Clinical Benefit Assessment of Vismodegib Therapy in Patients With Advanced Basal Cell Carcinoma

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Advanced basal cell carcinoma • Vismodegib • Clinical benefit • Independent panel review • ERIVANCE BCC

ABSTRACT

Purpose. Vismodegib was approved for the treatment of advanced basal cell carcinoma (aBCC) based on the pivotal ERIVANCE BCC study. The primary endpoint (objective response rate [ORR]) was assessed 9 months after the last patient was enrolled. To confirm the clinical benefit of vismodegib, an additional analysis was performed 12 months after the primary analysis.

Materials and Methods. ERIVANCE BCC was a multicenter, nonrandomized, two-cohort study of 104 patients with histologically confirmed aBCC. Patients received 150 mg oral vismodegib daily until disease progression, intolerable toxicity, or withdrawal. An independent review panel comprising three expert clinicians reviewed patient photographs individually and as a consensus panel to evaluate baseline disease severity and clinical benefit after vismodegib treatment in 71 patients with locally advanced BCC (laBCC).

Results. Sixty-three patients were efficacy evaluable; baseline and postprogression photographs for 61 were available for review. Baseline disease severity was judged as 5 or 4 (very severe or moderately severe) in 71.4%. Clinical benefit was observed in 76.2% (significant: 65.1%; some: 11.1%). Inter-panelist agreement (maximum difference ≤ 1 point among panelists' scores in 65.1% and 87.3% of patients for clinical benefit and baseline disease severity, respectively) and correlation between individual and panel reviews were strong. Clinical benefit scores showed good concordance with the protocol-specified ORR obtained by an independent review facility and with investigator-assessed response.

Conclusion. Clinical benefit assessed by independent review based on expert clinical judgment provides strong evidence that treatment with vismodegib results in clinically meaningful and durable responses in patients with laBCC. *The Oncologist* 2014;19:790–796

Implications for Practice: Based on the results of the pivotal ERIVANCE BCC trial, vismodegib was approved for use in patients with basal cell carcinoma not amenable to surgery or radiation. The current article demonstrates that expert independent clinical judgment of pretreatment and post-treatment lesion photographs from patients enrolled in ERIVANCE BCC was consistent with the investigator-assessed results previously reported. Strong consistency was also observed between independent reviewers' assessments of both baseline disease severity and overall clinical benefit. This independent panel review lends support to the clinically meaningful responses to vismodegib observed in ERIVANCE BCC.

INTRODUCTION

Basal cell carcinoma (BCC) is the most common human cancer. White persons have an approximate 30% lifetime risk of developing the disease [1, 2]. Most BCCs are treatable by surgery; however, in rare cases, BCC can progress to advanced BCC (aBCC), either locally advanced BCC (laBCC) or, in rare cases, metastatic BCC (mBCC) [3, 4]. An accurate estimate of aBCC incidence is difficult to obtain, in part, because of the lack of uniform reporting requirements for nonmelanoma skin cancer and the absence of a widely used staging system; however, aBCC is thought to represent approximately 1%–10%

of all BCC, with mBCC accounting for between 0.0028% and 0.5% [5–8]. BCC can be disfiguring or debilitating and can lead to significant morbidity [3, 9, 10]. In such cases, standard treatment (mainly surgery and, to a lesser extent, radiotherapy) may be inappropriate because of lesion size and location and the potential for further disfigurement or physical impairment [11, 12]. Therapeutic options available for such patients are limited.

Aberrant Hedgehog (Hh) pathway signaling, driven by specific genetic loss-of-function alterations in patched 1

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(*PTCH*) or activating mutations in smoothened (*SMO*) [13, 14], plays a critical role in the pathogenesis and progression of BCC [11, 15, 16]. Vismodegib is the first oral small molecule inhibitor of the Hh signaling pathway to be approved for treatment of advanced BCC based on results from the pivotal phase II ERIVANCE BCC study, in which patients with laBCC and mBCC received 150 mg oral vismodegib daily [17]. The primary endpoint, objective response rate (ORR), was assessed by an independent review facility. Because no standard endpoint was determined for laBCC when the study was designed, response was defined as a decrease $\geq 30\%$ in the externally visible lesion (or radiographic dimension, if applicable) or complete resolution of ulceration (if present at baseline). Investigators and the photographic independent review facility were instructed to include residual scarring when measuring externally visible lesions. Responses had to be confirmed at least 4 weeks after initial documentation. Progressive disease was defined as an increase $\geq 20\%$ in the externally visible or radiographic dimension, new ulceration, or a new lesion. If multiple target lesions were identified, the sum of the longest diameters was used. The primary endpoint, ORR, as assessed by the independent review facility, was met by 43% of patients with laBCC and 30% of patients with mBCC [17]. Investigator-assessed ORRs were 60% and 45% in patients with laBCC and mBCC, respectively. These findings were further supported by 12-month updated data on patients, with an additional 12-month follow-up after primary analysis (or minimum potential follow-up of 21 months) [18]. The most frequent adverse events (AEs) observed at the 12-month update included muscle spasms (71%), alopecia (65%), dysgeusia (54%), weight loss (50%), fatigue (40%), and nausea (33%). Serious AEs were reported in 32% of patients, and seven deaths resulting from AEs were noted [18].

