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Immunotherapy and Its Timing in Advanced Basal Cell Carcinoma Treatment

Clio Dessinioti[1], Alexander J. Stratigos[1]

1 Skin Cancer and Melanoma Unit, 1st Department of Dermatology-Venereology, National and Kapodistrian University of Athens, Andreas Sygros Hospital, Athens, Greece

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Corresponding Author: Alexander J Stratigos, Department of Dermato-Oncology, Andreas Sygros Hospital, Athens, Greece. E-mail: alstrat2@gmail.com

ABSTRACT For patients with advanced basal cell carcinoma (BCC), including locally advanced or metastatic BCC not amenable to curative surgery or radiotherapy, hedgehog pathway inhibitors (HHI) vismodegib and sonidegib are approved as first-line systemic treatment. Results from clinical trials highlight that the overall discontinuation rate of HHI treatment varies from 88% to 92% with vismodegib and is approximately 92% with sonidegib, and half of patients will discontinue HHI after approximately 8 to 12 months. The main factors weighing in on the decision to discontinue HHI include efficacy (tumor response), adverse events and patient decision. In clinical practice, some of the patients that stop HHI may be re-evaluated if the tumor becomes amenable to surgery, or restart HHI at a later time, while others will need to switch to immunotherapy, depending on the reasons for HHI discontinuation. In this review, we revisit the therapeutic decisions considering a switch from HHI to immunotherapy with anti-PD-1 agent cemiplimab and we highlight the place of cemiplimab in the therapeutic ladder for patients with advanced BCC. We discuss the evidence on the efficacy and safety of anti-PD-1 agents as second-line systemic monotherapy, or in combination with other treatments, and the emergence of checkpoint immunotherapy as a neoadjuvant treatment.

Introduction

Basal cell carcinoma (BCC) accounts for 75% of all skin cancers and is the most common malignant tumor in white populations. BCC and cutaneous squamous cell carcinoma (cSCC) are referred to as keratinocyte carcinomas (formerly known as nonmelanoma skin cancers) [1].The majority of BCCs is characterized by indolent biological behavior and is cured with surgical excision or topical treatments. However, in some cases, BCC can infiltrate locally into adjacent and deeper structures and cause extensive tissue destruction. Metastases are extremely rare (< 0.1%) and may affect the regional lymph nodes, lung, spine, bone marrow and pelvic bones [2].

Multiple factors are implicated in the development of sporadic BCC including exposure to ultraviolet radiation (sun or indoor tanning beds), older age, light skin and hair tones, tendency to sunburn, male sex, immunosuppression (solid organ transplantation) and genetic factors [3-6]. Gene alterations playing some role in BCC pathogenesis include mutations in *p53* (17p13), human type II oculo-cutaneous albinism-related gene (*OCA2*), agouti signaling protein (*ASIP*), tyrosinase (*TYR*) and melanocortin 1 receptor gene (*MC1R*, 16q24.3) [1,7,8]. Mutations in the Hedgehog (Hh) signaling pathway have been detected in practically all BCCs. The Hh signaling pathway is normally required for the hair follicle morphogenesis during development and regulation of the hair cycle in adulthood, while its aberrant activation, due to mutations in the *PTCH1* or *SMO* genes, leads to BCC carcinogenesis [9]. Loss-of-function somatic mutations in *PTCH1* (9q22.3) and activating mutations in the G-protein coupled receptor smoothened (SMO) have been detected in up to approximately 90% and 10% of BCC tumors, respectively [10].

In addition, cancer immunology via the innate and adaptive immune system plays a key role in the development of keratinocyte carcinomas. The PD-1 pathway is a checkpoint that plays a central role in the local immunosuppression in the tumor microenvironment [11,12]. PD-L1 is expressed on tumor and/or immune cells and the programmed cell death receptor-1 (PD-1) is expressed on immune cells, including CD8+ and CD4+ T-cells, B-cells and natural killer cells [11]. In response to endogenous anti-tumor immunity, cancer cells express on their surface the programmed cell death ligand-1 (PD-L1), in a process termed adaptive immune resistance [13]. Blocking the PD-1 pathway is regarded as "common denominator" for cancer therapy [14]. Regarding BCC, the expression of PD-L1 has been detected in tumors or the tumor microenvironment [15,16]. The percentage of positive PD-L1 expression (defined as greater than 5% positive immuno-histochemical staining) was 89.9% in tumor cells and 94.9% in tumor infiltrating lymphocytes of BCCs [15]. In another study, among 40 BCCs, 22% had PD-L1 expression on tumor cells, and 82% had PD-L1 expression on tumor-infiltrating lymphocytes and macrophages [16]. Also, BCC is one of the malignancies with the highest tumor mutational burden (TMB), which in turn has been associated with the presence of tumor neoantigens that may be targeted by immune cells activated with immunotherapy [17].

