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REVIEW

Targeted Therapy for Advanced Basal-Cell Carcinoma: Vismodegib and Beyond

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ABSTRACT

Basal-cell carcinoma is a commonly occurring skin malignancy that has the potential to progress into locally invasive or resistant disease, as well as spread distantly. Due to advances in the molecular understanding of the disease over the last two decades, it has been discovered that the Hedgehog pathway plays an important role in the pathogenesis of this disease and can be exploited as a treatment target. Several agents that inhibit the Hedgehog pathway have reached clinical studies and one drug, vismodegib, has recently been US Food and Drug Administration (FDA) approved based on clinical activity and tolerability in patients with advanced basal-cell carcinoma. This review will describe the clinical development of vismodegib, as well as the proper application of the drug in clinical practice. Other important clinical questions, such as mechanisms of resistance to vismodegib and the role of other Hedgehog pathway inhibitors currently in development will also be discussed.

Keywords: Basal-cell carcinoma; Hedgehog pathway inhibitors; LDE-225; Metastatic basal-cell carcinoma; Smoothened inhibitors; Vismodegib

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INTRODUCTION

Epidemiology

More than 2 million cases of nonmelanoma skin cancers were diagnosed in 2006 with approximately 80% of these being basal-cell carcinoma (BCC) [1]. Fortunately, BCC tumors rarely spread internally and are generally curable with local approaches such as surgical excision, radiotherapy, topical imiquimod, or photodynamic therapy [2]. However, in some cases BCC can progress to a point of significant local invasion such that surgical excision is not

feasible or removal is associated with excessive morbidity or disfigurement. Additionally, some BCC tumors are not amenable to radiotherapy due to being in sensitive locations, or they can recur post-radiation therapy making further localized approaches not possible. Finally, although very rare, BCC can metastasize to distant sites of the body, which is considered a terminal condition. Patients with metastatic BCC have a median survival of around 8 months [3]. Locally, invasive BCC that is not amenable to surgical or radiation approaches or metastatic BCC are termed advanced BCC, and until recently, limited treatment options were available for patients with advanced BCC. No cytotoxic chemotherapy has been approved for the treatment of advanced BCC; however, agents such as cisplatin have been used for patients with metastatic BCC with varied results [4].

Etiology

Similar to other skin malignancies, the risk of development of sporadic BCC has been linked to ultraviolet radiation exposure, skin type, family history, prior history of skin tumors, and immunosuppression [5–7]. However, a variety of hereditary syndromes can result in an increased risk of developing BCC tumors, including nevoid BCC syndrome, Bazex–Dupré–Christol syndrome, Rombo syndrome, Oley syndrome, and xeroderma pigmentosum [8]. Nevoid BCC syndrome, which is also known as Gorlin–Goltz syndrome or simply Gorlin syndrome, is an autosomal-dominant condition that results in a varying array of defects including, but not limited to events such as macrocephaly, frontal bossing, congenital cataracts, hypertelorism, palmar pits, spina bifida, polydactyly, and hypogonadism [9]. This condition, which was first described in 1960, is also associated with the potential for development of numerous BCC tumors and medulloblastoma. A landmark finding published in 1996 described a germline mutation of the patched gene (PTCH), which is found on chromosome 9q22.3, and accounts for the findings in Gorlin syndrome [10, 11]. There have been a variety of types of mutations in the PTCH gene, which have been described including insertion, deletion, missense, nonsense, and splice site mutations [12]. Interestingly, sporadic cases of BCC can also have mutations in the PTCH or smoothened (SMO) gene with abnormal Hedgehog pathway signaling playing a dominant role in most cases [13–15]. It is translation of these basic science findings to the clinic which has resulted in a new generation of targeted therapeutics for the treatment of both sporadic BCC and congenital BCC syndromes.

THE HEDGEHOG GROWTH SIGNALING PATHWAY

The Hedgehog pathway plays a critical role in embryonic development and is not active in most adult tissues, with the exception of stem cells, hair follicles, and skin cells in which the pathway is important for cell maintenance [16]. Key components of the Hedgehog pathway were first described in 1980 by Nusslein-Volhard et al. [17]. Hedgehog pathway signaling starts with the Hedgehog (Hh) ligand binding to a 12-pass transmembrane receptor known as PTCH, which is located in the primary cilium of the cell (Fig. 1). In 1993, three mammalian homologs of the Hh ligand were described, including Sonic Hedgehog (named after the popular Sega videogame), and also Indian Hedgehog and Desert Hedgehog (both named after real hedgehog species) [18, 19]. The

"Hedgehog" moniker was coined based on the description of *Drosophila melanogaster* (fruit fly) larvae, which took on the appearance of the spiky hedgehog when the gene was mutated.

