CT063

Phase Ib trial of ATRi tuvusertib + ATMi lartesertib (M4076) in patients with advanced solid tumors

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DDRiver SOLID TUMORS 320

CONCLUSIONS

- **Different doses of lartesertib combined with tuvusertib 180 mg QD using two different schedules were well tolerated**
- **As predicted, haematological DLTs occurred at the highest tested dose levels**
- **Evidence of clinical benefit was observed in this unselected patient population**
- **Exposure and PD of the tuvusertib + lartesertib combination were consistent with the respective monotherapies**
- **Tuvusertib 180 mg QD + lartesertib 150 mg QD 2 w on/2 w off was selected for investigation in expansion cohorts in patients with prostate and endometrial cancer**

INTRODUCTION

- ATR and ATM protein kinases play a critical role in the DNA damage response[1]
- Inhibition of ATR promotes DNA double-strand breaks, the repair of which requires ATM activation[1]
- ATR and ATM genes have a synthetic lethal relationship in cancer[2]
- The ATMi lartesertib potentiates the efficacy of an ATRi in vitro and in vivo[3]
- Tuvusertib and lartesertib are potent, selective, orally administered inhibitors of ATR and ATM, respectively.[4,5] Both are well tolerated as monotherapy in patients with solid tumors[6,7]
- DDRiver Solid Tumors 320 (NCT05396833) is an open-label, multicenter Phase 1b study
- Part A1 of the DDRiver Solid Tumors 320 study is investigating the safety, tolerability, and PK/PD profile of tuvusertib in combination with lartesertib in patients with metastatic or locally advanced unresectable solid tumors

METHODS

Study design

- Eligible patients were ≥18 years of age with metastatic or locally advanced unresectable solid tumors refractory to standard therapy. No restrictions on histology or genomic background were applied in this dose finding part
- Patients received ascending doses of tuvusertib and lartesertib starting with 90 mg tuvusertib QD and 50 mg lartesertib QD on a 2 w on/2 w off schedule. A 2 w on/1 w off schedule was also explored

Safety analysis

- Safety profiles were assessed through reporting and analysis of baseline medical conditions, AEs, physical examination findings, vital signs, ECGs and laboratory tests. DLTs were assessed over the first 28 days
- A dual-agent Bayesian model was used to support dose-escalation decisions based on safety, tolerability, and available PK data

PK analysis

- Plasma concentrations were analyzed using a validated LC/MS method. PK parameters of tuvusertib and lartesertib were determined by noncompartmental analysis using Phoenix® WinNonlin®

PD assay

- H2AX phosphorylation (γ-H2AX) was assessed using circulating lymphocytes as a surrogate for tumor tissue[8]
- PBMCs were stimulated with 4NQO (to induce ATR activity), bleomycin (to induce ATM activity), or control prior to staining with CD45 and γ-H2AX antibodies and analysis using a FacsCanto II (Becton Dickinson, Franklin Lakes, NJ, USA)

RESULTS

Safety

Table 1. DLTs by ascending dose (DLT-evaluable patients; N=37)

Dose (tuvusertib + lartesertib), mg	Cohorts	N	Patients with DLT	DLT AE terms by dose levels
2 week on/2 week off regimen				
90 + 50 QD	1	3	No	N/A
130 + 50 QD	2	4	No	N/A
130 + 100 QD	3	3	No	N/A
180 + 100 QD	4	3	No	N/A
180 + 150 QD	5+8+10	9	No	N/A, dose selected for expansion
180 + 200 QD	6	4	2	Patient 1: febrile neutropenia Grade 3, neutrophil count decreased Grade 4, anemia Grade 3, platelet count decreased Grade 4, candida infection Grade 2. Patient 2: neutrophil count decreased Grade 4
2 week on/1 week off regimen				
180 + 150 QD	7	4	2	Both had platelet count decreased Grade 3
180 + 100 QD	9+11	7	1	Neutrophil count decreased Grade 4

