DEBIO 0123-101, A PHASE 1 TRIAL OF DEBIO 0123 IN COMBINATION WITH CARBOPLATIN IN ADVANCED SOLID TUMORS: SAFETY, PHARMACOKINETIC, AND PRELIMINARY ANTITUMOR ACTIVITY DATA

ABSTRACT #3012

Hans Gelderblom[1], Mathilde Jalving[2], Ingrid Desar[3], Omar Saavedra[4], Jourik A. Gietema[2], Stefan van Ravensteijn[3], Nina Ajmone Marsan[1], Anne Bellon[5], Sandrine Micallef[5], Noemie Luong[5], Luke Piggott[5], Rikke Frederiksen Franzen[5], Esteban Rodrigo Imedio[5]

[1]Leiden University Medical Center, Leiden, The Netherlands; [2]University Medical Center Groningen, Groningen, The Netherlands; [3]Radboud University Medical Centre, Nijmegen, The Netherlands; [4]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [5]Debiopharm International SA, Lausanne, Switzerland

BACKGROUND

Debio 0123, an oral, brain-penetrant and highly selective inhibitor of the WEE1 kinase

- WEE1, a DNA damage-activated kinase, governs the G2/M cell cycle checkpoint, arresting the cell cycle to allow for DNA repair (Fig. 1)[1]
- Cells often rely on G2/M to avoid excess DNA damage accumulation[2]
- WEE1 is an attractive therapeutic target, as its inhibition, combined with mounting DNA damage, can induce mitotic catastrophe and apoptosis[3]
- Debio 0123 is a selective, potent, orally available ATP-competitive, brain-penetrant WEE1 inhibitor that has previously shown a proportional increase in target engagement from 150 mg in patient skin biopsies[4,5]

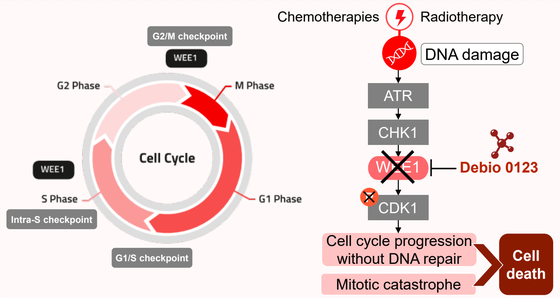


Figure 1. WEE1 inhibition reduces the phosphorylation (P) of CDK1, allowing cancer cells to proceed through the cell cycle with DNA damage, leading to mitotic catastrophe and cell death.

METHODS

- Debio 0123-101 is a Phase 1, dose-escalation study of Debio 0123 in patients (pts) with advanced solid tumors that recurred or progressed after platinum-containing therapy, where no standard therapy of proven benefit is available
- Approximately 60 pts are planned to be treated in this dual-arm study
  - In Arm A, Debio 0123 monotherapy is given in Cycle (C) 1 (Day [D] -3 and D1 to D3), then in combination with carboplatin (CP) from C2 (D1 to D3) until end of treatment (EOT)
  - In Arm B, Debio 0123 is given with CP (D1 to D3 and D8 to D10) from C1 to EOT
  - CP is given on D1 of each 21-day cycle in both arms

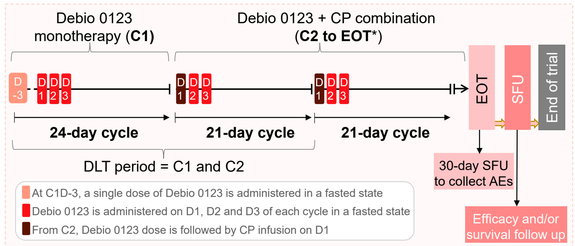


Figure 2. Arm A dose administration schedule of study treatment per dose level. *Maximum treatment duration is 2 years. DLT period = first two cycles (one mono- and one combination therapy cycle). Abbreviations: AE, adverse event; D, day; DLT, dose-limiting toxicity; EOT, end of treatment; SFU, safety follow up.

- Inclusion criteria include prior use of platinum-based therapy, a life expectancy of ≥3 months and an ECOG performance score of 0–1
- Exclusion criteria include a history of other malignancies requiring active treatment in the last 6 months, presence of brain tumors and/or symptomatic brain metastases and receipt of other investigational agents
- In Arm A, dose escalation is guided using a continual reassessment method; maximum tolerated dose (MTD) is defined as the highest dose level showing an acceptable estimated dose limiting toxicity (DLT) rate (<40%) (Fig. 3, Fig. 4)

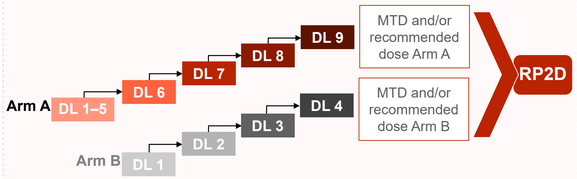


Figure 3. Debio 0123-101 dose escalation design. At initiation, Arm B DL 1 is one DL lower than the highest DL shown to be safe in Arm A. RP2D will be based on overall safety, efficacy, pharmacodynamic and pharmacokinetic data. Abbreviations: DL, dose level; MTD, maximum tolerated dose; RP2D, recommended Phase 2 dose.

