2018

PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma

L. Hernandez-Aya
Washington University School of Medicine in St. Louis
et al

ORIGINAL ARTICLE

PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma

M.R. Migden, D. Rischin, C.D. Schmults, A. Guminski, A. Hauschild, K.D. Lewis, C.H. Chung, L. Hernandez-Aya, A.M. Lim, A.L.S. Chang, G. Rabinowits, A.A. Thai, L.A. Dunn, B.G.M. Hughes, N.I. Khushalani, B. Modi, D. Schadendorf, B. Gao, F. Seebach, S. Li, J. Li, M. Mathias, J. Booth, K. Mohan, E. Stankevich, H.M. Babiker, I. Brana, M. Gil-Martin, J. Homsi, M.L. Johnson, V. Moreno, J. Niu, T.K. Owonikoko, K.P. Papadopoulos, G.D. Yancopoulos, I. Lowy, and M.G. Fury

ABSTRACT

BACKGROUND

No systemic therapies have been approved for the treatment of advanced cutaneous squamous-cell carcinoma. This cancer may be responsive to immune therapy, because the mutation burden of the tumor is high and the disease risk is strongly associated with immunosuppression. In the dose-escalation portion of the phase 1 study of cemiplimab, a deep and durable response was observed in a patient with metastatic cutaneous squamous-cell carcinoma.

METHODS

We report the results of the phase 1 study of cemiplimab for expansion cohorts of patients with locally advanced or metastatic cutaneous squamous-cell carcinoma, as well as the results of the pivotal phase 2 study for a cohort of patients with metastatic disease (metastatic-disease cohort). In both studies, the patients received an intravenous dose of cemiplimab (3 mg per kilogram of body weight) every 2 weeks and were assessed for a response every 8 weeks. In the phase 2 study, the primary end point was the response rate, as assessed by independent central review.

RESULTS

In the expansion cohorts of the phase 1 study, a response to cemiplimab was observed in 13 of 26 patients (50%; 95% confidence interval [CI], 30 to 70). In the metastatic-disease cohort of the phase 2 study, a response was observed in 28 of 59 patients (47%; 95% CI, 34 to 61). The median follow-up was 7.9 months in the metastatic-disease cohort of the phase 2 study. Among the 28 patients who had a response, the duration of response exceeded 6 months in 57%, and 82% continued to have a response and to receive cemiplimab at the time of data cutoff. Adverse events that occurred in at least 15% of the patients in the metastatic-disease cohort of the phase 2 study were diarrhea, fatigue, nausea, constipation, and rash; 7% of the patients discontinued treatment because of an adverse event.

CONCLUSIONS

Among patients with advanced cutaneous squamous-cell carcinoma, cemiplimab induced a response in approximately half the patients and was associated with adverse events that usually occur with immune checkpoint inhibitors. (Funded by Regeneron Pharmaceuticals and Sanofi; ClinicalTrials.gov numbers, NCT02383212 and NCT02760498.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Migden at the Departments of Dermatology and Head and Neck Surgery, University of Texas MD Anderson Cancer Center, 1400 Pressler St. #1452, Houston, TX 73030, or at mrmigden@mdanderson.org.

Drs. Migden and Rischin contributed equally to this article.

This article was published on June 4, 2018, at NEJM.org.

N Engl J Med 2018;379:341-51.
DOI: 10.1056/NEJMoa1805131

Cutaneous squamous-cell carcinoma is the second most common skin cancer; only basal-cell carcinoma has a higher incidence.[1,2] Risk factors for cutaneous squamous-cell carcinoma include chronic sun exposure, advanced age, skin that is sensitive to ultraviolet radiation, and immunosuppression.[3] In more than 95% of patients, the cancer is cured with surgery.[4] In a small percentage of patients, the tumor reaches an incurable state because it becomes metastatic or has locally advanced progression and is no longer amenable to surgery or radiation therapy. Advanced cutaneous squamous-cell carcinoma is a condition that encompasses these two incurable situations, and patients with this condition are considered for palliative systemic therapy, which can be administered as part of routine clinical practice.[5-7] In 2012, an estimated 3900 to 8700 people in the United States died from cutaneous squamous-cell carcinoma.[8]

Cutaneous squamous-cell carcinoma has the clinical and molecular hallmarks of a tumor that is likely to be responsive to systemic immune therapy: the mutation burden of the tumor is high, and the disease risk is increased among patients with immunosuppression.[9-11] Patients who have undergone solid-organ transplantation and are receiving immunosuppressive therapy have a risk of cutaneous squamous-cell carcinoma that is 65 to 250 times as high as the risk in the general population,[9] which suggests that immune surveillance is critical for preventing cutaneous squamous-cell carcinoma in immunocompetent people. Most patients with cutaneous squamous-cell carcinoma have hypermutated tumors because of chronic skin damage from ultraviolet light,[10,11] and patients who have tumors with a high mutation burden are more likely to have a response to immune therapy with a checkpoint inhibitor, possibly because the tumors have increased neoantigen expression.[12-14]

Cemiplimab is a high-affinity, highly potent human monoclonal antibody directed against programmed death 1 (PD-1).[15] In the dose-escalation portion of the phase 1 study of cemiplimab, a deep and durable response was observed in a patient with advanced cutaneous squamous-cell carcinoma.[16] We report the results of the phase 1 study for expansion cohorts of patients with locally advanced or metastatic cutaneous squamous-cell carcinoma, as well as the results of the primary analysis of the pivotal phase 2 study for a cohort of patients with metastatic disease (metastatic-disease cohort). The primary objective of the phase 2 study was to establish the clinical benefit of cemiplimab, as measured by an objective response rate. A key secondary objective was to assess the duration of response to cemiplimab within the limits of study follow-up.

