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A first-in-human Phase 1 study of the ATM inhibitor M4076 in patients with advanced solid tumors (DDRiver Solid Tumors 410): Part 1A results

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DDRiver SOLID TUMORS 410

CONCLUSIONS

- **M4076 achieved target exposure and engagement without significant hematological toxicities; maculo-papular rash was the most common dose-limiting toxicity (DLT)**
- **The maximum tolerated dose (MTD) of M4076 was 300 mg once-daily (QD)**
- **Exposure increased in a dose-related manner, with minimum accumulation after multiple doses**
- **M4076 is currently being evaluated in combination with M1774, an ataxia-telangiectasia and Rad3-related (ATR) inhibitor (DDRiver Solid Tumors 320, NCT05396833)**

INTRODUCTION

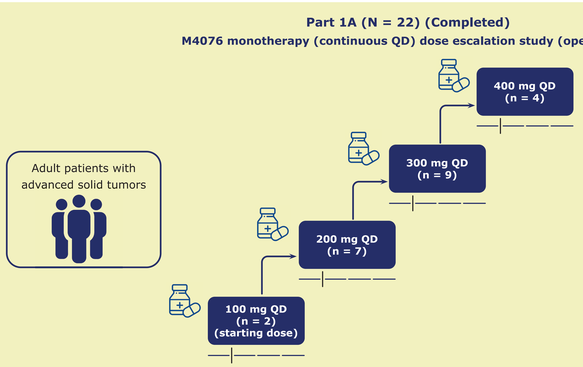
- M4076 is a potent and selective, orally administered inhibitor of ataxia-telangiectasia mutated (ATM), a key kinase involved in the regulation of cellular responses to double-strand break (DSB), particularly repair of DSBs by homologous recombination[1,2]
- In preclinical models, M4076 when combined with DNA damage-inducing therapy or other DDR inhibitors, caused unrestricted cell cycle progression and DNA damage accumulation, resulting in tumor cell death[3]
- DDRiver Solid Tumors 410 study evaluated the safety and tolerability M4076 monotherapy in patients with advanced solid tumors (NCT04882917)

OBJECTIVES

- Assess the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and MTD of M4076 in patients with advanced solid tumors in Part 1A of the DDRiver Solid Tumors 410 study

METHODS

Figure 1. Study design of Part 1A



Primary endpoints

- DLTs[a]
- AEs, TRAEs[a]
- Clinically significant changes in vital signs, laboratory parameters, and 12-lead ECG findings

Secondary endpoints

- PK
- PD (ATM pathway readout [γ-H2AX in serial *ex vivo* bleomycin stimulated blood samples])
- OR
- DoR
- PFS

- Each dose level included a DLT observation period (Period 1); treatment was continued in each subsequent period (Period ≥2) until disease progression, death, or End of Study **(Figure 1)**
- Safety monitoring committee (SMC) recommended dose escalation was guided by safety, along with Bayesian analysis, PK, and the PD profile of M4076
- DLT analysis set included all patients who received ≥1 dose of M4076 and met ≥1 of the following criteria:
  - Experienced ≥1 DLT during the DLT period, regardless of the number of M4076 doses administered
  - Received ≥80% of the planned cumulative dose during the DLT period and completed the DLT period
  - Received <80% of the planned total dose, but ≥80% dose of a different dose cohort and completed the DLT period

[a]National Cancer Institute Common Terminology Criteria for Adverse Events v5.0; [b]Response Evaluation Criteria in Solid Tumours v1.1 (assessed by investigator)
AEs, adverse events; **ATM**, ataxia-telangiectasia mutated; **DLT**, dose-limiting toxicity; **DoR**, duration of response; **ECG**, electrocardiogram; **OR**, overall response; **PD**, pharmacodynamics; **PFS**, progression-free survival; **PK**, pharmacokinetics; **QD,** once-daily; **TRAEs**, treatment-related AEs

RESULTS

- Between May 24, 2021 (study start date) and December 12, 2022 (last patient last visit), 22 patients had received M4076 at 4 different dose levels (100–400 mg QD), and all were included in the safety analysis set
- Patient baseline and demographic characteristics are summarized in **Table 1**
  - Median age was 58.5 years, with the majority being White (77.3%)
  - Most patients had an Eastern Cooperative Oncology Group Performance Status of 1 (81.8%)
  - Overall, 31.8% of patients had undergone ≥4 prior anti-cancer treatment regimens
- Primary tumor sites included ovary and prostate gland (n = 4 [18.2%] each); endometrium (n = 3 [13.6%]); rectum (n = 2 [9.1%]); colon, lung, nasopharynx, pancreas, pancreas (head), parotid gland, retroperitoneum, thyroid gland, and unknown site (n = 1 [4.5%] each)

