Long-Term Safety and Efficacy of Vismodegib in Patients With Advanced Basal Cell Carcinoma (aBCC): 18-Month Update of the Pivotal ERIVANCE BCC Study

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ABSTRACT

Background: Therapies for aBCC, which includes metastatic (m) and locally advanced (la) BCC, are limited. Abnormal Hedgehog pathway signaling is a key driver in BCC pathogenesis. Primary analysis of the pivotal ERIVANCE BCC trial of vismodegib, an oral Hedgehog pathway inhibitor (HPI), demonstrated an objective response rate (ORR) by independent review of 30% and 43% in mBCC and laBCC patients, respectively, with a median duration of response (DOR) of 7.6 months. We present safety and investigator (INV)-assessed efficacy results 18 months (29 May 2012) after primary analysis (26 Nov 2010).

Methods: Multicenter, international, nonrandomized study in patients (N = 104) with radiographically measurable mBCC or laBCC (surgery inappropriate due to multiple recurrence, or substantial morbidity or deformity anticipated) receiving 150 mg oral vismodegib daily until disease progression or intolerable toxicity. Key secondary endpoints included INV-assessed ORR, progression-free survival (PFS), DOR, overall survival (OS), and safety.

Results: At data cut-off, 21 patients continued to undergo protocol-specified assessments and 57 patients were in survival follow-up. The median dose intensity was comparable with primary analysis. ORR was 48.5%, mBCC; 60.3%, laBCC, comparable with the primary analysis. However, median DOR improved (mBCC = 14.7; laBCC = 20.3 months). The median OS for mBCC was 30.9 months but was not estimable in laBCC. Adverse events remained consistent, with muscle spasm, alopecia, dysgeusia, weight decrease, and fatigue most frequently reported. Eleven more deaths were reported in the update period after primary analysis; these occurred in survival follow-up and were not drug related.

Conclusions: Vismodegib is the first FDA-approved HPI; thus, long-term efficacy and safety data are particularly relevant. 18-Month update data confirmed prolonged responses and consistent safety in vismodegib-treated aBCC patients.

INTRODUCTION

- Limited therapeutic options are available for patients with advanced basal cell carcinoma (BCC), a disease that is locally advanced (laBCC) or metastatic (mBCC).
- The Hedgehog (Hh) signaling pathway is a key driver in the pathogenesis of BCC.
- Vismodegib is a first-in-class small molecule inhibitor of Hh pathway signaling[1-3] that has been approved by the US Food and Drug Administration (FDA) for the treatment of adults with mBCC, or with laBCC that has recurred following surgery, or who are not candidates for surgery, and who are not candidates for radiation.
- Primary analysis of the pivotal, multicenter, nonrandomized ERIVANCE BCC trial of vismodegib demonstrated an objective response rate (ORR) by independent review of 30% and 43% in mBCC and laBCC patients, respectively, with a median duration of response (DOR) of 7.6 months, thereby meeting its primary endpoint.[4]

OBJECTIVES

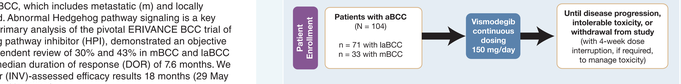
- The primary analysis of the ERIVANCE BCC study was based on data up to November 26, 2010, which was 9 months after the last patients were enrolled in the study.[4]
- Here we present results of an additional 18 months of follow-up (to May 29, 2012) of efficacy and safety endpoints, for a total minimum potential follow-up time of 27 months for all patients.

METHODS

ERIVANCE BCC Study Design

- Multicenter, international, nonrandomized, 2-cohort study (**Figure 1**)
- A control group was not used because of the following:
  - The primary endpoint was ORR.
  - Spontaneous responses were not reported in the literature.
  - Effective therapies were not available for this small patient population.
- Patients received oral vismodegib 150 mg once daily until disease progression, intolerable toxicity, or study discontinuation.
  - Dose interruption for up to 4 weeks was allowed for the management of toxicity.

Figure 1. Study design.



aBCC, advanced basal cell carcinoma; laBCC, locally advanced BCC; mBCC, metastatic BCC.

Patient Eligibility

- Patients were at least 18 years of age, with adequate organ function and Eastern Cooperative Oncology Group performance status ≤ 2.
- Patients with mBCC had Response Evaluation Criteria In Solid Tumors, version 1.0 (RECIST v1.0)–measurable disease (including nodal metastases), as confirmed by computed tomography or magnetic resonance imaging.
- Patients with laBCC had at least 1 lesion with longest diameter ≥ 10 mm that was considered inoperable, or for which surgery was considered inappropriate.
  - Surgery was deemed inappropriate if BCC had recurred after ≥ 2 surgical procedures and curative resection was deemed unlikely, and/or there was substantial morbidity, and/or deformity was anticipated from surgery.
- In the laBCC cohort, prior radiotherapy to ≥ 1 target lesion was required, unless medically contraindicated or inappropriate.

