

Real-World Treatment Patterns and Outcomes of Cemiplimab in Patients with Advanced Cutaneous Squamous Cell Carcinoma Treated in US Oncology Practices

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Background: Prior to the Food and Drug Administration approval of cemiplimab in 2018, the median overall survival (OS) for adult patients with advanced CSCC receiving systemic therapy was approximately 8 to 15 months. Limited real-world data are available on cemiplimab for this indication in the US.

Patients and Methods: This retrospective cohort study included US patients with advanced CSCC initiating cemiplimab monotherapy in a real-world database (2018–2021). A clinical trial–like sub-cohort was identified using select criteria. Time to treatment discontinuation (TTD), time to next treatment (TTNT), and OS were estimated using Kaplan–Meier methods. Cox proportional hazard models were used to examine prognostic factors associated with OS in the main cohort.

Results: The main cohort included 622 patients (n = 240 in the trial-like cohort). In the main cohort, the median age was 78 years, 77.8% were male, 21.4% were immunocompromised/immunosuppressed, and 63.8% had metastatic CSCC. Median (95% CI) TTD and TTNT were 8.0 (6.6–9.0) months and 16.4 (13.3–21.0) months, respectively, in the main cohort. Median (95% CI) OS was 24.8 (21.8–29.1) months in the main cohort (not reached in the trial-like cohort). In multivariable analyses, age <60 years (hazard ratio [HR], 0.37), Eastern Cooperative Oncology Group performance status <3–4 (HR range, 0.13–0.57), and primary CSCC location in the head and neck only versus extremities only (HR, 0.59) were associated with better OS. Similar OS was observed between patients who had immunosuppressing/immunocompromising conditions and those without.

Conclusion: These findings confirm the effectiveness of cemiplimab among a heterogeneous, real-world advanced CSCC patient population and substantiate the efficacy of cemiplimab observed in clinical trials.

Keywords: cutaneous squamous cell carcinoma, cemiplimab, immune checkpoint inhibitor, real-world study, skin cancer

Introduction

Cutaneous squamous cell carcinoma (CSCC) is the second most common skin cancer in the US.^{1–3} Most cases of CSCC are cured by surgery/radiation, but an estimated 1% to 5% of patients will develop advanced disease, which is associated with poor prognosis.⁴ Cemiplimab is a preferred systemic treatment option in US guidelines for patients with locally advanced, recurrent, or metastatic CSCC if curative radiation or surgery is not feasible.⁵

Cemiplimab was the first programmed death receptor-1 (PD-1) inhibitor approved by the US Food and Drug Administration (FDA) for the treatment of patients with metastatic CSCC or locally advanced CSCC who are not candidates for curative surgery or radiation, hereafter referred to as advanced CSCC. Prior to the approval of cemiplimab in 2018, there were no FDA-approved interventions for patients with advanced CSCC; patients who were not candidates for curative surgery or radiation or those treated with other systemic therapies experienced a median overall survival

(OS) of approximately 8 to 15 months.^{3,6–13} Pooled longer term data from the Phase 2 clinical trial for cemiplimab (NCT02760498; median follow-up, 15.7 months) showed an objective response rate of 46.1% and median progression-free survival of 18.4 months; median duration of response and median OS were not reached.¹⁴

To date, limited real-world data are available on cemiplimab in the treatment of advanced CSCC in the US, although a Phase 4 registry study is currently underway.¹⁵ There is a need to better understand the real-world patient characteristics, treatment patterns, and outcomes of patients with advanced CSCC treated with cemiplimab in the US. The objectives of this study were two-fold: 1) to describe patient characteristics, treatment patterns, time to treatment discontinuation (TTD), time to next treatment (TTNT), and OS; and 2) to explore potential prognostic factors (demographic and clinical characteristics) associated with OS among patients with advanced CSCC treated with cemiplimab monotherapy in largely community oncology clinical practices in the US.

Materials and Methods

Study Design and Data Source

This retrospective cohort study was conducted using data from adult patients with advanced CSCC initiating cemiplimab monotherapy between 2018 and 2021 in the nationwide de-identified Flatiron Health database derived from electronic health records (EHRs) in the US.¹⁶ During the study period, the de-identified data originated from approximately 280 US cancer clinics (approximately 800 sites of care). The longitudinal database contains de-identified patient-level data derived from structured and unstructured EHR data curated via technology-enabled chart abstraction.^{16,17} Data provided to third parties are de-identified to prevent re-identification and protect patient confidentiality. Patient-level structured data (EHR, obituaries, and Social Security Death Index) and unstructured EHR data (abstracted) were linked to generate a composite mortality variable, which has shown high sensitivity and specificity when compared with the National Death Index.¹⁸ Institutional Review Board approval of the study protocol for creating the advanced CSCC research database was obtained by Flatiron Health before the study was conducted and included a waiver of informed consent.

Study Population

Main Cohort

The main study cohort included adult patients who initiated cemiplimab monotherapy between September 28, 2018, and September 30, 2021, and had at least 2 visits in the Flatiron Health network on or after January 1, 2011, with a study end date of December 31, 2021 ([Supplemental Figure 1](#)). Patients were required to have a confirmed diagnosis of advanced CSCC on or before the index date, which was defined as the date of their first dose of cemiplimab monotherapy. Advanced CSCC diagnosis, defined as locally advanced CSCC not amenable to curative surgery or radiation or metastatic CSCC, was confirmed through technology-enabled manual review of EHR records and pathology reports by Flatiron Health-trained personnel. To ensure the full advanced CSCC treatment history was captured, the patient's first structured EHR record had to occur before or within 30 days after the advanced CSCC diagnosis date. The baseline period varied among patients based on data availability, with the earliest data extending back to January 1, 2011. Patients who first initiated cemiplimab in combination with other systemic treatment (ie, not as monotherapy) or who participated in a clinical trial on or before the index date were excluded.

