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REVIEW

New Emerging Treatment Options for Advanced Basal Cell Carcinoma and Squamous Cell Carcinoma

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ABSTRACT

Non-melanoma skin cancers, also known as keratinocyte tumors, have an increasing incidence worldwide, with basal cell carcinoma and squamous cell carcinoma being the most represented ones. Although surgery represents the gold-standard treatment for both tumors, some cases can progress to an advanced or a metastatic state and targeted therapy is required. Hedgehog signaling pathway has an important role in the development of basal cell carcinoma, and its inhibition is the key to new treatment options available for the treatment of locally advanced and metastatic basal cell carcinoma. Cutaneous squamous cell carcinoma is the second most frequent malignant skin cancer; when presenting in advanced or metastatic stage, alternative treatments are required; cemiplimab is a human monoclonal antibody directed against programmed cell death-1 receptor that acts by blocking T-cell inactivation and is the first drug approved for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma. Studies evaluating pembrolizumab, ipilimumab and nivolumab as alternative treatments for advanced squamous cell carcinoma are still underway. Objective of this review is to analyze and discuss the novel therapies for advanced basal cell carcinoma and squamous cell carcinoma to obtain a sharper perspective of the available treatment options.

Keywords: Basal cell carcinoma; Squamous cell carcinoma; Hedgehog inhibitor; Vismodegib; Sonidegib; Cemiplimab

Key Summary Points

Why carry out this study?

Surgical excision remains the main recommended therapy for easy-to-treat basal cell carcinoma (BCC), while difficult-to-treat BCC, including locally advanced BCC (laBCC) and metastatic BCC (mBCC), still represent the real challenge

The majority of cutaneous squamous cell carcinoma (cSCC)s are successfully treated with surgical excision and radiation therapy. However, treating metastatic cSCC and locally advanced cSCC (lacSCC) remains the main goal of clinical practice

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New emerging treatment options for advanced forms of BCC and squamous cell carcinoma (SCC) are required to offer non-invasive alternatives to patients not eligible for conventional treatments

What was learned from the study?

Hedgehog inhibitors (HHIs) are promising alternative treatments for patients with advanced basal cell carcinomas; vismodegib and sonidegib, two oral smoothened (SMO) antagonists, have already been approved for the treatment of adult patients with advanced basal cell carcinoma

Currently, US Food and Drug Administration (FDA) has granted Orphan Drug and Breakthrough Therapy Designation for topical patidegib gel formulation in patients with basal cell carcinoma nevus syndrome, also known as Gorlin syndrome

Cemiplimab has been approved by the European Medicines Agency (EMA) and Food and Drug Administration (FDA) for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma, not eligible for surgery or radiotherapy, and for adult patients with locally advanced or metastatic BCC intolerant to a HH pathway inhibitor

INTRODUCTION

Non-melanoma skin cancers, also known as keratinocyte carcinomas (KC)s, are the most frequent tumors in the Western world [1, 2]. In particular, basal cell carcinoma (BCC) accounts for 80% of KCs, with cutaneous squamous cell carcinoma (cSCC) representing the remaining 20% [2].

BCC incidence is increasing worldwide with a lifetime risk of 20–30% [3]. They present as asymptomatic, enlarging and often bleeding lesions usually located in sun-damaged areas [4].

Conversely, cSCC has a rising worldwide lifetime risk of 9–14% for men and 4–9% for women, respectively [5]. Solitary red scaly plaques or nodules located in sun-exposed areas are the most common clinical presentation of cSCC [6].

While cSCC can develop metastasis in 3–7% of cases, BCC metastasis are rare [2].

Regarding risk factors, most of them are shared: chronic UV exposure, tanning bed use, ionizing radiations, fair skin, age > 70 years, immunosuppression and chronic inflammation are the most common ones [2].

Unique risk factors include blistering sunburns and some genetic alterations (basal cell nevus syndrome, telomeric function gene variants) for BCC and human papilloma virus infection, immunosuppressive drugs, arsenic and genetic diseases (xeroderma pigmentosum, oculocutaneous albinism) for cSCC, respectively [2, 4, 7, 8].

