

## ORIGINAL ARTICLE

# Long-term efficacy and safety of sonidegib in patients with locally advanced and metastatic basal cell carcinoma: 30-month analysis of the randomized phase 2 BOLT study

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## Abstract

**Background** Patients with locally advanced basal cell carcinoma (laBCC) or metastatic BCC (mBCC), two difficult-to-treat populations, have had limited treatment options. Sonidegib, a hedgehog pathway inhibitor (HPI), was approved in laBCC based on results from the BOLT trial.

**Objective** To evaluate long-term efficacy and safety of sonidegib in laBCC and mBCC in the BOLT 18- and 30-month analyses.

**Methods** BOLT (NCT01327053, ClinicalTrials.gov), a double-blind phase 2 study, enrolled patients from July 2011 until January 2013. Eligible HPI-treatment-naïve patients with laBCC not amenable to curative surgery/radiotherapy or mBCC were randomized 1 : 2 to sonidegib 200 mg (laBCC,  $n = 66$ ; mBCC,  $n = 13$ ) or 800 mg (laBCC,  $n = 128$ ; mBCC,  $n = 23$ ). Tumour response was assessed per central and investigator review.

**Results** With 30 months of follow-up, among patients treated with sonidegib 200 mg (approved dose), objective response rates were 56.1% (central) and 71.2% (investigator) in laBCC and 7.7% (central) and 23.1% (investigator) in mBCC. Tumour responses were durable as follows: median duration of response was 26.1 months (central) and 15.7 months (investigator) in laBCC and 24.0 months (central) and 18.1 months (investigator) in mBCC. Five patients with laBCC and three with mBCC in the 200-mg arm died. Median overall survival was not reached in either population; 2-year overall survival rates were 93.2% (laBCC) and 69.3% (mBCC). In laBCC, efficacy was similar regardless of aggressive or non-aggressive histology. Sonidegib 200 mg continued to have a better safety profile than 800 mg, with lower rates of grade 3/4 adverse events (43.0% vs. 64.0%) and adverse events leading to discontinuation (30.4% vs. 40.0%).

†Affiliation at the time the study was conducted. HC and TY are no longer affiliated with Novartis Pharmaceuticals.

**Conclusion** Sonidegib continued to demonstrate long-term efficacy and safety in these populations. These data support the use of sonidegib 200 mg per local treatment guidelines.

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### Conflicts of interest

Dr Lear has served as a consultant or speaker for and received honoraria from Novartis Pharmaceuticals Corporation. Dr Migden has participated on advisory boards and received honoraria from Genentech, Inc.; Novartis Pharmaceuticals Corporation; and Eli Lilly and Company. Dr Lewis has received research funding paid to the institution from Novartis Pharmaceuticals Corporation. Dr Chang is a primary investigator for and has served as a consultant for and received research grant/funding paid to the institution from Novartis Pharmaceuticals Corporation. Dr Guminski has participated on advisory boards for Bristol-Myers Squibb, Pfizer Inc. and Sanofi; received honoraria from Novartis Pharmaceuticals Corporation; and received travel support from Astellas and Bristol-Myers Squibb. Dr Gutzmer has received research grants paid to the institution from Roche, Novartis Pharmaceuticals Corporation, Johnson & Johnson and Pfizer Inc.; received honoraria from Roche, Bristol-Myers Squibb, MSD, GlaxoSmithKline, Novartis Pharmaceuticals Corporation, Merck Serono, Ammiral, Janssen, Amgen Inc., Galderma and Boehringer Ingelheim; and served as a consultant for Roche, Bristol-Myers Squibb, MSD, GlaxoSmithKline, Novartis Pharmaceuticals Corporation, Ammiral, LEO Pharma Inc., Amgen Inc. and Pfizer Inc. Dr Dirix has no conflict of interest to declare. Dr Combemale has no conflict of interest to declare. Dr Stratigos has received a research grant from Roche and Novartis Pharmaceuticals Corporation and received honoraria from LEO Pharma Inc., Meda Pharmaceuticals Inc. and Janssen-Cilag. Dr Plummer has participated on an advisory board and received honoraria from Astex, Roche, Bristol-Myers Squibb, Vertex, Bayer, Pierre Faber, Novartis Pharmaceuticals Corporation and Clovis Oncology. Dr Castro was an employee of Novartis during the development of this manuscript and is currently an employee of Bristol-Myers Squibb. Dr Yi was an employee of Novartis during the development of this manuscript. Dr Mone is an employee and stockholder of Novartis Pharmaceuticals Corporation. Dr Zhou is an employee of Novartis Pharmaceuticals Corporation. Dr Trefzer has been an advisor for and received honoraria from F. Hoffmann-La Roche Ltd, participated on an advisory board and received honoraria from MSD, and has been a speaker and received honoraria from Novartis Pharmaceuticals Corporation. Dr Kaatz has participated on advisory boards and received honoraria from Roche, MSD, Novartis Pharmaceuticals Corporation, Bristol-Myers Squibb and Janssen. Dr Loquai has served as a consultant for Bristol-Myers Squibb, Roche, Novartis Pharmaceuticals Corporation, Amgen, BioNTech and MSD. Dr Kudchadkar has participated on an advisory board and received honoraria from Bristol-Myers Squibb and Genentech, Inc. Dr Sellami is an employee and stockholder of Novartis Pharmaceuticals Corporation. Dr Dummer has received research funding from Novartis Pharmaceuticals Corporation, MSD, Bristol-Myers Squibb, Roche and GlaxoSmithKline and has served as a consultant or participated on an advisory board for Novartis Pharmaceuticals Corporation, MSD, Bristol-Myers Squibb, Roche, GlaxoSmithKline, Amgen and Takeda.

