Efficacy and safety of cosibelimab in advanced cutaneous squamous cell carcinoma: Results from a Pivotal Open-label Study with a median follow-up of ≥2 years

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Background: Cosibelimab-ipdl, a high-affinity, programmed death-ligand 1–blocking antibody, is approved by the US Food and Drug Administration for treatment of adults with metastatic cutaneous squamous cell carcinoma (mCSCC) or locally advanced CSCC (laCSCC) who are not candidates for curative surgery or radiation.

Objective: To report long-term efficacy and safety outcomes from a pivotal study of cosibelimab in mCSCC or laCSCC.

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Methods: Patients received intravenous cosibelimab 800 mg every 2 weeks (mCSCC and laCSCC cohorts) or 1200 mg every 3 weeks (mCSCC cohort). The primary endpoint was objective response rate (ORR). Secondary endpoints included duration of response (DOR) and safety.

Results: With a median follow-up duration of 29.3 months for the mCSCC cohort (n = 78), ORR was 50.0% (complete response [CR], 12.8%), median DOR was not reached, and estimated 24-month DOR was 72.1%. With a median follow-up duration of 24.1 months for the laCSCC cohort (n = 31), ORR was 54.8% (CR, 25.8%), median DOR was not reached, and the estimated 24-month DOR was 80.2%. Immune-related adverse event rate was 27.6%; 3.6% grade 3, no grade ≥4 events.

Limitations: Nonrandomized; limited biomarker analysis.

Conclusion: Cosibelimab demonstrated robust and durable ORRs with increasing CR rates in advanced CSCC and low rates of severe immune-related adverse events. (J Am Acad Dermatol 2026;94:48-56.)

Key words: advanced cutaneous squamous cell carcinoma; cosibelimab; immune checkpoint inhibitors; immunotherapy; programmed death-ligand 1; skin cancer; skin neoplasms.

INTRODUCTION

Cutaneous squamous cell carcinoma (CSCC) is the second most common form of skin cancer; however, robust global estimates are limited, as CSCC is excluded from many national cancer registries, including those in the United States.[1,2] Historically, the prevalence ratio of basal cell carcinoma to CSCC cases was estimated at 4:1.[3,4] However, recent data from US insurance claims databases suggest this ratio is nearing 1:1, reflecting a relative increase in the incidence of CSCC.[4,5] In the United States, the estimated annual incidence of CSCC is 1.8 million cases, including ~40,000 advanced cases, with an estimated 15,000 deaths annually.[6,7]

CAPSULE SUMMARY

- Programmed death receptor-1 inhibitors have been shown to be efficacious for cutaneous squamous cell carcinoma (CSCC), but there are limited data on other immunotherapies in CSCC, including programmed death-ligand 1 (PD-L1) inhibitors.
- Cosibelimab, a PD-L1 inhibitor, shows long-term, durable responses with increasing complete response rates and a low incidence of severe immune-related adverse events, prompting priority consideration in clinical treatment strategies.

Before the introduction of immunotherapy, patients who presented with locally advanced CSCC (laCSCC) or metastatic CSCC (mCSCC) had poor prognosis and more limited treatment options, given the advanced stage of disease.[8] Locally advanced or metastatic disease is associated with substantial morbidity and mortality, with 10-year survival rates of <20% for patients with regional lymph node involvement and <10% for patients with distant metastases.[1,9] CSCC is characterized by high tumor mutational burden with a large amount of ultraviolet radiation–related mutations, thereby making CSCC tumors highly sensitive to immunotherapy.[3,10,11] Programmed death-ligand 1 (PD-L1) is often upregulated in CSCC tumors. Binding of PD-L1 to its receptor, programmed death receptor-1 (PD-1), in tumor cells leads to inhibition of peripheral T-cell activation, evasion of detection by immune cells, facilitation of tumor growth, and increased risk of metastasis.[3,12,13] As such, inhibiting the PD-L1/PD-1 pathway has been targeted by multiple pharmaceutical therapies to treat solid tumors, including CSCC. Cemiplimab and pembrolizumab, both PD-1–targeting monoclonal antibodies, are approved by the US Food and Drug Administration (FDA) for patients with mCSCC or laCSCC who are ineligible for curative surgery or radiotherapy. For eligible patients, immunotherapy is now the standard of care for this patient population.[3,14,15] This represents an important advancement in the management of CSCC; however, PD-1–blocking antibodies are associated with higher risk of severe adverse events (AEs) compared with PD-L1–blocking antibodies.[16] Higher incidences of grade ≥3 treatment-related AEs, including immune-related AEs (irAEs), have been reported for PD-1 inhibitors compared with PD-L1 inhibitors in other cancers, indicating the potential for PD-L1 therapies to have a more tolerable safety profile for patients with CSCC.[17,18]

Cosibelimab (UNLOXCYT; Checkpoint Therapeutics, Inc.) is a high-affinity, fully human monoclonal antibody that binds to PD-L1 and inhibits

Abbreviations used:

