



Immunotherapy for Non-melanoma Skin Cancer

Sophia Z. Shalhout¹ · Kevin S. Emerick⁴ · Howard L. Kaufman³ · David M. Miller^{1,2}

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Abstract

Purpose of Review The therapeutic landscape for non-melanoma skin cancer (NMSC) has recently expanded with the development of effective and targeted immunotherapy. Here, we provide an overview of the role of immunotherapy in the management of advanced cutaneous carcinomas.

Recent Findings Several agents were recently U.S. Food and Drug Administration (FDA)-approved for the treatment of locally advanced and metastatic cutaneous squamous cell carcinoma, Merkel cell carcinoma, and basal cell carcinoma. However, recent approvals in tissue-agnostic indications may also benefit other NMSCs including cutaneous adnexal solid tumors with high tumor mutation burdens or microsatellite instability. Furthermore, while FDA-approved indications will likely continue to expand, continued studies are needed to support the role of immunotherapy in the neoadjuvant, adjuvant, and refractory settings.

Summary Immunotherapy is emerging as the standard of care for several advanced NMSCs not amenable to surgery and radiation. Ongoing evaluation of the clinical trial landscape is needed to optimize enrollment and ensure continued innovation.

Keywords Immunotherapy · Basal cell carcinoma · Merkel cell carcinoma · Cutaneous squamous cell carcinoma · NMSC · FDA · Cutaneous adnexal carcinomas · Immune checkpoint blockade · Anti-PD-L1 · Anti-CTLA-4 · Anti-PD-1 · Non-melanoma skin cancer · Clinical trials · Immune checkpoint inhibitors · MCC · BCC · CSCC · Avelumab · Cemiplimab · Pembrolizumab · Nivolumab · Ipilimumab · Adjuvant trials · Neoadjuvant trials · Real-world evidence · Regulatory approvals · Accelerated approvals · Hedgehog inhibitors

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✉ David M. Miller
dmiller4@mgh.harvard.edu

Sophia Z. Shalhout
sshalhout@mgh.harvard.edu

Kevin S. Emerick
kevin_emerick@mei.harvard.edu

Howard L. Kaufman
hlkaufman@mgh.harvard.edu

¹ Department of Medicine, Division of Hematology/Oncology, Massachusetts General Hospital, Harvard Medical School, Bartlett Hall, Room 132, 15 Parkman St, Boston, MA 02114, USA

² Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, Bartlett Hall, Room 132, 15 Parkman St, Boston, MA 02114, USA

³ Department of Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

⁴ Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA, USA

Abbreviations

AE	Adverse events
BLA	Biologic license application
BCC	Basal cell carcinoma
CACs	Cutaneous adnexal carcinomas
CSCC	Cutaneous squamous cell carcinoma
CTLA-4	Cytotoxic T-lymphocyte-associated antigen 4
ECOG PS	Eastern Cooperative Oncology Group Performance Status
FDA	USA Food and Drug Administration
H&N	Head and neck
HHI	Hedgehog inhibitor
HIV	Human immunodeficiency virus
ICI	Immune checkpoint inhibitor
irAE	Immune-related adverse event
MCC	Merkel cell carcinoma
MCPyV	Merkel cell polyomavirus
MMR	Mismatch repair
MSI	Microsatellite instability
NDA	New drug application
NMSC	Non-melanoma skin cancer

pCR	Pathological complete response
PFS	Progression-free survival
PD-L1	Programmed death-ligand 1
PD-1	Programmed cell death 1 protein
RWE	Real world evidence
SOTRs	Solid organ transplant recipients
TMB	Tumor mutation burden

Introduction

Non-melanoma skin cancers (NMSCs) are exceedingly common, accounting for 30% of all cancer diagnoses. With an aging population that reflects high levels of cumulative ultraviolet exposure and immunosenescence, the incidence of NMSCs continues to rise [1]. NMSC comprises a heterogeneous group of malignancies including basal cell carcinoma (BCC), cutaneous squamous cell carcinoma (CSCC), Merkel cell carcinoma (MCC), and cutaneous adnexal tumors. Overall mortality is proportionally low, despite high incidence; however, the absolute number of deaths is comparable to melanoma [1]. BCC and CSCC rarely present as locally advanced or metastatic, as the majority present as localized tumors and are treated with curative surgery or radiotherapy. Furthermore, while MCC is one of the most aggressive NMSCs, with nodal and/or distant metastasis detected at presentation in one third of patients, it is a rare cancer [2].

