Vismodegib in patients with advanced basal cell carcinoma (STEVIE): a pre-planned interim analysis of an international, open-label trial

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Summary

Background The Hedgehog pathway inhibitor vismodegib has shown clinical benefit in patients with advanced basal cell carcinoma and is approved for treatment of patients with advanced basal cell carcinoma for whom surgery is inappropriate. STEVIE was designed to assess the safety of vismodegib in a situation similar to routine practice, with a long follow-up.

Methods In this multicentre, open-label trial, adult patients with histologically confirmed locally advanced basal cell carcinoma or metastatic basal cell carcinoma were recruited from regional referral centres or specialist clinics. Eligible patients were aged 18 years or older with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and adequate organ function. Patients with locally advanced basal cell carcinoma had to have been deemed ineligible for surgery. All patients received 150 mg oral vismodegib capsules once a day on a continuous basis in 28-day cycles. The primary objective was safety (incidence of adverse events until disease progression or unacceptable toxic effects), with assessments on day 1 of each treatment cycle (28 days) by principal investigator and coinvestigators at the site. Efficacy variables were assessed as secondary endpoints. The safety evaluable population included all patients who received at least one dose of study drug. Patients with histologically confirmed basal cell carcinoma who received at least one dose of study drug were included in the efficacy analysis. An interim analysis was pre-planned after 500 patients achieved 1 year of follow-up. This trial is registered with ClinicalTrials.gov, number NCT01367665. The study is still ongoing.

Findings Between June 30, 2011, and Nov 6, 2014, we enrolled 1227 patients. At clinical cutoff (Nov 6, 2013), 499 patients (468 with locally advanced basal cell carcinoma and 31 with metastatic basal cell carcinoma) had received study drug and had the potential to be followed up for 12 months or longer. Treatment was discontinued in 400 (80%) patients; 180 (36%) had adverse events, 70 (14%) had progressive disease, and 51 (10%) requested to stop treatment. Median duration of vismodegib exposure was 36·4 weeks (IQR 17·7–62·0). Adverse events happened in 491 (98%) patients; the most common were muscle spasms (317 [64%]), alopecia (307 [62%]), dysgeusia (269 [54%]), weight loss (162 [33%]), asthenia (141 [28%]), decreased appetite (126 [25%]), ageusia (112 [22%]), diarrhoea (83 [17%]), nausea (80 [16%]), and fatigue (80 [16%]). Most adverse events were grade 1 or 2. We recorded serious adverse events in 108 (22%) of 499 patients. Of the 31 patients who died, 21 were the result of adverse events. As assessed by investigators, 302 (66·7%, 62·1–71·0) of 453 patients with locally advanced basal cell carcinoma had an overall response (153 complete responses and 149 partial responses); 11 (37·9%; 20·7–57·7) of 29 patients with metastatic basal cell carcinoma had an overall response (two complete responses, nine partial responses).

Interpretation This study assessed the use of vismodegib in a setting representative of routine clinical practice for patients with advanced basal cell carcinoma. Our results show that treatment with vismodegib adds a novel therapeutic modality from which patients with advanced basal cell carcinoma can benefit substantially.

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Introduction

Basal cell carcinoma is the most common non-melanoma skin cancer in human beings, arising more frequently than all other cancers combined in adult patients.[1,2] Although most basal cell carcinomas follow an indolent course and can be treated curatively with surgery, a small proportion progress to an advanced stage.[2] Advanced basal cell carcinoma is inconsistently classified, partly because of its rarity, the heterogeneity of complex cases of basal cell carcinoma, and the scarce treatment options available.[3–5]

Moreover, because 80% of sporadic basal cell carcinomas arise in the head and neck,[6] advanced disease is often disfiguring and associated with substantial morbidity. Surgery and radiotherapy might be contraindicated for advanced basal cell carcinoma, either because of the extent of disease leading to risk of deformity or loss of function, or because of patients' medical history (eg, patients with

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Research in context

Evidence before this study

Aberrant activation of the Hedgehog signalling pathway is a key driver in the pathogenesis of basal cell carcinoma, and vismodegib is the first Hedgehog pathway inhibitor approved for the treatment of advanced, inoperable basal cell carcinoma. The phase 2 study ERIVANCE BCC showed that vismodegib offered clinical activity in patients with advanced basal cell carcinoma who were not eligible for surgery. Recently, data have been presented for sonidegib, another Hedgehog pathway inhibitor. We searched Medline and Embase with the search terms "basal cell carcinoma", "hedgehog pathway inhibitor", "vismodegib", "sonidegib", and "LDE225" for peer reviewed papers and abstracts published in the past 5 years (between Jan 1, 2010, and March 1, 2015).