Surgical excision represents the gold-standard treatment for both tumors [9]. However, this approach depends on tumor characteristics, such as stage, histopathological subtype, location and patients' comorbidities [10–12]. Surgical excision, including Mohs micrographic surgery and destructive treatment (topical treatments such as imiquimod, 5-fluoruracil; cryotherapy, laser therapy, radiation therapy or photodynamic therapy) remain the main recommended therapies for easy-to-treat BCC. Difficult-to-treat BCC, including locally advanced BCC (laBCC) and metastatic BCC (mBCC), still represent the real challenge [13].

Most cSCCs are successfully treated with surgical excision, photodynamic therapy, laser treatment, cryosurgery and radiation therapy. However, treating metastatic cSCC (mcSCC) and locally advanced cSCC (lacSCC) remain the main goal of clinical practice [14].

Thus, new emerging treatment options for BCC and cSCC are required to offer non-invasive alternatives and a tailored-tail therapy to patients not eligible for conventional treatments such as surgery or radiation therapy. Objective of this review is to analyze and discuss the novel therapies for advanced BCCs and

cSCCs to obtain a sharper perspective related to the available treatment options according to specific patients' characteristics.

METHODS

A search of the PubMed, Embase and clinicaltrials.gov databases was performed using the following research terms: "basal cell carcinoma," "cutaneous squamous cell carcinoma," "keratinocyte carcinoma," "vismodegib," "sonidegib," "patidegib," "taladegib," "cemiplimab" and "pembrolizumab". Reviews, metanalyses, clinical trials (CT), real-life studies (RLS), case reports and series were reviewed, and the most relevant articles were included. The assessment of treatment efficacy was made through overall survival (OS), progression-free survival (PFS), recurrence-free survival (RFS), disease-free survival (DFS), durable response rate (DRR) and overall response rate (ORR). Articles and trials regarding standard treatments, such as surgery or radiation therapy, used to treat KCs were excluded. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

NEW EMERGING THERAPIES FOR ADVANCED BCC

Basal Cell Carcinoma and Hedgehog Pathway Inhibition

Hedgehog (HH) pathway, usually silenced in adults, has a key role in different aspects of cell life such as organogenesis, patterning, proliferation, survival and differentiation [15]. It was originally discovered in Drosophila. The HH signaling cascade could be stimulated by three different ligands that are involved in this pathway: Sonic hedgehog (SHH), Indian hedgehog and Desert hedgehog. However, SHH is widely expressed in human tissues [16]. These ligands bind to the receptor Patched-1 (PTCH), a membrane receptor localized on the surface of target cells, which normally acts by inhibiting Smoothened (SMO), another membrane protein, thus initiating the HH signaling cascade [17]. The inhibition of SMO is relieved, resulting in an aberrant activation of the cascade.

In this pathway, SMO has a key role; it acts by activating HH signaling cascade and leads to the activation of the transcription factors for glioma-associated oncogene homolog 1 (Gli1), which activates angiogenetic and target genes (Bcl-2, Cyclin-D1 and Myc) [17]. In absence of SHH ligand, HH cascade is inactive and PTCH inhibits SMO activity preventing Gli1-target gene transcription. The HH pathway is involved in cell growth regulation and differentiation during embryogenesis and is not active in adult tissues. The aberrant activation of HH pathway is characterized by an increased cell proliferation and survival, implicated in the pathogenesis of different solid tumors including BCC. Patients with Gorlin syndrome present a germline mutation (single hit) in PTCH gene that relieves SMO inhibition leading to the development of multiple BCCs along with other tumors. Approximately 90% of cases of sporadic BCCs, instead, present a somatic mutation causing loss of function (two hits) in PTCH gene [18]. Thus, targeting the HH pathway is the active principle of the new oral drugs for the treatment of advanced BCCs. The HH inhibitors act by binding to SMO, thus preventing Gli1 release and tumor growth. The HH pathway and role of HH inhibitors are represented in Fig. 1.

The main features in terms of efficacy and safety of the HH inhibitors are reported in Table 1.

