Vismodegib, a Hedgehog Pathway Inhibitor in Advanced Basal Cell Carcinoma: STEVIE Study Primary Analysis in 1215 Patients

Johan Hansson,[1] Axel Hauschild,[2] Rainer Kunstfeld,[3] Jean-Jacques Grob,[4] Brigitte Dréno,[5] Laurent Mortier,[6] Paolo A. Ascierto,[7] Lisa Licitra,[8] Caroline Dutriaux,[9] Luc Thomas,[10] Nicolas Meyer,[11] Bernard Guillot,[12] Reinhard Dummer,[13] Petr Arenberger,[14] Kate Fife,[15] Ana Raimundo,[16] Emi Dika,[17] Natalie Dimier,[18] Ioannis Xynos,[18] Nicole Basset-Séguin[19]

[1]*Karolinska University Hospital, Solna, Stockholm, Sweden;* [2]*University Hospital Schleswig-Holstein, Kiel, Germany;* [3]*Medical University of Vienna, Vienna, Austria;* [4]*Aix-Marseille University, Timone Hospital APHM, Marseille, France;* [5]*Nantes University, Nantes, France;* [6]*University of Lille 2, Lille Regional University Hospital, Lille, France;* [7]*Istituto Nazionale Tumori Fondazione G. Pascale, Naples, Italy;* [8]*Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy;* [9]*University Hospital of Bordeaux, Bordeaux, France;* [10]*Lyon 1 University-Centre Hospitalier Lyon Sud and Lyons Cancer Research Center Lyon, France;* [11]*Paul Sabatier University, Larrey Hospital, Toulouse, France;* [12]*University Hospital of Montpellier, Montpellier, France;* [13]*University Hospital Zurich, Zurich, Switzerland;* [14]*University Hospital Vinohrady Prague and Charles University Third Medical Faculty, Prague, Czech Republic;* [15]*Cambridge University Hospital, Cambridge, UK;* [16]*Instituto Português de Oncologia do Porto Francisco Gentil, Porto, Portugal;* [17]*University of Bologna, Bologna, Italy;* [18]*Roche Products Ltd., Welwyn Garden City, UK;* [19]*Hôpital Saint Louis, Paris, France*

INTRODUCTION

- Basal cell carcinoma (BCC) is the most commonly diagnosed human cancer worldwide[1]
- Although most BCCs are curable by surgery, some may progress to advanced BCC (locally advanced or metastatic BCC), for which radiotherapy and surgery are inappropriate because cure is unlikely and/or because surgery might result in substantial deformity[2,3]
- More than 90% of BCCs exhibit abnormal activation of the Hedgehog signaling pathway[4]
- Vismodegib is a first-in-class, oral, selective Hedgehog pathway inhibitor approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of adults with metastatic BCC or with locally advanced BCC inappropriate for surgery or radiotherapy[5,6]
- More recently, another Hedgehog pathway inhibitor, sonidegib, was approved for use in patients with locally advanced BCC[7]
- The pivotal registration study, ERIVANCE BCC, demonstrated vismodegib objective response rate of 43% in locally advanced BCC and 30% in metastatic BCC, as assessed by an independent review facility[8]
- Subsequent analyses from ERIVANCE BCC have demonstrated long-term duration of response and a consistent efficacy and safety profile[9,10]
- The Safety Events in Vismodegib (STEVIE, ClinicalTrials.gov ID, NCT01367665) study was designed to further assess safety and efficacy of vismodegib in patients with advanced BCC in a real-world setting[11]
- Here we report results from the primary analysis of the total evaluable population (N = 1215), with a data cutoff of March 16, 2015

OBJECTIVES

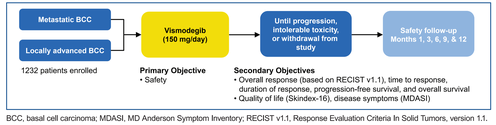
- The primary objective was safety
- Efficacy and quality-of-life variables were assessed as secondary objectives

METHODS

Study Design

- Single-arm, open-label, international study
- Eligible patients with locally advanced or metastatic BCC received oral vismodegib 150 mg/day continuously until disease progression, unacceptable toxicity, patient consent withdrawal, death, or other reasons (**Figure 1**)
- No dose reductions were allowed, but treatment interruption of up to 8 weeks was permitted for managing toxicity or temporary inability to swallow capsules

Figure 1. Study design.



