Biochemistry laboratory shift based on common terminology criteria in patients with advanced basal cell carcinoma receiving sonidegib 200 mg daily: Results from the 42-month BOLT study

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BACKGROUND

- Hedgehog inhibitors were developed to block aberrant Hedgehog signaling found in most sporadic basal cell carcinomas (BCCs); inhibition of the Hedgehog pathway is among the limited treatment options available for patients with advanced BCC[1,2]
- Sonidegib is a Hedgehog inhibitor that selectively targets Smoothened[3] and is approved in the US, the EU, Switzerland, and Australia for the treatment of adult patients with locally advanced BCC (laBCC) not amenable to curative surgery or radiation therapy[3–6]
  - Sonidegib is also approved to treat metastatic BCC (mBCC) in Switzerland and Australia[5,6]
- 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 daily demonstrated durable efficacy and consistent/manageable toxicity[7–10]
- Evaluation of clinical biochemistry in patients with advanced BCC provides valuable information on the tolerability and safety of sonidegib

OBJECTIVE

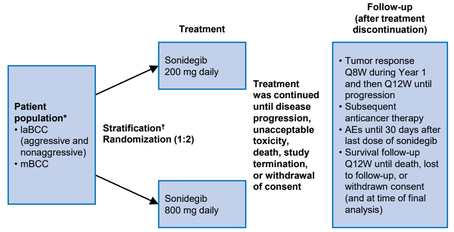
- To characterize changes in biochemistry laboratory values in patients receiving sonidegib 200 mg daily through 42 months of treatment for advanced BCC

METHODS

Study design

- BOLT was a randomized, double-blind, Phase 2 clinical trial conducted in 58 centers across 12 countries[10]
- Eligible patients had histologically confirmed laBCC or mBCC and were randomized 1:2 to receive sonidegib 200 or 800 mg orally daily, respectively (**Figure 1**)

Figure 1. BOLT study design



*Patients previously treated 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 LDE225 (sonidegib) **T**reatment; HHI, Hedgehog inhibitor; laBCC, locally advanced BCC; mBCC, metastatic BCC; Q8W, every 8 weeks; Q12W, every 12 weeks.

Assessments

- The primary efficacy endpoint was objective response rate (ORR) per central review (**Figure 2**)
- ORR was defined as the proportion of patients with a confirmed best overall response (determined based on consecutive assessments ≥4 weeks apart) of complete response or partial response

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 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 RECIST; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to tumor response.

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

Biochemistry assessments

- Clinical biochemistry assessments were ideally performed in fasted patients at screening, biweekly for 14 weeks, then every 4 weeks until Week 77, and then as clinically indicated until end of treatment
  - Assessments included alanine aminotransferase (ALT), albumin, alkaline phosphatase, amylase, aspartate aminotransferase (AST), total bilirubin, total calcium, cholesterol, plasma and serum creatine kinase (CK), creatinine, glucose, lipase, magnesium, phosphorus, potassium, and sodium
- Biochemistry evaluations were performed by a central laboratory until Week 182; after this, assessments were conducted locally
- Abnormal laboratory values constituted adverse events (AEs) if they fulfilled ≥1 of the following criteria:
  - Induced clinical signs or symptoms
  - Considered clinically significant
  - Required concomitant therapy or procedures
  - Required changes in study treatment

Safety assessments

- Safety assessments included AE monitoring and recording until 30 days after the last dose through regular monitoring of hematology, clinical chemistry, electrocardiograms, 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[11]

RESULTS

Patient demographics and baseline disease characteristics

- At baseline, 48 (60.8%) patients receiving sonidegib 200 mg daily (n = 79) were male; the median age of patients in this study was 67 years (**Table 1**)

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

	Sonidegib 200 mg (n = 79)
Age, years, mean (SD)	65.6 (15.7)
Age, years, median (range)	67 (25–92)
Sex, male	48 (60.8)
ECOG performance status	
0	50 (63.3)
1	19 (24.1)
2	8 (10.1)
Unknown	2 (2.5)
Stage	
laBCC	66 (83.5)
mBCC	13 (16.5)
Histologic/cytologic subtype	
Aggressive*	40 (50.6)
Nonaggressive†	38 (48.1)
Undetermined	1 (1.3)
Number of lesions	
0	0
1	30 (38.0)
≥2	49 (62.0)
Metastasis	14 (17.7)
Metastatic site	
Lung	10 (12.7)
Lymph nodes‡	1 (1.3)
Bone	2 (2.5)
Other§	4 (5.1)
Prior antineoplastic therapy	
Surgery	59 (74.7)
Radiotherapy	19 (24.1)

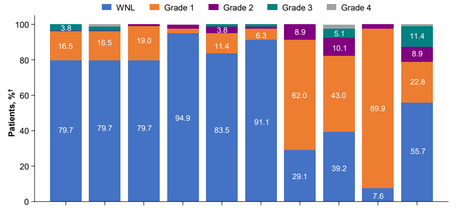
Data presented as n (%) unless otherwise indicated.
*Includes micronodular, infiltrative, multifocal, basosquamous, and sclerosing histological subtypes. †Includes nodular and superficial histological subtypes. ‡Includes axillary, parotid, submandibular, supraclavicular, and other. §Includes trunk, brain, head, liver, neck, and upper extremities.
BCC, basal cell carcinoma; ECOG, Eastern Cooperative Oncology Group; laBCC, locally advanced BCC; mBCC, metastatic BCC; SD, standard deviation.

