PHARMACODYNAMIC MARKER MODULATION OF THE SELECTIVE WEE1 INHIBITOR DEBIO 0123 IN PATIENT BIOPSIES FROM PHASE 1 CLINICAL TRIAL.

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SUMMARY

Debio 0123 is an investigational, orally bioavailable, highly selective, adenosine triphosphate (ATP)-competitive inhibitor of the WEE1 tyrosine kinase. WEE1 is a key regulator of cell cycle progression at both the G2/M and S phases of the cell cycle. At G2/M WEE1 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 presents an opportunity as a therapeutic strategy in cancer, either as monotherapy or in combination with other therapies[1], by inducing a reduction of phosphorylated CDC2 (pCDC2) and driving cancer cells prematurely into mitosis leading to mitotic catastrophe and apoptosis. Here we present data on modulation of pharmacodynamic marker pCDC2 upon treatment with Debio 0123 in tumor and skin biopsies from patients in Arm A of the Debio 0123-101 (NCT03968653) study (after 3 days of treatment), across all dose levels explored so far. In paired skin biopsies, a consistent reduction in pCDC2 was observed starting at the dose level 150 mg, becoming more pronounced with increasing doses. A correlation could be observed between Debio 0123 plasma exposure and pCDC2 reduction. Currently, a more intense dosing schedule is also being tested in Arm B. Overall, these data suggest Debio 0123 target engagement from a dose of 150mg onwards when administered for 3 days, being more pronounced at higher doses.

BACKGROUND

Debio 0123 mechanism of action

WEE1 acts at both the G2/M and S-phase checkpoints and is activated when DNA damage occurs or when cells undergo replication stress. At the G2/M checkpoint, CDC2 is phosphorylated by WEE1 and is inactive. When CDC25 dephosphorylates CDC2, or when WEE1 is inhibited, active CDC2 binds to cyclin B, which promotes entry into mitosis. Debio 0123 is a selective WEE1 inhibitor that affects the phosphorylation of CDC2 and forces the progression through the cell cycle despite the presence of DNA damage or replication stress. These properties make Debio 0123 amenable to combination with multiple chemotherapies with different mechanisms of action[1].

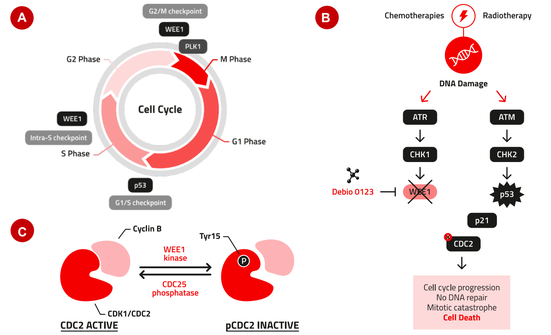

Figure 1. (A) Cell cycle checkpoints. In cancer cells. Wee1 is a key regulator of the G2/M and S-phase checkpoints where it leads to cell cycle arrest allowing DNA damage repair. **(B) WEE1 inhibition.** Inhibition of WEE1 reduces the phosphorylation of CDC2 (CDK1) permitting cells to proceed through the cell cycle with an accumulation of DNA damage leading to mitotic catastrophe and ultimately cell death. **(C) CDC2 activation**. When WEE1 is active, CDC2 is phosphorylated on tyrosine 15, cannot interact with Cyclin B and is inactive. Upon cell cycle reactivation, phosphatase CDC25 dephosphorylates CDC2, which allows the interaction with Cyclin B and allow the cell to progress through the cycle.

PHARMACODYNAMIC MARKER METHODS

Preclinical studies were performed for validation of antibodies, surrogate tissue and methods to be used in the Debio 0123-101 clinical trial. All studies were conducted in accordance with institutional and NCRI Guidelines for the welfare and use of animals in cancer research[2].

Western blot (WB): NCI-H1048 tumors were analysed by WB at 20µg/lane using CDC2 mouse mAb (CST #9116S), pCDC2 (Tyr15) rabbit mAb (CST #4539) and ACTB rabbit mAb (LI-COR 926-42210) as loading control.

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.

PHARMACODYNAMIC MARKER VALIDATION

Effect of Debio 0123 and PK/PD relationship in preclinical models has been presented in a previous publication[3]. To validate skin as a reliable surrogate tissue for monitoring Debio 0123 activity on pCDC2, tumor and skin tissues was assessed from NCI-H1048 SCLC xenografts treated with Debio 0123. Following Debio 0123 treatment, a significant reduction of pCDC2, by WB and IHC, was observed in tumors. An equivalent reduction was observed by IHC in the epidermal layer of the skin, demonstrating skin as a suitable surrogate tissue for target engagement upon treatment with Debio 0123.

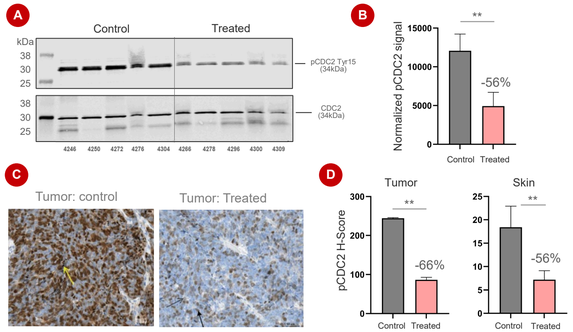

Figure 2. pCDC2 reduction in NCI-H1048 xenograft. (A) Detection of pCDC2 by western blot in tumors from mice treated for 3 days with 50mg/kg of Debio 0123 or control mice (treated with vehicle). Each column represents an independent tumor. **(B) Quantification of pCDC2 from (A)** normalized to total CDC2 levels. **(C) Representative images of IHC obtained from tumors** taken from animals treated with vehicle control or Debio 0123 as in (A). **(D) H-score quantification of pCDC2 signal** in tumor and skin samples obtained from animals treated as in (A), n=5 ±SEM

CLINICAL TRIAL DESIGN AND BIOPSY SAMPLING

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, 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.