AE:	adverse event
CI:	confidence interval
CR:	complete response
CSCC:	cutaneous squamous cell carcinoma
DOR:	duration of response
ECOG PS:	Eastern Cooperative Oncology Group performance status
FDA:	US Food and Drug Administration
irAE:	immune-related adverse event
ICH:	International Conference on Harmonisation
ICR:	independent central review
laCSCC:	locally advanced cutaneous squamous cell carcinoma
mCSCC:	metastatic cutaneous squamous cell carcinoma
NSCLC:	non−small cell lung cancer
ORR:	objective response rate
PD-1:	programmed death receptor-1
PD-L1:	programmed death-ligand 1
Q2W:	every 2 weeks
Q3W:	every 3 weeks
SD:	standard deviation
TEAE:	treatment-emergent adverse event

its interaction with the PD-1 and B7.1 receptors.[8,19,20] Additionally, cosibelimab has a functional fragment crystallizable domain capable of inducing antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity against tumor cells.[8,20] Modeling data demonstrate that cosibelimab sustains >99% tumor target occupancy to block the PD-L1 interaction with PD-1 and reactivate T cells to help restore an antitumor immune response.[20,21]

Pivotal results based on an initial predefined data cutoff from the open-label, multicenter, multiregional, multicohort, phase 1 trial of cosibelimab in patients with mCSCC or laCSCC (ClinicalTrials.gov identifier: NCT03212404) formed the basis of the FDA approval of cosibelimab-ipdl for the treatment of adults with mCSCC or laCSCC who are not candidates for curative surgery or radiation in December 2024.[19] These results demonstrated objective response rates (ORRs) of 47.4% (95% confidence interval [CI]: 36.0% to 59.1%) and 48.4% (95% CI: 30.2% to 66.9%) at a median follow-up of 15.4 months (range, 0.4-40.5 months) and 10.7 months (range, 2.7-22.3 months) in mCSCC and laCSCC, respectively, as of the data cutoff for the FDA marketing application (November 18, 2021).[19,22] The most frequent serious adverse reactions (≥2% of participants) were sepsis (2.8%), pneumonia (2.8%), and pyrexia (2.1%), with no reported treatment-related deaths.[19,22]

We present long-term follow-up data from the pivotal phase 1 trial of cosibelimab in patients with advanced CSCC who are not candidates for curative surgery or radiation, including data for the laCSCC cohort that have not previously been published.

METHODS

Patient population

This ongoing, open-label, multicenter, multicohort trial was conducted in 2 parts. Briefly, part 1 was a dose-escalation study to evaluate fixed doses of cosibelimab monotherapy administered every 2 weeks (Q2W) or every 3 weeks (Q3W) in participants with advanced cancers. Part 2 assessed the antitumor activity and safety of cosibelimab in various expansion cohorts of patients with advanced cancers, including pivotal cohorts of patients with mCSCC and laCSCC. Key inclusion and exclusion criteria are detailed in the Supplementary Methods available via Mendeley at https://data.mendeley.com/datasets/zgwsjgdkvt/1.

Study design

Patients received intravenous cosibelimab 800 mg Q2W (group 1, mCSCC; group 2, laCSCC) on days 1 and 15 of each 28-day treatment cycle or 1200 mg Q3W (group 3, mCSCC) on day 1 (Supplementary Figure 1, available via Mendeley at https://data.mendeley.com/datasets/zgwsjgdkvt/1). Cosibelimab dosing regimens of 800 mg Q2W and 1200 mg Q3W are comparable based on the pharmacokinetics-related criteria outlined in the FDA guidance for alternative dosing regimens for PD-L1−blocking antibodies.[22] Treatment was continued until confirmed complete response (CR), as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (for radiological scans) and clinical response criteria using bidimensional measurements in accordance with World Health Organization (WHO) criteria (for digital photography), worsening progressive disease, toxicity, or clinical deterioration, followed by a posttreatment follow-up period. Treatment following CR could be extended if specifically requested by the Investigator and deemed in the best interest of the patient. Both the investigator and an independent central review (ICR) conducted end-of-cycle tumor assessments between days 24 and 28 in cycles 2, 4, 6, and 8 and every 3 cycles thereafter for groups 1 and 2, and between days 17 and 21 in cycles 3, 6, 9, and 12 and every 4 cycles thereafter for group 3 (Supplementary Figure 1, available via Mendeley at https://data.mendeley.com/datasets/zgwsjgdkvt/1). There was no randomization, and neither patients nor study investigators were blinded. Patients were contacted by telephone quarterly about survival and tumor treatment status after treatment was stopped and the required follow-up visits were completed. The study design details were previously published (Supplementary Methods, available via

Mendeley at https://data.mendeley.com/datasets/zgwsjgdkvt/1).[8]

The study was conducted according to the principles of the Declaration of Helsinki, the International Conference on Harmonisation (ICH) Good Clinical Practice guidelines outlined in the ICH E6 Tripartite Guideline, and the Code of Federal Regulations Title 21 (part 312) at the various participating sites, with approval of an independent ethics committee or institutional review board. Written informed consent was obtained from each patient before study enrollment.