Assessments

- Physical examinations were performed on all patients at baseline and every 4 weeks thereafter.
- For laBCC, a novel composite endpoint for response rate was devised to evaluate therapeutic response; response was defined as meeting any of the following criteria: ≥ 30% reduction in tumor size by physical examination and/or radiography, and/or complete resolution of ulceration present at baseline.
- In patients with mBCC or radiologically evaluable laBCC, responses were assessed using RECIST v1.0 criteria.[5]
- Efficacy was assessed by both independent review facility (IRF) and the investigators (INV) for the primary analysis. Separate IRF assessed patient photographs (laBCC) and radiographically measurable BCC (mBCC and radiographically measurable laBCC). For this report, efficacy was assessed by INV only.
- The efficacy-evaluable population included all treated patients for whom the independent pathologist confirmed BCC in archival tumor tissue or on baseline biopsy.
- Adverse event (AE) data were collected for all patients from initial treatment with vismodegib until data cut-off on May 29, 2012. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Endpoints

- Endpoints assessed included ORR by IRF (primary endpoint) and INV; DOR by IRF and INV; progression-free survival (PFS) by IRF and INV; and overall survival (OS).

RESULTS

Patient Characteristics

- Over 13 months, 104 patients were enrolled at 31 sites in the USA, Europe, and Australia (n = 33 for the mBCC cohort; n = 71 for the laBCC cohort).
- Eight patients with laBCC were excluded from the efficacy analysis because the independent pathologist did not identify BCC in biopsy specimens taken at baseline or at postbaseline biopsy. No patients with mBCC were excluded.
- Baseline patient characteristics are shown in **Table 1**.

Table 1. Demographics and Baseline Characteristics (efficacy-evaluable population)

		mBCC (n = 33)	laBCC (n = 63)
Age	Mean (SD)	61.6 (11.4)	61.4 (16.9)
	Median (range)	62.0 (38-92)	62.0 (21-101)
Sex, n (%)	Male	24 (72.7)	35 (55.6)
	Female	9 (27.3)	28 (44.4)
Race, n (%)	White	33 (100)	63 (100)
laBCC, n (%)	Inoperable	–	24 (38.1)
	Surgery inappropriate	–	39 (61.9)
	Multiple recurrence	–	16 (25.4)
	Significant morbidity/deformity	–	32 (50.8)
	Radiation previously administered	–	13 (20.6)
	Radiation inappropiate/contraindicated	–	50 (79.4)

BCC, basal cell carcinoma; laBCC, locally advanced BCC; mBCC, metastatic BCC; SD, standard deviation.

- As of the data cut-off date of May 29, 2012, 21 (20.2%) patients were receiving study drug and continued to undergo protocol-specified assessments, with 83 (79.8%) patients discontinued from the primary assessment period (defined as the period during which patients undergo protocol-specified assessments) and 57 (54.8%) patients entered into the survival follow-up (**Table 2**).

Table 2. Patient Status

Patient Status, n (%)[a]	Metastatic BCC (n = 33)	Locally Advanced BCC (n = 71)	All Patients (N = 104)
In study period	4 (12.1)	17 (23.9)	21 (20.2)
Discontinued study period	29 (87.9)	54 (76.1)	83 (79.8)
Entered survival follow-up	22 (66.7)	35 (49.3)	57 (54.8)

BCC, basal cell carcinoma.
Note: Not all patients entered survival follow-up. Data cut-off date: May 29, 2012.
[a]Patient status as of the May 29, 2012, data cut-off date.

- Patient disposition at the 18-month update is shown in **Table 3**.

Table 3. Patient Disposition

Disposition, n (%)	Metastatic BCC (n = 33)	Locally Advanced BCC (n = 71)	All Patients (N = 104)
On treatment	4 (12.1)	17 (23.9)	21 (20.2)
Discontinued treatment			
Total	29 (87.9)	54 (76.1)	83 (79.8)
Adverse event	4 (12.1)	16 (22.5)	20 (19.2)
Death	1 (3.0)	2 (2.8)	3 (2.9)
Lost to follow-up	1 (3.0)	2 (2.8)	3 (2.9)
Physician's decision to discontinue treatment	3 (9.1)	3 (4.2)	6 (5.8)
Patient's decision to discontinue treatment	4 (12.1)	21 (29.6)	25 (24.0)
Disease progression	15 (45.5)	9 (12.7)	24 (23.1)
Other	1 (3.0)	1 (1.4)	2 (1.9)

BCC, basal cell carcinoma. Data cut-off date: May 29, 2012.