Vismodegib

Vismodegib (Erivedge®) is an oral, second-generation cyclopamine derivate that acts by binding to SMO, thus inhibiting the HH pathway [19]. It was approved in January 2012 by the Food and Drugs Administration (FDA) and in 2013 by the European Commission to treat patients aged $\geq$ 18 years with laBCC and mBCC who present recurrence of BCC following surgery or radiation therapy or those who are not candidates for surgery or radiotherapy. The approved dosage is 150 mg daily [19]. Vismodegib is controindicated in women who are either pregnant or breast-feeding because of its

potential embryotoxicity, as HH signaling plays a key role in early embryogenesis.

Its efficacy and safety have been evaluated in phase I and phase II clinical trials [20–23]. The first phase I study including 33 patients presenting with advanced BCCs was conducted in 2009; all patients were treated with 150 mg daily of oral vismodegib for a median duration of response of 12.8 months reporting an objective response rate (ORR) of 58% [20]. The ORR includes the percentage of patients reporting complete and partial response to treatment. The approval of the drug was related to a phase II, single-arm, two-cohort, multicenter trial (ERIVANCE) [21]. A total of 104 patients, divided in two cohorts (laBCC and mBCC) and receiving vismodegib 150 mg daily, were included in the study. The primary endpoint was the ORR, defined as ≥ 30% tumor size reduction or complete resolution of tumor ulceration in laBCC and as ≥ 30% decrease in sum of longest diameter of target lesions for mBCC. The laBCC group (n = 63) reported an ORR of 43% (95% CI 31–56), while, the mBCC group (n = 33) reported an ORR of 30% (95% CI 16–48) according to the efficacy analysis by independent review. ORRs of 60% and 46% for laBCC group and mBCC group, respectively, were reported by the investigator-assessed efficacy analysis. Regarding drug-related adverse event (AE)s, all patients experienced at least one AE, with muscle spasms, alopecia and dysgeusia being present in 71.2%, 66.3% and 55.8% of cases, respectively. Regarding severe AEs (grade ≥ 3), weight decrease (8.7%) and muscle spasms were the most frequently reported. Eight patients experienced grade 5 AEs, but the investigator did not consider any of the deaths related to the treatment. The 39-month follow-up confirmed the positive results, reporting an ORR of 60.3% and 48.5% for the laBCC and mBCC group, respectively. Vismodegib efficacy was also assessed by an expanded access study conducted on 119 patients with either laBCCs and mBCCs treated for a median duration of 5.5 months; 46.4% for the laBCC group and 30.8% for mBCC group were the ORRs reported [22]. Later, the STEVIE trial, a single-arm multicenter study, confirmed vismodegib efficacy on a larger cohort of patients (1215 patients; 1119 with laBCC and 96 with mBCC); in particular, an ORR of 69% (95% CI 66–71) and an ORR of 37% (95% CI 27–48) were reported in the laBCC and mBCC group, respectively [23]. The safety profile confirmed what was reported in previous trials; the occurrence of treatment-emergent adverse events (TEAEs) per 100 patient-years of exposure showed higher rates during the first

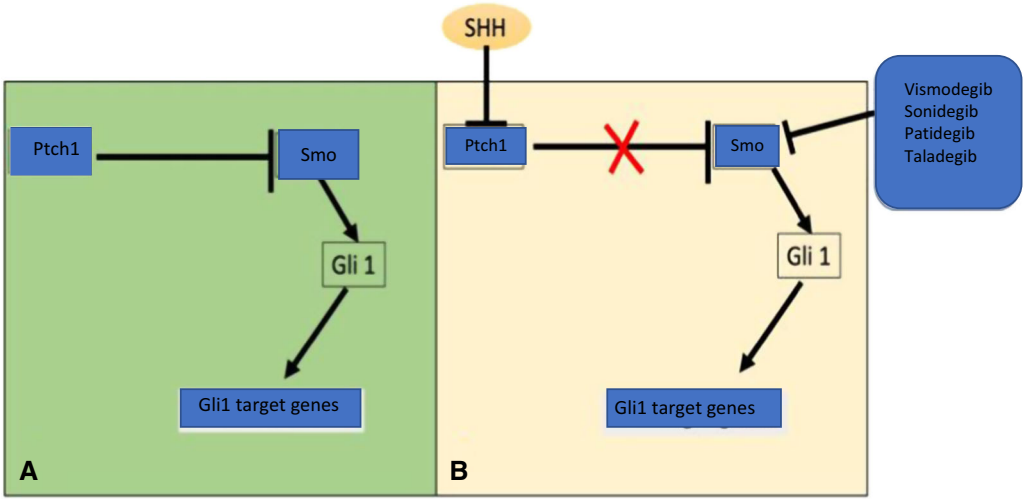

Fig. 1 **A** Normal Hedgehog pathway. **B** Dysregulated Hedgehog pathway with mechanism of action of investigated Hedgehog inhibitors. *Pthc1* Patched-1, *Smo* Smoothened, *Gli1* glioma-associated oncogene homolog 1, *SHH* Sonic Hedgehog

