U.S. Food and Drug Administration Approval: Vismodegib for Recurrent, Locally Advanced, or Metastatic Basal Cell Carcinoma

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Abstract

The data and regulatory considerations leading to the U.S. Food and Drug Administration (FDA) January 30, 2012 approval of Erivedge (vismodegib) capsules for the treatment of patients with recurrent, locally advanced, or metastatic basal cell carcinoma (BCC) are described. The FDA's approval decision was based primarily on the results observed in a single-arm, parallel cohort, international trial of vismodegib, administered orally at 150 mg daily until disease progression, in patients with pathologically confirmed, recurrent, locally advanced basal cell carcinoma (laBCC) or metastatic basal cell carcinoma (mBCC). An independent review committee confirmed an overall response rate (ORR) of 30.3% [95% confidence interval (CI): 15.6–48.2] in 33 patients with mBCC and an ORR of 42.9% (95% CI: 30.5–56.0) in 63 patients with laBCC; median response durations were 7.6 months and 7.6 months for patients with mBCC and laBCC, respectively. The most common adverse reactions were muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, diarrhea, decreased appetite, constipation, cough, arthralgias, vomiting, headache, ageusia, insomnia, and upper respiratory tract infection. Animal toxicology studies confirmed that vismodegib is a potent teratogenic agent. Approval was based on durable objective tumor responses supported by knowledge of the pathologic role of Hedgehog signaling in BCC and acceptable toxicity in a population without effective alternative therapies. Clin Cancer Res; 19(9); 2289–93. ©2013 AACR.

Introduction

Basal cell carcinoma (BCC) is a nonmelanotic skin cancer that arises from basal cells and is the most common form of cancer, with an estimated lifetime risk of 30% in non-Hispanic whites. The total number of BCC cases is difficult to estimate because cancer registries do not require reporting of BCC; when reported, BCC cases are usually combined with squamous cell carcinoma as nonmelanoma skin cancers (NMSC; ref. 1–2). A recent 2006 report estimated 3.5 million cases of NMSC and 2.2 million people received treatment based on Medicare claims. (3)

The initial management in most cases of BCC is surgical resection with assessment for positive margins (Mohs surgery), curettage, and electrodessication; for tumors with positive margins after attempted resection, radiation is recommended (4). The surgical cure rate for local disease is more than 90%, the specific mortality due to BCC is less than 0.1%, and the incidence of metastasis in BCC ranges from 0.0028% to 0.55% with reports in the literature of less than 400 cases (5). Fluorouracil cream and imiquimod cream are the only U.S. Food and Drug Administration (FDA)-approved drugs for localized BCC (laBCC) in patients who are not candidates for surgery or radiotherapy. Photodynamic therapy, not approved by the FDA for this indication, is another treatment option used in this population.

Treatment-resistant and metastatic BCC are very uncommon, resulting in disfigurement and morbidity, such as spinal cord compression (6) and lethal cerebral invasion (7). Case reports describe the limited activity of chemotherapy in metastatic BCC (mBCC; refs. 8–9). The 5-year survival rate is approximately 10% in patients with recurrent, unresectable, locally advanced BCC and metastatic BCC (10–12).

The role of the hedgehog (Hh) signaling pathway in the molecular pathogenesis of BCC is based on observations in 1996 of heritable mutations in patients with nevoid basal cell carcinoma syndrome (NBCCS), an autosomal dominant disorder with mutations in the human homolog of the patched 1 (PTCH) gene, characterized by...
multiple BCCs, keratoacysts of the jaw, palmar/plantar pits, spine and rib anomalies, and calcification of the falx cerebri (13, 14). The aberrant gene product PTCH produces ligand-independent activation of Smoothened (SMO) with constitutive activation of the Hh pathway and downstream activation of the glioma-associated oncogene family zinc finger (GLI) transcription factor and expression of multiple genes that control cell differentiation, tissue patterning, and cell proliferation (15, 16). Vismodegib binds to and inhibits SMO, thereby repressing Hh signaling.

Chemistry Manufacturing and Controls

Erivedge (vismodegib) is a synthetically derived new molecular entity. The chemical name for vismodegib is 2-Chloro-N-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl) benzamide. The commercial vismodegib drug product is a hard gelatin capsule containing 150 mg of vismodegib. Erivedge capsules are available in bottles of 28 capsules.

Nonclinical Pharmacology and Toxicology

The nonclinical data assessed included in vitro and in vivo pharmacology studies, single-dose and multiple-dose toxicology studies in rodents and dogs, a reproductive toxicology assessment in rats, and evaluation of genotoxicity. Repeat-dose toxicity studies of up to 6 months duration conducted in rats and dogs with daily administration of oral vismodegib have shown a less than dose-proportional increase in exposure (AUC) with increasing doses of vismodegib. The clinical adverse effects of vismodegib were predicted by these nonclinical studies.

