doi:10.36849/JDD.9954

 ORIGINAL ARTICLE

Efficacy and Safety of Cosibelimab for Advanced Cutaneous Squamous Cell Carcinoma: An Expert Consensus Panel

Brooke Bartley MD,[a] Angela Rosenberg DO,[a] Lauren DeBusk MD,[a] Aaron S. Farberg MD,[b,c,d] Scott M. Dinehart MD,[e] Shannon C. Trotter DO,[f,g] Lindsay Ackerman MD,[h] Daniel Groisser MD,[i,j] Todd Schlesinger MD FAAD FASMS,[k] James Q. Del Rosso DO,[l] Mark Lebwohl MD,[m] Darrell Rigel MD MS[a,n]

[a]Department of Dermatology, UT Southwestern, Dallas, TX
[b]Department of Dermatology, Baylor Scott and White Health System, Dallas, TX
[c]Bare Dermatology, Dallas, TX; [d]Department of Dermatology, University of North Texas Health Science Center at Fort Worth, Fort Worth, TX;
[e]Arkansas Dermatology, Little Rock, AR; [f]Ohio University Heritage College of Osteopathic Medicine, Dublin, OH;
[g]DOCS Dermatology, Canal Winchester, OH; [h]Medical Dermatology Specialists, US Dermatology Partners, Phoenix, AZ;
[i]Schweiger Dermatology Group, Nutley, NJ; [j]Department of Dermatology, Saint Barnabas Hospital, Livingston, NJ;
[k]Clinical Research Center of the Carolinas, Charleston, SC; [l]JDR Dermatology Research, Las Vegas, NV;
[m]Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY;
[n]Department of Dermatology, NYU Grossman School of Medicine, New York, NY

ABSTRACT

Background: Cutaneous squamous cell carcinoma (cSCC) represents a significant clinical challenge in patients with locally advanced (laCSCC) or metastatic (mCSCC) disease who are not candidates for surgery or radiation. In addition to PD-1 inhibitors, pembrolizumab and cemiplimab, cosibelimab, a PD-L1 inhibitor, has been recently approved by the US Food and Drug Administration (FDA) for laCSCC and mCSCC. Given its recent approval, practical guidance is needed to support clinician decision-making regarding cosibelimab's efficacy and safety.

Methods: A comprehensive literature review of PubMed and Google Scholar was completed for studies related to cosibelimab efficacy and safety in laCSCC and mCSCC. An expert panel of 9 dermatologists with significant expertise in the treatment of cSCC gathered to review the articles and create consensus statements on the role of cosibelimab in managing laCSCC and mCSCC. A modified Delphi process was used to approve each statement, and the strength of recommendation was assigned using the Strength of Recommendation Taxonomy (SORT) criteria.

Results: The literature search produced over 200 articles that met the criteria, and a screening of the studies for relevance resulted in 13 articles. The panel developed 6 consensus statements, with 5 unanimously adopted with a strength of "A".

Conclusion: Available data suggest that cosibelimab is an effective treatment for patients with laCSCC and mCSCC who are not candidates for surgery or radiation. Cosibelimab demonstrates a unique and favorable safety profile with no reported grade 4 or 5 immune-related adverse events after more than 2 years of follow-up.

J Drugs Dermatol. 2026;25(5):413-420. doi:10.36849/JDD.9954

INTRODUCTION

Cutaneous squamous cell carcinoma (cSCC) is the second most common skin cancer, with increasing incidence rates worldwide.[1] While most cases are successfully treated with surgical excision or radiation therapy, a subset of patients develop locally advanced cSCC (laCSCC) or metastatic cSCC (mCSCC) that is not amenable to standard treatments, presenting significant therapeutic challenges.[2,3]

cSCC features a high tumor mutational burden (TMB) and elevated prevalence in immunosuppressed individuals, indicating a circumvention of immune surveillance. The programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) checkpoint pathway plays a critical role in tumor immune evasion in cSCC. PD-1 is an inhibitory receptor primarily found on T cells that, when bound by its ligands, PD-L1 and PD-L2, found on antigen-presenting cells and many cancer cells, restrains T cells from full activation and proliferation, thereby suppressing antitumor responses. cSCC tumors exploit this pathway by overexpressing PD-L1 on tumor cells, which interacts with PD-1 receptors on T cells to promote T cell inhibition and immune evasion.[4] These characteristics make advanced cSCC an exceptionally prime candidate for immunotherapy.[2,5-10]

The treatment landscape for advanced cSCC has been transformed by the introduction of immune checkpoint inhibitors (ICIs). Cemiplimab (a fully human PD-1 monoclonal antibody) and pembrolizumab (a humanized PD-1 monoclonal

antibody) have received US Food and Drug Administration (FDA) approval for the treatment of laCSCC and mCSCC in patients who are not candidates for curative surgery or radiation. These PD-1-targeting therapies have led to significant improvements in advanced cSCC survival and quality of life.[11,12] However, treatment options are still limited for advanced cSCC patients, and side effects, including potentially life-threatening immune-related adverse events such as endocrinopathies, pneumonitis, colitis, hepatitis, and severe dermatologic reactions, can lead to discontinuation of treatment.[11-13]

Cosibelimab is a high-affinity, fully human monoclonal antibody targeting PD-L1 and is the most recently FDA-approved ICI for the treatment of laCSCC and mCSCC. While pivotal phase 1 studies have demonstrated its efficacy and safety in advanced cSCC, cosibelimab remains a newly approved therapy.[14,15] As such, expert evaluation of current clinical data is essential to guide optimal use in practice.

The purpose of this expert consensus panel was to review the published evidence on cosibelimab efficacy and safety in advanced cSCC and provide practical guidance to support clinicians as they integrate this newly approved therapy into the management of laCSCC and mCSCC.

