Abstract: P1241

Title: A NOVEL CEREBLON-BINDING MOLECULAR GLUE, SP-3164, SHOWS PRECLINICAL ACTIVITY IN NON-HODGKIN LYMPHOMAS

Abstract Type: Poster Presentation

Session Title: Lymphoma Biology & Translational Research

Background:

Relapsed and refractory non-Hodgkin's lymphomas (NHLs) are an area of high unmet need with patients seeking novel, chemotherapy-free options. One modality that has shown potential for treatment of NHLs is targeted protein degradation (TPD). The first-generation cereblon (CRBN)-binding molecular glue, lenalidomide, is used for treatment of various NHLs including mantle cell, follicular, and diffuse large B-cell lymphomas. SP-3164 is a next-generation CRBN-binding molecular glue with the potential for improved therapeutic and safety properties due to its novel use of deuterium-enabled chiral switching (DECS). To date, the majority of CRBN-binding molecular glues, including lenalidomide, pomalidomide, and avadomide, are glutarimides with an unstable chiral center that results in interconversion between the desired, active (*S*)-enantiomer and the inactive (*R*)-enantiomer. DECS stabilizes the chiral center and allows for the characterization of SP-3164, the stable, active (*S*)-enantiomer of avadomide. SP-3164 can potently degrade Ikaros and Aiolos (I/A), showing compelling activity in preclinical NHL models. Previously, we demonstrated SP-3164's differential activity compared to other I/A degraders and have shown that the (*R*)-enantiomer (SP-3165) does not induce protein degradation in cancer cells, resulting in minimal therapeutic activity. Instead, SP-3165 appears to support tumor growth in certain xenograft models. Additionally, we showed SP-3164's potent activity in an *in vivo* DLBCL model as a single agent and in combination with rituximab.

Aims:

To further characterize SP-3164's protein degradation and anticancer activity and demonstrate its therapeutic potential in NHLs, including follicular lymphoma (FL).

Methods:

Degradation of I/A in peripheral blood mononuclear cells (PBMCs) at various SP-3164 concentrations (10, 100, 1000 nM) and time points (2, 4, 6, and 24 hours) was assessed via Western blots. Additional *in vitro* studies included viability and cytokine secretion assays. *In vivo* bioavailability studies were conducted in BALB/c mice and xenograft studies were conducted in NOD/SCID mice.

Results:

Degradation of I/A in PBMCs was dose- and time-dependent, with >70% degradation being achieved at 24 hours across all tested concentrations and the 1000 nM treatment group achieving >70% degradation as early as 2 hours (PBMC viability was not affected following up to 96 hours of SP-3164 treatment). In addition to having direct anti-tumor effects, I/A degraders also exert anticancer effects via immunomodulation, which is critical for therapeutic activity in lymphomas. To study SP-3164's immunomodulatory effects, we treated T-cells with SP-3164 or SP-3165 and examined the response in a panel of cytokines. SP-3164 stimulated cytokine release (i.e., IL-2 and TNF-α) at significantly lower concentrations than SP-3165. Pharmacokinetic studies demonstrated that SP-3164 was highly bioavailable (F >100%). In an *in vivo* efficacy model of FL (DOHH2), SP-3164 (7.5 mg/kg BID PO) showed significant tumor growth inhibition (TGI) compared to vehicle. In addition, the combination of SP-3164 with venetoclax (50 mg/kg QD PO, 5 on/2 off) resulted in more significant TGI than either SP-3164 or venetoclax alone (Figure).

Summary/Conclusion:

SP-3164 is a novel, orally available, CRBN-binding molecular glue with potent immunomodulatory activity and

attractive therapeutic properties in NHL models, including FL. Further assessment of SP-3164's potential as a treatment for NHLs is warranted and a clinical trial is planned to start in 2023.

Keywords: Non-Hodgkin's lymphoma, Immunomodulation, B cell lymphoma