Treatment with two different doses of sonidegib in patients with locally advanced or metastatic basal cell carcinoma (BOLT): a multicentre, randomised, double-blind phase 2 trial

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Lancet Oncology 2015

Published Online
May 14, 2015
http://dx.doi.org/10.1016/S1470-2045(15)70100-2

See Online/Comment
http://dx.doi.org/10.1016/S1470-2045(15)70233-0

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Summary

Background Patients with advanced basal cell carcinoma have limited treatment options. Hedgehog pathway signalling is aberrantly activated in around 95% of tumours. We assessed the antitumour activity of sonidegib, a Hedgehog signalling inhibitor, in patients with advanced basal cell carcinoma.

Methods BOLT is an ongoing multicentre, randomised, double-blind, phase 2 trial. Eligible patients had locally advanced basal cell carcinoma not amenable to curative surgery or radiation or metastatic basal cell carcinoma. Patients were randomised via an automated system in a 1:2 ratio to receive 200 mg or 800 mg oral sonidegib daily, stratified by disease, histological subtype, and geographical region. The primary endpoint was the proportion of patients who achieved an objective response, assessed in the primary efficacy analysis population (patients with fully assessable locally advanced disease and all those with metastatic disease) with data collected up to 6 months after randomisation of the last patient. This trial is registered with ClinicalTrials.gov, number NCT01327053.

Findings Between July 20, 2011, and Jan 10, 2013, we enrolled 230 patients, 79 in the 200 mg sonidegib group, and 151 in the 800 mg sonidegib group. Median follow-up was 13·9 months (IQR 10·1–17·3). In the primary efficacy analysis population, 20 (36%, 95% CI 24–50) of 55 patients receiving 200 mg sonidegib and 39 (34%, 25–43) of 116 receiving 800 mg sonidegib achieved an objective response. In the 200 mg sonidegib group, 18 (43%, 95% CI 28–59) patients who achieved an objective response, as assessed by central review, were noted among the 42 with locally advanced basal cell carcinoma and two (15%, 2–45) among the 13 with metastatic disease. In the 800 mg group, 35 (38%, 95% CI 28–48) of 93 patients with locally advanced disease had an objective response, as assessed by central review, as did four (17%, 5–39) of 23 with metastatic disease. Fewer adverse events leading to dose interruptions or reductions (25 [32%] of 79 patients *vs* 90 [60%] of 150) or treatment discontinuation (17 [22%] *vs* 54 [36%]) occurred in patients in the 200 mg group than in the 800 mg group. The most common grade 3–4 adverse events were raised creatine kinase (five [6%] in the 200 mg group *vs* 19 [13%] in the 800 mg group) and lipase concentration (four [5%] *vs* eight [5%]). Serious adverse events occurred in 11 (14%) of 79 patients in the 200 mg group and 45 (30%) of 150 patients in the 800 mg group.

Interpretation The benefit-to-risk profile of 200 mg sonidegib might offer a new treatment option for patients with advanced basal cell carcinoma, a population that is difficult to treat.

Funding Novartis Pharmaceuticals Corporation.

Introduction

Aberrant activation of Hedgehog pathway signalling plays an important part in the pathogenesis of basal cell carcinoma,[1–3] which is the most commonly diagnosed cancer in fair-skinned individuals worldwide.[4–6] Most sporadic basal cell carcinomas have mutations in *PTCH1* (more than 85%) or *SMO* (around 10%) that lead to activation of signalling and expression of the Hedgehog pathway and its targets, including *GLI* family transcription factors.[1–3]

Most basal cell carcinomas are effectively treated with topical therapy, surgery, radiotherapy, or a combination of these,[4,6,7] but, treatment of locally advanced disease with large, neglected, and locally aggressive or recurrent tumours or metastatic disease is challenging.[5,8] Patients with advanced basal cell carcinoma might have substantial morbidity and disfigurement caused by tissue invasion and destruction.[5] Treatment options for these patients are limited and include the *SMO* inhibitor vismodegib,[9–11] chemotherapy, or a clinical trial.[4,6,7]

Sonidegib blocks Hedgehog signalling by selective inhibition of *SMO* expression.[12,13] This drug showed antitumour activity in patients with advanced basal cell carcinoma in a phase 1 study.[14] Exposure to the drug increased proportionally with low-dose increases (100, 200, and 400 mg daily) but less than proportionally at

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higher doses up to 3000 mg daily.[14] The Basal cell carcinoma Outcomes with LDE225 Treatment (BOLT) trial was started to assess the safety and antitumour activity of two doses of sonidegib, 200 mg and 800 mg daily, in patients with advanced disease. We report here the results of the BOLT primary analysis, which was based on data collected up to 6 months after randomisation of the last patient.

Methods

Study design and patients

BOLT is an ongoing multicentre, randomised, double-blind, phase 2 study that is being done in 58 centres in 12 countries (appendix).

Eligible patients were aged 18 years or older and had histologically confirmed, locally advanced basal cell carcinoma not amenable to radiotherapy or curative surgery, or metastatic basal cell carcinoma for which all existing available treatment options had been exhausted, and a WHO status grade of 0 (capable of all normal activity), 1 (ambulatory and capable of some light work but restricted in physically strenuous activity), or 2 (ambulatory, mobile more than 50% of waking hours, and capable of all self-care but unable to work).[15] Other inclusion criteria were adequate bone marrow (absolute neutrophil count $1·5\times10^9$ cells per L or higher, haemoglobin 90 g/L or higher, and platelet count of 100×10^9 cells per L or higher), liver function (total bilirubin concentration in serum no greater than 1·5 times the upper limit of normal (ULN); aspartate aminotransferase and alanine aminotransferase no greater than 2·5 times the ULN or no more than 5·0 times the ULN in patients with liver metastases), and renal function (creatine kinase concentration in serum no greater than 1·5 times the ULN; creatinine concentration in serum no greater than 1·5 times the ULN or 24 h creatinine clearance of 0·84 mL/s per m² or greater). Further details on eligibility are provided in the appendix. Exclusion criteria were previous treatment with sonidegib or another Hedgehog pathway inhibitor, major surgery, other antineoplastic therapy, having taken an investigational agent within 4 weeks before the start of the study or currently taking strong inhibitors or inducers of CYP3A4 or CYP3A5 expression or drugs metabolised by CYP2B6 or CYP2C9; gastrointestinal dysfunction or known malabsorption syndromes, neuromuscular disorders, or other uncontrolled medical disorders; treatment with drugs known to cause rhabdomyolysis (eg, statins), although use of pravastatin was allowed with extra caution; and pregnancy or breastfeeding. All patients were required to use highly effective methods of contraception throughout the study and for 6 months after the last treatment.

All patients were referred by their physicians and provided written informed consent before enrolment. The protocol and amendments were approved by the institutional review board, independent ethics committee, or research ethics board at each centre. The study was done in accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice and the Declaration of Helsinki.

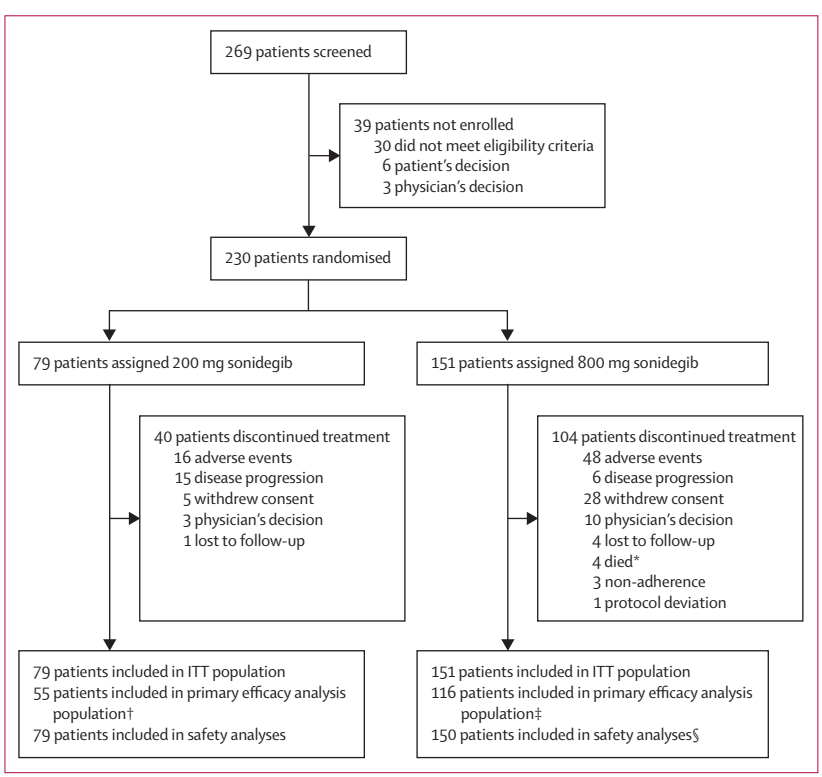

Figure 1: **Trial profile**
ITT=intention to treat. *Two patients with clinically important cardiac risk factors at baseline died of congestive cardiac failure (day 17) and cardiac death (day 196) and two died owing to disease progression on days 16 and 38. †24 patients excluded because of incomplete standard and annotated photographic assessments (n=12), no MRI at baseline (n=7), or both (n=5). ‡35 patients excluded because of incomplete standard and annotated photographic assessments (n=23), no MRI at baseline (n=7), or both (n=5). §One patient not treated was excluded from the safety analyses.

