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

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BACKGROUND
- Basal cell carcinomas (BCCs) can be categorized as aggressive or nonaggressive based on their histology.
  - Most BCCs have nonaggressive histology, including superficial and nodular subtypes.
  - Aggressive subtypes (eg, micronodular, infiltrative, or sclerotic) are rarer but have a higher rate of recurrence.
- 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.
- Sonidegib was approved based on results from the phase 2 Basal Cell Carcinoma Outcomes With LDE225 Treatment (BOLT) study (NC1701327053), which included patients with aggressive or nonaggressive laBCC subtypes.

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 assessed.
- Safety was assessed 30 days after the final treatment.

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

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Aggressive (n = 37)</th>
<th>Nonaggressive (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>59% (42-72)</td>
<td>52% (32.5-71.7)</td>
</tr>
<tr>
<td>DCR (%)</td>
<td>52% (46-65)</td>
<td>70% (50-82)</td>
</tr>
<tr>
<td>Kaplan-Meier (CM)</td>
<td>50% (29-75)</td>
<td>Not reached</td>
</tr>
<tr>
<td>≥2 ORS (5%) CM</td>
<td>52% (32.5-71.7)</td>
<td>Not reached</td>
</tr>
<tr>
<td>PFS, no. of median</td>
<td>11.2 ± 2.1</td>
<td>8.0 ± 2.5</td>
</tr>
<tr>
<td>OS, median (CM)</td>
<td>50% (29-75)</td>
<td>70% (50-95)</td>
</tr>
</tbody>
</table>

The observed safety profile of sonidegib remained similar to that of previous analyses, with the 200-mg dose continuing to show a favorable profile:
- >50% of patients with laBCC experienced grade 1 AEs.
- Most common AEs of any grade among patients with laBCC were muscle spasms, alopecia, dysgeusia, and nausea (Figure 4).

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.

REFERENCES

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