42-month results on the efficacy and safety of sonidegib in patients with aggressive and nonaggressive subtypes of locally advanced basal cell carcinoma

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BACKGROUND

- Sonidegib—a Hedgehog inhibitor (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 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/d demonstrated durable efficacy and consistent/manageable toxicity[5-8]

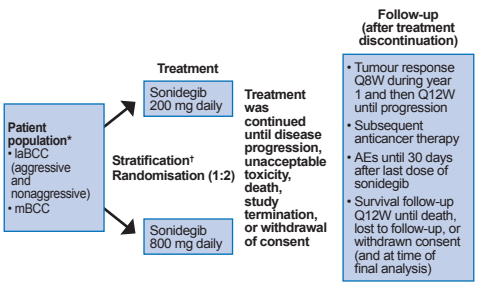
OBJECTIVE

- Here, we report final BOLT 42-month efficacy and safety results—the longest follow-up data available for an HHI—according to aggressive vs nonaggressive tumour histology among patients with laBCC receiving sonidegib 200 mg/d

METHODS

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

Figure 1. BOLT study design



*Patients who received prior treatment 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 **L**DE225 (sonidegib) **T**reatment; HHI, Hedgehog inhibitor; laBCC, locally advanced BCC; mBCC, metastatic BCC; Q8W, every 8 weeks; Q12W, every 12 weeks.

- 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 summarised in **Figure 2**
- Tumour response by central and investigator review was evaluated using the stringent modified Response Evaluation Criteria in Solid Tumors (mRECIST)
  - Includes assessment by magnetic resonance imaging complemented by colour photography and histology of multiple biopsy samples; complete response was defined as negative histology with complete disappearance of target lesions by all image modalities[5,7]

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

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

- For analysis by tumour histology, aggressive histological subtypes included micronodular, infiltrative, multifocal, basosquamous, and sclerosing; nonaggressive histological subtypes included nodular and superficial
- Safety/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 terminology v19, and toxicity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03[9]
- Data presented here are based on the approved 200-mg dose at 42 months

RESULTS

- At baseline, 58% of patients with laBCC receiving sonidegib 200 mg/d were male, and the median age was 67 years (**Table 1**)
- The majority of patients had an aggressive histologic subtype (56.1%) and ≥2 lesions (54.5%) (**Table 1**)

Table 1. Baseline demographics and disease characteristics

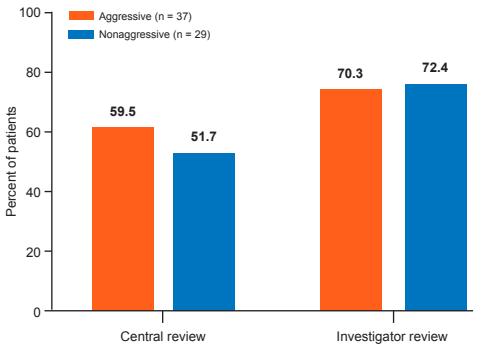
	Sonidegib 200 mg/d
Median age (range), years	67 (25–92)
Male	38 (57.6)
ECOG Performance Status	
0	44 (66.7)
1	16 (24.2)
2	4 (6.1)
Unknown	2 (3.0)
laBCC histologic subtype	
Aggressive*	37 (56.1)
Nonaggressive†	29 (43.9)
Number of lesions in patients with laBCC	
1	30 (45.5)
≥2	36 (54.5)
Prior antineoplastic therapy for laBCC	
Surgery	48 (72.7)
Radiotherapy	12 (18.2)

Data presented as n (%) unless otherwise indicated. n = 66.
*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.

Efficacy in patients with laBCC at 42 months

- Among all patients with laBCC who received sonidegib 200 mg/d, objective response rate (ORR) by central review was 56.1%
- ORR by central review was numerically higher for aggressive (59.5%) vs nonaggressive histology (51.7%) (**Figure 3**)
- ORR by investigator review was numerically higher overall relative to central review and similar for aggressive (70.3%) vs nonaggressive histology (72.4%) (**Figure 3**)

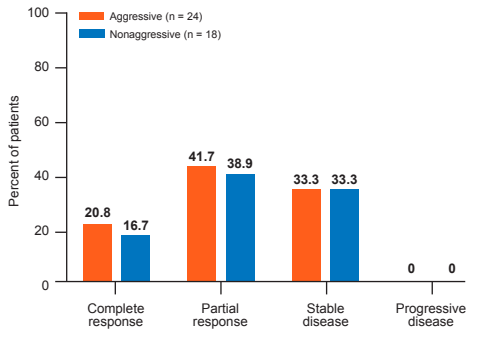
Figure 3. Objective response rate by central and investigator review using RECIST



Objective response rate is the proportion of patients with a confirmed complete or partial response by mRECIST as their best overall response. Aggressive includes micronodular, infiltrative, multifocal, basosquamous, and sclerosing histological subtypes; nonaggressive includes nodular and superficial histological subtypes.
mRECIST, modified Response Evaluation Criteria in Solid Tumours.(sonidegib) **T**reatment.

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

Figure 4. Best overall response by central review using RECIST

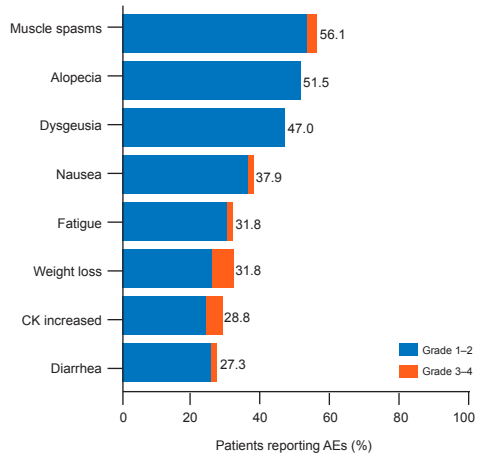


Aggressive includes micronodular, infiltrative, multifocal, basosquamous, and sclerosing histological subtypes; nonaggressive includes nodular and superficial histological subtypes.
RECIST, Response Evaluation Criteria in Solid Tumors.

Overall safety/tolerability at 42 months

- The safety profile of sonidegib 200 mg/d was manageable and consistent with prior analyses[5,6]
- After 42 months, 64/66 (97.0%) patients with laBCC receiving sonidegib 200 mg/d experienced an AE; the most frequent AEs in this population were muscle spasms (56.1%), alopecia (51.5%), dysgeusia (47.0%), and nausea (37.9%) (**Figure 5**)
- The majority of common AEs were grade 1–2 in severity (**Figure 5**)

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



AE, adverse event; CK, creatine kinase.

CONCLUSIONS

- After 42 months, sonidegib 200 mg/d demonstrated clinically meaningful responses in patients with laBCC evaluated by the stringent mRECIST criteria
- Sonidegib 200 mg/d was effective in patients with aggressive and nonaggressive tumour histology
- AEs were consistent with the known safety profile of sonidegib

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