In unresectable locally advanced or metastatic NMSC, systemic therapy may be indicated. Within the last decade, clinical benefit with immune checkpoint inhibitors (ICI) have supported U.S. Food and Drug Administration (FDA) approvals for advanced MCC, CSCC, and most recently, BCC. The aim of this review is to provide an update on the regulatory approvals for immunotherapy in the treatment of advanced NMSC with a focus on cutaneous carcinomas, including MCC, BCC, and CSCC as well as uncommon skin adnexal tumors such as sebaceous carcinoma and porocarcinoma. We also examine ongoing trials and real-world evidence investigating the role of ICIs in the adjuvant, neo-adjuvant, and refractory settings of advanced NMSCs and discuss challenges and prospects in the field. Other NMSCs such as cutaneous lymphoma, angiosarcoma, and Kaposi's sarcoma are beyond the scope of this review.

FDA-approved Front-line Immunotherapy in NMSCs

Cutaneous Squamous Cell Carcinoma

CSCC is the second most common skin cancer following BCC and maintains tumor features predictive of response to ICI therapy, including high tumor mutational burden

(TMB) and over representation among immunosuppressed patients [3]. With high mortality rates in patients with metastatic disease, the therapeutic potential of ICI in advanced CSCC gained early considerable interest. Initial reports of clinical benefit and response were described in limited case series and case reports [4, 5]. Following results of the EMPOWER CSCC-1 phase II (NCT02760498) and phase I (NCT02383212) pivotal trials, the FDA granted regular approval for the anti-PD-1 agent, cemiplimab, in September of 2018 for the treatment of locally advanced or metastatic CSCC in patients deemed ineligible for curative surgery or curative radiation (Table 1) <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&AppNo=761097>. Solid organ transplant recipients (SOTRs), patients who previously received ICI, those requiring immunosuppressants for autoimmune conditions, hepatitis/HIV infected, and patients with an ECOG PS ≥ 2 were excluded from enrollment. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&AppNo=761097>, [6••] An objective response rate (ORR) of ~50% was achieved with 7% of the phase II cohort achieving a complete response (CR). Cemiplimab was well tolerated with treatment cessation reported in only 7% and an adverse events (AEs) profile similar to other anti-PD-1 agents. [6••] Recent updates from the EMPOWER-CSCC-1 and NCT02383212 trials reveal continued durable response and favorable safety profiles [7, 8].

In June of 2020, the FDA approved pembrolizumab, an anti-PD-1 agent, for the treatment of patients with recurrent or metastatic CSCC not amenable to curative surgery or radiation, based on the results of the KEYNOTE-629 (NCT03284424) pivotal trial (Table 1) <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&AppNo=125514>, [9•]. An ORR of 34.3% (95% CI, 25.3–44.2%) was reported with 4% of the cohort achieving CR and a disease control rate of 52.4% (95% CI, 42.4–62.2%). [9•] Eighty-seven percent of the KEYNOTE-629 cohort received one or more previous lines of therapy. In keeping with clinical benefit observed in KEYNOTE-629, initial results from the CARSKIN (NCT02883556) trial where pembrolizumab is being evaluated as first-line monotherapy (e.g., chemotherapy-naïve) demonstrate an ORR of 41% (95% CI, 26–58%) (Table 2) [10].

