

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

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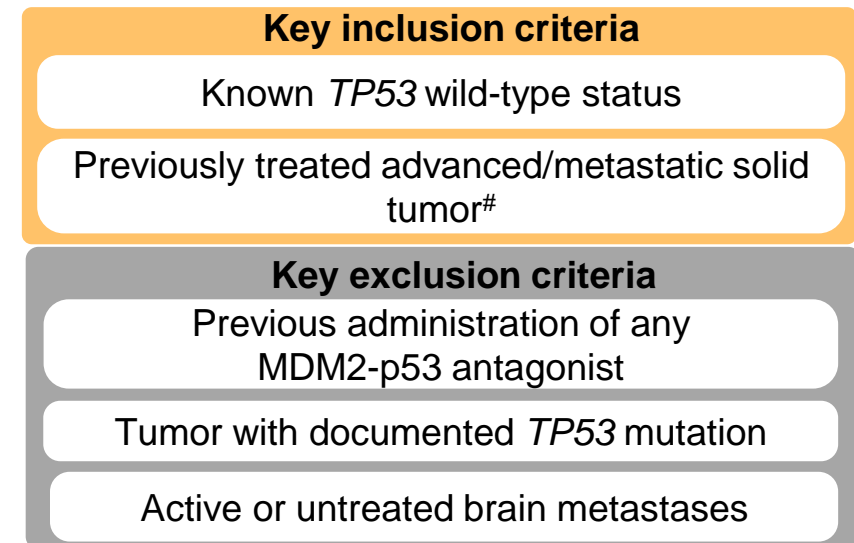
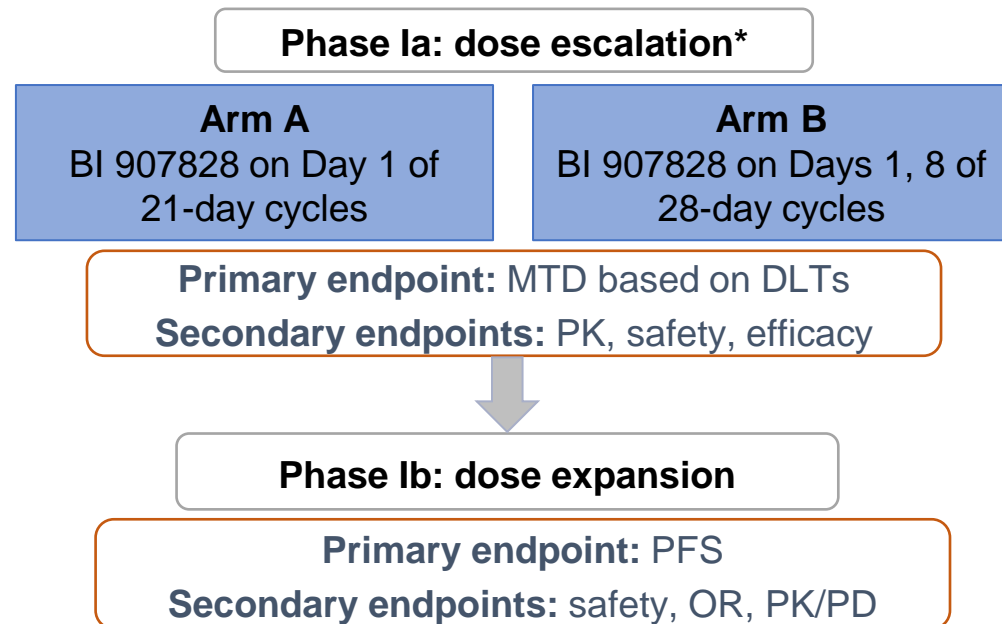
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Introduction and Objectives

- NCT03449381 is a Phase I study assessing the MDM2-p53 antagonist BI 907828 in patients with advanced/metastatic solid tumors
- **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

Methods



*Guided by Bayesian Logistic Regression Model; [#]Patients ineligible for standard-of-care treatments or for whom no treatment exists are eligible

DLTs, dose-limiting toxicities; MDM2, murine double minute 2; MTD, maximum tolerated dose; OR, objective response; p53, tumor protein p53; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics

Patients

- 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
 - Of these, 3 have been stable >1 year

	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)

Safety

- Most DLTs were grade 3/4 hematologic AEs
- **In Arm A**, 5 patients had a DLT: 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)
- **In Arm B**, 3 patients had a DLT: one grade 4 thrombocytopenia (45 mg), one grade 4 neutropenia associated with grade 4 thrombocytopenia (60 mg), and one grade 3 neutropenia (60 mg)