Table 1. Patient baseline and demographic characteristics

Parameters	100 mg n = 2	200 mg n = 7	300 mg n = 9	400 mg n = 4	Total N = 22
Median age (min, max), years	74.5 (70, 79)	54.0 (43, 62)	61.0 (44, 70)	55.5 (53, 65)	58.5 (43, 79)
Female, n (%)	1 (50.0)	5 (71.4)	4 (44.4)	3 (75.0)	13 (59.1)
Race, n (%)					
White	2 (100.0)	5 (71.4)	7 (77.8)	3 (75.0)	17 (77.3)
Other	0 (0.0)	2 (28.6)	2 (22.2)	1 (25.0)	5 (22.7)
ECOG PS					
0	0 (0.0)	1 (14.3)	2 (22.2)	1 (25.0)	4 (18.2)
1	2 (100.0)	6 (85.7)	7 (77.8)	3 (75.0)	18 (81.8)
Time since disease diagnosis[a], mean (SD), years	2.75 (0.35)	1.35 (1.08)	5.73 (4.46)	2.20 (1.13)	3.42 (3.48)
Prior anti-cancer treatment regimens received[a], n (%)					
1	0 (0.0)	2 (28.6)	0 (0.0)	1 (25.0)	3 (13.6)
2	1 (50.0)	1 (14.3)	0 (0.0)	0 (0.0)	2 (9.1)
3	1 (50.0)	1 (14.3)	3 (33.3)	0 (0.0)	5 (22.7)
≥4	0 (0.0)	3 (42.9)	2 (22.2)	2 (50.0)	7 (31.8)

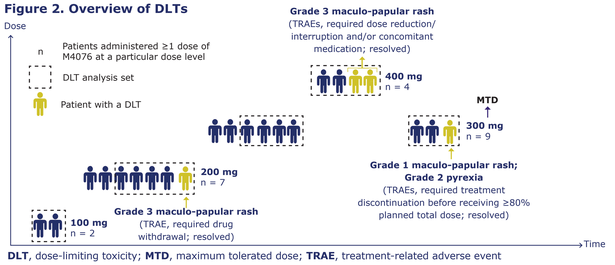
[a]Locally advanced, inoperable, or metastatic disease
ECOG PS, Eastern Cooperative Oncology Group Performance Status; **SD**, standard deviation

Safety

- Ten patients (45.5%) discontinued treatment prior to disease progression* (AEs, n = 5 [22.7%])
  - Four patients (18.2%) had M4076-related AEs that led to permanent treatment discontinuation
- Overall, 4 of 18 patients (22.2%) in the DLT analysis set experienced a total of 5 DLTs (per SMC decision) **(Figure 2)**
  - Maculo-papular rash was the most common DLT (4 events in 4 patients; 1 each in dose levels 200 mg and 300 mg, and 2 in 400 mg)
  - Pyrexia was reported in 1 patient in the 300 mg dose level
- Fatigue (n = 9 [40.9%]) was the most commonly reported treatment-emergent AE (TEAE) in both Periods 1 and ≥2 **(Figure 3)**
- Grade ≥3 TEAEs were reported in 13 (59.1%) patients (**Table 2**); 1 (4.5%) patient had a Grade 4 event (hypersensitivity reaction, 400 mg). Cytopenia (TEAE of special interest) was reported in 4 (18.2%) patients; all were anemia events Grade ≥3
- No deaths were reported during the study period; however, 3 (13.6%) patients died within 60 days of the last dose of M4076 and their deaths were unrelated to M4076
- MTD of M4076 was determined at 300 mg QD

*Progressive disease and death are included in study intervention/completion rather than discontinuation

Figure 2. Overview of DLTs



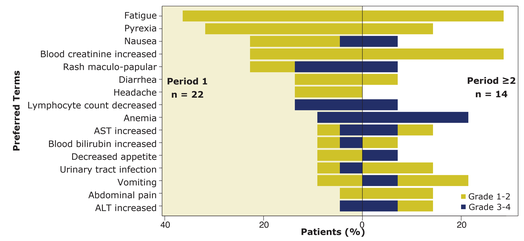
DLT, dose-limiting toxicity; **MTD**, maximum tolerated dose; **TRAE**, treatment-related adverse event