Table 1 Main features of the Sonic Hedgehog pathway inhibitors in clinical trials

Drug	Dosage	Tumor	Study	Patients	TTR	ORR	AE
Vismodegib [20]	Oral 150 mg QD	BCC	Phase I	33	NR	58%	NR
Vismodegib [21]	Oral 150 mg QD	BCC	ERIVANCE	Total: 104 mBCC: 33 (31.7%) laBCC: 63 (60.6%)	mBCC: 57 days laBCC: 140 days	Total: 53 (51.0%) mBCC: 30% laBCC: 43%	Muscle spasms (74, 71.2%) Alopecia (69, 66.3%) Dysgeusia (58, 55.8%)
Vismodegib [23]	Oral 150 mg QD	BCC	STEVIE	Total: 1215 mBCC: 96 (7.9%) laBCC 1119 (92.1%)	3.7 months	Total 769 (66.2%) mBCC: 31 (36.9%) laBCC: 738 (68.5%)	Muscle spasms 793 (65.3%) Alopecia 732 (60.2%) Dysgeusia 647 (53.3%)
Sonidegib [28]	Oral 200 mg QD	BCC	BOLD	Total: 79 mBCC: 13 (16.5%) laBCC: 66 (83.5%)	mBCC: 4.6 months laBCC: 3.8 months	36%	Muscle spasms 39 (49.4%) Alopecia 34 (43.0%) Dysgeusia 30 (38.0%)
	Oral 800 mg QD	BCC	BOLD	Total: 151 mBCC: 23 (15.2%) laBCC: 128 (84.8%)	mBCC: 1.0 months laBCC: 3.7 months	34%	Muscle spasms 100 (66.2%) Dysgeusia 89 (58.9%) Alopecia 83 (55.0%)
Patidegib [32]	Oral $\geq$ 130 mg QD	BCC	Phase I	Total: 94 BCC: 39	NR	20.5%	Fatigue 51 (54.3%) Alopecia 36 (38.3%) Muscle spasms 22 (23.4%)
Patidegib [36]	Topic 2% BD	BCC	Phase II	6	NR	NR	None
	Topic 4% BD	BCC	Phase II	6	NR	NR	None
Patidegib [37]	Topic 2% BD	BCC	Phase III	36	NR	NR	None

Table 1 continued

Drug	Dosage	Tumor	Study	Patients	TTR	ORR	AE
Taladegib [38]	Oral 50–1000 mg QD	BCC	Phase I	Total: 84 BCC: 47 (56.0%)	NR	46.8%	Dysgeusia 41 (48.8%) Fatigue 37 (44.0%) Nausea 36 (42.9%)
Taladegib [39]	Oral 100 mg	BCC	Phase I	3	NR	NR	Dysgeusia 3
	Oral 200 mg	BCC	Phase I	3	NR	NR	Dysgeusia 2 Decreased appetite 1
	Oral 400 mg	BCC	Phase I	13	NR	NR	Decreased appetite 11 Fatigue 9 Nausea 9

TTR Time to response, *ORR* objective response ratio, *AE* adverse event, *QD* once daily, *BCC* basal cell carcinoma, *mBCC* metastatic basal cell carcinoma, *laBCC* locally advanced basal cell carcinoma, *W* week, *BD* twice daily

year of treatment, thus suggesting no trend toward new TEAEs or grade 3 TEAEs as treatment duration increased. Moreover, vismodegib showed promising results in terms of efficacy and safety also when administered at a long-intermittent dosing regimen [24].

