A Phase I dose-escalation and expansion study evaluating the safety and efficacy of the MDM2–p53 antagonist brigimadlin (BI 907828) in patients with solid tumours

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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]
- Approximately 5–7% of tumours display *MDM2* amplification[2]; for example, in BTC, *MDM2* amplification occurs in 5–8% of cases[3,4]
- Brigimadlin (BI 907828) binds to MDM2 and prevents it from inactivating p53, thereby restoring wild-type p53 function[5]
- NCT03449381 is a Phase I study assessing brigimadlin in patients with advanced/metastatic solid tumours

BTC, biliary tract cancer; MDM2, mouse double minute 2 homolog; p53, protein 53

Objectives

- To assess the safety and evaluate the preliminary efficacy of brigimadlin in patients with advanced/metastatic solid tumours

Methods

Phase Ia (dose escalation): completed[6]
54 patients with locally advanced/metastatic solid tumours

Arm A
Brigimadlin on Day 1 of 21-day cycles

Arm B
Brigimadlin on Days 1 and 8 of 28-day cycles

Recommended dose for expansion:
Brigimadlin 45 mg q3w

Phase Ib (dose expansion): ongoing

Cohort 1
TP53 wild-type, *MDM2*-amplified sarcomas (any line)

Brigimadlin 30/45 mg q3w p.o.

Cohort 2
TP53 wild-type, *MDM2*-amplified solid tumours: NSCLC, gastric, urothelial, pancreatic, biliary tract (≥2L)

Brigimadlin 45 mg q3w p.o.

Phase Ib
Primary endpoint: PFS
Secondary endpoints: OR, OS, grade ≥3 TRAEs, PK parameters (C_{max}, $AUC_{0\text{-}inf}$)

Key inclusion criteria

- Known *TP53* wild-type status and *MDM2*-amplification (expansion phase only)
- ECOG performance status 0 / 1
- Patients with PD/relapse, no proven treatment available, or *MDM2*-amplified sarcomas who require 1L treatment (expansion phase only)

Key exclusion criteria

- Previous administration of any MDM2-p53 antagonist
- Known *TP53* mutation
- Symptomatic brain metastases

1/2L, first/second-line; AUC, area under the curve; C_{max}, maximum concentration; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; OR, objective response; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetic; p.o., orally; q3w, every 3 weeks; *TP53*, tumour protein 53; TRAE, treatment-related adverse event

References

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Key findings and conclusions

- This ongoing Phase I study is evaluating the safety and efficacy of the MDM2–p53 antagonist brigimadlin
- Brigimadlin demonstrated a manageable safety profile with a low discontinuation rate of 4.0%
- In patients who received brigimadlin q3w, median PFS was 7.0 months, ORR was 10.7%, DCR was 76.7%
- Efficacy was particularly encouraging in patients with *MDM2*-amplified BTC: 30.0% ORR, 80% DCR
- The dose-finding, safety and efficacy data from this study led to the Phase II/III Brightline-1 trial in patients with advanced DDLPS (NCT05218499), and further investigation in patients with BTC in the Phase IIa/IIb Brightline-2 trial (NCT05512377)

Patients

- Here, we focus on patients who received brigimadlin q3w in Phase Ia and Phase Ib
- As of 31st May 2023, 150 patients with solid tumours had received brigimadlin q3w (29 in Phase Ia, 121 in Phase Ib); median number of prior anti-cancer therapies was 2 (0–11)
  - A total of 10 patients had biliary tract cancer (BTC)

	All q3w patients (N=150)
Mean age, years (range)	59.6 (19–83)
Male, n (%)	83 (55.3)
Race, n (%)*	
Caucasian	115 (76.7)
Asian	27 (18.0)
African American	2 (1.3)
Native Hawaiian/other Pacific Islander	1 (0.7)
ECOG performance status, n (%)#	
0	83 (55.3)
1	64 (42.7)

*Data missing for 5 patients; #data missing for 3 patients

Safety

- In all q3w patients, the most common any-grade TRAEs were nausea (72.7%) and fatigue (58.7%)
  - Most common grade ≥3 TRAEs were neutropenia (30.6%), thrombocytopenia (24.0%) and anaemia (13.3%)

