Abstract

The incidence of advanced cutaneous squamous cell carcinoma (cSCC) is increasing; of the 1.3 million nonmelanoma skin cancers that arise each year, approximately 20% are cSCC, and between 2-5% of these cases ultimately metastasize. However, there is no established consensus on first-line systemic treatment for those patients who have locally advanced or metastatic disease. Major classes of systemic agents include chemotherapy, epidermal growth factor receptor (EGFR)-targeted therapy, and immunotherapy; each is associated with a distinct set of adverse effects, and availability of data from randomized controlled trials (RCTs) to definitively guide treatment are limited. While several chemotherapeutic agents have been described in case studies or small patient cohorts, only one RCT has been conducted, demonstrating a 34% overall response rate for a cisplatin-based regimen. EGFR-inhibitors evaluated for use in cSCC by RCT include cetuximab, panitumumab, and gefitinib; response rates ranged from 15-31% for these agents. Inhibitors of the immune checkpoint programmed death-1 (PD-1) have yielded promising outcomes in advanced cSCC; indeed, the PD-1 inhibitor pemolimab recently received FDA approval for use in advanced cSCC. Despite these advances, the preferred regimen for systemic treatment of cSCC remains unclear, particularly in immunocompromised populations. Herein we provide a review of the literature supporting the use of these modalities and a discussion of their clinical utility.

Semin Cutan Med Surg 38:E67-E74 © 2019 Frontline Medical Communications

Introduction

Epidemiology of cutaneous squamous cell carcinoma

Nonmelanoma skin cancer is the most common malignancy in the United States. Approximately 1.3 million cases of nonmelanoma skin cancers occur annually, with 80% of these being basal cell carcinoma and the remaining 20% cutaneous squamous cell carcinoma (cSCC). While the precise incidence is unknown because of the lack of reporting of cSCC to national tumor registries, it is widely recognized that the incidence of both localized and invasive cSCC has increased—based on data from the Rochester Epidemiology Project—by 263% over the last 30 years. The absolute number of cSCC patients in the United States who have nodal metastasis is estimated at 5,604 to 12,572, and the absolute number of cSCC-related deaths is estimated at 3,932 to 8,791 annually.

Estimating risk of metastasis

Most patients have an excellent prognosis following surgical removal, with or without concurrent radiation therapy. Mohs micrographic surgery has particularly been shown to reduce risk of local recurrence. However, a subset of cSCC tumors has increased risk for local recurrence or distant metastasis, and 2% to 5% of tumors will ultimately metastasize to regional lymph nodes or more distant sites. While no definitive guidelines exist to determine which patients require staging, several methods have been proposed. Until 2010, no cSCC-specific staging algorithm was available. However, in 2010, the American Joint Committee on Cancer (AJCC) proposed guidelines for staging cSCC that included features such as tumor diameter and depth, degree of differentiation, and tumor location. Finally, in 2013, the Brigham and Women’s Hospital (BWH) staging system was proposed and was subsequently validated in a cohort of 1,818 patients. Similar to the new AJCC guidelines, the BWH system recommends a T staging algorithm based on the presence or absence of risk factors including tumor diameter ≥2 cm, tumor invasion beyond subcutaneous fat, poorly differentiated histology, and perineural tumor invasion.

Findings from an independent 2016 meta-analysis of 36 studies of patients with cSCC yielded similar risk factors, overall supporting both the BWH system as well as the most recent AJCC guidelines. Current National Comprehensive Cancer Network clinical practice guidelines for cSCC further endorse this approach to stratifying high-risk and low-risk tumors.

A 2018 study by Fox et al. showed a statistically significant increase in sentinel lymph node biopsy positivity among BWH stage T1b tumors compared with T1-Ha in cSCC patients without palpable lymphadenopathy, leading to their recommendation that providers perform radiographic staging for all tumors with 2 to 4 cm of the BWH risk factors (stage T1b-III), even in the absence of palpable lymphadenopathy. While further data are necessary to validate this approach, given the overall paucity of decision-making tools that exist to guide management of early-stage cSCC, this study represents useful preliminary guidance towards identifying patients who require additional staging.

