SP-3164, A Novel Cereblon-Binding Protein Degrader, Shows Activity in Preclinical Lymphoma Models

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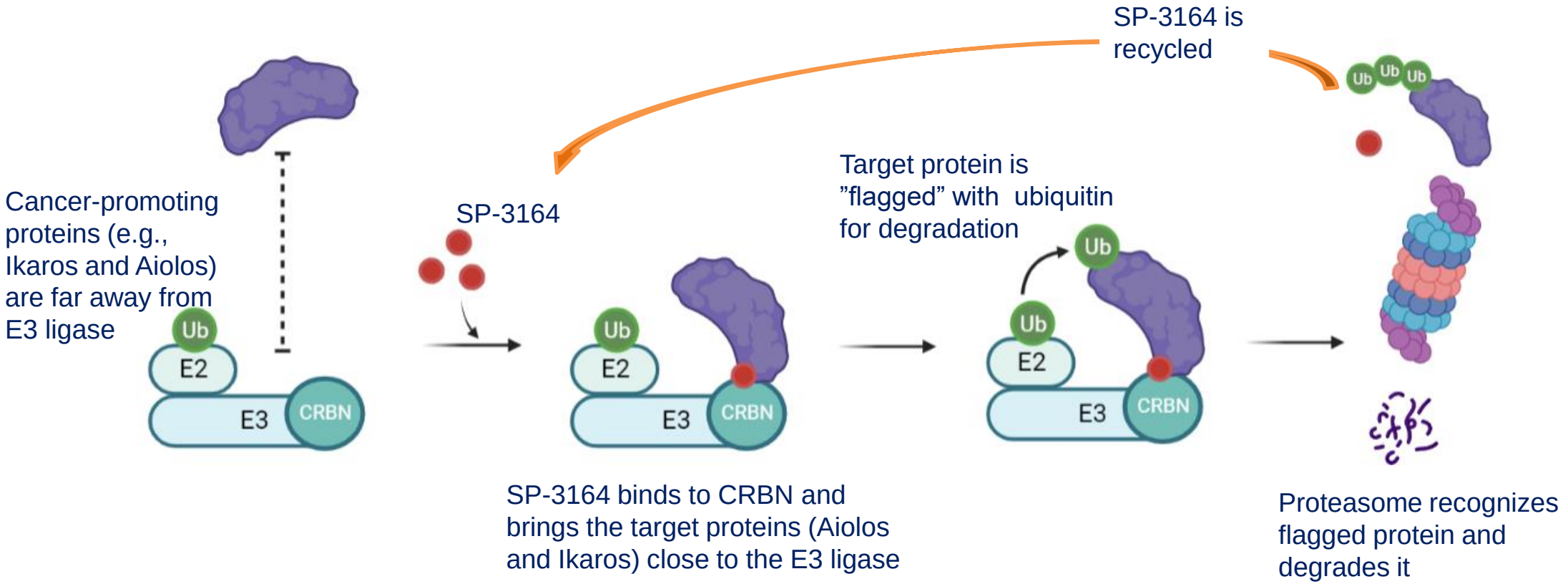
SP-3164 mechanism of action

Degradation of neosubstrates Ikaros and Aiolos

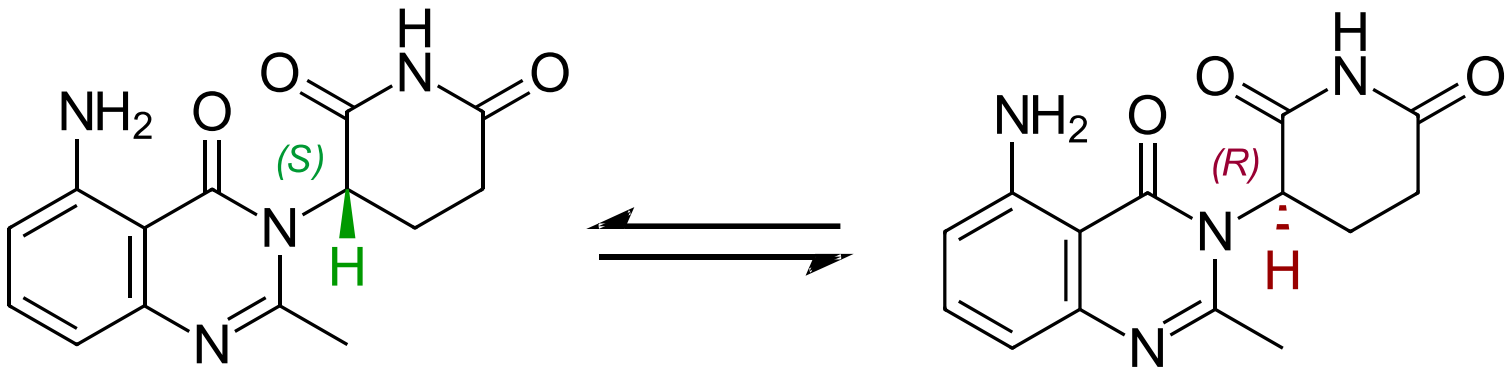
SP-3164 is a next generation cereblon binding Ikaros and Aiolos (I/A) protein degrader