In the absence of the Hh ligand, the PTCH receptor acts as a tumor suppressor by inhibiting the next protein in the pathway known as Smoothened (Smo), which is a G-protein-coupled receptor. When the Hh ligand binds to PTCH, the inhibitory effects on Smo are released allowing the signal to propagate. Although the mechanisms following Smo inhibition release have not been completely elucidated, Smo activation ultimately results in the release of inhibition of glioma-associated protein (Gli) through the suppressor of fused molecule (Sufu). The Gli family of proteins (Gli-1–3) are zinc finger transcription factors that are capable

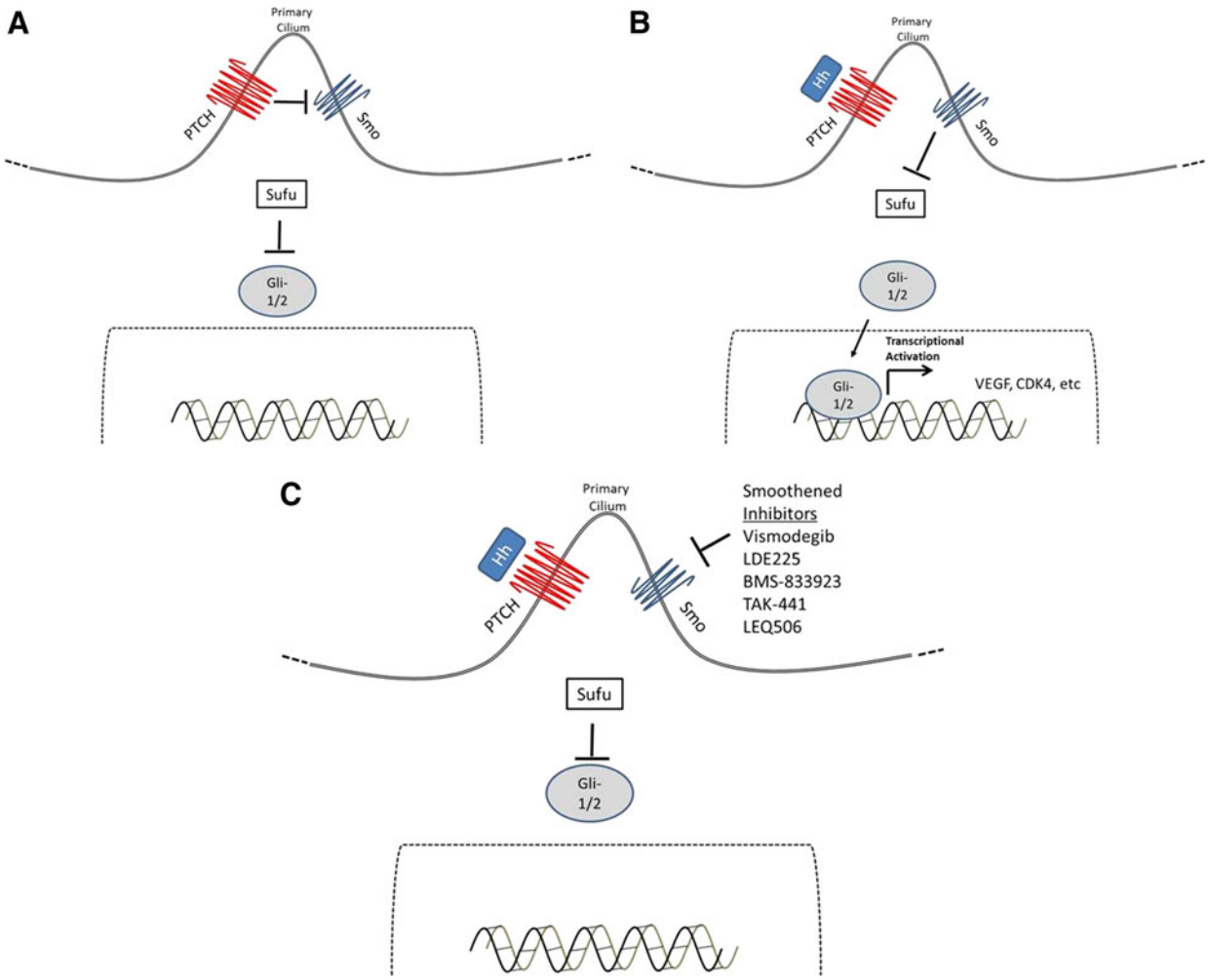

Fig. 1 The Hedgehog pathway in basal-cell carcinoma. In the majority of normal human cells, the hedgehog pathway is suppressed (**a**). The 12-pass transmembrane receptor Patched (PTCH) inhibits Smoothened (Smo), which through a series of incompletely elucidated steps, results in Suppressor of Fused (Sufu) inhibition of Glioma-1/2 (Gli-1/2) transcription factor function. However, in the presence of Hedgehog ligand (Hh) or mutation of PTCH or Smo, PTCH suppression of Smo is lifted resulting in inhibition of Sufu and release of Gli-1/2 transcriptional activity (**b**). Vismodegib and other Smo inhibitors block the Hedgehog pathway by inhibiting Smo resulting in suppression of Gli-1/2 transcriptional activation (**c**)

