DRUG PROFILE

Pembrolizumab as monotherapy in locally advanced cutaneous squamous cell carcinoma

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ABSTRACT

Introduction: Outcomes for patients with advanced cutaneous squamous cell carcinoma (cSCC) are poor, however recent approvals in programmed death-1 (PD-1) checkpoint inhibition have shown promise. Prior systemic treatments in this patient population included chemotherapy and anti-EGFR directed therapies, with limited long-term benefit. Studies investigating cemiplimab and pembrolizumab have recently revealed significant responses with many cases of sustained benefit in both locally advanced and recurrent and/or metastatic disease. While these treatments have shown improvement in outcomes, there are continued areas of need.

Areas covered: This review focuses on clinical evidence for PD-1 directed checkpoint inhibition in advanced cSCC. Excluded populations and new approaches involving immunotherapy are discussed.

Expert opinion: Immune checkpoint inhibition in advanced cSCC has shown impressive benefit. The clinical trials for both cemiplimab and pembrolizumab demonstrate similar responses and outcomes. Biomarkers for predicting response are an area of need. In addition, these trials excluded immunosuppressed patients due to hematological malignancies or prior organ transplant, which are populations with significantly increased risk of cSCC. Finally, a variety of novel approaches using checkpoint inhibition in cSCC are being investigated, with some encouraging preliminary results.

1. Introduction

Cutaneous squamous cell carcinoma (cSCC) is the second most common skin cancer with increasing incidence noted worldwide [1,2]. There are a variety of risk factors for cSCC, the most significant including ultraviolet (UV) light exposure, age, fair skin, and an immunosuppressed state [3]. While most patients present with early-stage, curable disease, approximately 2–5% of patients will develop locoregionally advanced or metastatic cSCC [4,5]. More advanced disease including nodal involvement at diagnosis portends 5 year disease-specific survival rates of 65–83% [6]. First-line treatment typically involves surgery followed by risk adapted adjuvant treatment or primary radiation in situations where surgery is infeasible, contraindicated, or not preferred by the patient [7].

Advanced cSCC encompasses locally advanced, recurrent, and/or metastatic disease no longer amenable to curative surgery or radiotherapy. Locally advanced cSCC is a unique situation in which a local tumor is unlikely to be cured with surgery or radiation or the patient is not a candidate for surgery or radiation due to high morbidity of treatment [8]. Systemic treatments are usually employed in these situations; however, overall prognosis is poor, with a 5 year overall survival (OS) rate of 11% [6]. Prior to the approval of checkpoint inhibitors for advanced cSCC, systemic treatment typically included chemotherapy or anti-epidermal growth factor receptor (EGFR) based treatments, with limited durable responses noted [9]. Genomic profiling of cSCC has demonstrated a mutational landscape dominated by tumor suppressor genes, a UV signature, and high tumor mutational burden (TMB) [10,11]. In addition, immunosuppression has a clear association with risk of cSCC, including higher rates in solid-organ transplant recipients and patients with chronic lymphocytic leukemia (CLL) [12,13]. Based on these findings, cSCC is considered an excellent target for checkpoint inhibition.

In this review, we will examine the data investigating the use of checkpoint inhibitors in advanced cSCC. We will place an emphasis on pembrolizumab in locally advanced disease, as incorporation of immunotherapy in this setting has led to dramatic responses and in a minority of cases curative options. In addition, we will discuss potential future approaches of combinatorial therapies with checkpoint inhibition, novel immunotherapies, and consideration of neoadjuvant checkpoint inhibition prior to surgical resection.

