Vismodegib and the Hedgehog Pathway: A New Treatment for Basal Cell Carcinoma

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ABSTRACT

Background: Vismodegib is an oral inhibitor of the Hedgehog pathway approved by the US Food and Drug Administration. It is the first systemic treatment for patients with locally advanced or metastatic basal cell carcinoma that is not amenable to surgery and radiation. This is the first drug to use the Hedgehog pathway to inhibit the proliferation of tumors and is also implicated in the development of other cancers such as medulloblastoma.

Objective: The goal of this review was to summarize the development, pharmacology, efficacy, and safety of vismodegib.

Methods: Relevant English-language literature was identified and then evaluated based on results from database searches of MEDLINE and EMBASE from 1975 to June 19, 2012. The terms searched included, but were not limited to, vismodegib, Erivedge, GDC-0449, basal cell carcinoma, and 2-chloro-N-[4-chloro-3-(pyridin-2-yl)phenyl]-4-(methylsulfonyl)benzamide. Additional literature was identified by assessing the reference lists of previously identified articles and through abstracts presented by the American Society of Clinical Oncology.

Results: A total of 70 full text citations were identified although two national conference proceedings were then excluded. An additional 10 published abstracts were also identified. A Phase II, nonrandomized, multicenter, international study demonstrated a 30.3% objective response rate in metastatic basal cell carcinoma and a 42.9% objective response rate in locally advanced basal cell carcinoma. The adverse effect profile for vismodegib is similar to other identified Hedgehog pathway inhibitors; muscle cramps (71.7%), alopecia (63.8%), and dysgeusia (55.1%) were the most common adverse effects seen in trials. A Phase II, randomized, placebo-controlled trial in Gorlin syndrome patients with basal cell carcinoma concluded that vismodegib was significantly better than placebo at reducing new basal cell carcinoma lesions (P < 0.001) and at decreasing the sum of the longest diameter of existing lesions (P = 0.003).

Conclusions: For patients with unresectable basal cell carcinoma or where resection would be cosmetically disadvantageous, vismodegib is an effective therapy with good response rates. At this time, the data are too limited to determine overall survival. The Hedgehog pathway is a newly identified area in which mutations or dysregulation can occur, leading to the development and progression of tumors. Studies continue to look at other cancers with involvement of the Hedgehog pathway.

Key words: basal cell carcinoma, Erivedge, GDC-0449, vismodegib.

INTRODUCTION

On January 30, 2012, vismodegib* became the first drug approved by the US Food and Drug Administration (FDA) for the treatment of locally advanced and metastatic basal cell carcinoma (BCC).1 This novel drug also introduced a new signaling target in the treatment of cancer, the Hedgehog (Hh) pathway. Most of the targeted oral agents approved to date are classified as tyrosine kinase inhibitors, or the “nibs,” based on their nomenclature of ending with “-tinib.” Vismodegib, with the “-degib” suffix, heralds a unique mechanism in which to attack signaling mutations within cells of the body that may lead to abnormal proliferation.

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BCC is the most common type of skin cancer and, together with squamous cell carcinoma, are labeled as nonmelanoma skin cancers.\(^2\)\(^,\)\(^3\) Skin cancers as a group are the most common form of cancer in the United States, with >3.5 million cases diagnosed annually.\(^3\) Melanoma is the most lethal, comprising <5% of all skin cancers but accounting for >75% of skin cancer deaths; nonmelanoma skin cancers account for <0.1% of all deaths attributed to cancer.\(^2\) Melanoma develops in the melanocytes (skin cells that make pigment), squamous cell carcinoma forms in the squamous cells (flat cells that form the surface of the skin), and BCC forms in the lower part of the epidermis (outer layer of the skin)\(^2\) (Figure 1), although there is some evidence to suggest that some BCCs may form from hair follicle stem cells.\(^4\)\(^,\)\(^5\)

BCCs account for 80% of nonmelanoma skin cancers.\(^6\) The number of these cancers has increased by an average of 4.2% every year between 1992 and 2006,\(^7\) with treatment of nonmelanoma skin cancers increasing by an estimated 77% during that same time period.\(^8\) For women aged <40 years, the diagnosis of BCC has doubled in the past 30 years.\(^9\) The risk of death is not defined, but expected to be quite low for BCC. However, outcomes can be cosmetically unacceptable or have significant morbidity, as many (>80%) will develop in sun-exposed areas such as the head and neck.\(^10\)–\(^12\) Metastases occur in only 0.55% of all cases and may develop years after its original presentation.\(^11\)–\(^13\)

