DEBIO 0123, A SELECTIVE, BRAIN PENETRANT WEE1 INHIBITOR IN CLINICAL DEVELOPMENT FOR PATIENTS WITH SOLID TUMORS

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SUMMARY

The WEE1 tyrosine kinase is activated upon DNA damage and is a key regulator of cell cycle progression. It influences entry into mitosis by modulating activity of cyclin-dependent kinase 1 (CDK1, also referred to as cell division cycle 2 [CDC2]). Inhibition of WEE1, in conjunction with additional genetic alterations and/or in addition to DNA damaging agents, results in mitotic catastrophe and apoptosis of cancer cells, and is an attractive approach for treating cancer[1].

Debio 0123 is an investigational, orally-available, selective ATP-competitive WEE1 inhibitor. Its main characteristics are an IC50 on WEE1 in the low nanomolar range, high selectivity, in particular lacking PLK1 and PLK2 inhibition, and good efficacy in animal models in several tumor types, as monotherapy or in combination with DNA damaging agents, such as etoposide and carboplatin.

Debio 0123 is being investigated in five clinical studies, as monotherapy and in combination with chemotherapy or targeted therapies, in patients with solid tumors. The drug has been considered well tolerated and safety profile manageable so far, with initial signals of antitumor activity. At the doses tested so far, a consistent pharmacodynamic effect on the downstream marker pCDC2 has been observed, suggesting target engagement.

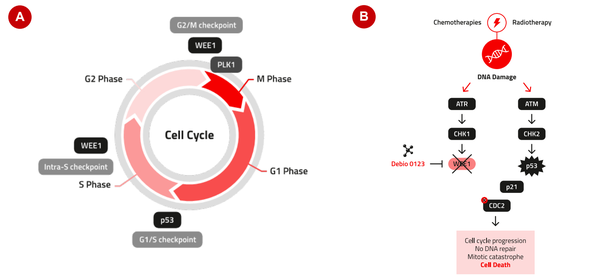


Figure 1. (A) Cell cycle checkpoints. In cancer cells, DDR pathways (such as ATM and ATR) are often upregulated due to genomic instability. WEE1 is a key regulator of the G2/M and S-phase checkpoints where it leads to cell cycle arrest allowing DNA damage repair. **(B) WEE1 inhibition.** Inhibition of WEE1 reduces the phosphorylation of CDC2 (CDK1) permitting cells to proceed through the cell cycle with an accumulation of DNA damage leading to mitotic catastrophe and ultimately cell death.

METHODS

The preclinical studies were conducted in accordance with institutional guidelines and NCRI Guidelines for the welfare and use of animals in cancer research[2].

Mouse xenograft models: NSCLC model: Briefly, 1x10^7 A427 tumor cells in 50% Matrigel were injected subcutaneously (sc) into the flank of male athymic nude mice. Animals were randomly assigned to treatment groups when tumors reached approximately 150 mm^3. **SCLC model**: Five x 10^6 NCI-H1048 SCLC tumor cells were inoculated in the flank of Balb/c female mice. **GBM model:** Male athymic nude mice were injected intracranially (i.c.) with 1x10^5 U87-MG-luc cells in Matrigel. **Animal treatment**: Animals were randomly assigned to treatment groups when tumors reached approximately 100-150 mm^3. Debio 0123 was orally administered once a day for up to 28 consecutive days (30mg/kg QD), carboplatin was administered once a week for up to 3 weeks (50mg/kg QW) and etoposide was administered once a week for up to 3 weeks (25mg/kg or 12.5mgkg QW)

***In vivo* brain exposure (Figure 3):** Plasma and brain exposures of Debio 0123, AZD1775 (adavosertib), and Zn-C3 (azenosertib) were assessed in healthy male Nu/Nu mice and healthy male Wistar Han rats (Debio 0123 only). Mice were treated orally, for four consecutive days, either with 30 mg/kg Debio 0123 once daily, 30 mg/kg AZD1775 twice daily on days 1 to 3 and once on day 4, or 80 mg/kg Zn-C3 once daily. Rats were treated with a single dose of 15 mg/kg Debio 0123. At designated time-points, terminal plasma and brain samples were collected. Plasma and brain homogenates were analyzed by LC-MS/MS to determine the test item concentrations.