Table 2. Safety overview

	M4076 monotherapy				
Number of patients, n (%)	**100 mg n = 2**	**200 mg n = 7**	**300 mg n = 9**	**400 mg n = 4**	**Total N = 22**
Any TEAE	2 (100.0)	7 (100.0)	9 (100.0)	4 (100.0)	22 (100.0)
Grade ≥3	0 (0.0)	6 (85.7)	4 (44.4)	3 (75.0)	13 (59.1)
Any treatment-related TEAE	1 (50.0)	2 (28.6)	8 (88.9)	4 (100.0)	15 (68.2)
Grade ≥3	0 (0.0)	1 (14.3)	1 (11.1)	2 (50.0)	4 (18.2)
Any serious TEAE	0 (0.0)	4 (57.1)	2 (22.2)	3 (75.0)	9 (40.9)
Any treatment-related serious TEAE	0 (0.0)	0 (0.0)	0 (0.0)	2 (50.0)	2 (9.1)
Any TEAESI Cytopenia[a]	0 (0.0)	1 (14.3)	2 (22.2)	1 (25.0)	4 (18.2)
Grade ≥3 (all anemia events)	0 (0.0)	1 (14.3)	2 (22.2)	1 (25.0)	4 (18.2)
TEAEs leading to permanent treatment discontinuation	0 (0.0)	2 (28.6)	2 (22.2)	1 (25.0)	5 (22.7)

[a]Includes lymphopenia, leukopenia/neutropenia, thrombocytopenia, anemia (Grade ≥3 or with complications)
TEAE, treatment-emergent adverse event; **TEAESI**, TEAE of special interest

Figure 3. TEAEs reported in ≥10% patients during DLT period (Period 1) vs. subsequent periods (Period ≥2)

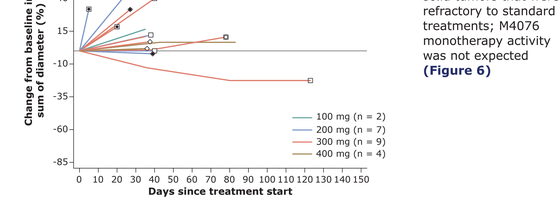


ALT, alanine aminotransferase; **AST**, aspartate aminotransferase; **DLT**, dose-limiting toxicity; **TEAE**, treatment-emergent adverse event

Pharmacokinetic analysis

- All 22 (100%) patients were included for PK analysis
- Based on non-compartmental PK analysis across dose groups, M4076 was rapidly absorbed with median T_{max} ~0.4–2h and mean elimination half-life ($t_{1/2}$) ~2–7h **(Figure 4)**
- Exposure increased in a dose-related manner, with minimum accumulation after multiple QD doses

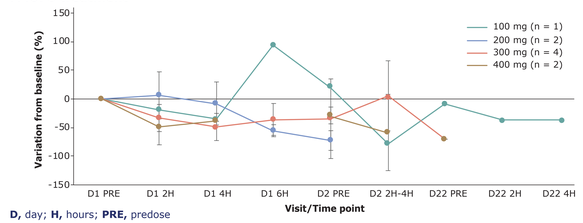
Figure 4. Plasma concentration–time profile across M4076 doses at steady state



Pharmacodynamic analysis

- PD analysis was done in 9 (40.9%) patients
- At ≥200 mg QD, unbound steady state plasma concentration exceeded *in vivo* pCHK2 IC_{90} throughout the dosing interval. PD evaluation was based on the modulation of γ-H2AX$_{Ser}$ (a direct ATM target) in *ex vivo* bleomycin-stimulated CD45+ lymphocytes, by flow cytometry
- PD analysis in blood showed a trend of reduction of γ-H2AX levels in the lymphocyte fraction from Day 1 to Day 2, reaching 80%–100% of target inhibition with the dose range 100–400 mg QD **(Figure 5)**

Figure 5. Target modulation: Changes in lymphocyte γ-H2AX levels during M4076 treatment



D, day; **H,** hours; **PRE,** predose

Efficacy

Figure 6. Best overall response

- Dose escalation was conducted in an unselected population of patients with advanced solid tumors that were refractory to standard treatments; M4076 monotherapy activity was not expected **(Figure 6)**

References: 1. Blackford AN, Jackson SP. *Mol Cell* 2017;66:801–817; **2.** Carrassa L, Damia G. *Cancer Treat Rev* 2017;60:139–151; **3.** Zimmermann A, *et al. Mol Cancer Ther* 2022;21:859–870.

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