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

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MALT1 in a paracaspase involved in NF-κB signaling

- MALT1 is one of the key regulators of physiological antigen receptor signaling in B and T cells, and is the component of the CARMA1-CBL10-MALT1 (CBM) signaling module which has an autoinhibitory function.

- Following antigen-receptor stimulation and the activation of CBM complex, MALT1 triggers NF-κB 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 RelA and XIAP.

- 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 single-digit nM IC50, excellent potency in the biochemical assay, and strong anti-proliferative effects on ABC-DLBCL cell lines.

SGR-1505 is an oral potent small molecule allosteric inhibitor of MALT1 that inhibits MALT1 enzymatic activity and demonstrates allosteric anti-proliferative activity in ABC-DLBCL cell lines, both BTK-sensitive (OCI-LY10) and BTK-resistant (OCI-LY3). When administered as a single agent and in combination with the approved Bruton’s tyrosine kinase inhibitor (BTKi) ibrutinib, SGR-1505 demonstrated tumoricidal 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 a first-in-human study to examine changes in gene expression from in vivo assays. We also compared SGR-1505 with a competitor Phase 1 candidate, JNJ-6633 (ex vivo).

SGR-1505 showed potential inhibition of cytokines ex vivo in the whole blood collected from the SGR-1505 treated 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 Multiplex Cytokine Assay. Results from a combined analysis of samples from multiple subjects up to 24h post-dosing on Day 2 and 8, showed potent S phase inhibition, as compared to JNJ-6633. Grey, G1 phase; Blue, S phase; and Black, G2 phase.

SGR-1505 showed stronger regulation of NF-κB and related pathway genes than JNJ-6633 in vivo DLBCL CDX model

Pathway enrichment heatmap of cell cycle related pathways, across multi-time point study, with 316 changes in cell cycle genes with >2 fold change in JNJ-6633 compared to SGR-1505. The legend shows a heatmap of significant pathway genes (p<0.001) for each time point of treatment with SGR-1505 or JNJ-6633. Changes in gene expression compared to JNJ-6633 are highlighted in blue, more severe changes in gene expression compared to SGR-1505 are highlighted in yellow.

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

Pathway enrichment heatmap showing the main gene set enrichment pathway gene expression changes in OCI-LY3 model. Tumor samples were collected after a single dose of 5 mg/kg of oral SGR-1505 or JNJ-6633. The legend shows a heatmap of significant pathway genes (p<0.001) for each time point of treatment with SGR-1505 or JNJ-6633. Changes in gene expression compared to JNJ-6633 are highlighted in blue, more severe changes in gene expression compared to SGR-1505 are highlighted in yellow.

Results

- SGR-1505 showed strong potential in the biochemical and cell based assays compared to JNJ-6633. Results from an ex vivo 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-κB and related pathway genes compared to JNJ-6633. Changes in gene expression in other 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, either compared to the chemically distinct JNJ-6633 compound and greater effects on NF-κB and related pathway gene expression.

- A Phase 1 clinical trial in patients with mature B cell neoplasms is currently ongoing (NCT05644021). 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

3. Phase 1 Study of JNJ-6633, a Binucleoside Pyrophosphate MALT1 Inhibitor, in Relapsed Relapsed- refractory B-cell (CLL/SLL), T-cell Lymphomas (ALCL) and Chronic lymphocytic leukemia (ALL). ASCO 2011; 30(Suppl 1) 4601
4. MALT1 inhibition targets a conserved mechanism of lymphoma development. Blood; May 18, 2020; 135(20):5537-44
6. 11th International Congress on Malignant Lymphomas (US Congress), Lugano, Switzerland, 14–17 June, 2011. Pages 151–132

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