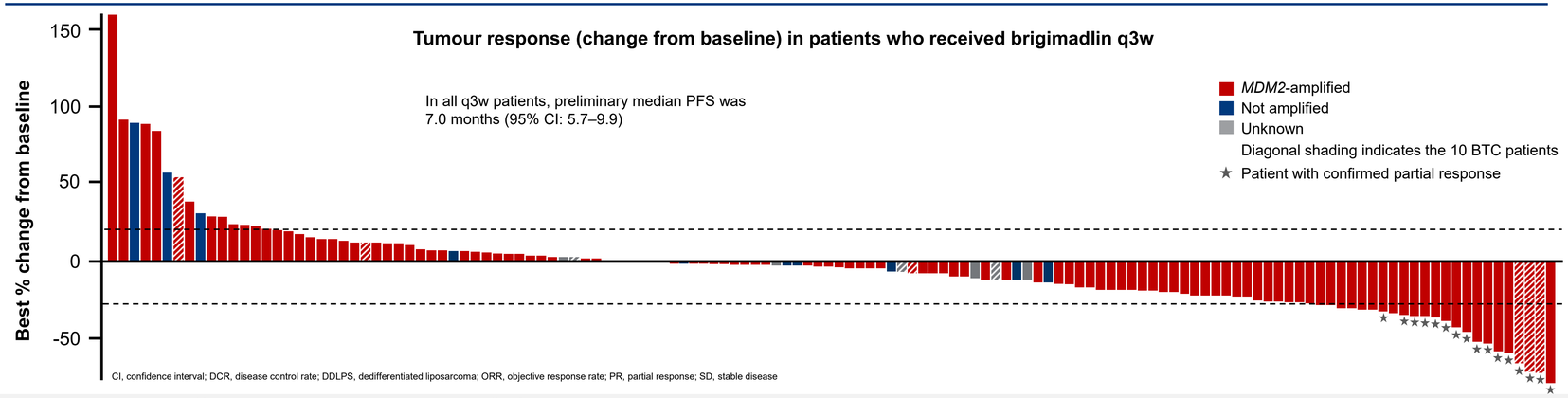
AEs, n (%)	All q3w patients (N=150)		45 mg q3w (n=106)	
Any-grade TRAEs	141 (94.0)		100 (94.3)	
Grade ≥3 TRAEs	76 (50.7)		55 (51.9)	
AEs leading to dose reduction/discontinuation	49 (32.7) / 6 (4.0)		35 (33.0) / 3 (2.8)	
Most common TRAEs*	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Nausea	109 (72.7)	9 (6.0)	76 (71.7)	7 (6.6)
Fatigue	88 (58.7)	8 (5.3)	64 (60.4)	6 (5.7)
Neutropenia	78 (52.0)	46 (30.6)	59 (55.7)	33 (31.1)
Thrombocytopenia	70 (46.7)	36 (24.0)	47 (44.3)	25 (23.6)
Vomiting	61 (40.7)	3 (2.6)	39 (36.8)	3 (2.8)
Decreased appetite	53 (35.3)	1 (0.7)	34 (32.1)	1 (0.9)
Anaemia	42 (28.0)	20 (13.3)	29 (27.4)	14 (13.2)
Leukopenia	32 (21.3)	16 (10.7)	24 (22.6)	12 (11.3)

*Any-grade TRAE occurring in >30% of patients or grade 3/4 TRAE occurring in >5% of patients
Percentages calculated using total number of patients per treatment as the denominator

Efficacy

- 16/150 (10.7%) patients who received brigimadlin q3w achieved a confirmed PR
- A further 99 (66.0%) patients had SD; disease control rate (PR + SD) was 76.7%
- Of the 10 BTC patients who received brigimadlin q3w, 3 (30.0%) achieved a PR
- A further 5 (50.0%) BTC patients had SD, giving a DCR of 80.0%

Efficacy



CI, confidence interval; DCR, disease control rate; DDLPS, dedifferentiated liposarcoma; ORR, objective response rate; PR, partial response; SD, stable disease

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