Immunohistochemistry (IHC): Tumor and skin biopsies embedded in FFPE blocks were kept at 4ºC to preserve the phospho epitope. Staining for pCDC2 was performed using the pCDC2 (Tyr15) rabbit mAb (CST #4539). The histopathological evaluation was performed by a blinded pathologist

REFERENCES

(1) Do K. et al., Cell Cycle. 2013 Oct 1;12(19):3159-64
(2) Workman et al., British Journal of cancer. (2010) 102, 1555-1577
Additional data were published in the following posters (available on www.debiopharm.com/medias/publications)
- O'Dowd et al., AACR 2019 abstract #4423
- Gelderblom et al., ESMO 2020, abstract #3893
- Piggott et al., AACR 2022 abstract #4894, AACR 2023 abstract #6185
- Gelderblom et al., ASCO 2023 abstract #3012
- Papadopoulos et al., ASCO 2022 #TPS2702
- Gelderblom et al., ESMO 2022 abstract #84P
- Roth et al., SNO abstract RTID-03

PRECLINICAL ACTIVITY – IN VITRO

Debio 0123 is a selective and orally available ATP-competitive inhibitor of the WEE1 kinase

WEE1 acts at both the G2/M and S-phase checkpoints making WEE1 inhibition amenable to combination with multiple chemotherapies with different mechanism of actions. Debio 0123 is a highly selective and potent WEE1 inhibitor[2]. Compared to AZD1775 and ZN-c3, Debio 0123 does not inhibit PLK1 or PLK2

High potency and selectivity

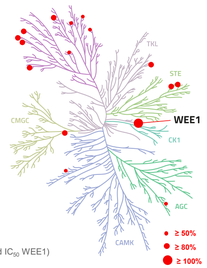
Target	Debio 0123 IC_{50} (nM)	AZD1775 IC_{50} (nM)	ZN-c3 IC_{50} (nM)[4]
WEE1	0.8	3.9	3.8

IC_{50} on WEE1 (ADP-competitive binding assay)

More selective than other WEE1i on PLK1/2

Target	Debio 0123 IC_{50} (nM)	AZD1775 IC_{50} (nM)	ZN-c3 IC_{50} (nM)[4]
PLK1	> 10 000	79	227
PLK2	> 10 000	79	40

IC_{50} on PLK1 and PLK2 (kinome screen) — Studies conducted using versions of AZD1775 and Zn-C3 synthesized by third-party contract research chemists, using publicly available information



Source: O'Dowd et al., AACR 2019 #4423[3].

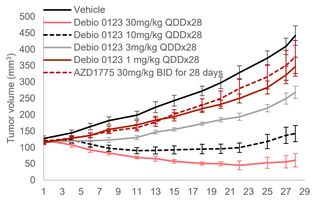
Figure 2. Cell free potency and selectivity profile screening at fixed concentration of 500nM (>100-fold IC_{50} WEE1)

PRECLINICAL– IN VIVO ACTIVITY

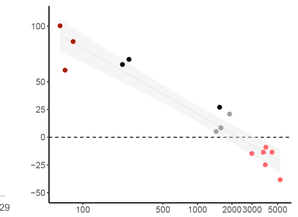
Debio 0123 induces tumor regressions in a NSCLC cancer model

When administered orally once daily for 28 consecutive days, Debio 0123 induced dose-dependent anti-tumoral activity and was well tolerated at all doses tested. At 30 mg/kg, treatment with Debio 0123 resulted in tumor regression.

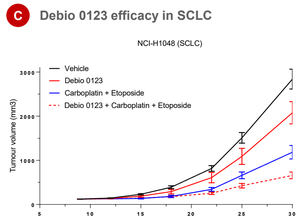
A Debio 0123 induces dose dependent antitumoral effects



B Debio 0123 exposure-efficacy relationship



C Debio 0123 efficacy in SCLC



D Debio 0123 efficacy in GBM

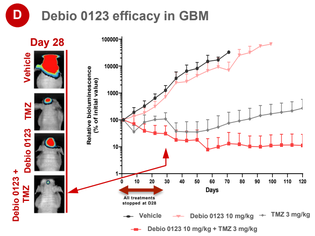
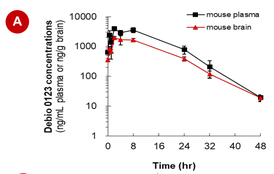