The greatest risk factor for BCC is ultraviolet radiation exposure from the sun, with ultraviolet A and B rays causing sunburns and DNA damage.\(^3\)\(^,\)\(^13\) Other factors that increase the risk of developing BCC include fair skin, older age, immunosuppression (especially after organ transplantation), environmental exposure (e.g., coal tars, petroleum, arsenic), and specific genetic conditions such as xeroderma pigmentosum, albinism, and Gorlin syndrome.\(^10\)

Gorlin syndrome, also known as basal cell nevus syndrome, is a rare autosomal dominant disorder in which those with the disease are prone to developing multiple BCCs at an early age, with occurrence of new lesions being common throughout their lifetime.\(^14\)–\(^17\) Biochemically, these patients have a mutation on the Patched 1 (PTCH1) gene of human chromosome 9q22.\(^15\) This mutation plays an important role in the regulation of the Hh pathway. In addition to an increased risk for BCCs, these patients have a 5% risk of developing medulloblastoma, a pediatric malignant tumor of the cerebellum, and are also at risk for developing rhabdomyosarcoma.\(^14\)–\(^16\)

Current first-line therapy for BCC consists of surgical removal and, potentially, radiation therapy. Most BCCs are cured by surgery but, in some cases, the cancer is unresectable or the surgery is deemed too disfiguring. These are considered locally advanced BCCs (laBCCs) and may metastasize without treatment. Nonsurgical treatment options can include photodynamic therapy, topical imiquimod, or 5-fluorouracil.\(^11\) Until vismodegib, there were no FDA-approved therapies for these cases, and median survival for metastatic disease varied from as little as 6 months to 3.6 years.\(^12\) Prior systemic treatment recommendations consisted of platinum-based therapy (cisplatin or carboplatin) or palliative and supportive care.\(^19\)

The Hh pathway was first elucidated in the fruit fly, Drosophila melanogaster.\(^16\)\(^,\)\(^18\) A mutation in the Hh gene led to embryo development that was covered with spiky processes, similar to the spiky appearance of a
hedgehog. Sonic Hh (SHH), Indian Hh, and Desert Hh are 3 ligands that have been identified which stimulate the Hh pathway; SHH was named after a popular video game character, and Indian Hh and Desert Hh were named after species of hedgehogs. The Hh pathway is important in regulating growth and development in embryogenesis, but it becomes almost dormant during adulthood, with activity limited to some regulation of tissue homeostasis, continuous renewal and repair of adult tissues, and stem cell maintenance.

Inappropriate activation of the Hh signaling pathway is associated with the development of some cancers, including BCC.

The genetic mutation observed in patients with Gorlin syndrome best characterizes the role of the Hh pathway in BCC pathogenesis. Many of these carcinomas have genetic alterations in the Hh signaling pathway that lead to pathway upregulation and abnormal proliferation. This signaling pathway begins at the primary cilium, which is present on most cells during interphase (Figure 2). At the base of the primary cilium of a cell is PTCH1, a 12-transmembrane domain protein. Normally, the role of PTCH1 is to inhibit activity of Smoothened (SMO), a 7-transmembrane serpentine receptor, by blocking it from entering the cilium. When an Hh ligand (SHH, Indian Hh, or Desert Hh) binds to PTCH1, the inhibition of SMO is interrupted, and SMO migrates from the intracellular endosome to the cell membrane of the cilium. SMO is activated within the cilium and signals downstream activation of the glioma-associated oncogene (GLI) family of zinc-finger transcription factors, which include GLI1, GLI2, and GLI3. GLI1 and GLI2 typically function as activators and GLI3 as a repressor. The GLI fac-

**Figure 2.** Hedgehog (Hh) signaling, vismodegib action, and acquired resistance. SMO = Smoothened; PTCH = patched gene of human chromosome 9q22; Sufu = suppressor of fused; GLI = glioma-associated oncogene. Reprinted with permission from the American Association for Cancer Research: Rudin CM, Vismodegib, Clinical Cancer Research, 2012;18(12):3218–3222. DOI:10.1158/1078-0432.CCR-12-0568.

