)
Restless legs syndrome	1 (1.7)	0
Rhinorrhoea	1 (1.7)	0
Road traffic accident	1 (1.7)	0
Sinusitis	1 (1.7)	0
Sepsis	1 (1.7)	1 (1.7)
Sciatica	1 (1.7)	0
Sinus headache	1 (1.7)	0
Skin disorder	1 (1.7)	0
Skin fissures	1 (1.7)	0
Skin plaque	1 (1.7)	0
Skin reaction	1 (1.7)	0
Sleep apnoea syndrome	1 (1.7)	0
Small intestinal hemorrhage	1 (1.7)	1 (1.7)
Soft tissue infection	1 (1.7)	0
Staphylococcal infection	1 (1.7)	0
Stomatitis	1 (1.7)	0
Suicidal ideation	1 (1.7)	1 (1.7)
Tinnitus	1 (1.7)	0
Toothache	1 (1.7)	0
Tremor	1 (1.7)	0
Trigeminal nerve paresis	1 (1.7)	0
Upper respiratory tract congestion	1 (1.7)	0

Vertigo	1 (1.7)	0
Wheezing	1 (1.7)	0
Wound	1 (1.7)	0

*****Events are listed as indicated on the case report form. Although rash and maculopapular rash may reflect the same condition, they were listed as two distinct events for the phase 2 safety report. Adverse events were coded according to Preferred Terms (MedDRA version 20.0), NCI grades were coded using CTCAE version 4.03. Events are listed in decreasing order of frequency. †The adverse event term of death was used for two patients. One was a patient with death due to progressive disease. The other patient was a 72-year-old man who died in his sleep, as described in the Results section. For the other two adverse events resulting in death that are described in the Results, the adverse event term was not death.

CSCC, cutaneous squamous cell carcinoma; CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute.

Table S8. Investigator-Assessed Treatment-Related Adverse Events in the Phase 2 Study

Treatment-related adverse events	Metastatic CSCC (N = 59)	
	Any grade	Grade ≥3
	Number of patients (percent)	
Any	44 (74.6)	7 (11.9)
Serious	6 (10.2)	5 (8.5)
Led to discontinuation	4 (6.8)	3 (5.1)
Led to death	0	0
Fatigue	8 (13.6)	0
Diarrhea	7 (11.9)	1 (1.7)
Maculo-papular rash	6 (10.2)	0
Pruritus	6 (10.2)	0
Rash	6 (10.2)	0
Cough	5 (8.5)	0
Decreased appetite	5 (8.5)	0
Nausea	5 (8.5)	0
Pneumonitis	5 (8.5)	2 (3.4)
Dry mouth	4 (6.8)	0
Dry skin	4 (6.8)	0
Increased alanine aminotransferase	4 (6.8)	0
Hypothyroidism	4 (6.8)	0
Arthralgia	3 (5.1)	0
Dizziness	3 (5.1)	0
Asthenia	2 (3.4)	0
Constipation	2 (3.4)	1 (1.7)
Dysgeusia	2 (3.4)	0
Headache	2 (3.4)	0

Increased aspartate aminotransferase	2 (3.4)	0
Increased blood immunoglobulin E	2 (3.4)	0
Infusion related reaction	2 (3.4)	0
Memory impairment	2 (3.4)	0
Abdominal pain	1 (1.7)	0
Abdominal distension	1 (1.7)	0
Abdominal pain lower	1 (1.7)	0
Actinic keratosis	1 (1.7)	0
Anemia	1 (1.7)	0
Chills	1 (1.7)	0
Colitis	1 (1.7)	1 (1.7)
Complex regional pain syndrome	1 (1.7)	0
Confusional state	1 (1.7)	1 (1.7)
Contusion	1 (1.7)	0
Decreased platelet count	1 (1.7)	0
Dermatitis	1 (1.7)	0
Drug eruption	1 (1.7)	0
Dry eye	1 (1.7)	0
Duodenal ulcer	1 (1.7)	1 (1.7)
Dyspnoea	1 (1.7)	0
Eczema	1 (1.7)	0
Face oedema	1 (1.7)	0
Generalised rash	1 (1.7)	0
Hyperphosphatemia	1 (1.7)	0
Hyperthyroidism	1 (1.7)	0
Hyperuricemia	1 (1.7)	0
Hypokalemia	1 (1.7)	0
Hypophysitis	1 (1.7)	1 (1.7)
Increased antinuclear antibody	1 (1.7)	0

