The Role of Systemic Therapy in Advanced Cutaneous Squamous Cell Carcinoma

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KEYWORDS

- Squamous cell cancer • Skin cancers • Cancer treatment protocols
- Immunotherapy

KEY POINTS

- Systemic therapy for head and neck cutaneous squamous cell carcinoma (HNCSCC) generally is reserved for patients with unresectable or distant metastatic disease.
- The agents used most commonly currently include platinum-based cytotoxic agents, agents targeting the epidermal growth factor receptor (EGFR) pathway, and programmed cell death protein 1 receptor (PD-1) immune checkpoint inhibitors.
- Although clinical trials studying systemic therapy for cutaneous squamous cell carcinoma (CSCC) have been limited, recent studies have led to US Food and Drug Administration approval of the PD-1 inhibitors cemiplimab and pembrolizumab for patients with locally advanced or metastatic disease.
- Recent data suggest that cisplatin-based concurrent chemoradiation does not provide benefit compared with radiation alone in the postoperative setting.
- Current clinical studies are examining PD-1 inhibitors as neoadjuvant and adjuvant therapy.

INTRODUCTION

Systemic therapy largely has been reserved for palliative treatment of cutaneous squamous cell carcinoma (CSCC) that cannot be treated with local therapy, but systemic agents have been employed in the adjuvant setting for very high-risk lesions. Until recently, data to guide the appropriate application have been limited. Efforts to

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develop large-scale clinical trials and the advent of immune checkpoint therapy have changed the landscape of systemic therapy for CSCC. This article defines advanced CSCC, because systemic therapy is reserved mostly for this subset of patients. Commonly used agents and the specific settings for which systemic therapy has either an established or potential benefit are discussed. Included is a review of immunotherapy in CSCC, discussing indications, outcomes, and new applications and clinical trials for advanced CSCC that are under way at the time of this publication.

DEFINITION OF ADVANCED CUTANEOUS SQUAMOUS CELL CARCINOMA

The discussion of systemic therapy in this review is relevant to advanced head and neck CSCC (HNCSCC). It is important to differentiate "high risk" from "advanced." High-risk features include location (ie, all areas of the head and neck are considered either moderate risk or high risk), poor differentiation, perineural invasion, immunosuppressed status of the patient, lymphatic or vascular invasion, and high-risk subtypes (ie, acantholytic, adenosquamous, desmoplastic, or metaplastic).[1] A patient may have high-risk features but not an advanced HNCSCC. Advanced HNCSCC suggests disease that has invaded to an extensive degree locally or has demonstrated regional and/or distant metastatic spread. These lesions carry significantly worse prognosis. A clear definition of advanced HNCSCC is debated, but it can be defined based on lesions that are deemed stage III or stage IV based on the American Joint Committee on Cancer (AJCC) staging guidelines. Physical examination and imaging for a suspected advanced CSCC are necessary to determine clinical stage prior to treatment. Features of stage III and stage IV disease, as defined by AJCC, 8th edition, are summarized in **Table 1**. These staging groups encompass patients with extensive local disease, who have developed lymph node spread, or who have distant metastasis. **Fig. 1** provides examples of patients with locally advanced and regionally and distant metastatic HNCSCC.

SYSTEMIC AGENTS USED TO TREAT ADVANCED CUTANEOUS SQUAMOUS CELL CARCINOMA

Until recently, data supporting a role for systemic therapy for patients with CSCC has been based mostly on small retrospective series and a few early clinical trials. Patients with unresectable or widely metastatic disease often require systemic therapy to mitigate their advanced disease, and thus agents have been chosen based on information extrapolated from other cancer types and/or hypothetical activity based on the biological properties of a given drug and the known biology of CSCC. In 2018, a phase I trial with an expansion phase II cohort of patients with advanced CSCC studying the immune checkpoint inhibitor, cemiplimab, demonstrated promising response rates,[2] which led to the rapid US Food and Drug Administration (FDA) approval of this agent for unresectable/metastatic CSCC. This event has dramatically changed the approach toward systemic treatment of this disease. This article reviews drugs that have been used to treat CSCC, including cytotoxic agents, molecular targeted agents, and immune checkpoint inhibitors.

