

# Cemiplimab for the Treatment of Advanced Cutaneous Squamous Cell Carcinoma: Appropriate Patient Selection and Perspectives

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**Abstract:** Five percent of patients with cutaneous squamous cell carcinoma develop locally advanced or metastatic disease that is not amenable to definitive surgical or radiation therapy. Cemiplimab, an antibody against programmed death receptor-1, was approved in the United States for the treatment of locally advanced and metastatic cutaneous squamous cell carcinoma in 2018. We performed a literature review on the use of cemiplimab in cutaneous squamous cell carcinoma, with an emphasis on efficacy, safety and tolerability, patient selection, and future directions. Embase and PubMed were searched for relevant terms, and 23 peer-reviewed journal articles presenting primary data on cemiplimab treatment in 5 or more subjects with cutaneous squamous cell carcinoma were included and summarized. Objective response rates in locally advanced and metastatic disease ranged from 42.9% to 50.8% in Phase I/II clinical trials and 32–77% (median 58%) in post-approval observational studies. Phase II trials looking at neoadjuvant use also had favorable response rates. Real-world studies demonstrated cemiplimab efficacy in periorbital tumors, tumors with large caliber perineural invasion, and tumors in solid organ transplant recipients. Cemiplimab was safe and well-tolerated in most patients. While side effects such as fatigue, diarrhea, pruritus, and rash were fairly common, only 9.8% of adverse events required cessation of therapy in phase II trials. Severe adverse events were primarily immune-mediated, including pneumonitis, myocarditis, myositis, and autoimmune hepatitis; the risk of treatment-related death was 3% in clinical trials. Further research on cemiplimab therapy in cutaneous squamous cell carcinoma is needed, and trials are now underway to obtain Phase IV long-term real-world data, further data on adjuvant and neoadjuvant use, and additional data in special populations such as stem cell and solid organ transplant recipients.

**Keywords:** cutaneous squamous cell carcinoma, cemiplimab, immunotherapy, immune checkpoint inhibitor, programmed death receptor-1 inhibitor

## Introduction

Cutaneous squamous cell carcinoma (CSCC) is the second most common type of skin cancer. Major risk factors for CSCC include chronic sun exposure, immunosuppression, and advancing age.<sup>1</sup> Although most CSCCs are low-risk and curable with surgical intervention, a subset of tumors display an aggressive phenotype and have a higher risk of poor outcomes including local recurrence, nodal metastasis, distant metastasis, and disease-specific death. High-risk factors that have been associated with poor outcomes include larger clinical diameter, greater depth of invasion, perineural invasion (PNI), and poor differentiation.<sup>2,3</sup> As the incidence of CSCC continues to increase, the morbidity is estimated to surpass that of melanoma over the next 5 years.<sup>4</sup>

Approximately 5% of patients with advanced cutaneous squamous cell carcinoma (aCSCC), including locally advanced (laCSCC) and metastatic CSCC (mCSCC), are not curable by surgical or radiation therapy.<sup>5,6</sup> Previous systemic treatment options for aCSCC were limited to cytotoxic chemotherapy and anti-epidermal growth factor receptor

(EGFR) therapy, with significant morbidity and poor durable response rates.<sup>7</sup> CSCC has a high mutational burden, and immune surveillance is critical to its pathogenesis,<sup>8</sup> leading to the investigation of immunotherapy options for advanced cases. In 2018, cemiplimab (Libtayo<sup>®</sup>; Regeneron, Tarrytown, New York, United States) - a human IgG4 antibody against programmed death receptor-1 (PD-1) - was approved by the United States Food and Drug Administration (US-FDA) for the treatment of laCSCC and mCSCC not amenable to definitive surgery or radiation.<sup>9</sup> We performed a literature review to summarize the data on the use of cemiplimab in CSCC, including effectiveness, safety and tolerability, and appropriate patient selection.