Increased blood alkaline phosphatase	1 (1.7)	0
Increased blood creatinine	1 (1.7)	0
Increased blood lactate dehydrogenase	1 (1.7)	0
Increased c-reactive protein	1 (1.7)	0
Influenza like illness	1 (1.7)	0
Irritability	1 (1.7)	0
Joint swelling	1 (1.7)	0
Lacrimation increased	1 (1.7)	0
Meningitis aseptic	1 (1.7)	1 (1.7)
Muscle spasms	1 (1.7)	0
Musculoskeletal pain	1 (1.7)	0
Myalgia	1 (1.7)	0
Nasal congestion	1 (1.7)	0
Neck pain	1 (1.7)	1 (1.7)
Neuritis	1 (1.7)	0
Neutropenia	1 (1.7)	0
Night sweats	1 (1.7)	0
Oesophagitis	1 (1.7)	1 (1.7)
Pain in extremity	1 (1.7)	0
Polyarthritis	1 (1.7)	1 (1.7)
Pyrexia	1 (1.7)	0
Renal failure	1 (1.7)	0
Skin reaction	1 (1.7)	0
Small intestinal hemorrhage	1 (1.7)	1 (1.7)
Tremor	1 (1.7)	0
Weight increased	1 (1.7)	0

*Events are listed as indicated on the case report form. Although rash and maculopapular rash may reflect the same condition, they were listed as two distinct events for the phase 2 safety report. Events were coded according to Preferred Terms (MedDRA version 20.0), NCI grades were coded using CTCAE version 4.03. Events are listed in decreasing order of frequency by any grade.

CSCC, cutaneous squamous cell carcinoma; CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute.

Table S9. Integrated Response Analysis by Central Review for All Patients with Metastatic CSCC*

	Phase 1 metastatic CSCC (N = 16)[†]	Phase 2 metastatic CSCC (N = 59)	Total (N = 75)
Best overall response, no. (%)			
Complete response	0	4 (6.8)	4 (5.3)
Partial response	7 (43.8)	24 (40.7)	31 (41.3)
Stable disease	4 (25.0)	9 (15.3)	13 (17.3)
Non-complete response/non-progressive disease[‡]	1 (6.3)	4 (6.8)	5 (6.7)
Progressive disease	3 (18.8)	11 (18.6)	14 (18.7)
Not evaluable[§]	1 (6.3)	7 (11.9)	8 (10.7)
Objective response, % (95% CI)	43.8 (19.8–70.1)	47.5 (34.3–60.9)	46.7 (35.1–58.6)
Durable disease control, % (95% CI) [¶]	62.5 (35.4–84.8)	61.0 (47.4–73.5)	61.3 (49.4–72.4)
Median observed time to response, months (range)[#]	1.9 (1.7–5.6)	1.9 (1.7–6.0)	1.9 (1.7–6.0)

*All patients with metastatic CSCC (i.e., distant and/or nodal metastatic disease) from the Phase 1 CSCC study (who met eligibility criteria for the Phase 2 study) and from the Phase 2 study are included in this analysis. [†]Does not include the penile squamous cell carcinoma patient (Table 1) from the phase 1 CSCC expansion cohorts (who had partial response per central review) because squamous cell carcinoma is not considered a cutaneous malignancy in the integrated analysis; does include the one metastatic CSCC patient from the dose escalation portion of the phase 1 study[1] (who also had partial response by central review). [‡]Patients with non-measurable disease on central

review of baseline imaging. [§]Includes missing and unknown tumor response. [¶]Defined as the proportion of patients without progressive disease for at least 105 days. [#]Data shown are from patients with confirmed complete or partial response (phase 1, N = 7; phase 2, N = 28; total, N = 35).

CI, confidence interval; CSCC, cutaneous squamous cell carcinoma; no., number.

Table S10. Response Analysis by Central Review for Phase 1 CSCC Expansion Cohort Patients Who Met the Definition of Locally Advanced CSCC Used in the Phase 2 study

	Locally Advanced CSCC* (N = 10)
Best overall response, no. (%)	
Complete response	0
Partial response	6 (60.0)
Stable disease	2 (20.0)
Non-complete response/non-progressive disease[†]	0
Progressive disease	0
Not evaluable[‡]	2 (20.0)
Objective response, % (95% CI)	60.0 (26.2–87.8)
Durable disease control, % (95% CI) [§]	70.0 (34.8–93.3)
Median observed time to response, months (range)[¶]	3.7 (1.8–7.3)

*Patients with locally advanced CSCC according to the Phase 2 definition (i.e. no nodal or distant metastasis) from the Phase 1 CSCC expansion cohorts were included in this analysis. [†]Patients with non-measurable disease on central review of baseline imaging. [‡]Include missing and unknown tumor response. [§]Defined as the proportion of patients without progressive disease for at least 105 days. [¶]Data shown are from patients with confirmed response; N = 6.

CI, confidence interval; CSCC, cutaneous squamous cell carcinoma.

Reference

1. Falchook GS, Leidner R, Stankevich E, et al. Responses of metastatic basal cell and cutaneous squamous cell carcinomas to anti-PD1 monoclonal antibody REGN2810. J Immunother Cancer 2016;4:70.