Debio 0123, a highly selective WEE1 inhibitor, in combination with carboplatin (C) and etoposide (E), in patients with recurrent small cell lung cancer (SCLC): determination of recommended dose (RD) from a phase 1 escalation

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BACKGROUND

Small cell lung cancer (SCLC)

- SCLC is an aggressive disease with poor prognosis, carrying a high mutational burden and genomic instability, with a high incidence of brain metastases [1]
- Limited treatment options are currently available for recurrent SCLC beyond lurbinectedin, topotecan, or rechallenge with platinum-based chemotherapy [2]
- The prognosis for recurrent SCLC patients remains poor and new therapies to improve current standard options are needed

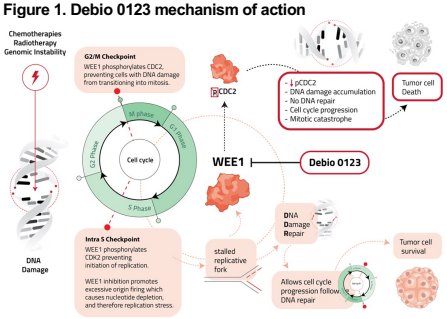
WEE1 kinase and Debio 0123

- WEE1 kinase, a key regulator of the S phase and G2/M cell cycle checkpoints, activates the DNA damage response (DDR) pathway before mitotic entry [3]
- The DDR pathway is often upregulated in cancer cells and blocking this pathway renders cells more vulnerable to DNA damage-inducing therapies [4]
- WEE1 inhibition leads to S phase and G2/M checkpoints abrogation, permitting mitosis without DNA repair, leading to mitotic catastrophe and subsequent cell death [5]

Debio 0123

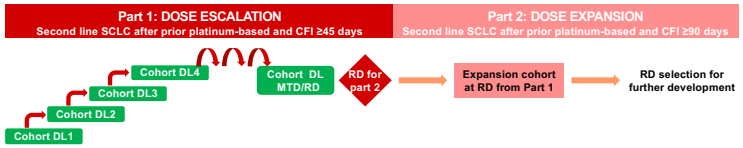
- Debio 0123 is an oral, brain-penetrant, highly selective, small-molecule WEE1 inhibitor (Figure 1)

Figure 1. Debio 0123 mechanism of action



STUDY DESIGN

- Debio 0123-SCLC-104 (NCT05765812) is a phase 1 interventional, non-randomized, open-label, multicentre study evaluating Debio 0123 combined with carboplatin (C) plus etoposide (E) in patients with recurrent SCLC after 1st line of platinum-based chemotherapy



Population

- Recurrent SCLC patients after 1st line of platinum-based chemotherapy, with ECOG 0-1 and adequate organ function. Patients must not have other cancer, symptomatic brain metastases, cardiac disease, gastrointestinal abnormality impacting absorption of orally Is drugs, or active infection disease.

Treatment

- 21-day cycle:
  - ✓ Debio 0123: P.O., 200, 300, or 400 mg, D1-D3 and D8-D10
  - ✓ Etoposide: IV, 100 mg/m^2, D1-D3
  - ✓ Carboplatin: IV, AUC5, D1

Methodology

- A Bayesian Logistic Regression Model-guided dose escalation of Debio 0123 was performed with a dose range from 200 to 400 mg

Objectives of the dose escalation part

- The **primary objective** was to identify the recommended dose (RD) and to characterize the safety and tolerability of Debio 0123 in combination with carboplatin and etoposide
- The **secondary objectives** were to assess the preliminary antitumor activity and pharmacokinetics of Debio 0123 in combination with carboplatin and etoposide

Debio 0123 combined with carboplatin and etoposide is **well tolerated** and leads to **antitumor activity** in patients with **recurrent SCLC** after platinum-based therapy

Abstract #: 8098

ABBREVIATIONS

AJCC, American Joint Committee on Cancer; AUC, Area under the curve; C, Carboplatin; CDC2, Cell division control 2; CDK2, Cyclin dependent kinase 2; CFI, Chemotherapy-free interval; CI, Confidence interval; CSF, Cerebrospinal fluid; DDR, DNA damage response; DL, Dose level; E, Etoposide; IV: Intravenous; ND, Not reached; NE, Not Evaluable; P.O.: Oral; PD, Progressive disease; PFS, Progression-free survival; PR, Partial response; Rad. PD, Radiographic progression; RD, Recommended dose; SCLC, Small cell lung cancer; SD, Stable disease; TEAE, Treatment emergent adverse event.

