Long-term Safety of Sonidegib in Basal Cell Carcinoma: 30-Month Results from the BOLT Trial

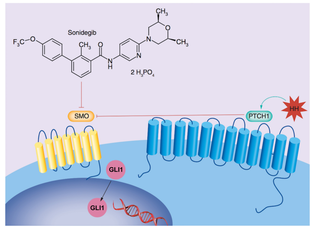
Ragini Kudchadkar, MD[1]; Anne Lynn S. Chang, MD[2]

[1]Associate Professor, Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, GA, USA; [2]Associate Professor, Dermatology, Stanford University School of Medicine, Redwood City, CA, USA.

BACKGROUND

- Basal cell carcinoma (BCC) is the most common form of skin cancer[1]
  - More than 4 million cases are diagnosed in the United States (US) each year[2]
- The incidence and prevalence of BCC is expected to increase as the population ages[3]
- ~95% of patients with BCC have mutations in the hedgehog (HH) signaling pathway components Patched-1 (PTCH1; >85%) or Smoothened (SMO; ~10%)[4]
- Sonidegib blocks the HH signaling pathway by selective inhibition of the SMO protein[5] (**Figure 1**)

Figure 1. Sonidegib Mechanism of Action



- Binding of HH signaling ligand to PTCH1 leads to release of SMO inhibition
- SMO activation causes GLI1 to cross the nuclear membrane, where it activates genes involved in tumorigenesis
- Sonidegib inhibits HH pathway signaling via SMO antagonism

GLI1, human glioma-associated oncogene homolog 1; HH, Hedgehog; PTCH1, Patched-1; SMO, Smoothened. (Adapted from [5])

- Sonidegib was approved based on results of the pivotal phase BOLT (**B**asal Cell Carcinoma **O**utcomes with **L**DE225 [sonidegib] **T**reatment) trial (NCT01327053)[6] (**Figure 2**)
- Sonidegib is approved in the US, the European Union, Switzerland, and Australia for the treatment of patients with locally advanced basal cell carcinoma (laBCC)[6]
- In Switzerland and Australia, sonidegib is also approved for the treatment of metastatic BCC (mBCC)[6]

OBJECTIVES

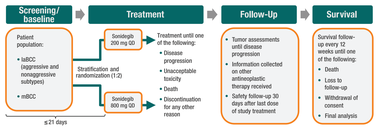
- Hedgehog pathway inhibitors are a relatively recent class of drugs
- Their long-term safety profile is not yet well characterized
- Safety was one of the key secondary endpoints from the BOLT clinical trial
- Adverse events (AEs) monitored at 30 months in laBCC and mBCC are reported here

METHODS

BOLT Study Design

- BOLT was a randomized, double-blind phase 2 clinical trial conducted in 58 centers across 12 countries[7] (**Figure 2**)
- Adults enrolled had either histologically confirmed laBCC (not amenable to curative surgery or radiation) or had mBCC (where all other treatment options had been exhausted)
- Patients received either 200 mg or 800 mg of sonidegib once daily (**Figure 2**)

Figure 2. BOLT Study Design



laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma; QD, once daily.

Safety/Monitoring AEs

- Monitoring of AEs was done according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03[8]
- AEs were assessed by central and investigator review from the first dose until 30 days after the last dose in patients who received at least one dose of sonidegib
- Muscle-related events were also assessed by an independent safety review and adjudication committee composed of three external experts

RESULTS

Patient Demographics and Disposition

- Two-hundred-thirty patients with laBCC (n=194) or mBCC (n=36) were enrolled between July 20, 2011, and January 10, 2013[9] (**Table 1**)
- Patients were randomized to sonidegib 200 mg (laBCC, n=66; mBCC, n=13) or 800 mg (laBCC, n=128; mBCC, n=23)[9]
- Baseline demographics were well balanced between arms

