457MO – A Phase I study of ATR inhibitor M1774 in patients with solid tumours (DDRiver Solid Tumours 301): Part A1 results

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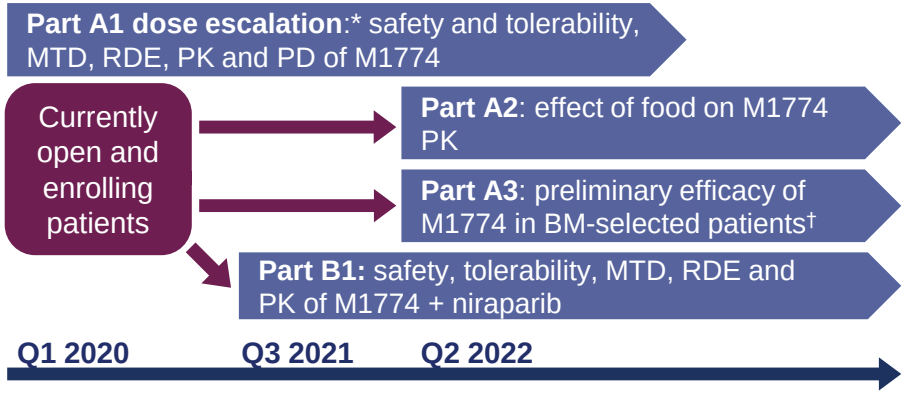
Background and methods

- ATR senses and responds to DNA replication stress by inducing cell cycle arrest; inhibition of ATR allows cell cycle progression and accumulation of unrepaired DNA damage, leading to tumour cell death[1,2]
- M1774 is a potent, selective, orally administered ATR inhibitor that has demonstrated antitumour activity in preclinical models[3,4]
- This open-label, phase I study (NCT04170153) aims to evaluate the safety, tolerability (including defining the MTD and RDE), PK, PD and preliminary efficacy of M1774, alone or in combination with niraparib, in patients with advanced solid tumours[4,5]

Study design



- M1774 was administered once daily as a single agent under fasting conditions. The starting dose level was 5 mg and was escalated, as determined by the SMC
- Dose levels were recommended by a Bayesian dose-toxicity model with overdose control
- Additional dosing regimens, including intermittent regimens, were explored for safety, tolerability and PK

*Patients in part A1 were not selected based on assessment of putative predictive biomarkers; †The three biomarker cohorts were *ATM, ARID1A* and *ATRX/DAXX*.
ATR, ataxia telangiectasia and Rad3-related protein kinase; BM, biomarker; MTD, maximum tolerated dose; PD, pharmacodynamics; PK, pharmacokinetics; RDE, recommended dose for expansion; SMC, safety monitoring committee

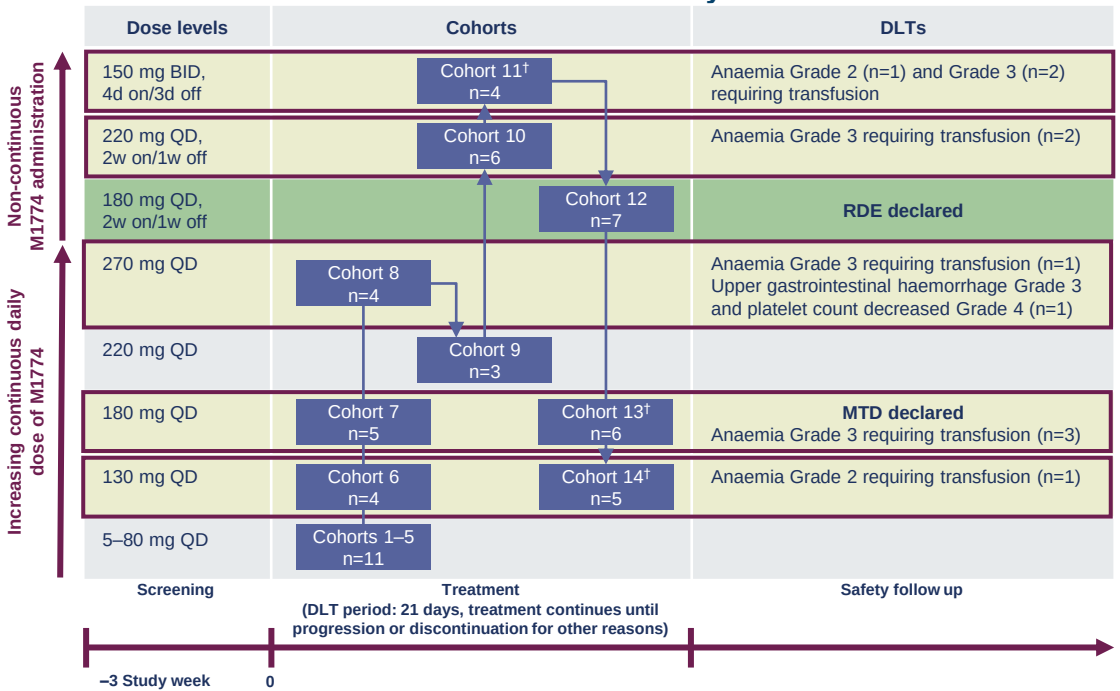
1. Carrassa L, Damia G. Cancer Treat Rev 2017;60:139–151; 2. Blackford AN, Jackson SP. Mol Cell 2017;66:801–817; 3. Zimmermann A, et al. Cancer Res 2022;82(12_Suppl):2588; 4. Yap TA, et al. J Clin Oncol 2021;39(15_Suppl):TPS3153; 5. ClinicalTrials.gov record. https://clinicaltrials.gov/ct2/show/NCT04170153 [last updated 27 April 2022; accessed 5 August 2022].