Although tumor response-based endpoints such as response rate (RR) and progression-free survival (PFS) are increasingly used and accepted, particularly for targeted molecular agents [19], these endpoints are dependent on accurate assessment of changes in the size of tumor lesions. Similarly, in skin cancers such as laBCC, endpoint assessment also includes review of photographic evidence of lesions and requires blinded, independent assessment to reduce bias. It has been reported that assessment of tumor lesions can be subject to interobserver and intraobserver variability [20–22]. Moreover, ORR by independent review facility is the most conservative assessment, and review of clinical photographs in the ERIVANCE BCC study suggested greater benefit than that measured by the independent review facility. In this analysis, we used photographs of lesions to better characterize both the severity of the disease at baseline and the clinical benefit derived from treatment in the ERIVANCE BCC study. Specifically, an ad hoc independent panel review consisting of three expert clinicians with experience treating aBCC reviewed all digital photographs of patients with laBCC at baseline and during treatment. In this paper, we present the methodology and results of this independent panel review. The independent panel review assessed clinical disease severity at baseline and overall clinical benefit on the basis of magnitude and duration of clinical response during vismodegib treatment. To our knowledge, this is the first description and application of an

independent panel review to assess clinical benefit in patients with aBCC.

MATERIALS AND METHODS

Study Design

The ERIVANCE BCC study design has been reported previously [17]. This phase II, single-arm, two-cohort, multicenter clinical trial was performed to evaluate the efficacy and safety of vismodegib in patients with aBCC. The study was conducted in accordance with U.S. Food and Drug Administration (FDA) regulations and the International Conference on Harmonization E6 Guideline for Good Clinical Practice. All enrolled patients received vismodegib 150 mg orally and daily until disease progression, intolerable toxicity, or study withdrawal. The primary endpoint was ORR, as assessed by independent review facility; secondary endpoints included investigator-assessed ORR, duration of response (DOR), and independent review facility- and investigator-assessed PFS. Safety parameters were also analyzed and adverse events graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 [23].

In the ERIVANCE BCC study, all laBCC patients were required to have at least one externally visible (target) lesion with a longest dimension ≥ 10 mm that was considered inoperable or surgery had to be deemed inappropriate in the opinion of a specialist in Mohs dermatologic, head and neck, or plastic surgery. Surgery was considered inappropriate if BCC had recurred after two or more surgeries and curative resection was unlikely and/or substantial morbidity and/or deformity was anticipated from the surgery. In addition, prior radiotherapy to one target lesion or more was required, unless medically contraindicated or inappropriate. Because a standard endpoint for laBCC did not exist when the ERIVANCE BCC study was designed, response was defined in collaboration with the FDA as a decrease $\geq 30\%$ in externally visible or radiographic dimensions (if applicable) or complete resolution of ulceration (if present at baseline). Investigators and independent reviewers were instructed to include residual scarring when measuring the externally visible dimension. As of November 28, 2011 (data cutoff for independent panel review), all patients had the potential to have been followed for at least 21 months. This was 12 months later than the protocol-specified primary analysis time point, which was only 9 months after the first treatment of the last enrolled patient (November 26, 2010) [17].

Independent Panel Review

Three independent physicians based in Europe with special expertise in dermatology, specifically, treatment of BCC and aBCC, were selected as reviewers in this analysis. They were not involved as investigators in the study or as consultants to Roche Molecular Systems. All were recommended by the independent review facility photographic vendor (Canfield Scientific, Fairfield, NJ, <http://www.canfieldsci.com>), and their qualifications were confirmed by a clinical representative of Roche. A predefined charter was provided by Roche for the independent panel review.

