Effects of sonidegib dose reduction or delay in locally advanced basal cell carcinoma: 42-month data from BOLT

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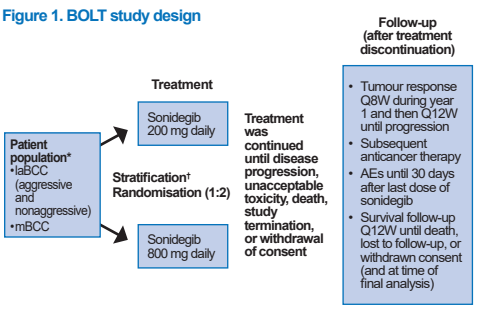
BACKGROUND

- Sonidegib is a Hedgehog inhibitor that selectively targets Smoothened1
- Sonidegib was approved in 2015 in the US, EU, Switzerland, and Australia for the treatment of adult patients with locally advanced basal cell carcinoma (laBCC) not amenable to curative surgery or radiation therapy[1–4]
  - Sonidegib is also approved for the treatment of metastatic BCC (mBCC) in Switzerland and Australia[3,4]
- Approval in laBCC was based on primary data from the phase 2 BOLT (**B**asal Cell Carcinoma **O**utcomes with **L**DE225 [sonidegib] **T**reatment) trial (NCT01327053)[5]
- Although the majority of adverse events (AEs) reported in the BOLT study were grade 1 or 2 in severity, AEs were a primary reason for early discontinuation[6]
- The impact of dose modification or treatment delay is important in the context of long-term efficacy
- Here we report 42-month objective response rates (ORRs) associated with sonidegib dose reduction or treatment delay in patients with advanced BCC enrolled in the BOLT study

METHODS

- BOLT was a randomised, double-blind, phase 2 clinical trial conducted in 58 centres across 12 countries[5] (**Figure 1**)

Figure 1. BOLT study design



*Patients who received prior treatment with sonidegib or other HHI were excluded. †Stratification was based on stage, disease histology for patients with laBCC (nonaggressive vs aggressive), and geographic region.
AE, adverse event; BCC, basal cell carcinoma; BOLT, **B**asal Cell Carcinoma **O**utcomes with **L**DE225 (sonidegib) **T**reatment; HHI, Hedgehog inhibitor; laBCC, locally advanced BCC; mBCC, metastatic BCC; Q8W, every 8 weeks; Q12W, every 12 weeks.

- Eligible patients had either histologically confirmed laBCC (not amenable to curative surgery or radiation) or mBCC (where all other treatment options had been exhausted)
- The primary endpoint was ORR per central review (**Figure 2**), using modified Response Evaluation Criteria in Solid Tumors (mRECIST) in patients with laBCC
  - mRECIST is a composite multimodal evaluation integrating magnetic resonance imaging (per RECIST v1.1[7]) standard and annotated colour photography (using bidimensional World Health Organization criteria[8]), and histology in multiple biopsies based on lesion surface area in the complex setting of posttreatment scarring, fibrosis, and ill-defined lesion borders

Figure 2. BOLT study endpoints

Primary	ORR → best overall confirmed response of CR or PR per central review according to mRECIST (laBCC) or RECIST v1.1 (mBCC)
Key Secondary	DOR and CR rates per central review according to mRECIST (laBCC) or RECIST v1.1 (mBCC)
Other Secondary	• OS • Safety • ORR and DOR per investigator review • PFS and TTR per central and investigator review

BCC, basal cell carcinoma; BOLT, **B**asal Cell Carcinoma **O**utcomes with **L**DE225 (sonidegib) **T**reatment; CR, complete response; DOR, duration of response; laBCC, locally advanced BCC; mBCC, metastatic BCC; mRECIST; modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; TTR, time to tumour response.

- Data analyses were performed at 6 months,[5] 12 months,[9] 18 months,[6] 30 months,[6] and 42 months; only data from the final analysis (data cutoff: July 8, 2016) are presented here
- Dose modifications were based on the worst grade of toxicity observed
  - Dose delays of ≤21 days and dose reductions were permitted for AEs suspected to be related to sonidegib (sample guidance provided in **Table 1**)
  - For patients treated with sonidegib 200 mg daily, one dose reduction was allowed (**Figure 3**)
  - For patients in the 800 mg daily group, a maximum of two dose reductions was allowed: first to 400 mg once daily and then to 200 mg once daily (**Figure 3**)