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### Introduction

Patients with locally advanced basal cell carcinoma (laBCC) or metastatic BCC (mBCC) have historically had limited treatment options.<sup>1</sup> Surgery, the primary course of treatment for most BCCs, and radiotherapy are often not viable options in advanced BCC.<sup>1–3</sup> In recent years, hedgehog (Hh) pathway inhibitors (HPIs) were developed to block aberrant Hh signalling that is found in most sporadic BCCs; HPIs have demonstrated efficacy in patients with laBCC and those with mBCC.<sup>4–13</sup>

Sonidegib (LDE225), which inhibits Hh signalling by targeting the Hh pathway component smoothed,<sup>6</sup> was approved (200 mg once daily) in the United States and Europe for the treatment of laBCC, in Australia for the treatment of laBCC and mBCC and in Switzerland for the treatment of advanced BCC that cannot be treated with curative surgery or radiotherapy.<sup>14–17</sup> These approvals were based on results from the pivotal phase 2 Basal Cell Carcinoma Outcomes With LDE225 Treatment (BOLT) study (NCT01327053), in which the primary analysis

was performed using data based on 6 months of follow-up.<sup>8,9</sup> Here, we report long-term efficacy and safety results from BOLT, with up to 30 months of follow-up after the last patient was randomized.

## Materials and methods

### BOLT study design and patients

BOLT is a randomized, double-blind, phase 2 study conducted in 58 centres across 12 countries that assessed the efficacy and safety of sonidegib 200 and 800 mg once daily, as described previously.<sup>8</sup> Patients  $\geq 18$  years of age with histologically confirmed disease, either laBCC not amenable to curative surgery or radiotherapy or mBCC, were eligible. Patients were required to have adequate organ function and a World Health Organization (WHO)<sup>18</sup> performance status  $\leq 2$ . Patients with previous HPI treatment were not eligible. Full inclusion and exclusion criteria were reported previously.<sup>8</sup>

Patients were randomized 1 : 2 to 200 or 800 mg based on previous data suggesting that 800 mg would show better efficacy.<sup>7</sup> Randomization was performed using the central Interactive Response Technology system (Cenduit, Allentown, PA). Stratification of patients was based on disease type (laBCC vs. mBCC), histological subtype (aggressive vs. non-aggressive) and geographic region. All patients and study personnel were blinded until the time of the primary analysis.

The study protocol was approved at each centre by independent ethics committee or institutional review board, and all patients provided written informed consent prior to enrolment.

### Sonidegib treatment and assessments

Sonidegib capsules were taken orally on a once-daily continuous schedule until disease progression, intolerable toxicity, withdrawal of patient consent, discontinuation at the discretion of the investigator, death or study termination. Tumour evaluations were conducted at baseline, during treatment and post-treatment follow-up (weeks 5 and 9, then every 8 weeks during year 1 and every 12 weeks thereafter), and at discontinuation using BCC-modified Response Evaluation Criteria In Solid Tumors (mRECIST)<sup>8,9</sup> for laBCC and RECIST v1.1<sup>19</sup> for mBCC. mRECIST<sup>8,9</sup> is a stringent multimodal assessment tool that incorporates magnetic resonance imaging (MRI) per RECIST v1.1<sup>19</sup> [ $\geq 30\%$  reduction in the sum of the longest diameters of target lesions required for a partial response (PR)], standard and annotated color photography per bidimensional WHO guidelines<sup>18</sup> ( $\geq 50\%$  reduction in the sum of the products of perpendicular diameters of target lesions required for a PR), and histology in multiple biopsies surveying the lesion area to determine a composite overall response. Complete responses (CRs) and PRs had to be confirmed on repeat assessments separated by  $\geq 4$  weeks. Fresh tumour biopsies were used to confirm CRs in the presence of confounding ulceration, cyst formation and/or

scarring/fibrosis. An independent review committee re-evaluated all central assessments for patients with laBCC.

In a prespecified analysis, responses were re-evaluated in patients with laBCC using BCC-RECIST-like, less-stringent criteria similar to those used in ERIVANCE, a phase 2 study of vismodegib.<sup>11</sup> Both mRECIST and BCC-RECIST-like integrate MRI per RECIST v1.1, standard and annotated color photography per WHO guidelines, and histology; however, the algorithm used to determine overall response for each is different: multiple scenarios exist for which the response is lower with mRECIST vs. BCC-RECIST-like (Table S1, Supporting Information).

Blood samples for pharmacokinetic (PK) assessments were collected from all patients through week 69; trough plasma concentrations were analysed at predose on weeks 1, 3, 5 and 9, then every 4 weeks through week 21 and every 12 weeks thereafter.

Adverse events (AEs) were monitored throughout the treatment period until 30 days following the last sonidegib dose according to Common Terminology Criteria for Adverse Events v4.03.<sup>20</sup>

### BOLT study outcomes

The primary study endpoint was objective response rate (ORR; proportion of patients with a best overall response of CR or PR) per central review. Secondary endpoints included ORR per investigator review; CR rate, duration of response (DOR) and progression-free survival (PFS) per central and investigator review; overall survival (OS); and safety.

