Debio 0123

Best-in-Class WEE1 Inhibitor

Non-Confidential Presentation

May 2023

Executive Summary

Debio 0123 is a Best-in-Class WEE1 Inhibitor in Clinical Development

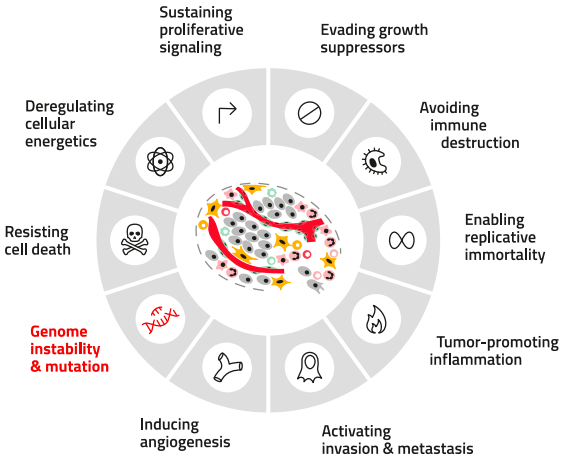
- Debio 0123 is an **oral**, **selective, brain penetrant and potent** small-molecule inhibitor of the WEE1 kinase
- **Efficacy demonstrated** in several preclinical *in vivo* models (monotherapy and in combination)
- **Currently studied in Phase 1 with first signs of safety and efficacy**
  - as single agent/monotherapy in solid tumors
  - in combination with carboplatin in patients with solid tumors (relapsed after platinum-containing therapies)
  - Further clinical development in SCLC and GBM
- Targeted approach leads to **favorable safety & tolerability profile to allow combinations**…
- …enabling opportunity to **combine** it with a wide array of cancer therapies/maximizing clinical dev options
- Expected time to **market 2030, composition of matter IP 2038, potential for market exclusivity up to 2043**

The Opportunity

Prolong life of cancer patients that are refractory or resistant to standard of care therapies

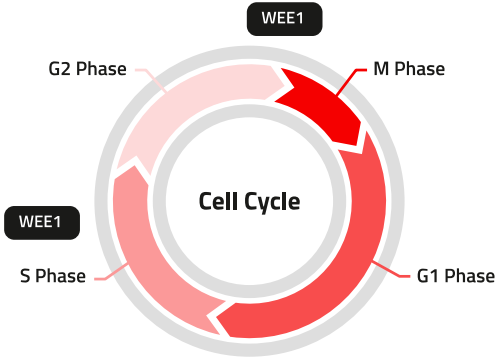
Therapy Resistance

WEE1 is a Key Cell Cycle Regulator in Response to DNA Damage



- In cancer cells, **DDR pathways are often upregulated** due to genomic instability
- This leads to **resistance to DNA damaging therapies**

- **Blocking DNA repair pathways** in cancer cells through inhibition of checkpoint kinases renders cells more vulnerable to DNA damaging therapies
- Failed DNA repair **will lead to anti-proliferative efficacy**



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Hanahan D, Weinberg RA. Cell. 2011;144(5):646-74

Target

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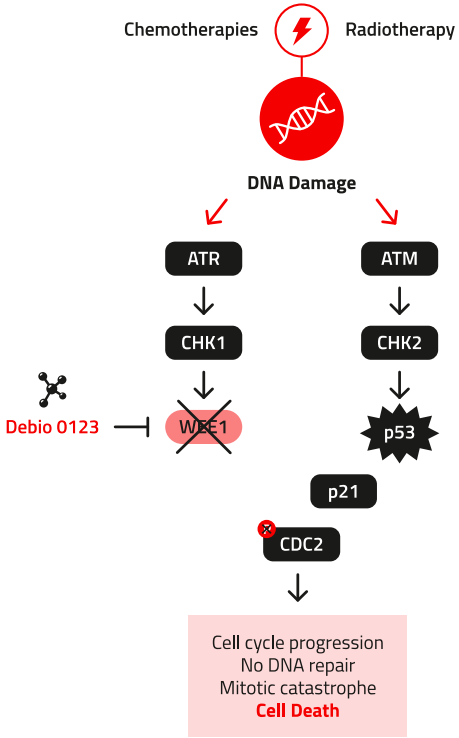
Debio 0123, a WEE1 Inhibitor

Inhibition of WEE1 Leaves Cancer Cells Vulnerable to Failed DNA Damage Repair, Leading to Cell Death

- **WEE1 inhibition** leads to cell-cycle progression despite unrepaired DNA damage
- Accumulation of damages and continued cell cycle induces **cell death**



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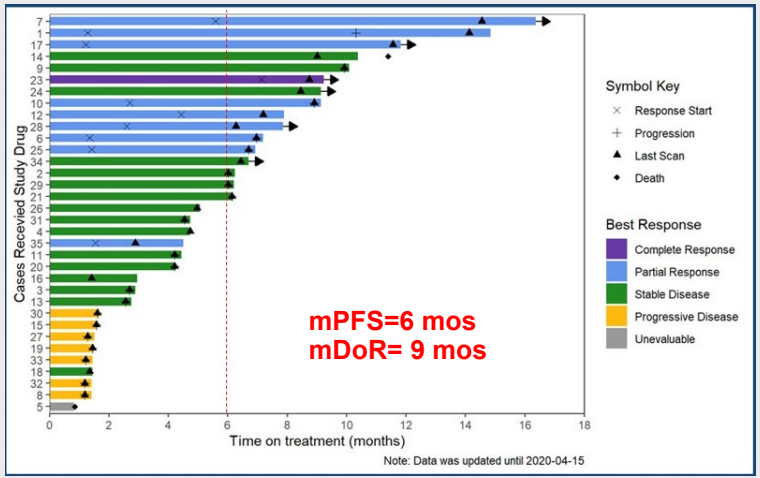
Target Validation