Added value of this study

In the STEVIE trial, comprising—to the best of our knowledge—the largest patient series reported with advanced basal cell carcinoma, the safety profile of vismodegib was consistent with that previously reported in other smaller vismodegib studies. Investigator-assessed responses were also consistent with those reported in the ERIVANCE BCC study, confirming proportions of tumour control.

Implications of all the available evidence

Vismodegib is tolerable and active in a population of patients with advanced basal cell carcinoma that is representative of patients treated in routine clinical practice. This study provides important safety and activity data associated with long-term vismodegib treatment.

basal cell naevus syndrome).[7,8] When surgery is inappropriate and patients cannot receive additional radiation therapy, Hedgehog pathway inhibitors can be a useful treatment option.

Aberrant activation of the Hedgehog signalling pathway is a key driver in the pathogenesis of basal cell carcinoma, with most basal cell carcinomas showing genetic alterations in pathway components.[9] Signalling mediated through the Hedgehog pathway is crucial for cell growth and differentiation during embryogenesis and early development, but is largely inactive in adults. The pathway is activated by the binding of Hedgehog ligand to PATCHED (PTCH1), a 12-pass transmembrane receptor, which relieves the inhibitory effects of PTCH1 on Smoothened (SMO), a seven-pass transmembrane protein and a member of the G-protein coupled receptor superfamily. Signal transduction by SMO leads to activation and nuclear localisation of GLI transcription factors and induction of target genes, many of which are involved in proliferation, survival, and differentiation. Most mutations in basal cell carcinoma are loss-of-function mutations in *PTCH1* (80–90%) or activating mutations in *SMO* (about 10%), resulting in constitutive pathway activation.[2,6]

Vismodegib is a first-in-class, oral, selective Hedgehog pathway inhibitor.[9,10] In a phase 2 study, 150 mg vismodegib once a day showed clinical benefit in patients with locally advanced or metastatic basal cell carcinoma who were not eligible for surgery, with 43% of patients achieving an objective response in locally advanced basal cell carcinoma and 30% in metastatic basal cell carcinoma by independent review (60% and 45%, respectively by investigator assessment), and median progression-free survival durations of 9·5 (IQR 7·2–12·8 for locally advanced basal cell carcinoma; 7·4–non-evaluable for metastatic basal cell carcinoma) months for both cohorts.[11,12] Although 51% of patients discontinued study treatment at data cutoff, a substantial proportion of patients achieved meaningful and durable responses with vismodegib. Vismodegib is the first Hedgehog pathway inhibitor approved for the treatment of advanced, inoperable basal cell carcinoma, and represents a promising new treatment option.[13] More recently, data for another Hedgehog pathway inhibitor (sonidegib) have been presented in patients with locally advanced or metastatic basal cell carcinoma.[14–16] Promising phase 1 data[14] resulted in a multicentre, randomised, double-blind phase 2 trial.[15]

The SafeTy Events in VIsmodEgib (STEVIE) study was designed to further assess the safety and efficacy of vismodegib in patients without other satisfactory treatment options. We report results of an interim analysis in 499 patients with the potential to be followed up for 12 months or longer.

Methods

Study design and patients

STEVIE is an ongoing, multicentre, open-label study being done at 167 regional referral centres and specialist clinics in 36 countries. Patient selection was established by investigators based on study eligibility criteria. Eligible patients were aged 18 years or older with histologically confirmed (per local guidelines) locally advanced basal cell carcinoma or metastatic basal cell carcinoma, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and adequate organ function. Patients with locally advanced basal cell carcinoma had to have been deemed ineligible for surgery (written confirmation from a surgical specialist that the tumour was deemed inoperable or that surgery was contraindicated). This definition included basal cell carcinoma that had recurred in the same location after two or more surgical procedures and curative resection was deemed unlikely, or if substantial morbidity or deformity from surgery was anticipated (eg, removal of all or part of a facial structure, such as nose, ear, eyelid,

eye; or requirement for limb amputation). Patients with measurable or non-measurable disease (per Response Evaluation Criteria in Solid Tumors [RECIST]; version 1.1) were allowed. Patients with basal cell naevus syndrome (Gorlin's syndrome) could enrol if all other criteria were met.

The study protocol was approved by the institutional review boards or independent ethics committees of participating study centres and the study was undertaken in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. An independent data safety monitoring board is monitoring patient safety on study. All patients provided written informed consent.

Procedures

All patients received 150 mg oral vismodegib capsules once a day on a continuous basis in 28-day cycles until disease progression, unacceptable toxic effects withdrawal of consent, death, or other reasons according to the treating physician. No dose reductions were allowed, but treatment interruption for up to 8 weeks was allowed for managing toxic effects. Adverse events were treated symptomatically and in accordance with local practices. No specific guidance on treatment of specific adverse events was provided to sites and investigators. Compliance was assessed by counts of unused capsules at each study visit.

