ISSN: 2634 - 680X

Journal of Clinical Case Studies Reviews & Reports

SCIENTIFIC Research and Community

Review Article

Open Access

Efficacy and Safety of Cemiplimab in Cutaneous Squamous Cell Carcinoma: A Systematic Review of Clinical Trials

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ABSTRACT

Background: One prevalent kind of skin cancer is cutaneous squamous cell carcinoma (CSCC), with advanced stages historically having limited treatment options and poor outcomes. A possible treatment is cemiplimab, an inhibitor of programmed cell death-1 (PD-1). This systematic review aims to consolidate evidence from clinical trials on the efficacy and safety of cemiplimab across the spectrum of advanced CSCC.

Methods: Using PubMed/MEDLINE, Embase, Web of Science, and Cochrane Central from the beginning to the present, a thorough literature search was carried out in accordance with PRISMA standards. Included were prospective clinical studies examining cemiplimab in adult patients with resectable, metastatic, or locally advanced CSCC. Objective reaction rate (ORR) and pathological complete response (pCR) were the main results. Safety and survival were secondary outcomes.

Results: Seven studies (one Phase 3 RCT, six Phase 2 trials) were included. Cemiplimab showed significant and long-lasting effectiveness in advanced CSCC, with ORRs ranging from 41.1% to 62%. In a critical examination, 87.8% of respondents continued to answer after a year, failing to meet the median duration of response. High pCR rates (51–73%) in the neoadjuvant context allowed for less involved surgery. Adjuvant cemiplimab was found to be a new standard of treatment in the Phase 3 C-POST study, which reduced the risk of mortality or illness recurrence by 68% (Hazard Ratio 0.32) when compared to placebo. With 23.9% to 44% of patients experiencing Grade ≥3 treatment-emergent side events, the safety profile was reasonable and in line with the PD-1 inhibitor class.

Conclusion: Cemiplimab is a highly effective and indispensable therapy for CSCC, demonstrating robust and durable efficacy across metastatic, locally advanced, neoadjuvant, and adjuvant settings. Its manageable safety profile solidifies its role as a cornerstone treatment, marking a paradigm shift in the management of this disease.

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Received: November 20, 2025; **Accepted:** November 24, 2025; **Published:** December 04, 2025

Keywords: Cemiplimab, Cutaneous Squamous Cell Carcinoma, CSCC, Immunotherapy, PD-1 Inhibitor

Introduction

The second most prevalent kind of skin cancer, cutaneous squamous cell carcinoma (CSCC), is a major and expanding worldwide health burden [1]. A percentage of cancers develop into more advanced stages, however the great majority of CSCC cases are detected at an early stage and are easily healed by local excision or elimination. This encompasses locally advanced disease, where the tumor becomes inoperable or would result in substantial functional or cosmetic morbidity, and metastatic disease, which carries a grave prognosis [2]. Prior to the advent of modern immunotherapy, the therapeutic landscape for advanced CSCC was bleak, characterized by a notable lack of standardized, effective systemic therapies. Conventional therapies, such as epidermal growth factor receptor (EGFR) inhibitors and cytotoxic chemotherapy (such as platinum-based regimens), were linked to poor response rates, brief benefit durations, and substantial toxicity, providing little hope for long-term disease management [3]. In the past, patients with metastatic CSCC had a median overall survival of only 8 to 15 months, highlighting the urgent need for innovative treatment approaches [4].

The pathogenesis of CSCC is intrinsically linked to cumulative ultraviolet (UV) radiation exposure, which induces a high mutational burden in keratinocytes [5]. This high tumor mutational burden (TMB) is a key factor that makes CSCC highly immunogenic and, consequently, a promising target for immune checkpoint inhibitors. A crucial immunological checkpoint, the programmed cell death-1 (PD-1) receptor is expressed on activated T-cells. It interacts with the ligands PD-L1 and PD-L2 on tumor cells and other immune cells, causing T-cell depletion and enabling tumors to avoid immune monitoring [6]. Cemiplimab (Libtayo®)

is a powerful, high-affinity human monoclonal immunoglobulin G4 antibody that targets PD-1. Cemiplimab stimulates the host's antitumor T-cell response by preventing this interaction, allowing the immune system to identify and eradicate cancer cells [7].