Table 1. Definition of baseline disease severity and clinical benefit scores

	Score				
	5	4	3	2	1
Baseline disease severity^a					
Cosmetic outcome	Disfigurement without possibility of reconstruction or prosthetics; severe	Disfigurement with need for reconstruction or prosthetics	Some disfigurement without need for reconstruction	Notable scarring without disfigurement	Limited to no scarring
Functional outcome	Significant impairment	Some impairment	Mild impairment	None	None
Clinical benefit	Significant clinical benefit	Some clinical benefit	No change	Somewhat worse	Significantly worse

^aSeverity index: 5, very severe; 4, moderately severe; 3, severe; 2, moderate; 1, mild.

Digital Photographic Procedures for Serial Photographic Documentation of laBCC

Clinical photographs were taken for the duration of the study using standardized equipment including a digital camera (Nikon D70s, 6MP, digital SLR; Nikon, Tokyo, Japan, <http://www.nikon.com>), a lens (Nikon 60-mm F2.8), a millimeter-scale attachment arm, a color card/patient identification (ID) holder, and standardized background material. Documentation at each photographic session included patient ID, including date and protocol, center, and visit number; a close-up view of the patient's target BCC area; and a global view of the patient's target BCC area. Tumors were assessed by means of physical examination (documented by standardized digital photography) at baseline and every 8 weeks thereafter. For patients with radiographically measurable disease (all patients with mBCC and some with laBCC), radiographic assessment of tumors was performed at baseline and every 8 weeks thereafter. Clinical benefit was assessed by a comparative review of change from baseline. Baseline images were displayed on a single projected screen, and postbaseline images were viewed on an adjacent screen sequentially for each patient. Each patient's BCC disease history, eligibility for inclusion in the study, and relevant past medical history were made available to the reviewer.

Baseline Disease Severity

Disease severity at baseline was based on the clinical judgment of each reviewer. The independent review panel performed an individual review of baseline disease severity in laBCC patients and scored each patient from 5 (very severe) to 1 (mild) based on an assessment of potential cosmetic outcome and functional score after surgical treatment, whichever was worse. A score of 5, for example, related to a cosmetic outcome of disfigurement without possibility for reconstruction or prosthetics and a functional outcome of significant impairment, and a score of 1 related to a cosmetic outcome limited to no scarring and good functional outcome (Table 1).

Clinical Benefit Measurement

Clinical benefit was based on the physician's global assessment of all target lesions (over all time points) for each patient, combining the magnitude and duration of benefit of treatment obtained by each patient. Clinical benefit was scored by each reviewer independently from 5 (significant clinical benefit) to 1 (significantly worse) (Table 1). For these reviews, all images of

patient target lesions were made available for independent panel review.

Assessments: Individual Review and Consensus Review

Assessments were done first by individual review and then by consensus review. For individual review, each reviewer entered scores and comments justifying the scores. For consensus review, scores and comments justifying the scores were collated from all three reviewers as a panel. If no agreement was noted among the three reviewers, "unable to assess" was entered, and the score was based on the median of individual scores in the analysis. Analyses of concordance between individual and consensus reviews were performed using Pearson and Spearman correlation coefficients.

RESULTS

Patient Baseline Characteristics

A total of 104 patients were enrolled in the ERIVANCE BCC study over a 13-month period at 31 sites in the U.S., Europe, and Australia [17]; 33 patients with mBCC and 71 patients with laBCC were included. Eight patients with laBCC were excluded from the efficacy analysis because the independent pathologist did not identify BCC in biopsy specimens obtained at baseline [17]. Among the laBCC patients ($n = 63$), 61 had photographs available at baseline and after treatment. The two patients who did not have photographs at baseline were not included in the independent review facility assessment.

Baseline Disease Severity

By consensus review, most patients ($n = 45$, 71.4%) had high baseline disease severity scores of 5 (very severe, 58.7%) and 4 (moderately severe, 12.7%), suggesting that treatment for these patients by alternative means would likely lead to disfigurement and/or (significant) functional impairment. Sixteen patients (25.4%) were assessed by consensus review as having a baseline disease severity score ranging from 1 to 3 (mild to severe) (Table 2). All of these patients met the protocol-defined inclusion criteria for laBCC. For two patients, no consensus could be reached; therefore, results were not evaluable.

Overall Clinical Benefit Score

By consensus review, 76.2% (48 of 63) of patients were judged to have gained significant clinical benefit (65.1%, clinical benefit score of 5) or some clinical benefit (11.1%, clinical benefit score of 4). Seven patients scored as significantly worse

Table 2. Consensus review of baseline disease severity scores in efficacy-evaluable locally advanced basal cell carcinoma patients

Baseline severity index ^a	No. of patients (n = 63)	Percentage
1	10	15.9
2	2	3.2
3	4	6.3
4	8	12.7
5	37	58.7
Missing	2	3.2

^aSeverity index: 1, mild; 2, moderate; 3, severe; 4, moderately severe; 5, very severe.

