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Primary Analysis of Phase 2 Results of Cemiplimab, a Human Monoclonal Anti–PD-1, in Patients with Locally Advanced Cutaneous Squamous Cell Carcinoma

Michael R. Migden,[1] Nikhil I. Khushalani,[2] Anne Lynn S. Chang,[3] Danny Rischin,[4] Chrysalyne D. Schmults,[5] Leonel Hernandez-Aya,[6] Friedegund Meier,[7] Dirk Schadendorf,[8] Alexander Guminski,[9] Axel Hauschild,[10] Deborah J. Wong,[11] Gregory A. Daniels,[12] Carola Berking,[13] Vladimir Jankovic,[14] Elizabeth Stankevich,[15] Jocelyn Booth,[14] Siyu Li,[14] Israel Lowy,[14] Matthew G. Fury,[14] Karl D. Lewis[16]

[1]Departments of Dermatology and Head and Neck Surgery, University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Department of Cutaneous Oncology, Moffitt Cancer Center, Tampa, FL, USA; [3]Department of Dermatology, Stanford University School of Medicine, Redwood City, CA, USA; [4]Department of Medical Oncology, Peter MacCallum Cancer Centre and University of Melbourne, Melbourne, Australia; [5]Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [6]Division of Medical Oncology, Department of Medicine, Washington University School of Medicine, St Louis, MO, USA; [7]Department of Dermatology, University Hospital Dresden, Dresden, Germany; [8]University Hospital Essen, Essen and German Cancer Consortium, Germany; [9]Department of Medical Oncology, Royal North Shore Hospital, St Leonards, Australia; [10]Schleswig-Holstein University Hospital, Kiel, Germany; [11]UCLA Department of Medicine, Los Angeles, CA, USA; [12]Division of Hematology and Oncology, University of California San Diego, Moores Cancer Center, La Jolla, CA, USA; [13]Department of Dermatology and Allergy, Munich University Hospital (LMU), Munich, Germany; [14]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [15]Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA; [16]University of Colorado Denver, School of Medicine, Aurora, CO, USA

Background

- Advanced cutaneous squamous cell carcinoma (CSCC), a term that comprises metastatic (nodal and/or distant) and locally advanced CSCC not amenable to surgery and/or radiotherapy, has a high mortality rate and poor prognosis.[1]
- Locally advanced CSCC is associated with substantial morbidity and has a major impact on quality of life and healthcare burden.[2,3]
- Previously available treatments for advanced CSCC (cytotoxic chemotherapy and epidermal growth factor receptor inhibitors) have low efficacy; durable responses are uncommon.[4,5]
- Until recently, there was no approved systemic therapy for patients with advanced CSCC.
- Cemiplimab is a high affinity, human, hinge-stabilized IgG4 monoclonal antibody to the programmed cell death (PD)-1 receptor that potently blocks the interactions of PD-1 with PD-ligand 1 (PD-L1) and PD-ligand 2 (PD-L2).[6]
  - In the US, cemiplimab-rwlc is the only Food and Drug Administration-approved treatment for patients with metastatic CSCC or locally advanced CSCC who are not candidates for curative surgery or curative radiation.[7]
- Cemiplimab produced substantial antitumor activity with durable responses in patients in the metastatic and locally advanced CSCC expansion cohorts in a Phase 1 study and in the primary analysis of patients with metastatic CSCC (Group 1) in a Phase 2 study (EMPOWER-CSCC-1; NCT02760498).[8]
- Here, we report data from the primary analysis and biomarker data of the patients with locally advanced CSCC (Group 2) from the Phase 2 study.

Objectives

- The primary objective of the Phase 2 study was to evaluate objective response rate (ORR; complete response + partial response according to independent central review [ICR]) per Response Evaluation Criteria In Solid Tumors (RECIST) 1.1[9] (for scans) and modified World Health Organization (WHO) criteria (for photos).
- Secondary objectives included estimation of ORR by investigator assessments (INV), duration of response, progression-free survival (PFS), overall survival (OS), and assessment of safety and tolerability of cemiplimab.
  - Durable disease control rate (defined as the proportion of patients without progressive disease for at least 105 days) was also assessed.
- Protocol-defined exploratory objectives included the association between PD-L1 immunohistochemistry (IHC) and tumor mutational burden (TMB) and clinical activity of cemiplimab.

