ORIGINAL ARTICLE

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

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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 10.1016/j.jaad.2013.09.012.)

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

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Funded by Roche-Genentech. Medical writing assistance was provided by Saema Magre, PhD, and Tony Serino, PhD, at ApotheCom and funded by F. Hoffmann-La Roche.

Disclosure: Dr Chang has received honoraria for participation on an advisory board for Genentech and has served as an investigator and received grants from Genentech and Novartis. Dr Solomon has received honoraria for participation on an advisory board for Genentech, and his institution has received grants from Genentech. Drs McKenna, Day, and Chen are salaried employees of and have received stock options from Genentech. Dr Weiss has served as an investigator for Infinity Pharma, Genentech, and Eli Lilly (no compensation received); has received honoraria as a speaker for Genentech, Quintiles, Medscape, Pfizer, and Eli Lilly; and his institution has received funds from Infinity Pharma, Genentech, and Eli Lilly for conducting clinical trials. Drs Hainsworth and Goldberg have no conflicts of interest to declare.

Accepted for publication September 5, 2013.

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Published online November 01, 2013.

0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2013.09.012

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

Abbreviations used:

AE:	adverse event
BCC:	basal cell carcinoma
BCNS:	basal cell nevus syndrome
ECOG:	Eastern Cooperative Oncology Group
FDA:	US Food and Drug Administration
ORR:	objective response rate
RECIST:	Response Evaluation Criteria in Solid Tumors
SMO:	Smoothened
TEAE:	treatment-emergent adverse event

initiation; had a history of other diseases or uncontrolled medical illnesses that would contraindicate vismodegib; were on concurrent antitumor therapy; or had a less than 12-week life expectancy.

Study design

This was an open-label, 2-cohort, multicenter study. All patients received 150 mg oral vismodegib once daily, with treatment cycles defined as every 28 days. Clinic visits occurred every 1 to 2 treatment cycles. The clinic visits included medical history; adverse event (AE) recording; ascertainment of concomitant medications; ECOG performance status; vital signs including weight; physical examination; complete blood cell count and metabolic panel; and urinalysis. Screening electrocardiography was also performed. Treatment was administered until investigator-assessed disease progression, unmanageable toxicities, patient or physician request to discontinue, or study termination by sponsor. Dose reduction was not permitted. Dose interruption up to 8 weeks was permitted to manage toxicity.

Safety analysis/assessment

The safety-evaluable population included patients receiving greater than or equal to 1 vismodegib dose. Safety was assessed by AE collection including incidence, type, severity, vismodegib discontinuation/interruption because of AEs, and on-study deaths (drug and nondrug related). Descriptions of all collected AEs were mapped to Medical Dictionary of Regulatory Activities terms (version 15.0) and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf).

Efficacy analysis/assessment

Patients receiving greater than or equal to 1 dose of vismodegib and having greater than or equal to 1 follow-up tumor assessment (or who died within 30 days of first dose of vismodegib) were included in the efficacy-evaluable population. Tumor responses were investigator-assessed according to RECIST version 1.0 criteria. Physical examinations were performed to assess measurable tumors within 7 days of treatment initiation, then every 4 to 8 weeks. Patients with radiographically measurable disease underwent computed tomography or magnetic resonance imaging assessment within 30 days before treatment initiation, then every 8 to 16 weeks thereafter. Patients with nonmeasurable disease, eg, bone metastases, were evaluated for disease progression by the clinical judgment of the treating physician. Objective tumor responses, defined as the best overall complete response or partial response, were confirmed by investigators using 2 consecutive tumor assessments performed at least 4 weeks apart according to RECIST version 1.0. For instance, if a tumor had a partial response followed by complete response but no second assessment of complete response, the tumor was labeled as partial response. For this study, appearance of a new cutaneous BCC was considered progressive disease if the lesion was larger than 5 mm and clearly documented as not previously present.

Statistical analysis

Patient data were collected through 30 days after the last vismodegib dose for the last patient enrolled. Efficacy and safety data were summarized by descriptive statistics. The association between tumor response and selected baseline characteristics of age, prior radiotherapy exposure, prior systemic cancer therapy, and number of involved sites was evaluated using Fisher exact test.

