4SC-202 plus Anti-PD1: Breaking PD1-refractoriness to increase efficacy of checkpoint inhibition in patients with advanced melanoma

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Abstract

Background: Despite successes in the treatment of melanoma patients with checkpoint inhibitors, most patients do not respond to checkpoint inhibition alone and a high unmet medical need remains for these patients. One promising approach is to enhance the immunogenicity and alter the tumor microenvironment from a more immune-deserted to an immune-inflamed phenotype by means of combination therapy. Epigenetic modulation has been reported as one key determining factor in shaping the immune microenvironment and compounds altering these processes (e.g. histone deacetylases (HDAC) inhibitors) are particularly promising.

Methods: Tumor bearing animals (CT26 and C38 syngenic models) were treated with 4SC-202, an orally available clinical stage combined HDAC class I/II/III inhibitor, or PD-L1 alone as well as in combination. Tumor growth was assessed continuously and after approx. 2 weeks of treatment tumors were excised and analyzed by flow cytometry and gene expression profiling. Additionally, animals not intended for these analyses were further monitored and tumor growth/survival was monitored.

Results: 4SC-202 treatment led to an increase of MHC molecules and enhanced expression of inflammatory markers like IFN-γ and various chemokines in tumors. Furthermore, detailed analysis of the tumor revealed that 4SC-202 strongly altered the immune cell composition and particularly the number of cytotoxic T cells (CTL) was markedly increased. Importantly, subsequent combination treatment of 4SC-202 with checkpoint inhibitors in syngenic animal models showed a strong synergistic effect resulting in significant longer survival in both models leading to 55% of tumor free animals (C38 model).

Treatment with 4SC-202 leads to increased infiltration of CD8+ T cells into tumor tissue.

Fig. 1: (A) Anti-tumor activity of 4SC-202 requires a functional immune system. (B, C) 4SC-202 enhances infiltration with cytotoxic CD8+ T cells in TME of CT26 tumors, whereas the total levels of CD8+ T cells remain unchanged. (D) Proposed mechanism of action: epigenetic modulation by 4SC-202 increases the recruitment of effector cells into the tumor rendering it more susceptible to treatment with checkpoint inhibitors.

Fig. 2: Combination of 4SC-202 and checkpoint inhibitor reduces tumor burden and increases survival in animal models.

Conclusion

Conclusion: Several preclinical tumor models have implicated remarkable immunomodulatory effects of 4SC-202 and the synergistic potential of combining with a checkpoint inhibitor. This epigenetically-driven modulation of the immune and tumor microenvironment by the HDAC class I/II/III Inhibitor 4SC-202 in Anti-PD1 refractory/non-responding cutaneous melanoma patients is hypothesized to sensitize the progressive tumor for the synergistic consecutive treatment of 4SC-202 in combination with Pembrolizumab to achieve clinical benefit. The Phase Ib/Ii SENITIZE study will test three dose cohorts of 4SC-202 for safety, tolerability and anti-tumor activity. A comprehensive biomarker panel analysis will be performed in sequential biopsies to investigate microenvironment changes on protein, gene expression and exosome level. The SENITIZE study is planned to enroll 30-40 patients in up to 6 certified skin cancer centers in Germany and recruitment will start soon. Initial topline data are expected to be available in 2018.

Contact and funding

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