## Methods

An electronic literature search was conducted in Embase and PubMed using terms related to cemiplimab and cutaneous squamous cell carcinoma, from database inception through November 7, 2022. Additional articles were identified by searching reference lists of included articles. Articles were included if they were published in peer-reviewed journals and presented primary data on five or more patients with CSCC treated with cemiplimab. Articles were excluded when CSCC data could not be separated from other tumor types, or when cemiplimab data could not be separated from other forms of treatment. The titles and abstracts, followed by the full texts of the remaining articles, were sorted by two reviewers (LM and SG). Conflicts were resolved by a third reviewer (KS).

## Results

The database search resulted in 338 articles, 23 of which met criteria and were included in the literature review.

### Efficacy of Cemiplimab in Advanced CSCC

#### Phase I Trial Data

From March 2016 to January 2017, an open-label, multi-institutional phase I study was completed to evaluate the safety and tolerability of cemiplimab in patients with locally advanced or metastatic CSCC.<sup>10</sup> Patients with a history of autoimmune disease treated with immunosuppressive medication within the last 5 years, prior anti-PD-1/PD ligand (PDL)-1 therapy, solid organ transplantation, and significant concurrent malignancies were excluded. A total of 26 patients with a median age of 73 years (range 55–88) received intravenous cemiplimab at a dose of 3 mg per kilogram (mg/kg) every 2 weeks for up to 48 weeks, or until they developed unacceptable side effects or disease progression.<sup>10</sup> Patients were evaluated by whole-body imaging every 8 weeks, and treatment response was measured by the Response Evaluation Criteria in Solid Tumors (RECIST) system, version 1.1.<sup>11</sup> At a median follow-up time of 11 months, the objective response rate (ORR) was 50% (95% confidence interval [CI] 30–70%) with a median observed time to response of 2.3 months (range 1.7–7.3). Additionally, the durable disease control rate (DCR; defined as the percentage of subjects without disease progression at 105 days) was 65% (95% CI 44–83%), and 54% of responders experienced a response lasting over 6 months.<sup>10</sup> Table 1 contains a summary of phase I clinical trial data.

#### Phase II Trial Data

Phase II trials evaluated the efficacy of cemiplimab for locally advanced CSCC, metastatic CSCC, and neoadjuvant treatment of resectable CSCC. In both the locally advanced and metastatic CSCC trials, subjects were excluded if they were immunosuppressed (including solid organ transplant patients) or had other concurrent malignancies.<sup>10,12–14</sup> For locally advanced CSCC not curable with resection or radiotherapy (labeled Group 2 in the combined data), 78 subjects were treated with intravenous cemiplimab 3 mg/kg IV every 2 weeks for up to 96 weeks.<sup>12,13</sup> At a median duration of follow-up of 15.5 months, the ORR was 44.9% (95% CI 33.6–56.6%) with a complete response (CR) rate of 12.8% and a partial response (PR) rate of 32.1%. The durable DCR was 62.8% (95% CI 51.1–73.5%), and median time to response was 2.1 months.<sup>13</sup> Tumors with a wide range of PDL-1 expression and mutational burden responded to cemiplimab therapy.<sup>12</sup>

For metastatic CSCC, both weight-based dosing (3 mg/kg every 2 weeks; Group 1) and fixed dosing (350 mg every 3 weeks; Group 3) for up to 96 weeks were evaluated.<sup>10,13,14</sup> Group 1 had 59 subjects, and Group 3 had 56. At a median duration of follow-up of 18.5 months for Group 1 and 17.3 months for Group 3, the ORRs were 50.8% (95% CI 37.5–64.1%) and 42.9% (95% CI 29.7–56.8%), respectively.<sup>13</sup> This included CR rates of 20.3% for Group 1 and 16.1% for Group 3. The

**Table I** Efficacy Data from Phase I and Phase II Clinical Trials Evaluating Cemiplimab for the Treatment of Advanced Cutaneous Squamous Cell Carcinoma