Retrospective studies of real-world assessment of response to immunotherapy, including pembrolizumab, cemiplimab, and nivolumab, offer insight into the patient population deemed trial ineligible, including solid organ transplant recipients (SOTRs) and patients with autoimmune conditions. ORR (31.5% to 58.7%) in the real-world setting appear comparable to trial results, independent of type and line of immunotherapy, and patient immunosuppression status [11–13]. However, a higher ECOG PS at baseline was

Table 1 FDA-approved agents for NMSCs and tissue-agnostic approvals

Skin cancer, indication	Therapeutic	Mechanism	Subjects enrolled	Approval date	BLA/NDA
BCC					
Superficial BCC	Fluorouracil	Anti-metabolite	54	1975–06-30	NDA016831
Superficial BCC	Imiquimod	TLR agonist	364	2004–07-14	NDA020723
Locally advanced/metastatic BCC	Vismodegib	Hedgehog inhibitor	96	2012–01-30	NDA203388
Locally advanced BCC	Sonidegib phosphate	Smoothed inhibitor	194	2015–07-24	NDA205266
Locally advanced/metastatic BCC, refractory setting	Cemiplimab-RWLC	PD-1 targeted antibody	112	2021–02-09	BLA761097
cSCC					
Locally advanced/metastatic cSCC	Cemiplimab-RWLC	PD-1 targeted antibody	108	2018–09-28	BLA761097
Recurrent/metastatic cSCC	Pembrolizumab	PD-1 targeted antibody	105	2020–06-24	BLA125514
MCC					
Metastatic MCC	Avelumab	PD-L targeted anti-body	88	2017–03-23	BLA761049
Locally advanced/metastatic MCC	Pembrolizumab	PD-1 targeted antibody	50	2018–12-19	BLA125514
Tissue agnostic					
Unresectable/metastatic solid tumors—MSI high or MMR-deficient	Pembrolizumab	PD-1 targeted antibody	149	2017–05-23	BLA125514
Solid tumors—TMB High	Pembrolizumab	PD-1 targeted antibody	102	2020–06-16	BLA125514

found as a likely predictor of progression on immunotherapy and risk–benefit assessment is warranted for considerations of potential organ transplant loss (Table 2, **See Potential Contraindications to Immunotherapy**) [11].

Although they do not carry a labeled indication for NMSC, other ICIs may have efficacy and clinical benefit in patients with advanced CSCC as described in limited case series and case reports. Nivolumab, a monoclonal anti-PD-1 agent, was assessed in seven patients where a progression-free survival (PFS) of 6–19.5 months was observed. A PR was noted in 5 patients treated with nivolumab and a CR was noted in a patient with poorly differentiated advanced CSCC treated with nivolumab and cetuximab [5, 14, 15]. Furthermore, several active clinical trials are assessing the response of nivolumab in the treatment of locally advanced and metastatic CSCC (Table 2, NCT04204837, NCT03834233). A few case reports suggest activity in CSCC treated with ipilimumab, the first-in-class CTLA-4 inhibitor, approved by the FDA for metastatic melanoma in 2011. One patient with metastatic CSCC refractory to chemotherapy experienced a CR after 4 cycles of ipilimumab [16].

Merkel Cell Carcinoma

MCC is an aggressive neuroendocrine skin cancer, representing less than 1% of NMSCs. MCC is associated with ultraviolet radiation exposure, advanced age, immunosuppression, and the Merkel cell polyomavirus (MCPyV). Before the era of immunotherapy, advanced MCC was treated with chemotherapy. While the majority of patients

show initial response to chemotherapy, the efficacy is short-lived (approximately 3 months), and there is no evidence of overall survival benefit [17]. Consequently, immunotherapy has emerged as the standard of care in first-line systemic therapy for advanced MCC.

Avelumab, an anti-PD-L1 agent, received accelerated FDA approval for the treatment of metastatic MCC in March of 2017. Part A of the JAVELIN (NCT02155647) Merkel 200 trial, an open-label, single-arm trial of patients with chemotherapy-refractory metastatic MCC (Table 1) reported an ORR of 33% (23.3–43.8%) with 11.4% of the subjects achieving a CR <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=761049>, [18]. Grade 3–4 AEs were reported in 10.1% [19]. Interim analysis of part B of the JAVELIN Merkel 200 trial reported an ORR of 62.1% (95% CI, 42.3–79.3%) in metastatic MCC patients treated with avelumab as first-line treatment [20]. Pembrolizumab also received an accelerated approval by the FDA in December of 2018 for the first-line treatment of recurrent locally advanced or metastatic MCC on the basis of KEYNOTE-017 (NCT02267603), a non-randomized, multi-center, open-label pivotal trial (Table 1) <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=125514>. The ORR was 56% (95% CI 41–70) and 24% (95% CI 13–38) of patients experienced a CR [21]. Furthermore, long-term observation studies of the expanded KEYNOTE-017 trial report continued durable disease control, a favorable OS and a manageable safety profile with pembrolizumab [22]. While currently