Endpoints

The primary objective was to evaluate ORR (CR + partial response) by ICR according to RECIST version 1.1 (for radiological scans) and clinical response criteria using bidimensional measurements in accordance with WHO criteria (for digital photography), assessed by the CSCC group. Key secondary objectives included evaluation of duration of response (DOR) by ICR as well as incidence and severity of treatment-emergent AEs (TEAEs) according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

RESULTS

Patient population

As of the March 31, 2023, data cutoff, 192 patients who were enrolled and treated in the 3 CSCC groups (group 1, mCSCC, n = 78; group 2, laCSCC, n = 58; group 3, mCSCC, n = 56) comprised the safety population (Supplementary Table II and Figure 2, available via Mendeley at https://data.mendeley.com/datasets/zgwsjgdkvt/1). Patients who were eligible (n = 109) for long-term efficacy assessment in group 1 mCSCC (n = 78) and group 2 laCSCC (n = 31) were included in the efficacy population (Table I), representing all patients included in the prespecified primary/interim analyses, as outlined in the statistical analysis plan (data cutoff: November 18, 2021). Patients with mCSCC had a mean (SD) age of 71.2 (12.9) years, 75.6% were male, and 88.5% were white; patients with laCSCC had a mean (SD) age of 76.5 (8.2) years, 61.3% were male, and 77.4% were white. Most patients had an Eastern Cooperative Oncology Group performance status of 1 (mCSCC, 70.5%; laCSCC, 54.8%) and had undergone prior cancer surgery (mCSCC, 60.3%; laCSCC, 80.6%) and radiation therapy (mCSCC, 65.4%; laCSCC, 77.4%), but the majority had not undergone prior systemic therapy (mCSCC, 91.0%; laCSCC, 96.8%).

Efficacy

With a median follow-up duration of 29.3 months (range, 0.4-52.0 months) for group 1 mCSCC and 24.1 months (range, 2.8-37.3 months) for group 2 laCSCC, the ORR per ICR was 50.0% (95% CI, 38.5%-61.5%) and 54.8% (95% CI, 36.0%-72.7%), respectively (Table II; Fig 1). Robust and durable reductions in the sum of target lesion diameters were observed for participants in both groups (Supplementary Figure 3, available via Mendeley at https://data.mendeley.com/datasets/zgwsjgdkvt/1). The CR rate was 12.8% and 25.8% for groups 1 and 2, respectively. Median DOR was not reached in both populations (group 1: range, 1.4-45.3+ months; group 2: range, 8.3-31.3+ months), with a median duration of follow-up for responding participants of 21.3 and 18.9 months for groups 1 and 2, respectively. The Kaplan-Meier–estimated probabilities of maintaining a response at 6, 12, and 24 months were 89.5%, 75.4%, and 72.1% in group 1 and 100%, 88.2%, and 80.2% in group 2, respectively (Table II; Fig 2).

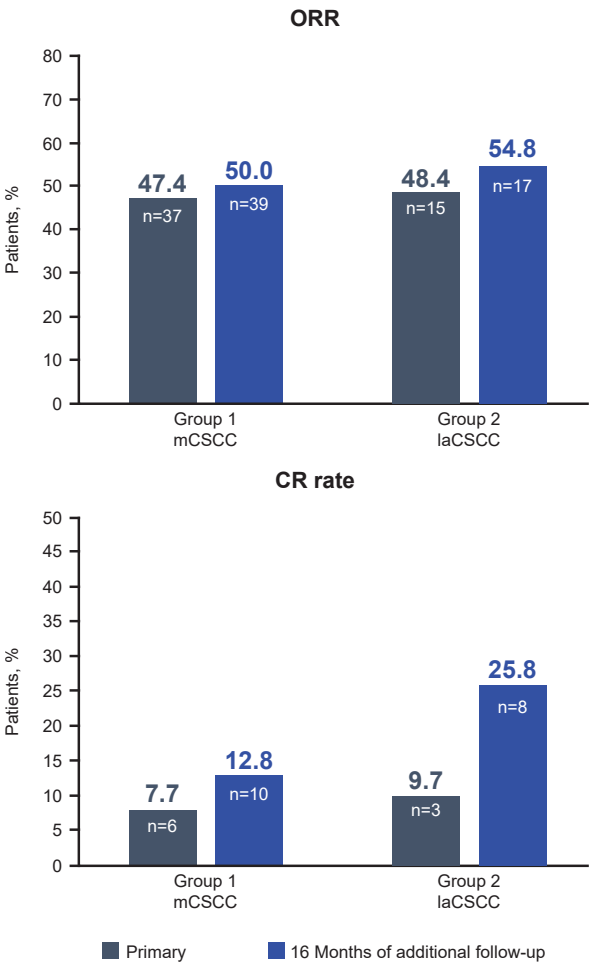

Fig 1. ORRs and CR rates per ICR at the primary/interim analyses and at 16 months of additional follow-up for the mCSCC and laCSCC cohorts. *CR*, Complete response; *ICR*, independent central review; *laCSCC*, locally advanced cutaneous squamous cell carcinoma; *mCSCC*, metastatic cutaneous squamous cell carcinoma; *ORR*, objective response rate.

