A Phase I dose-escalation study of the MDM2-p53 antagonist BI 907828 in patients with advanced solid tumors

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Introduction

• Evasion of cell-cycle arrest and apoptosis by inactivation of p53 is a key mechanism by which tumors promote survival and proliferation.
• The MDM2 antagonist is a critical regulator of p53; overexpression of MDM2 aids tumor proliferation.

BI 907828, a highly potent MDM2 wild-type antagonist, showed tumor efficacy in vivo, especially in TP53 wild-type murine xenografts and syngeneic models.

Objectives

• To determine the MTD (based on DLTs during Cycle 1), and to evaluate the safety and tolerability, PK, PD, and preliminary efficacy of BI 907828.

Methods

• DLTs, dose-limiting toxicities; MTD, maximum tolerated dose; PD, pharmacodynamics; PK, pharmacokinetics

Patients

• Here, we report results for the dose-escalation part of the study.
• At April 4, 2021, 54 patients with advanced solid tumors were treated with BI 907828; median (range) of 2 (1-11) prior systemic therapies:
  – Arm A: 29 patients, dose range 10-80 mg
  – Arm B: 25 patients, dose range 5-40 mg
  – 34.5% of patients in Arm A and 48.8% of patients in Arm B had soft tissue sarcomas

Key patient demographics and disease characteristics

<table>
<thead>
<tr>
<th>Feature</th>
<th>Arm A</th>
<th>Arm B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yrs (range)</td>
<td>59.1 (32-84)</td>
<td>55.0 (19-75)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>14 (55.2)</td>
<td>15 (60.0)</td>
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<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>15 (45.5)</td>
<td>16 (61.5)</td>
</tr>
<tr>
<td>Asian</td>
<td>5 (15.2)</td>
<td>5 (20.0)</td>
</tr>
<tr>
<td>African American</td>
<td>1 (3.4)</td>
<td>1 (4.0)</td>
</tr>
</tbody>
</table>

ECOG PS 0-1, n (%) | 11 (37.1) | 20 (80.0) |

Prior therapies, median (range) | 2 (1-11) | 2 (1-11) |

Key inclusion criteria

Known TP53 wild-type status
Previously treated advanced/metastatic solid tumor
Tumor with documented TP53 mutation
Active or untreated brain metastases

Key exclusion criteria

Prior therapies, median (range) = 27.9 ± 8.23 h post-dose

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• Data missing for 1 patient in Arm B. CCGC P6, Eastern Cooperative Oncology Group performance status.

Safety

• DLTs in Cycle 1
  – Most DLTs were grade 3/4 hematologic AEs:
    – Arm A: 5 patients with DLTs; one grade 3 nausea (45 mg), one grade 3 thrombocytopenia (45 mg), one grade 3 enterocolitis (60 mg), one grade 4 neutropenia (60 mg) and one grade 4 thrombocytopenia (40 mg)
    – Arm B: 3 patients with DLTs: one grade 4 thrombocytopenia (45 mg), one grade 4 neutropenia associated with grade 4 thrombocytopenia (60 mg), and one grade 3 neutropenia (60 mg)

• PK/PD analysis:
  – GDF15 level (biomarker of target engagement) correlated with exposure (AUC0-72h)

• Manageable safety profile, favorable PK properties, early signs of efficacy, especially in MDM2-amplified tumors

Efficacy

• This ongoing Phase I study is evaluating the safety and anti-tumor activity of the MDM2-p53 antagonist BI 907828

• Preliminary PK (Arm A) and PK/PD (Arms A + B)

• Key findings and conclusions

• PFS, progression-free survival; SR, serious AE

References

• Zhao Y, et al. Acta Biochim Biophys Sin (Shanghai) 2014;46(10):831-4

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