BGB-58067, a brain-penetrative MTA-cooperative PRMT5 inhibitor, demonstrates promising anti-tumor activity and favorable selectivity in tumors with MTAP-deletion

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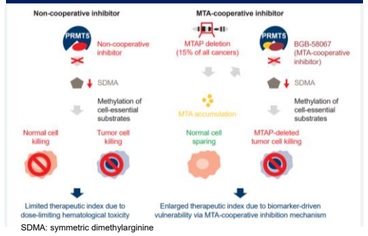
Introduction

Protein arginine methyltransferase 5 (PRMT5), as the major type II methyltransferase involved in multiple cellular activities, acts as an oncogene to promote tumorigenesis and progression; its overexpression is associated with poor clinical outcomes in a variety of cancers. PRMT5 was identified as a synthetic lethal target for cancers harboring homozygous deletion of the methylthioadenosine phosphorylase (MTAP) gene, as the homozygous MTAP-deletion was observed in 15% of all tumor types. 5'-methylthioadenosine (MTA) was found to accumulate in tumor cells with MTAP-deletion, which inhibited PRMT5 enzymatic activity and increased susceptibility to additional PRMT5 depletion. MTA-cooperative PRMT5 inhibitors have been developed as potential antitumor therapies in tumor types with MTAP-deletion as they selectively bind and stabilize the catalytically inactive PRMT5/MTA complex.

- BGB-58067 is a highly potent and selective MTA-cooperative PRMT5 inhibitor to demonstrate desirable *in vitro* and *in vivo* inhibition activities, as well as favorable selectivity and safety margin.
- BGB-58067 shows brain-penetrative potential, not being a substrate of P-gp or BCRP to demonstrate excellent unbound brain-to-plasma partition coefficient (Kp_{uu}) and robust intracranial anti-tumor activities.
- BGB-58067 is being assessed as monotherapy and in combination with other anti-cancer agents in a first-in-human, phase 1a/b, open-label, multicenter trial in patients with advanced solid tumors with MTAP deficiency (NCT06589596).

Mechanism of action of BGB-58067



SDMA: symmetric dimethylarginine

MTAP deletion occurs in various tumor types

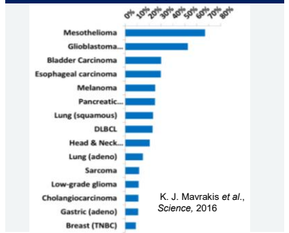


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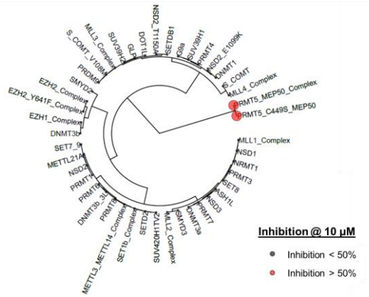
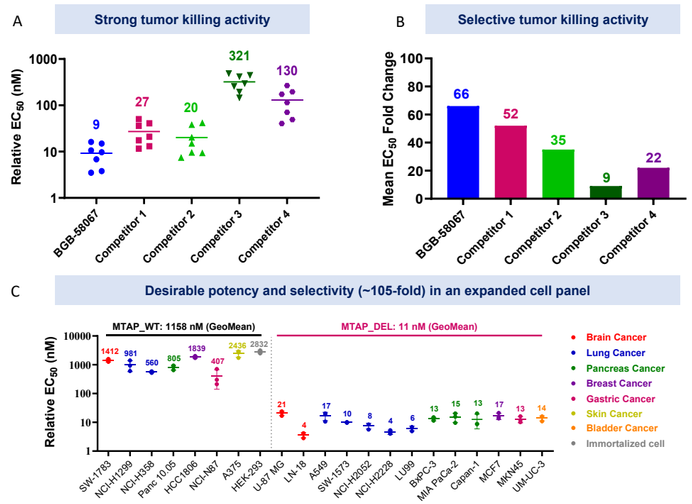
Figure 1. BGB-58067 is highly selective for PRMT5



BGB-58067 was screened at the concentration of 10 μM across a panel of 44 methyltransferases (Reaction Biology Corp.) and exibited high selectivity for PRMT5 (>98% inhibition) over other methyltransferases.

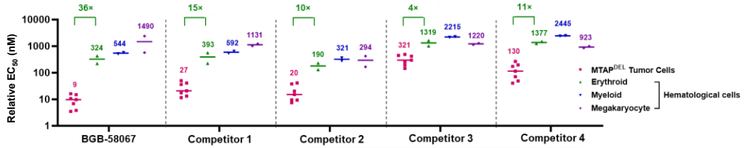
BGB-58067 was screened in an in vitro SafetyScreen87 study (Eurofins Panlabs) at 1 μM and did not show significant inhibition against any of the targets in the panel. (Not illustrated)

Figure 2. BGB-58067 has strong potency in MTAP^{Deletion} tumor cell lines and desirable selectivity against MTAP^{WT} tumor cell lines



(A) Dot plots showing mean cell killing EC_{50} value for PRMT5 inhibitors in different tumor cell lines with MTAP-deletion. (B) Fold change in mean EC_{50} value for cell killing in 2 MTAP^{WT} over 7 MTAP^{Deletion} tumor cell lines. (C) 21 tumor cell lines (8 MTAP-WT cell lines, 13 MTAP^{Deletion} cell lines) were tested in the cell viability inhibition assay. The average EC_{50} value were calculated from three independent assays.