Trial-Like Cohort

A trial-like cohort (a sub-cohort of the main cohort) was created by including patients who further met select inclusion and exclusion criteria of the cemiplimab R2810-ONC-1540 clinical trial.^{19–21} Patients were required to have at least 1 Eastern Oncology Cooperative Group performance status (ECOG PS) measurement within 30 days on or before the index date, with the highest ECOG PS being no greater than 1. Patients with any other malignancy receiving antineoplastic treatment within 3 years before the index date, any diagnosis of central nervous system metastasis (ICD-10-CM codes C79.3X or C79.4X) on or prior to the index date, immunocompromised or immunosuppressed status on or before the index date, or abnormal hepatic, renal, or bone marrow function within 30 days before or on the index date were excluded from the trial-like cohort.

Immunocompromised or immunosuppressed status was defined as having one or more diagnoses of the following: transplant (allogenic bone marrow transplant, solid organ transplant), hematological malignancies (leukemia, lymphoma, multiple myeloma), or other conditions (Addison's disease, celiac disease, Grave's disease, Hashimoto's thyroiditis, HIV, inflammatory bowel disease, lupus, multiple sclerosis, myasthenia gravis, pernicious anemia, psoriasis or psoriatic arthritis, rheumatoid arthritis, Sjogren's syndrome, type 1 diabetes, vasculitis). Transplants and other conditions were identified using ICD-9/ICD-10 diagnosis or procedure codes, and malignancies were identified using ICD-9/ICD-10 codes and abstracted data.

Abnormal organ or bone marrow function was defined as meeting any of the following: hemoglobin <9.0 g/dL, absolute neutrophil count $<1.5 \times 10^9/L$, platelet count $<75 \times 10^9/L$, serum creatinine $>1.5 \times$ upper level of normal (ULN), estimated creatinine clearance <30 mL/min, total bilirubin $>1.5 \times$ ULN (or $>3 \times$ ULN if liver metastases), transaminases $>3 \times$ ULN (or $>5.0 \times$ ULN if liver metastases), or alkaline phosphatase (ALP) $>2.5 \times$ ULN (or $>5.0 \times$ ULN if liver or bone metastases).

Variables

Baseline demographic and clinical characteristics included age, sex, race/ethnicity, region, practice type, insurance, ECOG PS, stage of disease at index date, number of prior lines of therapy (LOTs), immunocompromised or immunosuppressed status, concomitant malignancies, location of CSCC, and abnormal hepatic, renal, or bone marrow function. For ECOG PS and inadequate hepatic, renal, and bone marrow function, the measurement recorded closest to the index date was used when multiple measurements were available. The stage at the index date was defined as the stage recorded before or up to 14 days after the index date.

Treatment history before cemiplimab initiation included number of LOTs and type of treatment received between the advanced CSCC diagnosis date and index date. For the analysis of treatment patterns, treatment regimens were derived from systemic antineoplastic treatments documented in the EHR and indexed to the advanced CSCC diagnosis date. For each LOT, all drugs administered within 28 days of the initiation date of the first drug in the LOT were considered as one regimen; the LOT ended when the patient initiated a new drug after the 28-day window or discontinued all drugs in the regimen. Treatment discontinuation was defined as a gap of more than 90 days after the last administration date plus the median infusion interval (eg, 21 days for cemiplimab).

Outcomes

Treatment pattern outcomes included the line setting of cemiplimab in advanced CSCC and type of treatment by LOT (ie, chemotherapy, immunotherapy monotherapy, immunotherapy combination therapy, targeted therapy, or other regimens). TTD by LOT was defined as the time from the initiation of a certain LOT until the date of treatment-line discontinuation or death, whichever occurred first. Treatment-line discontinuation was defined as the initiation of a subsequent line, having a gap of more than 90 days with no systemic therapy following the last administration, or having a date of death while on the current LOT. The date of discontinuation was the last administration plus infusion interval or initiation of subsequent line or death, whichever occurred first. TTNT was defined as the time from the treatment initiation of a certain LOT to the date of initiation of a subsequent LOT or death, whichever occurred first. OS was defined as the time from the index date to the date of all-cause death. Patients were followed from the index date to the end of follow-up (ie, the date of last structured EHR activity), death, or the end of the study, whichever occurred first.

Statistical Analysis

Baseline characteristics and treatment history for each cohort were summarized using descriptive statistics. Continuous variables were reported as mean, SD, median, IQR, and range; categorical variables were reported as number and percentages. Follow-up time was calculated as the length of time between the index date and the last structured EHR activity date, death, or the end of the study, and was estimated using the reverse Kaplan–Meier method. Median (95% CI) TTD, TTNT, and OS were estimated using the Kaplan–Meier method for the main cohort and the trial-like cohort. For the main cohort, OS was also stratified by age, sex, immunocompromised/immunosuppressed status, ECOG PS, stage at index, index year, and line setting of cemiplimab. Hematological malignancies and prior transplants were presented separately as they were considered major immunocompromising/immunosuppressing conditions. To evaluate the potential prognostic

factors for OS in the main cohort, Cox proportional hazard (PH) models were used to derive unadjusted and adjusted hazard ratios (HRs) and 95% CIs for all baseline variables. Univariate Cox PH models were performed for each variable to assess its magnitude and statistical significance. Key variables known to be potentially important prognostic factors (eg, age, ECOG PS, immunocompromised/immunosuppressed status) and other variables found to be significant at a level of 0.2 were carried forward to the multivariate Cox model. Missing data were not imputed.

