Background FOXP3⁺ Regulatory T cells (Tregs) play a critical role in mediating tolerance to self-antigens but can repress anti-tumor immunity through multiple mechanisms. TGF-β is a potent immunosuppressive cytokine that acts as an essential factor during the differentiation of Treg cells. Therefore, targeted depletion of tumor-promoting Tregs is warranted to promote effective anti-tumor immunity while preserving peripheral homeostasis. CCR8 is a chemokine receptor that has recently been identified as a specific marker for tumor-infiltrating Tregs. Preclinical mouse tumor models have shown that the depletion of CCR8⁺ Tregs by anti-CCR8 monoclonal antibodies (mAbs) and FcγR engagement, but not ligand blockade, enables effective and long-lasting anti-tumor immunity in combination with PD-1 blockade. Several ADCC function-enhanced anti-CCR8 mAbs have been approved for clinical study both as a monotherapy and combined with PD-1 blockade. However, whether ADCP function enhancement would further potentiate anti-CCR8-mediated Treg depletion is still unknown. Here, we reveal an Fc-optimized anti-CCR8 mAb, which shows stronger ADCC and ADCP function than a wild-type IgG1 control. To explore potential combination strategies in the clinic, we also investigated the synergistic potential of combining the anti-CCR8 mAb with an anti-PD-L1 mAb fused to the extracellular domain of the human TGF-β receptor II (TGFβRII) via a flexible linker, to neutralize TGF-β (anti-PD-L1-β trap).

Methods Effector function-optimized anti-CCR8 mAbs were generated by the mutation of Fc residues plus expression in a fut8⁻ CHO cell line. ADCC and ADCP function was detected in both luciferase reporter cell line and primary cells. In vivo efficacy studies using anti-muCCR8-mG2a combined with an anti-PD-L1-β trap was conducted in a CT-26 colon carcinoma model.

Results Fc-optimized anti-CCR8 mAb showed stronger ADCC and ADCP function than the version containing wildtype IgG1 Fc in in vitro assays. The combination of anti-CCR8 mAb and anti-PD-L1-β trap more effectively controlled in vivo tumor growth compared to both monotherapies. We hypothesize that this potent anti-tumor immune response is propagated by the synergy of activating tumor infiltrating lymphocytes and the depletion of tumor-infiltrating Treg cells.

Conclusions We successfully generated an Fc-optimized anti-CCR8 mAb with both ADCC and ADCP enhancement. We also highlight the potential clinical combination benefit of anti-CCR8 mAbs with agents simultaneously blocking the PD1/L1 and TGF-β pathways.

Ethics Approval All mice were maintained under specified pathogen-free conditions, and all studies were approved by the Animal Care and Use Committee of HUST-Suzhou Institute for Brainsmatics.