SP-3164, a novel Ikaros and Aiolos molecular glue degrader with preclinical activity in non-Hodgkin lymphomas

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Daniela Y Santiesteban, PhD[1], Aundrietta D Duncan, PhD[1], Justine Delgado, PhD[1],Nadeem Q. Mirza, MD, MPH[1], Vincent Jacques, PhD[1,2], Sheila DeWitt, PhD[1,2] and Swami P Iyer, MD[3]

[1]Salarius Pharmaceuticals Inc., Houston, TX; [2]DeuteRx, LLC, Andover, MA; [3]Department of Lymphoma/Myeloma, The University of Texas at MD Anderson Center, Houston, TX

Introduction

SP-3164, an oral, next-generation molecular glue, is currently in IND-enabling studies and is expected to enter the clinic in 2023. SP-3164 interacts with the cereblon (CRBN) component of a CRL4 E3 ligase, inducing recruitment and subsequent degradation of hematological transcription factors, Ikaros (IKZF1) and Aiolos (IKZF3) (Figure 1). SP-3164 uses deuterium to stabilize the (*S*)-enantiomer of avadomide (CC-122), an extensively studied clinical compound, preventing interconversion to the undesired (*R*)-enantiomer (Figure 2). SP-3164 has shown compelling activity in non-Hodgkin lymphomas (NHL) and may have advantages over other molecular glues.

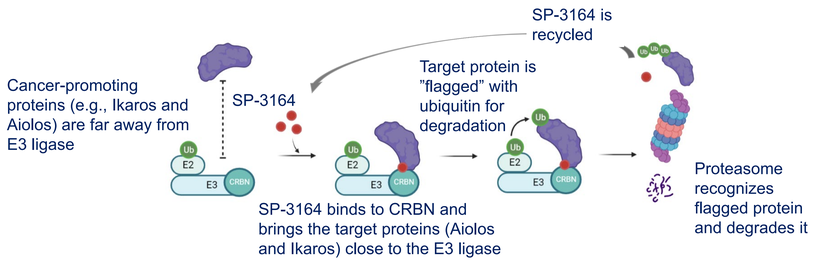


Figure 1. SP-3164's mechanism of action

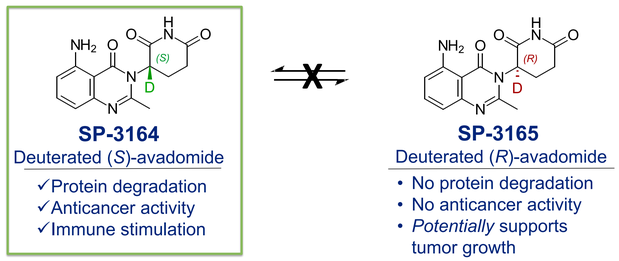


Figure 2. SP-3164 is the stabilized active species of avadomide

Objectives

- Demonstrate SP-3164's protein degradation effects and validate it as the active anticancer species of avadomide.
- Study SP-3164 antitumor activity in NHL models, including *in vivo* follicular lymphoma (FL), alone or in combination with approved agents.

Methods

- **Protein degradation**: NHL cells were cultured and treated with SP-3164, SP-3165, avadomide (AVA), or lenalidomide (LEN) for 6 hrs and Aiolos degradation was assessed by western blot.
- **Apoptosis/Degradation**: JeKo-1 cells were treated with SP-3164 for 48 hours and stained for cleaved caspase-3 and Ikaros and analyzed by flow cytometry. Data shown is relative to DMSO control.
- ***In vivo* efficacy:** Female CB17/SCID mice (n=10) were inoculated with 5X10^6 DOHH-2 (FL) cells and treated with test agent(s) when tumors reached ~110 mm^3. Tumor samples were collected at 2, 4, and 8 hrs after the last dosing and stained for Ikaros and Aiolos.

In vitro Results

SP-3164 Induces Rapid Aiolos Degradation

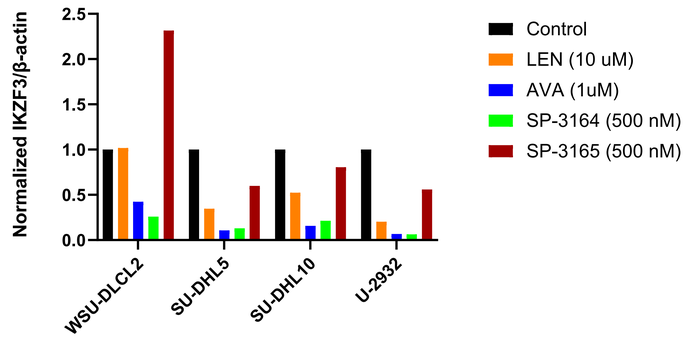


Figure 3. In DLBCL cells of different subtypes, SP-3164 (500 nM) resulted in rapid Aiolos degradation and compared favorably to AVA (1 μM) and LEN (10 μM), whereas SP-3165 (500 nM) did not result in meaningful Aiolos degradation.

