FIRST-IN-HUMAN PHASE 1 STUDY OF A NOVEL ORAL WEE1 INHIBITOR (DEBIO 0123) IN COMBINATION WITH CARBOPLATIN IN PATIENTS WITH ADVANCED SOLID TUMORS

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ABSTRACT #3893

BACKGROUND

The Wee1 tyrosine kinase is activated upon DNA damage and regulates the G2-M cell cycle checkpoint. Inhibition of Wee1, in conjunction with additional genetic alterations and/or addition of a DNA damaging agent, results in mitotic catastrophe and apoptosis of cancer cells, being an attractive approach for treating cancer. Debio 0123 is a potent and highly specific WEE1 inhibitor with an IC_{50} in the low nanomolar range. Debio 0123 was demonstrated to inhibit phospho-CDC2 which translated into an increase in DNA damage and premature entry into mitosis (AACR 2019, abstract 4423[1]). Debio 0123 combination with carboplatin was synergic in vitro. In vivo, Debio 0123 was demonstrated to increase antitumoral activity of carboplatin in models where neither agent was active alone.

Wee1, a central player in cell cycle and DNA damage response

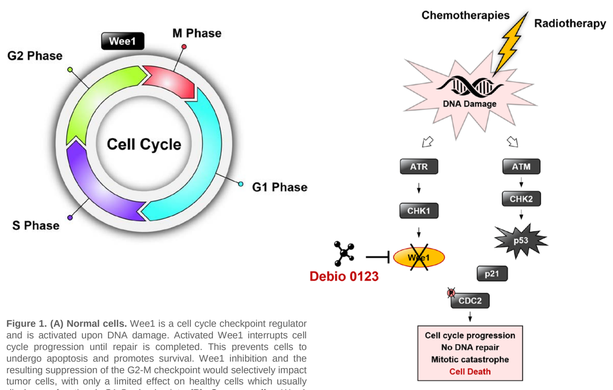


Figure 1. (A) Normal cells. Wee1 is a cell cycle checkpoint regulator and is activated upon DNA damage. Activated Wee1 interrupts cell cycle progression until repair is completed. This prevents cells to undergo apoptosis and promotes survival. Wee1 inhibition and the resulting suppression of the G2-M checkpoint would selectively impact tumor cells, with only a limited effect on healthy cells which usually display a functional G1-S checkpoint. **(B) Cancer cells.** Wee1 inhibition leads to cell-cycle progression despite unrepaired DNA damage with subsequent induction of cell death,

Debio 0123 is active in combination with carboplatin

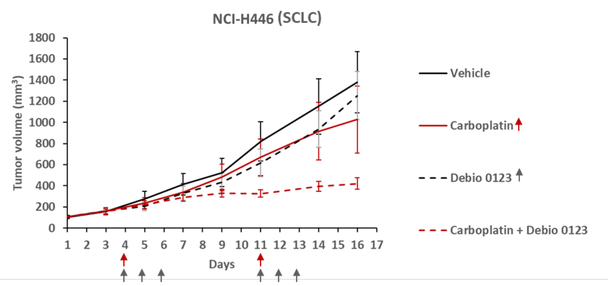


Figure 2. Anti-tumor activity of Debio 0123 combined with carboplatin in the subcutaneous NCI-H446 xenograft model in BALB/c nude mice. Carboplatin was administered iv once a week at 50 mg/kg (red arrows) and Debio 0123 was administered per oral gavage at 30 mg/kg for 3 consecutive days each week, starting on the day of Carboplatin (black arrows). Values shown are mean tumor volumes +/-SEM, N=5 animals per group.