### Statistical methods

Results were analysed based on two database cut-offs: 11 July 2014 and 10 July 2015 (18 and 30 months after the last patient was randomized, respectively). ORR and CR rates were estimated with 95% CIs. Kaplan–Meier nonparametric maximum likelihood estimates of median time and 95% CIs were estimated for DOR and PFS for each arm and by disease. Statistical comparisons of the 200- and 800-mg arms were not planned. Additional details on the statistical methods used in the study were published previously.<sup>8,9</sup>

## Results

### Patient demographics and disposition

Two-hundred and thirty patients with laBCC ( $n = 194$ ) or mBCC ( $n = 36$ ) were enrolled between 20 July 2011 and 10 January 2013. Patients were randomized to sonidegib 200 mg (laBCC,  $n = 66$ ; mBCC,  $n = 13$ ) or 800 mg (laBCC,  $n = 128$ ; mBCC,  $n = 23$ ; Fig. S1, Supporting Information). Baseline demographics were well balanced between arms.<sup>8,9</sup> Most patients with laBCC (200 mg, 56.1%; 800 mg, 58.6%) had aggressive tumour histology. By the data cut-off for the 18-month analysis (median follow-up, 26.3 months), 87.0% of patients (200 mg, 86.1%; 800 mg, 87.4%) had discontinued treatment; by the data cut-off

for the 30-month analysis (median follow-up, 38.2 months), 93.0% (200 mg, 92.4%; 800 mg, 93.4%) had discontinued treatment (Fig. S1, Supporting Information). The most common reasons for treatment discontinuation were AEs [30-month analysis (200 vs. 800 mg), 29.1% vs. 37.7%], progressive disease (36.7% vs. 14.6%) and patient decision (10.1% vs. 21.9%).

### Efficacy in patients with laBCC

ORRs in patients with laBCC increased compared with the primary analysis (Table 1; Table S2, Supporting Information). Tumour shrinkage was observed in most patients (Fig. S2, Supporting Information). In the 30-month analysis, ORRs in the 200-mg arm were 56.1% (central review) and 71.2% (investigator review); in the 800-mg arm, ORRs were 45.3% and 58.6%, respectively. Per central review, 26 of 37 patients with laBCC in the 200-mg arm who achieved an objective response by the 30-month data cut-off maintained the response (Fig. 1a; Fig. S3a, Supporting Information), and the estimated median DOR in the 200-mg arm was 26.1 months (15.7 months per investigator review). Among patients with laBCC who responded to treatment in the 800-mg arm, 38 of 58 maintained an objective response per central review (Fig. S3b, Fig. S4a, Supporting Information), and the estimated median DOR was 23.7 months (26.0 months per investigator review). At the 30-month data cut-off, the median durations of PFS among patients with laBCC were 22.1 months (central review) and 19.4 months (investigator review) in the 200-mg arm (Fig. 1b) and 22.0 and 28.0 months, respectively, in the 800-mg arm (Fig. S4b, Supporting Information).

Response in patients with laBCC was also assessed using BCC-RECIST-like criteria. Although ORRs and DORs were similar with both sets of criteria, CR rates were higher with BCC-RECIST-like criteria (Table S3, Supporting Information). In the 200-mg arm, CR rates in the 30-month analysis per central review were 21.2% (BCC-RECIST-like) vs. 4.5% (mRECIST).

Efficacy was similar among patients with laBCC with aggressive or non-aggressive histological subtypes. In the 30-month analysis, ORRs in patients with aggressive vs. non-aggressive histology in the 200-mg arm were 59.5% vs. 51.7% per central review and 70.3% vs. 72.4% per investigator review (Table 1); respective ORRs in the 800-mg arm were 44.0% vs. 47.2% per central review and 54.7% vs. 64.2% per investigator review (Table S2, Supporting Information). Tumour responses were durable regardless of tumour aggressiveness.

At the time of the 18-month analysis, efficacy in patients with laBCC was also assessed based on tumour burden at baseline. Responses were found to be durable regardless of tumour burden with both doses, with >58% of patients in each group having responses lasting >6 months (Table S4, Supporting Information).

Five patients with laBCC in the 200-mg arm died by the 30-month analysis; median OS was not yet reached and the

estimated 2-year OS was 93.2% (Table 1; Fig. 2). In the 800-mg arm, 11 patients with laBCC died; median OS was not reached and the estimated 2-year OS was 90.7% (Table S2, Fig. S5, Supporting Information). Numerically more deaths were reported in patients with aggressive (200 mg, 4; 800 mg, 8) vs. non-aggressive (200 mg, 1; 800 mg, 3) histology; median OS was not reached in either population with either dose, and 2-year OS rates were 91.8% vs. 94.7% (200 mg) and 86.6% vs. 95.8% (800 mg).

### Efficacy in patients with mBCC

Tumour shrinkage was reported in most patients with mBCC (Fig. S6, Supporting Information). ORRs in the 200-mg arm were 7.7% (central review) and 23.1% (investigator review) in the 30-month analysis, and estimated median DOR was 24.0 months (central review) and 18.1 months (investigator review; Table 2). ORRs in the 800-mg arm were 17.4% (central review) and 34.8% (investigator review); estimated median DOR was not reached per central review and was 10.2 months per investigator review (Table S5, Supporting Information). The disease control rate (CR + PR + stable disease) was high with sonidegib 200 mg (central, 92.3%; investigator, 84.6%) and 800 mg (central, 91.3%; investigator, 82.6%). The median PFS with sonidegib 200 mg was 13.1 months per central and investigator review (Fig. 1b) and with sonidegib 800 mg was 11.1 months per central review and 14.3 months per investigator review (Fig. S4b, Supporting Information).

