Vismodegib, a Hedgehog Pathway Inhibitor, in Advanced Basal Cell Carcinoma: STEVIE Study Interim Analysis in 300 Patients

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ABSTRACT

Background: Therapy options are limited for locally advanced (la) and metastatic (m) BCC. Aberrant Hedgehog (Hh) signaling is the key driver in BCC pathogenesis. Vismodegib, a first-in-class Hedgehog pathway inhibitor (HPI), is approved in the US for use in adults with advanced BCC (aBCC). STEVIE is an ongoing study focusing on the safety of vismodegib therapy in patients with aBCC. We present data from the third interim analysis (data cut-off: 19 October 2012), which also permits a preliminary assessment of the efficacy of vismodegib in the largest study conducted in patients with aBCC.

Methods: Adult patients with laBCC or mBCC received oral vismodegib 150 mg QD until progressive disease, unacceptable toxicity, or withdrawal. Safety is the primary objective of STEVIE (National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0). Secondary endpoints include efficacy variables. Recruitment is ongoing.

Results: This analysis included 300 patients with laBCC (n = 278) or mBCC (n = 22) from 11 countries with potential for ≥ 3 months of follow-up. Median treatment duration, including vismodegib interruption, was 176.5 days (range, 1-455 days). Common treatment-emergent AEs (TEAEs), typically ≤ grade 2, included muscle spasm (59.3%), alopecia (49.3%), and dysgeusia (41.0%) and were comparable with those in a prior analysis. Serious TEAEs occurred in 53 patients (17.7%). 131 (43.7%) patients discontinued from the study, mainly due to patient or investigator request (n = 41), AEs (n = 35), disease progression (n = 18) or death (n = 13; 7 due to AEs assessed by the investigator as unrelated to study drug, 3 due to AEs not possible to be assessed, 2 due to disease progression, and 1 due to cardiopulmonary failure). Preliminary best overall response in patients with available tumor assessments (n = 251) included complete response (17.5%), partial response (39.8%), stable disease (39.0%), and progressive disease (2.8%). Patient recruitment and monitoring are ongoing.

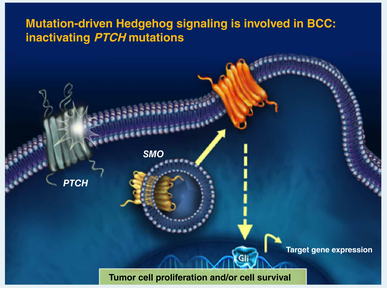
Conclusions: This third interim analysis of STEVIE confirms the previously observed vismodegib safety profile and provides further information about the high rate of tumor control with vismodegib in a large series of patients with aBCC.

This abstract has been updated from the original submission.

INTRODUCTION

- Basal cell carcinoma (BCC) is the most commonly diagnosed human cancer worldwide.[1]
- Most BCCs can be treated by surgery or radiation therapy; however, in rare cases, there is disease progression to advanced BCC, such as locally advanced (la) or metastatic (m) BCC.
- In laBCC, characteristics of the tumor (eg, size, location) and of the patient (eg, age, associated morbidities) make standard treatment by surgery ineffective, unreasonable, or unacceptable as it may lead to disfigurement or loss of function.[2,3]
- Aberrant Hedgehog (Hh) signaling, driven by specific genetic loss of function alterations in *Patched* (*PTCH*) or by activation mutations in *Smoothened* (*SMO*), is the key driver in BCC pathogenesis.[4,5]
  - Most BCCs have evidence of abnormal activation of the Hh signaling pathway (**Figure 1**).[6]
- Vismodegib (Erivedge®) is a first-in-class, oral, selective Hh pathway inhibitor[2,7,8] approved by the US Food and Drug Administration 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.[9]
- In the pivotal registration study (ERIVANCE BCC), the objective response rate to vismodegib treatment was 43% in laBCC and 30% in mBCC by independent review.[10]
- The SafeTy Events in VismodEgib (STEVIE) study is the largest study conducted in patients with advanced BCC and is designed to further assess vismodegib safety in this patient population.
- The data cut-off date for the third interim analysis of STEVIE was October 19, 2012: 300 patients with potential for ≥ 3 months of follow-up were included. Data allow a preliminary assessment of efficacy.
  - STEVIE recruitment is ongoing; the planned enrollment target is 1200 patients over approximately a 3.5-year period.

Figure 1. The Hedgehog signaling pathway.



