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A First-in-Human Phase I Study of ATR Inhibitor M1774 in Patients with Solid Tumors

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STUDY STATUS

- **Study is open and currently recruiting**
- **Patients have been enrolled to nine cohorts in Part A1**
- **Dose escalation is ongoing**

BACKGROUND

- The DNA damage response (DDR) is a complex surveillance and signaling network that has evolved to maintain genomic integrity, but can play a role in resistance to antitumor agents by repairing the DNA damage induced by chemotherapy and/or radiotherapy, allowing cells to survive treatment.[1–3]
- Ataxia telangiectasia and Rad3-related (ATR) protein kinase is a key kinase of the DDR and a major regulator of the replication stress response and can induce cell cycle arrest to prevent aberrant replication.[1,2,4]
- ATR inhibition is a promising treatment strategy as monotherapy for patients with advanced solid tumors harboring synthetically lethal conditions, such as inactivating mutations in *ARID1A*, *ATM*, and in *ATRX* and/or *DAXX* as a surrogate of alternative lengthening of telomeres (ALT) status.[5–8]
- M1774 is a potent, selective, orally administered ATR inhibitor that has been shown to exert antitumor activity in patient-derived xenograft tumors and acute myeloid leukemia xenograft tumors that express the ATR inhibition sensitizing mixed lineage leukemia fusion protein.
- This study (NCT04170153) aims to evaluate the safety and tolerability, maximum tolerated dose, recommended dose for expansion (RDE) and pharmacokinetics (PK) of M1774 (Part A1), the effect of food on M1774 PK (Part A2), and the preliminary efficacy of M1774 in patients with tumors harboring selected mutations (Part A3).

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STUDY DESIGN

This is a 3-part open-label Phase I study (Figure 1)

Part A1 – Dose escalation to RDE

- The first and second single-participant cohorts received 5 mg and 10 mg M1774 once daily on a 21-day cycle.
- The third and following cohorts include three or more participants per dose level.
- 18–24 evaluable participants are expected to be enrolled to determine the RDE.

Part A2 – Preliminary food effect

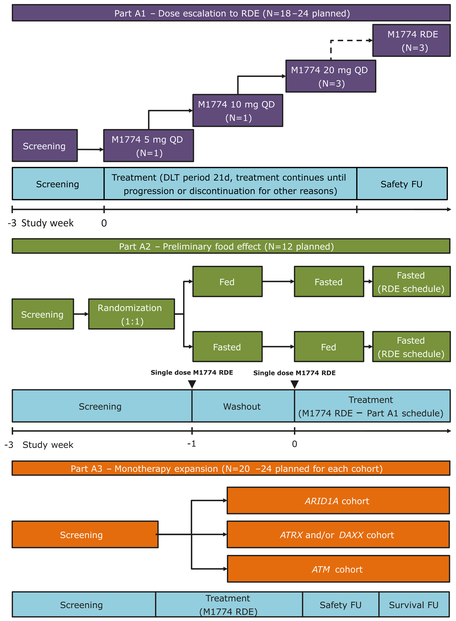
- Randomized, two-sequence two-period crossover design.
- Patients will receive a single dose of M1774 at RDE determined in Part A1, either in a fed or fasted condition, followed by a 1-week washout period.
- Patients will subsequently receive M1774 at the RDE determined in Part A1.

Part A3 – Preliminary efficacy study

- Patients with tumors harboring loss-of-function mutations in *ARID1A*, *ATRX* and/or *DAXX*, or *ATM*, will receive M1774 at the RDE determined in Part A1.
- Mutations are detected by next-generation sequencing, either by an approved local test or a central trial assay.

The objectives and endpoints for each Part are shown in **Table 1**.

Figure 1. Study design



DLT, dose-limiting toxicity; **FU**, follow-up; **QD**, once daily; **RDE**, recommended dose for expansion.

ELIGIBILITY, OBJECTIVES AND ASSESSMENTS

Inclusion criteria

- Aged ≥18 years.
- Eastern Cooperative Oncology Group performance status (ECOG PS) ≤1.
- Locally advanced or metastatic disease refractory to standard therapy or for which no standard therapy is judged appropriate.
- Adequate baseline hematological, renal and hepatic function.
- **Part A3 only:** tumors with loss of function mutations in *ARID1A*, *ATRX* and/or *DAXX*, or *ATM*; and measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.

