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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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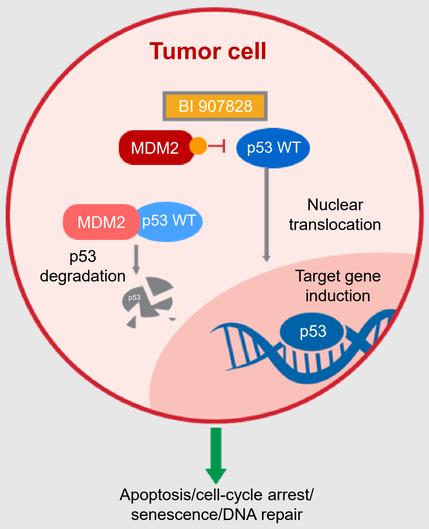
Introduction

- 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]
  - *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

Patients

Key inclusion criteria

Aged ≥18 years (≥20 years in Japan)
Pathologically documented advanced/metastatic solid tumor
Radiologically documented disease progression/relapse during or after all standard of care treatments
ECOG PS 0–1
Adequate organ function
Life expectancy ≥12 weeks at start of treatment
≥1 measurable target lesion (for Phase Ib only)

Key exclusion criteria

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

ECOG PS, Eastern Cooperative Oncology Group performance status; GDF-15, growth/differentiation factor 15 (formerly MIC-1)

Study design

Phase Ia — Dose escalation ~40 patients

Arm A	Arm B
One dose on day 1, every 21 days Starting dose: 10 mg	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 ~25 patients per cohort

Cohort 1	Cohort 2
TP53 wild-type and *MDM2*-non-amplified solid tumors	*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

AE, adverse event

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

Endpoints and assessments

Primary	
Phase Ia	Phase Ib
Dose-limiting toxicities†	Objective response‡
Maximum tolerated dose†	

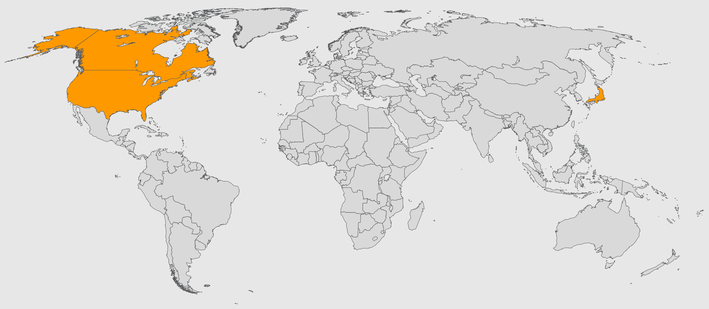
Secondary	
Phase Ia	Phase Ib
Pharmacokinetics	Disease control‡
	PFS‡
	Safety
	Pharmacokinetics

†During the first treatment cycle; ‡determined by investigator according to RECIST v1.1 (solid tumors) or RANO criteria (glioblastoma)

- 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; RANO, Response Assessment in Neuro-Oncology; 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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