Phase 2 study of cemiplimab in patients with advanced cutaneous squamous cell carcinoma (CSCC): Final analysis from EMPOWER-CSCC-1 Groups 1, 2, and 3

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Introduction

- CSCC is the second most common malignancy in the USA, with approximately 186,000–420,000 cases diagnosed each year.[1]
- While most cases of CSCC are cured by complete surgical excision, a small but substantial number of patients develop advanced disease, including locally advanced (laCSCC) or metastatic (mCSCC) disease.[2,3]
- Cemiplimab is a high-affinity, fully human, hinge-stabilized, immunoglobulin G4 anti–programmed cell death-1 (PD-1) antibody that blocks the interaction of the PD-1 receptor with its ligands, PD-L1 and PD-L2.[4]
- Cemiplimab is approved in the US and Europe, and by multiple other health authorities, for the treatment of patients with metastatic or locally advanced CSCC who are not candidates for curative surgery or curative radiation.[5–8] Additionally, cemiplimab is recommended for the treatment of patients with metastatic or locally advanced CSCC not amenable to curative surgery or curative radiation by the European Association of Dermato-Oncology, European Organization for Research and Treatment of Cancer, and the National Comprehensive Cancer Network.[9,10]
- In the primary and follow-up analysis from the EMPOWER-CSCC-1 Phase 2 study, cemiplimab demonstrated substantial clinical benefit and an acceptable safety profile in patients with advanced CSCC (NCT02760498).[11–14]
  - Cemiplimab achieved an objective response rate (ORR) of 46.1% in patients with advanced CSCC, with complete response rates of 20.3%, 12.8%, and 16.1% for Groups 1, 2, and 3, respectively.[11]
- Here, we provide the final update from study Groups 1, 2 and 3.

Objectives

- **Primary objective:** To assess the clinical benefits of cemiplimab as measured by ORR (complete + partial response) per independent central review (ICR).
- **Key secondary objectives:** Duration of response (DOR), progression-free survival (PFS), overall survival (OS), complete response rate, and safety and tolerability.

Methods

- EMPOWER-CSCC-1 is an open-label, non-randomized, multicenter, international Phase 2 study of patients with advanced CSCC (NCT02760498).
- Patients with histologically confirmed mCSCC or unresectable laCSCC received cemiplimab 3 mg/kg intravenous (IV) every 2 weeks for up to 96 weeks (Group 1, mCSCC; Group 2, laCSCC) or cemiplimab 350 mg IV every 3 weeks for up to 54 weeks (Group 3, mCSCC) (**Figure 1**).
- The data cutoff was March 1, 2022.

Results

Patients

- A total of 193 patients were enrolled (Group 1, n=59; Group 2, n=78; Group 3, n=56) with a median age of 72.0 years (range, 38–96). Most patients had a primary cancer site of the head and neck (n=131, 67.9%) (**Table 1**).
- Median duration of follow up was 15.7 months (range, 0.6–43.4) and median duration of exposure was 51.1 weeks (range, 2.0–109.3).

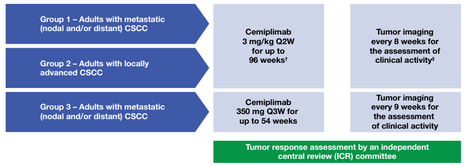
Response

- Tumor response per ICR, median PFS and OS remained generally consistent with the previous update (data cutoff: October 11, 2020) (**Table 2**).
- Median PFS was 22.1 months (95% confidence interval [CI], 10.4–32.3) and the overall median DOR was 41.3 months (95% CI, 38.8–46.3) (**Figures 2** and **3A**).
- Median OS was not reached. The Kaplan–Meier estimated probability of OS at 48 months was 61.8% (95% CI, 54.0–68.7) (**Figure 3B**).

Safety

- All but one patient (n=192, 99.5%) experienced at least one treatment-emergent adverse event (TEAE) of any grade (**Table 3**).
- The most common TEAE of any grade was fatigue (n=67, 34.7%), followed by diarrhea (n=53, 27.5%), nausea (n=46, 23.8%), and pruritus (n=41, 21.2%).

