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Systemic Therapies for Advanced Basal Cell and Cutaneous Squamous Cell Carcinomas: Novel Targeted Therapies and Immunotherapies

Mirela Krišto[1], Mirna Šitum[1], Romana Čeović[2]

[1]Department of Dermatology and Venereology, Sestre milosrdnice University Hospital Center, Zagreb, Croatia; [2]Department of Dermatovenereology, University Hospital Center Zagreb, School of Medicine, University of Zagreb, Zagreb, Croatia

Corresponding author:
Mirela Krišto, MD
Department of Dermatology and Venereology
Sestre milosrdnice University Hospital Center
Vinogradska cesta 29
10 000 Zagreb
Croatia
mgrdovi@gmail.com

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ABSTRACT Nonmelanoma skin cancers (NMSC), basal cell carcinoma (BCC), and cutaneous squamous cell carcinoma (cSCC) are the most common malignancies worldwide with a prevalence of epidemic proportions and continually rising global incidence rates, associated with increased morbidity rates and significant economic burden of their management. Although treatable cancers with low rates of metastasis and mortality, NMSCs reach an incurable state in small proportion of patients, becoming advanced, unresectable, or metastatic. Until recent years, patients with these conditions were considered for palliative radiotherapy and/or classical chemotherapies, which offer modest clinical benefit. Based on better understanding of the pathogenesis of these cancers, novel targeted therapies have been developed. We review novel systemic approaches for the treatment of aggressive forms of BCCs and cSCCs, with special emphasis on approved targeted molecular therapies and immunotherapies.

KEYWORDS: nonmelanoma skin cancer, advanced basal cell carcinoma, advanced cutaneous squamous cell carcinoma, hedgehog pathway inhibitors, immune checkpoint inhibitors

INTRODUCTION

Basal cell (BCC) and cutaneous squamous cell carcinomas (cSCC), jointly referred to as nonmelanoma skin cancers (NMSC), are the most commonly diagnosed malignant neoplasms in Caucasians in most countries around the world (1,2), with BCC being the most common type and comprising approximately 80% of these NMSCs (3,4). Generally, the incidence and mortality rates of NMSCs are difficult to establish in many countries since they are usually excluded from cancer registries and death is uncommon.

It is well known that incidence rates of these tumors are increasing worldwide (3,4). It is estimated that one in five Americans will develop skin cancer in their lifetime (1). According to one estimate in the US, about 5.4 million NMSCs are diagnosed each year, occurring in about 3.3 million Americans, indicating that some people have more than one (3,5). Incidence rates of BCC in the US have risen by approximately 2% per year, and there are significant increases among women and individuals younger than 40 years in

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whom the incidence doubled, while the incidence of cSCC in individuals younger than 40 years tripled (3,6-9). In western Europe, incidence rates of BCC have risen 2-3 times in the last few decades (2).

One study has estimated a diagnosis rate of 15–35 cSCC per 100 000 people, with an average increase of 2-4% per year (3). In the United States, up to 420 000 new cases of cSCC have been estimated to occur in 2012 (6). Australia has the highest incidence of cSCC in the world, with over 300 000 patients diagnosed per year (3).

NMSCs are treatable cancers and have low rates of metastasis and mortality compared with other malignomas; however, their high incidence rates and treatment costs contribute significantly to the rising economic burden of health care, making it the fifth most costly cancer in the US (4,10).

Metastatic disease is rare, occurring in only 0.0028-0.55% of BCCs, and mortality rate is quite low (11-13). However, more locally aggressive BCCs cause significant morbidity (14). Although only 5% of cSCC will become locally advanced, recur, or metastasize, this still represents a significant problem (6,15). They are associated with significant morbidity and are responsible for the majority of NMSC deaths (16). Their overall mortality rate is estimated between 1 and 5% (15,17).

Approximately 2,000 people in the US die each year from these cancers, however it is thought that this rate has been dropping in recent years due to improved treatment options (5).