STUDY OBJECTIVES

PRIMARY OBJECTIVE

Determine the recommended Phase 2 dose (RP2D) of Debio 0123 when administered in combination with CP

SECONDARY OBJECTIVES

Evaluate the safety, tolerability, pharmacokinetics and tumor response with Debio 0123

RESULTS

Patient demographics

- Arm A data with a cut-off date of April 30th 2023 is presented
- Overall, 38 pts were treated in Arm A; 2 pts continue treatment
- Most (78.9%) pts were female and the mean age was 59 years
- The most common primary solid tumor location was ovarian cancer (36.8%)

Debio 0123 combined with CP was well tolerated in Arm A

- The worst grade of Debio 0123-related treatment-emergent adverse events (TEAEs) were grade 1/2 in most pts
- Debio 0123-related TEAEs occurred in 68.4% of pts over all dose levels tested
- Serious Debio 0123-related TEAEs occurred in 10.5% of pts over all dose levels tested

Debio 0123-related TEAEs, n (%)	All pts (n=38)		Pts who received ≥200 mg (n=22)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Thrombocytopenia/ ↓ platelet count	12 (31.6)	3 (7.9)	11 (50.0)	3 (13.6)
Nausea	12 (31.6)	0	9 (40.9)	0
Anaemia	8 (21.1)	1 (2.6)	6 (27.3)	1 (4.5)
Normal QT interval	8 (21.1)	0	6 (27.3)	0
Fatigue	7 (18.4)	0	4 (18.2)	0
Leukopenia	5 (13.2)	1 (2.6)	4 (18.2)	1 (4.5)
Vomiting	5 (13.2)	0	5 (22.7)	0
Neutropenia/ ↓ neutrophil count	4 (10.5)	1 (2.6)	2 (9.1)	0
Electrocardiogram QT prolonged	3 (7.9)	1 (2.6)	3 (13.6)	1 (4.5)
Constipation	3 (7.9)	0	3 (13.6)	0
Dyspepsia	3 (7.9)	0	2 (9.1)	0
Alanine aminotransferase ↑	3 (7.9)	0	1 (4.5)	0
Aspartate aminotransferase ↑	2 (5.3)	1 (2.6)	0	0
Lipase ↑	2 (5.3)	1 (2.6)	0	0
Ejection fraction ↓	2 (5.3)	0	0	0
Diarrhoea	2 (5.3)	0	1 (4.5)	0
Gamma-glutamyltransferase ↑	2 (5.3)	0	1 (4.5)	0

The maximum tolerated dose (MTD) of Debio 0123 was 520 mg

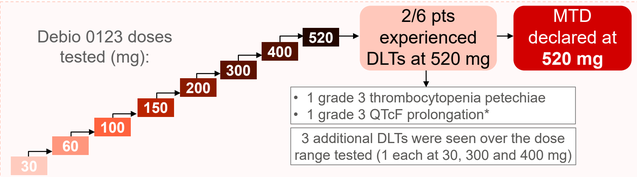
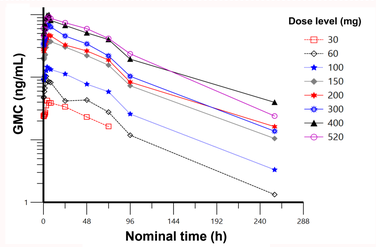


Figure 4. Dose-escalation of Debio 0123 to determination the MTD. Abbreviations: DLT, dose-limiting toxicity; MTD, maximum tolerated dose. *Pt with normal QTcF interval <450 msec and Δ 60.1 msec; pt ongoing.

Arm A pharmacokinetic (PK) and pharmacodynamic data

- PK analysis shows that Debio 0123 plasma levels and exposure parameters increase proportionally with dose



DL (mg)	N	C_{max} (ng/mL)	T_{max}* (h)	AUC_{24} (h*ng/mL)	T1/2 (h)	AUC_{INF} (h*ng/mL)
30	4	42	4	852	47	3117
60	4	108	3	1648	51	5868
100	3	163	4	2961	54	11300
150	4	397	5	7838	57	31815
200	4	491	5	9361	66	40534
300	3	718	5	13220	58	49286
400	9	980	4	18353	61	79986
520	5	954	6	19287	54	84479

Figure 5. PK analysis of Debio 0123 in Arm A. The graph shows geometric mean concentrations (GMC) of Debio 0123 over time after 3 daily doses. PK parameters of Debio 0123 after 3 daily doses (geometric mean, unless otherwise noted) are shown in the table. Median of T_{max} is reported. Abbreviations: AUC, area under the curve; DL, dose level; GM, geometric mean; PK, pharmacokinetics.