MATERIALS AND METHODS

Literature Search and Study Selection

A targeted literature review of PubMed and Google Scholar was completed from October 1 to October 10, 2025, using keywords "cosibelimab," "CK-301," "cutaneous squamous cell carcinoma," "cSCC," "PD-L1 inhibitor," "pembrolizumab," "cemiplimab," "locally advanced," "metastatic," and "immune-related adverse events" along with Boolean term "AND" for English-language original research articles, systematic reviews, meta-analyses, and conference posters or presentations. Package inserts for cosibelimab, cemiplimab, and pembrolizumab were also reviewed. The literature was screened for relevance to the efficacy and safety of cosibelimab and comparative checkpoint inhibitors in advanced cSCC.

The 9 experts who participated in the panel were selected for their expertise in the management of advanced cSCC. The articles and presentations that met the inclusion criteria were distributed, and each member of the panel assigned levels of evidence based on the Strength of Recommendation Taxonomy (SORT) criteria.[16] These levels included level 1 (good-quality patient-oriented evidence), level 2 (limited-quality patient-oriented evidence), or level 3 (other evidence such as consensus guidelines, usual practice, opinion, or disease-oriented evidence).[16]

TABLE 1.

Strength of Recommendation Taxonomy (SORT) Criteria Level of Evidence for References Used in Modified Delphi Process

Reference	Citation	Study Title	Level of Evidence	Consensus
1	Clingan (2023)[15]	Efficacy and Safety of Cosibelimab, an Anti-PD-L1 Antibody, in Metastatic cSCC	1	(9/9)
2	Gorelik (2017)[18]	Poster: Preclinical Characterization of a Novel Full Human IgG1 Anti-PD-L1 mAb CK-301	3	(9/9)
3	Hughes (2021)[12]	Pembrolizumab for Locally Advanced and Recurrent/Metastatic cSCC (KEYNOTE-629 Study): an Open-Label Nonrandomized, Multicenter, Phase II Trial	1	(9/9)
4	Idris (2025)[19]	PD-L1 Inhibitor Cosibelimab for cSCC: Comprehensive Evaluation of Efficacy, Mechanism, and Clinical Trial Insights	2	(9/9)
5	Lin (2021)[20]	Poster: Semi-mechanistic PK/Target-Occupancy Modeling to Support Dose Justification for Anti–PD-L1 Clinical Candidate CK-301 (cosibelimab)	3	(8/9)
6	Migden (2018)[11]	PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma	1	(9/9)
7	Muñoz-Couselo (2024)[21]	Poster: Cosibelimab in Advanced cSCC: Long-Term Efficacy and Safety Results from Pivotal Study	1	(9/9)
8	Muñoz-Couselo (2024)[22]	Poster: Pembrolizumab for Locally Advanced or Recurrent/Metastatic cSCC: Long-Term Results of the Phase 2 KEYNOTE-629 Study	1	(9/9)
9	Plock (2023)[23]	Poster: PD-L1 Inhibitor Cosibelimab: Poppk Supports Comparability of 800 Mg Q2W and 1200 Mg Q3W Dosing Regimens Based on Recent FDA Criteria	3	(9/9)
10	Rischin (2025)[13]	Adjuvant Cemiplimab or Placebo in High-Risk cSCC	1	(9/9)
11	Ruiz (2025)[14]	Efficacy and Safety of Cosibelimab in Advanced cSCC: Results From a Pivotal Open-Label Study With a Median Follow-up of ≥2 Years	1	(9/9)
12	Spagnuolo (2018)[24]	"Comparison of the Toxicity Profile of PD-1 versus PD-L1 Inhibitors in Non-Small Cell Lung Cancer": Is There a Substantial Difference or Not?	3	(9/9)
13	Wang (2019)[25]	Treatment-Related Adverse Events of PD-1 and PD-L1 Inhibitors in Clinical Trials: A Systematic Review and Meta-Analysis	2	(8/9)

Abbreviations: cSCC, cutaneous squamous cell carcinoma; IgG, Immunoglobulin G; mAb, monoclonal antibody; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; Q2W, every 2 weeks; Q3W, every 3 weeks

Development of Consensus Statements

The panel convened on October 22, 2025, to discuss the studies and create consensus statements on cosibelimab efficacy and safety in advanced cSCC. A modified Delphi process, a standard method for developing dermatology recommendations, was used and required a supermajority of six of nine votes for adoption through iterative real-time voting.[17] Consensus statements were assigned a strength of recommendation of A (consistent, good-quality evidence), B (inconsistent or limited-quality evidence), or C (consensus, opinion, or disease-oriented evidence).[16]

RESULTS

Literature Search and Study Selection

The literature search resulted in over 200 articles that met the search criteria. After a comprehensive screening process, 13 references were selected. Studies were included if they reported efficacy and/or safety outcomes for cosibelimab in cSCC or informed comparative safety and/or efficacy of PD-1/PD-L1 inhibitors in advanced cSCC.

Levels of Evidence Designation

For the 13 references that were evaluated, the panel assigned level 1 evidence to 7 references, level 2 evidence to 2 references, and level 3 evidence to 4 references. Although several references initially received mixed evidence ratings, subsequent roundtable discussions allowed the panel to review and clarify the data, resulting in a supermajority consensus for all literature provided (Table 1).

The panel developed 6 consensus statements regarding the efficacy and safety of cosibelimab in advanced cSCC. Five statements were approved unanimously (9/9); one received supermajority support (7/9) (Table 2).

