BGB-290-104: A Phase 1b/2 study to assess the safety, tolerability and efficacy of BGB-290 in combination with radiation therapy and/or temozolomide in subjects with first-line or recurrent/refractory glioblastoma

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Primary objectives:Phase 1b:Arm A (BGB-290 + radiation therapy [RT]): Subjects with first-line glioblastoma (GB) with unmethylated MGMT promoter (*unmethylated GB*)• To assess safety and tolerability of BGB-290 combined with RT• To identify dose-...

Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON48745

Source
ToetsingOnline

Brief title
BGB-290-104

Condition

- Other condition

Synonym
astrocytoma, primary brain tumour

Health condition

newly diagnosed and recurrent grade IV astrocytoma

Research involving
Human

Sponsors and support

Primary sponsor: BeiGene USA, Inc.
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: BGB-290, Glioblastoma, safety, tolerability

Outcome measures

Primary outcome

Phase 1b, all Arms

• Incidence and nature of DLTs

• Incidence, nature, and severity of AEs, graded according to the NCI-CTCAE,

v4.03

• Number of cycles (Arm C Only) and the dose intensity of each component of the

treatment regimens, and changes in vital signs and clinical laboratory test

results during and following study treatment

Phase 2, Arm A (BGB-290 + RT) and Arm B (BGB-290 + RT + TMZ)

• Modified disease control rate (DCR) as assessed using the modified Response

Assessment in Neuro-Oncology (mRANO), version 1.1

Phase 2, Arm C (BGB-290 + TMZ)

• Objective response rate (ORR) as assessed using mRANO

Secondary outcome

Phase 1b, all Arms:

• PK parameter for pamiparib of steady-state Ctrough

• Modified DCR (Arms A and B), DCR (Arm C), ORR and clinical benefit rate (CBR)

• Time-to-event endpoints: e.g., duration of response (DOR), progression-free survival (PFS) and overall survival (OS)

Phase 2, Arm A (BGB-290 + RT) and Arm B (BGB-290 + RT + TMZ):

• ORR and CBR as assessed using RANO criteria

• Time-to-event endpoints: e.g., DOR, PFS and OS Incidence, nature, and severity of AEs, graded according to NCI-CTCAE, v4.03

• The Dose intensity of each component of the treatment regimens, and changes in vital signs and clinical laboratory test results during and following study treatment

• PK parameter for pamiparib

Phase 2, Arm C (BGB-290 + TMZ):

• DCR and CBR as assessed using RANO criteria

• Time-to-event endpoints: e.g., DOR, PFS and OS

• Incidence, nature, and severity of AEs, graded according to NCI-CTCAE, v4.03

• Number of cycles and the dose intensity of each component of the treatment regimens, and changes in vital signs and clinical laboratory test results during and following study treatment

• PK parameter for pamiparub

Study description

Background summary

Glioblastomas (GB), the most aggressive subtype of gliomas, harbor a range of oncogenic mutations. These mutations are associated with resistance to both chemotherapy and radiation therapy (RT). A substantial number of these genetic alterations affect key players in deoxyribonucleic acid (DNA) repair pathways.

• Methylation of the O6-methylguanine-DNA methyltransferase (MGMT) gene promoter and Mismatch Repair (MMR) gene mutations:
• Downregulation of the p53 signaling pathway: Around 70% of GB patients were reported to have somatic mutations affecting the p53 pathway
• Downregulation of the retinoblastoma (RB) signaling pathway: RB1 and its paralogs p107 and p130 play a central role in DNA double strand break (DSB) repair by non-homologous end joining
• Upregulation of the epidermal growth factor receptor (EGFR)/Ras/phosphatidylinositol-3-OH kinase (PI3K) signaling pathway through PTEN alterations:

The high frequency of genetic alterations in GB affecting DNA repair pathways suggests that DNA-damaging agents or agents interfering with DNA repair may be able to provide clinical benefit for GB patients. This hypothesis is supported by the current standard of care for GB patients but has not been adequately explored for other classes of drugs, such as inhibitors of poly(ADP-ribose) polymerase (PARP).

