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 proliferation1 – The murine double minute 2 (MDM2) oncoprotein is a critical negative regulator of TP53, and overexpression of this protein aids tumor proliferation1 – 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 liposarcoma2,3
• 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 development4 – 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

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

Endpoints and assessments

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*During the first treatment cycle; †Determined by investigator according to RECIST v1.1 (solid tumors) or AHERA criteria (glioblastoma); ‡Determined by investigator according to 2019 WHO tumor response criteria

Study design

Phase Ia

Dose escalation

~40 patients

Cohorts of newly-enrolled patients will receive escalating doses of BI 907828 until MTD is reached

Phase Ib

Dose expansion

~25 patients per cohort

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

Endpoints and assessments

Objective response

TP53 wild-type and MDM2-non-amplified solid tumors

TP53 wild-type and MDM2-amplified solid tumors

Study 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

• 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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