A phase II, multicenter, open-label, 3-cohort trial evaluating the efficacy and safety of vismodegib in operable basal cell carcinoma

Howard Sofen, MD,[a] Kenneth G. Gross, MD,[b] Leonard H. Goldberg, MD, FRCP,[c] Harry Sharata, MD, PhD,[d] Tiffani K. Hamilton, MD,[e] Barbara Egbert, MD,[f,g] Benjamin Lyons, PhD,[h] Jeannie Hou, MD,[h] and Ivor Caro, MD[h]
Los Angeles, San Diego, Palo Alto, and South San Francisco, California; Houston, Texas; Madison, Wisconsin; and Atlanta, Georgia

Background: Vismodegib is approved for treatment of advanced basal cell carcinoma.

Objective: We sought to characterize vismodegib efficacy and safety in operable basal cell carcinoma.

Methods: Patients with new, operable, nodular basal cell carcinoma received vismodegib (150 mg/d) followed by excision and Mohs micrographic surgery to ensure clear margins. Cohort 1 received vismodegib for 12 weeks; cohort 2 received vismodegib for 12 weeks, then 24 weeks of observation before excision; and cohort 3 received vismodegib for 8 weeks on/4 weeks off/8 weeks on.

Results: In all, 24 patients enrolled in cohort 1, and 25 in cohorts 2 and 3. Complete histologic clearance was achieved by 42%, 16%, and 44% of patients in cohorts 1, 2, and 3, respectively. Muscle spasms (76%), alopecia (58%), and dysgeusia (50%) were the most frequent adverse events (AEs). Five (7%) patients discontinued treatment because of an AE. AE reversibility was evaluated in cohort 2 with 24 weeks of observation after treatment discontinuation.

Limitations: Nonrandomized, small cohort sizes, and short observation durations for some patients are limitations.

Conclusion: Primary efficacy end points were not met (predefined complete histologic clearance rate: >50% in cohorts 1 and 3; >30% in cohort 2). Safety was comparable when dosed continuously versus intermittently. Posttreatment reversibility of vismodegib-related AEs was demonstrated. (J Am Acad Dermatol 2015;73:99-105.)

Key words: basal cell carcinoma; hedgehog pathway inhibitor; vismodegib.

From the Department of Medicine/Dermatology, David Geffen School of Medicine at University of California—Los Angeles[a]; Skin Surgery Medical Group Inc, San Diego[b]; DermSurgery Associates, Houston[c]; Madison Skin and Research Inc[d]; Atlanta Dermatology, Vein and Research Center LLC[e]; Stanford University Medical School[f]; Department of Veterans Affairs Palo Alto Health Care System, Palo Alto[g]; and Genentech Inc, South San Francisco.[h]

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Reprint requests: Howard Sofen, MD, 8930 S Sepulveda Blvd, Suite 114, Los Angeles, CA 90045. E-mail: hsofen@ucla.edu.

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Aberrant activation of the hedgehog pathway is important in basal cell carcinoma (BCC) pathogenesis.[1] Vismodegib (Erivedge, Genentech, South San Francisco, CA), a hedgehog pathway inhibitor,[2,3] was approved by the US Food and Drug Administration (FDA) in 2012 and the European Medicines Agency in 2013 for treatment of adults with locally advanced or metastatic BCC.

This study evaluated activity of vismodegib in patients with smaller operable BCC by measuring the rate and durability of complete histologic clearance (CHC) of lesions. Safety with different durations of treatment and follow-up, including resolution of adverse events (AEs), was also assessed.

CAPSULE SUMMARY

- Vismodegib has demonstrated activity in advanced basal cell carcinoma. This study evaluated activity in operable basal cell carcinoma.
- Although complete histologic clearance was achieved in up to 44% and complete clinical response in 50% of patients receiving short course vismodegib, the prespecified level of efficacy was not achieved.
- This study demonstrated that vismodegib-related adverse events were reversible on treatment discontinuation.