RESULTS

Patient demographics and baseline characteristics

In all, 120 patients (locally advanced BCC n = 62, metastatic BCC n = 58) enrolled at 11 US sites. Of these, 119 patients (locally advanced BCC n = 62, metastatic BCC n = 57) were safety-evaluable and 95 (locally advanced BCC n = 56, metastatic BCC n = 39) were efficacy-evaluable (Fig 1). Demographic and baseline characteristics were similar for both locally advanced BCC and metastatic BCC cohorts (Table I). RECIST-measurable disease at baseline comprised 87.4% of patients enrolled. The remaining 12.6% of patients had biopsy-proven metastatic BCC to bone, classified as nonmeasurable disease by RECIST version 1.0, but evaluable on imaging. Seven patients with BCNS had biopsy-proven distantly metastatic BCC.

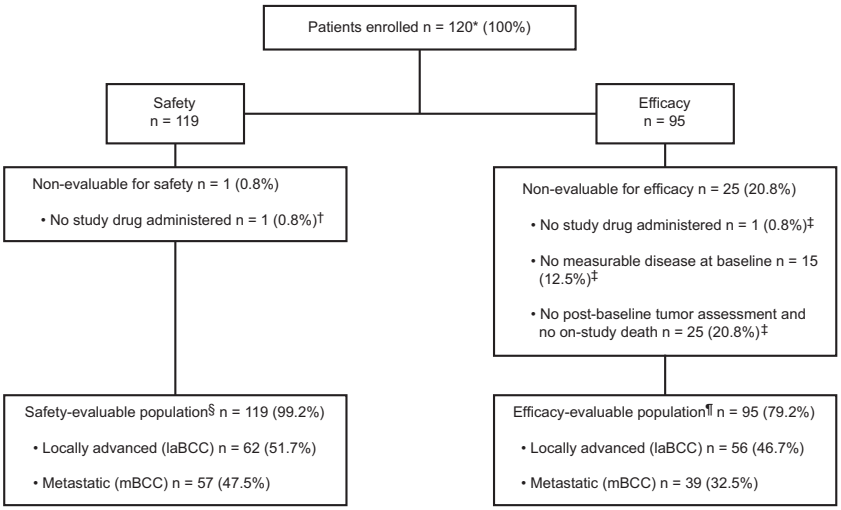

Fig 1. CONSORT schematic on patient enrollment. Percentages were based on patients enrolled (n = 120). *One patient was inadvertently assigned a new patient identification number after rejoining the study, 5 months after being lost to follow-up. All results for this patient were presented under the original patient identification number. †One patient was not included in the safety-evaluable population because the patient started the first cycle of treatment and then was lost to follow-up. As the drug bottle or drug diary was not returned to the site, it could not be confirmed how many (if any) doses had been taken. ‡Patients could be counted in more than 1 of the efficacy-nonevaluable reasons. §Defined as enrolled patients who had received at least 1 dose of vismodegib. ¶Defined as patients who had received at least 1 dose of vismodegib, had measurable disease at baseline, and had at least 1 follow-up tumor assessment or died within 30 days from the last dose of study drug. *laBCC*, Locally advanced BCC; *mBCC*, metastatic BCC.

Safety

Treatment exposure and study termination. The median duration of vismodegib treatment was 5.5 (range 0.4-19.6) months. The mean received dose was approximately 95% of planned. The median safety follow-up was 6.5 (range 1.4-20.6) months. The relatively short median duration of vismodegib treatment was reflective of FDA approval, at which point the sponsor terminated the study and patients were transitioned to commercially available vismodegib. The sponsor study termination was the primary reason for discontinuation. Of the 120 patients enrolled, 79 (locally advanced BCC n = 44, metastatic BCC n = 35) were transitioned to commercial drug. Other reasons for study discontinuation included disease progression (n = 16), subject decision (n = 7), loss to follow-up (n = 6), and AEs (n = 5).