Cytotoxic Agents

Various cytotoxic drugs have been utilized to treat advanced CSCC, including platinum-based agents, taxanes, vinca alkaloids, bleomycin, 5-fluorouracil (5-FU), methotrexate, doxorubicin, gemcitabine, and ifosfomide.[3] A majority of these agents, however, have been examined only in small series using a variety of regimens; thus, the responses to these agents are varied and not well characterized. Generally, limited

Table 1
Factors associated with advanced cutaneous squamous cell carcinoma

Features of Local Disease	American Joint Committee on Cancer Stage
Greatest tumor dimension ≥4 cm	T3
Minimal erosion of bone	T3
Perineural invasion in nerves >0.1 mm, deeper than dermis	T3
Clinical or radiologic evidence of nerve involvement	T3
Invasion depth >6 mm or deeper than subcutaneous fat	T3
Extensive cortical or medullary bone involvement	T4a
Invasion of the cranial base	T4b
Invasion through cranial foramen	T4b

Features of Metastatic Disease	American Joint Committee on Cancer Stage
Metastasis to an isolated ipsilateral lymph node, ≤3 cm in greatest dimension, ENE(−)	N1
Metastasis to an isolated ipsilateral lymph node, 3–6 cm in greatest dimension, ENE(−)	N2a
Metastasis to multiple ipsilateral lymph nodes, none >6 cm in greatest dimension, ENE(−)	N2b
Metastasis to bilateral or contralateral lymph nodes, none >6 cm in greatest dimension, ENE(−)	N2c
Metastasis to any lymph node, >6 cm in greatest dimension, ENE(−)	N3a
Metastasis to any lymph node, ENE(+)	N3b
Distant metastasis	M1

responses with early recurrence/progression have been typical.[3] Strategies that include platinum, alone or with other agents, have been employed most often. Outcomes reported across multiple small observational studies have been modest, with partial responses or stable disease reported in the 15% to 50% range.[3–6]

Molecular Targeted Agents

The molecular target that has received the most attention in CSCC is the epidermal growth factor receptor (EGFR) and its downstream pathways. EGFR is a transmembrane receptor among the ErbB family of receptors. EGFR is activated by extracellular epidermal growth factor (EGF) ligands, such as EGF and transforming growth factor-α. Activated EGFR triggers several tyrosine kinase cascades, including the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated (ERK) pathway, and phosphoinositide 3-kinase (PI3K) pathways.[7] EGFR has been shown to be overexpressed in CSCC, and an association with aggressive features has been reported.[8] EGFR inhibitors, including antibodies that block the EGFR receptor, and small molecules that block EGFR tyrosine kinase activity, have been employed and studied in small trials studying CSCC.[9–21] Cetuximab, a monoclonal antibody to EGFR, showed

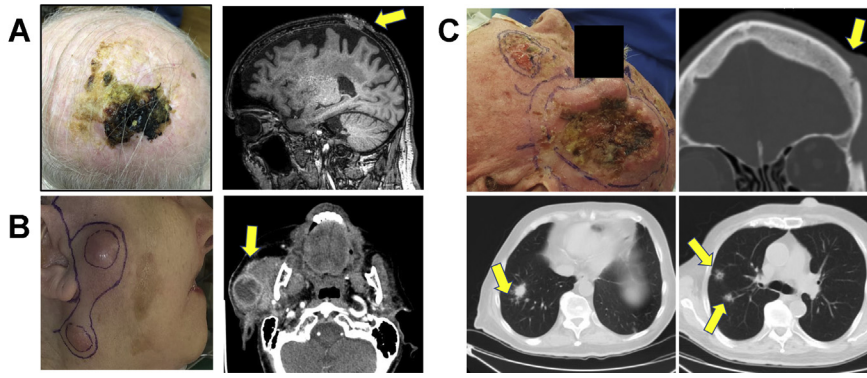

Fig. 1. Examples of patients with advanced CSCC. (*A*) Patient with advanced scalp squamous cancer, with evidence of bone invasion through the calvarium on T1 contrast MR imaging (*arrow*). (*B*) Patient with advanced regional metastasis to the parotid gland (*arrow*), on CT imaging with contrast, and upper neck lymph nodes. This patient presented with facial nerve paralysis consistent with clinical perineural invasion. (*C*) Patient with a left temple squamous cancer recurrent after surgery and radiation. Left temple exhibited minor bone invasion (*right upper panel* [*arrow*]). He developed pulmonary metastases in the right lung, noted as spiculated lesions on CT imaging (*lower panels* [*arrows*]).