DISCUSSION

Statement 1: *Available evidence indicates that cosibelimab is an effective treatment for mCSCC and laCSCC. (SORT Level A)*

Pivotal clinical trials have evaluated cosibelimab for the treatment of laCSCC and mCSCC, generating the current evidence for its clinical activity. In the pivotal multicenter, multi-cohort, non-randomized phase 1 trial of 78 patients with mCSCC treated with cosibelimab 800 mg IV every 2 weeks, the objective response rate (ORR) was 47.4%, including 7.7% complete responses (CRs) and 39.7% partial responses (PRs) (Table 3). With a median follow-up of 29.3 months, the median duration of response (DOR) was not reached, with a range of 1.4+ to 45.3+ months. Among responders, 85% had an observed DOR ≥6 months, and 67% had an observed DOR ≥12 months.[15]

Extended follow-up (≥2 years; median 24-29 months) in 192 patients with mCSCC and laCSCC showed sustained activity, with ORRs of 50.0% and 54.8%, CRs of 12.8% and 25.8%, and PRs of 37.2% and 29.0%, respectively. In the mCSCC cohort, the estimated 24-month DOR rate was 72.1%. In the laCSCC cohort (median follow-up, 24.1 months), median DOR was not reached (8.3-31.3+ months). Among responders, 100% had an observed DOR of ≥6 months and 88% had an observed DOR of ≥12 months, with an estimated 24-month DOR rate of 80.2%.[14]

Interpretation of these efficacy findings requires consideration of several important limitations. Although the available data demonstrated clear efficacy signals, the evaluable evidence would be strengthened by longer follow-up durations and larger patient cohorts to fully characterize cosibelimab's long-term efficacy and safety profile. Additionally, and more fundamentally, the classification of cSCC as "locally advanced" lacks standardization, creating inherent challenges in translating

TABLE 2.

Consensus statements Consensus Statements and Corresponding Strength of Recommendations *(consensus defined as ≥6 of 9 panelists; five statements approved unanimously [9/9] and one statement approved by supermajority [7/9]).*

Reference	Citation	Study Title
Available evidence indicates that cosibelimab is an effective treatment for metastatic and locally advanced cutaneous squamous cell carcinoma.	A	9/9
The efficacy of the PD-L1 inhibitor, cosibelimab, in cSCC is comparable to that of PD-1 inhibitors in similar patient populations.	A	9/9
Cosibelimab has a comparable safety profile and is characterized by lower level of high-grade adverse events compared to PD-1 inhibitors based on available data.	A	9/9
Given the current evidence, the absence of grade 4 and 5 immune-related adverse events with cosibelimab is clinically meaningful.	A	9/9
Given its favorable adverse event profile, cosibelimab may provide a clinical advantage compared to other systemic therapies for mcSCC and lacSCC.	A	9/9
The reduced risk for grade 4 and 5 adverse events with cosibelimab for the management of mcSCC and lacSCC may simplify clinical workflows and enhance patient safety.	B	7/9

Abbreviations: cSCC, cutaneous squamous cell carcinoma; laCSCC, locally advanced cutaneous squamous cell carcinoma; mcSCC, metastatic cutaneous squamous cell carcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1

TABLE 3.

Efficacy Data (ORRs, CRs, and PRs) With Associated Median Duration of Follow-up From Pivotal and Long-term Trials for ICIs in the Treatment of laCSCC and mCSCC†

Agent	Study / Dataset	Cohort	N	ORR (%)	CR (%)	PR (%)	Median Duration of Follow up (Months)
Cosibelimab	Phase 1 pivotal trial	mcSCC	78	47.4	7.7	39.7	15.4
Cosibelimab	Phase 1 extended follow-up (≥2 yrs)	mcSCC	78	50	12.8	37.2	29.3
Cosibelimab	Phase 1 extended follow-up (≥2 yrs)	laCSCC	31	54.8	25.8	29	24.1
Cemiplimab	Phase 1 Expansion Cohorts (EMPOWER-cSCC)	mcSCC or laCSCC	26	50	0	50	11.6
Cemiplimab	Phase 2 Cohorts (EMPOWER-cSCC)	mcSCC	59	47.4	6.8	40.6	9.4
Cemiplimab	EMPOWER-cSCC-1 long-term analysis Groups 1 – 3	mcSCC or laCSCC	193	47.2	20.3	26.9	42.5
Pembrolizumab	KEYNOTE-629	laCSCC	54	50	16.7	33.3	14.9
Pembrolizumab	KEYNOTE-629	mcSCC	105	35.2	10.5	24.8	11.4
Pembrolizumab	KEYNOTE-629 extended follow-up	laCSCC	54	51.9	22.2	29.6	52.4
Pembrolizumab	KEYNOTE-629 extended follow-up	mcSCC	105	35.2	12.4	22.9	64.7

Abbreviations: CR, complete response; laCSCC, locally advanced cutaneous squamous cell carcinoma; ICIs, immune checkpoint inhibitors; mcSCC, metastatic cutaneous squamous cell carcinoma; N, number; ORR, overall response rate; PR, partial response
†Comparisons across therapies are descriptive only. No head-to-head studies are available, and differences in trial design, patient populations, endpoints, and follow-up duration should be considered when interpreting these data.

trial results to clinical practice. Current staging systems and guidelines, including those from the National Comprehensive Cancer Network (NCCN), American Joint Committee on Cancer (AJCC), and Brigham and Women's Hospital (BWH), employ divergent risk stratification approaches without consensus on what constitutes locally advanced disease.[26-28] This definitional ambiguity introduces heterogeneity in both clinical practice and research populations, complicating the interpretation and application of treatment efficacy data to individual patients. When considering cosibelimab therapy, alignment between individual patient disease characteristics and those of the laCSCC population enrolled in pivotal trials is an important consideration, as efficacy estimates may not uniformly generalize to all patients classified as having "locally advanced" disease in routine practice.