Randomisation and masking

At the start of the trial, no active comparator drug was available and the use of a placebo group was not ethical in view of the preliminary activity reported in the phase 1 study.[14] Therefore, we decided to assess two doses of sonidegib. The 200 mg dose was the lowest dose tested that yielded exposure in the predicted active range and showed anti-tumour activity. The 800 mg dose was the highest well tolerated, biologically active dose in a continuous, once-daily dosing regimen.

On the basis of the phase 1 data on dose-dependent and exposure-dependent *GLI1* inhibition,[14] 200 mg sonidegib once daily was predicted to be less active than 800 mg once daily and, therefore, we randomly assigned patients to these doses in a 1:2 ratio. Randomisation was stratified by disease state (locally advanced *vs* metastatic), histological subtype for locally advanced disease (non-aggressive *vs* aggressive), and geographical region. An independent provider (Cenduit, Allentown, PA, USA) produced a randomisation list that the sites could access

online or via a voice-activated telephone system, from which patients were automatically assigned numbers linked to treatment groups and medication. The funder used a separate randomisation list to assign numbers to treatment packs. The patients, investigators or site staff, and the funder were unaware of dose allocations from the time of randomisation until the primary analysis. Unmasking was permitted if a second dose modification was deemed necessary or in the case of an emergency where knowledge of treatment might be required to ensure a patient's wellbeing. The packaging and labelling, appearance, odour, and dosing schedules were identical for both doses of sonidegib.

Procedures

Patients received 200 mg or 800 mg sonidegib orally once daily on a continuous dosing schedule. Dose escalation was not allowed. Dose interruptions of 21 days or fewer, or dose reductions were permitted for toxic effects deemed to be related to study treatment (appendix). For patients in the 800 mg group, a maximum of two dose reductions were allowed—first to 400 mg once daily, and then to 200 mg once daily. For patients in the 200 mg group, one dose reduction was allowed, which was to the matched placebo. Patients continued taking study treatment until documented disease progression (as confirmed by independent central review), intolerable toxic effects, withdrawal of consent, death, discontinuation at an investigator's discretion, dose interruption lasting longer than 21 days (unless the patient was responding to study treatment and had not progressed, in which case resumption of treatment was permitted at the investigator's discretion), use of a prohibited medication, start of another antineoplastic therapy, or study termination. Surgery, radiation therapy, and other investigational therapies were not allowed during study treatment. Medications to treat adverse events or manage cancer symptoms or concurrent stable disease and supportive care agents were permitted. End-of-treatment assessments included tumour response, collection of information on any antineoplastic therapies, and safety (up to 30 days).

Tumour assessments were done by the central review committee and investigators at baseline and at weeks 5 and 9 after treatment start, then every 8 weeks during year 1, every 12 weeks thereafter, and at the time of treatment discontinuation. We used modified Response Criteria In Solid Tumors (RECIST) to assess patients with locally advanced basal cell carcinoma and RECIST version 1.1[16] to assess those with metastatic basal cell carcinoma. Owing to potential ulceration, cyst formation, scarring, or fibrosis, and ill-defined lesion borders after treatment, RECIST version 1.1 is inadequate for assessment of response in patients with locally advanced disease. The modified RECIST complements the MRI findings used in RECIST version 1.1[16] with standard and annotated colour photography, as required by the bidimensional WHO guidelines (response defined as at least a 50% reduction in the sum of the products of perpendicular diameters)[15] and histology of multiple biopsy samples based on lesion surface area to assess depth, length, and width of lesions and granularity (appendix). An independent review committee reassessed all results for locally advanced basal cell carcinoma. Fresh tumour biopsy samples were taken to confirm complete responses or if response assessment was confounded by the presence of ulceration, cysts, scarring, or fibrosis, or a combination of these.

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See Online for appendix

	200 mg sonidegib (n=79)	800 mg sonidegib (n=151)
Age (years)	67 (25–92)	65 (24–93)
Age ≥65 years	47 (59%)	78 (52%)
Sex		
Female	31 (39%)	55 (36%)
Male	48 (61%)	96 (64%)
Ethnic origin		
White	71 (90%)	145 (96%)
Black	0	1 (<1%)
Other	8 (10%)	5 (3%)
Eastern Cooperative Oncology Group performance status		
0	50 (63%)	95 (63%)
1	19 (24%)	44 (29%)
2	8 (10%)	10 (7%)
Unknown	2 (3%)	2 (1%)
Predominant histological or cytological subtype		
Aggressive*	40 (51%)	76 (50%)
Non-aggressive†	38 (48%)	68 (45%)
Undetermined	1 (1%)	6 (4%)
Missing	0	1 (<1%)
Metastasis	14 (18%)	23 (15%)
Metastatic sites		
Lung	10 (71%)	12 (52%)
Lymph nodes‡	1 (7%)	7 (30%)
Bone	2 (14%)	5 (22%)
Other§	3 (21%)	7 (30%)
Number of lesions at baseline¶		
1	30 (38%)	57 (38%)
≥2	49 (62%)	93 (62%)
Previous antineoplastic therapy		
Surgery	60 (76%)	127 (84%)
Radiotherapy	19 (24%)	49 (32%)
Reason for enrolment‖		
Multiple tumour recurrence following surgery or radiotherapy	15 (19%)	47 (31%)
Radiotherapy contraindicated due to pre-existing disorder	1 (1%)	4 (3%)
Surgery or radiotherapy inappropriate due to location of lesion	33 (42%)	44 (29%)
Severe disfigurement expected with surgical resection	25 (32%)	43 (28%)

Data are number (%) or median (range). *Includes micronodular, infiltrative, multifocal, basosquamous, or sclerosing basal cell carcinoma. †Includes nodular and superficial basal cell carcinoma. ‡Includes axillary, parotid, submandibular, supraclavicular, and other. §Includes trunk, brain, head, liver, neck, and upper extremities. ¶One patient randomised to receive 800 mg sonidegib had no lesion data collected at baseline and was not treated. ‖Each patient enrolled provided only one reason.

***Table 1*: Demographics and disease history at baseline in the intention-to-treat population**

	200 mg sonidegib		800 mg sonidegib	
	laBCC (n=42)	mBCC (n=13)	laBCC (n=93)	mBCC (n=23)
Proportion of patients with objective response† (central review)	18 (43%, 28–59)	2 (15%, 2–45)	35 (38%, 28–48)	4 (17%, 5–39)
Complete response	2 (5%)	0	0	0
Partial response	16 (38%)	2 (15%)	35 (38%)	4 (17%)
Disease control‡	39 (93%)	12 (92%)	74 (80%)	19 (83%)
Proportion of patients with objective response† (investigator review)	28 (67%, 50–80)	3 (23%, 5–54)	54 (58%, 48–68)	8 (35%, 16–57)
Complete response	3 (7%)	0	12 (13%)	2 (9%)
Partial response	25 (60%)	3 (23%)	42 (45%)	6 (26%)
Disease control‡	39 (93%)	11 (85%)	82 (88%)	19 (83%)
Time to tumour response (months; central review)§	3·9 (2·1–4·0)	4·6 (1·8–7·4)	3·7 (2·0–3·8)	1·0 (1·0–2·1)
Time to tumour response (months; investigator review)§	1·9 (1·2–3·7)	1·0 (0·9–3·7)	1·8 (1·1–2·0)	2·7 (1·0–5·6)
Duration of tumour response (central review)¶				
Number of events per responders	3/18	0/2	1/35	1/4
Duration (months)	Not reached	Not reached	Not reached	8·3 (not estimable)
Event-free probability at 9 months (%)	82·1% (44·4–95·3)	100% (not estimable)	92·3% (56·6–98·9)	0 (not estimable)
Duration of tumour response (investigator review)¶				
Number of events per responders	5/28	0/3	6/54	1/8
Duration (months)	20·2 (10·1–20·2)	Not reached	Not reached	10·2 (not estimable)
Event-free probability at 9 months (%)	84·2% (58·3–94·7)	100% (not estimable)	80·6% (58·4–91·7)	100% (not estimable)
Progression-free survival (central review)‖				
Number of progression-free survival events	5	4	8	10
Duration (months)	Not reached	13·1 (5·6–13·1)	Not reached	7·6 (6·2–11·1)
Event-free probability at 12 months (%)	83·6% (58·9–94·1)	64·9% (24·9–87·4)	82·8% (67·3–91·4)	15·7% (1·0–47·7)
Progression-free survival (investigator review)‖				
Number of progression-free survival events	9	7	13	6
Duration (months)	22·0 (13·7–22·0)	13·1 (9·2–16·6)	Not reached	13·3 (not estimable)
Event-free probability at 12 months (%)	73·6% (50·2–87·2)	53·7% (21·0–78·1)	69·9% (51·7–82·4)	58·9% (21·8–83·2)

