Sonidegib Efficacy and Safety in Patients with Locally Advanced Basal Cell Carcinoma Based on Tumor Aggressiveness

Michael R. Migden, MD[1], and Reinhard Dummer, MD[2]

[1]Departments of Dermatology and Head and Neck Surgery MD Anderson Cancer Center, Houston, TX, USA
[2]Department of Dermatology, University of Zurich Hospital, Zurich, Switzerland

BACKGROUND

- Basal cell carcinomas (BCCs) can be categorized as aggressive or nonaggressive based on their histology[1,2]
  - Most BCCs have nonaggressive histology, including superficial and nodular subtypes[2]
  - Aggressive subtypes (eg, micronodular, infiltrative, or sclerosing) are rarer but tend to have a higher rate of recurrence[1,2]
- Sonidegib (LDE225) is a hedgehog (Hh) pathway inhibitor approved for the treatment of patients with locally advanced BCC (laBCC) not amenable to surgery or radiotherapy[3-5]
  - Sonidegib was approved based on results from the phase 2 Basal Cell Carcinoma Outcomes With LDE225 Treatment (BOLT) study (NCT01327053), which included patients with aggressive or nonaggressive laBCC subtypes[6]

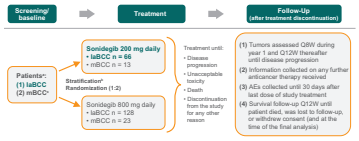
OBJECTIVE

- In patients with laBCC regardless of tumor aggressiveness, durable tumor responses were observed
  - These results are significant, given the higher rate of recurrence and higher chance of subclinical spread associated with aggressive laBCC subtypes
- Here we present the efficacy and safety of sonidegib 200 mg in patients with laBCC, based on tumor aggressiveness, from the BOLT 30-month analysis

METHODS

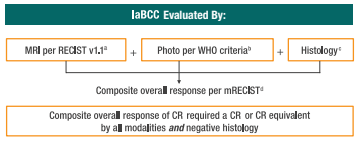
- BOLT was a multicenter, randomized, double-blind, phase 2 study that enrolled patients with laBCC (aggressive or nonaggressive) or metastatic BCC (mBCC; **Figure 1**)
- Patients with laBCC not amenable to curative surgery or radiotherapy were randomized in a 1:2 ratio to 200 mg or 800 mg once daily (QD); only results from the 200-mg QD dose will be discussed here
- Objective response rate (ORR: confirmed complete response [CR] + partial response [PR]). Duration of response, and progression-free survival (PFS) were assessed according to stringent criteria, defined as modified Response Evaluation Criteria In Solid Tumors (mRECIST; **Figure 2**), by central review
  - Overall survival (OS) was also assessed
- Safety was assessed until 30 days after the final treatment; Common Terminology Criteria for Adverse Events (CTCAE) v4.03 guidelines were used to evaluate adverse events (AEs)[6]

Figure 1: BOLT Study Design



[a]Patients treated with previous sonidegib or other hedgehog pathway inhibitors were excluded. [b]Stratification was based on stage, history, disease histology for patients with laBCC (aggressive vs nonaggressive), and geographic region. AEs, adverse events; laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma; Q8W, every 8 weeks; Q12W, every 12 weeks.

Figure 2: Stringent Tumor Response Evaluation Criteria



[a]Assessed by central review per RECIST v1.1.9. [b]Standard and annotated color photography assessed per WHO criteria.[3] Partial response ≥50% reduction in the sum of products of perpendicular diameters from baseline; progressive disease ≥25% increase in the sum of products of perpendicular diameters from the lowest point. [c]Histology was assessed in multiple biopsies surveying the lesion area. [d]Composite overall response was determined by an independent review committee that reread all available data, including histology reports for laBCC. CR, complete response; laBCC, locally advanced basal cell carcinoma; mRECIST, modified Response Evaluation Criteria In Solid Tumors; MRI, magnetic resonance imaging; WHO, World Health Organization.