Statement 2: *The efficacy of the PD-L1 inhibitor, cosibelimab, in cSCC is comparable to that of PD-1 inhibitors in similar patient populations. (SORT Level A)*

Although head-to-head trials comparing ICIs in advanced cSCC are not available, evaluating cosibelimab efficacy relative to cemiplimab and pembrolizumab provides an important therapeutic context. Cemiplimab demonstrated ORRs of 50% in advanced cSCC (mCSCC and laCSCC combined) and 47% in mCSCC alone in its pivotal phase 1 expansion cohort and phase 2 study.[11] Long-term analysis after 42.5 months of follow-up showed an ORR of 47.2% across both disease stages.[29]

Pembrolizumab in the KEYNOTE-629 trial demonstrated ORRs of 50.0% (laCSCC) and 35.2% (mCSCC), with an overall ORR of 40.3%.[12] Extended follow-up (52.4-64.7 months) showed ORRs of 51.9% and 35.2% in laCSCC and mCSCC cohorts, respectively (Table 3).[22]

Cosibelimab extended follow-up data (≥2 years) demonstrated ORRs of 50.0% in mCSCC and 54.8% in laCSCC, falling within a similar, and possibly higher, range compared to other ICIs. However, these comparisons require cautious interpretation given cosibelimab's limited long-term follow-up of approximately two years versus the nearly four to five years of mature data available for cemiplimab and pembrolizumab (Table 3).

Review of the pivotal trials confirms that all 3 agents were evaluated in clinically aligned patient populations: predominantly older adults with ECOG 0-1 performance status, strong male predominance, and advanced, unresectable cSCC stratified into locally advanced and metastatic cohorts (Table 4). This alignment supports meaningful contextual comparison and the conclusion that cosibelimab outcomes are comparable to those of PD-1 inhibitors in similar populations.

Although cosibelimab is the third ICI approved for cSCC, it is the only PD-L1 inhibitor. PD-1 inhibitors bind the PD-1 receptor on T cells, blocking interaction with both PD-L1 and PD-L2 ligands, while PD-L1 inhibitors bind the PD-L1 ligand, blocking interaction with PD-1 and B7.1, but preserving the PD-L2-PD-1

TABLE 4.

Comparison of Patient Populations Reported in Clinical Trials for Advanced cSCC Treated With Cosibelimab, Pembrolizumab, or Cemiplimab (Excluding Adjuvant Therapy Clinical Trial Data)†

Feature	Cosibelimab	Pembrolizumab (KEYNOTE-629)	Cemiplimab (EMPOWER-cSCC-1)
N	192	159	358
Cohorts	mcSCC / lacSCC	lacSCC / mcSCC	mcSCC / lacSCC
Age Range, years	71 – 77	72–75	71–76
Male, *n (%)*	19 – 59 (61.3% – 75.6%)	39 – 119 (72.2% – 76.2%)	48 – 130 (77.8% – 91.5%)
ECOG 0–1, *n (%)*	17 – 55 (54.8% - 70.5%)	32 – 101 (59.3% – 65.7%)	31 – 98 (51.3% - 61.0%)
PD-L1+ effect determined	Response not dependent on PD-L1+ status	Not specified	Response not dependent on PD-L1+ status
Prior systemic therapy, *n (%)*	1 – 7 (3.2% – 9.0%)	Not specified	5 – 33 (3.0% - 35.7%)
Follow-up duration, months	24–29 months	~52–64 months	~42.5 months

Abbreviations: cSCC, cutaneous squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group Performance Status; lacSCC, locally advanced cutaneous squamous cell carcinoma; mcSCC, metastatic cutaneous squamous cell carcinoma; N or n, number of study subjects; PD-L1, programmed death-ligand 1
†Comparisons across therapies are descriptive only. No head-to-head studies are available, and differences in trial design, patient populations, endpoints, and follow-up duration should be considered when interpreting these data.

interaction.[18,19] In addition to PD-L1 pathway blockade, preclinical in vitro studies have demonstrated that cosibelimab may exhibit secondary mechanisms of action that distinguish it from PD-1 inhibitors. Cosibelimab is an unmodified immunoglobulin G1 (IgG1) antibody with a functional Fc domain, which in vitro has been shown to mediate antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).[18,19] Through ADCC, natural killer cells are activated to release cytotoxic molecules, resulting in direct lysis of tumor cells. Through CDC, engagement of the Fc region initiates the classical complement cascade, leading to membrane attack complex formation and lysis of target cells.[19] Pre-clinical studies indicate that these Fc-mediated effects, including natural killer cell activation and complement engagement, are not observed with PD-1 inhibitors such as cemiplimab and pembrolizumab, which are IgG4 isotype antibodies engineered to minimize Fc-mediated immune activation.[30,31]

These dual-secondary mechanisms of action may contribute to its efficacy, possible longevity against tumor resistance seen in PD-1 inhibitors, and safety profile. However, the potential contribution of ADCC and CDC likely varies across patients due to differences in Fc receptor expression, heterogeneous PD-L1 expression on tumor cells, and the immunosuppressive tumor microenvironment.[19] Whether the similar efficacy across agents represents a broader class effect of PD-L1 pathway blockade or is specific to cosibelimab remains unclear and warrants further investigation through direct comparative studies.