METHODS

Study design

This nonrandomized, 3-cohort, open-label, phase II study was conducted at 9 sites in the United States (ClinicalTrials.gov identifier: NCT01201915). A Mohs experienced surgeon acted as principal investigator or subinvestigator.

Cohort 1 evaluated CHC rate after 12 weeks of treatment. Cohort 2 evaluated durability of CHC after a 12-week course and a 24-week observation period. To assess whether intermittent dosing improved tolerability, a protocol amendment added cohort 3 evaluating two 8-week treatment periods separated by a 4-week drug holiday (Fig 1).

The study was conducted per FDA regulations, International Conference on Harmonization E6 Guideline for Good Clinical Practice, and applicable local, state, and federal laws. Protocol approved by institutional review boards where applicable. Patients gave written informed consent.

Patients

Patients were 21 years of age or older, with new, operable, biopsy-confirmed, nodular BCC and willing to delay excision. One target lesion per patient located a sufficient distance from nontarget lesions avoided ambiguity in margin assessment. Enrollment in cohort 1 was limited to patients with lesions on the scalp/head/neck (0.5-2.0 cm) or cape area of the upper aspect of the trunk (1.0-3.0 cm). In cohorts 2 and 3, eligibility included lesions on the scalp/head/neck (0.5-2.0 cm) and on the greater trunk/limbs (1.0-3.0 cm). Patients had adequate baseline hematologic function and hepatic function. Cases with histologic subtypes other than nodular BCC, Gorlin syndrome, prior treatment with any hedgehog pathway inhibitor, and pregnancy or lactation were excluded.

Interventions

Patients received vismodegib at 150 mg/d. Dose reduction was not permitted. All target sites, even if clinically clear at the time of surgery, were excised by standard means, followed by Mohs micrographic surgery to obtain clear margins.

In cohorts 1 and 3, all patients underwent excision and Mohs micrographic surgery within 2 weeks of discontinuing treatment. In cohort 2, excised lesions and margins were evaluated with Mohs micrographic surgery at the end of a 24-week observation period.

Study assessments

The primary objective was to evaluate rate of CHC of target lesions at end-of-treatment period (cohorts 1 and 3) or after 24 weeks of observation (cohort 2). CHC was defined as absence of BCC in excised target site by histology.

After excision, specimens were sent to a central laboratory (Genentech Pathology, South San Francisco, CA) for histologic evaluation by an independent pathologist and examined for evidence of residual tumor (breadloafed). Secondary efficacy end point was time from vismodegib initiation to investigator-assessed complete clinical clearance. All tumor assessments were performed every 4 weeks.

AEs were recorded at each visit. All patients were followed up for safety until 30 days after Mohs micrographic surgery or last dose of study drug if Mohs micrographic surgery did not occur.

Statistical analysis

Evaluable patients received 1 or more doses of vismodegib and were included as nonresponders if they discontinued before evaluation for CHC or durable CHC. Study hypotheses were that the CHC rate would be more than 50% in cohorts 1 and 3, and the durable CHC rate would be more than 30% in cohort 2 (1-sided $\alpha = 0.10$).

Safety analyses included summaries of AEs, serious AEs (SAEs), treatment-emergent AEs, and AEs leading to discontinuation, graded according to

Abbreviations used:

AE: adverse event
BCC: basal cell carcinoma
CHC: complete histologic clearance
FDA: Food and Drug Administration
SAE: serious adverse event

the National Cancer Institute Common Terminology Criteria for AE, Version 4.0.

RESULTS

A total of 74 patients enrolled between October 5, 2010, and November 29, 2012: 24 in cohort 1, and 25 each in cohorts 2 and 3 (Fig 2). In all, 49 patients (66%) completed the study, and 25 (34%) discontinued early (patient decision to withdraw [n = 11; 15%], AEs [n = 4; 5%], lost to follow-up [n = 4; 5%], physician decision to withdraw [n = 3; 4%], and target lesion progression [n = 3; 4%, all from cohort 2]). Patient demographics and baseline disease characteristics are listed in Table I.