- Paired skin biopsies collected at baseline and C1D3 were analysed by immunohistochemistry for pCDK1; clear target engagement was observed from 150 mg, becoming more pronounced with increasing dose

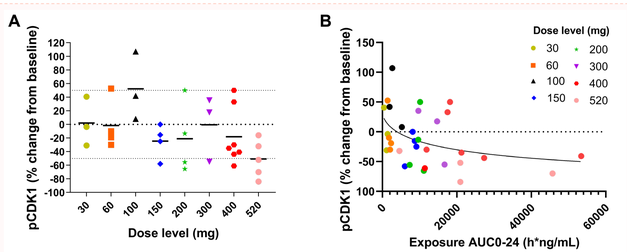


Figure 6. Changes in pCDK1 from baseline at increasing dose levels in skin biopsies. (A) Percentage change in H-score from biopsies collected following 3 daily doses of Debio 0123 from baseline. Each point represents change in a paired biopsy and mean indicated as a line; **(B)** Percentage of pCDK1 reduction vs Debio 0123 exposure (AUC_{24h}) following 3 days treatment with Debio 0123 (C1D3). The curve represents a non-linear regression.

Debio 0123 shows antitumor activity when combined with CP in pts with solid tumors who progressed with prior platinum-based chemotherapy

- 4/12 pts with platinum-resistant ovarian cancer had a PR; 1 pt is ongoing
- Median duration of response was 10.9 months

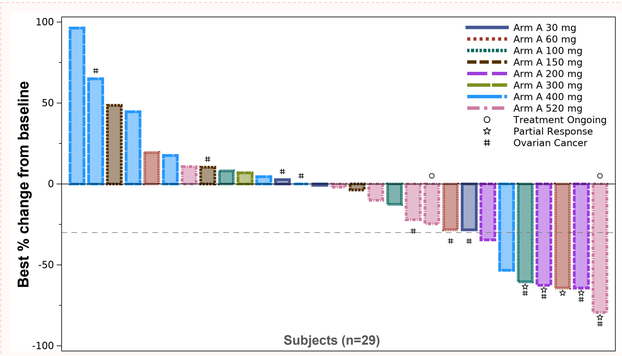


Figure 7. Sum of the longest diameters. Each bar represents an individual pt.

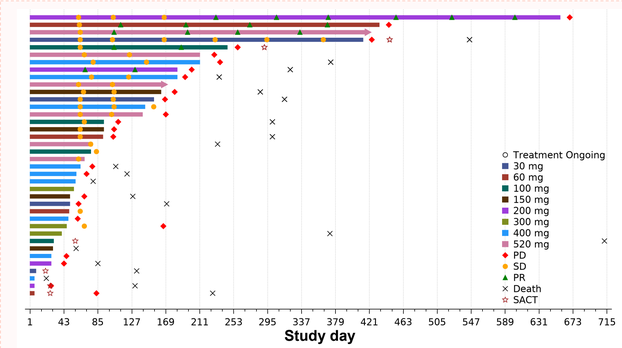


Figure 8. Treatment duration and tumor response per RECIST 1.1. Each bar represents an individual pt. Abbreviations: PD, progressive disease; PR, partial response; SACT, systemic anticancer therapy; SD, stable disease.

CONCLUSIONS

- **Debio 0123, in combination with CP, is well tolerated up to 520 mg and demonstrates a manageable safety profile like that for CP monotherapy**
- **Debio 0123 shows dose-proportional increases in exposure and evident target engagement from 150 mg that became more pronounced with higher doses**
- **The Debio 0123-CP combination led to antitumor activity in pts with cancers who had progressed with previous platinum-based chemotherapy, including confirmed responses in pts with platinum-resistant ovarian cancer**
- **Further evaluation of therapeutic Debio 0123 is warranted and dose escalation with a more intense schedule (Arm B) is currently ongoing**

REFERENCES

1. Squire CJ, et al. *Structure*. 2005;13:541–50.
2. Bucher & Britten. *Br J Cancer*. 2008;98:523–528
3. Di Rorà A, et al. *J Hematol Oncol*. 2020;13:126.
4. Gelderblom H, et al. *Poster at ESMO 2022* (84P)
5. Piggott L, et al. *Poster at AACR 2023* (#6185)

ACKNOWLEDGEMENTS

This study is funded by Debiopharm International SA. The authors would like to thank Marie-Laurence Yge for significant contribution to the project. Editorial assistance was provided by Dr Georgia Greaves at Cancer Communications & Consultancy Ltd.

DEBIO 0123 CLINICAL TRIALS

Debio 0123 is in Phase I clinical investigation as a monotherapy (NCT05109975), in combination with CP in advanced solid tumors (NCT03968653), in combination with temozolomide -/+ radiotherapy in glioblastoma (NCT05765812) and in combination with CP and etoposide in small cell lung cancer (NCT05815160).

STUDY CONTACTS

esteban.rodrigoimedio@debiopharm.com / rikke.frederiksenfranzen@debiopharm.com