Debio 0123, a highly selective WEE1 inhibitor in adult patients with advanced solid tumors: a phase 1 dose escalation and expansion monotherapy study

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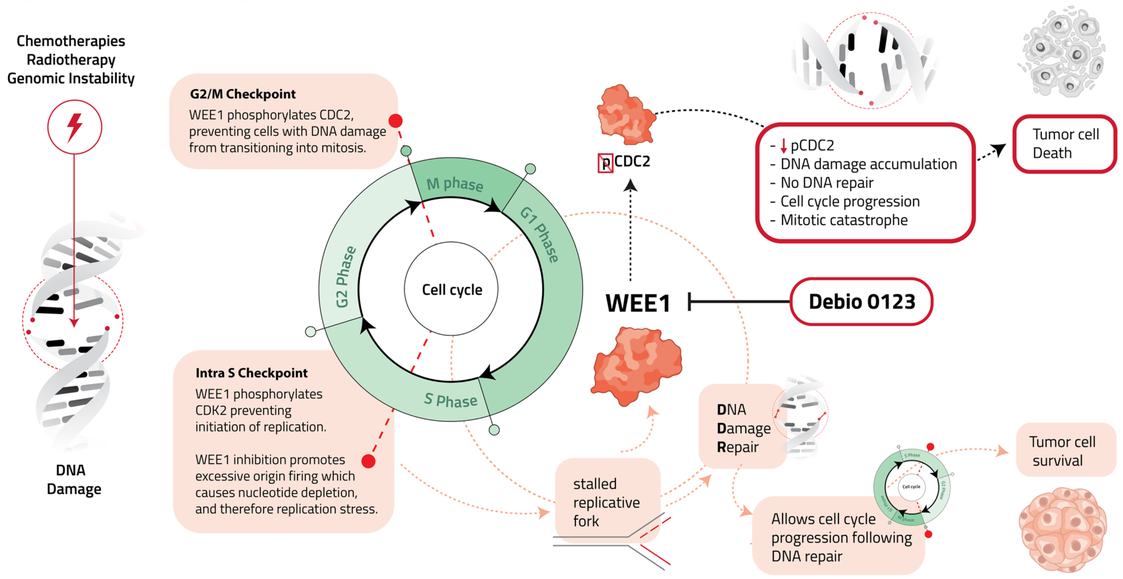
BACKGROUND

Debio 0123 is an oral, brain-penetrant, highly selective inhibitor of WEE1 kinase (Figure 1)

- Defective cell cycle checkpoints are common in many cancers with tumor cells relying on the G2 checkpoint to limit the accumulation of excessive DNA damage[1]
- WEE1, a DNA damage-activated kinase, governs the S-phase and G2/M checkpoints of the cell cycle[2]
- By phosphorylating cyclin-dependent kinase 1 (CDK1, also known as CDC2), WEE1 induces cell cycle arrest and enables DNA repair before cell cycle progression[2]
- WEE1 is therefore an attractive therapeutic target, as its inhibition induces mitotic catastrophe and apoptosis in cancer cells[3]

Figure 1. Debio 0123 a highly selective inhibitor of WEE1 kinase



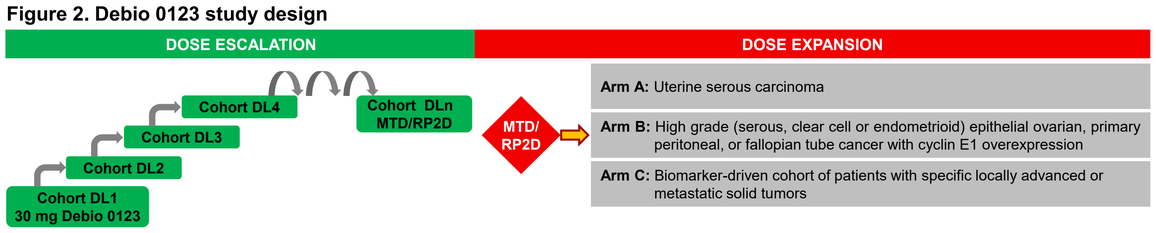
OBJECTIVES

- **The co-primary objective** of the expansion part of this trial was to 1) characterize the safety and tolerability, and 2) evaluate the anti-tumor activity of Debio 0123 when administered as monotherapy at the recommended phase 2 dose (RP2D) determined during the dose escalation of the study
- **Secondary objectives** were to determine other efficacy and pharmacokinetic profiles of Debio 0123 at the RP2D

TRIAL DESIGN

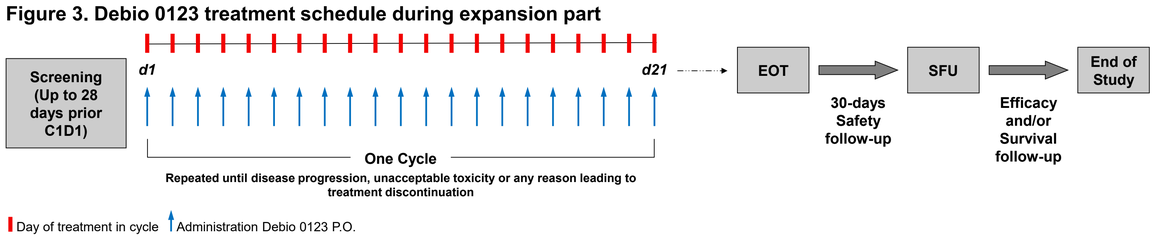
- Debio 0123-102 (NCT05109975) is a phase 1, open-label, multicenter, international study composed of 2 parts (Figure 2):
  - ✓ a dose-escalation part to determine the MTD and/or RP2D of oral Debio 0123 in patients with advanced solid tumors that recurred or progressed following prior therapy and/or for whom no standard therapy of proven benefit is available. Data were presented at ASCO 2024[4]
  - ✓ **a dose expansion part** evaluating the safety, tolerability, pharmacokinetics and preliminary antitumor activity of Debio 0123 in patients who recurred or progressed following prior therapy