Sonidegib

Sonidegib (LDE-225) is the second oral HH inhibitor approved for the treatment of adult patients with locally advanced BCC not eligible for curative surgery or radiation therapy. It was approved in July 2015 by the FDA under the trade name of Odomzo® and in August 2015 by the European Commission at the approved dosage of 200 mg daily [25]. Efficacy and safety of sonidegib have been evaluated in phase I and II clinical trials [26, 27]. The approval of the drug was based on the pivotal phase II multicenter study (BOLT) including 230 patients with laBCC and mBCC [28]. Patients were randomly divided into two groups: one receiving sonidegib at a dosage of 200 mg/daily (n = 79) and the other receiving 800 mg sonidegib daily (n = 151) with treatment continued until progressive disease, intolerable toxicity, withdrawal of consent or death.

The median follow-up was 13.9 months. In the primary efficacy analysis, an objective response was observed in 36% (95% CI 24–50) and 34% (95% CI 25–43) of patients receiving 200 mg and 800 mg sonidegib, respectively. Twenty-two percent of patients receiving 200 mg sonidegib and 54% of patients receiving 800 mg discontinued treatment. Ten percent of patients experienced mild-grade treatment-related adverse events (grade 1–2), including muscle spasms (49%), alopecia (43%), dysgeusia (38%), nausea (33%), raised blood creatine kinase (CK) levels (29%), fatigue (29%), decreased weight (27%), diarrhea (24%), decreased appetite (19%), myalgia (19%), headache (15%) and arthralgia (13%). The 30% of patients receiving sonidegib 200 mg once daily reported increased CK (4% grade 3; 3% grade 4), increased lipase (5%; all grade 3),

hypertension, asthenia and muscle spasms (all 3%; all grade 3). Secondary malignancies were also reported in 6% of patients. No deaths due to toxicity were reported. The 12- and 18-month follow-up confirmed sonidegib efficacy, and at the 30-month analysis, patients with laBCC and mBCC treated at the approved dosage of 200 mg daily reported an ORR of 71.2% and 33%, respectively, with a median duration of response of 15.7 months in laBCC and 18.1 months in mBCC patients [29, 30]. At the 42-month analysis of the BOLT trial, Dummer et al. confirmed sonidegib's long-term efficacy [31].

Patidegib

Patidegib, also known as saridegib or IPI-926, is a semysinthetic HH pathway inhibitor deriving from cyclopamine that selectively antagonizes the HH cascade by binding Smoothened receptor.

Jimeno et al. [32] conducted the first in-human phase I study, including 94 patients with advanced solid tumors treated with oral patidegib at different dosing regimen (ranging from 20 to 210 mg daily), to evaluate the pharmacokinetic profile, antitumor activity and dose-limiting toxicity. Thirty-nine patients had advanced BCC (5 were affected by Gorlin's syndrome); of these, 28 patients were considered evaluable, having received more than one dose and being vismodegib-naïve. Patidegib showed anti-tumor activity in patients who were vismodegib-naïve; complete response (CR) and partial response (PR) were assessed in two and six patients, respectively; however, two patients receiving patidegib after vismodegib treatment did not experience any objective response. Drug-related adverse events, including muscle spasms, fatigue, nausea and hair loss, were reported.

A Phase 2 double-blind, randomized, placebo-controlled trial evaluated the efficacy of patidegib gel compared to vehicle gel in 17 patients affected by Gorlin syndrome [33]. In particular, five patients were treated with placebo, six with patidegib 2% and six with patidegib 4% gel twice daily up to 26 weeks of treatment. Main objective of the study was to assess the change in BCC diameter, followed by the prevention of new BCCs. BCC > 5 mm in diameter of the face and > 9 mm in the other sites were defined as surgical eligible basal cell carcinoma (SEBs). At week 26, 2% and 4% topical patidegib caused tumor CR in 25% of SEBs ($p = 0.02$ compared with placebo), and a new facial BCC was assessed in 2/12 (16%) patidegib-treated patients ($p = 0.02$ for prevention). Moreover, patidegib 2% gel showed a reduction of 51.29% in the number of tumors from baseline, while patidegib 4% gel shown a reduction of 26.63%, demonstrating a better clinical effect at 2% vs. 4% concentration.

Safety of topical patidegib was also confirmed; no muscle cramps, hair loss and taste loss were reported [33]. Currently, the US Food and Drug Administration (FDA) has granted Orphan Drug and Breakthrough Therapy Designation for topical patidegib in patients with basal cell carcinoma nevus syndrome, also known as Gorlin syndrome [35].