Methods

Patients

The expansion cohorts of the phase 1 study involved adult patients who had advanced (locally advanced or metastatic) cutaneous squamous-cell carcinoma. Patients who had locally advanced disease were eligible for inclusion in the study if they were not candidates for surgery for one or both of the following reasons: they had disease recurrence after two or more surgical procedures and the treating clinicians expected that curative resection would be unlikely, or the treating clinicians anticipated that surgery would result in substantial complications or deformity. The phase 2 study was designed to involve adult patients who had metastatic cutaneous squamous-cell carcinoma with distant or regional metastasis or both (group 1), as well as adult patients who had locally advanced cutaneous squamous-cell carcinoma (group 2). The time point for the primary analysis was reached for the metastatic-disease cohort. Thus, we report the results of the phase 1 study for the expansion cohorts, as well as the results of the primary analysis of the phase 2 study for the metastatic-disease cohort. Results of the phase 2 study for the locally advanced–disease cohort are not included in this article, because the data are interim and the time point for the primary analysis (according to the statistical analysis plan) has not yet been reached.

For both studies, key eligibility criteria were an Eastern Cooperative Oncology Group performance status score of 0 or 1 (on a 5-point scale, with higher scores indicating greater disability), adequate organ function, and the presence of at least one lesion that could be measured according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.[17] Patients were excluded if they had ongoing or recent (within 5 years) autoimmune disease that was treated with systemic immunosuppressive therapy or if they had previously received treatment with anti–PD-1 or anti–programmed death ligand 1 therapy, had un-

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Expansion Cohorts of the Phase 1 Study (N=26)	Metastatic-Disease Cohort of the Phase 2 Study (N=59)
Age		
Median (range) — yr	73 (55–88)	71 (38–93)
≥65 yr — no. (%)	21 (81)	43 (73)
Male sex — no. (%)	21 (81)	54 (92)
ECOG performance status score — no. (%)†		
0	10 (38)	23 (39)
1	16 (62)	36 (61)
Primary site of cutaneous squamous-cell carcinoma — no. (%)		
Head or neck	18 (69)	38 (64)
Arm or leg	5 (19)	12 (20)
Trunk	2 (8)	9 (15)
Penis	1 (4)	0
Previous systemic therapy for cutaneous squamous-cell carcinoma — no. of patients (%)‡		
No regimens	8 (31)	26 (44)
Any regimen	15 (58)	33 (56)
1 regimen	15 (58)	22 (37)
≥2 regimens	0	11 (19)
Previous radiotherapy for cutaneous squamous-cell carcinoma — no. (%)	20 (77)	50 (85)
Extent of cutaneous squamous-cell carcinoma — no. (%)		
Distant metastasis	8 (31)	45 (76)
Regional metastasis only	8 (31)	14 (24)
Locally advanced progression only	10 (38)	0

* The expansion cohorts of the phase 1 study involved patients with metastatic or locally advanced cutaneous squamous-cell carcinoma. The metastatic-disease cohort of the phase 2 study involved patients with metastatic cutaneous squamous-cell carcinoma.
† Eastern Cooperative Oncology Group (ECOG) performance status scores are measured on a 5-point scale, with higher scores indicating greater disability.
‡ In the phase 1 cohorts, previous systemic therapies were unknown for 3 patients. In the phase 2 cohort, 14 patients had received previous systemic therapy for cutaneous squamous-cell carcinoma with palliative intent.

dergone solid-organ transplantation, or had concurrent cancer, unless the disease was indolent or was not considered to be life-threatening (e.g., basal-cell carcinoma). Patients who had hematologic cancer (e.g., chronic lymphocytic leukemia) were excluded from the phase 2 study. For details about the inclusion and exclusion criteria, see the study protocols, available with the full text of this article at NEJM.org.

STUDY DESIGN

The phase 1 study was an open-label, multicenter study of cemiplimab that involved patients with advanced solid-tumor cancers. The primary end point was the safety and side-effect profile of cemiplimab. The phase 2 study was a nonrandomized, global, pivotal study of cemiplimab involving patients with advanced cutaneous squamous-cell carcinoma. The primary end point was the response rate, as assessed by independent central review. For both studies, secondary end points included the duration of response, progression-free survival, overall survival, and toxic effects. An additional analysis was performed to evaluate the rate of durable disease control, which was defined as the proportion of patients who

Table 2. Tumor Response to Cemiplimab, as Assessed by Independent Central Review.*

Outcome	Expansion Cohorts of the Phase 1 Study (N=26)	Metastatic-Disease Cohort of the Phase 2 Study (N=59)
Best overall response — no. (%)†		
Complete response	0	4 (7)
Partial response	13 (50)	24 (41)
Stable disease	6 (23)	9 (15)
Progressive disease	3 (12)	11 (19)
Could not be evaluated‡	3 (12)	7 (12)
Nontarget lesions only§	1 (4)	4 (7)
Objective response — % (95% CI)	50 (30–70)	47 (34–61)
Durable disease control — % (95% CI)	65 (44–83)	61 (47–74)
Median observed time to response (range) — mo¶	2.3 (1.7–7.3)	1.9 (1.7–6.0)