of activating a number of target genes, which can result in an oncogenic effect on the cell. Among the genes that are upregulated through Gli transcriptional activation are PTCH1 (provides negative feedback of pathway), Gli-1 (positive pathway feedback), and other gene pathways that aid in the survival of the cell, such as angiogenesis [20, 21], cell cycle regulation [22], and antiapoptosis pathways [23]. The Hedgehog pathway also conducts significant crosstalk with other molecules and pathways including p53, Wnt, PI3 K/aKT/mTOR, and retinoic acid. These interactions create a complex network, which may promote a variety of resistance mechanisms for drug targeting of this pathway. A variety of diseases have been linked to abnormal Hedgehog pathway signaling besides BCC, including medulloblastoma, hematologic malignancies, and other solid tumors [24].

Cyclopamine, the first naturally occurring inhibitor of the Hedgehog pathway, was isolated from the *Veratrum californicum* (the California corn lily) plant [25]. Cyclopamine was named after its ability to induce cyclopia and holoprosencephaly in the progeny of animals that fed on the plant while pregnant, highlighting the alkaloid's role in impairing the Hedgehog pathway in developing embryos. Cyclopamine was first found to bind to the Smo receptor resulting in blockade of downstream Hh signaling pathway transduction [26]. This discovery has led to a variety of more potent and selective Smo antagonists, which have been developed and incorporated into clinical research for a variety of cancer types, including patients with advanced BCC.

METHODS

A PubMed search was utilized to retrieve the data presented in this review article. The search terms BCC, metastatic basal-cell carcinoma, smoothened inhibitor, Hedgehog pathway, vismodegib, LDE-225, and targeted therapy were used for this search. Additionally, abstracts from national cancer meetings were obtained via a similar search on the American Society of Clinical Oncology (ASCO) website and the European Society of Medical Oncology (ESMO) website.

VISMODEGIB (GDC-0449)

Vismodegib (GDC-0449) is a first-in-class, orally bioavailable inhibitor of Smo. Based on the efficacy and tolerability results of recent clinical studies, vismodegib received US Food and Drug Administration (FDA) approval on January 30, 2012. Table 1 [27–32] summarizes the critical studies that have explored the use of vismodegib for BCC.

The first study was published in 2009 by Von Hoff et al. [27] and described the results of a dose-escalation phase 1 trial of vismodegib in patients with metastatic or locally advanced BCC. In this study, 68 solid tumor patients, including 33 patients with metastatic or locally advanced BCC, were treated with three different doses of drug. The study consisted of two phases, a dose-escalation phase followed by an expansion cohort. In the dose escalation phase of the trial, patients received 150, 270, or 540 mg daily, with each dosing group including one BCC. Based on pharmacokinetic studies, 150 mg daily was chosen as the optimal dose from this first stage of the trial. The second stage involved expansion cohorts, including 12 non-BCC patients, 20 patients with advanced BCC (dosing included 150 or 270 mg/day), and 16 patients with solid tumors (10 of which had advanced BCC). Results of the complete study, including other solid tumor types, have been presented elsewhere and demonstrated activity in medulloblastoma in addition to BCC [31].

Table 1 Studies evaluating vismodegib for basal-cell carcinoma (BCC)

Trial	Design/ population	Number of patients	Drug dose	Results	References
Phase 1	Dose-escalation, refractory solid tumors	68 solid tumor patients (33 basal cell; 15 Locally advanced, 18 metastatic)	Variable dosing; dose of 150 mg daily chosen as optimum dose	mBCC: ORR 50% metastatic BCC; LaBCC: ORR 60%	27
Phase 2	Two cohort (La and metastatic)	104 patients (33 metastatic, 71 locally advanced)	150 mg daily	mBCC: ORR 30%, PFS 9.5 months; LaBCC: ORR 43%, PFS 9.7 months	29
Expanded access	Open-label, nonrandomized LaBCC and mBCC	120 patients (96 evaluable at time of report, 57 LaBCC; 39mRCC)	150 mg daily	mBCC: ORR 50%; LaBCC: ORR 34%	31
Phase 2 Basal-cell nevus syndrome	Randomized (2:1) placebo-controlled double blind	41 patients (26 vismodegib; 15 placebo)	150 mg daily or placebo	Vismodegib cohort: mean 2 new lesions per year; placebo cohort: mean 29 new lesions/year	32

LaBCC locally advanced BCC, *mBCC* metastatic BCC, *ORR* objective response rate, *PFS* progression-free survival

For those with BCC, key inclusion requirements included histologically confirmed locally advanced or metastatic BCC considered refractory to standard therapy, Eastern Cooperative Oncology Group (ECOG) performance status 0–2, absence of prolonged QT interval, and negative pregnancy test for females. Patients who had radiographically measurable disease had imaging studies at baseline and every 8 weeks with responses measured by Response Evaluation Criteria In Solid Tumors (RECIST) (version 1.0) criteria.