Efficacy

The predefined CHC rate of more than 50% was not met in either cohort 1 (10 of 24 patients, or 42% [P = .85]) or cohort 3 (11 of 25 patients, or 44% [P = .79]). In cohort 2, 4 of 25 (16%) patients achieved durable CHC lasting 24 weeks or more beyond the end of the 12-week treatment period (P = .97), which did not meet predefined threshold of more than 30% (Table II). Examples of 2 patients are presented in Fig 3.

Investigator-assessed complete clinical clearance was observed in 37 patients (50%), including 10

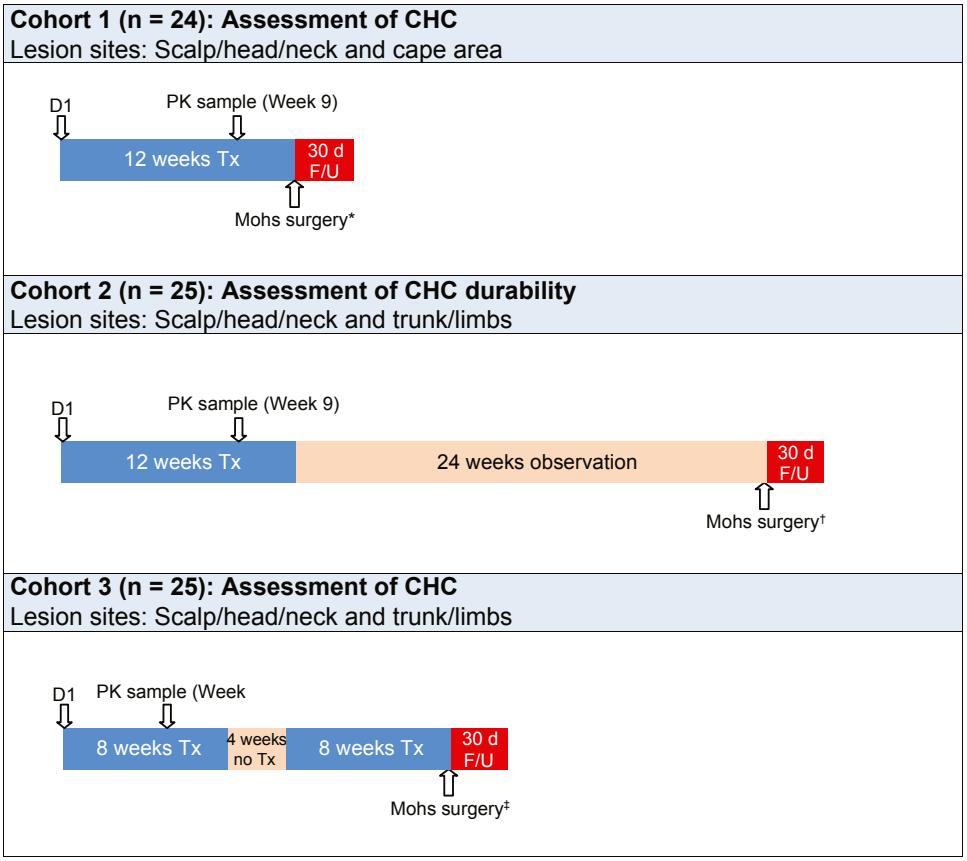

Fig 1. Treatment (*Tx*) interventions and assessments by cohort. *In patients who discontinued vismodegib Tx prematurely, the target lesion was removed with conventional excision and Mohs evaluation of margins was performed between weeks 13 and 15, or earlier if the investigator chose. †Patients who discontinued vismodegib before the completion of 8 weeks of Tx did not enter the 24-week observation period, but underwent excision and Mohs micrographic surgery between weeks 13 and 15; patients who discontinued between weeks 8 and 12 entered the observation period, and underwent excision and Mohs micrographic surgery at week 37. ‡Patients who discontinued early underwent target lesion excision and Mohs evaluation at week 20, or earlier if the investigator chose. *CHC*, Complete histologic clearance; *D1*, day 1; *F/U*, follow-up; *PK*, pharmacokinetic.

