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Pharmacodynamic and immunophenotyping analyses of ATR inhibitor M1774 in a Phase I study in patients with solid tumours (DDRiver Solid Tumors 301)

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CONCLUSIONS

- **Exposure-related target engagement suggested >80% target inhibition at ≥130 mg M1774**
- **M1774 treatment did not cause any consistent change in the levels of most immune cell subsets at all dose levels tested, including T and B lymphocytes, and myeloid-derived suppressor cells (MDSC)**
- **Transient decreases in monocytes and natural killer (NK) cell subsets were observed at doses ≥130 mg M1774, with recovery during treatment breaks**

INTRODUCTION

- Ataxia telangiectasia and Rad3-related (ATR) protein kinase is activated by exposure to single-stranded DNA, leading to cell cycle arrest and promoting DNA repair[1]
- 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, demonstrated antitumor activity in preclinical models[2]. Part A1 of the open-label, single-arm DDRiver Solid Tumors 301 (NCT04170153) Phase 1 trial evaluated the safety, tolerability, maximum tolerated dose, pharmacokinetics (PK) and pharmacodynamics (PD) of M1774[3]
- M1774 monotherapy in patients with advanced solid tumors was well-tolerated and a totality of evidence approach including quantitative model-based analyses suggested the recommended dose for expansion (RDE) as 180 mg M1774 QD 2 weeks on/1 week off[3]

OBJECTIVES

- Show M1774 target inhibition in surrogate tissue (PD) and examine the effect of treatment on immune cells in whole blood samples collected from the 55 patients in the dose escalation Part A1 of the study

METHODS

PD assay

- M1774 PD was explored by assessing the level of H2AX phosphorylation (γ-H2AX) by ATR in circulating lymphocytes as tumor surrogate tissue[4]
- Whole blood samples were collected before and 3 h after the first M1774 dose. The samples were stimulated either with 4NQO (4-Nitroquinoline N-oxide, Sigma, UK) or dimethyl sulfoxide, as control
- Following treatment with Lyse & Fix Solution and permeabilization, cells were stained with CD45 and Phospho-Histone H2A.X antibodies. Analysis was performed using a FacsCanto II (Becton Dickinson, Franklin Lakes, NJ, USA)
- The PK/PD relationship between AUC_{0-3h} and γ-H2AX was established 3 h post single-dose of M1774
- Percentage of γ-H2AX positive lymphocytes was used as main read-out and calculated as

$$\left[\frac{4NQO\ post\ treatment}{4NQO\ baseline}\times 100\right]-100^{*}$$

(*baseline γ-H2AX expression fixed at 100% as maximum expression within the dose level under evaluation)

Immunophenotyping assay

- For immunophenotyping, flow cytometry panels were used to detect 43 immune cell subsets, including T, B, and NK cells, MDSC and monocytes, in human whole blood samples
- Whole blood samples were collected at visits on day 1 and day 15 of cycles 1 and 2 before M1774 intake (cycle duration: 21 days)
- Analyses were performed at Q2 Solutions Global Central Laboratories in agreement and following Q2 Solution validated methods
- Relative changes (RC) to the baseline of each measurement were computed as follows:

$$\%RC=\left(\frac{measurement\ at\ each\ visit-measurement\ at\ baseline}{measurement\ at\ baseline}\right)\times 100$$

RESULTS

Pharmacodynamics

Figure 1. M1774 target inhibition

- Percentage decrease of γ-H2AX levels in *ex vivo* 4NQO stimulated lymphocytes at 3 h vs. pretreatment

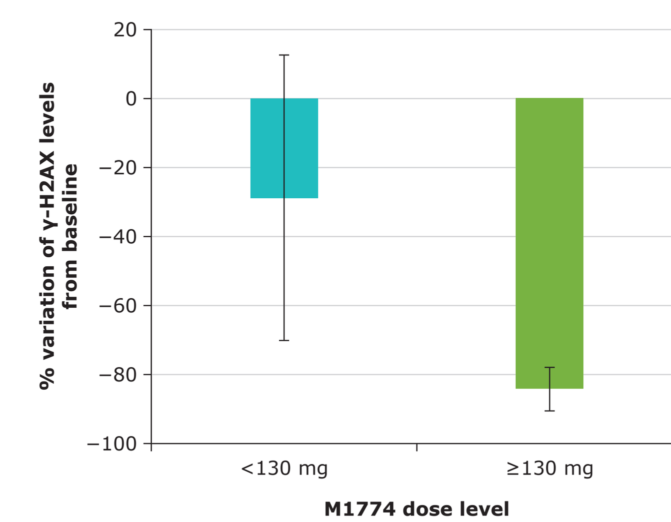
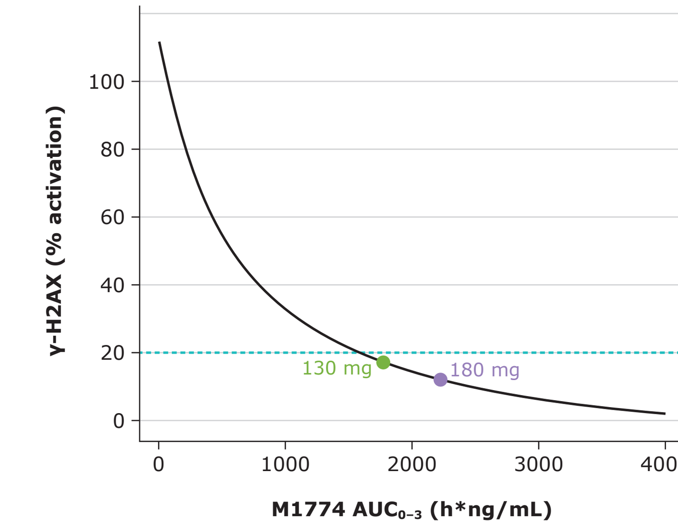