Methods

- Adult patients with locally advanced CSCC from Group 2 of EMPOWER-CSCC-1, a Phase 2, non-randomized, global, pivotal trial of cemiplimab in patients with advanced CSCC, are included in this primary analysis (**Figure 1**).
- Patients were eligible for inclusion if they had a CSCC lesion not amenable to surgery or radiotherapy according to the investigator.
- Acceptable reasons for surgery to be considered inappropriate were either:
  - CSCC with significant local invasion that precluded complete resection, or
  - CSCC that was technically amenable to surgery but clinically inappropriate (lesion in an anatomically challenging location for which surgery may result in severe disfigurement or dysfunction; lesion in the same location after two or more surgical procedures and with curative resection deemed unlikely, or other conditions deemed contraindicated for surgery).
- Acceptable reasons for radiotherapy to be considered inappropriate were:
  - Prior radiotherapy with further radiotherapy exceeding the threshold of an acceptable cumulative dose.
  - Judgement of the radiation oncologist that the tumor was unlikely to respond to radiotherapy, or
  - Risk-benefit assessment that radiotherapy was contraindicated for the patient.
- Severity of treatment-emergent adverse events (TEAEs) was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03).
- PD-L1 expression level was assessed by the PD-L1 IHC 22C3 assay (Agilent) in formalin-fixed paraffin embedded (FFPE) core needle or punch tumor biopsy samples and quantified as the percentage of tumor cells with detectable PD-L1 membrane staining (tumor proportion score [TPS]).
- TMB was estimated in the DNA samples extracted from the FFPE tumor biopsies using the analytically validated TruSight Oncology 500 (Illumina).
- The data cut-off date for this analysis was October 10, 2018.

Results

Baseline characteristics, disposition, and treatment exposure

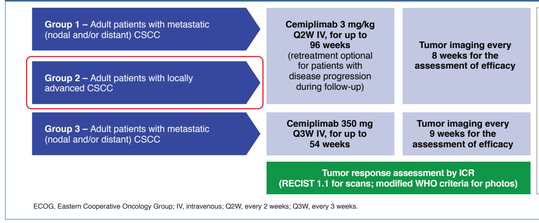
- A total of 78 patients were enrolled and treated with cemiplimab 3 mg/kg Q2W (**Table 1**).

Table 1. Patient demographics and baseline characteristics

	Locally advanced CSCC (N=78)
Median age, years (range)	74 (45–96)
≥65 years, n (%)	59 (75.6)
Male, n (%)	59 (75.6)
ECOG performance status, n (%)	
0	38 (48.7)
1	40 (51.3)
Primary CSCC site, n (%)	
Head/neck[1]	62 (79.5)
Extremity	14 (17.9)
Trunk	2 (2.6)
Prior cancer-related systemic therapy, n (%)[2]	12 (15.4)
Prior cancer-related radiotherapy, n (%)	43 (55.1)
Reasons patients were not considered candidates for surgery, n (%)	
CSCC lesion with significant local invasion that precluded complete resection	20 (25.6)
CSCC lesion in an anatomically challenging location for which surgery may result in severe disfigurement or dysfunction	30 (38.5)
CSCC lesion in the same location after two or more surgical procedures and with curative resection deemed unlikely	25 (32.1)
Other conditions deemed contraindicating for surgery	3 (3.8)
Reasons patients were not considered candidates for radiotherapy, n (%)	
Prior radiotherapy with further radiotherapy exceeding the threshold of an acceptable cumulative dose	10 (12.8)
Judgement of the radiation oncologist that the tumor was unlikely to respond to radiotherapy	17 (21.8)
Risk-benefit assessment that radiotherapy was contraindicated for the patient	38 (48.7)
Other conditions deemed contraindicating for radiotherapy	11 (14.1)
Missing	2 (2.6)

[1]Includes one patient with nodal metastasis who was incorrectly enrolled in the locally advanced Group 2 (instead of a metastatic group) due to protocol violation. Data for this patient were analyzed in Group 2 per intention-to-treat. [2]Ten patients had received one prior cancer-related systemic therapy and two had received ≥2 prior cancer-related systemic therapies.

