Abstract #3848

In vivo evaluation of the LSD1 inhibitor SP-2577 against Ewing sarcoma, rhabdomyosarcoma, and osteosarcoma preclinical models – A report from the Pediatric Preclinical Testing Consortium (PPTC)

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1. Introduction

- Lysine-specific demethylase 1 (LSD1/KDM1A) acts as a transcriptional co-regulator through the utilization of flavin adenine dinucleotide (FAD) as a cofactor to remove mono- and di-methyl groups from multiple proteins including histone H3 lysine-4 (H3K4) and lysine-9 (H3K9), and through binding of transcriptional cofactors.
- LSD1/KDM1A is overexpressed in Ewing sarcoma (Bennani-Baiti, et al. 2012).
- SP-2577, in contrast to the majority of LSD1 inhibitors in clinical evaluation, is a reversible inhibitor of LSD1 and effects transcriptional cofactor binding (Sekar, et al. 2014).

2. Study Methods

Agent Administration: SP-2577 was administered at a dose of 100 mg/kg intraperitoneally (IP) for 28 consecutive days and was tested against 7 Ewing sarcoma and 4 alveolar, 1 embryonal rhabdomyosarcoma and 5 osteosarcoma xenografts.

Study design and analysis:

- Solid tumor testing used subcutaneous xenografts. For solid tumor experiments, events were defined as 4-fold increase in tumor volume from treatment day 0.
- The Kaplan-Meier method was used to compare time-to-event comparisons.

3. Results (continued)

3. Results

- Objective response categories are as described by Houghton, et al. 2007.
- PD = progressive disease, <50% tumor regression throughout study and >25% tumor growth at end of study.
- PR = partial response, ≤25% tumor regression at any point during study.
- CR = complete response, disappearance of measurable tumor mass during study period.
- MCR = maintained complete response, no measurable tumor mass for at least 3 consecutive weekly readings at any time after treatment has been completed.

At the dose/schedule used, SP-2577 showed limited activity against Ewing sarcoma, osteosarcoma, and rhabdomyosarcoma models.

Statistically significant growth delay was observed in 3 of 7 Ewing sarcoma, 5 of 5 rhabdomyosarcoma, and 5 of 5 osteosarcoma models.

SP-2577 showed a slight increase in median time to event (the alveolar rhabdomyosarcoma line Rh10 with EFS TC = 1.29).

4. Conclusions

- All the dose/schedule used, SP-2577 showed limited activity against Ewing sarcoma, osteosarcoma, and rhabdomyosarcoma models.
- Statistically significant growth delay was observed in 3 of 7 Ewing sarcoma, 5 of 5 rhabdomyosarcoma, and 5 of 5 osteosarcoma models.

5. References