Translational research has linked the above mentioned genetic and molecular findings in BCC with the development of treatments targeting these underlying dysregulations. As a result, our therapeutic options have been enriched with the Hedgehog pathway inhibitors (HHI) vismodegib and sonidegib, and the anti-PD-1 agent cemiplimab, that have been regulatory approved for advanced BCC by the European Medicines Agency (EMA) in Europe. These treatments have been a breakthrough for the treatment of patients with advanced BCC as they have replaced conventional systemic chemotherapy, which was previously used for advanced BCC. Platinum-based chemotherapy was studied in a 1978 phase I-II clinical trial in various solid tumors, that reported one complete and one partial response in two patients with disseminated BCC [18], however further reports of chemotherapy for mBCC were generally limited by poor response, or short duration of response, short overall survival, and lack of serial tumor measurements [19,20].

In this review, we focus on patients with advanced BCC, including locally advanced and metastatic BCC, not amenable to curative surgery or radiotherapy and thus warranting systemic treatment. We highlight the current recommendations for the use of oral Hedgehog inhibitors and intravenous anti-PD-1 agents for the treatment of patients with advanced BCC. We discuss the evidence on the potential applicability of anti-PD-1 agents as first-line or second-line systemic monotherapy, or in combination with other treatments and the emergence of anti-PD-1 agents as a neoadjuvant treatment.

Systemic Treatments for Advanced BCC

Advanced BCC is classified as either locally advanced BCC (laBCC) or metastatic BCC (mBCC). Based on the possibility of treatment with surgery and/or radiotherapy with curative definitive intent, the term locally advanced BCC has been used to describe difficult-to-treat or high-risk BCCs in which current treatment modalities are contraindicated by tumor or patient factors [21-23]. Such factors may include tumor size and location that may pose technical difficulties of maintaining function and aesthetics, large numbers of BCCs, tumor subtype, multiple recurrences, and patient comorbidities and frailty [21-23].

Systemic treatments for advanced BCC include HHI and immunotherapy. Systemic therapy is considered for laBCC and mBCC, when curative surgery and RT are not feasible

[22,23]. A multidisciplinary board discussion is required to determine if BCC is not amenable to curative surgery and/or RT and further decide on the type of systemic therapy [22,23]. HHI for advanced BCC include vismodegib and sonidegib, which are taken orally. Vismodegib was approved in 2012 by the US FDA and in 2013 by EMA for the treatment of adults with symptomatic metastatic BCC or with locally advanced BCC inappropriate for surgery or radiotherapy [24]. Sonidegib was approved in 2015 by the US FDA and EMA for the treatment of adults with locally advanced BCC who are not amenable to curative surgery or radiotherapy [25]. Cemiplimab is a human programmed death receptor (PD)-1 monoclonal antibody that belongs to the family of immune checkpoint inhibitors (ICIs) [26]. Cemiplimab was approved in 2021 by the US FDA and in 2019 by EMA as monotherapy for the treatment of adult patients with metastatic or locally advanced BCC who have progressed on or are intolerant to a hedgehog pathway inhibitor [27]. It is administered by intravenous infusion over 30 minutes and the recommended dosage is 350 mg every 3 weeks until disease progression or unacceptable toxicity [27].In the following sections, we will discuss the evidence on the place of cemiplimab immunotherapy in the therapeutic ladder for patients with advanced BCC.

