Sonidegib Duration of Response in Advanced Basal Cell Carcinoma: Long-term Results from the Phase 2 BOLT Trial

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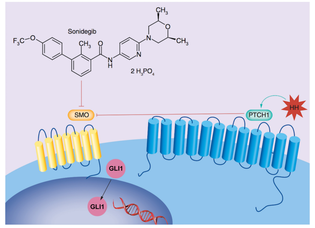
BACKGROUND

- 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]
- Treatment options for patients with locally advanced (laBCC) or metastatic BCC (mBCC) are limited[3,4]
- ~95% of patients with BCC have mutations in the hedgehog (HH) signaling pathway components Patched-1 (PTCH1; >85%) or Smoothened (SMO; ~10%)[5]
- Sonidegib is an inhibitor that blocks HH signaling by selective inhibition of the SMO protein[6] (**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 [6])

- 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)[7] (**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)[7]
- In Switzerland and Australia, sonidegib is also approved for the treatment of mBCC[7]

OBJECTIVES

- Hedgehog pathway inhibitors are a relatively recent class of drugs, and therefore their long-term duration of response (DOR) is not well characterized
- DOR was one of the key secondary endpoints from the BOLT clinical trial
- DOR results from the BOLT trial 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[8] (**Figure 2**)
- Adults enrolled had either histologically confirmed laBCC (not amenable to curative surgery or radiation) or mBCC (where all other treatment options had been exhausted)
- Patients received either 200 mg or 800 mg of sonidegib once daily (**Figure 3**)

Figure 2. BOLT Eligibility Criteria and Study Centers

Key Eligibility Criteria

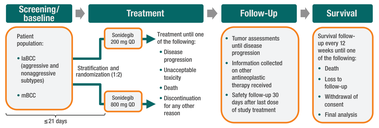
Adults (≥18 y) with histologically confirmed laBCC not amenable to radiotherapy or curative surgery, or mBCC for which all treatment options had been exhausted, and a WHO status grade of 0-2

	Sites	Randomized
Australia	2	12
Belgium	2	20
Canada	1	3
France	5	19
Germany	10	49
Greece	1	5
Hungary	2	5
Italy	1	3
Switzerland	3	6
Spain	3	3
United Kingdom	7	18
United States	21	87
TOTAL	58	230

STUDY CENTERS
58 sites worldwide

laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma; WHO, World Health Organization.

Figure 3. BOLT Study Design



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

Data Analyses

- 30-month analysis data will be shown here: data cutoff, July 10, 2015; median follow-up, 38.2 months
- Only data from the 200-mg treatment arm will be presented as this dose was found in earlier studies to be more tolerable and equally as effective as the higher dose

BOLT Primary and Secondary Endpoints

- The primary endpoint was objective response rate (ORR), which was defined as the proportion of patients with a best overall response of complete response (CR) or partial response (PR)
- Secondary endpoints included DOR, progression-free survival (PFS), and overall survival (OS) (**Table 1**)

Table 1. BOLT Study Endpoints

Primary endpoints	Objective response rate (best overall confirmed tumor response of complete or partial response) by central review
Secondary endpoints	• Complete response rate by central review • **Duration of response by central and investigator review** • Objective response rate by investigator review • Time to tumor response and progression-free survival by central and investigator review • Safety

- Tumors were evaluated using BCC-**m**odified **R**esponse **E**valuation **C**riteria **I**n **S**olid **T**umors (mRECIST) for laBCC, and by RECIST version 1.1 to access those with mBCC (**Figure 4**)

Figure 4. laBCC Evaluation per mRECIST

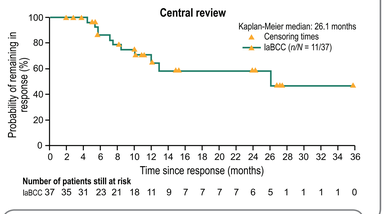
- BCC-mRECIST is a composite multimodal evaluation used to integrate MRI according to RECIST 1.1,[9] standard and annotated color photography using bi-dimensional WHO criteria,[10] and histology in multiple biopsies based on lesion surface area in the complex setting of post-treatment scarring, fibrosis, and ill-defined lesion borders

BCC, basal cell carcinoma; laBCC, locally advanced BCC; mRECIST, modified Response Evaluation Criteria in Solid Tumors; MRI, magnetic resonance imaging; WHO, World Health Organization.

RESULTS

- By central review, the median DOR for laBCC was 26.1 months[11] (**Figure 5**)
- By central review, the median DOR for mBCC was 24.0 months[11]

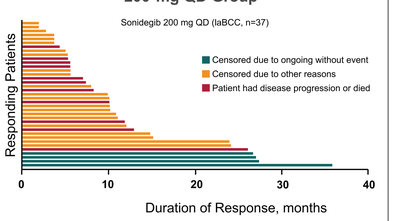
Figure 5. Kaplan-Meier Plot of DOR (Responders Only) for laBCC per Central Review in 200-mg QD Group



DOR, duration of response; laBCC indicates localized advanced basal cell carcinoma.

- Per central review, 70% (26 of 37) patients with laBCC in the 200-mg arm who achieved an objective response by the 30-month data cutoff maintained the response[11] (**Figure 6**)

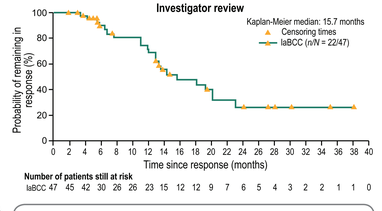
Figure 6. Waterfall Plot of DOR for laBCC (responders only) per Central Review in 200-mg QD Group



DOR, duration of response; laBCC, locally advanced basal cell carcinoma.

- By investigator review, the median DOR for laBCC was 15.7 months[11] (**Figure 7**)
- By investigator review, the median DOR was 18.1 months for mBCC[11]

Figure 7. Kaplan-Meier Plot of DOR (Responders Only) for laBCC per Investigator Review in 200-mg QD Group



DOR, duration of response; laBCC indicates locally advanced basal cell carcinoma.

- Patients who discontinued sonidegib before disease progression had durable responses, ranging from 25 weeks to 100 weeks (investigator review)
- The 2-year OS rates were 93.2% for laBCC and 69.3% for mBCC[11] (data not shown)

CONCLUSIONS

- With 30 months of follow-up, sonidegib continued to demonstrate durable responses in patients with laBCC or mBCC at the approved dosage of 200 mg once daily
- Importantly, patients with laBCC treated with sonidegib had sustained responses persisting beyond treatment discontinuation
- These results continue to support the use of sonidegib 200 mg QD for the treatment of patients with advanced BCC, in accordance with local guidelines

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DISCLOSURES

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.

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.

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