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tors enter the cell nucleus and promote or repress transcription of target genes, including PTCH1, GLI1, and various others. The transcribed target genes go on to regulate cell proliferation via the activation of cyclin D1 and other cyclin-dependent kinases.17,22 Suppressor of fused is a negative regulator of the Hh pathway as it binds to GLI, preventing activation of Hh target genes. Mutations can occur in various areas of the Hh pathway and, ultimately, inactivate PTCH1, causing abnormal proliferation of cells, potentially leading to several cancers (including BCC).15,22

In Gorlin syndrome, inhibition of the Hh pathway is impaired due to a mutation of the PTCH1 gene, allowing dysregulation of the Hh pathway with a resulting predisposition of developing BCC. The etiology of BCC in non–Gorlin syndrome patients in almost all cases is also linked to upregulated signaling of the Hh pathway.13,14,24 Therefore, suppression of the Hh pathway with an SMO antagonist such as vismodegib would theoretically prevent further basal cell proliferation caused by Hh pathway stimulation.

The goal of this review was to summarize the development, pharmacology, efficacy, and safety of vismodegib.

METHODS
Relevant English-language literature was identified and then evaluated based on results from database searches of MEDLINE and EMBASE from 1975 to June 19, 2012. The terms searched included, but were not limited to, vismodegib, Erivedge, GDC-0449, basal cell carcinoma, and 2-chloro-N-[4-chloro-3-(pyridin-2-yl)phenyl]-4-(methylsulfonyl)benzamide. A total of 70 full text citations were identified although two national conference proceedings were then removed. Additional literature was identified by assessing the reference lists of previously identified articles and through abstracts presented by the American Society of Clinical Oncology.

RESULTS
Chemistry
The chemical formula for vismodegib is C19H14Cl2N2O3S. Its chemical name is 2-chloro-N-[4-chloro-3-(pyridin-2-yl)phenyl]-4-(methylsulfonyl)benzamide. It is a crystalline-free base with a pKa of 3.8 and a molecular weight of 421.3 g/mol. The solubility as a free base is far greater at an acidic pH.

Mechanism of Action
Vismodegib is an antagonist of SMO as depicted in Figure 2. It binds and inactivates SMO and inhibits its translocation when PTCH1 is stimulated by Hh ligands (ie, SHH, Desert Hh, Indian Hh). Inhibition of the Hh pathway results in decreased downstream production of proliferation factors. Decreased proliferation factors should ultimately lead to suppression of BCC growth.

Resistance
Elucidation of resistance mechanisms to vismodegib has been relatively limited. Of note, 1 case report described a 26-year-old man with treatment-refractory metastatic medulloblastoma who developed resistance after 3 months despite an initial response.16 In this patient’s case, it was observed that a D473 resistance mutation had occurred in SMO that prevented vismodegib binding, thus losing efficacy against the tumor.

Dijkgraaf et al22 performed further investigation into mechanisms of resistance to vismodegib. First, in a simulation of the mutation that occurred in the previously mentioned case report,16 substitution of every amino acid for the aspartic acid at position 473 was performed, and vismodegib binding was assessed. All mutant variations were less sensitive to vismodegib than wild-type SMO. The study also assessed for other amino acid residue mutations that may confer resistance via alanine-scanning mutagenesis. It was determined that E518 is an important residue in vismodegib activity on SMO. Its mutation conferred complete resistance to vismodegib. Lastly, their study looked at potential compounds to treat Hh pathway resistance. Results showed that Hh pathway–resistant medulloblastoma allografts were sensitive to phosphoinositide-3-kinase inhibition. Another identified mechanism of vismodegib resistance is amplification of GLI2 downstream of SMO. Other plausible mechanisms exist but have yet to be confirmed.