2. Overview of systemic treatment landscape

Current systemic treatment used in advanced cSCC includes cytotoxic chemotherapy, anti-EGFR therapies, and most recently checkpoint inhibitors. Much of the data involving cytotoxic chemotherapy is based on small single-arm studies and case series, which demonstrate only modest benefit of these agents. Some of the early studies incorporated platinum
and 5-fluorouracil-based regimens, with notably high response rates of over 80% [14–16]. However, more recent studies in which patients received either chemotherapy or cetuximab have shown lower response rates [9,17]. The Dermatologic Cooperative Oncology Group (DeCOG) conducted a retrospective analysis including 190 patients with advanced cSCC [9]. Only 30 patients received systemic treatment, with 39 systemic therapies in total. Thirty-eight percent of patients received either single agent or combination chemotherapy. The ORR among patients receiving only chemotherapy was 40% (6/15), and the median duration of response for the entire population was only 5 months. Another retrospective study investigating systemic treatments in advanced cSCC included 82 patients [17]. The most common regimen was carboplatin and paclitaxel in 26.8% (22/82) of patients. The response rate for all first-line treatments was 18.3% in the entire population and 17.6% in the locally advanced cohort. The median duration of response for first-line treatment was 2.4 months and 4.1 months for the locally advanced population. These more recent retrospective studies show the limited responses of chemotherapy as well as the short duration of response, which limits the impact on survival.

EGFR-directed therapies have also shown only modest benefit in the treatment landscape of cSCC. Activation of EGFR leads to a phosphorylation cascade with multiple downstream pathways affected involving proliferation, apoptosis, invasion, angiogenesis, and metastasis [18]. Tumors in patients with cSCC are known to often overexpress EGFR, which provides the preclinical rationale for targeting EGFR in treatment [19]. In addition, overexpression of EGFR in cSCC correlates with metastatic potential [20]. The benefit of cetuximab in advanced cSCC was reported in a phase II clinical trial [21]. In this trial, chemotherapy naïve patients with unresectable or metastatic cSCC received single-agent cetuximab. There were 36 patients enrolled from October 2005 to April 2008. Only 8% of patients had distant metastatic disease, while the rest either had unresectable local disease (47%) or regional lymph node involvement (44%). The disease control rate at week 6 was 69% and the best overall response rate was 28%, with half of responders showing late responses between week 6 and 18. Interestingly, three patients that had a partial response underwent conservative surgical excision of the primary tumor and lymph node dissection after treatment. All three patients had residual disease noted on pathology, however one patient did remain disease free at 3 years. The overall survival was 8.1 months and median PFS was 4.1 months. The safety profile was similar to previously reported trials involving cetuximab. Notably, patients that developed an acneiform rash during treatment had a significantly prolonged median PFS of 4.5 vs 1.7 months and a trend toward improved survival, however no difference in DCR or RR. In this trial, only patients with EGFR expression were included, however EGFR expression levels were not associated with treatment efficacy. Panitumumab, a high affinity human IgG2 monoclonal antibody directed against human EGFR, has also been investigated in patients with advanced cSCC. An open label, uncontrolled, single center prospective phase II study enrolled patients from May 2010 to May 2012 [22]. In total 16 patients with locally advanced, recurrent, or metastatic cSCC not suitable for curative local received panitumumab infusions every 2 weeks for a maximum of 9 infusions. Of the 16 patients, 13 were considered locoregional without distant metastatic disease, 14 had received prior radiation, and 2 patients had received prior systemic chemotherapy for advanced cSCC. The ORR was 31% including 3 PR and 2 CR, and an additional 6 patients had SD. Median duration of response was 6 months and DCR at 6 weeks was 69% (11/16). Median PFS was 8 months and median OS was 11 months, with no relationship between skin toxicity and duration of response, PFS, or OS. Safety analysis showed a 31% rate of grade 3 or 4 toxicity mostly related to skin toxicity. EGFR expression levels were analyzed, and were not associated with treatment efficacy. These small phase II studies demonstrate benefit from anti-EGFR therapy, but unfortunately median survival in both trials is less than 1 year and responses are relatively short.

3. Checkpoint inhibition in advanced cSCC

Checkpoint inhibition has eclipsed chemotherapy and EGFR-directed therapies in recent years with recent approvals of first cemiplimab followed by pembrolizumab, both of which have now been approved in the locally advanced, recurrent, and/or metastatic disease setting when treatment with curative intent surgery or radiation is not possible. In the following sections we will discuss the mechanism of action of checkpoint inhibition and review the data for cemiplimab and pembrolizumab in advanced cSCC.