Article	Trial Phase	Treatment Groups	Cemiplimab Dosing	Median Follow Up (Months)	Efficacy Outcomes			
					ORR	CRR	PRR	DDCR
Migden et al 2018 <sup>10</sup>	Phase I	laCSCC or mCSCC (n=26)	3 mg/kg IV every 2 weeks for up to 48 weeks	11	50%	0%	50%	65%
	Phase II	mCSCC (n=59)	3 mg/kg IV every 2 weeks for up to 96 weeks	7.9	47%	7%	41%	61%
Migden et al 2020 <sup>12</sup>	Phase II	laCSCC (n=78)	3 mg/kg IV every 2 weeks for up to 96 weeks	9.3	44%	13%	31%	37%
Rischin et al 2021 <sup>13</sup>	Phase II (Extended follow-up)	Group 1: mCSCC (n=59)	3 mg/kg IV every 2 weeks for up to 96 weeks	18.5	50.8%	20.3%	30.5%	61%
		Group 2: laCSCC (n=78)	3 mg/kg IV every 2 weeks for up to 96 weeks	15.5	44.9%	12.8%	32.1%	62.8%
		Group 3: mCSCC (n=56)	350 mg IV q3 weeks for 54 weeks; optional up to 96 weeks	17.3	42.9%	16.1%	26.8%	57.1%
Rischin et al 2020 <sup>14</sup>	Phase II (Extended follow-up for weight-based dosing group)	mCSCC (n=56)	350 mg IV every 3 weeks for up to 54 weeks	8.1	41.1%	5.4%	35.7%	57.1%
		mCSCC (n=59)	3 mg/kg IV every 2 weeks for up to 96 weeks	16.5	49.2%	16.9%	32.2%	61%
<b>Neoadjuvant therapy</b>								
Gross et al 2022 <sup>15</sup>	Phase II	Resectable AJCC-8 stage II (at least 3cm), III, or IV (M0) CSCC (n=79)	350 mg IV every 3 weeks for up to four doses before resection	–	53% (path) 68% (imaging)	6%	62%	–
Ferrarotto et al 2021 <sup>16</sup>	Phase II	Primary or recurrent resectable CSCC-HN stage III–IV (AJCC-8) (n=20)	350 mg IV every 3 weeks for 2 cycles before resection	22.6	75% (path) 30% (imaging)	0%	75%	–

**Abbreviations:** laCSCC, locally advanced cutaneous squamous cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma; mg, milligrams; kg, kilograms; IV, intravenous; ORR, objective response rate; CRR, complete response rate; PRR, partial response rate; DDCR, durable disease control rate; AJCC, American Joint Committee on Cancer; cm, centimeter; HN, head and neck.

durable DCRs were 61% (95% CI 47.4–73.5%) for Group 1 and 57.1% (95% CI 43.2–70.3%) for Group 3.<sup>13</sup> Efficacy was comparable in subjects with nodal and distant metastases.<sup>10</sup>

In a pooled analysis combining all laCSCC and mCSCC data, median duration of response was not reached by the study end date, and 87.8% (95% CI 78.5–93.3%) of responders were estimated to have an ongoing response at 1 year.<sup>13</sup> Median progression-free survival (PFS) and median overall survival (OS) were also not reached by the end of the study.