Because of the infiltrative nature of GB, surgery alone is never curative. Therefore, the majority of patients are subsequently treated with RT, with or without chemotherapy. In 2005, Stupp and colleagues published a landmark study demonstrating a 2.5-month overall survival (OS) benefit with the addition of the alkylating agent temozolomide (TMZ) to surgery and RT . The results of this large trial established the role of TMZ, along with maximal safe resection and RT, for the treatment of newly diagnosed GB patients <65 years old. Preliminary evidence that inactivation of the MGMT protein conferred sensitivity to TMZ and TMZ*s efficacy in recurrent glioma served as supporting data for this large, randomized, Phase 3 trial. Subset analyses confirmed improved survival and sensitivity to TMZ for tumors deficient in MGMT (defined by MGMT promoter methylation) compared to those with adequate MGMT expression (defined by an unmethylated MGMT promoter).

Ionizing radiation used in the clinical treatment of GB generates mostly single-strand breaks (SSBs) and to a minor extent DSBs. Single-strand breaks are repaired through the BER pathway, operating via either the short patch or the long patch repair sub-pathways, which differ in the size of the repair

patch and the enzymes involved. A PARP-1 role in the short patch is well established, but its contribution in the long patch is still unclear. In non-replicating cells, PARP inhibition only delays the repair of SSBs induced by radiation with a minimal impact on cell survival. On the contrary, PARP inhibition markedly enhances radiosensitivity of proliferating cells since unrepaired SSBs
collide with the DNA replication machinery, generating DSBs. Thus, PARP inhibitors have the potential to increase the anti-tumor effect of RT by preventing DNA damage repair and increasing cytotoxic DNA damage.

PARP-1 and PARP-2 have a key role in the base excision repair (BER) of N-methylpurines (N7-methylguanine and N3-methyladenine) that are generated by TMZ. In the presence of a functional BER system these damaged bases are promptly repaired and limit TMZ cytotoxicity. The first step of the BER process is the excision of the modified base by N-methylpurine glycosylase (MPG) resulting in an apurinic/apyrimidinic (AP) site that is subsequently cleaved by apurinic/apyrimidinic endonuclease. The resultant DNA nicks are finally repaired by the coordinate intervention of PARP-1, DNA polymerase, XRCC1 and ligase III. Inhibition of PARP activity hampers PARylation of PARP-1 and PARP-2, interrupting the completion of the repair process mediated by BER . Combining PARP inhibition with DNA-damaging TMZ leads to increased DNA damage that results in apoptosis and/or growth arrest. Repeated treatments with TMZ and PARP inhibitors also downregulate transcription and delay recovery of BER
components in tumor cells . This mechanism might further enhance the cytotoxic effects of TMZ combined with a PARP inhibitor.

In glioma cells, pharmacological modulation of PARP activity increased growth inhibition by TMZ in both p53-wild-type and p53-mutant glioblastoma cells and markedly lowered the TMZ IC50 to levels below the concentration of TMZ that can be detected in the plasma or brain of treated patients. The most pronounced effect was observed in tumor cells resistant to TMZ due to high MGMT levels or to MMR deficiency. In fact, in short-term primary cultures of glioma cells derived from surgical specimens, the enhancement of chemosensitivity to TMZ induced by a PARP inhibitor was especially evident in MGMT-proficient cells. Moreover, in an MMR-deficient glioma cell line, in which an MGMT inhibitor would have been ineffective, the combination of TMZ with the PARP inhibitor reverted resistance to the methylating compound . These data suggest that GB patients who derive less benefit from current standard of care because of lack of MGMT promoter methylation may benefit from a combination regimen that includes a PARP inhibitor.

Non clinical data suggests BGB-290 is a highly potent and selective inhibitor of PARP1 and PARP2 that sets itself apart from other PARP inhibitors by combining potent DNA-trapping activity with good brain penetrance.

