Adverse events of special interest in patients with advanced basal cell carcinoma receiving sonidegib: Long-term 42-month results from the BOLT study

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BACKGROUND

- Sonidegib—a hedgehog inhibitor (HHI) that selectively targets Smoothened[1]—is approved in the US, the EU, 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]
- Through 42 months of the phase 2 BOLT (**B**asal Cell Carcinoma **O**utcomes with **L**DE225 [sonidegib] **T**reatment) trial (NCT01327053), sonidegib 200 mg/day demonstrated durable efficacy and consistent/manageable toxicity[5-9]

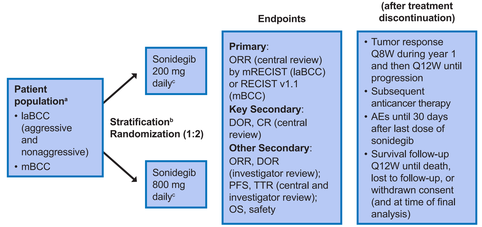
OBJECTIVES

- Here, we report the incidence and impact of HHI class-effect adverse events (AEs) from the BOLT 42-month results

METHODS

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

Figure 1. BOLT study design



[a]Patients previously treated with sonidegib or other HHI were excluded. [b]Stratification was based on stage, disease histology for patients with laBCC (nonaggressive vs aggressive), and geographic region. [c]Treatment was continued until disease progression, unacceptable toxicity, death, study termination, or withdrawal of consent.
AE, adverse event; BCC, basal cell carcinoma; BOLT, **B**asal Cell Carcinoma **O**utcomes with LDE225 (sonidegib) **T**reatment; CR, complete response; DOR, duration of response; HHI, hedgehog inhibitor; 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; Q8W, every 8 weeks; Q12W, every 12 weeks; TTR, time to tumor response.

- Eligible patients had either histologically confirmed laBCC (not amenable to curative surgery or radiation) or mBCC (for which all other treatment options had been exhausted)
- Primary and secondary endpoints are summarized in **Figure 2**

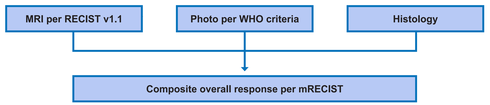
Figure 2. BOLT study endpoints

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 • ORR and DOR per investigator review • Safety • PFS and TTR per central and investigator review

BCC, basal cell carcinoma; BOLT, **B**asal Cell Carcinoma **O**utcomes with LDE225 (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 tumor response.

- Tumor response was evaluated by investigator review and by central review using modified Response Evaluation Criteria in Solid Tumors (mRECIST) for patients with laBCC and RECIST v1.1 for patients with mBCC (**Figure 2** and **Figure 3**)

Figure 3. Tumor evaluation per mRECIST (laBCC)



mRECIST is a composite multimodal evaluation used to integrate MRI according to RECIST v1.1,[10] standard and annotated color photography using bidimensional WHO criteria,[11] and histology in multiple biopsies based on lesion surface area in the complex setting of posttreatment scarring, fibrosis, and ill-defined lesion borders. Complete response is defined as a negative MRI, negative photo, and negative histology. Partial response is defined as ≥50% reduction in bidimensional format.
BCC, basal cell carcinoma; laBCC, locally advanced BCC; mRECIST, modified Response Evaluation Criteria in Solid Tumors; MRI, magnetic resonance imaging; WHO, World Health Organization.

- Safety/tolerability were assessed through monitoring and recording AEs; regular monitoring of hematology, clinical chemistry, and electrocardiograms; and routine monitoring of vital signs and physical condition
  - AEs were coded using the Medical Dictionary for Regulatory Activities terminology v19.0 and toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03[12]
  - Muscle-related events were evaluated by an independent Safety Review and Adjudication Committee
  - AEs of special interest for HHI-class drugs included muscle-related events, alopecia, nausea and/or vomiting, dysgeusia, decreased appetite and/or weight loss, fatigue/lethargy, diarrhea, hypersensitivity, second primary malignancies, QT prolongation, lipase and amylase elevations, fractures, and cardiac disorders
- 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
- Data presented here are based on the US Food and Drug Administration-approved 200-mg dose at 42 months

