Effect of concomitant medications on efficacy of sonidegib 200 mg daily 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 **L**DE225 [sonidegib] **T**reatment) trial (NCT01327053), sonidegib 200 mg/day demonstrated durable efficacy and consistent/manageable toxicity[11-15]

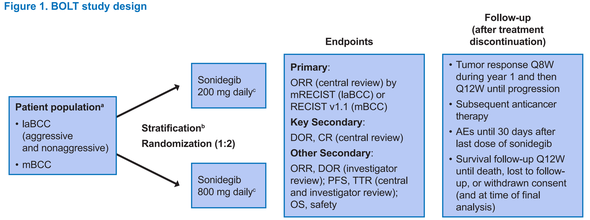
OBJECTIVES

- We present a post hoc analysis of efficacy per investigator review in patients with laBCC taking common concomitant medications with the approved sonidegib 200 mg/day dose

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 histology 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; Q8W, 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

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 tumor response.

- Tumor response was evaluated by central review using modified Response Evaluation Criteria in Solid Tumors (mRECIST) for patients with laBCC (**Figure 2**)
  - 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[7,10]
- Secondary post hoc assessments included best overall response and duration of response (DOR) in patients taking concomitant medications
- 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)[16]

RESULTS

- At baseline, 60.8% of the 79 patients receiving sonidegib 200 mg/day were male and had a median age of 67.0 years; the majority (83.5%) of patients had laBCC and 62.0% had ≥2 lesions (**Table 1**)

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

	Sonidegib 200 mg (n = 79)
Median age (range), years	67 (25–92)
Male	48 (61)
ECOG performance status	
0	50 (63)
1	19 (24)
2	8 (10)
Unknown	2 (3)
Stage	
laBCC	66 (84)
mBCC	13 (16)
Histologic/cytologic subtype	
Aggressive[a]	40 (51)
Nonaggressive[b]	38 (48)
Undetermined	1 (1)
Number of lesions	
1	30 (38)
≥2	49 (62)
Metastasis	14 (18)
Sites	
Lung	10/14 (71)
Bone	2/14 (14)
Axillary lymph node	1/14 (7)
Trunk	1/14 (7)
Other[c]	3/14 (21)
Prior antineoplastic therapy	
Surgery	59 (75)
Radiotherapy	19 (24)

Data presented as n (%) unless otherwise indicated.
[a]Includes micronodular, infiltrative, multifocal, basosquamous, and sclerosing histological subtypes. [b]Includes nodular and superficial histological subtypes. [c]Includes retro-orbital and left mandible, pelvic side wall and lung, and bilateral scalp.
BCC, basal cell carcinoma; ECOG, Eastern Cooperative Oncology Group; laBCC, locally advanced BCC; mBCC, metastatic BCC.

Overall efficacy at 42 months

- Clinically relevant objective response rates (ORRs) continued to be reported for patients receiving 200 mg/day of sonidegib at 42 months (**Table 2**)
- At 42 months, the ORR (95% Confidence Interval [CI]) was 48.1% (36.7%–59.6%) for all 79 patients receiving 200 mg/day of sonidegib
- Disease control rate exceeded 90% and further supports treatment benefit (**Table 2**)
- Sustained duration was confirmed, with a median duration of response of 26.1 months (**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; mBCC, metastatic BCC; NE, not estimable; ORR, objective response rate; PFS, progression-free survival; TTR, time to tumor response.

- Overall ORR (95% CI) by investigator review for patients with laBCC receiving sonidegib 200 mg/day (n = 66) was 71.2% (58.7%–81.7%, **Table 3**)
- Median DOR (95% CI) per investigator review for patients with laBCC receiving sonidegib 200 mg/day was 15.7% (12.0%–20.2%, **Table 3**)

Table 3. Objective response rate and duration of response per investigator review in patients with laBCC receiving sonidegib 200 mg daily

	All laBCC patients (n = 66)	Aggressive histology (n = 37)	Nonaggressive histology (n = 29)
ORR (95% CI)	71.2 (58.7–81.7)	70.3 (53.0–84.1)	72.4 (52.8–87.3)
DOR (95% CI)	15.7 (12.0–20.2)	20.2 (NE)	15.7 (11.0–20.2)

CI, confidence interval; DOR, duration of response; laBCC, locally advanced basal cell carcinoma; NE, not estimable; ORR, objective response rate.

