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Review

Molecular Cancer Therapeutics

Efficacy of Hedgehog Pathway Inhibitors in Basal Cell Carcinoma

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Abstract

Basal cell carcinoma (BCC) is the most commonly diagnosed cancer. While most BCCs are amenable to surgery, some tumors can reach a more advanced stage or metastasize, and become ineligible for surgical resection or radiotherapy. Abnormal activation of the Hedgehog (Hh) pathway is a key driver in BCC pathophysiology. Consequently, inhibitors of the Hh pathway have been developed. Molecules that inhibit the receptor protein Smoothened (SMO) are the most advanced in clinical development. Vismodegib is the first-in-class SMO inhibitor and has been approved in a number of countries for the treatment of metastatic or locally advanced BCC. Several molecules have demonstrated antitumoral activity, but treatment may be limited in duration by a number of side effects, and it is not yet established whether these agents are truly curative or whether continued treatment will be required. Resistance to SMO inhibition has been reported in the clinic for which incidence and mechanisms must be elucidated to inform future therapeutic strategies. Intermittent dosing regimens to improve tolerability, as well as neoadjuvant use of Hh pathway inhibitors, are currently under investigation. Here, we review the most recent outcomes obtained with Hh inhibitors under clinical investigation in BCC.
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Introduction

Basal cell carcinoma

Basal cell carcinoma (BCC) is the most common malignancy in the fair skin population. It accounts for around 80% of all nonmelanoma skin cancers (NMSC; ref.1). The major carcinogenic factor for BCC is sunlight exposure, which explains why these tumors are often located on the face, head, and neck regions. It is a slow growing tumor that can cause substantial morbidity due to its proximity to eyes, ears, or nose, its tendency to relapse, its multiplicity, and the potential to invade and destroy local tissues. BCCs belong to a heterogeneous group of tumors ranging from superficial (Fig. 1A) to disfiguring invasive tumors that can, although rarely, metastasize (Fig. 1B).

BCC incidence

BCC incidence is difficult to estimate because NMSCs are usually not included in cancer registries. From the available data, it is evident that there are marked geographical variations in occurrence. In Europe, incidence ranges from 44.6 to 128 per 100,000 inhabitants (2). In the United States, age standardized yearly rates have been estimated at up to 407 cases per 100,000 inhabitants in men and 212 cases per 100,000 inhabitants in women (3). Strikingly, in Australia an incidence of as high as 2% per year has been reported in some regions (4). There is a worldwide increase in NMSC incidence, potentially due to factors such as longer life expectancy and increased recreational exposure to sunlight (5).

BCC classification

There are three recognized clinical subtypes of BCC: nodular, superficial, and morpheaform (5). Four classical histologic variants are identified: nodular, superficial, infiltrating, and morpheaform, and two further, less common, histologic forms: metatypical BCC, defined as a BCC that includes squamous carcinomatous differentiation, and mixed, or composite, carcinoma defined as a combination of a BCC and a squamous cell carcinoma (SCC), with each component being clearly histologically distinguishable.

In contrast to most cancers, tumor–node–metastasis (TNM) classification is not often used for BCC as these tumors rarely metastasize. Various guidelines have aimed to evaluate prognostic factors for BCC, which relate mostly to their potential to locally relapse rather than spread to distant sites. In a recent update of European guidelines, BCCs are classified in three major groups according to risk probability: low, intermediary, and high risk (5). Prognostic factors upon which this classification is based include tumor size, histologic subtype, tumor site, definition of clinical margins, and failure of previous treatment. Most of these tumors are curable by surgery or, for superficial tumors, by nonsurgical methods such as photodynamic therapy or imiquimod treatment. In some cases, tumors can destroy adjacent structures, such as muscle, bone or cartilage. This is often due to neglect of the tumor for many years, though rarely BCCs can be fast growing. These situations relate to locally advanced BCC (laBCC), which are defined as tumors not eligible for surgery or radiotherapy, or where these options are unlikely to be curative. MRI or tomodensitometry may be necessary for the evaluation of such advanced tumors and an interdisciplinary approach is recommended to manage these patients. Eligibility of laBCCs for surgery can be confounded by the degree of tumor progression, the