Statement 3: *Cosibelimab has a comparable safety profile and is characterized by a lower level of high-grade adverse events compared to PD-1 inhibitors based on available data. (SORT Level A)*

The safety profile of cosibelimab has been evaluated through up to 2 years of follow-up. In the pivotal phase 1 trial (78 patients with mCSCC), 52.6% experienced grade ≥3 treatment-emergent adverse events (TEAEs), with no grade 4 or 5 TEAEs reported. Immune-related adverse events (irAEs) occurred in 23.1% of patients; only 2.6% experienced grade 3 irAEs, and no grade 4 or 5 irAEs occurred. There were no treatment-related deaths.[15]

Extended follow-up (≥2 years; 192 patients with mCSCC and laCSCC) demonstrated that 32.8% experienced serious TEAEs and 45.3% experienced grade ≥3 TEAEs. irAEs occurred in 27.6% of patients, with grade 3 events in 3.6%. Permanent discontinuation due to TEAEs occurred in 6.3%. Notably, no grade ≥3 pneumonitis, colitis, hepatitis, nephritis, or endocrinopathies were observed, and no grade 4 or 5 irAEs occurred. Adverse events led to death in 3.1% of patients, though all were considered unrelated to treatment.[14]

By comparison, cemiplimab long-term data showed 38.9-43.6% serious TEAEs, 45.5-49.2% grade ≥3 TEAEs, and 10.4-13.9% permanent discontinuation rates. Grade ≥3 irAEs occurred in 10.7-19.2% of patients, most commonly pneumonitis, autoimmune hepatitis, colitis, and diarrhea. TEAEs led to death in 2.6–8.5% of patients.[29] Pembrolizumab data from KEYNOTE-629 showed 70.4% TEAE incidence, with grade ≥3 and serious TEAEs in 11.3% and 10.1%, respectively. Permanent discontinuation occurred in 8.8%, grade ≥3 irAEs in 8.8%, and TEAEs led to death in 1.3%.[29]

These data suggest cosibelimab may offer improved safety and tolerability while maintaining efficacy. This is supported by a systematic review and meta-analysis of 125 trials (20,128 patients) showing PD-1 inhibitors were associated with significantly higher grade ≥3 treatment-related adverse events than PD-L1 inhibitors (OR 1.58; 95% CI 1.00-2.54) and higher rates of pneumonitis and hypothyroidism.[25]

Critical interpretive considerations must be noted. The minimum incidence required for an AE to be listed in the package insert differs among ICIs for cSCC. Cosibelimab includes AEs occurring in ≥10% of patients, cemiplimab includes those in ≥15%, and pembrolizumab lists only AEs occurring in ≥20% of patients.[32-34] These differences in reporting thresholds mean the cosibelimab package insert captures a greater number of low-frequency events, potentially creating the appearance of a broader adverse event profile while underestimating the true breadth for the comparator agents. Direct comparison of adverse event frequencies based solely on package insert data may therefore be misleading.

Additionally, while studied in generally comparable populations, the depth of safety evidence differs. PD-1 inhibitors have more mature datasets enabling clearer identification of uncommon or delayed toxicities, whereas the cosibelimab evidence base is earlier in development. The absence of grade 4 and 5 irAEs in available data from cosibelimab trials should not be interpreted as confirmation that such events do not occur; rather, the data suggest they are uncommon within the current follow-up window of two years. Ongoing monitoring and future long-term data remain essential to fully characterize cosibelimab's safety profile.

Statement 4: *Given the current evidence, the absence of grade 4 and 5 immune-related adverse events with cosibelimab is clinically meaningful. (SORT Level A)*

irAEs represent a significant concern with checkpoint inhibitor therapy. ICIs enhance T-cell activity not only against tumors but also against normal tissues, causing effects ranging from dermatologic manifestations to colitis, hepatitis, thyroid dysfunction, pneumonitis, and neurological complications.[35] Grade 4 events are life-threatening and require urgent intervention; grade 5 events result in death.[36,37] NCCN and American Society of Clinical Oncology (ASCO) guidelines recommend permanent discontinuation of immunotherapy for grade 4 or higher irAEs or for toxicities that fail to resolve with immunosuppression.[37,38] Prevention of these severe toxicities therefore has meaningful implications for patient safety, treatment duration, and mortality.

Clinical trial data for cosibelimab spanning approximately two years have documented no grade 4 or 5 and only 2.6% grade 3 irAEs,[14,15] contrasting with PD-1 inhibitors where grade ≥3 irAEs occurred in 8.8–19.2% of patients.[22,29] This difference extends beyond statistical measures to tangible patient care impacts: reduced mortality risk, fewer hospitalizations, less treatment interruption and/or discontinuation, and avoidance of long-term sequelae.

In practice, there is a critical difference between avoiding versus managing severe toxicities. For advanced cSCC, where treatment options have historically been limited, early detection and aggressive management of treatment-related adverse events has been necessary to maintain patients on life-saving therapy.[38] Cosibelimab offers an alternative paradigm: selecting a treatment that is less likely to cause severe toxicities. This avoidance-oriented approach may be particularly valuable when intensive monitoring is challenging, specialist access for irAE management is limited, patient comorbidities increase vulnerability to severe toxicities, or quality of life and tolerability are high priorities.[38]

Statement 5: *Given its favorable adverse event profile, cosibelimab may provide a clinical advantage compared to other systemic therapies for mCSCC and laCSCC. (SORT Level A)*

The safety profile of cosibelimab, particularly the absence of grade 4 or 5 irAEs in available studies, may translate into meaningful real-world clinical advantages for any patient undergoing treatment for laCSCC or mCSCC. While pembrolizumab and cemiplimab demonstrate comparable efficacy with similar objective response rates, these PD-1 inhibitors are associated with higher rates of grade ≥3 irAEs.[11,12,14,15,22,29] This distinction becomes particularly relevant in settings where prevention, rather than management, of severe toxicities offers tangible benefits.

Community practices, rural healthcare settings, and facilities without immediate subspecialist access may find the lower irAE rate particularly advantageous. Registry data show longer time to irAE diagnosis in private practices versus university hospitals.[39] One community-based study found that only 65% of patients with ICI-related colitis received subspecialist evaluation.[40]

Cosibelimab's safety profile may also expand treatment eligibility to patients who might otherwise be marginal candidates for checkpoint inhibition: elderly patients, those with multiple comorbidities, and patients with limited ability to attend frequent monitoring visits.[38] Notably, median ages in cSCC ICI trials ranged from 71–76 years (Table 4).[11,12,14,15,22,29] When quality of life and tolerability are high priorities or specialist access for irAE management is limited, cosibelimab's safety advantages may represent a clinically meaningful difference in benefit-risk assessment.

