Duration of response and progression-free survival with sonidegib 200 mg once daily until disease progression or start of new antineoplastic therapy in patients with locally advanced basal cell carcinoma: Results of the 42-month, randomized, double-blind BOLT study

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BACKGROUND

- Incidence of basal cell carcinoma (BCC) is increasing worldwide by an approximate 1% annually[1,2]
- In cases of advanced BCC, current treatment modalities (eg, surgery) are contraindicated[3,4]
- Hedgehog inhibitors (HHIs) were developed to block aberrant hedgehog signaling found in most sporadic BCCs, and inhibition of the hedgehog pathway is among the few treatment options available for patients with advanced BCC[5,6]
- Sonidegib—an HHI that selectively targets Smoothened[1]—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[7-10]
  - Sonidegib is also approved for the treatment of metastatic BCC (mBCC) in Switzerland and Australia[9,10]
- Through 42 months of the phase 2 BOLT (**B**asal Cell Carcinoma **O**utcomes with LDE225 [sonidegib] **T**reatment) trial (NCT01327053), sonidegib 200 mg/day demonstrated durable efficacy and consistent/manageable toxicity[11-15]

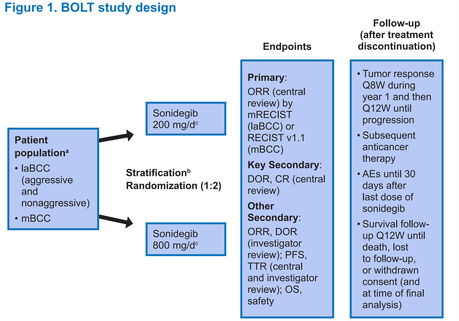
OBJECTIVES

- Here, we report duration of response (DOR) and progression-free survival (PFS), with start of new antineoplastic therapy considered progressive disease (PD), in aggressive and nonaggressive laBCC in a sensitivity analysis from the BOLT 42-month results

METHODS

- BOLT was a randomized, double-blind, phase 2 clinical trial conducted in 58 centers across 12 countries[11] (**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 history 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; 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 basal cell carcinoma; mBCC, metastatic basal cell carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QW, 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**

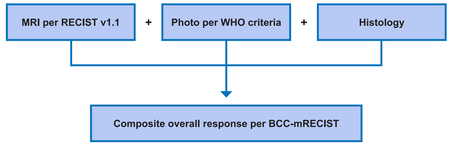
Figure 2. BOLT study endpoints

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 • Safety • ORR and DOR per investigator review • PFS and TTR per central and investigator 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 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 central review using modified Response Evaluation Criteria in Solid Tumors (mRECIST) for patients with laBCC (**Figure 2 and 3**)
  - Includes assessment by magnetic resonance imaging complemented by color photography and histology of multiple biopsy samples; complete response was defined as negative histology with complete disappearance of target lesions by all image modalities[11,14]

Figure 3. Tumor evaluation per mRECIST (laBCC)



BCC-mRECIST is a composite multimodal evaluation used to integrate MRI according to RECIST v1.1,[16] standard and annotated color photography using bidimensional WHO criteria,[17] 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.

- Tumor evaluations were to be continued per the study evaluation schedule (once every 8 weeks during the first year and once every 12 weeks thereafter) following discontinuation of study treatment prior to documented PD for any reason other than withdrawal of consent or death
  - Evaluations were performed until PD was determined per central review, the start of a new antineoplastic therapy, or loss to follow-up
  - New antineoplastic therapy was defined as any additional (secondary) anticancer therapy or surgery
  - For analysis by tumor histology, aggressive histological subtypes included micronodular, infiltrative, multifocal, basosquamous, and sclerosing; nonaggressive histological subtypes included nodular and superficial
- Safety and tolerability were assessed through monitoring and recording adverse events (AEs); regular monitoring of hematology, clinical chemistry, and electrocardiograms; and routine monitoring of vital signs and physical condition
  - AEs were coded using Medical Dictionary for Regulatory Activities (v19.0) terminology, and toxicity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (v4.03)[18]

RESULTS

- At baseline, 58% of patients with laBCC (n = 66) receiving sonidegib 200 mg/day were male, and the median age was 67 years (**Table 1**)
- More patients had an aggressive histologic subtype (56%) than a nonaggressive histologic subtype (44%)

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

	laBCC (n = 66)
Median age (range), years	67 (25–92)
Male	38 (57.6)
ECOG Performance Status	
0	44 (66.7)
1	16 (24.2)
2	4 (6.1)
Unknown	2 (3.0)
laBCC histologic subtype	
Aggressive[a]	37 (56.1)
Nonaggressive[b]	29 (43.9)
Number of lesions in patients with laBCC	
1	30 (45.5)
≥2	36 (54.5)
Prior antineoplastic therapy for laBCC	
Surgery	48 (72.7)
Radiotherapy	12 (18.2)

Data presented as *n* (%) unless otherwise indicated.
[a]Includes micronodular, infiltrative, multifocal, basosquamous, and sclerosing histological subtypes; [b]Includes nodular and superficial histological subtypes.
ECOG, Eastern Cooperative Oncology Group; laBCC, locally advanced basal cell carcinoma.