* The expansion cohorts of the phase 1 study involved patients with metastatic or locally advanced cutaneous squamous-cell carcinoma. The metastatic-disease cohort of the phase 2 study involved patients with metastatic cutaneous squamous-cell carcinoma.
† To determine the tumor response, results of whole-body imaging were evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. In the phase 2 study, digital medical photographs were evaluated according to protocol-specified composite response criteria.
‡ The data include patients who did not undergo imaging studies after the initiation of therapy or had imaging studies that could not be evaluated by independent central review.
§ The data include patients who had nontarget lesions only (i.e., lesions that could not be measured according to RECIST, version 1.1) and did not have disappearance of all lesions or unequivocal progression.
¶ The data are from patients who had a confirmed complete or partial response.

did not have progressive disease for at least 105 days. The treatment regimen was an intravenous dose of cemiplimab (3 mg per kilogram of body weight, administered over a period of 30 minutes) every 2 weeks. The duration of treatment was up to 48 weeks in the phase 1 study and up to 96 weeks in the phase 2 study or until the patient had unacceptable toxic effects or had confirmed disease progression.

STUDY OVERSIGHT

For both studies, the protocols and all amendments were approved by the institutional review board at each participating study site; the protocols, statistical analysis plans, and amendments are available at NEJM.org. The studies were conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. The patients provided written informed consent before enrollment.

The studies were sponsored by Regeneron Pharmaceuticals and Sanofi. They were designed by employees of Regeneron Pharmaceuticals in collaboration with the authors. The phase 2 study was overseen by a steering committee. For each study, efficacy results were reviewed by an independent central response-assessment committee. The data were collected by investigators, analyzed by statisticians employed by the sponsors, and interpreted by the authors, including employees of the sponsors. The authors had unrestricted access to the data, were responsible for all content and editorial decisions, and received no honoraria related to the development of the manuscript. The authors, in collaboration with the sponsors, made the decision to submit the manuscript for publication when the primary analysis of the phase 2 study was completed, in accordance with the statistical analysis plan.

The first draft of the manuscript was prepared by a medical writer, who was paid by the sponsors; the draft was based on comments that were provided by the authors on the manuscript outline, which was also prepared by the medical writer. Thereafter, the first draft was critically reviewed and revised by the authors. The sponsors provided comments on an early draft. The authors agreed to maintain confidentiality of the data until publication and vouch for the accuracy and complete-