Aside from surgical resection and RT as main standards of care. Glioblastomas

have a high prevalence of alterations affecting DNA repair. There is strong scientific rationale that PARP inhibitors may provide anti-tumor activity in GB, in particular when combined with standard-of-care DNA-damaging RT and/or TMZ. These novel combinations may furthermore be able to overcome resistance in GBs with unmethylated MGMT promoter.

Study objective

Primary objectives:
Phase 1b:
Arm A (BGB-290 + radiation therapy [RT]): Subjects with first-line glioblastoma (GB) with unmethylated MGMT promoter (*unmethylated GB*)
• To assess safety and tolerability of BGB-290 combined with RT
• To identify dose-limiting toxicity (DLT) and determine the maximum tolerated dose (MTD) or maximum administered dose (MAD) for BGB-290 combined with RT
• To select the recommended Phase 2 schedule for full-dose BGB 290 combined with RT Arm B (BGB-290 + RT + temozolomide [TMZ]): Subjects with first-line unmethylated GB
• To assess safety and tolerability of BGB-290 combined with RT and TMZ
• To identify DLTs and determine the MTD or MAD for TMZ combined with RT and the MTD/MAD for BGB-290 of Arm A
• To select the RP2D for TMZ combined with RT and the MTD/MAD for BGB-290 of Arm A Arm C (BGB-290 + TMZ): Subjects with recurrent/refractory GB
• To assess safety and tolerability of BGB-290 combined with TMZ
• To identify DLTs and determine the MTD or MAD for TMZ combined with full-dose BGB-290
• To select the RP2D for TMZ combined with full-dose BGB 290

Phase 2:
Arm A, Expansion 1 (BGB-290 + RT): Subjects with first-line unmethylated GB
• To assess the efficacy of BGB-290 combined with RT Arm B, Expansion 1 (BGB-290 + RT + TMZ): Subjects with first-line unmethylated GB
• To assess the efficacy of BGB-290 combined with RT and TMZ Arm C, Expansion 1 (BGB-290 + TMZ): Subjects with recurrent/refractory unmethylated GB
• To assess the efficacy of BGB-290 combined with TMZ Arm C, Expansion 2 (BGB-290 + TMZ): Subjects with recurrent/refractory methylated GB
• To assess the efficacy of BGB-290 combined with TMZ

Secondary

Phase 1b, all Arms
• To characterize the PK of BGB-290 in combination with RT and/or TMZ
• To make a preliminary assessment of BGB-290 efficacy in combination with RT and/or TMZ

Phase 2, all Arms
• To assess safety and tolerability of BGB-290 in combination with RT and/or TMZ

• To characterize the PK of BGB-290 in combination with RT and/or TMZ

Study design

This is an open-label, multi-center, multiple-dose, dose-escalation Phase 1b/2 study to determine the safety, pharmacokinetics (PK) and pharmacodynamics of BGB-290 in combination with RT and/or TMZ with two initial arms and a potential third arm. In Arm A, BGB-290 will be combined with RT in subjects with first-line glioblastoma (GB) with unmethylated MGMT promoter (*unmethylated GB*). In Arm B, depending on the safety of the Arm A combination, BGB-290 will be combined with both TMZ and RT in subjects with first-line unmethylated GB. In Arm C, BGB-290 will be combined with TMZ in subjects with recurrent/refractory GB with methylated or unmethylated MGMT promoter.

The dose escalation phase consists of the following:

Arm A: BGB-290 (60 mg BID) at increasing exposures of 2, 4, and 6 weeks in combination with RT for 6 to 7 weeks. After RT is completed, subjects will receive no further study treatment.

Arm B: Depending on the safety of the Arm A combination, the following combination may be explored: BGB-290 (as determined in Arm A) in combination with RT for 6 to 7 weeks and increasing doses of TMZ. After RT is completed, subjects will receive no further study treatment.