Another Phase II, double-blind and placebo-controlled clinical trial on 36 patients with sporadic nodular BCC treated with patidegib 2% once daily ($n = 6$), 2% twice daily ($n = 6$), 4% once daily ($n = 6$), 4% twice daily ($n = 6$) or placebo ($n = 12$) for 12 weeks confirmed topical patidegib efficacy and tolerability and compared the 2% and 4% patidegib gel formulations by evaluating adverse events and molecular efficacy (Gli1 mRNA level). Results showed that patidegib 2% gel has higher clinical and molecular efficacy than 4% gel [36]. Phase III trials (NCT04155190) and (NCT03703310), evaluating patidegib topical gel 2% efficacy in patients with Gorlin syndrome and with sporadic BCCs, are ongoing [37].

Taladegib

Taladegib, also known as LY2940680, is an anthranilamide derivative currently under study. It is a second-generation HH inhibitor acting by inhibiting SMO-receptor. A Phase I study, including 84 patients with advanced solid tumors, treated with different dosages (from 50 to 1000 mg) of taladegib once daily, showed its efficacy in treating patients with advanced BCC who had previously received Hedgehog inhibitor or not [38]. Of all the patients, 47 had BCC. Among these, a CR was

assessed in 5 (6.0%) patients and PR in 17 (20.2%). The most common AEs reported were dysgeusia (41, 48.8%) followed by fatigue (37, 44.0%), nausea (36, 42.9%) and muscle spasms (34, 40.5%) [38].

Another Phase I study including 19 Japanese patients with advanced solid tumors showed that taladegib should be used at doses of 100 mg or 200 mg in this population, not at the global recommended dosage of 400 mg. The main AE reported was dysgeusia (13/19, 68.4%) followed by decreased appetite (12/19, 63.2%), nausea (9/19, 47.4%), fatigue (9/19, 47.4%) and vomiting (6/19, 31.6%). However, no data on efficacy of taladegib in BCC were evaluated from this study [39]. Currently, there are different trials investigating the use of taladegib in several tumors such as small-cell lung cancer, medulloblastoma and gastroesophageal adenocarcinoma [40].

Immune Checkpoint Inhibitors for Cutaneous SCC

The immune system plays a key role in the development of KC [2]. In particular, most cSCCs with high mutation rates are strongly associated with immunosuppression [41], and the high expression of Programmed-Death - Ligand-1 (PD-L1) and Programmed-Death (PD-1) receptor has been assessed in these tumors [42]. Thus, targeting the PD-L1/PD-1 axis to avoid the cancer immune evasion is the rationale for developing treatments that have emerged in recent years.

The main features in terms of safety and effectiveness of the immune checkpoint inhibitors are reported in Table 2.

Cemiplimab

Cemiplimab (LIBTAYO®) is a human monoclonal antibody that acts by targeting PD-1, a membrane receptor which is expressed on activated T and B lymphocytes and macrophage, thus blocking its interaction with PD-L1 and PD-L2 [43].

It has been approved by the EMA and FDA-approved to treat adult patients affected by locally advanced and metastatic cutaneous squamous cell carcinoma who are not suitable for surgery or radiotherapy and as first-line treatment for adult patients presenting with non-small-cell lung cancer (NSCLC) expressing PD-L1, with no EGFR, ALK or ROS1 [44].

Recently, it has also received EMA approval for the treatment of locally advanced or metastatic BCC not responding to HH pathway inhibitor.

Two open-label, multi-center, nonrandomized studies (Study 1423, $n = 26$; Study 1540, $n = 193$ [EMPOWER-CSCC 1]) involving 219 patients with mcSCC or lacSCC evaluated the efficacy and tolerability of cemiplimab [44]. In study 1423, 26 patients (mcSCC:16; lacSCC:10) were treated with cemiplimab 3 mg/kg intravenously every 2 weeks up to 48 weeks [44]. The incidence of treatment-emergent AEs was the primary objective to be evaluated. An ORR (complete response rate of 7.7% and partial response rate of 42.3%) was reported in 50% of patients, whereas five patients reported stable disease (SD) and six presented progressive disease; two patients were not evaluable for response. A disease control rate of 65% and median time to response of 2.3 months (range: 1.7–7.3) were also reported.