Figure 2. Debio 0123 study design



- Patients in the dose expansion part will be treated with Debio 0123 once daily at the RP2D dose of 260 mg over a 21-day cycle (Figure 3)

Figure 3. Debio 0123 treatment schedule during expansion part



- **Sample size for the expansion part**: Up to 40 patients are anticipated to be enrolled in the expansion part of the study. A Bayesian Binomial analysis will estimate the objective response rate (ORR) using a non-informative Jeffreys prior (Beta (0.5, 0.5)). The analysis will be performed independently for each arm.

MAJOR ELIGIBILITY CRITERIA

Inclusion criteria	Exclusion criteria
• Age ≥18 years • ECOG PS 0-1 • Life expectancy of at least 3 months • Adequate organ functions • Measurable disease measured per RECIST version 1.1 • Arm A only ✓ Histologically or cytologically confirmed uterine serous carcinoma that recurred or progressed following at least 1 prior platinum-based line of therapy for management of advanced or metastatic disease • Arm B only: ✓ Histologically or cytologically confirmed, recurrent, high-grade epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer. Tumors must show cyclin-E1-protein overexpression ✓ Patients must have progressed after at least 1 prior platinum-based line of therapy for advanced/metastatic disease ✓ Documented progressive or recurrent disease since the last systemic anti-cancer therapy and prior to trial entry • Arm C only: ✓ Histologically or cytologically confirmed, locally advanced or metastatic solid tumors positive for a specific biomarker ✓ Disease progression under or following standard therapy since last systemic anti-cancer therapy and/or disease for which no effective standard therapy exists, is tolerated, or appropriate	• History of active second malignancies requiring therapy in the last 6 months • Major surgery ≤4 weeks prior to first dose of study treatment • Brain tumors and/or brain metastases • History of cardiac disease • LVEF <55% • QTcF >450 msec, history of congenital long QT syndrome, clinically significant conduction abnormality, or any conduction abnormality that may increase the risk of Torsade de pointe • Known infection requiring the systemic use of an antibiotic or antiviral agent • Inability or unwillingness to swallow oral medications • Clinically significant gastro-intestinal abnormality that would affect the absorption of the drug • Unresolved AEs or toxicities due to previous treatments • Prior exposure to any WEE1 inhibitor

ASSESSMENTS

Assessment	Details
Disease evaluation	• CT scan MRI will be performed at screening, C3D1 and every 12 weeks thereafter until disease progression or start of a new anti-cancer treatment.
Adverse events	• AEs will be monitored from time of inclusion until 30 days after the last dose of Debio 0123 • AEs will be coded according to MedDRA, version 19.0 or later, and summarized per system organ class and preferred term • Severity will be graded per NCI-CTCAE version 5.
Pharmacokinetics	• Blood samples will be taken before and 4 hours after Debio 0123 administration on days 1 and 15 of cycle 1 and 2, then on day 1 of cycles 3 to 5

ANALYSIS

Assessment	Details
Efficacy	• Will be assessed in the patients who received at least 1 dose of Debio 0123 and a measurable disease according to RECIST v 1.1 at baseline and at least one evaluable post-baseline tumor assessment. • Objective response rate, best objective response, and disease control rate will be reported using percentages and corresponding 95% confidence interval • Event rates over time for (time to progression, progression-free survival, duration of response, and overall survival) will be determined using the Kaplan Meier method
Safety	• Will be assessed in the patients who received at least 1 dose (full or partial) of Debio 0123 • TEAEs will be summarized by number and percentage of patients
Pharmacokinetics	• Will be assessed in the patients who received at least 1 dose of Debio 0123 and with at least 1 post dose measurable Debio 0123 concentration • Concentrations of Debio 0123 and N32-desmethyl-Debio 0123 will be measured by LC-MS/MS • Pharmacokinetic parameters will be derived from a population pharmacokinetic approach using non-linear mixed-effects modeling

CURRENT STATUS

- The 260 mg dose (RP2D) of Debio 0123 once daily used in this expansion part of the study was selected based on cumulative safety/antitumor activity, pharmacokinetics, and exposure-response relationships of the dose escalation part[4]
- Enrollment is ongoing in Switzerland, Spain, and United States
- As of the 28-APR-2025, 32 patients have already been treated in the expansion part of the study

ABBREVIATIONS

AE: Adverse event; CDK1: cyclin-dependent kinase 1; CT: Computed tomography; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EOT, end of treatment; LVEF: Left ventricular ejection fraction; MedDRA: Medical Dictionary for Regulatory Activities; MRI: Magnetic resonance imaging; NCI-CTCAE v5.0: National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0; P.O.: per os; QTcF: QT interval corrected using Fridericia's formula; RECIST v.1.1: Response Evaluation Criteria in Solid Tumors version 1.1; RP2D: recommended phase 2 dose; SFU: safety follow-up; TEAE: treatment-emergent adverse event.

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