substantial activity as a single agent in CSCC, with a disease control rate of 69% and response rate of 28%. Another monoclonal antibody to EGFR, panitumumab, has shown a similar response rate.[10] Cetuximab also has been implemented concurrently with radiation (RT),[15] with platinum therapy,[17] and more recently in active trials in combination with immune checkpoint inhibitors.[22] Small molecule EGFR tyrosine kinase inhibitors, such as erlotinib and gefitinib, as well as a multikinase inhibitor that includes EGFR, lapatinib, also have been evaluated—results resemble those of anti-EGFR antibodies.[11–14,19,21]

Agents targeting signaling molecules downstream of EGFR also are under active investigation. Cobimetinib is a small molecule inhibitor of MEK, a downstream MAPK/ERK signaling molecule that is being actively studied in CSCC.[22] mTOR inhibitors are an area of interest for patients with CSCC—because many of these lesions arise among patients who require immunosuppression for organ transplant survival, the concurrent antineoplastic properties of mTOR inhibitors, perhaps coupled with other PI3K inhibitors, are an area of active study.[23,24] Overall, targeting EGFR and downstream pathways carries substantial promise in CSCC; however, more robust clinical trials are necessary to establish definitive benefit in the appropriate settings.

Immune Checkpoint Inhibitors—Programmed Cell Death Protein 1 Receptor Pathway Blockade

Immune checkpoint inhibitors are drugs that block molecules that typically repress the immune response. There is strong rationale for these agents in CSCC. CSCCs are common among immunosuppressed individuals, and this disease has been shown to carry a high mutation burden[25]—a biomarker for response to immune checkpoint inhibitors in several different cancer types.[26] A key immune checkpoint is the programmed cell death protein 1 receptor (PD-1), which is expressed on cytotoxic T-lymphocytes and activated by its ligands, programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2). PD-1 activation leads to T-cell apoptosis and

repression of the immune response. Tumor cells can up-regulate these ligands, typically PD-L1, to evade immune surveillance. Recently, several drugs have been developed that target this pathway. As discussed previously, cemiplimab, a monoclonal antibody that targets PD-1, demonstrated a 47% response rate among patients with locally advanced or metastatic CSCC, with a large proportion of these patients exhibiting benefit for over 6 months.[2] These results led to FDA approval of this agent for patients with unresectable/metastatic CSCC. More recently, pembrolizumab, another anti–PD-1 antibody, demonstrated a 34% objective response rate, a 52% disease control rate, and a median progression-free survival of 6.9 months among 105 patients with recurrent or metastatic advanced CSCC,[27] also leading to FDA approval. The PD-1 inhibitor, nivolumab, and the PD-L1 inhibitor atezolizumab, also are under active investigation for patients with CSCC.[22] These agents are showing substantial promise, especially for patients with HNCSCC, where locoregionally advanced disease often poses significant challenges among patients with multiply recurrent disease, second primary disease burden, and advanced age. Immune checkpoint inhibitors are being studied further in new combination approaches as well as in the neoadjuvant and adjuvant settings.[22]

INDICATIONS AND APPLICATIONS FOR SYSTEMIC THERAPY FOR ADVANCED CUTANEOUS SQUAMOUS CELL CARCINOMA

Curative treatment of HNCSCC relies on surgical resection and/or radiation therapy (RT) to ablate existing locoregional disease. The primary role of systemic therapy in HNCSCC is for palliative treatment of patients with incurable locoregional or distant disease.[1,28] Systemic therapy also has been considered in both the adjuvant and neoadjuvant settings; however, a definitive role in these settings has not yet been established. Available guidelines for the application of systemic therapy in HNCSCC and commonly used systemic agents and their utility in HNCSCC are reviewed in the following sections.