Switching From Hedgehog Pathway Inhibitors to Anti-PD-1 Immunotherapy for Advanced BCC

Hedgehog pathway inhibitors (HHI) vismodegib (150 mg/day) and sonidegib (200 mg/day) are approved as first-line systemic treatment for patients with advanced BCC. The reported overall discontinuation rate of HHI treatment is 88% to 92% with vismodegib and 92% with sonidegib [28-30]. Median vismodegib treatment duration was 8.6 (range: 0-44) months in the STEVIE study and 12.7 (range: 1.1-47.8) months in the ERIVANCE BCC study [28,29]. Median sonidegib treatment duration was 11 months [30]. These results from clinical trials highlight that half of patients with advanced BCC will discontinue HHI after approximately 8 to 12 months. The main factors weighing in on the decision to discontinue HHI, include efficacy (tumor response), adverse events and patient decision. In clinical practice, some of the patients that discontinue HHI may be re-evaluated for surgical excision if the tumor becomes amenable to surgery, or restart HHI at a later time, while others will need to switch to immunotherapy, depending on the reasons for HHI discontinuation. The results of clinical trials of HHI treatment in patients with laBCC, that may affect decision to switch treatment are presented in Table 1. The therapeutic decisions considering a switch from HHI to cemiplimab are shown in Figure 1.

First, regarding efficacy, the overall response rate (ORR: complete response or partial response) with vismodegib in the primary analysis of the pivotal ERIVANCE BCC trial was 45% for mBCC and 60% for laBCC [31]. The final 39-month update of this trial reported that investigator-assessed ORR was 48.5% for mBCC (all partial responses) and 60.3% for laBCC. Also, there was stable disease in 42.4% of mBCC [29]. At the 39-month study, disease progression was the reason to discontinue vismodegib in 51.5% of patients with mBCC and in 16.9% of patients with laBCC [29]. Similar results have been shown with sonidegib [30,32-35]. Secondary acquired resistance of BCC with a secondary loss of response may occur during HHI treatment and is frequently due to mutation of SMO [36,37]. A study of 9 patients with primary or secondary resistance to vismodegib reported absence of response after switch to sonidegib, suggesting a class-relating effect [38]. However, the early discontinuation of sonidegib in 4 patients, due to adverse events or patient decision, may have contributed for not observing a response [38,39]. Regarding those patients that achieve a complete response with vismodegib and stop treatment, the median relapse-free survival was 18.4 months or 24 months [40,41]. Relapse in complete responders is attributed to a persisting, slow-cycling tumor cell population, induced by vismodegib via a shift in tumor cell identity and activation of the Wnt pathway [42,43]. When BCC relapses in complete responders, re-treatment with vismodegib can be successful (response in 65.7% or 85%) but some patients will not respond again [40,41,44]. These results highlight that non-responding patients could be considered for switching from HHI to second-line anti-PD-1 immunotherapy (Figure 1).

Second, although adverse events are mostly reversible after HHI withdrawal and are usually of mild or moderate severity, they can be considerably distressing to patients and are a frequent cause of drug discontinuation [45-47]. Adverse events occur in all (100%) patients treated with HHI and are class-related, e.g. they are similar for vismodegib and sonidegib [29,31,46,48]. Adverse events more frequently observed in clinical trials with HHI include muscle cramps in 49%-71%, alopecia in 55%-66%, dysgeusia in 38% to 71%, weight loss in 16% to 52%, fatigue in 16% to 43%, loss of appetite in 11% to 31% and diarrhea in 8% to 27% [46]. During HHI treatment, the procedures to assess BCC response and monitor for adverse events, and the management of adverse events, have been reviewed previously and are outside the scope of this article [46,47,49].

The STEVIE study reported long-term safety results among patients with mBCC or laBCC treated with vismodegib for at least 12 months [50]. Among 499 patients, 400 (80%) discontinued treatment, including 180/499 (36%) due to adverse events, 14% due to disease progression, and 10% due to patient request [50]. Among the 180 patients who discontinued vismodegib due to adverse events, those were of mild severity (grade 1 or 2) in 106 patients (59%), and most

Table 1. Summary of results of clinical trials of HHI treatments in patients with advanced BCC, that may affect decision to switch to anti-PD-1 immunotherapy: response, rates and reasons of discontinuation.

