BGB-21447, a BCL-2 inhibitor, shows high potential in BCL-2 overexpressing B cell non-Hodgkin lymphomas (NHL) cancers in preclinical studies

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INTRODUCTION

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) , suggesting a more potent BCL-2 inhibitor is needed.

Biologically, DLBCL has ≥20% BCL-2 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, another BCL-2 inhibitor with high potency, 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.

CONCLUSIONS

BGB-21447 is a BCL-2 inhibitor with substantially greater potency than venetoclax and strong potential in indications such as DLBCL and solid tumors where venetoclax has suboptimal efficacy. Clinical trials are needed to validate these results.

ACKNOWLEDGEMENTS

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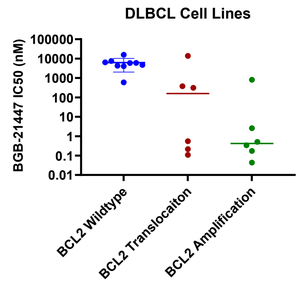
RESULTS

Figure 1: BGB-21447 sensitive DLBCL cancer cells tend to enrich BCL2 amplifications or translocations

A.

Cell lines	COO	BGB-21447 IC50 (nM)	BCL2 amp/translocation by FISH
TMD8	ABC	0.51	amp
OCI-LY3	ABC	808.3	amp
OCI-LY10	ABC	0.34	amp
RI-1	ABC	0.043	amp
U2932	ABC	0.17	amp
SU-DHL-2	ABC	4035	no
SU-DHL-6	GCB	2.59	amp
DB	GCB	13844	t(14;18)
Pfeiffer	GCB	378.6	t(14;18)
SU-DHL-4	GCB	313.8	t(14;18)
RL	GCB	0.21	t(14;18)
Toledo	GCB	0.10	t(14;18)
DOHH2	GCB	0.54	t(14;18)
SU-DHL-8	GCB	594.1	no
SU-DHL-5	GCB	5950	no
Farage	GCB	7572	no
SU-DHL-10	GCB	6418	no
HT	GCB	4272	no
Will-1	GCB	6016	no
OCI-LY7	GCB	4693	No
WSU-DLCL2	GCB	15755	No

B.



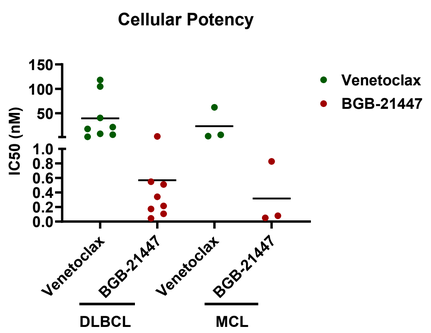
C.

DLBCL cell lines		BCL2 translocation/ amplification	
		Yes	No
BGB-21447 sensitive (IC50 <10nM)	Yes	8	0
	No	7	9

- The Fisher exact test statistic value is 0.0223.

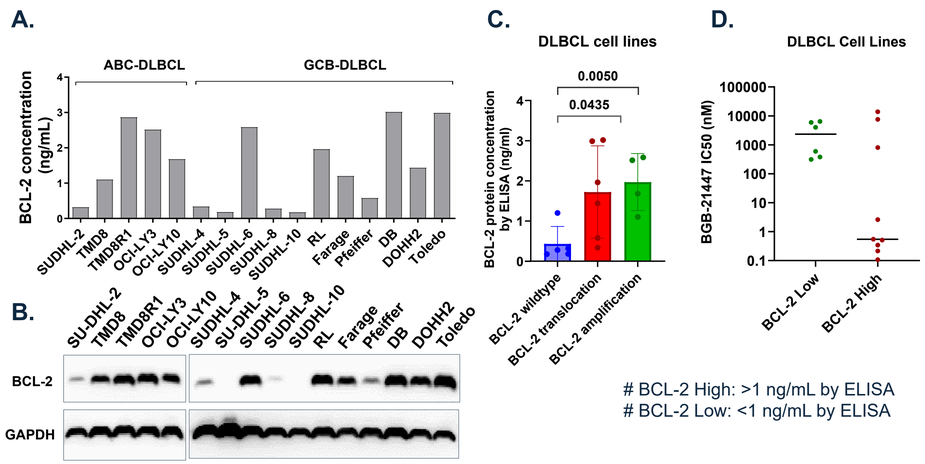
*The potency of BGB-21447 in DLBCL cancer cell lines. **A.** A table summarizes the IC50 of BGB-21447 in DLBCL cancer cell lines as well as BCL2 genetic alterations and cell of origin (COO) subtyping of selected DLBCL cell lines. **B-C.** Further analysis of data in A suggested that BGB-21447 sensitive DLBCL cells tend to enrich BCL2 genetic alterations.*

Figure 3: BGB-21447 is a BCL-2 inhibitor with more than 50-fold higher potency than venetoclax in different B lymphoma cancer cell lines *in vitro*



The potency of BGB-21447 was profiled in a panel of BCL2 dependent DLBCL and MCL cancer cell lines in vitro by using venetoclax as control. In almost all cell lines, BGB-21447 showed about 100-fold more potent activity than venetoclax.

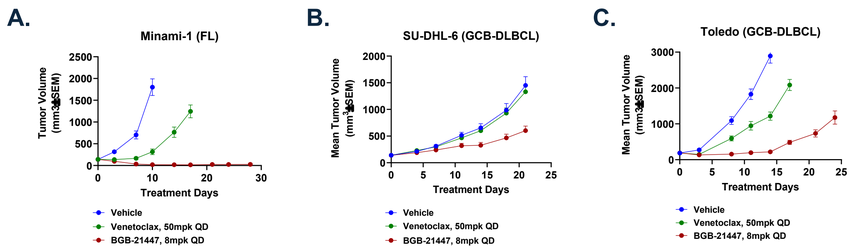
Figure 2: BCL-2 protein level in cancer cells correlates with BCL2 translocation or amplification, as well as BGB-21447 sensitivity



BCL-2 High: >1 ng/mL by ELISA
BCL-2 Low: <1 ng/mL by ELISA

*BCL-2 protein level and their correlation to BGB-21447 sensitivity in DLBCL cell lines. **A.** BCL-2 protein levels in DLBCL cell lines were examined by ELISA, variable protein levels were observed among cell lines. **B.** BCL-2 protein level examined by western blot correlates to ELISA concentration. **C.** Cell lines with BCL-2 genetic alterations tend to have higher protein levels. **D.** BGB-21447 sensitive cell lines tend to be enriched in cell lines with high protein levels.*

Figure 4: BGB-21447 demonstrates better anti-tumor activity in NHL xenograft models with BCL-2 high expression or BCL2 genetic alterations



#Toledo and Minami-1 have t(14;18) translocation, while SU-DHL-6 has amplification; they are all BCL-2 high expressed cancer cells.

*In vivo activity of BGB-21447 was further profiled in BCL-2 high expressing NHL xenografts . **A-C.** BGB-21447 at 8mpk QD showed significant better anti-tumor activity in all NHL xenograft models compared to venetoclax at 50mpk QD, a clinically relevant dose with exposure close to 1200mg QD in human.*