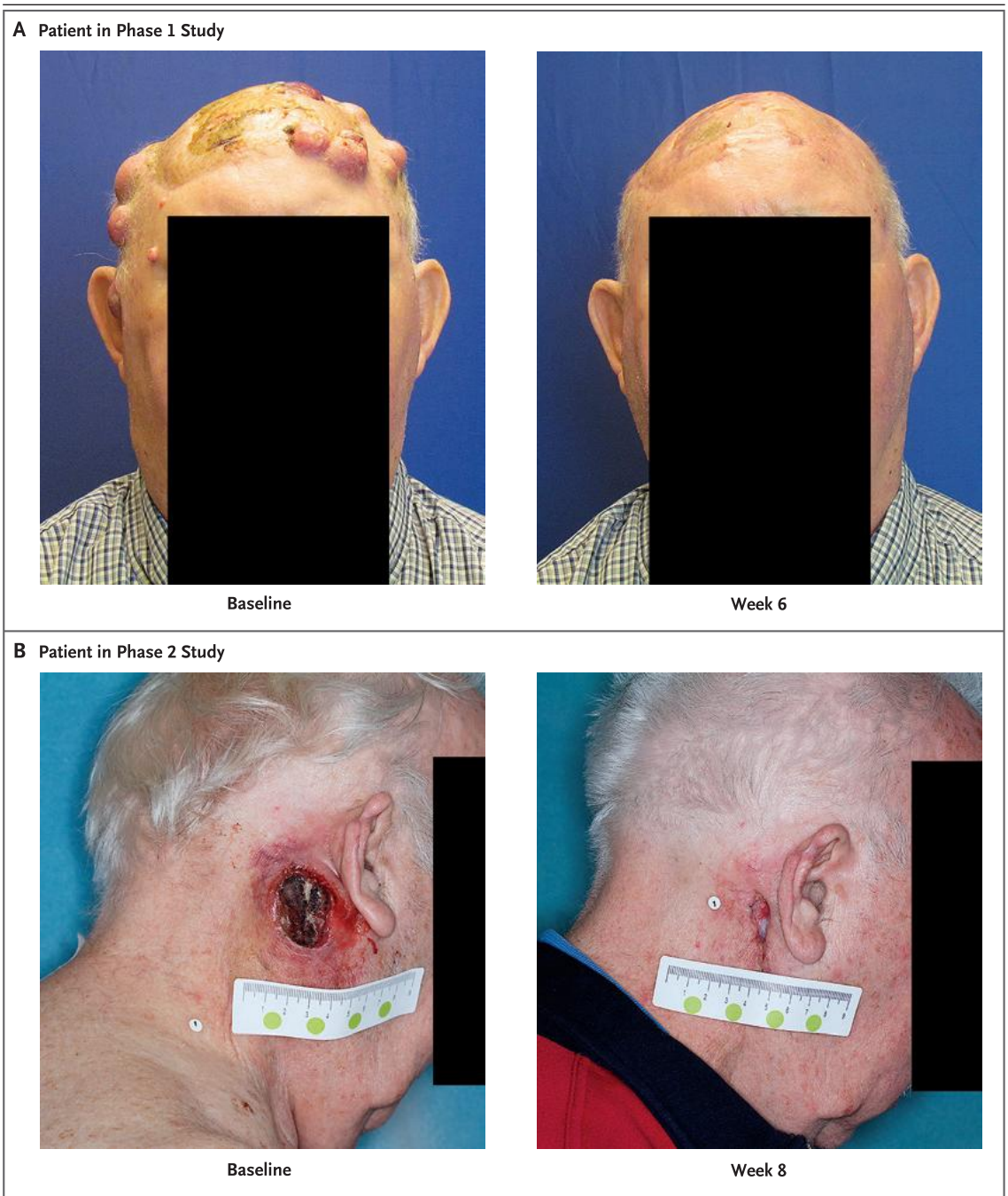


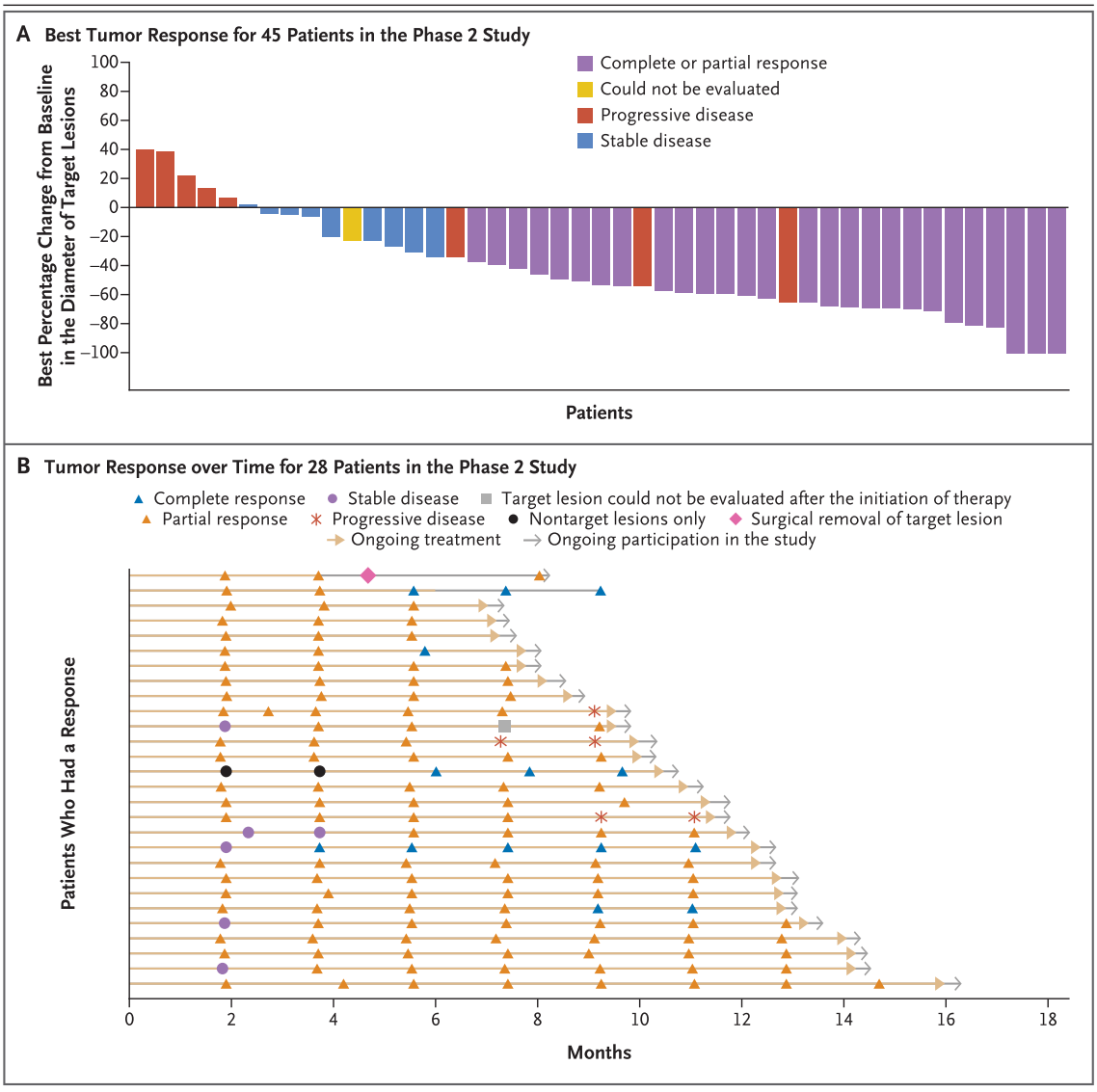
Figure 1. Effect of Cemiplimab in Patients with Advanced Cutaneous Squamous-Cell Carcinoma.

Panel A shows a 62-year-old patient at baseline and after 6 weeks of treatment with cemiplimab. Panel B shows an 83-year-old patient, who had undergone multiple surgeries for cutaneous squamous-cell carcinoma, at baseline and after 8 weeks of treatment with cemiplimab.

ness of the data and the fidelity of the studies to the protocols.

