A Phase Ia/Ib, open-label, multicenter, dose-escalation study of BI 907828 (MDM2-p53 antagonist) in adult patients with advanced or metastatic solid tumors

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Introduction

- Evasion of cell-cycle arrest and apoptosis by inactivation of the tumor protein p53 (TP53) is a key mechanism by which tumors promote survival and proliferation\(^1\)
  - The murine double minute 2 (MDM2) oncoprotein is a critical negative regulator of TP53, and overexpression of this protein aids tumor proliferation\(^1\)
  - \textit{MDM2} gene copy number is increased in an average of 7% of human cancers, and this may be as high as 90% of tumors in some cancer types, such as liposarcoma\(^2,3\)
- Small molecule inhibitors of the MDM2-p53 interaction (MDM2-p53 antagonists) are being developed as novel anti-cancer drugs
  - Several MDM2-p53 antagonists, designed to restore p53 function in tumors with wild-type p53, are currently in early clinical development\(^4\)
- BI 907828 is a potent MDM2-p53 antagonist that has shown efficacy in mouse models of human cancer, both with and without MDM2 gene copy number increases

MDM2, murine double minute 2; p53, tumor protein 53; WT, wild type
Study design and objectives

• NCT03449381 is a Phase Ia/Ib, open-label, multicenter, dose-escalation trial of BI 907828
• The primary objectives of Phase Ia (dose-escalation) are to determine: maximum tolerated dose (MTD); recommended dose for expansion (RDE); safety and tolerability
• Secondary objectives for Phase Ia include pharmacokinetics (PK) and preliminary anti-tumor activity. Further objectives include pharmacodynamics (PD; GDF-15 induction in plasma)
• The primary objectives of Phase Ib (dose expansion) are to assess the efficacy, safety, and PK profiles at the RDE, and to determine the recommended dose for Phase II

GDF-15, growth/differentiation factor 15 (formerly MIC-1)
# Patients

## Key inclusion criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
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<tbody>
<tr>
<td>Aged ≥18 years (≥20 years in Japan)</td>
<td>Pathologically documented advanced/metastatic solid tumor</td>
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<tr>
<td>Radiologically documented disease progression/relapse during or after</td>
<td>Adequate organ function</td>
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<td>all standard of care treatments</td>
<td>Life expectancy ≥12 weeks at start of treatment</td>
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<td>ECOG PS 0–1</td>
<td>≥1 measurable target lesion (for Phase Ib only)</td>
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ECOG PS, Eastern Cooperative Oncology Group performance status
Patients cont’d

Key exclusion criteria

<table>
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<th>Criteria</th>
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<tr>
<td>Previous administration of any MDM2-p53 antagonist</td>
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<tr>
<td>Tumor with documented mutation in TP53</td>
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<tr>
<td>Active or untreated brain metastases (from non-brain tumors)</td>
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<td>Current use of warfarin, factor Xa inhibitors, or direct thrombin inhibitors</td>
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<td>History of bleeding diathesis</td>
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<td>Major surgery within 12 weeks prior to start of study treatment</td>
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Study design

Phase Ia
- Dose escalation
  - Arm A: One dose on day 1, every 21 days, starting dose: 10 mg
  - Arm B: One dose on days 1 and 8, every 28 days, starting dose: 50% of the dose level at which at least two grade ≥2 non dose-limiting AEs occur in cycle 1 in Arm A
- Cohorts of newly-enrolled patients will receive escalating doses of BI 907828 until MTD is reached

Phase Ib
- Dose expansion
  - Cohort 1: TP53 wild-type and MDM2-non-amplified solid tumors
  - Cohort 2: TP53 wild-type and MDM2-amplified solid tumors
- Treatment dose and schedule for Phase Ib will be determined based on the safety and PK/PD data of Phase Ia

In both phases, treatment will continue until disease progression or unacceptable toxicity.

AE, adverse event; MTD, maximum tolerated dose; PD, pharmacodynamics; PK, pharmacokinetics
## Endpoints and assessments

### Primary

<table>
<thead>
<tr>
<th>Phase Ia</th>
<th>Phase Ib</th>
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<tr>
<td>Dose-limiting toxicities†</td>
<td>Objective response‡</td>
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<tr>
<td>Maximum tolerated dose†</td>
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### Secondary

<table>
<thead>
<tr>
<th>Phase Ia</th>
<th>Phase Ib</th>
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<tr>
<td>Pharmacokinetics</td>
<td>Disease control‡</td>
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<td></td>
<td>PFS‡</td>
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<td></td>
<td>Safety</td>
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<td></td>
<td>Pharmacokinetics</td>
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</tbody>
</table>

†During the first treatment cycle; ‡determined by investigator according to RECIST v1.1 (solid tumors) or RANO criteria (glioblastoma). RANO, Response Assessment in Neuro-Oncology; PFS, progression-free survival.
Endpoints and assessments cont’d

- In Phase Ia, tumor assessment will occur every 6 (Arm A) or 8 (Arm B) weeks for the first 6 months, and then every 12 weeks until PD or start of subsequent anti-cancer therapy
- MTD will be based on the number of patients with DLTs during the first treatment cycle in both arms of Phase Ia
- PFS will be analyzed by Kaplan–Meier curves
  - PFS = time from the start of BI 907828 treatment to the date of PD or death, whichever occurs first
- DC = CR, PR, or SD per investigators’ assessment until PD or start of subsequent anti-cancer therapy
- OR = CR or PR per investigators’ assessment, where best overall response is assessed from start of treatment until PD, death, or last evaluable tumor assessment
- Safety analyses will be carried out in a descriptive fashion
- Interim safety analyses will be performed in Phase Ia by the SMC after each dose cohort, and used to determine the next dose level

CR, complete response; DC, disease control; DLT, dose-limiting toxicity; OR, objective response; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SMC, safety monitoring committee
Current status

- Patient screening started in June 2018
- The first patient was enrolled in June 2018
- Target enrollment is up to 40 patients in Phase Ia and 50 patients in Phase Ib, across 3 countries
Key points

Objectives:
• MTD and RDE, safety and tolerability, PK, PD, and preliminary efficacy of the MDM2-p53 antagonist BI 907828 in patients with advanced solid tumors

Study design:
• Open-label, multicenter, dose-escalation Phase Ia/Ib trial

Endpoints:
• Primary: DLTs, MTD, OR
• Secondary: PK, DC, PFS, safety

Status: Currently enrolling for Phase Ia in centers across the USA, Canada, and Japan
References

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