Muscle-related adverse events in patients receiving sonidegib: Results from the 42-month BOLT study

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BACKGROUND

- Sonidegib—a Hedgehog inhibitor (HHI) that selectively targets Smoothened[1]—is approved in the US, the EU, 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[3,5]
- 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[1,6-9]
- While sonidegib is well tolerated, the prevalence of muscle-related adverse events (AEs) remains a treatment challenge for HHIs
  - All-grade muscle spasms were reported in 49% of patients after 6 months of treatment with sonidegib and in 68% of patients after 9 months of treatment with vismodegib[1,10]

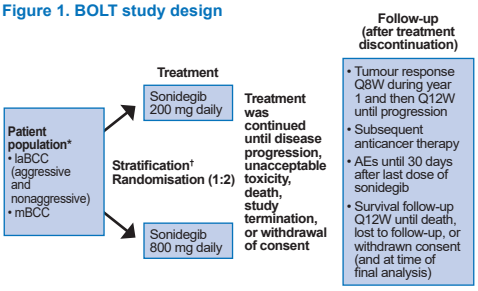
OBJECTIVE

- To describe the clinical impact of muscle-related AEs in patients receiving sonidegib for laBCC and mBCC using 42-month data from BOLT

METHODS

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

- Safety/tolerability were assessed through monitoring and recording AEs; regular monitoring of haematology, clinical chemistry, and electrocardiograms; and routine monitoring of 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]
  - Muscle-related events were evaluated by an independent Safety Review and Adjudication Committee comprising experts on muscle toxicity
- Blood creatine kinase (CK) was measured prior to treatment or within 72 hours of the first dose, then every week during the first 2 months, and then every 4 weeks thereafter while on sonidegib
- Dose modifications were based on the worst grade of toxicity observed
  - Dose delays of ≤21 days and dose reductions were permitted for AEs suspected to be related to sonidegib (sample guidance provided in **Table 1**)

Table 1. Recommended dose modifications and delays

Suspected treatment-related muscle toxicity	
Normal CK with muscle-related symptoms (eg, pain, spasms, cramps)	• Grade 1 or 2 symptoms: Continue sonidegib at same dose; consider symptomatic treatment for muscle-related toxicity • Grade 3: Hold sonidegib dose for up to 21 days; measure CK; resume sonidegib at a reduced dose if resolved or improved to grade 1
Grade 1 or 2 CK elevation*	• Asymptomatic (no new onset or worsening of muscle cramps, myalgia, or other muscle symptoms): Continue sonidegib at same dose • Symptomatic: Continue sonidegib at same dose, monitor CK ≥QW
Grade 3 or 4 CK elevation*	• Hold sonidegib • Check blood and/or urine myoglobin • Monitor renal function • Measure CK at least twice weekly • Consider electromyography and muscle biopsy • Consider resuming sonidegib at a reduced dose if renal function is not impaired and resolution to grade ≤1 occurs within 21 days • Discontinue patient from study in the presence of renal impairment (serum creatinine >2X ULN)

*Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, v4.03.[10]
CK, creatine kinase; QW, weekly; ULN, upper limit of normal.

RESULTS

- At baseline, 60.8% of the 79 patients receiving sonidegib 200 mg/d 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 2**)

Table 2. Baseline demographics and disease characteristics in patients receiving sonidegib 200 mg daily

	Sonidegib 200 mg/d 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*	40 (51)
Nonaggressive†	38 (48)
Undetermined	1 (1)
Number of lesions	
1	30 (38)
≥2	49 (62)
Metastasis	14 (18)
Site	
Lung	10/14 (71)
Axillary lymph nodes	1/14 (7)
Bone	2/14 (14)
Trunk	1/14 (7)
Other§	3/14 (21)
Prior antineoplastic therapy	
Surgery	59 (75)
Radiotherapy	19 (24)

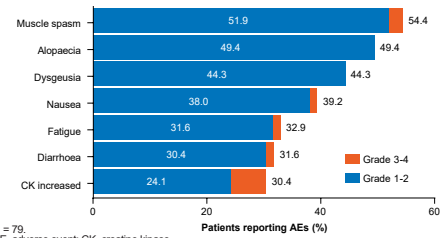
Data presented as n (%) unless otherwise indicated.
*Includes micronodular, infiltrative, multifocal, basosquamous, and sclerosing histological subtypes. †Includes nodular and superficial histological subtypes. §Includes retro-orbital and left mandible, pelvic side wall and lung, and bilateral scalp.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

- At 42 months, the objective response rate for patients receiving sonidegib 200 mg/day was the same as at 30 months for both patients with laBCC (n = 66: 56.1% [95% confidence interval (CI), 43.3, 68.3]) and mBCC (n = 13: 7.7% [95% CI, 0.2, 36.0])[7]

Overall safety/tolerability at 42 months

- Median duration of sonidegib exposure was 11.0 months in the 200 mg/day arm
- Overall, 54 (68.4%), 34 (43.0%), and 19 (24.1%) patients were exposed to sonidegib 200 mg/day for ≥8, ≥12, and ≥20 months, respectively
- The most common all-grade AEs reported in patients receiving sonidegib 200 mg/day were muscle spasms (54.4%), alopaecia (49.4%), dysgeusia (44.3%), nausea (39.3%), fatigue (33.0%), diarrhoea (31.7%), decreased weight (30.5%), and increased CK (30.4%); 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



N = 79.
AE, adverse event; CK, creatine kinase.