Results

Patient Selection and Characteristics

In total, 622 patients were included in the main cohort and 240 patients in the trial-like cohort (Figure 1); over 60% of the patients would have been ineligible for the cemiplimab clinical trial. In the main cohort, the median (IQR) age at cemiplimab initiation was 78 (70–83) years, and 43.6% of patients were aged 80 years or older; 77.8% were male and 72.0% were White (Table 1). The median (IQR) time from the first advanced CSCC diagnosis to the index date was 1.3 (0.5–6.2) months. Most (63.8%) patients had metastatic CSCC (44.1% regional metastasis, 19.8% distant metastasis) and 45.7% of patients had

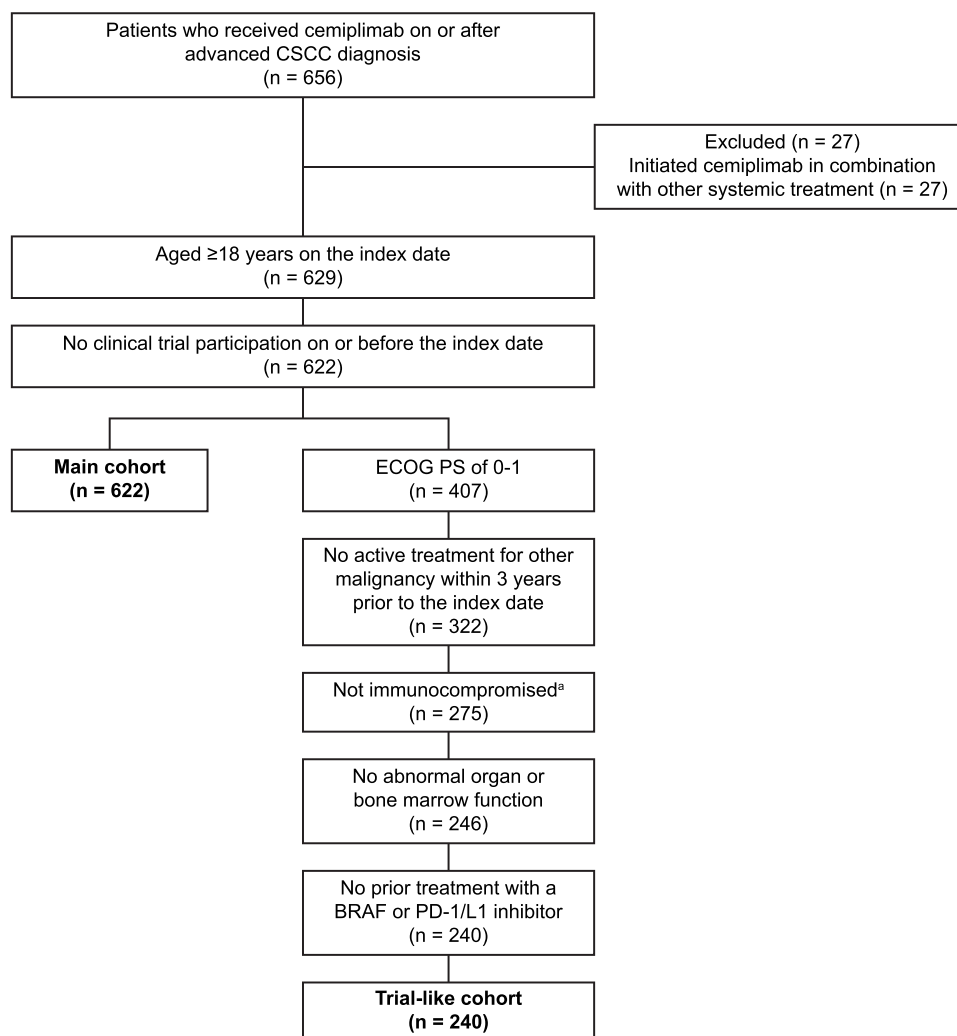


Figure 1 Study cohort selection.

Notes: ^aImmunocompromised/immunosuppressed status defined as having 1 or more of the following on or before the index date: prior transplant (allogenic bone marrow transplant, solid organ transplant), hematological malignancies (leukemia, lymphoma, multiple myeloma), or other conditions (Addison's disease, celiac disease, Grave's disease, Hashimoto's thyroiditis, HIV, inflammatory bowel disease, lupus, multiple sclerosis, myasthenia gravis, pernicious anemia, psoriasis or psoriatic arthritis, rheumatoid arthritis, Sjogren's syndrome, type 1 diabetes, vasculitis).

Abbreviations: BRAF, B-Raf proto-oncogene, serine/threonine kinase; CSCC, cutaneous squamous cell carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-1/L1, programmed death receptor-1/ligand-1.

Table I Baseline Demographics and Clinical Characteristics

	Main Cohort (N = 622)	Trial-Like Cohort (N = 240)
Age at index, years, median (Q1–Q3)	78 (70–83)	76 (68–83)
Months of follow-up, median (95% CI)	16.6 (14.9–18.7)	15.3 (13.1–18.0)
Age at index, years, n (%)		
18–59	49 (7.9)	21 (8.8)
60–69	101 (16.2)	45 (18.8)
70–79	201 (32.3)	83 (34.6)
≥80	272 (43.6)	91 (37.9)
Male sex, n (%)	484 (77.8)	178 (74.2)
Race, n (%)		
White	448 (72.0)	174 (72.5)
Other ^a	121 (19.5)	42 (17.5)
Missing	53 (8.5)	24 (10.0)
Ethnicity, n (%)		
Non-Hispanic or Latino	606 (97.4)	231 (96.3)
Hispanic or Latino	16 (2.6)	9 (3.8)
Region, n (%)		
Midwest	50 (8.0)	19 (7.9)
Northeast	42 (6.8)	14 (5.8)
South	300 (48.2)	113 (47.1)
West	64 (10.3)	27 (11.3)
Unknown/other	166 (26.7)	67 (27.9)
Practice type, n (%)		
Academic	128 (20.6)	52 (21.7)
Community	494 (79.4)	188 (78.3)
Insurance type, n (%)		
Commercial	424 (68.2)	164 (68.3)
Medicare or Medicaid	112 (18.0)	44 (18.3)
Other	63 (10.1)	24 (10.0)
Missing	23 (3.7)	8 (3.3)
ECOG PS, n (%)		
0	167 (26.8)	97 (40.4)
1	240 (38.6)	143 (59.6)
≥2	111 (17.8)	NA
Missing	104 (16.7)	NA
Stage at index, n (%)		
Locally advanced not amenable to curative intent surgery or radiation	225 (36.2)	87 (36.3)
Regional metastatic	274 (44.1)	99 (41.3)
Distant metastatic	123 (19.8)	54 (22.5)
Line setting of cemiplimab, n (%)		
1	528 (84.9)	209 (87.1)
2+	94 (15.1)	31 (12.9)

(Continued)

Table 1 (Continued).