Of the 33 patients enrolled with BCC, 17 patients received GDC-0449 at a dose of 150 mg daily, 15 received 270 mg daily, and one patient received a dose of 540 mg daily. Additionally, 15 patients (45%) had locally advanced BCC and 18 patients (55%) had metastatic BCC. Prior treatments, included surgery ($n = 28$, 85%), radiation therapy ($n = 19$, 58%), and systemic therapy ($n = 15$, 45%). Of the 18 patients with metastatic BCC, there were 15 with radiographically measurable disease, with seven of these having a partial response (>30% shrinkage of tumor size). Two additional patients had partial responses based on imaging and physical exam. Seven patients had stable disease and two patients had progressive disease as their best response. The overall response rate (ORR) was 50% for metastatic BCC. Of the 15 patients with locally advanced BCC, there were two complete responses, seven patients with partial response, four patients with stable disease, and two patients with progressive disease as best response. The ORR for locally advanced BCC was 60%. At the time of study publication, the median duration of response was 8.8 months and ongoing. In terms of toxicities, there were no dose-limiting adverse effects noted. There was an isolated case of grade

4 asymptomatic hyponatremia. Grade 3 events included fatigue, hyponatremia, weight loss, dyspnea, muscle spasm, and prolonged QT interval. Correlative molecular studies in select patients showed mutations in the PTCH1 gene in nine of ten specimens analyzed, loss of heterozygosity of the PTCH1 gene in one patient's tumor, SMO-M2 mutations in one patient, PTCH1 mutations in normal skin of a patient with basal-cell nevus syndrome, and elevated Gli-1 mRNA expression in 25 of 26 biopsied tumors. Of the four patients with progressive disease, one patient was not found to have Hedgehog pathway signaling, whereas two of the others analyzed did have signaling suggesting other more important driving mutations for these patients.

Pivotal Phase 2 Study of Vismodegib

The findings of the phase 1 trial by Von Hoff et al., led to exploration of vismodegib (GDC-0449) in a multicenter, international, two-cohort phase 2 trial in patients with metastatic or locally advanced BCC [28]. In this study, 104 patients with locally advanced or metastatic BCC were enrolled to receive vismodegib 150 mg by mouth daily. The primary endpoint of the study was objective response rate. There was no control group or randomization performed in the study, and the two cohorts evaluated were divided based on the presence of metastatic or locally advanced BCC. For the patients with metastatic BCC, RECIST criteria (version 1.0) were employed. Independent review was used to assess radiographs and photographic images (for locally advanced patients). For locally advanced BCC patients, independent pathologic evaluation was performed to determine whether the response was partial or complete (absence of residual BCC in biopsy specimen). Key eligibility requirements included histologically confirmed metastatic or locally advanced BCC, ECOG performance status of 0–2, radiographically measurable disease (for metastatic patients), at least one 10 mm or greater skin lesion (for locally advanced patients), and surgical or radiotherapeutic management was inappropriate (locally advanced patients). Women of childbearing potential or men with female partners of childbearing potential were required to use two methods of contraception. Thirty-three metastatic BCC patients and 71 patients with locally advanced BCC were enrolled and received treatment [28].

Most patients with metastatic BCC had three or more measurable target lesions (61%) with the most frequent sites of metastasis being lung and lymph nodes. Prior treatments for patients with metastatic disease included surgery (97%), radiation (58%), and systemic therapy (30%). The objective response rate for patients with metastatic BCC was 30% upon independent review (45% site review). An additional 64% of metastatic patients had stable disease as best response on independent review (45% on site review), and 3% had progressive disease (6% site review). The median progression-free survival (PFS) was found to be 9.5 months for the metastatic cohort with a median duration of treatment of 10.0 months. In a subsequent presentation of the updated results of this study, median overall survival was found to be 24.1 months for patients with metastatic BCC [29].

Of the patients with locally advanced BCC, 38% were considered to have inoperable disease, with remainder considered to have surgically inappropriate due to multiple recurrences (25%), considerable chance for deformity or morbidity (51%), or both reasons (14%). In terms of radiotherapy, 21% had target

lesions that were refractory to prior radiation, and 79% had lesions that were considered to be contraindicated or inappropriate for radiotherapy. The median objective response rate was found to be 43% upon independent review (60% site review). There were 38% of patients with stable disease (24% site review) and 13% with progressive disease (10% site review) as best response. The median PFS for locally advanced BCC patients was found to be 9.5 months with a median duration of treatment of 9.7 months. Of the patients who had biopsy to confirm response, 54% had no pathologic evidence of disease upon sampling. Median overall survival for patients with locally advanced BCC has not been reached [29].