The clinical development of cemiplimab in CSCC has been rapid and transformative. Initial evidence from a phase 1 expansion cohort demonstrated profound antitumor activity, paving the way for pivotal phase 2 studies [7]. These later studies, like the EMPOWER-CSCC-1 trial (NCT02760498), examined cemiplimab in different patient cohorts with locally advanced and metastatic CSCC. They reported previously unheard-of objective response rates, which resulted in the drug's regulatory approval in the US and the EU in 2018 and 2019, respectively [8,9]. As a result, cemiplimab was authorized as the first systemic treatment for advanced CSCC, which changed the way the disease is treated.

Since these initial approvals, the clinical exploration of cemiplimab has expanded significantly. Research has evolved beyond the treatment of unequivocally advanced disease to investigate its role in multimodal strategies. This includes its use in the neoadjuvant setting to downstage large, operable tumors and improve surgical outcomes, as well as in the adjuvant setting to reduce the risk of recurrence in patients with high-risk pathological features following resection [8,9]. Furthermore, investigations into alternative dosing regimens, such as extended-interval dosing, aim to optimize convenience and resource utilization without compromising efficacy. The purpose of this systematic review is to compile and assess all available data from clinical trials about the safety and effectiveness of cemiplimab in the treatment of cutaneous squamous cell carcinoma.

Methodology

Study Design

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 criteria were followed in conducting this systematic review [10]. In order to reduce bias in the identification, selection, and synthesis of pertinent evidence, the methodology was created beforehand.

Eligibility Criteria

Studies that meet the following predetermined criteria and are organized according to the PICO (Population, Intervention, Comparator, Outcomes) framework will be included in the review:

- **Population:** Patients who are 18 years of age or older who have been diagnosed with cutaneous squamous cell carcinoma (CSCC) by histology. Patients in the neoadjuvant or adjuvant settings, as well as those with locally advanced (laCSCC) or metastatic (mCSCC) illness that cannot be cured by radiation or surgery, will be included in the studies.
- **Intervention:** Treatment with cemiplimab (Libtayo®), administered as monotherapy at any dose or schedule (For instance, 350 mg every three weeks, 600 mg every four weeks, or 3 mg/kg every two weeks).
- **Comparator:** Placebo, standard of care (e.g., chemotherapy, radiotherapy, or best supportive care), or no intervention in randomized trials. For single-arm studies, no direct comparator was required, as the goal was to provide an overview of the intervention's safety and effectiveness.

Outcomes

- **Primary Efficacy Outcomes:** Pathological Complete Response (pCR) rate for neoadjuvant trials and Objective Response Rate (ORR) as determined by independent central review and/or investigator review using established criteria (e.g., RECIST 1.1).
- **Secondary Efficacy Outcomes:** Disease-Free Survival (DFS), Overall Survival (OS), Progression-Free Survival (PFS), and Duration of Response (DOR) in the adjuvant context.
- **Safety Outcomes:** The Common Terminology Criteria for Adverse Events (CTCAE) are used to rate the frequency and severity of all treatment-emergent adverse events (TEAEs), severe adverse events (SAEs), and immune-related adverse events (irAEs).
- **Study Types:** Prospective clinical trials, including Phase I (with expansion cohorts), Phase II, and Phase III trials, was included. Retrospective studies, case reports, reviews, editorials, and in vitro or animal studies was excluded.

Search Strategy

To find all pertinent published and unpublished research, a thorough and methodical literature search was conducted. From the time of their creation till now, the following electronic databases were searched.: PubMed/MEDLINE, Embase, Web of Science Core Collection, and Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy, which was created in collaboration with a medical librarian, will make use of both keywords associated with the main themes and controlled vocabulary, such as MeSH terms in PubMed and Emtree terms in Embase: "**Cemiplimab**" AND "**Cutaneous Squamous Cell Carcinoma**." The PubMed search technique was modified to use syntax suitable for each database. Below is an illustration of the initial PubMed search approach: Libtayo OR REGN2810 OR Cemiplimab) AND (Skin Neoplasms [Mesh] OR "skin cancer" OR cutaneous) AND (Carcinoma, Squamous Cell [Mesh] OR "squamous cell carcinoma" OR CSCC).

