4SC-202: Epigenetic modulator and potential combination partner for checkpoint inhibitors

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**Introduction**

4SC-202 is an orally available, small molecule epigenetic modulator which inhibits HDAC class I and LSD1. The compound has been evaluated in a phase I clinical trial in hematological malignancies (TOPAS) where it was found to be safe and efficacious (1 CR, 1 PR; clinical benefit observed in 83% of the patients).

Here, we report that 4SC-202 is able to modify the tumor microenvironment leading to an increased influx of immune effector cells mediating an inflamed tumor type. Importantly, combination of 4SC-202 and checkpoint inhibitors show synergistic effects suggesting useful combinations in the clinic.

**4SC-202 induces a T-cell inflamed phenotype**

Figure 1: Anti-tumor activity of 4SC-202 requires a functional immune system and reshapes the tumor microenvironment.

A. Anti-tumor effects after treatment with 4SC-202 were observed in CT26 syngeneic mouse models (left panel) but not in nude/irradiated animals (right panel).

B. 4SC-202 leads to a change in immune-cell composition in CT26 tumors: particular the amount of CD8+ T-cells increased (upper left panel).

**4SC-202 enhances tumor immunogenicity**

Figure 2: Gene expression analysis after 4SC-202 treatment.


B. Gene expression analysis in cells: MHC (left panel) and co-stimulatory molecules (right panel); AML = THP-1, HL-60, Molm-13.

**4SC-202 does not exert toxicity to immune cells**

Figure 3: 4SC-202 treatment does not affect viability of immune cells.

A. Treatment with 4SC-202 increases the overall number of CD8+ T-cells in tumor, however overall count in blood remains unchanged.

B. 4SC-202 is less toxic to immune cells when compared to other HDAC inhibitors; IC50 values are displayed.

**Clinical relevance and conclusion**

We demonstrated that at clinically relevant exposure 4SC-202:

- Induces a T-cell inflamed phenotype
- Reduces the number of immunosuppressive MDSC in tumor microenvironment
- Increases immunogenicity by up-regulation of TAA, and MHC presentation machinery
- Is not toxic for tumoridial immune cells
- Converts tumors into PD-1/ PD-L1 blockade susceptible inflamed phenotype in vivo

- 4SC-202 is an ideal combination partner for checkpoint inhibitors due to its immune priming capacity, its excellent safety profile and the oral formulation which allows convenient application and flexible dosing schedule.

- Next step comprises translation of preclinical data into clinical Phase II trial.