Data are number (%), number (%, 95% CI), median (95% CI), or % (95% CI). laBCC=locally advanced basal cell carcinoma. mBCC=metastatic basal cell carcinoma. *Patients with fully assessable laBCC tumours and all patients with mBCC. †Proportion of patients with a confirmed best overall response (on repeat assessments ≥4 weeks apart) of compelete response or partial response. ‡Complete response, partial response, or stable disease. §Time from randomisation to first observed objective response. ¶ Time from first observed objective response to disease progression or death from any cause. ‖Time from randomisation to first documented disease progression or death from any cause.

Table 2*: Activity of sonidegib by treatment group in the primary efficacy analysis population

Fresh tumour biopsy samples were assessed at screening (fresh or archived), week 9, week 17, and at the end of treatment to measure *GLI1* expression by quantitative RT-PCR in all valid samples. We measured changes in *GLI1* expression from baseline and assessed associations between these and best overall response and time to onset of grade 2 or worse increased creatine kinase concentration. The presence of basal cell carcinoma was histologically confirmed before *GLI1* analyses.

Changes in disease-related symptoms, functioning, and quality of life were assessed by investigators at baseline and at weeks 9 and 17 during treatment then every 8 weeks during year 1 and every 12 weeks thereafter with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (QLQ-C30)[17] and its associated module specific for head and neck cancers (H&N35).[18] We prespecified use of the subscales most relevant to patients with advanced basal cell carcinoma: physical functioning, social functioning, pain, and fatigue for QLQ-C30, and trouble with social contact, head and neck pain, and weight loss for H&N35. Proportions of patients with improvement, no change, or decline from baseline were calculated on the basis of best reported score after baseline. Median time to deterioration, defined as a worsening of at least 10 points in a score from baseline without a subsequent improvement, was also calculated for each subscale.

Safety, including monitoring of adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03,[19] was assessed by central review and by investigators from the first dose until 30 days after the last dose in patients who received at least one dose of sonidegib. Details on further study assessments are provided in the appendix. Muscle-related events were also assessed by an independent safety review and adjudication committee of three external experts.

Outcomes

The primary endpoint was the proportion of patients who achieved an objective response among those with

	200 mg sonidegib		800 mg sonidegib	
	laBCC (n=66)	mBCC (n=13)	laBCC (n=128)	mBCC (n=23)
Proportion of patients with objective response* (central review)	31 (47%, 35–60)	2 (15%, 2–45)	45 (35%, 27–44)	4 (17%, 5–39)
Complete response	2 (3%)	0	0	0
Partial response	29 (44%)	2 (15%)	45 (35%)	4 (17%)
Disease control†	60 (91%)	12 (92%)	100 (78%)	19 (83%)
Proportion of patients with objective response* (investigator review)	43 (65%, 52–76)	3 (23%, 5–54)	73 (57%, 48–66)	8 (35%, 16–57)
Complete response	5 (8%)	0	15 (12%)	2 (9%)
Partial response	38 (58%)	3 (23%)	58 (45%)	6 (26%)
Disease control†	59 (89%)	11 (85%)	110 (86%)	19 (83%)
Time to tumour response (months; central review)‡	3·9 (3·6–4·2)	4·6 (1·8–7·4)	3·7 (2·6–3·8)	1·0 (1·0–2·1)
Time to tumour response (months; investigator review)‡	1·9 (1·8–3·7)	1·0 (0·9–3·7)	1·9 (1·2–2·0)	2·7 (1·0–5·6)
Duration of tumour response (central review)§				
Number of events per responders	4/31	0/2	3/45	1/4
Duration (months)	Not reached	Not reached	Not reached	8·3 (not estimable)
Event-free probability at 9 months (%)	82·4% (53·9–94·1)	100% (not estimable)	82·7% (53·9–94·3)	0 (not estimable)
Duration of tumour response (investigator review)§				
Number of events per responders	10/43	0/3	10/73	1/8
Duration (months)	20·2 (10·1–20·2)	Not reached	Not reached	10·2 (not estimable)
Event-free probability at 9 months (%)	73·7% (52·2–86·7)	100% (not estimable)	77·0 (59·3–87·8)	100% (not estimable)
Progression-free survival (central review)¶				
Number of events	7	4	10	10
Duration (months)	Not reached	13·1 (5·6–13·1)	Not reached	7·6 (6·2–11·1)
Event-free probability at 12 months (%)	83·5% (64·6–92·9)	64·9% (24·9–87·4)	85·5% (73·0–92·5)	15·7% (1·0–47·7)
Progression-free survival (investigator review)¶				
Number of events	15	7	17	6
Duration (months)	16·6 (13·7–22·0)	13·1 (9·2–16·6)	Not reached	13·3 (not estimable)
Event-free probability at 12 months (%)	68·8% (50·7–81·4)	53·7% (21·0–78·1)	71·4% (56·8–81·8)	58·9% (21·8–83·2)

Data are number (%), number (%, 95% CI), median (95% CI), or % (95% CI). laBCC=locally advanced basal cell carcinoma. mBCC=metastatic basal cell carcinoma. *Proportion of patients with a confirmed best overall response (on repeat assessments ≥4 weeks apart) of complete response or partial response. †Complete response, partial response, or stable disease. ‡Time from randomisation to first observed objective response. §Time from first observed objective response to disease progression or death from any cause. ¶Time from randomisation to first documented disease progression or death from any cause.

***Table 3*: Activity of sonidegib by treatment group in the intention-to-treat population**

fully assessable (by modified RECIST) locally advanced tumours and all patients with metastatic basal cell carcinoma (primary efficacy analysis population, by central review). Additionally, we assessed anti-tumour activity in the intention-to-treat (ITT) population (full analysis set), which included all patients randomised, irrespective of whether they received the study drug. Secondary endpoints were the proportion of patients who achieved complete response, time to tumour response, duration of tumour response, duration of progression-free survival, and safety. Exploratory endpoints included patient-reported outcomes and assessment of *GLI1* expression.

Statistical analysis

The study was designed to accrue around 210 patients for the ITT population to ensure around 150 patients would be included in the primary efficacy analysis population (100 patients in the 800 mg sonidegib group and 50 patients in the 200 mg sonidegib group) if treatment were continued beyond the interim analysis. The study success criterion was set at a point estimate of 30% or more patients achieving an objective response in either treatment group in the primary efficacy analysis population, with the lower bound of the 95% CI exceeding 20%. This sample size was chosen to provide good control for false-positive results (2·4% error rate for 200 mg sonidegib and 0·3% error rate for 800 mg sonidegib if the true proportion of patients achieving an objective response was 20% or less). It also provided sufficient power to detect anti-tumour activity with either dose. No statistical tests comparing the two treatment groups were planned because the 800 mg dose was predicted to have greater antitumour activity than the 200 mg dose.[14]

The proportions of patients who achieved objective response and complete response were estimated by treatment group, with 95% exact binomial CIs, in the