Risk factors for NMSC include chronic sun exposure, longer life expectancy, fair skin type, genetic disorders (e.g. Gorlin syndrome, xeroderma pigmentosum), history of NMSC, and immunosuppression (5,14,18,19). Exposure to ultraviolet (UV) light, particularly UVB, represents the greatest risk factor for the development of NMSC with a clear mutational signature of UV radiation (20,21). A history of blistering sunburns in younger age and exposure to UV radiation early in life as well as intermittently throughout life have been associated with BCC (22,23). In the past decade, indoor tanning has emerged as a significant risk factor for skin cancer, including early-onset BCC (24,25).

Chronically immunosuppressed patients (e.g. solid organ transplant recipients) are at high risk not only for NMSC but also for more aggressive phenotypes of these skin cancers due to impaired immunosurveillance (26,27). The risk of developing cSCC in this group of patients is 65 to 250 times as high as the risk in the general population (26-28), and the risk of BCC is significantly increased at a factor of 7 to 20 as compared with the normal population (29).

For the vast majority of NMSCs (more than 95%), surgery is the curative treatment of choice as it provides the best means of controlling that the entire tumor is removed (30). Besides excisional surgery as the gold standard, Mohs micrographic surgery and ablative methods can also be used.

Nonsurgical methods represent a therapy option for certain patients, as cure rates approach those provided by surgery in many cases, and other advantages are lower overall costs and more cosmetically acceptable outcomes (31,32).

These methods include superficial field therapies, such as photodynamic therapy, 5-fluorouracil (5-FU), imiquimod, and intralesional interferon alfa-2b, for low-risk, superficial tumors, as well as primary or adjuvant radiotherapy for patients not amenable to surgery.

However, in a small percentage of patients, the tumor reaches an incurable state because it becomes metastatic or locally advanced and is no longer amenable to surgery or radiotherapy. Advanced cSCC and advanced BCC are two conditions that involve these two incurable situations, and patients with these conditions are considered for palliative systemic therapy. Chemotherapy has been used to treat these patients, although no standard chemotherapeutic regimen exists and it remains unknown if any of it can provide long-term survival or quality-of-life benefits.

In recent years, knowledge of the pathogenesis of NMSCs has led to the development of improved therapy options for advanced cases. Herein we review recently available insights concerning the treatment of locally advanced and metastatic BCC and cSCC, with a special emphasis on novel targeted therapy and immunotherapy.

Advanced BCC

Although locally destructive with a low rate of metastasis and mortality, BCC can progress to an advanced stage in a small portion of patients, encompassing metastatic BCC (mBCC) and locally advanced BCC (laBCC), whereby becoming more difficult to treat (5,14,33,34). Metastatic disease occurs more frequently with large, untreated and aggressive primary tumors or with recurrent tumors (11,35,36). The most frequent sites of metastasis are the bone, lung, liver, and regional lymph nodes (11,36). It is estimated that once metastases develop the median overall survival is between 8 months and 7.3 years, with recently improving survival rates due to improved treatment options (12,13,36).

Large, aggressive or recurrent tumors or those that penetrate deeper into the underlying skin and

surrounding tissues are generally considered laBCC (33,37). When located in a difficult-to-treat areas (e.g. periorbital), those kinds of tumors can be challenging for effective surgery without causing significant morbidity, loss of function, or disfigurement, and may not be amenable to radiotherapy. LaBCCs are also associated with high recurrence risk (33,37).

Since there is no widely accepted definition of laBCC, several multidisciplinary groups of experts have recently proposed guidelines for defining laBCC in an attempt to facilitate proper diagnosis and effective treatment (33,38). According to one UK group, BCCs staged ≥II according to the American Joint Committee on Cancer guidelines are considered locally advanced (39), as well as those in whom current treatment options are contraindicated by disease- (tumor size, location, number, histological subtype, and recurrent disease) or patient-driven factors (age, effects on quality of life, patient opinion on therapy, genodermatosis, and immunosuppression) (33).

Management of patients with aBCC should include physicians with experience in this field and whenever possible a multidisciplinary team made of dermatologists, Mohs surgeons, head and neck surgeons, plastic surgeons, oncologists, radiologists, and pathologists, to help determine the best course of treatment (33,40).