In the 30-month analysis, 11 patients (200 mg, 3; 800 mg, 8) with mBCC had died. With sonidegib 200 mg, the estimated median OS was not reached, and the estimated 2-year OS was 69.3% (Fig. 2). With sonidegib 800 mg, the estimated median OS was 36.7 months, and the estimated 2-year OS was 69.1% (Fig. S5, Supporting Information).

### Sonidegib PK

Sonidegib PK was evaluated based on the 18-month data cut-off (by which time all patients had completed the scheduled PK assessments). Mean sonidegib plasma concentrations rose until week  $\approx$ 13–17 with daily 200 and 800 mg dosing (Fig. S7, Supporting Information). By week 17, an approximate steady state was reached for both doses. Sonidegib demonstrated under dose-proportional increases in plasma exposure between the two doses tested: at week 17, the geometric mean trough concentration was 689 ng/mL with 200 mg and 1574 ng/mL with 800 mg, corresponding to a  $\approx$ 2.3-fold increase in trough concentration over a fourfold dose increase.

### Safety

No new safety concerns emerged with an additional 24 months of follow-up since the primary analysis. At the 30-month data cut-off, the median duration of exposure was 11.0 months (range, 1.3–41.3 months) in the 200-mg arm and 6.6 months

**Table 1** Efficacy in patients with laBCC treated with sonidegib 200 mg by central and investigator review

Patients with laBCC	Sonidegib 200 mg QD				
	Primary analysis*	18-month analysis†	30-month analysis‡		
	All patients n = 66	All patients n = 66	All patients n = 66	Patients with aggressive histology§ n = 37	Patients with non-aggressive histology¶ n = 29
ORR, n (%); 95% CI**					
Central review	31 (47.0); 34.6–59.7	37 (56.1); 43.3–68.3	37 (56.1); 43.3–68.3	22 (59.5); 42.1–75.2	15 (51.7); 32.5–70.6
Investigator review	43 (65.2); 52.4–76.5	47 (71.2); 58.7–81.7	47 (71.2); 58.7–81.7	26 (70.3); 53.0–84.1	21 (72.4); 52.8–87.3
BOR, n (%)††					
CR					
Central review	2 (3.0)	3 (4.5)	3 (4.5)	2 (5.4)	1 (3.4)
Investigator review	5 (7.6)	6 (9.1)	6 (9.1)	3 (8.1)	3 (10.3)
PR					
Central review	29 (43.9)	34 (51.5)	34 (51.5)	20 (54.1)	14 (48.3)
Investigator review	38 (57.6)	41 (62.1)	41 (62.1)	23 (62.2)	18 (62.1)
SD					
Central review	29 (43.9)	23 (34.8)	23 (34.8)	12 (32.4)	11 (37.9)
Investigator review	16 (24.2)	14 (21.2)	13 (19.7)	8 (21.6)	5 (17.2)
PD					
Central review	1 (1.5)	1 (1.5)	1 (1.5)	1 (2.7)	0
Investigator review	1 (1.5)	1 (1.5)	1 (1.5)	0	1 (3.4)
Unknown					
Central review	5 (7.6)	5 (7.6)	5 (7.6)	2 (5.4)	3 (10.3)
Investigator review	6 (9.1)	4 (6.1)	5 (7.6)	3 (8.1)	2 (6.9)
DOR‡‡					
Events§§/responders, n/n; KM median (95% CI), months					
Central review	4/31; NR	10/37; NR	11/37; 26.1 (NE)	7/22; 26.1 (NE)	4/15; NR
Investigator review	10/43; 20.2 (10.1–20.2)	21/47; 14.3 (12.0–20.2)	22/47; 15.7 (12.0–20.2)	9/26; 20.2 (NE)	13/21; 15.7 (11.0–20.2)
PFS¶¶					
Events§§, n; KM median (95% CI), months					
Central review	7; NR	15; 22.1 (NE)	16; 22.1 (NE)	11; 22.1 (NE)	5; NR
Investigator review	15; 16.6 (13.7–22.0)	26; 19.4 (16.6–22.6)	28; 19.4 (16.6–23.6)	12; 19.0 (NE)	16; 19.4 (9.2–22.6)
OS***					
Deaths, n; KM median (95% CI), months	1; NR	3; NR	5; NR	4; NR	1; NR
2-year OS (95% CI), %	–	–	93.2 (80.2–97.8)	91.8 (70.9–97.9)	94.7 (68.1–99.2)

BOR, best overall response; CR, complete response; DOR, duration of response; KM, Kaplan–Meier; laBCC, locally advanced basal cell carcinoma; NE, not estimable; NR, not reached; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; QD, once daily; SD, stable disease; –, indicates not reported.

\*Data cut-off, 28 June 2013; median follow-up (200- and 800-mg arms), 13.9 months.

†Data cut-off, 11 July 2014; median follow-up (200- and 800-mg arms), 26.3 months.