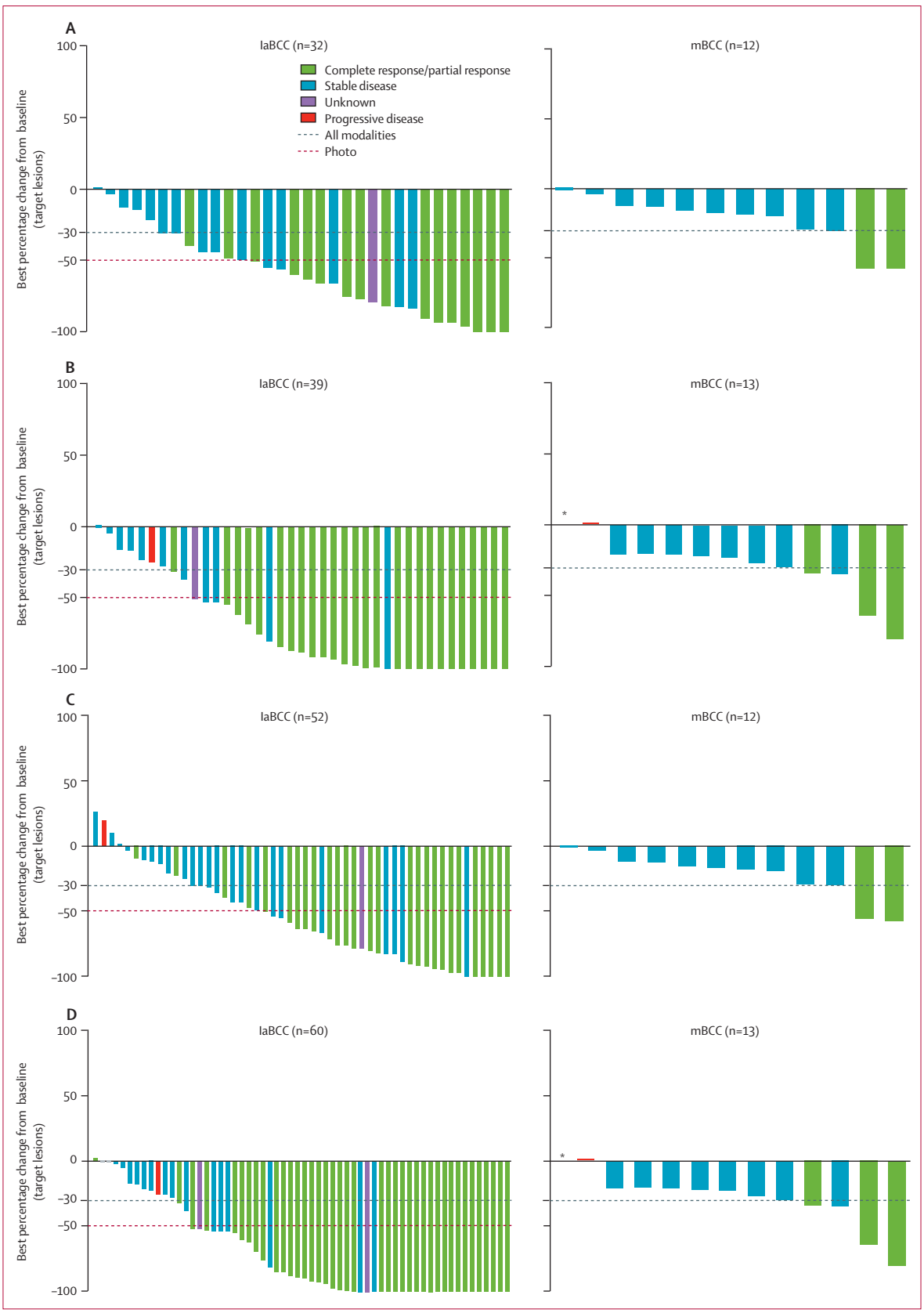

***Figure 2*: Changes from baseline in the sum of target lesions in the 200 mg group, by disease status**

(A) Central review of patients in the primary efficacy analysis population. (B) Investigator review of patients in the primary efficacy analysis population. (C) Central review of patients in the intention-to-treat population. (D) Investigator review of patients in the intention-to-treat population. laBCC=locally advanced basal cell carcinoma. mBCC=metastatic basal cell carcinoma. *One patient whose best percentage change was available but was contraindicated by an overall lesion response of progressive disease.

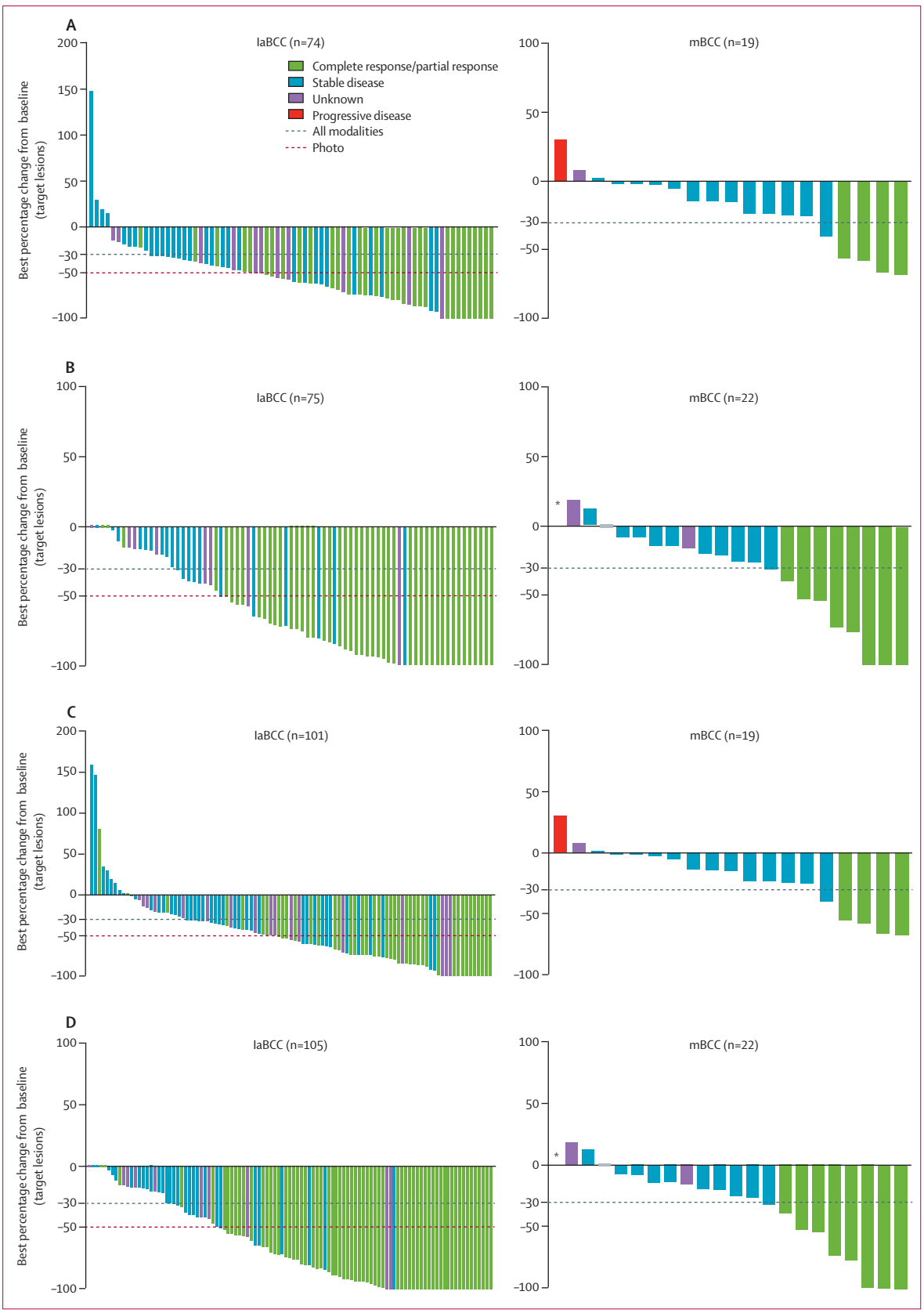

***Figure 3*: Changes from baseline in the sum of target lesions in the 800 mg group, by disease status**

(A) Central review of patients in the primary efficacy analysis population. (B) Investigator review of patients in the primary efficacy analysis population. (C) Central review of patients in the intention-to-treat population. (D) Investigator review of patients in the intention-to-treat population. laBCC=locally advanced basal cell carcinoma. mBCC=metastatic basal cell carcinoma. *One patient whose best percentage change was available but was contraindicated by an overall lesion response of progressive disease.