Table 1. Patient Demographics and Disease History

Sonidegib Dose (QD)	200 mg (n=79)	800 mg (n=151)
Median age (range), years	67 (25-92)	65 (24-93)
Male, %	61	64
Eastern Cooperative Oncology Group performance status, %		
0	63	63
1	24	29
2	10	7
Unknown	3	1
Aggressive histological/cytological subtype for patients with laBCC based on randomization/stratification, %	n=66	n=128
Aggressive subtype[a]	56	59
Nonaggressive subtype[b]	44	41
Metastasis, %	18	15
Metastatic sites, % of total patients with metastasis		
Lung	71	52
Lymph nodes[c]	7	30
Bone	14	22
Other[d]	21	30
Prior antineoplastic therapy, %		
Surgery	75	83
Radiotherapy	24	32

[a]Includes micronodular, infiltrative, multifocal, basosquamous, and sclerosing histological subtypes. [b]Includes nodular and superficial histological subtypes. [c]Includes axillary, parotid, submandibular, supraclavicular, and other. [d]Includes trunk, brain, head, liver, neck, and upper extremities. laBCC indicates locally advanced basal cell carcinoma; QD, once daily.

- At the time of the 30-month analysis, >90% of patients in each arm had discontinued treatment[9] (**Table 2**)
- AEs leading to treatment discontinuation in the 200-mg arm occurred in 29% of patients compared to 38% in the 800-mg arm[9]
- More patients receiving sonidegib 200 mg QD were able to stay on treatment until disease progression compared fo in the 800-mg QD group[9]

Table 2. Patient Disposition

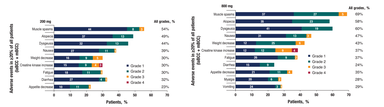
Sonidegib Dose (QD)	200 mg (n=79)		800 mg (n=150)	
Analysis	**Primary[a]**	**30-Month[b]**	**Primary[a]**	**30-Month[b]**
Median duration of exposure (range), months	8.9 (1.3-21.4)	11.0 (1.3-41.3)	6.5 (0.3-19.1)	6.6 (0.3-43.5)
Treatment ongoing, %	49	8	31	6
Treatment discontinued, %	51	92	69	94
Primary reasons for discontinuation, %				
Adverse event	20	29	32	38
Progressive disease[c]	19	37	4	15
Patient decision[d]	6	10	19	22
Physician decision[d]	4	13	7	9
Loss to follow-up	1	3	3	3
Death	0	1	3	3
Nonadherence	0	0	2	3
Protocol deviation	0	0	1	1

[a]Data cutoff: June 28, 2013; median follow-up was 13.9 months in both treatment arms combined. [b]Data cutoff: July 10, 2015; median follow-up was 38.2 months in both treatment arms combined. [c]Improved tolerability of the 200-mg dose allowed more patients to stay on treatment until disease progression than with the 800-mg dose. [d]Discontinuations due to patient or physician decision were primarily attributed to adverse events. QD, once daily.

Adverse Events Profile for laBCC and mBCC Combined

- At 30 months, the most common (>20% of patients) AEs associated with a once-daily 200-mg dose of sonidegib were muscle spasms (54%; 51% grades 1-2), alopecia (50%; all grades 1-2), dysgeusia (44%; all grades 1-2), and nausea (39%; 38% grades 1-2)
- Few grade 3-4 AEs were reported[9]
- Increased creatine kinase (CK) and rhabdomyolysis were the most commonly reported serious AEs among all patients
  - Because there was no renal impairment, none of the cases of rhabdomyolysis were confirmed by an independent review and adjudication committee of experts on muscle toxicity
  - Rhabdomyolysis was defined as CK concentrations >10-fold higher than baseline + 1.5-fold increase in creatinine concentration in serum from baseline[9]

Figure 3. Adverse Events (AEs) Reported in ≥20% of All (laBCC and mBCC) Patients Treated with Sonidegib

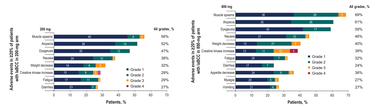


laBCC, locally advanced basal cell carcinoma, mBCC metastatic BCC.