	Main Cohort (N = 622)	Trial-Like Cohort (N = 240)
Index year		
2018	39 (6.3)	16 (6.7)
2019	212 (34.1)	77 (32.1)
2020	213 (34.2)	90 (37.5)
2021	158 (25.4)	57 (23.8)
Diagnosis to index date, median (IQR), months	1.3 (0.5–6.2)	1.1 (0.5–5.5)
Immunocompromised/immunosuppressed status, n (%) ^b		
None	489 (78.6)	240 (100.0)
Hematological malignancy	101 (16.2)	NA
Other immunodeficiency	21 (3.4)	NA
Prior transplant	11 (1.8)	NA
Any malignancy diagnosed before index date, n (%)	284 (45.7)	61 (25.4)
Any treatment for other malignancy within 3 years before index date, n (%)	130 (20.9)	0 (0)
Primary location of CSCC, n (%)		
Head and neck only	345 (55.5)	128 (53.3)
Extremities only	91 (14.6)	44 (18.3)
Trunk only	30 (4.8)	10 (4.2)
Other	31 (5.0)	16 (6.7)
Multiple sites	125 (20.1)	42 (17.5)

Notes: ^aOther race includes people who selected Asian or Black or African American or other. ^bImmunocompromised/immunosuppressed status defined as having 1 or more of the following on or before the index date: prior transplant (allogenic bone marrow transplant, solid organ transplant), hematological malignancies (leukemia, lymphoma, multiple myeloma), or other conditions (Addison's disease, celiac disease, Grave's disease, Hashimoto's thyroiditis, HIV, inflammatory bowel disease, lupus, multiple sclerosis, myasthenia gravis, pernicious anemia, psoriasis or psoriatic arthritis, rheumatoid arthritis, Sjogren's syndrome, type 1 diabetes, vasculitis).

Abbreviations: CI, confidence interval; CSCC, cutaneous squamous cell carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; NA, not applicable; Q, quartile.

another malignancy. More than one-fifth (21.4%) of patients were immunocompromised or immunosuppressed, including 16.2% with a hematological malignancy, 3.4% with another immunodeficiency, and 1.8% with a prior transplant. ECOG PS was available in 83.3% of patients, among whom 17.8% had an ECOG PS of 2 or higher. About 85% of patients initiated cemiplimab in the first-line setting.

Similar patient characteristics were observed in the trial-like cohort except for those that were implemented as inclusion/exclusion criteria by design (Table 1). Differences in select baseline characteristics were observed for the main cohort when stratified by stage at index (Supplemental Table 1). For example, the subgroup of patients with locally advanced CSCC had a greater proportion of female patients and older patients than the regional metastatic CSCC and distant metastatic CSCC subgroups.

Median (95% CI) follow-up estimated using the reverse Kaplan–Meier method was 16.6 (14.9–18.7) months in the main cohort and 15.3 (13.1–18.0) months in the trial-like cohort (Table 1). The median (IQR) duration of the baseline period (time from the first EHR record to the index date) was 14.2 (2.2–56.4) months in the main cohort and 7.0 (1.3–29.6) months in the trial-like cohort.

Treatment Patterns

In the main cohort (N = 622), most patients (n = 528; 84.9%) initiated cemiplimab monotherapy as first-line systemic therapy (Figure 2). Of the patients initiating first-line cemiplimab monotherapy, 95 (18.0%) received second-line systemic therapy, whereas 294 (55.7%) were censored. For patients who initiated cemiplimab monotherapy in the second line (n = 76; 12.2% of the main cohort), the first-line treatments were mostly chemotherapy (n = 40) or targeted therapies (n = 32).