Adverse events. Almost all safety-evaluable patients (n = 116; 97.5%) experienced a treatment-emergent AE (TEAE). These were typically grades 1 and 2, with few patients experiencing AEs of grade 3 (n = 24), grade 4 (n = 9), and grade 5 (death; n = 2). Common ($\geq$15% incidence) TEAEs are listed in Table II. The median time to onset of common TEAEs was generally less than 60 days after treatment initiation; however, alopecia and decreased weight had longer onset times (median 87 and 175 days, respectively). Most TEAEs (eg, muscle spasm, dysgeusia, alopecia) occurred within the first 7 treatment cycles (Fig 2). Among women of childbearing potential (n = 8), 4 developed amenorrhea or irregular menses; 1 patient had amenorrhea for longer than 6 months (grade 3), 1 patient for more than 3 to 6 months (grade 2), and 2 patients for 1 to 3 months (grade 1). All amenorrhea AEs were ongoing at study termination.

Serious AEs, TEAE-related withdrawal, and study deaths. Eighteen patients (locally advanced BCC n = 9, metastatic BCC n = 9) reported serious AEs that were grade 3 (n = 12), grade 4 (n = 6), or grade 5 (n = 2). Muscle spasm (n = 1, grade 3) was the only vismodegib-related serious AE reported. Seven patients discontinued vismodegib because of AEs (2 were drug related and 5 unrelated). In the locally advanced BCC cohort, TEAEs leading to discontinuation included 1 patient each with wound complication, muscle spasm, worsening/recurrence of pre-existing conditions such as B-cell lymphoma, mesothelioma, and squamous cell carcinoma. In the metastatic BCC cohort, AEs leading to treatment discontinuation included 1 patient with fatigue and

Table I. Patient demographics and baseline disease characteristics in the safety-evaluable population

Demographic	All patients (n = 119)	laBCC (n = 62)	mBCC (n = 57)
Median age, y (range)	62.0 (24-100)	61.0 (26-92)	63.0 (24-100)
Male, n (%)*	88 (73.9)	43 (69.4)	45 (78.9)
White, n (%)	116 (97.5)	60 (96.8)	56 (98.2)
ECOG performance status, n (%)			
0	69 (58.0)	39 (62.9)	30 (52.6)
1	41 (34.5)	19 (30.6)	22 (38.6)
2	9 (7.6)	4 (6.5)	5 (8.8)
Patients with basal cell nevus syndrome, n (%)	19 (16.0)	12 (19.4)	7 (12.3)
BCC history			
Mean time from initial diagnosis of BCC to study treatment, y (±SD)	8.6 (12.5)	12.1 (15.0)	4.9 (7.7)
Patients with measurable disease at baseline, n (%)	104 (87.4)	56 (90.3)	48 (84.2)
Patients with laBCC, n (%)	62 (52.1)	62 (100)	—
Inoperable	—	27 (43.5)	—
Surgery medically contraindicated, n (%)	—	35 (56.5)	—
Recurrent BCC unlikely to be curatively resected	—	10 (16.1)	—
Anticipated substantial morbidity and/or deformity from surgery	—	28 (45.2)	—
Other contraindications to surgery	—	2 (3.2)	—
No. of laBCC and/or mBCC sites involved, n (%)			
≤3	—	56 (90.3)	49 (86.0)
>3	—	6 (9.7)	8 (14.0)
Site of disease, n (%)			
Lung	—	—	30 (52.6)
Skin	—	61 (98.4)	29 (50.9)
Face	—	40 (64.5)	5 (8.8)
Scalp	—	24 (38.7)	6 (10.5)
Neck	—	14 (22.6)	12 (21.1)
Trunk	—	11 (17.7)	6 (10.5)
Arm	—	7 (11.3)	3 (5.3)
Leg	—	4 (6.5)	—
Other skin site	—	12 (19.4)	16 (28.1)
Lymph node	—	—	16 (28.1)
Bone	—	—	16 (28.1)
Liver	—	—	4 (7.0)
Other site	—	4 (6.5)†	12 (21.1)‡
Previous treatments, n (%)			
Surgery	111 (93.3)	57 (91.9)	54 (94.7)
Radiotherapy	55 (46.2)	20 (32.3)	35 (61.4)
Systemic therapy	31 (26.1)	11 (17.7)	20 (35.1)

BCC, Basal cell carcinoma; *ECOG*, Eastern Cooperative Oncology Group; *laBCC*, locally advanced BCC; *mBCC*, metastatic BCC.
*Percentages are based on n value in top row.
†Other sites for laBCC included medial canthus, right eye, dura, shoulder, and orbit.
‡Other sites included left axilla and clavicle, brain, chest, sacrum, periorbital, kidney, ocular, left axilla, right axilla, T10-T12, lumbar spine, and left gingivobuccal sulcus oral cavity.