Outcomes

The primary endpoint was safety (incidence of adverse events until disease progression or unacceptable toxic effects), with assessments on day 1 of each treatment cycle (28 days) by the principal investigator and co-investigators at the site. Assessments included adverse events, assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0), limited physical examination (ie, restricted to assessment of specific systems or areas of interest, including those with previously abnormal findings or associated with symptomatic or laboratory evidence of toxic effects), vital signs, ECOG performance status, and laboratory parameters.

Secondary endpoints included investigator-assessed objective response based on clinical assessments according to RECIST (version 1.1; complete response defined as the disappearance of all target lesions, any pathological lymph nodes [target or non-target] needed to have a reduction in short axis to less than 10 mm and partial response defined as at least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters[17]), duration of response, time to response, progression-free survival, overall survival, and quality of life assessed by Skindex-16. We assessed measurable tumours accessible by physical examination every 4 to 8 weeks. If necessary, CT and MRI scans were done every 8 to 16 weeks. RECIST assessments from the investigators were reviewed by Roche against the tumour measurements reported; there was no central review.

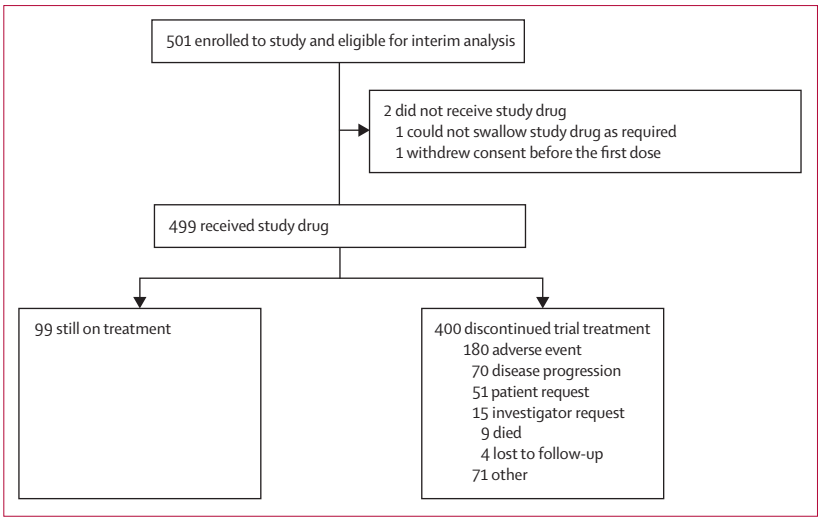

Figure 1: **Trial profile**
The most common reasons for "other" included complete response (42 [8%]), patient request to discontinue but agreed to continue in follow-up (n=9 [2%]), non-compliance (4 [<1%]), and protocol violation (3 [<1%]).

Statistical analysis

The planned sample size was roughly 1200 patients to provide an adequate safety database and allow the adverse event incidence rate to be estimated within 1·6–1·8% of the true adverse event rate, assuming an observed incidence of 10% (ie, within a 95% Clopper-Pearson CI of 8·4–11·8) and with a precision to estimate an adverse event of 1% frequency to within a frequency of 0·5 to 1% of the true adverse event rate. Overall recruitment for STEVIE has been completed, with 1227 patients enrolled between June 30, 2011, and Nov 6, 2014. The primary analysis will be done when roughly 1200 patients have the potential to be followed for at least 1 year.

This interim analysis was pre-specified to include available safety and efficacy data from 500 enrolled patients with the potential to be followed for 12 months or longer at clinical cutoff (Nov 6, 2013). The evaluable safety population included all patients who received at least one dose of study drug. We included patients with histologically confirmed basal cell carcinoma who received at least one dose of study drug in the analysis of progression-free survival. Patients with histologically confirmed, measurable basal cell carcinoma who received at least one dose of study drug were included in all other efficacy analyses. No hypothesis tests were planned for either the basal cell carcinoma or basal cell carcinoma subpopulations. We used SAS (version 9.2) for statistical analyses.

This trial is registered with ClinicalTrials.gov, number NCT01367665.