Pharmacokinetics
Pharmacokinetic properties of vismodegib were studied in a 2-part, Phase I, open-label trial.19,23,25 In part 1, a total of 20 patients were evaluated at 1 of 3 different doses (150, 270, or 540 mg) on day 1, followed by a washout period of 6 days and then daily administration at the same dose beginning on day 8. An additional 48 patients were added in part 2 of this trial to assess the following: vismodegib’s safety at the
150-mg dose (12 patients), patients with BCC at the 150- and 270-mg dose (20 patients), and a new 150-mg formulation evaluation (16 patients). Concentrations of the 3 different doses in part 1 revealed little decline over the 6-day washout period. After daily dosing, it was observed that steady state was achieved earlier than would be expected (7–14 days) and did not differ significantly between the 3 doses. Less than 1% of total drug concentration was observed unbound in plasma at steady state. The nonlinear kinetics seen in the daily administration with respect to dose and time is explained by vismodegib’s high affinity for binding with \( \alpha_1 \)-acid glycoprotein (AAG). A strong linear correlation was seen with total steady-state concentrations of the drug and AAG plasma levels. Vismodegib seems to bind to AAG first, and any remaining unbound drug then binds with human serum albumin. The recommended starting dose for the Phase II trials was determined to be 150 mg.

The pharmacokinetics of the 33 patients with BCC within the 2-part study was reported by Von Hoff et al. Three of the 20 subjects in part 1 had BCC, and each received 1 of the 3 vismodegib doses (150, 270, or 540 mg). The remaining 30 patients enrolled in part 2 were given either 150 mg (16 patients) or 270 mg (14 patients). The remaining 30 patients enrolled in part 2 were given either 150 mg (16 patients) or 270 mg (14 patients). Median \( C_{\text{max}} \) was found to be 23.0 \( \mu \)M. The median steady-state concentration was 16.1 \( \mu \)M, with a median time to steady-state of 14 days (range, 7–22 days). Further evaluation revealed that absorption of vismodegib was saturable at doses >150 mg and did not result in higher steady-state concentrations of the drug (median steady-state level of 19.8 \( \mu \)M for the 150-mg dose and 15.9 \( \mu \)M for the 270-mg dose).

Another pharmacokinetic study by the same group assessed the differences between daily, three times a week (TIW), or once weekly dosing of vismodegib at 150 mg. The study subjects were stratified according to baseline AAG levels and randomized to 1 of the 3 groups. Both total and unbound drug levels were measured. Total and unbound levels dropped significantly in the TIW and once weekly doses compared with the daily dosing group. Unbound levels dropped by >50% in one half of the TIW group and in all patients in the weekly dosing group.

A group of healthy women of nonchildbearing potential were studied in another Phase I trial to assess single-dose versus 7-day continuous dosing of vismodegib. AAG levels were monitored to ensure similarity between the 2 dosing groups. In the single-dose cohort, oral vismodegib was administered; 2 hours later (the approximate time of maximum plasma concentration of the oral form), radiolabeled vismodegib was administered intravenously. The other cohort received vismodegib orally for 7 days and was then given the same radiolabeled vismodegib intravenously 2 hours later. Plasma levels were drawn after both dosage forms in each group and again demonstrated the nonlinear pharmacokinetics of the drug. Clearance and volume of distribution at steady state were increased and bioavailability was decreased after continuous daily dosing due to changes in the unbound concentration. This finding explains the lack of excessive accumulation of the drug after multiple dosing, which would be expected in a drug with the \( t_{1/2} \) that was exhibited in the single dose. Compared with the single dose, unbound levels of vismodegib increased 2.4-fold with continuous dosing at 7 days. The fraction unbound did not return to levels similar to the single-dose concentrations until approximately day 35.

**Absorption**

Bioavailability after a single 150-mg dose was 31.8% in 1 study. The effect of food on absorption has been presented in abstract form only. Single doses of 150 mg were studied in the setting of a high-fat meal, low-fat meal, or with fasting overnight. The researchers reported a trend toward a higher \( C_{\text{max}} \) in patients receiving a high-fat meal versus fasting for a single dose, but no statistically significant differences were found between the 3 groups with regard to steady-state \( C_{\text{max}} \), steady-state \( T_{\text{max}} \), or steady-state \( \text{AUC}_{0-24} \). Grade 3 or greater adverse effects were similar between the groups as well. The use of proton pump inhibitors, histamine2-blockers, or antacids may alter the solubility of vismodegib, causing decreased absorption of the drug. At a pH of 1, the solubility is 0.99 mg/mL in contrast to 0.0001 mg/mL at a pH of 7. No formal studies have been done to date to evaluate whether agents used to decrease the pH of the stomach would affect systemic exposure of vismodegib.
Metabolism
Vismodegib is minimally metabolized, with >98% of the drug excreted unchanged. Metabolic pathways include oxidation, glucuronidation, and pyridine ring cleavage. The 2 most abundant oxidative metabolites in feces were produced in vitro by recombinant cytochrome P450 (CYP) 2C9 and CYP3A4/5. However, drug exposure is not expected to be altered because patients were treated concomitantly with CYP3A4 inhibitors and inducers in trials with little change in exposure.29 Results of in vitro studies suggest that vismodegib is an inhibitor of CYP2C8, CYP2C9, CYP2C19, and the BRCP (breast cancer resistance protein) transporter. Rosiglitazone, a CYP2C8 substrate, was given with vismodegib at steady state with no clinically significant change in levels, suggesting that there is no clinically significant inhibition of vismodegib with CYP2C8.30 Vismodegib was also found in vitro to be a substrate of the p-glycoprotein transporter. The manufacturer cautions that systemic exposure and the subsequent adverse effects may be increased when given concomitantly with drugs that inhibit p-glycoprotein, such as clarithromycin, erythromycin, or azithromycin.29