Treating invasive cSCC

Despite recent advances in the staging of cSCC and standardization of high-risk features associated with increased metastasis, there is no established consensus on first-line systemic treatment for those patients who have locally advanced disease not adequately managed with resection and/or radiation, or for those who de-
velop distant metastases. While several agents have been shown to have clinical benefit, the optimal approach to treating patients with advanced disease remains unclear. Major classes of treatment modalities include chemotherapy, epidermal growth factor receptor (EGFR)-targeted therapy, and immunotherapy. Herein, we provide a review of the literature supporting the use of these modalities and a discussion of their clinical utility.

**Chemotherapy**

Data regarding the efficacy of chemotherapy in advanced cSCC are limited; the lack of large randomized controlled trials (RCTs) has necessitated extrapolation of chemotherapy regimens used in squamous cell carcinomas (SCCs) from other primary sites. However, a small number of trials have validated the use of certain agents not only as palliative adjuncts but also as tools aimed at achieving long-term remission or cure. Chemotherapeutic agents that have been investigated as mono- or adjunctive therapies primarily include alkylating agents, antimetabolites, anthracyclines, and retinoids. The greatest body of literature exists in support of cisplatin, either alone or in combination with 5-fluorouracil (5-FU), as a therapeutic option in patients who require additional treatment beyond surgery and radiotherapy.

**Alkylating agents**

Cisplatin and carboplatin are alkylating compounds that induce apoptotic death by introducing cross-links into DNA. The subsequent genetic disruption in mitosis and cell division and inhibits major DNA repair pathways. Cisplatin has been shown to have a well-described side effect profile; its principal toxicities include emesis, nephrotoxicity, neurotoxicity, and ototoxicity. Carboplatin is associated with significant myelosuppression but fewer renal and neurologic effects and is generally considered to be better tolerated than cisplatin. However, in certain solid malignancies, including head and neck SCC, cisplatin has been shown to have better efficacy; perhaps for this reason, few reports exist describing the use of carboplatin in cSCC.

The first report of cisplatin-based therapy in cSCC was published in 1989; since then, several additional case series have described outcomes in small cohorts of patients receiving cisplatin combined with 5-FU, doxorubicin, bleomycin, or vindesine (Table). Overall response rate (ORR) observed in these studies varied from 34% to 86%. The largest among them was composed of 28 patients who received cisplatin and doxorubicin alone or as neoadjuvant treatment. The chemotherapy-only group showed an ORR of 66% among the chemotherapy-only group (15 patients, 33% complete response [CR], 33% partial response [PR]). The multimodality group had an initial ORR of 69% following chemotherapy (13 patients, 23% CR, 46% PR); they subsequently had an ORR of 100% following surgery or radiation.

Just one RCT has been performed to assess the utility of a cisplatin-containing regimen in cSCC. The 2002 study assessed the utility of the combination of interferon alpha (IFNα), 13-cis-retinoic acid, and cisplatin in 39 patients with regionally advanced or metastatic cSCC. The overall and complete response rates were 34% and 17%, respectively, with median durations of 9 and 35.4 months, respectively. The response rate was higher in locally advanced (67%) than metastatic (17%) disease (P = .007). Median survival was 14.6 months. One-, 2-, and 5-year survival rate estimates were 58%, 32%, and 21%, respectively.

A single prospective case series investigated the utility of carboplatin or cisplatin as a single systemic agent in combination with radiotherapy for treating locally advanced disease. Twenty-one patients were enrolled in the study. Of the 19 evaluable patients, 10 achieved CR (53%); the remaining 9 had PR (47%) with chemotherapy plus radiation, 2 of whom subsequently achieved CR following salvage surgery.

**Antimetabolites**

5-FU and its produg capecitabine are antimetabolite agents that inhibit RNA and DNA biosynthesis by inducing misincorporation of fluoronucleotides into nucleic acid structures. Efficacies of these agents are thought to be equivalent; however, toxicity profiles vary. In some tumor types, high levels of thymidylate phosphorylase expression result in preferential metabolism of capecitabine to 5-FU, theoretically producing less systemic toxicity. Nevertheless, both can cause prominent gastrointestinal side effects, including nausea, diarrhea, and stomatitis, as well as neutropenia, hand-foot syndrome, and—less commonly—cardiotoxicity. 5-FU and capecitabine have been used to treat advanced cSCC with variable outcomes.