However, Kaplan–Meier curves estimated the median PFS to be 18.4 months (95% CI 10.3–24.3), and the probability of PFS and OS at 24 months to be 44.2% (95% CI 36.1–52.1%) and 73.3% (95% CI 66.1–79.2%), respectively.<sup>13</sup> Quality of life scores improved as early as cycle 2, with statistically significant improvement by cycle 3 and clinically meaningful improvement ( $\geq 10$ -point change) by cycle 12. This included significant improvement in emotional functioning, social functioning, and pain.<sup>13</sup>

Two phase II studies evaluated neoadjuvant cemiplimab therapy for resectable CSCC.<sup>15,16</sup> Gross et al included American Joint Commission on Cancer 8th Edition (AJCC-8) stage T2 tumors that were at least 3 cm in diameter, T3 tumors, and T4 tumors located on any anatomic site. Seventy-nine subjects received intravenous cemiplimab 350 mg every 3 weeks for up to 4 cycles prior to definitive resection. The pathologic complete response rate (defined as no tumor cells present on the excision specimen) was 53%, and the pathologic major response rate (defined as tumor cells in up to 10% of the excision specimen) was 13%. ORR by imaging (using RECIST 1.1) was 68%, with 6% having a complete response and 62% a partial response.<sup>15</sup> Ferrarotto et al included only T3 and T4 (by AJCC-8) head and neck CSCCs. Twenty subjects (including 13 primary and 7 recurrent tumors) received 2 doses of cemiplimab 350 mg every 3 weeks prior to resection. The ORR was 30% (95% CI 11.9–54.3%), with all having a partial response by RECIST 1.1. A pathologic response was seen in 75% of subjects, including a complete response in 55% and a major response in 20%.<sup>16</sup> Table 1 contains a summary of phase II clinical trial data.

### Real World Efficacy Data

Post-approval observational studies of cemiplimab for the treatment of CSCC are important to review as they include a broader range of patients treated in real-world settings. This includes patients with advanced age, multiple comorbidities, lower performance status, and immunosuppression. Overall, the ORR ranged from 32% to 77% in observational studies, with a mean of 55% and a median of 58%. This includes partial response rates ranging from 23% to 47% and CR rates ranging from 8% to 33%.<sup>17–24</sup> The DCR ranged from 47% to 72% in real-world studies, with a median of 62%.<sup>18–20,24,25</sup> Factors associated with higher response rates included age,<sup>20</sup> higher performance status, and primary tumors on the head and neck.<sup>21,23</sup> Immune status,<sup>21</sup> frailty, sex, and body mass index (BMI) did not impact response rates.<sup>23</sup> Median duration of response was 12 months in one study,<sup>24</sup> and was not reached in others.<sup>19,21</sup> Median progression-free survival, when reached by data cut-off, ranged from 5.9 to 9.13 months.<sup>19–22</sup> Overall, efficacy in the real-world setting has been comparable to that seen in clinical trials.

One retrospective cohort study evaluated the effect of cemiplimab and radiotherapy combination therapy compared to cemiplimab treatment alone. This resulted in an ORR of 41.6% in the combination therapy group and 47.6% in the cemiplimab monotherapy group. However, the combination therapy group demonstrated an earlier radiologic disease response, with a median duration of 3 months (versus 5.5 months in the monotherapy group) and a prolonged treatment response even after discontinuation of PD-1 blockade.<sup>26</sup>

Several studies evaluated unique scenarios, such as the use of cemiplimab to treat periorbital CSCC, CSCC with large caliber PNI, and CSCC in SOTRs. For periorbital CSCC, treatment with cemiplimab resulted in response rates between 82% and 100% and negated the need for orbital exenteration in most cases.<sup>27–29</sup> In a single center retrospective cohort study evaluating the response of large caliber PNI to immunotherapy, all seven subjects treated with cemiplimab experienced stable or improved neurologic symptoms, one had a complete radiologic response, and five had partial radiologic responses.<sup>30</sup> While most real-world studies did not include transplant recipients, Tsung et al studied the use of cemiplimab in six solid organ transplant recipients (SOTRs) with metastatic head and neck CSCC. The DCR in this study was 83%, including one subject with stable disease, three with a partial response, and one with a complete response. Half of the subjects received a systemic steroid regimen as prophylaxis for organ rejection, and one subject in the group that did not receive steroids developed rejection.<sup>31</sup>

