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PHASE 1B/2 STUDY TO ASSESS THE CLINICAL EFFECTS OF BGB-290 IN COMBINATION WITH RADIATION THERAPY AND/OR TEMOZOLOMIDE IN PATIENTS WITH FIRST-LINE OR RECURRENT/REFRACTORY GLIOBLASTOMA

BeiGene

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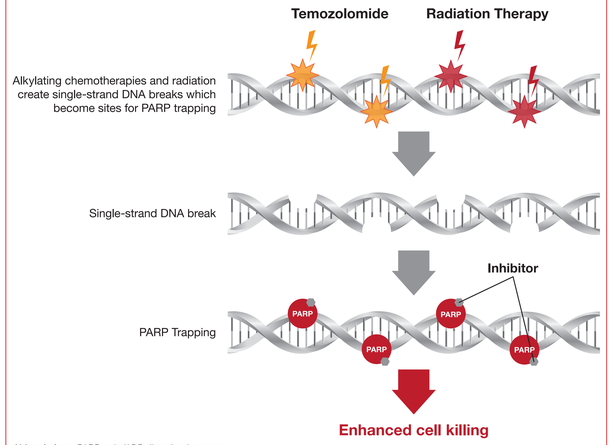
BACKGROUND

- Glioblastomas (GBMs) represent the most aggressive type of malignant tumor originating in the brain[1]
- Glioblastomas harbor a wide range of oncogenic mutations associated with resistance to chemotherapy and RT[2]
  - These mutations primarily affect key mediators involved in DNA repair mechanisms[2]
- Poly (ADP-ribose) polymerase (PARP) proteins are involved in DNA repair, genome stability and programmed cell death, and play a key role in base excision repair of DNA damage induced by chemotherapy agents (TMZ) or by RT[3]
- Inhibition of PARP activity (**Figure 1**):
  - Increases growth inhibition induced by TMZ in p53 wild-type and mutant GBM cells[4]
  - Enhances the radiosensitivity of proliferating cells resulting in double-strand DNA breaks[5,6]
- Small-molecule PARP inhibitors have demonstrated sustained antitumor effects in patients with BRCA1/BRCA2- mutant tumors[7]
- BGB-290 is a potent and selective PARP1/2 inhibitor that has shown potent PARP trapping, brain penetrance, and antitumor activity in preclinical xenograft models[8]
- Interim results from an ongoing Phase 1 study of patients with advanced solid tumors demonstrated that BGB-290 was well tolerated with promising antitumor activity in ovarian cancer[9]
- This Phase 1b/2 study (NCT03150862) has been planned to assess the safety, tolerability, and efficacy of BGB-290 in combination with RT or TMZ in patients with first-line or recurrent/refractory GBM

Figure 1: Rationale for Combining BGB-290 with Temozolomide/Radiation Therapy



Abbreviations: PARP, poly (ADP-ribose) polymerase.

METHODS

Overall Design and Study Objectives

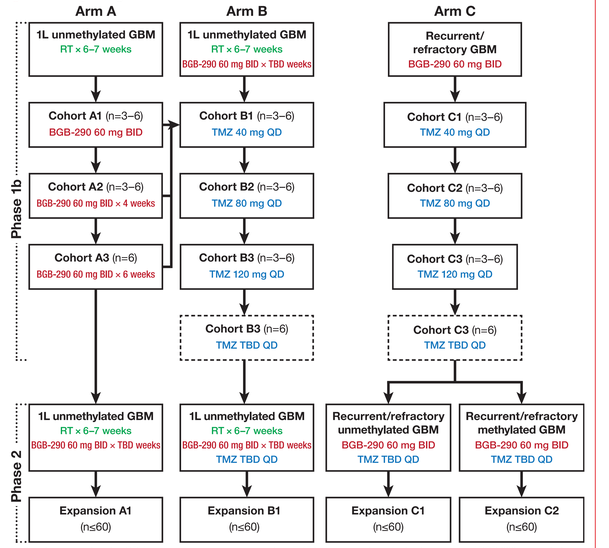
- This open-label, dose-escalation/dose-expansion Phase 1b/2 study was designed to determine the safety, tolerability (including dose-limiting toxicities [DLTs] and maximum tolerated dose [MTD] or maximum administered dose), pharmacokinetics, pharmacodynamics, and antitumor effects of BGB-290 at the recommended Phase 2 dose (60 mg by mouth [PO] twice daily [BID]) in combination with RT and/or TMZ
  - The Phase 1b component will consist of 3 dose-escalation arms (**Figure 2**)
    - **Arm A:** BGB-290 will be combined with RT in patients with first-line GBM with unmethylated O6-methylguanine-DNA methyltransferase (MGMT) promoter ('unmethylated GBM')
    - **Arm B:** BGB-290 will be combined with both TMZ and RT in patients with first-line unmethylated GBM
    - **Arm C:** BGB-290 will be combined with increasing doses of TMZ in patients with recurrent/refractory methylated or unmethylated GBM
  - For the Phase 2 dose-expansion cohort, ≤60 patients may be enrolled in each arm (**Figure 2**)
    - In Arm C, 2 expansion cohorts (unmethylated GBM and methylated GBM) with ≤60 patients each may be opened
- Patients will be enrolled from 15 to 40 sites across the United States, Europe, and Australia

