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M1774, a novel potent and selective ATR inhibitor, shows antitumor effects as monotherapy and in combination

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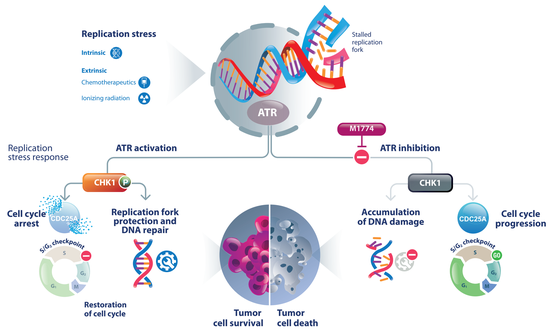
CONCLUSIONS

- **M1774 is a potent, orally administered, selective ataxia telangiectasia-mutated and Rad3-related (ATR) kinase inhibitor with differential anti-proliferative activity in tumor cells**
- **M1774 is active in xenograft models harboring ataxia telangiectasia-mutated (ATM) or AT-rich interaction domain 1A (ARID1A) mutations**
- **Synergistic activity with specific DNA-damaging agents, poly adenosine diphosphate-ribose polymerase (PARP) inhibitors, and ATM inhibitors was demonstrated**
- **In combination with DNA-damaging agents (cisplatin, gemcitabine) and DNA damage response (DDR) inhibitors (niraparib, M4076) strong anti-tumor activity was observed in xenograft models**
- **M1774 is currently being investigated in a Phase I clinical trial in patients with advanced solid tumors (DDRiver Solid Tumors 301, NCT04170153)**

INTRODUCTION

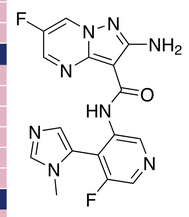
- ATR is activated by single-stranded DNA and recruited to stalled replication forks in response to replication stress[1]
- Activated ATR phosphorylates and activates checkpoint kinase 1 (CHK1), which in turn induces S/G2 cell cycle arrest through degradation of cell division cycle 25A (CDC25A) and promotes DNA repair, ultimately restoring replication fork progression[1]
- ATR inhibition by small molecule inhibitors such as M1774 abrogates the S/G2 cell cycle checkpoint as well as the restoration of replication forks, resulting in tumor cell death[1,2]



ATR, ataxia telangiectasia-mutated and Rad3-related

RESULTS

Table 1. Structure, activity and selectivity of ATR inhibitor M1774

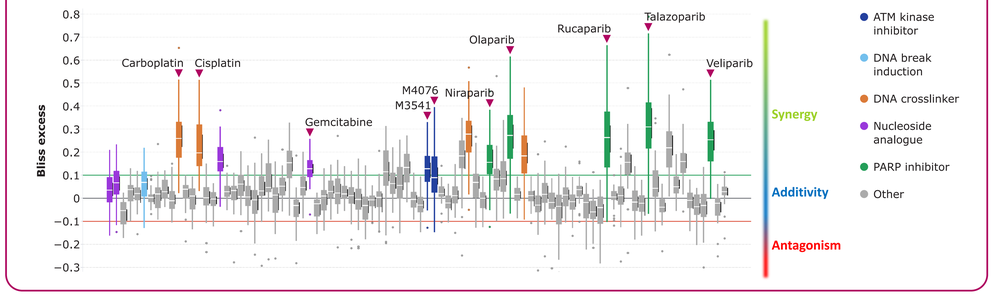
Kinase assays	Ki [nM]	Structure
ATR	<0.2	
ATM	4040	
DNA-PK	290	
Cell-based assays	**IC_{50} (nM)**	
ATR: 4NQO-induced pSer345 CHK1 in HT29	5	
ATM: NCS-induced pSer139 H2AX in MO59J (DNA-PK null)	19.800	
DNA-PK: NCS-induced pSer139 H2AX in HT144 (ATM null)	2300	
HCT116, proliferation inhibition; cytotoxicity	24, 26	
HFL1, proliferation inhibition; cytotoxicity	1.870; 11.000	
Cancer cell line panel (#93)	23 – >1.000 (median 120)	
Selectivity	**Kinases <175-fold split**	
Kinase selectivity*	4/321 tested	

ATR, ataxia telangiectasia-mutated and Rad3-related; **ATM**, ataxia telangiectasia mutated; **DNA-PK**, DNA-dependent protein kinase

- M1774 is a potent inhibitor of ATR
- In cell-based assays, M1774 has >100-fold selectivity for ATR over ATM and DNA-dependent protein kinase (DNA-PK)
- In large panel kinase profiling, minimal inhibitory activity was observed against unrelated kinases, with at least 175-fold selectivity for ATR over 317 out of 321 kinases tested
- A broad range of antiproliferative activities (IC_{50} 23 nM – 1 µM) was observed in a panel of 93 cancer cell lines