	All patients (n=499)	Locally advanced (n=468)	Metastatic (n=31)
Men	297 (60%)	278 (59%)	19 (61%)
Women	202 (40%)	190 (41%)	12 (39%)
Women of childbearing potential*	29 (14%)	27 (14%)	2 (17%)
Age (years)	72·0 (57–83)	72·0 (57–83)	63·0 (58–73)
<65 years	192 (38%)	175 (37%)	17 (55%)
≥65 years	307 (62%)	293 (63%)	14 (45%)
Time since first diagnosis (years)	8·20 (2·47–17·67)	7·89 (2·29–17·77)	9·87 (5·20–16·07)
Histologically confirmed diagnosis			
Yes	497 (99·6%)	466 (99·6%)	31 (100%)
No	2 (0·4%)	2 (0·4%)	0 (0%)
Ineligibility for surgery			
Inoperable	204/468 (44%)	204 (44%)	..
Surgery contraindicated	264/468 (56%)	264 (56%)	..
Unlikely to be curatively resected	121/468 (26%)	121 (26%)	..
Risk of substantial morbidity and/or deformity	141/468 (30%)	141 (30%)	..
Other†	39/468 (8%)	39 (8%)	..
Previous radiotherapy			
Yes	134 (27%)	113 (24%)	21 (68%)
No	365 (73%)	355 (76%)	10 (32%)
Inappropriate	220 (44%)	216 (46%)	4 (13%)
Contraindicated	145 (29%)	139 (30%)	6 (19%)
Sites of disease			
Skin	474 (95%)	462 (99%)	12 (39%)
Extremity	67 (13%)	65 (14%)	2 (6%)
Head	369 (74%)	365 (78%)	4 (13%)
Neck	58 (12%)	54 (12%)	4 (13%)
Trunk	110 (22%)	106 (23%)	4 (13%)
Other skin	86 (17%)	82 (18%)	4 (13%)
Lymph nodes	8 (2%)	0	8 (26%)
Lymph nodes locoregional	1 (<1%)	1 (<1%)	0
Bone	11 (2%)	0	11 (35%)
Lung	20 (4%)	0	20 (64%)
Liver	4 (<1%)	0	4 (13%)
Other site	13 (3%)	7 (2%)	6 (19%)
Unknown site	1 (<1%)	1 (<1%)	0
Disease status‡			
Measurable	484 (97%)	455 (97%)	29 (94%)
Non-measurable	14 (3%)	12 (3%)	2 (6%)
Number of target lesions at baseline	484 (1, 1–5)	455 (1, 1–5)	29 (2, 1–5)
Gorlin's syndrome§			
Yes	98/485 (20%)	96/454 (21%)	2/31 (6%)
No	387/485 (80%)	358/454 (79%)	29/31 (94%)
ECOG performance status			
0	309 (62%)	296 (63%)	13 (42%)
1	128 (26%)	117 (25%)	11 (36%)
2	62 (12%)	55 (12%)	7 (23%)

Data are n (%), n (median, IQR). ECOG=Eastern Cooperative Oncology Group.*Percentages are calculated based on number of females. †Patients who refused surgery or had other contraindications for medical or surgical reasons. ‡One patient (<1%) had an unknown disease status. This patient was in the locally advanced basal cell carcinoma population. §Gorlin syndrome was captured in medical history only, with no formal diagnosis made on study. Gorlin syndrome status was missing for eight patients and unknown for six. All 14 patients had locally advanced basal cell carcinoma.

Table 1: **Baseline characteristics and demographics of all patients given study drug**

Role of the funding source

This study was designed by the investigators and representatives of the funder. Funder representatives participated in study design, study steering committee meetings, gathering, analysis, or interpretation of the data, writing of the report, and had access to the raw data. The funder was responsible for data gathering and analysis. All authors contributed to the interpretation of the data and subsequent writing, reviewing, and amendment of the manuscript. The funder funded writing and editorial support. All authors vouch for the accuracy and completeness of the reported data and attest that the study conformed to the protocol and statistical analysis plan. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between June 30, 2011, and Nov 6, 2013, 1227 patients were enrolled in 17 countries (Australia, Austria, Belgium, Bulgaria, Canada, Denmark, France, Germany, Israel, Italy, the Netherlands, New Zealand, Russia, Spain, Sweden, Switzerland, and the UK; appendix) At clinical cutoff (Nov 6, 2013), 499 patients (468 with locally advanced basal cell carcinoma and 31 with metastatic basal cell carcinoma) had received study drug and had the potential to be followed up for 12 months or longer (figure 1). 468 (94%) of 499 patients who received study treatment had locally advanced basal cell carcinoma and 31 (6%) had metastatic basal cell carcinoma. Table 1 shows baseline characteristics. At the time of clinical cutoff, 99 (20%) patients were receiving ongoing treatment with vismodegib. The median duration of exposure to vismodegib was 36·4 weeks (IQR 17·7–62·0); 36·3 weeks (17·6–60·0) for locally advanced basal cell carcinoma, and 52·0 weeks (23·3–76·0) for metastatic basal cell carcinoma. Treatment was discontinued in 400 (80%) patients (figure 1).