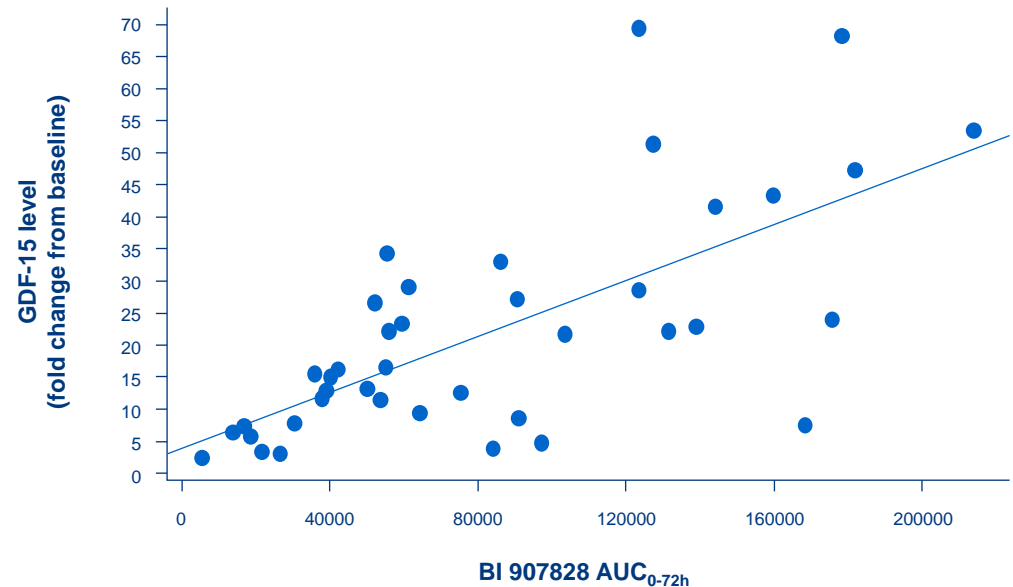
Adverse events, n (%)	N=54	
Any-grade TRAE	50 (92.6)	
Grade 3/4 TRAE	16 (29.6) / 8 (14.8)	
Serious AEs (any cause)	18 (33.3)	
Most common TRAEs*	Any grade	Grade 3/4
Nausea	40 (74.1)	3 (5.6)
Vomiting	27 (50.0)	1 (1.9)
Thrombocytopenia	24 (44.4)	14 (25.9)
Fatigue	22 (40.7)	1 (1.9)
Decreased appetite	17 (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.
AE, adverse event; DLTs, dose-limiting toxicities; TRAE, treatment-related adverse event.

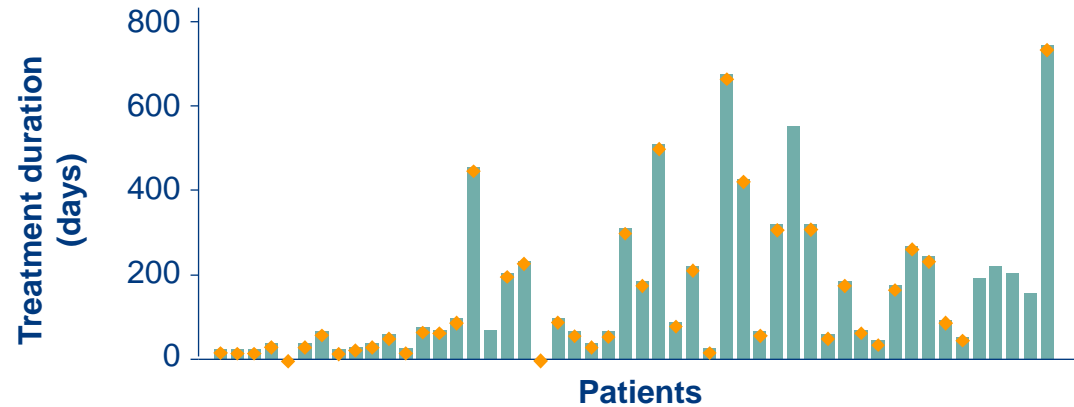
Preliminary PK (Arm A) and PK/PD (Arms A + B)

- 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

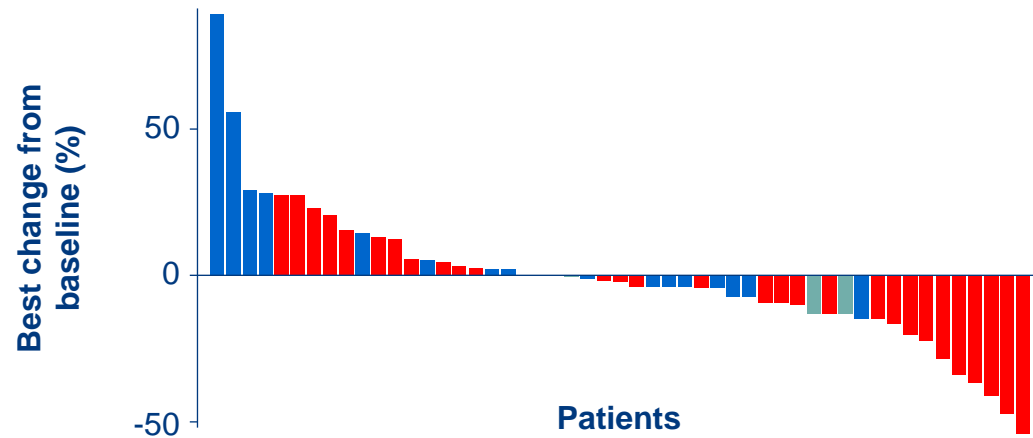
BI 907828 exposure (AUC_{0-72h}) was correlated with GDF-15 level (biomarker of target engagement) at 72 h post-dose



Efficacy results



- As of April 2021, 5 patients had 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

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 were 60 mg in Arm A and 45 mg in Arm B
- PK/PD analysis demonstrated that GDF-15 levels in plasma (target engagement) correlated with exposure (AUC_{0-72h})
- These data suggest a manageable safety profile, favorable PK properties and early signs of efficacy, especially in MDM2-amplified tumors