Figure 2. M1774 PK/PD relationship

- Model-predicted γ-H2AX levels (% activation) vs. area under the curve (AUC) of plasma concentration time curve of 3 h post single M1774 dose (AUC_{0-3})
- Dots represent γ-H2AX activation at M1774 130 mg and 180 mg dose groups. The dashed line marks the 20% activation threshold which is equivalent to the 80% threshold for target inhibition
- The PK/PD relationship between inhibition of γ-H2AX activation and AUC_{0-3h} post single dose M1774 across dose groups indicated exposure-related target engagement suggesting >80% target inhibition at ≥130 mg M1774[5]



RESULTS

Immunophenotyping

Figure 3. Representative examples of aggregated data from immunocyte subsets grouped by M1774 dose levels above and below 130 mg QD or BID

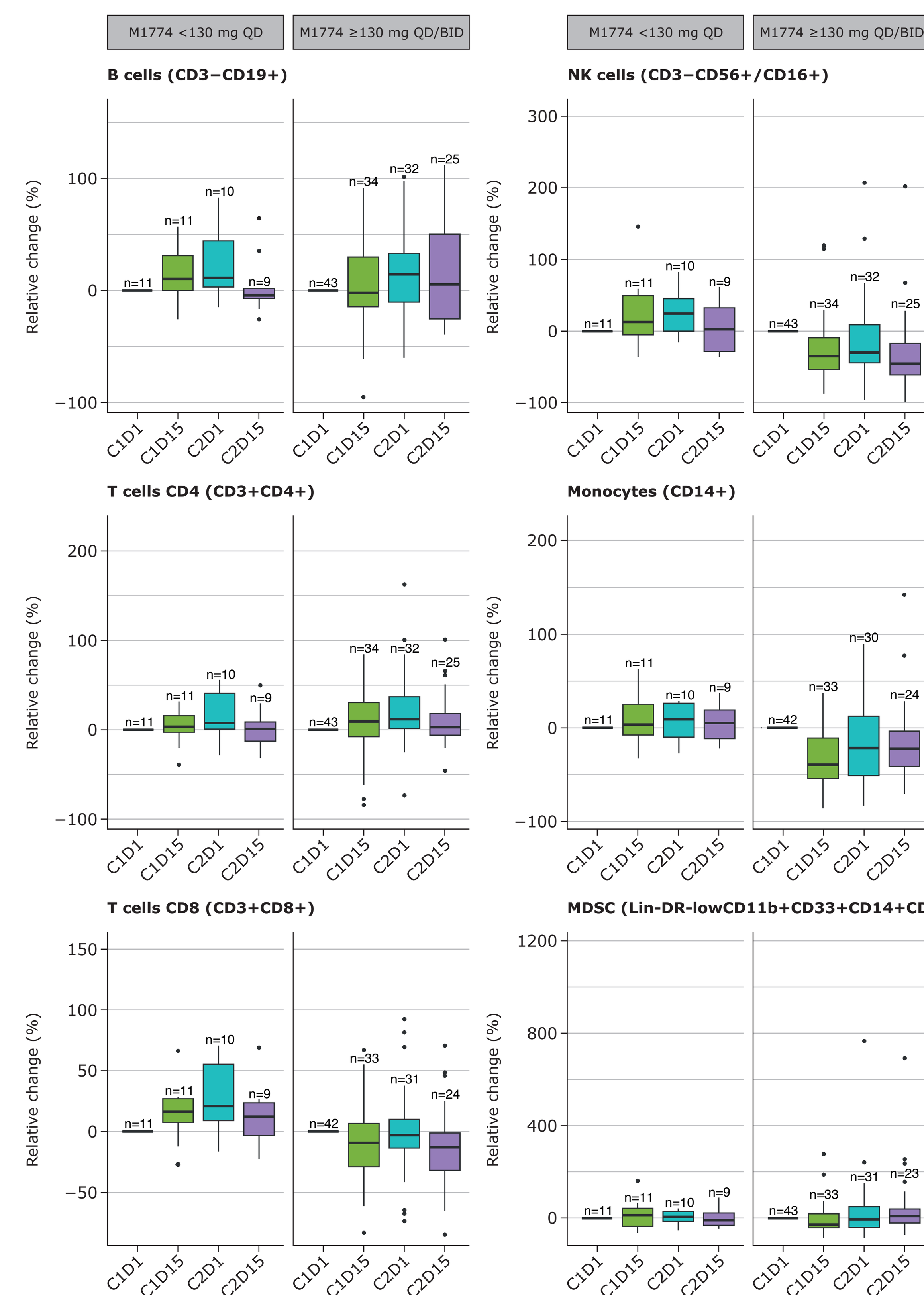
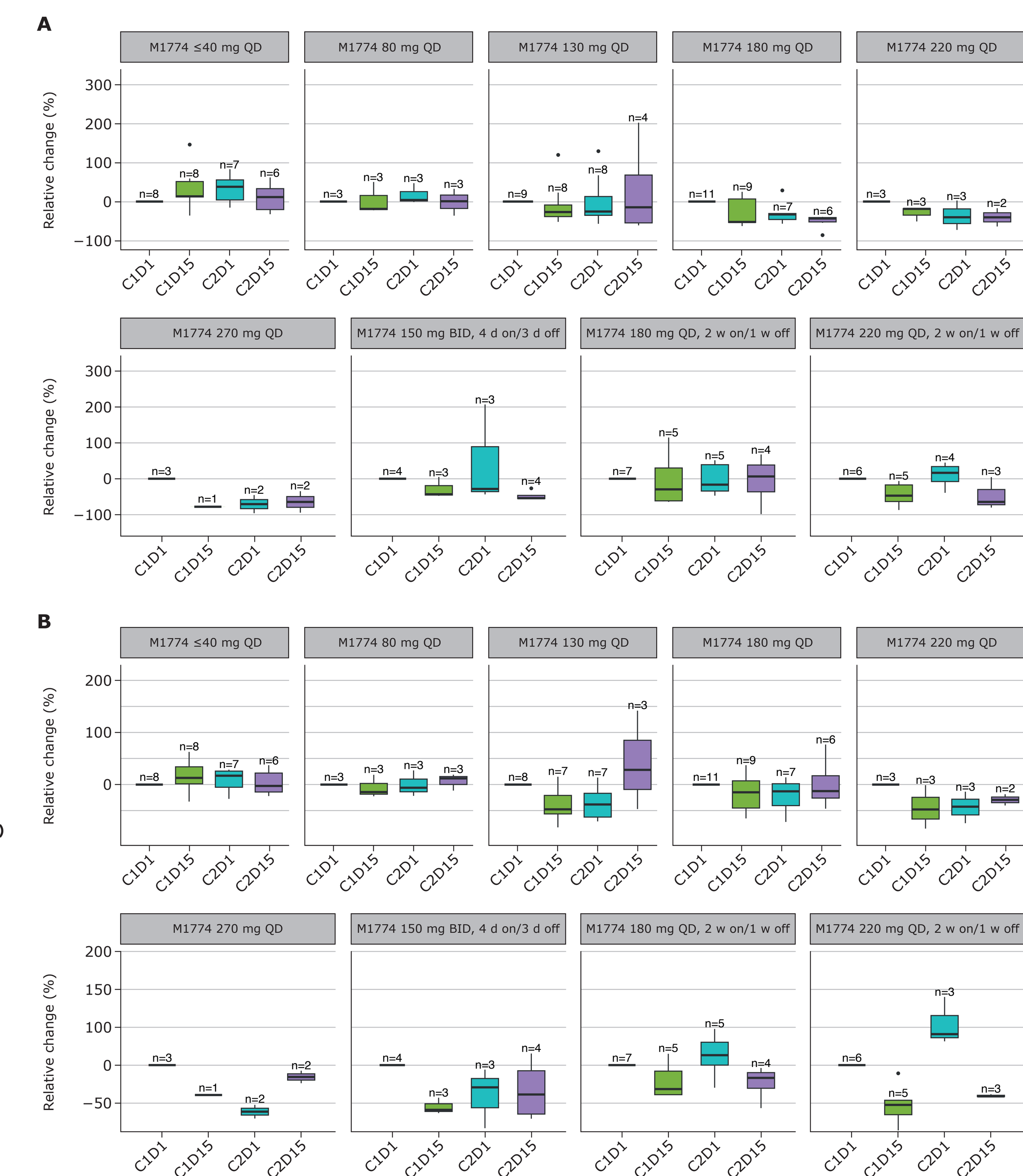


Figure 4. Aggregated data grouped by single M1774 dose levels for NK cells (A) and monocytes (B)



For each parameter, measurements obtained at each visit are grouped by dose level. Each graph visualizes the relative change [%RC] from baseline of each measurement. **C**, cycle; **D**, day; **MDSC**, myeloid-derived suppressor cells; **NK**, natural killer; **QD**, once daily

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