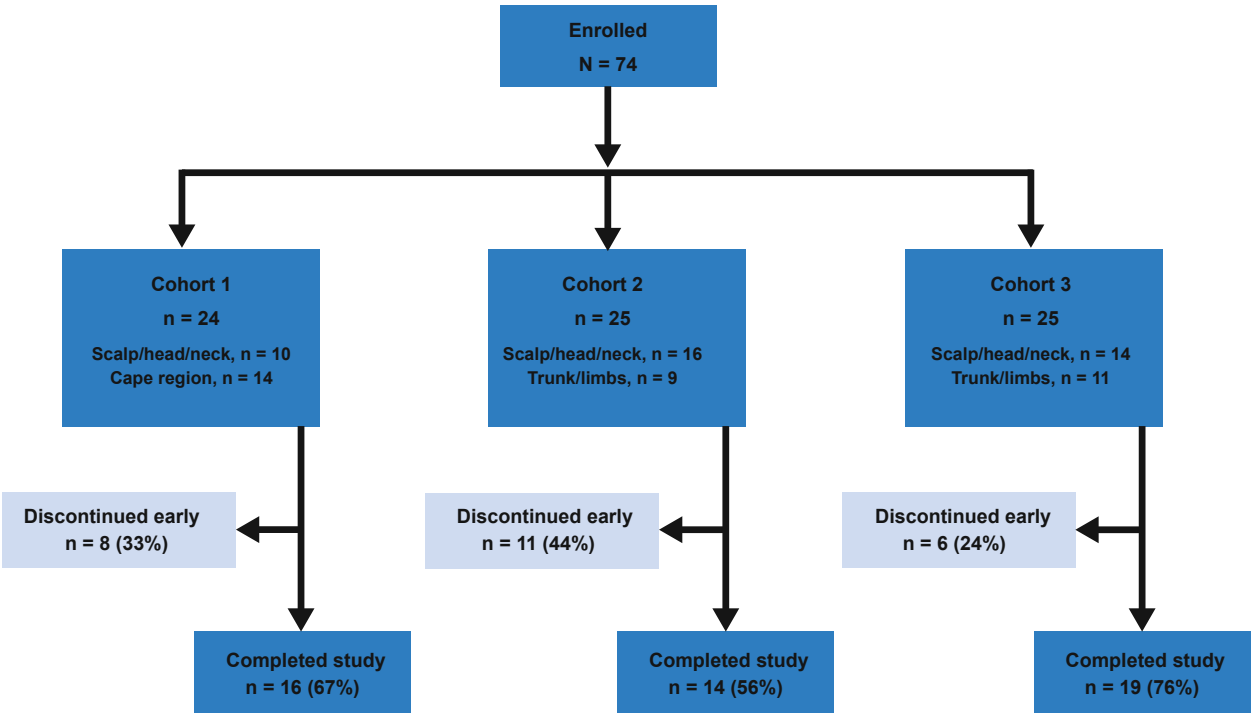

Fig 2. Patient disposition.

Table I. Demographic data and baseline characteristics

Demographic or baseline characteristic	Cohort 1 n = 24	Cohort 2 n = 25	Cohort 3 n = 25	All patients N = 74
Age, y				
Median (range)	59.0 (43-81)	65.0 (40-86)	61.0 (47-89)	61.5 (40-89)
Sex, n (%)				
Male	19 (79)	22 (88)	17 (68)	58 (78)
Female	5 (21)	3 (12)	8 (32)	16 (22)
Race, n (%)				
White	23 (96)	25 (100)	25 (100)	73 (99)
Native American	1 (4)	0	0	1 (1)
Longest diameter of nodular BCC, cm				
Median (range)	1.2 (1-3)	1.5 (1-2)	1.2 (1-3)	1.3 (1-3)
Concomitant medications, n (%)				
Any	22 (92)	25 (100)	24 (96)	71 (96)

BCC, Basal cell carcinoma.