- Of the 42 patients enrolled, 37 were DLT-evaluable
- 5 patients experienced DLTs
- No DLTs were observed in 9 patients receiving tuvusertib 180 mg QD + lartesertib 150 mg QD 2 w on/2 w off

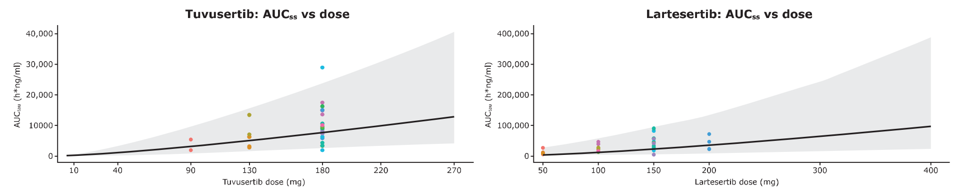
Table 2. Grade ≥3 TEAEs affecting ≥2 patients and any-grade TEAEs affecting >20% of patients (all cohorts, N=42)

TEAEs	Grade ≥3 n (%)	Any grade n (%)
Anemia	9 (21.4)	26 (61.9)
Platelet count decreased	5 (11.9)	9 (21.4)
Fatigue	3 (7.1)	18 (42.9)
Neutrophil count decreased	3 (7.1)	5 (11.9)
Abdominal pain	2 (4.8)	7 (16.7)
Nausea	0	19 (45.2)
Vomiting	0	18 (42.9)
Aspartate aminotransferase increased	0	9 (21.4)

- All 42 patients had at least one TEAE, and the majority of TEAEs were Grade 1 or 2
- Three patients died due to disease progression: one in the tuvusertib 90 mg QD + lartesertib 50 mg QD 2 w on/2 w off regimen on study day 85, one in the tuvusertib 180 mg QD + lartesertib 150 mg QD 2 w on/2 w off regimen on study day 23, and one in the tuvusertib 180 mg QD + lartesertib 150 mg QD 2 w on/1 w off regimen on study day 46

Pharmacokinetics of tuvusertib and lartesertib

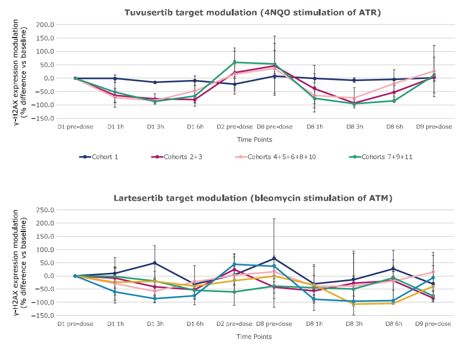
Figure 1. Relationship between tuvusertib and lartesertib monotherapy doses and AUC_{ss} using a power model in comparison to observed preliminary tuvusertib and lartesertib AUC_{ss} in their combination



- Symbols represent preliminary individual patients' tuvusertib AUC_{ss} data in combination with lartesertib; the solid black line and the shaded grey area represent the model-predicted AUC_{ss} for tuvusertib and lartesertib and 97.5% prediction interval, respectively
- Exposure of tuvusertib + lartesertib in combination was consistent with their respective monotherapy exposures, indicating no clinically meaningful mutual drug–drug interactions

Pharmacodynamics of tuvusertib and lartesertib

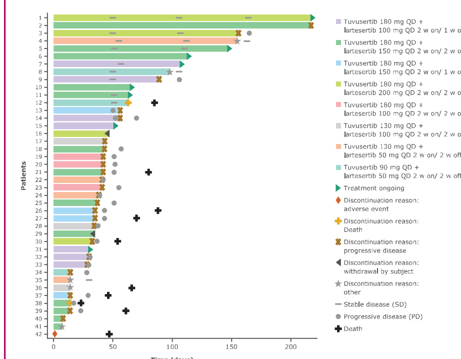
Figure 2. Analysis of γ-H2AX in circulating lymphocytes following treatment with tuvusertib and lartesertib


