[ABSTRACT: RTID-03]

A Phase 1/2 study of the WEE1 inhibitor Debio 0123 in combination with temozolomide +/– radiotherapy in adults with recurrent or newly diagnosed glioblastoma

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BACKGROUND

Glioblastoma (GBM)

- GBM is the most aggressive and common type of cancer originating in the brain
- Patients (pts) with GBM have a very poor prognosis for survival[1–3]
- GBM tumors can be difficult to target due to their fast-growing nature and the blood-brain-barrier which creates an obstacle to available treatments[2]
- Newly diagnosed GBM treatment is typically multi-faceted, including surgery and chemo- and/or radiotherapy;[1,2] however, even with best standard-of-care (SOC), recurrence is often inevitable and effective treatment options are limited[4]

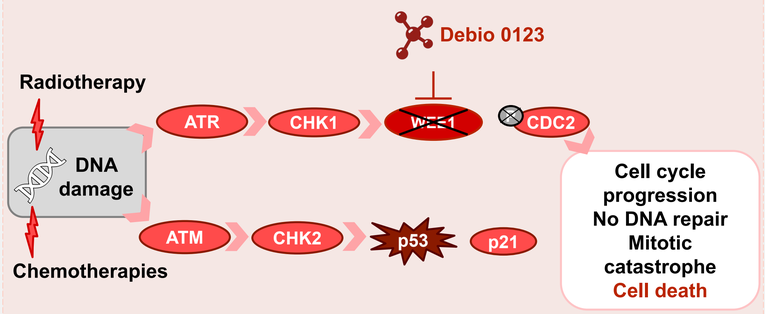
WEE1 kinase

- WEE1 kinase, a key regulator of the S phase and G2/M cell cycle checkpoints, activates the DNA damage response (DDR) pathway before mitotic entry[5]
- The DDR pathway is often upregulated in cancer cells due to genomic instability, leading to resistance to DNA-damaging therapies[6,7]
- Blocking DNA repair pathways via checkpoint kinase inhibition renders cells more vulnerable to DNA damage-inducing therapies[8]
- WEE1 inhibition leads to S phase and G2/M abrogation, permitting mitosis without DNA repair, leading to mitotic catastrophe and subsequent cell death[9]

Debio 0123

- Debio 0123 is an oral, brain-penetrant, highly selective, small-molecule WEE1 inhibitor[10]
- Preclinically, Debio 0123 has been shown to effectively penetrate the brain and WEE1 target engagement has been observed in early-phase clinical trials[11]
- Debio 0123 has demonstrated improved response to radiotherapy (RT) *in vitro* and to temozolomide (TMZ) in mouse models of GBM, supporting clinical investigation of Debio 0123 in combination with TMZ+/–RT[10]

Figure 1. Debio 0123 mechanism of action[12]



STUDY DESIGN

- We present the design of a Phase 1/2, interventional, non-randomized, open-label, multicenter study of Debio 0123 in pts with recurrent and newly diagnosed GBM
- A Bayesian logistic regression model-based decision is being used to guide the dose escalation for both Phase 1 Arm A and Arm B
- This two-part study, initiated in March 2023, is registered as NCT05765812

Phase 1 Arm A: assessing Debio 0123 with TMZ-based chemotherapy to identify the recommended Phase 2 dose (RP2D) of Debio 0123

- Dose limiting toxicity (DLT)-evaluable pts with either recurrent or progressive GBM isocitrate dehydrogenase (IDH)-wildtype (WT), Grade 4 (per WHO 2021 criteria)[13] **or** astrocytoma, IDH-mutant, Grade 3 (per WHO 2021 criteria)[13] will be enrolled, receiving escalating doses of Debio 0123 with TMZ in 28-day cycles, administered as capsules

Phase 1 Arm B: assessing Debio 0123 with concomitant TMZ and RT to identify the RP2D of Debio 0123

- DLT-evaluable pts with newly diagnosed GBM IDH-WT, Grade 4 will be enrolled, receiving escalating doses of Debio 0123 with concomitant TMZ and RT for 6 weeks
- Radiotherapy will be administered in accordance with the local clinical practice and RTOG or EORTC guidelines[14]