‡Data cut-off, 10 July 2015; median follow-up (200- and 800-mg arms), 38.2 months.

§Aggressive histological subtypes of BCC include micronodular, infiltrative, multifocal, basosquamous and sclerosing.

¶Non-aggressive histological subtypes of BCC include nodular and superficial.

\*\*Proportion of patients with a BOR of CR or PR on repeat assessments  $\geq 4$  weeks apart.

††Best response recorded from the time of randomization until the earliest occurrence of disease progression, start of other antineoplastic therapy or data cut-off date.

‡‡Time from first observed objective response (CR or PR) until disease progression or death due to any cause (responder data only).

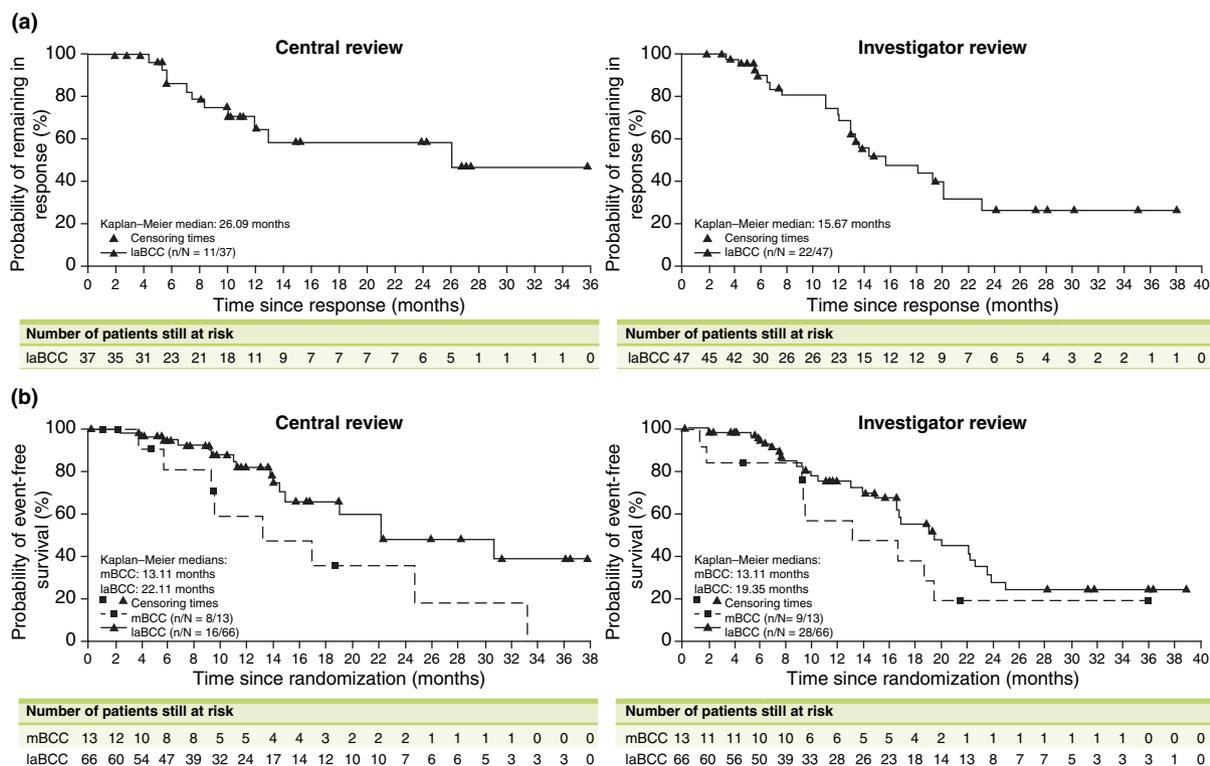
§§Progressive disease or death due to any cause.

¶¶Time from randomization to first documented disease progression or death due to any cause.

\*\*\*Time from randomization to the date of death due to any cause or the last date the patient was known to be alive.

(range, 0.3–43.5 months) in the 800-mg arm. The incidence of many of the most common AEs was lower with sonidegib 200 mg than 800 mg, including muscle spasms, alopecia, dysgeusia, nausea, weight decreased, creatine kinase (CK) increased,

fatigue, appetite decreased, myalgia and vomiting (Fig. 3). The most common AEs reported in patients with laBCC (Fig. S8, Supporting Information) and mBCC (Fig. S9, Supporting Information) were similar. Among all patients, grade 3/4 AEs



**Figure 1** Duration of response (DOR) in patients with locally advanced basal cell carcinoma (laBCC) and progression-free survival (PFS) by central and investigator review in patients with laBCC or metastatic BCC (mBCC) treated with sonidegib 200 mg. (a) Kaplan–Meier plots of DOR in patients with laBCC who responded to treatment with sonidegib 200 mg per central ( $n = 37$ ) and investigator ( $n = 47$ ) review. (b) Kaplan–Meier plots of PFS in patients with laBCC ( $n = 66$ ) and mBCC ( $n = 13$ ) treated with sonidegib 200 mg per central and investigator review.