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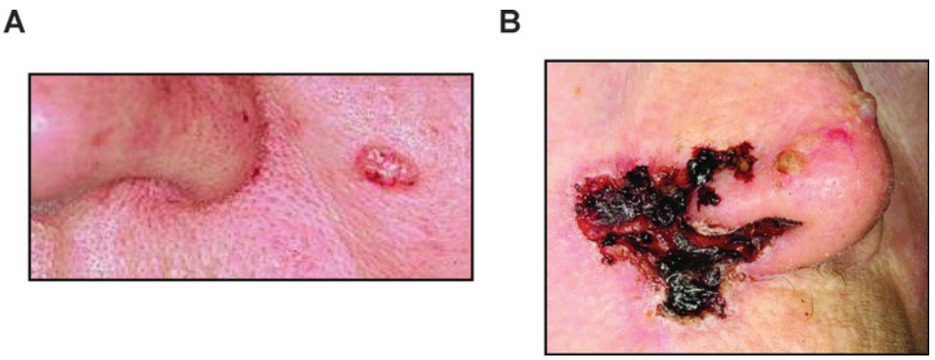

Figure 1.
BCC is a heterogeneous group of tumors ranging from a simple typical nodular lesion on the cheek (A) to much more aggressive and difficult to treat cases such as in B, where the tumor invades the lateral part of the nose, adjacent cheek, and upper labial skin and for which surgical removal has great morbidity in this elderly patient.

likelihood of achieving free margins, the high morbidity of surgical procedures or the presence of a contraindication. In addition, the use of radiotherapy may be complicated by factors such as prior radiotherapy, location, size, or contraindication to radiotherapy. Cytotoxic chemotherapies are not approved for nonresectable BCC. However, cisplatin and doxorubicin have been administered to patients (6) but are not well tolerated in this typically elderly population. Therefore, until recently these patients could only be offered palliative care.

Metastasis incidence in BCC is estimated to range from 0.0028% to 0.55% of cases (7). It is most frequently observed in the regional lymph nodes, followed by the lungs and liver (8). The prognosis of metastatic BCC (mBCC) is very poor, with a mean survival ranging from 8 months to 3.6 years. A recent mBCC literature review collated data from 172 cases and concluded that patients with distant metastases (DM; lung > bone > distant lymph nodes > liver) tended to be younger at the point of diagnosis than those with regional metastases (RM; regional lymph node > soft tissue or skin) and had a worse prognosis (24 months in patients with DM vs. 87 months for patients with RM; ref. 9). LaBCC and mBCC are hereafter referred to as advanced BCC (aBCC).

The Hh Signaling Pathway

Initially discovered in *Drosophilia melanogaster*, the Hh pathway is evolutionarily conserved and plays a key role in early development. It is largely inactive in the adult except for a few tissues such as the skin. For a comprehensive review of the Hh pathway, we direct the reader to a recent review on the subject (10). At the cell surface, reception of the Hh signal involves a number of transmembrane proteins, including the negative regulator Patched (PTCH), the positive regulator SMO, and the coreceptors BOC, CDO, GAS1. In vertebrates, the primary cilium, an antenna-like cellular projection, is critical for Hh signal transduction (11). In the absence of Hh ligands, PTCH localizes in the cilium and represses SMO activity, preventing its accumulation in the cilium. Upon Hh ligand binding to PTCH, SMO migrates to the tip of the cilium and initiates a signaling cascade that culminates in the activation of GLI transcription factors and their translocation to the nucleus through a still poorly characterized process involving molecules such as protein kinase A (PKA), KIF7 and the negative regulator SUFU. The 3 GLI family members (GLI1–3) are the final effectors of the pathway and regulate the transcription of key Hh target genes implicated in the control of cell differentiation, proliferation, and survival (Fig. 2A and B).

The Hh Pathway and Cancer

Two major mechanisms of involvement of the Hh pathway in human cancers have been identified: ligand-independent and ligand-dependent.

Ligand-independent

Mutations of different effectors of the pathway such as PTCH, SMO, and SUFU lead to constitutive activation of the Hh pathway independently of Hh ligand. These mutations have been reported in BCC (12–16), a subpopulation of medulloblastoma (17, 18), meningiomas without NF2 mutations (19, 20), and ameloblastomas (21). Variants in PTCH1 are found in other cancers, such as ovarian and endometrial (http://cancer.sanger.ac.uk/cancergenome/projects/cosmic/), however, their relevance to these diseases is not established.

Ligand-dependent

Hh ligands have been reported to be overexpressed in epithelial tumors, a subject that has been reviewed previously (22). Studies that have proposed autocrine requirements for Hh ligand have generally been confounded by off-target effects caused by the use of high levels of SMO inhibitors, such as cyclopamine (23). Hh ligand produced by tumor cells generally acts in a paracrine manner to activate the pathway in the surrounding stromal fibroblasts, as demonstrated for pancreatic carcinogenesis (24). One reported exception is the case of a reverse paracrine mechanism, where Hh ligand is secreted by bone marrow stroma in B-cell malignancies (25). While manipulation of the Hh pathway in the tumor microenvironment slowed down tumor growth in a xenograft model (26), SMO inhibitors used in genetically engineered mouse models of pancreatic ductal adenocarcinoma have led to ambiguous results (27, 28). Moreover, SMO inhibitors have so far failed to show any benefit in clinical trials, including pancreatic (29), colon (30), and ovarian (31) cancers, suggesting that more robust effects in preclinical models are required for translation in the clinic.

