SGR-1505 is a potent MALT1 protease inhibitor with a potential best-in-class profile

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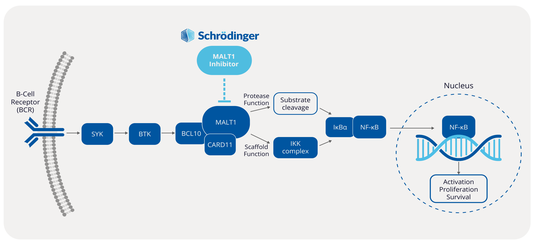
MALT1 is a paracaspase involved in NF-kB signaling

- MALT1 is one of the key regulators of physiological antigen receptor signalling in B cells and T cells, and is the only component of the CARMA1-BCL10-MALT1 (CBM) signalosome which has proteolytic activity.
- Following antigen-receptor stimulation and the activation of CBM complex, MALT1 triggers NF-kB signaling and lymphocyte activation. MALT1 targets key proteins in a negative feedback loop mediating termination of the NF-κB response: a) as a scaffolding protein to activate the Inhibitor of IκB Kinase (IKK) complex and b) as a protease to inactivate negative regulators such as RelB and A20.
- Constitutive activation of the NF-κB signaling pathway is a molecular hallmark of activated B cell like diffuse large B cell lymphoma (ABC-DLBCL), and mutations that trigger constitutive MALT1 protease activity (such as on CD79 and CARD11) cause malignant B cell signaling in multiple B-cell malignancies.



Background

Previously, we described the discovery of novel MALT1 inhibitors with anti-proliferative effects in non-Hodgkin B-cell lymphoma cells and the strong anti-tumor activity of our MALT1 inhibitors across multiple tumor models as well as combination potential with agents including standard-of-care.[1,2] SGR-1505 is an oral potent small molecule allosteric inhibitor of MALT1 that inhibits MALT1 enzymatic activity and demonstrates anti-proliferative activity in ABC-DLBCL cell lines, both BTKi-sensitive (OCI-LY10) and BTKi-resistant (OCI-LY3). When administered as a single agent and in combination with the approved Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib, SGR-1505 demonstrated tumorostatic and regressive antitumor activity in ABC-DLBCL cell line-derived xenograft and patient-derived xenograft models. These data suggest that SGR-1505-mediated MALT1 inhibition has therapeutic potential for patients with selected B-cell lymphomas.

Here we further characterized SGR-1505, in a series of *in vitro* and *ex vivo* assays, as well as RNA-seq analysis to examine changes in gene expression from *in vivo* tumor samples. We also compared SGR-1505 with a competitor Phase I candidate, JNJ-67856633 (JNJ-6633).[3,4]

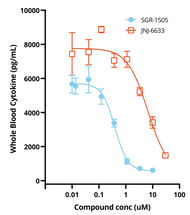
SGR-1505 showed excellent potency in the biochemical assay and strong anti-proliferative effects on ABC-DLBCL cell lines

	Assay	SGR-1505		JNJ-6633	
		IC_{50}, nM	IC_{90}, nM	IC_{50}, nM	IC_{90}, nM
Biochemical assay	MALT1 Biochemical Assay	1.3	7	73	485
Cell-based assay	BCL10 Cleavage Assay in OCI-LY10 Cells	22	63	98	334
	IL10 Secretion Assay in OCI-LY10 Cells	36	211	267	2,816
	Antiproliferative Assay in OCI-LY10 Cells	71	181	430	5,670
	NF-kB Reporter Assay in Jurkat Cells	37	113	242	4,122

SGR-1505 is at least ten-fold more potent than JNJ-6633 in a human primary T cell-based assay

Whole blood was collected from 3 healthy donors, stimulated with anti-CD3/CD28, and titrated with increased concentration of either SGR-1505 or JNJ-6633. Cytokine was measured using MesoScale Diagnostics (MSD) after 20hr of incubation.

