A Phase Ia/Ib, dose-escalation/expansion study of the MDM2–p53 antagonist BI 907828 in patients with advanced/metastatic sarcoma

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Introduction

- Evasion of cell-cycle arrest and apoptosis by inactivation of p53 is a key mechanism by which tumours promote survival and proliferation.1
- The MDM2 oncoprotein is a critical regulator of p53; overexpression of MDM2 aids tumour proliferation.1

- BI 907828, a highly potent MDM2–p53 antagonist, showed antitumour efficacy in vivo, especially in TP53 wild-type MDM2-amplified DDLPS preclinical xenograft and syngeneic models.1

- NCT03449381 is a Phase I study assessing BI 907828 in patients with advanced/metastatic sarcoma (DDLPS-de-differentiated liposarcoma; MDM2, murine double minute 2; p53, tumor protein p53).

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 in patients with advanced solid tumours, particularly confirmed advanced/metastatic sarcoma.

- Here, we report results for the Phase Ia dose-escalation part, including efficacy data in patients with advanced/metastatic sarcoma.

Methods

Key findings and conclusions

- This ongoing Phase I study is evaluating the safety and antitumour activity of the MDM2–p53 antagonist BI 907828.

- BI 907828 is associated with a manageable safety profile.

- Encouraging preliminary efficacy in patients with sarcoma, particularly in MDM2-amplified tumours:
  - 82.1% disease control rate
  - Three of eight patients with WDLPDs achieved a PR
  - All 11 DDLPS patients achieved SD
  - Estimated median PFS was 10.8 months (range, 1.3–21.0 months)

Patients

- At 12 July 2021, 54 patients with advanced solid tumours had been treated with BI 907828:
  - Arm A: 29 patients, dose range 10–40 mg
  - Arm B: 25 patients, dose range 5–80 mg

- Other subtypes were high-grade leiomyosarcoma, leiomyosarcoma, GIST, adenocarcinoma, dermatofibrosarcoma protuberans, osteosarcoma, chondrosarcoma, MDM2 amplification in WDLPD, and myxoid chondrosarcoma.

Key patient demographics and disease characteristics

<table>
<thead>
<tr>
<th>Arm</th>
<th>A (n=29)</th>
<th>B (n=25)</th>
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<tbody>
<tr>
<td>Age, mean±SD</td>
<td>57.9±11.9</td>
<td>56.9±11.6</td>
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<tr>
<td>Sex</td>
<td>16 (55.2)</td>
<td>16 (64.0)</td>
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<tr>
<td>Race</td>
<td>10 (34.5)</td>
<td>13 (52.0)</td>
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<td>Caucasian</td>
<td>9 (31.0)</td>
<td>10 (40.0)</td>
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<tr>
<td>Asian</td>
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<td>5 (20.0)</td>
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<tr>
<td>African American</td>
<td>3 (10.3)</td>
<td>4 (16.0)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (6.9)</td>
<td>1 (4.0)</td>
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</tbody>
</table>

- ECOS Sarcoma Cooperative Oncology Group risk status performance status (ECOS, adrenocortical carcinoma; GIST, gastrointestinal stromal tumour; WDLPD, well-differentiated liposarcoma; DDLPS, dedifferentiated liposarcoma).

- Of 28 patients with sarcoma, 23 achieved ≥2SD; the disease control rate (SD) was 82.1%.

- Three of 8 patients with WDLPD achieved a PR (all were MDM2-amplified).

- All 11 patients with WDLPDs achieved SD as best overall response.

- The estimated median PFS was 10.8 months (range, 1.3–21.0 months).

Safety

Tumour response over time

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- Three of 8 patients with WDLPDs achieved a PR (all were MDM2-amplified).
- All 11 patients with WDLPDs achieved SD as best overall response.
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Efficacy in patients with advanced/metastatic sarcoma

References