ASSESSMENTS

In both studies, the patients were assessed for a response to cemiplimab every 8 weeks by means of imaging studies. Results of whole-body imaging were evaluated according to RECIST, version 1.1.[17] In the phase 2 study, digital medical photographs of the skin were evaluated according to protocol-specified composite response criteria. Confirmatory imaging studies were obtained no less than



4 weeks after the initial documentation of a response. Patients who received at least one dose of cemiplimab were assessed for toxic effects during the treatment phase; the assessment included adverse-event reporting, laboratory tests, electrocardiograms, and measurement of vital signs. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

STATISTICAL ANALYSIS

The results are presented in accordance with the intention-to-treat principle. The data cutoff points were October 2, 2017, for the expansion cohorts of the phase 1 study and October 27, 2017, for the metastatic-disease cohort of the phase 2 study. For the phase 1 cohorts, the analysis did not include formal hypothesis testing. For the phase 2 cohort, the primary analysis was based on a single-stage exact binomial design, with a null hypothesis that the response rate would be 15% or less. We calculated that a sample of 50 patients would give the phase 2 study 85% power to reject the null hypothesis if the true response rate was at least 34%. In accordance with the statistical analysis plan for the phase 2 study, the primary analysis was conducted 6 months after the first dose of cemiplimab had been administered in the last patient to be enrolled.

Figure 2 (facing page). Tumor Response to Cemiplimab among Patients in the Phase 2 Study Who Had Metastatic Cutaneous Squamous-Cell Carcinoma.

Panel A shows the best percentage change from baseline in the sum of the diameters of the target lesions for each of the 45 patients in the metastatic-disease cohort of the phase 2 study who underwent imaging studies after the initiation of therapy, as well as the best response for each patient. The results of imaging studies were assessed by independent central review. Target lesions were lesions that could be measured according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1; patients could have up to two target lesions per organ and five total target lesions. Nontarget lesions were lesions that could not be measured according to RECIST, version 1.1; patients with nontarget lesions only were considered to have a noncomplete response or nonprogressive disease, unless there was disappearance of all lesions or unequivocal progression. Measurements that were obtained after disease progression were excluded. A partial response was defined as a decrease in the sum of the target-lesion diameters of at least 30%, and progressive disease was defined as an increase in the sum of the target-lesion diameters of at least 20%. Three patients who had a decrease in the sum of the target-lesion diameters of at least 30% were classified as having progressive disease (red bars below baseline) because they had a new lesion or progression of a nontarget lesion. One patient had stable disease according to RECIST, version 1.1, but could not be evaluated overall (yellow bar) because the digital medical photographs could not be evaluated. The graph does not show data for the following patients (although they were included in the primary analysis): 3 patients who had new lesions or progression of nontarget lesions but had target lesions that could not be evaluated after the initiation of therapy, 1 patient who had a complete response but had nontarget lesions only at baseline, 4 patients who had nontarget lesions only, and 6 patients who had a target lesion that could not be evaluated after the initiation of therapy. Panel B shows the time to response and the duration of response for the 28 patients in the metastatic-disease cohort of the phase 2 study who had a response. Of the 28 patients, 23 continued to have a response at the time of data cutoff, 3 had progressive disease, 1 had surgical removal of the responsive target lesion and thus had censored data after surgery (top line), and 1 had a confirmed complete response but had censored data after being lost to follow-up (second line from the top). One of the 23 patients who continued to have a response (14th line from top) had nontarget lesions only and was deemed by independent central review to have a complete response after the lesions disappeared.

RESULTS

EXPANSION COHORTS OF THE PHASE 1 STUDY

From March 2016 through January 2017, a total of 26 patients with advanced cutaneous squamous-cell carcinoma were enrolled in expansion cohorts of the phase 1 study and were treated with cemiplimab. The median age was 73 years (range, 55 to 88). With respect to previous treatments for cutaneous squamous-cell carcinoma, 15 patients (58%) had received previous systemic therapy and 20 (77%) had received previous radiotherapy. Data on baseline characteristics, disposition, and exposure to cemiplimab are summarized in Table 1, and in Tables S1 and S2 in the Supplementary Appendix, available at NEJM.org.

The median follow-up was 11.0 months (range, 1.1 to 17.0). The most common adverse events of any grade were fatigue (occurring in 27% of the patients), as well as constipation, decreased appetite, diarrhea, hypercalcemia, hypophosphatemia, nausea, and urinary tract infection (each occurring in 15% of the patients). There were five deaths: three were due to disease progression, one was due to an unknown cause in a patient who had discontinued treatment because of disease progression and was subsequently lost to follow-up, and one was due to an adverse event. Details about the fatal adverse event are provided in Table S3 in the Supplementary Appendix. Adverse events that were assessed by investigators to be related to the treatment are shown in Table S4 in the Supplementary Appendix.

The response rate, as assessed by independent central review, was 50% (95% confidence interval [CI], 30 to 70) (Table 2). The rate of durable disease control was 65% (95% CI, 44 to 83). The median observed time to response was 2.3 months (range, 1.7 to 7.3). The duration of response exceeded 6 months in 7 of the 13 patients who had a response (54%). Figure 1A shows a patient who had a rapid tumor reduction after 6 weeks of treatment with cemiplimab.

METASTATIC-DISEASE COHORT OF THE PHASE 2 STUDY

Patient Characteristics

From May 2016 through April 2017, a total of 59 patients with metastatic cutaneous squamous-cell

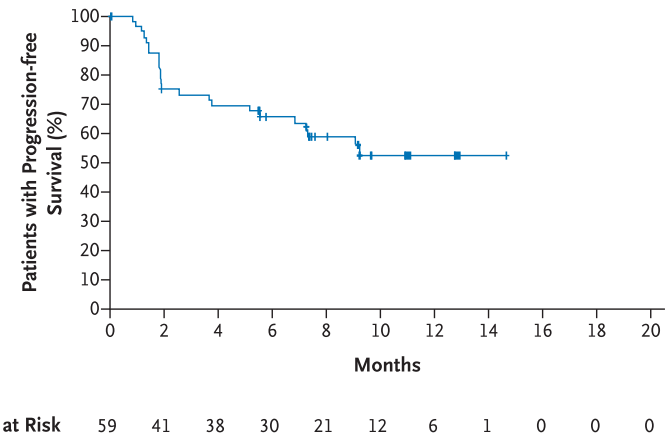


Figure 3. Kaplan–Meier Curves for the Probability of Progression-free Survival among Patients in the Phase 2 Study Who Had Metastatic Cutaneous Squamous-Cell Carcinoma.

