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

Poster #390

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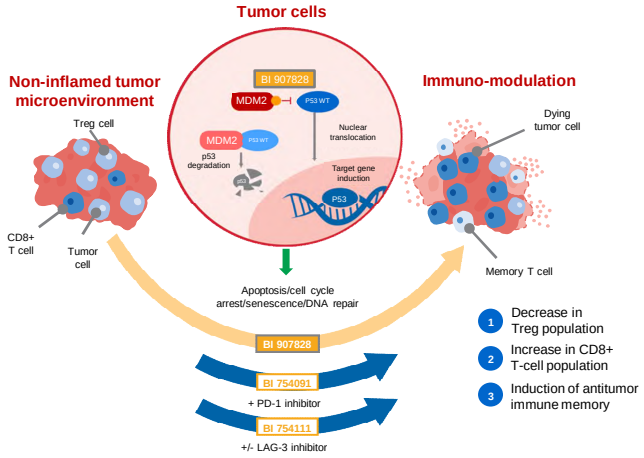
Introduction

- 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



CD8, cluster of differentiation 8; LAG-3, lymphocyte activating 3; MDM2, murine double minute 2; PD-1, programmed cell death protein-1; TP53, tumor protein p53; 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

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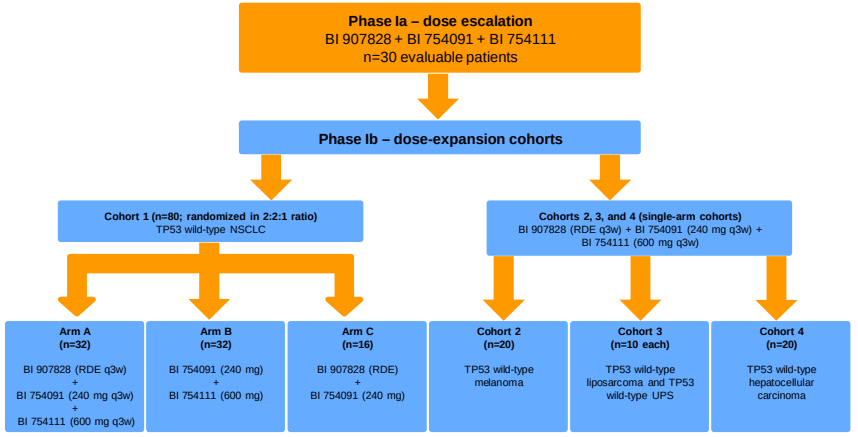

MTD, maximum tolerated dose; PK, pharmacokinetics; q3w, every 3 weeks; RDE, recommended dose for expansion (determined in Phase Ia); UPS, undifferentiated pleomorphic sarcoma

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Patients

Key inclusion criteria

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

Key exclusion criteria

- Previous administration of any MDM2-p53 antagonist or anti-LAG-3 antibody
- 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

Endpoints and assessments

Phase Ia

Primary	Secondary
MTD based on DLTs	PK parameters (C_{max} and $AUC_{0\text{-}tz}$ of BI 907828, BI 754091 and BI 754111) in Cycle 1

Phase Ib

Primary	Secondary
Objective response according to RECIST v1.1	Objective response according to iRECIST
	Disease control according to RECIST v1.1 and iRECIST
	PFS*

*In cohort 3, the PFS rate at 12 and 24 weeks will also be assessed

$AUC_{0\text{-}tz}$, area under curve from 0 to the time of the last quantifiable data point; C_{max}, maximum plasma concentration; DLTs, dose-limiting toxicities; MTD, maximum tolerated dose; PFS, progression-free survival; PK, pharmacokinetics; 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

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