CT271

Translational analyses of ATR inhibitor M1774 in a Phase I study in patients with solid tumors (DDRiver Solid Tumors 301)

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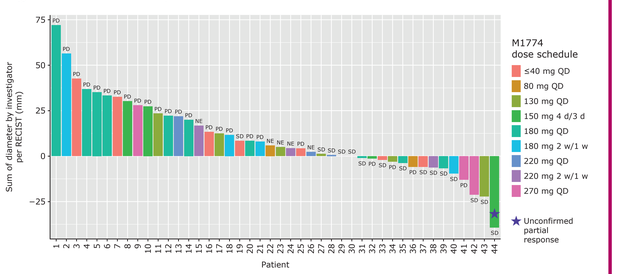
CONCLUSIONS

- **M1774 induced frequent molecular responses (MRs) in patients treated with doses in the predicted efficacious concentration range**
- **The presence of *TP53* alterations was significantly associated with MR**
- **MRs are enriched in patients with radiological disease stabilization and longest treatment duration**
- **Complete MRs were detected for mutations in the genes *ARID1A*, *ATRX*, *DAXX* that are being used for participant selection in the ongoing biomarker expansion cohorts of the DDRiver Solid Tumors 301 study**

INTRODUCTION

- Ataxia telangiectasia and Rad3-related (ATR) protein kinase plays a critical role in the DNA damage response
- ATR inhibition allows unhindered cell cycle progression through specific checkpoints, promoting the accumulation of unrepaired DNA damage and tumor cell death[1]
- M1774, a potent, selective, orally administered ATR inhibitor with antitumor activity in preclinical models, was evaluated as monotherapy in Part A1 of the first-in-human, open-label, single-arm study DDRiver Solid Tumors 301 (NCT04170153)[2,3]
- M1774 was well-tolerated and pharmacodynamic analyses showed that maximum target engagement was reached from the dose of 130 mg once daily (QD), and totality of evidence including quantitative model-based analyses suggested the recommended dose for expansion (RDE) as M1774 180 mg 2 weeks on/1 week off[2]
- One patient with platinum and PARP inhibitor-resistant *BRCA* wild type ovarian cancer and *ATRX* mutation on local tumor testing achieved a RECIST v1.1 partial response (unconfirmed)[2]

Figure 1. Clinical response and M1774 dose levels



Change in target lesion sum of longest diameters and best response (RECIST v1.1) is shown per patient.
NE, not evaluable; **PD**, progressive disease; **QD**, once daily; **SD**, stable disease

OBJECTIVES

- Explore the molecular portrait and evolution of the underlying disease of patients treated with M1774, by measuring the changes in allele frequencies of somatic tumor DNA alterations in circulating tumor DNA (ctDNA)
- Analyze the MRs to M1774 treatment in relationship to clinical benefit

METHODS

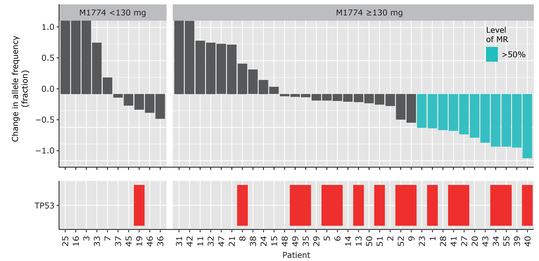
- Blood samples for plasma ctDNA analyses were collected from study participants on day 1 of each treatment cycle (21 days) and at disease progression
- A total of 123 samples from 55 study participants were analyzed by Next Generation Sequencing at Guardant Health, Redwood City, CA, USA using the OMNI panel. On-treatment ctDNA samples were collected for 44/55 participants:
  - 122/123 (99%) samples were processed successfully
  - 121/122 (99%) samples sequenced had detectable ctDNA after filtering for putative clonal hematopoiesis
- MR is defined as best delta mean Variant Allele Fraction (VAF) <50%

$$Best\ delta\ mean\ VAF = min(treati)\ \frac{VAF_{baseline} - VAFtreati}{VAF_{treati}}$$

  - Somatic putative clonal hematopoiesis of indeterminate potential mutations were excluded
  - VAF at baseline <0.3% were excluded
  - "Baseline variants" not detected at treatment received VAF = 0.0001
- High functional impact of a mutation was given when it belonged to one of the following categories:
  - Frameshift
  - Nonsense
  - splice_donor
  - splice_acceptor
  - Pathogenic by Clinvar[4]

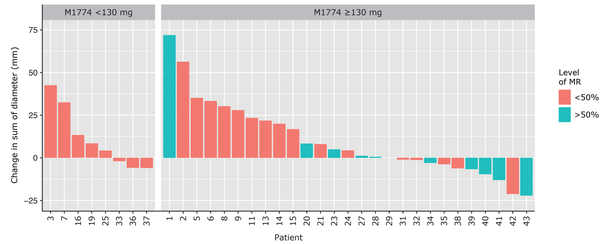
RESULTS

Figure 2. Molecular responses are enriched in subjects treated with M1774 active doses