1 with clostridial infection. Overall AE and serious AE rates were not significantly different between locally advanced BCC and metastatic BCC cohorts.

In this study, death because of disease progression was not considered a grade-5 AE. Three patients died on study (metastatic BCC, n = 2; locally advanced BCC, n = 1), defined as during or within 30 days of receiving the last treatment dose. Reported causes in the locally advanced BCC cohort included recurrence of a previously treated squamous cell carcinoma and wound complication. The cause of death of the patient in the metastatic BCC cohort was disease progression. None of the deaths were considered by the investigator to be treatment related.

Efficacy

Objective response and best overall response rate. In efficacy-evaluable patients (locally advanced BCC n = 56, metastatic BCC n = 39), objective responses achieved by patients with locally advanced BCC and metastatic BCC were

Table II. Common (≥ 15% incidence) treatment-emergent adverse events with vismodegib in the safety-evaluable population

Common AE (≥ 15% incidence)	Median time to AE onset, d (95% CI)	All AEs, n (%)	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)
Muscle spasm	37 (28-44)	84 (70.6)	63 (52.9)	19 (16.0)	2 (1.7)	0	0
Dysgeusia	41 (30-52)	84 (70.6)	68 (57.1)	16 (13.4)	0	0	0
Alopecia	87 (74-104)	69 (58.0)	57 (47.9)	12 (10.1)	0	0	0
Diarrhea	38 (22-116)	30 (25.2)	23 (19.3)	5 (4.2)	1 (0.8)	1 (0.8)	0
Nausea	30 (11-130)	23 (19.3)	19 (16.0)	4 (3.4)	0	0	0
Fatigue	42 (16-120)	23 (19.3)	14 (11.8)	8 (6.7)	1 (0.8)	0	0
Weight decrease	175 (114-293)	19 (16.0)	12 (10.1)	7 (5.9)	0	0	0

AE, Adverse event; *CI*, confidence interval (95% distribution-free confidence limits for percentiles).
Percentages were based on safety-evaluable patients (n = 119).

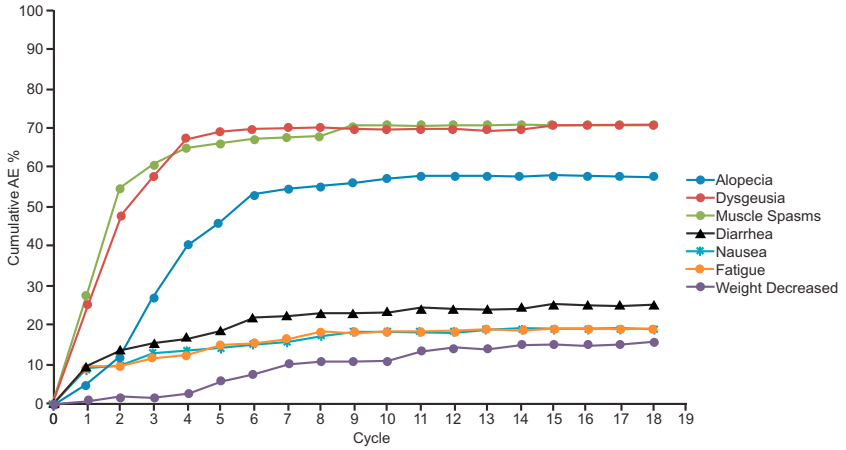

Fig 2. Cumulative occurrence of adverse events (*AEs*) by cycle. AEs with earlier onset included muscle spasm and dysgeusia. AEs with later onset included alopecia and weight loss.

46.4% and 30.8%, respectively (Fig 3). Eight patients (8.4% of all study patients) achieved complete response (locally advanced BCC n = 6, metastatic BCC n = 2), whereas 30 patients (31.6% of all study patients) achieved partial response (locally advanced BCC n = 20, metastatic BCC n = 10). In all, 47 patients (49.5% of all study patients) experienced stable disease (locally advanced BCC n = 27, metastatic BCC n = 20). In total, 94.6% patients in the locally advanced BCC cohort and 82.1% patients in the metastatic BCC cohort had complete response, partial response, or stable disease. No patient with locally advanced BCC had progressive disease, whereas 3 patients with metastatic BCC exhibited progressive disease (Table III).