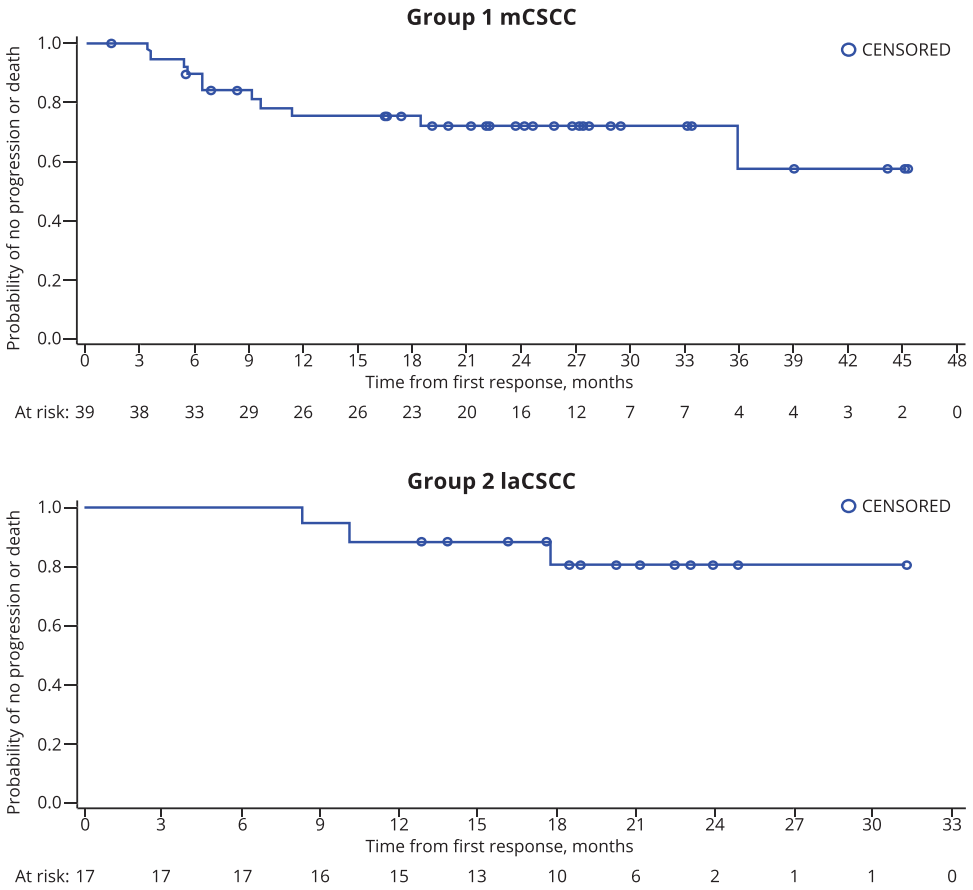

Fig 2. Kaplan-Meier curves of DOR per ICR in patients with mCSCC and laCSCC. *CR*, Complete response; *DOR*, duration of response; *ICR*, independent central review; *laCSCC*, locally advanced cutaneous squamous cell carcinoma; *mCSCC*, metastatic cutaneous squamous cell carcinoma; *PR*, partial response. DOR is measured from the time measurement criteria are first met for response (CR or PR, whichever is first recorded) until the first date of recurrent or progressive disease (radiographic), or death due to any cause.

Exploratory subgroup analyses by demographics are presented in Supplementary Figure 4 (available via Mendeley at https://data.mendeley.com/datasets/zgwsjgdkvt/1). Samples for baseline tumor PD-L1 status assessment were available for 70.5% and 87.1% of the group 1 and 2 cohorts, respectively. The ORR by ICR was 51.0% (19 of 37) among participants with PD-L1–positive (≥1%) tumors and 44.0% (8 of 18) among participants with PD-L1–negative tumors in the mCSCC cohort. For participants in the laCSCC cohort, the ORR by ICR was 53.0% (10 of 19) among participants with PD-L1–positive (≥1%) tumors and 38.0% (3 of 8) among participants with PD-L1–negative tumors. There was no statistical correlation between response and PD-L1 status for participants in both cohorts.

Safety

TEAEs were reported in 181 patients (94.3%; Table III); 63 patients (32.8%) experienced ≥1 serious TEAE. The most common TEAEs of any grade were fatigue (22.9%), anemia (20.3%), constipation (16.1%), and diarrhea (15.1%). Fifty-three patients (27.6%) experienced irAEs, of which only 7 patients (3.6%) were classified as grade 3 irAEs, which included increased transaminases (n = 2), acute generalized exanthematous pustulosis, increased aspartate aminotransferase, cholestatic jaundice, pemphigoid, and pruritic rash (n = 1 each). There were no reported grade ≥4 irAEs. Permanent treatment discontinuation due to TEAEs, regardless of attribution, occurred in 12 patients (6.3%); the most common reason was COVID-19 or COVID-19 pneumonia (1.6%). The most common treatment-related TEAEs of any grade were pruritus and fatigue (each, 12.0%) and rash (8.9%; Supplementary Table III available via Mendeley at https://data.mendeley.com/datasets/zgwsjgdkvt/1). The most common grade ≥3 TEAE was anemia (5.2%). There were no events of grade ≥3 pneumonitis, colitis, hepatitis, nephritis, or endocrinopathies. TEAEs led to death in 6 patients

Table I. Patient demographics and baseline characteristics (efficacy population, N = 109)