Tuvusertib target modulation (4NQO stimulation of ATR)
γ-H2AX expression modulation (% difference vs baseline)
D1 pre-dose
D1 1h
D1 3h
D1 6h
D2 pre-dose
D8 pre-dose
D8 1h
D8 3h
D8 6h
D9 pre-dose
Time Points
Cohort 1
Cohorts 2+3
Cohorts 4+5+6+8+10
Cohorts 7+9+11
Lartesertib target modulation (bleomycin stimulation of ATM)
Cohorts 1+2
Cohorts 3+4
Cohorts 5+8+10
Cohort 6
Cohort 7
Cohorts 9+11

- Complete or almost complete target inhibition was observed 1–6 h after tuvusertib ≥130 mg, with rebound above baseline after 24 h
- Variable target inhibition was observed across all time points at lartesertib ≥100 mg

Preliminary efficacy

Figure 3. Swimmer plot showing responses to combination of tuvusertib and lartesertib


Patients
Time (days)
Tuvusertib 180 mg QD + lartesertib 100 mg QD 2 w on/ 1 w off
Tuvusertib 180 mg QD + lartesertib 150 mg QD 2 w on/ 2 w off
Tuvusertib 180 mg QD + lartesertib 150 mg QD 2 w on/ 1 w off
Tuvusertib 180 mg QD + lartesertib 200 mg QD 2 w on/ 2 w off
Tuvusertib 180 mg QD + lartesertib 100 mg QD 2 w on/ 2 w off
Tuvusertib 130 mg QD + lartesertib 100 mg QD 2 w on/ 2 w off
Tuvusertib 130 mg QD + lartesertib 50 mg QD 2 w on/ 2 w off
Tuvusertib 90 mg QD + lartesertib 50 mg QD 2 w on/ 2 w off
Treatment ongoing
Discontinuation reason: adverse event
Discontinuation reason: Death
Discontinuation reason: progressive disease
Discontinuation reason: withdrawal by subject
Discontinuation reason: other
Stable disease (SD)
Progressive disease (PD)
Death

- 42 patients were treated, which is the basis of the safety and preliminary efficacy analyses
- Six patients (2 with ovarian cancer, 2 with uterine cancer, 1 with prostate cancer, 1 with melanoma) had stable disease >16 w. As of 4 January 2024, 3 of these patients remain on treatment

Abbreviations: AE, adverse event; **ATM**, ataxia telangiectasia-mutated; **ATMi**, ATM inhibitor; **ATR**, ataxia telangiectasia-mutated and Rad3-related; **ATRi**, ATR inhibitor; **AUC_{ss}**, area under the curve at steady state; **AUC_{tau}**, area under the curve for dosing interval; **C**, cohort; **D**, day; **DLT**, dose-limiting toxicity; **ECG**, electrocardiogram; **LC/MS**, liquid chromatography/mass spectrometry; **NA**, not applicable; **PD**, pharmacodynamics; **PK**, pharmacokinetics; **PMBCs**, peripheral blood mononuclear cells; **QD**, once daily; **TEAE**, treatment-emergent adverse event; **w**, week.

References: 1. Blackford AN, Jackson SP. *Mol Cell* 2017;66:801–17; **2.** Kantindze OL, et al. *Trends Cancer* 2018;4:755–68; **3.** Turchick A, et al. *Mol Cancer Ther* 2023;22:859–72; **4.** Zimmermann A, et al. *MCT* 2022;21:859–70; **5.** Zimmermann A, et al. *Cancer Res* 2022;82:2588; **6.** Yap T, et al. *Clin Cancer Res* 2024 (epub; doi:10.1158/1078-0432.CCR-23-2409); **7.** Siu L, et al. *Cancer Res* 2023;83:CT171; **8.** Reaper PM, et al. *Nat Chem Biol* 2011;7:428–30.

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