3.1. Mechanism of action

Pembrolizumab and cemiplimab are both humanized monoclonal IgG4 kappa anti-PD1 antibodies, which inhibit the ability of PD1 ligand 1 (PD-L1) and PD-L2 to bind to the PD-1 receptor [23,24]. Upon binding to PD1, pembrolizumab does not engage Fc receptors or activate complement, so is devoid of any cytotoxic activity [25]. Similarly, cemiplimab does not mediate complement-dependent cytotoxicity [24]. Based on numerous clinical trials, checkpoint inhibitors targeting CTLA-4, PD-1, and PD-L1 have been FDA approved to treat a variety of malignancies [26].

Over the years, there has been extensive research into the relationship between the immune system and development of cancer [27]. Tumor-specific antigens theoretically should elicit
an immune response resulting in removal of malignant cells by means of immune surveillance. However, through a variety of mechanisms, tumor cells are able to escape detection. One mechanism of evasion is through manipulation of checkpoint pathways, such as PD-1, which can either promote or inhibit the immune system and T cell function [28]. Early findings noted the upregulation of PD-1 ligands in many malignancies [29]. In addition, PD-1 is highly expressed on functionally impaired tumor antigen-specific T cells found within the tumor microenvironment [30]. These findings have led to the development of drugs inhibiting multiple-checkpoint pathways including PD-1. A schema describing the mechanism of action of PD-1 checkpoint inhibitors is shown in Figure 1.

Cutaneous SCC has a clear association with the immune system, as patients with immune dysfunction including organ transplant recipients have a significantly higher incidence than the general population [12]. Unsurprisingly, transplant patients taking fewer immunosuppressive drugs have a lower risk of developing skin cancers [31]. Ultraviolet light susceptibility also plays an important role, as organ transplant patients with skin types prone to sunburn are more likely to develop cutaneous SCC [32]. The high somatic mutational frequency with a signature of exposure to UV light in aggressive cSCC has been confirmed with whole-exome sequencing [11]. Studies have also shown a correlation between increasing tumor mutational burden and ORR to PD-1 inhibition [33]. These properties make cutaneous SCC a particularly attractive target for immune checkpoint inhibition-based treatment.

3.2. Adverse effects of checkpoint inhibitors

As a consequence of increasing the activity of the immune system, checkpoint inhibitors can have immune-related adverse effects (irAEs). The mechanism of action of these adverse effects is multifactorial and continues to be investigated. Possible etiologies include the influence of checkpoint inhibitors on immunologic homeostasis and increased T-cell activity against antigens present in healthy tissue as well as tumor [34]. Some commonly affected organ systems include the skin, endocrine glands, gastrointestinal tract, liver, and lungs, however auto-immune side effects affecting most organs have been described [35]. Many of these toxicities can be serious and lead to death, however, this occurs rarely,
with the incidence of fatal adverse events estimated to be between 0.3% and 1.3% [36]. A meta-analysis investigated the incidence of irAEs included patients with advanced melanoma receiving checkpoint inhibitors from 35 clinical trials [37]. The study found increased irAEs in patients receiving ipilimumab, a CTLA-4 inhibitor, and in those receiving combination CTLA-4 and PD-1 directed therapy. The most common all-grade potential irAEs in patients receiving single-agent pembrolizumab included hypothyroidism in 8.2%, arthralgias in 7.7%, and hyperglycemia in 5.6%. Noteworthy grade 3 or higher irAEs in patients receiving single-agent pembrolizumab included adrenal insufficiency in 0.7%, hypophysitis in 0.7%, autoimmune colitis in 0.6%, pneumonitis in 0.3%, and autoimmune hepatitis in 0.2%. Management of irAEs is dependent on the grade and type of toxicity. However, typically if grade 2 or higher toxicity develops, the checkpoint inhibitor is held and immunosuppression with high-dose corticosteroids started [38].

### 3.3. Clinical efficacy of cemiplimab in advanced cSCC

Cemiplimab was FDA approved in September 2018 for treatment of locally advanced and/or metastatic cSCC. The approval was based on data from two clinical trials with data published in 2018 and 2020 [39,40]. Data from these trials will be described below and in Table 1.