	Vismodegib (150 mg/day)			Sonidegib (200 mg/day)	
	ERIVANCE study (39-month update) [29]	STEVIE study (median follow-up: 17.9 m) [28]		BOLT study (30- month and 42-month update) [30,34]	
Outcome	N =63 laBCC	N =1119 laBCC	N =1215 total	N =66 laBCC	N =79 total
Investigator-assessed ORR, N (%)	38 (60.3)	738 (68.5)	769 (66.2)	47 (71.2%) [34]	NR
CR	20	360 (33.4)	364 (31.4)	6 (9.1)	
PR	18	378 (35.1)	405 (34.9)	41 (62.1)	
SD	15	270 (25.1)	309 (26.6)	13 (19.7)	
PD	6	21 (1.9)	30 (2.6)	1 (1.5)	
Median duration of response in responders, m (95% CI)	26.2 (9.0-37.6)	23 (20.4-26.7)	22.7 (20.3-24.8)	26.1 (central review) [30,34]	NR
Median treatment duration, m (range)	12.7 (1.1-47.8)	NR	8.6 (0-44)	NR	11.0 [30]
Discontinuation, N (%)	64/71 (90.1)	NR	1068 (88)	NR	73 (92.4%) [30]
Main reason for discontinuation					
Patient decision	23 (32.4)		113 (9.3)		8 (10.1)
Adverse event	17 (23.9)		349 (28.7)		23 (29.1)
Progressive disease	12 (16.9)		189 (15.5%)		29 (36.7)
Physician decision	7 (9.9)		76 (6.3)		10 (12.6)
Death	2 (2.8)		37 (3)		1 (1.3)
Lost to follow-up	2 (2.8)		21 (1.7)		2 (2.5)
Other	1 (1.4)		283 (23.3)		

CI = confidence interval; CR = complete response; laBCC = locally advanced BCC; m = months; N = number; NR = not reported; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease.

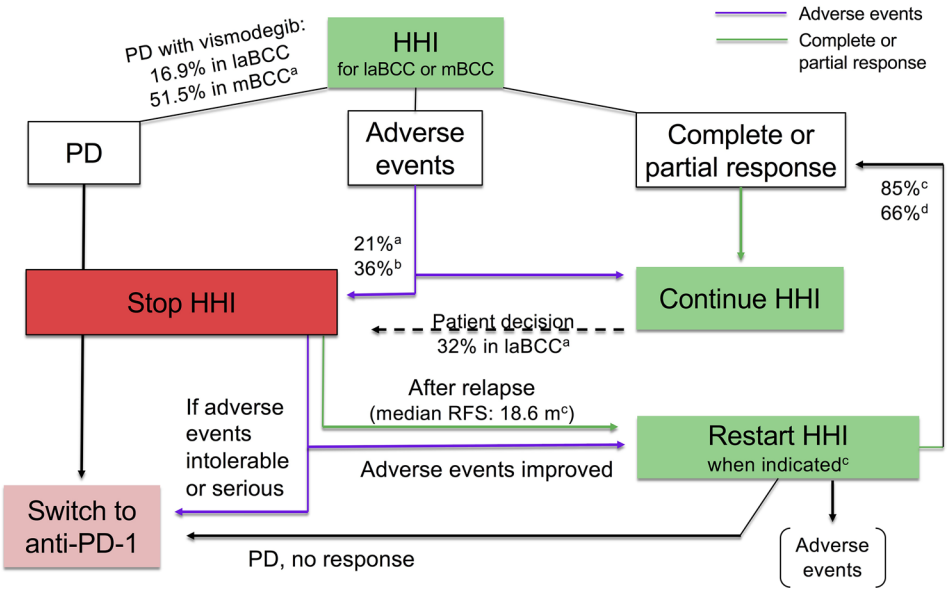

Figure 1. A schematic of therapeutic decisions on switching from hedgehog pathway inhibitors to anti-PD-1 immunotherapy with cemiplimab.

HHI = hedgehog pathway inhibitors; laBCC = locally advanced basal cell carcinoma; mBCC = metastatic basal cell carcinoma; PD = progressive disease; RFS = relapse-free survival.

[a] results from the final update of the ERIVANCE BCC study [29]
[b] results from STEVIE study [50]
: results from Herms [40]
[d] results from Bassompierre [41]

had complete or partial response [50]. The primary analysis of STEVIE study in 1215 patients with advanced BCC showed similar results, and the leading cause of vismodegib discontinuation were adverse events (28.7%) [28] (Table 1). In the final update of the ERIVANCE BCC study, overall 92.3% patients discontinued vismodegib, mainly because of disease progression (27.9%), patient decision (26%) and adverse events (21.2%) [29]. In the group of laBCC, 90.1% discontinued vismodegib, but the leading cause of discontinuation was patient decision (32.4%), followed by adverse events (23.9%) and disease progression (16.9%) [29]. In the 42-month update of the BOLT study, of those who discontinued sonidegib, 29.1% discontinued due to adverse events, despite the fact that most had only mild (grade 1 or 2) adverse events [30,33] (Table 1).