WEE1 is a Clinically Validated Target

Adavosertib in Recurrent Uterine Serous Carcinoma in Monotherapy

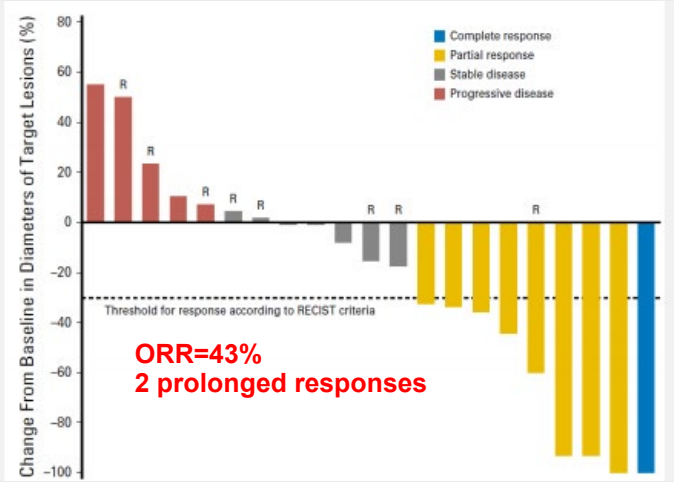


2020 ASCO ANNUAL MEETING

Primary EPs

- ORR = 29%, incl. 3% CR
- PFS6 = 60%

Adavosertib in TP53mut R/R Ovarian Cancer in Combination with Carboplatin



Journal of Clinical Oncology®

Other EPs

- mPFS = 5.3 mos
- mOS = 12.6 mos

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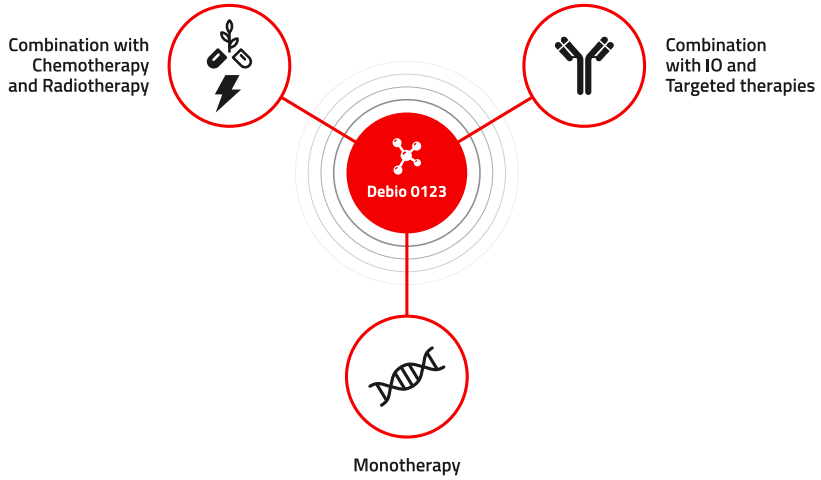
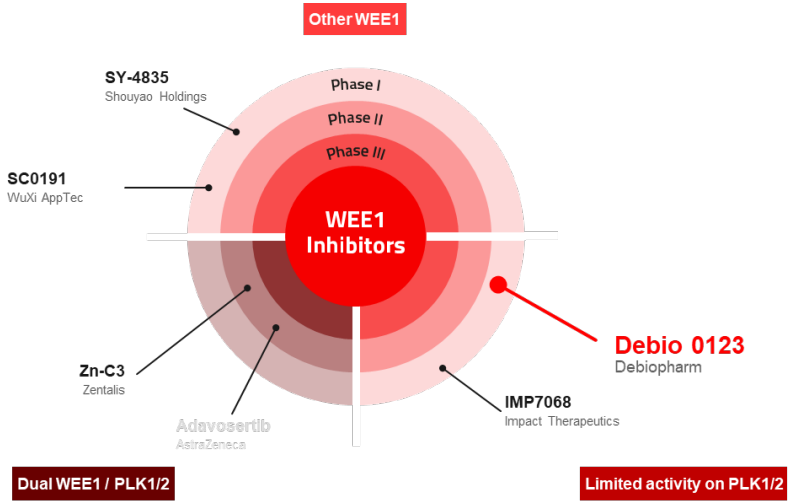
Sources: Joyce Liu at ASCO 2020; Leijen et al (2016). Note: adavosertib= AZD-1775

The WEE1 Target

WEE1 is an Attractive & Promising Target for Future Anticancer Therapy





- WEE1 inhibition has demonstrated antitumoral efficacy in the clinics[#]
- WEE1 targeting by Debio 0123 offers multiple opportunities for development

- WEE1 is a hot target in oncology, with several programs currently in clinical development
- Debio 0123 is a potential best-in-class, first-choice WEE1 inhibitor