The Hh Pathway and BCC

The role of the Hh pathway in BCC was initially identified in patients with basal cell nevus syndrome (BCNS). BCNS is an autosomal-dominant disease characterized by multiple developmental abnormalities such as palmoplantar pits and odontogenic cysts, and predisposition to multiple neoplasias, including BCC and medulloblastoma (15, 16). BCNS is most frequently associated with germline mutations in *PTCH1*. Following this discovery,

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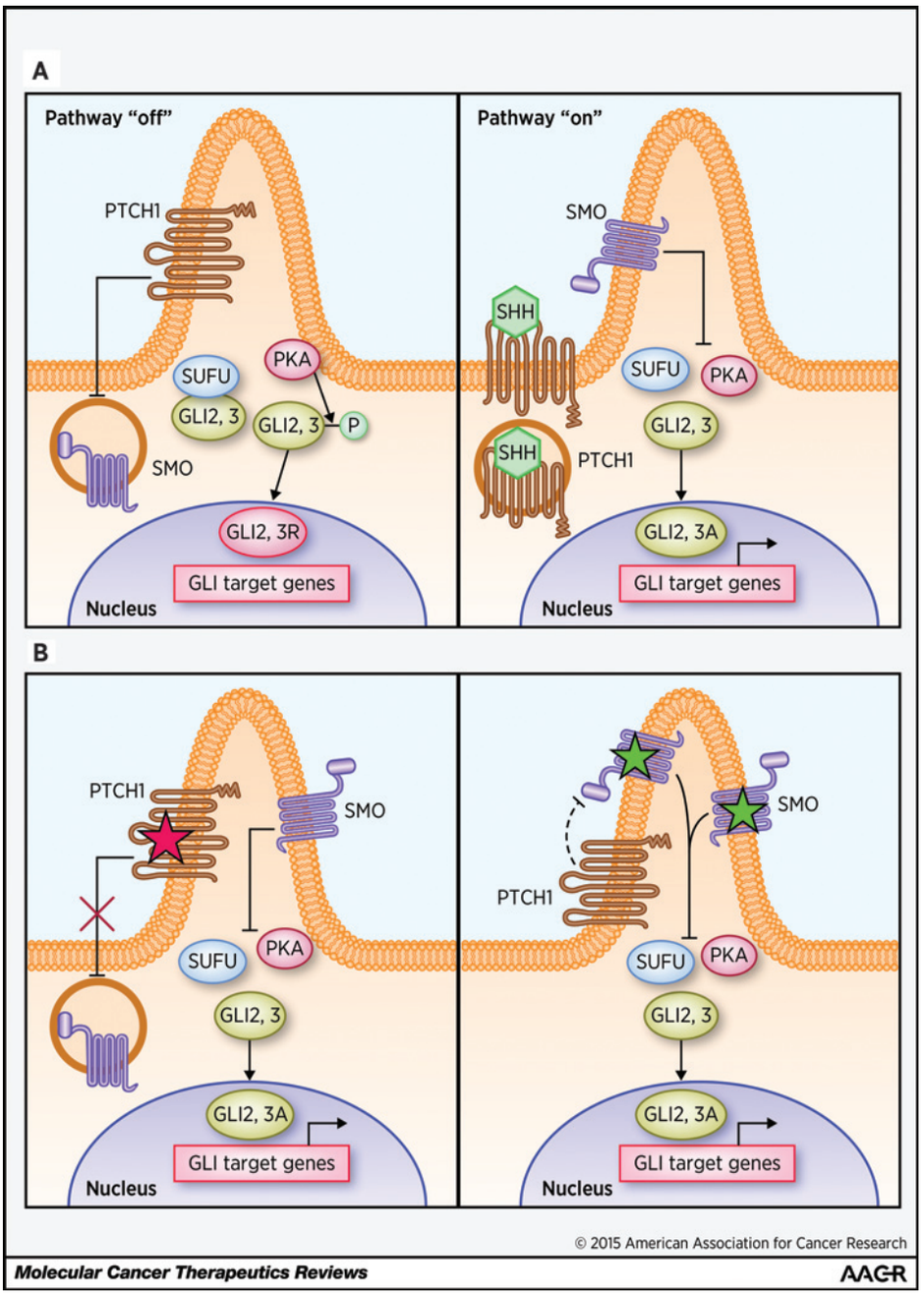