Up to now, treatment options for patients with these tumors have been limited to surgery, radiotherapy, and consideration of chemotherapy, since there is no evidence of consistent efficacy with any chemotherapeutic regimen (41-43). However, rising knowledge of the pathogenesis of BCCs in recent years, specifically comprehension of the Hedgehog (Hh) pathway, made a leap towards development of inhibitors targeting this pathway which have shown a great promise in this difficult-to-treat disease.

Hedgehog pathway and targeted inhibitors

The Hh signaling pathway is an evolutionary conserved pathway of signal transmission from the cell membrane to the nucleus (44). It is essential for cell differentiation, proliferation, and tissue patterning during embryonic development (45,46). The Hh pathway is mostly inactive or poorly active in adults (44) and is involved in the maintenance of certain tissues and stem cells under normal conditions (46,47). However, aberrant activation of the Hh pathway has been detected in the development and promotion of several tumor types, including BCC, medulloblastoma, and gastrointestinal carcinomas (34). The signaling Hh pathway includes the ligands, i.e. three homologues of the Hh gene, Sonic (Shh), Desert (Dhh) and Indian (Ihh), patched receptors (PTCH1, PTCH 2), signal transducer smoothened (SMO), and glioma-associated oncogene (Gli) transcription factors (Gli1, Gli2, Gli3) (34). Signaling is initiated when 1 of the 3 Hh ligands binds to the extracellular region of the PTCH1, thereby relieving the inhibition that unbound PTCH1 exerts on the SMO (48-51). SMO can then activate downstream signaling that culminates with the expression of the Gli transcription factors that promote proliferation, survival, and differentiation, and represent the key genes involved in BCC tumorogenesis (14,52). BCC was first to be associated with aberrant Hh signaling when mutations in the PTCH1 gene were identified as the driving mutations in patients with Gorlin syndrome, often having numerous BCCs (53-55). Most spontaneous BCCs were found to have inactivating mutations in PTCH1 in 85-90% of cases and activating mutations in SMO in about 10% of cases (52-54,56,57).

Therefore, several of the small-molecule targeted therapies have focused on SMO inhibition.

Vismodegib (GDC-0449), a small-molecule compound optimized for selective and potent SMO inhibition, was the first Hh pathway inhibitor (HPI) which demonstrated clinical efficacy in patients with aBCC (58,59). It was followed by sonidegib (LDE225), another SMO inhibitor, with efficacy and safety profile similar to that of vismodegib (60,61). Additional SMO inhibitors, such as itraconazole, LY2940680, BMS-833923 and PF-044449913, are in various stages of clinical development for the treatment of patients with aBCC and other advanced cancers (62-64).

Vismodegib

Vismodegib is a first-in-class orally bioavailable agent which gained Food and Drug Administration (FDA) approval in 2012 for use in adult patients with mBCC or laBCC that has recurred following surgery or who are not candidates for surgery or radiotherapy (51,65,66). In the initial phase I trial by Von Hoff *et al*. that evaluated dose and toxicity of the drug and tumor responses, 33 patients with aBCC (18 with mBCC and 15 with laBCC) were enrolled and treated with vismodegib at one of three doses (150, 270 or 540 mg daily) (58). The median duration of treatment was 9.8 months and the objective response rate (ORR) was 58% (18 out of 33 patients responded); 2 patients had a complete response (CR), defined as 100% regression of the visible/palpable lesions; 6 patients had a partial response (PR), defined as more than 50% reduction in tumor diameter (58). The median duration of response (DOR) was 12.8 months. Of the patients

who did not respond, 11 had stable disease (SD) and 4 had progressive disease (PD). Molecular evaluation of tumor tissue was been included in the study and found elevated Gli mRNA levels in tissue samples of some patients with PD, raising the question of possible resistance (58).

Approval of vismodegib 150 mg once daily was granted based on the clinical efficacy demonstrated in the ERIVANCE phase II study by Sekulic *et al*. (59,65,66). This international, 2-cohort, single-arm trial enrolled 104 patients, 33 patients with mBCC and 71 patients with laBCC, who were treated with vismodegib 150 mg daily (59,67).