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[#] Moore et al., *CCR* 2021, Liu *et al*., *JCO* 2021, Leijen et al., *JCO* 2016

Our answer

A potent and selective WEE1 inhibitor to exploit DDR dependency of cancer cells

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Executive Summary

Well-Differentiated, Clinical-Stage WEE1 Inhibitor

	adavosertib (Astra Zeneca)	ZN-c3 (Zentalis Pharma)	Debio 0123
Status	Discontinued (Ph 2) due to safety concerns	Phase 2	**Phase 1**
Structure similarity to adavosertib	–	adavosertib-like§	**DIFFERENT CHEMOTYPE**
Brain Penetration Preclinical	No	No	**YES**
PLK1/2 inhibition	Yes	Yes	**NO**
Dosing	BID / QD	QD	**QD**
Addressed indications	Mainly gynecological	Gynecological, osteosarcoma, other solid tumors	**SCLC, GBM***

§ Huang et al., *J. Med. Chem.* 2021
# Moore et al., *CCR* 2021, Leijen et al., *JCO* 2016, Embaby et al., ASCO 2022

Differentiation
Selectivity

Debio 0123 is a Selective WEE1 Inhibitor with High Potency

High potency and selectivity

Target	Debio 0123 IC_{50} (nM)	adavosertib IC_{50} (nM)	Zn-C3 IC_{50} (nM)
WEE1	0.8	3.9*	3.8*

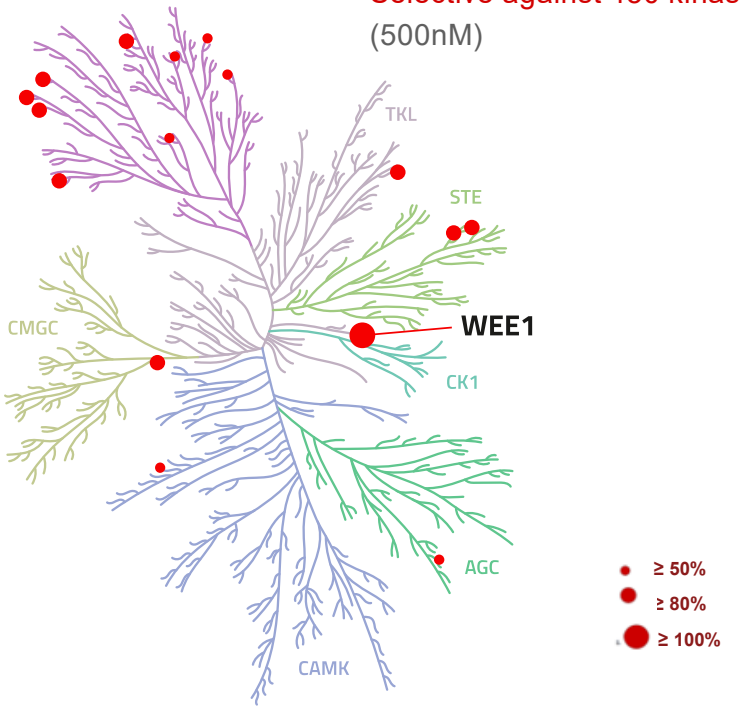
IC_{50} on WEE1 (ADP-competitive binding assay)

More selective than competition on PLK1/2

Target	Debio 0123 IC_{50} (nM)	adavosertib IC_{50} (nM)	Zn-C3 IC_{50} (nM)*
PLK1	> 10 000	79	227
PLK2	> 10 000	79	40

IC_{50} on PLK1 and PLK2 (kinome screen)

Selective against 450 kinases
(500nM)



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

Source: unpublished data

* Huang et al., *J. Med. Chem.* 2021, 64, 17, 13004-13024

Studies conducted using versions of adavosertib synthesized by third-party contract research chemists, using publicly available information

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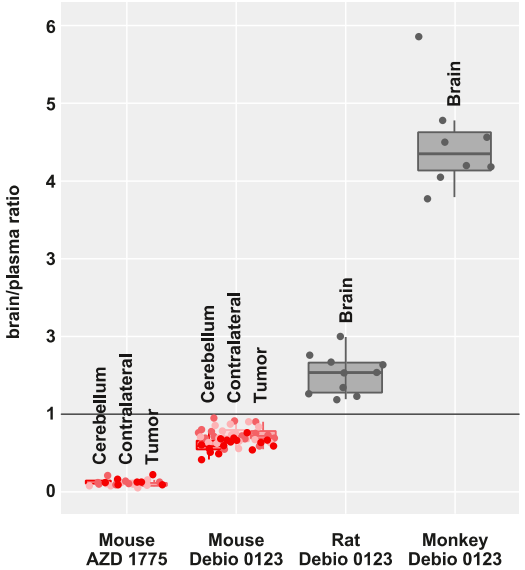
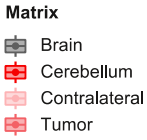
Differentiation

Brain Penetration

Debio 0123 Shows Favorable Brain Penetration in Different Species

Shows similar penetration across brain tumor and healthy brain

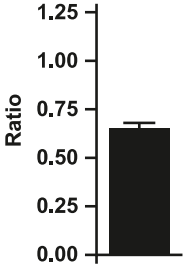




Mouse: 4h after last dose

Rat & monkey: 24h after last dose

- In the mouse, the brain to plasma ratio is similar to that of Temozolomide (TMZ)[1] ⟶
- AZD1775 penetrates poorly into brain