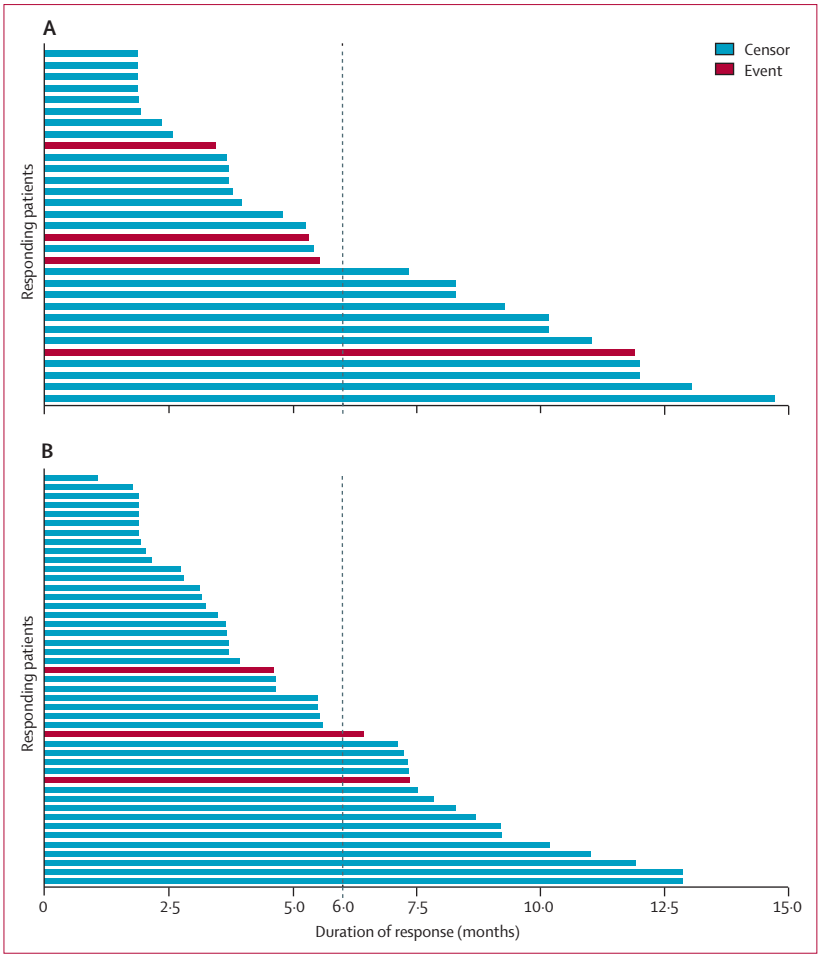

***Figure 4*: Central review of duration of treatment response in patients with locally advanced basal cell carcinoma**

(A) 200 mg sonidegib (n=31). (B) 800 mg sonidegib (n=45). For patients with metastatic disease, the duration of response was 20·3 months for the responder in the 200 mg group and 5·9, 7·7, 8·3, and 10·2 months in the 800 mg group; all censored except for 8·3 months. Censor=patients censored because of continued objective response or other reasons at the data cutoff date. Event=patients who progressed or died due to any reason after objective response.

primary efficacy analysis and ITT populations. The differences between the treatment groups were also summarised. For time-to-event analyses (time-to-tumour response, duration of tumour response, and duration of progression-free survival), we used the Kaplan-Meier non-parametric maximum likelihood estimates to calculate median (or other percentiles) times and 95% CIs by treatment group. Additional statistical methods for exploratory endpoints are provided in the appendix.

An interim analysis of safety and antitumour activity to assess futility was done by independent statisticians at least 16 weeks after the 48th patient received his or her first dose of study treatment. Results of this analysis indicated that the study should continue with both doses.

All analyses were done with SAS version 9.3. BOLT is registered with ClinicalTrials.gov, number NCT01327053.

Role of the funding source

The study was designed by the funder in collaboration with RD. Protocol amendments were developed with guidance from MRM, AG, RG, and JTL. The funder had no role in data collection. The funder had a role in data analysis, data interpretation, and writing of the report. 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 July 20, 2011 and Jan 10, 2013, we enrolled 230 patients, 194 with locally advanced and 36 with metastatic basal cell carcinoma, of whom 79 were randomly assigned to receive 200 mg sonidegib and 151 to receive 800 mg sonidegib (figure 1). Baseline characteristics were generally similar in the two groups (table 1). The median total size of target lesions was 12·1 cm² (range 0·7–639·3) in patients with locally advanced disease assessed by standard annotated photography, and 4·9 cm (1·5–15·8) in patients with metastatic disease assessed by central review with CT or MRI. Median follow-up was 13·9 months (IQR 10·1–17·3). At the time of the primary analysis, 144 (63%) patients had discontinued treatment, primarily due to adverse events, the patient's decision, or disease progression (figure 1, appendix).

Tumour assessments after baseline were available for 227 (99%) patients at the time of the primary analysis. In the primary efficacy analysis population, central review showed that 20 (36%, 95% CI 24–50) of 55 patients in the 200 mg dose group and 39 (34%, 25–43) of 116 patients in the 800 mg group achieved an objective response (table 2). In the ITT population, 33 (42%, 95% CI 31–53) of 79 patients in the 200 mg group and 49 (32%, 25–41) of 151 patients in the 800 mg group achieved an objective response, as assessed by central review (table 3). Responses by type of disease are shown in tables 2 and 3. The proportions of patients who achieved objective responses by central review were consistent across the primary efficacy analysis and ITT populations. In both populations the responses, as assessed by investigator review were higher (tables 2, 3). When assessed by histology and geographical region, the proportions of patients who achieved an objective response did not differ substantially between the subgroups assessed (appendix). Differences in proportions of patients who achieved objective responses between the two dose groups are provided in the appendix.

Secondary endpoints were consistent in the primary efficacy analysis and ITT populations (tables 2, 3). By central review, disease control was seen in more than 90% of patients treated with 200 mg sonidegib (tables 2, 3), as was the proportion of patients who had reduction from baseline in the sum of target lesions (figure 2). Disease control was achieved by around 80% of patients treated with 800 mg sonidegib; the proportion of patients treated with 800 mg sonidegib who had

reductions in tumour burden was similar to that noted in the 200 mg group (figure 3). By investigator review, reductions in the sum of target lesions from baseline were similar to or higher than those reported by central review (figures 2, 3).

Of the 76 patients with locally advanced basal cell carcinoma who had an objective response, only seven (four in the 200 mg dose group and three in the 800 mg dose group) had disease progression or died before the primary analysis data cutoff. Therefore, median duration of tumour response could not be calculated in either group. Responses lasting longer than 6 months in patients with locally advanced disease were seen in 12 (39%) of 31 responders taking 200 mg sonidegib and 17 (38%) of 45 responders taking 800 mg sonidegib (figure 4). Objective responses in patients with metastatic disease were maintained in five of six patients at the time of the primary analysis data cutoff. Median time to tumour response, duration of tumour response, and progression-free survival are shown in tables 2 and 3.

Most patients treated with sonidegib had stable or improved disease-related symptoms, functioning, and health status (table 4). With 200 mg sonidegib, deterioration was seen for fatigue and weight loss, with median times to deterioration being 13·7 months (95% CI 9·3–not estimable) and 16·6 months (13·9–not estimable), respectively. In the 800 mg sonidegib group, deterioration was seen in physical functioning, social functioning, fatigue, and weight loss: median time to deterioration for physical functioning 11·1 months (95% CI 9·0–not estimable), for social functioning 11·3 months (7·6–not estimable), for fatigue 5·6 months (5·5–9·4), and for weight loss 16·5 months (10·7–16·6).

Median durations of exposure to sonidegib for patients were 8·9 months (IQR 6·5–12·4) in the 200 mg dose group and 6·5 months (3·4–10·8) in the 800 mg dose group. Duration of exposure and relative dose intensity are shown in the appendix. Nearly all patients (72 [91%] of 79) in the 200 mg sonidegib group took treatment for 4 months or longer, compared with 105 (70%) of 150 in the 800 mg group.

The most common adverse events (muscle spasms, dysgeusia, alopecia, nausea, increased creatine kinase concentration in serum, weight decrease, and fatigue) were generally less frequent in the 200 mg sonidegib group than in the 800 mg sonidegib group (table 5). Raised creatine kinase concentration was the most frequently reported grade 3–4 adverse event, followed by increased lipase concentration elevations (table 5). Fewer adverse events leading to dose interruptions or reductions (25 [32%] of 79 *vs* 90 [60%] of 150) or treatment discontinuation (17 [22%] *vs* 54 [36%]) occurred in patients in the 200 mg than in the 800 mg sonidegib group. The most frequent adverse events leading to discontinuation of treatment were muscle spasms (three [4%] of 79 in the 200 mg sonidegib group *vs* 13 [9%] of 150 in the 800 mg sonidegib group), dysgeusia (two [3%] *vs* seven [5%]), weight decrease (two [3%] *vs* seven [5%]), and nausea (two [3%] *vs* six [4%]). Differences in the incidence of adverse events between treatment groups are provided in the appendix.