Muscle-related toxicity

- The most frequent muscle-related AEs (incidence ≥5%; all grades) were muscle spasms (54.4%), CK increase (30.4%), myalgia (19.0%), muscular weakness (5.1%), and musculoskeletal pain (5.1%) (**Table 3**)
- Grade 3 and 4 AEs were few and included CK increase (6.3%; n = 5), muscle spasms (2.5%; n = 2), and rhabdomyolysis (1.3%; n = 1) (**Table 3**)
  - However, the investigator-reported case of rhabdomyolysis was not confirmed by an independent Safety Review and Adjudication Committee

Table 3. Muscle-related adverse events reported in ≥1% of patients receiving sonidegib 200 mg daily

	All grade	Grade 3–4
Muscle spasms	43 (54.4)	2 (2.5)
CK increase	24 (30.4)	5 (6.3)
Myalgia	15 (19.0)	0
Muscle weakness	4 (5.1)	0
Musculoskeletal pain	4 (5.1)	0
Blood creatinine increase	2 (2.5)	0
Chromaturia	2 (2.5)	0
Rhabdomyolysis	1 (1.3)	1 (1.3)
Hypocalcemia	1 (1.3)	0
Acute kidney injury	1 (1.3)	0

Data are presented as n (%). N = 79.
CK, creatine kinase.

Time to adverse event onset

- Median time to first onset of grade ≥3 muscle-related AE other than CK increase was 4.6 months (range 1.9–11.0; n = 7)
- Median time to onset of CK increase (grade ≥2; n = 14) was 12.9 weeks (range, 2–39), which resolved to grade ≤1 in 12 patients in a median time of 12.0 days (95% CI, 8.0, 14.0)
- Muscle-related AEs and CK increase often overlapped. Of the 48 patients with grade ≥1 CK increase, 72.9% experienced muscle-related symptoms. Of the 31 patients who had no CK increase, 48.4% also had muscle-related symptoms (**Table 4**)

Table 4. Onset of muscle-related symptoms by worst creatine kinase elevation in patients receiving sonidegib 200 mg daily

	No CK increase n = 31	Grade ≥1 n = 48	Grade ≥2 n = 14	Grade ≥3 n = 6	Grade ≥4 n = 2
No symptoms	16 (51.6)	13 (27.1)	3 (21.4)	1 (16.7)	0
Presence of symptoms	15 (48.4)	35 (72.9)	11 (78.6)	5 (83.3)	2 (100.0)
Symptoms prior to CK increase*	-	27 (56.3)	10 (71.4)	5 (83.3)	2 (100.0)
Symptoms after CK increase†	-	8 (16.7)	1 (7.1)	0	0

*At least 1 muscle-related symptom occurred prior to or on the same day of the first CK increase. †The first muscle-related symptom occurred after the first CK increase.
Data are presented as n (%) for the highest grade of CK increase postbaseline.
CK, creatine kinase.

Dose adjustments, interruption, and discontinuation

- In total, 16.5% of patients (13/79) had a dose adjustment during the study period. Only 1 was due to a muscle-related AE (muscle weakness)
- Temporary interruption due to muscle-related AEs occurred in 6/79 patients (7.6%)
  - One patient with grade 4 CK increase and grade 2 myalgia, 1 with grade 3 CK increase and grade 3 rhabdomyolysis, 1 with grade 2 muscle spasms, 1 with grade 2 CK increase, 1 with grade 3 CK increase, and 1 with grade 4 CK increase
- Discontinuation due to muscle-related AEs occurred in 5 patients (6.3%)
  - One with grade 1 muscle spasms, 1 with grade 2 muscle spasms, 2 with grade 3 muscle spasms, and 1 patient with grade 2 elevated CK; these events were deemed related to the study drug

Table 5. Dosing alterations in patients receiving sonidegib 200 mg daily

	All cause	Due to any AE	Due to muscle-related AE
Dose reduced	13 (16.5)	5 (6.3)	1 (1.3)
Dose interrupted*	54 (68.4)	33 (41.8)	6 (7.6)
Discontinued drug	73 (92.4)	24 (30.4)	5 (6.3)

*Includes patients with 1 and ≥2 dose interruptions.
Data are presented as n (%). N = 79.
AE, adverse event.

Concomitant statins and muscle toxicity

- Of the 79 patients receiving sonidegib 200 mg/day, 12 (15.2%) were receiving concomitant statins
  - Pravastatin was the most common concomitant statin (n = 9)
- Of patients on any statin, 58.3% (7/12) experienced grade 1–2 muscle symptoms and 66.7% (8/12) had a CK increase. No patient taking statins experienced a grade 3–4 muscle-related AE or CK increase
- Of the patients not taking statins, 64.2% (43/67) experienced any grade muscle symptom and 4.5% (3/67) reported grade 3–4 events; 59.7% (40/67) reported a CK increase with 9% reporting a grade 3–4 CK increase

CONCLUSIONS

- Overall safety findings for patients with laBCC and mBCC receiving sonidegib 200 mg/d at 42 months were consistent with observations at 30 months[7]
- Muscle-related AEs—most notably muscle spasms and elevated CK—were common, occurring in 54.4% and 30.4% of patients, respectively; however, most of these events were grade <3
- For most patients with elevated CK, resolution occurred within 14 days
- Discontinuations due to muscle-related AEs were low and manageable, with only 1 due to increased CK
- Though only a small number of patients in this analysis were receiving concomitant statins, there appear to be no differences in muscle toxicity
- Overall, sonidegib represents a viable treatment option for patients with advanced BCC

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