Results of the primary analysis found that most patients experienced tumor shrinkage in the laBCC cohort: ORR (CR+PR) was 43%, CR was achieved in 21% (defined as absence of BCC per histological assessment) and PR achieved in 22% (≥30% decrease of target lesions). SD was observed in 38%, whereas 13% had PD (≥20% increase in target lesion size or new ulceration/lesion). The median DOR in this cohort was 7.6 months, and the median progression-free survival (PFS) was 9.5 months.

In the mBCC cohort, the ORR was 30%; all responses were PRs. SD and PD were reported in 64% and 3%, respectively. Most patients with mBCC (73%) experienced tumor shrinkage. The median DOR was 7.6 months and the median PFS was 9.5 months (59,67).

The ERIVANCE study evaluated safety using the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 (59,68). In the primary analysis, the median duration of exposure to vismodegib was about 10 months in both cohorts of patients (59). All patients experienced ≥1 adverse events (AE), but most of them had only grade 1/2 AEs (67). The most common AEs were muscle spasms (68%), alopecia (63%), dysgeusia (51%), decreased weight (46%), fatigue (36%), nausea (29%), decreased appetite (23%), and diarrhea (22%). Thirteen patients (12%) discontinued treatment due to AEs, particularly due to muscle spasms. More severe AEs were reported in 25% of patients. Sixteen patients died by the time of primary analysis, but none of the deaths were considered related to vismodegib. The median duration of exposure in all patients was 12.9 months (67).

The safety and efficacy of vismodegib 150 mg once daily was assessed in 2 additional studies, an expanded access study (69) and the Safety Events in Vismodegib (STEVIE) study (70).

The expanded access study was an open-label, 2-cohort, multicenter US study which enrolled 119 patients, 62 patients with laBCC and 57 patients with mBCC (69). The median duration of exposure was only 5.5 months due to earlier termination of study appearing after FDA approval of vismodegib. In the laBCC cohort, the ORR was 46%, and in the mBCC cohort ORR was 31%. The safety profile of vismodegib was similar to that observed in ERIVANCE; most patients experienced at least one AE, primarily graded 1/2. The most common AEs were muscle spasms (71%), dysgeusia (71%), alopecia (58%), and diarrhea (25%) (69).

STEVIE, the largest vismodegib trial to date, was an open-label, multicenter study that evaluated safety (primary objective) and efficacy of vismodegib in 499 patients (468 patients with laBCC and 31 patients with mBCC) who were followed for ≥ 12 months (70). ORR was observed in 66.7% of patients with laBCC and 37.9% of those with mBCC. The median time to response was 2.7 months and the median DOR was 22.7 months. Most patients experienced ≥1 AE, and the most common AEs were similar to those reported in ERIVANCE, i.e. muscle spasms (64%), alopecia (62%), dysgeusia (54%), weight loss (33%), asthenia (28%), decreased appetite (25%), and ageusia (22%). 36% of patients discontinued therapy due to AEs (59,67,70). Other more serious AEs include significant fatigue, hyponatremia, hypocalcemia, and atrial fibrillation (71).

Sonidegib

Sonidegib gained approval in 2015 in the US and Europe for the treatment of adults with laBCC who are not candidates for curative surgery or radiotherapy (72). In Switzerland and Australia, sonidegib is also approved for the treatment of patients with mBCC (73,74). Approval of sonidegib 200 mg once daily was granted based on efficacy and safety demonstrated in the international, randomized, double-blind, phase II Basal Cell Carcinoma Outcomes With LDE225 Treatment (BOLT) study (61,72-74). The BOLT study included long-term follow-up data of 194 patients with laBCC and 36 patients with mBCC, randomized 1:2 into the sonidegib 200 mg and 800 mg daily treatment arms (61). More patients were randomized to receive sonidegib 800 mg based on phase 1 data, indicating that the higher dose would provide better efficacy (60). However, in BOLT sonidegib 200 mg demonstrated a better benefit-risk profile than sonidegib 800 mg (61); therefore further discussion has focused primarily on the 200-mg dose. The median follow-up in this study was 13.9 months. In primary analysis the ORR in patients with laBCC was 47% with CRs, PRs, SD, and PD reported in 3%, 44%, 44%, and 1.5 % of patients, respectively (61,75). Most patients experienced reduction in target lesion size. Similar efficacy of sonidegib was observed in patients

with aggressive and nonaggressive histological subtypes of laBCC (75).