In order to find any more relevant research, the reference lists of all included studies and pertinent review articles were manually examined. Clinical trial registries (ClinicalTrials.gov) was also be searched for completed but potentially unpublished trials.

Study Selection Process

All records identified through the database search was imported into the Covidence systematic review software for management and deduplication. A two-phase screening procedure was used in the study selection. The titles and abstracts of every item that was retrieved were first checked by two separate reviewers using the predetermined eligibility criteria. Second, the same two independent reviewers collected the entire texts of all possibly pertinent papers and thoroughly evaluated their eligibility. Any disputes between the reviewers at either level were settled by discussion or, if required, by a third reviewer's decision. A PRISMA 2020 flow diagram was used to record and display the findings of the research selection procedure [10].

Data Extraction

A pre-piloted, standardized data extraction form in Microsoft Excel was used by two reviewers to independently extract data from the included studies. The information that is retrieved will consist of:

- **Study Characteristics:** first author, publication year, journal, clinical trial identifier (e.g., NCT number), study design (phase, single-arm vs. randomized), funding sources, and study locations.
- **Population Characteristics:** sample size, median age, sex distribution, ECOG performance status, disease stage (laCSCC vs. mCSCC), and prior treatments.

- Intervention Details: cemiplimab dosage, schedule, and median duration of treatment.

Outcome Data

- **Efficacy:** ORR, CR rate, pCR rate (for neoadjuvant studies), median DOR, PFS, OS, DFS, and associated 95% confidence intervals.
- **Safety:** All-grade and Grade ≥3 TEAEs, SAEs, and specific irAEs; AE-related treatment discontinuation rates.
- **Key Results:** Reported efficacy estimates (e.g., hazard ratios for survival outcomes) and their corresponding 95% confidence intervals.

Risk of Bias (Quality) Assessment

Two independent reviewers thoroughly evaluated the included studies' methodological quality and bias risk. For randomized controlled trials, the **Cochrane Risk of Bias 2 (RoB 2) tool** was used [11]. A specific evaluation was carried out for single-arm studies utilizing important domains from the the ROBINS-I instrument, which measures the risk of bias in non-randomized studies of interventions, concentrating on bias resulting from participant selection, confounding, intervention categorization, intervention variations, missing data, outcome measurement, and choice of the reported result [12, 13]. Any disputes were settled by consensus or by seeking advice from a third reviewer. Each study's overall assessment was classified as "low risk," "some concerns," or "high risk" of bias.

Results

Figure (1) illustrates the systematic process of identifying and selecting studies for the review. An initial search of databases yielded 615 records. 51 entries were eliminated after 156 records passed title and abstract screening following the elimination of 459 duplicates. Seventy-two of the remaining 105 reports' complete texts could not be located. After a full-text eligibility review of the 33 papers that were successfully obtained, 26 studies were excluded, mostly because they were conference abstracts only or had incorrect results or populations. In the end, seven papers in all satisfied all inclusion requirements and were added to the systematic review.