Using HHI as first-line treatment followed by anti-PD-1 therapy as second-line treatment may increase the tumor likelihood to respond to anti-PD-1 therapy. The treatment with HHI promotes adaptive immune responses, upregulates MHC-I expression and increases the intra-tumor infiltration with CD4+ and cytotoxic CD8+ T cells [51]. Another study showed significantly higher PD-L1 immunohistochemical staining intensity in tumor cells of previous treated BCC versus naïve BCC (32% versus 7%, respectively). Previous treatments included HHI, platinum chemotherapy, gefitinib, topical chemotherapy, surgery, and radiotherapy [15]. The evidence on the efficacy and safety of anti-PD-1 immunotherapy for advanced BCC is presented in the following sections.

Efficacy and Safety of Anti-PD-1 Immunotherapy as Second-line Systemic Therapy for Advanced BCC

The investigation of anti- PD-1 agents for advanced BCC followed the clinical trials and regulatory approval of anti-PD-1 immunotherapy for the treatment of other advanced skin cancers, including cutaneous melanoma and squamous cell carcinoma. Anti-PD-1 immunotherapy for advanced BCC was first reported in various case reports treated with cemiplimab, nivolumab, or pembrolizumab, mostly with benefit [52-64].

Regulatory approvals for BCC indications were based on a pivotal phase 2 open-label, multicenter, single-arm trial that assessed cemiplimab monotherapy in patients with advanced BCC (ClinicalTrials.gov identifier NCT03132636) [65,66]. This pivotal trial included 84 patients with laBCC (group 2) previously treated with HHI, who were not candidates for further HHI therapy due to progression of disease (71%), or no better than stable disease after 9 months of HHI therapy (8%), or intolerance (38%) [65]. Patients received cemiplimab 350 mg by IV infusion every 3 weeks for up to 93 weeks. At a median follow-up of 15 months (IQR 8-18), an objective response (by independent central review) was observed in 31%, including 6% with complete response and 25% with partial response. The response rate was similar across subgroups regarding age, sex, and intolerance or progression/lack of response to previous HHI. Cemiplimab was discontinued in 62% of patients, due to disease progression (35%), adverse event (16%), or patient decision (6%) [65] (Table 2).

In this pivotal study, the safety profile of cemiplimab for BCC was consistent with that of other anti-PD-1 agents for cutaneous melanoma and cSCC. Treatment-emergent adverse events grade 3 or 4 occurred in 48% of patients, including hypertension, colitis, and fatigue. Immune-related adverse events (none of grade 4 or 5) occurred in 25% of patients and included hypothyroidism (10%), hyperthyroidism (2%), thyroiditis (2%), adrenal insufficiency (2%), immune-related colitis (4%), and hypophysitis, immune-mediated hepatitis and maculopapular rash (each in one patient) (Table 2) [65].

The UNICANCER AcSe NIVOLUMAB phase 2 basket trial (NCT03012581) evaluated nivolumab in a relatively small number of 32 patients with advanced BCC, including 29 laBCC and 3 mBCC. Patients received nivolumab 240 mg by IV infusion every 2 weeks for up to 24 months [67]. The median follow-up was 17 months (IQR 12-23). In this study, the objective response (radiologically) was assessed early at 12 weeks, and was observed in 22%, including 3.1% with complete response and 18.8% with partial response (Table 2). Adverse events occurred in 28% of patients and almost half were considered treatment related. Only one related adverse event led to treatment discontinuation. More frequent adverse events were diabetes mellitus, colitis, pneumonitis, myocardial infarction, lymphopenia and bullous pemphigoid [67].

The above mentioned findings of clinical trials show the efficacy of second-line anti-PD-1 ICI in some patients while others will not respond, indicating a considerable group of patients with primary or secondary resistance to anti-PD-1 therapy. To overcome these limitations, the use of anti-PD-therapies against earlier stages of cancer as neo-adjuvant treatment has been considered [11].

Is There a Place for Anti-PD-1 Agents as Neoadjuvant or Adjuvant Treatment for Advanced BCC?

The aim of neoadjuvant (presurgical) treatment for advanced skin cancer has traditionally been to improve the operability of tumors. Currently there is no treatment approved for advanced BCC in the neoadjuvant setting. Neoadjuvant vismodegib was used in the VISMONEO phase 2 trial in 55 patients with locally advanced BCC of the face, and resulted in downstaging in surgical resection complexity in 44 (80%), of whom 27 had complete response. A recurrence

Table 2. Results from clinical trials with anti-PD-1 immunotherapy for advanced BCC.