- Improves upon approved 1st generation I/A degraders, i.e., lenalidomide and pomalidomide



Avadomide, an Extensively Studied CELMoD®

Exists as a Mixture of 2 Enantiomers



S-enantiomer **R-enantiomer**

Avadomide (CC-122)

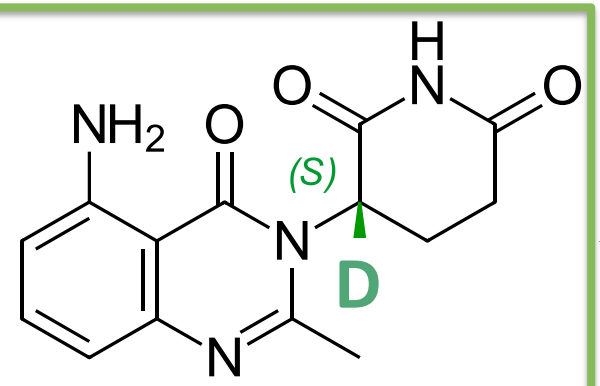
a 1:1 mixture of 2 interconverting enantiomers

✓ Studied in 10 clinical trials in >400 patients

CELMoD – Cereblon E3 Ligase Modulation Drugs, a registered trademark of Celgene / BMS

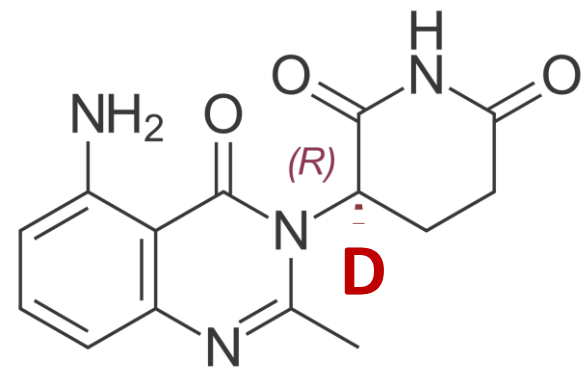
SP-3164: The Deuterium-Stabilized S-Enantiomer of Avadomide

- Stabilization of avadomide enantiomers with deuterium blocks interconversion



SP-3164
Deuterated S-avadomide

- ✓ Cereblon binder
- ✓ Anti-cancer activity
- ✓ Immune stimulation



SP-3165
Deuterated R-avadomide

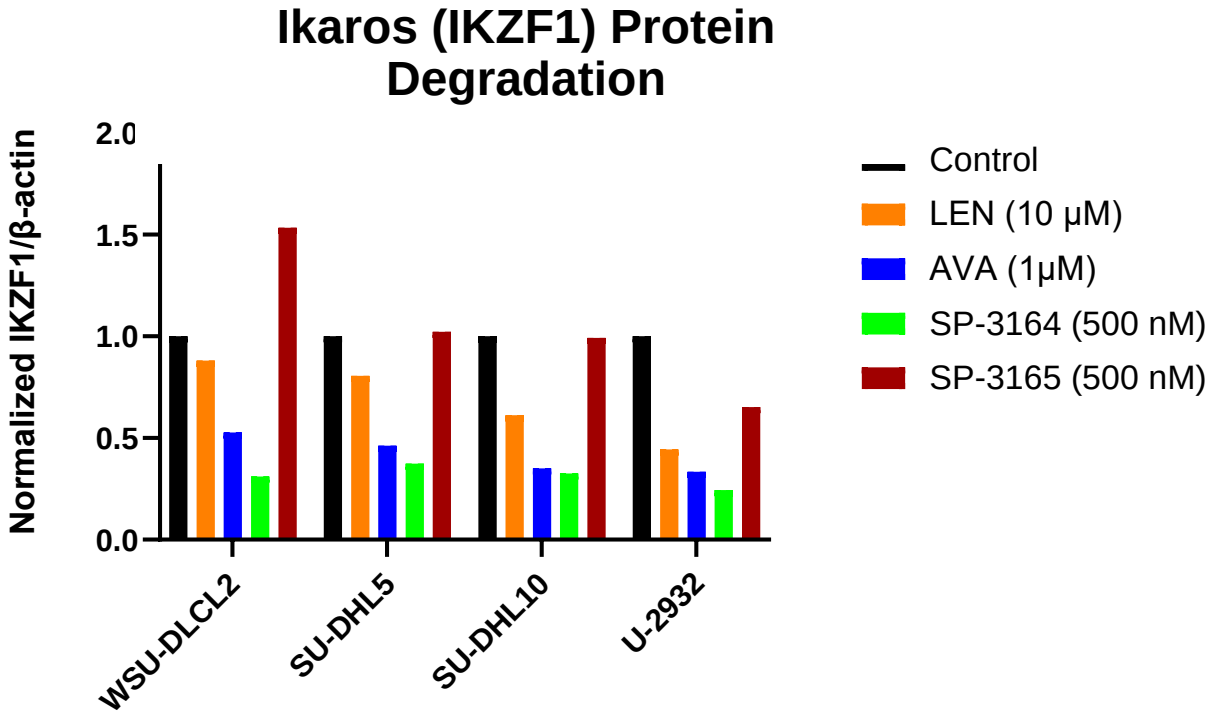
- Does not bind cereblon
- Minimal neosubstrate degradation
- *Potentially* supports tumor growth