Figure 2.
Schematic overview of the core components of the Hh pathway. A, in the absence of Hh ligands, PTCH1 is localized in and around the primary cilium, where it represses the activity of SMO. Protein kinases, including PKA, phosphorylate the GLI proteins, GLI2 and GLI3. SUFU sequesters GLIs in the cytosol. This leads to their proteolytic cleavage to generate the repressor forms (GLI2R and GLI3R, respectively). In the presence of SHH ligand, PTCH1 exits, and SMO accumulates in, the primary cilium. The activation of SMO results in the dissociation of the GLI–SUFU complex and the transport of full-length, activated GLI2 and GLI3 proteins to the nucleus, bypassing proteolytic processing. B, in BCC, hyperactivation of Hh signaling can be caused by mutations and/or copy loss of PTCH1 (PTCH2 has yet to be associated with carcinogenesis). The loss of PTCH1 activity leads to uncontrolled activation of SMO (left panel). In sporadic BCCs, constitutively activating SMO mutations have been identified, which render SMO refractory to the inhibitory activity of PTCH1 and therefore cause unrestrained activation of the pathway (right panel).

somatic mutations in *PTCH1*, often associated with loss of heterozygosity, have been found in approximatively 90% of sporadic BCCs (13, 14). In addition, sporadic BCCs without *PTCH1* mutations have been reported to harbor gain-of-function *SMO* mutations (12, 32). A few cases of familial *SUFU* mutations have been identified, which have very recently been linked to BCC occurrence (33, 34).

Murine models with mutations in Hh pathway components develop similar patterns of tumors depending on the strain background including BCC and medulloblastoma, confirming that the Hh pathway is a driver in these cancers (35, 36). Interestingly, these mouse models do not develop any of the tumor types where Hh ligand overexpression has been suggested to play a role, indicating that Hh signaling does not represent a major driver of disease in these tumors. Other genetic and epigenetic changes may be implicated in the various clinicohistologic subtypes of BCC described above but have not yet been identified.

Development of Hh Pathway Inhibitors

Small-molecule regulation of SMO

Given that most ligand-independent Hh pathway cancers are driven by inactivation of PTCH1 or activation of SMO, targeting the pathway at the level of SMO or downstream was a viable

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strategy. This was achieved in nature by cyclopamine, a natural product isolated from corn lilies, responsible for inducing cyclopia in newborn sheep, and discovered to be a SMO inhibitor (37). However, the relatively poor oral solubility and specificity of cyclopamine, with consequent off-target effects (38), precluded its use in humans. High-throughput *in vitro* screens led to the discovery of a large number of other synthetic SMO antagonists, including the now FDA-approved therapeutic vismodegib (Table 1).

Preclinical efficacy models

As described above, mice with mutations in *Ptch1* or *Smo* genes leading to constitutive activation of the Hh pathway develop BCC and medulloblastoma. These mouse models were critical to the development and testing of HPIs because there were no cell line or xenograft models available for tumors driven by Hh pathway mutation. These models were used to test the effect of Hh pathway inhibition on tumors in their native environment, or following transplantation under the skin of recipient animals to generate allografts.

The activity of an Hh antagonist (Hh-Antag) was first explored in *Ptch1*$^{+/-}$ *Trp53*$^{-/-}$ mice (39), a spontaneous medulloblastoma model, where it was shown to inhibit the Hh pathway, leading to tumor regression and improved survival. Moreover, in subcutaneous allograft models generated from *Ptch1*$^{+/-}$ mice, it was shown that vismodegib could induce complete regression of tumors (40, 41). Importantly, in both the autochthonous and allograft models, it was demonstrated that the near complete