The phase II trial EMPOWER-cSCC 1 had assessment of the ORR as primary objective [45]. One hundred ninety-three patients were enrolled and divided into three groups: group 1 ($n = 59$ patients) with mcSCC receiving cemiplimab 3 mg/kg every 2 weeks, group 2 ($n = 78$ patients) with lacSCC receiving 3 mg/kg biweekly and group 3 ($n = 56$ patients) with mcSCC receiving a dose of 350 mg intravenously every 3 weeks [46].

A median time to response of 1.9 months was reported for group 1 and 2, whereas, a median time of 2.1 was described for group 3. Interestingly, group 2 reported an ORR of 44% (CR: 13%; PR: 31%). Durable response for a period $\geq$ 6 months was seen in 68% of patients. Regarding the other two cohorts of patients enrolled, Group 1 showed an ORR in 49% of patients and patients in group 3 reported an ORR of 41.1% [45, 46]. Finally, a multicenter, prospective, non-interventional phase IV trial, CASE (CemiplimAb-rwlc Survivorship and Epidemiology, NCT03836105), designed with the

Table 2 Main features of the immune checkpoint inhibitors in clinical trials

Drug	Dosage	Tumor	Study	Patients	TTR	ORR	AE
Cemiplimab [44]	Iv 3 mg/kg Q2W	cSCC	Study 1423	26	2.3 months	13 (50.0%)	Fatigue 7 (26.9%) Constipation 4 (15.4%) Decreased appetite 4 (15.4%)
Cemiplimab [44–46]	Iv 3 mg/kg Q2W	mcSCC	EMPOWER-CSCC 1 (group 1)	59	1.9 months	29 (49.2%)	Diarrhea 16 (27.1%) Fatigue 14 (23.7%) Nausea 10 (16.9%)
	Iv 3 mg/kg Q2W	lacSCC	EMPOWER-CSCC 1 (group 2)	78	1.9 months	34 (43.6%)	Fatigue 32 (41.0%) Diarrhea 21 (26.9%) Pruritus 21 (26.9%)
	Iv 350 mg Q3W	mcSCC	EMPOWER-CSCC 1 (group 3)	56	2.1 months	23 (41.1%)	Fatigue 16 (28.6%) Diarrhea 10 (17.9%) Nausea 10 (17.9%)
Cemiplimab [50]	Iv 350 mg Q3W	BCC	Phase II	84	4.3 months	26 (31.0%)	Fatigue 25 (29.8%) Diarrhoea 20 (23.8%) Asthenua 18 (21.4%)

Table 2 continued

Drug	Dosage	Tumor	Study	Patients	TTR	ORR	AE
Pembrolizumab [52]	Iv 200 mg Q3W	cSCC	KEYNOTE-629	Total: 159 lacSCC: 54 (34.0%) mcSCC: 105 (66.0%)	2.0 months	40.3 lacSCC: 50.0 mcSCC: 35.2	Pruritus 29 (18.2%) Fatigue 23 (14.5%) Asthenia 20 (12.6%)

TTR time to response, *ORR* objective response ratio, *AE* adverse event, *Q2W* every 2 weeks, *Q3W* every 3 weeks, *BCC* basal cell carcinoma, *mcSCC* metastatic cutaneous squamous cell carcinoma, *lacSCC* locally advanced cutaneous squamous cell carcinoma

aim of assessing several data from patients with lacSCC or mcSCC in treatment with cemiplimab at the labeled dosage (350 mg IV, Q3W) in a real-life experience, is still ongoing [47].

Data from real-life experiences confirmed the safety and the efficacy of cemiplimab in both locally advanced and metastatic cSCC, as assessed in clinical trials [48, 49].

Recently, an open-label, multicenter, non-randomized Phase II trial, including 119 patients with laBCC or mBCC resistant or intolerant to HH, evaluated the efficacy of endovenous cemiplimab 350 mg every 3 weeks for up to 93 weeks [44]. Stratigos et al. [50] reported the results from 84 evaluable patients. Six showed CR, while PR was observed in 21 patients. Moreover, 82 (97.6%) patients reported at least one AE, with fatigue being the most frequently reported (25, 29.8%).