Serious adverse events were reported in 11 (14%) of 79 patients in the 200 mg sonidegib group and 45 (30%) of 150 in the 800 mg sonidegib group. The most frequently reported serious adverse events were rhabdomyolysis (one (1%) of 79 in the 200 mg group and

	200 mg sonidegib		800 mg sonidegib	
	laBCC	mBCC	laBCC	mBCC
EORTC QLQ-C30[17]				
Physical functioning				
Number of respondents	61	13	110	20
Improvement from baseline	22 (36%)	9 (69%)	35 (32%)	8 (40%)
No change from baseline	29 (48%)	3 (23%)	38 (35%)	10 (50%)
Decline from baseline	10 (16%)	1 (8%)	37 (34%)	2 (10%)
Social functioning				
Number of respondents	61	13	109	20
Improvement from baseline	16 (26%)	5 (38%)	22 (20%)	7 (35%)
No change from baseline	40 (66%)	6 (46%)	75 (69%)	12 (60%)
Decline from baseline	5 (8%)	2 (15%)	12 (11%)	1 (5%)
Pain				
Number of respondents	61	13	110	20
Improvement from baseline	19 (31%)	6 (46%)	36 (33%)	11 (55%)
No change from baseline	36 (59%)	7 (54%)	52 (47%)	7 (35%)
Decline from baseline	6 (10%)	0	22 (20%)	2 (10%)
Fatigue				
Number of respondents	61	13	109	20
Improvement from baseline	23 (38%)	6 (46%)	21 (19%)	8 (40%)
No change from baseline	26 (43%)	6 (46%)	55 (50%)	8 (40%)
Decline from baseline	12 (20%)	1 (8%)	33 (30%)	4 (20%)
EORTC H&N35[18]				
Trouble with social contact				
Number of respondents	58	13	110	19
Improvement from baseline	25 (43%)	4 (31%)	33 (30%)	8 (42%)
No change from baseline	27 (47%)	7 (54%)	68 (62%)	9 (47%)
Decline from baseline	6 (10%)	2 (15%)	9 (8%)	2 (11%)
Head and neck pain				
Number of respondents	60	13	112	20
Improvement from baseline	11 (18%)	3 (23%)	20 (18%)	4 (20%)
No change from baseline	47 (78%)	9 (69%)	78 (70%)	12 (60%)
Decline from baseline	2 (3%)	1 (8%)	14 (13%)	4 (20%)
Weight loss				
Number of respondents	58	12	110	19
Improvement from baseline	9 (16%)	2 (17%)	8 (7%)	5 (26%)
No change from baseline	49 (84%)	8 (67%)	89 (81%)	14 (74%)
Decline from baseline	0	2 (17%)	13 (12%)	0

laBCC=locally advanced basal cell carcinoma. mBCC=metastatic basal cell carcinoma. EORTC=European Organisation for Research and Treatment of Cancer. QLQ-C30=Quality of Life Questionnaire-Core 30. H&N35=Head and Neck Cancer Module 35. *In patients who completed questionnaires at baseline and at least once after baseline, and based on best score change.

Table 4*: Patients' self-reported quality of life

	200 mg sonidegib (n=79)					800 mg sonidegib (n=150)				
	Total‡	Grade 1	Grade 2	Grade 3	Grade 4	Total‡	Grade 1	Grade 2	Grade 3	Grade 4
Any adverse event	75 (95%)	14 (18%)	37 (47%)	21 (27%)	3 (4%)	150 (100%)	15 (10%)	51 (34%)	68 (45%)	16 (11%)
Muscle spasms	39 (49%)	33 (42%)	4 (5%)	2 (3%)	0	100 (67%)	57 (38%)	35 (23%)	8 (5%)	0
Alopecia	34 (43%)	27 (34%)	6 (8%)	1 (1%)§	NA	83 (55%)	53 (35%)	30 (20%)	NA	NA
Dysgeusia	30 (38%)	23 (29%)	7 (9%)	0	0	89 (59%)	65 (43%)	23 (15%)	1 (<1%)§	0
Nausea	26 (33%)	18 (23%)	7 (9%)	1 (1%)	0	68 (45%)	46 (31%)	18 (12%)	4 (3%)	0
Blood creatine kinase increased¶	23 (29%)	11 (14%)	7 (9%)	3 (4%)	2 (3%)	56 (37%)	19 (13%)	18 (12%)	11 (7%)	8 (5%)
Fatigue	23 (29%)	14 (18%)	9 (11%)	0	0	54 (36%)	40 (27%)	11 (7%)	3 (2%)	0
Weight decreased	21 (27%)	11 (14%)	9 (11%)	1 (1%)	0	57 (38%)	18 (12%)	31 (21%)	8 (5%)	0
Diarrhoea	19 (24%)	18 (23%)	1 (1%)	0	0	33 (22%)	23 (15%)	10 (7%)	0	0
Appetite decreased	15 (19%)	9 (11%)	6 (8%)	0	0	46 (31%)	27 (18%)	13 (9%)	6 (4%)	0
Myalgia	15 (19%)	12 (15%)	3 (4%)	0	0	39 (26%)	29 (19%)	7 (5%)	3 (2%)	0
Headache	12 (15%)	9 (11%)	3 (4%)	0	0	20 (13%)	17 (11%)	2 (1%)	1 (<1%)	0
Arthralgia	10 (13%)	8 (10%)	1 (1%)	1 (1%)	0	12 (8%)	10 (7%)	1 (<1%)	1 (<1%)	0
Constipation	6 (8%)	5 (6%)	0	1 (1%)	0	20 (13%)	18 (12%)	2 (1%)	0	0
Pneumonia	5 (6%)	2 (3%)	3 (4%)	0	0	5 (3%)	0	3 (2%)	2 (1%)	0
Vomiting	5 (6%)	4 (5%)	0	1 (1%)	0	39 (26%)	33 (22%)	4 (3%)	2 (1%)	0
Asthenia	6 (8%)	1 (1%)	3 (4%)	2 (3%)	0	8 (5%)	5 (3%)	3 (2%)	0	0
Lipase increased¶	6 (8%)	1 (1%)	1 (1%)	4 (5%)	0	12 (8%)	3 (2%)	1 (<1%)	7 (5%)	1 (<1%)
Hypertension	5 (6%)	2 (3%)	1 (1%)	2 (3%)	0	11 (7%)	0	7 (5%)	4 (3%)	0
Anaemia	2 (3%)	1 (1%)	1 (1%)	0	0	10 (7%)	2 (1%)	5 (3%)	2 (1%)	1 (<1%)
Dyspnoea	2 (3%)	2 (3%)	0	0	0	7 (5%)	4 (3%)	1 (<1%)	2 (1%)	0
General physical health deterioration	2 (3%)	0	1 (1%)	1 (1%)	0	3 (2%)	1 (<1%)	1 (<1%)	1 (<1%)	0
Hypotension	2 (3%)	1 (1%)	0	1 (1%)	0	3 (2%)	2 (1%)	0	1 (<1%)	0
Syncope	2 (3%)	1 (1%)	0	1 (1%)	0	4 (3%)	0	1 (<1%)	3 (2%)	0
Alanine aminotransferase increased¶	1 (1%)	0	0	1 (1%)	0	6 (4%)	1 (<1%)	1 (<1%)	4 (3%)	0
Amylase increased¶	1 (1%)	0	0	1 (1%)	0	6 (4%)	4 (3%)	1 (<1%)	0	1 (<1%)
Aspartate aminotransferase increased¶	1 (1%)	0	0	1 (1%)	0	7 (5%)	1 (<1%)	2 (1%)	4 (3%)	0
Atrial fibrillation	1 (1%)	0	0	1 (1%)	0	3 (2%)	1 (<1%)	1 (<1%)	1 (<1%)	0
Rhabdomyolysis‖	1 (1%)	0	0	1 (1%)	0	5 (3%)	0	0	2 (1%)	3 (2%)
Dehydration	0	0	0	0	0	8 (5%)	0	5 (3%)	3 (2%)	0
Hypogeusia	0	0	0	0	0	8 (5%)	1 (<1%)	5 (3%)	2 (1%)	0
Blood myoglobin increased	0	0	0	0	0	3 (2%)	1 (<1%)	0	1 (<1%)	1 (<1%)
Hyperkalaemia¶	0	0	0	0	0	3 (2%)	0	0	3 (2%)	0

