Debio 0123

Best-in-Class WEE1 Inhibitor

Non-Confidential Presentation

October 2023

Debio 0123
Executive Summary

Best-in-Class WEE1 Inhibitor in Clinical Development
Available for Licensing

Debio 0123 is a potent, oral, brain-penetrant, and highly selective small-molecule inhibitor of the **WEE1** kinase

- Good efficacy in multiple preclinical *in vivo* models
- No targeting of the PLK1/2 axis

Currently in **Phase 1** clinical development as single agent, and in combination with SOC in patients with solid tumors

- **Better safety/tolerability** profile to date *vs.* other clinical-stage WEE1 inhibitors, either as monotherapy or in combination with carboplatin
- Signals of **antitumor activity** and consistent WEE1 **target engagement** observed in patients
- Further clinical development plan is ongoing

Excellent opportunity to **combine** it with a wide array of cancer therapeutic regimens allowing to address **multiple indications** and maximize clinical development options

Expected time to **market 2030**, with current market **exclusivity up to 2043**

Debio 0123
Executive Summary

Well-Differentiated, Clinical-Stage WEE1 Inhibitor

	adavosertib (AZD-1775) (AstraZeneca)	**azenosertib** (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 / Low[¶]	No / Low[†,¶]	**YES**[¶]
PLK1/2 inhibition	Yes	Yes	**NO**
Clinical safety profile	High rate of hematological & GI toxicity	Significant rate of hematological toxicity	**LOW RATE of hematological & GI toxicity**
Clinical efficacy profile	31-43% ORR[#]	In same range as adavosertib	**In same range as adavosertib**
Addressed indications	Mainly gynecological	Gynecological, osteosarcoma, CRC, AML	**SCLC, GBM***

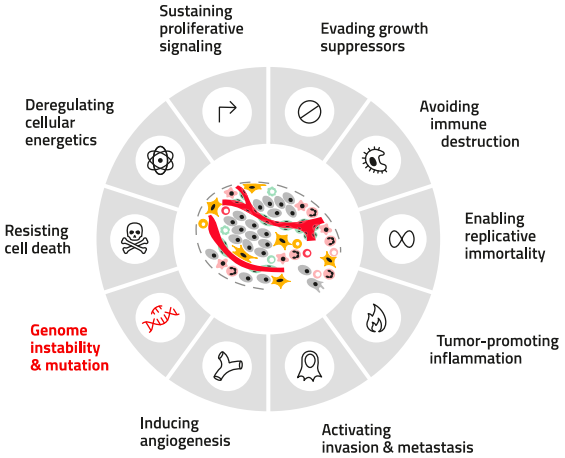
[§] Huang et al., *J. Med. Chem.* 2021
[†] Shwetal et al., AACR 2023 abstract # 2796
[¶] Piggott et al, AACR 2023 abstract #6185
[#] Moore et al., *CCR* 2021, Leijen et al., *JCO* 2016, Embaby et al., ASCO 2022

The Target

WEE1

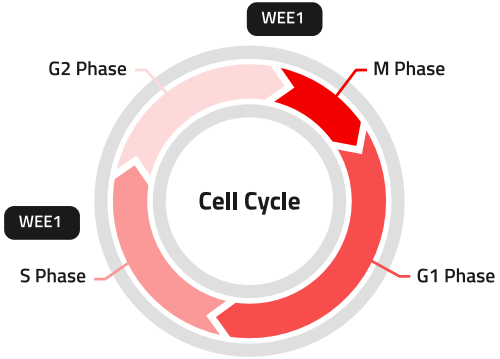
Mechanism of Action

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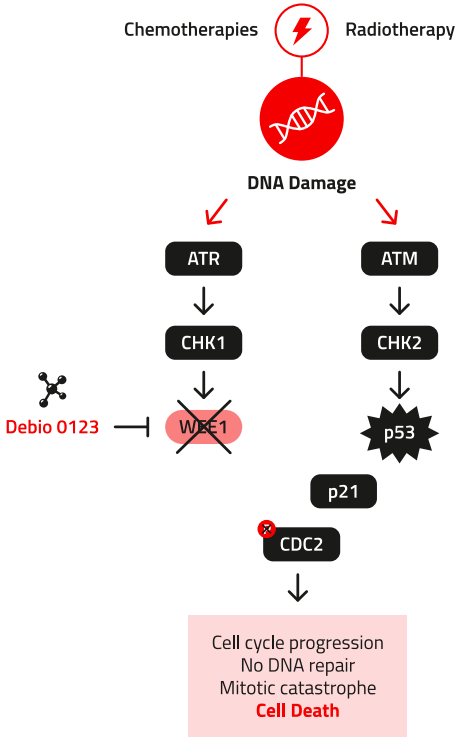
Hanahan D, Weinberg RA. Cell. 2011;144(5):646-74

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**
- Expected synergies with deficiencies in other DDR pathways