TRIAL DESIGN

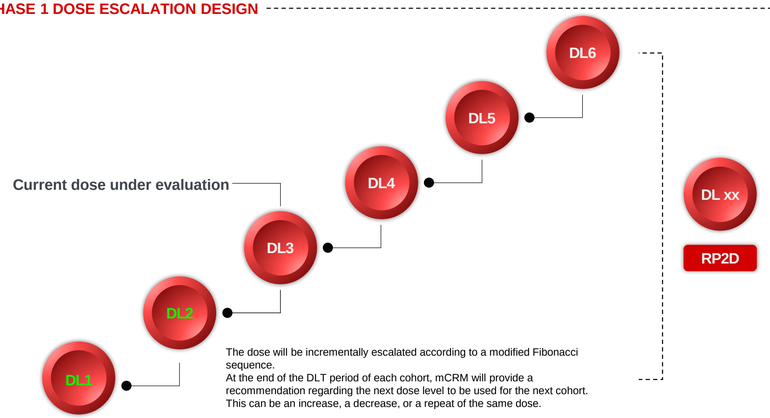
Methods

This is a phase 1, multi-center, open-label, dose escalation study of Debio 0123 as monotherapy (first cycle only) and in combination with carboplatin, from cycle 2 in subjects with advanced solid tumors that recurred or progressed following prior platinum therapy.

Primary objective: determination of the recommended phase 2 dose (RP2D) of Debio 0123 when administered in combination with carboplatin using a modified Continual Reassessment Method (mCRM). Patients receive Debio 0123 orally once daily for the first 3 days of a 21-day cycle as monotherapy during first cycle and in combination with carboplatin in following cycles.

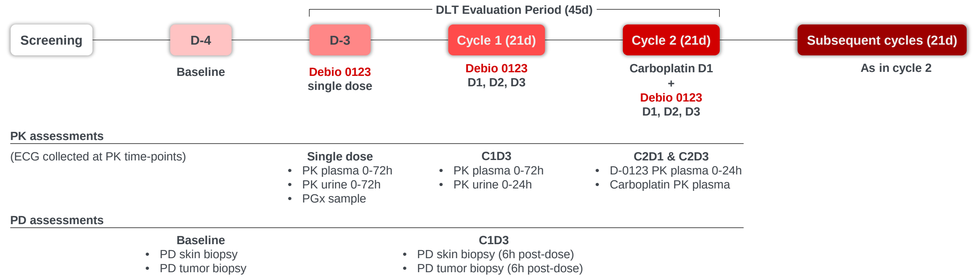
Secondary objectives: includes determination of occurrence of dose-limiting toxicities (DLT) and characterization of the pharmacokinetics of Debio 0123 and its active metabolite, which are evaluated after single and repeated administration when administered alone or in combination with carboplatin. Potential risk of QTc prolongation is evaluated by exposure-response modeling. Pharmacodynamics biomarkers including phospho-CDC2 are explored in pre- and post-treatment tumors and skin biopsies. Recruitment started in July 2019. Cohort 2 has been completed.

PHASE 1 DOSE ESCALATION DESIGN



The dose will be incrementally escalated according to a modified Fibonacci sequence.
At the end of the DLT period of each cohort, mCRM will provide a recommendation regarding the next dose level to be used for the next cohort.
This can be an increase, a decrease, or a repeat of the same dose.

EACH DOSING COHORT IN DOSE ESCALATION CONSISTS OF



STUDY ENDPOINTS

Primary

- Determine the Recommended Phase 2 Dose (RP2D) of Debio 0123 when administered in combination with Carboplatin

Secondary

- Occurrence of DLTs
- Incidence of treatment-emergent Serious Adverse Events (SAEs) and Incidence and severity of treatment-emergent adverse events (TEAEs) and laboratory abnormalities, graded according to NCI-CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) version 5.0 criteria
- Incidence of treatment discontinuations and treatment modifications due to adverse events (AEs) and laboratory abnormalities
- Change in vital signs, electrocardiograms (ECG), and ECOG PS (Eastern Cooperative Oncology Group performance status)
- PK parameters of Debio 0123 (and of its metabolite) in monotherapy and urine after single dose on Cycle Day -3 and following 3 days of once daily dosing (i.e., after the last dose on Cycle 1 Day 3)
- PK parameters of Debio 0123 (and of its metabolite) and carboplatin and other PK parameters as deemed appropriate) in combination after dosing on Cycle 2 and subsequent cycles
- Relationship between plasma concentration of Debio 0123 (and its metabolite) and changes in QTcF
- Tumor response according to RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1 criteria: best overall response (BOR), disease control rate, best change in tumor size
- Median and 1- and 2-years rates of progression-free survival (PFS) and overall survival (OS)