National Comprehensive Cancer Network Guidelines

The National Comprehensive Cancer Network (NCCN) has published clinical guidelines commonly used to assist with decision making in the care of cancer patients. In operable patients with HNCSCC, the guidelines hold few definitive recommendations regarding the use of systemic therapy.[1,28] If systemic therapy is being considered, multidisciplinary team discussion is recommended, ideally in the setting of a tumor board. The guidelines also suggest consideration of concurrent chemotherapy if nodal disease is excised incompletely or if there is residual disease where further surgery is not feasible. Systemic therapy is not recommended for local disease amenable to surgery or in cases of fully resected regional disease. The NCCN guidelines do suggest consideration of concurrent chemoradiation therapy (CCRT) within the context of a clinical trial if extracapsular nodal extension (ENE) is identified on pathology after neck dissection.[1] This recommendation is under scrutiny, however, due to recent data. The recently published multi-institutional randomized phase III Trans-Tasman Radiation Oncology Group (TROG) 05.01 Trial compared RT versus carboplatin in addition to RT in the adjuvant setting for high-risk CSCC, and there was no significant improvement observed in the carboplatin/RT arm.[29] Thus, the benefit of adding chemotherapy in this setting has not been established (discussed in more detail later).

For inoperable patients, systemic therapy alone can be used if curative treatment is not feasible. For concurrent use with RT, cisplatin, cisplatin plus 5-FU, EGFR inhibitors, or carboplatin is suggested. If concurrent curative RT is not feasible, the guidelines

suggest the PD-1 inhibitor cemiplimab as the preferred option. If immunotherapy is not possible, platinum-based regimens or EGF receptor (EGFR) inhibitors are suggested. The guidelines also recommend clinical trial enrollment in this setting. When cemiplimab is being considered, other anti–PD-1 inhibitors could be effective in this setting based on the recently reported clinical experiences and preliminary data from ongoing trials. In cases of regional recurrence or distant metastatic disease, the preference of NCCN is cemiplimab.[1] Clinical trial platinum-based regimens or EGFR inhibitors are alternatives.

LOCALLY ADVANCED UNRESECTABLE DISEASE AND METASTATIC DISEASE

Regimens that have been examined and have shown some success in the unresectable and recurrent/metastatic setting include platinum-based chemotherapy, targeted agents, and immunotherapy.

The response rate with platinum-based regimens is reasonably high in CSCC.[5,6,30,31] In a small cohort of unresectable patients, combined treatment with cisplatin plus 5-FU plus bleomycin resulted in 31% complete response (CR) rate, and a 54% partial response rate. Most patients went on to definitive treatment.[6] The experience of systemic therapies at Roswell Park Comprehensive Cancer Center was published in 2016. They found that platinum-based regimens were superior to taxanes and EGFR therapies.[32] Dereure and colleagues[9] studied carboplatin in combination with cetuximab with disappointing results, including a 21% response rate, with no CRs, and a 2.6-month survival rate. In a prospective phase II study, concurrent radiation and platinum-based therapy was administered to locally or regionally advanced unresectable CSCC patients.[33] Of 19 patients, an impressive 10 (53%) achieved a CR with 2 others salvaged by surgery. The overall CR was 63%.[33] These regimens tend to be toxic, especially compared with potential targeted agents and immune checkpoint inhibitors as alternatives. Toxicity is important, particularly for a majority of patients who suffer from advanced CSCC, who often are elderly and/or immunosuppressed persons.[6] Responses to platinum agents tend to not be highly durable.[20,32]

EGFR targeted antibodies and tyrosine kinase inhibitors have been examined in recurrent/metastatic CSCC based on the principle that many tumors overexpress EGFR.[34] Erlotinib[11] and gefitinib[21] both have been studied in phase II trials in this context. The response rate to gefitinib was impressive, at 45%, when administered before definitive treatment in locally advanced patients.[21] CR was seen in 18%. Patients with unresectable/incurable disease, however, had a much lower response rate (11%).[21] Erlotinib, a similar agent, was studied in locally advanced unresectable or metastatic patients, and the results were disappointing.[11] Of the 29 patients who completed the treatment course, only 3 patients (10%) had a confirmed partial response. The remainder exhibited stable disease or progressed. Median progression-free survival was 4.7 months. Patients with chronic lymphocytic leukemia were excluded from the study.[11] Panitumumab, the humanized EGFR monoclonal antibody, also was studied as a single agent in incurable CSCC.[10] In 16 patients, the overall response rate was 31%, with 2 CRs.[10] Cetuximab similarly has been studied as first-line therapy in this population. In a phase II trial, the combined complete and partial response rate was 28%.[16] For unresectable locally advanced HNCSCC, concurrent RT with cetuximab or platinum-based regimens has been compared retrospectively adjuvant and definitive settings.[15,35] An analysis of 12 patients treated with concurrent cetuximab and radiation demonstrated CR of 36% and partial response of 27%, but toxicities were high.[35] In a comparative study, the clinical outcomes between the 2 regimens were improved slightly with cetuximab versus platinum regimens, but