Adverse events from vismodegib in this study included muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, loss of appetite, and diarrhea. There were 13 patients (12%) who discontinued treatment due to adverse events, with the most common reason being muscle spasms. Molecular analysis of mRNA expression of Gli-1 and PTCH2 were measured and shown to have similarly high levels in both the locally advanced and metastatic cohorts.

An expanded access study of vismodegib has also been conducted to help further understand the activity of the agent and allow access of the drug to locally advanced/metastatic BCC patients prior to FDA approval [29]. Final results of the expanded access study were recently presented at ESMO 2012. Of the 120 patients enrolled, 96 patients were evaluable for response and showed evidence of clinical activity with 26 of 57 locally advanced patients having a response (45.6%, investigator assessed), and 12 of 39 patients with metastatic patients having a response (30.4%, investigator assessed). No patients in the locally advanced BCC cohort and 7.7% of the metastatic BCC cohort experienced progressive disease as best overall response. Side effects were similar to that seen in the pivotal phase 2 trial and included muscle spasms, dysgeusia, alopecia, nausea, weight loss, fatigue, and diarrhea [29].

Use of Vismodegib in Basal-Cell Nevus Syndrome

Vismodegib has also been prospectively evaluated in patients with basal-cell nevus syndrome (Gorlin syndrome) [30]. In a randomized, double-blind, placebo-controlled trial, 42 patients with basal-cell nevus syndrome were enrolled to determine the anti-BCC efficacy. The primary endpoint of the study was the comparative rate of appearance of new surgically resectable BCC lesions between the treatment and placebo arms. Surgically resectable BCC lesions were defined as being $\geq$3 mm on the nose or around the eyes, $\geq$5 mm on other areas of the face, and $\geq$9 mm on the trunk or limbs. Other endpoints included an evaluation of the frequency of smaller BCC lesions, reduction in the size of existing surgically resectable lesions, duration of the effect of vismodegib after discontinuation, and safety. Additionally, evaluation of changes in Hedgehog pathway gene expression was measured by quantitative polymerase chain reaction (PCR) analysis of Gli-1 at baseline and at 1 month after start of therapy. Eligibility for the trial required a clinical diagnosis of basal-cell nevus syndrome as defined by at least two major criteria and at least ten surgically eligible BCC lesions at study entry or that were removed during the 2 years prior to enrollment. Treatment included vismodegib at 150 mg by mouth daily or matching placebo for up to 18 months or until intolerable adverse effects or clinically worsened disease. Clinically worsening disease was defined as >60 new surgically eligible

BCCs or a doubling of the longest diameter of existing or new BCC lesions. Patients could have surgical resection of BCC lesions if it was decided necessary by the primary dermatologist [30].

Of the 42 patients enrolled, 41 patients were randomized in a 2:1 fashion and received treatment. The two arms were well balanced based on age, weight, and number of BCC lesions at baseline (44 lesions per patient in the vismodegib arm vs. 37 lesions per patient in the placebo arm, $P = 0.79$). Patients in the vismodegib arm were found to have a significantly reduced number of new surgically eligible BCC lesions compared to the placebo group (mean of two new lesions per year for vismodegib compared to 29 new lesions per year for the placebo group, $P < 0.001$). Additionally, vismodegib was shown to reduce the mean size of existing BCC lesions (longest diameter) compared to placebo (–65% for vismodegib vs. –11% for placebo, $P = 0.003$). Vismodegib-treated patients also had fewer surgical resections of BCC lesions compared to placebo (0.31 surgeries per patient compared to 4.4 for placebo, $P < 0.001$). Tumor responses were seen in all tumors treated with vismodegib with some near-complete responses. At the time of the report, 54% of patients had discontinued treatment with vismodegib due to adverse events. Common side-effects from vismodegib included dysgeusia, muscle cramps, hair loss, and weight loss [30].

Histologic and molecular studies confirmed the anti-BCC effect and molecular pathway targeting of vismodegib. In lesions that appeared clinically resolved, residual BCC tumor cells were seen in only 17% of biopsied specimens ($n = 1$ of six). Evaluation of Gli-1 mRNA expression by PCR demonstrated a 90% decrease compared to pre-treatment biopsy specimens ($P < 0.001$). Reduction in Ki67 expression was also seen, but there was no change in apoptosis (as measured by cleaved caspase 3). In patients who stopped vismodegib and had at least 3 months post-treatment follow-up ($n = 4$), it took several months (~ 18) for the sum of the longest diameter of existing lesions to reach their baseline size. Additionally, the rate of new lesions in vismodegib-receiving patients after discontinuation of drug was less than that for those on placebo (0.69 new per month compared to 2.4 new per month for placebo) [30].