Most patients (491 [98%] of 499) had at least one adverse event; the most common were muscle spasms (317 [64%]), alopecia (307 [62%]), dysgeusia (269 [54%]), weight loss (162 [33%]), asthenia (141 [28%]), decreased appetite (126 [25%]), ageusia (112 [22%]), diarrhoea (83 [17%]), nausea (80 [16%]), and fatigue (80 [16%]; appendix). Table 2 summarises the most common treatment-emergent adverse events in 10% or more of patients by severity. For all patients, median time to first onset of common adverse events irrespective of grade were 2·83 months (95% CI 2·30–3·68) for muscle spasms, 5·55 months (4·86–5·75) for alopecia, and 6·51 months (3·71–9·56) for dysgeusia. Eight (28%) of the 29 women of childbearing potential had eight events of irregular menses or amenorrhea. We recorded serious adverse events in 108 (22%) of 499 patients. At the clinical cutoff, three events had resolved after discontinuation of vismodegib and five events were ongoing. Adverse events leading to discontinuation of vismodegib were grades 1

or 2 in 106 (21%) of 499 patients and grades 3 (56 [11%]) or 4 (11 [2%]) in 499 patients.

The most common adverse events leading to treatment discontinuation were muscle spasms (44 [9%]), dysgeusia (29 [6%]), weight loss (24 [5%]), asthenia (22 [4%]), alopecia (21 [4%]), decreased appetite (19 [4%]), ageusia (14 [3%]), and fatigue (12 [2%]). Response data were available for 103 of the 106 patients who discontinued because of a grade 1–2 adverse events. 75 (73%) of 103 patients had achieved complete or partial response before discontinuation, and of these 48 (47%) had achieved a complete response. As expected, because of a longer follow-up, there was a higher incidence of common adverse events (all grades) in patients given vismodegib for 12 months or longer compared with those given the drug for less than 12 months (table 3). These adverse events were generally grade 1 or 2, and most common adverse events were attributed to vismodegib. The incidences of grade 3 or worse adverse events occurring in patients given vismodegib for less than 12 months, and in those given the drug for 12 months or longer were similar (130 [41%] of 314 patients *vs* 84 [45%] of 185 patients), and we recorded no clinically relevant differences except for weight decrease (four [1%] *vs* 14 [8%]). To adjust for exposure and compare adverse events arising during the first year of treatment with those after this, we did an additional, post-hoc analysis of rates of adverse events per 100 patient-years occurring with vismodegib treatment for less than 12 months, and 12 months or longer. Adverse events were lower after 12 months or longer of exposure (appendix). Serious adverse events were reported in 108 (22%) of 499 patients, with the most common being pneumonia (nine [2%]), general physical health deterioration (seven [1%]), squamous cell carcinoma (five [1%]), and dehydration (five [1%]).

At clinical cutoff, 31 (6%) of 499 patients had died. 21 deaths were attributed to adverse events, five to progressive disease (three locally advanced basal cell carcinoma and two metastatic basal cell carcinoma), and five to other reasons, including deterioration in general health status (two patients), and old age, cardiac decompensation, and multi-organ failure (one patient each). 19 (90%) of 21 deaths were deemed unrelated to vismodegib by the investigator. Two cases were assessed to be possibly treatment-related due to the timing between the onset of event and administration of vismodegib. Nevertheless, both events were recorded in patients with confounding medical histories (cardiorespiratory arrest 29 days after vismodegib discontinuation in an 86-year-old man with chronic lymphocytic leukaemia and myocardial infarction 301 days after the initiation of vismodegib and 2 days after the most recent dose in a 54-year-old patient with a history of pulmonary embolism). These deaths were reviewed and adjudicated by an independent data safety monitoring board and were deemed not assessable because of insufficient clinical data; however, both were thought unlikely to be related to vismodegib.

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Any	85 (17%)	191 (38%)	170 (34%)	23 (5%)	21 (4%)
Muscle spasms	165 (33%)	114 (23%)	38 (8%)	0	0
Alopecia	178 (36%)	127 (25%)	2 (<1%)	0	0
Dysgeusia	156 (31%)	102 (20%)	11 (2%)	0	0
Asthenia	76 (15%)	51 (10%)	12 (2%)	1 (<1%)	1 (<1%)
Decreased appetite	76 (15%)	39 (8%)	11 (2%)	0	0
Weight decreased	72 (14%)	71 (14%)	17 (3%)	1 (<1%)	0
Diarrhoea	64 (13%)	16 (3%)	3 (<1%)	0	0
Nausea	59 (12%)	20 (4%)	1 (<1%)	0	0
Ageusia	55 (11%)	46 (9%)	10 (2%)	1 (<1%)	0
Fatigue	50 (10%)	18 (4%)	11 (2%)	1 (<1%)	0

Data are n (%). Treatment-emergent adverse events were defined as occurring between the first administration of study drug and 30 days after the last administration of study drug, inclusive. Patients were counted only once with each preferred term for the most severe case of that preferred term.

