Preclinical characterization of BGB-11417, a potent and selective Bcl-2 inhibitor with superior anti-tumor activities in haematological tumour models

BGB-11417 in blood cancer models

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The ability to evade apoptosis is a hallmark of cancer. B-cell lymphoma-2 (Bcl-2), an anti-apoptosis protein, is overexpressed and leads to oncogenesis or drug resistance in various tumor types, including lymphoma and leukemia. Bcl-2 is a well-validated target for B cell malignancies as demonstrated by a Bcl-2 inhibitor venetoclax which was recently approved for the treatment of chronic lymphocytic leukemia (CLL) and is currently in phase III clinical development for other hematologic malignancies. With longer term treatment, recurrent mutation G101V in Bcl-2 has been reported to mediate resistance to venetoclax in patients with CLL. Herein, we report the pharmacological properties of BGB-11417, a highly potent and selective BCL-2 inhibitor, in preclinical models. BGB-11417 potently inhibited both wildtype and G101V-mutated Bcl-2 in SPR binding assay with IC_{50} of 0.035 and 0.28 nM, respectively. BGB-11417 was a more potent Bcl-2 inhibitor than venatoclax in both enzymatic and cellular assays. In a binding assay for BH3 peptide and Bcl2, BGB-11417 and venatoclax showed an IC_{50} of 0.014 nM and 0.2 nM, respectively. In addition, BGB-11417 potently inhibited the proliferation of a Bcl-2 dependent

acute lymphoblastic leukemias (ALL) cell line RS4;11 with an IC_{50} of 0.81 nM, but not a Bcl-xL dependent T-ALL cell line Molt-4. Moreover, BGB-11417 exhibited potent cell killing activity against a variety of lymphoma and leukemia cell lines, including follicular lymphomas (FL), mantle cell lymphomas (MCL), diffuse large B-cell lymphomas (DLBCL) and acute myeloid leukemias (AML). BGB-11417 was also highly selective, showing ≥2000folds selectivity to Bcl-xL, BCL-W, MCL-1 and BCL2A1. In pharmacokinetics (PK) and pharmacodynamics (PD) studies, oral administration of BGB-11417 displayed a clear PK and PD correlation in RS4;11 ALL xenografts as shown by the increase of cleaved caspase 3 level with the increase of BGB-11417 concentration in tumor tissue. Furthermore, BGB-11417 demonstrated significantly greater efficacy than venetoclax in human ALL, MCL and DLBCL xenograft models without body weight loss. Collectively, BGB-11417 is a potent and highly selective Bcl-2 inhibitor with superior anti-tumor activities compared with venetoclax in preclinical studies. The phase I study of BGB-11417 for treatment of hematological cancers is ongoing.