In the metastatic-disease cohort of the phase 2 study, the median progression-free survival had not been reached at the time of data cutoff. The estimated probability of progression-free survival from baseline through 12 months was 53% (95% CI, 37 to 66), as assessed by independent central review.

carcinoma were enrolled in the metastatic-disease cohort of the phase 2 study and were treated with cemiplimab. The median age was 71 years (range, 38 to 93). With respect to previous treatments for cutaneous squamous-cell carcinoma, 33 patients (56%) had received previous systemic therapy and 50 (85%) had received previous radiotherapy (Table 1). Data on disposition and exposure to cemiplimab are shown in Tables S5 and S6 in the Supplementary Appendix. The median follow-up was 7.9 months (range, 1.1 to 15.6).

Clinical Efficacy

The response rate, as assessed by independent central review, was 47% (95% CI, 34 to 61), and the rate of durable disease control was 61% (95% CI, 47 to 74). A partial response was observed in 24 patients and a complete response in 4 patients (Table 2). Characteristics of the tumor responses are shown in Figure 2, and in Figure S1 in the Supplementary Appendix.

The median observed time to response was 1.9 months (range, 1.7 to 6.0) (Table 2). The median duration of response had not been reached at the time of this analysis. However, the duration of response exceeded 6 months in 16 of the 28 patients who had a response (57%). Among the 28 patients with confirmed responses, 3 had subsequent disease progression and data on the duration of response were censored for 2 (Fig. 2B). At the time of data cutoff, 23 of the 28 patients who had a response (82%) continued to have a response and to receive cemiplimab.

According to independent central review, neither the median progression-free survival nor the median overall survival had been reached at the time of data cutoff. The estimated probability of progression-free survival at 12 months was 53% (95% CI, 37 to 66) (Fig. 3), and the estimated probability of overall survival at 12 months was 81% (95% CI, 68 to 89) (Fig. S2 in the Supplementary Appendix). Figure 1B shows the effect of cemiplimab on the natural course of advanced cutaneous squamous-cell carcinoma in a patient with metastatic disease and an externally visible lesion. (For additional examples, see Fig. S3 in the Supplementary Appendix.)

In subgroup analyses, similar efficacy was observed in patients with regional metastatic disease and in those with distant metastatic disease. A response was observed in 22 of 45 patients with distant metastasis (49%; 95% CI, 34 to 64) and in 6 of 14 patients with regional metastasis (43%; 95% CI, 18 to 71).

Adverse Events

The most common adverse events were diarrhea (occurring in 27% of the patients), fatigue (24%), nausea (17%), constipation (15%), and rash (15%) (Table 3, and Table S7 in the Supplementary Appendix). Four patients (7%) discontinued treatment because of an adverse event. Adverse events of grade 3 or higher that occurred in more than one patient were cellulitis, pneumonitis, hypercalcemia, pleural effusion, and death.

Overall, there were 11 deaths: 8 were due to disease progression, and 3 were due to adverse events. A 93-year-old man presented on study day 35 with fever and cough with purulent sputum, and he died from complications of pneumonia on day 38. A 72-year-old man died in his sleep on study day 41. A 90-year-old man who had disease progression (as assessed by independent central review) on study day 57 had a duodenal ulcer and esophagitis that resolved on day 64; the patient subsequently had hypercalcemia and deep-vein thrombosis and died on day 92. No autopsies were performed on these three patients. Adverse events that were assessed by investigators to be related to the treatment are shown in Table S8 in the Supplementary Appendix.

DISCUSSION

Advanced cutaneous squamous-cell carcinoma is a life-threatening condition for which no systemic therapies have been approved. The study of cemiplimab for the treatment of advanced cutaneous squamous-cell carcinoma was underpinned by the recognition that a high mutation burden may render these tumors sensitive to effector T cells in the context of immune checkpoint blockade.[18] In addition, the dramatically increased risk of cutaneous squamous-cell carcinoma among people with immunosuppression pointed to an important role for immune surveillance for this cancer. In the dose-escalation portion of the phase 1 study of cemiplimab, an objective response was observed in a patient with metastatic cutaneous squamous-cell carcinoma.[16] We report results showing robust efficacy of cemiplimab in the phase 1 study in expansion cohorts of patients with advanced cutaneous squamous-cell carcinoma, as well as in the phase 2 study in a cohort of patients with metastatic disease. The response rates were consistent in the phase 1 cohorts and the phase 2 cohort (50% and 47%, respectively), as were the characteristics of the tumor responses.

