RESULTS OF A PHASE 1, DOSE-FINDING STUDY OF DEBIO 0123 AS MONOTHERAPY IN ADULT PATIENTS WITH ADVANCED SOLID TUMORS — SAFETY, PHARMACOKINETIC, AND PRELIMINARY ANTITUMOR ACTIVITY DATA

ABSTRACT# 3120

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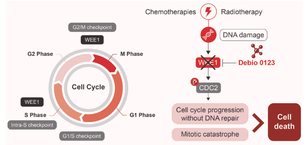
BACKGROUND

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

- Defective cell cycle controls 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 permits 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 is a highly selective inhibitor of WEE1 kinase



WEE1 inhibition reduces the phosphorylation (P) of CDC2, allowing cancer cells to proceed through the cell cycle without DNA damage repair, leading to mitotic catastrophe and cell death.

OBJECTIVES

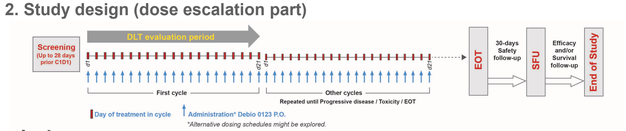
- The primary objective of the dose escalation part of this study was to establish the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) of Debio 0123 when administered daily as monotherapy
- Secondary objectives were to determine the safety, tolerability, pharmacokinetic profiles and preliminary antitumor activity of Debio 0123

STUDY DESIGN OF THE ESCALATION PART AND METHODS

Study design

- Debio 0123-102 (NCT05109975) is a phase 1 dose escalation study evaluating the safety, tolerability, pharmacokinetics and preliminary antitumor activity of Debio 0123 in patients with advanced solid tumors followed by a dose expansion part
- Eligibility criteria in the dose escalation part included patients who had relapsed or progressed following prior therapy and/or for whom no standard therapy was available. Additional eligibility criteria included a life expectancy of ≥3 months and ECOG PS 0-1
- A Bayesian Logistic Regression Model-guided dose escalation of Debio 0123 was performed with a dose range from 30 mg to 350 mg
  - Patients were treated with Debio 0123 once daily, over a 21-day cycle (Figure 2)

Figure 2. Study design (dose escalation part)



Safety analysis

- Safety was assessed on the safety population that included all the enrolled patients who received at least 1 dose of Debio 0123 as per NCI-CTCAE v5.0

Pharmacokinetic and pharmacodynamic analysis

- Pharmacokinetic (PK) analysis was performed on patients' plasma collected over 8 hours on the first day and at steady state on cycle 2 day 1 (C2D1). Samples were analyzed using LC-MS/MS. PK parameters were derived using non-compartmental analysis and population PK model to estimate interindividual variability
- Pharmacodynamic analysis was performed on patient paired skin biopsies, taken pre-dose and on C1D15. Phospho-CDC2 (p-CDC2) levels were assessed in the epidermis by immunohistochemistry. p-CDC2 expression was quantified using H-score and a change from baseline was calculated in evaluable skin biopsy samples

Antitumor activity

- Antitumor activity was assessed according to RECIST v1.1 criteria

RESULTS

Patient demographics

Table 1. Patient demographics (Data cutoff October 24, 2023)

	All patients (N=27)
Mean age, years (range)	63 (45–80)
Sex	
Female (%)	18 (67)
Cancer type, n (%)	
Ovarian cancer	10 (37)
Colon cancer	5 (19)
Others	12 (44)
ECOG PS score, n (%)	
0	17 (63)
1	10 (37)

Safety

- Blood creatine increased and Fredericia-corrected QT (QTcF) prolongation were the most frequent any grade treatment-related adverse events (TRAEs), seen in 10 (37%) patients each (Table 2)
- The most common grade ≥3 TRAEs were QTcF prolongation and fatigue which were seen in 3 (11%) and 2 (7%) patients respectively, and mainly at 350 mg (Table 2)
- Three patients had dose-limiting toxicities: grade 3 fatigue, grade 3 QTcF prolongation (both at a dose of 350 mg) and grade 3 rash (at 260 mg dose)
- A total of 4 (15%) and 7 (26%) patients required dose reductions and treatment interruptions, respectively. Two (7%) patients had treatment discontinuation due to TRAEs
- The MTD was established at 260 mg

Table 2. Treatment-related adverse events

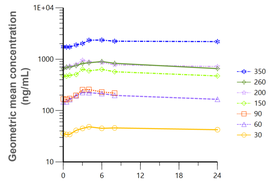
TRAE	Any grade TRAE If ≥ 10% incidence in All Doses		Grade ≥3 TRAE	
	≤ 260 mg (N=21)	All Doses (N=27)	≤ 260 mg (N=21)	All Doses (N=27)
Any TRAE, n (%)	19 (90)	25 (93)	4 (19)	9 (33)
Preferred Term, n (%)				
Blood creatine increased	7 (33)	10 (37)	0	0
QTcF prolongation	6 (29)	10 (37)	0	3 (11)
Nausea	5 (24)	9 (33)	0	0
Vomiting	4 (19)	7 (26)	0	0
QT interval normal[a]	5 (24)	7 (26)	0	0
Dysgeusia	5 (24)	6 (22)	0	0
Fatigue	5 (24)	6 (22)	1 (5)	2 (7)
Diarrhea	4 (19)	5 (19)	0	0
Aspartate aminotransferase increased	2 (10)	4 (15)	0	1 (4)
Lipase increased	2 (10)	4 (15)	0	0
Rash maculo-popular/Rash/Rash papular	4 (19)	4 (15)	1 (5)	1 (4)
Alanine aminotransferase increased	1 (5)	3 (11)	0	1 (4)
Decreased appetite	2 (10)	3 (11)	0	0
Pruritus	3 (14)	3 (11)	0	0