Figure 1. EMPOWER-CSCC-1 study design (NCT02760498)



ECOG, Eastern Cooperative Oncology Group; IV, intravenous; Q2W, every 2 weeks; Q3W, every 3 weeks.

- At the time of data cut-off, five patients (6.4%) had completed the planned treatment, 24 (30.8%) remained on treatment, and 49 (62.8%) had discontinued treatment mainly due to disease progression (n=17; 21.8%) and adverse events, investigator's decision, complete response to cemiplimab, and patient's decision (each n=6; 7.7%).
- The median duration of exposure to cemiplimab was 7.9 months (range: 0.5–22.1) and the median number of doses administered was 17 (range: 1–48).
- The median duration of follow-up at the time of data cut-off was 9.3 months (range: 0.8–27.9).

Clinical activity

- By ICR, ORR was 43.6% (95% confidence interval [CI]: 32.4–55.3) with 10 patients experiencing a complete response and 24 experiencing a partial response (**Table 2**). By INV, ORR was 52.6% (95% CI: 40.9–64.0; 13 complete responses and 28 partial responses). By ICR, disease control rate was 79.5% (95% CI: 68.8–87.8).

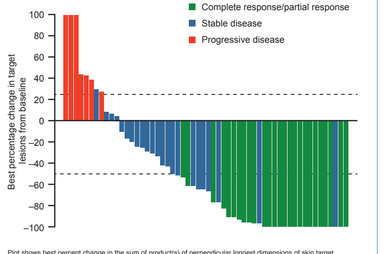
Table 2. Tumor response assessment by ICR

	Locally advanced CSCC (N=78)
Best overall response, n (%)	
Complete response	10 (12.8)
Partial response	24 (30.8)
Stable disease	28 (35.9)
Progressive disease	9 (11.5)
Not evaluable[1]	7 (9.0)
ORR, % (95% CI)[2]	43.6 (32.4–55.3)
Disease control rate, % (95% CI)	79.5 (68.8–87.8)
Durable disease control rate, % (95% CI)[3]	62.8 (51.1–73.5)
Median observed time to response, months (range)[4]	1.9 (1.8–8.8)

[1]Includes missing and unknown tumor response. [2]Not included among the responders are two patients who had progressive disease at initial response assessments per ICR, followed by subsequent responses (one partial response and one complete response). By INV, the ORR was 52.6% (95% CI: 40.9–64.0; 13 complete responses and 28 partial responses). [3]Defined as the proportion of patients without progressive disease for at least 105 days. [4]Data shown are from patients with confirmed complete or partial response.

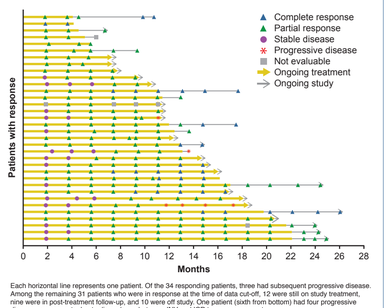
- Rapid, deep, and durable reductions in target lesions were frequently observed (**Figures 2** and **3**); examples of reductions in visible CSCC lesions following treatment with cemiplimab are shown on **Figure 4**.
- By ICR, median duration of response had not been reached at data cut-off.
  - Responses have lasted ≥12 months for 12 patients (Kaplan-Meier estimated event-free probability at 12 months in patients with confirmed complete or partial response was 87.8% [95% CI: 66.7–95.9]).
  - The longest duration of response at data cut-off was 24.2 months and was ongoing.

