4SC-202 increases CTLs in tumor microenvironment and primes tumors for checkpoint therapy

**4SC-202, a class I HDAC inhibitor, increases immunogenicity of tumor cells**

4SC-202 is an orally available small molecule in clinical development. 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 range of 85%. 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 mode-of-action of 4SC-202 in syngeneic models alone and in combination with checkpoint inhibitors. To ensure clinical relevance, clinically equivalent dosage regimen was used.

**4SC-202 increases inflammatory signature and the number of cytotoxic T cells in tumor microenvironment (TME)**

A. 4SC-202 increases infiltration of TME with CTLs

CT26 tumor was analyzed by FACS and by IHC in C26 and C38 models at the end of study. 4SC-202 was given orally (20 BID: 20 mg/kg BID, 60 SID: 60 mg/kg SID)

B. C. 4SC-202 increases inflammatory signature

Effect of 4SC-202 on gene expression in CT26 tumor was analyzed by RNA-Seq. animals were treated with 20 mg/kg BID daily dose.

**4SC-202 synergizes with immune checkpoint blockade resulting in durable responses and increased survival**

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

A. CT26: 20 mg/kg BID 4SC-202 was combined with an anti-PD-L1 antibody (10F9G2) given te with 10 µg/kg for two weeks. C. C38: 4SC-202 at indicated doses was combined with an anti-PD-1 antibody (MP1-14) given te with 10 µg/kg for two weeks; individual tumor growth curves on the right; B. In both models treatment with 4SC-202 increased the number of intratumoral CTLs

D-F. Combination of 4SC-202 with PD-1/PD-L1 blockade results in durable responses and significant survival increase in C38 and CT26 tumor models

D. CT26 and C38 models were performed as described in A and C. E. In the models, 60 mg/kg SID 4SC-202 + anti-PD-L1 combination versus vehicle was tested in C38 model, most tumors proceeded to regrow after treatment cessation resulting in 85% durable complete responses in this experiment

**4SC-202 primes tumors for therapy with inhibitory immune checkpoint antibodies**

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 therapy. Treatment with 4SC-202 enhanced inflammatory signature and infiltration of tumors with cytotoxic T cells, resulting in a high rate of durable responses, and increased survival in combination with PD-1/PD-L1 antibodies.

Thus, 4SC-202’s immune priming capacity offers a unique opportunity to increase response rate and survival in PD-1/PD-L1 refractory/non-responding patients. Combination with PD-1 blockade is now under evaluation in a Phase Ib/II in advanced melanoma patients refractory/non-responding to anti-PD1 antibodies (‘SENSITIZE’, NCT03278665).

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