Figure 1. Study design



Key inclusion criteria	Key exclusion criteria
• ECOG performance status of 0 or 1 • Adequate organ function • Groups 1 and 3: – At least one lesion measurable by RECIST version 1.1 • Group 2: – At least one lesion measurable by digital medical photography – CSCC lesion that is not amenable to surgery or radiation therapy per investigators' assessment	• Ongoing or recent (within 5 years) autoimmune disease requiring systemic immunosuppression • Prior treatments with anti-PD-1 or anti-PD-L1 therapy • History of solid organ transplant, hematologic malignancies, or concurrent malignancies (unless indolent or not considered life threatening; e.g., basal cell carcinoma)

†Retreatment optional for patients with disease progression during follow-up.
‡Confirmatory scans performed no sooner than 4 weeks following initial documentation of tumor response. The severity of TEAEs was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03).
CSCC, cutaneous squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; Q2W, every 2 weeks; Q3W, every 3 weeks; RECIST 1.1, Response Evaluation Criteria In Solid Tumors version 1.1; TEAE, treatment-emergent adverse event.

Table 1. Patient demographics and baseline characteristics

	Advanced CSCC (n=193)
Age, years, median (range)	72.0 (38–96)
Male, n (%)	161 (83.4)
ECOG performance status, n (%)	
0	86 (44.6)
1	107 (55.4)
Primary CSCC site: head and neck, n (%)	131 (67.9)
mCSCC, n (%)	115 (59.6)
laCSCC, n (%)	78 (40.4)
Patients with cemiplimab as first-line therapy, n (%)	128 (66.3)
Patients with prior systemic therapy, n (%)†	65 (33.7)
Duration of exposure to cemiplimab, weeks, median (range)	51.1 (2.0–109.3)
Number of cemiplimab doses administered, median (range)	18.0 (1–48)

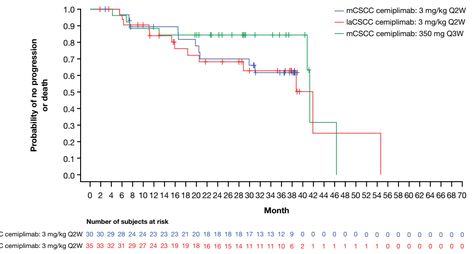
†Settings for prior lines of therapy included metastatic disease, adjuvant, chemotherapy with concurrent radiation, or other, and the most common types of prior systemic therapy were platinum compounds (n=46/65, 70.8%) and monoclonal antibodies (n=18/65, 27.7%).
CSCC, cutaneous squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group; laCSCC, locally advanced cutaneous squamous cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma.

Table 2. Tumor response per ICR

PD-L1 (22C3)	Group 1 (mCSCC) 3 mg/kg Q2W (n=59)	Group 2 (laCSCC) 3 mg/kg Q2W (n=78)	Group 3 (mCSCC) 350 mg Q3W (n=56)	Total (n=193)
Duration of follow-up, months, median (range)	18.5 (1.1–41.0)	15.5 (0.8–43.2)	17.3 (0.6–43.4)	15.7 (0.6–43.4)
ORR, % (95% CI)	50.8 (37.5–64.1)	44.9 (33.6–56.6)	46.4 (33.0–60.3)	47.2 (39.9–54.4)
Complete response, n (%)	12 (20.3)	10 (12.8)	11 (19.6)	33 (17.1)
Partial response, n (%)	18 (30.5)	25 (32.1)	15 (26.8)	58 (30.1)
DOR, months, median (95% CI)	NR (20.7–NE)	41.9 (20.5–54.6)	41.3 (40.8–46.3)	41.3 (38.8–46.3)
PFS, months, median (95% CI)	18.4 (7.3–53.2)	18.5 (11.1–43.8)	21.7 (3.8–43.3)	22.1 (10.4–32.3)
OS, months, median (95% CI)	57.7 (29.3–NE)	NR (58.3–NE)	48.4 (29.5–NE)	NR (56.0–NE)

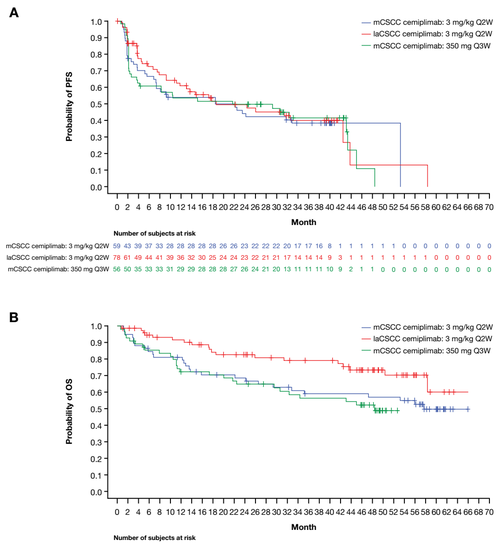
CI, confidence interval; DOR, duration of response; ICR, independent central review; laCSCC, locally advanced cutaneous squamous cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma; NE, not evaluable; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; Q3W, every 3 weeks.