not regulatory approved, the efficacy of nivolumab in advanced MCC has been assessed in the phase I/II Check-Mate 358 (NCT02488759) trial and an ORR of 68% was reported (Table 2) [23].

Basal Cell Carcinoma

BCC is the most common cancer and has an increasing incidence rate. Currently, two therapies targeting the hedgehog pathway are FDA-approved for the upfront treatment of recurrent, metastatic, or locally advanced BCC not amenable to surgery or radiation. The hedgehog signaling pathway is often dysregulated in BCCs through mutations in either PTCH1 or SMO genes. Vismodegib was the first hedgehog inhibitor (HHI) approved by the FDA in 2012 based on the phase II ERIVANCE (NCT00833417) trial (Table 1). An ORR of 47.6% for locally advanced BCC and 30% for metastatic BCC was observed at 12 months [24, 25]. At 39 months of follow-up, updated trial results reported an ORR of 60.3% and 48.5% for locally advanced and metastatic BCC, respectively [24].

Sonidegib is the second oral FDA-approved HHI for the upfront treatment of BCC (Table 1). Approved in 2015, sonidegib is indicated for the treatment of locally advanced BCC that has recurred following surgery or radiation therapy, or in candidates deemed ineligible for surgery or radiation. The phase II BOLT (NCT01327053) pivotal trial revealed an ORR of 56.1% with a median duration of response of 26.1 months and a 93.2% 2-year survival rate for locally advanced BCC. An ORR of 7.7% was reported for metastatic BCC (Table 1) [26].

There are currently no FDA approvals for first-line or upfront immunotherapy for BCCs that are locally advanced or metastatic. However, since BCC bears one of the highest TMBs, they are likely good candidates for treatment with ICI. Currently, pivotal trial data in the first-line setting are lacking, but several case reports with anti-PD-1 agents [28–30] and anti-CTLA-4 therapy [31] report activity and responses in advanced disease. A recent phase Ib study showed antitumor activity against advanced BCC with pembrolizumab. Seven patients received pembrolizumab plus vismodegib and nine patients received pembrolizumab alone [32]. The ORRs were 44% and 29% at 18 weeks and the PFS at 1 year were 62% and 83% for the monotherapy versus combination therapy cohorts, respectively (Table 2). Although not directly compared due to the non-randomized design of the study, the authors concluded combination therapy was not superior to monotherapy. The use of pembrolizumab in BCC has also been noted in 5 case reports with complete [30, 33] and partial [29, 34, 35] responses achieved, as well as a report of progressive disease of metastatic BCC bony lesions [30] on therapy. Nivolumab [28, 36] and cemiplimab [27] have also shown efficacy against

advanced BCC. A patient with HHI-refractory recurrent metastatic BCC achieved a PR with cemiplimab [27]. Two patients with metastatic BCC were treated with nivolumab with one achieving a PR and PFS of 116 weeks [28] and the other patient achieved SD and PFS of 22 weeks [4].

Clinical trials investigating upfront ICIs in locally advanced, unresectable, or metastatic BCC are ongoing. This includes a non-randomized open-label Phase II trial (NCT03521830) where patients receive nivolumab alone or nivolumab in combination with ipilimumab. Additionally, there is a phase I/II trial (NCT02690948) investigating pembrolizumab monotherapy versus pembrolizumab plus vismodegib (Table 2).