The initial publication in 2018 included data from a phase I study expansion cohort of cemiplimab in patients with locally advanced and/or metastatic cSCC as well as data from the metastatic cohort of a phase 2 study [39]. The phase I study was an open-label and multicenter study involving patients with advanced solid-tumor malignancies. From March 2016 to January 2017 a total of 26 patients with advanced cSCC received cemiplimab in the expansion cohort. In this cohort, 38% (10/26) patients had locally advanced disease, and the rest had either distant or regional metastatic disease. In terms of prior treatment for cSCC, 15 patients had received previous systemic treatment and 20 patients had received prior radiation treatment. There was an objective response in 50% of patients (13/26), all of which were PR, with a durable disease control of 65%. The phase 2 study was a nonrandomized global study of cemiplimab in patients with advanced cSCC. From May 2016 to April 2017 a total of 59 patients with metastatic cSCC were enrolled, 56% (33/59) of whom had received previous systemic treatment and 85% (50/59) had received previous radiation therapy. Objective responses were noted in 47% (28/59) with 7% (4/59) achieving a CR, and durable disease control in 61% of patients. The estimated probability of PFS at 12 months was 53% and estimated probability of OS at 12 months was 81%. The adverse events were consistent with prior trials involving PD-1 inhibitors.

The locally advanced cohort of the phase 2 study was published in 2020 [40]. This portion of the trial enrolled 78 patients between June 2016 and April 2018. By central review, an objective response was noted in 44% (34/78) of patients, with a CR in 13% and PR in 31%. Most disease responses occurred by the first assessment, with a median time to response of 1.9 months. The disease control rate was 79% (62/78) and durable disease control, defined as SD or better for at least 105 days, was 63% (49/78). Both median PFS and median OS were not reached at the data cutoff. The estimated proportion of patients with a 12 month PFS was 58% and 12 month OS was 93%. There were benefits seen regardless of PD-L1 status as well as TMB levels.

Overall, the data from the phase I and phase II trials of cemiplimab in the advanced cSCC revealed relatively high response rates as well as durable disease control, which ultimately resulted in better outcomes than any other prior therapy leading to FDA approval.

### 3.4. Clinical Efficacy of Pembrolizumab in Advanced cSCC

The use of pembrolizumab in locally advanced and metastatic cSCC has been investigated in two clinical trials, KEYNOTE-629 and CARSKIN. Both of these trials included patients with locally advanced as well as recurrent and/or metastatic (R/M) disease. The data from these trials is summarized below and in Table 1.

KEYNOTE-629 was an open-label, single-arm, phase II study with two cohorts, locally advanced disease and R/M disease. Patients with locoregionally recurrent disease incurable by surgery or radiation and/or metastatic cSCC were included in the R/M cohort. The first interim analysis from KEYNOTE-629 was published in 2020 and included data from the R/M cohort only [41]. This cohort enrolled 105 patients between October 2017 and June 2018, of which 91 received at least one prior systemic treatment. The ORR was 34.3% (36/105), with a CR and PR in 3.8% (4/105) and 30.5% (32/105) patients, respectively. Stable disease was noted in 29.5% (31/105) of patients and with SD of ≥12 weeks included DCR was 52.4% (55/105). The median time to response was 1.5 months and median duration of response was not reached. Median PFS was 6.9 months with a 32.4% 12-month PFS rate, while median OS was not reached with a 60.3% 12-month survival rate. First-line patients were allowed in the trial after an amendment, with a total of 14 patients enrolled. The ORR in the first-line group was 50%. Patients saw benefit regardless of PD-L1 status. Interestingly, 29 patients continued treatment beyond initial progressive disease, with 8 patients having a later response including one CR. Safety analysis was consistent with prior trials involving checkpoint inhibitors with expected mild-to-moderate TRAEs noted. This initial data led to the FDA approval of pembrolizumab in recurrent or metastatic cSCC in June 2020.