Main exclusion criteria

- Unstable angina, myocardial infarction, congestive heart failure or a coronary revascularization procedure within 180 days of study entry.
- Active fungal, bacterial or viral infection.
- Treatment with live/live-attenuated vaccine 30 days before dosing (no restrictions regarding SARS-CoV-2 vaccinations).
- Major surgery 4 weeks prior to study intervention.
- Anticancer treatment within 28 days of study intervention.
- Prior treatment with an ATR and/or checkpoint kinase 1 (CHK1) inhibitor.

Table 1. Primary objectives and endpoints

Primary objectives		Primary endpoints
Part A1	• To determine safety, tolerability and the MTD of M1774 as a single agent in participants with solid tumors.	• Occurrence of DLTs during the DLT observation period. • Occurrence of TEAEs, treatment-related AEs, and deaths. • Occurrence of abnormalities (Grade ≥3) in laboratory test values. • Occurrence of markedly abnormal vital sign measurements. • Occurrence of clinically significant abnormal ECGs.
	• To determine the RDE.	• In addition to the safety profile, PK and PD data will be used to identify the RDE.
Part A2	• To assess the effect of food on the PK of M1774 administered as a single dose under fed/fasting conditions in a cohort of participants.	• PK profile and fed/fasted ratio of M1774 in terms of: AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}, when administered as a single dose with or without food.
Part A3	• To further characterize safety of M1774 as a single agent.	• Occurrence of TEAEs and treatment-related AEs. • Occurrence of abnormalities (Grade ≥3) in laboratory test values. • Occurrence of markedly abnormal vital sign measurements. • Occurrence of clinically significant abnormal ECGs.
	• To evaluate the efficacy of M1774.	• Objective response (confirmed CR or PR) by RECIST Version 1.1.

AE, adverse event; **ATR**, ataxia telangiectasia and Rad3-related; **CR**, complete response; **DLT**, dose-limiting toxicity; **ECG**, electrocardiogram; **MTD**, maximum tolerated dose; **PD**, pharmacodynamics; **PK**, pharmacokinetics; **PR**, partial response; **RECIST**, Response Evaluation Criteria in Solid Tumors; **RDE**, recommended dose for expansion; **TEAE**, treatment-emergent adverse event.

STATISTICAL ANALYSES

Part A1

- Dose escalation is determined by the safety monitoring committee and guided by a Bayesian 2-parameter logistic regression model with overdose control.
- The DLT observation period is 3 weeks.
- Paired tumor biopsies and serial peripheral blood mononuclear cell (PBMC) samples will be used to evaluate markers of ATR activation and inhibition such as p-CHK1 and γ-H2AX, and assess M1774 pharmacodynamics (PD).

Part A2

- Paired tumor biopsies and serial PBMC samples will be used to evaluate markers of ATR activation and inhibition such as p-CHK1 and γ-H2AX and assess M1774 PD.
- The effects of food on PK of M1774 will be assessed with a mixed effects model for the randomized two-sequence two-period cross-over design.
- After six participants are enrolled, the data will be reviewed, and a decision made whether an additional six participants will be enrolled.

Part A3

- After nine evaluable participants are enrolled in each of the three biomarker-defined cohorts, the antitumor-efficacy of M1774 in these participants will be determined. If one or more responders are observed, enrollment will continue to a total of 20 evaluable participants per cohort. Evaluable participants must have central confirmation of the presence of the corresponding mutation in liquid biopsy collected before dosing.
- The primary efficacy endpoint is objective response according to RECIST Version 1.1. Tumor assessment will be performed until disease progression, irrespective of study treatment discontinuation.

STUDY CONTACT

- The coordinating investigator for this study is Professor Johann S. de Bono, MB ChB, FRCP, MSc, PhD, FMedSci (Johann.DeBono@icr.ac.uk)
- For further information, please visit www.ClinicalTrials.gov (NCT04170153) or www.merckgroup.com

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