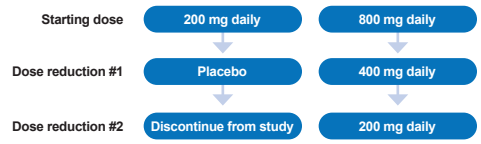
Table 1. Recommended dose modifications and dose delays for suspected treatment-related muscle toxicity

Suspected Treatment-Related Muscle Toxicity	
Normal CK with muscle-related symptoms (eg, pain, spasms, cramps)	• Grade 1 or 2 symptoms: Continue sonidegib at same dose; consider symptomatic treatment for muscle-related toxicity • Grade 3: Hold sonidegib dose for up to 21 days; measure CK; resume sonidegib at a reduced dose if resolved or improved to grade 1 occurs
Grade 1 or 2 CK elevation*	• Asymptomatic (no new onset or worsening of muscle cramps, myalgia, or other muscle symptoms): Continue sonidegib at same dose • Symptomatic: Continue sonidegib at same dose, monitor CK at least QW
Grade 3 or 4 CK elevation*	• Hold sonidegib dose • Check blood and/or urine myoglobin • Monitor renal function • Measure CK at least twice weekly • Consider electromyography and muscle biopsy • Consider resuming sonidegib at a reduced dose if renal function is not impaired and resolution to ≤1 occurs within 21 days • Discontinue patient from study in the presence of renal impairment (serum creatinine >2X ULN)

*Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, v4.03.[9]
CK, creatine kinase; QW, once weekly; ULN, upper limit of normal.

- Subgroup analyses included:
  - Incidence of, and primary reason for, dose reduction
  - Incidence of, and primary reason for, treatment delay
  - ORR in patients with and without dose reduction or delay

Figure 3. Dose modification steps for sonidegib



RESULTS

Dose reductions and treatment delays (Table 2)

- Dose reductions and treatment delays were primarily instituted for AEs
- Overall, treatment delay was more common than dose reduction (66% vs 30%)
- Dose reduction was more frequent in patients treated with 800 mg (37%) vs 200 mg (17%)
- The primary reason for sonidegib dose reduction was muscle-related AEs, affecting one (1.3%) patient in the sonidegib 200 mg arm (muscle weakness and myalgia) and 21 (14%) patients in 800 mg arm (muscle spasms and increased creatine kinase)

Table 2. Dose reduction and treatment delay in sonidegib-treated patients with advanced BCC: BOLT 42-month analysis

	Sonidegib 200 mg/day	Sonidegib 800 mg/day	All
Patients randomised, n	79	151	230
Patients treated, n	79	150	229
Patients with any dose reduction, n (%) 1 reduction 2 reductions	13 (17) 13 (17) 0	55 (37) 44 (29) 11 (7)	68 (30) 57 (25) 11 (5)
Reasons for dose reduction, n Adverse events Dosing error Lack of efficacy	13* 12 1 0	55* 57 3 1	68* 69 4 1
Days full dose received, % Median Range	99.1 8.1–100	94.2 2.6–100	97.6 2.6–100
Patients with any delay in treatment, n (%) 1 delay ≥2 delays	54 (68) 19 (24) 35 (44)	98 (65) 34 (23) 64 (43)	152 (66) 53 (23) 99 (43)
Actual days of sonidegib treatment, % Median Range	99 77–100	98 47–100	99 47–100
Reasons for treatment delay, n (%) Adverse event Dosing error Technical issue Dispensing error	54* 31 (39) 28 (35) 18 (23) 0	98* 77 (51) 47 (31) 24 (16) 1 (0.7)	152* 108 (47) 75 (33) 42 (18) 1 (0.4)

*A patient with multiple reasons for dose change or delay is only counted once in the total row.
BCC, basal cell carcinoma; BOLT, **B**asal Cell Carcinoma **O**utcomes with **L**DE225 (sonidegib) **T**reatment.