This study has highlighted several important points regarding the treatment of patients with basal-cell nevus syndrome with a Smo inhibitor. Although active treatment with vismodegib was able to control the rate of new lesions and decrease the size of existing lesions, the treatment was intolerable for many patients, making long-term use challenging. Although the rate of new lesions after discontinuation of vismodegib was still lower than those in the placebo arm, the effect was much less prominent than when these patients were on active treatment. These findings confirm an inhibitory effect of Smo blockade on BCC tumor cell growth over time; however, few patients are likely to have a long-term benefit due to either primary resistance which develops in a small population of tumor cells or the toxicity ceiling of the drug prevents prolonged use and thus incomplete tumor cell kill. As Gorlin syndrome represents a lifelong disease with continuous potential for the development of BCC tumors, the ideal treatment would be one that is effective and tolerable enough for continued use (perhaps a topical therapy).

LDE225

Via cell-based high-throughput screening, LDE225 was identified as a selective, potent inhibitor of Smo, which is currently in clinical development for BCC and other cancer types [31]. It has been evaluated in a phase 1

dose-escalation study, which was reported at ASCO in 2010 [32]. In this study, patients with advanced solid tumors were treated with varied doses of LDE225 (100, 200, 400, and 800 mg) with the primary goal of determining the maximally tolerated dose (MTD). At the time of the presentation, 25 patients had been treated with no dose-limiting toxicities noted. Common side-effects included fatigue, nausea, vomiting, anorexia, muscle cramps, and dysgeusia. Additionally, at the time of the report one patient with medulloblastoma had obtained an objective response, whereas five other patients had at least stable disease for 4 months (including one BCC patient). A reduction in Gli-1 mRNA expression was noted in skin samples of patients with the level of reduction correlating with dose of LDE225.

LDE225 has subsequently entered testing in a phase 2 randomized trial for patients with locally advanced or metastatic BCC in 2011, which is currently ongoing. In this study, patients are randomized to one of two different doses of LDE225. The primary endpoint of the study is objective response rate by 6 months with secondary endpoints including duration of response, PFS, and safety. Additionally, a trial of LDE225 in patients who have progressed on another Smo-inhibitor (e.g., vismodegib) is currently being conducted, which will shed light on the role of cross-resistance with these inhibitors (ClinicalTrials.gov number: NCT01529450).

LDE225 has also been evaluated in the management of nevoid BCC syndrome. In this trial, eight patients were treated with 0.75% LDE225 and vehicle [33]. Lesions on each patient were randomized to the active LDE225 cream or vehicle only. There were a total of 27 lesions treated with either the LDE225 cream or vehicle twice daily for 4 weeks. Fourteen lesions received vehicle whereas 13 lesions received LDE225 cream. There were clinical responses in all lesions treated with LDE225 except one. Clinical responses included three complete clinical responses and nine partial responses. Clinical response was seen in only one of the 14 lesions treated with the vehicle. Both the LDE225 cream and vehicle were well tolerated with no reported skin toxicities. Systemic absorption of LDE225 was below the limit of detection in 50% of the patients with the highest concentration noted in the other four patients being 0.11 ng/mL. Correlative analysis on biopsied tumors after LDE225 topical treatment revealed downregulation of Hedgehog pathway gene targets, such as Gli-1, Gli-2, PTCH1, and PTCH2. Certainly, for patients with numerous localized BCCs, such as in nevoid BCC syndrome, the use of topical LDE225 appears to be a rational approach as it avoids systemic exposure that predisposes to more side-effects.

OTHER Smo Inhibitors in Development

A variety of other agents that inhibit Smo are in clinical development. These agents have been evaluated, or are currently being evaluated, in phase 1 clinical studies. These include BMS-833923, which has been described in a phase 1 clinical trial in advanced solid tumors [34]. This study was reported in 2010 at ASCO, and at the time of the report 18 patients had been treated with BMS-833923 at doses ranging from 30 to 240 mg. One patient with Gorlin syndrome who was treated with the 240 mg dose had a confirmed partial response, and another patient with medulloblastoma had stable disease lasting for more than 11 months. Further updates from this trial are expected. Currently, trials with BMS-833923 are ongoing in small cell lung cancer, chronic myeloid leukemia (CML),

multiple myeloma, and gastrointestinal malignancies. Several other Smo inhibitors are being evaluated in first-in-human clinical studies. This includes TAK-441 (Millennium, Cambridge, MA, USA; ClinicalTrials.gov number: NCT01204073) and LEQ506 (Novartis, Basel, Switzerland; ClinicalTrials.gov number: NCT01106508), which are also in early phase studies with advanced solid tumors.