BCC, basal cell carcinoma; MDASI, MD Anderson Symptom Inventory; RECIST v1.1, Response Evaluation Criteria In Solid Tumors, version 1.1.

Key Eligibility Criteria

Inclusion Criteria

- Key inclusion and exclusion criteria for the study are included in **Table 1**

Table 1. Key Eligibility Criteria

Inclusion criteria	Exclusion criteria
Patients aged ≥18 years with a histologically confirmed diagnosis of locally advanced/metastatic BCC, ECOG PS ≤2, and adequate organ function	Concurrent non–protocol-specified antitumor therapy
For patients with locally advanced BCC, ≥1 histologically confirmed lesion deemed inoperable or surgery deemed inappropriate, and radiotherapy must have been previously administered, unless inappropriate	Completion of most recent antitumor therapy <21 days before initiation of treatment
For patients with metastatic BCC, histologic confirmation of distant metastasis	Uncontrolled medical illness
Patients with Gorlin syndrome must meet criteria for locally advanced/metastatic BCC	History of other disease that contraindicates the use of an investigational drug or that may affect interpretation of the study results
Patients eligible for enrollment with measurable and/or nonmeasurable disease, as defined by RECIST v1.1	

BCC, basal cell carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; RECIST v1.1, Response Evaluation Criteria In Solid Tumors, version 1.1.

Outcomes

- The primary end point was safety (incidence of treatment-emergent adverse events [TEAEs] according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03
- Secondary end points included overall response rate (investigator-assessed according to Response Evaluation Criteria In Solid Tumors, version 1.1 [RECIST v1.1]) in those patients with measurable disease; time to response; duration of response; progression-free survival and overall survival; and quality of life (assessed by Skindex-16 and impact of treatment on disease symptoms in patients with metastatic BCC assessed using the MD Anderson Symptom Inventory)
- Physical examinations were performed at screening and every 4-8 weeks thereafter
- Tumor evaluation by imaging techniques (if required) was performed every 8-16 weeks

Statistical Considerations

- A sample size of approximately 1200 patients allows the true adverse event (AE) incidence rate to be estimated within 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) and with a precision to estimate an AE of 1% frequency to within 0.5%-1% of the true AE rate

RESULTS

Patient Characteristics

- Recruitment for STEVIE was completed with 1232 patients enrolled between June 30, 2011, and September 2, 2014, at 167 sites in 36 countries
- 17 patients were excluded from the safety and efficacy analysis (no documented exposure based on return of drug dispensed)
- Patient demographics and baseline patient characteristics are shown in **Table 2**

Table 2. Patient Demographics and Baseline Characteristics

Characteristic	Locally advanced BCC n = 1119	Metastatic BCC n = 96	Total N = 1215
Age, years			
Mean (SD)	69.7 (16.1)	66.6 (13.0)	69.5 (15.9)
Median (range)	72.0 (18-101)	67.0 (34-95)	72.0 (18-101)
Sex, n (%)			
Male	634 (56.7)	60 (62.5)	694 (57.1)
ECOG PS, n (%)			
0	662 (59.2)	39 (40.6)	701 (57.7)
1	316 (28.3)	42 (43.8)	358 (29.5)
2	138 (12.3)	15 (15.6)	153 (12.6)
Gorlin syndrome, n (%)			
Yes	214 (19.2)	5 (5.2)	219 (18.1)
No	899 (80.8)	91 (94.8)	990 (81.9)
Type of locally advanced BCC, n (%)			
Inoperable	433 (38.7)	–	433 (35.6)
Surgery contraindicated	686 (61.3)	–	686 (56.5)
Recurrent BCC unlikely to be curatively resected	328 (29.3)	–	328 (27.0)
Anticipated substantial morbidity or deformity	385 (34.4)	–	385 (31.7)
Prior radiotherapy, n (%)			
Yes	312 (27.9)	59 (61.5)	371 (30.5)
No	806 (72.0)	37 (38.5)	843 (69.4)
Contraindicated	340 (30.4)	11 (11.5)	351 (28.9)
Inappropriate	466 (41.6)	26 (27.1)	492 (40.5)

