Phase 1b/2 study to assess the clinical effects of BGB-290 in combination with radiation therapy (RT) and/or temozolomide (TMZ) in patients with first-line or recurrent/refractory glioblastoma

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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 TMZ. In glioblastoma (GB) cells, pharmacological modulation of PARP activity increased growth inhibition induced by TMZ in both p53-wild type and-mutant GB cells lowering the TMZ IC_{50}. RT used in the clinical treatment of GB generates mostly single-strand breaks (SSBs). 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 generating double-strand breaks. Thus, PARP inhibitors have the potential to increase the therapeutic index of RT by increasing DNA damage mainly in highly replicating tumor cells, but sparing non-cycling normal tissues. BGB-290, a potent and selective inhibitor of PARP1/2, has demonstrated potent PARP trapping, brain penetrance and antitumor activity in preclinical intracranial xenograft models.

Trial design

This open-label, dose-escalation/dose-expansion Phase 1b/2 study was designed to determine the safety, tolerability, pharmacokinetics, pharmacodynamics, and antitumor effects of BGB-290 at the recommended Phase 2 dose (60 mg PO BID) in combination with RT and/or TMZ. The Phase 1b component will consist of 3 dose-escalation arms. Arm A: BGB-290 will be combined with RT in patients with first-line GB with unmethylated *MGMT* promoter ('unmethylated GB'); Arm B: BGB-290 will be combined with both TMZ and RT in patients with first-line unmethylated GB; Arm C: BGB-290 will be combined with increasing doses of TMZ in patients with recurrent/refractory methylated or unmethylated GB. Once a recommended Phase 2 regimen has been established, up to 60 patients may be enrolled in the dose-expansion (Phase 2) cohort for that arm. In Arm C, 2 expansion cohorts with up to 60 patients each may be opened: 1 for unmethylated GB and 1 for methylated GB.

Clinical trial identification