DNA Damage Response Inhibitors (DDRi)

Phase 1 study: tuvusertib—advanced solid tumors

DDRiver™ SOLID TUMORS 301

Tuvusertib is investigational and not approved for use. Niraparib in combination with tuvusertib is not approved for use.
The safety and efficacy of this combination in advanced solid tumors has not been established.
There is no guarantee tuvusertib will be approved in any indication by any health authority worldwide.

Sponsor: Affiliates of Merck KGaA, Darmstadt, Germany

Study design (NCT04170153) [Active, not recruiting]

DDRiver Solid Tumors 301: Phase 1, first-in-human, open-label study

Key eligibility criteria

- Patients with metastatic/locally advanced solid tumors refractory to or not appropriate for standard therapy
- ECOG PS ≤1
- Must have clinically controlled brain metastases that do not include meningeal carcinomatosis
- Patients must be able to comply with restrictions for medications or food

N=161

A1: monotherapy dose escalation to RDE
RDE: 180 mg tuvusertib QD, 2 weeks on/1 week off[1]

Tuvusertib PO QD (fasted)

A2: preliminary food effect assessment

Tuvusertib single-dose PO at RDE[a] (fed/fasted), followed by a 1-week washout

A3: monotherapy expansion

Tuvusertib PO QD at RDE[a] in patients with LOF mutations in *ARID1A*, *ATM*, and *ATRX* and/or *DAXX*

B1a: combination therapy dose finding

Niraparib PO QD + Tuvusertib PO QD (different doses) in patients with baseline body weight <77 kg or platelet <150,000 per mm^3
RDEs:
1.Tuvusertib 90 mg QD + niraparib 200 mg QD 1 week on/1 week off [2]
2.Tuvusertib 180 mg QD + niraparib 100 mg QD 1 week on/1 week off[2]

A4: Japan dose confirmation monotherapy

Tuvusertib PO QD at RDE[a] (fasted)[b]

A5: China dose confirmation monotherapy

Tuvusertib PO QD at RDE[a] (fasted)[b]

B1b: combination therapy dose finding

Niraparib PO QD + Tuvusertib PO QD (B1a RDEs[c] + different doses) in patients with baseline body weight ≥77 kg or platelet ≥150,000 per mm^3

Endpoints

Primary	Parts A1, A4, A5, B1: DLTs, safety, RDE Part A2: PK (fed/fasted) Part A3: OR[d], safety
Secondary	PK/PD, clinical benefit[e], DOR, PFS, OS, OR[d], safety

Study start date
December 2019

Est. primary completion date
January 2026

Locations

Sites in US, China, Japan, Spain and UK

[a]180 mg tuvusertib QD, 2 weeks on/1 week off. [b]Additional schedules may be evaluated if needed. [c]Tuvusertib 90 mg QD + niraparib 200 mg QD 1 week on/1 week off and Tuvusertib 180 mg QD + niraparib 100 mg QD 1 week on/1 week off. [d]Assessed by investigator per RECIST version 1.1. [e]Defined as OR or SD for ≥6 months.
DLT, dose-limiting toxicity; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; Est. estimated; LOF, loss of function; OR, objective response; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; PO, orally; QD, once daily; RDE, recommended dose for expansion; SD, stable disease.
1. Yap TA, et al. *Clin Cancer Res.* 2024;30(10):2057-2067. 2. Yap TA, et al. *J Clin Oncol*. 2024;42(16_suppl).

For more information on this clinical trial, scan the QR code.

EMD SERONO

DNA Damage Response Inhibitors (DDRi)

Phase 1b study: tuvusertib—advanced solid tumors

DDRiver™ SOLID TUMORS 320

Tuvusertib and lartesertib (M4076) are investigational and not approved for use. Lartesertib and avelumab in combination with tuvusertib is not approved for use. The safety and efficacy of this combination in advanced solid tumors has not been established. There is no guarantee tuvusertib and lartesertib (M4076) will be approved in any indication by any health authority worldwide.

Sponsor: Affiliates of Merck KGaA, Darmstadt, Germany

Study design (NCT05396833) [recruiting]

DDRiver Solid Tumors 320: Phase 1b, open-label, multicenter study

Key eligibility criteria

- Patients with unresectable locally advanced or metastatic solid tumors refractory to standard therapy, or for whom no standard therapy is judged appropriate by the investigator, or who cannot tolerate standard of care treatment
- ECOG PS ≤1

N=72

A1: Dose escalation to RDE
RDE: 180 mg tuvusertib QD + 150 mg lartesertib QD, 2 weeks on/2 weeks off[1]

Tuvusertib PO QD + **lartesertib PO QD**
until disease progression, death, discontinuation, or end of study

A1.1: Food effect assessment (low-fat meal)

Tuvusertib PO QD + **lartesertib PO QD**
until disease progression, death, discontinuation, or end of study

A1.2: Relative bioavailability assessment (Tablet vs Capsule)

Tuvusertib PO QD + **lartesertib PO QD**
until disease progression, death, discontinuation, or end of study

A2: LOF in *ATM* in prostate cancer

Tuvusertib PO QD + **lartesertib PO QD** at RDE[a]
until disease progression, death, discontinuation, or end of study

A3: LOF in *ARID1A* in endometrial cancer

Tuvusertib PO QD + **lartesertib PO QD** at RDE[a]
until disease progression, death, discontinuation, or end of study

A2/A3: Tablet (test) versus capsule (reference) formulation

Tuvusertib PO QD + **lartesertib PO QD**
until disease progression, death, discontinuation, or end of study

B1: combination therapy

Tuvusertib PO QD + **avelumab IV QD**
until disease progression, death, discontinuation, or end of study

Endpoints

Primary	Parts A1, B1: DLTs, safety, PD (biomarker) Part A1.1: PK (fed/fasted) Part A1.2: PK Part A2/A3: OR[b], safety
Secondary	Parts A1, B1: PK, ECG changes, OR[b], ADA (part B1 only) Part A1.1: PK (fed/fasted), Part A1.1, A1.2, A2/A3: safety Part A2/A3: PK, DOR[b], clinical benefit[c], PFS[d]

Study start date
June 2022

Est. primary completion date
March 2026

Locations
Sites in US, Canada, Spain, and Republic of Korea

[a]180 mg tuvusertib QD + 150 mg lartesertib QD, 2 weeks on/2 weeks off. [b]Per RECIST v1.1. [c]Defined as OR or SD for ≥6 months; [d]Assessed by investigator per RECIST v1.1, modified according to PCWG-3.
ADA, anti-drug antibody; DLT, dose-limiting toxicity; DOR, duration of response; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; Est. estimated; IV, intravenous; OR, objective response; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; PCWG-3, Prostate Cancer Working Group 3; PO, orally; QD, once daily; RDE, recommended dose for expansion; SD, stable disease.

1. Siu LL, et al. *Cancer Research* 2024;84(7_Supplement):CT063.

For more information on this clinical trial, scan the QR code.

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