A Phase Ia/Ib, dose-escalation/expansion study of BI 907828 in combination with BI 754091 and BI 754111 in patients with advanced solid tumors

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Introduction

• The anti-tumor activity of MDM2-p53 antagonists has been demonstrated through reactivation of the tumor suppressor gene TP53 and, potentially, an additional immune-modulatory effect\(^1\)
  – BI 907828 is a highly potent MDM2-p53 antagonist that has shown anti-tumor activity in preclinical studies\(^1\)
• BI 754091 is an antibody that binds to the PD-1 receptor, blocking the interaction with its ligands\(^2\)
• BI 754111 is an anti-LAG-3 antibody that has been shown to reverse the negative regulation of T-cell activation in preclinical models\(^3\)
• There is evidence that blockade of the PD-1 pathway leads to over-expression of other checkpoint inhibitors, including LAG-3, which may represent an escape pathway; therefore, blocking multiple immune checkpoints could improve patient outcome\(^4\)
• Preclinical studies have demonstrated the synergistic anti-tumor effect of a combination of MDM2-p53 antagonist (BI 907828) with anti-PD-1 (BI 754091) and anti-LAG-3 (BI 754111) antibodies in several syngeneic models\(^5\), driving the rationale for this study

LAG-3, lymphocyte activating 3; MDM2, murine double minute 2; PD-1, programmed cell death protein-1; TP53, tumor protein p53
Non-inflamed tumor microenvironment

Tumor cells

Immuno-modulation

CD8+, cluster of differentiation 8; Treg, regulatory T cells; wt, wild-type
Study design and objectives

Study design
• Open-label, multicenter, dose-escalation Phase Ia/Ib trial (NCT03964233)

Objectives
• To determine the MTD, PK, efficacy, safety, and tolerability of BI 907828 when combined with BI 754091 and BI 754111 in patients with advanced solid tumors

MTD, maximum tolerated dose; PK, pharmacokinetics
Study design and objectives (cont’d)

**Phase Ia – dose escalation**
BI 907828 + BI 754091 + BI 754111
n=30 evaluable patients

**Phase Ib – dose-expansion cohorts**

**Cohort 1** (n=80; randomized in 2:2:1 ratio)
TP53 wild-type NSCLC

- **Arm A** (n=32)
  - BI 907828 (RDE q3w)
  - BI 754091 (240 mg q3w)
  - BI 754111 (600 mg q3w)

- **Arm B** (n=32)
  - BI 754091 (240 mg q3w)
  - BI 754111 (600 mg q3w)

- **Arm C** (n=16)
  - BI 907828 (RDE)
  - BI 754091 (240 mg)

**Cohorts 2, 3, and 4** (single-arm cohorts)

- **Cohort 2** (n=20)
  - TP53 wild-type melanoma
  - BI 907828 (RDE q3w)
  - BI 754091 (240 mg q3w)
  - BI 754111 (600 mg q3w)

- **Cohort 3** (n=10 each)
  - TP53 wild-type liposarcoma and TP53 wild-type UPS
  - BI 907828 (RDE)
  - BI 754091 (240 mg)

- **Cohort 4** (n=20)
  - TP53 wild-type hepatocellular carcinoma

q3w, every 3 weeks; RDE, recommended dose for expansion (determined in Phase Ia); UPS, undifferentiated pleomorphic sarcoma
# Patients

## Key inclusion criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
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<tbody>
<tr>
<td>Aged ≥18 years</td>
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<tr>
<td>Pathologically documented advanced/metastatic solid tumor</td>
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<td>≥1 measurable target lesion (for Phase Ib only)</td>
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<td>Radiologically documented disease progression/relapse during or after all standard of care treatments</td>
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<td>At least one prior treatment</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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<td>Life expectancy ≥12 weeks at start of treatment</td>
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## Key exclusion criteria

<table>
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<tr>
<th>Criteria</th>
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<tr>
<td>Previous administration of any MDM2-p53 antagonist or anti-LAG-3 antibody</td>
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<tr>
<td>Tumor with documented mutation in TP53</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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ECOG PS, Eastern Cooperative Oncology Group performance status
## Endpoints and assessments

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<thead>
<tr>
<th>Phase Ia</th>
<th>Phase Ib</th>
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<tr>
<td><strong>Primary</strong></td>
<td><strong>Secondary</strong></td>
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<tr>
<td>MTD based on DLTs</td>
<td>PK parameters ($C_{\text{max}}$ and AUC$_{0-tz}$ of BI 907828, BI 754091 and BI 754111) in Cycle 1</td>
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<tr>
<td><strong>Primary</strong></td>
<td><strong>Secondary</strong></td>
</tr>
<tr>
<td>Objective response according to RECIST v1.1</td>
<td>Objective response according to iRECIST</td>
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<tr>
<td>Disease control according to RECIST v1.1 and iRECIST</td>
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<tr>
<td>PFS*</td>
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*In cohort 3, the PFS rate at 12 and 24 weeks will also be assessed.

AUC$_{0-tz}$, area under curve from 0 to the time of the last quantifiable data point; $C_{\text{max}}$, maximum plasma concentration; DLTs, dose-limiting toxicities; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumors.
Study status

First patient enrolled: June 2019

Target enrollment:
Phase Ia: 30 patients

Target enrollment:
Phase Ib: 140 patients
References

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