Table 2: **Most common treatment-emergent adverse events in ≤10% patients by severity (n=499)**

	All TEAEs		Grade 3–5 TEAEs	
	<12 months' exposure (n=314)	≥12 months' exposure (n=185)	<12 months' exposure (n=314)	≥12 months' exposure (n=185)
Any TEAE	307 (98%)	184 (99%)	130 (41%)	84 (45%)
Muscle spasms	169 (54%)	148 (80%)	21 (7%)	17 (9%)
Alopecia	154 (49%)	153 (83%)	1 (<1%)	1 (<1%)
Dysgeusia	139 (44%)	130 (70%)	8 (3%)	3 (2%)
Weight loss	80 (25%)	82 (44%)	4 (1%)	14 (8%)
Asthenia	76 (24%)	65 (35%)	9 (3%)	5 (3%)
Decreased appetite	74 (24%)	52 (28%)	7 (2%)	4 (2%)
Ageusia	75 (24%)	37 (20%)	6 (2%)	5 (3%)
Fatigue	50 (16%)	30 (16%)	9 (3%)	3 (2%)
Nausea	38 (12%)	42 (23%)	0	1 (<1%)
Diarrhoea	32 (10%)	51 (28%)	1 (<1%)	2 (1%)

Data are n (%). For the most common treatment-emergent adverse events (TEAEs) of any grade, event occurring in 10% or more of patients are reported. Events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version (version 4.0).

Table 3: **Incidence of treatment-emergent adverse events according to duration of vismodegib exposure (≥12 months *vs* <12 months; n=499)**

	All patients (n=482*)	Patients with locally advanced basal cell carcinoma (n=453)	Patients with metastatic basal cell carcinoma (n=29)
Complete	155 (32%)	153 (34%)	2 (7%)
Partial	158 (33%)	149 (33%)	9 (31%)
Stable disease	128 (27%)	118 (26%)	10 (34%)
Progressive disease	15 (3%)	11 (2%)	4 (14%)
Missing/not evaluable	26 (5%)	22 (5%)	4 (14%)

Data are n (%). *Excludes patients without histologically confirmed disease (n=3) and without measurable disease (n=14).

Table 4: **Best response to treatment**

See Online for appendix

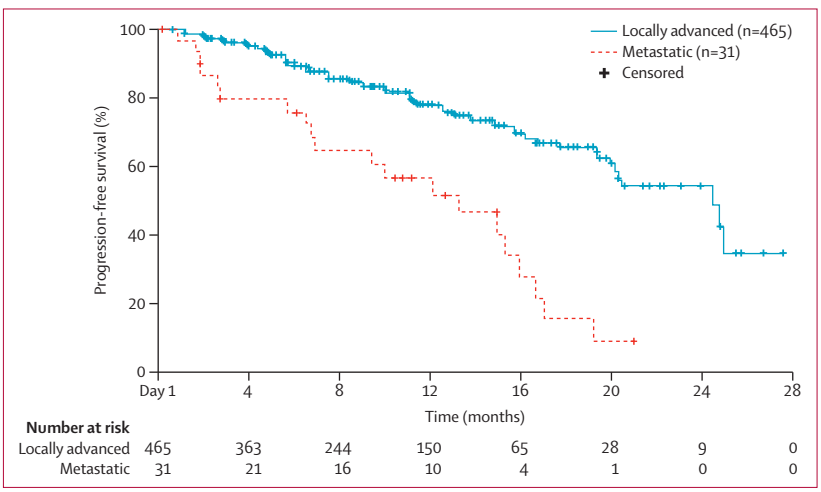

Figure 2: **Kaplan-Meier plot of progression-free survival in patients who had histologically confirmed basal cell carcinoma**

Of the 482 patients with RECIST-measurable disease, investigator-assessed best responses were noted in 313 (64·9%, 95% CI 60·5–69·2) patients, with objective responses in 302 (66·7%; 62·1–71·0) of 453 patients with locally advanced basal cell carcinoma and 11 (37·9%, 20·7–57·7) of 29 with metastatic basal cell carcinoma (table 4). Of 14 patients with non-measurable disease at baseline (assessed by RECIST [version 1.1] and allowed as per the protocol), three (21%) had objective responses (two [17%] of 12 patients with locally advanced basal cell carcinoma and one [50%] of two patients with metastatic basal cell carcinoma). All three of these objectives responses were complete responses. In the combined population with a response, median time to response was 2·7 months (95% CI 2·0–2·8), with a median duration of 22·7 months (95% CI 16·8–NE). In patients with locally advanced basal cell carcinoma experiencing a response, median time to best response was 2·6 months (95% CI 2·0–2·8) and median duration of response was 22·7 months (95% CI 16·8–NE). In patients with metastatic basal cell carcinoma experiencing a response, median time to best response was 2·8 months (95% CI 1·8–3·7) and median duration of response was 10·0 months (95% CI 5·7–NE). Treatment with vismodegib was consistently associated with clinically meaningful improvement in the emotional domain of the Skindex-16 questionnaire in patients with locally advanced basal cell carcinoma (data not shown).