Figure 2. Clinical activity of tumor response to cemiplimab in patients who underwent medical photography evaluation per modified WHO criteria by ICR



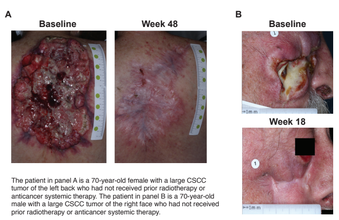
Plot shows best percent change in the sum of product(s) of perpendicular longest dimensions of skin target lesion(s) from baseline for 56 patients who had baseline skin target lesions and underwent at least one evaluable post-baseline medical photography evaluation per modified WHO criteria by ICR. Lesion measurements after progression are excluded. Horizontal dashed lines indicate WHO criteria for partial response (≥50% decrease in the sum of products of skin target lesion diameters) and progressive disease (≥25% increase in the sum of products of skin target lesion diameters). Twenty-two patients who either did not have baseline skin target lesion or did not have evaluable post-baseline photography assessment are not included in the figure but are included in the overall response analysis (Table 2) per intention-to-treat. Eight patients had tumor reductions that met criteria for response on photographic measurements but are classified as stable (blue bars >50% reduction in target lesions), either because there was no subsequent scan to confirm response (seven patients) or because composite response assessment was stable disease (one patient). Eight of 34 patients with objective response are not shown in this plot because the composite response assessments per ICR included consideration of radiology results.

Figure 3. Time to and duration of response in responding patients



Each horizontal line represents one patient. Of the 34 responding patients, three had subsequent progressive disease. Among the remaining 31 patients who were in response at the time of data cut-off, 12 were still on study treatment, nine were in post-treatment follow-up, and 10 were off study. One patient (sixth from bottom) had four progressive disease assessments due to discordance between INV and ICR tumor assessments.

Figure 4. Examples of reductions in visible CSCC lesions following treatment with cemiplimab



The patient in panel A is a 70-year-old female with a large CSCC tumor of the left back who had not received prior radiotherapy or anticancer systemic therapy. The patient in panel B is a 70-year-old male with a large CSCC tumor of the right face who had not received prior radiotherapy or anticancer systemic therapy.

- In a subgroup analysis regarding the different reasons that patients were considered to not be candidates for curative surgery, clinical activity with cemiplimab was observed in all subgroups (**Table 3**).

Table 3. Response and disease control rates by ICR by reasons patients were considered not candidates for surgery

% (95% CI)	CSCC lesions with significant local invasion that precluded complete resection (n=20)	CSCC lesions in anatomically challenging locations for which surgery may result in severe deformity or dysfunction (n=30)	CSCC lesions in the same location after two or more surgical procedures and with curative resection deemed unlikely (n=25)
ORR	50.0 (27.2–72.8)	56.7 (37.4–74.5)	24.0 (9.4–45.1)
Disease control rate	80.0 (56.3–94.3)	86.7 (69.3–96.2)	68.0 (46.5–85.1)

- Neither median PFS nor median OS had been reached at the time of data cut-off.
  - The Kaplan-Meier estimated progression-free probability at 12 months was 58.1% (95% CI: 43.7–70.0).
  - The Kaplan-Meier estimated probability of survival at 12 months was 93.2% (95% CI: 84.4–97.1).