Figure 2. Kaplan–Meier curves of DOR per ICR



CSCC, cutaneous squamous cell carcinoma; DOR, duration of response; ICR, independent central review; laCSCC, locally advanced cutaneous squamous cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma; Q2W, every 2 weeks; Q3W, every 3 weeks.

Figure 3. Kaplan–Meier curves of (A) PFS and (B) OS



CSCC, cutaneous squamous cell carcinoma; ICR, independent central review; laCSCC, locally advanced cutaneous squamous cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; Q3W, every 3 weeks.

- Grade ≥3 TEAEs were reported in 95 patients (49.2%). The most common Grade ≥3 TEAEs were hypertension (n=9, 4.7%), cellulitis, and anemia (each n=8, 4.1%), pneumonia (n=8, 4.1%), pneumonitis (n=6, 3.1%), sepsis (n=5, 2.6%), and fatigue (n=5, 2.6%).
- In total, 19 patients (9.8%) experienced at least one sponsor-identified Grade ≥3 immune-related adverse event, the most common of which were pneumonitis (n=6, 3.1%), diarrhea, and autoimmune hepatitis (each n=2, 1.0%).
- Twenty patients (10.4%) discontinued treatment due to TEAEs of any grade (**Supplementary Table 1**). Beyond what has previously been reported,[6–8] no new TEAE-related deaths occurred.

Table 3. TEAEs†

	Advanced CSCC, n=193	
TEAEs, n (%)	Any grade	Grade ≥3
Any	192 (99.5)	95 (49.2)
Serious	75 (38.9)	60 (31.1)
Leading to discontinuation	20 (10.4)	13 (6.7)
Leading to death	5 (2.6)	5 (2.6)
Occurring in ≥10% of patients (any grade)		
Fatigue	67 (34.7)	5 (2.6)
Diarrhea	53 (27.5)	2 (1.0)
Nausea	46 (23.8)	0
Pruritus	41 (21.2)	0
Constipation	28 (14.5)	1 (0.5)
Vomiting	25 (13.0)	1 (0.5)
Arthralgia	34 (17.6)	1 (0.5)
Cough	32 (16.6)	0
Rash	32 (16.6)	1 (0.5)
Anemia	22 (11.4)	8 (4.1)
Hypothyroidism	22 (11.4)	0
Actinic keratosis	23 (11.9)	0
Rash, maculo-papular	23 (11.9)	1 (0.5)
Upper respiratory tract infection	21 (10.9)	0
Headache	21 (10.9)	0

†TEAEs occurring in ≥10% of patients are reported here. Adverse events were coded according to the Preferred Terms of the Medical Dictionary for Regulatory Activities, version 22.1. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.
RTI, respiratory tract infection; TEAE, treatment-emergent adverse event.

Conclusions

- This final update to the EMPOWER-CSCC-1 study confirms the efficacy, durability, and safety profile of cemiplimab in patients with advanced CSCC.
- No new safety concerns were identified on longer follow-up.
- Cemiplimab remains a standard-of-care option for metastatic or locally advanced CSCC patients who are not candidates for curative surgery or radiation.

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Acknowledgments

The authors thank the patients, their families, all other investigators, and all investigational site members who participated in this study. Medical writing and editorial support under the direction of the authors was provided by Sameen Yousaf, PhD, of Prime (Knutsford, UK) and funded by Regeneron Pharmaceuticals, Inc., and Sanofi according to Good Publication Practice guidelines. Responsibility for all opinions, conclusions and data interpretation lies with the authors.

Disclosure

Michael R Migden reports honoraria and travel expenses from Regeneron Pharmaceuticals, Inc., Sanofi, Novartis, Genentech, Eli Lilly, and Sun Pharma; and institutional research funding from Regeneron Pharmaceuticals, Inc., Novartis, Genentech, and Eli Lilly.

Presented at Winter Clinical Derm 2023, January 13–18, 2023 (encore of previous presentation at the European Society of Medical Oncology [ESMO] 2022, September 8–13, Migden MR et al.). Reused with permission.