Phase 2: assessing the efficacy of the Phase 1 Arm A RP2D of Debio 0123

- Externally controlled, open-label study comparing the efficacy of Debio 0123 with TMZ at the RP2D of Phase 1 Arm A vs SOC in pts with recurrent GBM IDH-WT
- Up to 41 pts with recurrent or progressive GBM IDH-WT Grade 4 after first-line concurrent TMZ-RT will be evaluated per arm
- Pts in the experimental arm will receive Debio 0123 at the RP2D of Phase 1 Arm A and TMZ in each 28-day cycle for up to 2 years
- The external control arm includes data from pts treated with SOC therapy from recently completed historical clinical trials (HCTs)
- Propensity score methods will be used to balance baseline and disease-specific prognostic factors of external control arm pts to pts receiving Debio 0123

Figure 2. Debio 0123 study design schematic

NCT05765812

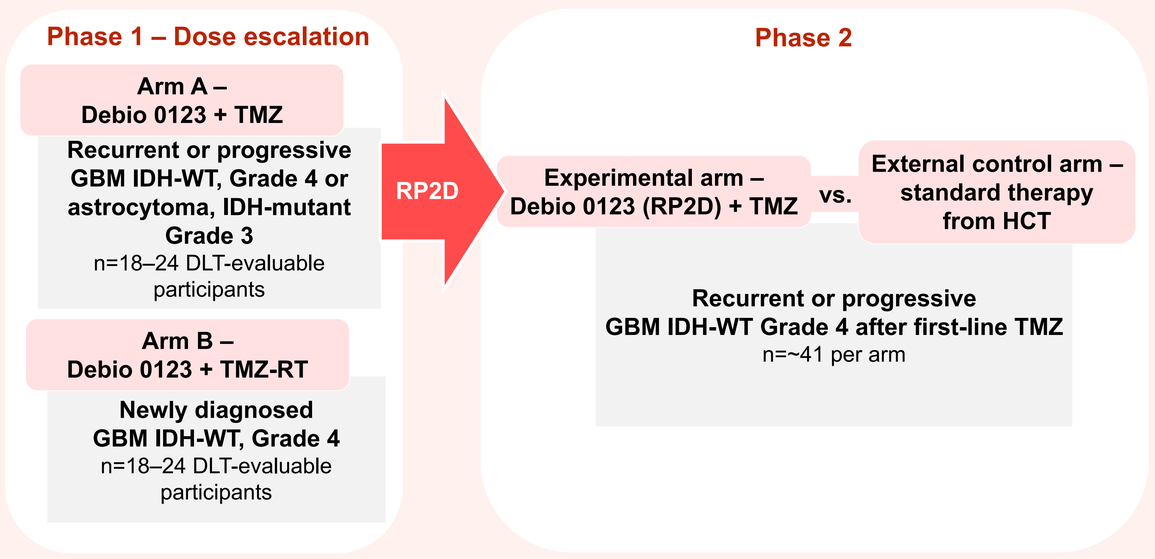
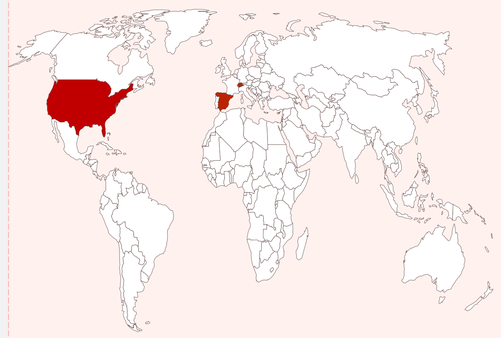


Figure 3. Study status and patient enrollment



The study is currently ongoing with enrollment taking place across Spain, Switzerland, and the US

STUDY OBJECTIVES

Phase 1

To establish the RP2D of Debio 0123 in combination with TMZ (Arm A) and in combination with TMZ and RT (Arm B) and to characterize the safety and tolerability of these combinations in adult pts with GBM

Phase 2

To assess the efficacy of Debio 0123 at the RP2D in combination with TMZ compared with SOC in adult pts with recurrent GBM