Table 1. Selected clinical trials with SMO inhibitors

SMO inhibitor	NCT identifier	Study phase	Patient population	Comments	Treatment regimen/comparator	Patients enrolled (*n*)
Vismodegib (GDC-0449; Curis/Roche)	NCT00607724	I	La BCC and mBCC		Continuous, dose escalation	33
	NCT00833417 (ERIVANCE)	II	La BCC and mBCC		Continuous	104
	NCT01367665 (STEVIE)	II	La BCC and mBCC		Continuous	1,200
	NCT00957229 (GORLIN)	II	BCNS; mutiple operable BCCs		Continuous	41
	NCT01835626	II	LaBCC	Combination with radiotherapy	Continuous	24
	NCT01815840 (MIKI)	II	Mutiple operable BCCs		Intermittent	200
	NTC01556009	II	Multiple operable BCCs		Intermittent/ photodynamic therapy	24
	TBD	II	Operable BCC	Neoadjuvant before classical surgery	Continuous	Unknown
	NCT01543581	II	Operable BCC	Neoadjuvant before Moh's surgery	Continuous/placebo	81
	NCT01201915	II	Operable BCC	Neoadjuvant before Moh's surgery	Continuous, various schedules	74
	NCT02067104	II	High risk of BCC	Chemoprevention study	Continuous/placebo	56
	NCT01700049	II	Various BCC subtypes	Response in various BCC subtypes	Continuous	36
Sonidegib (LDE225; Novartis)	NCT01529450	I	LaBCC and mBCC	Previously treated with non-LDE225 SMO inhibitor	Continuous	22
	NCT01208831	I	Solid tumors		Continuous	100
	NCT01327053	II	LaBCC and mBCC		Continuous, two dose levels	270
	NCT01350115	II	BCNS		Dose escalation	42
LEQ-506 (Novartis)	NCT01106508	I	Solid tumors		Dose escalation	71
Taladegib (LY2940680; Eli Lilly)	NCT01226485	I	Solid tumors		Dose escalation	70
	NCT01919398	I	Solid tumors		Dose escalation	12
BMS-833923 (Bristol-Myers Squibb)	NTC00670189	I	Solid tumors, including laBCC and mBCC		Dose escalation	70
TAK-441 (Millenium)	NTC01204073	I	Solid tumors, including BCC		Dose escalation	46

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suppression of the pathway (>90%) was required to see tumor regression (39, 42). The impressive activity of Hh inhibitors in these preclinical models supported the testing of these molecules in patients (Table 1).

Clinical experience with vismodegib (formerly known as GDC-0449)

Phase I. The initial phase I study of vismodegib was a dose-escalation study that evaluated doses ranging from 150 to 540 mg orally daily (43). Early data showed objective antitumoral activity in 18 of 33 aBCC patients with a median duration of vismodegib treatment of 9.8 months. Among these 18 patients, 2 achieved CR and 16 PR. The remaining patients had either stable disease ($n = 11$) or progressive disease ($n = 4$). Most patients responded within the first 2 months, but later responses were also observed. Of the 33 patients with aBCC, 8 patients experienced grade 3 adverse events (AE), which included fatigue, hyponatremia, muscle spasms, and atrial fibrillation. According to the pharmacokinetic properties observed in this phase I study, a 150 mg daily regimen was selected as the dose for future studies.

Phase II: ERIVANCE. The phase II ERIVANCE BCC study included 104 patients and the primary endpoint was objective response rates of over 20% (laBCC) and 10% (mBCC) assessed by independent review (44). At 9 months, the efficacy of vismodegib for both laBCC and mBCC was confirmed with overall response rates in 43% and 30% of laBCC and mBCC patients, respectively. Similar to the phase I study, common adverse events included muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, decreased appetite, and diarrhea. Serious adverse events (SAE) were reported in 25% of patients. Grade 5 AE (death) were reported in 7 patients; investigator assessments indicated these were unrelated to vismodegib treatment. These patients all had clinically significant risk factors or coexisting conditions at baseline that confounded the assessment of causality. This initial assessment of efficacy was followed up by an exploratory assessment of clinical benefit performed by independent clinical experts 12 months after the primary analysis. This panel considered the severity of the disease at baseline and the response to treatment on study and concluded that 71.4% of patients had severe disease before treatment and that 76.2% patients experienced clinical benefit (45). Additional exploratory analysis was performed in May 2012 to assess the durability of response and showed that 13 patients who did not have progressive disease at time of study discontinuation were still alive and available for follow up. Six of the 13 patients remained progression-free for more than one year. The other 7 patients showed at least one worsening target or nontarget lesion since treatment discontinuation. These data are derived from a very small number of patients and so it remains to be established if treatment with vismodegib can in some cases be curative or if combination with additional agents will be required (46).

A follow-up analysis of the ERIVANCE BCC study, performed 30 months after the primary analysis, confirmed the safety, efficacy, and tolerability results of the initial analysis. The investigator-assessed response rate was 48.5% in mBCC and 60.3% for laBCC. The duration of response increased from 7.6 to 12.9 months in mBCC and from 14.8 to 26.2 months in laBCC (47). While 17 additional deaths were reported none were considered to be related to the drug by the investigator (47). The efficacy observed in this phase II trial lead to the FDA approval of vismodegib, which is the first-in-class small-molecule SMO inhibitor for the treatment of aBCC.