1 TMZ= GBM SoC; Source: De Gooijer M.C et al., Neoplasia Vol. 20, No. 7, 2018

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Studies conducted using versions of AZD1775 synthesized by third-party contract research chemists, using publicly available information

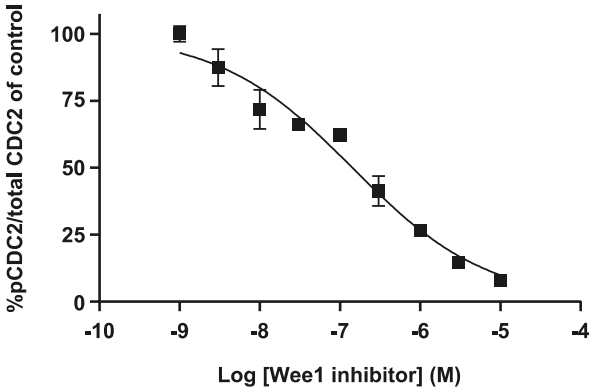
Target engagement

Debio 0123 Demonstrates Strong & Sustained Target Engagement

Target engagement *in vitro*

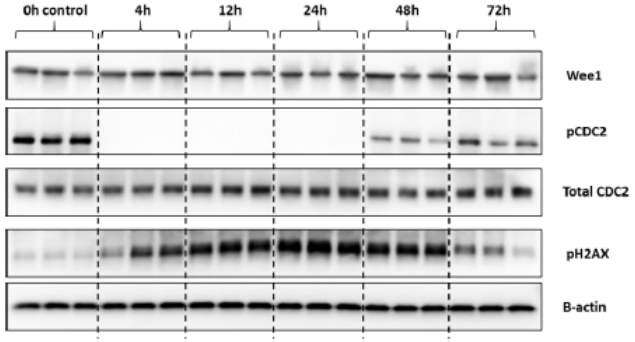
IC_{50} on pCDC2: 142nM

pCDC2 by ELISA in HT29 cells treated with Debio 0123



Strong & sustained target engagement *in vivo*

Debio 0123 (30mg/kg, p.o.)



- Complete & sustained knock down of pCDC2 up to 24h with Debio 0123 at 30mpk , p.o.
- Strong & sustained g-H2AX induction observed with Debio 0123 over 48h

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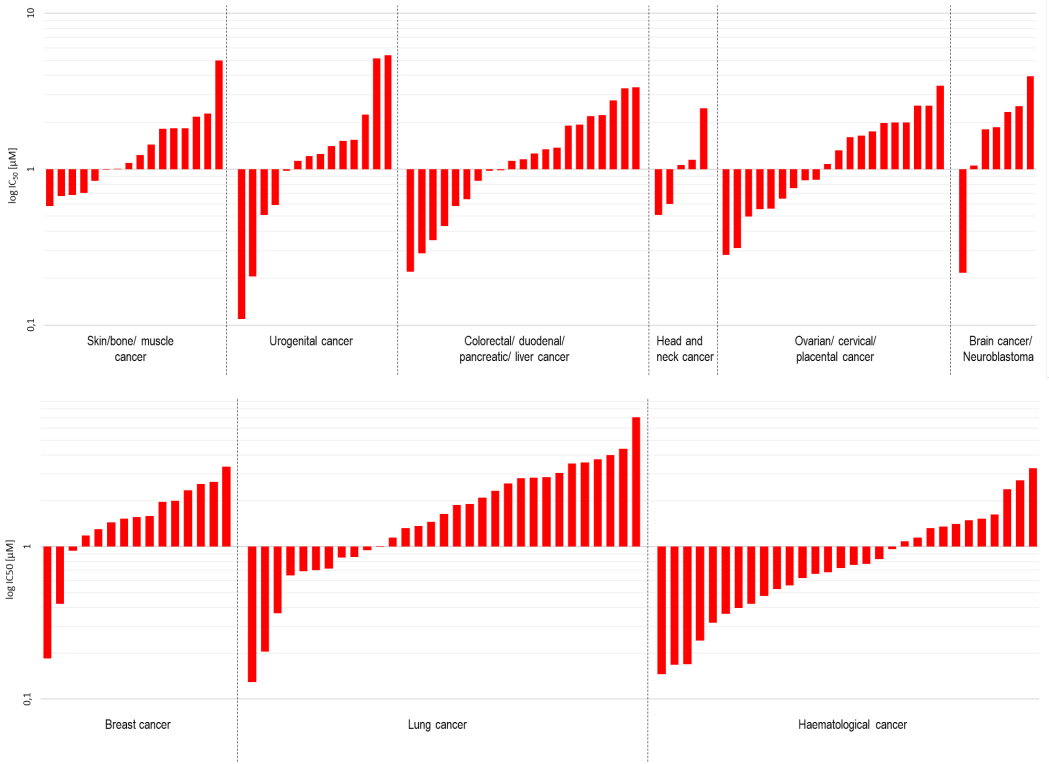
Single Agent Activity

Debio 0123 Shows a Broad Range of Activity *in vitro*

Median IC50 value was 1.23 µM (range: 0.109 to 7.08 µM), showing a good response of cancer cells to Debio 0123 across various histotypes.

