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A PHASE 1B/2 STUDY TO ASSESS THE SAFETY, TOLERABILITY, AND CLINICAL ACTIVITY OF BGB-290 IN COMBINATION WITH TEMOZOLOMIDE IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC SOLID TUMORS

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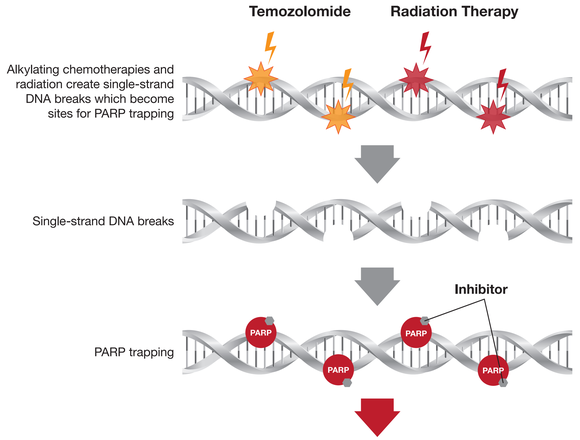
BACKGROUND

- Poly (ADP-ribose) polymerase (PARP) proteins are a family of DNA-binding and repair proteins that play a key role in the base excision repair of DNA damage caused by the DNA-alkylating agent, temozolomide (TMZ)
- By inhibiting PARP activity, PARP inhibitors exert cytotoxic effects on tumors, trapping PARP proteins on DNA, further augmenting cell death (Figure 1)
- Cancer cells with homologous recombination deficiencies (HRDs) are more susceptible to PARP inhibitors via a mechanism known as synthetic lethality, which occurs when 2 conditions in combination are lethal but neither agent alone is lethal[1]
- BGB-290 is a potent and selective inhibitor of PARP1/2 that has demonstrated synergistic cytotoxicity with TMZ in vitro, in both cell lines and animal models, and trapping activity both in vitro and in vivo
- 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[2]
- This Phase 1b/2 study (NCT03150810) has been planned to evaluate the effects of recommended Phase 2 dose (RP2D) of BGB-290 (60 mg twice daily [BID]) with escalating doses of TMZ, starting from 40 mg/day in patients with locally advanced and metastatic tumors[3-7]

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



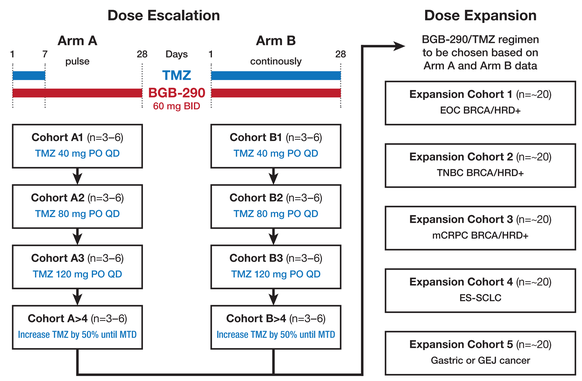
Abbreviations: PARP, poly (ADP-ribose) polymerase.

METHODS

Overall Design and Study Objectives

- This open-label, Phase 1b/2 dose-escalation/dose-expansion study (Figure 2) is designed to evaluate BGB-290 at the RP2D (60 mg administered orally [PO] BID) in combination with TMZ in patients with locally advanced and metastatic solid tumors
  - Patients will be enrolled from approximately 25 sites in the United States, Europe, Asia, and the Pacific region
  - The Phase 1b dose-escalation component will follow a 3+3 design to establish the maximum tolerated dose (MTD) of TMZ in combination with BGB-290 in approximately 50 patients with solid tumors
  - The Phase 2 component will further evaluate the safety, tolerability, and antitumor activity of the recommended combination dose and is scheduled to enroll approximately 100 patients with 5 different tumor types

Figure 2: Study Design



Abbreviations: BID, twice daily; ES-SCLC, extensive-stage small cell lung cancer; EOC; epithelial ovarian carcinoma; HRD, homologous recombination deficiency; GEJ, gastroesophageal junction; mCRPC; metastatic castration-resistant prostate cancer; PO, orally; QD, once daily; TMZ, temozolomide; TNBC; triple-negative breast cancer.