Separated Adverse Events Profile for laBCC and mBCC

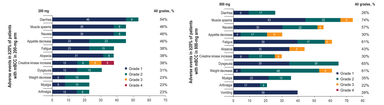
- The most common AE for sonidegib at either dosage in laBCC was muscle spasms[9] (**Figure 4**)
- The most common AE for 200 mg QD in mBCC was diarrhea; for 800 mg QD, it was muscle spasm[9] (**Figure 5**)

Figure 4. Adverse Events (AEs) Reported in ≥20% of laBCC Patients Treated with Sonidegib



laBCC, locally advanced basal cell carcinoma.

Figure 5. Adverse Events (AEs) Reported in ≥20% of mBCC Patients Treated with Sonidegib



mBCC, metastatic basal cell carcinoma.

- A total of 8 deaths were reported in BOLT, none of which were deemed related to treatment[9]
  - 4 deaths occurred in patients with laBCC; 1 death occurred in the 200-mg arm, and 3 deaths occurred in the 800-mg arm[9]
  - 4 deaths occurred in patients with mBCC; all occurred in the 800-mg arm[9]

CONCLUSIONS

- At the BOLT 30-month analysis, sonidegib treatment demonstrated long-term safety and tolerability, with no new safety concerns emerging in patients with either laBCC or those with mBCC
- Sonidegib 200 mg demonstrated a better benefit–risk profile compared with sonidegib 800 mg QD
- These data support the use of sonidegib 200 mg for the treatment of patients with laBCC or mBCC according to local treatment guidelines

REFERENCES

1. Mohan SV, Chang ALS. Advanced basal cell carcinoma: epidemiology and therapeutic innovations. *Curr Dermatol Rep.* 2014;3(1):40-45.
2. Rogers HW, Weinstock MA, Feldman SR, Coldiron BM. Incidence estimate of nonmelanoma skin cancer (keratinocyte carcinomas) in the US population, 2012. *JAMA Dermatol* 2015;151(10):1081-1086.
3. Kish T, Corry L. Sonidegib (Odomzo) for the systemic treatment of adults with recurrent, locally advanced basal cell skin cancer. *P T.* 2016;41(5):322-325.
4. Epstein EH. Basal cell carcinomas: attack of the hedgehog. *Nat Rev Cancer.* 2008;8(10):743-754.
5. Chen L, Aria AB, Silapunt S, Lee HH, Migden MR. Treatment of advanced basal cell carcinoma with sonidegib: perspective from the 30-month update of the BOLT trial. *Future Oncol.* 2017 Nov 9. doi: 10.2217/fon-2017-0457. [Epub ahead of print]
6. Burness CB. Sonidegib: first global approval. *Drugs.* 2015;75(13):1559-1566.
7. Migden MR, Guminski A, Gutzmer R. Treatment with two different doses of sonidegib in patients with locally advanced or metastatic basal cell carcinoma (BOLT): a multicentre, randomised, double-blind phase 2 trial. *Lancet Oncol.* 2015;16(6):716-728.
8. US Department of Health and Human Services. *Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.* Washington, DC: National Institutes of Health; May 28, 2009 (v4.03: June 14, 2010). NIH Publication No. 09-5410. Available at: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.
9. Lear JT, Migden MR, Lewis KD, et al. Long-term efficacy and safety of sonidegib in patients with locally advanced and metastatic basal cell carcinoma: 30-month analysis of the randomized phase 2 BOLT study. *J Eur Acad Dermatol Venereol.* 2017 Aug 28. doi: 10.1111/jdv.14542. [Epub ahead of print]

ACKNOWLEDGMENTS

The funding for this presentation was contributed by Sun Pharmaceutical Industries Ltd. Writing assistance was provided by Beverly E. Barton, PhD, and Nicola Donelan, PhD, of ScioScientific, LLC.

DISCLOSURES

Dr. Kudchadkar has participated on advisory boards, received research funding from Merck, consulting fees from Bristol-Myers Squibb, and received honoraria from Genentech, Inc., Novartis Pharmaceuticals Corporation, Sun Pharmaceutical Industries Ltd., and Eli Lilly & Company.

Dr. Chang has received honoraria for participation on an advisory board for Genentech, Inc., and has served as an investigator and received grants from Genentech, Inc. and Novartis Pharmaceuticals Corporation.

Presented at 2018 Winter Clinical Dermatology Conference – Hawaii, Lahaina, Hawaii, USA