DEBIO 0123, A SELECTIVE 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 currently being tested in two clinical studies, as monotherapy and in combination with carboplatin, in patients with advanced solid tumors. At the highest doses tested so far, a consistent pharmacodynamic effect on the downstream marker pCDC2 has been observed, suggesting target engagement.

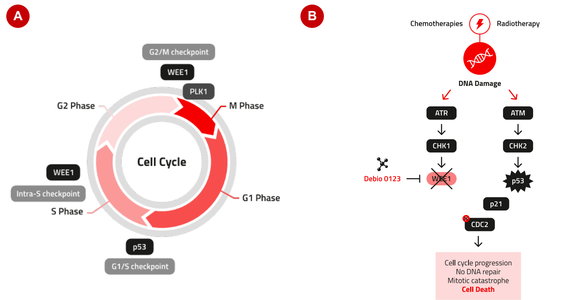

Figure 1. (A) Cell cycle checkpoints. In cancer cells, DDR pathways (such as ATM and ATR) are often upregulated due to genomic instability. WEE1 is a key regulator of the G2/M and S-phase checkpoints where it leads to cell cycle arrest allowing DNA damage repair. **(B) WEE1 inhibition.** Inhibition of 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. **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)

Western blot (WB): Effects of Debio 0123 on downstream signaling were analyzed by WB in tumor lysate. Antibody references: tCDC2: CST #9116S, pCDC2 (Tyr15): CST #9111s, phospho histone H2A.X: CST #2577s and B-Actin: CST 12620S.

Immunohistochemistry (IHC): Tumor and skin biopsies embedded in FFPE blocks were kept at 4°C 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
- Papadopoulos et al., ASCO 2022 abstract #TPS2702
- Gelderblom et al., ESMO 2022 abstract #84P

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, Debio 0123 does not inhibit PLK1 or PLK2.

High potency and selectivity

IC_{50} on WEE1: 0.8nM

Selective against 450 kinases (500nM)

More selective than competition

Target	AZD1775 IC_{50} (nM)	Debio 0123 IC_{50} (nM)
WEE1	43	41
PLK1	79	> 10 000
PLK2	79	> 10 000

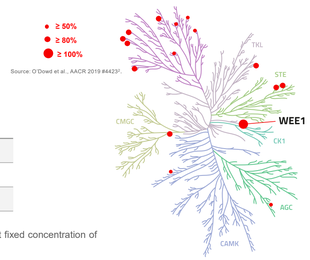

Figure 2. Cell free potency and selectivity profile screening at fixed concentration of 500nM (>100-fold IC_{50} WEE1)

PRECLINICAL ACTIVITY – IN VIVO MONOTHERAPY

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.

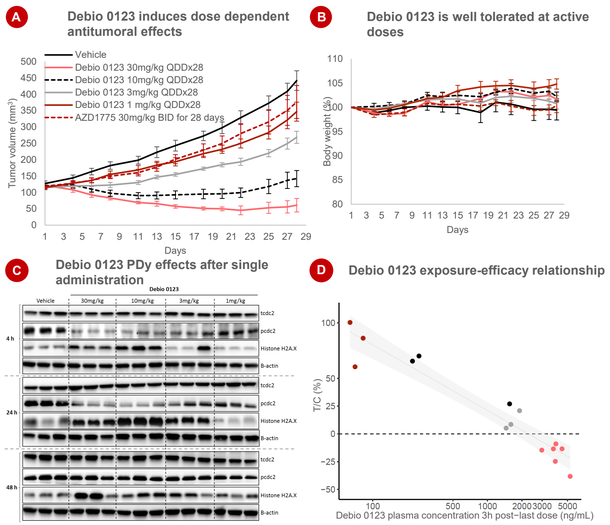

Figure 3: A) Tumor volumes and **B) Body weight** over the 28 days treatment period. Values shown are mean tumor volumes +/-SEM (A) and mean percent of body weight change (%) +/-SEM (B), N=6 animals per group. **C) Effects on downstream cellular markers after one administration**. Tumor-bearing animals received one single administration of Debio 0123. Tumors were collected at 4h, 24h, and 48h post administration. Expression of the indicated proteins was assessed by Western blot analysis. Quantification of P-CDC2/total CDC2, γH2AX levels at 4h, 24h and 48. N=3 animals per group, all 3 animals are shown. **D) 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.

PRECLINICAL ACTIVITY – IN VIVO COMBINATION

Debio 0123 improves SCLC response to carboplatin and etoposide *in vivo*

The NCI-H1048 model was used to evaluate the efficacy and tolerability of Debio 0123 in combination with carboplatin and etoposide as a triple combination. Debio 0123 monotherapy resulted in a moderate anti-tumor response and SOC carboplatin/etoposide treatment resulted in a significant inhibition of tumor growth. Triple combination of Debio 0123, carboplatin and etoposide resulted in a significant anti-tumor response compared to vehicle (TGI 72%, p<0.01), Debio 0123 monotherapy (TGI 68%, p<0.01) and carboplatin/etoposide (TGI 44%, p<0.01) treatments. All treatments were well tolerated with no significant body weight loss in the treated animals.