Table 3. Consensus review assessment of clinical benefit scores in efficacy-evaluable locally advanced basal cell carcinoma patients

Clinical benefit score ^a	No. of patients (n = 63)	Percentage
1	7	11.1
2	4	6.4
3	2	3.2
4	7	11.1
5	41	65.1
Missing	2	3.2

^aClinical benefit score: 1, significantly worse; 2, somewhat worse; 3, no change; 4, some clinical benefit; 5, significant clinical benefit.

Table 4. Correlation between baseline disease severity and clinical benefit by consensus review

Baseline severity index ^a	Clinical benefit score ^b				
	1	2	3	4	5
1	0	0	0	2	8
2	0	1	0	0	1
3	0	0	0	0	4
4	0	0	0	1	7
5	7	3	2	4	21

^aSeverity index: 1, mild; 2, moderate; 3, severe; 4, moderately severe; 5, very severe.

^bClinical benefit score: 1, significantly worse; 2, somewhat worse; 3, no change; 4, some clinical benefit; 5, significant clinical benefit.

(clinical benefit score of 1), and four patients were scored as having somewhat worse clinical benefit (clinical benefit score of 2). No change was assigned to two patients (clinical benefit score of 3), only one of whom was efficacy evaluable; the other was nonevaluable (Fig. 1; Table 3).

Correlation Between Consensus Review Assessments of Baseline Disease Severity and Clinical Benefit

Of 12 patients assessed by consensus review to have baseline disease of mild (baseline disease severity score 1, $n = 10$) or moderate (score 2, $n = 2$) severity, 11 (92%) were assessed to have derived some clinical benefit (clinical benefit score 4, $n = 2$) or significant clinical benefit (clinical benefit score 5, $n = 9$)

Figure 1. Consensus review of clinical benefit score by patient (only efficacy-evaluable patients were included; two patients were not included because no baseline photographs were available). Clinical benefit was assessed by comparative review of change from baseline: 1 = significantly worse; 2 = somewhat worse; 3 = no change; 4 = some clinical benefit; 5 = significant clinical benefit.

Figure 2. Examples of photographic documentation used for independent review facility and independent panel review assessment. **(A):** Patient 20620: baseline disease severity score of 5, clinical benefit score of 5. **(B):** Patient 20521: baseline disease severity score of 1, clinical benefit score of 5. **(C):** Patient 20507: baseline disease severity score of 4, clinical benefit score of 5. **(D):** Patient 20523: baseline disease severity score of 4, clinical benefit score of 5. **(E):** Patient 20500: baseline disease severity score of 5, clinical benefit score of 3. **(F):** Patient 20504: baseline disease severity score of 5, clinical benefit score of 1.

Table 5. Individual review inter-reader variability for baseline disease severity

Range ^a	No. of patients (n = 63)	Percentage
0	23	36.5
1	18	28.6
2	10	15.9
3	9	14.3
4	1	1.6

^aRange = maximum difference among three readers' scores for each patient.

Table 6. Individual review inter-reader variability for clinical benefit

Range ^a	No. of patients (n = 61)	Percentage
0	33	52.4
1	22	34.9
2	3	4.8
3	2	3.2
4	1	1.6

^aRange = maximum difference among three readers' scores for each patient.

(Table 4). Of the remaining 49 patients assessed by consensus review to have severe (baseline disease severity score 3, $n = 4$), moderately severe (baseline disease severity score 4, $n = 8$), or very severe (baseline disease severity score 5, $n = 37$) disease at baseline, 37 (73%) were assessed to have derived some or significant clinical benefit. The condition of 11 patients (22%) was considered to have worsened (i.e., clinical benefit score of 1 or 2) during vismodegib treatment, and 10 of those patients had a baseline independent panel review consensus assessment of very severe disease (baseline disease severity score of 5). Two of the 11 patients had progressive disease unrelated to BCC: one had a growing lesion subsequently found to be squamous cell carcinoma, and the other had a sarcoma diagnosed on day 55. Nine of the 11 patients had extensive lesions involving scalp ($n = 6$) or nose ($n = 3$) with cartilaginous destruction. One patient had a very large lesion threatening the jugular vein, and scalp lesions were noted by two of three independent panel reviewers to have improved. Examples of the photographic documentation of lesions used for independent review facility and independent panel review assessment are presented in Figure 2.