The use of 5-FU monotherapy in advanced cSCC was examined in a prospective study conducted in 2000 by Cartei et al. Therein, outcomes were described for 14 patients treated with oral 5-FU (mammitol-coated 5-FU tablets), with a daily dose of 100 mg/m² for days 1 through 3, 150 mg/m² for days 4 through 7, and 175 mg/m² thereafter. Treatment resulted in PR in 2 patients (14.3%) and stable disease (SD) in 7 (50%), with a median duration of response of 30 months. Of note, no patient in this study was thought to have metastatic disease.

Capecitabine has shown promising results in small studies of locally advanced cSCC. The utility of systemic capecitabine with subcutaneous IFNα was investigated in a 2004 prospective case series of 4 patients with advanced cSCC. Capecitabine 950 mg/m²/d was given on days 1 through 14, and IFNα 3 x 3 million units was given 3 times weekly; ORR was 100% with 2 patients experiencing CR and 2 with PR.

A case series of 10 solid organ transplant recipients treated with capecitabine to reduce cSCC burden was reported in 2013. Low-dose oral capecitabine (0.5-1.5 g/m²) was given to 10 patients for days 1 through 14 of 21-day treatment cycles. The average incidence of SCC was reduced by an average of 68% during the first 12 months of treatment. Seven of 10 participants required dose adjustments, and 2 of these discontinued capecitabine because of common side effects, including fatigue, nausea, hand and foot syndrome, gout, and renal insufficiency. Similar results have been reported in case reports describing the use of oral capecitabine to prevent cSCC recurrence in lung transplant recipients.

**Retinoids**

Retinoids—including acitretin, isotretinoin, and etretinate—inhibit cell proliferation and promote apoptosis through unclear mechanisms. While they are not thought to alter the course of an existing tumor, they may have utility in preventing new cSCC from developing.
arising. They are therefore particularly beneficial in organ transplant recipients requiring chronic immunosuppression, as this is a well-described risk factor for cSCC. Not only does cSCC arise at an increased rate in immunosuppressed individuals, these cancers are more likely to follow aggressive disease courses than cSCC in immunocompetent individuals; rates of metastasis have been reported as high as 8%.\(^3^5,^3^6\)

A retrospective study conducted by Harwood et al. in 2005 demonstrated a significant reduction in cSCC occurrence in organ transplant recipients treated with acitretin over 3 years.\(^3^5\) Additionally, two earlier RCTs have been conducted comparing acitretin to placebo administered over 6 to 12 months for prevention of cSCC in transplant recipients; both noted a significant reduction in number of cSCC lesions that arose in the treatment groups compared with the placebo groups over the surveillance period. However, in both studies, treatment groups experienced significant dose-limiting toxicities (headache, hyperlipidemia, mucocutaneous effects), and in several patients, a “rebound effect” was observed wherein numerous cSCC lesions arose shortly after discontinuing acitretin.\(^3^7,^3^8\)

Unfortunately, similar efficacy has not been demonstrated in treating existing SCC or preventing recurrence in immunocompetent patients. A single phase 3 study has been conducted in the immunocompetent cSCC population; patients receiving 13-cis-retinoic acid and IFN\(\alpha\) reported neither improvement of the recurrence-free interval nor a preventive effect in terms of additional SCCs on the skin.\(^2^9\) Similar findings have been yielded in the immunocompetent head and neck SCC patients; 13-cis-retinoic acid has been shown in RCTs to be ineffective in this population.\(^1^0\)

### Targeted therapy

The epidermal growth factor receptor (EGFR) is the most common molecular target in cSCC treatment. EGFR is a transmembrane...
receptor with tyrosine kinase activity belonging to a family of 4 related proteins: EGFR, HER-2, HER-3, and HER-4. Activation of EGFR results in autophosphorylation and subsequent activation of 2 major intracellular pathways: RAS–rapidly accelerated fibrosarcoma (RAF)-MEK-MAPK, resulting in gene transcription and cell proliferation, and the phosphoinositide 3-kinase (PI3K)-Akt pathway, which results in activation of anti-apoptotic signals. It is important to note that, although overexpression of EGFR in cSCC tumors has been shown to be an independent negative prognostic factor—and may confer radioresistance—there appears to be no correlation between level of EGFR expression and response to anti-EGFR therapy.

