A Phase Ia/Ib, dose-escalation/expansion study of BI 907828 in combination with immune checkpoint inhibitor(s) in patients with advanced solid tumors

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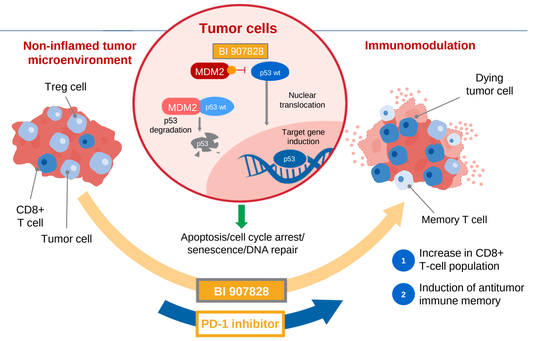
Introduction

- BI 907828, an MDM2–p53 antagonist, inhibits the interaction between the tumor suppressor p53 and its negative regulator MDM2.[1] This leads to stabilization of p53, followed by target gene induction that may result in cell cycle arrest or apoptosis in tumors with *TP53*-wt status[2]
- Preclinical data show that combining an MDM2–p53 antagonist with immune checkpoint inhibitors produces anti-tumor effects in multiple tumor types[2,3]
- The recommended dose for expansion for BI 907828 monotherapy was previously established as 45 mg q3w[4]



- In the present trial (NCT03964233), treatment was initiated as a triplet combination of BI 907828 plus ezabenlimab (an anti-PD-1 monoclonal antibody) plus BI 754111 (anti-LAG-3). During the course of the Phase Ia part, other studies indicated a lack of added efficacy when BI 754111 was combined with ezabenlimab;[5] therefore, the study design was updated to switch the dose escalation to the doublet combination of BI 907828 plus ezabenlimab
- We present results from patients enrolled in the Phase Ia part who received BI 907828 plus ezabenlimab

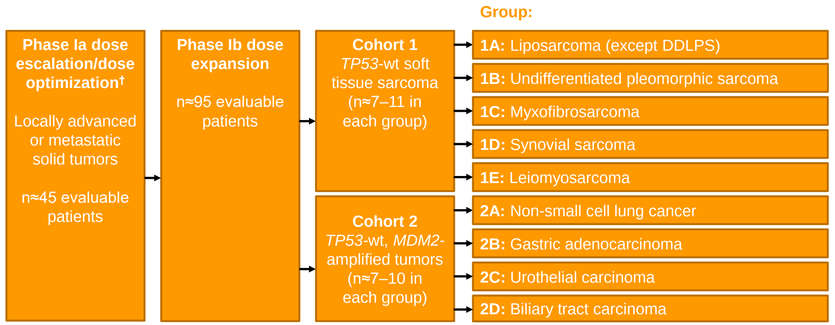
CD8, cluster of differentiation 8; LAG-3, lymphocyte-activation gene 3; MDM2, murine double minute 2 homolog; p53, protein 53; PD-1, programmed cell death protein 1; *TP53*, tumor protein 53; Treg, regulatory T cell; q3w, every three weeks; wt, wild type

Objectives

- Determine the safety, tolerability, and recommended Phase II dose of the doublet combination therapy of BI 907828 with ezabenlimab in a variety of *TP53*-wt cancers
- Determine early efficacy signals of the combination for further development

Methods

- Administration: BI 907828 (10–45 mg, oral) and ezabenlimab (240 mg, 1 hour infusion) on Day 1 of 21-day cycles



†Phase Ia back-fill cohorts and dose optimization cohorts at dose levels of BI 907828 in combination with ezabenlimab where preliminary efficacy has been observed will be populated to evaluate the optimal dose of BI 907828 for the Phase Ib part of the trial
DDLPS, dedifferentiated liposarcoma

Key findings and conclusions

- This Phase Ia/Ib study (NCT03964233) is assessing BI 907828, an MDM2–p53 antagonist, combined with immune checkpoint inhibitor(s) in *TP53*-wt cancers
- The doublet combination of BI 907828 plus ezabenlimab showed a manageable safety profile and early signs of antitumor activity
- Recruitment is ongoing

Scan this QR code or visit the URL for an electronic copy of the poster, supplementary content, and acknowledgments‡

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Endpoints and eligibility criteria

Phase Ia

Primary endpoints:
- Number of patients with DLTs during the first treatment cycle
- MTD based on number of DLTs

Secondary endpoints:
- PK parameters: C_{max}, $AUC_{0\text{-}tz}$ of BI 907828 and ezabenlimab
- Number of patients with DLTs during the entire treatment period

Phase Ib

Primary endpoints:
- Objective response per RECIST 1.1
- Progression-free survival

