1149 TARGETING REGULATORY T CELLS WITH CTM033, A NOVEL ANTI-CCR8 ANTIBODY, INHIBITED TUMOR GROWTH

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Background Regulatory T cells (Tregs) are potent suppressors of immune activation in the periphery and tumor microenvironment and high density of Tregs are associated with poor response to immune oncology (IO) therapies. CCR8 was selectively expressed on tumor infiltrating Tregs across multiple cancer types, but its expression on peripheral Tregs or other proinflammatory effector T cells was negligible. Moreover, CCR8+ Tregs were identified as a highly suppressive cell population within tumors which hampered the efficacy of immunotherapy. Recent studies also showed the CCR8 and its ligand CCL1 potentiated Tregs via an autocrine loop, implying CCL1-CCR8 axis may play a pivotal role in restraining antitumor immunity.

Methods The binding activity and specificity of anti-CCR8 antibody CTM033 was determined by a panel of flow cytometry based assays. Antagonistic activity of CTM033 against CCL1-CCR8 signaling was assessed by β-arrestin, calcium flux and migration assay. Antibody-dependent cell-mediated cytotoxicity (ADCC) function was evaluated by reporter assays and primary cells mediated killing against tumor infiltrating Tregs. The anti-tumor efficacy of CTM033 was evaluated in a MC38 syngeneic mouse model where the murine CCR8 gene was replaced by its human counterpart. Finally, Biacore and ADCC assay was performed to determine the ADCC-enhancing strategies.

Results CTM033 specifically bound to human CCR8 with subnanomolar activity and did not bind to closely related chemokine receptors and other unrelated proteins. CTM033 also potently inhibited CCL1-mediated β-arrestin recruitment, calcium flux, and migration of hCCR8+ cells. Furthermore, to maximize ADCC effect, different strategies were screened to determine the best approach for efficient Treg depletion. In vivo efficacy study suggested CTM033 monotherapy showed significant inhibition of tumor growth with evidence of intratumoral Treg depletion while sparing peripheral Treg subset.

Conclusions CTM033 is a humanized antibody against CCR8 with high affinity. CTM033 efficiently blocked CCL1-CCR8 pathway and induced ADCC function to deplete Tregs in the tumor microenvironment. Targeting CCR8+ Treg by CTM033 showed single agent activity in a preclinical model. Therefore, current data support anti-CCR8 is a promising approach for the cancer treatment that warrants further development.

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