Impact of sonidegib dose reductions and treatment delays on efficacy outcomes

- In the 200 mg arm, ORRs by central review were:
  - Similar between all patients (48%) and subgroups with (46%) and without (49%) dose reduction or delay (**Table 3**)
  - Similar between all patients with laBCC (56%) and subgroups with (50%) and without (57%) dose reduction or delay (**Table 4**)
- In the 800 mg daily arm, ORRs increased in the setting of at least 1 dose reduction in both the overall population (58%) and the subset of patients with laBCC (67%) but were not formally (statistically) tested (**Table 5**)
- In the 200 mg arm, the impact of dose reduction on duration of response (DOR) and progression-free survival could not be determined given the low number of events. In contrast, dose reduction in the 800 mg arm was associated with a DOR similar to that of the overall treated population

Table 3. Objective response rate by central review at 42 months in sonidegib-treated patients with advanced BCC and without dose reduction or delay

	Sonidegib 200 mg/day ORR, % (95% CI)	Sonidegib 800 mg/day ORR, % (95% CI)
All patients (laBCC + mBCC)	n = 79 **48** (37–60)	n = 151 **42** (34–50)
No dose reduction or delay	n = 66 **49** (36–61)	n = 96 **32** (23–43)
≥1 dose reduction or delay	n = 13 **46** (19–75)	n = 55 **58** (44–71)
Patients with laBCC	n = 66 **56** (43–68)	n = 128 **46** (37–55)
No dose reduction or delay	n = 54 **57** (43–71)	n = 80 **34** (24–45)
≥1 dose reduction or delay	n = 12 **50** (21–79)	n = 48 **67** (52–80)

BCC, basal cell carcinoma; CI, confidence interval; laBCC, locally advanced BCC; mBCC, metastatic BCC ; ORR, objective response rate.

Table 4. Duration of response by central review at 42 months in sonidegib-treated patients with advanced BCC with and without dose reduction or delay*

	Sonidegib 200 mg/day n = 79	Sonidegib 800 mg/day n = 151
All patients (laBCC + mBCC) Events/responders, n/N Median, month (95% CI)	13/38 **26.1** (NE)	24/63 **23.3** (12.2–29.6)
No dose reduction or delay Events/responders, n/N Median, month (95% CI)	12/32 **24.0** (NE)	13/31 **14.7** (8.3–26.4)
≥1 dose reduction or delay Events/responders, n/N Median, month (95% CI)	1/6 **NE** (NE)	11/32 **24.8** (NE)
All patients with laBCC Events/responders, n/N Median, month (95% CI)	12/37 **26.1** (NE)	23/59 **23.3** (12.2–29.6)
No dose reduction or delay Events/responders, n/N Median, month (95% CI)	11/31 **26.1** (NE)	12/27 **14.7** (8.8–26.4)
≥1 dose reduction or delay Events/responders, n/N Median, month (95% CI)	1/6 **NE** (NE)	11/32 **24.8** (NE)

*Median DOR was calculated using the Kaplan-Meier method.
BCC, basal cell carcinoma; CI, confidence interval; DOR, duration of response; laBCC, locally advanced BCC; mBCC, metastatic BCC; NE, not estimable.

Table 5. Progression-free survival by central review at 42 months in sonidegib-treated patients with advanced BCC with and without dose reduction or delay*

	Sonidegib 200 mg/day n = 79	Sonidegib 800 mg/day n = 151
All patients (laBCC + mBCC) Events/patients, n/N Median, month (95% CI)	25/79 **22.1** (14.4–33.1)	46/151 **21.5** (16.1–28.4)
No dose reduction or delay Events/patients, n/N Median, month (95% CI)	22/66 **22.1** (14.4–30.7)	28/96 **16.7** (12.1–28.4)
≥1 dose reduction or delay Events/patients, n/N Median, month (95% CI)	3/13 **NE** (NE)	18/55 **24.9** (16.6–42.8)
All patients laBCC Events/patients, n/N Median, month (95% CI)	17/66 **22.1** (NE)	33/128 **24.9** (19.2–33.4)
No dose reduction or delay Events/patients, n/N Median, month (95% CI)	15/54 **22.1** (14.4–39.6)	20/80 **21.5** (13.2–33.4)
≥1 dose reduction or delay Events/patients, n/N Median, month (95% CI)	2/12 **NE** (NE)	13/48 **29.3** (19.3–43.3)

*Median PFS was calculated using the Kaplan-Meier method.
BCC, basal cell carcinoma; CI, confidence interval; laBCC, locally advanced BCC; mBCC, metastatic BCC; NE, not estimable; PFS, progression-free survival.

CONCLUSIONS

- These data support the long-term efficacy of sonidegib at the approved dose of 200 mg daily
- Sonidegib dose reductions and treatment delays are feasible without negatively impacting treatment efficacy
- Proactive management of AEs, including dose adjustment and treatment delays, may improve tolerability and optimise sonidegib treatment duration

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DISCLOSURES

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