- At 42 months, ORRs (95% confidence interval) in patients with laBCC (n = 66) and mBCC (n = 13) receiving sonidegib 200 mg were 56.1% (43.3%–68.3%) and 7.7% (0.2%–36.0%), respectively; disease control rate (summed complete response, partial response, and stable disease rates) exceeded 90% in all patients

Biochemistry assessments

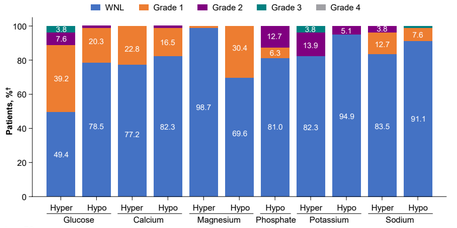
- Through 42 months of treatment with sonidegib 200 mg, most biochemistry laboratory values had shifts ≤Grade 2, with the majority being ≤Grade 1 (**Figure 3**)
- Observed Grade 3 shifts included elevations in ALT, amylase, AST, bilirubin, plasma CK, serum CK, glucose, lipase, and potassium; 1 patient developed hyponatremia (**Table 2**)
- Grade 4 shifts were minimal and included elevations in AST, serum CK, and lipase (**Table 2**)

Figure 3A. Distribution of biochemistry shifts for enzyme, protein, and lipid parameters in patients receiving sonidegib 200 mg daily*



*n = 79. †Values <3.8% are not shown within corresponding bars. ‡Values for plasma CK were not included, as 86.1% of data values were missing for this parameter.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; WNL, within normal limits.

Figure 3B. Distribution of biochemistry shifts for glucose and electrolyte parameters in patients receiving sonidegib 200 mg daily*



*n = 79.
†Values <3.8% are not shown within corresponding bars.
WNL, within normal limits.

Table 2. Distribution of biochemistry shifts for parameters with Grade 3 or 4 shifts in patients receiving sonidegib 200 mg daily*

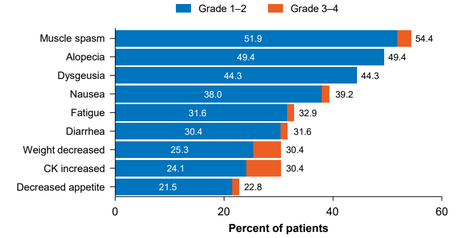
	Within normal limits	Grade 1	Grade 2	Grade 3	Grade 4
ALT	63 (79.7)	13 (16.5)	0	3 (3.8)	0
Amylase	66 (83.5)	9 (11.4)	3 (3.8)	1 (1.3)	0
AST	63 (79.7)	13 (16.5)	0	2 (2.5)	1 (1.3)
Bilirubin	72 (91.1)	5 (6.3)	1 (1.3)	1 (1.3)	0
Plasma CK	8 (10.1)	1 (1.3)	1 (1.3)	1 (1.3)	0
Serum CK	31 (39.2)	34 (43.0)	8 (10.1)	4 (5.1)	2 (2.5)
Hyperglycemia	39 (49.4)	31 (39.2)	6 (7.6)	3 (3.8)	0
Lipase	44 (55.7)	18 (22.8)	7 (8.9)	9 (11.4)	1 (1.3)
Hyperkalemia	65 (82.3)	0	11 (13.9)	3 (3.8)	0
Hyponatremia	72 (91.1)	6 (7.6)	0	1 (1.3)	0

All data presented as n (%).
*n = 79.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase.

Safety and tolerability at 42 months

- The majority of AEs were Grade 1–2 in severity
- The most common all-grade AEs in patients receiving sonidegib 200 mg daily were muscle spasms (54.4%), alopecia (49.4%), and dysgeusia (44.3%; **Figure 4**)

Figure 4. Adverse events reported in ≥20% of patients receiving sonidegib 200 mg daily



CK, creatine kinase.

CONCLUSIONS

- Through 42 months of treatment with sonidegib 200 mg daily, most patients experienced no biochemistry changes or Grade 1 biochemistry shifts
- Overall safety findings at 42 months were consistent with observations at 30 months[9]

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