4SC-202 induces inflamed tumor microenvironment, strongly enhances tumor infiltration with cytotoxic T cells and primes tumors for anti-PD1/PD-L1 therapy

T. Wulf1, K. Kronthaler1, S. Schrefler1, U. Pamitzke1, A.C. Bretz1, R. Baumgartner1, S. Hamm1
14SC AG, Martinsried, Germany

4SC-202, clinical stage epigenetic immune modulator

Various HDAC inhibitors were described as beneficially affecting anti-tumoral immune response. Although different HDAC inhibitors were investigated in syngeneic tumor models, the mode of anti-tumoral action is not yet fully understood.

Here, we analyzed the anti-tumoral efficacy and mode-of-action of 4SC-202, an orally available clinical stage epigenetic small molecule inhibitor specifically targeting histone deacetylases HDAC class I as well as the lysine-specific demethylase LSD1.

To ensure that the conclusions would be relevant for the clinical situation clinically equivalent doses were used. 4SC-202 increased the number of cytotoxic CD8+ T cells (CTL) in tumor microenvironment (TME) of T-cell-inflamed C38 tumors as well as of non-T-cell-inflamed CT26 tumors without affecting the number of CTLs in blood (Fig. 1).

Furthermore, 4SC-202 enhanced Th1 signature and chemokine network in TME of CT26 tumors, and reduced pro-inflammatory IL-1β and IL-23 (Fig. 2 A and B). Of note, a broad-spectrum HDAC inhibitor tested in the same model demonstrated anti-tumoral efficacy but did not affect the number of CTLs in tumors demonstrating that HDAC inhibitors employ different MOAs for their anti-tumoral response and that the effect on CTLs is not attributed to HDAC inhibition in general.

4SC-202 enhances infiltration of TME with cytotoxic T cells and increases IFN-γ and chemokine expression

A C38 tumors are characterized by high infiltration with T cells, especially with CD8+ T cells. CT26 tumors comprise only low number of CTLs (CD8+ T-cell-inflamed). To evaluate 4SC-202 increases CTL number in TME of both tumor types, especially in non-inflamed CT26 tumors (38 doses as indicated: CT26: 20 mg/kg BID; immune cells analyzed by FACS at the end of study).

4SC-202 primes cancer for checkpoint blockade

Since the T cell abundance is pre-requisite for the efficacy of PD1/PD-L1 blockade, combination of 4SC-202 with an PD1/PD-L1 blockade was tested in C38 and CT26 models. The combined treatment was more efficacious than monotherapies (Fig. 3) and resulted in significantly longer survival in both models with 55% tumor-free animals in C38 model (Fig. 4).

4SC-202 has already demonstrated a favorable safety profile in a Phase I clinical trial with relapsed or refractory hematological malignancies with two objective responses (1 CR, 1 PR) and disease stabilizations in several patients. 4SC-202’s immune priming capacity offers further options for clinical development of 4SC-202 in combination with PD1/PD-L1 blockade as well as with other cancer immunotherapy approaches.

Contact: www.4sc.com, Email: svetlana.hamm@4sc.com