RESULTS

- 66 patients with laBCC received 200 mg QD sonidegib
  - Of these, 37 (56%) patients had aggressive laBCC subtypes and 29 (44%) had nonaggressive subtypes
- 92% of patients were no longer receiving sonidegib as of the cut-off date for the 30-month analysis
- Median duration of exposure was 11.1 months
- Most common reasons for discontinuation were AEs (29%) and progressive disease (37%)

Efficacy

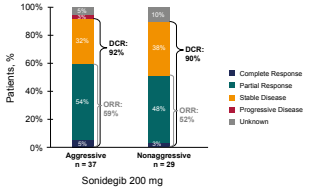
- ORRs per central review were similar for patients with aggressive or nonaggressive laBCC subtypes (**Table 1**; **Figure 3**)
  - In patients with aggressive subtypes, ORR per central review was 59% in the 200-mg treatment arm
  - In patients with nonaggressive subtypes, ORR per central review was 52% in the 200-mg treatment arm

Table 1: Sonidegib Efficacy in laBCC at 30 Months

	Sonidegib 200 mg QD	
Central Review	**Aggressive[a] (n = 37)**	**Nonaggressive[b] (n = 29)**
Best overall response, n (%) • CR[c] • PR[c] • SD • PD • Unknown	 2 (5) 20 (54) 12 (32) 1 (3) 2 (5)	 1 (3) 14 (48) 11 (38) 0 3 (10)
ORR (95% CI); % CR, % PR	59 (42-75); 5,54	52 (32.5-71); 3, 48
DCR, %[d]	92	90
DOR, no. of events[e]/ responders; Median (95% CI), mo	7/22; 26.1 (not estimable)	4/15; Not reached
Kaplan-Meier-estimated median (95% CI), mo[e]	26.1 (NE)	NE
PFS, no. of events; Median (95% CI), mo	11; 22.1 (not estimable)	5; Not reached
OS, median (95% CI), mo; 2-yr OS (95% CI), %	Not reached; 92 (71-98)	Not reached; 95 (68-99)

[a]Includes micronodular, infiltrative, multifocal, basosquamous, and sclerosing laBCC; [b]Includes nodular and superficial laBCC; [c]Required confirmation on repeat assessments >4 weeks apart; [d]CR+PR+SD; [e]KM-estimated time from first CR or PR until disease progression or death due to any cause (among responders). CR, complete response; DCR, disease control rate; DOR, duration of response; ORR, overall response rate; OS, overall survival; PR, partial response; PFS, progression-free survival, QD, once daily; SD, stable disease.

Figure 3: Best Overall Response by laBCC Subtype at 30 Months



DCR, disease control rate; laBCC, locally advanced BCC; ORR, objective response rate.

Progression and Survival

- PFS and OS were similar for patients with aggressive or nonaggressive laBCC subtypes (**Table 2**)
- Overall, 5 deaths in patients with laBCC in the 200-mg arm were reported by the data cutoff date
- Median OS was not reached for either histological subgroup in either arm

Table 2: PFS and OS in Patients by laBCC Subtype

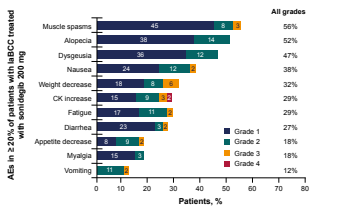
	Sonidegib 200 mg QD	
	Aggressive (n = 37)	**Nonaggressive (n = 29)**
PFS events, n (%)	11 (30)	5 (17)
KM-estimated media PFS duration (95% CI), months	21.1 (NE)	NE
Deaths, n (%)	4 (11)	1 (3)
KM-estimated 2-uear OS (95% Ci), %	92 (71-98)	9 (68-99)

CI, confidence interval; KM, Kaplan-Meier; laBCC, locally advanced BCC; OS, overall survival; PFS, progression-free survival

Safety

- The observed safety profile of sonidegib remained similar to that of previous analyses, with the 200-mg dose continuing to show a favorable profile[7,8,10]
- >50% of patients with laBCC experienced grade 1/2 AEs
- The most common AEs of any grade among patients with laBCC were muscle spasms, alopecia, dysgeusia, and nausea (**Figure 4**)
- There were no treatment-related deaths
- There were no significant differences noted between the subtypes

Figure 4: Adverse Events Regardless of Cause in ≥20% of Patients with laBCC



AE, adverse event; CK, creatinine kinase; laBCC, locally advanced BCC.

CONCLUSIONS

- With 30 months of follow-up, patients with aggressive or nonaggressive laBCC subtypes experienced durable responses when given sonidegib 200 mg daily
- The efficacy of sonidegib was similar for patients with aggressive or nonaggressive laBCC subtypes in this analysis
- No new safety concerns were detected, and sonidegib 200 mg demonstrated a good benefit–risk profile
- Together, these data support the use of sonidegib 200 mg daily in patients with laBCC regardless of tumor aggressiveness, in accordance with local guidelines

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