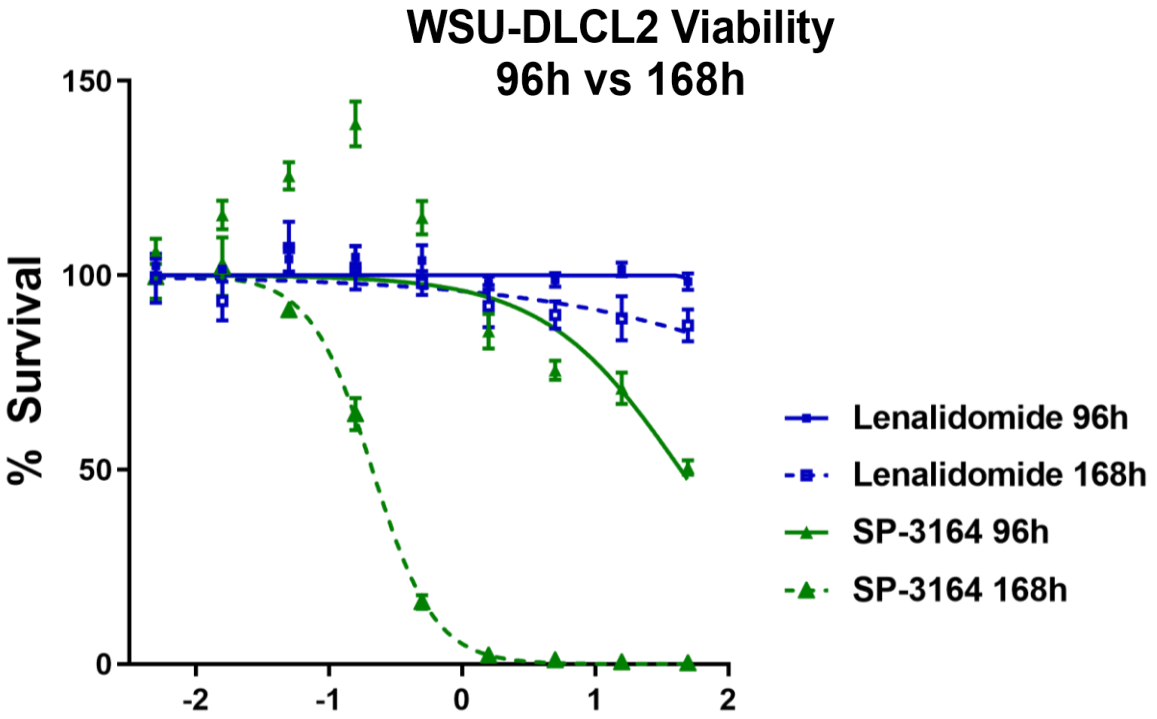
- An NCE with its own, issued composition of matter patent
- Potential for **improved efficacy and safety compared to avadomide**