Phase II: STEVIE. The STEVIE study is an ongoing global phase II safety study, which included approximately 1,200 patients with laBCC or mBCC. For STEVIE, vismodegib was administered orally at a dose of 150 mg once daily until progression or intolerable toxicity. The primary objective of the STEVIE study is safety. The interim analysis of the first 300 patients (laBCC, $n = 278$ and mBCC, $n = 22$) with the potential to be followed 3 months after initial therapy revealed that after a median treatment duration at data cut-off of 5.8 months (range 1–14.9 months) 55.4% laBCC and 68.2% mBCC were still under treatment and the remainder had discontinued the drug, mostly due to adverse events and in more rare cases due to disease progression (48). As observed for previous trials, the most common treatment emergent AEs (TEAE) were muscle spasms, alopecia, dysgeusia, ageusia, fatigue, weight loss, decreased appetite, and nausea. SAE occurred in 17.7% of patients and 13 deaths (4.3%) were reported, of which 3 were due to disease progression, 7 were not related to the drug and 3 could not be assessed. This interim analysis showed a vismodegib safety profile consistent with that seen in the pivotal ERIVANCE BCC study. The secondary objective of the study is overall response. The preliminary best overall response in patients with available data ($n = 251$) showed the following: 17.5% of CR, 39.8% or PR, 39% of stable disease and 2.8% of progressive disease. Thus, these preliminary efficacy data show tumor response and control in nearly all patients with aBCC.

Survival. Overall survival cannot be assessed effectively for laBCC because superficial BCC is rarely linked to mortality, and is generally slow growing. However, for patients with mBCC in the ERIVANCE study, the median overall survival was 33.4 months (49). The largest combined cohort to date with the longest follow-up were the phase I and phase II studies with vismodegib and demonstrated that, compared with historical data, the one year survival rate was 84.4% [95% confidence interval (CI), 73.9–95.0%] for vismodegib-treated mBCC patients with distant metastasis versus 58.6% for non-vismodegib–treated patients collected from the literature (49). The median survival of 2.8 years (95% CI, 2.0 to not estimable) versus 2.0 years suggested a potential survival benefit for these very poor prognosis cases.

Other studies. Vismodegib was made available for compassionate use through an expanded access program in the United States and the recently published results also confirmed the antitumor efficacy of vismodegib (50). In this small number of cases, responses appeared to be negatively associated with prior systemic therapy ($n = 9$) such as other Hh inhibitors ($n = 5$) or cisplatin in patients with laBCC, suggesting that these patients have either more aggressive tumors, or that vismodegib is more effective as a primary treatment. However, in this study, lack of response was not associated with prior systemic therapy in patients with mBCC.

The efficacy of vismodegib was also tested in patients with BCNS with a high BCC burden (around 40 lesions at baseline; ref. 50). Forty-one patients were randomized (2:1) to receive oral vismodegib 150 mg daily or placebo for a planned treatment period of 18 months. The rate of new surgically eligible BCCs was lower with vismodegib than with placebo (2 vs. 29 cases per group per year), as was the size of existing clinically significant BCC (−65% vs. −11%). Some patients achieved complete responses

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and none progressed while on drug. At the time of the report, 54% of patients receiving vismodegib discontinued the drug due to AEs. Among lesions that appeared to be clinically resolved, residual tumors were present in only 17% of biopsy samples. In a *post hoc* analysis of 7 patients who stopped vismodegib, 0.69 new surgically eligible BCCs developed per month after treatment discontinuation, a rate that is considerably less than that among patients receiving placebo, which was 2.4 per month (51). However, most surgically eligible BCCs regrew once the drug was stopped, underscoring the likelihood that in these cancer-prone patients maintained treatment with vismodegib may be required. Interestingly, palmoplantar pits of BCNS disappeared during vismodegib treatment. In addition, vismodegib treatment reduced the size of odontogenic cysts by at least 50% from baseline and could represent an alternative to surgery for some patients (52).

Vismodegib has currently obtained marketing authorization in several countries including the United States, Europe Union, Canada, Mexico, Switzerland, Australia, and South Korea, for mBCC and laBCC that has recurred after surgery or that is deemed inappropriate for surgery or radiotherapy. A number of studies are ongoing to extend or optimize its use in patients with BCC, such as intermittent dosing of the drug to improve tolerability or for its use as a neoadjuvant treatment to decrease the morbidity of surgical procedures (see Table 1). Accordingly, a recent publication reported that vismodegib treatment for 3 months or longer reduces the surgical defect area from baseline, which is of great clinical interest to physicians and patients with lesions located in sensitive locations that require treatment (53).

