4SC-202 primes tumor microenvironment for treatment with cancer immunotherapy

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4SC-202, clinical stage epigenetic immune modulator

4SC-202 is an orally available class I specific HDAC inhibitor. Phase I in 24 heavily pre-treated patients with hematological indications demonstrated favorable safety profile and efficacy with one CR, one PR and a disease control rate of 63%.

We have demonstrated that 4SC-202 increases immunogenicity of tumor cells by upregulating expression of tumor associated antigens, MHC class I and II, and co-stimulatory molecules. Here, we analyzed efficacy and mode-of-action of 4SC-202 in syngeneic models alone and in combination with checkpoint inhibitors and agonistic 4-1BB antibody. To ensure clinical relevance, clinically equivalent dosage regimen was used.

4SC-202 increases inflammatory signature and number of CTLs in tumor microenvironment (TME)

4SC-202 synergizes with PD-1/PD-L1 blockade resulting in increased survival and durable responses

A/B. Combination of 4SC-202 with PD-1/PD-L1 blockade resulted in beneficial anti-tumoral effect and increased survival in CT26 and C38 tumor models.

C. In C38 tumors the combination resulted in up to 83% durable complete responses.

D. In both models treatment with 4SC-202 increased the number of intratumoral CTLs.

4SC-202 combination with PD-1/LAG3 blockade results in more pronounced tumor regression

Triple combination of 4SC-202 + anti-PD-1 + anti-LAG3 was superior to all mono- and double therapies in C38 model.

Anti-LAG3 antibody exerted additional effect in 4SC-202/anti-PD-1 combination only. C38 model: treatment with 10 µg/kg 4SC-202 was given orally at 20 mg/kg BID, anti-PD-1 antibody (MPM-21) and anti-LAG3 (C10096) were given i.p. with 10 µg/kg TF for two consecutive weeks. A. mean values + SD, n=20, B. Individual tumor growth curves.

4SC-202 synergizes with agonistic 4-1BB antibody

4SC-202 strongly increases anti-tumoral effect and response rate to agonistic 4-1BB antibody

A. 4SC-202 increased infiltration of cytotoxic T cells (CTLs) into TME

CT26 mice were analyzed by FACS and by IHC in CT26 and C38 models at the end of study. 4SC-202 was given orally (p.o. 20 mg/kg 4SC-202) once daily for 20 days. B/C. In CT26 tumors 4SC-202 increased inflammatory signature and IFNγ expression and decreased expression of IL-1 and IL-23.

D. Expression of CD8 and CD3 T-cells and IFNγ significantly correlated with CTL infiltration and anti-tumoral response

Effect of 4SC-202 on gene expression in CT26 tumors was analyzed by RNA-Seq. Animals were treated with 20 mg/kg BID class. Tumor samples were harvested at the end of study.

4SC-202 primed tumor microenvironment for treatment with cancer immunotherapy

Although anti-PD1/PD-L1 antibodies are the new standard of care in many solid tumor indications, a high proportion of patients do not respond to this therapy. Treatment with 4SC-202 enhanced inflammatory signature and infiltration of tumors with cytotoxic T cells in various tumor models, qualifying this substance for combination with immune approaches targeting functionality of anti-tumoral T cells. We have demonstrated that 4SC-202 increases the response rate to agonistic 4-1BB antibody and synergizes with PD-1/PD-L1 blockade resulting in a high rate of durable responses, and increased survival.

Furthermore, the triple combination of 4SC-202 with anti-PD-1 and anti-LAG3 antibodies was superior to double combinations and led to tumor regression in nearly all animals.

Thus, 4SC-202’s immune priming capacity may offer an unique complementary approach to improve anti-tumor activity in combination with immunotherapy. Combination with PD-1 blockade is now under evaluation in a Phase Ib/II in advanced melanoma patients refractory/non-responding to anti-PD-1 antibodies (‘SENSITIZE’, NCT03278665).