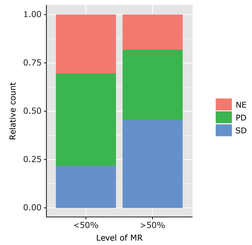
MR per patient. Reduction of somatic allele frequencies from baseline by more than 50% is highlighted in blue. *TP53* mutation status (red) is shown below. MRs were observed in 11/34 (32%) patients treated with more than M1774 130 mg QD; none were observed in the 10 patients treated with lower M1774 doses. *TP53* mutations were significantly associated with MR, independently of the tumor type (Wilcoxon rank-sum test P<0.01).
MR, molecular response; **QD**, once daily

Figure 3. Molecular responses are enriched in subjects with radiological disease stabilization



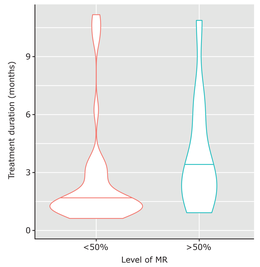
5/10 (50%) patients with molecular responses showed a reduction in sum of tumor diameter, compared with 5/16 (31%) of those without MRs. **MR**, molecular response

Figure 4. Clinical benefit is enriched in the presence of molecular responses



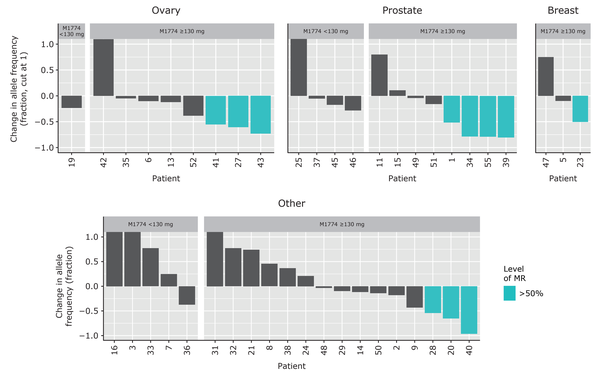
Frequency of clinical response by RECIST v1.1 in patient cohorts with, and without MR.
MR, molecular response; **NE**, not evaluable; **PD**, progessive disease; **SD**, stable disease

Figure 5. Treatment duration is prolonged in the presence of molecular responses



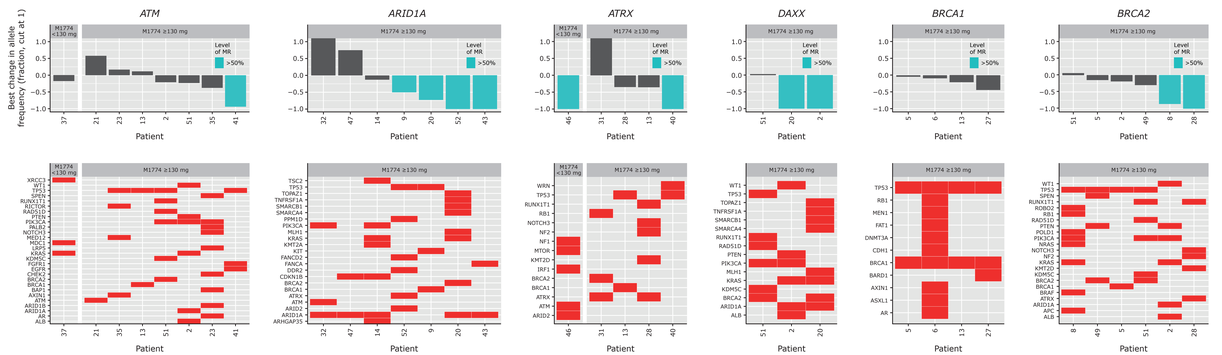
Duration of treatment in patients with and without MR.
MR, molecular response

Figure 6. Molecular responses are enriched in BRCA-associated tumors



MRs were enriched in patients with ovarian cancer (3/8, 38%), prostate cancer (4/8, 50%), and breast cancer (1/3, 33%), but less frequent in other histologies (3/15, 25%). **MR**, molecular response

Figure 7. Complete molecular responses are observed in participants with mutations predictive of ATRi sensitivity



Molecular responses were enriched in genes associated with ATR inhibitor activity by a synthetic lethality mechanism.[5-7] Complete MRs were achieved for any mutations in *ARID1A* (2/7), *ATRX* (2/5), *DAXX* (2/3), and *BRCA1/2* (1/10). Additional mutated genes with high impact mutations per patient are shown in the oncoprints. Some patients harbored multiple mutations predictive of ATRi sensitivity and are shown more than once. **ATR**, Ataxia telangiectasia and Rad3-related

References: 1. Blackford AN, Jackson SP. *Mol Cell.* 2017;66:801–17; **2.** Yap T, et al. *Ann Oncol.* 2022;33(suppl_7):S747–8; **3.** Zimmermann A, et al. *Cancer Res.* 2022;82(12_Suppl):2588; **4.** Landrum MJ, et al. *Nucleic Acids Res.* 2014;42(1):D980–5; **5.** Williamson CT, et al. *Nat Commun.* 2016;7:13837; **6.** Reaper PM, et al. *Nat Chem Biol.* 2011;7(7):428–30; **7.** Flynn RL, et al. *Science.* 2015;347(6219):273–7.

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