the flawed methodology of this study inhibits the ability draw any definitive conclusions.[15]

Immune checkpoint inhibitors have been studied in advanced unresectable locoregional disease and recurrent/metastatic CSCC, and cemiplimab and pembrolizumab (both PD-1 inhibitors), have been approved by the FDA for this indication. Cemiplimab is well tolerated and effective. A phase I/II study by Migden and colleagues[2] reported an objective response rate of approximately 50% of patients with locally advanced unresectable or metastatic CSCC. These responses generally were durable, with a duration of response exceeding 6 months in 57% of patients. Toxicities occurred in the minority of patients and were consistent with those typical of checkpoint inhibitors.[2] In another phase II trial, cemiplimab also showed excellent results among 78 patients with locally advanced disease deemed unresectable and ineligible for radiation, with a CR rate of 13% and partial response rate of 31%.[36] In the KEYNOTE-629 trial published in 2020, investigators administered single-agent pembrolizumab to 105 patients with recurrent or metastatic disease not amenable to surgery or radiation. The response rate was 34.4% with a median progression-free survival of 6.9 months. The 6-month progression-free survival rate was 50.4%. There were grades 3 to 5 toxicities in 5.7% of patients, including 1 death, but generally side effects were mild. They also reported response regardless of PD-L1 combined positive score.[27] Based on this study, the FDA approved pembrolizumab for the treatment-recurrent/metastatic CSCC. Patients with chronic lymphocytic leukemia or immunosuppressed states, including solid organ transplant patients, usually are excluded from immunotherapy trials. The transplant rejection rate is unacceptably high with immunotherapy, reportedly 52% for nivolumab, 27% for pembrolizumab, and 25% for ipilimumab.[37] Studies are emerging to examine markers that will identify which patients would respond to particular immune checkpoint therapies.

In summary, systemic therapy for CSCC has relied on cytotoxic agents, such as cisplatin and EGFR targeted therapy, based on limited reports. More recently, PD-1 checkpoint inhibitors have emerged as the preferred systemic treatment modality. **Fig. 2** provides examples of patients with both advanced local and metastatic disease who have responded exquisitely to PD-1 immune checkpoint inhibition.

Adjuvant Chemotherapy and Chemoradiation

As discussed previously, the seminal study guiding current decision making in the postoperative setting for advanced CSCC is the randomized phase III TROG 05.01 Trial, published in 2018.[29] Prior to this trial, rationale for adjuvant cytotoxic platinum-based chemoradiation regimens for patients with high-risk disease (ie, with positive surgical margins and/or ENE of lymph node disease) was extrapolated from studies that established benefit from concurrent cisplatin with radiation among high-risk head and neck aerodigestive squamous cell carcinoma patients.[38,39] In the TROG 05.01 Trial, carboplatin was the agent of choice for the concurrent chemoradiation therapy (CCRT) treatment arm. This was compared with adjuvant radiation (RT) alone. For both study arms, the rate of freedom from local relapse (FFLR) at 5-years was 83% in the RT arm and 87% in the CCRT arm, which were not significantly different. There also was no significant difference in overall survival. Locoregional failure rate was 7% in both arms. They included an analysis among patients with ENE, which was present in approximately equal proportions in each arm and found no significant difference in FFLR between arms among this subcohort.[29] Other studies have confirmed that there is no survival advantage for radiation alone versus chemoradiation in the postoperative setting for patients with regionally metastatic HNCSCC.[40,41] Tanvetyanon and colleagues[42] reported a decreased risk of recurrence or death with