PD-L1 immunohistochemistry and TMB

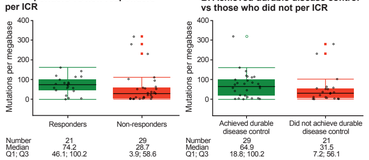
- Cemiplimab was highly active in both PD-L1 positive (TPS ≥1%) and PD-L1 negative (TPS <1%) subgroups (**Table 4**).
  - Of the 17 patients with PD-L1 TPS of <1%, ORR by ICR was 35.3% (95% CI: 14.2–61.7).
  - Of the 31 patients with PD-L1 TPS of ≥1%, ORR by ICR was 54.8% (95% CI: 36.0–72.7).
- Among 21 responders and 29 non-responders (per ICR) with samples available for analysis, median TMBs were 74.2 and 28.7 mutations per megabase, respectively (**Figure 5A**).
- Among 29 patients who achieved durable disease control and 21 patients who did not (per ICR), median TMBs were 64.9 and 31.5 mutations per megabase, respectively (**Figure 5B**).
- Preliminary analysis also suggests associations between high TMB and 12-month PFS and OS.
  - Among 12 patients who were progression-free for ≥1 year and 19 who progressed or died in <1 year, median TMBs were 57.5 and 35.1 mutations per megabase, respectively.
  - Among 29 patients who survived for ≥1 year and 3 who died in <1 year, median TMBs were 57.1 and 37.6 mutations per megabase, respectively.
    - However, many patients have not had sufficient follow-up to reach the 12-month landmark analysis.

Table 4. Tumor response per ICR by PD-L1 status

	PD-L1 <1% (N=17)	PD-L1 ≥1% (N=31)	PD-L1 ≥1–<5% (N=3)	PD-L1 ≥5–<50% (N=21)	PD-L1 ≥50% (N=7)
Best overall response, n (%)					
Complete response	1 (5.9)	4 (12.9)	0	4 (19.0)	0
Partial response	5 (29.4)	13 (41.9)	2 (66.7)	8 (38.1)	3 (42.9)
Stable disease	8 (47.1)	7 (22.6)	1 (33.3)	4 (19.0)	2 (28.6)
Progressive disease	2 (11.8)	3 (9.7)	0	1 (4.8)	2 (28.6)
Not evaluable	1 (5.9)	4 (12.9)	0	4 (19.0)	0
ORR, % (95% CI)	35.3 (14.2–61.7)	54.8 (36.0–72.7)	66.7 (9.4–99.2)	57.1 (34.0–78.2)	42.9 (9.9–81.6)
Disease control rate, % (95% CI)	82.4 (56.6–96.2)	77.4 (58.9–90.4)	100 (29.2–100)	76.2 (52.8–91.8)	71.4 (29.0–96.3)
Durable disease control rate, % (95% CI)	58.8 (32.9–81.6)	67.7 (48.6–83.3)	100 (29.2–100)	66.7 (43.0–85.4)	57.1 (18.4–90.1)

A total of 48 patients had samples available for tumor PD-L1 status assessment.

Figure 5. Slight trend to associations between clinical activity of cemiplimab and TMB



Panel A depicts TMB for responders (complete or partial response) versus non-responders (stable disease, progressive disease, or not evaluable) per ICR. Panel B depicts TMB for patients who achieved durable disease control (patients without progressive disease for at least 105 days) versus those who did not. Black lines in each box denote median; lower and upper boundaries of box denote lower quartile and upper quartile (IQR), respectively; and upper and lower whiskers indicate maximum (Q3 + 1.5*IQR) and minimum (Q1 − 1.5*IQR) values, respectively. Individual patients are indicated by open black circles. Open black circles beyond the whiskers are outliers. Open green circles and closed red boxes are duplicates of the outliers (the plots are overlap of boxplots and scatter plots). TMB data are not available for 28 patients due to lack of pre-treatment tumor sample for TMB analysis.