Demographic/characteristic, n (%)	Group 1 mCSCC 800 mg Q2W (n = 78)	Group 2 laCSCC 800 mg Q2W (n = 31)
Sex		
Female	19 (24.4)	12 (38.7)
Male	59 (75.6)	19 (61.3)
Age		
<65 y	22 (28.2)	2 (6.5)
≥65 y	56 (71.8)	29 (93.5)
Race		
Asian	6 (7.7)	0
Black or African American	1 (1.3)	0
White	69 (88.5)	24 (77.4)
Other race	0	1 (3.2)
Missing*	2 (2.6)	6 (19.4)
Ethnicity		
Hispanic or Latino	3 (3.8)	5 (16.1)
Not Hispanic or Latino	73 (93.6)	19 (61.3)
Unknown	0	1 (3.2)
Missing*	2 (2.6)	6 (19.4)
Country/region		
Asia	6 (7.7)	0
Australia/New Zealand	45 (57.7)	13 (41.9)
Europe	19 (24.4)	17 (54.8)
South Africa	8 (10.3)	1 (3.2)
ECOG PS		
0	23 (29.5)	14 (45.2)
1	55 (70.5)	17 (54.8)
Primary CSCC site		
Head/neck	46 (59.0)	28 (90.3)
Extremity	18 (23.1)	2 (6.5)
Trunk	9 (11.5)	1 (3.2)
Other	5 (6.4)	0
Type of metastatic disease		
Distant	52 (66.7)	NA
Nodal	26 (33.3)	NA
Prior cancer-related surgery		
Yes	47 (60.3)	25 (80.6)
No	31 (39.7)	6 (19.4)
Prior radiation therapy		
Yes	51 (65.4)	24 (77.4)
No	27 (34.6)	7 (22.6)
Prior systemic therapy		
Yes	7 (9.0)	1 (3.2)
No	71 (91.0)	30 (96.8)

CSCC, Cutaneous squamous cell carcinoma; *ECOG PS*, Eastern Cooperative Oncology Group performance status; *laCSCC*, locally advanced CSCC; *mCSCC*, metastatic CSCC; *NA*, not applicable; *Q2W*, every 2 weeks.

*Some sites in Europe did not report race and ethnicity owing to privacy laws.

Table II. Tumor response to cosibelimab by ICR (efficacy population, N = 109)

	Group 1 mCSCC 800 mg Q2W (n = 78)	Group 2 laCSCC 800 mg Q2W (n = 31)
Median follow-up duration (95% CI), months	29.3 (25.3-34.8)	24.1 (22.6-26.9)
ORR (95% CI), %	50.0 (38.5-61.5)	54.8 (36.0-72.7)
Best overall response, n (%)		
Complete response	10 (12.8)	8 (25.8)
Partial response	29 (37.2)	9 (29.0)
Stable disease	11 (14.1)	10 (32.3)
Progressive disease	20 (25.6)	3 (9.7)
Not evaluable	8 (10.3)	1 (3.2)
Median observed time to response (min-max), months	1.9 (1.6-16.9)	3.6 (1.7-10.1)
Median DOR (min-max), months	NR (1.4-45.3+)	NR (8.3-31.3+)
Median follow-up duration for durability of response, months	21.3	18.9
KM-estimated 6-month DOR probability (95% CI), %	89.5 (74.3-95.9)	100 (NE)
KM-estimated 12-month DOR probability (95% CI), %	75.4 (57.9-86.4)	88.2 (60.6-96.9)
KM-estimated 24-month DOR probability (95% CI), %	72.1 (54.1-84.0)	80.2 (49.6-93.3)

CI, Confidence interval; *DOR*, duration of response; *ICR*, independent central review; *KM*, Kaplan-Meier; *laCSCC*, locally advanced cutaneous squamous cell carcinoma; *mCSCC*, metastatic cutaneous squamous cell carcinoma; *NE*, not evaluable; *NR*, not reached; *ORR*, objective response rate; *Q2W*, every 2 weeks.

(3.1%); all events were considered unrelated to cosibelimab treatment. Of these 6 participants, 2 died of COVID-19, 1 died of COVID-19 pneumonia, 1 with a history of cardiovascular disease died of cardiac arrest, 1 died of Fournier's gangrene, and 1 died of sepsis. The safety profile of cosibelimab was generally comparable across groups and dosing regimens.

DISCUSSION

Cosibelimab is the first PD-L1–targeting monoclonal antibody approved by the FDA for the treatment of adults with mCSCC or laCSCC who are not

Table III. Summary of TEAEs regardless of attribution (safety population, N = 192)

	Advanced CSCC	
TEAE, n (%)	**Any grade**	**Grade ≥3**
Any TEAE	181 (94.3)	87 (45.3)
Any serious TEAE	63 (32.8)	
Immune-related TEAE	53 (27.6)	7 (3.6)
Most common immune-related TEAEs (≥1%)		
Hypothyroidism	17 (8.9)	—
Hyperthyroidism	9 (4.7)	—
Rash	8 (4.2)	—
Pruritus	6 (3.1)	—
Adrenal insufficiency	3 (1.6)	—
Arthralgia	3 (1.6)	—
Rash maculopapular	3 (1.6)	—
Transaminases increased	2 (1.0)	2 (1.0)
Pneumonitis	2 (1.0)	—
Most common TEAEs (≥10%)		
Fatigue	44 (22.9)	4 (2.1)
Anemia	39 (20.3)	10 (5.2)
Constipation	31 (16.1)	1 (0.5)
Diarrhea	29 (15.1)	—
Pruritus	26 (13.5)	—
Nausea	25 (13.0)	—
Rash	24 (12.5)	1 (0.5)
Asthenia	22 (11.5)	1 (0.5)
Arthralgia	21 (10.9)	—
Skin lesion	20 (10.4)	—
Headache	20 (10.4)	—
TEAEs leading to discontinuation	12 (6.3)	—
TEAEs leading to death	6 (3.1)	—

CSCC, Cutaneous squamous cell carcinoma; *TEAE*, treatment-emergent adverse event.

candidates for curative surgery or radiation.[19] Here, we present the long-term data of cosibelimab from the pivotal phase 1 trial in advanced CSCC, including data for the laCSCC cohort that have not previously been published, to continue characterization of the safety and efficacy profile of cosibelimab. Overall, cosibelimab was associated with long-term efficacy in participants with mCSCC and laCSCC, as evidenced by clinically meaningful ORRs, high CR rates, and durable DORs. Consistent with the primary/interim analyses, cosibelimab was associated with a low rate of grade 3 irAEs and no grade ≥4 irAEs.