- At 42 months, the objective response rate (95% confidence interval [CI]) in patients with laBCC was 56.1% (43.3%–68.3%) (**Table 2**)

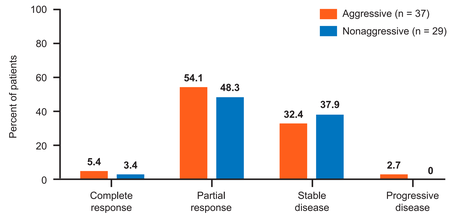
Table 2. Efficacy outcomes per central review in patients with laBCC receiving sonidegib 200 mg daily

	laBCC (n = 66)
ORR, % (95% CI)	56.1 (43.3, 68.3)
CR, % (95% CI)	4.5 (0.9, 12.7)
DCR, %	90.9
DOR, median, months (95% CI)	26.1 (NE)
PFS, median, months (95% CI)	22.1 (NE)
TTR, median, months (95% CI)	4.0 (3.8, 5.6)

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

- Best overall response by central review was similar between patients with aggressive and nonaggressive histology (**Figure 4**)

Figure 4. Best overall response by central review using mRECIST



Aggressive includes micronodular, infiltrative, multifocal, basosquamous, and sclerosing histological subtypes; nonaggressive includes nodular and superficial histological subtypes.
mRECIST, modified Response Evaluation Criteria in Solid Tumors.

Outcomes in patients starting new antineoplastic therapy

- Median DOR (95% CI) per central review in all laBCC patients (n = 66) was 13.0 (not estimable [NE]) months and median PFS (95% CI) was 19.0 (14.0–30.7) months
- Median DOR (95% CI) in patients starting new antineoplastic therapy with aggressive (n = 37) laBCC was 13.0 (7.4–35.7) months and NE for patients with nonaggressive (n = 29) laBCC; median PFS (95% CI) in patients starting new antineoplastic therapy with aggressive and nonaggressive laBCC was 14.9 (13.2–30.7) and 22.1 (NE) months, respectively
- DOR 12-month event-free probability percent estimate with laBCC, aggressive laBCC, and nonaggressive laBCC was 63.2%, 54.6%, and 75.0%, respectively (**Table 3**)

Table 3. Duration of response and progression-free survival per central review in laBCC patients with new antineoplastic therapy

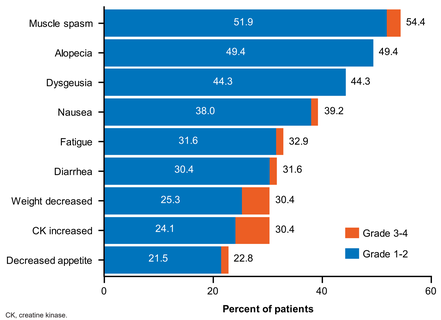
	All laBCC patients (n = 66)	Aggressive histology (n = 37)	Nonaggressive histology (n = 29)
DOR			
n/N (%)	15/37 (40.5)	10/22 (45.5)	5/15 (33.3)
PD, n (%)	15 (40.5)	10 (45.5)	5 (33.3)
Median (95% CI)	13.0 (NE)	13.0 (7.4–35.7)	NE
% Event-free probability estimate (95% CI)			
6 months	86.8 (68.5–94.8)	83.6 (57.3–94.4)	91.7 (53.9–98.8)
9 months	72.5 (52.4–85.3)	71.6 (44.6–87.1)	75.0 (40.8–91.2)
12 months	63.2 (41.7–78.6)	54.6 (26.2–76.1)	75.0 (40.8–91.2)
PFS			
n/N (%)	23/66 (34.8)	16/37 (43.2)	7/29 (24.1)
PD, n (%)	23 (34.8)	16 (43.2)	7 (24.1)
Median (95% CI)	19.0 (14.0–30.7)	14.9 (13.2–30.7)	22.1 (NE)
% Event-free probability estimate (95% CI)			
6 months	93.0 (82.4–97.3)	88.3 (71.7–95.4)	100 (NE)
9 months	90.9 (79.5–96.1)	88.3 (71.7–95.4)	94.7 (68.1–99.2)
12 months	80.8 (65.9–89.7)	80.1 (60.3–90.7)	81.6 (52.8–93.7)

The start of any anticancer therapy different from sonidegib is considered disease progression.
CI, confidence interval; DOR, duration of response; laBCC, locally advanced basal cell carcinoma; n, total number of events included in the analysis (an event is disease progression or death due to any cause); N, total number of patients included in the analysis; NE, not estimable; PD, progressive disease; PFS, progression-free survival.

Safety and tolerability

- Overall, the safety profile of sonidegib 200 mg/day was manageable and consistent with prior analyses[11,13]
- 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%), alopecia (49.4%), and dysgeusia (44.3%) (**Figure 5**)

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



CK, creatine kinase.

CONCLUSIONS

- Patients with laBCC receiving sonidegib 200 mg/day experienced durable tumor response until disease progression or start of new antineoplastic therapy
- Safety and tolerability of sonidegib 200 mg/day at 42 months was consistent with earlier data

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