CHS-114: a Cytolytic Anti-CCR8 Antibody that Depletes Tumor-Infiltrating Regulatory T Cells as a Treatment for Head and Neck Squamous Cell Carcinoma

N. Rajapakekar1, R. Haines1, M. Panduro2, Y. Yang1, Y. Rani2, V. Palombella1, J. Hiff1, R. Masi1, X. Wang1, V. Kapoor1, T. Lalvallée1, and J. Mohan1

1Cohere BioSciences, Redwood City, CA 2Surface Oncology, Cambridge, MA

**Background**

- FOXP3+ regulatory T (Treg) cells play a crucial role in orchestrating immune responses across several tissues, including the tumor microenvironment (TME).
- Intratumoral Treg cells support an immunosuppressive TME and increase the frequency correlates with poor clinical prognosis.
- Chemokine receptor B8 (CCR8) is highly upregulated by intratumoral Treg cells compared to peripheral counterparts and other immune cells.
- Monoclonal antibodies targeting CCR8 have been developed to deplete tumor Treg cells. This is an attractive strategy to reinvigorate the TME and enhance anti-tumor immune responses.

**CHS-114** is an engineered antibody that selectively targets human CCR8 and preferentially induces depletion of CCR8 Treg cells and not T effector (Teff) cells.

These preclinical studies aimed to characterize the expression of CCR8 in human tissues and study the effects of CHS-114-mediated depletion of CCR8 Treg cells.

**CHS-114 is currently in a Phase I clinical study** (NCT03563653).

**Intratumoral Treg Cells Highly Express CCR8 and Are Resistant in HNSCC Tumors**

**Results**

- Levels of CCR8 Treg cells are more abundant in HNSCC samples that express HPV. Although CCR8+ T cells do not appear to correlate with clinical stage or HPV status.
- Representative images of IHC for FOXP3 and CCR8 in a HNSCC sample indicating a high density of CCR8 (IF) staining in CCR8+ T cells compared to FOXP3+ T cells.
- Quantitation of CCR8+ T cells in clinical stage IV disease and of (D) CCR8+ cells by FOXP3 on HNSCC samples (n = 35-39 samples).

**CHS-114 Binds to HCCRs and Induces AADC and ADCC Activity**

- Representative images of mPD-L1 IHC at 10x.
- Human PBMC were incubated with serial dilutions of CHS-114 or an isotype control antibody (n = 3-4).
- A) Survival of human primary subcutaneous B16F10 tumors treated with anti-murine CCR8 mAb, anti-murine PD-L1, or control antibodies. B) Flow cytometric analysis of human tumor-infiltrating lymphocytes in B16F10 tumors on Day 8 of study. C) Density of infiltrating CCR8+ T cells. (Treatment initiated 6 days post-implantation, mean tumor volume of 71 mm3; A) n = 10 per group; B and C) n = per group per treatment.

**Dose-Dependent Depletion of CCR8 Treg Cells by CHS-114 in a Splenectomy Mouse Model**

- CHS-114 treatment at 10 mg/kg led to decreased FOXP3+ Treg cells, decreased detectable CCR8 expression, and increased CCR8+ T cells in the spleens compared to isotype control.
- Representative images of FOXP3+ CCR8+ and CCR8+ T cells in HNSCC tumors.
- CHS-114-mediated depletion of CCR8 Tregs in HNSCC tumors with PD-L1+ and PD-L1- tumors.
- CHS-114 treatment of mice resulted in a reduction in CCR8+ Treg cells in the spleens of humanized mice.

**Dose-Dependent Activation of Myeloid Cells in Response to CHS-114 Treatment**

- CHS-114 treatment leads to increased expression of macrophage markers M1 and M2, respectively, dose-dependent induction of macrophage activation, and monocytes in response to 10 mg/kg CHS-114.
- Other activation markers, CD80, CD206, and CD244, were not induced with either dose of CHS-114.

**Conclusions**

- CHS-114 expression is highly enriched within the TME and predominantly expressed on intratumoral Treg cells.
- CCR8 Treg are abundant in HNSCC tumors, which an activated phenotype, and their frequency correlates with PD-L1+ status.
- In dissociated HNSCC tumors, CHS-114 activated NK cells and specifically induces cytolytic activity toward tumor-infiltrating Treg.
- The mechanism of action is demonstrated in humanized mice: CHS-114 depletes human CCR8+ Treg cells in vivo, resulting in the expansion of CD8+ T cells and activation of murine myeloid cells.

- Anti-CCR8 and anti-PD-1 combination treatment improves overall survival in a checkpoint inhibitor-resistant melanoma mouse model by promoting expansion of CD8+ T cells in the TME.
- Molecular evaluation and in vitro studies highlight CHS-114 as a potentially relevant indication to evaluate the therapeutic activity of an anti-CCR8 in monotherapy or in combination with an anti-CCR8/anti-PD-1 combination therapy.
- CHS-114, a CCR8-specific cytotoxically inducing antibody that preferentially depletes CCR8 Treg cells and not T eff cells, is currently being evaluated in a Phase I clinical trial (NCT03563653).