Sonrotoclax (BGB-11417), a selective BCL-2 inhibitor, demonstrates better efficacy than venetoclax and lisaftoclax (APG-2575) in hematological cancer cells, xenografts, and human bloods

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Presentation Number

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INTRODUCTION

BCL-2 overexpression is a hallmark of hematologic malignancies and is associated with evasion of cell death as well as drug resistance, particularly in chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), and acute myeloid leukemia (AML). BCL-2 inhibitors such as venetoclax (Ven) counteract this by disrupting BCL-2 interaction with pro-apoptotic proteins (e.g., BIM, BAX), thereby activating apoptosis.

Despite ven's clinical success, limitations including tumor lysis syndrome and suboptimal complete remission (CR) rates in CLL, and other indications underscore the need for improved inhibitors. Lisaftoclax (Lisa) is also a selective BCL-2 inhibitor in development. In addition to this, sonrotoclax (Sonro), a BCL-2 inhibitor with shorter half life and improved selectivity showed higher ORR and CR rate in CLL patients compared to Ven and Lisa. This study further investigates how Ven, Lisa, and Sonro is different across different cancer cell lines, resistant mutations and human whole blood.

METHODS

RS4;11 and KMS-12-PE cells with BCL-2-G101V mutation, a common resistance mechanism in Ven-treated CLL patients, were generated via ENU mutagenesis. OCI-LY10 cells expressing BTK-WT, C481S, T474I, L528W, and A428D mutations (associated with BTK inhibitor resistance) were engineered using lentiviral transduction. *In vitro* cytotoxicity was assessed via CellTiter-Glo (CTG) assay. To evaluate BCL-2:BIM complex disruption by BCL-2 inhibitors in a physiologically relevant setting, human whole blood from healthy donors was incubated with compounds for 36 hours, followed by quantification of BCL-2:BIM complexes using an MSD assay.

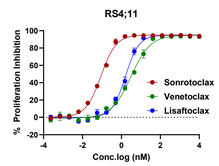
RESULTS

Figure 1: Sonro demonstrates higher potency than Ven and Lisa in cancer cell lines from different indications *in vitro*

A.

Indication	Cell lines	IC50 (nM) of Compounds		
		Sonrotoclax	Venetoclax	Lisaftoclax
MCL	REC-1	0.8456	40.96	15.66
	Mino	0.1328	4.721	1.472
AML	MV-4-11	0.3879	6.198	4.889
	OCI-AML-2	0.3879	6.198	4.889
	MOLM-13	1.203	12.32	10.05
	KG-1a	7.315	176.7	58.57
MM	KMS-12PE	0.624	10.7	5.6
	KMS-27	0.02	12.5	10.3
	KMS-28BM	2.19	91.35	33.06
	NCI-H929	0.026	8.55	3.62
B-ALL	RS4;11	0.089	3.07	1.61

B.



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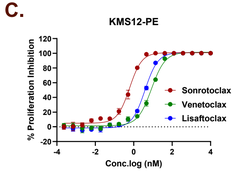
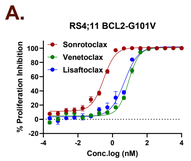


The potency of BCL-2 inhibitors in different cancer cell lines. ***A.*** *A table of the number of IC50s (concentrations of 50% inhibition) for different BCL-2 inhibitors in in vitro cytotoxicity assay.* ***B-C.*** *Representative dose-response curves of BCL-2 inhibitors (from A.) in two commonly used cell lines in literatures for BCL-2 inhibitors.*

Figure 2: Sonro exhibits higher potency than Ven and Lisa in ven resistant cancer cells

A.



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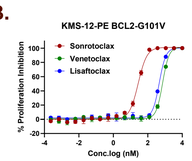
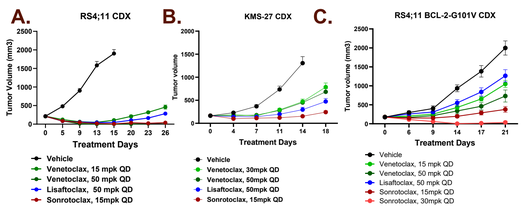


C.