ELIGIBILITY

KEY INCLUSION CRITERIA
Phase 1 Arm A and Phase 2
Age ≥18 years old
Measurable or non-measurable disease as per RANO criteria by gadolinium (Gd)-based contrast-enhanced brain magnetic resonance imaging (MRI)
Pts receiving corticosteroids must be on stable or decreasing dose of ≤4 mg daily dexamethasone 7 days prior to start of study treatment
≤1 (Phase 2) or ≤2 (Phase 1 Arm A) prior treatment lines; first-line must be TMZ-RT
Karnofsky Performance Status (KPS) ≥60
Phase 1 Arm A
Histopathologically proven diagnoses of either: GBM, IDH-wildtype, Grade 4 (per WHO 2021);[13] may include secondary GBMs (i.e., progression from low-grade gliomas) **OR** astrocytoma, IDH-mutant, Grade 3 (per WHO 2021)[13]
Phase 1 Arm B
New, histologically proven diagnosis of GBM, IDH-WT Grade 4 (per WHO 2021);[13] may include secondary GBMs (i.e., progression from low-grade gliomas)
KPS ≥70
Phase 2
Histopathologically proven diagnosis of GBM, IDH-WT, Grade 4 (per WHO 2021)[13]

KEY EXCLUSION CRITERIA
Phase 1 and 2
Chemotherapy, monoclonal antibodies/biologics, investigational treatment, or RT with curative intent with 28 days prior to starting study treatment
Prior exposure to any WEE1 inhibitor
Left ventricular ejection fraction <55%
Phase 1 Arm A and Phase 2
Prior treatment with bevacizumab, other VEGF inhibitors, or VEGF-receptor signalling inhibitors
Phase 1 Arm A
Prior treatment with >2 lines of therapy for GBM IDH-wildtype, Grade 4, or for astrocytoma, IDH-mutant, Grade 3
Phase 1 Arm B
Prior radiation, chemotherapy, biological therapy, interstitial brachytherapy, implanted chemotherapy, therapeutics delivered by local injection or convection-enhanced delivery for GBM
Phase 2
Prior treatment with >1 line of systemic therapy for GBM IDH-wildtype, Grade 4. Combination therapy with TMZ and RT with/without subsequent TMZ treatment is considered as 1 line

SUMMARY

- WEE1 kinase, a key regulator of cell cycle progression and DDR pathway activation, is often upregulated in tumor cells and therefore represents an interesting therapeutic target for cancers
- Debio 0123 is a brain-penetrant, highly-selective WEE1 inhibitor that has been shown to improve response to RT *in vitro* and to TMZ in mouse models
- Phase 1 of this study will identify the RP2D of Debio 0123 in combination with TMZ+/-RT and Phase 2 will assess the safety and efficacy of the RP2D established in Phase 1 Arm A in pts with recurrent, progressive GBM
- The study is ongoing and enrolling pts in the US, Spain and Switzerland

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ABBREVIATIONS

CDC2, cell division control 2; CHK1/2, checkpoint kinase 1/2; CxRT, chemoradiotherapy; DDR, DNA damage response; DLT, dose-limiting toxicity; ECG, electrocardiogram; EORTC, European Organisation for Research and Treatment of Cancer; GBM, glioblastoma; Gd-based, gadolinium-based; HCT, historical clinical trials; IDH-WT, isocitrate dehydrogenase-wildtype; KPS, Karnofsky Performance Score; MRI, magnetic resonance imaging; OR, objective response; pts, patients; RANO, Response Assessment in Neuro-Oncology; RP2D, recommended Phase 2 dose; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; SOC, standard of care; TEAE, treatment-emergent adverse event; TMZ, temozolomide; WHO, World Health Organisation; VEGF, vascular endothelial growth factor

CONFLICTS OF INTEREST

LRS reports research support from Merck and BTG, PLC; Advisory board for BTG, PLC; Consulting fees from ONO Pharmaceuticals. ERI is an employee of Debiopharm International SA and reports shares in BioNtech. SM, AB, MO, LP and VR are employees of Debiopharm International SA. PR, KPP, MV, JTY, NKM, JMS, VM, JGPL and JR have nothing to declare.

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