The ORR in patients with mBCC was 15%, including 2 patients with PRs (61). Disease control (CR+PR+SD) was observed in 92% of patients and most of them experienced tumor reduction. The median PFS was 13.1 months, and PD or death was reported in only 4 patients (61).

In BOLT 12-month analysis, sonidegib continued to demonstrate sustained and meaningful tumor responses (75).

In the primary analysis, the most common AEs (200/800 mg; any grade) evaluated per CTCAE v4.03, which generally occurred more often with the 800-mg dose, were muscle spasms (49%/67%), alopecia (43%/55%), dysgeusia (38%/59%), nausea (33%/45%), elevated creatine kinase (CK) levels (29%/37%), fatigue (29%/36%), weight loss (27%/38%), and diarrhea (24%/22%) (61).

The most frequently reported grade 3/4 AEs (200/800 mg) were elevated CK and lipase levels. Discontinuation of treatment was observed in 20% and 32% of patients in the 200 mg and 800 mg arms, respectively, mainly due to muscle spasms, dysgeusia and weight loss. The most common serious AEs (200/800 mg) were elevated CK levels and rhabdomyolysis (61). In the primary analysis, 4 patients receiving sonidegib 800 mg died while on treatment, but none of these deaths were considered related to treatment (61).

Generally, the safety profile of sonidegib was similar to that of vismodegib (59,61,67,69,70), indicating that many of the AEs, such as muscle spasms and dysgeusia, are class effects (40). Both drugs carry a risk of severe birth defects or fetal death when a pregnant woman is exposed to them (40).

Other hedgehog pathway inhibitors

Other HPIs, such as itraconazole, BMS-833923, taladegib (LY2940680), and PF-04449913 are in various stages of clinical development; however no clinical data exists for treatment in aBCC (62-64). Itraconazole, a commonly used antifungal agent, demonstrated some efficacy and safety in patients with sporadic BCCs in an exploratory phase 2 study with PRs and SD reached in 4 patients (21%) each (62). On average, patients who received this drug had a 24% reduction in lesion area. AEs were generally mild and reversible (62).

Hedgehog pathway resistance and other implications

Although most patients with aBCC achieve disease control with HPI therapy, some of the patients are intrinsically resistant to treatment and others become resistant during it (59,61,67,76-79). In other words, primary and secondary drug resistances to HPIs are different (78,79). New heterozygous missense SMO mutations were sequenced in recurrent BCC tissues resistant to vismodegib (78,79). In cases of secondary resistance, isolated SMO mutations were not present in primary tumors that originally responded to treatment, but in distinct recurrent BCC nodules, suggesting a heterogenous and dynamic mechanism of resistance that can rapidly arise in recurrent tumor tissue (79). In case of primary resistance, genotyping patient tumors could identify patients with mutations and help avoid unnecessary treatment with a SMO inhibitor (34).

More interestingly, a resistance to sonidegib was also observed in a study of 9 patients with aBCC resistant to vismodegib, suggesting that chemoresistance can occur between different SMO inhibitors (80).

Disease recurrence in patients who initially responded to HPI treatment may be due to residual tumor cells escaping the cytotoxic effects of HPI therapy or becoming resistant to it (77). A study that analysed tumor biopsy specimens from patients with laBCC treated with vismodegib and who experienced recurrence following an initial response, found reactivation of Hh signal pathway, often associated with SMO mutations in or near the drug-binding pocket (inhibiting vismodegib binding) or in other SMO areas (likely contributing to SMO activation) (77). Thus, recurrence was associated with the proliferation of resistant, possibly preexisting subclones that emerged after the elimination of larger HPI-sensitive cell populations (77).