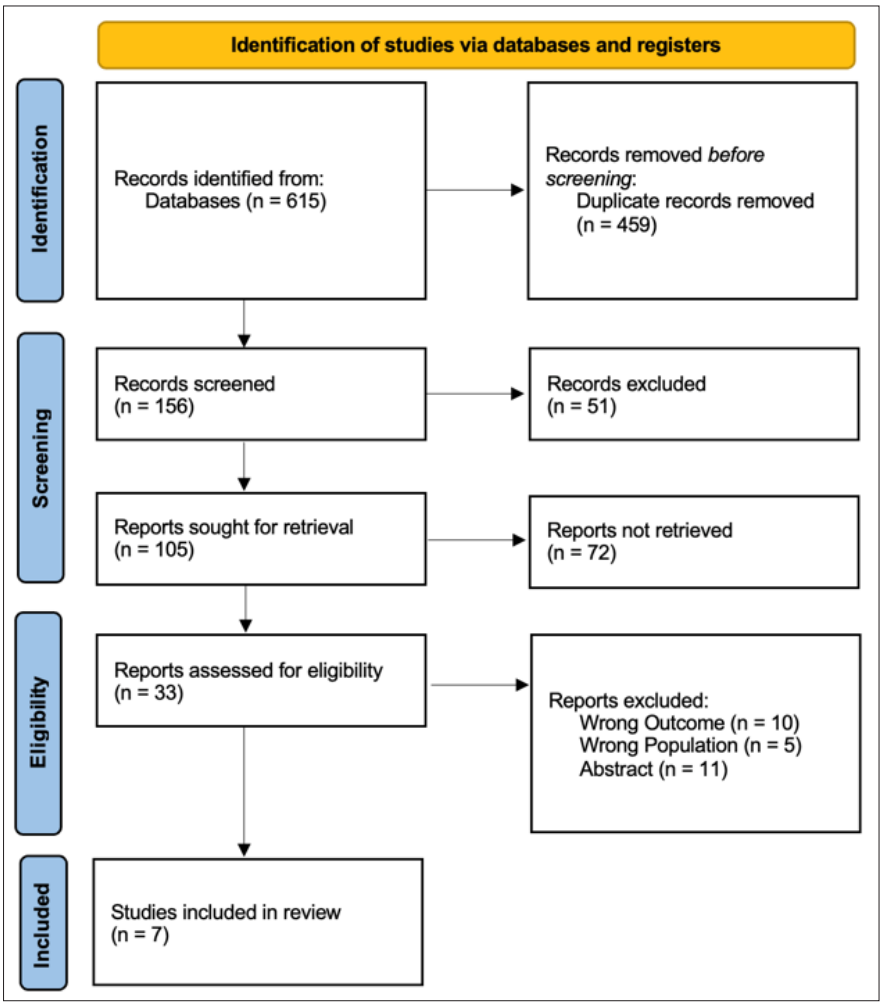

Figure 1: Prisma 2020 Flow Diagram for Study Selection

Table 1 outlines the fundamental design and demographic elements of the seven included studies. This table reveals that the evidence base consists primarily of Phase 2 trials, with one pivotal Phase 3 randomized controlled trial [14-20]. The patient populations varied across the studies, encompassing different stages of cSCC, including metastatic (mCSCC), locally advanced (laCSCC), and resectable disease in both neoadjuvant and adjuvant settings [14-19]. The sample sizes ranged from 11 to 415, with a notable predominance of male participants and patients with a good performance status (ECOG 0-1) where reported [14,16-18].

Table 2 synthesizes the critical efficacy and safety outcomes, demonstrating the consistent clinical activity of cemiplimab across various treatment paradigms. The objective response rates (ORR) in advanced disease settings were substantial, ranging from 41.1% to 62%, with a considerable percentage of patients attaining a complete response (CR) [15, 19, 20]. The durability of these responses was a key finding, with an estimated 87.8% of respondents continuing to answer after a year, and one integrated study showing a median duration of response (mDOR) that was not attained [15]. In the surgical settings, the pathological complete response (pCR) rates with neoadjuvant cemiplimab were remarkably high, at 51% and 73%, translating into excellent short-term survival outcomes, such as a 12-month event-free survival of 89% [14, 18]. Above all, the Phase 3 C-POST study demonstrated that cemiplimab significantly decreased the risk of disease recurrence or mortality by 68% (Hazard Ratio 0.32) in comparison to placebo, setting a new benchmark in the adjuvant context [17].

The survival data and the impact on treatment plans further underscore the drug's efficacy. Overall survival (OS) was encouraging across studies, with a 24-month probability of 73.3% in advanced cSCC and 92% at 12 months in the neoadjuvant study [15,18]. The neoadjuvant studies also reported that achieving a pCR often allowed for less extensive surgery than originally planned [14]. Regarding safety, the profile of cemiplimab was manageable and consistent with the known class effects of anti-PD-1 therapy. In the adjuvant study, the incidence of treatment-emergent adverse events (TEAEs) of Grade 3 or higher varied from 23.9% to 44% in one of the earlier phase 2 studies, with fatigue and diarrhea being among the most common any-grade events [16, 17, 19].