Data from the second interim analysis of KEYNOTE-629 was subsequently published in July 2021 [42], which included data from both the locally advanced and R/M cohorts. The trial enrolled patients from 59 centers in 10 countries between November 2017 and September 2019. In total, 159 patients were enrolled, of which 54 were considered locally advanced. Most patients in the locally advanced cohort (85.2%) had a CPS of 1 or higher. Of the 54 locally advanced patients, 12 received prior systemic treatment for curative intent. The ORR was 50.0% (27/54) with a CR in 16.7% (9/54) and a PR in 33.3% (18/54). Including 8 patients that had SD for at least 12 weeks, the DCR was 64.8%. Among the 27 patients with a confirmed response, 77.8% had ongoing responses at the data cutoff date, with 84.1% of responses estimated to last ≥12 months. The estimated PFS rates at 6 and 12 months were 60.9% and
| Drug         | Trial               | Group          | Number of Patients | ORR | CR  | PR  | SD  | PD  | DCR |
|--------------|---------------------|----------------|-------------------|-----|-----|-----|-----|-----|-----|
| Cemiplimab   | Phase I Dose        | Locally Advanced | 10                | 60% | 0%  | 60% | 20% | 0%  | 70% |
|              | Escalation          | R/M            | 16                | 43.8% | 0%  | 43.8% | 25% | 18.80% | 62.9% |
|              | Phase 2             | Locally Advanced | 78                | 44% | 13% | 31% | 36% | 12% | 63% |
|              |                     | R/M            | 59                | 47.50% | 6.80% | 40.70% | 15.30% | 18.60% | 61% |
| Pembrolizumab| KEYNOTE-629         | Locally Advanced | 54                | 50% | 16.70% | 33.30% | 24.10% | 16.70% | 64.8% |
|              |                     | R/M            | 105               | 35.20% | 10.50% | 24.80% | 28.60% | 26.70% | 52.4% |
|              | CARSKIN             | All patients   | 57                | 42% | 7%  | 35% | 18% | 32% | 60% |

| Drug         | Median time to response (months) | Median DOR (months) | Median PFS (months) | Estimated 12-month PFS | Estimated 12-month OS |
|--------------|----------------------------------|---------------------|---------------------|------------------------|-----------------------|
| Cemiplimab   | 3.7                              | N/A                 | N/A                 | N/A                    | N/A                   |
| Pembrolizumab| NR                               | NR                  | NR                  | 58%                    | 93%                   |
| CARSKIN      | 6.7e                             | 25.3e               | NR                  | 75.50%                 |                       |

Superscripts: a: Stable disease or better at 105 days; b: Stable disease or better at 84 days; c: From primary cohort only (n = 39)

Abbreviations: CR: complete response; DCR: disease control rate; N/A: not reported; NR: not reached; ORR: objective response rate; PD: progressive disease; PR: partial response; R/M: recurrent/metastatic; SD: stable disease
54.5%, respectively, and the estimated OS rates at both 12 and 18 months was 73.6%. Data for response based on PD-L1 CPS were provided for the total population, which showed increasing responses as PD-L1 expression increased but responses noted regardless of PD-L1 status. Specifically, an ORR of 42.6% in the 115 PD-L1 CPS ≥1 patients and 20.0% in the 15 PD-L1 CPS of <1. In terms of adverse events, both trials had mild-to-moderate treatment-related AE with no new safety concerns noted. This second analysis led to the 2nd FDA approval of pembrolizumab in July 2021 for the treatment of locally advanced cSCC that is not curable by surgery or radiation.

Complementing the findings of the KEYNOTE 629 study, the CARSKIN trial was an open-label, uncontrolled, multicenter phase II study conducted in 25 French centers [43]. The trial enrolled patients with locally advanced surgically unresectable disease or metastatic disease with documented progression between March 2017 and September 2018. There were 39 patients in the primary cohort and an additional 18 in the expansion cohort, all of which were chemotherapy and anti-EGFR naïve. The patient population included 12% with unresectable local disease, 63% with regional lymph node involvement, and 25% with distant metastatic disease. The ORR at 15 weeks (primary endpoint) for all patients was 42% (24/57), with a PR in 35.1% (20/57) and a CR in 7.0% (4/57). It should be noted that some patients had responses after week 15. The disease control rate for all patients was 59.6% (34/57). In the primary cohort the ORR for the locally advanced disease was 40% (2/5) and regional disease was 40% (10/25). The primary cohort’s median PFS was 6.7 months and median OS was 25.3 months. Of note, two patients underwent surgery of initially unresectable regional disease after pembrolizumab administration. Among the 42 patients with PD-L1+ disease, the ORR was 55% (23/42), which was higher than the 12 PD-L1 - patients with ORR 17% (2/12). However, DCR in PD-L1- patients was 50% (6/12), indicating potential benefit. Progression of disease occurred in about one-third of patients with most occurring in the first weeks of treatment indicating primary resistance. Unfortunately, two patients exhibited what appeared to be hyperprogression secondary to checkpoint inhibition. Overall safety analysis was consistent with prior studies and thought to be acceptable.