Given the above, alternative treatment strategies may prove beneficial in patients with aBCC. One approach is to target Hh signaling downstream of SMO in order to bypass acquired mutations affecting SMO inhibitor binding, i.e. through inhibition of the Gli transcription factors. GANT61 is an inhibitor of Gli1/2 transcriptional activity that has shown promising preclinical results in numerous tumor types (81-83).

Anti-programmed death-1 (PD-1) immunotherapy may be another emerging treatment option. One case report described achievement of near complete remission of HPI-resistant mBCC following anti-PD-1 antibody treatment (84).

Combination of HPIs and surgery (neoadjuvant therapy) could also prove beneficial for some patients to help achieve long-term responses and reduce the disfigurement associated with complex surgeries (40,85).

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Patients on HPI therapy often discontinue treatment due to mostly low-grade AEs and many of them consequently experience recurrence (61,67). Managing AEs and educating patients in order to prolong their time on therapy could help achieve deeper and more long-lasting responses, with intermittent HPI dosing schedules being one potential option (40,71).

In conclusion, HPIs have proven to be an effective treatment option for patients with aBCC. While the results of this treatment have been promising, there still remain questions regarding durability of the response, long-term tolerability of AEs, and more importantly acquisition of resistant mutations over time.

Advanced cSCC

In a small percentage of patients, cSCC reaches an incurable state referred to as advanced cSCC, because it becomes metastatic or locally advanced and is no longer amenable to surgery or radiotherapy (86). Several risk factors have been identified for recurrence and metastasis, such as large tumor diameter, poor histological differentiation, and immunosuppression (16).

Patients with this condition are considered for palliative radiotherapy and/or classical chemotherapies, which offer modest clinical benefit (87-89). Platin derivates, i.e. cisplatin or carboplatin, have been commonly used as the first-line molecules for advanced unresectable or metastatic cSCC but with limited clinical trial experience (88,90). Other molecules used for either advanced or metastatic disease include 5-FU, bleomycin, methotrexate, adriamycin, taxanes, gemcitabine, or ifosfamide alone or in combination (19), with RRs for single agents varying widely from 17 to 78% (91,92). Platins and 5-FU are often used as palliative treatment alone or in combination with radiotherapy (92). Combinations of cisplatin with either 5-FU, doxorubicin, or bleomycin have demonstrated some degree of efficacy, achieving CR in some cases (93). Polychemotherapies seem more effective than monochemotherapy but result in more side-effects and poor tolerance. There is currently no standard treatment of metastatic disease (94).

Newer treatment options with improved response rates are based on better understanding of the pathogenesis of cSCC.

Epidermal growth factor receptor (EGFR) and its family members are often overexpressed or activated in human carcinomas, including cSCC, and may contribute to enhance uncontrolled proliferation (94). Previous studies have shown that up to 80% of cSCC and 100% of metastatic cSCC express EGFR (95).

Additionally, recent studies have indicated that cSCC is highly mutated, displaying a complex genetic background (96). The high mutation burden of the tumor, i.e. increased neoantigen expression due to chronic skin damage from UV light and dramatically increased risk of cSCC among immunosuppressed people pointed to an important role of immunosurveillance for preventing cSCC in immunocompetent people (97-99). Therefore, cSCC has the clinical and molecular features of a tumor that is likely to be responsive to systemic immunotherapy with checkpoint inhibitors (100-102).

Immune checkpoint inhibitors, in particular monoclonal antibodies, are able to activate a T-cell-specific immune response and have shown impressive success in some adult malignancies, such as malignant melanoma, non-small-cell lung cancer, head and neck SCCs, and recently also in cSCC (94).

Cemiplimab is a high-affinity, highly potent human monoclonal antibody directed against PD-1 receptor expressed on activated T and B lymphocytes and macrophages, blocking its interaction with PD-ligand 1 (PD-L1) and 2 (PD-L2) on the surface of tumor (103,104). Binding of the PD-1 receptor to PD-L1 and PD-L2 results in suppression of T-cell effector function, which enables tumor cells expressing these ligands to avoid destruction by the immune system. Inhibition of PD-1 binding to PD-L1/PD-L2 has been shown to reverse this mechanism and has been associated with a response in several cancers, including cSCC (103).

