Expanded access study of patients with advanced basal cell carcinoma treated with the Hedgehog pathway inhibitor, vismodegib

Anne Lynn S. Chang, MD,[a] James A. Solomon, MD, PhD,[b,c,d] John D. Hainsworth, MD,[e] Leonard Goldberg, MD,[f] Edward McKenna, PharmD, BCOP,[g] Bann-mo Day, PhD,[g] Diana M. Chen, MD,[g] and Glen J. Weiss, MD[h]

Stanford, California; Ormond Beach and Orlando, Florida; Nashville, Tennessee; Urbana, Illinois; Houston, Texas; San Francisco, California; and Scottsdale, Arizona

Background: Vismodegib, a first-in-class Hedgehog pathway inhibitor, was US Food and Drug Administration (FDA) approved for advanced basal cell carcinomas (BCCs) based on a single, nonrandomized, phase-II trial. Consequently, additional clinical data are critical to confirm the efficacy and safety of vismodegib.

Objective: We sought to assess efficacy and safety of vismodegib, while providing early drug access to patients with advanced BCC and limited treatment options.

Methods: This was an open-label, multicenter study in patients with advanced BCC inappropriate for radiotherapy or surgery. Patients received 150 mg vismodegib daily until disease progression or intolerable toxicity. Tumor response was assessed via Response Evaluation Criteria in Solid Tumors version 1.0.

Results: A total of 119 patients with advanced BCC took vismodegib for a median of 5.5 months. Objective responses occurred in 46.4% of locally advanced BCC and 30.8% of patients with metastatic BCC. Response was negatively associated with prior systemic therapy in patients with locally advanced BCC (P = .002). Mean follow-up for safety was 6.5 months, with muscle spasms (70.6%), dysgeusia (70.6%), alopecia (58.0%), and diarrhea (25.2%) as the most common adverse events.

Limitations: Abbreviated follow-up time because of study termination upon FDA approval was a limitation.

Conclusion: This study provides important clinical data supporting the efficacy and safety of vismodegib. Larger studies are underway to assess predictors of response and long-term outcomes. (J Am Acad Dermatol 2014;70:60-9.)

Key words: basal cell carcinoma; basal cell nevus syndrome; expanded access; Hedgehog pathway inhibitor; locally advanced; metastatic; vismodegib.

From the Stanford University School of Medicine[a]; Ameriderm Research, Ormond Beach[b]; Sarah Cannon Research Institute, Nashville[c]; University of Illinois, Urbana Champaign, College of Medicine[d]; University of Central Florida, College of Medicine, Orlando[e]; Dermsurgery Associates, Houston[f]; Genentech Inc, South San Francisco[g]; and Virginia G. Piper Cancer Center Clinical Trials at Scottsdale Healthcare.[h]

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Reprint requests: Anne Lynn S. Chang, MD, Department of Dermatology, Stanford University School of Medicine, 450 Broadway St, Mail Code 5334, Redwood City, CA 94063. E-mail: alschang@stanford.edu.

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Basal cell carcinoma (BCC) is the most common human malignancy, with an estimated 1.6 million new patients treated in the United States in 2006.[1-3] Most BCCs are effectively cured, but in some cases may progress to advanced BCC (refers to both locally advanced and distantly metastatic BCCs).[4-6] Locally advanced BCCs can be debilitating and lead to significant morbidity.[4,7,8] Surgery or radiotherapy may be untenable choices[9,10] because of potential loss of vital function with these treatments.[7,11,12] In metastatic BCC, a rare but often fatal condition, distant metastases may preclude surgery or radiation.[6,13,14]

Conventional chemotherapy such as cisplatin has been reported to improve tumor response, but improvements in progression-free survival or overall survival have not been demonstrated.[15] Chemotherapy has also been examined as an adjuvant to radiation but this has not demonstrated improved survival either.[16] Hence, effective treatment for advanced BCCs represented a significant unmet medical need.

Smoothened (SMO) inhibitors are highly targeted therapies based on the biology of BCCs. Aberrant Hedgehog pathway signaling, driven by genetic loss of function alterations in Patched or activating mutations in SMO,[17,18] is critical in BCC pathogenesis.[10,19,20] Loss of Patched contributes to approximately 90% of sporadic BCCs, whereas SMO-activating mutations occur in approximately 10% of sporadic BCCs.[21-23] Hence, Hedgehog pathway inhibitors represent a novel therapeutic option for BCC treatment.[19,24]

Vismodegib is the first US Food and Drug Administration (FDA)-approved oral, small-molecule, Hedgehog pathway inhibitor effective in advanced BCC.[5,9,14,24,25] In a phase-II BCC study (ERIVANCE), 104 patients with advanced BCC received vismodegib, with a 43% response in locally advanced BCC and a 30% response in metastatic BCC groups.[14] Because of significant unmet medical need in patients with advanced BCC, vismodegib received priority FDA approval after this phase-II clinical trial.[26,27]

Despite FDA approval, additional clinical data in a greater number of patients with advanced BCC are critical to confirm the safety and efficacy of vismodegib. This study provided an opportunity for patients with advanced BCC and limited treatment options to receive early drug access. Furthermore, this study is the largest peer-reviewed, published study to date on vismodegib in patients with advanced BCC, allowing exploratory analysis of factors that predict advanced BCC response to vismodegib.

CAPSULE SUMMARY

- Vismodegib was approved by the US Food and Drug Administration for advanced basal cell carcinoma after a single phase-II clinical trial.
- To our knowledge, this is the largest completed trial to date on vismodegib, with 119 patients with this rare condition.
- This study confirms prior safety and efficacy and explores clinical factors associated with tumor response.

METHODS

Study patients

After approval from institutional review boards, and in accordance with Declaration of Helsinki guidelines, all patients provided written informed consent for trial participation. This study was registered as NCT01160250 on Clinicaltrials.gov.

Inclusion criteria

Eligible patients were 18 years or older; had adequate organ function; had an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less; and had measurable, evaluable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 criteria.[28] BCC metastatic to the bone, termed "nonmeasurable" disease by RECIST version 1.0 was included. Patients with locally advanced BCC had at least 1 histologically confirmed lesion 10 mm or larger in diameter with written confirmation from a surgical specialist that the tumor was inoperable, or that surgery was contraindicated. Surgery was considered inappropriate if BCC recurred in the same location after 2 or more surgical procedures and curative resection was deemed unlikely, or when there was substantial morbidity and/or deformity anticipated. Patients with locally advanced BCC were required to have had prior radiation therapy to greater than or equal to 1 target lesion unless contraindicated or inappropriate. Histologic confirmation of locally advanced BCC and metastatic BCC lesion(s) was required in all cases. Patients with basal cell nevus syndrome (BCNS) could enroll if they met inclusion criteria. Women of childbearing potential and men with female partners of childbearing potential were required to use medically reliable contraception because of vismodegib teratogenicity.

Exclusion criteria

Patients were ineligible to participate if they had major organ dysfunction; were pregnant, lactating, or unwilling to practice birth control; had completed antitumor therapy less than 21 days before treatment