	Stratigos, 2021 [65]	Veron, 2022 [67]
Anti-PD-1 agent	Cemiplimab	Nivolumab
N	84 laBCC	29 laBCC and 3 mBCC
Prior systemic treatment HHI (vismodegib or sonidegib) Chemotherapy	 All NR	 All 17 (53%)
Median FU, m	15	17
ORR (ICR), n (%) Complete Response Partial Response Stable Disease Progressive Disease Not evaluable	26 (31%) 5 (6%) 21 (25%) 41 (49%) 9 (11%) 8 (10%)	At 12 weeks 21.9% 1 (3.1%) 6 (18.8%) 14 (43.8%) 11 (34.3%)
Median time to response (IQR), m	4.3 (4.2, 7.2)	5.3
Disease control rate, n (%)	67 (80%)	21 (65.7%)
Duration of response in responders Median ≥ 12 months	 Not reached 11 (46%)	 13.8 m
Estimated duration of response at 12 months (95% CI)	85% (61-95)	
Estimated 1-year PFS (95%C CI)	57% (44-67)	
Estimated 2-year OS (95%C CI)	80% (63-90)	
OS, median	Not reached	
Discontinued	52 (62%)	
Median treatment duration, w (IQR)	47 (27-80)	32

DDC = durable disease control; HHI = Hedgehog inhibitors vismodegib or sonidegib; ICR = independent central review; IQR = interquartile range; laBCC = locally advanced basal cell carcinoma; mBCC = metastatic basal cell carcinoma; m = months; N = number of patients; NR = not reported; OS = overall survival; PFS = progression-free survival; w = weeks.

was noted in 36% at 3-year follow-up [68]. Also, the NCCN guidelines recommend that for patients with high-risk BCC in whom surgery may cause significant functional damage, neoadjuvant vismodegib followed by PDEMA may be considered [22].

Regarding neoadjuvant immunotherapy, most evidence comes from studies in cutaneous melanoma, and there are limited studies in keratinocyte cancers, eg cSCC and BCC. The effects of systemic checkpoint inhibitors in the neoadjuvant setting for melanoma surpass improved operability as, even more importantly, impact the long-term tumor control and possibly survival through the induction of a systemic immune response to cancer cells [11,69]. In resectable advanced (stage IIIB-IV) cutaneous melanoma, the combined neoadjuvant plus adjuvant pembrolizumab regimen (200 mg IV every 3 weeks, in 3 doses before surgery and the remaining 15 doses after surgery) was studied in the randomized SWOGS1801 trial compared to standard-care adjuvant pembrolizumab (18 doses after lymph-node dissection). The estimated event-free survival was 72% in the neoadjuvant plus adjuvant group versus 49% in the adjuvant group (HR: 0.58, P = 0.004). There was a similar frequency of grade 3 or higher adverse events of 12% in the neoadjuvant-adjuvant group and 14% in the adjuvant-only group [70]. The PRADO melanoma trial investigated whether surgery and/or subsequent adjuvant therapy could be omitted in the case of a major (complete or near complete) pathological response (0% or 0% to ≤10% viable tumor cells in surgical specimen, respectively). In these cases, the landmark two-year recurrence-free survival and distant-metastasis-free survival were 93% and 98% respectively [71].

In resectable cSCC with primary tumors with diameter of at least 3 cm or with nodal metastasis (stage II, III or IV M0), a phase 2 study evaluated neoadjuvant cemiplimab (350 mg every 3 weeks for up to 4 doses) followed by surgery in 79 patients. A pathological complete response was observed in 40 patients (51%), and a pathological near-complete response in 10 patients (13%). The results on relapse-free survival have not been reported yet [72]. The NCCN version 1.2023 guidelines recommend that neoadjuvant cemiplimab may be considered in patients with cSCC with nodal metastasis who are considered borderline resectable, unresectable, or for whom surgery may carry a high morbidity [73].

Table 3. Clinical trials on neoadjuvant immunotherapy in patients with advanced basal cell carcinoma.