Elimination
Vismodegib is eliminated primarily by the hepatic route with 82% recovered in feces and 4.4% recovered in urine.31 The estimated t1/2 of the drug is 12 days after a single dose and 4 days after continuous once-daily administration. A trial has been designed to study vismodegib in patients with renal or hepatic impairment, but these populations have not been included in the trials produced thus far.

Population pharmacokinetic analyses demonstrated that weight (range, 41–140 kg), age (range, 26–89 years), creatinine clearance (range, 30–80 mL/min), and sex do not have a clinically meaningful influence on the systemic exposure of vismodegib.29

In the pediatric population, steady-state concentrations were 10262 M after 85 mg/m2 and 170262 M after 170 mg/m2. Clearance was 0.86 mL/min/m2 at steady state, with an estimated cerebrospinal fluid penetration of 1.3% relative to total vismodegib concentration in the plasma.32 The concentration of unbound vismodegib measured in the cerebrospinal fluid of patients was similar to the unbound concentration in plasma, suggesting that effective levels of drug do reach the central nervous system.

**THERAPEUTIC EFFICACY/CLINICAL TRIALS**

**Phase I**
Some key Phase I trials and their essential results are summarized in Table I.23,27,32

**Phase II/III**
Two Phase II studies investigating vismodegib in BCC have been published, including the pivotal Phase II trial that earned vismodegib its FDA approval.23 No Phase III studies have been initiated or are planned.

<table>
<thead>
<tr>
<th>ClinicalTrials.gov Identifier</th>
<th>Cancer Type</th>
<th>Key Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT0060772423 Solid tumors (focus: mBCC and laBCC)</td>
<td>Established dose of 150 mg orally daily for subsequent trials Efficacy: 18 of 33 patients with objective response, 11 of 33 with stable disease, 4 of 33 with progressive disease; median duration of therapy, 9.8 months</td>
<td></td>
</tr>
<tr>
<td>NCT0082245832 Refractory medulloblastoma</td>
<td>Pediatric study population; 1 grade 3 GGT elevation; BSA dosing schema for ongoing Phase II trial (PBTC-032/NCT01239316)</td>
<td></td>
</tr>
<tr>
<td>NCT00991718,27 NCT01173536 Healthy women of nonchildbearing potential</td>
<td>Pharmacokinetic considerations explored; no QTc interval prolongation noted at therapeutic doses</td>
<td></td>
</tr>
</tbody>
</table>

mBCC = metastatic basal cell carcinoma; laBCC = locally advanced basal cell carcinoma; GGT = γ-glutamyl transpeptidase; BSA = body surface area.
Sekulic et al\(^2\) performed the trial that led to vismodegib being FDA approved. It was an international, single-arm, multicenter, open-label, 2-cohort trial. They enrolled 104 patients with either mBCC (n = 33) or laBCC (n = 71). Patients with Gorlin syndrome were eligible for enrollment. Patients received 150 mg of oral vismodegib daily until an end point of disease progression or unacceptable toxicity was reached. The primary indicator of efficacy was objective response rate (ORR). This rate included both partial and complete responses and was defined as a ≥30% decrease in disease. Disease progression was defined as a ≥20% increase in lesion size or identification of new BCC lesions.