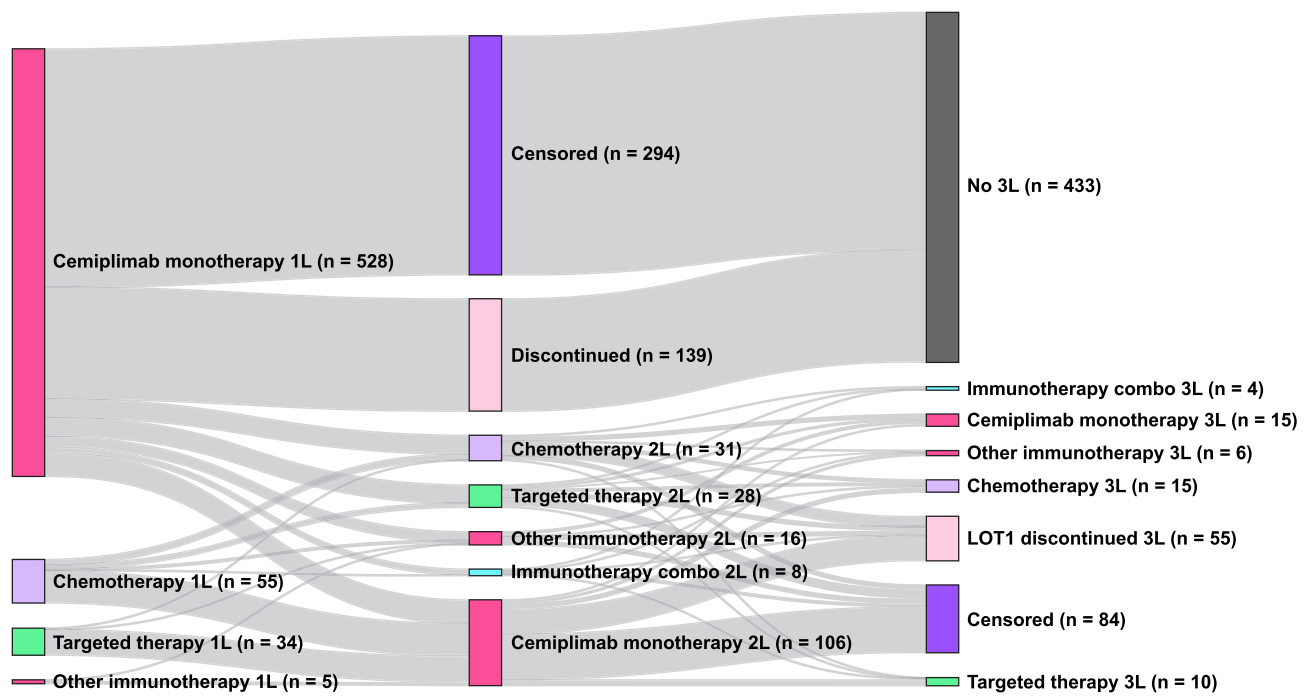


Figure 2 Sankey diagram.^a

Notes: ^aCemiplimab patients were indexed across first, second, and third lines (most were indexed on LOT1). Targeted therapy included afatinib, cetuximab, erlotinib, gefitinib, lapatinib, panitumumab, dabrafenib, or vemurafenib. Other immunotherapy included atezolizumab, avelumab, durvalumab, nivolumab, pembrolizumab, ipilimumab, cemiplimab, interferon alfa-2a, or pegylated interferon alfa 2a.

Abbreviations: 1L, first line; 2L, second line; 3L, third line; LOT1, first line of therapy.

Time to Treatment Discontinuation

The median (95% CI) TTD of cemiplimab was 8.0 (6.6–9.0) months in the main cohort and 8.8 (7.1–12.4) months in the trial-like cohort (Figure 3). The Kaplan–Meier probability (95% CI) of treatment discontinuation or death at 6 months was 43% (39%–47%) in the main cohort and 38% (31%–45%) in the trial-like cohort. The Kaplan–Meier probability (95% CI) of treatment discontinuation or death at 12 months was 63% (59%–68%) in the main cohort and 58% (50%–65%) in the trial-like cohort. By 24 months, the Kaplan–Meier probability (95% CI) of continuing cemiplimab treatment was 17% (13%–22%) in the main cohort and 23% (16%–32%) in the trial-like cohort.

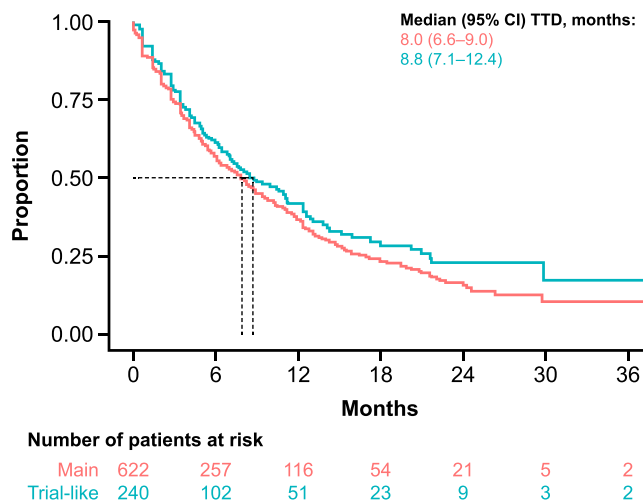


Figure 3 TTD in the main and trial-like cohorts.

Abbreviation: TTD, time to treatment discontinuation.

Time to Next Treatment

The median (95% CI) TTNT from cemiplimab initiation was 16.4 (13.3–21.0) months in the main cohort and 25.3 months (16.4 months to not estimable [NE]) in the trial-like cohort (Figure 4). The Kaplan–Meier probability (95% CI) of initiating next LOT or death at 12 months was 43% (38%–47%) in the main cohort and 35% (28%–42%) in the trial-like cohort.

Overall Survival

Median (95% CI) OS was 24.8 (21.8–29.1) months in the main cohort and not reached in the trial-like cohort during a median follow-up of 16.6 and 15.3 months, respectively (Figure 5). The Kaplan–Meier probability (95% CI) of OS at 12 months was 67% (63%–71%) in the main cohort and 73% (67%–80%) in the trial-like cohort. The probability (95% CI) of OS at 24 months was 51% (46%–56%) in the main cohort and 62% (54%–71%) in the trial-like cohort.

Stratified analysis of OS in the main cohort is shown in Figure 6. As expected, patients who were older (ie, aged ≥ 80 years) (Figure 6A) or with an ECOG PS of 2 or greater (Figure 6B) had numerically shorter median OS. No differences in median OS were observed by sex (Figure 6C) or disease stage at index. Median (95% CI) OS by stage at index was 22.6 (19.7–NE)

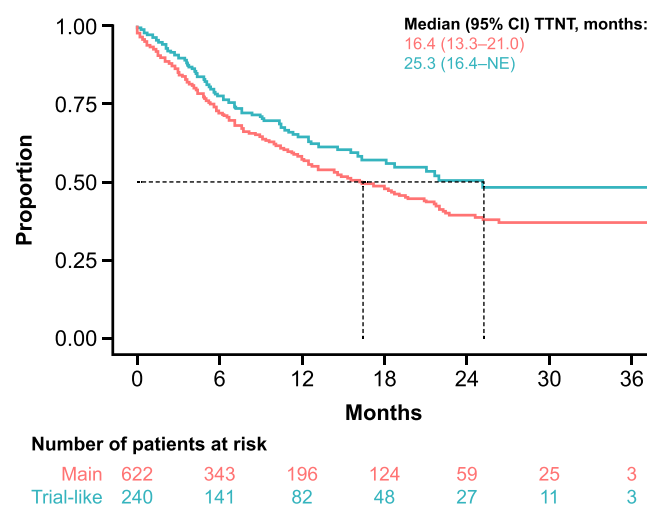


Figure 4 TTNT in the main and trial-like cohorts.