Statement 6: *The reduced risk for grade 4 and 5 adverse events with cosibelimab for the management of mCSCC and laCSCC may simplify clinical workflows and enhance patient safety. (SORT Level B)*

The potential for reduced severe adverse events with cosibelimab may simplify clinical workflow management and patient safety monitoring protocols. This statement received supermajority approval (7/9), reflecting some panel variability

regarding the strength of supporting evidence. The workflow simplification recommendation is driven largely by expert consensus rather than direct clinical study evidence. However, available data showing a favorable adverse event profile with lower high-grade events and no grade 4 or 5 irAEs suggest patients may remain on cosibelimab longer due to improved safety and tolerability, resulting in fewer treatment interruptions and discontinuations.[38]

Extended follow-up data from cosibelimab clinical trials demonstrated increasing complete response (CR) rates over time in both mCSCC and laCSCC cohorts. In the mCSCC cohort, CR rates increased from 7.7% to 12.8%, accompanied by a decrease in partial responses (PRs) from 39.7% to 37.2%, suggesting conversion of partial to complete responses with continued therapy. Similarly, in the laCSCC cohort, CR rates increased substantially from 9.7% in the primary analysis to 25.8% with extended follow-up, alongside a reduction in PRs from 38.7% to 29.0%.[14,15] Collectively, these findings support the clinical benefit of maintaining patients on uninterrupted treatment to allow for deepening of responses over time.

CONCLUSION

A comprehensive expert panel literature review developed six consensus statements on cosibelimab's efficacy and safety in managing laCSCC and mCSCC. The panel concluded that cosibelimab demonstrates comparable efficacy to current PD-1 inhibitors, with ORRs of 50–54.8% across mCSCC and laCSCC cohorts. The absence of grade 4 and 5 irAEs in available studies was noted to be clinically meaningful and may confer advantages to any patient undergoing treatment for laCSCC or mSCC, and especially to those in settings with limited capacity for intensive adverse event monitoring.

While cosibelimab's total evidence base remains more limited than that of cemiplimab and pembrolizumab, and longer-term follow-up is needed, available data support cosibelimab as an effective and relatively well-tolerated option for patients with advanced cSCC who are neither surgical nor radiation candidates. These consensus recommendations can guide clinicians in treatment decision-making as they integrate this newest therapeutic option into practice for advanced cutaneous squamous cell carcinoma.

DISCLOSURES

Brooke Bartley MD, Angela Rosenberg DO, Daniel Groisser MD, and Lauren DeBusk MD have no conflicts of interest to disclose. Aaron S. Farberg MD is on advisory boards for Ortho Dermatologics, Regeneron Pharmaceuticals, Sun Pharma, and Castle Biosciences, Inc. Scott M. Dinehart MD serves as a speaker and consultant for Genentech, Regeneron Pharmaceuticals/Sanofi, Castle Biosciences, and Sun Pharma; and participates in clinical research with 3M Pharmaceuticals, Eli Lilly, Pfizer, Horizon Therapeutics, Leo Pharma, Galderma, Dermira, Amgen, Connetics, Novartis, Genentech, Sanofi, Genmab, Dow Pharma, Abbott Laboratories, Dermik, MedImmune, Rapt Therapeutics, Aclaris Therapeutics, AbbVie, Biocon, Incyte, Castle Biosciences, Bristol Myers Squibb, Xencor, Merck, Ventyx, Daiichi Sankyo, Brexogen, Apogee, Regeneron Pharmaceuticals, and Sun Pharma. Shannon C. Trotter DO has a professional relationship with Castle Biosciences, Inc. Lindsay Ackerman MD is a consultant/advisor, speaker, or investigator for AbbVie, Alumis, Amgen, Apogee, Apollo, ArGEN-X, Artacus, AstraZeneca, Biofrontera, Boehringer-Ingelheim, Bristol Myers Squibb, Castle Biosciences, ChemoCentryx, Corevitas (Corrona), DermTech, Eli Lilly, Exact Biosciences, GlaxoSmithKline, Helsinn, Incyte, Janssen, Kyowa Kirin, Leo, Merck, Mindera, Novartis, Pfizer, Regeneron, Sanofi, Soligenix, Sun Pharma, Takeda, Timber, Trevi, UCB, Veradermics, and ZuraBio. Todd Schlesinger MD FAAD FASMS is an investigator and/or consultant for AbbVie, Almirall, Apogee, Arcutis, Benev, Biofrontera, Bristol Myers Squibb, Crown Aesthetics, Eli Lilly, Flint Clinical, Genentech, Janssen, LEO Pharma, Oruka, Pfizer, Regeneron, Sun Pharma, Verrica, and UCB; served as an investigator for AbbVie, Allergan, Almirall, Arcutis, Aslan, Biofrontera, Bristol Myers Squibb, Boehringer Ingelheim, Cara Therapeutics, Castle Biosciences, Concert (acquired by Sun Pharma), Cutanea Life Sciences, Dermavant Sciences, Eli Lilly, Galderma, HighlightII, Incyte, Janssen, Nimbus Therapeutics, Medicus, Novartis, Processa, Prolacta, Regeneron, Sanofi, SkinCure Oncology, Takeda, Trevi, and Verrica; is a shareholder in Bristol Myers Squibb, Chronicle Medical Software, Derma-Gene, Eli Lilly, Propedix and Remedly; has served as a consultant for Beiersdorf, Estee Lauder, Dermsquared, HTL Biotechnology, LaRoche Posay, L'Oreal, MJH Life Sciences, and RBC Consultants; and has received salary from Avant-Health. James Q. Del Rosso DO has received grants from JDR Dermatology Research and personal fees from James Q. Del Rosso DO, LLC during the conduct of the study. He has received personal fees from Galderma, Almirall, Sun Pharma, Vyne, Leo Pharma, Sente, Journey, Main Pharma, Cutera, Bausch (Ortho), Amgen, Arcutis, Biofrontera, Blue Medicines, Bluefin, Botanix, Cage Bio, Incyte, Organon, MoonLake, Pelthos, Regeneron, Sanofi, Takeda, and Verrica outside the submitted work. Mark Lebwohl MD has received grants and/or research funding from AbbVie, Arcutis, Avotres, Boehringer Ingelheim, Bristol-Myers Squibb, Cara Therapeutics, Clexio, Dermavant Sciences, Eli Lilly and Company, Incyte Corporation, Inozyme, Janssen Research and Development LLC/Johnson & Johnson, Oruka, Pfizer Inc., Sanofi-Regeneron, and UCB; serving as a consultant for AbbVie, Added Health, Aikium, Almirall, AltruBio Inc., Alumis, Amgen, Apogee, Arcutis Inc., AstraZeneca, Atomwise, Avotres Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Castle Biosciences, Celltrion, Corevitas, Dermavant Sciences, Dermsquared, Edessa, Eli Lilly and Company, Evommune Inc., Forte Biosciences, Galderma, Genentech, Janssen/Johnson & Johnson, Incyte Corporation, LEO Pharma, Mayne Pharmaceuticals, Meiji Seika Pharma, Mindera, Mirium Pharmaceuticals, MoonLake, Oruka, Pfizer