Assay	SGR-1505		JNJ-6633	
	IC_{50}, nM	IC_{90}, nM	IC_{50}, nM	IC_{90}, nM
MALT1 Biochemical Assay	240	1,353	5,357	78,096

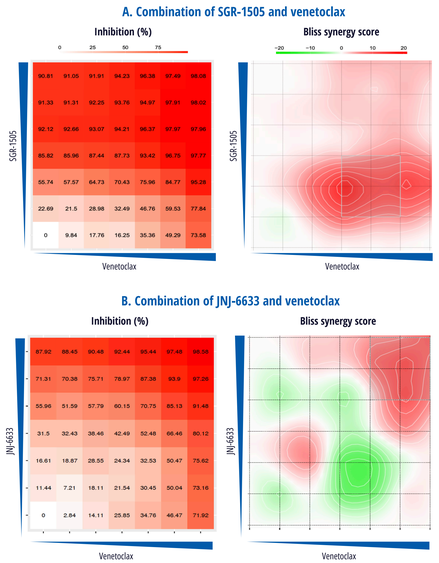


SGR-1505 showed potent inhibition of cytokines *ex vivo* in the whole blood collected from the SGR-1505-102 healthy volunteer study

Whole Blood was collected from healthy subjects dosed with oral SGR-1505 tablets and stimulated with anti-CD3/CD28. Cytokine was measured using MesoScale Diagnostics (MSD) after 20hr of incubation.

Assay		SGR-1505	
		EC_{50}, nM	EC_{90}, nM
Ex Vivo Whole Blood Assay from Healthy subjects (SGR-1505-102 Study)	Inhibition of cytokine release from *ex vivo* stimulation of human whole blood collected from healthy volunteers that were dosed with SGR-1505	843 - 1744	2,438 - 5,580

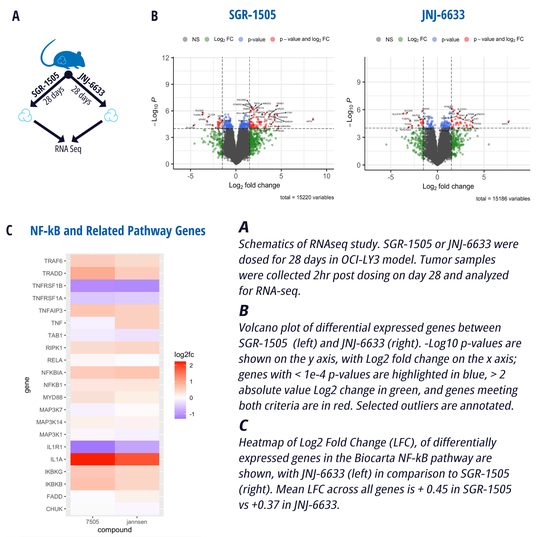
SGR-1505 with venetoclax shows stronger combination effect compared to JNJ-6633 in DLBCL cell line



A *In vitro combination of SGR-1505 and venetoclax in OCI-LY3 cells following the treatment for 4 days; (left) matrix of % of inhibition in the CTG assay; (right) Bliss synergy score calculated by synergyfinder*

B *In vitro combination of JNJ-6633 and venetoclax in OCI-LY3 cells following the treatment for 4 days*

SGR-1505 shows stronger regulation of NF-kB and related pathway genes than JNJ-6633 in *in vivo* DLBCL CDX model

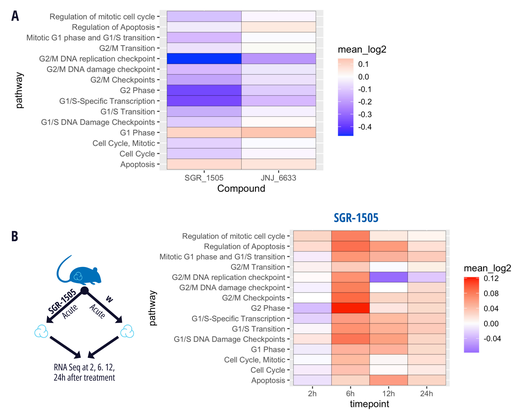


A *Schematics of RNAseq study. SGR-1505 or JNJ-6633 were dosed for 28 days in OCI-LY3 model. Tumor samples were collected 2hr post dosing on day 28 and analyzed for RNA-seq.*

