A Phase Ia/Ib, dose-escalation/expansion study of the MDM2–p53 antagonist BI 907828 in patients with advanced/metastatic sarcoma

#1548P

Mrinal Gounder,[1*] Manish R. Patel,[2] Noboru Yamamoto,[3] Todd M. Bauer,[4] Scott Laurie,[5] Alejandro Perez-Pitarch,[6] Junxian Geng,[7] Jan Cheng,[7] Mehdi Lahmar,[6] Patricia LoRusso[8]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Sarah Cannon Research Institute, Florida Cancer Specialists & Research Institute, Sarasota, FL, USA; [3]National Cancer Center Hospital, Tokyo, Japan; [4]Sarah Cannon Research Institute Tennessee Oncology, Nashville, TN, USA; [5]The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada; [6]Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany; [7]Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT, USA; [8]Yale University School of Medicine, Yale Cancer Center, New Haven, CT, USA

Introduction

- Evasion of cell-cycle arrest and apoptosis by inactivation of p53 is a key mechanism by which tumours promote survival and proliferation[1]
- The MDM2 oncoprotein is a critical negative regulator of p53; overexpression of MDM2 aids tumour proliferation[1]
- BI 907828, a highly potent MDM2-p53 antagonist, showed antitumour 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 tumours

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 in patients with advanced solid tumours, particularly advanced/metastatic sarcoma
- Here, we report results for the Phase Ia dose-escalation part, including efficacy data in patients with advanced/metastatic sarcoma

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 tumour†

Key exclusion criteria

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

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

Patients

- At 12 July 2021, 54 patients with advanced solid tumours had been treated with BI 907828
  - Arm A: 29 patients, dose range 10–80 mg
  - Arm B, 25 patients, dose range 5–60 mg
- 28 (51.9%) patients had advanced sarcomas
  - The most common subtypes were DDLPS (11 patients) and WDLPS (8 patients)
  - Other subtypes were high-grade leiomyosarcoma, leiomyosarcoma, GIST, adenosarcoma, dermatofibrosarcoma, osteosarcoma, rhabdomyosarcoma, UPS, and myxoid chondrosarcoma

Key patient demographics and disease characteristics

	Arm A (n=29)	Arm B (n=25)
Mean age, years (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)	3 (0–11)	2 (0–8)

*Data missing for one patient in Arm B

ECOG PS, Eastern Cooperative Oncology Group performance status; DDLPS, de-differentiated liposarcoma; GIST, gastrointestinal stromal tumour; UPS, undifferentiated pleomorphic sarcoma; WDLPS, well-differentiated liposarcoma

Key findings and conclusions

- This ongoing Phase I study is evaluating the safety and antitumour activity of the MDM2–p53 antagonist BI 907828
- BI 907828 is associated with a manageable safety profile
- Encouraging preliminary efficacy in patients with sarcoma, particularly in *MDM2*-amplified tumours:
  - 82.1% disease control rate
  - Three of eight patients with WDLPS achieved a PR
  - All 11 DDLPS patients achieved SD
  - Estimated median PFS was 10.8 months (range, 1.3–21.0 months)

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- The Phase Ib dose expansion is ongoing; RDE 45 mg q3w

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Initial safety data for the Phase Ia cohort were originally presented at ASCO 2021.
*Corresponding author email address: gounderm@mskcc.org

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

Dose level	DLTs in Cycle 1
Arm A: five patients had DLTs	
45 mg	Grade 3 nausea
	Grade 3 thrombocytopenia
60 mg	Grade 3 enterocolitis
	Grade 3 febrile neutropenia
80 mg	Grade 4 neutropenia
	Grade 4 thrombocytopenia
Arm B: three patients had DLTs	
45 mg	Grade 4 thrombocytopenia
60 mg	Grade 3 neutropenia
	Grade 4 neutropenia
	Grade 4 thrombocytopenia

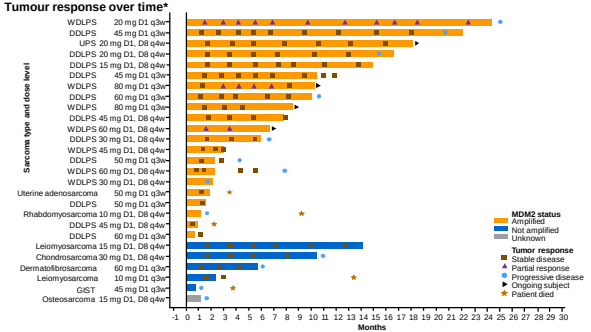
- MTDs were confirmed as 60 mg in Arm A and 45 mg in Arm B
- The RDE was selected as 45 mg q3w
- 18 patients received at least 1 cycle of treatment at RDE in Phase Ib: three DLTs were reported (two grade 3 anaemia and one grade 4 thrombocytopenia)

AEs, n (%)	N=54	
Any-grade TRAE	50 (92.6)	
Grade 3/4 TRAE	23 (42.6) / 10 (18.5)	
Serious AEs (any cause)	18 (33.3)	
AEs leading to dose reduction / discontinuation	19 (35.2) / 4 (7.4)	
Most common TEAEs*	**Any grade**	**Grade 3/4**
Nausea	47 (87.0)	3 (5.6)
Vomiting	30 (55.6)	2 (3.7)
Fatigue	29 (53.7)	1 (1.9)
Thrombocytopenia	26 (48.1)	16 (29.6)
Decreased appetite	22 (40.7)	0
Diarrhoea	22 (40.7)	1 (1.9)
Neutropenia	18 (33.3)	13 (24.0)
Anaemia	18 (33.3)	6 (11.1)

AE, adverse event; q3w, every 3 weeks; RDE, recommended dose for expansion; TEAEs, treatment-emergent AEs; TRAEs, treatment-related AEs. *Any-grade TEAE occurring in >30% of patients or grade 3/4 TEAE occurring in >5% of patients

Efficacy in patients with advanced/metastatic sarcoma

Tumour response over time*



- Of 28 patients with sarcoma, 23 achieved ≥SD; the disease control rate (≥SD) was 82.1%
- Three of 8 patients with WDLPS achieved a PR (all were *MDM2*-amplified)
  - One remained on treatment >2 years
- All 11 patients with DDLPS achieved SD as best overall response
  - The estimated median PFS was 10.8 months (range, 1.3–21.0 months)

D, day; PR, partial response; q4w, every 4 weeks; SD, stable disease. *No response data available for one patient with WDLPS

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