A Phase I dose-escalation study of the MDM2-p53 antagonist BI 907828 in patients with advanced solid tumors

#3016

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Introduction

- Evasion of cell-cycle arrest and apoptosis by inactivation of p53 is a key mechanism by which tumors promote survival and proliferation[1]
- The MDM2 oncoprotein is a critical negative regulator of p53; overexpression of MDM2 aids tumor proliferation[1]
- BI 907828, a highly potent MDM2-p53 antagonist, showed anti-tumor efficacy *in vivo*,[2] especially in *TP53* wild-type MDM2-amplified DDLPS patient-derived xenografts and syngeneic models
- NCT03449381 is a Phase I study assessing BI 907828 in patients with advanced/metastatic solid tumors

DDLPS, de-differentiated liposarcoma; MDM2, murine double minute 2; p53, tumor protein p53

Objectives

- To determine the MTD (based on DLTs during Cycle 1), and to evaluate the safety and tolerability, PK, PD, and preliminary efficacy of BI 907828

DLTs, dose-limiting toxicities; MTD, maximum tolerated dose; PD, pharmacodynamics; PK, pharmacokinetics

Methods

Phase Ia: dose escalation*

Arm A
BI 907828 on Day 1 of 21-day cycles

Arm B
BI 907828 on Days 1, 8 of 28-day cycles

Primary endpoint: MTD based on DLTs
Secondary endpoints: PK, safety, efficacy

Phase Ib: dose expansion

Primary endpoint: PFS
Secondary endpoints: safety, OR, PK/PD

Key inclusion criteria

- Known *TP53* wild-type status
- Previously treated advanced/metastatic solid tumor#

Key exclusion criteria

- Previous administration of any MDM2-p53 antagonist
- Tumor with documented *TP53* mutation
- Active or untreated brain metastases

*Guided by Bayesian Logistic Regression Model
#Patients ineligible for standard-of-care treatments or for whom no treatment exists are eligible
AEs, adverse events; OR, objective response; PFS, progression-free survival

Patients

- Here, we report results for the dose-escalation part of the study
- At April 4, 2021, 54 patients with advanced solid tumors were treated with BI 907828; median (range) of 2 (0–11) prior systemic therapies
  - Arm A: 29 patients, dose range 10–80 mg
  - Arm B, 25 patients, dose range 5–60 mg
- 34.5% of patients in Arm A and 48.0% of patients in Arm B had soft tissue sarcomas

Key patient demographics and disease characteristics

	Arm A (n=29)	Arm B (n=25)
Mean age, yrs (range)	59.1 (32–83)	55.0 (19–75)
Male, n (%)	16 (55.2)	15 (60.0)
Race, n (%)*		
Caucasian	19 (65.5)	18 (72.0)
Asian	9 (31.0)	5 (20.0)
African American	1 (3.4)	1 (4.0)
ECOG PS 0 / 1, n (%)	11 (37.9) / 18 (62.1)	17 (68.0) / 8 (32.0)
Prior therapies, median (range)	2 (0–11)	2 (0–8)

*Data missing for 1 patient in Arm B. ECOG PS, Eastern Cooperative Oncology Group performance status

Key findings and conclusions

- This ongoing Phase I study is evaluating the safety and anti-tumor activity of the MDM2-p53 antagonist BI 907828
- DLTs and grade 3/4 AEs were most commonly thrombocytopenia and neutropenia
- MTDs: 60 mg in Arm A and 45 mg in Arm B
- PK/PD analysis: GDF-15 levels in plasma (target engagement) correlated with exposure ($AUC_{0\text{-}72h}$)

- Manageable safety profile, favorable PK properties and early signs of efficacy, especially in MDM2-amplified tumors

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References

1. Zhao Y, et al. Acta Biochim Biophys Sin (Shanghai) 2014;46:180–9;
2. Rudolph D, et al. Abstract 4866: Cancer Res 2018; 78:4866.

Safety

DLTs in Cycle 1

- Most DLTs were grade 3/4 hematologic AEs
- Arm A: 5 patients with DLTs, one grade 3 nausea (45 mg), one grade 3 thrombocytopenia (45 mg), one grade 3 enterocolitis (60 mg), one grade 4 neutropenia (80 mg) and one grade 4 thrombocytopenia (80 mg)
- Arm B: 3 patients with DLTs, one grade 4 thrombocytopenia (45 mg), one grade 4 neutropenia associated with grade 4 thrombocytopenia (60 mg), and one grade 3 neutropenia (60 mg)

AE, adverse event; TRAE, treatment-related AE

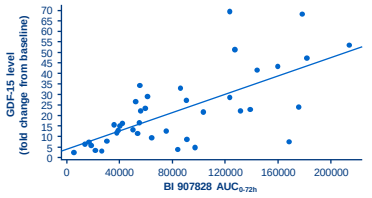
Adverse events, n (%)	N=54	
Any-grade TRAE	50 (92.6)	
Grade 3/4 TRAE	16 (29.6) / 8 (14.8)	
Serious AEs (any cause)	18 (33.3)	
Most common TRAEs*	**Any grade**	**Grade 3/4**
Nausea	40 (74.1)	3 (5.6)
Vomiting	27 (50.0)	1 (1.9)
Thrombocytopenia	24 (44.4)	14 (25.9)
Fatigue	22 (40.7)	1 (1.9)
Decreased appetite	17 (31.5)	0
Neutropenia	15 (27.8)	11 (20.4)

*Any-grade TRAE occurring in >30% of patients or grade 3/4 AE occurring in >5% of patients

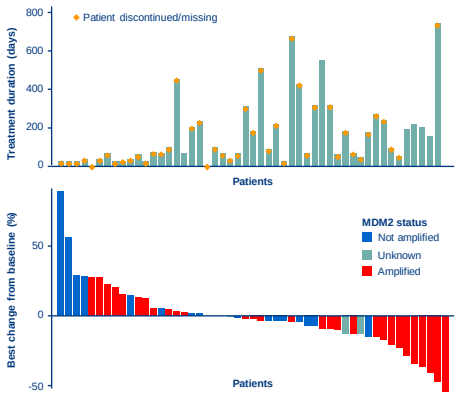
Preliminary PK (Arm A) and PK/PD (Arms A + B)

- T_{max} was reached between 3.5 and 5.5 h
- Mean plasma exposures (C_{max} and $AUC_{0\text{-}inf}$) increased with dose, with no significant deviation from linearity over the dose range 5–60 mg
- gMean clearance/F = 4.5–11.0 mL/min
- gMean apparent volume of distribution/F = 23.6–35.1 L
- gMean half-life after the 1st dose = 27.9–59.4 h
- Inter-patient variability in exposure was moderate

BI 907828 exposure ($AUC_{0\text{-}72h}$) was correlated with GDF-15 level (biomarker of target engagement) at 72 h post-dose



Efficacy



- 5 patients achieved a PR
  - 1 patient with MDM2-amplified pancreatic adenocarcinoma (41% tumor shrinkage)
  - 1 patient with biliary adenocarcinoma (54% tumor shrinkage)
  - 3 patients with MDM2-amplified well differentiated liposarcoma;
    1 patient treated at the 20 mg dose level (Arm A) stayed on treatment >2 years
- 5 of 11 DDLPS patients were progression-free beyond 9 months
  - Of these, 3 have been stable for >1 year

PR, partial response

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