Results

Demographics and dose outcomes

- Median age was 62 years (range 33–82), 58% of patients were female and the most common primary tumour types were prostate (26%), ovary (16%), breast (6%) and pancreas (6%)
- 11 patients experienced DLTs during the predefined observation period of 21 days*
  - 10 of 11 DLTs were anaemia requiring blood transfusion
- The Bayesian model suggested the MTD of M1774 was 180 mg QD when given continuously; no MTD has been formally established for the intermittent 2w on/1w off schedule
- RDE for M1774 was declared at a dose of 180 mg 2w on/1w off due to this schedule having a better safety profile versus 180 mg QD continuously*

Part A1: dose escalation cohorts to RDE (N=55) over 14 cohorts and DLTs by dose



*As determined by the SMC; †One participant not evaluable for DLTs

BID, twice daily; d, day; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; QD, once daily; RDE, recommended dose for expansion; SMC, safety monitoring committee; w, week

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Results

Safety outcomes

- Overall, the most frequently reported TEAE(s) of:
  - Any grade were anaemia (70.9%), nausea (61.8%) and fatigue (40.0%)
  - Grade ≥3 were anaemia (36.4%), neutrophil count decreased (7.3%) and lymphocyte count decreased (7.3%)
  - Grade ≥4 was platelet count decreased (3.6%) at dose levels exceeding the MTD
- No deaths were considered to be related to M1774

MTD RDE

TEAEs (% patients)	M1774 dosing cohorts (N=55)									
	≤40 mg QD (n=8)	80 mg QD (n=3)	130 mg QD (n=9)	180 mg QD (n=11)	220 mg QD (n=3)	270 mg QD (n=4)	220 mg QD 2w on/1w off (n=6)	150 mg BID 4d on/3d off (n=4)	180 mg QD 2w on/1w off (n=7)	Total (N=55)
Any TEAE	6 (75.0)	3 (100.0)	9 (100.0)	11 (100.0)	3 (100.0)	4 (100.0)	6 (100.0)	4 (100.0)	6 (85.7)	52 (94.5)
Any treatment-related TEAE	5 (62.5)	1 (33.3)	9 (100.0)	11 (100.0)	3 (100.0)	4 (100.0)	6 (100.0)	4 (100.0)	5 (71.4)	48 (87.3)
Any serious treatment-related TEAE	0 (0.0)	0 (0.0)	1 (11.1)	1 (9.1)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.5)
Any treatment-related TEAE leading to dose reduction	0 (0.0)	0 (0.0)	1 (11.1)	1 (9.1)	1 (33.3)	3 (75.0)	0 (0.0)	3 (75.0)	1 (14.3)	10 (18.2)
Any treatment-related Grade 3 TEAE	0 (0.0)	0 (0.0)	2 (22.2)	7 (63.6)	1 (33.3)	2 (50.0)	3 (50.0)	4 (100.0)	0 (0.0)	19 (34.5)
Any treatment-related Grade 4 TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (25.0)	0 (0.0)	2 (3.6)
Deaths	2 (25.0)	1 (33.3)	0 (0.0)	2 (18.2)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (10.9)