Efficacy in patients taking concomitant medications and sonidegib 200 mg/day

- The ORR for patients receiving sonidegib 200 mg/day and concomitant medications were comparable to all patients receiving only sonidegib 200 mg/day
- Patients receiving salicylic acid derivatives had the highest ORR of patients taking common concomitant medications (**Table 4**)

Table 4. Best overall response, progression-free survival, and time to tumor response per investigator review in patients with laBCC receiving concomitant medications and sonidegib 200 mg daily

	Any concomitant medications (n = 37)	NSAIDs (n = 7)	Glucocorticoids (n = 10)	SADs (n = 9)
ORR (95% CI)	73.0 (55.9–86.2)	71.4 (29.0–96.3)	80.0 (44.4–97.5)	88.9 (51.8–99.7)
CR, % (95%, CI)	2.7 (0.1–14.2)	0 (0–41.0)	0 (0–30.8)	0 (0–33.6)
DCR, %	94.6	100.0	100.0	100.0
PFS, median (95%, CI)	39.6 (NE)	NE	NE	19.0 (NE)
TTR, median (95% CI)	3.9 (2.1–6.6)	1.9 (NE)	3.9 (1.9–9.3)	5.6 (1.9–7.4)

CI, confidence interval; CR, complete response; DCR, disease control rate; laBCC, locally advanced basal cell carcinoma; NE, not estimated; NSAID, nonsteroidal anti-inflammatory drug; ORR, objective response rate; PFS, progression-free survival; SAD, salicylic acid derivative; TTR, time to tumor response.

- Overall, 26.3% of patients taking common concomitant medications along with sonidegib 200 mg/day had progressive disease (**Table 5**)

Table 5. Duration of response per investigator review in patients with laBCC receiving concomitant medications and sonidegib 200 mg daily

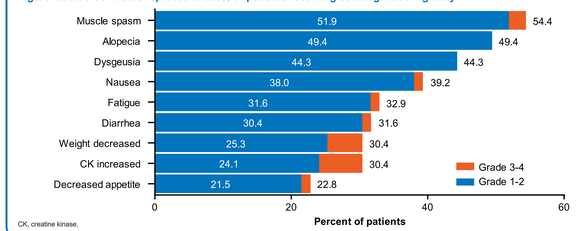
	Any concomitant medications (n = 37)	NSAIDs (n = 7)	Glucocorticoids (n = 10)	SADs (n = 9)
n/N1	5/19	3/5	3/8	2/9
PDs, n (%)	5 (26.3)	2 (40)	2 (25)	2 (22)
DOR, median, months (95% CI)	NE (NE)	12.9 (3.4–13.6)	18.2 (NE)	NE (NE)

CI, confidence interval; DOR, duration of response; laBCC, locally advanced basal cell carcinoma; NE, not estimated; NSAID, nonsteroidal anti-inflammatory drug; ORR, objective response rate; PD, progressive disease; SAD, salicylic acid derivative.

Safety and tolerability

- The safety profile of sonidegib 200 mg/day was manageable and consistent with previous analysis[1-5]
- At 42 months, 64/66 (97.0%) patients with laBCC receiving sonidegib 200 mg/day experienced an AE
- The most frequent AEs in this population were muscle spasms (54.4%), alopecia (49.4%), dysgeusia (44.3%), and nausea (39.2%)
- The majority of AEs were grade 1–2 in severity (**Figure 3**)

Figure 3. Adverse events reported in ≥20% of patients receiving sonidegib 200 mg daily



CK, creatine kinase.

CONCLUSIONS

- Sonidegib 200 mg/day led to clinically meaningful outcomes in patients with laBCC through 42 months of treatment, with a manageable tolerability profile[11-15]
- Common concomitant medications had no impact on efficacy
- The safety profile of sonidegib 200 mg daily was manageable and consistent with previous analysis[11,13]

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ACKNOWLEDGMENTS

Medical writing and editorial support were provided by Jennifer Meyering, RN, MS, CMPP, of AlphaBioCom, LLC, and funded by Sun Pharmaceutical Industries, Inc.

DISCLOSURES

MM has participated on advisory boards and received honoraria from Genentech; Novartis Pharmaceuticals Corporation; Sun Pharmaceutical Industries, Inc.; and Regeneron Pharmaceuticals. JL has received personal fees from Novartis Pharmaceuticals Corporation. LL and NS are employees of Sun Pharmaceutical Industries, Inc. AG has participated on advisory boards for Bristol-Myers Squibb, Pfizer, and Sanofi; received honoraria from Novartis Pharmaceuticals Corporation; and received travel support from Astellas and Bristol-Myers Squibb. RD has received grants and personal fees from Bristol-Myers Squibb; GlaxoSmithKline; Merck Sharpe and Dohme; Novartis Pharmaceuticals Corporation; Roche; and Sun Pharmaceutical Industries, Inc.

Presented at Fall Clinical Dermatology Conference for PAs & NPs 2020, April 3–5, Orlando, FL, USA