→ Efforts are ongoing to identify predictive biomarkers to support further development in monotherapy

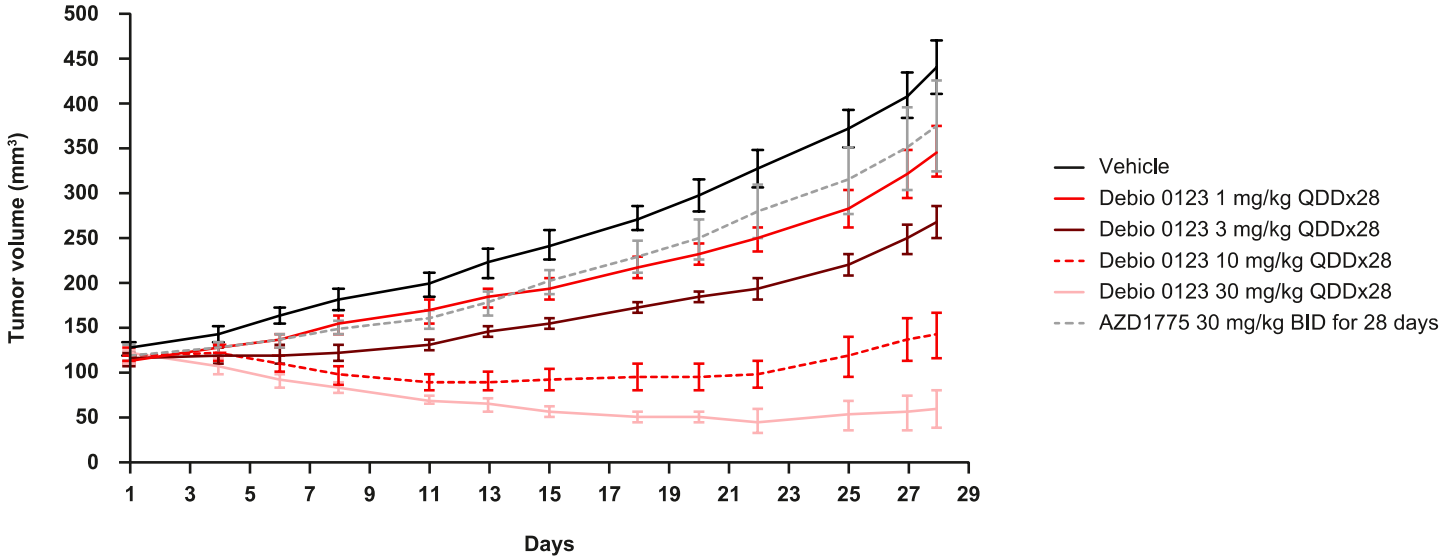


Source: O'Dowd *et al.*, AACR 2019 #4423.

Single agent activity

Debio 0123 Outperforms adavosertib *in vivo*

NSCLC model (A427)



Source: O'Dowd *et al.*, AACR 2019 #4423.

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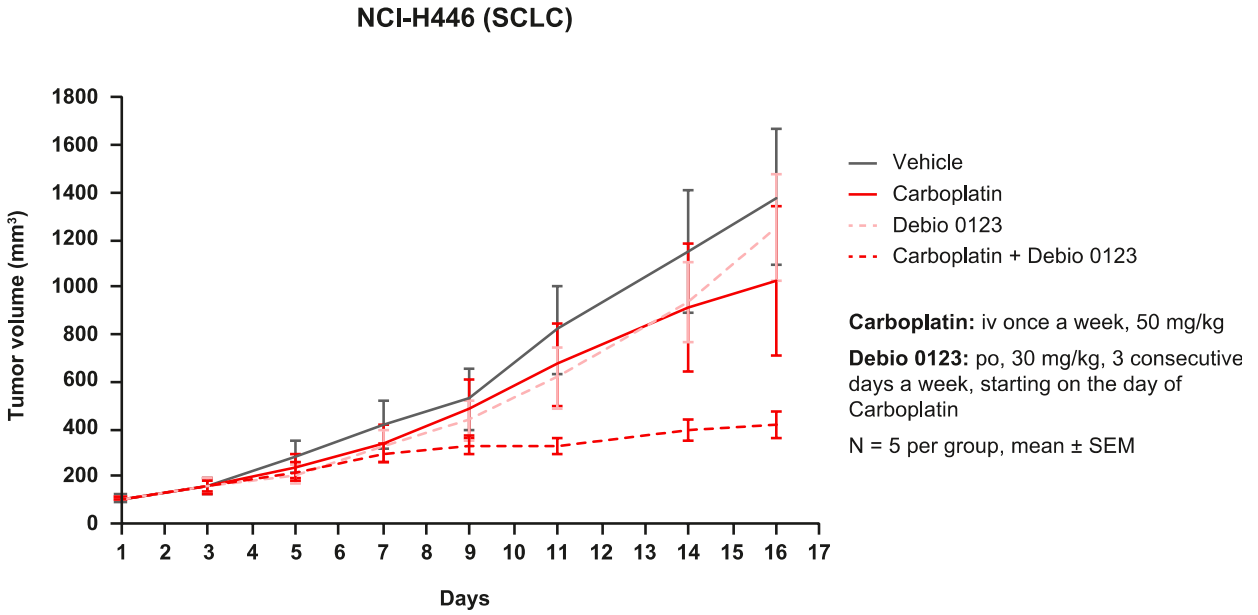
Combination Treatment

Debio 0123 Shows Strong Activity in Combination with Carboplatin

- Synergy *in vitro* in several cell lines and in vivo in one xenograft model



Source: Gelderblom *et al*, ESMO 2020 #3893.