Abnormal activation of the Hh signaling pathway is thought to play a critical role in the pathogenesis and progression of BCC by mutations that either inactivate *PTCH* or activate *SMO*.[6]

BCC, basal cell carcinoma; Gli, Gli family of transcription factors – downstream effectors; Hh, Hedgehog; *PTCH*, *Patched* – Hedgehog ligand receptor; *SMO*, *Smoothened* – cell surface signal transducer.

OBJECTIVES

- **Primary**: To assess the **safety** of vismodegib in patients with laBCC or mBCC, using National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0)
- **Secondary**: To assess **overall response** (overall response rate [ORR]) in patients with measurable disease using Response Evaluation Criteria In Solid Tumors, version 1.1 (RECIST v1.1)
  - Other efficacy parameters: time to response, duration of response (DOR), progression-free survival (PFS), and overall survival (OS)

METHODS

STEVIE Study Design

- Single-arm, open-label, international multicenter study
- Eligible patients with advanced BCC receive vismodegib 150 mg orally once daily until investigator-assessed disease progression, unexpected toxicity, or withdrawal (**Figure 2**). One cycle of therapy is defined as 28 days of treatment.
  - Temporary dose interruptions for up to 8 weeks are allowed for the management of toxicity.

Figure 2. Study design.

BCC, basal cell carcinoma.

Key Patient Eligibility

Inclusion Criteria

- ≥ 18 years of age with histologically confirmed laBCC or mBCC, with adequate organ function and Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 2
- For laBCC: ≥ 1 histologically confirmed lesion that is considered inoperable or surgery contraindicated; patient must have been previously administered radiotherapy (unless contraindicated or inappropriate) and must have experienced disease progression after irradiation
- For mBCC: histologic confirmation of distant metastasis
- Patients with Gorlin's syndrome meeting the criteria for laBCC or mBCC
- Enrollment eligibility based on measurable and/or nonmeasurable disease, as defined by RECIST v1.1

Exclusion Criteria

- Concurrent non–protocol-specified antitumor therapy
- Completion of most recent antitumor therapy < 21 days before initiation of treatment
- Uncontrolled medical illnesses (eg, infection requiring treatment with intravenous antibiotics)
- History of other disease that contraindicates the use of an investigational drug or might affect interpretation of study results

Assessments

- Physical examinations are performed at screening and every 4 weeks thereafter.
- All study assessments (eg, vital signs, ECOG PS, laboratory analyses) during the treatment phase are performed every 4 weeks with the exception of computed tomography and/or magnetic resonance imaging for tumor evaluation, which take place every 8 to 16 weeks or as per institutional standards.

Statistical Analysis

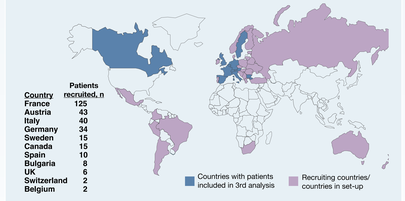
- A sample size of approximately 1200 patients was planned for this study. With this sample size, the true adverse event (AE) incidence rate can be estimated to be between 1.6% and 1.8% if an observed incidence of 10% is assumed (ie, within a 95% Clopper-Pearson confidence interval [CI] of 8.4%-11.8%).
- Evaluations of safety were conducted on the safety population, which included all patients who received at least one dose of study medication.
  - Safety variables were summarized descriptively.
  - AEs were assessed according to the NCI CTCAE v4.0 grading system.
  - ORR was assessed and summarized via best overall response.
  - Median time of OS and PFS were obtained via the Kaplan-Meier approach, and the corresponding 95% CI for the median was provided.

RESULTS

Patient Characteristics

- This analysis includes 300 patients with laBCC (n = 278) or mBCC (n = 22) from 10 European countries (n = 285) and Canada (n = 15), with potential for ≥ 3 months of follow-up (**Figure 3**).

Figure 3. Patient recruitment by country.



- Patient demographics and baseline characteristics are shown in **Table 1**.