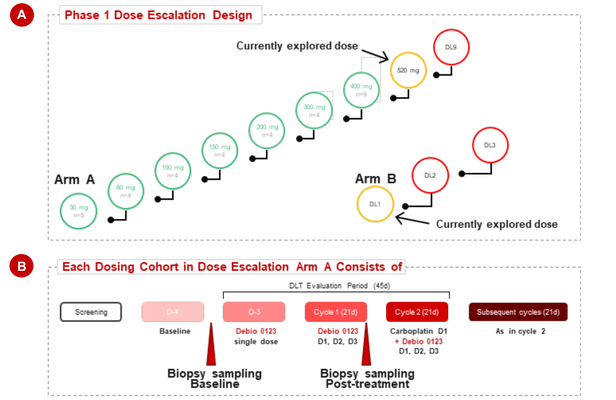

Figure 3. (A) Trial design. The trial has a mCRM design, with a DLT period over 45 days. At the end of the DLT period of each cohort, mCRM provides a recommendation regarding the next dose level to be used for the next cohort, based on a power model. The currently explored dose in Arm A is 520mg. **(B) Details of DLT period and biopsy sampling timepoints in 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).

RESULTS

Reduction of pCDC2 in paired skin biopsies

Paired skin biopsies collected during the study (baseline and C1D3) were analysed by IHC for pCDC2. A consistent signal reduction was observed from the 150 mg dose level onwards, becoming more pronounced with increasing dose levels.

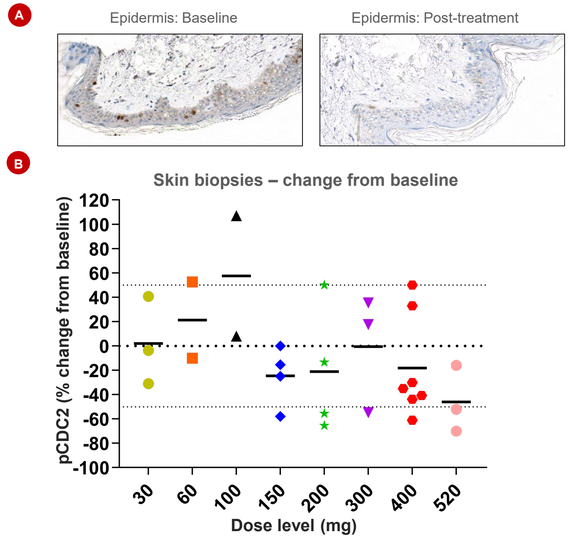

Figure 4. pCDC2 detection in skin biopsies. (A) Representative images of pCDC2 staining by IHC in paired skin biopsies. (B) pCDC2 change from baseline at increasing dose levels. Percentage change in H-score from biopsies collected following 3 daily doses of Debio 0123 from baseline. Each point represents change in a paired biopsy. The line in each column represents the mean.

CLINICAL TRIALS

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).

ACKNOWLEDGMENTS

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CONFLICTS OF INTEREST

First author declares no conflict of interest.

Study is sponsored by Debiopharm.

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(2) Workman et al., British Journal of cancer. (2010) 102, 1555-157
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PK/PD relationship in skin biopsies

PK parameters were calculated after 3 daily administration of Debio 0123. A correlation is observed between exposure (AUC_{24h}) at cycle 1 day 3 (C1D3) and percentage decrease in pCDC2 from baseline.

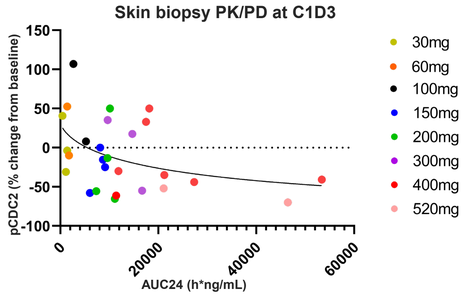

Figure 5. PK/PD relationship across increasing dose levels. Percentage of pCDC2 reduction vs Debio 0123 exposure (AUC_{24h}) following 3 days treatment with Debio 0123 (C1D3). The curve represents a non-linear regression calculated in GraphPad Prism.

Target engagement in tumors

Paired tumor biopsies are collected following patient consent and where feasible. pCDC2 is detected by IHC, similarly to skin biopsies. A reduction in pCDC2 (up to 64%) has been observed in some tumors following 3 daily doses of Debio 0123, further indicating target engagement. In Figure 6, we show an example of reduction seen in one patient treated at the dose of 400mg.

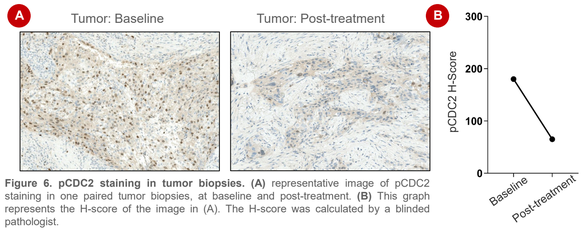

Figure 6. pCDC2 staining in tumor biopsies. (A) representative image of pCDC2 staining in one paired tumor biopsies, at baseline and post-treatment. **(B)** This graph represents the H-score of the image in (A). The H-score was calculated by a blinded pathologist.

CONCLUSIONS

- Preclinical studies have demonstrated that skin is a good surrogate tissue for the detection of WEE1 inhibition activity by analysing pCDC2 levels.
- pCDC2 reduction has been observed in both skin and tumor tissue obtained from patients following Debio 0123 treatment, indicating target engagement.
- 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.

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