Adverse events are based on the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.03 guidelines.[19] NA=not applicable. *Reported during treatment and within 30 days of study drug discontinuation. †Grade 3 or 4 adverse events that occurred in single patients are not listed in this table: in the 200 mg group, grade 3 amenorrhoea, dizziness, facial pain, femoral neck fracture, lumbar vertebral fracture, and malignant melanoma, and grade 4 blood creatine kinase MB increased and blood uric acid increased; in the 800 mg group, grade 3 abscess, abscess limb, angina pectoris, arterial haemorrhage, blood alkaline phosphatase increased, blood glucose increased, blood pressure increased, bradycardia, bundle branch block left, cataract, dental caries, dysphagia, failure to thrive, hand fracture, haematuria, hepatic enzyme increased, hepatotoxicity, intervertebral disc degeneration, muscle contracture, muscular weakness, myositis, nephropathy toxic, paraesthesia, pseudomonas infection, respiratory failure, small intestinal obstruction, somnolence, spinal fracture, squamous cell carcinoma, superinfection, transitional cell carcinoma, upper gastrointestinal haemorrhage, and vertigo, and grade 4 B-cell lymphoma, brain neoplasm, cardiac death, congestive cardiac failure, and prostate cancer. ‡Patients with multiple adverse events are counted only once. §Event was reported in error. ¶Data differ from those in the appendix, where values are based on biochemistry laboratory analyses. ‖None of the cases of rhabdomyolysis reported by investigators was confirmed by the independent safety review and adjudication committee on muscle toxicity.

Table 5: **Most common adverse events reported by investigators in >10% of patients and all grade 3 or 4 adverse events*†**

three (3%) of 150 in the 800 mg group), and raised concentration of creatine kinase in serum (one (1%) of 79 in the 200 mg group and five (3%) of 150 in the 800 mg group; appendix). No case of rhabdomyolysis identified by investigators was confirmed by the independent safety review committee, who defined rhabdomyolysis as creatine kinase concentrations more than ten times higher than baseline plus a 1·5-fold increase in creatinine concentration in serum from baseline. Correlations between muscle-related adverse events and raised creatine kinase concentration are provided in the appendix.

Secondary malignancies were noted in five (6%) of 79 patients in the 200 mg group and in 11 (7%) of 150 patients in the 800 mg group. New malignant disease included squamous cell carcinoma (seven; three in the

200 mg group, four in the 800 mg group), malignant melanoma (two; one in each group), prostate cancer (two; one in each group), and one case each of vulval cancer, brain neoplasm, lung neoplasm, transitional cell carcinoma, and B-cell lymphoma (all in the 800 mg group; appendix). Four patients died while taking study treatment, all in the 800 mg sonidegib group (appendix), but none of these deaths was deemed to be related to sonidegib. Two patients with locally advanced basal cell carcinoma and clinically relevant cardiac risk factors died due to congestive cardiac failure (one on day 17) and cardiac death (one on day 196). Two patients with metastatic disease died due to disease progression, one on day 16 and one on day 38.

Baseline characteristics of patients assessed for *GLI1* expression were similar to those of the ITT population (appendix). Decreases in *GLI1* expression from baseline at weeks 9 and 17 were similar in the two treatment groups (median decreases of more than 90% at both timepoints; appendix). At week 17, substantial decreases from baseline in *GLI1* expression were seen in patients with disease control, whereas in the only patient with progressive disease who had tumour available for *GLI1* assessment, a net increase of 10% in *GLI1* expression was noted (figure 5, appendix). Additionally, at week 17, patients in the 800 mg sonidegib group who had greater *GLI1* inhibition from baseline (low *GLI1* group) had a higher risk of grade 2 or worse increases in creatine kinase concentrations than patients with greater *GLI1* inhibition from baseline in the 200 mg sonidegib group (figure 5, appendix).

Discussion

In this study, both 200 mg and 800 mg sonidegib showed antitumour activity in patients with advanced basal cell carcinoma, which is a population with limited therapeutic options.[4,6,7,9,10] The proportion of patients who achieved an objective response exceeded prespecified criteria for activity, and was consistent in the primary efficacy analysis and ITT populations.

The modified RECIST criteria we used for locally advanced disease were stringent, as classification of complete response required confirmation in multiple biopsy samples (based on lesion surface area) and results were assessed by an independent review committee. Thus, even if all biopsy samples were negative, this feature alone was insufficient to define a complete response; achievement of a partial response or stable disease was possible on the basis of the MRI or photography findings. To distinguish scarring or fibrosis from residual disease is difficult with MRI and, therefore, the number of patients with a complete response in this trial might be underestimated. Additionally, the definition of tumour response assessed by photography was at least a 50% reduction in the sum of target lesions.[15] The low proportion of patients with complete response in our study might be explained by these stringent

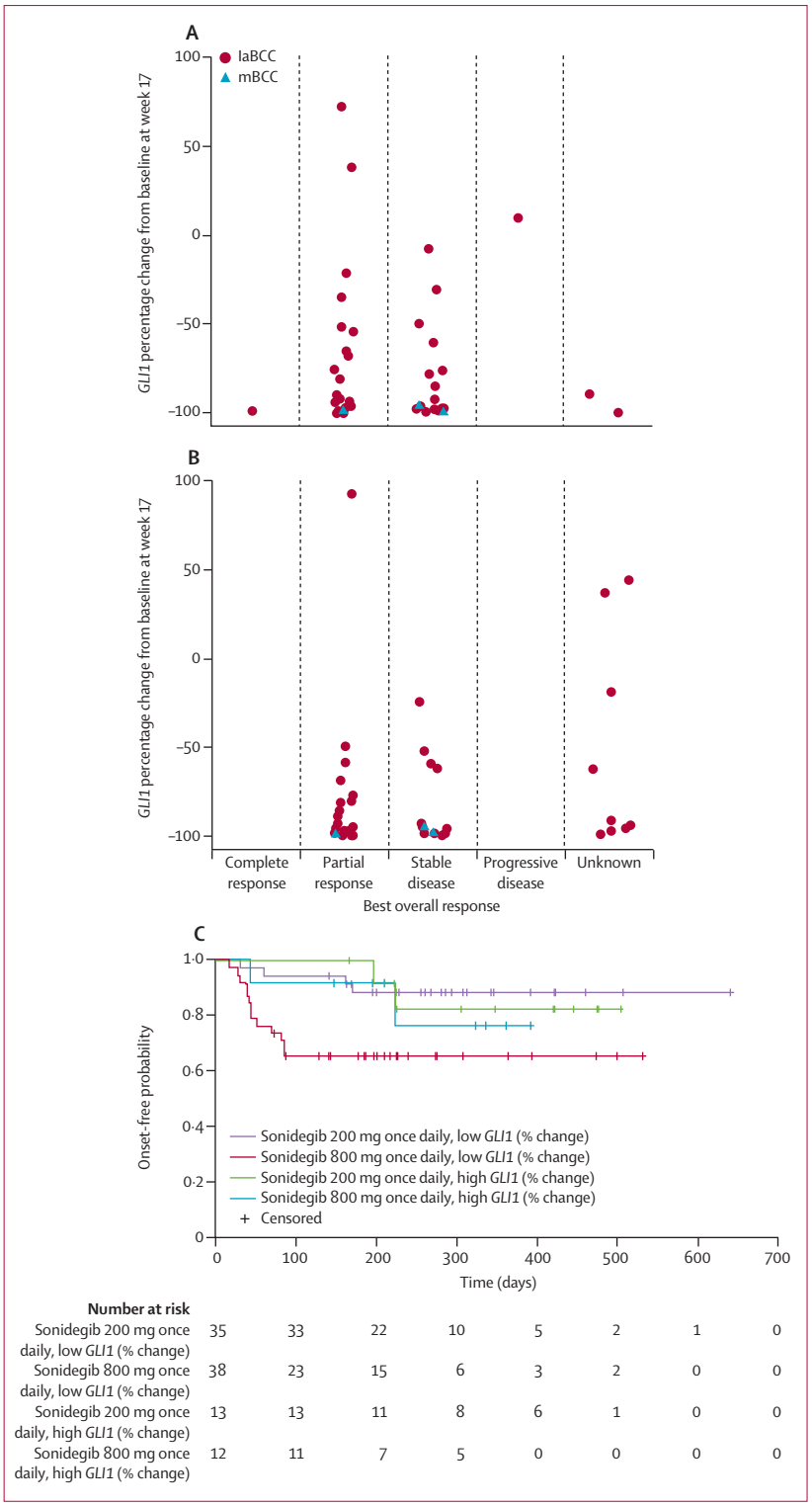

Figure 5: **Association between percentage change in *GLI1* expression from baseline at week 17 and best overall response and time to grade 2 or worse increase in creatine kinase concentration**
(A) 200 mg sonidegib (n=48). (B) 800 mg sonidegib (n=50). (C) Time to grade 2 or worse increase in creatine kinase concentration by dose of sonidegib and by percentage change in *GLI1* expression from baseline (low and high were, respectively, below and above the third quartile of percentage change from baseline). laBCC=locally advanced basal cell carcinoma. mBCC=metastatic basal cell carcinoma.