Cemiplimab had similar efficacy for the treatment of metastatic and locally advanced cutaneous squamous-cell carcinoma. After integrating the results for the 75 patients who had metastatic disease in the two studies (the 59 patients in the metastatic-disease cohort of the phase 2 study plus the 16 patients in the phase 1 study who met the criteria for metastatic disease that were used in the phase 2 study), the response rate was 47% (95% CI, 35 to 59) (Table S9 in the Supplementary Appendix). Of the 10 patients in the expansion cohorts who met the criteria for locally advanced disease that were used in the phase 2 study (i.e., no regional or distant metastasis), 6 had an objective response (Table S10 in the Supplementary Appendix). These results indicate that advanced cutaneous squamous-cell carcinoma tumors, whether metastatic or locally advanced, are responsive to cemiplimab. The phase 2 study of cemiplimab for locally advanced cutaneous squamous-cell carcinoma is ongoing.

Most adverse events that were assessed by investigators to be related to the treatment were grade 1 or 2 events, and 8% and 7% of the patients in the phase 1 cohorts and the phase 2 cohort, respectively, discontinued treatment because of adverse events. Despite the advanced age of the patients, no new safety signals were reported in these cohorts.[19-21]

Table 3. Adverse Events.*

Event	Metastatic-Disease Cohort of the Phase 2 Study (N=59)	
	Any Grade	Grade ≥3
	no. of patients (%)	
Any	59 (100)	25 (42)
Serious	21 (36)	17 (29)
Led to discontinuation of treatment	4 (7)	3 (5)
Associated with an outcome of death	3 (5)	3 (5)
Occurred in ≥5 patients		
Diarrhea	16 (27)	1 (2)
Fatigue	14 (24)	1 (2)
Nausea	10 (17)	0
Constipation	9 (15)	1 (2)
Rash	9 (15)	0
Cough	8 (14)	0
Decreased appetite	8 (14)	0
Pruritus	8 (14)	0
Headache	8 (14)	0
Dry skin	6 (10)	0
Maculopapular rash	6 (10)	0
Vomiting	6 (10)	0
Anemia	5 (8)	1 (2)
Hypothyroidism	5 (8)	0
Increased alanine aminotransferase	5 (8)	0
Pneumonitis	5 (8)	2 (3)

* 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 safety report of the phase 2 study. Adverse events were coded according to the Preferred Terms of the *Medical Dictionary for Regulatory Activities*, version 20.0. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. A complete list of adverse events that occurred in the metastatic-disease cohort of the phase 2 study is provided in Table S7 in the Supplementary Appendix.

Our results show the efficacy of cemiplimab for the treatment of cutaneous squamous-cell carcinoma in immunocompetent patients. We did not enroll immunocompromised patients, and thus we cannot comment on the efficacy of cemiplimab among such patients.

Our results are consistent with an emerging theme regarding the high efficacy of immune

checkpoint blockade for the treatment of hypermutated cancers, since the mutation burden of cutaneous squamous-cell carcinoma is similar to that reported for advanced solid tumors with microsatellite instability.[10,11,14,22] A pivotal phase 2 study of cemiplimab for the treatment of advanced basal-cell carcinoma in immunocompetent patients is in progress (ClinicalTrials.gov number, NCT03132636).

In conclusion, among patients with advanced cutaneous squamous-cell carcinoma, cemiplimab induced a response in approximately half the patients and was associated with adverse events that are similar to those seen with other PD-1 inhibitors.

Supported by Regeneron Pharmaceuticals and Sanofi. Medical-writing assistance, provided by Emmanuel Ogunnowo, Ph.D., of Prime (Knutsford, United Kingdom), was funded by Regeneron Pharmaceuticals and Sanofi, according to Good Publication Practice guidelines. Dr. Lim was supported by a Clinician Research Fellowship from the Department of Health and Raine Medical Research Foundation. Dr. Thai was supported by a Fellowship in Head and Neck and Lung Oncology from the Spotlight Foundation.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patients and their families.

APPENDIX

The authors' full names and academic degrees are as follows: Michael R. Migden, M.D., Danny Rischin, M.D., Chrysalyne D. Schmults, M.D., Alexander Guminski, M.D., Ph.D., Axel Hauschild, M.D., Karl D. Lewis, M.D., Christine H. Chung, M.D., Leonel Hernandez-Aya, M.D., Annette M. Lim, M.D., Ph.D., Anne Lynn S. Chang, M.D., Guilherme Rabinowits, M.D., Alesha A. Thai, M.D., Lara A. Dunn, M.D., Brett G.M. Hughes, M.D., Nikhil I. Khushalani, M.D., Badri Modi, M.D., Dirk Schadendorf, M.D., Bo Gao, Ph.D., Frank Seebach, M.D., Siyu Li, Ph.D., Jingjin Li, Ph.D., Melissa Mathias, M.D., Jocelyn Booth, M.B.A., Kosalai Mohan, Ph.D., Elizabeth Stankevich, B.S., Hani M. Babiker, M.D., Irene Brana, M.D., Ph.D., Marta Gil-Martin, M.D., Jade Homsi, M.D., Melissa L. Johnson, M.D., Victor Moreno, M.D., Ph.D., Jiaxin Niu, M.D., Ph.D., Taofeek K. Owonikoko, M.D., Ph.D., Kyriakos P. Papadopoulos, M.D., George D. Yancopoulos, M.D., Ph.D., Israel Lowy, M.D., Ph.D., and Matthew G. Fury, M.D., Ph.D.