Objectives

- The primary objectives of this study are to determine the safety and tolerability of oral BGB-290 when administered in combination with oral TMZ (pulsed and continuous), determine the MTD or maximum administered dose for BGB-290 combined with TMZ (pulsed and continuous), and to select the RP2D and dosing schedule of BGB-290 in combination with TMZ
- Characterization of the pharmacokinetic (PK) profiles of BGB-290 and TMZ and preliminary antitumor activity of BGB-290 in combination with TMZ are secondary endpoints
- Evaluation of candidate biomarkers in tumor tissue and in peripheral circulation as potential markers of response, resistance, or disease progression is an exploratory endpoint

Study Population

- Adult patients (≥18 years old) with a confirmed malignancy that has progressed to advanced or metastatic stage with no option for effective standard therapy were enrolled
- Eastern Cooperative Oncology Group (ECOG) performance status ≤1
- Patient must have adequate bone marrow, liver, and renal function
- Patients are excluded if they have a hypersensitivity to any TMZ or dacarbazine, prior treatment with a PARP inhibitor (except for iniparib), chemotherapy, biologic therapy, immunotherapy, investigational agent within 3 weeks prior to treatment initiation, or are refractory to platinum-based therapy

Dose-Expansion Phase

- The dose-expansion phase will investigate BGB-290 in patients with selected tumor types (Table 1); all patients in all dose-expansion cohorts must have measurable disease per RECIST v1.1 except prostate cancer patients
  - Subjects with only non-measurable bone lesions must have either progression with 2 or more new lesions or have PSA progression within the 6-week period before study drug administration

Table 1: Tumor-Specific Cohorts

Treatment Cohort	Tumor type*	Estimated sample size
Cohort 1†	Platinum-sensitive, high-grade epithelial, non-mucinous, BRCA/HRD+ ovarian cancer, fallopian cancer, or primary peritoneal cancer (EOC)	20
Cohort 2†	Triple-negative BRCA/HRD+ breast cancer (TNBC)	20
Cohort 3†	Metastatic castration-resistant BRCA/HRD+ prostate cancer (mCRPC)	20
Cohort 4‡	Extensive-stage small cell lung cancer (ES-SCLC)	20
Cohort 5‡	Gastric or gastroesophageal junction cancer	20

*Patients who are considered refractory to platinum-based therapy are not eligible for any of the diseasespecific cohorts.
†Patients are required to have either HRD or BRCA1/2 mutation status at the time of enrollment.
‡Patients are required to have had <3 prior lines of therapy.
Abbreviations: HRD, homologous recombination deficiency.

TREATMENT

- The dose-escalation phase consists of 2 arms:
  - **Arm A:** continuous BGB-290 (60 mg BID) in combination with increasing doses of TMZ (fixed doses of 40, 80, 120 mg once daily [QD] and higher, if tolerated) administered on Days -1–7 of each 28-day cycle
  - **Arm B:** BGB-290 (60 mg BID) in combination with increasing doses of TMZ (fixed doses of 40, 80, 120 mg QD and higher, if tolerated) administered continuously
- Following a modified 3+3 dose-escalation guideline, a minimum of 3 patients will be enrolled in Arm A, dose level 1, before patients are enrolled into Arm B, dose level 1
- The decision to proceed to the next dose cohort will be on the basis of dose-limiting toxicity (DLT)
  - 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 will be enrolled in that cohort, for a minimum of 6 evaluable patients
- The dose-expansion phase will begin once the safety and tolerability have been reviewed for the dose-escalation cohorts and the preferred dose and treatment schedule of BGB-290 plus TMZ has been determined

STUDY ASSESSMENTS AND STATISTICAL ANALYSES

- Safety/tolerability of BGB-290 will be assessed by monitoring DLTs and AEs (per NCI-CTCAE v4.03) as well as results from physical examinations, 12-lead electrocardiograms, vital signs assessments, and clinical laboratory evaluations
- Antitumor effects will be assessed based on RECIST v1.1
  - For patients with prostate cancer, prostate-specific antigen and tumor lesion will be evaluated together to determine the tumor response based on Prostate Cancer Working Group 2 criteria
  - For patients with ovarian cancer, tumor responses may also be evaluated using RECIST v1.1 combined with Gynecological Cancer Intergroup carcinoma antigen 125 criteria
- Trial data will be summarized using descriptive statistics; no formal hypothesis testing is planned for this study

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