Inter-reader Variability of Individual Review Scores for Baseline Disease Severity and Clinical Benefit

Inter-reader variability of individual review scores for both baseline disease severity and clinical benefit was small. For baseline disease severity in 65.1% (41 of 63) of patients, the maximum difference among the three individual readers' scores was 0 or 1 point (Table 5). For clinical benefit in 87.3% (55 of 61) of patients, the maximum difference among the three individual readers' scores was 0 or 1 point (Table 6). Both κ [24] and Kendall's [25] statistics of concordance of the three readers' scores for baseline disease severity and clinical benefit are presented in Table 7. Only one patient was considered nonevaluable because of lack of agreement among the reviewers.

Strong concordance between individual and panel reviews was seen for both baseline disease severity and overall clinical benefit using Pearson and Spearman correlation coefficients. Pearson coefficients for baseline disease severity and clinical benefit were 0.896 and 0.925, respectively; Spearman coefficients were 0.903 and 0.933, respectively.

Table 7. Concordance of three reviewers' scores for baseline disease severity and clinical benefit

Concordance	Baseline disease severity score	Clinical benefit score
κ statistics for nominal response		
Overall statistics	0.260	0.372
<i>p</i> value	<.0001	<.0001
Kendall's coefficient for ordinal response		
Coefficient	0.828	0.775
<i>p</i> value	<.0001	<.0001

Consensus Review Assessment of Clinical Benefit Versus Independent Review Facility or Investigator Assessments of Response

Clinical benefit, a global clinical response accounting for baseline disease severity as well as magnitude and duration of response, showed good concordance with ORR assessed by independent review facility (65%) and investigator (65%) (Table 8). Independent review facility and investigator were single time point responses during the treatment course. The γ for the consensus review of clinical benefit versus independent review facility and investigator assessment (responder vs. nonresponder) is 0.8 and 0.5, respectively [26].

DISCUSSION

A durable reduction in the size of unresectable and potentially disfiguring skin tumors has been considered a direct clinical benefit of vismodegib [27]. In the 12-month update of the ERIVANCE BCC study, 33% of patients with mBCC and 48.5% of patients with laBCC achieved a response to vismodegib; in both of these groups, a median duration of response of 7.6 months was demonstrated by independent assessment [18]. The protocol-specified independent review facility- and investigator-assessed endpoints in the ERIVANCE BCC study were based primarily on tumor measurements, including scarring and healing of ulceration. Results of the current independent panel review analysis, based on independent clinical judgment of pretreatment and post-treatment photographs, were consistent with the primary efficacy endpoint (ORR) results in ERIVANCE BCC.

Consensus review confirmed that most patients with laBCC had significant disease burden at baseline (71.4%) and that most (76.2%) derived clinical benefit from vismodegib treatment. Of those patients with mild or moderate baseline disease severity, 91.7% achieved some or significant clinical benefit. Among patients with severe, moderately severe, or very severe baseline disease severity, 73.5% achieved some or significant clinical benefit. Of patients whose condition worsened with treatment, 91.7% had very severe baseline disease severity.

In this analysis, assessment and scoring of each independent reviewer showed good concordance for baseline disease severity and overall clinical benefit. With only one patient considered nonevaluable because of lack of agreement

Table 8. Consensus review of clinical benefit versus independent review facility or investigator assessment

Assessment	Clinical benefit ^a		Concordance
	Nonresponder	Responder	
Independent review facility ^b			41/63 (65%)
Nonresponder	13	20	
Responder	2	28	
Investigator ^b			41/63 (65%)
Nonresponder	9	16	
Responder	6	32	

^aFor consensus review assessment of clinical benefit, a "responder" has a clinical benefit score of 4 (some clinical benefit) or 5 (significant clinical benefit), and a "nonresponder" has a clinical benefit score of 1 (significantly worse), 2 (somewhat worse), or 3 (no change).

^bFor independent review facility/investigator assessment, a "responder" has partial or complete response, and a "nonresponder" has stable disease, progressive disease, or missing data.

among the three reviewers, strong consistency is evident in the experts' clinical assessments.

CONCLUSION

The independent panel review assessment by clinical experts provides strong evidence that treatment with vismodegib results in clinically meaningful responses in patients with laBCC who are not suitable candidates for surgical excision.

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DISCLOSURES

Brigitte Dreno: Roche (C/A); **Ivor Caro:** Roche/Genentech (E, OI); **Huibin Yue:** Roche/Genentech (E); **Dirk Schadendorf:** Roche, GSK, Novartis, BMS, Delcath, Merck, Amgen (C/A); Merck (RF). The other author indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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