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Translational, PK, and PD analyses of tuvusertib + niraparib in a Phase I open-label multicenter dose-escalation study in patients with advanced solid tumors (DDRiver Solid Tumors 301)

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DDRiver SOLID TUMORS 301

CONCLUSIONS

- **Tuvusertib exposure when administered with niraparib was consistent with monotherapy exposure, suggesting a lack of clinically meaningful mutual drug–drug interactions**
- **Robust target modulation was observed at tuvusertib doses ≥130 mg**
- **Approximately 44% of evaluable patients had a molecular response**
- **Molecular responses were more frequent in:**
  - **Patients receiving tuvusertib ≥130 mg**
  - **Patients with stable disease or non-complete response/ non-progressive disease**
  - **Patients with *BRCA1*-mutated tumors versus patients with *BRCA1*-wild type tumors**
- **Tuvusertib + niraparib is being further explored in patients with PARPi-resistant epithelial ovarian cancer (DDRiver EOC 302; NCT06433219)**

INTRODUCTION

- The DNA damage response (DDR) is a complex cellular signalling network that maintains genomic integrity in response to constant exposure to endogenous and exogenous insults[1]
- Ataxia telangiectasia and Rad3-related kinase (ATR) and poly-ADP ribose polymerase (PARP) are essential components of the DDR[2,3]
- Tuvusertib (M1774) is a potent, orally administered and selective ATR inhibitor with a manageable safety profile observed in patients with advanced solid tumors[4]
- Combining tuvusertib with the PARP inhibitor niraparib may induce synthetic lethality, triggering replication fork collapse, mitotic catastrophe and cancer cell death[5-8]
- Part B1 of the DDRiver Solid Tumors 301 study (NCT04170153) is assessing this combination; acceptable tolerability and preliminary efficacy have been observed[9]
- Here, we report tuvusertib pharmacokinetics (PK), changes in levels of phosphorylated histone variant H2AX (γ-H2AX; a pharmacodynamic [PD] biomarker of ATR inhibition), as well as a retrospective analysis of molecular response (MR) from Part B1 of the DDRiver Solid Tumors 301 study (**Figure 1**)

Figure 1. Overall DDRiver Solid Tumors 301 study design

In **Part A1** of DDRiver 301, tuvusertib 180 mg QD was determined as the MTD, with anemia as the main toxicity[4]

Part A1 dose escalation: safety and tolerability, MTD, RDE, PK, and PD of **tuvusertib monotherapy**

Part A2: effect of food on tuvusertib PK

Part A3: preliminary efficacy of tuvusertib in biomarker-selected patients

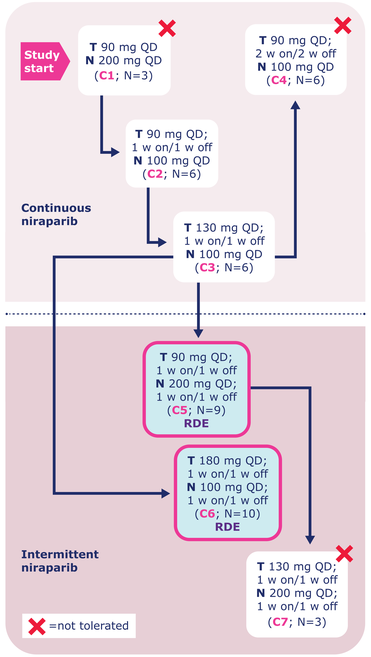
Part B1: safety, tolerability, MTD, RDE, PK, PD, and preliminary efficacy of **tuvusertib** + **niraparib**

MTD, maximum tolerated dose; **PD**, pharmacodynamics; **PK**, pharmacokinetics; **QD**, once daily; **RDE**, recommended dose for expansion

