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

Authors: *Amy Jiang, Jinyan Chen, Xiaoxin Liu, Hongyu Chen, Huijun Kang, Jie Li, Haiying Li, Bo Zhang, Chenge Zhao, Hao Zhu, Xin Zhou, Sanjia Xu, Xing Zhou, Shifan Ma, Ming Fang, Min Xu, Lan Hua, Chuanxiu Yang, Yue Wu, Beibei Jiang, Xi Wu, Sean Lin, Fan Wang, Ye Liu, Zhitao Wan, Jing Li, Zhiwei Wang, Yu Shen, Lai Wang, Xiaomin Song***
BeOne Medicines, Beijing 102206, P.R. China.

Abstract: PRMT5 was identified as a synthetic lethal target for cancers harboring homozygous deletion of the MTAP gene. MTA was found to accumulate in tumor cells with MTAP-deletion, which inhibited PRMT5 enzymatic activity and increased susceptibility to additional PRMT5 depletion. The homozygous MTAP-deletion was observed in 15% of all tumor types. 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 to inhibit PRMT5 enzymatic activity. BGB-58067 is a highly potent and selective MTA-cooperative PRMT5 inhibitor with good brain penetration potential that is developed by BeOne Medicines. BGB-58067 is highly selective for PRMT5 over other methyltransferase family members. It shows strong killing potency and good selectivity (> 50-fold) in the cancer cell lines panel with MTAP-deletion over cell lines with MTAP-WT. BGB-58067 very weakly hits on normal hematological cells and demonstrates preferable selectivity (> 30-fold) than competitors. BGB-58067 induces robust anti-tumor activities in multiple cell line derived xenograft models. BGB-58067 demonstrates desirable pharmacokinetics properties and low DDI risk. It exhibits excellent unbound brain-to-plasma partition coefficient to support robust intracranial anti-tumor activities. BGB-58067 shows favorable nonclinical safety profile in the GLP studies, as well as good selectivity in an in vitro SafetyScreen87-off target profiling study. In conclusion, BGB-58067 demonstrates robust potency and selectivity, providing a favorable safety margin for patients, with high potential for the treatment of brain tumors and brain metastases.