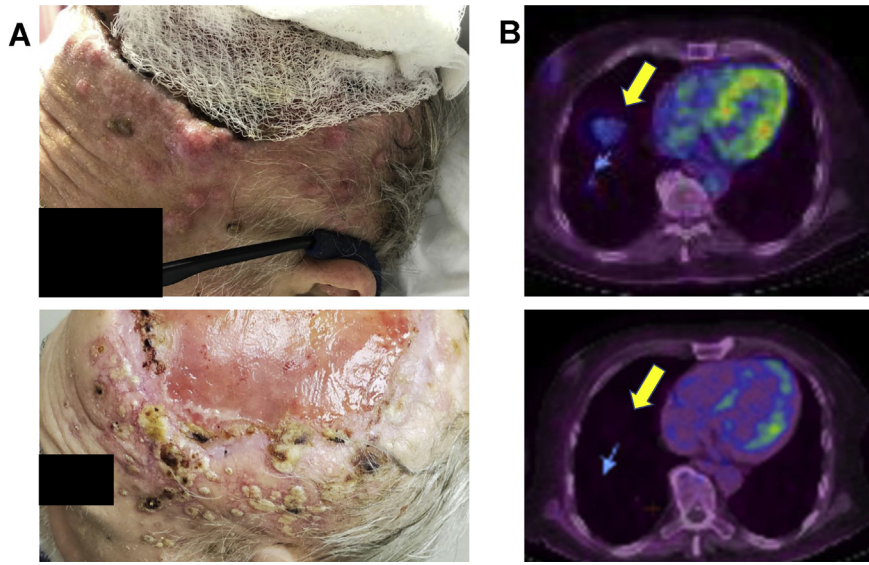

Fig. 2. Examples of patients with advanced CSCC who have responded to PD-1 inhibitor treatment. (*A*) Patient who developed extensive dermal metastases that rapidly developed 6 weeks after wide resection of a large, advanced scalp squamous cancer (*arrows*). The patient reduced his immunosuppressive medication for a renal transplant allograft and was given 2 cycles of cemiplimab, with an outstanding response (*lower panel*). (*B*). Example PET–computed tomography imaging from a patient with advanced scalp CSCC who developed pulmonary metastases (*upper panel* [*arrow*]). Durable CR after 1 year of ongoing cempilimab treatment (*lower panel* [*arrow*]).

CRT rather than RT alone in a retrospective study, but they did not find a difference in overall survival. ENE certainly is a poor prognosticator in CSCC.[40,43] Unlike mucosal squamous cell carcinoma, however, it is not clear that there is a benefit from adding chemotherapy for positive margins or ENE.[29,41]

Data regarding postoperative adjuvant therapy with other agents are limited. At least 1 small retrospective study has compared postoperative cetuximab with radiation to concurrent cisplatin and radiation,[15] with both exhibiting similar outcomes. Currently, immune checkpoint inhibitors are being evaluated as adjuvant agents combined with radiation in the postoperative setting. At the time this article was written, there is 1 active trial examining cemiplimab in this setting (NCT03969004), a second trial examining cemiplimab both before and after surgery (NCT04428671), and a trial examining concurrent pembrolizumab and radiation in the postoperative setting (NCT03833167).

For patients who are unresectable and receiving radiation as primary treatment, data supporting concurrent systemic therapy are limited to small case series and retrospective reports. Platinum-based agents commonly are used, but the most effective agents, which include the agents discussed in this review, are not known. In most cases, primary CRT is considered for patients with very advanced local disease (unresectable) or for patients with extensive comorbidities who would not tolerate surgery. It is likely that immune checkpoint therapy will play a major role in these settings, either as a single agent or perhaps given concurrently with radiation.

Table 2
Summary of key completed systemic therapy trials for patients with cutaneous squamous cell carcinoma

Trial, Year	Study Design	N	Outcome
Maubec et al,[16] 2011	Phase II, single arm, cetuximab, unresectable	36	DCR 69% at 6 wk; overall RR 28%; CR 6%
TROG 05.01,[29] 2018	Postoperative CCRT (carboplatin) vs RT	157 (RT) vs 153 (CRT)	FFLRR 83% (RT) vs 87% (CRT) at 5 y. DM 7% both arms
Migden et al,[2] 2018	Phase I/II, cemiplimab, locally advanced/metastatic	26 (phase I) 59 (phase II)	RR 47%–50%; duration of response >6 mo in 57%
KEYNOTE-629,[27] 2020	Phase II, pembrolizumab, recurrent/metastatic	105	DCR 52%; objective RR 34%

Abbreviations: DCR, disease control rate; DM, distant metastasis; RR, response rate.