Objective response rate (ORR) associations. Exploratory analysis of demographic or clinical factors that associate with ORR was performed. Because of sample size limitation, the associations selected were limited to age, use of prior radiotherapy, use of prior systemic chemotherapy, and the number of concurrent sites involved with BCC (Table IV). ORR was not significantly associated with age, number of sites involved, or use of prior radiotherapy in either the locally advanced BCC or the metastatic BCC cohorts. However, the ORR for patients with locally advanced BCC was significantly different in those with versus without previous systemic chemotherapy (0% and 55%, respectively; P = .002). All patients with locally advanced BCC who received prior systemic therapy experienced stable disease as best overall response. Duration of treatment was similar for patients with locally advanced BCC with or without prior systemic treatment (5.7 vs 6.4 months). Prior systemic therapies reported by the treating investigators included: vismodegib (n = 4), IPI-926, another Hedgehog pathway inhibitor, dasatinib, rofecoxib, photodynamic therapy, and cisplatin plus pemetrexed (n = 1 each) for an underlying mesothelioma, with target BCC concurrently exposed to this treatment. With removal of rofecoxib and photodynamic therapy as systemic therapy for BCCs, the negative association was still significant (P = .01). Sample size

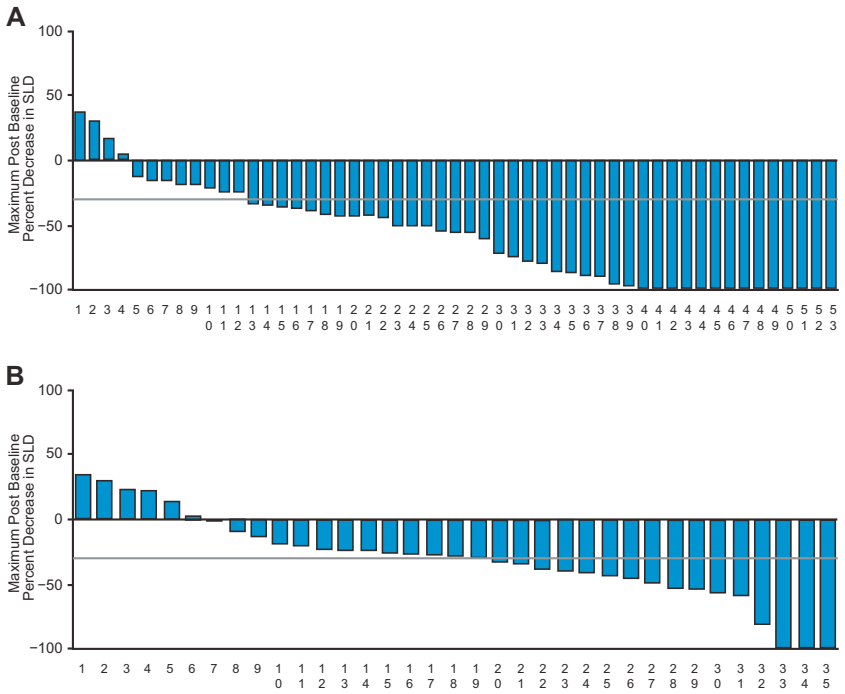

Fig 3. Maximum postbaseline percentage decrease in the sum of the longest diameters (*SLD*) of measurable lesions in patients. Data for patients with locally advanced (**A**) and metastatic (**B**) basal cell carcinoma. Each column represents an individual patient.

