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POSTER ABSTRACTS

621.LYMPHOMAS: TRANSLATIONAL-MOLECULAR AND GENETIC

Sgr-1505 Is a Potent MALT1 Protease Inhibitor with a Potential Best-in-Class Profile

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Background: MALT1 (Mucosa-associated lymphoid tissue lymphoma translocation protein 1) is a component of the MALT1-BCL10-CARD11 complex downstream from the Bruton Tyrosine Kinase (BTK) on the B-cell receptor signaling pathway. MALT1 is a key mediator of nuclear factor kappa B (NF-κB) signaling, which is the main driver of a subset of B-cell lymphomas. MALT1 is considered a potential therapeutic target for several subtypes of non-Hodgkin B-cell lymphomas and chronic lymphocytic leukemia (CLL), including tumors with acquired BTK inhibitor (BTKi) resistance. Constitutive activation of the NF-κB is a molecular hallmark of activated B cell-like diffuse large B cell lymphoma (ABC-DLBCL), and MALT1 may have utility as a treatment option for ABC-DLBCL.

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 (ref 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) (ref 3, 4).

Results: SGR1505 potency and downstream effects were evaluated in a series of biochemical and cell based assays. SGR-1505 showed excellent potency in the biochemical assay and strong anti-proliferative effects on ABC-DLBCL cells. SGR-1505 was more potent than JNJ-6633 in all assays tested (Table 1). These results are also consistent with the result from a human primary T-cell based assay, where SGR-1505 showed at least ten-fold better potency than JNJ-6633.

RNA-seq analysis was conducted to examine changes in gene expression from *in vivo* tumor samples. Greater modulation of BIOCARTA NF-kB pathway genes was seen with SGR-1505 compared to JNJ-6633, as measured by mean absolute change in gene expression. At 6 hr and later timepoints, we also observed a trend of increases in genes related to cell cycle pathways, such as cell cycle, DNA damage, and apoptosis.

SGR-1505 is being evaluated in the SGR-1505-102 phase 1 study, which is an ongoing first-in-human, single center, dose escalation study to evaluate the safety, tolerability, PK and PD of SGR-1505 tablets in healthy participants (ACTRN12623000358640p). Preliminary data showed changes in target engagement markers at concentrations predicted by the in vitro and ex vivo assays, consistent with MALT1 protease inhibition.

Conclusions: SGR-1505, a MALT1 protease small molecule inhibitor, consistently demonstrated better potency in *in vitro* and *ex vivo* assays when compared to the clinical-stage JNJ-6633 compound and greater effects on NF-kB pathway gene expression in *in vivo* tumor samples based on RNA-seq analysis. Changes in biological pathways mediated by MALT1 were also observed at relevant doses in the ongoing SGR-1505 healthy volunteer study. Currently, a phase 1 clinical trial in patients with mature B cell neoplasms is also ongoing (NCT05544019). The data presented suggests SGR-1505 has a potential best-in-class profile and supports advancing the ongoing clinical development of SGR-1505.

Disclosures Yin: *Schrödinger:* Current Employment. **Ye:** *Schrödinger:* Current Employment. **Marshall:** *Schrödinger:* Current Employment. **Tan:** *Schrödinger:* Current Employment. **Paull:** *Schrödinger:* Current Employment. **Nie:** *Schrödinger:* Current Employment. **Trzoss:** *Schrödinger:* Current Employment. **Krilov:** *Schrödinger:* Current Employment. **Feng:** *Schrödinger:* Current Employment. **Pelletier:** *Schrödinger:* Current Employment. **Bell:** *Schrödinger:* Current Employment. **Skrdla:** *Schrödinger:* Current Employment. **Calkins:** *Schrödinger:* Current Employment. **Grimes:** *Schrödinger:* Current Employment. **Wright:** *Schrödinger:* Current Employment. **Akinsanya:** *Schrödinger:* Current Employment.

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