Table 1. Patient Demographics and Baseline Characteristics

Variable		laBCC (n = 278)	mBCC (n = 22)	Total (N = 300)
Age, y	Mean (SD)	69.6 (17.82)	64.6 (13.04)	69.2 (17.54)
	Median (range)	73.0 (18-98)	62.5 (42-96)	72.5 (18-98)
Sex, n (%)	Male	165 (59.4)	16 (72.7)	181 (60.3)
	Female	113 (40.6)	6 (27.3)	119 (39.7)
ECOG PS, n (%)	Grade 0	174 (63.7)	9 (40.9)	183 (62.0)
	Grade 1	67 (24.5)	8 (36.4)	75 (25.4)
	Grade 2	32 (11.7)	5 (22.7)	37 (12.5)
Type of laBCC, n (%)	Inoperable	129 (46.4)	–	–
	Surgery contraindicated	149 (53.6)		
	Recurrent BCC unlikely to be curatively resected	77 (27.7)	–	–
	Anticipated substantial morbidity or deformity	72 (25.9)		

ECOG PS, Eastern Cooperative Oncology Group performance status; laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma; SD, standard deviation.

Treatment Exposure

- Median treatment duration at data cut-off was 5.8 months (range, 1 to 14.9 months).
- At data cut-off, a total of 169 (56.3%) patients were receiving ongoing treatment, while 131 (43.7%) patients discontinued study medication, mainly owing to AEs (n = 35), patient or investigator request (n = 41), disease progression (n = 18), or death (n = 13) (**Table 2**).

Table 2. Patient Disposition at Data Cut-off

	laBCC (n = 278)	mBCC (n = 22)	Total (N = 300)
Treatment ongoing	154 (55.4)	15 (68.2)	169 (56.3)
Treatment discontinued	124 (44.6)	7 (31.8)	131 (43.7)
Main reason for study drug discontinuation			
Adverse event	35 (12.6)	0 (0.0)	35 (11.7)
Patient request[a]	35 (12.6)	1 (4.5)	36 (12.0)
Death	11 (4.0)	2 (9.1)	13 (4.3)
Investigator request[a]	5 (1.8)	0 (0.0)	5 (1.7)
Progression of disease	15 (5.4)	3 (13.6)	18 (6.0)
Other	21 (7.6)	0 (0.0)	21 (7.0)
Lost to follow-up	1 (0.4)	1 (4.5)	2 (0.7)
Missing	1 (0.4)	0 (0.0)	1 (0.3)

All data are presented as n (%). [a]Information on the patient/physician decision to discontinue treatment was not recorded in the study. laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma.

Safety and Tolerability

- Treatment-emergent adverse events (TEAEs), defined as occurring between the first administration and 30 days after the last administration of study drug, inclusive, were reported in 278 (92.7%) patients and were typically mild or moderate (grade 1/2) in severity.
  - Common TEAEs, defined as those occurring in ≥ 10% of the safety population, included muscle spasms (59.3%), alopecia (49.3%), and dysgeusia (41.0%) at any grade.
    - The most common grade 3/4 TEAEs were muscle spasms (5.0%) and ageusia (3.0%) (**Table 3**).

Table 3. Most Common Treatment-Emergent Adverse Events (TEAEs)

	(N = 300)		
TEAE,[a] n (%)	All	Grade 3	Grade 4
Muscle spasms	178 (59.3)	15 (5.0)	0 (0.0)
Alopecia	148 (49.3)	3 (1.0)	0 (0.0)
Dysgeusia	123 (41.0)	6 (2.0)	0 (0.0)
Ageusia	77 (25.7)	9 (3.0)	2 (0.7)
Asthenia	70 (23.3)	5 (1.7)	0 (0.0)
Weight decreased	48 (16.0)	3 (1.0)	0 (0.0)
Decreased appetite	47 (15.7)	4 (1.3)	0 (0.0)
Nausea	43 (14.3)	0 (0.0)	0 (0.0)
Fatigue	38 (12.7)	5 (1.7)	0 (0.0)

[a]Most common TEAEs shown are those reported in ≥ 10% of the safety population.

- Serious TEAEs occurred in 53 (17.7%) patients (74 events); most (71%) were considered not related to the study drug (**Table 4**).
- There were 13 deaths reported in the study; of these:
  - 2 were due to disease progression (1 patient each for laBCC and mBCC)
  - 9 were due to AEs assessed by the investigator as unrelated to study drug (pneumonia [2 patients], multi-organ failure, rectal cancer, cardiac arrest, chronic obstructive pulmonary disease, non-Hodgkin lymphoma, sudden death, myocardial infarction [1 patient each])
  - 1 was due to an AE assessed by the investigator as related to treatment (cardiopulmonary failure)
  - 1 was due to "other reason" (multi-organ failure)