At the clinical cutoff date (Nov 6, 2013), median progression-free survival in the intention-to-treat population (n=496) was 20·2 months (95% CI 19·3–NE); it was 24·5 months (95% CI 20·1–NE) in patients with locally advanced basal cell carcinoma and 13·1 months (95% CI 6·7–15·7) in patients with metastatic basal cell carcinoma (figure 2). Because of a low number of events and limited survival follow-up, overall survival data were not deemed mature and are, therefore, not presented; of note, of 31 deaths so far, 28 were patients with locally advanced basal cell carcinoma and three were patients with metastaic basal cell carcinoma. Median follow-up was 12·7 months (95% CI 12·1–13·3) in patients with locally advanced basal cell carcinoma and 12·9 months (9·6–17·8) in patients with metastatic basal cell carcinoma.

Discussion

This interim analysis of the STEVIE trial is, to the best of our knowledge, the largest patient series ever reported with advanced basal cell carcinoma and provides important safety and efficacy data associated with long-term vismodegib treatment. The recorded safety profile is consistent with the safety profile of vismodegib recorded in earlier analyses of this study and in other studies of vismodegib in patients with advanced basal cell carcinoma;[11,12] we recorded no new safety signals. Common adverse events included muscle spasms, alopecia, dysgeusia, weight decreased, asthenia, decreased appetite, ageusia, diarrhoea, fatigue, and nausea. Preliminary findings from other Hedgehog pathway inhibitors in development, such as sonidegib, show similar adverse events including muscle spasms, alopecia, and taste disturbances (dysgeusia or ageusia).[14–16] These are deemed to be class effects associated with on-target inhibition of the Hedgehog signalling pathway.[2] Adverse events leading to discontinuation were mainly mild or moderate, and commonly associated with vismodegib treatment, conforming with previously described patterns of discontinuation of vismodegib due to the chronic and cumulative nature of low-grade toxic effects.[2] Most patients who discontinued because of grade 1 or 2 adverse events had experienced response before discontinuation, which might have affected the decision for discontinuation due to an adverse event. To minimise patient dropout due to adverse events, especially for patients who need long-term treatment, clinical activities are in progress to assess whether alternative dosing regimens could increase tolerability (eg, in patients with several basal cell carcinomas, including patients with Gorlin's syndrome; MIKIE study [NCT01815840]).[18] Fatal adverse events were recorded in 21 patients, two of which were deemed potentially related to study treatment by the investigator. The study was done in elderly patients; a review of all deaths suggested no definite pattern, and all patients who died on study had significant comorbidities and risk factors. The patient safety on study is monitored by the data safety monitoring board.

Onset of the most common adverse events was typically within the first 6 months of treatment. With increasing exposure (ie, in those given vismodegib for ≥12 months), common adverse events generally occurred at a higher rate compared with those treated for less than 12 months. However, most adverse events remained mild or moderate in severity. The incidence of grade 3–5 adverse events was similar in patients given vismodegib for 12 months or longer and those given the drug for less than 12 months

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with the exception of weight decrease, which was more frequent in patients receiving long-term treatment. These data suggest that long-term exposure does not lead to increased severity of adverse events, although nutrition care should be advised.

In this interim analysis, vismodegib showed similar clinical activity to that recorded in the pivotal ERIVANCE BCC study.[12] Durable reduction in skin tumours, which are unresectable and often disfiguring, has been considered a direct clinical benefit[19] and led to the approval of vismodegib in the USA and the EU. The proportions of patients with an investigator-assessed overall response were consistent with those in the ERIVANCE BCC primary analysis (60% and 45%, respectively) and the 30-month (final) analysis of the ERIVANCE BCC study (60% and 49%, respectively),[20] despite differences in the method of response assessment between the two studies. In ERIVANCE BCC, metastatic basal cell carcinoma was assessed by RECIST (version 1.0), whereas locally advanced basal cell carcinoma was assessed by a composite endpoint of radiographic imaging, physical examination, and histological assessment based on RECIST. Response duration and progression-free survival noted here also seemed to compare favourably with the investigator-assessed final analysis of the ERIVANCE BCC study,[20] although data are not yet fully mature. Although the median duration of exposure was relatively short, at 36·4 weeks, the median duration of response was 22·7 months, which is clinically meaningful in this patient population with advanced basal cell carcinoma and no other treatment options. Nonetheless, patients with advanced basal cell carcinoma will progress, and further treatments are needed for patients who become resistant to vismodegib. A limitation of the present analysis is the absence of independent central review, which was used in ERIVANCE BCC,[12] and lack of subset analysis of Gorlin's syndrome patient subset—analysis of this subpopulation will be done with the primary analysis.