RESULTS

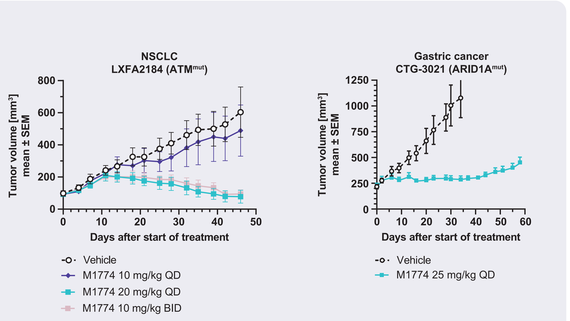
Figure 1. Bliss synergy analysis of M1774 drug combination profiling



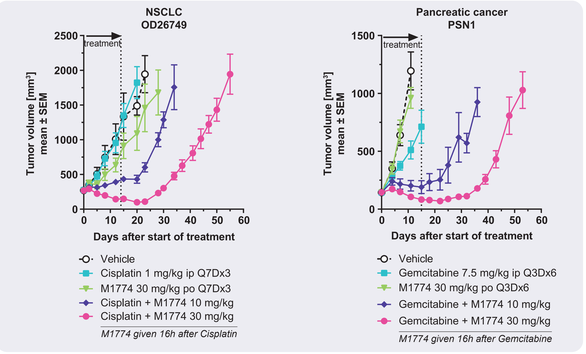
- Pairwise combination of M1774 with 90 standard of care and investigational agents for oncology
- PARP inhibitors, platinum-containing anti-cancer drugs, antimetabolites, and ATM inhibitors identified as synergistic combination partners
- Combination data were generated in 35 cancer cell lines (5-day compound incubation; readout: sulforhodamine B staining)
- Box plots show the distribution of Bliss scores for each combination

Figure 2. In vivo activity of M1774 as monotherapy and combination with DNA-damaging agents and DDR inhibitors in xenograft models in mice

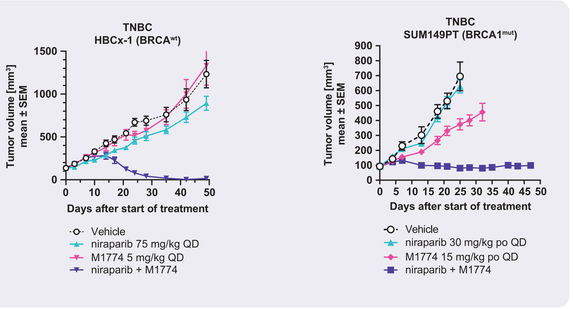
Single-agent activity in ATM- and ARID1A-mutated models



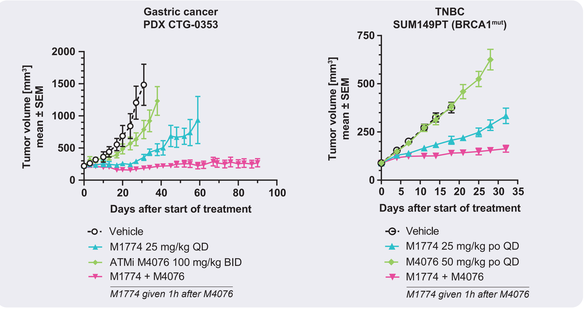
Combination with DNA-damaging chemotherapeutic agents



Combination with PARP inhibitor niraparib



Combination with ATM inhibitor M4076



ARID1A, AT-rich interaction domain 1A; **ATM**, ataxia telangiectasia mutated; **BID**, twice a day; **BRCA**, breast cancer gene; **DDR**, DNA damage response; **ip**, intraperitoneal administration; **NSCLC**, non small cell lung cancer; **PARP**, poly adenosine diphosphate-ribose polymerase; **po**, oral administration; **QD**, every day; **SEM**, standard error of the mean; **TNBC**, triple negative breast cancer

- M1774 was usually well tolerated with no additional body weight loss compared to chemotherapeutic agent or DDR inhibitor alone
- Combination of M1774 with niraparib at 75 mg/kg resulted in body weight loss in a fraction of mice (up to 20% in 3/14 mice treated with combination regimen), while combination with niraparib at a dose of 30 mg/kg was well tolerated

1. Blackford N, Jackson P. *Mol Cell.* 2017;66:801–817; 2. Yap TA, et al. *J Clin Oncol.* 2021;39:15(suppl TPS3153).

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