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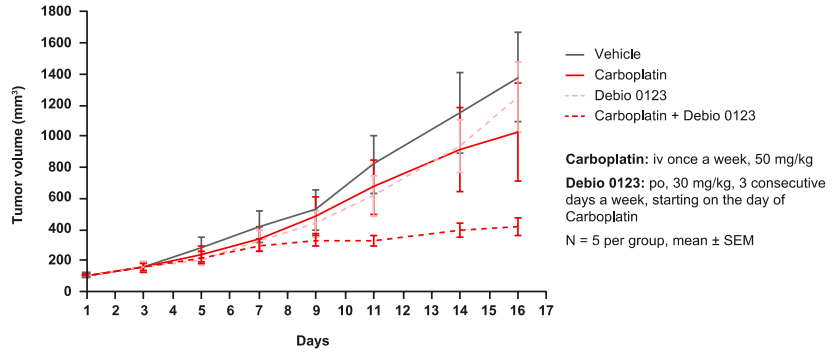
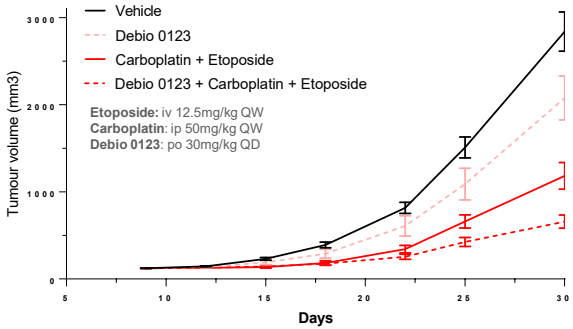
In vivo

Debio 0123 Shows Strong Activity in Combination with Carboplatin and Etoposide in Lung Cancer Models

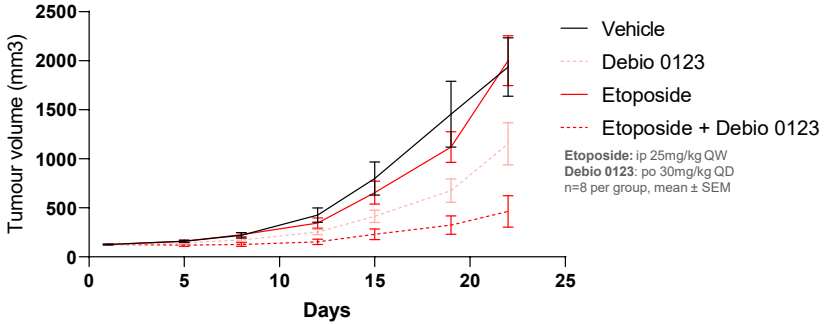
NCI-H446 (SCLC)



NCI-H1048 (SCLC)



NCI-H1048 (SCLC)