Translational data (exploratory)

- PD effect of Debio 0123 in paired (i.e. before-during treatment) tumor and skin biopsies
- Associations between potential predictive biomarkers in blood and tumor tissue and efficacy (if data permit)
- Correlation of TP53 status and tumor response according to RECIST v1.1.
- Relationship between Debio 0123 (and its metabolite) plasma exposure and PD effect, safety and efficacy
- Genetic variations in DMET or other genes associated with differences in the PK disposition or safety of Debio 0123

MAIN INCLUSION CRITERIA

- Signed written informed consent before undertaking any study-specific procedures.
- Age ≥ 18 years.
- Histologically or cytologically confirmed locally advanced or metastatic solid and non-bleeding tumors that had recurred or progressed following standard therapy, has not responded to standard therapy or for which no standard therapy of proven benefit is available.
- Able and willing to undergo tumor biopsy unless archived tumor sample is available.
- Previous platinum-based chemotherapy (carboplatin or cisplatin).
- ECOG performance score 0-1.
- Life expectancy of at least 3 months in the best judgement of the Investigator
- Adequate bone marrow function
- For women if relevant: Negative pregnancy test and willingness to use highly effective contraception methods
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.

MAIN EXCLUSION CRITERIA

- History of other malignancies requiring active treatment in the last 6 months.
- Brain tumors and/or brain metastases unless they are asymptomatic, stable on recent imaging (not dated more than 30 days from the inclusion date) and have not required active treatment in the last 3 months.
- History of myocardial infarction or stroke within 6 months, congestive heart failure greater than NYHA (New York Heart Association) class II, unstable angina pectoris, unexplained recurrent syncope, cardiac arrhythmia requiring treatment or family history of sudden death from cardiac-related causes, any cardiotoxicity experienced after previous chemotherapy.
- Left ventricular ejection fraction (LVEF) below the normal range (< 55%)
- Baseline Fridericia's corrected QT (QTcF) interval greater than 470 msec (female) or greater than 450 msec (male), history of congenital long QT syndrome, the presence in the screening ECG of a conduction abnormality that in the opinion of the Investigator would preclude safe participation in this study.
- Concomitant use of a drug with a known risk of QTc prolongation.
- Not recovered from AEs or toxicities due to previous treatments to a Grade >1 specified in NCI-CTCAE v 5.0 except hemoglobin (not less than 9.6 g/dL or 6 mmol/L), albumin (< 2.5 g/dL or 25g/L), and alopecia.
- Hypersensitivity to carboplatin or any of the excipients
- Any psychological familial, sociological or geographical condition potentially preventing compliance with the study protocol schedule
- Subjects who are exposed to high levels of UV light for example occupational exposure to sunlight.

CLINICAL TRIAL INFORMATION

NCT03968653

https://clinicaltrials.gov/ct2/show/NCT03968653

CONCLUSIONS

- Debio 0123 is a highly selective and potent Wee1 inhibitor able to prevent CDC2 / Cdk1 phosphorylation currently being investigated in FiH trial in combination with carboplatin in patients with solid tumors.
- Dose level 1 and 2 was well tolerated with manageable toxicity

CONFLICTS OF INTEREST

First author has no conflict of interest. Study is sponsored by Debiopharm.

REFERENCES

(1) O'Dowd et al., Antitumor activity of the novel oral highly selective Wee1 inhibitor Debio 0123. AACR 2019 #4423.

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