NCE: new chemical entity

SP-3164 is the active species of avadomide

Confirmed via protein degradation and viability studies

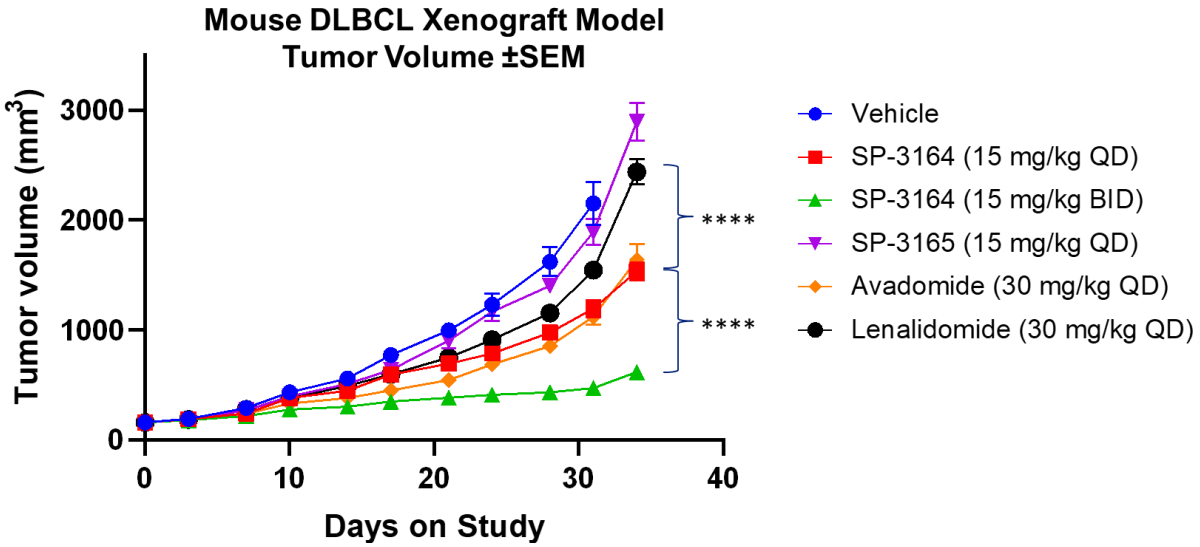




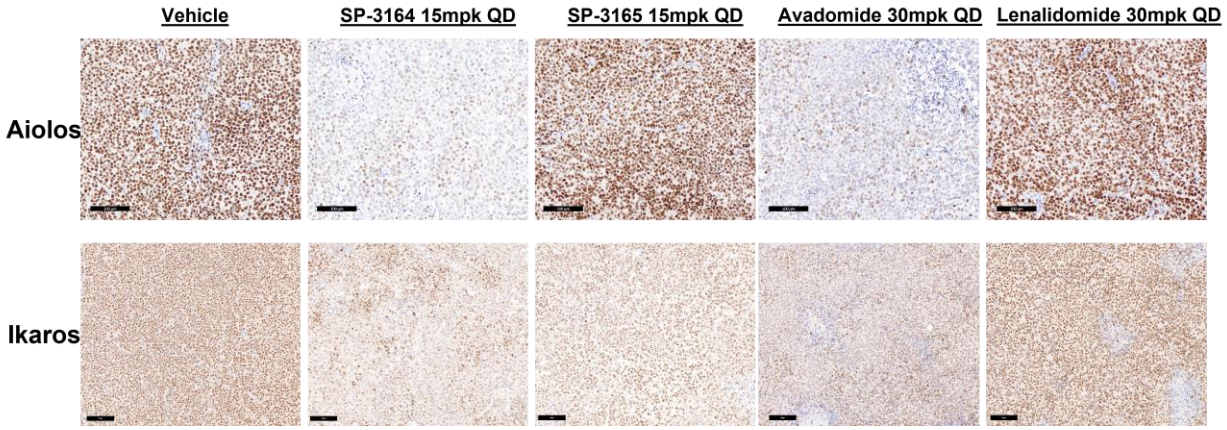
- SP-3164 efficiently degrades Ikaros across DLBCL cell lines
- SP-3165 exhibits minimal neosubstrate degradation
- SP-3164 (500 nM) is comparable or better than CC-122 (1 μM), better than LEN (10 μM)

In WSU DLCL2 cells, longer treatment (168 hr vs 96 hr) revealed increased sensitivity to SP-3164 (IC50 0.217μM vs not reached).