BCC, basal cell carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation.

Treatment Exposure

- At data cutoff, median duration of treatment was 263 days (8.6 months) and 147 patients (12%) were receiving ongoing treatment, whereas 1068 patients (88%) had discontinued treatment, mainly due to TEAEs (n = 349), disease progression (n = 189), patient request (n = 113), physician decision (n = 76), deaths (n = 37), loss to follow-up (n = 21), or other reasons (n = 283) (**Table 3**)
- Median dose intensity was 97.7% (97.6% in the locally advanced BCC cohort and 98.9% in the metastatic BCC cohort)

Table 3. Patient Disposition at Data Cutoff

	Locally advanced BCC n = 1119	Metastatic BCC n = 96	Total N = 1215
Treatment ongoing, n (%)	131 (11.7)	16 (16.7)	147 (12.1)
Discontinued, n (%)	988 (88.3)	80 (83.3)	1068 (87.9)
Main reason for treatment discontinuation, n (%)			
AE	340 (30.4)	9 (9.4)	349 (28.7)
Progression of disease	152 (13.6)	37 (38.5)	189 (15.6)
Patient request	104 (9.3)	9 (9.4)	113 (9.3)
Investigator request	72 (6.4)	4 (4.2)	76 (6.3)
Death	32 (2.9)	5 (5.2)	37 (3.0)
Lost to follow-up	19 (1.7)	2 (2.1)	21 (1.7)
Other[a]	269 (24.0)	14 (14.6)	283 (23.3)

AE, adverse event; BCC, basal cell carcinoma.
[a]The "Other" category includes 124 patients (10.2%) who discontinued treatment but agreed to safety follow-up. This category also includes 96 patients (7.9%) who discontinued due to complete response/remission.

Safety

- TEAEs, defined as occurring between the first administration and 30 days after the last administration of study drug, inclusive, were reported in 1192 patients (98%)
- The most common all-grade TEAEs were muscle spasm (66.4%), alopecia (61.5%), dysgeusia (54.6%), weight decreased (40.6%), and decreased appetite (24.9%) (**Table 4**)
- The majority of TEAEs (54%) were mild to moderate
- Incidence of grade 3 and 4 TEAEs is listed in **Table 4**

Table 4. Most Common TEAEs[a]

TEAE	Patients with TEAEs, n (%) N = 1215		
	All	Grade 3	Grade 4
Muscle spasm	807 (66.4)	94 (7.7)	1 (<0.1)
Alopecia	747 (61.5)	15 (1.2)	1 (<0.1)
Dysgeusia	663 (54.6)	25 (2.1)	1 (<0.1)
Weight decreased	493 (40.6)	47 (3.9)	1 (<0.1)
Decreased appetite	303 (24.9)	20 (1.6)	0
Asthenia	291 (24.0)	22 (1.8)	1 (<0.1)
Nausea	218 (17.9)	4 (0.3)	0
Ageusia	213 (17.5)	15 (1.2)	1 (<0.1)
Fatigue	201 (16.5)	19 (1.6)	1 (<0.1)
Diarrhea	197 (16.2)	8 (0.7)	0
Arthralgia	124 (10.2)	4 (0.3)	0

TEAE, treatment-emergent adverse event.
[a]The most common TEAEs shown are those in >10% of patients.