From February 2, 2009, to November 26, 2010, a total of 96 of 104 patients were evaluated for ORR.\(^2\) According to baseline characteristics, the study population was 100% white, 61% male, and had a median age of 62 years. In the mBCC group (n = 33), there were 10 confirmed partial responses (30.3%) and no complete responses. The 30.3% ORR was significantly greater (\(P = 0.001\)) than the hypothesized 10% ORR. In the laBCC group (n = 63), there were 13 complete responses (20.6%) and 14 partial responses (22.2%). The 42.9% ORR was significantly greater (\(P < 0.001\)) than the hypothesized 20% ORR. Further breakdown of responses are listed in Table II. For both mBCC and laBCC, the median response duration was 7.6 months. Overall survival data had not matured by the time the study was published. Updated data with an additional 6 months of follow-up were presented at the 2012 American Society of Clinical Oncology annual meeting.\(^3\) The presented data supported the previously reported significant clinical effects and adverse effect profile.

The other Phase II trial, by Tang et al,\(^1\) investigated vismodegib therapy in patients with Gorlin syndrome. It was a randomized, double-blind, placebo-controlled trial involving 3 clinical centers with a primary end point of reduction in the incidence of new BCCs that were eligible for surgical resection versus placebo. Forty-one patients were randomized in a 2:1 ratio to receive 150 mg of oral vismodegib or placebo daily for 18 months. At the second interim analysis, the data and safety monitoring board concluded that there was a significant difference (\(P = 0.0113\)) between treatment and placebo groups. The significant results are listed in Table III.

### Safety/Tolerability
As a class, the Hh inhibitors exhibit adverse effects of muscle spasms/cramps, alopecia, and dysgeusia.\(^1\) Unsurprisingly, these adverse effects have played a prominent role in studies assessing vismodegib. Data on patients from 4 studies were compiled to evaluate the adverse effect profile and are summarized in Table IV.\(^2\) A total of 138 patients with BCC received vismo-

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Vismodegib (n = 26)</th>
<th>Placebo (n = 15)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New surgically eligible BCCs per year, median</td>
<td>2</td>
<td>25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reduction in size (sum of longest diameters) of existing surgically eligible BCCs, median</td>
<td>−71%</td>
<td>−21%</td>
<td>0.003</td>
</tr>
</tbody>
</table>

BCC = basal cell carcinoma.
degib; severe adverse effects were seen rarely. The most common reactions were muscle cramps, alopecia, dysgeusia, weight loss, and fatigue. Grade 3 or 4 fatigue was seen in >5% of patients. Although nausea was seen in ~30% of patients, the incidence of grade 3 nausea (ie, unable to adequately take in enough calories or fluid and potential need for parenteral nutrition, tube feedings, or hospitalization) was only 0.7%. Notably, 3 of 10 premenopausal women administered vismodegib for BCC developed amenorrhea.29 Only 1 patient displayed QTc interval prolongation in a Phase I study.23 In the pediatric trial reported to date, a Phase I medulloblastoma study investigating vismodegib found 1 grade 3 dose-limiting toxicity (increased γ-glutamyl transpeptidase at a dose of 170 mg/m²); no grade 4 toxicities were seen.32

The Phase II trial by Tang et al14 was placebo-controlled and therefore clearly illustrates the adverse effects of vismodegib versus an inert placebo. In this study, patients receiving vismodegib were significantly more predisposed to experiencing dysgeusia, muscle cramps, alopecia, and weight loss compared with patients taking placebo. Also of note from this study were patient medication discontinuation rates. After a mean 8 months of administration, 7 (27%) of 26 patients had discontinued therapy due to adverse effects. On discontinuation, resolution of dysgeusia and muscle cramps occurred within 1 month and hair growth within 3 months.

Sekulic et al24 reported 7 fatal events occurring during their trial, including hypovolemic shock, myocardial infarction, meningeal disease, and ischemic stroke. The relationship between vismodegib and these events is unknown. Fifty-seven percent of the patients receiving vismodegib had at least 1 adverse effect. Twenty-five percent of patients with laBCC chose to discontinue therapy on their own accord, although the reason for discontinuation was not documented. The authors of this trial attributed discontinuation to either long-term, low-grade adverse effects such as dysgeusia and muscle cramps or patient perception that the maximal benefit had already been achieved by vismodegib therapy.