Study Population

- Adult patients (≥18 years old), who have a histopathologically confirmed Grade IV GBM (based on the World Health Organization [WHO] criteria), a supratentorial component, and an Eastern Cooperative Oncology Group performance status ≤1 were enrolled
- Patients must have adequate bone marrow, liver, and renal function
- Patients enrolled in Arms A and B must be naïve to RT, chemotherapy, or systemic therapy for lower grade central nervous system tumors, and have documented unmethylated MGMT promoter status determined by methylation-specific polymerase chain reaction
- Patients enrolled in Arm C must have:
  - No prior systemic therapy other than TMZ for GBM WHO Grade IV
  - Progressive disease >2 months after completion of first-line therapy
  - At least 1 measurable lesion defined by modified Response Assessment in Neuro-Oncology (mRANO v1.1) criteria
- Patients were excluded if they had:
  - Chemotherapy, biologic therapy, immunotherapy, or investigational therapy ≤21 days (or ≤5 half-lives, whichever is shorter) prior to Day 1 of treatment
  - Uncontrolled seizure disorder or active bleeding disorder
  - Active infection requiring systemic treatment; known human immunodeficiency virus infection or active viral hepatitis
  - Current evidence of cardiac dysfunction or disease including myocardial infarction, class III/IV heart failure (New York Heart Association Functional Classification)
  - Active inflammatory gastrointestinal disease, chronic diarrhea, known diverticular disease, or previous gastric resection or lap band surgery

TREATMENTS

Figure 2: Study Design



Unmethylated and methylated GBM are allowed during dose escalation; TMZ to be administered for the time period of BGB-290 administration; [1]BGB-290 and TMZ to be administered on Days 1–21 of each 28-day cycle.
Abbreviations: 1L, first-line; BID, twice daily; GBM, glioblastoma; QD, once daily; RT, radiation therapy; TBD, to be determined; TMZ, temozolomide.

- **Arm A:** BGB-290 60 mg PO BID will be administered continuously; RT will be administered QD × 5 days per week for 6–7 weeks with 1.8–2 Gy/fraction for a total dose of up to 60 Gy
  - Three cohorts were treated with varying durations of RT
- **Arm B:** The dose of BGB-290 in the opening of Arm B will depend on the safety observed in Arm A; RT will be administered QD × 5 days per week for 6–7 weeks with 1.8–2 Gy/fraction for a total dose of up to 60 Gy; TMZ doses of 40–120 mg QD will be administered for the duration of BGB-290 treatment
  - After RT is completed, patients will receive no further study treatment
- **Arm C:** BGB-290 60 mg PO BID will be administered continuously; TMZ, at doses of 40–120 mg (Cohorts 1–3), will be given for Days 1–21 of each 28-day cycle
- Across all 3 arms, dose escalation will follow a modified 3+3 dose-escalation criteria, where, a minimum of 3 patients will be enrolled
  - If none of the first 3 evaluable patients enrolled in a given cohort experience a DLT, dose escalation may proceed
  - If 1 of the first 3 evaluable patients enrolled in a given cohort experiences a DLT, additional patients (for a minimum of 6 evaluable patients) will be enrolled in that cohort
- If a DLT is observed in at least one-third of patients, the MTD will have been exceeded, and dose escalation will be stopped; additional patients will be assessed for DLTs at the preceding dose level
- For Arms A and B, the DLT assessment window will depend on the time period of BGB-290 administration during RT and will consist of the time period of combination treatment plus 4 weeks (+3 days) after last scheduled combination treatment
- For Arm C, the DLT assessment window will encompass the first cycle of 28 days (+2 days)

STUDY ASSESSMENTS AND STATISTICAL ANALYSES

- Safety and tolerability of BGB-290 will be assessed by monitoring DLTs and AEs (per the NCI-CTCAE v4.03) as well as results from physical examinations, 12-lead electrocardiograms, and clinical laboratory evaluations
- Standard steady-state PK endpoints will be determined (eg, area under the plasma concentration–time curve [AUC], maximum observed plasma concentration [C_{max}], lowest observed plasma concentration [C_{trough}], time to maximum observed plasma concentration [t_{max}])
- Antitumor effects will be evaluated every 8 weeks (or as clinically indicated) using mRANO v1.1
- Descriptive statistics will be used to evaluate antitumor activity and tolerability of combination regimens

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Please address any questions or comments regarding this poster to Clinicaltrials@beigene.com.