Because of the lack of a widely used uniform staging system and uniform reporting guidelines for non-melanoma skin cancer, little is known about patients with advanced basal cell carcinoma. However, efforts are underway to further describe this population. Demographic comparisons of this study with the US disease registry and the scientific literature[4] confirm similarities, suggesting that experiences from the STEVIE safety study might be similar to those encountered in clinical practice.[21,22]

The care of patients with advanced basal cell carcinoma and assessment of patient eligibility for treatment with vismodegib and other Hedgehog pathway inhibitors needs a multidisciplinary approach. Close follow-up of patients after treatment initiation is necessary to manage side-effects and assess continued benefit to treatment. Patients might experience prolonged response after treatment discontinuation or could receive additional treatment including surgery.[23,24] Treatment with vismodegib might lead to tumour shrinkage and reduce the basal cell carcinoma surgical defect area before surgery;[25–27] however, further research will be needed to define optimum combination of vismodegib with surgical approaches.

In conclusion, interim results of the STEVIE study show that vismodegib is tolerable in a patient population that is representative of patients treated in routine clinical practice with a safety profile consistent with that previously reported in other studies.[9,10] Investigator-assessed response rates are consistent with those reported in the ERIVANCE BCC study and confirm rates of tumour control.

Contributors

NB-S, AH, and JH designed the study; AH, J-JG, RK, BD, LM, PAA, LL, CD, LT, TJ, NM, BG, RD, KF, DSE, and JH collected data; NB-S, AH, J-JG, RK, BD, LM, PAA, LL, LT, TJ, NM, RD, KF, DSE, SW, AF, IX, JH analysed and interpreted data; and NB-S, AH, J-JG, RK, BD, LM, PAA, LL, CD, LT, TJ, NM, BG, RD, KF, DSE, SW, AF, IX, and JH contributed to writing the report.

Declaration of interests

NB-S was a visiting scientist at Genentech (February to September, 2014) and reports personal fees from consulting for Roche and being an investigator for Roche trials. AH reports personal fees from consulting for Amgen, Bristol-Myers Squibb, Celgene, Eisai, GlaxoSmithKline, Medimmune, MelaSciences, Merck Serono, MSD and Merck, Novartis, Oncosec, and Roche Pharma, honoraria for Amgen, Bristol-Myers Squibb, Celgene, Eisai, GlaxoSmithKline, Medimmune, MelaSciences, Merck Serono, MSD and Merck, Novartis, Oncosec, and Roche Pharma, and grants for Amgen, Bristol-Myers Squibb, Celgene, Eisai, GlaxoSmithKline, MelaSciences, Merck Serono, MSD and Merck, Novartis, Oncosec, and Roche Pharma. J-JG reports personal fees for advisory boards for Novartis, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Meda, and Electra. RK reports personal fees from Hoffmann-La Roche, personal fees from Menarini Pharma, personal fees from Novartis, outside the submitted work. BD reports personal fees from Roche, outside the submitted work. LM reports personal fees from Roche during the conduct of the study. PAA reports grants and personal fees from Bristol-Myers Squibb, grants and personal fees from Roche-Genentech, personal fees and non-financial support from Merck Sharp & Dohme, personal fees from Glaxo SmithKline, grants and personal fees from Ventana, personal fees from Novartis, personal fees from Amgen, outside the submitted work. LL reports personal fees from Eisai, Bristol-Myers Squibb, Amgen, Boehringer Ingelheim, Merck Serono, DebioPharm, VentiRx, AstraZeneca, SOBI, Novartis, Bayer, GlaxoSmithKline, Lilly, and grants from Eisai, Exelixis, Amgen, Boehringer Ingelheim, Merck Serono, Pfizer, AstraZeneca, Novartis, Roche, Lilly, and other from Merck Serono, DebioPharm, SOBI, Bayer, outside the submitted work. TJ reports investigator funds for Roche. NM reports personal fees from Roche, outside the submitted work. BG reports personal fees from Roche, during the conduct of the study; personal fees from Bristol-Myers Squibb, personal fees from MSD, personal fees from Leo Pharma, outside the submitted work. RD reports grants and other from Roche, grants and other from Bristol-Myers Squibb, and grants and an advisory and consultant relationship with GlaxoSmithKline, Novartis, and MSD, outside the submitted work. KF reports grants from Roche during the conduct of the study, personal fees from Roche, personal fees from Roche, personal fees from GlaxoSmithKline, non-financial support from Roche, non-financial support from Novartis, outside the submitted work. DSE reports personal fees from Roche, outside the submitted work. SW, AF, and IX report salary from Roche. JH reports personal fees from Roche, personal fees from GlaxoSmithKline, personal fees from Bristol-Myers Squibb, personal fees from Novartis, during the conduct of the study. CD and LT declare no competing interests.

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