Currently available anti-EGFR therapies are monoclonal antibodies that bind to the extracellular or adenosine triphosphate (ATP)-binding domains of EGFR, inhibiting EGFR autophosphorylation and downstream signaling. The major toxicity seen with EGFR inhibitors is a papulopustular ( acneiform) rash that occurs in most (45%-100%) patients receiving EGFR inhibitors. Other common toxicities include gastrointestinal effects (diarrhea, nausea), neurologic effects (fatigue, neuropathy), neutropenia, hypermagnesemia, and infusion reactions.

**Cetuximab**

Cetuximab is a monoclonal antibody that competitively inhibits the extracellular domain of EGFR, preventing ligand binding. Until 2011, only case reports were available to suggest the clinical utility of cetuximab for treating cSCC. In 2011, Maubec et al. reported a phase 2 trial investigating the use of cetuximab in patients with unresectable cSCC. Patients with locally advanced, regional, or metastatic cSCC received an initial dose of intravenous cetuximab 400 mg/m², followed by weekly 1-hour infusions of 250 mg/m². Disease control rate (CR, PR, SD) and ORR (CR, PR) were 69% and 11%, respectively, in the intention-to-treat population at the 6-week study endpoint; the best overall study ORR was 28% (median treatment duration for enrolled patients was 15 weeks). Grade 3 to 4 cetuximab-related adverse events led to discontinuation of cetuximab in 4 patients, but no infusions were postponed, and no dose reduction was required. Of note, high expression of EGFR in SCCs (defined as positive expression of EGFR in >80% of tumor cells by immunohistochemistry [IHC]) was observed in 72% of patients; however, tumor EGFR expression levels were not associated with treatment efficacy, a finding consistent with studies done in the colorectal and head and neck literature.

Subsequent to the Maubec et al. trial, a number of case reports and series have been published reporting positive results with cetuximab in cSCC patients. However, despite the modest benefits described in the trial, no further clinical trials have been performed to complete validation of cetuximab monotherapy as a therapeutic option.

**Panitumumab**

Panitumumab is another monoclonal antibody targeting the extracellular domain of EGFR. Its use has been primarily validated in colorectal cancer, a setting in which it has shown noninferiority to cetuximab. The drug was investigated as a monotherapy for nonresectable cSCC in a 2014 single-arm phase 2 study in which 16 patients received panitumumab 6 mg/kg every 2 weeks for at least 3 cycles and a maximum of 9 cycles. ORR was 31% (2 patients with CR, 3 patients with PR); an additional 37% had SD. Mean progression free survival (PFS) and overall survival (OS) were 8 and 11 months, respectively. Grade 3 to 4 adverse effects occurred in 31% of patients; most of these were cutaneous, and indeed, 1 patient discontinued the drug because of cutaneous toxicity. Later, another case report described the use of panitumumab for palliative treatment of metastatic cSCC in a patient who had anaphylactic response to cetuximab. Panitumumab was selected as alternate therapy in this patient given its lower rate of infusion reactions. The patient received panitumumab 6 mg/kg every 14 days; CR was observed after 15 cycles and persisted for 6 months after drug discontinuation.

**Gefitinib**

While cetuximab and panitumumab act on EGFR extracellular binding site, gefitinib blocks EGFR’s ATP-binding site, rendering it unable to activate by autophosphorylation. In a 2006 phase 2 study evaluating the utility of gefitinib in metastatic recurrent cSCC, Glisson et al. observed a 15% response rate and a 45% disease control rate (DCR) among 20 evaluable patients. Later, similar results were yielded in a 2017 single-arm phase 2 clinical trial conducted by William et al. investigating gefitinib monotherapy in patients with unresectable cSCC. A total of 40 patients were treated with gefitinib 250 mg orally daily until disease progression or intolerable toxicity. ORR was 16%; an additional 35% had SD at 8 weeks of treatment. Among these, median duration of response and PFS were 31.4 months and 3.8 months, respectively. While this suggests only modest activity, the adverse event profile was determined to be favorable; most participants experienced grade 1 to 2 side effects, including rash, fatigue, and diarrhea, and 16% of participants experienced grade 3 side effects.

**Erlotinib**

Erlotinib, like gefitinib, acts on EGFR’s ATP-binding site. In 2007, W. Read reported 3 patients with unresectable cSCC who were treated with erlotinib monotherapy. One patient developed CR and then disease recurrence when erlotinib was discontinued 8 months later; the other 2 patients had partial responses. Another case report in 2011 described a patient with regionally invasive cSCC that recurred after surgery and chemoradiotherapy who had stable disease for 4 months on erlotinib monotherapy prior to disease progression.

