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Phase Ib study of elimusertib in combination with niraparib in participants with advanced solid tumors

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INTRODUCTION

- Elimusertib is an orally available, potent, and highly selective inhibitor of the ataxia telangiectasia and Rad3-related (ATR) protein kinase, with anti-tumor activity in preclinical models of various solid tumors and lymphomas[1]
  - ATR is a key regulator of the DNA damage response (DDR) and replication stress response that are essential for cell survival and represents a potential therapeutic target, particularly in tumors with DDR defects[2,3]
- The first-in-human study (NCT03188965) explored 2 different schedules for single-agent elimusertib: 3 days on/4 days off and 3 days on/11 days off
  - In the dose-expansion phase, clinical benefit (stable disease or objective response at 120 days) was reported in 40% (14/35) of participants with ovarian cancer treated with 40 mg twice daily on a 3 days on/4 days off schedule, including participants resistant to platinum and previously treated with a poly ADP-ribose polymerase inhibitor (PARPi)[4]
- Niraparib is a PARPi approved for ovarian cancer in the maintenance setting (regardless of biomarker status) and in the non-maintenance setting (requires appropriate biomarker status)[5,6]
  - Niraparib inhibits PARP-1 and PARP-2, which bind damaged regions of DNA and facilitate proper repair[7]
- Preclinical evidence suggests that combined inhibition of parallel DDR pathways acts synergistically to improve anti-tumor responses[1,8]
- This Phase Ib trial (NCT04267939) will evaluate elimusertib in combination with niraparib for the treatment of participants with advanced solid tumors

STUDY DESIGN AND OBJECTIVES

- This is a Phase Ib, non-randomized, open-label, single-arm, multiphase study of elimusertib in combination with niraparib in participants with recurrent advanced solid tumors
- The primary objectives are to determine the safety, tolerability, maximum tolerated dose (MTD), and/or recommended Phase II dose (RP2D) of elimusertib in combination with niraparib
- The secondary objectives are to obtain a preliminary assessment of anti-tumor activity and to characterize the pharmacokinetics of elimusertib in combination with niraparib
- Exploratory objectives include retrospective biomarker analyses of tumor tissue collected at baseline and cell-free DNA collected at baseline and during treatment

Eligibility

- Select inclusion and exclusion criteria are presented in Table 1

Table 1. Select inclusion and exclusion criteria

Inclusion criteria
Male or female aged ⩾18 years
A histologically confirmed diagnosis of the following indications: • Dose-escalation phase: recurrent advanced solid tumors (excluding prostate cancer due to a licensing constraint), with disease progression after standard-of-care therapy for metastatic disease, with tumor-associated DDR deficiency and/or *CCNE1* gene amplification • Dose-expansion phase: recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer – Sub-population 1: PARPi-naïve with platinum-resistant or refractory disease (recurrence with a platinum-free interval <6 months from last platinum-based regimen) with tumor-associated DDR deficiency; must not have had >3 therapies since the development of platinum resistance – Sub-population 2: disease progression on PARPi (including niraparib) administered as maintenance as well as an active line of therapy; must not have received a further line of therapy after disease progression on PARPi
Disease progression and measurable disease, as defined by RECIST v1.1[9]
Archival tissue <12 months old, otherwise a fresh tumor tissue sample at baseline should be obtained
Eastern Cooperative Oncology Group performance status of 0 or 1
Life expectancy of at least 12 weeks
Adequate bone marrow function (hemoglobin ⩾10 g/dL; platelets ⩾150×10⁹/L; neutrophils ⩾1.5×10⁹/L), organ function (heart, kidney, liver), and coagulation

Exclusion criteria
Inability to swallow oral medication
Any chronic gastrointestinal condition that is known to affect absorption
Significant acute gastrointestinal disorders with diarrhea as a major symptom or CTCAE grade ⩾2 diarrhea of any etiology
Known hypersensitivity to study drugs
History of myelodysplastic syndrome, acute myeloid leukemia, or organ allograft transplantation (including allogenic bone marrow transplant)
Ongoing or active uncontrolled infection of CTCAE grade ⩾2 that requires systemic treatment
Immunocompromised participants
Pleural effusion or ascites that causes respiratory compromise (CTCAE grade ⩾2 dyspnea)
Active hepatitis B or C virus infection that requires treatment
Moderate or severe hepatic impairment (ie, Child-Pugh class B or C)
Previous or concurrent cancer that is distinct in primary site or histology from the cancer being evaluated in this study[a]
Must have recovered from adverse events caused by previous therapies (to CTCAE grade ⩽1)
History of brain or meningeal tumors or active symptomatic or untreated brain metastases
Evidence or history of bleeding disorders
Significant cardiovascular disease
Serious non-healing wound, ulcer, or bone fracture

