Efficacy following discontinuation of sonidegib treatment in patients with locally advanced basal cell carcinoma: Results from the BOLT 42-month analysis

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SYNOPSIS

- Hedgehog pathway inhibitors (HHIs) block dysregulated Hedgehog signaling in sporadic basal cell carcinomas (BCCs) and represent one of the few treatment options available for patients with advanced BCC[1,2]
- Sonidegib, an HHI that selectively targets Smoothened,[3] is approved in the US, EU, Switzerland, and Australia to treat adults with locally advanced BCC (laBCC) not amenable to curative surgery or radiotherapy[3-6]
  - Additionally, sonidegib is approved in Switzerland and Australia for the treatment of metastatic BCC (mBCC)[5,6]
- Sonidegib 200 mg once daily demonstrated durable efficacy and consistent/manageable toxicity through 42 months of treatment in the Phase 2 BOLT (**B**asal Cell Carcinoma **O**utcomes with **L**DE225 [sonidegib] **T**reatment) trial (NCT01327053)[7-10]
- Pharmacokinetic modeling suggests that inhibition of the hedgehog pathway can be maintained following discontinuation of sonidegib due to its long half-life of approximately 28 days
- This analysis presents the efficacy of sonidegib 200 mg daily in patients with laBCC who discontinued treatment without progressive disease (PD)

OBJECTIVE

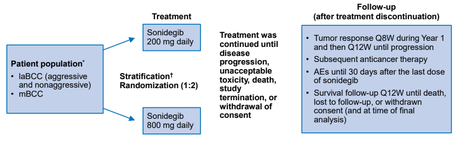
- To determine the clinical benefit of sonidegib for patients who discontinued treatment

METHODS

Study design

- BOLT was a randomized, multicenter, double-blind, Phase 2 trial of patients with histologically confirmed laBCC or mBCC (**Figure 1**)
- Enrolled patients were randomly assigned 1:2 to receive oral sonidegib 200 or 800 mg daily

Figure 1. BOLT study design



*Patients previously treated with sonidegib or another HHI were excluded.
†Stratification was based on stage, disease histology for patients with laBCC (nonaggressive vs aggressive), and geographic region.
AE, adverse event; BOLT, **B**asal Cell Carcinoma **O**utcomes with LDE225 (sonidegib) **T**reatment; HHI, Hedgehog inhibitor; laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma; Q8W, every 8 weeks; Q12W, every 12 weeks.

Efficacy assessments

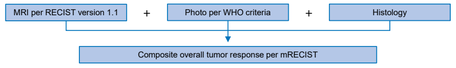
- Efficacy endpoints in BOLT are summarized in **Figure 2**
  - Central review was conducted by an independent blinded organization
- The primary efficacy endpoint for patients with laBCC in the pivotal BOLT analysis was objective response rate (ORR) per central review using modified Response Evaluation Criteria in Solid Tumors (mRECIST; **Figures 2** and **3**)
- Tumor measurements were performed by central review of color photographs or magnetic resonance imaging (MRI) scans within 21 days of starting treatment. Further tumor response evaluations were performed at Weeks 5, 9, and 17 (±3 days) and subsequently every 8 weeks (±3 days) during the first year and every 12 weeks (±3 days) thereafter
  - Measurable lesions were those that could be accurately measured in ≥1 dimension as ≥10 mm with MRI scans or color photographs

Figure 2. BOLT study endpoints

Primary	ORR → best overall confirmed response of CR or PR per central review according to mRECIST (laBCC) or RECIST version 1.1 (mBCC)
Key secondary	DOR and CR rates per central review according to mRECIST (laBCC) or RECIST version 1.1 (mBCC)
Other secondary	• OS • ORR and DOR per investigator review • Safety • PFS and TTR per central review

BOLT, **B**asal Cell Carcinoma **O**utcomes with LDE225 (sonidegib) **T**reatment; CR, complete response; DOR, duration of response; laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma; 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.

Figure 3. laBCC tumor evaluation by mRECIST methodology



laBCC, locally advanced basal cell carcinoma; mRECIST, modified RECIST; MRI, magnetic resonance imaging; RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization.

Safety assessments

- Safety and tolerability were assessed through monitoring and recording of adverse events (AEs)

RESULTS

- Of the 230 patients enrolled in BOLT, 79 were randomized to sonidegib 200 mg daily
- Among patients receiving sonidegib 200 mg daily, the median age at baseline was 67.0 years, and 60.8% were male (**Table 1**)
- The majority (62.0%) had ≥2 lesions, and 66 (83.5%) had laBCC

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 (%) of patients unless otherwise indicated.
*Includes micronodular, infiltrative, multifocal, basosquamous, and sclerosing histological subtypes.
†Includes nodular and superficial histological subtypes.
ECOG, Eastern Cooperative Oncology Group; laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma.

- Of the 66 patients with laBCC who received sonidegib 200 mg, 37 discontinued treatment before PD (**Table 2**)
- AEs were the most common reason for treatment discontinuation, which included 17 patients (45.9%)

Table 2. Disposition of patients with laBCC who discontinued before progressive disease

	Sonidegib 200 mg (n = 37)
Treatment exposure, months, median (range)	10.12 (2.8–30.9)
Reasons for treatment discontinuation, n (%)	
AE	17 (45.9)
Lost to follow-up	2 (5.4)
Physician decision	9 (24.3)
Withdrawal by patient	8 (21.6)
Death	1 (2.7)

AE, adverse event; laBCC, locally advanced basal cell carcinoma.