### Dosing/Administration

The FDA-approved dosing of vismodegib is 150 mg orally daily until disease progression or unacceptable toxicity is experienced. A Phase I trial assessed higher dosing regimens, including 270 mg daily (23 patients) and 540 mg daily (4 patients).19,25 The increase in dose did not reflect an increase in systemic exposure to vismodegib due to its nonlinear kinetics. Although there was no noted increase in toxicity with higher doses, there was also no added clinical benefit.

### Special Populations

#### Pregnancy and Breastfeeding

Vismodegib is listed as a pregnancy category D medication.29 In rat studies, vismodegib was found to be teratogenic at a corresponding 20% of the recommended daily dose. Teratogenesis in rats included craniofacial abnormalities, open perineum, retardations in normal growth, and absence or fusion of digits. When exposed to concentrations equivalent to the recommended human dose, vismodegib was found to be embryolethal in rats. Vismodegib’s prescribing information includes a black box warning that embryo-fetal death and severe birth defects could occur with exposure.

The development of the first compound to inhibit the Hh pathway came from the isolation of cyclopamine and jervine from corn lilies. Teratogenic effects (including cyclopia) were noted in sheep feeding on this plant.17 Recognizing that the Hh pathway is important in embryogenesis, it would suggest that exposure of a fetus to vismodegib could produce significant abnor-

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle spasms</td>
<td>71.7</td>
<td>3.6</td>
</tr>
<tr>
<td>Alopecia</td>
<td>63.8</td>
<td>-</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>55.1</td>
<td>-</td>
</tr>
<tr>
<td>Weight loss</td>
<td>44.9</td>
<td>7.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>39.9</td>
<td>5.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>30.4</td>
<td>0.7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>29.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>25.4</td>
<td>-</td>
</tr>
<tr>
<td>Constipation</td>
<td>21.0</td>
<td>-</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>15.9</td>
<td>0.7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13.8</td>
<td>-</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>4.3</td>
<td>-</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>1.4</td>
<td>-</td>
</tr>
<tr>
<td>Azotemia</td>
<td>2.2</td>
<td>-</td>
</tr>
</tbody>
</table>

Grading according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.
malities. The manufacturer encourages women exposed to vismodegib during pregnancy, either directly or through seminal fluid, to participate in the drug’s pregnancy pharmacovigilance program. As this implies, men taking vismodegib must also exercise contraceptive precautions due to the risk of teratogenesis. It is unknown if vismodegib is excreted in breast milk, but it is recommended that breastfeeding not occur if a woman is receiving the drug based on the same reasoning that it should be avoided during pregnancy.

**Pediatrics**

The safety and efficacy of vismodegib in pediatric populations have not been well established. In animal studies, adverse effects at 20% to 40% of the human exposure range were observed that would be of concern in the pediatric population. These adverse effects included closure of the epiphysial growth plate and abnormalities in the development of incisor teeth (degeneration of odontoblasts, formation of fluid-filled cysts in dental pulp, ossification of the root canal, and hemorrhage resulting in breakage or tooth loss). Because inhibition of the Hh pathway may have application in the treatment of medulloblastoma, pharmacokinetics, efficacy, and toxicities are being assessed in an ongoing Phase II study of its use in pediatric patients aged 3 to 21 years who have medulloblastoma.

**Geriatrics**

To date, there have been an insufficient number of patients ≥65 years of age in studies of vismodegib to determine whether there are any differences in the pharmacokinetics or safety and efficacy in the geriatric population. Because the majority of BCCs occur in the older population, this group will need to be assessed in the postmarketing phase.

**Pharmacoeconomics**

The estimated cost of nonmelanoma skin cancer in patients with Medicare coverage is approximately $426 million per year, which ranks as the fifth most costly cancer in this population. The overall cost in the United States is approximately $650 million annually. Most costs are associated with services received during the physician’s office visit, with the dermatologist managing up to 82% of the visits in some studies through office-based surgical procedures. However, economic analyses have only looked at the treatment of early-stage nonmelanoma skin cancers in which surgical excision is used, sometimes in combination with radiation or topical therapy. No analysis is currently available for treatment in those patients with advanced cancer that is unresectable. It is difficult to systematically assess the economics of advanced BCC due to the lack of histology-specific International Classification of Diseases, Ninth Revision, codes for BCC that were not created until October 2011. The introduction of vismodegib is a new area in which to look at economic impact because there is nothing to compare it with beyond symptomatic management. According to the manufacturer, the wholesale acquisition cost is $7500 per 28 days, and the median duration of treatment for most patients in the pivotal Phase II trial was ~10 months.