Cosibelimab demonstrated robust and durable ORRs and CR rates in patients with mCSCC and laCSCC. After 16 months of additional follow-up, these results showed deepening of responses over time, resulting in higher ORR and CR rates than reported at the primary/interim analyses.[8] The response rates are comparable to those reported in long-term studies of pembrolizumab and cemiplimab in patients with advanced CSCC albeit with longer median follow-up durations (pembrolizumab: 63.1 months; cemiplimab: 42.5 months).[23,24] Median DOR was not reached for both the mCSCC and laCSCC cosibelimab cohorts. Kaplan-Meier–estimated probability of survival at 24 months was 72.1% and 80.2% for the mCSCC and laCSCC cohorts, respectively, suggesting ongoing durable responses to cosibelimab treatment. These durable responses are especially significant for patients with CSCC presenting as tumors in the head and neck region, forming the majority of primary CSCC sites, which can be challenging to manage surgically due to the heightened risk of disfigurement and morbidity.[25]

PD-L1 expression has demonstrated predictive value for clinical response in certain cancers, including non–small cell lung cancer (NSCLC) and bladder cancer.[12] Our preliminary analysis showed that cosibelimab was associated with durable responses irrespective of baseline tumor PD-L1 status in both cohorts. This suggests that PD-L1 expression alone cannot predict clinical response to cosibelimab in patients with advanced CSCC. Similar observations have been reported with cemiplimab, although results have been inconsistent with pembrolizumab.[24,26-29] Future studies are warranted to explore whether other candidate biomarkers or clinical factors may be important for clinical decision-making.

Overall, cosibelimab had a manageable safety profile, regardless of attribution, with notable low rates of grade 3 irAEs, no grade ≥4 irAEs, and no treatment-related deaths. The rate of severe irAEs reported in this study (3.6%) is lower than those reported in studies with PD-1–targeting agents (pembrolizumab: 8.8%; cemiplimab: 10.7% to 19.2%).[24,30,31] This may be due to preservation of the PD-L2/PD-1 interaction, which may maintain levels of checkpoint signaling, resulting in decreased blockade of the negative inhibitory signal and decreased autoimmunity. Additionally, the PD-L2/PD-1 interaction reduces PD-L2 binding to other molecules (eg, repulsive guidance molecule b), which could contribute to irAEs (eg, pneumonitis) with PD-1-targeting agents.[16,18,32] Studies of patients aged ≥65 years with NSCLC have found the incidence of irAEs to be high.[33] This is relevant for patients with advanced CSCC as the median age for patients in the cosibelimab trial and other PD-1 inhibitor trials is >70 years.[24,26-30] Management of elderly patients is complicated by potential comorbidity, frailty, organ dysfunction, and polypharmacy; therefore, selecting a drug with low rates of severe irAEs is very important.[33] Furthermore, the safety profile of cosibelimab makes it an attractive agent to study further in special CSCC populations at higher risk of toxicities, such as solid

organ transplant recipients and patients with a history of hematologic malignancies or autoimmune disorders, where irAEs limit utilization.[34-36]

Study limitations have been described in the primary mCSCC publication and include the single-cohort design, short duration of follow-up at data cutoff, limited biomarker analysis, and absence of pathologic confirmation of complete response in externally visible target lesions.[8] However, the data presented herein provide longer-term follow-up with sustained efficacy. These results further support that cosibelimab at 800 mg Q2W and 1200 mg Q3W has a manageable safety profile and provides clinically meaningful activity for patients with mCSCC and laCSCC, as evidenced by ORR and DOR.

CONCLUSION

In this pivotal study of patients with mCSCC and laCSCC, cosibelimab was associated with robust and clinically meaningful ORRs ≥50% and CR rates, durable DORs, and a manageable safety profile with low rates of grade 3 irAEs and no grade ≥4 irAEs. These results provide additional support for the use of cosibelimab in patients with mCSCC and laCSCC.