An Italian multi-institutional retrospective study evaluated the impact of the coronavirus-19 (COVID-19) pandemic on cemiplimab treatment in CSCC. In a cohort of 54 patients, 57% continued treatment and 31% stopped due to the pandemic. Only two patients, both of whom were hospitalized at the time, were infected with COVID-19; both patients died of COVID-19 pneumonia. The authors noted the overall safety of immunotherapy during the pandemic and cautioned against stopping treatment due to the risk of tumor progression.<sup>32</sup>

Finally, two retrospective studies evaluated the use of PET-CT to assess response to cemiplimab treatment. Historically, CT and MRI are used to monitor response to therapy according to the RECIST 1.1 system. In these studies, PET-CT (using the PERCIST 1.0 grading system) performed well in monitoring response to therapy.<sup>33,34</sup> McLean et al demonstrated that tumor responses were discordant between CT/MRI and PET-CT, with 73% of subjects achieving a complete response on PET-CT and only 7% achieving a complete response on CT/MRI. They hypothesized that PET-CT is more precise and that in many cases apparent tumor on CT/MRI may actually be scar tissue.<sup>34</sup>

## Safety and Tolerability

Table 2 includes the most common treatment emergent adverse events across all included studies. In phase II clinical trials, 99.5% of the 193 total subjects developed at least one adverse event while on treatment, and 48.7% developed a severe adverse event (National Cancer Institute Grade 3 or higher). However, only 17.1% of severe adverse events were believed to be treatment-related, and only 9.8% of adverse events required cessation of therapy. The most common adverse events were fatigue and GI distress. The most common severe treatment-related adverse effects were pneumonitis (2.6%) and autoimmune hepatitis (1.6%).<sup>13</sup> There were six total adverse-event related deaths (3%). Of these, two deaths from pneumonia and one from hypercalcemia and deep vein thrombosis were felt to be related to cemiplimab; the others were not related or only possibly related to treatment.<sup>10,12,14</sup>

Safety data in the real-world setting has been comparable to clinical trials, despite inclusion of patients with a broader range of ages and comorbidities. The overall treatment related adverse event rate in larger observational studies ranged from 33% to 58%, 8–9% of which were considered serious events.<sup>18,19,21</sup> As in phase II trials, fatigue and diarrhea were most commonly reported, along with pruritus, rash, anemia, pneumonitis, pancreatitis, and musculoskeletal pain.<sup>18,19,21</sup> Hepatic disorders were the third most common adverse event in one study;<sup>21</sup> another found a 5.1% risk of immune

**Table 2** The Most Common Adverse Events in Clinical Trials and Real-World Observational Studies of Cemiplimab Treatment for Advanced Cutaneous Squamous Cell Carcinoma. Adverse Events with a Frequency of 1.1% or Less are Not Included in This Table

Severity of Adverse Events	Frequency (%)
Any adverse event	33.6
Grade 3 or higher adverse event	20.9
Adverse event requiring drug discontinuation	5.9
Types of Adverse Events	Frequency (%)
Fatigue	14.5
Diarrhea	11.0
Nausea/vomiting	7.5
Rash	4.0
Pruritus	2.5
Arthralgia	2.3
Pneumonitis	2.1
Hypothyroidism	1.6
Myalgia	1.6
Transaminitis	1.5
Hypertension	1.5

hepatitis and noted that cemiplimab should be considered even in patients with baseline liver disease.<sup>25</sup> Interrupted therapy due to side effects occurred in 23.4% of subjects in one study<sup>19</sup> and 55% in another.<sup>24</sup> Treatment discontinuation rates ranged from 5.3% to 41%.<sup>18,19,21,24</sup> Deaths related to cemiplimab treatment were rare and included cases of pneumonitis, myocarditis, toxic epidermal necrolysis, myositis, and pneumonia.<sup>18,21,24</sup>