Treatment Exposure

- Duration of treatment, dose intensity, and total cumulative dose are shown in **Table 4**.
  - Median dose intensity was comparable with that in the primary analysis.

Table 4. Treatment Exposure

	Metastatic BCC (n = 33)	Locally Advanced BCC (n = 71)	All Patients (N = 104)
Duration (months) of treatment received			
Mean (SD)	14.4 (8.68)	15.8 (10.38)	15.3 (9.85)
Median	13.27	12.68	12.93
Minimum-maximum	0.7-30.7	1.1-36.6	0.7-36.6
Dose intensity, %			
Mean (SD)	96.3 (5.98)	94.0 (8.58)	94.7 (7.89)
Median	98.89	97.17	97.76
Minimum-maximum	77.4-102.5	58.5-107.5	58.5-107.5
Total cumulative dose, g			
Mean (SD)	63.0 (37.48)	67.7 (44.87)	66.2 (42.54)
Median	60.45	52.05	57.60
Minimum-maximum	2.9-134.4	3.8-156.2	2.9-156.2

BCC, basal cell carcinoma; SD, standard deviation. Data cut-off date: May 29, 2012.

Efficacy

- At the 18-month update, ORRs remained similar to those reported at the primary analysis in patients with mBCC and laBCC (**Table 5**).
- Median DOR improved in both cohorts (mBCC: 14.7 vs 12.9 months; laBCC: 20.3 vs 7.6 months) since the primary analysis (data cut-off November 26, 2010).
  - An example of a responder is presented in **Figure 2**.
  - Kaplan-Meier estimates of DOR by INV assessment for efficacy-evaluable patients are shown in **Figure 3**.
- The median PFS for mBCC patients was 9.3 months and for laBCC patients was 12.9 months (**Figure 4**).
- The median OS for mBCC patients was 30.9 months but was not estimable in laBCC patients (**Figure 5**).

Table 5. Summary of Investigator-Assessed Efficacy Results and Survival Results

	Data Cut-off of November 26, 2010 (Primary Analysis)			Data Cut-off of May 29, 2012		
	Metastatic BCC (n = 33)	Locally Advanced BCC (n = 63)	Total (N = 96)	Metastatic BCC (n = 33)	Locally Advanced BCC (n = 63)	Total (N = 96)
Patients with objective response, n (%) [95% CI]	15 (45.5) [28.1-62.2]	38 (60.3) [47.2-71.7]	53 (55.2) [44.7-65.4]	16 (48.5) [30.8-66.2]	38 (60.3) [47.2-71.7]	54 (56.3) [45.7-66.4]
Complete response	0	20	20	0	20	20
Partial response	15	18	33	16	18	34
Stable disease	15	15	30	14	15	29
Progressive disease	2	6	8	2	6	8
Median duration of response, months (95% CI)	(n = 15) 12.9 (5.6-12.9)	(n = 38) 7.6 (7.4-NE)	(n = 53) 9.5 (7.4-12.9)	(n = 16) 14.7 (5.6-17.0)	(n = 38) 20.3 (9.0-NE)	(n = 54) 16.8 (9.5-NE)
Median PFS, months (95% CI)	9.2 (7.4-NE)	11.3 (9.5-16.8)	11.1 (9.3-12.9)	9.3 (7.4-16.6)	12.9 (10.2-31.4)	12.8 (9.5-18.0)
Median OS, months (95% CI)	NE (13.9-NE)	NE (17.6-NE)	NE (16.9-NE)	30.9 (18.1-NE)	NE (NE-NE)	NE (NE-NE)
1-Year survival rate, % (95% CI)	75.5 (57.3-93.6)	91.6 (83.5-99.7)	NA	78.7 (64.7-92.7)	93.1 (86.6-99.6)	NA

BCC, basal cell carcinoma; CI, confidence interval; NA, not available; NE, not estimable; OS, overall survival; PFS, progression-free survival.
The 95% CI for response rate was computed using the Blyth-Still-Casella method.

Figure 2. Example of a responder after vismodegib treatment.

- Age of responder 68
- Substantial deformity anticipated from surgery; radiation contraindicated
- Lesion assessed by physical exam/photo and RECIST v1.0

Figure 3. Kaplan-Meier plot of duration of objective response by investigator (INV) assessment.

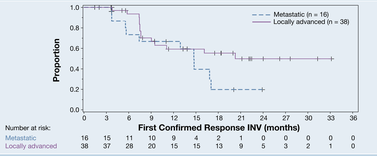


Figure 4. Kaplan-Meier plot of progression-free survival by investigator (INV) assessment.

