3. Results (continued)

The objective response categories are as described by Houghton, et al. 2012). The Kaplan-Meier method was used to compare time-to-event comparisons made. For comparing treatment groups, comparison between treatment groups used a p-value of 0.0167 for declaring significance to correct for the multiple groups, comparison between treated and control groups. For comparing treatment tumor volume from treatment day 0.

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 between treated and control groups. For comparing treatment groups, comparison between treatment groups used a p-value of 0.0167 for declaring significance to correct for the multiple comparisons made.
- The 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
- PD1 = when PD and the mouse's time to event ≤ 200% the KM Kaplan-Meier (KM) median time-to-event in control group
- PD2 = when PD but, additionally, time-to-event is > 200% of the median time-to-event in control group
- SD = stable disease, <50% tumor regression throughout study and 25% tumor growth at end of study
- PR = partial response, ≥50% tumor regression at any point during study but measurable tumor throughout study period
- 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.

3. Results (continued)

Figure 1. A. Responses of rhabdomyosarcoma xenografts to SP-2577. Mice received SP-2577 (100 mg/kg daily x 28 days) when tumors were 200-400mm3). Lines show growth of individual tumors, Control (red); SP-2577 treated (blue). The solid (bold) lines show median response. B. Relative tumor volume C. Kaplan-Meier probability plots for Event-Free Survival (EFS).

Figure 2. A. Responses of osteosarcoma xenografts to SP-2577. Mice received SP-2577 (100 mg/kg daily x 28 days) when tumors were 200-400mm3). Lines show growth of individual tumors, Control (red); SP-2577 treated (blue). The solid (bold) lines show median response. B. Relative tumor volume C. Kaplan-Meier probability plots for Event-Free Survival (EFS).

Figure 3. A. Responses of Ewing sarcoma xenografts to SP-2577. Mice received SP-2577 (100 mg/kg daily x 28 days) when tumors were 200-400mm3). Lines show growth of individual tumors, Control (red); SP-2577 treated (blue). The solid (bold) lines show median response. B. Relative tumor volume C. Kaplan-Meier probability plots for Event-Free Survival (EFS).

Figure 4. Pharmacodynamic effects of SP-2577 that were studied included c-Myc, N-Myc, HOXM1, histone H3, and histone H3(K4) dimethyl levels. Tissues were collected 4 hours after dose 7 (100 mg/kg daily) of SP-2577. There were no consistent decreases in histone H3(K4) dimethyl levels, and there was no obvious decrease in either c-Myc or N-Myc, whereas HOXM1 was slightly increased by treatment in two Ewing sarcoma models.

4. Conclusions

- At the dose/schedule used, SP-2577 showed limited activity against Ewing sarcoma, osteosarcoma, and rhabdomyosarcoma models.
- Statistically significant growth delay was observed in 7 Ewing sarcoma, 3 of 5 rhabdomyosarcoma, and 5 of 5 osteosarcoma models. However, a single modest but statistically significant 20% increase in median time to event (the alveolar rhabdomyosarcoma line Rh10 with EFS T/C = 2.79).

SP-2577 showed no effect on levels of c-Myc and N-Myc. HOXM1 showed a slight increase in tumors of animals treated with SP-2577 suggesting under the conditions used only moderate target engagement was achieved.


- 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 (Sankar, et al. 2014).

5. References

Sehrawat A, Gao L, Wang Y, Bankhead A, 3rd, McWeeney SK, King CJ, et al. LSD1 activates a lethal transcriptional coregulator 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 (Sankar, et al. 2014).


Academy of Sciences of the United States of America. 2018;115(18):E4179-E88


Supported by: U01 CA199297, U01 CA199221 and U01 CA199222

Presented at: AACR 2019

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