(42%) in cohort 1, 9 (36%) in cohort 2, and 18 (72%) in cohort 3. Median time to complete clinical clearance (in those who achieved it) was 59.5 days (95% confidence interval 28-80) in cohort 1, 84 days (95% confidence interval 27-120) in cohort 2, and 60 days (95% confidence interval 55-86) in cohort 3 (Table III).

Safety

In all, 73 patients (99%) developed 1 or more treatment-emergent AEs (Table IV, available at http://www.jaad.org). Most frequent AEs (≥30% of patients) included muscle spasms (76%), alopecia (58%), dysgeusia (50%), and ageusia (30%). Grade-3 AEs occurred in 14 patients (19%), with muscle

Table II. Complete histologic clearance rate with vismodegib in cohorts 1, 2, and 3

BCC histopathology	Cohort 1 n = 24	Cohort 2 n = 25*	Cohort 3 n = 25
Patients achieving CHC, n	10	4	11
CHC rate, %	42	16	44
95% CI	22.1-63.4	4.5-36.1	24.4-65.1
P value	.85	.97	.79

Hypotheses were formally tested using a 1-sided exact binomial test at the 1-sided $\alpha = 0.10$ level. The 95% CI for response rates was calculated using the Clopper-Pearson exact method.
BCC, Basal cell carcinoma; *CHC*, complete histologic clearance; *CI*, confidence interval.
*Four patients did not have evaluable data for durable CHC and were included in the analysis as nonresponders.