Apoptosis Correlates with Ikaros Degradation

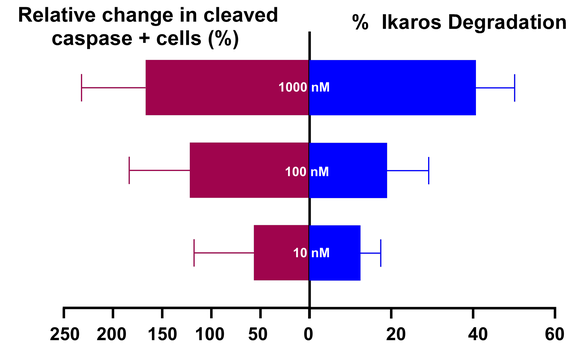
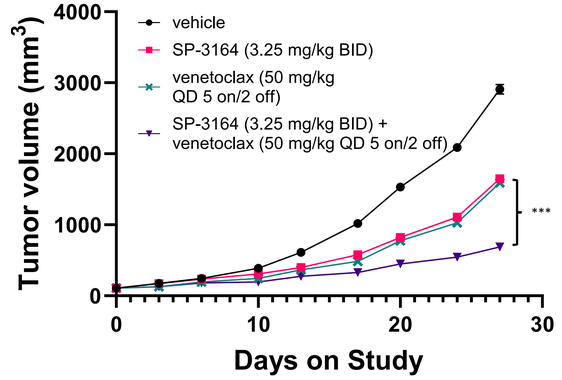


Figure 4. JeKo-1 apoptosis, as measured by cleaved caspase 3 expression, correlated with extent of Ikaros degradation at 48 hours.

In vivo Results

A.



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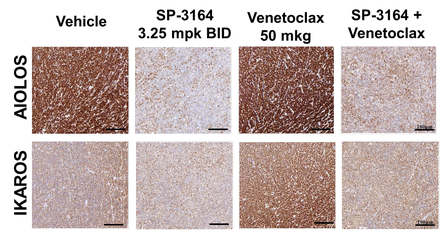

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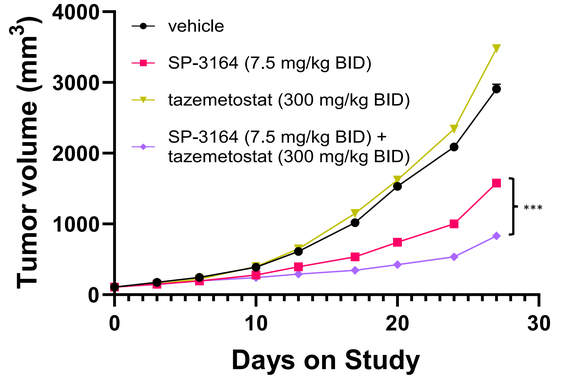

Figure 5. SP-3164's activity was studied in a mouse model of FL (DOHH-2) as a single agent and in combination. **A.** In combination with venetoclax, SP-3164 showed improved tumor growth inhibition (TGI) compared to either agent alone. **B.** IHC analysis showed SP-3164 treatment resulted in Ikaros and Aiolos degradation in the tumor. **C.** SP-3164 performed better than the approved agent, tazemetostat (TAZ), which had no effect. In combination, SP-3164 sensitized cells to TAZ resulting in improved TGI. (***p ≤0.001)

Conclusions

- SP-3164, the deuterium-stabilized (*S*)-enantiomer of avadomide, is a novel molecular glue with compelling antitumor activity in NHL models.
- Protein degradation (PD) studies validate SP-3164 as the active species and that the (*R*)-enantiomer has minimal PD effects.
- In *in vivo* FL studies, SP-3164 showed compelling single agent TGI and when combined with venetoclax or tazemetostat resulted in more pronounced TGI.
- The presented data support clinical investigation of SP-3164 and a trial is planned for 2H of 2023.

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Email: dsantiesteban@salariuspharma.com