Treatment-emergent adverse events

- TEAEs regardless of attribution are summarized in **Table 5**.
- Grade ≥3 TEAEs that occurred in more than one patient were hypertension (n=6; 7.7%), pneumonia (n=4; 5.1%), hyperglycemia and cellulitis (each n=3; 3.8%), and breast cancer, fall, hyponatremia, lymphopenia, muscular weakness, pneumonitis, sepsis, and urinary tract infection (each n=2; 2.6%).
- Grade ≥3 TEAEs that led to treatment discontinuation were pneumonitis (n=2; 2.6%) and encephalitis, hepatitis, increased aspartate aminotransferase, pneumonia, and proctitis (each n=1; 1.3%).
- Treatment-related adverse events (TRAEs) occurred in 62 patients (79.5%) with 10 patients (12.8%) experiencing the following grade ≥3 TRAEs:
  - Pneumonitis (n=2; 2.6%) and autoimmune hepatitis, death, dizziness, encephalitis, hepatitis, hypophosphatemia, increased aspartate aminotransferase, increased lipase, myocarditis, pneumonia, and proctitis (each n=1; 1.3%).
- Six patients (7.7%) experienced serious grade ≥3 TRAEs as follows: pneumonitis (n=2; 2.6%), and autoimmune hepatitis, death, encephalitis, myocarditis, pneumonia, and proctitis (each n=1; 1.3%).
- A total of 12 grade ≥3 immune-related adverse events occurred in eight patients (10.3%):
  - Pneumonitis (n=2; 2.6%) and autoimmune hepatitis, encephalitis, hepatitis, hypophosphatemia, increased aspartate aminotransferase, increased lipase, myocarditis, pneumonia, and proctitis (each n=1; 1.3%).
- Two patients (2.6%) had TEAEs with outcome of death:
  - An 86-year-old man developed infectious pneumonia on study with a fatal outcome.
  - An 82-year-old man with a medical history of aspiration pneumonia developed aspiration pneumonia on Study Day 14. The patient died on Study Day 24 due to unknown cause. The death was considered related to study treatment.

Table 5. TEAEs regardless of attribution

TEAEs	Locally advanced CSCC (N=78)	
n (%)	Any grade	Grade ≥3
Any	78 (100)	34 (43.6)
Serious	23 (29.5)	19 (24.4)
Led to discontinuation	6 (7.7)	5 (6.4)
With an outcome of death[1]	2 (2.6)	2 (2.6)
Occurred in at least 10% of the patient population by any grade[2]		
Fatigue	33 (42.3)	1 (1.3)
Diarrhea	21 (26.9)	0
Pruritus	21 (26.9)	0
Nausea	17 (21.8)	0
Cough	15 (19.2)	0
Abdominal pain	11 (14.1)	0
Rash	10 (12.8)	0
Vomiting	9 (11.5)	1 (1.3)
Actinic keratosis	8 (10.3)	0
Anemia	8 (10.3)	1 (1.3)
Arthralgia	8 (10.3)	1 (1.3)
Back pain	8 (10.3)	0
Basal cell carcinoma	8 (10.3)	1 (1.3)
Constipation	8 (10.3)	0
Dry skin	8 (10.3)	0
Hypothyroidism	8 (10.3)	0
Maculopapular rash	8 (10.3)	0

[1]One death was considered unrelated to study treatment and the other was considered related to treatment; see poster notes for further details. [2]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 in the safety report. Included in this table are TEAEs of any grade that occurred in at least 10% of the patient population. Events are listed in decreasing order of frequency by any grade.

Conclusions

- Cemiplimab 3 mg/kg Q2W showed substantial antitumor activity, durable responses, and acceptable safety profile in patients with locally advanced CSCC.
- Cemiplimab provided clinical benefit for patients in which local invasion precluded complete surgical resection and for those in which complete surgical resection was technically possible but might have resulted in disfigurement or loss of function.
  - Further prospective study of cemiplimab in advanced CSCC in both the preoperative (neoadjuvant) and postoperative (adjuvant) settings is planned.
- The safety profile is consistent with that previously described for cemiplimab and other PD-1 inhibitors.
- Durable responses and disease control occurred at all measured TMB levels.
  - Exploratory analyses suggest slight enrichment for cemiplimab response in high TMB tertile.
  - These data do not support the clinical utility of either TMB or PD-L1 expression in predicting outcome among patients with advanced CSCC treated with cemiplimab.
- Combined with the 12-month follow-up data of the patients with metastatic CSCC (Group 1) from the Phase 2 study (see poster number 9526), these results confirm that cemiplimab is highly active in advanced CSCC tumors.

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For any questions regarding this poster presentation, please contact mrmigden@mdanderson.org.

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