[a]QT interval normal: QTcF is <450 msec but there is a delta from baseline of >30 msec and ≤60 msec

Pharmacokinetics and pharmacodynamics

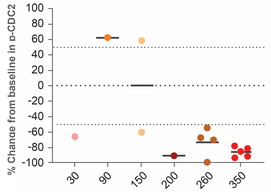
- Debio 0123 plasma exposure increased dose-proportionally from 150 to 350 mg (Table 3)
- The steady state of plasma exposure was achieved after about 15 days of continuous, daily treatment (Figure 3)
- Target engagement (assessed as a reduction in p-CDC2 in paired skin biopsies) was observed consistently from a dose of 200 mg (Figure 4)
- A relationship between exposure expressed as AUC over the cycle and the relative change from baseline in p-CDC2 was observed (Figure 5 – compilation of two studies)

Figure 3. Steady state pharmacokinetic plasma exposure of Debio 0123 at C2D1



Profiles shown are mean values per dose level (mg)

Figure 4. Debio 0123 inhibits CDC2 phosphorylation



Each dot represents a single patient

Efficacy

Debio 0123 preliminary antitumor activity

- Stable disease for ≥5 weeks was the best overall response seen in 8 (32%) patients (Figure 6)
- Two patients with ovarian cancer had 17% and 20% reductions respectively in target lesions (Figure 7) despite requiring dose reductions after the first cycle; one of these also had a CA-125 response
- A trend was observed between Debio 0123 exposure and tumor shrinkage (not shown)

Figure 6. Swimmer plot showing duration of responses to treatment with Debio 0123

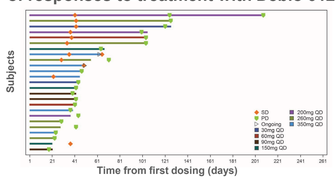
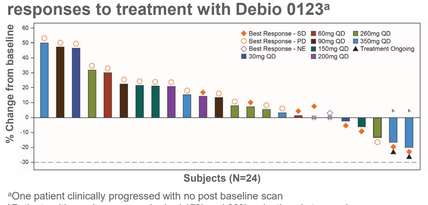


Figure 7. Waterfall plot showing best overall responses to treatment with Debio 0123[a]



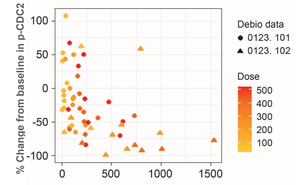
[a]One patient clinically progressed with no post baseline scan
[b]Patients with ovarian cancer who had 17% and 20% reductions in tumor size

Table 3. Estimated pharmacokinetic parameters per dose level

Dose (mg)	N	C_{max}[a] (µmol/L)	AUC_{24}[a] (µmol.h/L)
30	2	0.01	0.18
60	2	0.04	0.40
90	2	0.05	0.78
150	3	0.11	0.93
200	3	0.16	1.02
260	6	0.13	1.05
350	1	0.37	3.87

[a]Main Debio 0123 parameters (geometric mean) derived from the population PK model at steady state. Data are summarized per dose level

Figure 5. Exposure-response relationship



Based on data from the current study and another one with a 3 days on 18 days off schedule in monotherapy

CONCLUSIONS

- Continuous daily dosing of Debio 0123 as a monotherapy was well tolerated up to 260 mg with a manageable safety profile. The MTD was declared at 260 mg
- Debio 0123 displayed dose proportional pharmacokinetics
- The RP2D of 260 mg once daily was selected based on cumulative safety/antitumor activity, pharmacokinetics, and exposure-response relationships
- A 3-arm expansion phase, including biomarker-selected cohorts, is now ongoing. Arm A includes patients with recurrent uterine serous carcinoma. Arm B includes patients with high-grade epithelial ovarian cancer with high cyclin E1. Arm C is a biomarker-driven cohort

ABBREVIATIONS

AUC, area under the serum concentration curve vs. time; AUC24, AUC for 0–24 hours; C, cycle; CDK1, cyclin-dependent kinase 1; C_{max}, maximum peak serum concentration; D, dose; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EOT, end of treatment; MTD, maximum tolerated dose; NCI-CTCAE v5.0, National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0; NE, not evaluable; p-CDC2, phospho-CDC2; PD, progressive disease; QD, once daily; QTcF; Fredericia-corrected QT; RECIST v.1.1, Response Evaluation Criteria in Solid Tumors version 1.1; P.O., per os (orally); RP2D, recommended phase 2 dose; SD, stable disease; SFU, safety follow-up; TRAE, treatment-related adverse event.

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