MECHANISMS OF RESISTANCE TO SMO INHIBITION

Although treatment of BCC with vismodegib and similar agents has resulted in dramatic responses, resistance to Smo inhibition occurs resulting in new tumor development or growth of previously responding tumors. A recent analysis into the mechanism of resistance to vismodegib has recently shed light into the complex nature of this process [35]. In a patient with medulloblastoma with a known PTCH mutation, the initial response to vismodegib was seen with subsequent progression of disease [36]. Comparison of before treatment tumor samples and samples obtained from a vismodegib-resistant tumor demonstrated a novel finding. The pre-existing PTCH mutation found in the pre-treatment tumor was still present in the resistant tumor; however, a new mutation in SMO (D473) was seen. Similar to alterations in BCR–ABL, which confer resistance of CML cells to imatinib, this SMO-D473 mutation was found to confer resistance to vismodegib. Further evaluation implicated that this particular mutation affected vismodegib binding to Smo. A panel evaluating other point mutations in this particular location uncovered potential oncogenic properties with autoactivation of Smo signaling [37]. Evaluation of other Smo inhibiting agents, demonstrated several potential candidates that could inhibit wild-type Smo and this new D473 mutation. Thus development of next-generation Smo inhibitors, which have a broader Smo inhibitory profile, could be a key to unlocking more durable benefits. Additionally, inhibition of downstream molecules, such as Gli, could have benefits to patients with Smo-inhibitor refractory tumors or as vertical inhibition combination strategies with current Smo inhibitors. Several Gli-inhibitor molecules have been discovered, including GANT 58 and GANT 61; however, agents such as these have yet to be evaluated in clinical studies [38]. Finally, other pathways play important roles via either downstream Hedgehog pathway regulation or Hedgehog pathway crosstalk. Some BCC cell lines that demonstrate Smo-inhibitor resistance rely on the PI3 K-Akt pathway. Coinhibition of Smo and PI3 kinase in these Smo-inhibitor resistant cell lines has demonstrated subsequent tumor responsiveness to treatment, implicating possible horizontal pathway inhibition strategies, which could be employed clinically [39]. Although, the mechanisms of resistance to Smo inhibitors remains incompletely evaluated, further information is likely to be forthcoming as ongoing trials are collecting tumor samples upon progression, which should further guide future treatment development strategies.

PRACTICAL CONSIDERATIONS FOR THE USE OF VISMODEGIB

Vismodegib represents a first-in-class medication for use in patients with locally advanced or metastatic BCC. As with any new drug, there is a learning curve to overcome in the community. Before the clinical

development and approval of vismodegib, there was little thought of using systemic therapy in these patients as chemotherapy has little activity. Advanced BCC patients are cared for by a wide range of disciplines including dermatologists, Mohs surgeons, plastic surgeons, otolaryngologists, and radiation oncologists. With the approval of vismodegib, medical oncologists now have a larger role to play. Common questions include: Who is the appropriate patient to receive this agent? How long should treatment with vismodegib be continued in someone with a complete response? What is done for patients who do not tolerate the medication? What do we do upon progression? Certainly, some of these questions can be answered with evidence-based support; however, others remain the focus of ongoing and future research.

Practical Management of Locally Advanced BCC

Based on the author's current knowledge, eligible patients can be broken down into two categories: locally advanced BCC and metastatic BCC. Although metastatic BCC is easy to pick out as these patients have clinically apparent metastatic deposits on radiographs, the locally advanced BCC patients are a little trickier. Some of these locally advanced BCC patients present to the treating physician after years of neglect with their tumors slowly growing to involve deep structures. This happens for a variety of reasons, including patient denial or lack of access to medical care due to psychiatric disorders, financial constraints, or social isolation. Other situations in which this occurs are due to patient predisposition with risk factors, such as extensive sun exposure, Gorlin syndrome, immunosuppression, or development of lesions in very sensitive areas.

Although the reason for development of locally advanced BCC varies, the identification of these patients can be guided from an evidence-based approach (Table 2). The definition of the locally advanced BCC patient eligible for the pivotal vismodegib study can be simplified to those with (1) recurrent BCC after surgery or radiotherapy, or (2) patients that were deemed ineligible for surgery and radiotherapy. There are many scenarios that can lead to one of these two classifications and these are outlined in Table 1. Although some BCCs that are locally recurrent after surgery can proceed to radiotherapy as a salvage option, location of the BCC matters. BCC lesions around the eyes or other sensitive areas are common and radiotherapy can definitely be more challenging or impossible for these locations of involvement. In the pivotal study, patients who had lesions that had recurred after at least two attempts at surgical resection were included. Additionally, patients who were not deemed surgical candidates because surgical resection would result in significant deformity or morbidity were included. Also, in clinical practice, some patients may be deemed ineligible for surgery or radiotherapy due to a high number of lesions. These patients may be Gorlin syndrome patients or they may be patients with extensive UV exposure or immunosuppression who have numerous lesions, making surgery or radiotherapy impractical. Finally, other patients to consider for vismodegib with localized disease include patients with comorbid conditions that preclude extensive surgical resection and general anesthesia and who are also not candidates for radiotherapy.