Abbreviations: NE, not estimable; TTNT, time to next treatment.

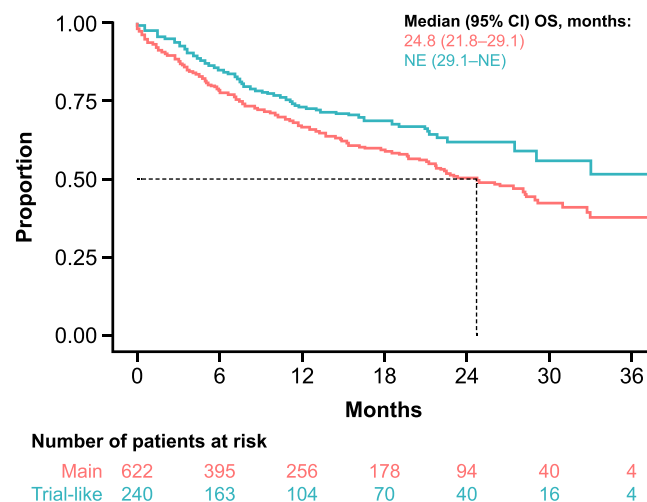


Figure 5 OS in the main and trial-like cohorts.

Abbreviations: NE, not estimable; OS, overall survival.

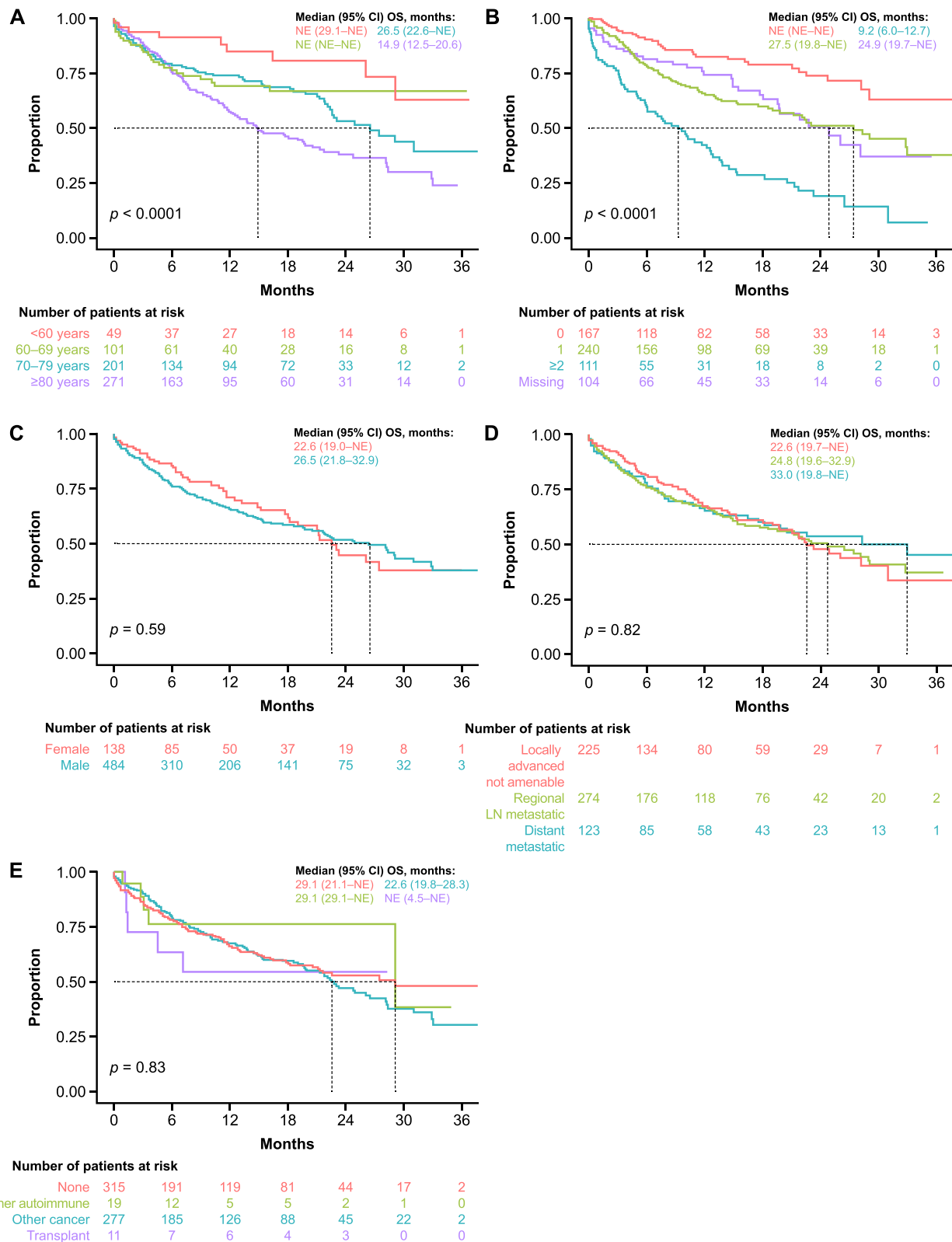


Figure 6 OS in main cohort stratified by (A) age, (B) ECOG PS, (C) sex, (D) stage at index, and (E) immunocompromised/immunosuppressed status. **Abbreviations:** ECOG PS, Eastern Cooperative Oncology Group performance status; LN, lymph node; NE, not estimable; OS, overall survival.

months for patients with locally advanced CSCC not amenable to curative surgery or radiation compared with 26.5 (21.2–33.0) months for patients with regional or distant metastatic CSCC (Figure 6D). No clear separation in OS was observed between patients who had immunosuppressing or immunocompromising conditions (Figure 6E); the sample size was small for patients with prior history of allogenic bone marrow or solid organ transplant. The Kaplan–Meier probability (95% CI) of OS at 12 months was 70% (62%–79%) in patients with immunocompromising/immunosuppressing conditions and 66% (60%–72%) in patients without. Median (95% CI) OS by stage at index was 21.3 (14.7–NE) months for patients with an index year of 2018 and 27.5 (22.6–33.0) months for patients with an index year of 2019 (Supplemental Figure 2; the median was not estimable for patients with an index year of 2020 or 2021). A multivariate Cox PH model produced an HR of 0.86 (95% CI, 0.58–1.27) associated with OS for patients with hematological malignancies vs patients without immunocompromising/immunosuppressing conditions (Supplemental Figure 3). Median (95% CI) OS was greater in patients who received cemiplimab monotherapy in the first line (24.8 [21.8–29.1] months) than in the second or third line (18.6 [12.2–NE] months).