- ORR assessed by central review was 60.6% for all patients and 57.1% for patients with laBCC receiving sonidegib 200 mg who discontinued treatment before PD (**Figure 4**)
  - Per investigator review, ORR was 71.2% for all patients and 73.0% for patients who discontinued treatment before PD

Figure 4. Overview of objective response rates in patients receiving sonidegib 200 mg daily

laBCC, locally advanced basal cell carcinoma; ORR, objective response rate; PD, progressive disease.

- Per central review, median duration of response (DOR; 95% confidence interval [CI]) was 26.1 (12.0, not estimable [NE]) months for all patients with laBCC and NE (12.0, NE) months for patients with laBCC who discontinued before PD (**Table 3**)
- Per investigator review, median DOR (95% CI) was 15.7 (12.0, 20.2) months for all patients with laBCC and 20.2 (12.0, NE) months for patients with laBCC who discontinued treatment before PD

Table 3. Overview of treatment duration of response in patients with laBCC

	All patients	Patients who discontinued sonidegib 200 mg before PD
Central review, n	66	35
Event, n (%)	12 (18.2)	2 (5.7)
Censored,* n (%)	28 (42.4)	18 (51.4)
DOR, months, median (95% CI)	26.1 (12.0, NE)	NE (12.0, NE)
KM estimate, % (95% CI)		
Month 12	69.25 (46.54, 83.82)	83.33 (27.31, 97.47)
Month 18	50.50 (26.56, 70.32)	66.67 (19.46, 90.44)
Month 36	40.40 (16.25, 63.62)	NE (NE, NE)
Month 42	NE (NE, NE)	NE (NE, NE)
Investigator review, n	66	37
Event, n (%)	22 (33.3)	8 (21.6)
Censored,* n (%)	25 (37.9)	19 (51.4)
DOR, months, median (95% CI)	15.7 (12.0, 20.2)	20.2 (12.0, NE)
KM estimate, % (95% CI)		
Month 12	68.28 (49.81, 81.14)	75.82 (46.71, 90.42)
Month 18	47.68 (29.40, 63.89)	56.16 (24.76, 78.78)
Month 36	27.81 (12.81, 45.07)	NE (NE, NE)
Month 42	27.81 (12.81, 45.07)	NE (NE, NE)

*DOR was censored at the date of the last adequate tumor assessment for the patient whose disease had not progressed and had not received further anti-cancer therapy.
CI, confidence interval; DOR, duration of response; KM, Kaplan Meier; laBCC, locally advanced basal cell carcinoma; NE, not estimable; PD, progressive disease.

- Per central review, the median progression-free survival (PFS; 95% CI) was 22.1 (14.8, NE) months for all patients with laBCC and NE (13.8, NE) months for patients who discontinued treatment before PD (**Table 4**)
- Per investigator review, the median PFS was 19.4 (16.6, 23.6) months for all patients with laBCC compared to 22.0 (16.6, NE) months for patients with laBCC who discontinued treatment before PD

Table 4. Overview of progression-free survival in patients with laBCC

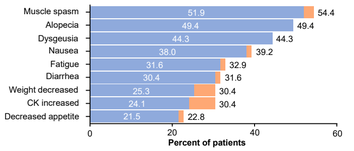
	All patients	Patients who discontinued sonidegib 200 mg before PD
Central review, n	66	35
Event, n (%)	16 (24.2)	2 (5.7)
Censored,* n (%)	50 (75.8)	33 (94.3)
PFS, months, median (95% CI)	22.1 (14.8, NE)	NE (13.8, NE)
KM estimate, % (95% CI)		
Month 12	82.06 (66.72, 90.78)	100 (100, 100)
Month 18	65.82 (45.89, 79.88)	90.00 (47.30, 98.53)
Month 36	38.30 (15.87, 60.62)	67.50 (16.21, 91.86)
Month 42	38.30 (15.87, 60.62)	NE (NE, NE)
Investigator review, n	66	37
Event, n (%)	28 (42.4)	8 (21.6)
Censored,* n (%)	38 (57.6)	29 (78.4)
PFS, months, median (95% CI)	19.4 (16.6, 23.6)	22.0 (16.6, NE)
KM estimate, % (95% CI)		
Month 12	75.57 (60.79, 85.42)	91.30 (68.34, 97.85)
Month 18	55.12 (38.19, 69.17)	76.30 (46.14, 90.97)
Month 36	24.21 (11.07, 40.09)	NE (NE, NE)
Month 42	24.21 (11.07, 40.09)	NE (NE, NE)

*PFS time was censored for any patient who was alive and progression-free on the date of last adequate tumor assessment , or when he/she received any other anti-cancer therapy.
CI, confidence interval; KM, Kaplan Meier; laBCC, locally advanced basal cell carcinoma; NE, not estimable; PD, progressive disease; PFS, progression-free survival.

Safety

- Overall, the safety profile of sonidegib 200 mg daily was manageable and consistent with the prior analyses[7,10]
- 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 5**)

Figure 5. AEs reported in ≥20% of patients receiving sonidegib 200 mg daily



AE, adverse event; CK, creatine kinase.

CONCLUSION

- Sonidegib 200 mg daily demonstrated clinical benefit beyond treatment discontinuation
- Patients who discontinued sonidegib before PD had objective responses prior to the last treatment dose

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DISCLOSURES

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