Another practical question is the use of vismodegib in the preoperative setting to attempt to convert an unresectable or difficult to resect lesion into one that can be managed

Table 2 Identification of locally advanced basal-cell carcinoma (BCC) patients who are appropriate for vismodegib use

Potential reasons to need systemic therapy for BCC
Recurrent disease despite two or more surgical resections
Surgical resection not possible due to inability to completely resect
Resection or radiation would result in too much disfigurement or morbidity
Too many lesions to resect or radiate (e.g., numerous sporadic lesions, Gorlin syndrome, immunosuppression, etc.)
Patient is not an operable candidate due to significant comorbidities
Recurrence after radiotherapy
Radiation not possible due to close proximity of adjacent organs or structures

easier. Although this would be considered a common-sense application of this medication, which has great potential to reduce lesion sizes, this approach needs to be evaluated in clinical studies. Currently, trials evaluating the preoperative use of vismodegib in patients with BCC are ongoing (ClinicalTrials.gov numbers: NCT01543581, NCT01201915).

Although some patients who are initiated on vismodegib have a complete response, a more typical outcome is partial response. The duration of this response varies but for the average patient, the BCC tumor does recur and management after vismodegib remains an important unanswered question. Certainly, patients may have the option of receiving surgical therapy or radiotherapy if the treatment with vismodegib resulted in a response that changed the feasibility of further local options. For patients who still cannot have further therapy, identification of a clinical trial is crucial to advancing our understanding of how to manage these patients. Currently, a trial of LDE225 in patients previously treated with vismodegib or other Smo inhibitors is ongoing (ClinicalTrials.gov number: NCT01529450). Also for patients with multiple localized BCCs, such as in Gorlin syndrome, use of vismodegib may be required for a long period of time raising the question of intermittent dosing to either reduce the chance of BCC resistance as well as to improve tolerability of the agent. To further understand the feasibility of this approach, an ongoing trial exploring intermittent dosing is being performed with vismodegib compared to photodynamic therapy (ClinicalTrials.gov number: NCT01556009).

Practical Management of Patients with Metastatic BCC

As previously stated, these patients are fortunately not as common as and are much easier to identify than those with locally advanced BCC. It is important for patients with locally advanced BCC to have imaging examinations using computed tomography (CT) or positron-emission tomography (PET) to rule out metastatic disease. Patients with metastatic BCC can have sites of involvement including lung, liver, and bone, so the examination needs to encompass these areas. Although patients with oligometastatic disease can be considered for metastatectomy or stereotactic radiosurgery, patients with more extensive disease or surgically unfit patients should be considered for systemic therapy with vismodegib or referred for clinical trial. The treatment goals for these patients are typically different than those with locally advanced disease. As metastatic BCC is a terminal

condition, certainly quality of life plays a large role in their goals of care. Although vismodegib has been shown to result in an average survival of approximately 2 years, vismodegib can be difficult for some patients to tolerate. Therefore, short treatment breaks could be employed to help the patient maintain their therapy and response for a longer period of time.

FUTURE DIRECTIONS

The introduction of selective, potent inhibitors of the Hedgehog pathway has led to improved outcomes for patients with advanced BCC who previously had limited systemic treatment options. Vismodegib represents a first-in-class Smo inhibitor, which has shown prominent clinical activity in phase 2 trials for patients with advanced BCC and Gorlin syndrome. Unfortunately, most patients treated with this drug eventually have disease progression. This is anticipated for other Smo inhibitors in development as well. Therefore, it is critical that further research to help our understanding of Smo inhibitor resistance be performed. Many of the trials that are ongoing are actively collecting samples from progressing lesions for molecular analysis. It is anticipated that more than one mechanism of resistance will be identified. Early evaluation of one patient who has progressed on vismodegib has revealed that mutation in the Smo molecule can occur, which interferes with vismodegib binding. This mutation is quite similar to the mutations noted in BCR–ABL, which develop in response to exposure to imatinib. This finding opens the door for the evaluation of agents that bind to both wild-type and mutant SMO as a means of overcoming vismodegib resistance. Additionally, agents that target downstream molecules in the Hedgehog pathway, such as Gli or other pathways, which contribute to Hedgehog pathway inhibitor resistance, such as the PI3kinase pathway are also candidates for overcoming resistance. Certainly, these are areas that need to be further explored as new agents that have similar activities are introduced. Finally, it is important to evaluate these agents earlier in the disease process as potential adjuvant or neoadjuvant adjuncts to traditional approaches, which may result in better outcomes and hopefully prevent the devastating occurrences of locally advanced and metastatic forms of BCC.

CONCLUSION

The identification of the Hedgehog pathway's role in BCC, as well as drugs that are able to target this pathway, has led to a critical proof-of-concept translation of these agents into the clinical management of advanced BCC. The first-in-class Smo inhibitor, vismodegib, has given the clinician an important tool in treating patients with this devastating disease. It is critically important that physicians understand when and how to use this novel agent in the management of these patients. Other agents that work similarly to vismodegib are in development and are expected to expand the clinical options for these patients even further. Research into mechanisms of resistance of Smo inhibitors, identification of other relevant molecular targets and an understanding of the use of Hedgehog pathway inhibitors in earlier stage disease remains a crucial next step to improving outcomes for patients BCC.

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