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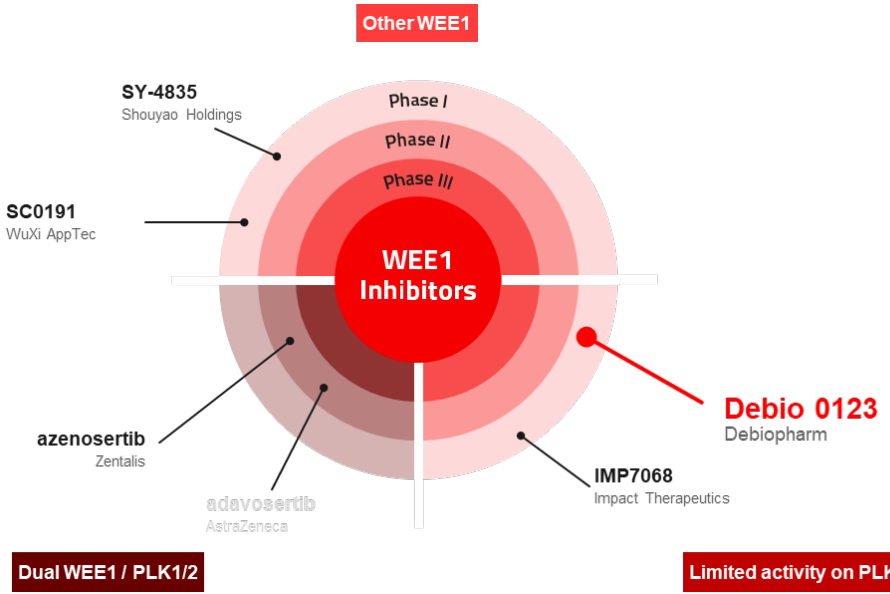
The WEE1 Target

WEE1 is an Attractive & Promising Target for Future Anticancer Therapy



- WEE1 is a hot target in oncology pursued in the clinics
- Debio 0123 is a potential best-in-class, first-choice WEE1 inhibitor
- WEE1 inhibition has demonstrated antitumoral efficacy in the clinics[#]
- WEE1 targeting by Debio 0123 offers multiple opportunities for development

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

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Our Compound

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

In vitro profile

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*

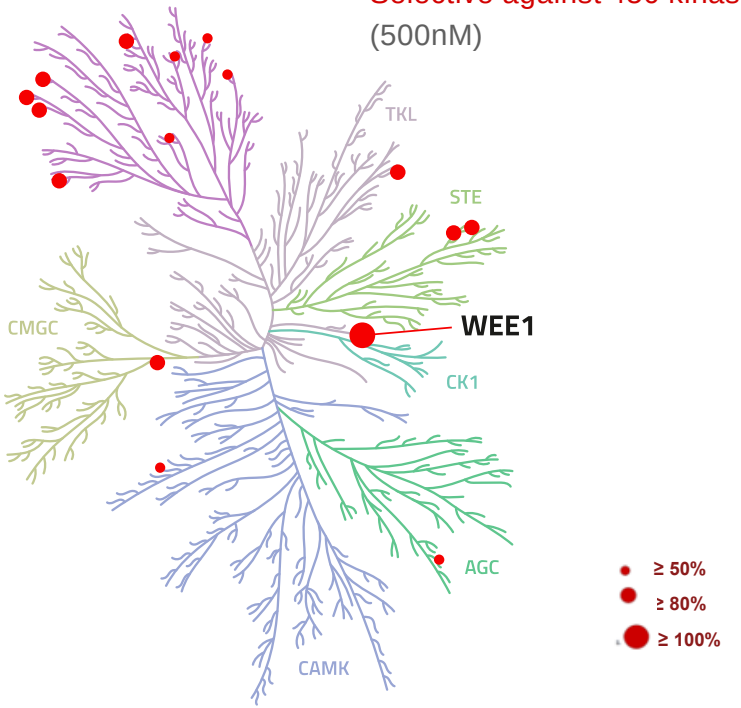
IC_{50} on WEE1 (ADP-competitive binding assay)

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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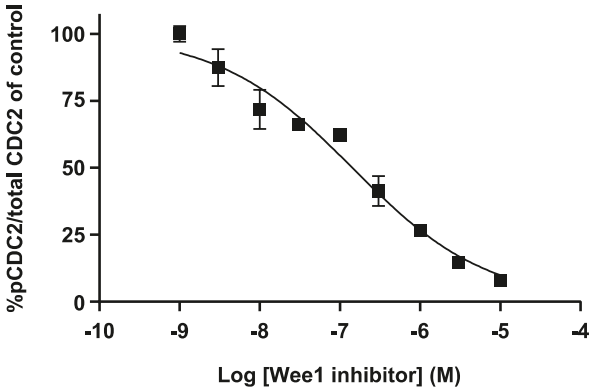
Target engagement