Cemiplimab

Cemiplimab was approved in September 2018 in the US for the treatment of patients with metastatic cSCC or locally advanced cSCC who are not candidates for curative surgery or radiation (105,106). Cemiplimab is undergoing regulatory assessment in the EU for the same indication (104).

The recommended dosage of cemiplimab is 350 mg administered as an intravenous (IV) infusion over 30 min once every 3 weeks until disease progression or the emergence of unacceptable toxicity (105).

Due to immune response inhibition, cemiplimab has the potential to cause immune-mediated adverse reactions that may be severe and potentially fatal. On this basis, patients receiving cemiplimab should be monitored for signs and symptoms of immune-mediated adverse reactions with prompt medical management when detected (105).

Approval of cemiplimab was based on the efficacy and safety demonstrated in the 2-phase study.

The phase 1 study was an open-label, multicenter study that involved patients with advanced solid-tumor cancers (86). The primary end point was the safety and side-effect profile of cemiplimab. In the dose-escalation portion of the phase 1 study, a deep and durable response was observed in a patient with advanced cSCC (107). Adult patients with advanced cSCC were involved in the expansion cohorts of the phase 1 study (86).

The phase 2 study was a nonrandomized, global, pivotal study involving patients with advanced cSCC (86). This study was designed to involve adult patients who had metastatic cSCC with distant or regional metastasis or both (group 1), as well as adult patients who had locally advanced cSCC (group 2). The primary end point was the response rate (86).

For both studies, secondary end points included DOR, PFS, overall survival, and toxic effects. The time point for the primary analysis was reached for the metastatic-disease cohort. The phase 2 study for locally advanced cSCC is ongoing.

Adult patients who had locally/regionally advanced disease with either recurrence after two or more surgical procedures or in whom surgery would result in substantial complications or deformity, as well as adult patients with metastatic cSCC were included (86). For both studies, key inclusion criteria included Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate organ function, and at least one lesion measurable by Response Evaluation Criteria In Solid Tumors (RECIST) v1.1.10.

Exclusion criteria were ongoing or recent (within 5 years) autoimmune disease that was treated with systemic immunosuppressive therapy, previous treatment with anti-PD-1 or anti-PD-L1 therapy, solid-organ transplantation, or concurrent cancer, unless the disease was indolent or was not considered to be life-threatening (e.g. BCC) (86).

The treatment regimen was an IV dose of cemiplimab (3 mg per kilogram of body weight, administered over a period of 30 minutes) every 2 weeks. The duration of treatment was up to 48 weeks in the phase 1 study and up to 96 weeks in the phase 2 study or until the patient had unacceptable toxic effects or had confirmed disease progression (86).

In both studies, the patients were assessed for a response to cemiplimab every 8 weeks by means of imaging studies.

A total of 26 patients (10 with metastatic and 16 with locally advanced cSCC) were enrolled in expansion cohorts of the phase 1 study. Regarding previous treatments for cSCC, 58% had received previous systemic therapy and 77% previous radiotherapy. The median follow-up was 11.0 months (86).

The ORR was 50%. The rate of durable disease control was 65%. The median observed time to response was 2.3 months. The DOR exceeded 6 months in 7 of the 13 patients who had a response (54%) (86).

The most common AEs of any grade were fatigue (27%), constipation, decreased appetite, diarrhea, hypercalcemia, hypophosphatemia, nausea, and urinary tract infection (each occurring in 15% of the patients) (86,108-110). There were 5 deaths: 3 due to disease progression, 1 due to an unknown cause, and 1 due to an AE.

A total of 59 patients were enrolled in the metastatic-disease cohort of the phase 2 study. Regarding previous treatments for cSCC, 56% had received previous systemic therapy and 85% previous radiotherapy. The median follow-up was 7.9 months (86).

The ORR was 47% and the rate of durable disease control was 61%. A PR was observed in 24 patients and a CR in 4 patients. The median observed time to response was 1.9 months. The median DOR had not been reached at the time of the analysis. However, the DOR exceeded 6 months in 16 of the 28 patients who had a response (57%) (86).