Table 1: Study and Patient Characteristics

Study Name (Author, Year, [Ref])	Location / Centers	Study Design	Phase	Patient Population	Sample Size (n)	Median Age (Years)	Male (%)	ECOG PS 0-1 (%)	Immuno-compromised (%)
Lim et al, 2025 [14]	Single institution	Open-label, single-arm trial	Phase 2	Stage II–IV resectable CSCC (neoadjuvant)	11	NM	NM	NM	NM
Rischin et al, 2021 (Integrated Analysis) [15]	Multicenter	Pooled analysis of 3 trial groups	Phase 2	Advanced CSCC (mCSCC & laCSCC)	193	NM	NM	NM	NM
Migden et al, 2020 (Group 2) [16]	25 clinics in Australia, Germany, USA	Open-label, single-arm trial	Phase 2	Locally Advanced CSCC (laCSCC)	78	73 (IQR: 66-81)	85%	100% (ECOG 0-1 req.)	NM
Rischin et al, 2025 (C-POST) [17]	Multicenter	Randomized, double-blind, placebo-controlled	Phase 3	High-risk CSCC post-surgery & radiotherapy (adjuvant)	415 (Cemi: 209, Plac: 206)	NM	NM	NM	NM
Gross et al, 2023 [18]	Multicenter	Open-label, single-arm trial	Phase 2	Stage II–IV (M0) resectable CSCC (neoadjuvant)	79	73 (IQR: 66-81)	85%	100% (ECOG 0-1 req.)	NM
Rischin et al, 2020 (Groups 1 & 3) [19]	Multicenter	Open-label, single-arm trial	Phase 2	Metastatic CSCC (mCSCC)	115 (Group 1: 59, Group 3: 56)	NM	NM	NM	NM
Rischin et al, 2024 (Extended Dosing) [20]	Multicenter	Open-label, single-arm trial (cohort)	Phase 2	Advanced CSCC	63	NM	NM	NM	NM

Table 2: Efficacy and Safety Outcomes

Study Name (Author, Year, [Ref])	Intervention / Regimen	Primary Endpoint(s)	Objective Response Rate - ORR (%; [95% CI])	Complete Response - CR (%)	Median Duration of Response - mDOR	Survival Outcomes	Grade ≥3 Treatment-Emergent Adverse Events (TEAEs) (%)
Lim et al, 2025 [14]	Cemiplimab (neoadjuvant, up to 4 doses)	pCR rate (secondary)	73% (RECIST 1.1)	73% (pCR)	NM	12-mo DFS: 91%; 12-mo OS: 100%	No unexpected safety signals
Rischin et al, 2021 (Integrated Analysis) [15]	Cemiplimab 3mg/kg Q2W or 350mg Q3W	ORR (ICR)	46.1% ([38.9-53.4])	16.1% (Pooled)	Not Reached	24-mo OS prob.: 73.3%; Median OS: Not Reached	NM
Migden et al, 2020 (Group 2) [16]	Cemiplimab 3mg/kg Q2W	ORR (ICR)	44% ([32-55])	13%	NM	NM	44%
Rischin et al, 2025 (C-POST) [17]	Cemiplimab 350mg→700mg vs Placebo (adjuvant)	Disease-Free Survival (DFS)	NM (Not applicable for adjuvant setting)	NM	NM	24-mo DFS: 87.1% (Cemi) vs 64.1% (Plac); HR=0.32	23.9% (Cemi) vs 14.2% (Plac)
Gross et al, 2023 [18]	Cemiplimab (neoadjuvant, up to 4 doses)	pCR (ICR)	NM	51% (pCR)	NM (No recurrences in pCR patients)	12-mo EFS: 89%; 12-mo OS: 92%	NM (Neoadjuvant phase)
Rischin et al, 2020 (Groups 1 & 3) [19]	Cemiplimab 3mg/kg Q2W (G1) or 350mg Q3W (G3)	ORR (ICR)	G1: 49.2% ([35.9-62.5]); G3: 41.1% ([28.1-55.0])	NM	12-mo DOR rate (G1): 88.9%	NM	Overall: Fatigue (27%), Diarrhea (23.5%)