Debio 0123 Demonstrates Strong & Sustained Target Engagement

Target engagement *in vitro*

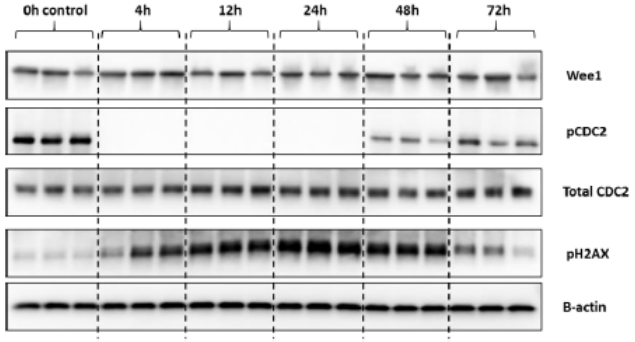
IC_{50} on pCDC2: 142nM

pCDC2 by ELISA in HT29 cells treated with Debio 0123



Strong & sustained target engagement *in vivo*

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



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

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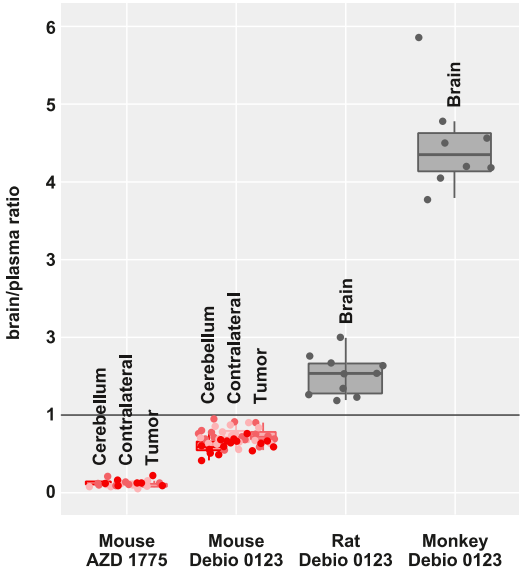
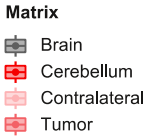
Differentiation
Brain Penetration

Debio 0123 Shows Favorable Brain Penetration in Different Species

Shows similar penetration across brain tumor and healthy brain

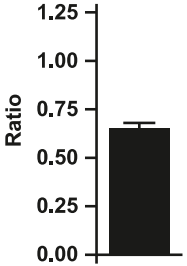




Mouse: 4h after last dose

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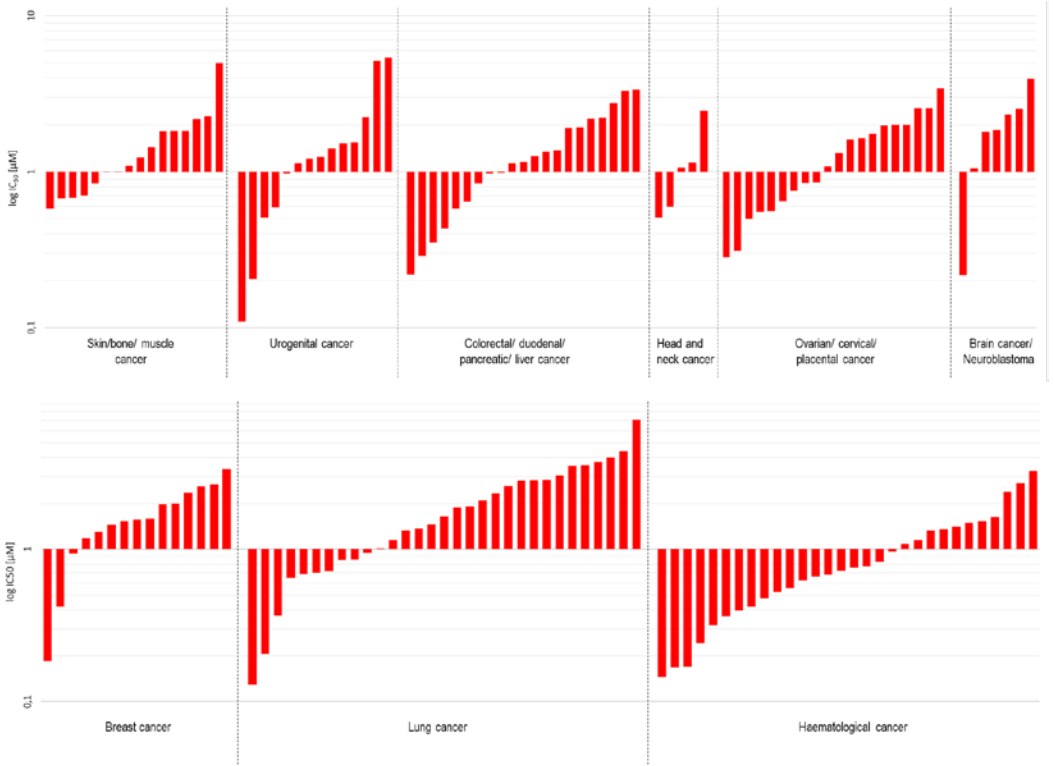
Studies conducted using versions of AZD1775 synthesized by third-party contract research chemists, using publicly available information

