

ANTI-CCR8 ANTIBODY CHS-114 (SRF114) DEPLETES TUMOR-INFILTRATING REGULATORY T CELLS IN DISSOCIATED TUMORS FROM PATIENTS WITH HEAD AND NECK SQUAMOUS CELL CARCINOMA

<http://dx.doi.org/10.1136/jitc-2023-SITC2023.1354>

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Background Depletion of intratumoral regulatory T cells (iTregs) represents an attractive therapeutic strategy to enhance anti-tumor responses. Transcriptional and flow cytometric analyses have identified the chemokine receptor CCR8 as being preferentially expressed on iTregs compared to peripheral Tregs and other immune cell types. Treatment of mouse tumor models with anti-CCR8 antibodies depletes iTregs, reduces tumor growth, and enhances anti-PD-1 anti-tumor activity in PD-1 resistant tumors. This highlights the therapeutic potential of anti-CCR8 depleting antibodies as a potential treatment for cancer patients and enhancing PD-1 therapy possibly in PD-1 resistant tumors.

CHS-114 (formerly SRF114) is an afucosylated anti-CCR8 antibody designed to deplete human iTregs. Here, we evaluate the phenotype, frequency, and localization of CCR8⁺ Tregs within resected tumor samples from patients with head and neck squamous cell carcinoma (HNSCC) and other indications. We also examine CHS-114-mediated iTreg depletion, immune effector cell activation, and cytokine production in dissociated tumor cells (DTC) from HNSCC samples.

Methods CCR8⁺ iTregs were characterized by flow cytometry and by immunofluorescence on formalin-fixed, paraffin-embedded (FFPE) samples. DTCs were cultured with CHS-114 to examine immune cell activation and iTreg depletion. The activity of anti-CCR8 treatment was assessed in humanized mice and the B16F10 tumor model.

Results CCR8 expression in the tumor microenvironment is highly restricted to iTregs. Across several solid tumor types, >50% of iTregs are CCR8⁺ cells. Immunofluorescence on FFPE samples shows that CCR8⁺ iTregs predominantly localize in the stroma but can also be found within tumor nests. CCR8⁺ cells are also present within tertiary lymphoid structures (TLS) and therefore potentially involved in constraining TLS-mediated anti-tumor immune responses. HNSCC exhibited a high abundance and frequency of CCR8⁺ iTregs (>70%). CCR8⁺ iTreg levels correlated with PD-L1 status but not with disease stage or HPV status. Furthermore, HNSCC CCR8⁺ iTregs exhibited a highly activated phenotype indicated by increased expression of FOXP3, HLA-DR, and Ki-67 compared to CCR8⁻ Tregs. SRF114 treatment of HNSCC DTC samples resulted in selective depletion of Tregs, NK cell activation, and IFN γ production. In mouse models, CHS-114 and a murine surrogate exhibited potent CCR8⁺ Treg depletion in vivo, resulting in CD8⁺ T-cell expansion, activation of myeloid cells, and inhibition of tumor growth.

Conclusions CHS-114 (SRF114) depletes CCR8⁺ Treg cells in vitro and in vivo. Molecular epidemiology studies highlight HNSCC as a tumor type with a high prevalence of CCR8⁺ iTregs to evaluate the anti-tumor activity of an anti-CCR8 antibody. CHS-114 (SRF114) is currently being evaluated in a Phase 1 clinical trial (NCT05635643).

Ethics Approval All animal studies were conducted under a protocol approved by and in compliance with policies set by the Institutional Animal Care and Use Committee, protocol # 2023-SUR-03.