The authors' affiliations are as follows: the Departments of Dermatology and Head and Neck Surgery, University of Texas MD Anderson Cancer Center, Houston (M.R.M.), and South Texas Accelerated Research Therapeutics (START), San Antonio (K.P.P.) — both in Texas; the Department of Medical Oncology, Peter MacCallum Cancer Centre and University of Melbourne, Melbourne, VIC (D.R., A.A.T.), the Department of Medical Oncology, Royal North Shore Hospital, St. Leonards, VIC (A.G.), the Department of Medical Oncology, Sir Charles Gairdner Hospital, Perth, WA (A.M.L.), and Royal Brisbane and Women's Hospital and University of Queensland, Brisbane (B.G.M.H.) — all in Australia; the Department of Dermatology, Brigham and Women's Hospital (C.D.S.), the Department of Dermatology, Harvard Medical School (C.D.S.), and the Department of Medical Oncology, Dana–Farber Cancer Institute (G.R.) — all in Boston; Schleswig-Holstein University Hospital, Kiel (A.H.), and University Hospital Essen, Essen and German Cancer Consortium, Essen (D.S.) — both in Germany; University of Colorado Denver, School of Medicine, Aurora (K.D.L.); the Departments of Head and Neck–Endocrine Oncology (C.H.C.) and Cutaneous Oncology (N.I.K.), H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; the Division of Medical Oncology, Department of Medicine, Washington University School of Medicine, St. Louis (L.H.-A.); the Department of Dermatology, Stanford University School of Medicine, Redwood City (A.L.S.C.), and the Division of Dermatology, City of Hope, Duarte (B.M.) — both in California; the Department of Medicine, Head and Neck Medical Oncology, Memorial Sloan Kettering Cancer Center, New York (L.A.D.), and Regeneron Pharmaceuticals, Tarrytown (F.S., M.M., K.M., G.D.Y., I.L., M.G.F.) — both in New York; Regeneron Pharmaceuticals, Basking Ridge, NJ (B.G., S.L., J.L., J.B., E.S.); University of Arizona Cancer Center, Tucson (H.M.B.), and Banner MD Anderson Cancer (J.H.) and the Department of Medical Oncology, Banner MD Anderson Cancer Center (J.N.), Gilbert — all in Arizona; Medical Oncology Department, Vall D'Hebron University Hospital (I.B.), and Institut Català D'Oncologia, L'Hospitalet de Llobregat (M.G.-M.), Barcelona, and START Madrid-FJD, Hospital Fundación Jiménez Díaz, Madrid (V.M.) — all in Spain; Sarah Cannon Research Institute, Nashville (M.L.J.); and the Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta (T.K.O.).

REFERENCES

1. Rogers HW, Weinstock MA, Feldman SR, Coldiron BM. Incidence estimate of nonmelanoma skin cancer (keratinocyte carcinomas) in the U.S. population, 2012. JAMA Dermatol 2015;151:1081-6.
2. Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol 2012;166:1069-80.
3. Stratigos A, Garbe C, Lebbe C, et al. Diagnosis and treatment of invasive squamous cell carcinoma of the skin: European consensus-based interdisciplinary guideline. Eur J Cancer 2015;51:1989-2007.
4. Kauvar AN, Arpey CJ, Hruza G, Olbricht SM, Bennett R, Mahmoud BH. Consensus for nonmelanoma skin cancer treatment, part II: squamous cell carcinoma, including a cost analysis of treatment methods. Dermatol Surg 2015;41:1214-40.
5. Hillen U, Leiter U, Haase S, et al. Advanced cutaneous squamous cell carcinoma: a retrospective analysis of patient profiles and treatment patterns — results of a non-interventional study of the DeCOG. Eur J Cancer 2018;96:34-43.
6. Jarkowski A III, Hare R, Loud P, et al. Systemic therapy in advanced cutaneous squamous cell carcinoma (CSCC): the Roswell Park experience and a review of the literature. Am J Clin Oncol 2016;39:545-8.
7. Cranmer LD, Engelhardt C, Morgan SS. Treatment of unresectable and metastatic cutaneous squamous cell carcinoma. Oncologist 2010;15:1320-8.
8. Karia PS, Han J, Schmults CD. Cutaneous squamous cell carcinoma: estimated incidence of disease, nodal metastasis, and deaths from disease in the United States, 2012. J Am Acad Dermatol 2013;68:957-66.
9. Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. N Engl J Med 2003;348:1681-91.
10. Pickering CR, Zhou JH, Lee JJ, et al. Mutational landscape of aggressive cutaneous squamous cell carcinoma. Clin Cancer Res 2014;20:6582-92.
11. Chalmers ZR, Connelly CF, Fabrizio D, et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Genome Med 2017;9:34.
12. McGranahan N, Furness AJ, Rosenthal R, et al. Clonal neoantigens elicit T cell immunoreactivity and sensitivity to

immune checkpoint blockade. Science 2016;351:1463-9.
13. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology: mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 2015;348:124-8.
14. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017;357:409-13.
15. Burova E, Hermann A, Waite J, et al. Characterization of the anti-PD-1 antibody REGN2810 and its antitumor activity in human PD-1 knock-in mice. Mol Cancer Ther 2017;16:861-70.
16. 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.
17. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
18. Goodman AM, Kato S, Bazhenova L, et al. Tumor mutational burden as an independent predictor of response to immunotherapy in diverse cancers. Mol Cancer Ther 2017;16:2598-608.
19. Weber JS, Postow M, Lao CD, Schadendorf D. Management of adverse events following treatment with anti-programmed death-1 agents. Oncologist 2016;21:1230-40.
20. Zimmer L, Goldinger SM, Hofmann L, et al. Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. Eur J Cancer 2016;60:210-25.
21. Spain L, Diem S, Larkin J. Management of toxicities of immune checkpoint inhibitors. Cancer Treat Rev 2016;44:51-60.
22. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509-20.