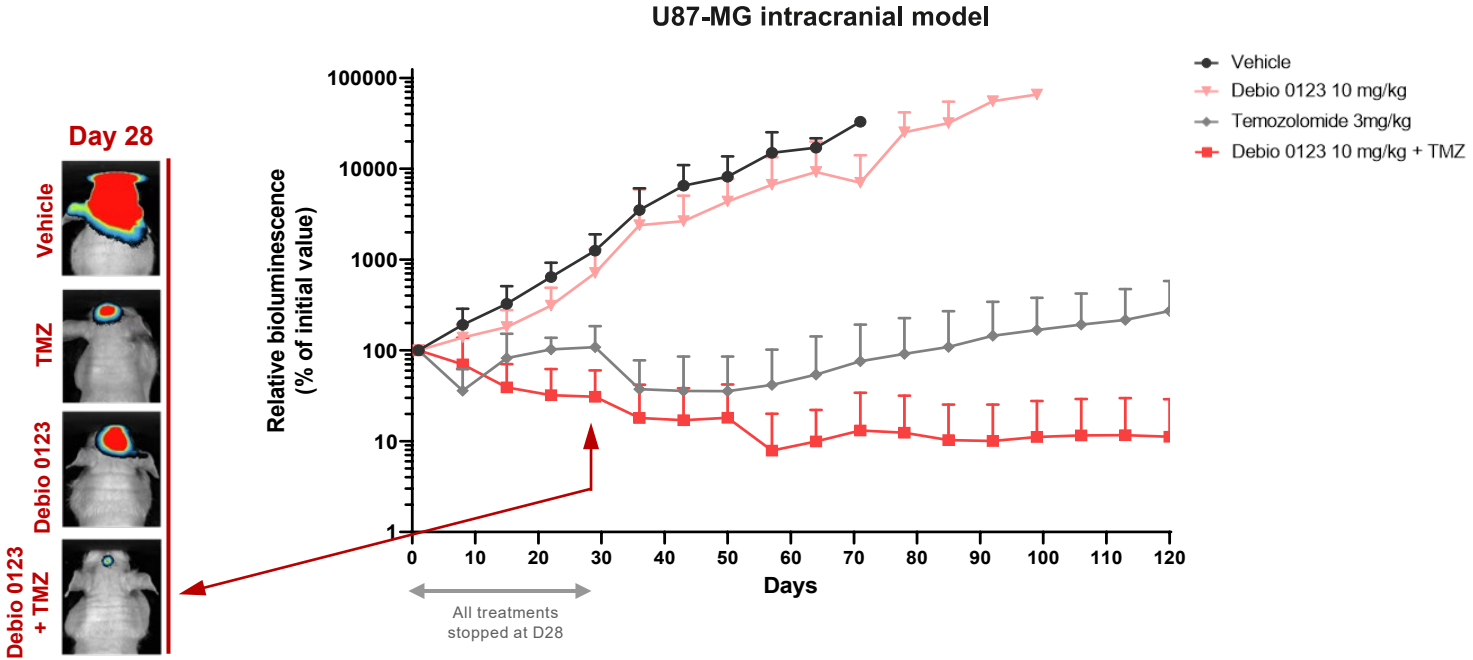


- Strong anti-tumor efficacy observed in combination with carboplatin or etoposide
- Triple combination significantly improves tumor response over SOC carboplatin/etoposide
- All treatments were well tolerated, including triplet combination

Glioblastoma

Debio 0123 + Temozolomide Leads to Sustained Regressions

In vivo



- Sustained complete regressions observed in 75% of animals treated with Debio 0123 + TMZ

Unpublished data

Our Development Path

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Clinical Overview

Our Clinical Studies

Ongoing Studies

Debio 0123-101 / **Phase 1** / Combination with carboplatin / NCT03968653

- In advanced solid tumors that recurred or progressed following prior cisplatin or carboplatin-containing therapy
- Primary Completion Date expected in April 2023

Debio 0123-102 / **Phase 1b** / Single agent / NCT05109975

- *Part A*: dose escalation in advanced solid tumors / Primary Completion Date expected in December 2023
- *Part B*: expansion in advanced tumor types

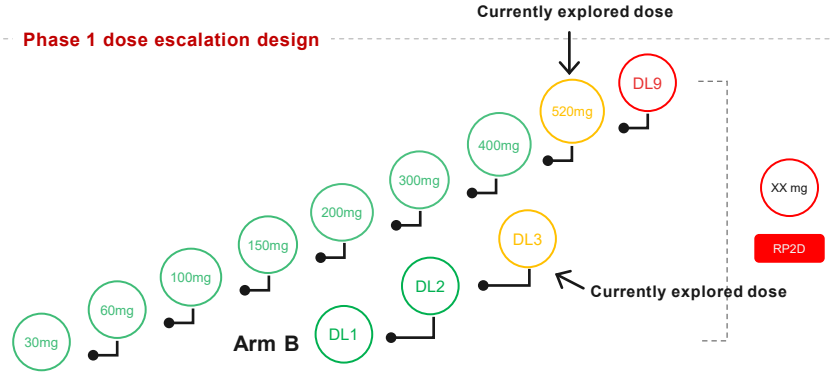
Debio 0123-SCLC-104 / **Phase 1** / Combination with Carboplatin/Etoposide / NCT05815160

- *Part A*: dose escalation in relapsed SCLC
- *Part B*: expansion in relapsed SCLC
- **Debio 0123-GBM-105** / **Phase 1/2** / Combination with Temozolomide or Temozolomide + Radiotherapy / NCT05765812
- *Phase 1*: dose escalation in combination with (A) TMZ in recurrent GBM or anaplastic astrocytoma, and (B) TMZ + RT in newly diagnosed GBM or anaplastic astrocytoma
- *Phase 2*: combination with TMZ in recurrent GBM

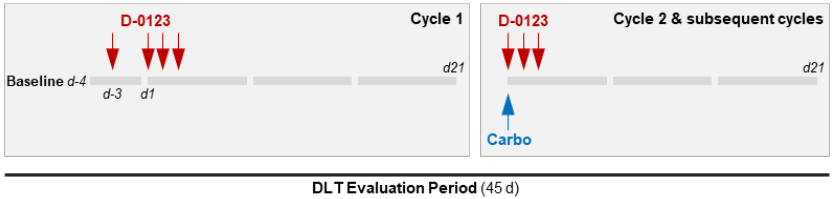
Carboplatin Combination

Debio 0123-101 Phase 1 Trial
Design

Phase 1 dose escalation design



Schedule of Administration & DLT Assessment



Main inclusion criteria

- 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

Endpoints

Safety

- Determine the Recommended Phase 2 Dose (RP2D) when administered in combination with Carboplatin (expected at the latest Q2/Q3-2022)
- Monitor adverse events and dose-limiting toxicities

Efficacity

- Response rate (RECIST v1.1), PFS, OS, etc…

Translational data (exploratory)