## Discussion

Immunotherapy has revolutionized the treatment of advanced malignancies, including CSCC. Cemiplimab, a PD-1 immune checkpoint inhibitor, is currently the only FDA-approved systemic treatment for laCSCC and mCSCC not curable with surgery or radiation. Prior to the advent of cemiplimab, systemic therapy options for CSCC were limited to platinum-based chemotherapy and EGFR inhibitors, both of which had limited efficacy and poor tolerability. Phase I and II clinical trials and real-world observational studies have demonstrated that cemiplimab is effective, safe, and well-tolerated in most patients. While adverse events are relatively common, most of these are minor and do not require treatment cessation. Fatal adverse events are rare and tend to be immune-mediated. Overall, the potential benefits of cemiplimab therapy outweigh the risks in patients with advanced CSCC, but patient selection is important.

## Patient Selection

Cemiplimab is FDA approved for the treatment of aCSCC. This includes mCSCC and laCSCC, the latter of which is defined as deeply invasive and/or unresectable tumors that are not amenable to definitive treatment with surgery or radiotherapy. Cemiplimab has also shown promise for neoadjuvant treatment of resectable tumors in phase II clinical trials. Although not without risk, cemiplimab therapy has been shown to be well tolerated by most patients, including patients with advanced age, lower functional status, multiple comorbidities, and immunosuppression in real-world studies. In addition, most adverse effects respond well to interruptions in or cessation of treatment.

Phase I and II clinical trials excluded solid organ transplant recipients. Immune checkpoint inhibitors (ICIs) are used with great caution in SOTRs due to the risk of immune-mediated graft rejection. However, these patients are significantly more likely to develop CSCCs and poor CSCC outcomes,<sup>35,36</sup> so having treatment options for advanced disease in these patients is critical. Post-approval observational studies of cemiplimab for the treatment of CSCC included 22 SOTRs, and the organ rejection rate across all studies was 13.6%.<sup>21,23,25,31</sup>

In 2022, a systematic review evaluated the safety of ICIs in advanced malignancies, including 18.5% CSCC. This revealed a 41% risk of organ rejection and a 24% risk of complete graft failure across the entire cohort. However, as subjects were significantly more likely to die of tumor progression (64%) than organ rejection (24%), the benefit of ICI therapy appears to outweigh the risks when no other treatment options are available.<sup>37</sup> Limited data suggest that prophylactic systemic steroid regimens may help decrease the risk of rejection in SOTRs.<sup>31</sup>

## Future Directions

Further research on the use of cemiplimab in advanced CSCC is needed. This includes additional long-term and real-world data, further studies in SOTRs (including the best strategy to prevent graft rejection), and additional trials evaluating neoadjuvant and adjuvant use. Future research should also focus on the use of biomarkers to predict treatment response, the timing of treatment cessation in long-term responders, optimal efficacy and safety monitoring, and strategies to prevent and manage adverse events. Finally, other immunotherapy options (including head-to-head clinical trials) and combination therapies should also be explored.

Multiple new trials are now underway to address some of these knowledge gaps. CASE (CemiplimAb-rwlc Survivorship and Epidemiology) is a Phase IV, prospective, non-interventional long-term follow-up study of aCSCC patients treated with cemiplimab in real-world settings (NCT03836105).<sup>38</sup> In addition, several clinical trials evaluating the efficacy and safety of cemiplimab in the adjuvant and/or neoadjuvant setting for locally advanced, resectable CSCC are actively enrolling (NCT03969004, NCT03916627, NCT04315701, and NCT4428671).<sup>39-42</sup> Finally, NCT04339062 is an open-label, phase I/II trial evaluating the use of cemiplimab in stem cell and renal transplant patients with aCSCC.<sup>43</sup>

## Conclusions

In conclusion, cemiplimab is a promising treatment option for locally advanced and metastatic CSCC and is overall well tolerated. Further research is needed to confirm long-term efficacy and safety in the real-world setting, in special populations, and for adjuvant and neoadjuvant indications.

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