The Hh pathway is a major regulator of embryonic development; thus, embryo-fetal toxicity was an expected outcome of inhibiting this pathway (17). Embryo-fetal developmental toxicity was confirmed in rats, with teratogenic effects observed at 10 mg/kg/day corresponding to a systemic exposure at approximately 20% of the human exposure at the recommended dose of 150 mg/day. Vismodegib was not genotoxic in vitro or in vivo. Carcinogenicity studies were not required before approval; however, pilomatrixcoma, a benign cutaneous neoplasm, was observed in rats (n = 2) in the chronic toxicity study.

Clinical Pharmacology

The absolute bioavailability of vismodegib after a single 150 mg oral dose was 31.8% with saturable absorption as evidenced by the lack of dose-proportional increases in exposure after single doses of 270 mg or 540 mg compared with 150 mg (18). Food intake did not affect vismodegib exposure at steady state.

Vismodegib was highly bound (>99%) to human serum albumin. Vismodegib and its metabolites were eliminated primarily by the hepatic route (19). The estimated elimination half-life (t1/2) of vismodegib was 4 days after continuous once-daily dosing.

The solubility of vismodegib was pH dependent with solubility of 0.1 at pH 7 and 990 µg/mL at pH 1. Drugs that alkalize the upper gastric tract (proton pump inhibitors, H2-receptor antagonists, and antacids) may decrease the solubility and bioavailability of vismodegib.

Clinical Trial Design

A single multicenter, open-label, parallel cohort trial (SHH4476g) enrolling 96 patients with pathologically confirmed laBCC or mBCC provided the primary efficacy data for this application (20). The safety data for patients with BCC consisted of a pooled subset of 138 patients who received vismodegib in 1 of 3 trials: SHH4476g, SHH3925g (a dose-finding trial), and SHH4610g (a dose optimization trial). The total safety database consisted of more than 400 subjects who received vismodegib monotherapy for BCC or other malignancies.

Trial SHH4476g was a fixed-dose, parallel cohort, multicenter, international trial. Eligibility criteria included age of 18 years or more, ECOG performance status ≤ 2, adequate bone marrow and hepatic function, histologic confirmation of BCC, measurable disease, and agreement to use highly effective contraception during and for at least 2 months (men) or 7 months (women) after drug discontinuation. Patients with laBCC were required to have at least one lesion 10 mm or more in the longest diameter, a determination by a Mohs dermatologic surgeon, head and neck surgeon, or plastic surgeon that the lesion was inoperable or medically contraindicated, and received prior radiation unless radiation was contraindicated or medically inappropriate. Medical contraindications to surgery were recurrent BCC in the same location after 2 or more operations with further surgery unlikely to result in curative resection, or anticipated substantial morbidity and deformity from surgery (e.g., removal of all or part of a facial structure, such as nose, ear, eyelid, eye; or requirement for limb amputation). Contraindications to radiation were tumor location, prior cumulative radiation dose, or diagnosis of NBCCS.

Patients received 150 mg of vismodegib daily until disease progression, intolerable adverse reactions attributable to vismodegib, or withdrawal of consent. Tumor assessments were conducted every 8 weeks and at the end of the trial or at early termination.

The primary objective was durable objective response rate as assessed by an independent review facility (IRF) based on radiologic, photographic, and histopathologic data. The IRF reviewers were not provided demographic data or clinical site determinations of response. Secondary end points included IRF-determined response duration, progression-free survival (PFS), overall survival (OS), and patient-reported outcomes.

Objective tumor response was based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 for the mBCC cohort. For the laBCC cohort, protocol-specific criteria for tumor response required at least one of the following criteria: (i) 30% or more reduction in lesion size [sum of the longest diameter (SLD)] from baseline in target lesions by radiographic assessment; (ii) 30% or more reduction in SLD from baseline in externally visible
dimension of target lesions; and (iii) complete resolution of ulceration in all target lesions. Complete response was defined as objective response as defined above with no residual BCC on sampling tumor biopsy.

The planned sample size of 100 patients was based on the following: 4:1 laBCC to mBCC patient ratio, 80% power to detect a response rate of 37% in the mBCC cohort and 34% in the laBCC cohort. All safety and efficacy results were presented as descriptive statistics.

Clinical Trial Results

One hundred four patients enrolled in Trial SHH4467g across 31 sites in Europe and the United States; 100% of patients with mBCC and 89% with laBCC had histologically confirmed BCC.