In February of 2021, cemiplimab received an accelerated FDA approval for the treatment of patients with locally advanced or metastatic BCC who experienced progression of disease on HHI or for HHI-therapy intolerant patients. Approval was based on the results of a phase II (NCT03132636) open-label, multicenter, non-randomized trial (Table 1). An ORR of 21% and 29% were reported for patients with metastatic and locally advanced BCC, respectively <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=761097>. With a recent FDA-approval for immunotherapy in the HHI-refractory setting, continued studies and trials (Table 2) are likely to lead to an expansion in FDA-approved indications in advanced BCC.

Rare Cutaneous Adnexal Carcinomas

Cutaneous adnexal carcinomas (CACs) represent a heterogeneous group of rare skin cancers including porocarcinoma and sebaceous carcinoma with limited effective systemic therapy options for advanced disease [37]. These malignancies display differentiation toward skin-primary adnexal structures such as eccrine or apocrine glands. Limited case reports in the literature have illustrated tumor response to ICIs in various CACs. For example, a patient with metastatic porocarcinoma achieved a clinical and radiological CR when treated with pembrolizumab [38] and a patient with widely metastatic sebaceous carcinoma experienced a near CR with pembrolizumab [39] CACs [40] and sebaceous carcinomas with high PD-L1 expression levels have been previously reported [41].

There are currently no FDA-approved immunotherapeutics for CACs specifically. However, the regulatory approval of tumor tissue-agnostic indications for pembrolizumab may play a role in the management of advanced CACs (Table 1). In May of 2017, the FDA approved pembrolizumab for the treatment of unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair (MMR) deficient tumors that have progressed following prior treatment. The accelerated approval was based on

the trial results of patients with MSI-H or MMR-deficient cancers treated with pembrolizumab identified across five clinical trials (NCT01876511, NCT02460198, NCT01848834, NCT02054806, NCT02628067; Table 1). An ORR of 39.6% with 7.4% achieving a CR was reported <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=125514>. The rationale for assessing MSI status in sebaceous carcinoma is supported by data reporting germline variants in the MMR genes MSH2, MSH6, and MLH1 in 8–29% of patients [43–45]. Individuals with sebaceous carcinomas, non-polyposis colorectal cancer, and germline loss of MMRs are characterized as having Muir-Torre syndrome (OMIM 158,320) and their tumors demonstrate microsatellite instability [46]. Furthermore, in June of 2020, the FDA approved a second tumor tissue-agnostic indication for pembrolizumab for unresectable or metastatic tumor mutational burden-high (TMB-H) [≥ 10 mutations/megabase] solid tumors that have progressed following prior treatment (Table 1) <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=125514>. The efficacy was investigated in the open-label, multicenter, non-randomized KEYNOTE-158 (NCT02628067) trial where an ORR of 29% and 37% was reported for the TMB ≥ 10 mutations/megabase cohort and TMB ≥ 13 mutations/megabase cohort, respectively. For advanced and metastatic CACs, tumors may be assessed for MSI, MMR status, and TMB levels for potential treatment with pembrolizumab since no satisfactory treatment options are available. Future studies are required to ascertain clinical benefit and response to pembrolizumab and other ICIs for the treatment of advanced CACs, especially since no CACs or NMSCs were included in the tissue-agnostic trials.

Immunotherapy Rechallenge

Despite the success of upfront ICI in advanced NMSCs, many patients develop resistance to immunotherapy after an initial response or do not have tumor response at all. The use of sequential ICIs or ICIs in combinatorial regimens represent a potentially promising approach for patients that do not have durable benefit from ICI. For example, a multi-institutional retrospective case series ($N=13$) assessed rescue therapy for ICI-refractory MCC (Table 2) [47]. Second-line ICI treatment in MCC patients that progressed on earlier ICI treatment revealed an ORR of 31%. In addition, a case report details a patient with metastatic MCC who progressed on pembrolizumab monotherapy 10 months after initiating ICI [48]. However, a durable response and CR was achieved when treated with concurrent radiation with pembrolizumab. Further

investigation is required to determine if second-line ICIs or combination radiation therapy might improve systemic responses to NMSC tumors initially refractory to ICI.

