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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Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting, Chicago, IL, USA, May 31 – June 4, 2019
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\(^1\)
  - \(MDM2\) 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>
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<tr>
<td>Pathologically documented advanced/metastatic solid tumor</td>
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<tr>
<td>Radiologically documented disease progression/relapse during or after</td>
<td>all standard of care treatments</td>
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<td>ECOG PS 0–1</td>
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<tr>
<td>Adequate organ function</td>
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<tr>
<td>Life expectancy ≥12 weeks at start of treatment</td>
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<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>
<thead>
<tr>
<th>Criterion</th>
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<tbody>
<tr>
<td>Previous administration of any MDM2-p53 antagonist</td>
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<tr>
<td>Tumor with documented mutation in <em>TP53</em></td>
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<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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In both phases, treatment will continue until disease progression or unacceptable toxicity.

**Study design**

**Phase Ia**
- **Dose escalation**
  - ~40 patients
  - **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

**Phase Ib**
- **Dose expansion**
  - ~25 patients per cohort
  - **Cohort 1**
    - TP53 wild-type and MDM2-non-amplified solid tumors
    - Treatment dose and schedule for Phase Ib will be determined based on the safety and PK/PD data of Phase Ia
  - **Cohort 2**
    - TP53 wild-type and MDM2-amplified solid tumors

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

<table>
<thead>
<tr>
<th>Primary</th>
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<th>Secondary</th>
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<tbody>
<tr>
<td><strong>Phase Ia</strong></td>
<td><strong>Phase Ib</strong></td>
<td><strong>Phase Ib</strong></td>
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<tr>
<td>Dose-limiting toxicities(^\dagger)</td>
<td>Objective response(^\dagger)</td>
<td>Disease control(^\dagger)</td>
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<tr>
<td>Maximum tolerated dose(^\dagger)</td>
<td></td>
<td>PFS(^\dagger)</td>
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<tr>
<td>Pharmacokinetics</td>
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<td>Safety</td>
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<td></td>
<td></td>
<td>Pharmacokinetics</td>
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\(^\dagger\)During the first treatment cycle; \(^\dagger\)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
Acknowledgments

• This study is funded by Boehringer Ingelheim. The authors were fully responsible for all content and editorial decisions, were involved at all stages of poster development and have approved the final version.
• Medical writing assistance, supported financially by Boehringer Ingelheim, was provided by Beth de Klerk, of GeoMed, an Ashfield company, part of UDG Healthcare plc, during the development of this poster.
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