METHODS

- Patients with metastatic or locally advanced unresectable solid tumors refractory to standard treatment were enrolled
  - No patients were selected according to tumor biomarkers
- Continuous tuvusertib (90 mg once daily [QD]) or intermittent tuvusertib (90–180 mg QD; 1 week on/1 week off or 2 weeks on/2 weeks off) and continuous niraparib (100 or 200 mg QD) or intermittent niraparib (100 or 200 mg QD; 1 week on/1 week off) schedules were explored, according to the Bayesian Partial Ordering Continual Reassessment Method (POCRM) model (**Figure 2**)
- Collected plasma PK samples for tuvusertib were analyzed using validated liquid chromatography/mass spectroscopy methods and parameters were determined by non-compartmental analysis using Phoenix® WinNonlin®
- PD analysis measured γ-H2AX in serial blood samples, stimulated ex vivo with 4-nitroquinoline N-oxide (4-NQO; specific for ATR inhibition)
- Samples for the circulating tumor DNA (ctDNA) analysis were collected at baseline, and mostly at day 1 of cycle 2, and at end of treatment (EOT); sometimes additional samples were collected (day 1 of cycle 3, 4 and 6; day 15 of cycle 2)
  - Guardant Infinity® was used to detect somatic alterations, including single nucleotide variants (SNVs), and methylation-based signatures in plasma samples
  - MR was defined as >50% reduction in ctDNA, according to changes from baseline in variant allele fraction or tumor-specific DNA methylation levels
  - MRs reported here were the best ctDNA change from baseline to the most recent sampling timepoint
- Alterations in 53 cancer-associated genes were analyzed to assess the gene alteration landscape and its correlation with MR using a Wilcoxon test

Figure 2. Dose-finding steps (N=43)[9]



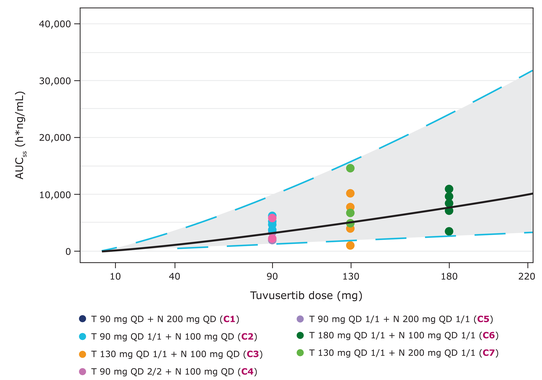
C, cohort; **N**, niraparib; **QD**, once daily; **RDE**, recommended dose for expansion; **T**, tuvusertib; **w**, week

RESULTS

PK analysis

- Tuvusertib exposure when combined with niraparib was consistent with monotherapy exposure, suggesting a lack of clinically meaningful mutual drug–drug interactions (**Figure 3**)

Figure 3. Relationship of tuvusertib AUC_{ss} and dose[a]



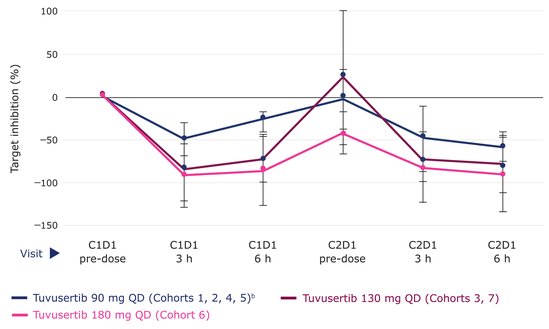
[a]Symbols represent individual patient tuvusertib AUC_{ss} data in combination with niraparib; the solid black line and the shaded gray area represent the model-predicted AUC_{ss} and the 97.5% probability interval from tuvusertib monotherapy, respectively

1/1, 1 w on/1 w off; **2/2**, 2 w on/2 w off; **AUC_{ss}**, area under the drug concentration-time curve at steady state; **AUC_{tau}**, area under the drug concentration-time curve over dosing interval; **C**, cohort; **N**, niraparib; **T**, tuvusertib; **QD**, once daily; **w**, week