Adjuvant and Neoadjuvant Immunotherapy

Although ICI treatment strategies for metastatic disease have been successful, therapeutic approaches to preclude the development of advanced disease in high-risk NMSC remain an unmet need. Improved recurrence-free survival (RFS) has been shown with ICI use in resected melanoma [49–51], and similar strategies are being investigated in NMSC (Table 2). A phase III (NCT03969004) trial is randomizing patients with high-risk CSCC after surgery and radiation therapy to either treatment with adjuvant cemiplimab or placebo. A phase II trial (NCT03057613) is assessing patients with resected CSCC of the head and neck treated with radiation therapy in combination with adjuvant pembrolizumab. A phase III double-blinded placebo-controlled study (NCT03833167) is assessing adjuvant pembrolizumab in patients with resected high-risk CSCC (Table 2).

There are also randomized trials examining anti-PD-1 or anti-PD-L1 inhibitors in the adjuvant setting for MCC. The phase III STAMP trial (NCT03712605) is randomizing patients with stage I–IIIB MCC. MCC patients with stage I disease and negative sentinel lymph nodes are excluded from enrollment. Following resection, patients are treated with either pembrolizumab or standard-of-care observation. Avelumab is also being investigated in the adjuvant setting. The phase III ADAM trial (NCT03271372) is an ongoing, multicenter, randomized, double-blind study comparing adjuvant avelumab versus placebo in patients with MCC that has metastasized to the lymph nodes and who have undergone surgery and/or radiation. The phase II I-MAT trial (NCT04291885) is a prospective, placebo-controlled study for patients with stage I–III MCC also aiming to explore the role of avelumab in the adjuvant setting. Nivolumab is being investigated in the adjuvant setting in the phase II ADMEC-O trial (NCT02196961). Enrolled patients receive nivolumab monotherapy in completely resected MCC versus standard-of-care observation. Adjuvant ipilimumab monotherapy failed to demonstrate prevention of disease progression in the adjuvant setting for resected MCC and resulted in pronounced AEs [52]. A phase I trial (NCT03798639) is randomizing patients with stage IIIA/B MCC to receive either nivolumab and radiation therapy or nivolumab in combination with ipilimumab to assess these two different immunotherapy regimens in the adjuvant setting (Table 2).

While the ability to offer patients many clinical trial options for adjuvant ICIs is important, it poses challenges as well. Due to experiencing relatively slow accrual, the

Table 2 Real-world evidence and active clinical trials using ICI in NMSCs

Upfront setting	Study design	Agent(s)	Published findings
CSCC			
Unresectable	Phase II [CARSKIN] (NCT02883556)	Pembrolizumab	41% ORR [10]
Unresectable/metastatic	Phase II (NCT02721732)	Pembrolizumab	-
Locally adv/recurrent	Phase II (NCT02964559)	Pembrolizumab	-
Locally adv/metastatic	Phase II (NCT03284424)	Pembrolizumab	-
Locally adv/metastatic	Retrospective, single institution (N = 76)	Pembrolizumab, cemiplimab, nivolumab	34% ORR [11]
Locally adv/metastatic	Retrospective, single institution (N = 61)	Pembrolizumab, cemiplimab, nivolumab	31.5% ORR [12]
Locally adv/metastatic	Retrospective, multi-institution (N = 46)	Pembrolizumab, cemiplimab, nivolumab	58.7% ORR [13]
Locally adv/metastatic	Interventional clinical trial (NCT03834233)	Nivolumab	-
Locally adv/metastatic	Interventional clinical trial (NCT04204837)	Nivolumab	-
MCC			
Virus-associated diseases (MCC)	Phase I/II [CheckMate 358] (NCT02488759)	Nivolumab	68% ORR [23]
Advanced, refractory to initial ICI therapy	Retrospective, multi-institution (N = 13)	Pembrolizumab, avelumab, nivolumab	31% ORR [47]
BCC			
Advanced BCC	Phase Ib(N = 16)(NCT02690948)	Pembrolizumab + vismodegib or pembrolizumab alone	29% ORR combination [32]; 44% ORR pembrolizumab [32]
Locally adv/metastatic	Phase II(NCT03521830)	Nivolumab + ipilimumab or nivolumab alone	-
Adjuvant setting			
CSCC			
Resected H&N CSCC	Phase II(NCT03057613)	Adjuvant pembrolizumab with postoperative XRT	-
Resected high-risk CSCC	Phase III(NCT03833167)	Adjuvant pembrolizumab	-
Resected high-risk CSCC	Phase III(NCT03969004)	Adjuvant cemiplimab or placebo	-
MCC			
Resected stage I–IIIB MCC	Phase III [STAMP](NCT03712605)	Pembrolizumab or observation	-
Resected MCC with nodal metastasis	Phase III [ADAM](NCT03271372)	Avelumab or placebo	-
Resected stage I–III MCC	Phase II [I-MAT](NCT04291885)	Avelumab or placebo	-
Resected MCC	Phase II [ADEMC-O] (NCT02196961)	Nivolumab or observation	-
Resected stage IIIA–IIIB MCC	Phase I(NCT03798639)	Nivolumab + radiation or nivolumab + ipilimumab	-
BCC			
Advanced BCC of H&N	Phase Ib(NCT04323202)	Neoadjuvant-adjuvant pembrolizumab	-
Neoadjuvant setting			
CSCC			
Stage III–IV H&N CSCC	Phase II(NCT03565783)	Neoadjuvant cemiplimab	30% ORR [57•]
MCC			
Stage IIA–IV MCC	Phase I/II [CheckMate 358] (NCT02488759)	Neoadjuvant nivolumab	47.2% pCR [58•]

