Abstract #3077

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

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Summary

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 long term treatment, recurrent mutation G101V in Bcl-2 has been reported to mediate resistance to venetoclax in patients with CLL.

BGB-11417 is a highly potent and selective Bcl-2 inhibitor. It potently inhibited both wildtype and G101V-mutated Bcl-2 in Surface Plasmon Resonance (SPR) binding assay with K_D of 0.035 and 0.28 nM, respectively. It inhibited Bcl-2 protein activity at much lower concentrations compared to venetoclax in both of biochemical and cellular assays. BGB-11417 was also highly selective for Bcl-2, showing ≥2000 folds selectivity to Bcl-X_L, Bcl-w, Mcl-1 and Bcl2A1. In pharmacokinetics (PK) and pharmacodynamics (PD) studies, oral administration of BGB-11417 induced rapid and robust apoptosis and displayed a clear PK and PD correlation in RS4;11 ALL xenografts. Furthermore, BGB-11417 demonstrated significantly greater efficacy than venetoclax in human acute lymphoblastic leukemia (ALL), mantle cell lymphoma (MCL) and DLBCL (diffuse large B-cell lymphoma) xenograft mouse models.

Collectively, BGB-11417 is a highly potent and 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.

Methods

- Potency and selectivity of BGB-11417 were measured in SPR binding assay, time-resolved fluorescence resonance energy transfer (TR-FRET) assays and cell-based functional assays
- PK/PD analysis: Animals bearing RS4;11 xenograft tumors were treated with BGB-11417 at 0, 5, 15 or 50 mg/kg. Active caspase 3 levels in the tumor tissue were determined by ELISA. Plasma and tumor concentrations of BGB-11417 were determined at 0.5, 2, 4, 8, 12 and 24 hours post-dosing
- Efficacy study: Tumor cells were implanted subcutaneously in female NCG mice. Transplanted animals were randomized according to transplantation sequence and body weight. Tumor volume was measured twice weekly

Results

BGB-11417 potently and selectively inhibits Bcl-2

Table 1. Potency and selectivity profile of BGB-11417

In vitro assays	BGB-11417	venetoclax
SPR binding assay K_D (nM)		
Bcl-2 WT	0.035	1.3
Bcl-2 G101V	0.28	34
TR-FRET assay IC_{50} (nM)		
Bcl-2 WT	0.014	0.20
Bcl-X_L	28	65
Mcl-1	>10000	>10000
Bcl-w	1803	2730
Bcl2A1	>10000	>10000
Cell survival assay IC_{50} (nM)		
RS4;11 cell line	0.42	3.4
Molt4 cell line	2314	2790

Abbreviation: IC_{50}, 50% inhibitory concentration

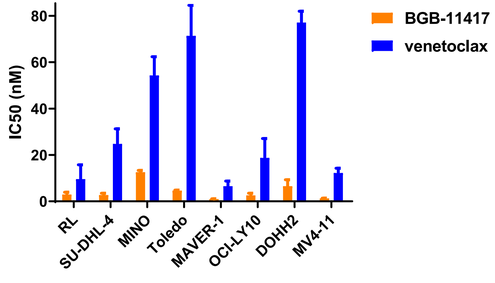

Figure 1. BGB-11417 exhibited potent cell-killing activity against a variety of hematological cancer cells.

BGB-11417 induces rapid and robust apoptosis in RS4;11 ALL tumor xenografts

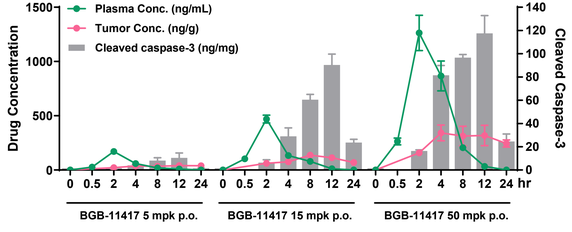

Figure 2. Time- and dose-dependent effects of BGB-11417 treatment on apoptotic marker, cleaved caspase-3 in human RS4;11 ALL xenografts in female NCG mice. Animals bearing RS4;11 xenograft tumors were treated as indicated by oral gavage for single dosing. Data were presented as mean active caspase-3 ser29 concentration ± standard error of the mean (SEM) of 3 animals in each group.

BGB-11417 performs superiorly to venetoclax in hematological xenograft models

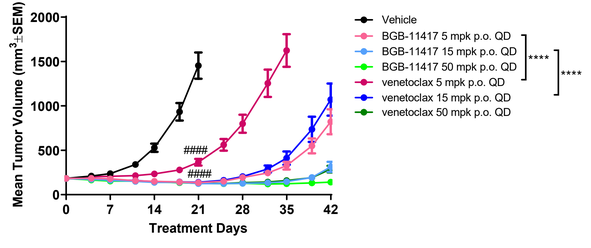

Figure 3. The effect of BGB-11417 on tumor growth in human RS4;11 ALL xenograft model. Mice were divided into 7 groups with 10 mice per group. #### p< 0.0001 all treatment groups versus vehicle by one-way ANOVA; **** p< 0.0001 versus venetoclax by one-way ANOVA.

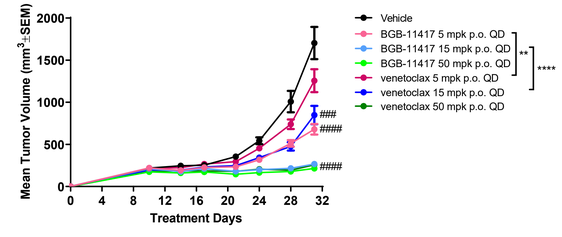

Figure 4. The effect of BGB-11417 on tumor growth in human Toledo DLBCL xenografts. Mice were divided into 7 groups with 10 mice per group. ### p< 0.001,#### p< 0.0001 versus vehicle by one-way ANOVA; ** p< 0.01, **** p< 0.0001 versus venetoclax by one-way ANOVA.

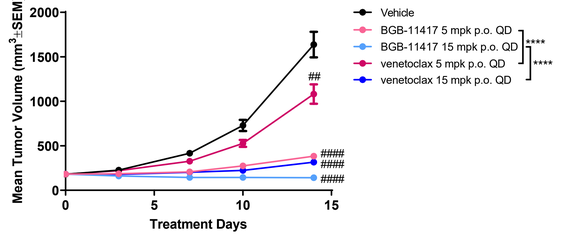

Figure 5. The effect of BGB-11417 on tumor growth in human MAVER-1 MCL xenografts. Mice were divided into 5 groups with 10 mice per group. ## p< 0.01,#### p< 0.0001 versus vehicle by one-way ANOVA; **** p< 0.0001 versus venetoclax by one-way ANOVA.

Conclusion

- BGB-11417 is a potent Bcl-2 inhibitor, with greater potency compared with venetoclax
- BGB-11417 has excellent selectivity profile for Bcl-2 against Bcl-xL, Mcl-1, Bcl-w and Bcl2A1
- BGB-11417 demonstrates remarkable efficacy in several preclinical tumor models, better than venetoclax at the same doses tested