The studies outlined above are summarized in Table 1. The data outlines the remarkable benefit of PD-1 directed treatment in patients with advanced cSCC. Both cemiplimab and pembrolizumab have shown promising efficacy, with overall similar response rates and patient outcomes. Similar responses are also seen in the locally advanced compared to the recurrent and/or metastatic populations.

4. Expert opinion

The data reviewed here summarize the limited benefit of chemotherapy and anti-EGFR therapies in advanced cSCC. Although moderate response rates and occasional disease control are noted with these treatments, the responses are typically short lived. In contrast, more recent trials involving checkpoint inhibitors in advanced cSCC have shown high response rates with prolonged duration of response. Based on these recent trials, both cemiplimab and pembrolizumab are FDA approved for treatment of locally advanced cSCC as well as for R/M cSCC. In the subset of patients with locally advanced cSCC receiving checkpoint inhibitors, the benefit is on par with those with R/M disease. As outlined above, the response rates in treatment naïve patients were approximately 40–50% and duration of responses were frequently 12 months or longer [39–43]. On cross trial comparison, cemiplimab and pembrolizumab have similar benefit. Given that these trials have clinically comparable patient populations, the similar outcomes have a confirmatory nature. Both have quickly transitioned to the preferred front-line therapy for advanced cSCC. While the benefit seen in these trials is remarkable, it should be noted these are relatively small-phase I/II non-randomized trials. These treatments must be used judiciously as, despite the excellent outcomes, curative surgical or radiation approaches remain the standard of care when possible.

Cutaneous SCC is primarily a disease of the elderly, and given the frailty of this population an important emphasis of treatment is minimizing toxicity and maintaining quality of life. A pre-specified exploratory analysis from Keynote-629 investigated health related quality of life (HRQoL) using a variety of assessments compared at baseline and at 12 weeks on study [44]. The assessments found patients treated with pembrolizumab had stable overall global health status, quality of life, functioning, and symptoms. In addition, patients that had a response to treatment had a correlation with benefit in HRQoL. As the median age in the study was 72 years, with a range of 29–95, these results also seem to indicate that advanced age is not a barrier to potential benefit.

The long duration of response to checkpoint inhibitors in several types of cancers, including advanced cSCC, leads to the question ‘how long is treatment necessary?’ While many clinical trials investigating checkpoint inhibitors continue treatment for 2 years, there are numerous examples in clinical practice and the literature of patients having sustained responses after just a few cycles of therapy. A recent article highlights this finding, in which a 92 year old patient with advanced cSCC received 3 cycles of cemiplimab resulting in a CR [45]. The patient subsequently decided to stop treatment, and at 6 months of follow-up remained disease free. Data of checkpoint inhibitor use in the melanoma field may also help answer this question. A single institution observational cohort study of 52 patients that discontinued PD-1 directed treatment after 6–18 months (median 11.1 months) showed 75% of patients remained without disease progression at a median follow-up of 20.5 months [46]. Although these findings are interesting, additional research is needed to determine the ideal time to discontinue checkpoint inhibitors in responders.

As of now, there does not appear to be a good biomarker of response for patients who may benefit from checkpoint inhibition. Some trials showed a trend toward improved response rates in PD-L1 positive patients; however, benefit was seen regardless of PD-L1 status. More specific gene expression studies and analysis of the tumor microenvironment were not incorporated into the cemiplimab or pembrolizumab studies, however, a neoadjuvant checkpoint inhibitor study by Ferrarotto et al. in cSCC showed that an inflamed tumor microenvironment with increased CD8+ T cells and Th1 cells were noted in pretreatment samples of patients that
achieved a pCR or MPR [47]. Conversely, an immunosuppressive tumor microenvironment was noted in patients without pathologic response or PD. Additional predictive markers of response would be beneficial, as up to a third of patients with advanced cSCC do not benefit from checkpoint inhibition.