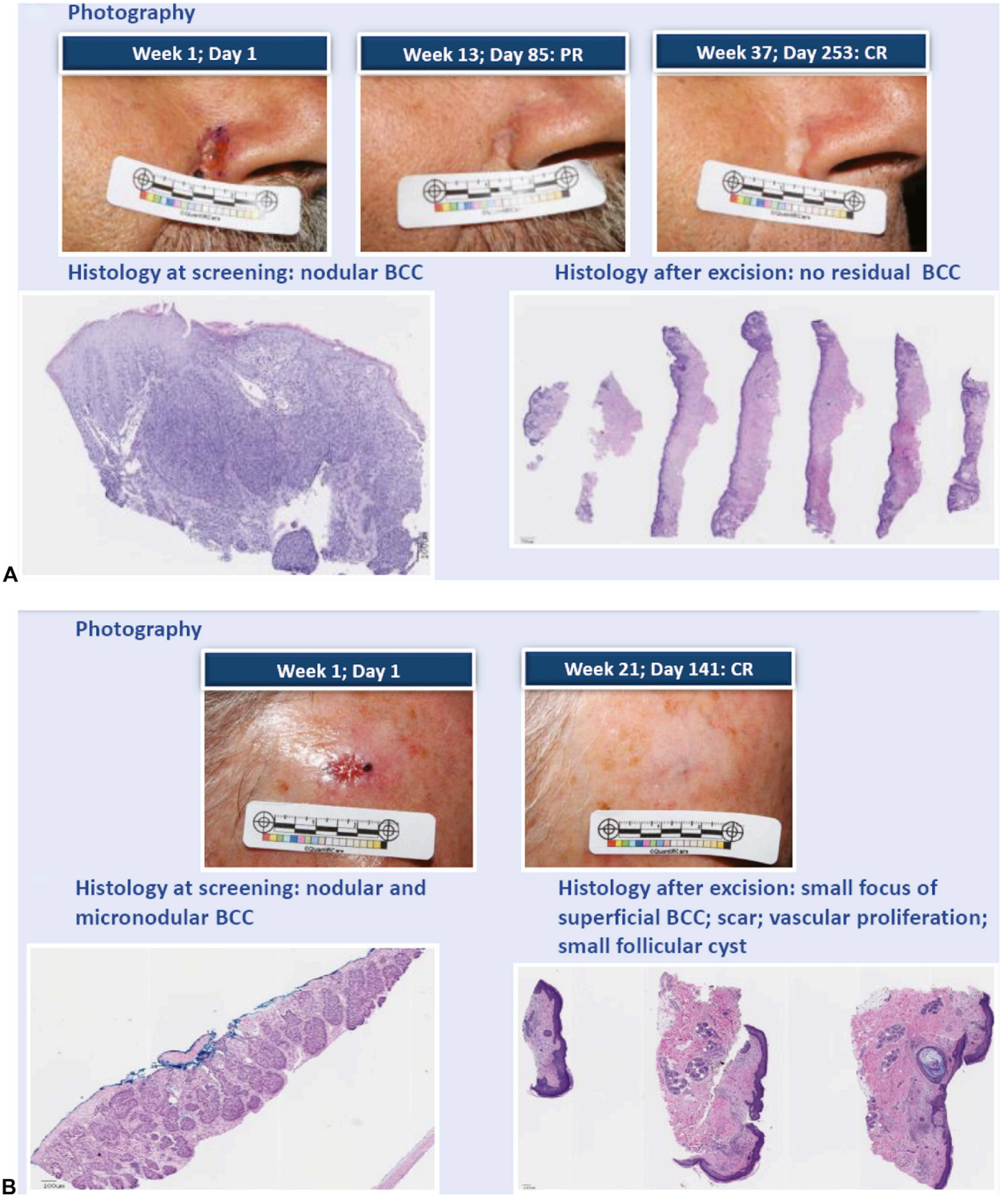

Fig 3. Case examples of patients treated with vismodegib. **A**, Complete histologic clearance after excision (patient 23036; white male, 59 years of age). **B**, Small focus of residual disease on histologic analysis after excision (patient 23056; white male, 57 years of age). *BCC*, Basal cell carcinoma; *CR*, complete response; *PR*, partial response.

spasms the most frequently reported. No grade-4 AEs or deaths were reported. SAEs were reported in 6 patients (8%) including atrial fibrillation, hemorrhoidal hemorrhage, small intestinal hemorrhage, hepatitis, bladder cancer, liposarcoma, and ischemic stroke. Most SAEs were considered

Table III. Investigator-assessed complete clinical clearance in all cohorts

	n	Investigator-assessed CCC, n (%)	Median (95% CI) time to investigator-assessed CCC, d
Cohort 1	24	10 (42)	59.5 (28-80)
Cohort 2	25	9 (36)	84 (27-120)
Cohort 3	25	18 (72)	60 (55-86)
Total	74	37 (50)	

Kaplan-Meier method used to estimate median time to CCC; 95% CIs computed using Brookmeyer-Crowley method.
CCC, Complete clinical clearance; *CI*, confidence interval.

unrelated to vismodegib treatment by investigators; 1 patient experienced an SAE of hepatitis and hemorrhoidal hemorrhage. The event of hepatitis was considered related and resolved within 2 months of study drug discontinuation.

Treatment was discontinued because of AEs in 2 patients from cohort 1 (8%), 1 from cohort 2 (4%), and 1 (4%) from cohort 3. Dysgeusia was the most frequent AE leading to discontinuation (n = 3; 4%), followed by muscle spasm (n = 2; 3%), and alopecia (n = 2; 3%).