Neoadjuvant and Induction Systemic Therapy

Limited studies exist evaluating neoadjuvant or induction systemic therapy prior to definitive treatment of advanced CSCC. Neoadjuvant cetuximab alone or cetuximab plus platinum plus 5-FU was examined in a trial of 34 patients who were mostly elderly; 92% of patients who initially had unresectable tumors became operable, and a pathologic CR was identified in 65% of those patients. The 2 patients who did not proceed to surgery still did well and were alive at greater than 21 months of follow-up.[17] Immune checkpoint inhibitors currently are the agents of choice for emerging neoadjuvant treatment strategies, with several planned or recently opened trials.[22] Several clinical trials are under way to examine this promising strategy. The preliminary results of a phase II trial of neoadjuvant cemiplimab in advanced HNCSCC (NCT03565783) were presented at the American Society of Clinical Oncology annual

Table 3
List of several[a] current clinical trials examining programmed cell death protein 1 receptor inhibitor therapy for new indications for patients with cutaneous squamous cell carcinoma

Agent	Setting	National Clinical Trial (NCT) Number
Cemiplimab	Recurrent stage III or IV, prior to surgery	NCT03565783
	Recurrent, intralesional injection prior to surgery	NCT03889912
	Adjuvant, after surgery and radiation	NCT03969004
	Stages II–IV, neoadjuvant	NCT04154943
Pembrolizumab	High-risk locally advanced, adjuvant after surgery and RT	NCT03833167
	With postoperative RT	NCT03057613
	Combination with cetuximab	NCT03082534
Nivolumab	Metastatic in immunosuppressed patients, alone or with ipilimumab	NCT 03816332

Each agent also is being studied in the unresectable/metastatic setting, and in combination strategies with novel agents.

Please visit ClinicalTrials.gov to find a comprehensive and updated list of clinical trials active for CSCC.

[a] Note this list is not a comprehensive list of all active trials studying immune checkpoint inhibitors.

meeting in 2019.[44] Of 20 patients included, there were no surgical delays. Overall response was 30% and a pathologic CR was observed in 55%. Despite planned post-operative radiation, 55% did not received this. No recurrences were observed at the median follow-up of 3.8 months.[44] There otherwise are few data regarding induction and neoadjuvant therapy with chemotherapy or targeted agents in CSCC.

SUMMARY

The role of systemic therapy for advanced CSCC traditionally has been understudied and limited. Cisplatin-based regimens and agents targeting the EGFR pathway have been utilized most. Recent advances are helping to clarify precise applications for systemic regimens and are leading to strategies using new agents. Specifically, adjuvant cisplatin-based CRT for advanced resectable CSCC has been called into question based on the results of the TROG 05.01 Trial,[29] and the PD-1 inhibitors cemiplimab and pembrolizumab now are FDA approved for the treatment of unresectable/metastatic CSCC. A selection of key clinical trials that help guide current application of systemic agents is presented in **Table 2**. New trials likely will lead to more wide indications for immune checkpoint inhibitors and molecularly targeted agents. **Table 3** highlights several active clinical trials studying new applications of immune checkpoint inhibitors in CSCC.

CLINICS CARE POINTS

- Advanced HNCSCC should undergo careful pathologic and imaging review by a multidisciplinary team that specializes in this disease in order to determine the appropriate role for systemic therapy.
- Because many patients with advanced and recurrent HNCSCC are elderly and/or immunocompromised, cases where systemic therapy may be considered often are challenging. This emphasizes the need for multidisciplinary decision making based on the best available data in a field that is progressing rapidly.
- Based on recent level I evidence (TROG 05.01), adjuvant platinum-based chemoradiation in the postoperative setting is not superior to radiation alone for patients with advanced resectable HNCSCC.
- PD-1 inhibitors now play an important role in the management of patients with unresectable and/or metastatic HNCSCC.

DISCLOSURE

Dr C.P. McMullen and Dr T.J. Ow have no commercial or financial conflicts of interest to disclose related to this article.

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