BID, twice daily; d, day; MTD, maximum tolerated dose; QD, once daily; RDE, recommended dose for expansion; TEAE, treatment-emergent adverse event; w, week

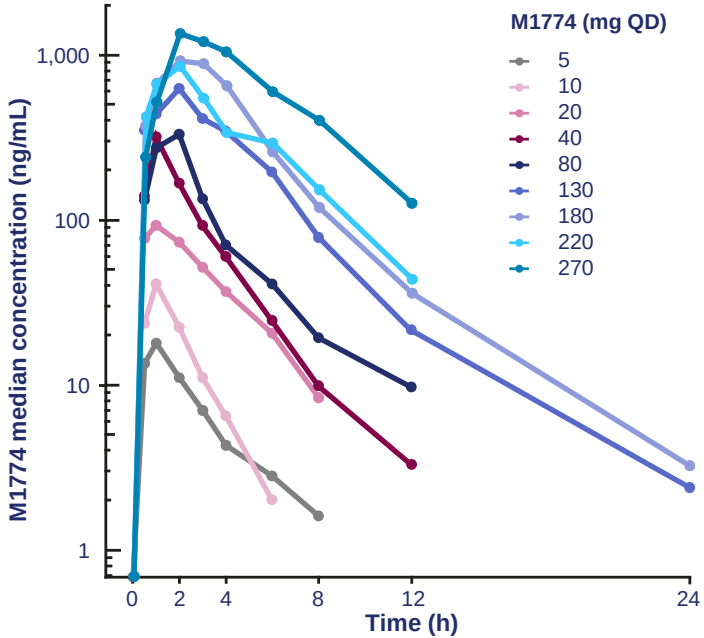
Results

PK and PD outcomes

- M1774 was rapidly absorbed, with median T_{max} ranging from approximately 0.5–3.5 hours and mean $t_{1/2}$ ranging from approximately 1.2–5.6 hours
- M1774 exposure was approximately dose proportional up to 180 mg QD and slightly more than proportional at higher doses
- **At 180 mg QD, average observed concentration at steady state was ≈30 fold higher than the *in vitro* pCHK1 IC_{90}**

- ɣ-H2AX is a molecular marker for monitoring DNA damage initiation and resolution[1]
- With M1774 doses of 130 mg QD or higher, ɣ-H2AX levels in *ex vivo* 4-NQO-treated patient PBMCs were reduced by >80% 3 hours after the first dose, showing target engagement [data not shown]

PK profiles of M1774 following single oral dose administration

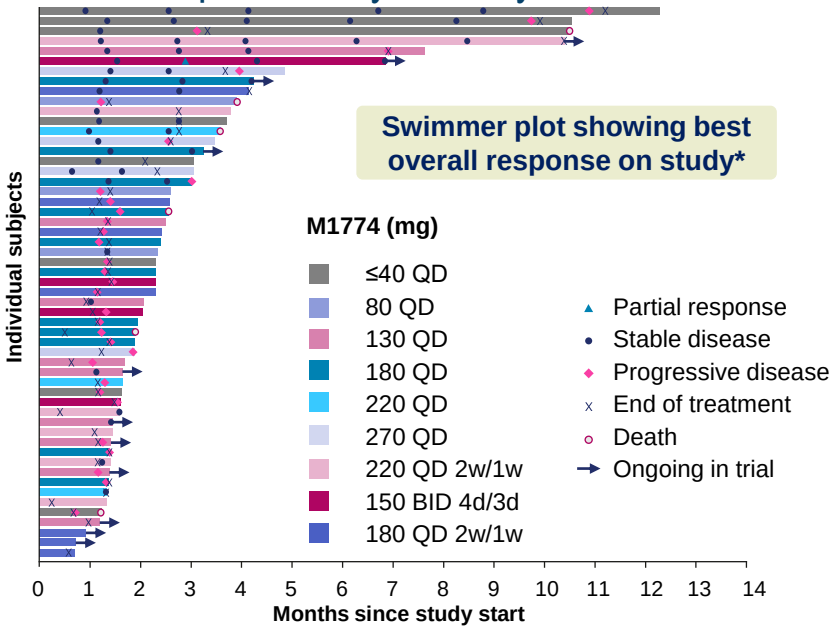


4-NQO, 4-nitroquinoline 1-oxide; h, hours; H2AX, H2A histone family member X; IC_{90}, concentration of a drug required for 90% inhibition; PBMC, peripheral blood mononuclear cells; pCHK1, phosphorylated checkpoint kinase 1; PD, pharmacodynamics; PK, pharmacokinetics; QD, once daily; $t_{1/2}$, drug half-life; T_{max}, time to maximum drug concentration

