Title: BGB-21447, a next generation Bcl-2 inhibitor, shows high potential in Bcl-2 overexpressing non-Hodgkin lymphomas (NHL) cancers in preclinical studies

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Background:

Venetoclax's success in CLL/SLL and AML validates Bcl-2 as a therapeutic target in hematologic malignancies. However, suboptimal efficacy has limited its development in DLBCL and multiple myeloma (MM) , raising uncertainty about whether Bcl-2 is an effective target in these diseases or if a more potent Bcl-2 inhibitor is needed.

Biologically, DLBCL has ≥20% BCL2 genetic alterations or ≥50% overexpression in patients), while Bcl-2 overexpression is also commonly observed in MM patients . These findings underscore the relevance of targeting Bcl-2 in both indications. In this study, we evaluate the potential of BGB-21447, a next-generation Bcl-2 inhibitor structurally distinct from sonrotoclax (BGB-11417), mainly in DLBCL/B-NHL via preclinical studies.

Methods:
Cell viability was assessed by CTG assay *in vitro*. Xenografts were established by subcutaneously inoculating cancer cells into NCG mice for in vivo efficacy evaluation. Bcl-2 protein levels were quantified using western blot and ELISA.

Results:

A panel of 21 DLBCL cell lines (15 GCB-DLBCL and 6 ABC-DLBCL) was tested for sensitivity to BGB-21447. In vitro CTG assays showed that 8/21 DLBCL cell lines responded to BGB-21447 with single-digit nanomolar (nM) potency, while the others were resistant. Sensitivity did not correlate with cell-of-origin subtype, but was enriched in cell lines with BCL2 genetic alterations, such as BCL2 amplification or t(14;18) translocation. Bcl-2 protein expression analysis revealed that these genetic alterations were associated with high Bcl-2 protein levels, as determined by western blot and ELISA. Notably, only cell lines with high Bcl-2 protein level were sensitive to BGB-21447, suggesting Bcl-2 protein expression as a potential predictive biomarker.

In vitro studies in Bcl-2-dependent DLBCL and MCL cell lines demonstrated that BGB-21447 is over 50-fold more potent than venetoclax, indicating strong potential in indications where venetoclax efficacy is limited. This was further supported by in vivo studies: BGB-21447, at 4 or 8 mpk QD (clinically achievable doses), showed significant anti-tumor activity in Toledo xenografts, while venetoclax at 50mpk QD (doses relevant to 1200 mg QD in humans) showed only partial efficacy. In SU-DHL-6 xenografts, venetoclax at 50 mpk QD had minimal effect, whereas BGB-21447 at 8 mpk significantly inhibited tumor growth. Similar trends were observed in Minami-1 (FL model) xenografts, where BGB-21447 induced complete tumor

regression, while venetoclax at 50 mpk QD showed partial activity.

Conclusions:
These findings indicate that BGB-21447 is a Bcl-2 inhibitor with substantially greater potency than venetoclax and strong potential in indications such as DLBCL where venetoclax has suboptimal efficacy. Clinical trials are needed to validate these results.