Study ID	Phase (Status)	Therapy	Enrollment, N	BCC classification	Main outcomes
NCT05929664 [74]	II (active, not yet recruiting)	Cemiplimab	35	laBCC of the head and neck requiring greater than 30% auriculectomy, rhinectomy, upper or lower lip resection, orbital exenteration (due to lid or orbital involvement), facial nerve sacrifice or Brigham and Women's stage 2b or 3 disease of head and neck	Primary: ORR, DCR Secondary: SBR, pCR, mPR, adverse events, quality of life
NCT04323202 [75]	I (active, not recruiting)	Pembrolizumab	13	Locoregionally advanced, resectable BCC of the head and neck	Primary: Pathologic response assessed by tumor volume. Secondary: Adverse events, one-year recurrence rates

BCC = basal cell carcinoma; DCR = disease control rate; laBCC = locally advanced basal cell carcinoma; mPR = major pathologic response; ORR= objective response rate; pCR = pathologic complete response; SBR = surgical/clinical benefit rate.

For advanced BCC, neoadjuvant anti-PD-1 immunotherapy is currently investigated in clinical trials which are summarized in Table 3 [74,75]. For laBCC, neoadjuvant nivolumab was used in 2 patients with laBCC as first-line treatment [76]. Neoadjuvant cemiplimab is investigated in patients with advanced BCC requiring greater than 30% auriculectomy, rhinectomy, upper or lower lip resection, orbital exenteration (due to lid or orbital involvement), facial nerve sacrifice or Brigham and Women's stage 2b or 3 disease of head and neck [74].Neoadjuvant pembrolizumab is investigated in patients with resectable high-risk BCC [75]. There is no recommendation on adjuvant anti-PD-1 treatment for resected advanced BCC outside the context of clinical trials in current guidelines [21,23].

Have Anti-PD-1 Agents Been Combined With Other Treatments for Advanced BCC?

Current guidelines recommend cemiplimab as monotherapy for advanced cSCC and for advanced BCC [22,73,77,78]. The need to combine anti-PD-1 with another treatment may arise in the case of failure of BCC to respond to anti-PD-1 in some patients, as described in the studies above and in case reports, if new BCCs develop during anti-PD-1 immunotherapy for other indications or despite response of the index advanced BCC [53,79-81]. In these lines, the combination of anti-PD-1 therapy with HHI, or talimogene laherparepvec for advanced BCC is currently evaluated in clinical trials.

The combination of pembrolizumab 200 mg IV every 3 weeks with vismodegib (in 7 patients) showed lower responses compared to pembrolizumab alone (in 9 patients) in the proof-of-concept study by Chang et al, for advanced BCC. The ORR at 18 weeks was and 29% for the combination regimen and 44% for the pembrolizumab monotherapy [82]. A case of laBCC which developed during cemiplimab therapy for lacSCC, was treated with concomitant sonidegib with a clinical response. The combination treatment was well tolerated and the patient received 31 cycles of cemiplimab and 10 cycles of sonidegib. The patient died due to sepsis that was considered unrelated to treatment [80]. Ongoing clinical trials aim to investigate the combination of cemiplimab with pulsed sonidegib therapy, and the combination of nivolumab plus relatlimab or ipilimumab for patients with laBCC or mBCC [83,84].

The combination of immunotherapeutic agents, such as immune checkpoint inhibitors and intralesional oncolytic viruses, is studied with the aim to improve the T-cell exhaustion, prolong the duration of response and delay resistance, associated with immune checkpoint inhibitor therapy [85,86]. Talimogene laherparepvec was approved in 2015 as the first engineered oncolytic herpes simplex virus type 1 (HSV-1) for the treatment of advanced melanoma [85,87]. Oncolytic viruses selectively infect and induce the lysis of cancer cells with subsequent release of tumor-derived antigens, express immunostimulatory cytokines and chemokines, such as granulocyte-macrophage colony-stimulating factor (GM-CSF) expressed by T-VEC, and may trigger a systemic anti-tumor response [85,87]. Intra-tumoural immunotherapy with T-VEC is being studied in clinical trials, in combination with panitumumab for

advanced cSCC, and in combination with nivolumab for advanced BCC [88,89].

Is There Evidence for Anti-PD-1 Agents as First-line Systemic Therapy for Advanced BCC?