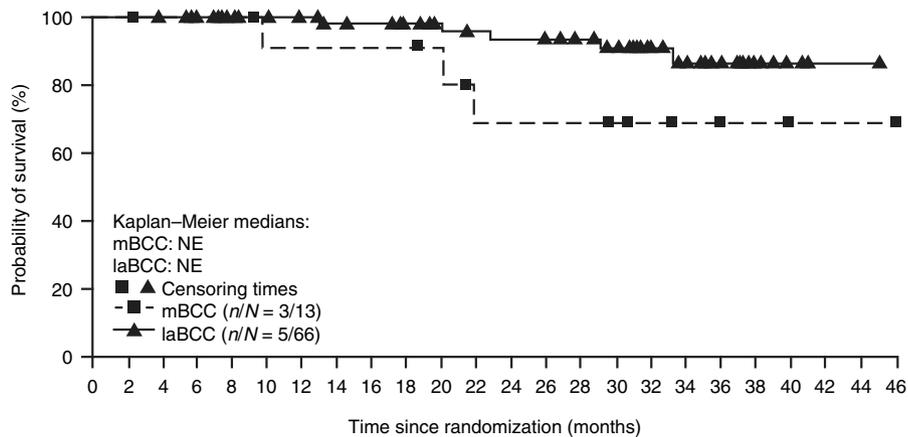
occurred less frequently with sonidegib 200 mg (43.0%) than with 800 mg (64.0%); similar results were reported for grade 3/4 AEs suspected to be related to treatment, with a lower incidence in the 200-mg arm (30.4%) than the 800-mg arm (43.3%). Increased CK was the most common grade 3/4 AE (10.9%; 200 mg, 6.3%; 800 mg, 13.3%); only one additional patient (800 mg) had a grade 3/4 increase in CK after the primary analysis cut-off. The median time to onset (range) of grade 2/3/4 CK elevation was 12.9 (2–39) and 6.7 (2–40) weeks in the 200- and 800-mg arms, respectively; the median time to resolution (95% CI) to grade  $\leq 1$  was 12.0 (8.0–14.0) and 15.0 (9.0–15.0) days, respectively.

AEs requiring dose interruption and/or reduction were reported in 43.0% and 66.7% of patients in the 200- and 800-mg arms, respectively; the most common AEs leading to dose interruption/reduction (200 mg vs. 800 mg) were muscle spasms (1.3% vs. 16.7%), CK increased (6.3% vs. 12.0%), and nausea (6.3% vs. 12.0%). AEs leading to treatment discontinuation also occurred less frequently with the 200-mg dose (30.4%) than the 800-mg dose (40.0%), with most (60.7%; 200 mg, 54.2%; 800 mg, 63.3%) being grade 1/2. The most common AEs leading

to discontinuation (200 mg vs. 800 mg) were muscle spasms (5.1% vs. 8.0%), weight decreased (2.5% vs. 6.0%), dysgeusia (3.8% vs. 4.7%) and alopecia (1.3% vs. 6.0%).

Serious AEs (SAEs) irrespective of cause were reported in 20.3% and 38.7% of patients treated with sonidegib 200 mg and 800 mg, respectively (Table S6, Supporting Information); SAEs related to sonidegib treatment occurred in 3.8% and 16.0%, respectively. Increased CK and rhabdomyolysis were the most commonly reported SAEs among all patients (2.6% each; 200 mg, 1.3% each; 800 mg, 3.3% each); due to a lack of renal impairment, none of the cases of rhabdomyolysis were confirmed by an independent review and adjudication committee of experts on muscle toxicity.<sup>8</sup>

On-treatment deaths were reported in eight patients (200 mg, 1; 800 mg, 7), four of whom had laBCC (200 mg, 1; 800 mg, 3) and four had mBCC (800 mg, 4); none of these deaths were considered treatment related. Four on-treatment deaths [two due to progressive disease (both with mBCC) and one each due to congestive cardiac failure (laBCC) and cardiac death (laBCC)] were reported in the primary analysis,<sup>8</sup> and four occurred following the primary analysis, including one



Number of patients still at risk																								
mBCC	13	13	12	12	12	10	10	10	10	10	9	6	6	6	6	5	4	3	2	2	1	1	1	0
laBCC	66	66	65	63	58	55	53	49	48	45	41	39	38	37	35	32	21	18	13	6	3	1	1	0

**Figure 2** Overall survival (OS) in patients with locally advanced basal cell carcinoma (laBCC) or metastatic BCC (mBCC) treated with sonidegib 200 mg. Kaplan–Meier plot of OS in patients with laBCC ( $n = 66$ ) or mBCC ( $n = 13$ ) treated with sonidegib 200 mg. NE, not estimable.

patient treated with sonidegib 200 mg (laBCC) who died of acute respiratory distress on study day 612, and three patients treated with 800 mg who died of cardiac arrest (laBCC), sepsis (mBCC) and respiratory arrest (mBCC) on study days 349, 391 and 433, respectively.

## Discussion

With long-term follow-up in BOLT, sonidegib 200 and 800 mg continued to demonstrate sustained efficacy in patients with laBCC (regardless of histology) and mBCC. Since the time of the primary analysis, ORRs in the 200-mg arm improved in patients with laBCC and remained similar in patients with mBCC. Higher rates of response were observed by investigator vs. central review, which could be due to investigators having the opportunity to physically examine lesions that are often complicated by post-treatment ulceration, cyst formation, scarring/fibrosis and ill-defined borders.<sup>8</sup> Responses in patients with laBCC were durable regardless of tumour burden at baseline, with most patients (central, 70.3%; investigator, 53.2%) who responded to treatment with sonidegib 200 mg maintaining an objective response at the 30-month data cut-off. Moreover, when responses in patients with laBCC were scored using less-stringent response criteria (BCC-RECIST-like criteria, similar to criteria used in ERIVANCE<sup>11</sup>), CR rates were similar to those reported with vismodegib in ERIVANCE.<sup>12</sup> This analysis underscores the efficacy of sonidegib in patients with laBCC. However, efficacy in patients with disease that recurred following prior HPI therapy is unknown because these patients were excluded from BOLT.

