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

Authors: M. Johnson[1], B. Benson[2], R. Wei[3], R. Brachmann[2], M.D. Galsky[4]; [1]Tennessee Oncology, Sarah Cannon Research Institute, Nashville, TN, US, [2]Clinical Development, BeiGene USA, Inc, Emeryville, US, [3]BioStatistics, BeiGene USA, Inc, Emeryville, US, [4]Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, US

Background

Poly (ADP-ribose) polymerase (PARP) proteins are a family of DNA binding and repair proteins and are thought to play a key role in the base excision repair of DNA damage generated by temozolomide (TMZ), a DNA-alkylating agent. PARP inhibitors (PARPis) represent a class of antitumor agents that exert their cytotoxic effects by inhibiting PARP activity. Some PARPis are capable of trapping PARP proteins on DNA, further augmenting cell death. BGB-290 is a potent and selective inhibitor of PARP1/2 and has demonstrated PARP trapping capacity. Synergistic cytotoxicity has been observed *in vitro* and *in vivo* when BGB-290 is combined with low dose TMZ

Trial design

This open-label, Phase 1b/2 dose-escalation/dose-expansion study is designed to evaluate BGB-290 at the recommended Phase 2 dose (60 mg administered orally twice daily [PO BID]) in combination with TMZ in patients with locally advanced and metastatic solid tumors. 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 ~50 patients with solid tumors. Dose escalation will evaluate the safety, tolerability and pharmacokinetics of BGB-290 (60 mg BID) plus escalating doses of TMZ administered once daily (QD) either on Days 1-7 (Arm A) or continuously (Arm B) of each 28-day cycle. The phase 2 component will further evaluate the safety, tolerability and antitumor activity of the recommended combination dose and schedule in ~20 patients with one of five different tumor types (**Table**). Enrollment into these expansion cohorts will occur simultaneously and independent of each other. Subjects will continue to receive treatment in 28-day cycles until confirmed disease progression, intolerable toxicity, or discontinuation/withdrawal.

Treatment Arm	Tumor type	Estimated sample size
Cohort 1	Platinum-sensitive high grade epithelial, non-mucinous, ovarian cancer, fallopian cancer or primary peritoneal cancer with either known deleterious or suspected deleterious germline or somatic BRCA1/2 mutation or with DNA HRD	20
Cohort 2	Triple negative breast cancer with either known deleterious or suspected deleterious germline or somatic *BRCA1/2* mutation or with DNA HRD	20

Cohort 3	Metastatic castration-resistant prostate cancer with either known deleterious or suspected deleterious germline or somatic BRCA1/2 mutation or with documented HRD	20
Cohort 4	Extended stage small cell lung cancer who have been treated with ≤2 prior regimens	20
Cohort 5	Gastric or gastroesophageal junction cancer who have been treated with ≤ 2 prior regimens	20

Clinical trial identification