Table 4. Summary of Serious TEAEs and Deaths on Study

	N = 300
Serious TEAEs (occurring in ≥ 5 patients)	53 (17.7)
Deaths	13 (4.3)
Common reasons for serious TEAEs[a]	
Infections and infestations	12 (4.0)
Neoplasms (benign, malignant, and unspecified, including cysts and polyps)	10 (3.3)
General disorders and administration site conditions	8 (2.7)
Cardiac disorders	5 (1.7)
Metabolism and nutrition disorders	5 (1.7)
Nervous system disorders	5 (1.7)
Gastrointestinal disorders	5 (1.7)

All data are presented as n (%). [a]Calculated as a percentage of total (N = 300) patients.
TEAEs, treatment-emergent adverse events.

Preliminary Efficacy

- A total of 251 of 300 patients had RECIST-measurable disease at baseline and at least one postbaseline assessment.

Best Overall Response: (RECIST-Confirmed) All Cycles

- Preliminary efficacy data for best overall response in patients with available tumor assessments (n = 251) are shown in **Table 5**.
- The median time to first best response was 57 days (range, 13 to 363 days).

Table 5. Summary of Preliminary Best Overall Response (RECIST-Confirmed)

Best Overall Response by Investigator Assessment Over All Cycles	Second Interim Analysis (n = 150)	Third Interim Analysis (n = 300)
Patients with measurable disease at baseline	130	276
At least one postbaseline assessment, n (%)	124 (100)	251 (100)
Complete response, n (%)	24 (19.4)	44 (17.5)
Partial response, n (%)	69 (55.6)	100 (39.8)
Stable disease, n (%)	27 (21.8)	98 (39.0)
Progressive disease, n (%)	4 (3.2)	7 (2.8)
Unevaluable, n (%)	–	2 (0.8)
Missing (no postbaseline assessment)	6	25

RECIST, Response Evaluation Criteria In Solid Tumors.

Patient Case Studies

- Patient case studies, as documented by photographic evidence at baseline and after treatment, further support preliminary efficacy data for vismodegib treatment in patients with advanced BCC (**Figures 4** to **6**).

Figure 4. Surgery possible but with severe anatomic damage. Resolution of large BCC lesion of the head with vismodegib treatment.

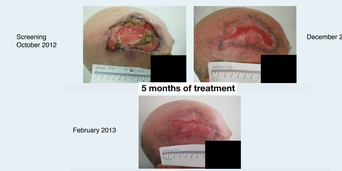


Figure 5. Failure of surgery. Resolution of multi-recurrent basal cell carcinoma with extension in the orbit achieved with vismodegib, although severe anatomic damage from previous surgery remains.

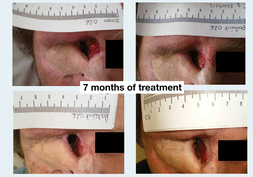
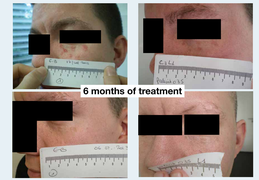


Figure 6. Anatomic site is difficult to access for surgery. Complete preservation of the eyelid after resolution of a cluster of small basal cell carcinomas.



CONCLUSIONS

- This third interim analysis of STEVIE included the first 300 patients with laBCC or mBCC with potential for ≥ 3 months of follow-up.
- The most common TEAEs were predominantly mild or moderate in severity.
  - This third interim analysis, similar to the previous interim analysis (n = 150), supports the vismodegib safety profile as seen in the pivotal ERIVANCE BCC study.[10]
- Preliminary efficacy data analysis showed a high rate of tumor control in patients with advanced BCC, who previously lacked adequate treatment options, with an investigator assessment of best overall response (complete response + partial response) of 144/251 (57%).
- Future analyses from STEVIE, with longer follow-up, will provide further information on the safety profile of vismodegib in patients with laBCC or mBCC.

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ACKNOWLEDGMENTS

The authors would like to thank the participating investigators, patients and their families, and current and past members of the Roche and Genentech vismodegib teams. This study was funded by F. Hoffmann-La Roche Ltd. Support for third-party writing assistance for this poster was provided by F. Hoffmann-La Roche Ltd.

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.

http://bit.ly/1tB2cyKj

Presented at the 2013 Annual Meeting of the American Society of Clinical Oncology (ASCO); May 31-June 4, 2013; Chicago, IL, USA