Table 2 (continued)

BCC	Phase Ib(NCT04323202)	Neoadjuvant-adjuvant pembrolizumab	-
Advanced BCC of H&N			

feasibility of trials in this setting are being re-examined due to the competing trial aspect. The challenge to recruit to adjuvant trials is further compounded by the growth of neoadjuvant strategies. Administration of ICI prior to resection of high-risk lesions has the potential to be advantageous for several reasons, though these studies often have significant overlap in the patient population targeted by adjuvant trials. Nevertheless, despite these logistical complexities, neoadjuvant treatment is emerging as a very active area of investigation as upfront ICI may not only reduce tumor burden and facilitate resection, but possibly also enhance tumor-specific immune responses [53]. Furthermore, pathological examination of neoadjuvantly treated tumors at the time of resection offers the potential to identify biomarkers of response and survival. Although not without their challenges, results from early neoadjuvant ICI strategies in melanoma have produced encouraging results [54–56]. In NMSC, the phase II open-label (NCT03565783) trial assessed the role of cemiplimab in the neoadjuvant setting for stage III–IV CSCC of the head and neck (Table 2). Early reports reveal an ORR of 30% with a pathological complete response (pCR) achieved in 55% of patients.[57•]

Nivolumab was assessed in the neoadjuvant setting for patients with resectable stage IIA–IV MCC in the CHECK-MATE 358 Trial (NCT02488759).[58•] A pCR was achieved in 47.2% of the cohort and responses were independent of TMB, MCPyV, or PD-L1 status. During the observation study period, no patient with a pCR had tumor relapse. A pathological complete response to neoadjuvant avelumab was also reported in a patient with MCC [59]. In BCC, a single-arm phase IB (NCT04323202) neoadjuvant-adjuvant study will investigate pembrolizumab therapy administered prior to and following resection in advanced disease of the head and neck.

Potential Contraindications to Immunotherapy

Additional safety profile considerations of ICIs are warranted since patients with advanced NMSCs are often immunosuppressed and/or of advanced age. Patients with a long-standing history of immunosuppressive medications, hematological malignancy, or HIV require consideration for ICI since these cohorts are often excluded from trials. For example, the use of ICIs in transplant recipients may be challenging due to enhanced T-cell activation potentially leading to allograft rejection [60]. Current trial data is limited and data from case series and reports reveal significant

risk of allograft rejection but consistent durable disease control [61–63]. Further studies are needed to determine the safety profile of ICIs in immunosuppressed populations with advanced NMSCs. A specific emphasis on research efforts aimed at determining suitable therapy regimens optimized for graft preservation without reducing ICI antitumor activity would be beneficial to this group. Data from case reports and case series reveal responses to ICI in immunosuppressed NMSC patients may be comparable to immunocompetent patients [11, 12]. Notably, a recent case series reported a PR of advanced CSCC in an HIV patient [4].