Squamous cell carcinoma and vismodegib treatment

There are a handful of reports suggesting a potential relationship between the occurrence of SCC in patients with BCC and treatment with vismodegib (54–56). This is a difficult issue to analyze for the following reasons: (i) these patients are at risk of developing both BCC and SCC, (ii) some BCCs can have squamous features, such as basosquamous carcinoma, (iii) cases treated by vismodegib had only a small part of their tumor analyzed by histology and it makes it difficult to rule out the potentially heterogeneous nature of the initial tumor. Molecular analyses are required to better define and characterize these types of tumors. Therefore, further studies are needed to critically address this issue.

Other Hh pathway inhibitors in the clinic

Other SMO inhibitors including BMS-833923 (XLI139; ref. 57), taladegib (LY2940680; ref. 58), PF-04449913 (59), LEQ506 (60), and sonidegib (LDE225; ref. 61) are currently being tested in phase I clinical trials in patients with advanced solid tumors including aBCC. Of these, sonidegib is the most advanced in the clinic (62). The phase I dose escalating study in solid tumors showed a maximum tolerated oral dose of 800 mg per day (61). In this study, 16 patients with BCC were included and 6 (37.5%) achieved an objective tumor response (PR or CR). Treatment-related grade 1/2 AEs were experienced by >10% of patients and included nausea, dysgeusia, anorexia, vomiting, muscle spasms, myalgia, increased serum creatine kinase (CK), fatigue/asthenia, and alopecia. Some grade 3/4 AEs were observed but no drug-related deaths were reported. Myalgia was associated with elevated creatine kinase (CK) most of the time. A phase II randomized 1:2 study comparing two doses (200 and 800 mg) of sonidegib in laBCC ($n = 194$) and mBCC ($n = 36$) showed antitumoral efficacy at both doses with better tolerability at the lower dose (62).

Preclinical studies aimed at identifying FDA-approved drugs with inhibitory activity on the Hh pathway revealed itraconazole and arsenic trioxide (ATO) as potential Hh pathway inhibitors (63, 64). Itraconazole is currently used to treat fungal infections and ATO is approved for the treatment of patients with acute promyelocytic leukemia. Unlike the complete tumor regression observed in preclinical models with HhAntag and vismodegib, itraconazole and ATO treatment resulted in a modest delay in tumor growth, consistent with these compounds only partially inhibiting Hh signaling (see Fig. 4C in ref. 63). In line with the suboptimal inhibition of the pathway by itraconazole observed preclinically, this molecule has so far yielded poor clinical efficacy with no complete responses observed with a treatment regimen of 200 or 400 mg/day (65). Consistent with the need to almost completely suppress Hh activity to see tumor responses, the authors note that itraconazole-treated patient BCCs experienced only a 65% reduction in Hh pathway activity. Similar to itraconazole, we anticipate limited efficacy of ATO for the treatment of BCCs.

Topical SMO inhibitors

The use of topical administration of SMO inhibitors is appealing because it could circumvent TEAEs observed with systemic therapies and allow for long-term dosing or use on operable tumors. A topical formulation of CUR61414 showed good antitumoral activity on BCCs from *K14-CreERT2*; *Ptch1*$^{+/-}$; *Trp53*$^{fl/fl}$ mice; however, it failed to induce tumor shrinkage in humans potentially due to species effects on potency or poor bioavailability in human skin (66). A topical formulation of LDE225 was also studied in 8 patients with BCNS presenting 27 BCCs, who received 0.75% sonidegib cream or vehicle (67). Among the 13 sonidegib-treated BCCs, 3 CR and 9 PR were observed, whereas only one PR was observed in the 14 vehicle -treated BCCs. However, further studies with the LDE225 topical cream were not pursued. These results highlight the challenges of topical delivery in an indication where the efficacy of surgical removal is very high.

SMO Inhibitor Resistance in BCC

Drug resistance is a major challenge to the long-term efficacy of targeted cancer therapies and unfortunately Hh inhibitors are no exception. Two major types of resistance can be observed. Primary resistance is defined as BCC tumors that do not respond to the drug and corresponds to <30% reduction in tumor size by RECIST (for mBCC). Overall response rates in the pivotal phase II study were 30% or 45% in mBCC cohort and 43% or 60% in the laBCC cohort based on independent review or investigator assessment, respectively. However, a *post hoc* clinical benefit assessment by independent clinical experts showed that 76.2% benefited from the treatment (45). The nonresponders included patients with stable or progressive disease. While the latter are truly resistant to the drug, it is not clear whether stable disease should be classified as drug-resistant. Primary resistance was predicted by a genomic analysis of Hh-driven medulloblastoma patient tumors and revealed variants in genes downstream of *SMO*, such as *SUFU*

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mutations, or amplification of *MYCN*, a Hh target gene (68). In medulloblastoma, mechanisms of primary resistance should be characterized and inform clinical decisions on SMO inhibitor use. However, it is worth noting that the genetic alterations associated with BCC typically affect *PTCH1* and *SMO* (14), and so anticipating primary resistance is more challenging.