SP-3164 Demonstrates Single-Agent Activity in DLBCL

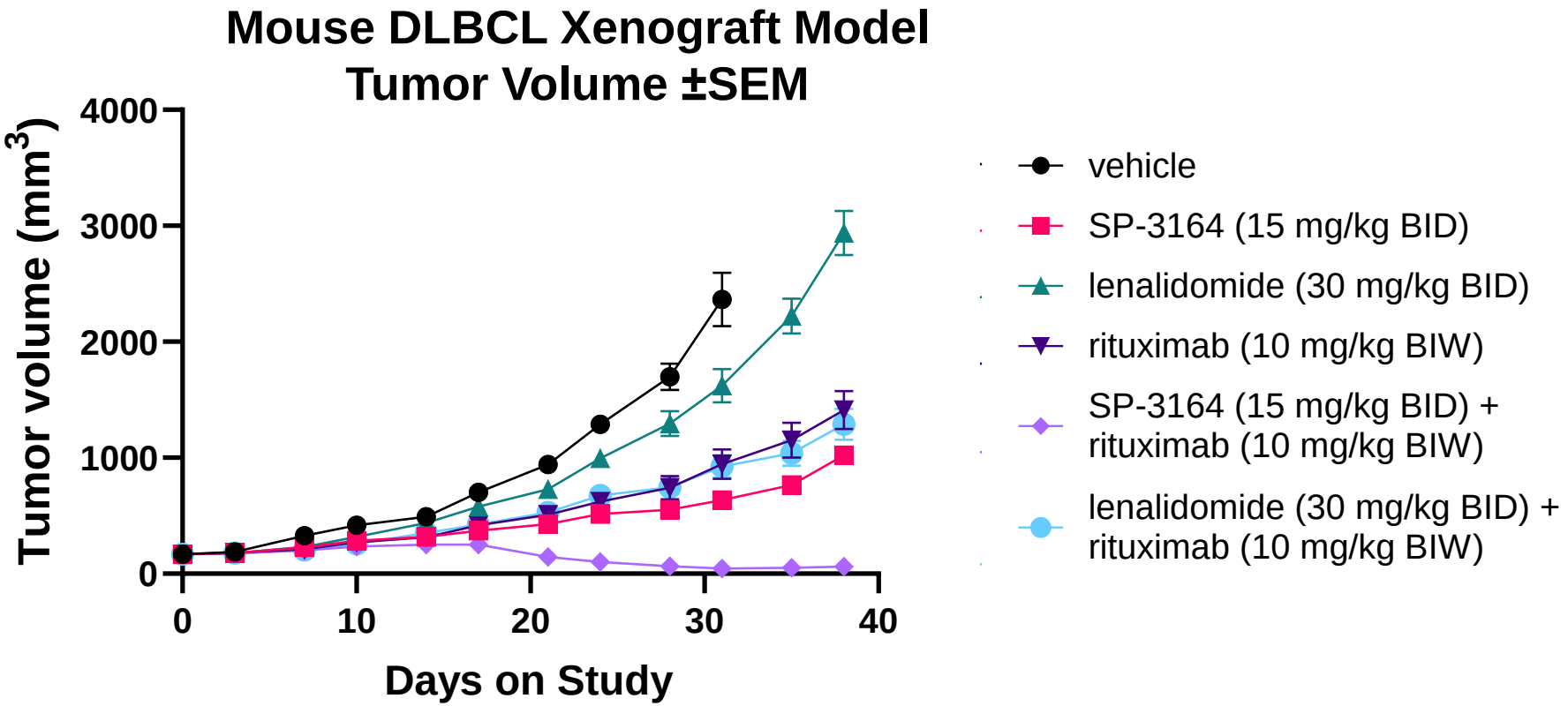


Degradation of Aiolos and Ikaros in tumors



- SP-3164 demonstrated pronounced antitumor activity as single agent outperforming lenalidomide and comparable to avadomide while SP-3165 lacked significant antitumor activity (**** p≤ 0.0001).
- Due to SP-3164's shorter half-life compared to avadomide, SP-3164 was studied BID resulting in the largest inhibitory effect.
- Treatment with SP-3164 caused degradation of Aiolos and Ikaros in tumors as shown by representative IHC images at t=6hr.

SP-3164 Shows Synergistic Activity with rituximab in DLBCL



- SP-3164's activity in combination with rituximab was compared to the approved regimen, lenalidomide and rituximab in the WSU-DLCL2 DLBCL model.
- The combination of SP-3164 and rituximab resulted in sustained regressions with 50% of mice being tumor-free, significantly better than the lenalidomide and rituximab regimen (****p ≤0.001).

Conclusions

- SP-3164 is a novel molecular glue that exists as the deuterium-stabilized, active (*S*)-enantiomer of avadomide and has compelling antitumor activity in NHL models.
- Preclinical studies validate SP-3164 as the active species and show that the (*R*)-enantiomer, SP-3165, has no antitumor effects.
- In *in vivo* DLBCL studies, SP-3164 showed synergistic activity with rituximab (anti-CD20), resulting in tumor regressions and performing significantly better than the approved regimen, lenalidomide and rituximab.
- The presented data support clinical investigation of SP-3164 and a trial is planned for 2023.