Table 1 provides the demographic and disease characteristics of the 96 patients with histologically confirmed BCC.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>mBCC (n = 33)</th>
<th>laBCC (n = 63)</th>
<th>Total (n = 96)</th>
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<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>62</td>
<td>62</td>
<td>62</td>
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<tr>
<td>Range</td>
<td>38–92</td>
<td>21–101</td>
<td>21–101</td>
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<td></td>
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<tr>
<td>18–65</td>
<td>19 (57.6%)</td>
<td>33 (52.4%)</td>
<td>44 (45.8%)</td>
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<tr>
<td>&gt;65</td>
<td>14 (42.4%)</td>
<td>30 (47.6%)</td>
<td>44 (46.4%)</td>
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<tr>
<td>Sex</td>
<td></td>
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<tr>
<td>Male</td>
<td>24 (72.7%)</td>
<td>35 (55.6%)</td>
<td>59 (61.5%)</td>
</tr>
<tr>
<td>Female</td>
<td>9 (27.3%)</td>
<td>28 (44.4%)</td>
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<td>Race</td>
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<tr>
<td>White</td>
<td>33 (100%)</td>
<td>63 (100%)</td>
<td>96 (100%)</td>
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<td>NBCCS</td>
<td>33 (100%)</td>
<td>43 (68.3%)</td>
<td>76 (79.2%)</td>
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<td>20 (31.7%)</td>
<td>20 (20.8%)</td>
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<td>42 (66.7%)</td>
<td>68 (70.8%)</td>
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<td>5 (5.2%)</td>
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<td>2 (3.2%)</td>
<td>2 (2.1%)</td>
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<td>48 (76.2%)</td>
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<td>1</td>
<td>19 (57.6%)</td>
<td>13 (20.6%)</td>
<td>32 (33.3%)</td>
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<td>2</td>
<td>1 (3.0%)</td>
<td>2 (3.2%)</td>
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<tr>
<td>Prior cancer treatment</td>
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<td>32 (97.0%)</td>
<td>59 (93.7%)</td>
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<tr>
<td>Prior surgery</td>
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<td>32 (97.0%)</td>
<td>56 (88.9%)</td>
<td>88 (91.7%)</td>
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<tr>
<td>Prior radiation</td>
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<tr>
<td>Yes</td>
<td>19 (57.6%)</td>
<td>17 (27%)</td>
<td>36 (37.5%)</td>
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<tr>
<td>Systemic treatment</td>
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<tr>
<td>Yes</td>
<td>10 (30.3%)</td>
<td>7 (11.1%)</td>
<td>17 (17.7%)</td>
</tr>
</tbody>
</table>

Twenty-one percent were diagnosed with NBCCS. The median age of the efficacy population was 62 years (54% were at least 65 years old), 62% male and 100% white. For the mBCC cohort (n = 33), 97% had prior surgery (97%) and systemic therapies (30%). For the laBCC cohort (n = 63), 94% had prior surgery (89%), radiotherapy (27%), and systemic/topical therapies (11%) and had received prior treatments for a median of 10.2 months. The most common reason for not receiving radiation was NBCCS in 20 patients (37.7%). FDA estimated the tumor burden in the laBCC subgroup by summing the longest diameters reported for all externally visible tumors identified at screening. The median tumor burden was 56.6 cm (range 6.6–305 cm).

The overall response rate (ORR) in patients with mBCC was 30.3% (95% CI: 15.6–48.2) and 42.9% (95% CI: 30.5–56.0) in patients with laBCC. All 10 responses in the mBCC cohort were partial responses. In the laBCC cohort of the 63 evaluable patients, 13 (20.6%) and 14 (22.2%) achieved complete and partial responses, respectively. The median response duration was 7.6 months (95% CI: 5.62, not estimable) and 7.6 months (95% CI: 5.7, 9.7) for patients with mBCC and laBCC, respectively.

The safety profile of vismodegib monotherapy was primarily evaluated in 138 patients with BCC. The median duration of treatment was approximately 10 months (range 0.7–36 months); 111 patients received Erivedge for 6 months or longer. The validity of pooling the safety information across these 3 trials was based on the lack of evidence for an exposure–toxicity relationship for common adverse reactions. For serious adverse reactions, a larger safety database of more than 400 patients with various malignancies receiving vismodegib doses ranging from 150 to 540 mg was evaluated.

The most common adverse reactions in patients with BCC receiving vismodegib (≥10%) were muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, diarrhea, decreased appetite, constipation, arthralgias, vomiting, and ageusia (Table 2). Seven patients (5.1% of overall study population) died within 30 days of receiving the last vismodegib dose; 4 deaths were potentially treatment related: acute myocardial infarction, hypovolemic shock, death not otherwise specified, and meningeal disorder. The most common serious adverse reactions (≥1%) in patients receiving vismodegib were death (2.2%), pneumonia (2.2%), cardiac failure (1.4%), gastrointestinal hemorrhage (1.4%), pulmonary embolism (1.4%), deep vein thrombosis (1.4%), and hemorrhage (1.4%). The lack of a randomized control makes the attribution of the serious adverse events to vismodegib uncertain, given the expected background rate of such serious events in older patient population.