Inc., Sanofi-Regeneron, Revolo, Seanergy, Strata, Sun Pharma, Takeda, Trevi Therapeutics, and Verrica Pharmaceuticals Inc.; and serving in other professional roles for the Facilitation of International Dermatology Education. Darrell Rigel MD MS is an investigator, consultant and/or speaker for: Almirall, Apogee, Beiersdorf, Inc., Castle Biosciences, Eli Lilly and Company, Ferndale Laboratories, Inc., Gore Range Capital, Kenvue, Pfizer, Primus Pharmaceuticals, SciBASE, SkinCure Oncology, Sun Pharmaceutical Industries Ltd., Takeda Pharmaceuticals, VYNE Therapeutics

REFERENCES

1. Tokez S, Hollestein L, Louwman M, Nijsten T, Wakkee M. Incidence of multiple vs first cutaneous squamous cell carcinoma on a nationwide scale and estimation of future incidences of cutaneous squamous cell carcinoma. *JAMA Dermatol.* 2020;156(12):1300-1306. doi:10.1001/jamadermatol.2020.3677
2. Wysong A. Squamous-cell carcinoma of the skin. *N Engl J Med.* 2023;388(24):2262-2273. doi:10.1056/NEJMra2206348
3. Kauvar AN, Arpey CJ, Hruza G, et al. Consensus for nonmelanoma skin cancer treatment, part II: squamous cell carcinoma, including a cost analysis of treatment methods. *Dermatol Surg.* 2015;41(11):1214-40. doi:10.1097/DSS.0000000000000478
4. Stevenson ML, Kim R, Meehan SA, Pavlick AC, Carucci JA. Metastatic cutaneous squamous cell carcinoma: the importance of T2 stratification and hematologic malignancy in prognostication. *Dermatol Surg.* 2016;42(8):932-935. doi:10.1097/DSS.0000000000000798
5. Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. *N Engl J Med.* 2003;348(17):1681-91. doi:10.1056/NEJMra022137
6. Pickering CR, Zhou JH, Lee JJ, et al. Mutational landscape of aggressive cutaneous squamous cell carcinoma. *Clin Cancer Res.* 2014;20(24):6582-92. doi:10.1158/1078-0432.CCR-14-1768
7. Chalmers ZR, Connelly CF, Fabrizio D, et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. *Genome Med.* 2017;9(1):34. doi:10.1186/s13073-017-0424-2
8. Boutros A, Cecchi F, Tanda ET, et al. Immunotherapy for the treatment of cutaneous squamous cell carcinoma. *Front Oncol.* 2021;11:733917. doi: 10.3389/fonc.2021.733917
9. Winter L, Ries J, Vogl C, et al. Comparative analysis of inhibitory and activating immune checkpoints PD-1, PD-L1, CD28, and CD86 in non-melanoma skin cancer. *Cells.* 2024;13(18). doi:10.3390/cells13181569
10. Choi FD, Kraus CN, Elsensohn AN, et al. Programmed cell death 1 protein and programmed death-ligand 1 inhibitors in the treatment of nonmelanoma skin cancer: a systematic review. *J Am Acad Dermatol.* 2020;82(2):440-459. doi:10.1016/j.jaad.2019.05.077
11. Migden MR, Rischin D, Schmults CD, et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. *N Engl J Med.* 2018;379(4):341-351. doi:10.1056/NEJMoa1805131
12. Hughes BGM, Muñoz-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. doi:10.1016/j.annonc.2021.07.008
13. Rischin D, Porceddu S, Day F, et al. Adjuvant cemiplimab or placebo in high-risk cutaneous squamous-cell carcinoma. *N Engl J Med.* 2025;393(8):774-785. doi:10.1056/NEJMoa2502449
14. Ruiz ES, Muñoz-Couselo E, Montaudié H, et al. 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. *J Am Acad Dermatol.* doi:10.1016/j.jaad.2025.09.009
15. 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. doi:10.1136/jitc-2023-007637
16. Alam M, Rauf M, Ali S, et al. A systematic review of completeness of reporting in randomized controlled trials in dermatologic surgery: adherence to consort 2010 recommendations. *Dermatol Surg.* 2016;42(12):1325-1334. doi:10.1097/DSS.0000000000000902
17. Diamond IR, Grant RC, Feldman BM, et al. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. *J Clin Epidemiol.* 2014;67(4):401-409. doi:10.1016/j.jclinepi.2013.12.002
18. Gorelik L, Avgerinos G, Kunes Y, et al. Abstract 4606: Preclinical characterization of a novel fully human IgG1 anti-PD-L1 mAb CK-301. *Cancer Res.* 2017;77(13 Supplement). doi:10.1158/1538-7445.AM2017-4606
19. Idris OA, Westgate D, Saadaie Jahromi B, et al. PD-L1 inhibitor cosibelimab for cutaneous squamous cell carcinoma: comprehensive evaluation of efficacy, mechanism, and clinical trial insights. *Biomedicines.* 2025;13(4):889. doi:10.3390/biomedicines13040889