Prognostic Factors for OS

The results of the Cox model showed that younger age (HR [95% CI], 0.37 [0.18–0.75] for <60 years compared to ≥80 years) and primary location of CSCC in the head and neck only (HR [95% CI], 0.59 [0.40–0.87] compared to extremities only) were associated with better OS in the main cohort (Supplemental Figure 3). As expected, patients with lower ECOG PS also had better OS (HR [95% CI], 0.13 [0.07–0.22] for an ECOG PS of 0; 0.27 [0.17–0.44] for an ECOG PS of 1; and 0.57 [0.34–0.96] for an ECOG PS of 2, compared to an ECOG PS of 3 to 4). Missing ECOG PS was also associated with better OS (HR [95% CI], 0.26 [0.15–0.46]).

Discussion

In this retrospective study, we found that the effectiveness of cemiplimab among patients with advanced CSCC in a real-world US setting was comparable to that observed in the phase 2 cemiplimab clinical trial. The OS in our real-world trial-like cohort approached that in the cemiplimab clinical trial, with 24-month survival probability of 62% (95% CI, 54%–71%) in our trial-like cohort (median follow-up, 16.6 months) versus 73% (95% CI, 66%–79%) in the cemiplimab clinical trial (median follow-up, 15.7 months); median OS was not reached in either study.¹⁴ Pembrolizumab was approved for advanced CSCC in 2020 based on the KEYNOTE-629 trial which demonstrated a median OS of 26.4 months (95% CI, 19.5 months–NR); survival probability at 24 months was 52.7% (95% CI, 43.8%–60.9%). Differences in patient characteristics existed between trials and might have also contributed to differences in outcomes in addition to treatments. The median age at index in our real-world population was 76 and 78 years in the main and trial-like cohorts, respectively, reaching the US life expectancy, which was 76.1 years at birth overall, 73.2 years for males, and 79.1 years for females in 2021.²² Although the median age difference between our trial-like cohort and the cemiplimab clinical trial cohort was only 4 years (76 vs 72 years, respectively),¹⁴ it should be noted that mortality is expected to increase substantially as age increases. A greater proportion of patients in our real-world cohort had metastatic disease compared with the cemiplimab clinical trial population (63.8% vs 59.6%, respectively).¹⁴ Compared with the cemiplimab clinical trial, more patients in our real-world trial-like cohort received cemiplimab in the first-line setting (87.1% vs 66.3%, respectively).¹⁴ In our real-world analysis, greater median OS was observed with first-line (vs second- or third-line) cemiplimab, as expected. Further, our study found a median TTNT, a proxy for progression-free survival (PFS), of 16.4 months in the main cohort and 25.3 months in the trial-like cohort, which was consistent with the median PFS reported in the cemiplimab trial of 18.4 (95% CI: 10.3–24.3) months.¹⁴ This was also a marked improvement on the previously reported median TTNT of 7.5 months from Vo et al in patients receiving their first systemic therapy (9/4/14–6/30/17) prior to the introduction of cemiplimab.²³ The median TTD in our study of about 8–9 months was in line with reports by Hober et al²⁴ of median treatment duration of 11.3 months (range 13–516 days) for complete responders versus 7.5 months (range 43–595 days) for partial responders. It should be noted that differences might exist between studies in terms of patient populations, outcome definitions, and statistical method of estimating treatment duration (ie, the Kaplan–Meier method). Approximately 17% of patients remained on cemiplimab treatment by 24 months in the current study, though the sample size was small due to the limited follow-up time.

Few previous studies have described real-world outcomes with cemiplimab or other PD-1 inhibitors for advanced CSCC in the US. Two US studies have described real-world outcomes with pembrolizumab, nivolumab, and cemiplimab

for advanced CSCC. Shalhout et al reported median OS of 3.3 years (95% CI: 1.8 years to not reached) and a 12-month OS rate of 72% (95% CI: 62%–84%) in 76 patients with advanced CSCC treated with PD-1 inhibitors, of whom 38 received cemiplimab (analyses were not stratified by the PD-1 inhibitor received).²⁵ Hanna et al reported median OS of 8.0 months (95% CI: 7.6–12.3 months) and a 12-month OS rate of 46.1% among 61 patients with advanced CSCC treated with pembrolizumab, nivolumab, or cemiplimab (the number of patients treated with cemiplimab was not stated) at a median follow-up of 8.5 months.²⁶ It should be noted that the Hanna et al study sample included a higher proportion of patients with distant metastasis (77% vs 20%), those who were immunocompromised or immunosuppressed (31% vs 21%), or those with an ECOG PS of 2 or higher (23% vs 18%) compared with our main cohort.²⁶

The CASE study is the only US study to date to report real-world outcomes for patients with advanced CSCC treated with cemiplimab alone.²⁷ It has not yet reported OS outcomes but reported overall response rates of 37.4% overall and 42.9% in patients who were immunocompromised or immunosuppressed (ie, allogenic bone marrow or solid organ transplantation, inflammatory bowel diseases, leukemia, lupus, lymphoma, multiple myeloma, multiple sclerosis, rheumatoid arthritis, polycythemia vera, myeloproliferative disorder, or chronic obstructive pulmonary disease with prednisone).²⁷

