Trial in progress: 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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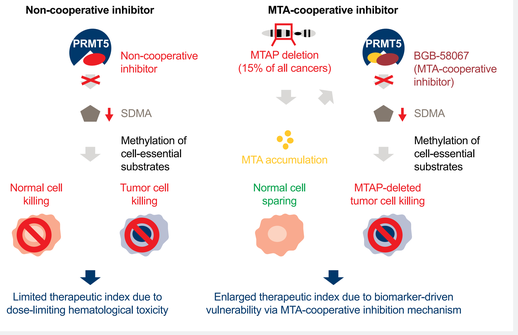
Introduction

- Protein arginine methyltransferase 5 (PRMT5) is a type II arginine methyltransferase that catalyzes the formation of monomethylated arginine (MMA) and symmetric dimethylarginine
  - PRMT5 participates in the methylation of substrates involved in cellular activities, including transcription, RNA splicing, DNA damage repair, apoptosis, and cell-cycle regulation[1]
  - PRMT5 may act as an oncogene,[1] with its overexpression associated with poor outcomes in a range of cancers, including lung, colon, pancreas, and bladder cancer, and glioblastoma multiforme[1-5]
- Homozygous loss of the *methylthioadenosine phosphorylase* (*MTAP*) gene occurs in 15% of all tumor types,[6] leading to the accumulation of methylthioadenosine (MTA), which partially inhibits PRMT5 and increases the susceptibility of these tumor cells to additional PRMT5 inhibition[7-9]

Figure 1. Mechanism of Action of BGB-58067



MTA, methylthioadenosine; MTAP, methylthioadenosine phosphorylase; PRMT5, protein arginine methyltransferase 5; SDMA, symmetric dimethylarginine.

- BGB-58067 is an oral, highly potent, brain-penetrant, MTA-cooperative PRMT5 inhibitor that selectively inhibits PRMT5 in tumors with MTAP deletion (**Figure 1**)
  - Preclinical evidence has shown the effectiveness of BGB-58067 in inhibiting PRMT5-mediated signaling and in its *in vivo* antitumor activity[10]
- BGB-58067 is being assessed as monotherapy in a first-in-human, phase 1a/b, open-label, international, multicenter trial in patients with advanced solid tumors with MTAP deficiency (NCT06589596)

Methods

Trial design

- This first-in-human, phase 1, open-label, international, multicenter trial consists of two parts: phase 1a (dose escalation/safety expansion) and phase 1b (dose expansion/optimization) (**Figure 2**)