20. Lin L, Hilbert J, Gorelik L, et al. Semi-mechanistic pharmacokinetic and target-occupancy modeling to support dose justification for anti-PD-L1 clinical candidate CK-301 (cosibelimab) in oncology patients. Poster presented at: Society for Immunotherapy of Cancer 24th Annual Meeting; 2019; National Harbor, MD.
21. Muñoz-Couselo E, Montaudié H, Berciano-Guerrero MA, et al. 1136P cosibelimab in advanced cutaneous squamous cell carcinoma (CSCC): Longer-term efficacy and safety results from pivotal study. *Ann Oncol.* 2024; 35:S745-S746. doi:10.1016/j.annonc.2024.08.2139
22. Muñoz-Couselo E, 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. doi:10.1200/JCO.2024.42.16_suppl.955
23. Plock N, Kleijn HJ, Neighbours L, Oliviero J. PD-L1 inhibitor cosibelimab: PopPK supports comparability of 800 mg q2w and 1200 mg q3w dosing regimens based on recent FDA criteria. Poster presented at: Population Approach Group Europe (PAGE) Meeting; June 2023; A Coruña, Spain.
24. Spagnuolo A, Gridelli C. "Comparison of the toxicity profile of PD-1 versus PD-L1 inhibitors in non-small cell lung cancer": is there a substantial difference or not? *J Thorac Dis.* 2018;10(Suppl 33):S4065-S4068. doi:10.21037/jtd.2018.09.83
25. 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. doi:10.1001/jamaoncol.2019.0393
26. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Cutaneous Squamous Cell Carcinoma. Version 1.2026. Published 2025. Available at: https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf. Accessed October 3, 2025.
27. Ruiz ES, Karia PS, Besaw R, Schmults CD. Performance of the American Joint Committee on cancer staging manual, 8th edition vs the Brigham and Women's Hospital tumor classification system for cutaneous squamous cell carcinoma. *JAMA Dermatol.* 2019;155(7):819-825. doi:10.1001/jamadermatol.2019.0032
28. Kim JYS, Kozlow JH, Mittal B, et al. Guidelines of care for the management of cutaneous squamous cell carcinoma. *J Am Acad Dermatol.* 2018;78(3):560-578. doi:10.1016/j.jaad.2017.10.007
29. 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. doi:10.1016/j.jaad.2024.06.108
30. Hutchins B, Starling GC, Mccoy MA, et al. Biophysical and immunological characterization and in vivo pharmacokinetics and toxicology in nonhuman primates of the anti-PD-1 antibody pembrolizumab. *Mol Cancer Ther.* 2020;19(6):1298-1307. doi:10.1158/1535-7163.MCT-19-0774.
31. Burova E, Hermann A, Waite J, et al. Characterization of the anti-PD-1 antibody REGN2810 and its antitumor activity in human PD-1 knock-in mice. *Mol Cancer Ther.* 2017;16(5):861-870. doi:10.1158/1535-7163.MCT-16-0665.
32. Libtayo (cemiplimab-rwlc) [package insert]. Regeneron Pharmaceuticals Inc; 2025. Available at: https://www.regeneron.com/downloads/libtayo_fpi.pdf. Accessed October 6, 2025.
33. Keytruda (pembrolizumab) [package insert]. Merck Sharp & Dohme Corp;2025. Available at: https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf. Accessed October 7, 2025.
34. Unloxcyt (cosibelimab) [package insert]. Checkpoint Therapeutics; 2025. Available at: https://unloxcyt.com/final-uspi_-SUN-11-2025.pdf. Accessed October 9, 2025.
35. Yan T, Yu L, Zhang J, et al. Achilles' heel of currently approved immune checkpoint inhibitors: Immune-related adverse events. *Front Immunol.* 2024;15:1292122. doi:10.3389/fimmu.2024.1292122
36. Geenen MM, Cardous-Ubbink MC, Kremer LCM, et al. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. *JAMA.* 2007;297(24):2705-2715. doi:10.1001/jama.297.24.2705
37. Schneider BJ, Naidoo J, Santomasso BD, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. *J Clin Oncol.* 2021;39(36):4073-4126. doi:10.1200/JCO.21.01440
38. Thompson JA, Schneider BJ, Brahmer J, et al. NCCN guidelines® insights: Management of immunotherapy-related toxicities, version 2.2024. *J Natl Compr Canc Netw.* 2024;22(9):582-592. doi:10.6004/jnccn.2024.0057
39. Ertl C, Tomsitz D, Rizzo F, et al. Real-world management and outcomes of immune-related adverse events in German cancer care: A multicenter analysis using the SERIO registry. *Oncologist.* 2025;30(10). doi:10.1093/oncolo/oyaf275
40. Rampersad A, Abrams G, Bauer C. P067 immune checkpoint inhibitor colitis in a community-based hospital system. *Am J Gastroenterol.* 2021;116(Suppl 1):S17-S18. doi:10.14309/01.ajg.0000798868.27587.86

AUTHOR CORRESPONDENCE

Brooke Bartley MD

E-mail:..... Brooke.R.Bartley@gmail.com