Panel: Research in context

Systematic review

When this trial was designed, no other *SMO* inhibitor had been approved by health authorities. Since the trial's inception, vismodegib has been approved for use in patients with locally advanced or metastatic basal cell carcinoma if surgery, radiation therapy, or both, are not deemed appropriate.[9–11] Vismodegib was approved on the basis of data from the phase 2 ERIVANCE trial.[24] We searched PubMed with the terms "hedgehog" or "smoothened" in combination with "inhibitor" and "advanced basal cell carcinoma" for articles published from Oct 1, 2009, to Oct 1, 2014, but identified no randomised, double-blind trials of Hedgehog pathway inhibitors in patients with advanced basal cell carcinoma. The only reports of large, phase 2 trials of Hedgehog pathway inhibitors in such patients were the primary and expanded access reports of the ERIVANCE trial.[24,25] The data from that trial showed that *SMO* inhibitors were efficacious in patients with advanced basal cell carcinoma, who have limited treatment options.

Interpretation

Our findings support the usefulness of *SMO* inhibitors for the treatment of patients with advanced basal cell carcinoma. The number of patients with disease control was high, and few patients had disease progression while taking sonidegib. Limited quality-of-life data exist for patients with advanced basal cell carcinoma, but it is clear that many patients have physical and emotional distress.[29] Treatment with sonidegib resulted in preservation of or improvement in quality of life for most patients. Together, our data show a positive benefit-to-risk profile with sonidegib, which could be a promising new option for the treatment of patients with advanced basal cell carcinoma.

response criteria and, potentially, by the extent of tumour burden and proportion of patients with metastatic disease who had bone metastases, which are associated with poor prognosis,[20] and lung metastases (table 1).

The number of patients with disease control strongly supports a treatment benefit with sonidegib. Moreover, substantial and sustained Hedgehog pathway inhibition (indicated by reduced *GLI1* expression) was seen in patients with disease control, which is consistent with the role of Hedgehog pathway signalling in the pathogenesis of basal cell carcinoma,[1–3] and indicates an association between *GLI1* inhibition and tumour response. Sonidegib was associated with early (from 1 month) and sustained responses (tables 2, 3). Median progression-free survival was not reached for patients with locally advanced basal cell carcinoma in either dose group by central review, but was 13·1 months (95% CI 5·6–13·1) with 200 mg sonidegib and 7·6 months (6·2–11·1) with 800 mg sonidegib in patients with metastatic disease. Duration of response and progression-free survival could not be assessed in patients with locally advanced basal cell carcinoma because less than 10% of patients had disease progression. The duration of response to sonidegib seen in this study is notable in view of the primary and secondary resistance that has been reported in patients treated with Hedgehog pathway inhibitors,[21,22] although we did not analyse the molecular mechanisms of resistance. Molecular analyses might lead to identification of the characteristics of tumours resistant to Hedgehog pathway inhibition.

Sonidegib was associated with a manageable safety profile in this study, with the 200 mg dose offering a more favourable profile than the 800 mg dose. The most frequently reported adverse events were typically grade 1–2 and were consistent with the safety profiles of other Hedgehog pathway inhibitors (muscle spasms, alopecia, dysgeusia, nausea, fatigue, decreased weight, diarrhoea, and decreased appetite), which suggests a class effect.[8,14,23–27]

Among patients with the greatest inhibition of *GLI1* expression from baseline, those treated with 800 mg sonidegib had a greater risk of grade 2 or worse increases in creatine kinase concentration than those treated with 200 mg sonidegib. This treatment effect was managed by dose adjustment or interruption and had no associated sequelae. The investigator-reported cases of rhabdomyolysis were not confirmed by the independent safety review and adjudication committee on muscle toxicity. Increased concentrations of creatine kinase were also reported in a patient treated with vismodegib.[28]

Duration of exposure was longer in patients who received 200 mg sonidegib than in those who received 800 mg sonidegib because of improved tolerability. Fewer discontinuations because of adverse events were reported in patients treated with 200 mg sonidegib and, therefore, more patients in this group took treatment until disease progression. Of note, 45 (63%) of the 71 patients who discontinued sonidegib because of adverse events experienced only grade 1–2 events. On the basis of improved tolerability (ie, longer duration of treatment, lower rate of most adverse events, and lower discontinuation rate) and similar treatment activity and Hedgehog pathway inhibition in the two dose groups, the overall benefit-to-risk profile is more favourable for 200 mg sonidegib than for 800 mg sonidegib. Improved management of adverse events in patients treated with sonidegib 800 mg might lead to lengthened treatment exposure, although it is questionable whether additional benefits are possible.

Quality of life for patients with advanced basal cell carcinoma can be poor because of the emotional distress caused by scarring and disfigurement, particularly for patients with visible lesions.[29] Most patients treated with sonidegib in our study experienced stable or improved quality of life, which is an important consideration for this population.[27]

Our findings suggest that 200 mg sonidegib could be a promising treatment option for patients with advanced basal cell carcinoma, which is a difficult population to treat, and support the usefulness of *SMO* inhibitors (panel).

Contributors

MRM, AG, RG, TY, MM, JTL, DS, and RD contributed to the study design. MRM, AG, RG, LD, KDL, PC, RMH, RK, UT, MK, CL, AJS, H-JS, RP, ALSC, FC, JTL, and RD collected data. All authors analysed and interpreted the data, participated in the development of the report and approved the final submitted version. The steering committee consisted of MRM, AG, RG, JTL, and RD.

Declaration of interests
MRM has received personal fees from Eli Lilly, Genentech, and Novartis. AG has received personal fees from Novartis. RG has received grants, personal fees, and non-financial support from Roche; grants and personal fees from Novartis; personal fees from GlaxoSmithKline; grants from Johnson & Johnson; personal fees and non-financial support from Bristol-Myers Squibb; personal fees from Amgen, Almirall Hermal, Boehringer Ingelheim, Janssen, Leo, MerckSerono, and Merck Sharpe and Dohme; and grants from Deutsche Forschungsgemeinschaft. KDL and RMH have received research funding from Novartis. RK has received personal fees from Bristol-Myers Squibb and Genentech. UT has received personal fees from Hofmann-La Roche. SG, TY, and DS are employed by Novartis and own stock. CP and MM are employed by Novartis. MK has received personal fees from Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharpe and Dohme, Novartis, and Roche Pharma. CL has received personal fees from Bristol Myers-Squibb, GlaxoSmithKline, Novartis, Ribological, and Roche. AJS has received personal fees from Leo, Novartis, and Roche. H-JS has received grants from F Hoffmann-La Roche and Roche. RP has received research funding from Novartis and personal fees from AstraZeneca, Bristol-Myers Squibb, Clovis, GlaxoSmithKline, Merck Sharpe and Dohme, Roche, and Vertex. ALSC has received research funding from Novartis. JTL has received personal fees from Novartis. RD has received grants and personal fees from Bristol Myers-Squibb, GlaxoSmithKline, Merck Sharpe and Dohme, Novartis, and Roche. The other authors declare no competing interests.

Acknowledgments
This study was funded by Novartis. We thank the patients and their families, the study investigators, their clinical teams, and the study site staff, and the members of the study committees. We also thank the Novartis BOLT clinical study team. Medical editorial assistance was provided by Jillian Brechbiel and Karen Miller-Moslin (Articulate Science, Hamilton, NJ, USA). Financial support for editorial assistance was provided by Novartis Pharmaceuticals Corporation. We thank the independent data monitoring committee (Mark R Pittelkow, Jürgen C Becker, and Stephen L George), the efficacy independent review committee (Vernon K Sondak, James Grichnik, and Lawrence Schwartz), and the muscle safety review and adjudication committee (Robert S Rosenson, Vinay Chaudhry, and Paul D Thompson).

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