Challenges and Future Directions

Despite exceptional responses to ICIs in NMSCs, the associated immune-related AEs (irAE) require careful monitoring. Thus, clinical research efforts should aim to identify new ICI regimens that enhance tumor response while reducing toxicity and irAE severity. In addition, continued efforts to identify predictive and prognostic biomarkers of response and resistance to anti-CTLA-4 and anti-PD-L1/PD-1 therapies may help identify patients with NMSC that are likely to benefit from therapy. A possible cause of failure to respond to ICIs is the lack of costimulatory signals in the tumor microenvironment. Current active research is focused on promoting response by utilizing costimulatory checkpoint agonists and innate immune targets such as OX40 agonists, oncolytic viruses, and STING/Toll-like receptor (TLR) agonists currently under investigation in patients with multiple solid tumors, including advanced NMSC. Furthermore, specific assessment of the role of ICIs in advanced CACs are required.

Lastly, we must consider barriers to enrollment to ongoing clinical studies—such as trial rollout and study design—to maintain continued progress. For example, launching synchronous studies in the neoadjuvant and adjuvant settings simultaneously can impair enrollment to both, as there is often significant overlap in these patient populations. Furthermore, we have found that certain elements of trial design have had substantial effects on recruitment. For example, enrolling patients on adjuvant ICI trials following adjuvant radiotherapy has proved challenging. Patients have expressed a preference to undergo only one therapy in the adjuvant setting and “reserve” immunotherapy for the relapsed setting. Similarly, we have found that the decision to incorporate a placebo as compared to a “standard-of-care” comparator arm has greatly affected trial participation, especially in the

time of the COVID-19 pandemic. While placebo arms play an important role in decreasing bias and confounders, they can negatively affect recruitment. Patients have been less enthusiastic about returning to clinic regularly for prolonged periods of time (e.g., every 2–6 weeks for an entire year) if there is a significant chance they are not going to receive the investigational agent. This is of particular concern in the NMSC population, which on average, is typically older with numerous comorbidities and increasingly reliant on others for transportation to clinic.

Of course, these challenges are not unique to the NMSC patient population. However, in the absence of a high-level assessment of the trial landscape, the NMSC field may turn one of its greatest assets into its biggest liability. The robust clinical activity of immunotherapy in NMSC has attracted attention by a great number of pharmaceutical companies. Patients with NMSC can provide a relatively straight-forward path to a new Biological License Application (BLA) or a supplemental efficacy indication. Consequently, the number of trials in the NMSC space has increased significantly over the last few years and that growth is likely to continue in the years to come. And while a multitude of therapeutic trial options has a theoretical advantage, a bigger concern is competition of these trials for a relatively stable patient population. Thus, without improved communication between sponsors, academicians and patient advocacy groups, we run the real risk of opening trials that fail to meet their enrollment goals and primary endpoints.

Conclusions

Anti-PD-1/PD-L1 and CTLA-4 inhibitors have improved survival for many advanced NMSC patients. Immunotherapy is playing an increasingly critical role in the management of advanced disease and is considered standard of care for upfront systemic therapy in locally advanced and unresectable MCC and CSCC, and more recently in HHI-refractory BCC. Potentially, ICIs and other forms of immunotherapy may also play an important role in the neoadjuvant and adjuvant settings as well, with several trials currently underway. Continued evaluation of the clinical trial landscape is needed to optimize enrollment and ensure perpetual innovation.

Declarations

Conflict of Interest Sophia Z. Shalhout declares that she has no conflict of interest. Kevin S. Emerick has received honoraria for participating on advisory boards for Regeneron, Sanofi Genzyme, and Jounce Therapeutics. Howard L. Kaufman is an employee of Immuneering Corporation. David M. Miller honoraria for participating on advisory boards for Checkpoint Therapeutics, EMD Serono, Pfizer, Merck, Regeneron, and Sanofi Genzyme.

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● Of importance

●● Of major importance

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