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Conflicts of interest

ESR has served as a consultant for Checkpoint Therapeutics, Feldan Therapeutics, Merck & Co., Regeneron Pharmaceuticals, and Replimune. EM-C has served as a consultant and/or scientific advisor for Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Pierre Fabre, Roche, Sanofi, and Regeneron; received research funding from Merck Sharp & Dohme, Sanofi, and Bristol Myers Squibb; served as a speaker for Amgen, Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Pierre Fabre, and Regeneron; and served as a principal investigator for clinical trials for Amgen, Bristol Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Pierre Fabre, Roche, Sanofi, Replimune, Iovance, and Bioinvent. HM has served as a consultant and/or scientific advisor for Bristol Myers Squibb, Merck Sharp & Dohme, and Pierre Fabre. MAB-G has served as a consultant, in an advisory role, or on a speakers' bureau for Bristol Myers Squibb, Merck Sharp & Dohme, Regeneron, Novartis, and Pierre Fabre; and received financial support for travel or accommodation expenses from Bristol Myers Squibb, Merck Sharp & Dohme, Regeneron, Novartis, and Pierre Fabre. GQ has served as a consultant for Sanofi. CN has served as a consultant or member of an advisory board for Bristol Myers Squibb, Merck Sharp & Dohme, Regeneron, and Novartis; and received financial support for travel and accommodation expenses from Bristol Myers Squibb, Merck Sharp & Dohme, and Novartis. SD has received research funding from Bristol Myers Squibb, Merck Sharp & Dohme, and Pierre Fabre; honoraria from Bristol Myers Squibb, Merck Sharp & Dohme, and Regeneron; financial support for travel expenses from Bristol Myers Squibb and Merck Sharp & Dohme; and served as a member of a Data Safety Monitoring Board/advisory board for Bristol Myers Squibb and Merck Sharp & Dohme. RL has served as a consultant and/or scientific advisor for AstraZeneca, Merck Sharp & Dohme, and Sanofi and been a speaker for Merck Sharp & Dohme. MM has served as a scientific advisor and speaker for Merck Sharp & Dohme. DB has served on an advisory board for and received honoraria from Merck Sharp & Dohme. DH has received reimbursements for serving as a clinical investigator for the CK-301-101 trial sponsored by Checkpoint Therapeutics. SF has received honoraria from Merck Sharp & Dohme, MundiPharma, Roche, and Sanofi and serves as a board director for ICON Oncology Holdings Pty (Ltd), Drs. Alberts Bouwer Jordaan Inc., and Gamma Knife South Africa. DRM serves as director for Phoenix Pharma. JO is an employee of Checkpoint Therapeutics and holds stock and other ownership interests in the company and has served in leadership roles at Checkpoint Therapeutics. LNW is an employee of Checkpoint Therapeutics and holds stock and other ownership interests in the company. WGG is an employee of Checkpoint Therapeutics and holds stock and other ownership interests in the company and has served in leadership roles at Checkpoint Therapeutics. MCAG, JC, RYT, MB-B, HS, AT, and PC have no conflicts of interest to declare.

REFERENCES

1. Stanganelli I, Spagnolo F, Argenziano G, et al. The multidisciplinary management of cutaneous squamous cell carcinoma: a comprehensive review and clinical recommendations by a panel of experts. *Cancers (Basel)*. 2022;14(2):377.
2. Wehner MR. Underestimation of cutaneous squamous cell carcinoma incidence, even in cancer registries. *JAMA Dermatol*. 2020;156(12):1290-1291.
3. Boutros A, Cecchi F, Tanda ET, et al. Immunotherapy for the treatment of cutaneous squamous cell carcinoma. *Front Oncol*. 2021;11:733917.
4. 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(10):1081-1086.
5. Lukowiak TM, Aizman L, Perz A, et al. Association of age, sex, race, and geographic region with variation of the ratio of basal cell to cutaneous squamous cell carcinomas in the United States. *JAMA Dermatol*. 2020;156(11):1192-1198.
6. The Skin Cancer Foundation. Most Americans Unaware of a Widespread and Potentially Life-Threatening Skin Cancer, According to Skin Cancer Foundation Survey. Accessed May 5, 2025. https://www.skincancer.org/press/2019-cscc-survey/