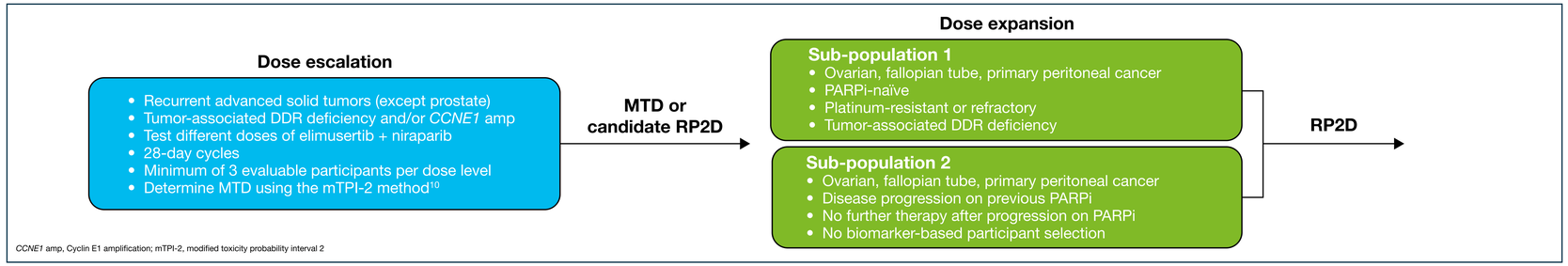
[a]Cervical carcinoma *in situ*, basal cell carcinoma of the skin, and superficial bladder tumors (Ta, Tis, and T1) are acceptable if proper treatment has already been provided and there is no evidence of that disease for >3 years, or if there is a low risk of recurrence

CTCAE, Common Terminology Criteria for Adverse Events; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1

Study outline

- The overall study outline is shown in Figure 1

Figure 1. Schema of the Phase Ib study



CCNE1 amp, Cyclin E1 amplification; mTPI-2, modified toxicity probability interval 2

- Participants will undergo screening to determine eligibility
  - Pre-screening for deleterious DDR gene alterations (dose-escalation and dose-expansion sub-population 1 only)
  - General screening for up to 28 days before study intervention (all participants)
- Following screening, participants will be treated in 28-day cycles
- During dose escalation, dose-limiting toxicities will be evaluated during the first cycle and the optimal dose for evaluation in dose expansion will be determined
- During the dose-escalation phase, the MTD and/or candidate RP2D will be determined using a stepwise dose-escalation design based on the modified toxicity probability interval method[10]
- The optimal dose identified during the dose-escalation phase will be further evaluated in 2 cohorts during the dose-expansion phase, and the final RP2D will be determined through analysis of safety, pharmacokinetics, pharmacodynamic target engagement, and preliminary efficacy
- Treatment will continue until disease progression or unacceptable toxicity, or until another criterion for withdrawal from the study is met

STUDY ENDPOINTS AND EVALUATION

- Tumor response and progression will be evaluated using RECIST v1.1[9]
- Toxicities will be graded using National Cancer Institute CTCAE version 5.0[11]
- Concentration–time courses and pharmacokinetic characteristics will be assessed
- Tumor tissue will be collected at baseline, and cell-free DNA will be collected at baseline and during treatment, for retrospective biomarker analyses
- The study endpoints are shown in Table 2

Table 2. Study endpoints

Primary endpoints	Secondary endpoints	Exploratory endpoints
Safety and tolerability • Incidence and severity of TEAEs, SAEs, and DLTs	**Efficacy** • Per investigator assessment • Incidence of participants with CR, PR, SD, or PD consistent with RECIST v1.1 • Objective response rate • Disease control rate	**Efficacy** • Per investigator assessment • Duration of response • Progression-free survival • Overall survival
Dose finding • Frequency of DLTs in dosing cycle 1 to determine the MTD (dose-escalation part only) • Incidence and severity of TEAEs and SAEs to determine the RP2D	**Pharmacokinetics** • C_{max} and AUC_{0-8} of elimusertib after single-dose and multiple-dose administrations	**Biomarker data** • Retrospective analyses using tumor tissue and cell-free DNA

AUC_{0-8}, area under the curve from 0 to 8 h after dose administration; C_{max}, maximum (or peak) concentration; CR, complete response; PD, progressive disease; PR, partial response; SAE, serious adverse event; SD, stable disease; TEAE, treatment-emergent adverse event

KEY MESSAGES

- **Participants:** Recurrent advanced or metastatic cancers relapsing following standard-of-care therapy, with a focus on biomarker-based participant selection (eg, those with DDR defects)
- **Elimusertib:** Investigational ATR inhibitor currently being investigated as monotherapy (NCT03188965) and in combination with niraparib or chemotherapy
- **Niraparib:** PARPi approved for the treatment of ovarian cancer in maintenance and non-maintenance settings. PARPi have demonstrated anti-tumor activity against several additional cancer types, including those with DDR defects (eg, *BRCA* mutations)
- **Elimusertib + niraparib:** Combined inhibition of ATR and PARP blocks independent DNA repair pathways, resulting in enhanced cytotoxicity in preclinical tumor models that harbor intrinsic DDR deficiencies, increased DNA damage, or replication stress
- **Phase Ib study (NCT04267939):** Non-randomized, open-label trial evaluating the safety, pharmacokinetics, and preliminary efficacy of elimusertib in combination with niraparib for the treatment of participants with advanced solid tumors. This trial is ongoing in the USA

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For more information on this study, please contact TYap@mdanderson.org

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