Secondary resistance is defined as patients presenting with tumor regrowth after an initial response. Secondary resistance to vismodegib was first reported in a patient with metastatic medulloblastoma (69, 70) and more recently, it has been described for several patients with BCC (71). A biopsy from one of the metastatic lesions from the vismodegib-resistant metastatic medulloblastoma mentioned above revealed an acquired mutation in SMO that disrupted drug binding (69). To date, this is the only functionally characterized mechanism of resistance to a SMO inhibitor in the clinic; however, *SMO* mutations were recently observed in a vismodegib-resistant patient with BCC (72). Preclinical models of medulloblastoma have been used to investigate further potential mechanisms of resistance to the SMO inhibitors vismodegib and sonidegib, and have identified alternative genetic alterations including amplification of *Gli2*, an effector and downstream target of SMO, or activation of an alternative pathway such as the PI3K pathway (73), which was subsequently demonstrated to reduce, but not completely block, the response to vismodegib (74). It remains to be determined whether the mechanisms of resistance identified in medulloblastoma will be relevant to BCC. These data also suggest clinical resistance will not be specific to vismodegib as it can be observed with other SMO inhibitors (73). A phase II trial studying the efficacy of LDE225 in patients with aBCC showed no response in 9 patients previously treated with a SMO inhibitor suggesting that cross-resistance between two different drugs of the same class may occur (75).

Final Remarks and Perspectives

The prognosis and care of patients with aBCC have been dramatically improved by the development of SMO inhibitors that confer potent antitumor activity. Overall, the majority of patients with aBCC benefit from inhibition of the Hh pathway, consistent with the majority of cases harboring genetic alterations in Hh pathway components (13, 14). Tumor responses are generally observed within the first 2 months of treatment but some late responses have been observed up to 10 months after start of treatment. Despite this apparent success, important challenges remain to be addressed. First, the available data indicates that some patients with aBCC and BCNS relapse when the drug is discontinued. This implies that residual disease is present and favors tumor regrowth after treatment discontinuation. It is therefore unclear if these targeted treatments are truly curative or whether sustained therapy is required to maintain responses. This is challenging because side effects associated with on-target activity of SMO inhibitors significantly reduce patient compliance, posing a challenge to long-term treatment. Second, some patients exhibit primary resistance to SMO inhibitors. While progressive disease under treatment clearly reflects drug resistance, stable disease is more complicated to classify for this slow growing tumor. Tumor growth kinetics after treatment discontinuation may help to better define disease control in this subset of patients. Analysis at the histopathologic, clinical, and molecular features of these tumors is important to understand why these patients do not respond to SMO inhibitors and to help identify treatment strategies that could help to overcome such resistance. Third, as observed in medulloblastoma, secondary resistance to SMO inhibitors is starting to emerge in BCC but still needs to be thoroughly investigated at the molecular level. The frequency at which secondary resistance develops is not yet well established. A deeper understanding of the most common resistance mechanisms is needed to design next generation therapeutic strategies to treat these tumors. These may include the use of other SMO inhibitors when resistance mutations occur in the drug target itself, targeting components downstream of SMO, such as GLI, or combination therapy with drugs targeting other pathways such as PI3K. A promising future therapeutic option for downstream targeting of the Hh pathway is the use of bromodomain inhibitors, which were shown to inhibit GLI transcription and have recently entered the clinic for the treatment of other cancers (76).

Patients with BCNS also benefit from SMO inhibitors. In these patients with very high tumor burden, drug treatment not only shrinks existing tumors but also prevents the development of new BCC lesions and resolve palmoplantar pits and odontogenic cysts. However, as described above, TEAEs will limit the necessary long-term regimens required in this patient population. Future studies should be focused on identifying intermittent dosing regimens to improve tolerability without impairing efficacy. Finally, neoadjuvant use of SMO inhibitors to decrease surgical morbidity could be a promising avenue of investigation. Further exploration of the efficacy of SMO inhibitors in different BCC subtypes, analysis of residual disease, and analysis of the molecular mechanisms of resistance to SMO inhibitors should help to optimize the use of these inhibitors.

Disclosure of Potential Conflicts of Interest

N. Basset-Seguin has speakers bureau honoraria from and is a consultant/advisory board member for Roche. F.J. de Sauvage has ownership interest (including patents) in Roche. No potential conflicts of interest were disclosed by H.J. Sharpe.

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Molecular Cancer Therapeutics

Efficacy of Hedgehog Pathway Inhibitors in Basal Cell Carcinoma

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