

# BGB-21447, a Next-Generation Bcl-2 Inhibitor, Demonstrates Superior Potency and Overcomes Venetoclax Resistance in Preclinical Models of Hematologic Malignancies #4663

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## Introduction

Bcl-2, a pivotal anti-apoptotic gatekeeper, maintains cellular survival by sequestering pro-apoptotic proteins. Aberrant overexpression or activation of Bcl-2 is a hallmark of numerous hematologic malignancies, where it drives tumorigenesis, predicts poor prognosis, and confers resistance to conventional chemotherapies<sup>1</sup>.

**Venetoclax (VEN) is a first-in-class Bcl-2 inhibitor. Nevertheless, significant unmet needs persist:**

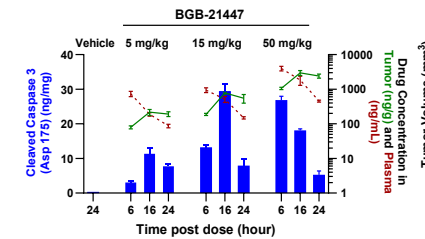
- VEN is approved for CLL/SLL and AML; however, its clinical benefit remains sub-optimal.
- Multiple acquired resistant *BCL2* mutations (e.g. G101V 16-50% and D103Y 3-17%) in CLL<sup>2-4</sup>.
- VEN showed modest efficacy in NHL (ORR = 38 and 18% in FL and DLBCL)<sup>5</sup>.

**BGB-21447 is a 2<sup>nd</sup> generation Bcl-2 inhibitor covering both WT Bcl-2 & broad mutations**

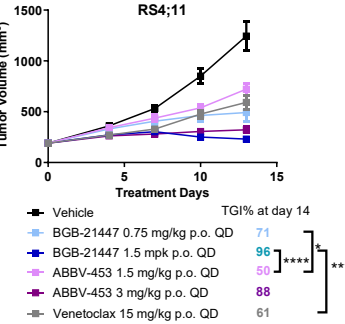
- **Remarkably better potency than VEN on WT Bcl-2**
  - Highly selective for Bcl-2 over other Bcl-2 family members
  - Remarkably better potency than VEN across hematologic cell lines (11- to 58- folds lower EC<sub>50</sub>).
  - Robust PD and superior antitumor activity to VEN in multiple tumor models
- **Highly potent against broad Bcl-2 mutations arising post VEN treatment**
  - Highly potent against broad Bcl-2 mutations, including G101V, D103Y/E/V, V156D, A113G, R129L.
  - Mutant xenograft models revealed superior PD and efficacy versus VEN
- **Phase 1 trials ongoing in metastatic breast cancer [NCT06756932]**

## BGB-21447 demonstrates robust PD and superior antitumor activity to VEN in *in-vivo* tumor models

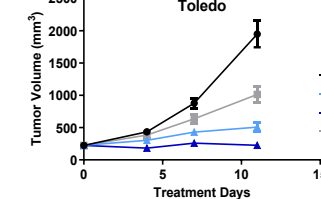
### Robust cleaved caspase-3 activation in RS4;11 leukemia CDX model