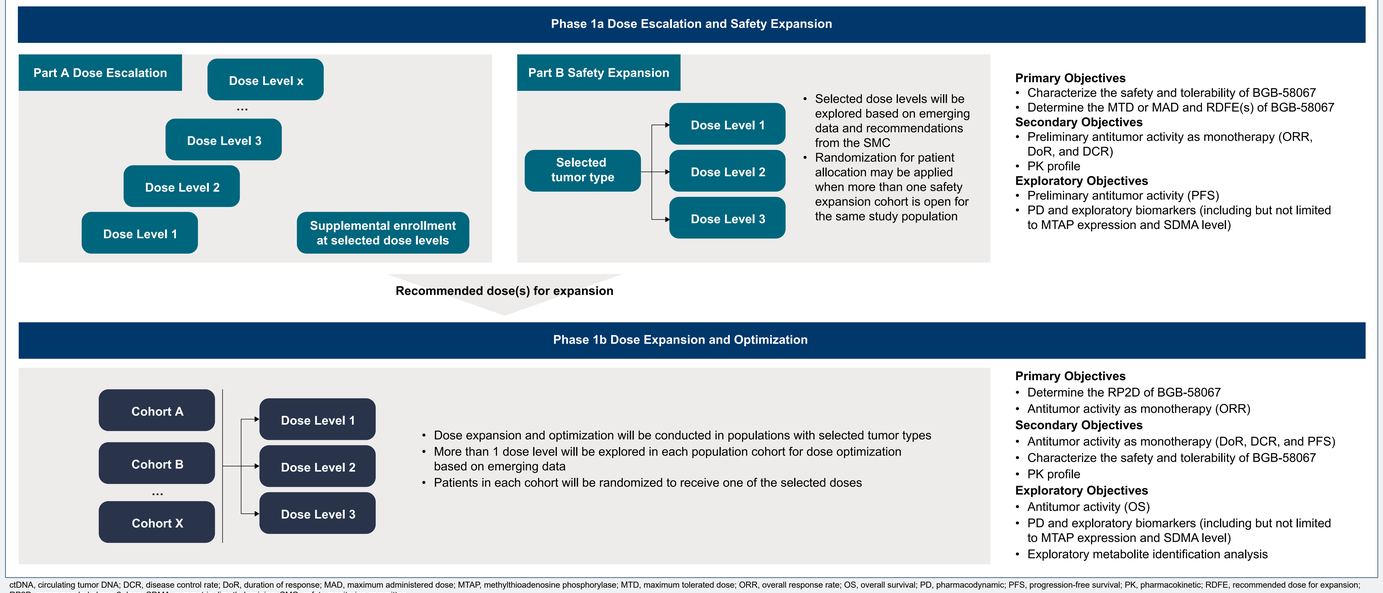
Key eligibility criteria

- Inclusion Criteria:
  - Patients with advanced, metastatic, or unresectable solid tumors, who have previously received standard systemic therapy or for whom treatment is not available or not tolerated
  - ECOG Performance Status of 0 or 1 or Karnofsky Performance Scale ≥70
  - Life expectancy ≥3 months
  - Evidence of homozygous loss of *MTAP* or lost MTAP expression in the tumor tissue
- Exclusion Criteria:
  - Prior treatment with any PRMT5 inhibitor or methionine adenosyltransferase 2a inhibitor
  - Active leptomeningeal disease or symptomatic spinal cord compression
  - Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage
  - Any malignancy ≤2 years before first dose of study drug except for the specific cancer under investigation in this study and any locally recurring cancer that has been treated curatively
- Please refer to ClinicalTrials.gov, NCT06589596, for further eligibility criteria

Analysis and Statistical Methods

- Dose escalation will be guided using the modified toxicity probability interval method[11]
- Patient demographics, safety, pharmacokinetics, and efficacy will be summarized by dose level and for all patients. Quantitative data will be described by standard descriptive statistics. Qualitative data will be summarized by frequency tables with number and proportion in each category
- Efficacy endpoints such as overall response rate and disease control rate will be summarized by dose level along with their 95% confidence intervals. The time-to-event endpoints, including duration of response, progression-free survival and overall survival will be analyzed using the Kaplan–Meier method

Figure 2. Study Design



ctDNA, circulating tumor DNA; DCR, disease control rate; DoR, duration of response; MAD, maximum administered dose; MTAP, methylthioadenosine phosphorylase; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; PD, pharmacodynamic; PFS, progression-free survival; PK, pharmacokinetic; RDFE, recommended dose for expansion; RP2D, recommended phase 2 dose; SDMA, symmetric dimethylarginine; SMC, safety monitoring committee.

Study Status

- This trial opened for enrolment in October 2024 and is anticipated to close in November 2026
- As of March 2025, this trial is actively recruiting patients in Australia, China, Korea, Spain, and the United States. For a list of participating sites, please refer to ClinicalTrials.gov, NCT06589596

Figure 3. Participating Countries

References

1. Stopa N, et al. *Cell Mol Life Sci*. 2015;72:2041-2059
2. Li X, et al. *J Cell Mol Med*. 2021;25:3537-3547
3. Lee MKC, et al. *Cancers (Basel)*. 2021;13:5136
4. Tan L, et al. *Aging (Albany NY)*. 2020;12:8728-8741
5. Banasavadi-Siddegowda YK, et al. *Neuro Oncol*. 2018;20:753-763
6. Bedard GT, et al. *J Biol Chem*. 2024;300:105492
7. Kryukov GV, et al. *Science*. 2016;351:1214-1218
8. Cottrell KM, et al. *J Med Chem*. 2024;67:6064-6080
9. Engstrom LD, et al. *Cancer Discov*. 2023;13:2412-2431
10. Data on File. BeiGene
11. Guo W, et al. *Contemp Clin Trials*. 2017;58:23-33

Disclosures

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