RESULTS

- At baseline, 60.8% of the 79 patients receiving sonidegib 200 mg/day were male and had a median age of 67.0 years; the majority (83.5%) of patients had laBCC and 62.0% had ≥2 lesions (**Table 1**)

Table 1. Baseline demographics and disease characteristics in patients receiving sonidegib 200 mg daily

	Sonidegib 200 mg (n = 79)
Median age (range), years	67 (25–92)
Male	48 (61)
ECOG performance status	
0	50 (63)
1	19 (24)
2	8 (10)
Unknown	2 (3)
Stage	
laBCC	66 (84)
mBCC	13 (16)
Histologic/cytologic subtype	
Aggressive[a]	40 (51)
Nonaggressive[b]	38 (48)
Undetermined	1 (1)
Number of lesions	
1	30 (38)
≥2	49 (62)
Metastasis	14 (18)
Sites	
Lung	10/14 (71)
Bone	2/14 (14)
Axillary lymph node	1/14 (7)
Trunk	1/14 (7)
Other[c]	3/14 (21)
Prior antineoplastic therapy	
Surgery	59 (75)
Radiotherapy	19 (24)

Data presented as n (%) unless otherwise indicated.
[a]Includes micronodular, infiltrative, multifocal, basosquamous, and sclerosing histological subtypes. [b]Includes nodular and superficial histological subtypes.[c]Includes retro-orbital and left mandible, pelvic side wall and lung, and bilateral scalp.
BCC, basal cell carcinoma; ECOG, Eastern Cooperative Oncology Group; laBCC, locally advanced BCC; mBCC, metastatic BCC.

Overall efficacy at 42 months

- Clinically relevant objective response rates (ORRs) continued to be reported for patients receiving 200 mg/day of sonidegib at 42 months (**Table 2**)
- At 42 months, the ORR (95% confidence interval) was 48.1% (36.7%–59.6%) for all 79 patients receiving 200 mg/d of sonidegib
- Disease control rate exceeded 90% and further supports treatment benefit (**Table 2**)
- Sustained duration was confirmed, with a median duration of response of 26.1 months (**Table 2**)

Table 2. Efficacy outcomes per central review in patients with advanced BCC receiving sonidegib 200 mg daily

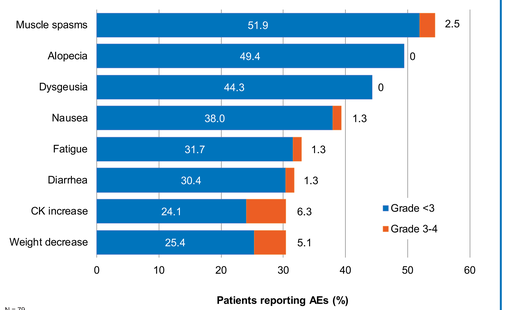
	laBCC (n = 66)	mBCC (n = 13)
ORR, % (95% CI)	56.1 (43.3, 68.3)	7.7 (0.2, 36.0)
CR, % (95% CI)	4.5 (0.9, 12.7)	0 (0.0, 24.7)
DCR, %	90.9	92.3
DOR, median, months (95% CI)	26.1 (NE)	24.0 (NE)
PFS, median, months (95% CI)	22.1 (NE)	13.1 (5.6, 33.1)
TTR, median, months (95% CI)	4.0 (3.8, 5.6)	9.2 (NE)

BCC, basal cell carcinoma; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; laBCC, locally advanced BCC; mBCC, metastatic BCC; NE, not estimable; ORR, objective response rate; PFS, progression-free survival; TTR, time to tumor response.

Overall safety/tolerability at 42 months

- Median duration of sonidegib exposure was 11.0 months in the 200 mg/day group
- Overall, 54 (68.4%), 34 (43.0%), and 19 (24.1%) patients were exposed to sonidegib 200 mg/day for ≥8, ≥12, and ≥20 months, respectively
- The majority of AEs were grade 1−2 in severity
- The most common all-grade AEs in patients receiving sonidegib 200 mg/day were muscle spasms (54.4%, n = 43), alopecia (49.4%, n = 39), dysgeusia (44.3%, n = 35), nausea (39.3%, n = 31), fatigue (33.0%, n = 26), diarrhea (31.7%, n = 25), weight decrease (30.5%, n = 24), and creatine kinase (CK) increase (30.4%, n = 24) (**Figure 4**)