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RESULTS

At data cut off (28 March 2025), 16 patients (mean age of 63.3 years, 7 [43.8%] females) were treated with Debio 0123 at dose levels of 200 mg (N=10), 300 mg (N=3) and 400 mg (N=3). SCLC stages (AJCC) were IV (8 patients [50.0%]), IVA (2 [12.5%]), and IVB (6 [37.5%]).

Figure 1: PK profiles of Debio 0123 on C1D10

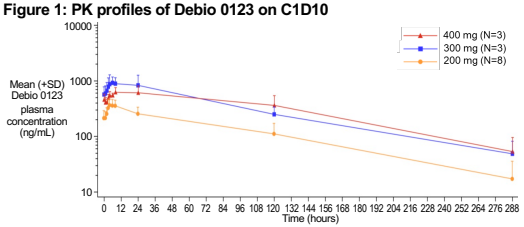


Table 1: Brain penetration of Debio 0123

Dose level	N	Mean CSF/plasma ratio (%)
200 mg	5	34
300 mg	2	35
400 mg	2	40
Overall	**9**	**36**

N: number of patients
CSF/plasma ratio = (concentration of Debio 0123 in CSF / concentration of free fraction of Debio 0123 in plasma) * 100

Table 2: Treatment-related adverse events seen in ≥10% of patients overall

	Any grade		Grade ≥3	
Preferred Term	RD (200 mg) (N=10) n (%)	All doses (N=16) n (%)	RD (200 mg) (N=10) n (%)	All doses (N=16) n (%)
Any Debio 0123-Related TEAE	9 (90.0)	14 (87.5)	4 (40.0)	8 (50.0)
Neutropenia/Neutrophil count decrease	4 (40.0)	6 (37.5)	3 (30.0)	5 (31.3)
Thrombocytopenia/Platelet count decreased	2 (20.0)	3 (18.8)	1 (10.0)	2 (12.5)
Anaemia	2 (20.0)	4 (25.0)	0	2 (12.5)
Asthenia/Fatigue/Malaise	1 (10.0)	3 (18.8)	0	0
Nausea	3 (30.0)	5 (31.3)	0	0
Diarrhoea	2 (20.0)	2 (12.5)	1 (10.0)	1 (6.3)
Vomiting	1 (10.0)	3 (18.8)	0	0
ALT increased/AST increased	1 (10.0)	2 (12.5)	0	1 (6.3)
Lipase increased	1 (10.0)	2 (12.5)	0	0

Figure 2: Treatment duration and tumor response (N=16)

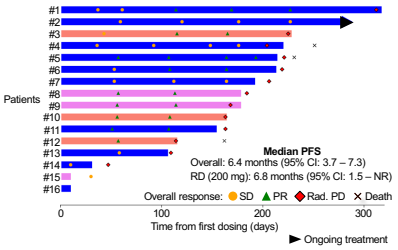
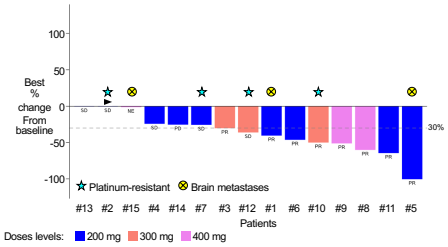


Figure 3: Best percentage change from baseline (N=15)



CONCLUSION

- Manageable safety profile of Debio 0123 (up to 200 mg [RD]) + C + E in line with the expected profile for platinum-based chemotherapy rechallenge
- Debio 0123 CSF/plasma ratio of about 40% suggests Debio 0123 ability to cross the blood-brain-barrier
- Promising antitumor activity at RD in platinum-sensitive (CFI ≥90 days) (n=7; 4 PR, 2 SD; ORR=57%) and platinum-resistant (CFI ≥45 and <90 days; 2 SD) patients with recurrent SCLC (including stable brain metastases at baseline) after prior platinum-based therapy
- Further investigation of Debio 0123 at 200 mg in patients with a CFI ≥90 days is ongoing