Table III. Best overall response (Response Evaluation Criteria in Solid Tumors[26]) to vismodegib treatment at study termination

Responses	laBCC (n = 56)	mBCC (n = 39)
Objective response, n (%)* [95% CI]	26 (46.4) [33.0-60.3]	12 (30.8) [17.0-47.6]
Complete response, n (%)	6 (10.7)	2 (5.1)
Partial response, n (%)	20 (35.7)	10 (25.6)
Stable disease, n (%)	27 (48.2)	20 (51.3)
Progressive disease, n (%)	0	3 (7.7)
Unevaluable/missing, n (%)	3 (5.4)	4 (10.3)
Median (range) time to objective response, mo†	2.6 (1.0-11.0)	2.6 (1.4-12.6)

CI, Confidence interval (based on the Clopper-Pearson method); *laBCC*, locally advanced BCC; *mBCC*, metastatic BCC.
*Percentages were based on n in the top row.
†Response assessments every 4-8 wk by physical examination and every 8-16 wk by radiographic examination.

precluded multivariate analysis. Prior systemic therapy did not lead to a significantly different ORR in the metastatic BCC cohort.

Illustrative patient case studies

Case study 1: Differential shrinkage in locally advanced BCCs after retreatment with vismodegib. An 84-year-old man with a long history of locally advanced BCCs enrolled in the current expanded access study after a 9-month course of vismodegib (150 mg daily) through the phase-II clinical trial (ERIVANCE BCC). Left scalp and preauricular locally advanced BCCs achieved partial response and he discontinued from ERIVANCE 7 months earlier for personal reasons. In the current study, target lesions on the left ear and left chin demonstrated a partial response, and the nontarget left scalp and preauricular locally advanced BCCs demonstrated complete response and visible tumor shrinkage (Fig 4, *A*), respectively, after 8 months of retreatment. Hence, retreatment can be beneficial but responses to vismodegib in different BCCs within an individual can vary.

Case study 2: Periocular BCCs in a patient with BCNS shows complete response.* A 55-year-old man with BCNS presented with multiple locally advanced BCCs* including 2 periocular BCCs—right medial canthus and left lateral canthus (Fig 4, *B* I)—and a 13-cm BCC on the right scalp eroding calvarium. The patient received 150 mg vismodegib once daily. His periocular lesions responded with complete regression. He continued on vismodegib after study termination and the periocular lesions have remained clear without evidence of disease at 24 months

*Note: Additional description of the scalp BCC has been published in *JAMA Dermatology* (Vignette section) 2013;149:639-41. Current photographs are not previously published.

Table IV. Association of baseline variables and objective response by univariate analysis

Outcome	laBCC cohort (n = 56)			mBCC cohort (n = 39)		
Age, y	**<65**	**≥65**	***P* value**	**<65**	**≥65**	***P* value**
n	32	24	1.000	21	18	1.000
Objective response, n (%)	15 (47)	11 (46)		6 (29)	6 (33)	
Median treatment duration, mo	5.3	7.7		6.2	5.2	
Prior radiotherapy	**Yes**	**No**	***P* value**	**Yes**	**No**	***P* value**
n	15	41	.561	23	16	.174
Objective response, n (%)	8 (53)	18 (44)		5 (22)	7 (44)	
Median treatment duration, mo	6.9	5.4		5.5	7.2	
Prior systemic therapy	**Yes**	**No**	***P* value**	**Yes**	**No**	***P* value**
n	9	47	.002	13	26	.714
Objective response, n (%)	0 (0)	26 (55)		3 (23)	9 (35)	
Median treatment duration, mo	5.7	6.4		5.1	6.3	
No. of sites involved (laBCC and/or mBCC)	**1 Site**	**>1 Sites**	***P* value**	**1 Site**	**>1 Sites**	***P* value**
n	30	26	.295	16	23	1.000
Objective response, n (%)	16 (53)	10 (38)		5 (31)	7 (30)	
Median treatment duration, mo	7.0	5.0		5.8	5.7	

laBCC, Locally advanced BCC; *mBCC*, metastatic BCC.
Percentages were based on N in each subgroup cohort. *P* values (uncorrected) were derived from Fisher exact test.
Objective response was significantly associated with the number of prior systemic treatments.
Prior systemic treatments were: Smoothened inhibitor drugs (including drugs besides vismodegib) and nontargeted chemotherapy.

follow-up (Fig 4, *B* II). His scalp lesion partially responded and the residual BCC was excised with negative margins. This case illustrates the use of vismodegib in periocular lesions where surgery may risk vision loss.