Figure 4. Adverse events reported in ≥30% of patients receiving 200 mg daily



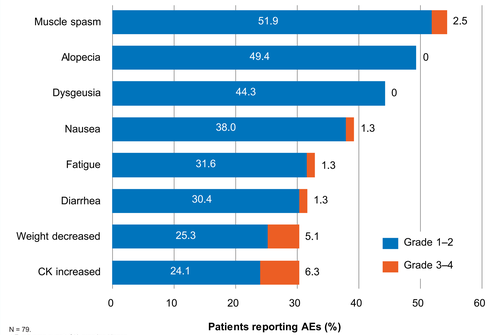
N = 79.
AE, adverse event; CK, creatine kinase.

- Of all 79 patients receiving sonidegib 200 mg/day, 16.5% of patients (n = 13) had a dose reduction and 68.4% (n = 54) had ≥1 dose interruption; 44.3% (n = 35) had ≥2 dose interruptions

Adverse events of special interest at 42 months

- Incidence and severity of HHI class-effect AEs at 42 months were consistent with reports at 30 months
- The most common all-grade AEs of special interest in patients receiving sonidegib 200 mg/day (N = 79) were all muscle-related events (68.4%); muscle spasms (54.4%); alopecia (49.4%); dysgeusia (44.3%); and nausea (39.2%) (**Figure 5**)

Figure 5. Adverse events of special interest reported in ≥30% of patients receiving sonidegib 200 mg daily



N = 79.
AE, adverse event; CK, creatine kinase.

- Most AEs of special interest were of grade <3. The most common grade 3/4 AEs of special interest (occurred in ≥5%) were increased CK (6.3%, n = 5); weight loss (5.1%, n = 4); lipase and amylase elevations (6.3%, n = 5); nausea and/or vomiting and their complications (5.1%, n = 4); and fatigue and asthenia (5.1%, n = 4)
  - The majority of high-grade AEs were reversible with interruptions in treatment
  - The time-to-first onset of grade 3/4 muscle-related events ranged from 1.9 to 11.0 months in patients receiving sonidegib 200 mg/day
- Few AEs of special interest required discontinuation of sonidegib or reductions in dose (**Table 3**)

Table 3. Adverse events of special interest leading to discontinuation or dose adjustments in patients receiving sonidegib 200 mg daily

Adverse event	Leading to discontinuation	Requiring dose adjustment
Muscle-related events	5 (6.3)	1 (1.3)
Fatigue and asthenia	5 (6.3)	1 (1.3)
Decreased appetite and/or weight loss	4 (5.1)	0
Dysgeusia	3 (3.8)	1 (1.3)
Nausea and/or vomiting	3 (3.8)	0
Second primary malignancies	2 (2.5)	0
Increased lipase	2 (2.5)	3 (3.8)
Alopecia	1 (1.3)	1 (1.3)
Hypersensitivity	1 (1.3)	0
Fractures	1 (1.3)	0
Cardiac disorders	0	0

N = 79.
Data are presented as n (%).

- Muscle-related events leading to discontinuation were grade 2 muscle spasms (n = 1), grade 3 muscle spasms (n = 3), and grade 3 blood CK increase (n = 1). The event requiring dose adjustment was muscle weakness
- Fatigue and asthenia events leading to discontinuation were grade 3 asthenia (n = 1), grade 2 asthenia (n = 2), and grade 1/2 fatigue (n = 2); there were no lethargy events leading to discontinuation
- Decreased appetite and weight loss events leading to discontinuation were grade 1/2 decreased appetite (n = 2) and grade 2 weight loss (n = 2)
- No new second primary malignancies were reported at 42 months in patients receiving sonidegib 200 mg/day. The 2 events leading to discontinuation were grade 3 invasive papillary breast carcinoma and grade 2 prostate cancer; both were determined not related to the study drug

CONCLUSIONS

- Patients receiving sonidegib 200 mg/day experienced consistent and robust efficacy and manageable tolerability, with rare grade 3/4 AEs and discontinuations
- Safety and tolerability of sonidegib 200 mg/day at 42 months was consistent with earlier data
- AEs of special interest associated with HHI-class drugs were manageable and few led to discontinuations or dose reductions in patients receiving sonidegib 200 mg/day

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