**Immunotherapy**

Immune checkpoint inhibitors (ICIs)—including inhibitors of programmed cell death 1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T-lymphocyte antigen 4 (CTLA-4)—function by activating a primarily T-cell-mediated antitumor immune response. Their use has been well described in several solid tumor types, including melanoma and head and neck SCC; however, there have been fewer studies to date investigating their use.
in cSCC. However, there is strong rationale for their application in cSCC. It is thought that chronic UV exposure to skin leads to induction of regulatory T cells and suppression of Langerhans cell activity; indeed, the tumor microenvironment of cSCC is characterized by a reduced number of peritumoral CD8+ T cells and high numbers of regulatory T cells. Other findings that suggest that immunotherapy may be particularly effective in cSCC include the frequency of cSCC in the immunosuppressed population, as well as the responses observed in cutaneous lesions to topical imiquimod, a toll-like receptor 7 activator that functions by increasing pathogen recognition by the immune system.

While only a few case reports exist describing the use of CTLA-4 inhibition in cSCC, PD-1 inhibitors cemiplimab, nivolumab, and pembrolizumab have been used with varying rates of success. Of note, while PD-L1 is expressed in up to 26% of SCC tumors, it is not clear whether the level of PD-L1 expression correlates with response to PD-1 pathway blockade. Common adverse effects seen with use of ICIs include fatigue, rash, diarrhea, musculoskeletal pain, and immune-mediated inflammatory disorders, particularly pneumonitis, hepatitis, and dermatitis.

**Cemiplimab**

Cemiplimab is a high-affinity human monoclonal antibody directed against PD-1 that was approved by the Food and Drug Administration (FDA) in December 2018 for use in metastatic or locally advanced cSCC. FDA approval was based on data yielded by an initial dose-escalation phase 1 clinical trial (NCT02383212) and a phase 2 trial (NCT02760498) assessing clinical response in patients with cSCC. The initial cemiplimab dose-escalation phase 1 study was performed in 2016 in patients with various solid tumors, with preliminarily encouraging responses among cSCC and basal cell carcinoma populations. FDA approval was based on data reported from the phase 1 expansion cohort as well as the phase 2 trial in patients with locally advanced or metastatic cSCC. In the phase 1 component of the study, 26 patients with locally advanced or metastatic cSCC were treated with cemiplimab 3 mg/kg every 2 weeks for up to 48 weeks; among the 26 patients treated, 13 (50%) had PR; an additional 6 (23%) had SD. In the phase 2 study, 59 patients were treated with the same dose for up to 96 weeks. Of these, 24 patients (41%) had PR; an additional 9 (15%) had SD. The rate of adverse events was similar in both arms of the study; fatigue occurred in 27% of patients, and constipation, diarrhea, hypercalcemia, hyperphosphatemia, and nausea all occurred in 15% of patients.

**Nivolumab**

Nivolumab, like cemiplimab, is a monoclonal antibody against PD-1; while it is used extensively in melanoma, only case reports exist to support its use in cSCC. A 2018 case series reported the use of nivolumab in 3 patients with advanced cSCC whose disease had progressed despite chemotherapy. Two of the patients had partial response that lasted at least 12 months; the third patient had stable disease for 3 months at the time of publication. Another case described in a separate 2018 report initially had pseudoprogression of disease following initiation of nivolumab but then developed PR, which was sustained for at least 12 months.

**Pembrolizumab**

While pembrolizumab, another monoclonal antibody targeting PD-1, has been approved by the FDA to treat recurrent metastatic SCC of the head and neck, no clinical trials to investigate its use in cSCC exist. Nevertheless, several case reports have described promising responses in patients with advanced cSCC. Since 2016, a total of 5 cases of patients experiencing either PR or CR to pembrolizumab have been reported.