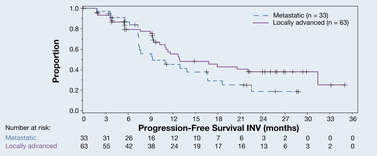
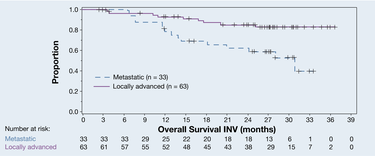


Figure 5. Kaplan-Meier plot of overall survival by investigator (INV) assessment.



Safety and Tolerability

- The vismodegib AE profile for this safety update was consistent with that previously reported.
- Treatment-emergent AEs were reported by all 104 patients. The most frequently reported AEs included muscle spasms (71.2%), alopecia (65.4%), dysgeusia (54.8%), weight decreased (51.0%), fatigue (42.3%), and nausea (32.7%) (**Table 6**).
  - Fifty-four (51.9%) patients reported grade 3 to 5 AEs, with the most common including weight decreased (7 patients; 6.7%), muscle spasms (6 patients; 5.8%), and fatigue (5 patients; 4.8%).
  - Amenorrhea was reported in 2 of 6 (33.0%) women of child-bearing potential at the updated analysis.

Table 6. Treatment-Emergent Adverse Events (total and by grade) Occurring in ≥ 10% of All Treated Patients

Adverse Event, n (%)[a]	NCI CTCAE Grade (N = 104)					
	Total	1	2	3	4	5
Any adverse events	104 (100.0)	11 (10.6)	38 (36.5)	34 (32.7)	13 (12.5)	7 (6.7)
Muscle spasms	74 (71.2)	49 (47.1)	19 (18.3)	6 (5.8)	0	0
Alopecia	68 (65.4)	48 (46.2)	20 (19.2)	0	0	0
Dysgeusia	57 (54.8)	31 (29.8)	26 (25.0)	0	0	0
Weight decreased	53 (51.0)	29 (27.9)	17 (16.3)	7 (6.7)	0	0
Fatigue	44 (42.3)	32 (30.8)	7 (6.7)	4 (3.8)	1 (1.0)	0
Nausea	34 (32.7)	25 (24.0)	9 (8.7)	0	0	0
Decreased appetite	28 (26.9)	18 (17.3)	7 (6.7)	3 (2.9)	0	0
Diarrhea	28 (26.9)	20 (19.2)	5 (4.8)	3 (2.9)	0	0
Constipation	20 (19.2)	14 (13.5)	6 (5.8)	0	0	0
Cough	20 (19.2)	16 (15.4)	4 (3.8)	0	0	0
Vomiting	18 (17.3)	15 (14.4)	3 (2.9)	0	0	0
Arthralgia	17 (16.3)	12 (11.5)	4 (3.8)	1 (1.0)	0	0
Headache	15 (14.4)	12 (11.5)	3 (2.9)	0	0	0
Nasopharyngitis	13 (12.5)	11 (10.6)	2 (1.9)	0	0	0
Squamous cell carcinoma	12 (11.5)	3 (2.9)	5 (4.8)	3 (2.9)	0	0
Ageusia	12 (11.5)	8 (7.7)	4 (3.8)	0	0	0
Hypogeusia	11 (10.6)	10 (9.6)	1 (1.0)	0	0	0

NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.
[a]MedDRA preferred term.

- Serious AEs were reported in 36 (34.6%) patients.
- At the May 29, 2012, data cut-off, there were no additional deaths due to AEs compared with the primary analysis.
  - A total of 27 (26.0%) deaths have been reported compared with 16 (15.4%) deaths in the primary analysis.
  - All 11 additional deaths reported in this update period occurred in survival follow-up, and none were drug related.
  - The most common causes of death included progressive disease (15 patients; 14.4%) and AEs (7 patients; 6.7%).

CONCLUSIONS

- Vismodegib is the first FDA-approved HPI; thus, long-term efficacy and safety data are particularly important.
- Data from the 18-month update confirm:
  - Increased durability of response in vismodegib-treated patients with aBCC
  - Longer-term safety profile of vismodegib consistent with that reported in the primary analysis

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Roche is developing vismodegib under a collaboration agreement with Curis, Inc. Vismodegib was discovered by Genentech and was jointly validated by Genentech and Curis through a series of preclinical studies. Through this collaboration, Genentech (USA), Roche (outside the USA excluding Japan and Korea), and Chugai Pharmaceuticals (Japan) are responsible for the clinical development and commercialization of vismodegib. Corresponding author: Aleksandar Sekulic (sekulic.aleksandar@mayo.edu).

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