The rate of survival in patients with BCC is extremely high<sup>21,22</sup>; however, the prognosis for patients with advanced

BCC is less clear.<sup>1</sup> In patients with laBCC, the survival rate is unknown due in part to a lack of reporting of these data in patient registries. In patients with mBCC, the median survival prior to 1990 was estimated to be  $\approx 8$  months and recently has been estimated to be as high as  $\approx 7$  years due to improved therapies, including HPIs.<sup>23–25</sup> In BOLT, the median OS in patients with laBCC was not reached with either dose by the 30-month analysis, and the estimated 2-year OS was  $>90\%$  in both arms; in patients with mBCC, the median OS was not yet reached with sonidegib 200 mg and was 36.7 months with 800 mg, and the estimated 2-year OS was  $\approx 69\%$  in both arms. These survival rates are similar to those reported with vismodegib [85.5% (laBCC) and 62.3% (mBCC) at 2 years in ERIVANCE], the only other approved HPI.<sup>13</sup>

The PK of sonidegib is different from that of vismodegib. Vismodegib exposure did not increase above the 150-mg daily dosage due to saturated protein binding, and the half-life was 4 days after repeated dosing.<sup>26,27</sup> In contrast, sonidegib exposure increased 2.3-fold between 200 and 800 mg and reached an approximate steady state at  $\approx 17$  weeks. Previously, PK exposure–response and exposure–safety analyses including the 200- and 800-mg doses (based on the 18-month data cut-off) showed no exposure–efficacy relationship but a reduced risk of grade 3/4 CK elevation with lower exposure, further supporting the favourable benefit–risk profile of sonidegib 200 mg vs. 800 mg.<sup>28</sup> Additionally, in a population PK model, sonidegib had a predicted elimination half-life of 29.6 days and an accumulation ratio of 21.<sup>29</sup>

Sonidegib 200 mg continued to be better tolerated than sonidegib 800 mg, and no additional safety concerns were reported

**Table 2** Efficacy in patients with mBCC treated with sonidegib 200 mg by central and investigator review

Patients with mBCC	Sonidegib 200 mg QD n = 13		
	Primary analysis*	18-month analysis†	30-month analysis‡
<b>ORR, n (%); 95% CI§</b>			
Central review	2 (15.4); 1.9–45.4	1 (7.7)¶; 0.2–36.0	1 (7.7); 0.2–36.0
Investigator review	3 (23.1); 5.0–53.8	3 (23.1); 5.0–53.8	3 (23.1); 5.0–53.8
<b>BOR, n (%)**</b>			
<b>CR</b>			
Central review	0	0	0
Investigator review	0	0	0
<b>PR</b>			
Central review	2 (15.4)	1 (7.7)¶	1 (7.7)
Investigator review	3 (23.1)	3 (23.1)	3 (23.1)
<b>SD</b>			
Central review	10 (76.9)	11 (84.6)	11 (84.6)
Investigator review	8 (61.5)	8 (61.5)	8 (61.5)
<b>PD</b>			
Central review	0	0	0
Investigator review	2 (15.4)	2 (15.4)	2 (15.4)
<b>Unknown</b>			
Central review	1 (7.7)	1 (7.7)	1 (7.7)
Investigator review	0	0	0
<b>DOR††</b>			
Events/responders, n/n‡‡;			
KM median (95% CI), months			
Central review	0/2; NR	0/1; NR	1/1; 24.0 (NE)
Investigator review	0/3; NR	1/3; 17.7 (NE)	2/3; 18.1 (17.7–18.4)
<b>PFS§§</b>			
Events, n; KM median (95% CI), months‡‡			
Central review	4; 13.1 (5.6–13.1)	6; 13.1 (NE)	8; 13.1 (5.6–33.1)
Investigator review	7; 13.1 (9.2–16.6)	8; 13.1 (NE)	9; 13.1 (9.2–19.4)
<b>OS¶¶</b>			
Deaths, n; KM median (95% CI), months			
Central review	1; NR	3; NR	3; NR
2-year OS (95% CI), %			
Central review	–	–	69.3 (31.2–89.1)

BOR, best overall response; CR, complete response; DOR, duration of response; KM, Kaplan–Meier; mBCC, metastatic basal cell carcinoma; NE, not estimable; NR, not reached; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; QD, once daily; SD, stable disease; –, indicates not reported.

\*Data cut-off, 28 June 2013; median follow-up (200- and 800-mg arms), 13.9 months.

†Data cut-off, 11 July 2014; median follow-up (200- and 800-mg arms), 26.3 months.

‡Data cut-off, 10 July 2015; median follow-up (200- and 800-mg arms), 38.2 months.

§Proportion of patients with a BOR of CR or PR on repeat assessments ≥4 weeks apart.

¶BOR of one patient changed from a PR to SD due to identification of a new lesion by central rereview in a photograph received after the cut-off for the primary analysis (28 June 2013).