Although the reported trial showed the efficacy and safety of cemiplimab for the treatment of patients with advanced BCC, to date, only one case from real-life experience has already been described in the literature [51].

Pembrolizumab

Pemrbolizumab is a PD-1 inhibitor recently approved by the FDA for the treatment of patients with recurrent or metastatic cSCC not curable by radiation or surgery.

The efficacy and safety of pembrolizumab in cSCC have been evaluated in a multicenter, non-randomized, Phase II trial (KEYNOTE-629) evaluating 159 patients with locally advanced, metastatic or recurrent cSCC treated with endovenous infusions of 200 mg pembrolizumab every 3 weeks. CR and PR were observed in 20 and 44 treated patients, respectively. One hundred ten patients reported drug-related AEs with pruritus being the most represented one ($n = 29$) [52].

To date, there is only a limited investigator-initiated, proof-of-concept study evaluating the efficacy and safety of pembrolizumab in patients with difficult-to-treat BCCs [53].

Nivolumab and Ipilimumab

Nivolumab and ipilimumab are two immune checkpoint inhibitors acting by blocking PD1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA4), respectively. Even if these drugs are currently approved for melanoma [54, 55], in the literature there are only a few cases reporting their use in cSCC and/or BCC [56–59]. However, several multicenter trials evaluating their efficacy in treating advanced BCC and SCC are ongoing [60–64].

DISCUSSION

KC are the most frequent tumors in the Western world [1, 2], with an increasing incidence of both BCC and cSCC worldwide. Although surgery represent the gold-standard treatment for these tumors, sometimes they can progress to

invasive forms, locally invading the underlying structures or metastatizing, thus requiring alternative options. In recent years, the challenging scenario of advanced and metastatic BCCs and cSCCs has changed with the introduction of new treatments. HH inhibitors (vismodegib and sonidegib) and the anti PD-1 cemiplimab are the therapeutic options already approved for the treatment of advanced BCCs and advanced cSCC, respectively [26, 43, 65].

Vismodegib and sonidegib act by inhibiting SMO receptor, thus blocking the HH signalling pathway, which has a key role in BCC pathogenesis. Several studies showed their efficacy in reducing tumor size up to complete regression of the disease [19, 25]. Moreover, HH inhibitors could also be used in patients with Gorlin syndrome, as studies showed complete regression of BCC and absence of progressive disease in a large proportion of treated patients. Muscle spasms, dysgeusia, diarrhea, fatigue, weight loss and alopecia are the AEs most frequently reported during HH inhibitor treatment; the correct management of AEs and use of supportive care to reduce their intensity should be an important strategy to adopt to avoid treatment discontinuation. Among the new emerging HH inhibitors, patidegib and taladegib are two promising molecules whose efficacy and safety are undergoing clinical investigations, and further studies are still required [32, 38]. In particular, topical formulation of patidegib could be a valid option for patients untreatable with oral HH inhibitors.

cSCC is the second cause of death from skin cancer, only preceded by melanoma, with an increasing worldwide incidence. Although most cSCCs are treated with surgery, $\leq 5\%$ of patients may present with non-resectable disease, including locally advanced (lacSCC) or metastatic (mcSCC) disease [6]. The introduction of checkpoint inhibitors has revolutionized the therapeutic scenario of advanced cSSC. Targeting the PD-L1/PD-1 axis seems to be the new objective of several studies to allow the treatment of lacSCC and mcSCC. Although cemiplimab and pembrolizumab have been recently FDA approved for the treatment of locally advanced and metastatic cSCCs, different studies investigating the efficacy and safety of nivolumab and ipilimumab in treating these tumors are ongoing [44, 54, 55]. The effectiveness of cemiplimab has been reported in clinical trials with $> 30\%$ of patients achieving an ORR. Similarly, ORR was reached in $> 40\%$ of patients treated with pembrolizumab.

As for most targeted therapies, drug resistance represents a challenge; the development of new molecules targeting different proteins involved in the HH pathway or in the PD-L1/PD-1 axis will allow overcoming resistance to treatment. Further data from clinical investigations and real-life experiences are still required to analyze the efficacy and tolerability of these drugs in the daily practice routine.

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