Single Agent Activity

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

- Broad sensitivity to Debio 0123 monotherapy across multiple indications
- Median IC_{50} value 1.23 µM (range: 0.109 to 7.08 µM)
  - ➢ Good response across various histotypes
- To support further development in monotherapy, efforts are ongoing to identify predictive biomarkers

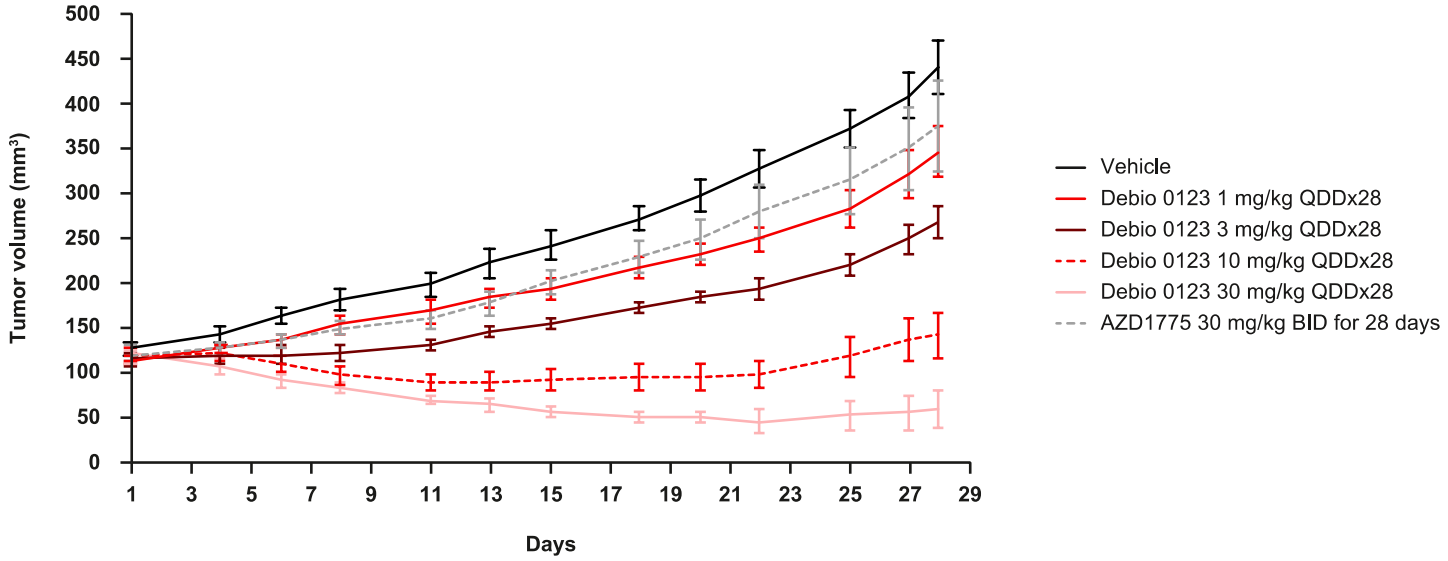


Source: O'Dowd *et al.*, AACR 2019 #4423.

Single agent activity

Debio 0123 Outperforms adavosertib *in vivo*

NSCLC model (A427)



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

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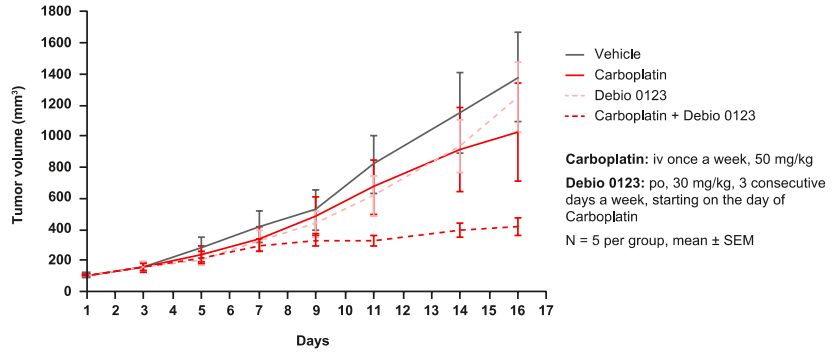
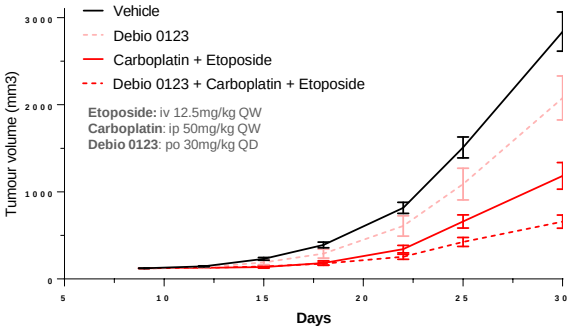
Combination Treatment