Arm C: BGB-290 (60 mg BID) in combination with increasing doses of TMZ administered on Days 1 to 21 of each 28-day cycle. The dose expansion phase consists of the following:

Once the safety, tolerability, PK, pharmacodynamic, and preliminary anti-tumor activity have been reviewed for the dose escalation cohorts of each of the arms, up to approximately 60 subjects may be enrolled in expansion cohorts for each of the three arms at a dose level below or equal to the MTD or MAD for that arm. In Arm C, two expansion cohorts may be opened, one for unmethylated GB and one for methylated GB. Approximately 60 subjects may be enrolled during the dose escalation phase, and the four dose expansion cohorts may comprise 240 subjects for a potential
approximate total of 300 subjects enrolled in this study.

Adverse events during and after the treatment period with study drug(s) will be followed and documented as outlined in Protocol Sections 7.4 and 9. AEs will be graded according to NCI-CTCAE v4.03. To determine the PK properties of BGB-290, blood samples will be taken at various time points as outlined in ProtocolSection 7.8 and Protocol Appendix 1.

Disease status will be assessed using mRANO criteria, v1.1. Subjects will undergo tumor assessments at screening and then every 8 weeks, or as clinically

indicated.In the absence of unacceptable toxicities or disease progression, subjects may be offered continued study treatment. Regardless of discontinuation of one or more study treatment(s), subjects should continue on study with regular follow-up (Protocol Sections 6.3 and 6.4). Subjects who have discontinued all study treatments should return to the clinic for an end-of-treatment (EOT) visit within 7 days of stopping all study treatment. Subjects in Arms A and B who have completed all study treatments per protocol will have their EOT visit at the end of the rest phase, 28 days after RT was completed. After the EOT visit, subjects should have regular follow-up for safety, efficacy and survival as outlined in Protocol Section 6.4. Subjects will be followed for survival and further anti-cancer therapy information post progression via
phone contact (with the subject*s guardian, if applicable) approximately every 12 weeks as per Protocol Appendix 1.

Intervention

Patients should take their precribed doses of TMZ and BGB-290.

BGB-290:
Arm A, Arm B, and Arm C: 60 mg will be administered PO BID, once in the morning and once in the evening 12 hours apart, continuously.
Radiation therapy:
Arm A and Arm B: RT will be administered QD × 5 days/week for 6 to 7 weeks with 1.8 to 2 Gy/fraction for a total dose of up to 60 Gy.
Temozolomide:
Arm B and Arm C: flat-dosing will be used for TMZ. The first dose level of 40 mg QD corresponds to 23 mg/m2 assuming an average body surface area of 1.73 m2. Subsequent dose levels of 80 mg and 120 mg correspond to 46 mg/m2 and 69 mg/m2, respectively will be administered PO QD.

Furthermore their data of Medical history and demographic data will be collected They must undergo physicial and vital signs examinations. An electrocardiogram and MRI scans will be made. Blood and urine will be collected.

Study burden and risks

BGB-290 has been studied in nonclinical toxicity and Phase 1 clinical studies. BGB-290 toxicities are largely consistent with the safety profile shared by other PARP inhibitors with the important exception that BGB-290 may cause less myelosuppression. PARP inhibitors, including BGB-290, show at least partial overlap with the safety profile of RT and/or TMZ. Therefore, subjects of this study may experience AEs typical for these study treatments at a higher frequency and/or severity. In addition, subjects may encounter AEs that are uniquely caused by the novel combination(s). Given the dire prognosis of GB

patients and the limited treatment options, the risk of combining BGB-290 with RT and/or TMZ appears acceptable in the context of a Phase 1 study with close monitoring through AE reporting, recording of vital signs and ECGs, clinical laboratory testing and tumor assessments.
As outlined in Sections 0 and 1.4, scientific rationale and supportive data are strong for combining PARP inhibitors with RT and/or TMZ in GB. This warrants evaluation of these combinations in GB patients, as the overall risk-benefit assessment appears favorable.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