Figure 3: A) Tumor volumes over the 28 days treatment period. Values shown are mean tumor volumes +/-SEM **B) Debio 0123 exposure-efficacy relationship**. Values shown are individual % T/C Value = [(individual tumor volume on Day 28 – individual starting volume) / (mean vehicle tumor volume on Day 28 – mean vehicle starting volume)] X100 as a function of Debio 0123 plasma concentration at 3h post last dose in corresponding animals, for all the tested dose levels. The black dotted line indicates the threshold for tumor regression. **C) Debio 0123 shows potent antitumor efficacy *in vivo* in combination with carboplatin/etoposide.** NCI-H1048 tumors were treated with 30mg/kg QD Debio 0123, 12.5mg/kg QW etoposide/ 50mg/kg QW carboplatin alone or in combination (n=10). **D) Debio 0123 shows potent antitumor efficacy *in vivo* in combination with Temozolomide.** Mice bearing U87-MG-luc tumors implanted intracranially were treated with 10mg/kg QD Debio 0123, 3mg/kg TMZ QD alone or in combination (n=8) and tumor growth monitored through luminescence imaging (representative examples of images following 28 days of each treatment group shown in left panel)

PRECLINICAL – IN VIVO BRAIN PENETRATION

Debio 0123 crosses the BBB in animal species

Following oral administration of 30 mg/kg QDx4 Debio 0123 in mice or 15 mg/kg single dose, in rats, concentration data show that Debio 0123 is able to cross the BBB and distributes into the brain. The brain to plasma AUC ratios of Debio 0123 were 0.49 in mice, and 0.60 in rat. Moreover, the brain to plasma AUC ratio in mice was over 10-fold higher for Debio 0123 than AZD1775 (ratio of 0.048) or Zn-C3 (ratio of 0.028), demonstrating Debio 0123´s favorable brain penetration properties.



C

	Debio 0123	AZD1775	Zn-C3
Brain to plasma ratio	0.49	**0.05**	**0.03**

Figure 4 (A) Debio 0123 exhibits favorable brain exposure properties in rodents compared to AZD1775 or Zn-C3. (A) Mouse plasma and brain exposures (n=3 per timepoint) of Debio 0123 on day 4, following 30 mg/kg oral, once daily administration of Debio 0123. (B) Rat plasma and brain exposures of Debio 123 following a single oral dose of 15 mg/kg Debio 0123. (C) Brain to plasma ratios comparison of WEE1 inhibitors in mice.

CLINICAL DEVELOPMENT

Debio 0123 is currently under phase 1 clinical investigation as a monotherapy (Debio 0123-102, NCT05109975) and in combination with chemotherapy in patients with advanced solid tumors (Debio 0123-101, NCT03968653, Debio 0123-104, NCT05815160, Debio 0123-105, NCT05765812).

Debio 0123-102 is a phase 1 study of Debio 0123 given as monotherapy in adult subjects with advanced solid tumors.

Debio 0123-101 is a phase 1 study of Debio 0123 in combination with carboplatin, in adult subjects with advanced solid tumors that recurred or progressed following prior platinum therapy. In Arm A, Debio 0123 is given for the first 3 days every cycle (21 days), as monotherapy in the first cycle, and then in combination with carboplatin of each subsequent cycle. In Arm B, a more intense dosing schedule is investigated.

Debio 0123-104: is a phase 1 study of Debio 0123 in combination with carboplatin + etoposide, in adult subjects with small cell lung cancer (SCLC) that recurred or progressed after previous standard platinum-based therapy.

Debio 0123-105: is a phase 1/2 study of Debio 0123 in combination with TMZ +/-RT, in adult subjects with recurrent or newly diagnosed glioblastoma.

CLINICAL DEVELOPMENT – SAFETY

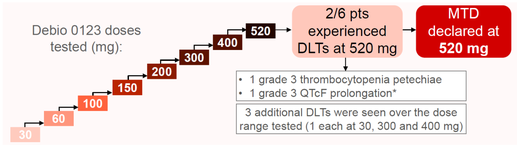


Figure 5. Dose escalation of Debio 0123 in Debio 0123-101 study to determine MTD in combination with carboplatin in arm A. *Pt with normal QTcF interval <450 msec and Δ 60.1 msec; remained on study until progression. DLT, dose-limiting toxicity; MTD, maximum tolerated dose.