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

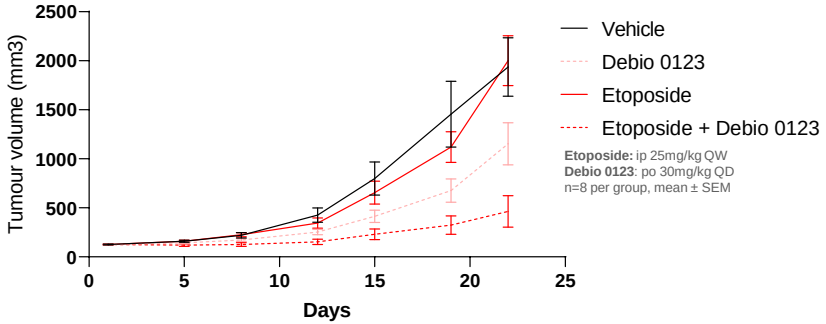
NCI-H446 (SCLC)



NCI-H1048 (SCLC)



NCI-H1048 (SCLC)



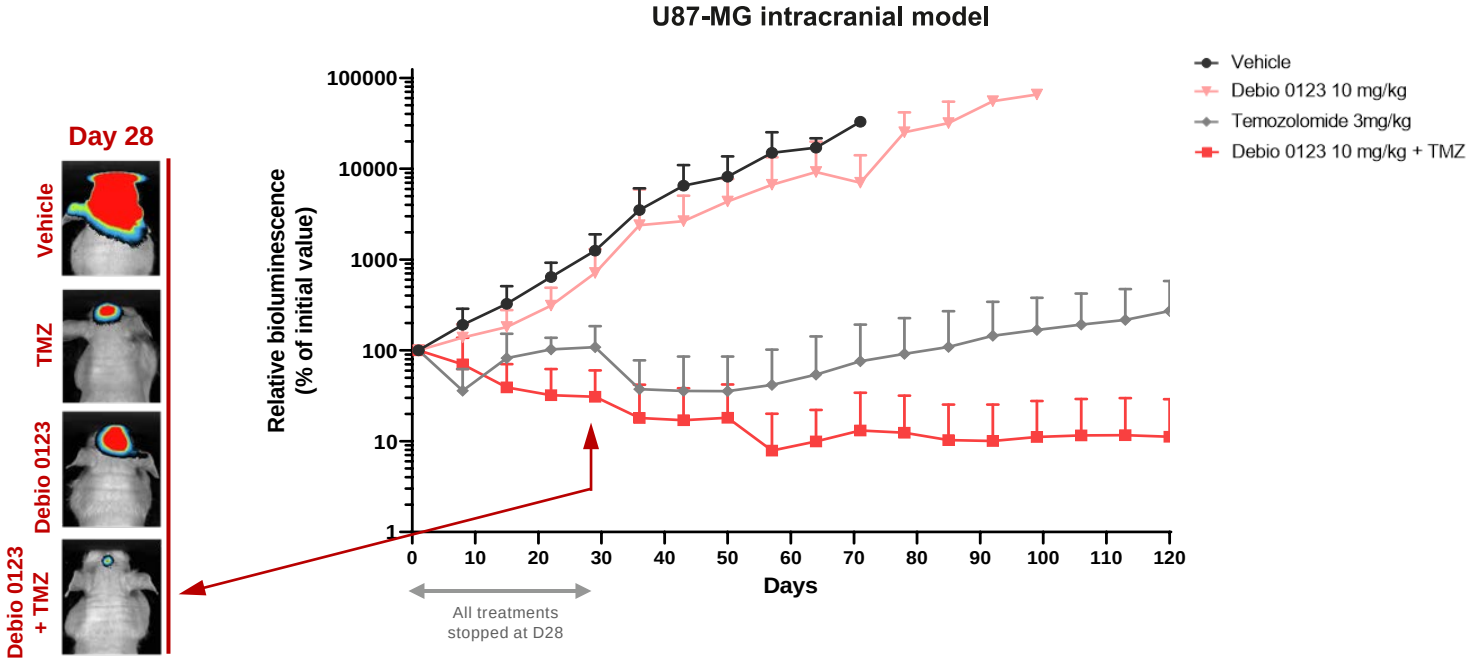
- Strong anti-tumor efficacy observed in combination with carboplatin or etoposide
- Triple combination significantly improves tumor response over SOC carboplatin/etoposide
- All treatments were well tolerated, including triplet combination

Sources
Gelderblom *et al,* ESMO 2020 abstract #3893
Piggott *et al,* AACR 2022 abstract #4894

Glioblastoma

Debio 0123 + Temozolomide Leads to Sustained Regressions

In vivo



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

Source
Piggott *et al*, AACR 2023 abstract #6185

Our Development Path

Clinical Overview

Our Clinical Studies

Ongoing Studies

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

- Dose escalation exploring 2 schedules of Debio 0123 (D1-D3 arm A and D1-D3, D8-D10 arm B), in advanced solid tumors that recurred or progressed following prior cisplatin or carboplatin-containing therapy

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

- *Part A*: dose escalation in advanced solid tumors
- *Part B*: expansion in specific advanced tumor types in case of efficacy signal

Debio 0123-SCLC-104 / **Phase 1** / Combination with carboplatin / etoposide / NCT05815160