ALL PATIENTS
1) Age >=18 years old

2) Confirmed diagnosis of glioblastoma (WHO Grade IV).
3) Ability to undergo serial MRIs.
4) ECOG status <= 1.
5) Adequate bone marrow function.
6) Adequate renal and hepatic function.
7) Ability to swallow whole capsules. ;Subjects in Arms A and B (not Arm C) must also meet inclusion criteria:
8) No previous treatment for GB except surgery.
9) Able to start radiation therapy <= 49 days after surgery but >= 14 days after a biopsy or >=28 days after an open biopsy or craniotomy with adequate wound healing.
10) Documented unmethylated MGMT promoter status.;Subjects in Arm C ESCALATION only must also meet inclusion criteria:
11) Documentation of MGMT promoter status
• It is preferable to determine MGMT status by MS-PCR. Other acceptable platforms include pyrosequencing methodologies and MSHRM assays with comparable sensitivity, applied to archival or fresh tumor tissue.
12) No prior systemic chemotherapy other than TMZ for GB and nd no prior anti-angiogenic therapy
13) Histologically confirmed secondary glioblastoma
14) Progressive disease > 2 months after completion of first line therapy.
15) Disease that is evaluable or measurable by mRANO ;Subjects in Arm C EXPANSION only must also meet inclusion criteria:
16) Histologically confirmed de novo (primary) glioblastoma with unequivocal first progressive disease (PD) after RT with concurrent/adjuvant TMZ chemotherapy as defined by one or more of the following:
• PD >= 3 months after the end of radiotherapy
• PD that is clearly outside the radiation field
• PD that has been unequivocally proven by surgery/biopsy
17) Disease that is measurable as defined by RANO criteria
18) Documentation of MGMT promoter status.
For full list of inclusion criteria refer to the study protocol.

Exclusion criteria

ALL PATIENTS
1) Chemotherapy, biologic therapy, immunotherapy or investigational agent <=21 days (or <=5 half-lives, whichever is shorter) prior to Day 1
2) Unresolved acute effects of any prior therapy of Grade >=2, except for AEs not constituting a safety risk by investigator judgement
3) Major surgical procedure, open biopsy, or significant traumatic injury <=28 days prior to Day 1, or anticipation of need for major surgical procedure during the course of the study
• Placement of vascular access device is not considered major surgery.
4) Other diagnosis of malignancy
• Except for surgically excised non-melanoma skin cancer, adequately treated carcinoma in situ of the cervix, localized prostate cancer treated with curative intent, adequately treated

low-stage bladder cancer, ductal carcinoma in situ treated surgically with curative intent, or a malignancy diagnosed >2 years ago with no current evidence of disease and no therapy <=2 years prior to Day 1
5) Active infection requiring systemic treatment
6) Active cardiac disease, inflammatory gastrointestinal disease, bleeding disorder (for details see protocol)
7) Anticoagulation with heparin, warfarin, or other anticoagulants (for details see protocol)8) Use <=10 days (or <=5 half-lives, whichever is shorter) prior to Day 1 or anticipated need for food or drugs known to be strong or moderate CYP3A inhibitors or strong CYP3A inducers including known enzyme inducing anti-epileptic drugs;For subjects in Arms B and C (NOT applicable to Arm A)
9) Known hypersensitivity to any temozolomide component or to dacarbazine (DTIC)
10) Have hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption
For full list of exclusion criteria see protocol.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	31-01-2019
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BGB-290
Generic name:	pamiparib

Product type:	Medicine
Brand name:	Temozolomide Accord
Generic name:	Temozolomide
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	05-09-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-01-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-02-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-02-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-04-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-04-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	04-11-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-01-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-10-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2017-001554-33-NL
ClinicalTrials.gov	NCT03150862
CCMO	NL62708.056.17

Study results

Date completed:	24-11-2020

Results posted: 02-09-2022

First publication
22-01-2022