Several studies outside of the US have described real-world outcomes for cemiplimab. In a retrospective study of patients with advanced CSCC enrolled in an early-access program for cemiplimab in France, median OS was not reached and the one-year OS rate was 63.1% overall; no significant OS differences were observed by immune status or previous systemic treatment status, but OS was significantly shorter for patients with higher ECOG PS (36% for ECOG PS ≥ 2 vs 73% for ECOG PS < 2 ; $p < 0.0001$).²⁴ In a single-center, real-world study of cemiplimab among elderly, frail patients with advanced CSCC in Italy, the 10-month OS rate was 57.6%; median OS was 18 (range, 1–23) months, but the small sample size limited reliable estimation.²⁸ In a retrospective analysis of patients with advanced CSCC treated with cemiplimab from the UK Named Patient Scheme, median OS was 12.6 months, and the 12-month OS rate was 60.5%.²⁹ In a retrospective single-center analysis of patients with advanced CSCC treated with cemiplimab in France, median OS was 24.1 (95% CI, 16.4–31.8) months.³⁰ Although reasons for differences in median OS observed across studies are unknown, they may be attributed to potential differences in patient characteristics such as disease stage, prior treatment, or unmeasured prognostic factors.

When stratified by stage at index, we did not find differences in OS between patients with locally advanced CSCC and those with metastatic CSCC; these results are similar to those observed by stage in other real-world studies of historical standard of care, where OS did not seem to differ substantially between patients with locally advanced CSCC and those with metastatic CSCC.^{3,23} In our analysis, patients who were immunocompromised or immunosuppressed seemed to be able to achieve similar OS to those who were not immunocompromised or immunosuppressed, though the number of patients who had prior allogenic or solid organ transplants was too small for meaningful interpretation. Similar to the Hober et al study,²⁴ immunocompromised or immunosuppressed status was not shown to be a significant predictor of OS in our multivariate analysis.

In our real-world analysis, younger age, primary location of CSCC in the head and neck only, and lower ECOG PS were associated with better OS. The finding that patients with primary CSCC location in the head and neck only had better OS than those in the extremities only is an interesting area for future research to identify potential reasons for this difference. One retrospective study of patients with advanced CSCC treated with cemiplimab in the named patient program-compassionate use in Italy did not find any baseline factor to be associated with the overall response rate in their multivariate analysis.³¹

This analysis contributes to the literature on real-world patient characteristics, treatment patterns, and survival in patients with advanced CSCC initiating cemiplimab monotherapy in oncology clinical practice settings in the US. However, the study has some limitations. Although we used OS as an outcome, disease-specific survival is used more often in CSCC, given the elderly population. Related, our study period coincided with the COVID-19 pandemic, and the clear separation in OS curves for the 2020 index year cohort suggests a potential effect of the pandemic on survival outcomes. Despite efforts to derive a trial-like cohort, these patients may not resemble those in the trial as not all inclusion and exclusion criteria were applied due to limited data availability and achievable operationalization of trial criteria in the real-world data. Comorbidities (eg, immunocompromised or immunosuppressed status) were defined using

structured EHR data only, which might underestimate the actual disease burden. While we are confident in the identification of the first systemic treatment after advanced CSCC diagnosis, there may be limitations in determining whether patients had received prior systemic therapy, surgery, or radiation before advanced CSCC diagnosis due to the limited baseline period duration. Data for certain baseline characteristics such as ECOG PS were missing for some patients. Medical care delivered outside of the participating centers, as well as non-oncology care, are not captured in the real-world database, including radiotherapy and surgery. Information on disease progression or relapse was not available in this study database. Real-world endpoints such as TTD and TTNT, as proxy measures for PFS, may not reflect disease progression and do not capture reasons for discontinuation. Finally, the study population primarily reflects the experience of patients with advanced CSCC treated with cemiplimab mainly in the community oncology setting and might not be representative of all such patients in clinical practice (eg, patients treated in academic centers or in the dermatology setting).

Conclusion

Among patients with advanced CSCC initiating cemiplimab monotherapy in the real-world setting, our study findings indicate that median OS was more than 2 years and as high as 26.5 months for those with regional or distant metastatic CSCC. This contrasts with pre-cemiplimab reports for other systemic non-immunotherapies, which have an OS of 8 to 15 months in advanced CSCC. Further, OS for patients in the real-world trial-like cohort approached that reported in clinical trials, even though patients in our real-world trial-like cohort were older, and a greater proportion had metastatic disease. Similar OS was observed in patients with immunosuppressing/immunocompromising conditions vs those without. These findings confirm the effectiveness of cemiplimab in advanced CSCC among a heterogeneous, real-world patient population and substantiate the efficacy of cemiplimab as observed in clinical trials.

Data Sharing Statement

The data that support the findings of this study have been originated by Flatiron Health, Inc. Requests for data sharing by license or by permission for the specific purpose of replicating results in this manuscript can be submitted to dataaccess@flatiron.com.

Ethics Approval

Institutional review board approval of the study protocol for creating this research database was obtained by Flatiron Health before the study was conducted and included a waiver of informed consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Wenzhen Ge, Ning Wu, Chieh-I Chen, Timothy J Inocencio, Frank Seebach, and Matthew Fury are employees of Regeneron Pharmaceuticals, Inc. and are Regeneron Pharmaceuticals, Inc. stockholders. Patrick R. LaFontaine is an employee of Sanofi and is a Sanofi stockholder. James Harnett is an employee of Regeneron Pharmaceuticals, Inc. and is a Regeneron Pharmaceuticals, Inc. and Pfizer stockholder. Emily Ruiz has received advisory board and consulting fees from Feldan Therapeutics, Regeneron Pharmaceuticals, Inc., Merck & Co, and Checkpoint Therapeutics. She also reports grants for co-investigation from Regeneron Pharmaceuticals, Inc., Merck, and Castle Biosciences, outside the submitted work. The authors report no other conflicts of interest in this work.

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