There are also subpopulations of patients with cSCC which bear mention where the utility of checkpoint inhibition is unclear or contraindicated. Patients with advanced cSCC and concomitant hematologic malignancies or an immunosuppressed state were excluded from clinical trials investigating checkpoint inhibition. As these patients are immunocompromised, the incidence and aggressiveness of cutaneous malignancies is known to be increased [48]. There was a small retrospective study investigating the use of checkpoint inhibition for cutaneous cancers in patients with a variety of hematologic malignancies [49]. The study only included 15 patients with cSCC with a response rate of 26.7% (4/15). Noting the small sample size, the authors concluded immune checkpoint inhibition therapy outcomes were inferior in patients with cSCC, which was not observed in the malignant melanoma and Merkel cell carcinoma populations. Treatment with checkpoint inhibitors may be offered in these patients after a discussion of risks and benefits highlighting the paucity of data and possible inferior outcomes. In contrast, patients with organ transplants are at risk for irreversible allograft rejection, making the use of checkpoint inhibition particularly unsafe. A single-center retrospective study examined the safety and efficacy of immune checkpoint inhibition in patients with solid organ transplants [50]. There were seven patients included in the analysis, with a response noted in five patients and evidence of graft rejection in two patients. Interestingly, three patients received prophylactic prednisone with treatment and none showed evidence of graft rejection. Finally, a prospective, real-world, multi-center, longitudinal study called the cemiplimab-rwlc survivorship and epidemiology study (CASE) published data from an initial cohort of immunosuppressed and/or immunocompromised patients with advanced cSCC [51]. There were 26 patients enrolled in the study that were designated immunocompromised or immunosuppressed either due to a history of prior organ transplant, autoimmune disorder, or hematologic malignancy. Among the 19 that had enrolled prior to their third dose of cemiplimab, the ORR was 47%. Although the published data involves a small cohort, the initial analysis indicates similar benefit to the clinical trials that excluded these patients. Given the very small numbers in these studies it is difficult to make any conclusions, but additional research in this area is needed.

Given the impressive outcomes in advanced cSCC, investigation into integrating checkpoint inhibition into curative treatment in high-risk patients has also begun. One approach has been to use immune checkpoint inhibition in the neoadjuvant setting. The goal of neoadjuvant systemic treatment in cSCC has been studied either to convert unresectable disease to resectable or to improve outcomes in resectable disease. Earlier studies of the neoadjuvant approach included anti-EGFR therapies with or without chemotherapy, which had varied outcomes that were not compelling enough to integrate into standard of care practice [52,53]. More recently, checkpoint inhibition has been investigated in this setting with an investigator-initiated, single institution, pilot phase II trial involving locoregionally advanced, resectable cSCC of the head and neck [47]. A total of 20 patients received two infusions of cemiplimab prior to curative intent surgery, which was planned 21 or more days after the second infusion. While only 30% of patients had an objective response, 75% of patients achieved either a pCR or major pathologic response (defined as ≤10% viable tumor). On a case by case basis, 11 of these patients did not receive the planned adjuvant radiation therapy, and none of these patients had recurred at the time of analysis. Overall, the study showed moderate radiological responses with impressive pathological responses that led to omission of adjuvant radiation in some patients. However, the study was a single arm, small, non-randomized study and thus larger studies are necessary to confirm these findings in order to guide how best to incorporate checkpoint inhibition into treatment of locally advanced cSCC.