- TEAEs were reported in 769 of 788 patients (97.9%) who received <12 months' treatment with vismodegib and in 423 of 427 patients (99.1%) who received ≥12 months' treatment. Because of the longer exposure period, patients who received ≥12 months' treatment experienced a higher incidence of TEAEs
- To address the impact of longer exposure, rate of occurrence of TEAEs (number of events per 100 patient-years) was calculated, comparing the rates of new TEAEs that occurred within the first 12 months and after 12 months of exposure
- A total of 1060.5 events per 100 patient-years occurred during the first 12 months and 391.6 events per 100 patient-years occurred after the first 12 months
- Grade ≥3 TEAEs also showed numerically higher rates per 100 patient-years in the first 12 months of treatment (93.6 events) than with exposure after 12 months of treatment (58.3 events)
- Serious TEAEs occurred in 289 patients (24%; 260 locally advanced; 29 metastatic BCC) and included pneumonia (1.5%), cutaneous squamous cell carcinoma (1.0%), and general physical health deterioration (1.0%)
- A total of 110 of 1215 patients (9.1%) died while on study or during follow-up, and 5.8% of deaths were a result of AEs (**Table 5**)

Table 5. Summary of Deaths on Study

	Locally advanced BCC n = 1119	Metastatic BCC n = 96	Total N = 1215
Deaths, n (%)	92 (8.2)	18 (18.8)	110 (9.1)
Main reason for death, n (%)			
AE	65 (5.8)	6 (6.3)	71 (5.8)
Progression of disease	15 (1.3)	12 (12.5)	27 (2.2)
Other[a]	12 (1.1)	0	12 (1.0)

AE, adverse event; BCC, basal cell carcinoma.
[a]Reasons for "Other" included unknown; natural causes; cardiac decompensation; general state alteration; deterioration of general state; clinical deterioration taking into consideration patient age; old age; and disease progression of mediastinal squamous cell carcinoma.

- Grade 5 (fatal) TEAEs occurred in 46 patients (3.8%); 7 of these deaths were considered by the investigator to be related to vismodegib but showed presence of comorbidities/risk factors in each case, thereby confounding the assessment of causality:
  - Myocardial infarction (n = 2): history of myocardial infarction and pulmonary embolism, smoking
  - Pancreatitis (n = 1): history of gastric hemorrhage and gastrectomy, concomitant medication
  - Pulmonary embolism (n = 1): lung cancer, obesity
  - Ischemic stroke (n = 1): hypertension
  - Cardiorespiratory arrest (n = 1): chronic lymphocytic leukemia
  - Renal failure (n = 1): dialysis, compromised vascular catheter
- The age range of these 7 patients was 54-86 years
- These deaths were medically reviewed and adjudicated by an independent data and safety monitoring board
- 6 of the 7 cases were considered unrelated to study drug
  - 1 case was not assessable because of insufficient clinical data (cardiorespiratory arrest)
- TEAEs that led to treatment discontinuation were reported in 380 patients (31%)
- The most frequently reported TEAEs that led to treatment discontinuation are presented in **Table 6**
- The majority of TEAEs that led to treatment discontinuation were mild to moderate: 56.6% of patients discontinued because of grade 1-2 TEAEs

Table 6. Most Common TEAEs That Led to Treatment Discontinuation

TEAE	Patients with TEAEs, n (%)		
	Locally advanced BCC n = 1119	Metastatic BCC n = 96	Total N = 1215
Muscle spasm	84 (7.5)	1 (1.0)	85 (7.0)
Dysgeusia	55 (4.9)	0	55 (4.5)
Weight decreased	46 (4.1)	1 (1.0)	47 (3.9)
Alopecia	39 (3.5)	0	39 (3.2)
Decreased appetite	37 (3.3)	0	37 (3.0)
Asthenia	35 (3.1)	0	35 (2.9)
Fatigue	25 (2.2)	2 (2.1)	27 (2.2)
Ageusia	23 (2.1)	0	23 (1.9)
Nausea	12 (1.1)	1 (1.0)	13 (1.1)

BCC, basal cell carcinoma; TEAE, treatment-emergent adverse event.