B *Volcano plot of differential expressed genes between SGR-1505 (left) and JNJ-6633 (right). -Log10 p-values are shown on the y axis, with Log2 fold change on the x axis; genes with < 1e-4 p-values are highlighted in blue, > 2 absolute value Log2 change in green, and genes meeting both criteria are in red. Selected outliers are annotated.*

C *Heatmap of Log2 Fold Change (LFC), of differentially expressed genes in the Biocarta NF-kB pathway are shown, with JNJ-6633 (left) in comparison to SGR-1505 (right). Mean LFC across all genes is + 0.45 in SGR-1505 vs +0.37 in JNJ-6633.*

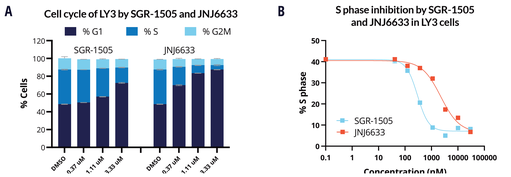
SGR-1505 exclusively regulates cell cycle related pathway genes in *in vivo* DLBCL CDX model



A *Pathway enrichment heatmap of cell-cycle related pathways, across multi-time point study of SGR-1505 and JNJ-6633 from the chronic efficacy studies in OCI-LY3 model. Intensity of color represents mean expression values across pathway genes (positive fold change: red; negative: blue).*

B *Pathway enrichment heatmap showing the mean Log2 Fold Change of all genes in cell cycle related pathways from an acute SGR-1505 study in OCI-LY3 model. Tumor samples were collected after a single dose of SGR-1505 treatment at 2, 6, 12, and 24hr. The largest increase across pathways is observed at the 6h timepoint, followed by continued positive activity at 12 and 24h.*

SGR-1505 induces G1 arrest in DLBCL cells



Flow based cell analysis of OCI-LY3 cells treated with SGR-1505 for 72 hours demonstrated more potent S phase inhibition, as compared to JNJ-6633. Grey, G1 phase; Blue, S phase; and Black, G2/M phase

Percentage of S phase of OCI-LY3 cells treated with SGR-1505 and JNJ-6633 for 72 hours

Results

- SGR-1505 showed excellent potency in the biochemical and cell based assays compared to JNJ-6633. Results from an *in vitro* human primary T-cell activation assay measuring cytokine production from whole blood collected from healthy donors suggested SGR-1505 is least ten-fold more potent than JNJ-6633.
- Consistent with the *in vitro* T-cell activation assay, SGR-1505 led to similar changes in cytokine production in an *ex vivo* assay in the whole blood collected from our ongoing healthy volunteer clinical trial (the SGR-1505-102 study).
- When tested in combination with venetoclax, SGR-1505 showed stronger combination effect compared to JNJ-6633.
- Using RNA-seq analysis, SGR-1505 showed greater modulation of NF-kB and related pathway genes compared to JNJ-6633. Changes in genes related to cell cycle pathways, such as cell cycle, DNA damage, and apoptosis were identified and exclusively associated with SGR-1505 treatment. Consistent with the gene expression analysis, SGR-1505 treatment induced G1 arrest effect in DLBCL cell line at much lower doses compared to JNJ-6633.

Conclusions

- SGR-1505, a MALT1 protease small molecule inhibitor, consistently demonstrated stronger potency and better combinability with venetoclax when compared to the clinical-stage JNJ-6633 compound and greater effects on NF-kB and related pathway gene expression.
- A Phase 1 clinical trial in patients with mature B cell neoplasms is currently ongoing (NCT05544019). The data presented here suggests SGR-1505 has a potential best-in-class profile and supports advancing the ongoing clinical development of SGR-1505.

References

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4. Phase 1 study of JNJ-67856633, a first-in-human MALT1 inhibitor, in relapsed/refractory (R/R) B-cell non-hodgkin lymphoma (B-NHL) and chronic lymphocytic leukemia (CLL). *Hematological Oncology* Volume 41: 17th International Conference on Malignant Lymphoma, Palazzo dei Congressi, Lugano, Switzerland, 13–17 June, 2023, Pages 131–132

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