- *Part A*: dose escalation in relapsed SCLC (CTFI ≥ 45d)
- *Part B*: expansion in relapsed SCLC (CTFI ≥ 90d)

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 / Controlled with a Synthetic Control Arm approach (non-randomized trial)

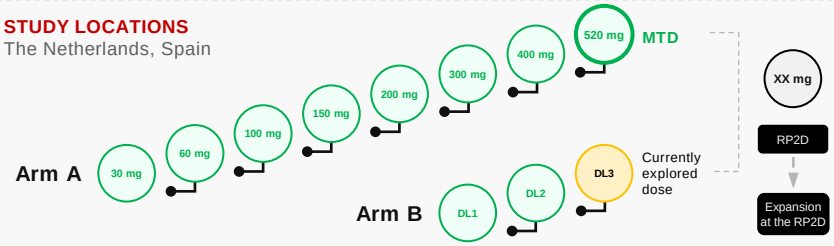
Clinical Development

Debio 0123-101 & -102 Phase 1 Trials

Design of Dose Escalation Parts

DEBIO 0123-101 Phase 1 Trial / Combination with carboplatin

STUDY LOCATIONS
The Netherlands, Spain



ENDPOINTS

- **SAFETY** (RP2D, AEs, DLTs) / **EFFICACY** (ORR, PFS, OS, …) / **PK, food-effect and effect of high gastric pH** / **TRANSLATIONAL** (PDy, biomarkers, …)

ADMINISTRATIONS & DLT ASSESSMENT

Arm A

- **Cycle 1** (24d)
  - **Debio 0123** (*p.o.*)
- **From Cycle 2 onwards** (21d)
  - **Debio 0123** (*p.o.*)
  - Carboplatin (*i.v.*)

DLT ASSESSMENT PERIOD
Covers Cycles 1 & 2 (45d)

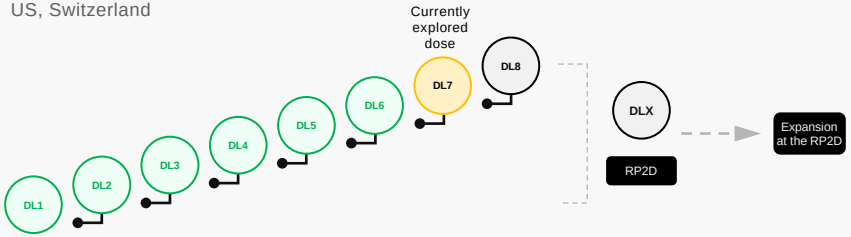
Arm B (all cycles) (21d)

- **Debio 0123** (*p.o.*)
- Carboplatin (*i.v.*)

DLT ASSESSMENT PERIOD
Covers Cycle 1 (21d)

DEBIO 0123-102 Phase 1 Trial / Monotherapy

STUDY LOCATIONS
US, Switzerland



ADMINISTRATIONS & DLT ASSESSMENT

All cycles (21d)

- **Debio 0123** (*p.o.*)

DLT ASSESSMENT PERIOD
Covers Cycle 1 (21d)

ENDPOINTS

- **SAFETY** (RP2D, AEs, DLTs)
- **EFFICACY** (ORR, PFS, OS, …)
- **TRANSLATIONAL** (PDy, biomarkers, …)

Clinical Development

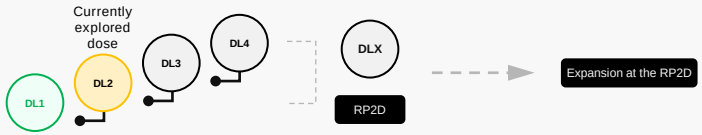
Debio 0123-SCLC-104 & -GBM-105 Trials

Design of Dose Escalation Parts

DEBIO 0123-SCLC-104 Phase 1 Trial / Combination with carboplatin / etoposide

STUDY LOCATIONS

US, Spain



ADMINISTRATIONS & DLT ASSESSMENT

All cycles (21d)

- **Debio 0123** (*p.o.*)
- Carboplatin (*i.v.*)
- Etoposide (*i.v.*)

DLT ASSESSMENT PERIOD
Covers Cycle 1 (21d)

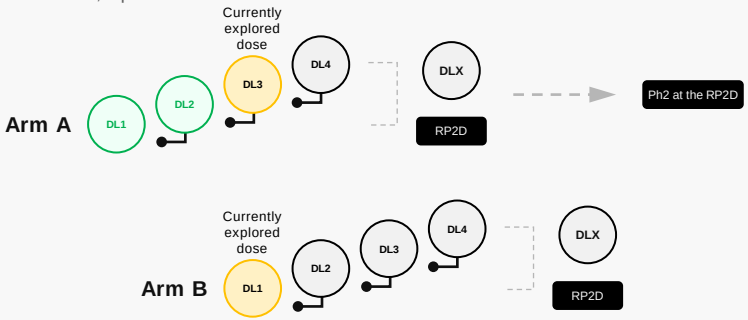
ENDPOINTS

- **RP2D**
- **SAFETY** (AEs, DLTs, ...) and **EFFICACY** (ORR, PFS, OS, ...)
- **TRANSLATIONAL** (PDy, biomarkers, ...)