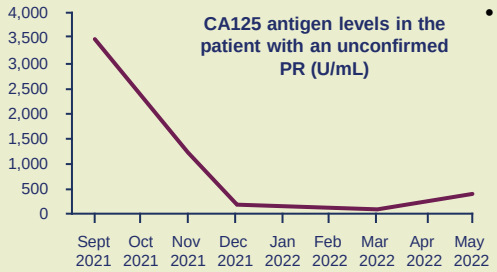
1. Dickey JS, et al. Chromasoma 2009;118:683–692

Results

Part A1: preliminary efficacy

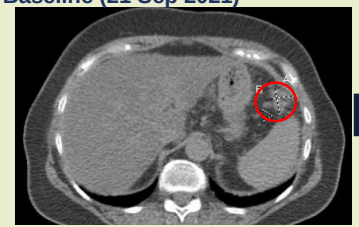


- In 13/35 patients in cohorts 1–11, LoF mutations were detected by NGS in baseline circulating tumour DNA samples, among them *BRCA1/2* (6), *ATM* (3), *ARID1A* (4) and *ATRX* (2)

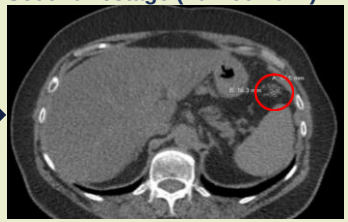


- One patient with platinum- and PARP inhibitor-resistant $BRCA_{wt}$ ovarian cancer with p53 and *ATRX* mutations† and receiving M1774 at a dose of 150 mg BID 4d on/3d off‡ achieved a RECIST v1.1 PR†

Baseline (21 Sep 2021)



Second restage (20 Dec 2021)



*Bar length indicates time from treatment start to date subject last known to be alive; †Not yet centrally confirmed; ‡Dose was modified twice: 120 mg BID 4d on/3d off (DM1) then 90 mg BID 4d on/3d off (DM2)
ARID1A, AT-rich interactive domain-containing protein 1A; *ATM*, ataxia-telangiectasia-mutated; *ATRX*, alpha thalassemia/mental retardation syndrome X-linked; BID, twice daily; *BRCA1/2*, breast cancer gene 1 and breast cancer gene 2; *BRCAwt*, breast cancer gene wild-type; d, day; DM, dose modification; LoF, loss of function; NGS, next generation sequencing; PARP, poly (adenosine diphosphate [ADP]-ribose) polymerase; QD, once daily; PR, partial response; RECIST v1.1, Response Criteria in Solid Tumours version 1.1; w, week.

Conclusions

- These early data show that the ATR inhibitor M1774 is well tolerated at doses up to 180 mg QD in patients with advanced solid tumours
    - At doses up to and including 180 mg QD, anaemia is the most frequently reported AE, with no significant neutropenia or thrombocytopenia reported
- M1774 exposure is approximately dose proportional up to 180 mg QD and slightly more than proportional at higher doses
- M1774 administered at doses of 130 mg QD and higher reduces γ-H2AX levels in PBMCs by >80%, demonstrating target engagement
- RDE for M1774 was declared at a dose of 180 mg 2w on/1w off because this schedule was better tolerated than the MTD schedule (180 mg QD continuously)*
- There was no protocol-mandated biomarker selection for part A1; nevertheless, preliminary signs of efficacy were observed
- The DDRiver 301 study is ongoing, with part A2 (effects of food on M1774 PK), part A3 (biomarker-selected cohorts) and part B1 (niraparib combination cohort) open and enrolling patients
- Another phase I study, DDRiver 320 (NCT05396833), is assessing M1774 in combination with DDRis and immune checkpoint inhibitors in patients with advanced solid tumours

*As determined by the SMC
γ-H2AX, phosphorylated H2AX; AE, adverse event; ATR, ataxia telangiectasia and Rad3-related protein kinase; DDRi, DNA damage response inhibitors MTD, maximum tolerated dose; PBMC, peripheral blood mononuclear cell; PK, pharmacokinetics; QD, once daily; RDE, recommended dose for expansion; SMC, safety monitoring committee