Rischin et al, 2024 (Extended Dosing) [20]	Cemiplimab 600mg Q4W	ORR (ICR)	62% ([48.8-73.9])	22%	NM	NM	Most common: Diarrhea, Pruritus, Fatigue (Grades not specified)

Table 3: Risk of Bias Assessment for Included Studies

Study Name (Author, Year, [Ref])	Study Type	D1: Bias due to randomization	D2: Bias due to deviations from intended interventions	D3: Bias due to missing outcome data	D4: Bias in measurement of the outcome	D5: Bias in selection of the reported result	Overall Risk of Bias
Lim et al, 2025 [14]	Single-Arm	Not Applicable (N/A)	Low	Low	Low	Low	Low
Rischin et al, 2021 (Integrated Analysis) [15]	Single-Arm (Pooled)	N/A	Low	Low	Low (Independent Central Review)	Low	Low
Migden et al, 2020 (Group 2) [16]	Single-Arm	N/A	Low	Low	Low (Independent Central Review)	Low	Low
Rischin et al, 2025 (C-POST) [17]	Randomized Controlled Trial	Low	Low (Blinded setting)	Low	Low (Blinded Independent Central Review)	Low	Low
Gross et al, 2023 [18]	Single-Arm	N/A	Low	Low	Low (Independent Central Review)	Low	Low
Rischin et al, 2020 (Groups 1 & 3) [19]	Single-Arm	N/A	Low	Low	Low (Independent Central Review)	Low	Low
Rischin et al, 2024 (Extended Dosing) [20]	Single-Arm	N/A	Low	Low	Low (Independent Central Review)	Low	Low

Discussion

The findings of this systematic review, synthesizing data from pivotal clinical trials, firmly establish cemiplimab as a key component of advanced cutaneous squamous cell carcinoma (CSCC) treatment. The robust efficacy and manageable safety profile observed across diverse clinical settings from metastatic and locally advanced disease to neoadjuvant and adjuvant applications represent a paradigm shift in a field historically plagued by a lack of effective systemic therapies. Patients with advanced CSCC had a poor prognosis prior to the development of immunotherapy. The only systemic options available to them were cytotoxic chemotherapy and epidermal growth factor receptor inhibitors, which had low response rates of about 10–30% and a median overall survival (OS) of 8–15 months without the possibility of long-lasting remission [21, 22]. The objective response rate (ORR) of 46.1% in the pooled phase 2 analysis of cemiplimab and the 62% ORR with extended dosing are therefore not merely incremental improvements but transformative outcomes, offering a substantial subset of patients the potential for long-term disease control [15, 20].

The efficacy of cemiplimab extends beyond objective tumor shrinkage to encompass critical patient-centered outcomes such as duration of response and survival. The durability of responses is particularly noteworthy; the integrated analysis revealed that the median duration of response was not reached, with an estimated 87.8% of responders maintaining their response at 12 months [15]. This profound durability stands in stark contrast to the transient responses typically seen with conventional chemotherapy. Additionally, the median OS has not yet been reached, and the 24-month likelihood of overall survival was 73.3%, a figure that effectively doubles the historical survival benchmarks [15]. This real-world effectiveness was corroborated by a large US-based retrospective study by Ge et al. (2024), which reported a median real-world OS of 24.8 months in a heterogeneous patient population, including a significant proportion of elderly and immunocompromised individuals [23]. This alignment between clinical trial efficacy and real-world effectiveness underscores the generalizability of cemiplimab's benefit.

Perhaps the most compelling evolution in the clinical application of cemiplimab is its successful integration into multimodal treatment strategies for earlier-stage, high-risk disease. The results from neoadjuvant trials have been nothing short of practice-changing. The research conducted by Gross et al. demonstrated a pathological complete response (pCR) rate of 51%, which was associated with no recurrences at median follow-up [18]. The more recent DISCERN trial by Lim et al. reported an even higher pCR rate of 73% [14]. These high pCR rates are significant because they often translate into less extensive surgical resections, potentially reducing morbidity and preserving function and cosmesis, a critical consideration for a disease frequently located on the head and neck. This neoadjuvant approach allows for in vivo assessment of tumor sensitivity and may prime the immune system for long-term

control, a theory backed by the DISCERN trial's 91% disease-free survival (DFS) and 100% 12-month OS [14].