Figure 3. BGB-58067 demonstrates excellent selectivity to spare normal hematological cells

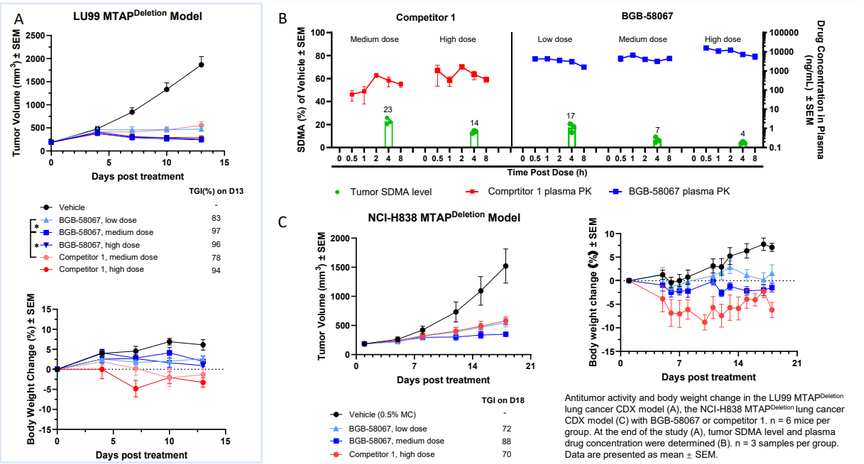


Dot plots showing mean cell killing EC_{50} values for PRMT5 inhibitors in MTAP^{Deletion} tumor cell lines and hematological cells (erythroid, myeloid, megakaryocyte; each dot represents a donor). Fold change in mean EC_{50} value for cell killing in erythroid over 7 MTAP^{Deletion} tumor cell lines.

Table 1. BGB-58067 has favorable pharmacokinetics/DDI properties

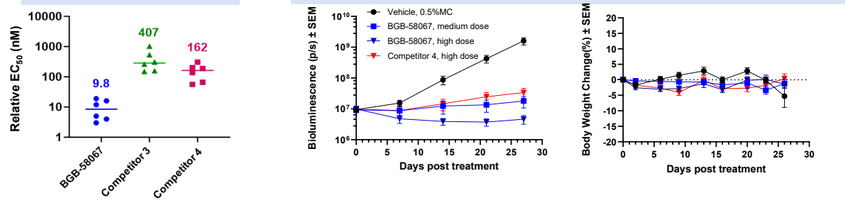
ADME/DDI	• High permeability and not a substrate of P-gp or BCRP, enabling optimal absorption and brain penetration • Low DDI risks as a perpetrator or victim
PK	• Medium-to-low clearance in both rodent and non-rodent species • Good bioavailability in both rodent and non-rodent species

Figure 4. BGB-58067 demonstrates robust *in vivo* anti-tumor activity in MTAP^{Deletion} CDX models



Antitumor activity and body weight change in the LU99 MTAP^{Deletion} lung cancer CDX model (A), the NCI-H838 MTAP^{Deletion} lung cancer CDX model (C) with BGB-58067 or competitor 1. n = 6 mice per group. At the end of the study (A), tumor SDMA level and plasma drug concentration were determined (B). n = 3 samples per group. Data are presented as mean ± SEM.

Figure 5. BGB-58067 exhibits strong potency in MTAP^{Deletion} brain tumor cells and strong intracranial anti-tumor activity



Dot plots showing the mean cell killing EC_{50} value for PRMT5 inhibitors in different MTAP^{Deletion} brain tumor cell lines (A). Antitumor activity and body weight change in the U-87 MG-luc MTAP^{Deletion} intracranial model (B) with BGB-58067 or Competitor 4. n = 8 mice per group. Data are presented as mean ± SEM.

Table 2. BGB-58067 is not a P-gp or BCRP substrate and shows excellent brain-penetrative activity

Parameters		BGB-58067	Competitor 3	Competitor 4
In vitro permeability	P_{app} A-B/Efflux ratio (MDCR-hP-gp, x10^{-6} cm/s)	9.7/1.0	16.0/1.2	22.1/1.6
	P_{app} A-B/Efflux ratio (MDCR-hBCRP, x10^{-6} cm/s)	8.7/1.0	28.6/0.8	14.8/1.0
In vivo	Kp_{uu}, brain (mouse)	18%	6.8%	17.1%
	Kp_{uu}, CSF (cyno)	55%	23%	46%

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