The incidence of muscle spasms evenly distributed across cohorts (cohort 1, 79%; cohort 2, 76%; cohort 3, 72%), with a median time to onset of 34, 26, and 27 days and median duration of 61, 73, and 115 days in cohorts 1, 2, and 3, respectively (Table V, available at http://www.jaad.org). A lower incidence of alopecia was observed in cohort 1 (33%) compared with cohorts 2 (68%) and 3 (72%). Median time to onset was 115, 75, and 68 days in cohorts 1, 2, and 3, respectively, and occurred after treatment discontinuation in 7 of 8 patients in cohort 1 and 9 of 17 patients in cohort 2. Median duration was 64, 89, and 134 days in cohorts 1, 2, and 3, respectively (Table V). The incidence of dysgeusia was 38%, 52%, and 60% in cohorts 1, 2, and 3, respectively. Median time to onset of dysgeusia was 24, 41, and 26 days in cohorts 1, 2, and 3, respectively. Median duration was 63 and 82 days in cohorts 1 and 2, respectively, and could not be estimated in cohort 3 (Table V). Median time to onset was 21, 15, and 15 days and median duration was 108, 134, and 124 days in cohorts 1, 2, and 3, respectively (Table V).

Importantly, the longer observation period in cohort 2 enabled exploration of reversibility of common AEs (Table V). Muscle spasm: 16 of 19 patients achieved full resolution within 6 weeks of end of treatment, and the remaining three grade-1 AEs resolved within 12 weeks of end of treatment. Among the 17 patients with alopecia, 4 patients had grade 1 alopecia ongoing at study end. For dysgeusia, 11 of 13 patients achieved resolution within 12 weeks of end of treatment, whereas the remaining 2 patients had ongoing grade-1 dysgeusia at study end (after 24 weeks' follow-up). Of 5 patients reporting ageusia in cohort 2 (all grade 1), all events fully resolved within 12 weeks of end of treatment.

DISCUSSION

This study did not achieve its predefined primary end points of independent pathologist-determined CHC, either in cohort 1 after 12 weeks of continuous vismodegib treatment, or in cohort 3 after 16 weeks of intermittent vismodegib treatment, or durable CHC in cohort 2 after 24 weeks of follow-up. However, the treatment regimens in this study were somewhat well tolerated as noted by the low discontinuation rate (4 patients [5%] discontinued treatment because of AEs). To date, more than 4000 patients with BCC have received treatment with vismodegib, and its AE profile has shown general consistency across populations and indications,[3-5] although individual incidences may vary with treatment duration.[6] In our study, the safety profile of vismodegib (150 mg daily) was comparable when dosed as a short-term continuous regimen or intermittently, and was generally consistent with clinical experience.[7]

Our data generally showed reversibility of muscle spasms, dysgeusia, and ageusia in the 6 to 12 weeks after drug discontinuation, and reversibility of delayed-onset alopecia in most patients during the 24-week follow-up period in cohort 2. Several differences in AEs were noted among cohorts, including incidences and times to onset. It is difficult to conclude whether these observations could be related to differences in total treatment exposures and follow-up periods, or a combination of factors, because of the small number of patients in each cohort. Moreover, patient assignment to cohorts was not randomized, limiting comparisons across cohorts.

Conclusions

The efficacy and safety of vismodegib continues to be investigated. Further studies are needed to evaluate any cumulative toxicity with extended treatment times and to explore strategies to ameliorate common AEs.[6] The prespecified level of efficacy was not achieved in patients with operable BCC. However, this study showed good reversibility of the most common AEs (muscle spasm, alopecia, dysgeusia, and ageusia) associated with vismodegib.