DEBIO 0123-GBM-105 Phase 1/2 Trial / Combination with temozolomide ± RT

STUDY LOCATIONS

US, Switzerland, Spain



ADMINISTRATIONS & DLT ASSESSMENT

Arm A (all cycles) (28d)

- **Debio 0123** (*p.o.*)
- Temozolomide (*p.o.*)

DLT ASSESSMENT PERIOD
Covers Cycle 1 (21d)

Arm B (6 weeks (42d)

- **Debio 0123** (*p.o.*)
- Temozolomide (*p.o.*)
- Radiotherapy

DLT ASSESSMENT PERIOD
Covers 6 weeks (42d)

ENDPOINTS

- **RP2D**
- **SAFETY** (AEs, DLTs, ...) and **EFFICACY** (ORR, PFS, OS, ...)
- **TRANSLATIONAL** (PDy, biomarkers, ...)

Debio 0123-101 Trial
Combination with Carboplatin

Debio 0123 has Shown Lower Hematological & GI Toxicity vs. Competitors when Combined with Carboplatin*

	Neutropenia		Thrombocytopenia		Anemia		Diarrhoea		Nausea		Vomiting	
	All	Gr ≥ 3	All	Gr ≥ 3	All	Gr ≥ 3	All	Gr ≥ 3	All	Gr ≥ 3	All	Gr ≥ 3
adavosertib[1,2] N= 46 (23 + 23)	35-43%	**22-39%**	70%	**48-52%**	61%	**9-48%**	70%	**4-17%**	78-83%	**4-13%**	48-56%	**0-13%**
azenosertib[3] N=14	50.0%	**7.1%**	64.3%	**35.7%**	71.4%	**28.6%**	35.7%	**0%**	42.9%	**0%**	14.3%	**0%**
Debio 0123[4] N=38	10.5	**2.6**	31.6	**7.9**	21.1%	**2.6%**	5.3%	**0%**	31.6%	**0%**	13.2%	**0%**

*No head-to-head comparison has been done and results are coming from different studies, and different patient populations.

References

1. Moore KM et al. *Clin Cancer Res* 2022;28:36-44 Carboplatin, cohort C
2. Leijen S et al. *J Clin Oncol* 2016;34:4354-4361
3. Liu J. et al, ASCO 2023 Abstract #5513
4. Gelderblom H. et al., ASCO 2023 Abstract #3012

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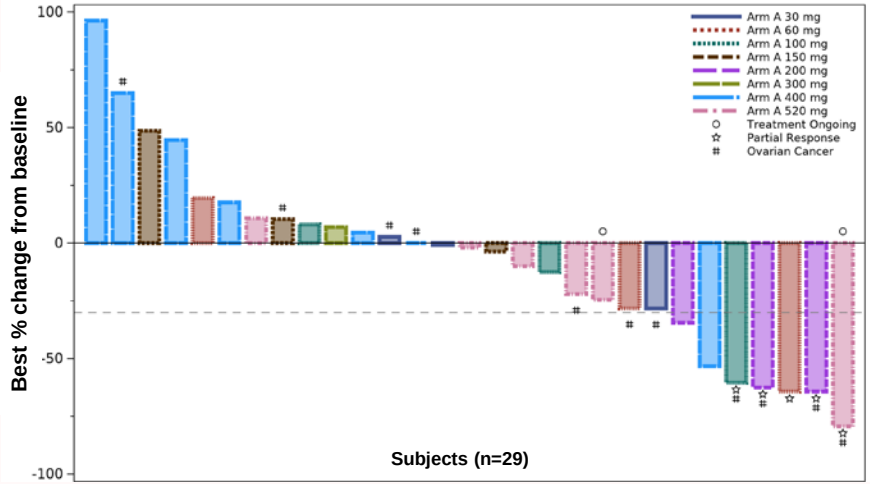
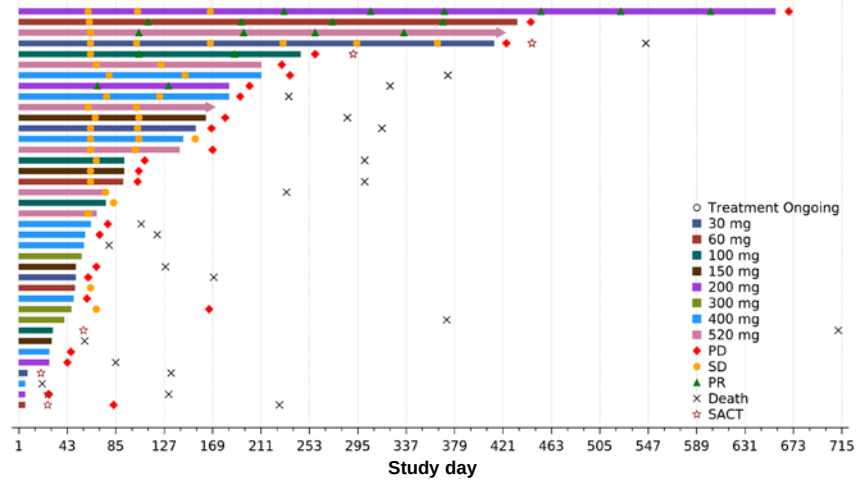
Debio 0123-101 Trial
Combination with Carboplatin