PD analysis

- Reduction in γ-H2AX in peripheral blood mononuclear cells immediately after dosing served as a proximal PD marker for tuvusertib
- In line with monotherapy outcomes, almost complete inhibition of γ-H2AX expression was observed after tuvusertib 130 and 180 mg doses (**Figure 4**)

Figure 4. Target modulation[a] according to tuvusertib dose



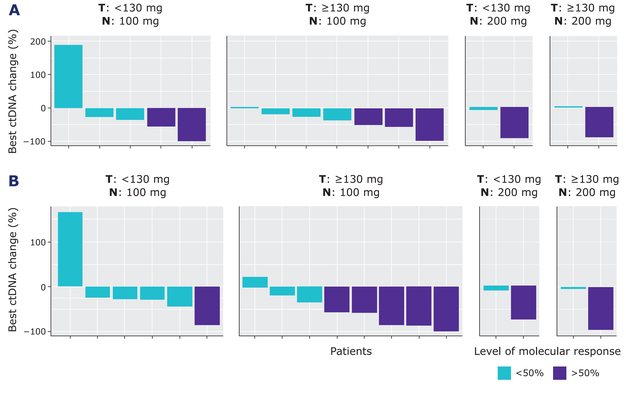
[a]4-NQO-only valid data used for analysis; [b]Only one patient available in Cohort 1 with a C1D1 6 h valid time point

γ-H2AX, phosphorylated histone variant H2AX; **4-NQO**, 4-nitroquinoline N-oxide; **C**, cycle; **D**, day; **h**, hour; **PD**, pharmacodynamic; **QD**, once daily

Molecular response

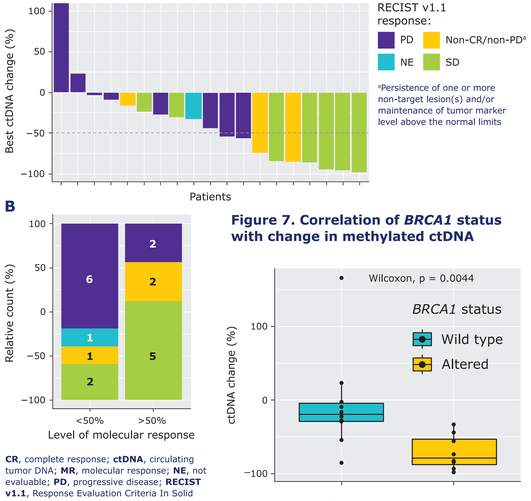
- Overall, 16 patients were MR-evaluable according to variant allele frequencies and 18 were MR-evaluable according to ctDNA methylation
- MRs were observed in 44% and 60% of evaluable patients receiving tuvusertib at doses ≥130 mg by mutation-based (**Figure 5A**) and methylation-based (**Figure 5B**) ctDNA assay, respectively
- MRs were more frequent at tuvusertib doses of ≥130 mg, compared with doses <130 mg, particularly when assessed with the methylation-based ctDNA assay (MR rates of 60.0% vs 25.0%; **Figure 5B**)
- SD or non-CR/non-PD were more frequent in patients with MR (78%) compared to those without MR (30%; **Figure 6AB**)
- Alterations in *BRCA1* were associated with greater reductions in ctDNA during treatment, compared with wild-type *BRCA1* (p=0.0044) (**Figure 7**)

Figure 5. Best change in ctDNA with different tuvusertib and niraparib dose levels according to reduction in mutation-based ctDNA (A; N=16) and methylated ctDNA (B; N=18)



ctDNA, circulating tumor DNA; **N**, niraparib; **T**, tuvusertib

Figure 6. Best change in methylated ctDNA and correlation with clinical response (A) and correlation of clinical response with MR (B)



CR, complete response; **ctDNA**, circulating tumor DNA; **MR**, molecular response; **NE**, not evaluable; **PD**, progressive disease; **RECIST v1.1**, Response Evaluation Criteria In Solid Tumors version 1.1; **SD**, stable disease

Figure 7. Correlation of *BRCA1* status with change in methylated ctDNA

ctDNA, circulating tumor DNA

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