Discovery and development of BLU-285: A potent, highly selective inhibitor of KIT and PDGFRα activation loop mutants

Abstract: KIT and PDGFRα activation loop mutants are recognized drivers of disease in subsets of patients with systemic mastocytosis (SM), gastrointestinal stromal tumors (GIST) and acute myeloid leukemia (AML). For the patients with primary activation loop mutations in PDGFRα and KIT Exon 17, there are no approved treatments that target these driver mutations. In patients with acquired mutations in the activation loop of KIT, despite advances in treatment options, patients still experience disease progression during or after treatment with available therapies. BLU-285 is a potent, highly selective oral inhibitor that targets KIT Exon 17 and PDGFRα D842 activation loop mutants. Blueprint Medicines is currently conducting Phase 1 clinical trials for BLU-285 in advanced SM and unresectable, treatment-resistant GIST. We will describe the discovery of BLU-285, including an in-depth mechanistic understanding of kinase activation loop mutants. The discussion will include kinome-wide selectivity structure-activity relationships (SAR) and the optimization of overall drug properties. The pharmacokinetics, in vivo potency and direct target engagement in i) a KIT D816 mutant in vivo model of SM, and ii) a TKI-refractory KIT activation loop-driven GIST patient derived xenograft (PDX) model will also be described.