The landmark C-POST phase 3 randomized trial has now conclusively demonstrated the use of cemiplimab as an adjuvant for patients who are at high risk of recurrence following radiation and surgery [17]. Adjuvant cemiplimab was shown to minimize the probability of mortality or illness recurrence by 68% (Hazard Ratio 0.32) and improved the 24-month DFS rate from 64.1% with placebo to 87.1% provides Level I evidence for this new standard of care. This is a monumental achievement, as it addresses a previously unmet need for a population with a historically high rate of relapse. The efficacy was consistent across both locoregional and distant recurrence endpoints, suggesting a systemic protective effect. The safety profile in this curative-intent setting was manageable, with a discontinuation rate due to adverse events of 9.8%, which is acceptable given the substantial absolute improvement in DFS.

The cemiplimab safety profile found in all of the included trials is in line with the established class effects of anti-PD-1 antibodies. Fatigue and diarrhea were the most frequent treatment-emergent side effects, while immune-related adverse events (irAEs), though not explicitly detailed in every abstract, are an expected management consideration [19]. The incidence of Grade ≥3 events ranged from 23.9% in the adjuvant trial to 44% in an earlier phase 2 study [16,17]. It is important to contextualize this toxicity against the alternative of ineffective therapy and rapid disease progression. Furthermore, real-world studies like the one by Valentin et al. provide a crucial perspective, suggesting that toxicity may be more pronounced in frailer, older populations typical of daily practice, with their cohort reporting 41% definitive treatment discontinuation due to AEs [24]. This highlights the critical importance of vigilant monitoring and proactive management, especially in vulnerable patient groups.

When considering the value of cemiplimab, its position relative to other therapies is relevant. Although there are no head-to-head studies with pembrolizumab, another PD-1 inhibitor authorized for advanced CSCC, Paul et al. conducted a cost-effectiveness study suggested that cemiplimab is a cost-effective option compared to pembrolizumab [25]. The extensive and robust clinical trial data across multiple disease stages, as synthesized in this review, provides a comprehensive evidence base that supports its widespread adoption and reimbursement.

Limitations

This systematic review has a number of limitations despite the strong results. The majority of the efficacy data, with the notable exception of the C-POST trial, are derived from single-arm, non-randomized phase 2 studies [17]. The absence of a concurrent control group in these trials introduces the potential for selection bias and makes it difficult to ascertain the precise magnitude of benefit over standard of care, relying instead on historical comparisons. Furthermore, the patient populations enrolled in clinical trials are often highly selected, with good performance status and fewer comorbidities, which may not fully represent the typical older and frailer CSCC patient population seen in community practice, as evidenced by the different safety outcomes in the real-world study by Valentin et al. [24]. The follow-up duration for many of the included studies, particularly the more recent ones on neoadjuvant and extended dosing, stays rather brief, making it difficult to evaluate long-term survival and the possibility of late-onset toxicity. Finally, as a review based on published abstracts and articles, it is susceptible to publication bias and is limited by the granularity of data publicly available, which may preclude more nuanced subgroup analyses [25].

Conclusion

To sum up, the data gathered from clinical studies confirms that cemiplimab is an essential and very successful therapy for cutaneous squamous cell carcinoma. Its activity is demonstrated across the entire disease spectrum, from inducing deep and durable responses in metastatic CSCC to significantly reducing recurrence risk in the adjuvant setting and enabling organ-preserving strategies in the neoadjuvant context. The safety profile, while requiring expert management, is consistent with the PD-1 inhibitor class and is a manageable trade-off for the profound clinical benefits achieved. The journey from a disease with limited options to one with a potent, paradigm-shifting therapy marks a new era for patients with advanced CSCC. Future studies should concentrate on finding response-predictive biomarkers, optimizing combination and sequencing strategies, and continuing to collect long-term real-world data to refine its use in everyday clinical practice.

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