DISCUSSION

To our knowledge, this is the largest peer-reviewed, published study to date of vismodegib in advanced BCCs. In light of priority review and approval of vismodegib by the FDA based on a single phase-II study,[14] this study contributes important additional data confirming the safety and efficacy of vismodegib for advanced BCCs. The observed safety profile based on incidence and severity of AEs is comparable with the phase-II study with no new safety signals observed. Longer follow-up times will be critical to assess long-term outcomes and the safety profile of vismodegib treatment. The international vismodegib safety study, STEVIE (NCT01367665), which aims to enroll 1200 patients, will likely address these important questions.

This clinical study (with ORR 46% in patients with locally advanced BCC and 31% in patients with metastatic BCC) shows similar overall clinical activity to the phase-II BCC study (with ORR 43% in patients with locally advanced BCC and 30% in those with metastatic BCC). This is despite several differences in response assessment between the 2 studies. First, this expanded access study used RECIST criteria for both cohorts and did not use independent review to assess the tumor responses to vismodegib. Second, a few patients (6 of 119) in this study had been exposed to an SMO inhibitor before enrollment, which was not the case in the phase-II study.

Data on clinical factors that predict ORR, as explored in this study, will be useful for clinicians to identify patients with advanced BCC most likely to benefit from vismodegib. Although this study has a relatively small sample size for ORR predictions, a prospective, observational, US disease registry (RegiSONIC; NCT01604252) is currently underway to assess effects of different treatments in advanced BCC and may provide additional data about predictors of tumor response.

In conclusion, this study provides important additional clinical data supporting vismodegib as a useful treatment for advanced BCCs. Given the complexity of many of these patients, and the recent availability of vismodegib for commercial use, multidisciplinary efforts among dermatologists, medical oncologists, radiation oncologists, otolaryngologists, and surgical oncologists may be needed to optimize patient outcomes.

The authors would like to thank all the patients and their families for participating in this study. The authors would also like to thank the following investigators for

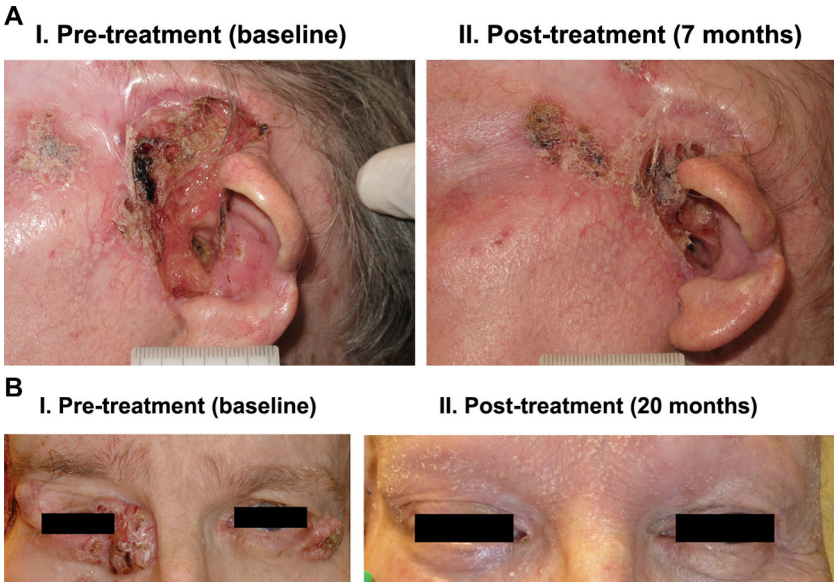

Fig 4. Case studies of patients with advanced basal cell carcinoma (BCC). **A**, Retreatment with vismodegib demonstrating a mixed response, with left preauricular showing stable disease followed by progressive disease even though a separate scalp lesion showed complete response. **B**, A patient with basal cell nevus syndrome and periocular locally advanced BCCs in the right medial canthus and left lateral canthus with durable complete response after study end, as followed up in dermatology clinic 20 months after vismodegib initiation. All photographs are presented in this article with the consent of the patients obtained by the authors.

their participation in the conduct of the study: Philip Friedlander, Joel Gelfand, Omid Hamid, Patricia LoRusso, Thomas Olencki, Anthony Oro, Aleksandar Sekulic, and Lisa Blaydorn.

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