The current US NCCN guidelines (version 1.2023) and the European guideline update 2023, have issued recommendations regarding the place and timing of anti-PD-1 immunotherapy for advanced BCC [22,23]. The British guidelines (2021) were prepared before the approval of cemiplimab for advanced BCC and do not include a recommendation on anti-PD-1 immunotherapy [21]. The NCCN guidelines recommend cemiplimab according to the US FDA approval, as a monotherapy for patients with laBCC or mBCC previously treated with an HHI or for whom an HHI is not appropriate [22].

Currently, when a patient is eligible for systemic therapy, including HHI or anti-PD-1 therapy, anti-PD-1 agents are recommended as second-line systemic therapy for patients with advanced BCC previously treated with HHI. The European guideline update 2023 on BCC, recommends that anti-PD-1 immunotherapy should be offered as second-line treatment in patients who progress or have contraindications to hedgehog inhibitors [23]. In the clinical trials of vismodegib and cemiplimab for laBCC, a similar treatment duration was reported with cemiplimab (median 12 months) and vismodegib (median 12 months)[2] the objective response rate was 31% with cemiplimab and 60% with vismodegib, and the median duration of response in responders was not reached with cemiplimab and was 26 months with vismodegib [29,65]. However, a direct comparison of these studies cannot be made as they included heterogeneous patients; cemiplimab was used in a highly challenging group of patients who had progressed or not responded or were intolerant to previous HHI treatment.

At the moment, there is no validated predictive biomarker to select those patients with advanced BCC more likely to benefit from anti-PD-1 ICI, thus guiding the choice of anti-PD-1 immunotherapy as first-line therapy for advanced BCC [26]. PD-L1 positivity by immunohistochemistry has been shown in some advanced BCC tumors, but it has not been associated with clinical responses to anti-PD-1 immunotherapy [15,57,65,90]. A high TMB has been consistently reported in advanced BCC [65,91]. Also, a higher TMB has been reported in advanced BCCs with response to anti-PD-1 therapy, however the median TMB in non-responders was 23 mt/Mb, that is above the defined high TMB threshold of ≥10 mut/Mb [65,92]. In the pivotal phase 2 clinical trial of cemiplimab for laBCC, exploratory biomarker data showed similar response to cemiplimab by PD-L1 immunohistochemistry status of tumor cells (PD-L1<1%, N = 35, versus PD-L1 ≥1%, N = 15) [65]. There was similar, albeit high, median TMB (58 versus 23 mut/MB) and similar median MHC-I expression level on tumor cells (37, IQR 21-72 versus 21, IQR 5-62), in responders versus non-responders, respectively. Notably, among some patients with high TMB levels who did not have objective response, major histocompatibility complex I (MHC-I) expression was low or absent [65]. The downregulation of MHC-I has been implicated in lower antigen modification and presentation, contributing to a possible lower immunogenicity of BCC compared to cSCC [93]. Recently, the dysregulation of regulatory non-coding RNAs, including microRNA (miRNA), has been identified in BCC. Some miRNAs may act as tumor suppressors while others act as oncogenes (oncomiR), and miRNAs have been associated with specific high-risk BCC subtypes, suggesting a potential prognostic role. In addition, several miRNAs have been shown to affect drug resistance to BRAF inhibition in melanoma, underscoring the possibility to add predictive information for response to therapy [94].

Conclusions

Anti-PD-1 agents offer a therapeutic option in patients with advanced BCC not amenable to curative surgery or radiotherapy, who have progressed or are intolerant to an HHI. For laBCC treated with second-line cemiplimab, the possibility of a response in approximately one third of patients and of a prolonged duration of response, make anti-PD-1 immunotherapy an important treatment solution. In addition, results from melanoma trials underscore the emergence of neoadjuvant immunotherapy with anti-PD-1 agents as a treatment positively affecting the prognostic outcomes in skin cancer. Treating advanced BCC with immunotherapy can achieve durable response in some patients, however there is a considerable number of patients who will not respond or will lose response. The use of biomarkers for Identifying and treating those patients more likely to respond to anti-PD-1 therapy is a promising area of active research towards personalized treatment.

Clinical and translational research has led to a paradigm shift in the treatment of advanced BCC with the advent of targeted therapies, eg HHI and anti-PD-1 immune checkpoint blockade. However, important treatment gaps still remain on the management of those patients that have resistance or unacceptable toxicities with HHI and anti-PD-1 agents. For the challenges that lie ahead, precision medicine and rigorous clinical research aim to provide further data to guide evidence-based decisions on the optimal timing and combination of treatments for patients with advanced BCC.

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