Secondary endpoints:
- Objective response per iRECIST
- Disease control per RECIST 1.1, iRECIST
- Overall survival
- Number of patients with DLTs during the entire treatment period

Key inclusion criteria

- ECOG PS 0–1
- Disease progression or relapse during SoC or ineligible for SoC§
- *TP53*-wt status (expansion cohorts)¶
- *MDM2* amplification (Ib Cohort 2)

Key exclusion criteria

- Previous administration of any MDM2–p53 or MDMX (MDM4)–p53 antagonist
- Symptomatic brain metastases
- *TP53* mutation (expansion cohorts)¶
- History of bleeding diathesis

§Patients ineligible for SoC treatments or for whom no treatment exists are eligible; ¶Phase Ib and expansion cohorts in Phase Ia
$AUC_{0\text{-}tz}$, area under the concentration-time curve in plasma over the time interval from 0 to the last quantifiable time point; C_{max}, maximum measured plasma concentration; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; iRECIST, immunotherapy RECIST; MTD, maximum tolerated dose; PK, pharmacokinetic; RECIST, Response Evaluation Criteria In Solid Tumors; SoC, standard of care

Patients

- In the Phase Ia part, 11 patients received the triplet combination (BI 907828 plus ezabenlimab with BI 754111) at the 10/20/30/45 mg dose levels (n=3/3/3/2, respectively). No DLTs were reported in Cycle 1; the MTD was not reached
- As of 20 Jan 2022, 15 patients have received the doublet combination (BI 907828 plus ezabenlimab) at 30/45 mg dose levels (n=10/5, respectively)
- Among these, histologies were: biliary duct carcinoma (n=3); LPS (n=2); DDLPS, endometrial carcinoma, esophageal carcinoma, invasive urothelial carcinoma, leiomyosarcoma, myxoid liposarcoma, myoepithelial carcinoma, pleomorphic liposarcoma, (n=1 each); other (n=2)

Characteristic	Triplet (n=11)	Doublet (n=15)
Median age, years (range)	56 (29–72)	59 (22–74)
Male, n (%)	4 (36)	10 (67)
Ethnicity, n (%)		
Asian	3 (27)	5 (33)
White	8 (73)	6 (40)
Missing	0 (0)	4 (27)
ECOG PS		
0	3 (27)	8 (53)
1	8 (73)	7 (47)
Clinical Stage (if available)		
I	0 (0)	1 (7)
III	1 (9)	2 (13)
IV	9 (82)	8 (53)

TRAEs in patients receiving BI 907828 plus ezabenlimab	Any grade, n (%)	Grade 3/4, n (%)
Total with TRAEs	12 (80)	6 (40)
Most common TRAEs		
Nausea	11 (73)	1 (7)
Vomiting	8 (53)	0
Decreased appetite	6 (40)	0
Anemia	5 (33)	3 (20)
Thrombocytopenia	5 (33)	4 (27)
White blood cell count decreased	4 (27)	1 (7)
Neutropenia	3 (20)	1 (7)
Fatigue	3 (20)	0
Malaise	3 (20)	0

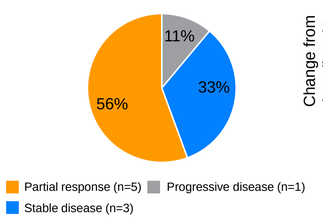
Table shows TRAEs affecting ≥3 patients. AE, adverse event; LPS, liposarcoma; TRAE, treatment-related AE

Safety

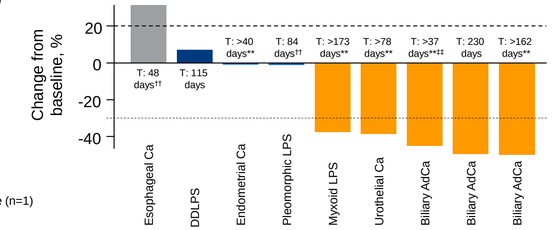
Among patients receiving BI 907828 plus ezabenlimab:
- One patient had a DLT during Cycle 1:
  - G2 neutropenia causing Cycle 2 delay (45 mg)
- Four DLTs were reported after Cycle 1:
  - G3 anemia (30 mg); G2 thrombocytopenia causing dose delay (45 mg); G3 neutropenia and G4 thrombocytopenia (45 mg)
- Most common grade ≥3 AEs were:
  - Anemia (n=6); thrombocytopenia (n=4); lymphopenia (n=3)

Efficacy

Best response among response-evaluable patients who received BI 907828 plus ezabenlimab (n=9)



Best change from baseline among response-evaluable patients who received BI 907828 plus ezabenlimab (n=9)



**Treatment ongoing; ††PFS event; ‡‡Response confirmed after 20 January 2022 (primary site: intrahepatic cholangiocarcinoma)
AdCa, adenocarcinoma; Ca, carcinoma; T, time to PFS event/censoring

References

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