Discussion

The FDA granted vismodegib regular approval on January 30, 2012 for the treatment of adults with mBCC or with laBCC with recurrence following surgery or who are not candidates for surgery or radiation. Approval was based on demonstration of durable tumor shrinkage as determined by an independent radiology review facility, with an ORR of...
In patients with locally advanced disease and a response rate of 30% (95% CI 16%, 48%) in patients with metastatic disease, with a median duration of response of 7.6 months in both cohorts. While the number of patients evaluated was small, confidence in the findings was supported by the well-characterized role of the Hh signaling pathway in development of BCC, present in both patients with NBCCS and in sporadic cases of BCC and the laboratory confirmation that vismodegib inhibits this pathway.

The regulatory standard for drug approval under the Federal Food, Drug, and Cosmetic Act of 1962 requires demonstration of substantial evidence of efficacy in adequate and well-controlled clinical trials. However, the FDA may exercise regulatory discretion in determining the number of trials required to provide substantial evidence, based on robustness of the findings and feasibility of additional trials, as discussed in the FDA’s Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 1998). Given the very low incidence of inoperable or metastatic BCC patients and robust treatment effects observed in the trial review, the FDA determined that a second trial in this population would be practically impossible.

When a disease is both serious and lacks effective alternative therapy, evaluation of treatment effects in randomized trials may also not be feasible. However, evidence of clinical benefit can be evaluated in single-arm trials, as the FDA has done for other cancers that are refractory. In single-arm trials, the “control” is external and generally historical in nature, thus time-to-event end points such as PFS or OS cannot be assessed as these are highly dependent on the characteristics of the population studied. However, objective tumor shrinkage in the absence of effective treatment (i.e., spontaneous remissions) is extremely rare regardless of selection criteria or population characteristics, therefore response rate and response durability can be directly attributed to drug treatment. The FDA may consider evidence of durable objective response to be a surrogate likely to predict an effect on clinical benefit such as reduction in mortality or morbidity, under an accelerated approval, or evidence of direct benefit. This judgment is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. In this instance, the FDA concluded that the independently confirmed response rates of 30% in patients with mBCC and 43% in patients with lBCC with median response durations of 7.6 months in both cohorts met the criteria for a clinically meaningful effect and direct clinical benefit. Photographic evidence of lesions established the disfiguring and morbid nature of the lBCC lesions, such that the durable reduction in lesions size was evidence of benefit. Among patients with mBCC, although the observed response rate was lower, the durability of responses, tolerable side effect profile of vismodegib, and lack of alternative therapy supported a conclusion of clinical benefit. Finally, as discussed earlier, an understanding of the drug’s mechanism of action, confirmed in nonclinical studies, which affected a well-described pathway in the disease process further supported confidence in these results, leading the FDA to conclude that the effect on tumor shrinkage was robust.

The approval of vismodegib follows the precedent set with cutaneous T-cell lymphoma (CTCL) and Kaposi’s sarcoma, where durable reduction in skin tumors, which are unresectable and often disfiguring, has been considered direct clinical benefit. Bexarotene and romidepsin each received regular approval for the treatment of advanced CTCL, based on similar evidence of efficacy (30% response rate and 34%–35% response rate, respectively) and similar sized safety databases of fewer than 200 patients.

The major potential toxicity of vismodegib based on preclinical studies is to the fetus of a woman exposed to vismodegib during pregnancy. A contraindication to use (Pregnancy Category X) was considered inappropriate as Erivedge is labeled for the treatment of a serious and life-threatening disease for which there are limited treatment options and other safer alternatives are not available. In addition, similar teratogenic findings have been identified with both older “nontargeted” drugs and with recently approved targeted therapies, vandetanib, crizotinib, and vemurafenib. The FDA determined that the teratogenic risk of vismodegib could be minimized through appropriate product labeling and voluntary educational efforts by the commercial sponsor. These
plans emphasize the need for contraception in females and barriers in males.

Vismodegib is the first systemic drug approved for the treatment of BCC and the first in the class of the Hh pathway inhibitors. While virtually all NBCCS and most BCC tumors seem to have PTCH1-activating mutations, thus obviating the need for genetic testing, further development of agents that target the Hh signaling pathway in other tumor primary tumors, such as medulloblastoma, is likely to require genetic tests to identify patient subsets likely to benefit (21).

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

References
Clinical Cancer Research

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