Early Signals of Antitumor Activity in a Heavily Pre-treated Patient Population*





Platinum-Resistant Ovarian Cancer Response	N (%) (total 12 Pts evaluable)
Complete response (CR)	0 (0%)
Partial Response (PR)	4 (33.3%)
Overall response rate (ORR)	**33.3%**
Stable Disease (SD)	6 (50%)
Disease control rate (DCR)	**83.3%**

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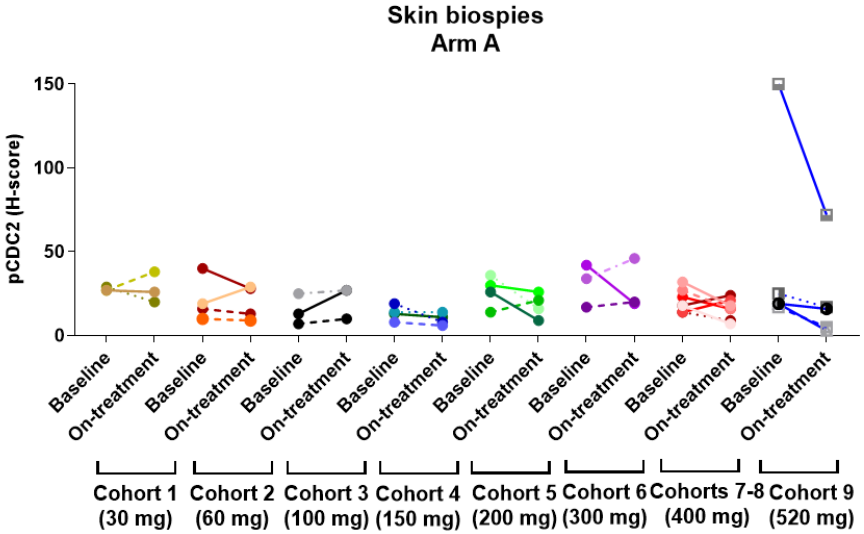
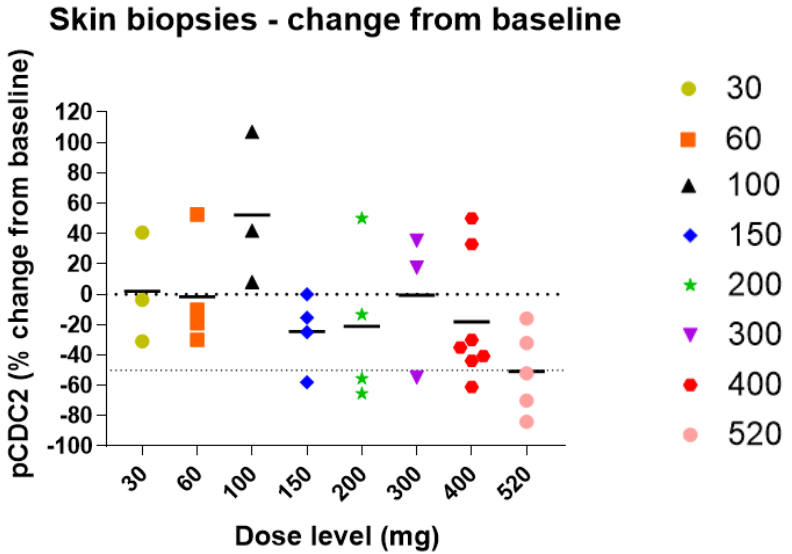
Source
Gelderblom *et al*, ASCO 2023 Abstract #3012

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 150 mg onwards
- Up to 95% reduction in pCDC2 observed in the skin
- up to 64% reduction in pCDC2 also observed in tumor biopsies

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Source
Gelderblom *et al*, ASCO 2023 Abstract #3012

Value Proposition

Differentiation Factors

Once-a-Day, Oral WEE1 Inhibitor

Clinical-stage WEE1 inhibitor with best-in-class potential

More attractive profile vs. other WEE1i (adavosertib and azenosertib)

1. **Higher selectivity – No inhibition of PLK1/2**
   - Better safety / tolerability profile to date
   - More favorable combinability allowing to address multiple indications
   - Preliminary clinical efficacy in line with other WEE1 inhibitors

2. **Brain-penetrant drug with favorable tissue distribution profile**

3. **Oral, 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

LARGE MARKET POTENTIAL

Multiple combinations potential
across a broad range of indications

Monotherapy in selected patients

CLEAR PATH TO MARKET IDENTIFIED

2030
Expected time to market

EXPECTED PATENT PROTECTION

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

Interested?

Find out more!

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