**DISCUSSION**

Vismodegib is an exciting development in the world of targeted oncologic therapy, introducing a novel mechanism for fighting cancer. BCC is the most common skin cancer, and there have been few options for those patients with locally advanced or metastatic disease. The number of patients within this stage of BCC is small, and there have been only a few studies to give a complete picture of the drug and its adverse effects. Additional information will continue to accrue from postmarketing data as well as from studies incorporating vismodegib into chemotherapy and other targeted therapy regimens. One of the 2 Phase II studies used the gold standard design of a randomized, placebo-controlled trial but was limited only to patients with Gorlin syndrome. This study was halted at the second interim analysis based on the data safety and monitoring board’s recommendation regarding statistically significant improvements in the treatment arm. A placebo-controlled study in patients with mBCC and laBCC, with the exclusion of those with Gorlin syndrome, would more accurately portray the safety and efficacy of vismodegib for its FDA-approved indication. However, no Phase III studies are planned because there are no other viable therapies, and it would be considered unethical at this point.

More information about vismodegib in different populations is needed. A trial on renal and hepatic dysfunction with vismodegib is ongoing at the time of this writing, but there are still limited data in the pediatric and geriatric populations. Studies are currently underway to look at safety and efficacy in the pediatric medulloblastoma population. Because BCC is prevalent in the older population, more data on toxicity and pharmacokinetics.
will need to be collected. Vismodegib is a promising therapy with a novel mechanism, but its clinical experience to date is within a limited patient population.

Resistance patterns of the Hh inhibitors have not yet been clearly defined but will be closely assessed in patients undergoing therapy. There are currently no proven salvage therapies available for Hh pathway resistance. Further investigation into second-line therapies for those who fail to improve or whose disease progresses with vismodegib therapy will continue to be researched. Preliminary identification of the role of phosphoinositide-3-kinase inhibitors or other pathways as a potential salvage therapy in Hh pathway resistance may potentially provide more options.

The adverse effects profile of vismodegib is something to watch closely during treatment and is very relevant when considering therapy in a patient. Although the majority of toxicities were grade 1 or 2 in the studies, there is now an understanding that even low-grade toxicities become more of a problem when they are associated with an anticancer agent that has to be taken every day. As evidenced by Phase II trial results, adherence was compromised by the toxicities that some of the patients experienced. The discontinuation rate by patients from low-grade adverse effects such as dysgeusia and muscle cramps was 12% (13 of 104 patients) and 27.0% (7 of 26 patients) in 2 Phase II studies despite the observed clinical efficacy in treating their disease. To decrease adverse effects, other means of delivery, including topical application or intralesion injection of vismodegib have been suggested, although another Hh pathway inhibitor given topically showed no beneficial results.

Although preclinical data suggest that the Hh pathway may play a role in development of a number of cancers, results have been most promising in BCC, medulloblastoma, pancreatic adenocarcinoma, and hematologic malignancies. Disappointing results have been seen in some early trials with other solid tumors such as ovarian and colorectal cancer and even some studies in pancreatic cancer. Developing more useful correlative studies and identifying specific biomarkers may aid in the design of future studies to better understand the Hh pathway. Research is ongoing to determine the activity of vismodegib in the treatment of these and many other cancers as well as assessing additional semisynthetic Hh pathway inhibitors that may be more selective or potent. Of interest, another Hh pathway inhibitor being tested is itraconazole, which acts on SMO as well, although the antagonism is distinctly different from vismodegib and other cyclopamine derivatives.

CONCLUSIONS

Vismodegib is a novel agent now available in the ever-growing arena of targeted cancer therapies. Its clinical data, despite limited in quantity, have been impressive. This agent should serve as a key therapy in further investigations into cancers with underlying mutations or enhancements in the Hh pathway. Presently, vismodegib is a step forward for a patient population that has had limited options when the disease is unresectable or where unacceptable cosmetic outcomes would occur. Additional studies will further elucidate vismodegib’s role in the treatment of BCC as well as other cancers.

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CONFLICTS OF INTEREST

Dr. Harris was responsible for the development of an online publication for a major health-system pharmacy organization as editor and project manager for Lippincott, Williams and Wilkins. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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