At the time of data cutoff, 82% of patients continued to have a response and to receive cemiplimab. A response was observed in 49% of patients with distant metastasis and 43% of patients with regional metastasis (86).

The most common AEs were diarrhea (27%), fatigue (24%), nausea (17%), constipation (15%), and rash (15%) (86,108-110). Four patients (7%) discontinued treatment because of an AE. Severe AEs (grade ≥3) were cellulitis, pneumonitis, hypercalcemia, pleural effusion, and death. Overall, there were 11 deaths: 8 due to disease progression and 3 due to AEs.

Severity of AEs was graded according to the CTCAE v4.03 (86). Most AEs related to the treatment were grade 1 or 2 events.

In conclusion, cemiplimab had similar efficacy for the treatment of metastatic and locally/regionally advanced cSCC. Final data from the cSCC expansion cohorts of the phase 1 study and metastatic-disease cohort of the phase 2 study show that cemiplimab demonstrated an acceptable risk/benefit profile with substantial antitumor activity (in approximately half the patients) and durability of responses. Concerning the side-effect profile, cemiplimab was associated with AEs that are similar to those seen with other PD-1 inhibitors.

Other targeted therapies for advanced cSCC

There are almost no data regarding the use of either the anti-CTLA4 antibody ipilimumab or other anti-PD-1 agents, such as nivolumab or pembrolizumab, for the treatment of cSCC. There are single case reports of anti-PD-1 therapy with nivolumab and pembrolizumab for advanced unresectable or metastatic cSCC demonstrating a clinical effect and tolerability (111-114), but their use in the treatment of advanced cSCC is still off-label.

Anti-EGFR therapies alone or in combination with chemotherapy and radiotherapy have demonstrated clinical benefits (94). Cetuximab and panitumumab are two monoclonal EGFR-targeting antibiodies that have been evaluated in cSCC. Cetuximab is a chimeric monoclonal IgG1 antibody that prevents ligand-induced activation of EGFR and mediates a variety of antitumor activities (115). So far, the most important study in cSCC is a phase II trial of Maubec *et al*. (116), in which cetuximab was used as first-line single-drug therapy in 36 patients reaching a 69% disease control rate at week 6. Two CR and eight PR with acceptable skin toxicity have been achieved. In another report, neoadjuvant therapy with cetuximab alone or in combination with platinum salt and 5-FU have been proposed as a valid option for locally advanced cSCC (117). Cetuximab combined with radiotherapy has also shown interesting results in terms of response rate, disease-free survival, and overall survival (118,119).

Panitumumab demonstrated responses as a single-agent in patients with locally advanced cSCC in a phase II study (120).

Oral agents targeting the EGFR pathway include gefitinib and erlotinib. Gefitinib, which affects the ATP-binding site of EGFR, inhibits autophosphorylation and receptor activation. In a small phase II neoadjuvant study in patients undergoing resection or radiotherapy, it demonstrated CR in 18.2% and PR in 27.3% (121).

Similarly, erlotinib, another orally available EGFR inhibitor, has demonstrated responses in advanced cSCC alone (122) or in combination with other therapies (123,124).

Generally, EGFR pathway inhibition is well tolerated but results in modest disease control. Another problem is resistance to EGFR inhibition which develops relatively rapidly (125).

CONCLUSION

Until recent years, advanced (inoperable) and metastatic forms of NMSCs were limited to palliative treatment options which offer modest clinical benefit. Better understanding of the pathogenesis of these cancers, especially Hh signaling pathway and the role of immunosurveillence, has led to a breakthrough in the development of novel targeted agents and immunotherapies which are decreasing morbidity for those afflicted with refractory forms of NMSCs. Both HPI and immune checkpoint inhibitors have demonstrated satisfactory and sustainable antitumor activity with acceptable side-effect profiles. However, there still remain important questions regarding long-term benefits, tolerability of adverse effects, and acquisition of resistant mutations over time. Further clinical trials and real-world data are needed to better characterize their practical value and make better-informed treatment decisions.

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