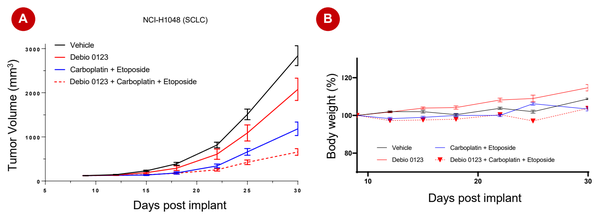

Figure 4 Debio 0123 shows potent antitumor efficacy *in vivo* in combination with carboplatin/etoposide. (A) NCI-H1048 tumors were treated with 30mg/kg QD Debio 0123, 12.5mg/kg QW etoposide/ 50mg/kg QW carboplatin alone or in combination (n=10). **(B)** Relative mean body weight during treatment.

CLINICAL DEVELOPMENT – TRIAL DESIGN

Debio 0123 is currently under phase I clinical investigation as a monotherapy (Debio 0123-102, NCT05109975) and in combination with carboplatin in patients with advanced solid tumors (Debio 0123-101, NCT03968653).

Debio 0123-102 is a phase 1, multi-center, open-label, dose escalation study of Debio 0123 given as monotherapy. More details on the trial design were published in Papadopoulos et al., ASCO 2022.

Debio 0123-101 is a phase 1, multi-center, open-label, dose escalation study of Debio 0123 in combination with carboplatin, in 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 only, and then in combination with carboplatin of each subsequent cycle. In Arm B, a more intense dosing schedule is investigated. Optional paired tumor and/or skin biopsies were collected during the study when patients consented and where feasible.

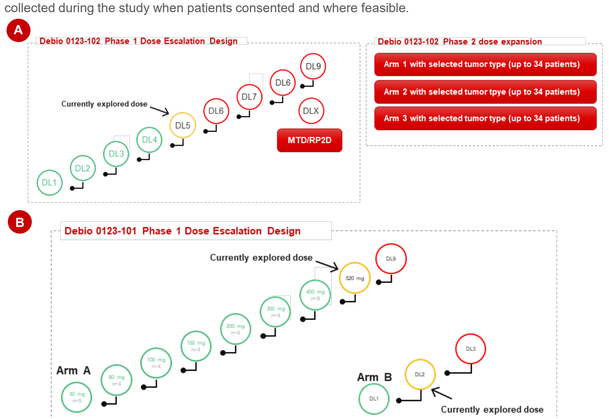

Figure 5. Trial design. (A) Debio 0123-102 (monotherapy): The trial has a mCRM (modified continual reassessment method) design, with a DLT period over 21 days. At the end of the DLT period of each cohort, mCRM provides a recommendation regarding the next dose level to be used for the next cohort, based on a power model. Dose level 5 is currently explored. **(B) Debio 0123-101 (combination with carboplatin):** The trial has a mCRM design, with a DLT period over 45 days. At the end of the DLT period of each cohort, mCRM provides a recommendation regarding the next dose level to be used for the next cohort, based on a power model. The currently explored dose in Arm A is 520mg

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.

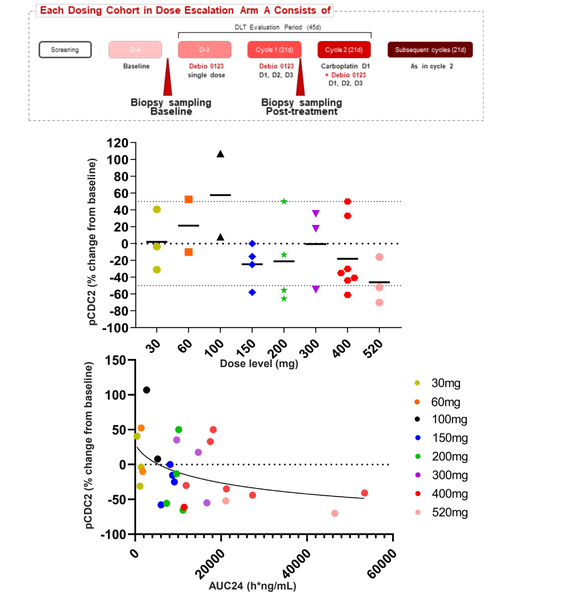

Figure 6. pCDC2 detection in skin biopsies. (A) Details of DLT period and biopsy sampling timepoints in Debio 0123-101 Arm A. Baseline biopsies, skin and/or tumor, are taken prior treatment start, usually on day -4 (D-4). Post-treatment biopsies are taken on cycle 1 after 3 days administration of Debio 0123 (C1D3). **(B) 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. **(C) 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 ATP-competitive inhibitor of WEE1 kinase that shows efficacy as monotherapy in a preclinical NSCLC model and displays strong exposure-efficacy relationship.
- Debio 0123 significantly improves response to standard of care carboplatin/etoposide treatment *in vivo* in a model of SCLC and is well tolerated.
- Debio 0123 is being explored in 2 ongoing clinical trials, as monotherapy and in combination with carboplatin.
- In clinical samples, target engagement is observed starting from the dose of 150mg and becomes more robust through increasing dose levels, showing a positive correlation with exposure in plasma.

CONTACT

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