TEAEs in >10% patients, n (%)	All Patients N=38		200-520mg N=22	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Thrombocytopenia	12 (31.6)	3 (7.9)	11 (50)	3 (13.6)
Nausea	12 (31.6)	0	9 (40.9)	0
Anaemia	8 (21.1)	1 (2.6)	6 (27.3)	0
Normal QT interval	8 (21.1)	0	4 (18.2)	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)	1 (2.6)	3 (13.6)	0

Figure 6. TEAEs in Debio 0123 101 ARM A combination carboplatin study

Safety profile:
- Not adding significant toxicity over carboplatin monotherapy
- Infrequent Grade 3 TRAEs across all doses evaluated
- Preliminary therapeutic range 200-520mg range

Manageable safety profile:
- Minimal dose reductions
- Serious TEAEs occurred in 10.5% of pts across all doses tested
- Grade 3 QT prolongation with normal QTcF interval <450 msec and Δ 60.1 msec; remained on study for >25 cycles

CLINICAL DEVELOPMENT – ANTITUMOR ACTIVITY

33% response rate observed in platinum-resistant ovarian cancer patients

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

4/12 patients with platinum-resistant ovarian cancer had a PR

Median duration of response was 10.9 months

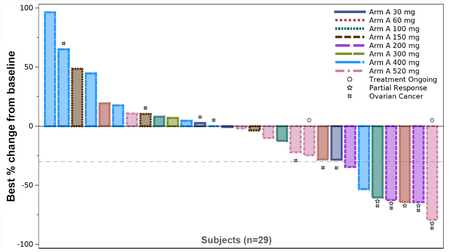


Figure 7. Sum of the longest diameters. Each bar represents an individual patient

CLINICAL DEVELOPMENT – PK/PD

Reduction of pCDC2 and PK/PD relationship in paired skin biopsies

In the Debio 0123-101 trial Arm A, paired skin biopsies were collected during the study (baseline and C1D3/post-treatment) and were analyzed by IHC for pCDC2. A consistent signal reduction was observed from the 150 mg dose level onwards, becoming more pronounced with increasing dose levels.

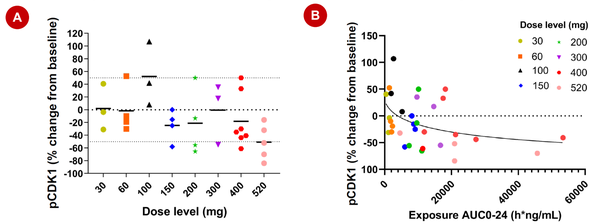


Figure 8. pCDC2 detection in skin biopsies. Baseline biopsies, skin and/or tumor, are taken prior treatment start. Post-treatment biopsies are taken on cycle 1 after 3 days administration of Debio 0123 (C1D3). **(A) pCDC2 change from baseline at increasing dose levels.** Percentage change in H-score from biopsies collected following 3 daily doses of Debio 0123 from baseline. Each point represents change in a paired biopsy. The line in each column represents the mean. **(B) PK/PD relationship across increasing dose levels.** Percentage of pCDC2 reduction vs Debio 0123 exposure (AUC_{24}) following 3 days treatment with Debio 0123 (C1D3). The curve represents a non-linear regression calculated in GraphPad Prism.

CONCLUSIONS

- Debio 0123 is a selective and orally available and brain penetrant inhibitor of WEE1 kinase that shows efficacy as monotherapy and displays strong exposure-efficacy relationship.
- Debio 0123 significantly improves response to standard of care treatments, carboplatin/etoposide in SCLC and TMZ in GBM, *in vivo*.
- Debio 0123 is being explored in 5 clinical trials, as monotherapy and in combination with carboplatin in solid tumors, TMZ in GBM, carboplatin/etoposide in SCLC and lunresertib.
- In clinical samples, target engagement is observed with up to 86% pCDC2 reduction and becomes more robust through increasing dose levels, showing a positive correlation with exposure in plasma.

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