Compounds	BCL-2 G101V (IC50, nM)	
	RS4;11	KMS12-PE
Sonrotoclax	0.30	50.14
Venetoclax	8.47	1198.15
Lisaftoclax	4.93	668.35

The potency of BCL-2 inhibitors in cancer cells expressing BCL-2-G101V—a mutation present in ~30% of Ven-relapsed CLL patients. ***A-B.*** *Sonro showed >10 fold higher potency than Ven and Lisa, who presented similar activity.* ***C.*** *A table summarizes the number of IC50s in* ***A.*** *and* ***B.***

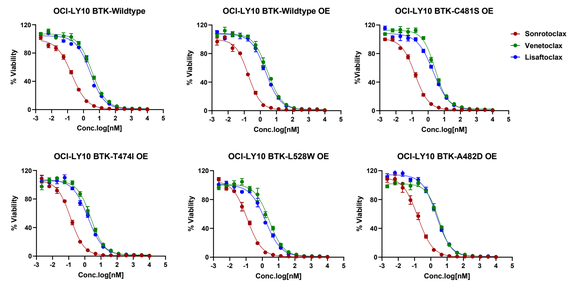
Figure 3: Sonro presents better efficacy than Ven and Lisa in xenografts



Cancer cells were inoculated subcutaneously into NOG mice for in vivo efficacy evaluation. ***A-C.*** *Sonro at the same or lower dose showed better efficacy than Ven and Lisa in xenografts.*

Figure 4: Sonro maintains higher potency than Ven and Lisa in B lymphoma cancer cell lines expressing BTK mutations that are resistant to BTK inhibitors

A.



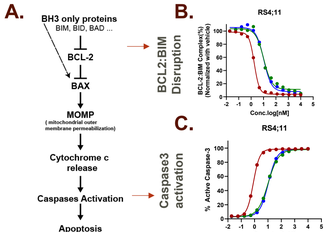
B.

OCL-LY10	IC50 (nM) of Compounds		
	Sonrotoclax	Venetoclax	Lisaftoclax
BTK-Wildtype	0.18	3.32	2.63
BTK-Wildtype OE	0.17	2.82	2.12
BTK-C481S OE	0.15	2.77	2.07
BTK-T474I OE	0.13	2.33	1.56
BTK-L528W OE	0.11	2.60	1.56
BTK-A428D OE	0.16	3.15	2.21

Potency of BCL-2 inhibitors in OCI-LY10 cells harboring BTKi resistance mutations (C481S, T474I, L528W, A428D). ***A.*** *Sonro maintained consistent higher activity than Ven and Lisa in BTK mutant cells as in parental cells.* ***B.*** *Table of IC50 numbers in A.*

Figure 5: Sonro is more efficient than Ven and Lisa in disrupting BCL-2:BIM complex and inducing apoptosis

A.



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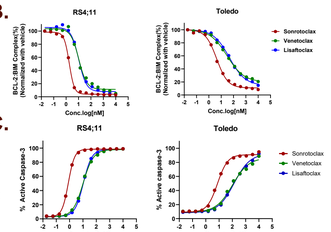


C.

D.

Cell lines	IC50 (nM) of BCL-2:BIM disruption		
	Sonrotoclax	Venetoclax	Lisaftoclax
RS4;11	1.77	10.39	10.35
Toledo	4.29	29.63	46.14

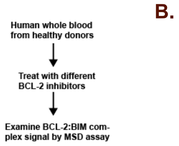
E.

Cell lines	IC50 (nM) of Caspase 3 activation		
	Sonrotoclax	Venetoclax	Lisaftoclax
RS4;11	0.80	10.26	10.81
Toledo	7.63	101.3	136.2

Potency of BCL-2is in triggering apoptosis. ***A.*** *A diagram of intrinsic apoptosis signaling.* ***B.*** *Sonro showed higher potency in disrupting BCL-2:BIM complex—a very proximal and direct effect of BCL-2i—in cancer cells.* ***C.*** *Sonro also showed higher potency in activating Caspase 3, an executioner of apoptosis.* ***D-E.*** *Tables of IC50 numbers in B & C.*

Figure 6: Sonro retains higher efficiency in disrupting BCL-2:BIM complex than Ven and Lisa in human blood

A.



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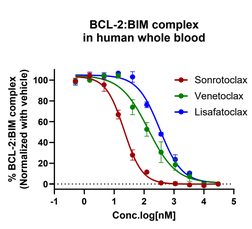

C.

Compouds	BCL-2:BIM Disruption	
	IC50 (nM)	IC90 (nM)
Sonrotoclax	21.35	98.2
Venetoclax	137.6	1469
Lisaftoclax	335.8	2234

The activity of BCL-2 inhibitors to disrupt BCL-2:BIM complex in human blood was profiled by using titration of the total drug concentration in human whole blood ***A.*** *A diagram highlights the flow of human whole blood assay.* ***B.*** *Sonro showed higher potency in disrupting BCL-2:BIM in human blood.* ***C.*** *Table of IC50 and IC90 number from B.*

CONCLUSIONS

Sonrotoclax demonstrates significant advantage over venetoclax and lisaftoclax in preclinical studies, including higher potency in BCL-2-dependent cancers, which translates into better efficacy against BCL-2-G101V and BTK resistance mutations, and enhanced target engagement in human whole blood. These findings highlight Sonro's great potential to address unmet needs in hematologic malignancies, including improved efficacy with better therapeutic outcomes and overcome resistance mechanisms.