A first-in-human phase 1a/b study of BGB-58067, an MTA-cooperative PRMT5 inhibitor, in patients with advanced solid tumors and MTAP deficiency

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Background: Protein arginine methyltransferase 5 (PRMT5) is an enzyme that methylates substrates involved in cellular activities, including transcription, RNA splicing, DNA damage repair, apoptosis, and cell-cycle regulation, and may act as an oncogene in multiple tumor types. Overexpression of PRMT5 is associated with poor clinical outcomes in a variety of cancers, including lung, colon, pancreas, and bladder cancer, and glioblastoma multiforme. Homozygous loss of the methylthioadenosine phosphorylase (*MTAP)* gene occurs in 15% of all tumor types, leading to the accumulation of methylthioadenosine (MTA), which partially inhibits PRMT5 and increases the susceptibility of these tumor cells to additional PRMT5 inhibition. BGB-58067 is an oral, highly potent, brain-penetrant, MTA-cooperative PRMT5 inhibitor that selectively inhibits PRMT5 in tumors with *MTAP* deletion. Preclinical evidence has shown the effectiveness of BGB-58067 in inhibiting PRMT5-mediated signaling and in its *in vivo* antitumor activity.

Methods: This study is a first-in-human, phase 1a/b, open-label, international, multicenter trial to evaluate the safety/tolerability, pharmacokinetics (PK), pharmacodynamics, and preliminary antitumor activity of BGB-58067 in patients with advanced solid tumors with *MTAP* deficiency (NCT06589596). In the dose-escalation and safety-expansion phase (phase 1a), sequential cohorts of patients will receive increasing dose levels of BGB-58067 given orally as monotherapy. In the dose-expansion and optimization phase (phase 1b), patients with select tumor types will receive BGB-58067 at the recommended dose(s) for expansion (RDFE[s]). Eligible patients are ≥18 years of age with pathologically confirmed advanced, metastatic, or unresectable solid tumors who have previously received standard systemic therapy or for whom treatment is not available or tolerated and with evidence of homozygous loss of the *MTAP* gene or lost MTAP expression in the tumor tissue.

For phase 1a, the primary objectives are to assess the safety/tolerability of BGB-58067 and to determine the maximum tolerated dose or maximum administered dose and RDFE(s); secondary objectives are to assess the preliminary antitumor activity (objective response rate [ORR], duration of response [DOR], and disease control rate [DCR], per investigator) and PK of BGB-58067. For phase 1b, the primary objectives are to determine the recommended phase 2 dose and to assess the antitumor activity (ORR per investigator); secondary objectives are to further assess antitumor activity (DOR, DCR and progression-free survival per investigator) and safety/tolerability of BGB-58067.

As of December 2024, the trial is actively recruiting patients in Australia, China, and the United States.