Efficacy

- 1161 patients in the efficacy-evaluable population had measurable disease and histologically confirmed disease at baseline
- Best overall confirmed responses (as assessed by investigator according to RECIST v1.1) were noted in 769 patients (66.2%): 738 of 1103 patients with locally advanced BCC (68.5%) and 31 of 89 patients with metastatic BCC (36.9%) (**Table 7**)
- Tumor or disease control is assumed from the number of complete and partial responses and number of stable disease combined
  - From these results, disease control was estimated to be 92.9%

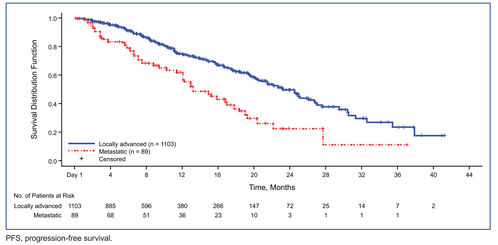
Table 7. Best Overall Response Rate (RECIST v1.1-confirmed)

Efficacy parameter	Locally advanced BCC n = 1103	Metastatic BCC n = 89	Total N = 1192
Patients with measurable disease at baseline, n	1077	84	1161
Best overall response rate			
Responder, n (%) [95% CI]	738 (68.5) [65.66-71.29]	31 (36.9) [26.63-48.13]	769 (66.2) [63.43-68.96]
Complete response, n (%)	360 (33.4)	4 (4.8)	364 (31.4)
Partial response, n (%)	378 (35.1)	27 (32.1)	405 (34.9)
Stable disease, n (%)	270 (25.1)	39 (46.4)	309 (26.6)
Progressive disease, n (%)	21 (1.9)	9 (10.7)	30 (2.6)
Missing or NE, n (%)	48 (4.5)	5 (6.0)	53 (4.6)
Median time to response, months (95% CI)	3.7 (2.9-3.7)	NE (5.49-NE)	3.7 (3.5-3.7)
Median duration of response, months (95% CI)	23.0 (20.4-26.7)	13.9 (9.2-NE)	22.7 (20.3-24.8)

BCC, basal cell carcinoma; CI, confidence interval; NE, not evaluable; RECIST v1.1, Response Evaluation Criteria In Solid Tumors, version 1.1.

- Median (95% CI) progression-free survival in patients with histologically confirmed disease and measurable or nonmeasurable disease at baseline was 22.1 (20.3-24.7): 23.2 months (21.4-26.0) in the locally advanced cohort and 13.1 months (12.0-17.7) in the metastatic BCC cohort (**Figure 2**)
- Median overall survival in patients with histologically confirmed disease and measurable or nonmeasurable disease at baseline was not estimable because the overall survival data are not mature for patients in the efficacy-evaluable population (both cohorts)

Figure 2. Kaplan-Meier curve of PFS.



PFS, progression-free survival.

CONCLUSIONS

- STEVIE is the largest study ever conducted in BCC and provides important safety and efficacy data associated with long-term vismodegib treatment in an advanced BCC patient population typically encountered in routine clinical practice
- Safety results from this primary analysis of STEVIE were consistent with the previously reported safety profiles[8,9]
- Long-term exposure was not associated with worsening of severity or frequency of TEAEs
- Investigator-assessed response rates showed a high rate of tumor control, including many complete and durable responses

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Roche is developing vismodegib under a collaboration agreement with Curis, Inc. Vismodegib was discovered by Genentech and 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.
Contact Dr. Johan Hansson at johan.hansson@ki.se for questions or comments.

http://bit.ly/1ZdYcQB