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REFERENCES

1. Epstein EH. Basal cell carcinomas: attack of the hedgehog. *Nat Rev Cancer*. 2008;8(10):743-754.

2. Macha MA, Batra SK, Ganti AK. Profile of vismodegib and its potential in the treatment of advanced basal cell carcinoma. *Cancer Manage Res*. 2013;5:197-203.
3. Sekulic A, Migden MR, Oro AE, et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. *N Engl J Med*. 2012;366(23):2171-2179.
4. LoRusso PM, Rudin CM, Reddy JC, et al. Phase I trial of hedgehog pathway inhibitor GDC-0449 in patients with refractory, locally-advanced or metastatic solid tumors. *Clin Cancer Res*. 2011;17(8):2502-2511.
5. Kaye SB, Fehrenbacher L, Holloway R, et al. A phase II, randomized, placebo-controlled study of vismodegib as maintenance therapy in patients with ovarian cancer in second or third complete remission. *Clin Cancer Res*. 2012;18(23):6509-6518.
6. Rudin CM. Vismodegib. *Clin Cancer Res*. 2012;18(12):3218-3222.
7. Chang AL, Solomon JA, Hainsworth JD, et al. Expanded access study of patients with advanced basal cell carcinoma treated with the hedgehog pathway inhibitor, vismodegib. *J Am Acad Dermatol*. 2014;70(1):60-69.

Table IV. Treatment-emergent adverse events reported in 5% or more of patients overall

AE* by MedDRA-preferred term, n (%)	Cohort 1 n = 24	Cohort 2 n = 25	Cohort 3 n = 25	All patients N = 74
Any AE	24 (100)	25 (100)	24 (96)	73 (99)
Muscle spasm	19 (79)	19 (76)	18 (72)	56 (76)
Alopecia	8 (33)	17 (68)	18 (72)	43 (58)
Dysgeusia	9 (38)	13 (52)	15 (60)	37 (50)
Ageusia	10 (42)	5 (20)	7 (28)	22 (30)
Fatigue	5 (21)	3 (12)	7 (28)	15 (20)
Nausea	5 (21)	2 (8)	6 (24)	13 (18)
Decreased appetite	3 (13)	1 (4)	4 (16)	8 (11)
Madarosis	3 (13)	2 (8)	3 (12)	8 (11)
Constipation	1 (4)	3 (12)	3 (12)	7 (9)
Diarrhea	2 (8)	1 (4)	3 (12)	6 (8)
Dyspepsia	2 (8)	1 (4)	2 (8)	5 (7)

AE, Adverse event; *MedDRA*, Medical Dictionary for Regulatory Activities.
*AEs occurring during treatment or follow-up phase. AEs were summarized by MedDRA (Version 16.0) system organ class and preferred term.

Table V. Median time to onset of selected adverse events, and median time to adverse event resolution, by cohort

AE	Cohort	n	Median (95% CI) time to AE onset, d	Median (95% CI) AE duration/ time to resolution, d	No. (%) of patients with AE ongoing at study treatment end
Muscle spasm	1	19	34 (15-43)	61 (15-43)	1 (5)
	2	19	26 (21-39)	73 (63-85)	0 (0)
	3	18	27 (14-50)	114.5 (39-152)	3 (17)
Alopecia	1	8	114.5 (58-135)	64 (13-64)	5 (62.5)
	2	17	75 (60-95)	89 (59-165)	4 (24)
	3	18	67.5 (57-74)	134 (29-140)	16 (89)
Dysgeusia	1	9	24 (8-63)	63 (3-107)	2 (22)
	2	13	41 (19-54)	82 (59-123)	2 (15)
	3	15	26 (12-32)	NE (145-NE)*	11 (73)
Ageusia	1	10	20.5 (8-38)	108 (51-134)	3 (24)
	2	5	15 (6-35)	134 (76-150)	0 (0)
	3	7	15 (11-27)	124 (42-173)	4† (57)

Cohort 1 received vismodegib for 12 weeks; cohort 2 received vismodegib for 12 weeks, then 24 weeks of observation before excision; and cohort 3 received vismodegib for 8 weeks on/4 weeks off/8 weeks on.
AE, Adverse event; *CI*, confidence interval; *NE*, not estimable.
*Range, 36-181 days.
†One patient with ageusia in cohort 3 discontinued the study before the 4-wk treatment break.