### Superior efficacy in RS4;11 leukemia CDX model

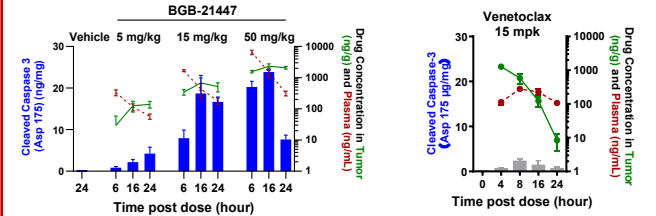


### Robust efficacy in VEN insensitive Toledo NHL CDX model

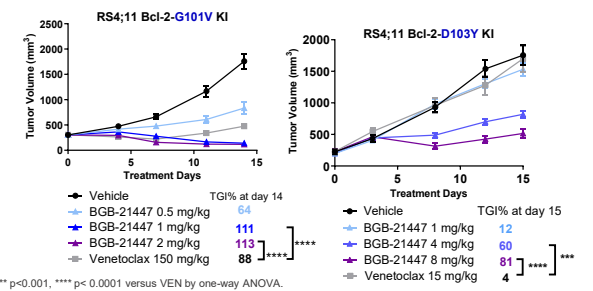


## BGB-21447 demonstrates robust PD and superior antitumor activity in Bcl-2 mutant tumor models

### Robust cleaved caspase-3 activation in RS4;11 Bcl-2 G101V KI CDX model



### Robust efficacy in VEN-resistant RS4;11 Bcl-2 G101V and Bcl-2 D103Y KI CDX models

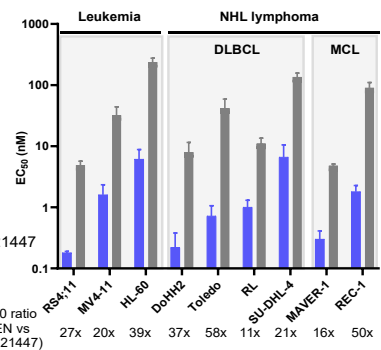


## BGB-21447 exhibits remarkably better potency than VEN against WT Bcl-2 across multiple hematologic cancer cell lines in *in-vitro* assays

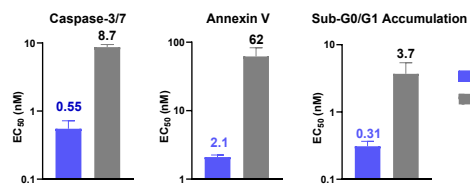
### Highly selective for Bcl-2 over other Bcl-2 family members

Bcl-2 family member	Selectivity folds to Bcl-2 BGB-21447
Bcl-xL	121
Bcl-W	2,507
Mcl-1	> 7.14 x10 <sup>4</sup>
Bcl2A1	> 7.14 x10 <sup>4</sup>

### Superior potency to VEN against a variety of hematologic cancer cell lines



### Stronger intrinsic apoptosis than VEN in RS4;11

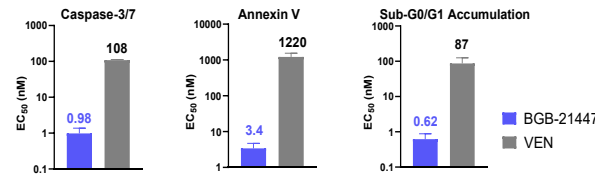


## BGB-21447 is highly potent against broad Bcl-2 mutations arising with the VEN progression in *in-vitro* assays

### Higher potency than VEN against a broad spectrum of Bcl-2 mutants

	Biochemical IC <sub>50</sub> (nM)		RS4; 11 Bcl-2 <sup>mut</sup> OE Cell viability, IC <sub>50</sub> (nM)	
	BGB-21447	VEN	BGB-21447	VEN
Bcl-2-G101V	0.29 ± 0.040	19 ± 0.58	15 ± 1.0	3854 ± 172
Bcl-2-D103Y	0.17	8.9	44 ± 4.9	4731 ± 454
Bcl-2-D103E	-	-	29 ± 7.2	4614 ± 1170
Bcl-2-D103V	-	-	41 ± 5.2	3890 ± 273
Bcl-2-V156D	0.30	4.8	25 ± 4.9	3401 ± 516
Bcl-2-A113G	0.23	0.45	17 ± 1.2	1367 ± 393
Bcl-2-R129L	0.11	0.61	11 ± 1.2	642 ± 147

### Stronger intrinsic apoptosis than VEN in RS4;11 Bcl-2 G101V OE cell line



## Conclusion

- BGB-21447 is a 2<sup>nd</sup> generation Bcl-2 inhibitor with remarkably better potency than VEN against WT Bcl-2, offering new opportunities for treatment of multiple hematologic malignancies and solid tumors.
- BGB-21447's strong potency against a broad spectrum of Bcl-2 mutations arising during VEN progression indicates that it could overcome VEN resistance caused by Bcl-2 mutations.

## Reference

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3. Blombery P, et al. Blood. 2020 Mar 5;135(10):773-777
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5. Davids MS, et al. J Clin Oncol. 2017 Mar 10;35(8):826-833.

WT: Wildtype; NHL: Non-Hodgkin's Lymphoma; CLL: Chronic Lymphocytic Leukemia; SLL: Small Lymphocytic Lymphoma; AML: Acute Myeloid Leukemia; FL: Follicular Lymphoma; DLBCL: Diffuse large B-cell lymphoma; MCL: Mantle Cell Lymphoma; PD: Pharmacodynamics; OE: overexpression; KI: knock-in