\*\*Best response recorded from the time of randomization until the earliest occurrence of disease progression, start of other antineoplastic therapy or data cut-off date.

††Time from first observed objective response (CR or PR) until disease progression or death due to any cause (responder data only).

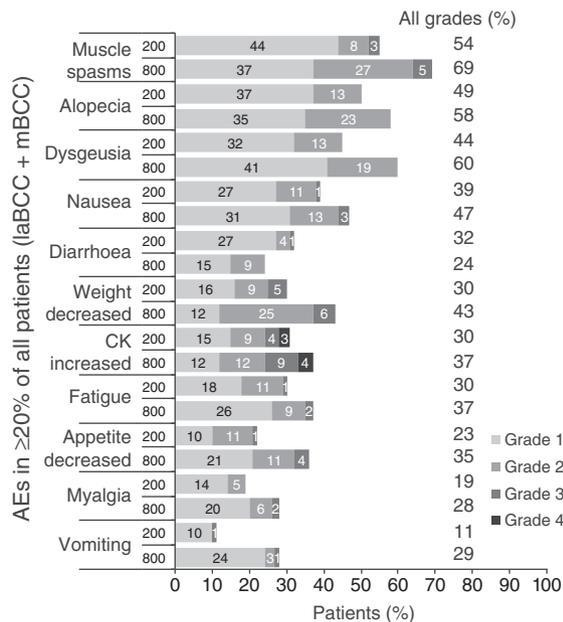
‡‡Progressive disease or death due to any cause.

§§Time from randomization to first documented disease progression or death due to any cause.

¶¶Time from randomization to the date of death due to any cause or the last date the patient was known to be alive.

with either dose. Lower incidences of grade 3/4 AEs, SAEs and AEs leading to discontinuation were observed with 200 mg vs. 800 mg. The majority of the most common AEs were generally grade 1 or 2 and were similar to those reported with other HPIs<sup>10–12,30–39</sup>; muscle-related AEs and the increase in CK that

can accompany these AEs are thought to be a class effect of HPIs.<sup>11,12,30,31,35,39</sup> Muscle-related AEs were effectively managed with dose adjustments or interruptions. In the future, patients who experience sonidegib-related AEs will be managed using this approach in an attempt to prolong exposure and enhance



**Figure 3** Adverse events (AEs), regardless of causality, reported in  $\geq 20\%$  of all patients treated with sonidegib, by treatment arm. The most common AEs reported in patients treated with sonidegib 200 mg ( $n = 79$ ) or 800 mg ( $n = 150$ ) assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events v4.03.<sup>20</sup> Reported AEs include those that occurred during treatment and within 30 days of treatment discontinuation. For a patient who had multiple occurrences of the same AE, the AE is reported only once at the highest severity rating. CK, creatine kinase; laBCC, locally advanced basal cell carcinoma; mBCC, metastatic BCC.

treatment benefit. In addition, future clinical trials designed to optimize the treatment regimen of HPIs may further improve outcomes.

Overall, these results support the use of sonidegib 200 mg as a treatment option for patients with advanced BCC according to local guidelines.<sup>14–17</sup>

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## Supporting information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Composite overall response in locally advanced basal cell carcinoma (laBCC) determined by mRECIST and BCC-RECIST-like criteria

**Table S2.** Efficacy in patients with locally advanced basal cell carcinoma (laBCC) treated with sonidegib 800 mg by central and investigator review

**Table S3.** Efficacy in patients with locally advanced basal cell carcinoma (laBCC) by central and investigator review per BCC-recist-like criteria (30-month analysis)

**Table S4.** Efficacy in patients with locally advanced basal cell carcinoma (laBCC) by baseline tumor burden by treatment arm (18-month analysis)

**Table S5.** Efficacy in patients with metastatic basal cell carcinoma (mBCC) treated With Sonidegib 800 mg by central and investigator review

**Table S6.** Serious adverse events reported in  $\geq 1\%$  of patients in either arm, regardless of causality (30-month analysis)

**Figure S1.** BOLT trial profile.

**Figure S2.** Waterfall plots of best change from baseline in the size of target lesions in patients with locally advanced basal cell carcinoma (laBCC).

**Figure S3.** Duration of response (DOR) in patients with locally advanced basal cell carcinoma (laBCC).

**Figure S4.** Kaplan–Meier plots of duration of response (DOR) in patients with locally advanced basal cell carcinoma (laBCC) and of progression-free survival (PFS) in patients with laBCC and metastatic BCC (mBCC) treated with sonidegib 800 mg by central and investigator review.

**Figure S5.** Kaplan–Meier plot of overall survival (OS) in patients with locally advanced basal cell carcinoma (laBCC) and metastatic BCC (mBCC) treated with sonidegib 800 mg.

**Figure S6.** Waterfall plots of best change from baseline in the size of target lesions in patients with metastatic basal cell carcinoma (mBCC).

**Figure S7.** Mean trough-concentration time profiles for sonidegib 200 or 800 mg.

**Figure S8.** Adverse events (AEs), regardless of causality, reported in  $\geq 20\%$  of patients with locally advanced basal cell carcinoma (laBCC) treated with sonidegib, by treatment arm.

**Figure S9.** Adverse events (AEs), regardless of causality, reported in  $\geq 20\%$  of patients with metastatic basal cell carcinoma (mBCC) treated with sonidegib, by treatment arm.