7. The Skin Cancer Foundation. Squamous Cell Carcinoma Overview. Accessed May 5, 2025. https://www.skincancer.org/skin-cancer-information/squamous-cell-carcinoma/
8. Clingan P, Ladwa R, Brungs D, et al. Efficacy and safety of cosibelimab, an anti-PD-L1 antibody, in metastatic cutaneous squamous cell carcinoma. *J Immunother Cancer*. 2023;11(10):e007637.
9. Greco S, Pugliese G, Rimini M, Depenni R. Treatment of locally advanced and metastatic cutaneous squamous cell carcinoma. Article in Italian. *Recenti Prog Med*. 2021;112(6):69e-74e.
10. Pickering CR, Zhou JH, Lee JJ, et al. Mutational landscape of aggressive cutaneous squamous cell carcinoma. *Clin Cancer Res*. 2014;20(24):6582-6592.
11. Yarchoan M, Hopkins A, Jaffee EM. Tumor mutational burden and response rate to PD-1 inhibition. *N Engl J Med*. 2017;377(25):2500-2501.
12. Davis AA, Patel VG. The role of PD-L1 expression as a predictive biomarker: an analysis of all US Food and Drug Administration (FDA) approvals of immune checkpoint inhibitors. *J Immunother Cancer*. 2019;7(1):278.
13. Kamiya S, Kato J, Kamiya T, et al. Association between PD-L1 expression and lymph node metastasis in cutaneous squamous cell carcinoma. *Asia Pac J Clin Oncol*. 2020;16(2):e108-e112.
14. LIBTAYO®. Package insert. Regeneron Pharmaceuticals. Inc; 2021.
15. Vafaei S, Zekiy AO, Khanamir RA, et al. Combination therapy with immune checkpoint inhibitors (ICIs): a new frontier. *Cancer Cell Int*. 2022;22(1):2.
16. Wang Y, Zhou S, Yang F, et al. Treatment-related adverse events of PD-1 and PD-L1 inhibitors in clinical trials: a systematic review and meta-analysis. *JAMA Oncol*. 2019;5(7):1008-1019.
17. Baxi S, Yang A, Gennarelli RL, et al. Immune-related adverse events for anti-PD-1 and anti-PD-L1 drugs: systematic review and meta-analysis. *BMJ*. 2018;360:k793.
18. Pillai RN, Behera M, Owonikoko TK, et al. Comparison of the toxicity profile of PD-1 versus PD-L1 inhibitors in non-small cell lung cancer: a systematic analysis of the literature. *Cancer*. 2018;124(2):271-277.
19. UNLOXCYT™. Prescribing information. Checkpoint Therapeutics. Inc.; 2024.
20. Gorelik L, Avgerinos G, Kunes Y, Marasco WA. Preclinical characterization of a novel fully human IgG1 anti-PD-L1 mAb CK-301. Washington, DC: Poster presented at: The American Association for Cancer Research Annual Meeting; April 1-5, 2017.
21. Lin L, Hilbert J, Gorelik L, et al. Semi-mechanistic PK and target-occupancy modeling to support dose justification for anti-PD-L1 clinical candidate CK-301 (cosibelimab) in oncology patients. National Harbor, MD: Poster presented at: The Society for Immunotherapy of Cancer 34th Annual Meeting; November 6-10; 2019.
22. US Food and Drug Administration. Pharmacokinetic-Based Criteria for Supporting Alternative Dosing Regimens of Programmed Cell Death Receptor-1 (PD-1) or Programmed Cell Death-Ligand 1 (PD-L1) Blocking Antibodies for Treatment of Patients with Cancer Guidance for Industry. Accessed March 17, 2025. https://www.fda.gov/media/151745/download
23. Couselo EM, Hughes BGM, Mortier L, et al. Pembrolizumab (pembro) for locally advanced (LA) or recurrent/metastatic (R/M) cutaneous squamous cell carcinoma (cSCC): long-term results of the phase 2 KEYNOTE-629 study. *J Clin Oncol*. 2024;42(16 suppl):9554.
24. Hughes BGM, Guminski A, Bowyer S, et al. A phase 2 open-label study of cemiplimab in patients with advanced cutaneous squamous cell carcinoma (EMPOWER-CSCC-1): final long-term analysis of groups 1, 2, and 3, and primary analysis of fixed-dose treatment group 6. *J Am Acad Dermatol*. 2025;92(1):68-77.
25. McLean LS, Lim AM, Webb A, et al. Immunotherapy to avoid orbital exenteration in patients with cutaneous squamous cell carcinoma. *Front Oncol*. 2021;11:796197.
26. Hughes BGM, Munoz-Couselo E, Mortier L, et al. Pembrolizumab for locally advanced and recurrent/metastatic cutaneous squamous cell carcinoma (KEYNOTE-629 study): an open-label, nonrandomized, multicenter, phase II trial. *Ann Oncol*. 2021;32(10):1276-1285.
27. Grob JJ, Gonzalez R, Basset-Seguin N, et al. Pembrolizumab monotherapy for recurrent or metastatic cutaneous squamous cell carcinoma: a single-arm phase II trial (KEYNOTE-629). *J Clin Oncol*. 2020;38(25):2916-2925.
28. Maubec E, Boubaya M, Petrow P, et al. Phase II study of pembrolizumab as first-line, single-drug therapy for patients with unresectable cutaneous squamous cell carcinomas. *J Clin Oncol*. 2020;38(26):3051-3061.
29. Migden MR, Khushalani NI, Chang ALS, et al. Cemiplimab in locally advanced cutaneous squamous cell carcinoma: results from an open-label, phase 2, single-arm trial. *Lancet Oncol*. 2020;21(2):294-305.
30. Munoz-Couselo E, Hughes BGM, Mortier L, et al. Pembrolizumab for locally advanced or recurrent/metastatic cutaneous squamous cell carcinoma: long-term results of the phase 2 keynote-629 study. *Int Arch Addict Res Med*. 2024;9(1):041.
31. Rischin D, Migden MR, Lim AM, et al. Phase 2 study of cemiplimab in patients with metastatic cutaneous squamous cell carcinoma: primary analysis of fixed-dosing, long-term outcome of weight-based dosing. *J Immunother Cancer*. 2020;8(1):e000775.
32. Xiao Y, Yu S, Zhu B, et al. RGMb is a novel binding partner for PD-L2 and its engagement with PD-L2 promotes respiratory tolerance. *J Exp Med*. 2014;211(5):943-959.
33. Rong Y, Bentley JP, Bhattacharya K, et al. Incidence and risk factors of immune-related adverse events induced by immune checkpoint inhibitors among older adults with non-small cell lung cancer. *Cancer Med*. 2024;13(1):e6879.
34. Jiang R, Fritz M, Que SKT. Cutaneous squamous cell carcinoma: an updated review. *Cancers (Basel)*. 2024;16(10):1800.
35. Zavdy O, Coreanu T, Bar-On DY, et al. Cutaneous squamous cell carcinoma in immunocompromised patients-a comparison between different immunomodulating conditions. *Cancers (Basel)*. 2023;15(6):1764.
36. Lai M, Pampena R, Cornacchia L, et al. Cutaneous squamous cell carcinoma in patients with chronic lymphocytic leukemia: a systematic review of the literature. *Int J Dermatol*. 2022;61(5):548-557.