**Ipilimumab**

Ipilimumab is a monoclonal antibody targeting CTLA-4. It is frequently combined with PD-1 blockade in treating metastatic melanoma, but its utility in cSCC has not been defined. A 2017 report described a patient who was receiving chemotherapy for metastatic cSCC and subsequently developed concurrent metastatic melanoma. Chemotherapy was stopped, and ipilimumab monotherapy was initiated; he subsequently developed CR of both malignancies, which was sustained for at least 8 months. Another report described a renal transplant recipient with metastatic cSCC who was treated with a combination of ipilimumab and nivolumab after disease progression on carboplatin-based chemotherapy and cetuximab; while he ultimately developed CR after 4 cycles, the treatment was complicated by acute rejection of his transplanted kidney, and later sudden cardiac death was thought to be related to renal failure.

**Combination therapy and future directions**

Herein we have reviewed chemotherapeutic, molecularly targeted, and immunotherapeutic agents that have evidence for use in advanced-stage cSCC. While the number of studies describing the use of these agents is increasing, much of this body of literature consists of case reports and small series; there remains a paucity of clinical trials involving large patient cohorts. The preferred regimen for treating invasive or metastatic cSCC has therefore remained unclear, and national practice guidelines continue to recommend reliance on tumor board and expert opinion to guide management on case-by-case bases. However, with the recent FDA approval of cemiplimab, the first FDA-approved treatment for metastatic cSCC, along with the expanding application of ICIs in many solid tumor types, the landscape of cSCC management will likely shift to include immunotherapy as a cornerstone of treatment.

Nevertheless, there remains a limited understanding of the role of other treatment platforms as therapeutic adjuncts to immunotherapy. With the exception of chemotherapy, in which cisplatin is typically combined with either 5-FU or another second agent, most of the trials and case studies described herein report monotherapeutic regimens.

There is a limited body of literature describing multiplatform regimens that combine agents from different therapeutic classes. The best described multiplatform combination regimen is cetuximab combined with chemotherapy; a 2015 study of 25 patients who received cetuximab with cisplatin and 5-FU reported a 65% CR rate, with PFS and OS reported as 8.5 months and 26 months, respectively. In a recent retrospective cohort study of 14 patients who received cetuximab as monotherapy or in combination with carboplatin, mean PFS was significantly improved in patients re-
ceiving combination therapy.92 Fewer reports exist to support the combination of EGFR-targeted therapy with immunotherapy; however, a single, recent case report described CR in advanced cSCC with combined cetuximab and nivolumab.93 These limited but promising reports underscore the need for further investigation into multimodality treatments.

The future of cSCC management must focus not only on elucidation of roles of existing agents but also discovery of additional therapeutic targets. Targeted agents have been limited to EGFR inhibitors thus far. Downstream signaling cascade molecules from EGFR, including RAF and PI3K, might be considered desirable therapeutic targets in cSCC given the success of EGFR inhibition. However, the RAF inhibitor vemurafenib has, in fact, been found to cause cSCC in 15% to 30% of patients who receive it as monotherapy for treatment of metastatic melanoma, a phenomenon blamed on paradoxical MAPK pathway activation.94 A more promising target may be the PI3K/Akt/mechanistic target of rapamycin (mTOR) pathway, which is thought to be activated by UV exposure and the intact function of which is essential for maintenance of epidermal homeostasis.95

Finally, additional efforts will be necessary in defining the optimal treatment of cSCC in the immunocompromised population. While ICIs have been implemented successfully in some cases, concerning reports have arisen describing organ rejection in the setting of immunotherapy. As cemiplimab and other ICIs become the future of cSCC management must focus not only on elucidation of roles of existing agents but also discovery of additional therapeutic targets. Targeted agents have been limited to EGFR inhibitors thus far. Downstream signaling cascade molecules from EGFR, including RAF and PI3K, might be considered desirable therapeutic targets in cSCC given the success of EGFR inhibition. However, the RAF inhibitor vemurafenib has, in fact, been found to cause cSCC in 15% to 30% of patients who receive it as monotherapy for treatment of metastatic melanoma, a phenomenon blamed on paradoxical MAPK pathway activation.94 A more promising target may be the PI3K/Akt/mechanistic target of rapamycin (mTOR) pathway, which is thought to be activated by UV exposure and the intact function of which is essential for maintenance of epidermal homeostasis.95

Finally, additional efforts will be necessary in defining the optimal treatment of cSCC in the immunocompromised population. While ICIs have been implemented successfully in some cases, concerning reports have arisen describing organ rejection in the setting of immunotherapy. As cemiplimab and other ICIs become

References
Systemic therapy for advanced cutaneous squamous cell carcinoma