Hematology 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 the majority of sporadic basal cell carcinomas (BCCs); inhibition of the Hedgehog pathway is among the few treatment options available for patients with advanced BCC[1,2]
- Sonidegib is a Hedgehog inhibitor that selectively targets Smoothened[3] and is approved at a dose of 200 mg daily 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 200 mg daily 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 safety parameters, such as hematology laboratory values in patients with advanced BCC provides valuable information on the tolerability and safety of sonidegib

OBJECTIVE

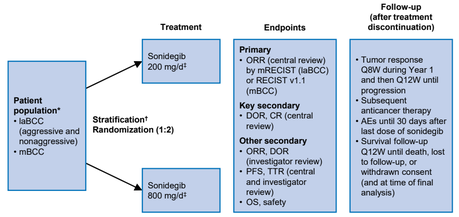
- To determine hematology laboratory abnormalities in patients receiving sonidegib 200 mg daily through 42 months of treatment for advanced BCC

METHODS

Study design

- BOLT was a randomized, double-blind, Phase 2 clinical trial conducted in 58 centers across 12 countries[10]
- Eligible patients had either 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. ‡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 **L**DE225 (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.

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 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 **L**DE225 (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

Hematology assessments

- Hematology assessments were performed at screening, biweekly for 14 weeks, then every 4 weeks until Week 77, and then followed as clinically indicated until end of treatment
  - Assessments included hemoglobin, platelet counts, complete red blood cell counts, and total white blood cell counts
  - Differential white blood cell counts included neutrophils, lymphocytes, monocytes, eosinophils, and basophils
- Hematology evaluations were performed by a central laboratory until Week 182; following Week 182, hematology assessments were conducted locally
- Abnormal laboratory values constituted adverse events (AEs) if they fulfilled ≥1 of the following criteria:
  - Induced clinical signs
  - Considered clinically significant
  - Required concomitant therapy or procedures
  - Required changes in study treatment

Safety

- 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%) of the 79 patients receiving sonidegib 200 mg daily were male (**Table 1**)
  - The median age was 67 years

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

	All patients (n = 79)
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)
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.
BCC, basal cell carcinoma; ECOG, Eastern Cooperative Oncology Group; laBCC, locally advanced BCC; mBCC, metastatic BCC.

- At 42 months, ORRs (95% confidence interval) in patients with laBCC (n = 66) and mBCC (n = 13) receiving sonidegib 200 mg daily were 56.1% (43.3%–68.3%) and 7.7% (0.2%–36.0%), respectively (**Table 2**)
- Disease control rate exceeded 90% in patients with both laBCC and mBCC
- Sustained duration was confirmed, with a median duration of response of 26.1 months in patients with laBCC

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

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

Results are for the intention-to-treat population.
BCC, basal cell carcinoma; CI, confidence interval; 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.

Hematology assessments

- In patients receiving sonidegib 200 mg daily, 24.1% of patients had Grade 1 anemia and 3.8% of patients had Grade 1 hyperhemoglobinemia (**Table 3**)
  - Zero patients had a Grade 3 or 4 hemoglobin shift
- Overall, 16.5%, 8.9%, and 2.5% of patients had Grade 1, 2, or 3 lymphocytopenia, respectively (**Table 3**)
- Grade 1 or 2 neutropenia was detected in 6.3% and 1.3% of patients, respectively
- Leukocytosis was not observed in any patients

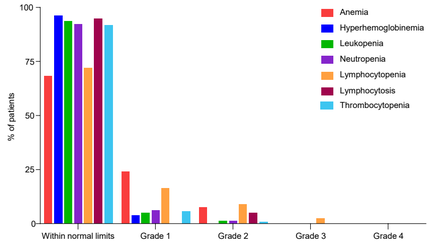
Table 3. Hematologic shifts in patients receiving sonidegib 200 mg daily

	Within normal limits	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	54 (68.4)	19 (24.1)	6 (7.6)	0	0
Hyperhemoglobinemia	76 (96.2)	3 (3.8)	0	0	0
Leukopenia	74 (93.7)	4 (5.1)	1 (1.3)	0	0
Neutropenia	73 (92.4)	5 (6.3)	1 (1.3)	0	0
Lymphocytopenia	57 (72.2)	13 (16.5)	7 (8.9)	2 (2.5)	0
Lymphocytosis	75 (94.9)	0	4 (5.1)	0	0

All data presented as n (%).

- Overall, 6.3% and 1.3% of patients had Grade 1 or 4 thrombocytopenia, respectively (**Figure 3**)
  - Zero patients had a Grade 2 or 3 shift in thrombocytes
- 92.4% of patients had no shift in thrombocyte counts

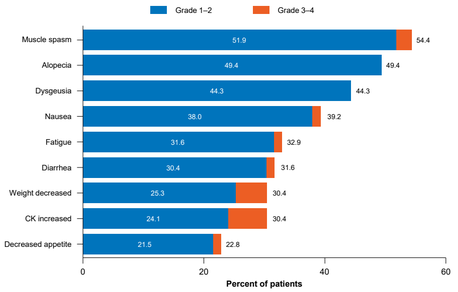
Figure 3. Hematology shifts in patients receiving sonidegib 200 mg daily



Safety and tolerability at 42 months

- Overall, the safety profile of sonidegib 200 mg daily was manageable and consistent with prior analyses[9,10]
- In patients receiving sonidegib 200 mg daily, the median duration of exposure was 11.0 months
- Overall, 54 (68.4%), 34 (43.0%), and 19 (24.1%) patients were exposed to sonidegib 200 mg daily 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 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 hematology changes or Grade 1 hematology shifts
- Overall safety findings at 42 months were consistent with observations at 30 months[9]
- Overall, patients with laBCC and mBCC receiving sonidegib 200 mg daily experienced consistent and robust efficacy and manageable tolerability

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MM participated in advisory boards and received honoraria from Genentech, Novartis, Sun Pharma, and Regeneron. **AG** has participated on advisory boards for Bristol-Myers Squibb, Pfizer, and Sanofi; received honoraria from Novartis; and received travel support from Astellas and Bristol-Myers Squibb. **RG** serves as a consultant to Almirall, Amgen, Bristol-Myers Squibb, Merck Serono, Merck Sharp & Dohme, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi Genzyme, Sun Pharma, and 4SC, has received travel grants and honoraria for lectures from Almirall, Amgen, Bristol-Myers Squibb, Merck Serono, Merck Sharp & Dohme, Novartis, Pierre Fabre, Roche, and Sun Pharma, and received research funding from Amgen, Johnson & Johnson, Merck Serono, and Novartis. **CL** acted as a speaker for, participated in an advisory board for, and received honoraria from Bristol-Myers Squibb, Roche, Novartis, and Merck Sharp & Dohme. **NS** is an employee of Sun Pharmaceutical Industries, Inc. **PF** has participated in clinical trials (investigator), been on an advisory board, been a consultant, received speaker's bureau/honoraria, and/or received research and/or travel grants from AbbVie, Akaal, Amgen, Arcutis, Aslan, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Botanix, Celgene, Celtaxsys, CSL, Cutanea, Dermira, Eli Lilly and Company, Galderma, Geneseq, Genetech, GSK, Hexima, Janssen, LEO Pharma, Mayne Pharma, MedImmune, Merck, Novartis, Pfizer, Regeneron, Reistone, Roche, Sanofi, Sun Pharma, UCB, and Valeant.