Although the outcomes for patients with advanced cSCC have improved with checkpoint inhibition compared to previous systemic therapy, most patients still die from their disease and thus ongoing research into novel therapies is warranted. As we continue to expand our understanding of checkpoint inhibitors in responders, numerous resistance mechanisms have been proposed. Examples of these mechanisms include T-cell exhaustion, co-expression of other inhibitory receptors, upregulation of alternative checkpoints, and higher proportion of inhibitory cells in the tumor microenvironment such as regulatory T-cells [54]. There are a myriad of ongoing clinical trials that are incorporating different strategies in an attempt to improve upon single-agent immunotherapy. Table 2 provides a sample of the active clinical trials and the novel approaches for advanced cSCC. These include trials incorporating combinations of immunotherapy and targeted therapy, combinations of novel immunotherapies, intralesional injections in combination with immunotherapy, and personalized vaccine-based treatment. Additionally, there are studies evaluating the role that radiation may play in enhancing the response to immunotherapy as well as trials of photomunotherapy, a novel drug and device treatment that combines monoclonal antibodies such as cetuximab to a dye that can be photoactivated to induce selective tumor cell death. Lastly, there are trials of a microbiota transplant to patients who have failed immunotherapy from patients who have responded to immunotherapy based on preliminary evidence of this approach in patients with melanoma.

In conclusion, the use of checkpoint inhibition in advanced cSCC has shown significant responses and some prolonged responses. These benefits are seen in both the locally advanced and R/M setting and outcomes are similar in the trials involving cemiplimab and pembrolizumab. Additional research is needed in particularly vulnerable populations, such as immunosuppressed patients, as well as with novel therapeutics for patients who do not respond well to single-agent checkpoint inhibition.
Table 2. Novel clinical trial approaches for patients with advanced cSCC.

| Therapeutic approach | Ongoing trial examples | References |
|----------------------|------------------------|------------|
| **Targeted therapy with checkpoint inhibition** | 1. Avelumab With or Without Cetuximab in Treating Patients With Advanced Skin Squamous Cell Cancer | [55,56] |
| | 2. Study of NKTR 255 in Combination With Cetuximab in Solid Tumors | |
| **Immunotherapy – immunotherapy combinations** | 1. High-Risk Skin Cancers With Atezolizumab Plus NT-17 | [57–59] |
| | 2. A Study of SAR442425 Combined With Cemiplimab for the Treatment of Participants With Various Advanced Skin Cancers | |
| | 3. A Study of SOT101 in Combination With Pembrolizumab to Evaluate the Efficacy and Safety in Patients With Selected Advanced Solid Tumors | |
| **Intralesional injections in combination with checkpoint inhibition** | 1. Talimogene Laherparepvec and Nivolumab in Treating Patients With Refractory Lymphomas or Advanced or Refractory Non-melanoma Skin Cancers | [60–63] |
| | 2. A Clinical Study to Assess the Efficacy and Safety of Alpha DaRT224 for the Treatment of Patients With Recurrent Cutaneous Squamous Cell Carcinoma | |
| | 3. Immunotherapy With IFx-Hu2.0 Vaccine for Advanced Non-melanoma Skin Cancers | |
| | 4. A First-in-Human Study of CDK-002 (exoSTING) in Subjects With Advanced/Metastatic, Recurrent, Injectable Solid Tumors | |
| **Vaccine** | 1. Personalized Neoantigen Peptide-Based Vaccine in Combination With Pembrolizumab for the Treatment of Advanced Solid Tumors, The PNeoVCA Study | [64] |
| **Radiation in combination with checkpoint inhibition** | 1. The UNSCARRRed Study: UNRestable Squamous Cell Carcinoma Treated With Avelumab and Radical Radiotherapy (UNSCARRRed) | [65,66] |
| | 2. Radiotherapy in Combination With Atezolizumab in Locally Advanced Borderline Resectable or Unresectable Cutaneous SCC | |
| **Photoimmunotherapy with checkpoint inhibition** | 1. RM-1995 Photoimmunotherapy, as Monotherapy or Combined With Pembrolizumab | [67,68] |
| | 2. An Open-label Study Using ASP-1929 Photoimmunotherapy in Combination With Anti-PD1 Therapy in EGFR Expressing Advanced Solid Tumors | |
| **Microbiome** | 1. Microbiota Transplant to Cancer Patients Who Have Failed Immunotherapy Using Feces From Clinical Responders (MITRIC) | [69] |

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