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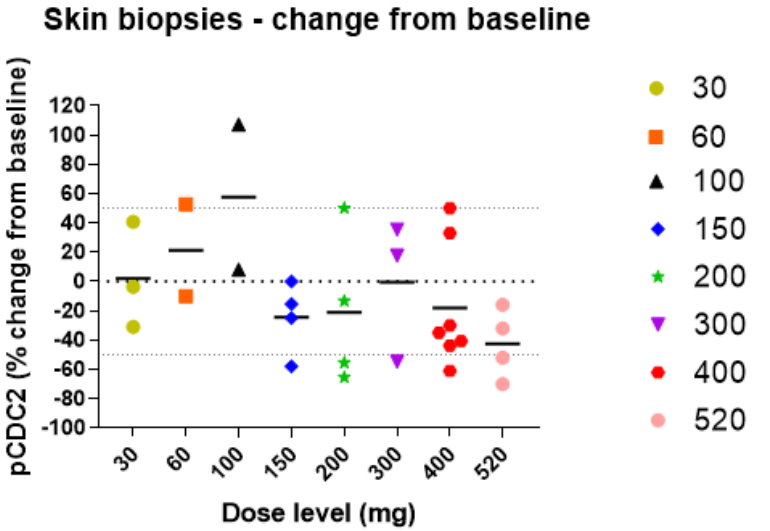
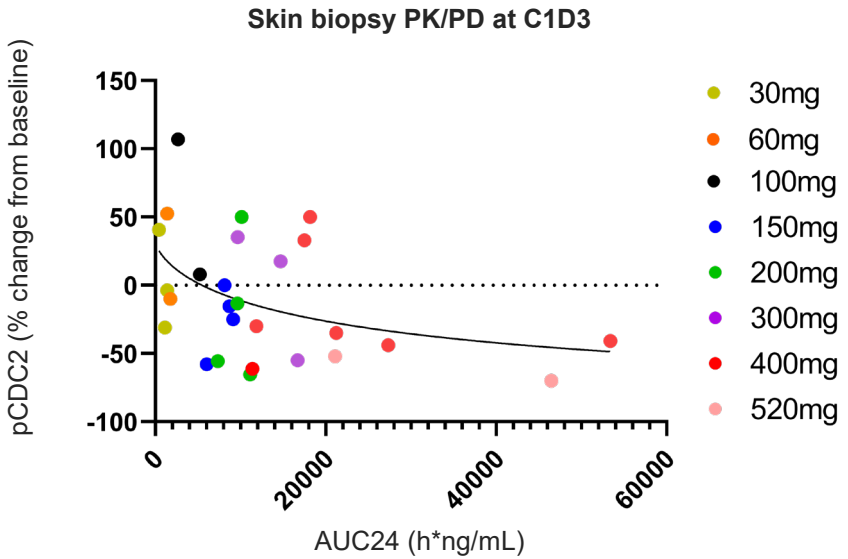
Study design (TIP) presented by Prof. Gelderblom H., ESMO 2020 #3893

Debio 0123-101 Trial
Combination with Carboplatin

Pharmacodynamics (ARM A)
Reduction of pCDC2 Observed in Skin Biopsies





- 15 out of 21 skin biopsies show pCDC2 reduction from 150mg onwards
- Up to 70% reduction in pCDC2 observed in the skin
- up to 64% reduction in pCDC2 also observed in tumor biopsies

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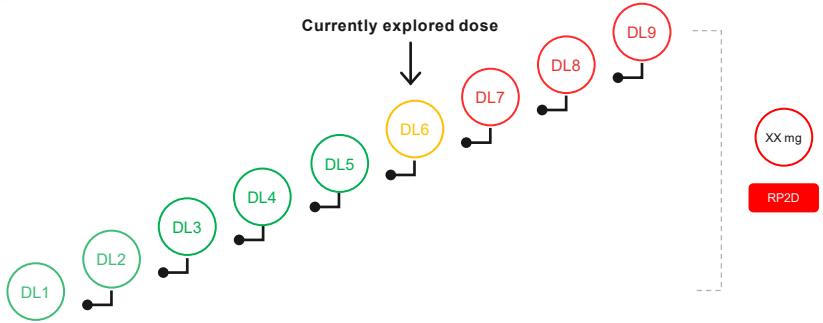
Monotherapy

Debio 0123-102 Phase 1 Trial

Dose Escalation Part

Phase 1 Dose Escalation Design



Key Eligibility Criteria

Inclusion criteria

- Histologically or cytologically confirmed locally advanced or metastatic solid tumors
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) PS 0-1

Exclusion Criteria

- Symptomatic or unstable brain metastases
- History of cardiac disorders
- Inability to swallow oral medication or abnormalities affecting drug absorption

Endpoints

Safety

- Determine the Recommended Phase 2 Dose (RP2D)
- Monitor adverse events and dose-limiting toxicities

Efficacy

- Response rate (RECIST v1.1), PFS, OS, etc…

Translational data (exploratory)

Our value proposition

Differentiation Factors

Once-a-Day, Oral WEE1 Inhibitor

Most advanced best-in-class WEE1 inhibitor

More attractive profile vs. competitors (adavosertib and ZN-c3)

1. **Higher selectivity**
   - Potential for better safety / tolerability profile
   - More favorable combinability
2. **Favorable tissue distribution profile**
3. **QD dosing**: convenience for patients

Market-ready formulation

- Suitable for pediatrics

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Value Proposition

Maximal Value & Commercial Opportunities Unlocked with Debio 0123

OPPORTUNITY TO INCREASE MARKET POTENTIAL

Potential for combinations with a broad range of cancer therapies across a broad range of indications

Monotherapy in selected patients

LAUNCH in 1st indication

2030
Expected time to market

PATENT PROTECTION

Composition of Matter:
Expiration date: 2038 + max 5 years (country-by-country)

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Interested?

Find out more!

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Contact informations

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