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Preclinical Evaluation of JTX-1811, an Anti-CCR8 Antibody with Enhanced ADCC Activity, For Preferential Infiltrating Regulatory T cells

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ABSTRACT

Introduction: Immune checkpoint blockade (ICB) has reinvigorated the treatment of many cancers, yet still most patients do not respond to PD-1/PDL-1 or CTLA4 inhibitors. Thus, new Immuno-Oncology (IO) therapies that could potentially benefit non-responding patients are greatly needed. Jounce has generated specific gene edited TCR and CAR T cell therapies for a variety of genetic diseases for novel IO targets. Regulatory T cells (Tregs) are a unique attractive cell type for targeting as they may contribute to resistance to ICB. While Tregs are critical for immune homeostasis and preventing tissue damage, they are often present in large numbers within tumors where they may suppress anti-tumor immunity. Therapeutic strategies that specifically deplete tumor-infiltrating Tregs (TITRs) while sparing peripheral and normal tissue Tregs are highly desirable. Using a Creg gene signature, we have found a strong correlation with TITRs and CCR8-Cold Chemokine Receptor 8 (CCR8) across multiple tumor types. CCR8 may be differentiated from other known Treg targets in this regard, as its expression was found to be highly variable in TITRs.

Methods and Results: We first assessed CCR8 levels on TITRs across multiple tumor types and compared expression to Tregs in normal colon tissue or peripheral blood. On average, peripheral blood Tregs had notably higher CCR8 expression and normal colon tissue Tregs showed 4-5 fold lower levels of CCR8 than TITRs. We then generated a panel of monoclonal antibodies (mAbs) that bind specifically to CCR8 but not other family members, and block CCR8 signaling induced by its ligand CCL18. The ability of these mAbs to mediate anti-tumor-dependent immune killing was confirmed in a mouse xenograft model and in a human colon cancer cell line that was driven to disease when Tregs were depleted. When target-expressing CCR8 at levels equivalent to normal tissue Tregs, TITRs of 1 × 10^6 cells/mL were obtained to confirm CCR8 antibody reactivity. CCR8-expressing TITRs robust ADCC was observed, but only using antibodies in which the Fc portion of FcγRIII was allomodulated. Thus, allomodulated anti-CCR8 antibodies demonstrated a therapeutic window where TITRs but not normal tissue Tregs could be depleted. An Fc-competent, mouse-specific, anti-CCR8 antibody showed single agent tumor growth inhibition across several murine tumor models - including models in which PD-1/PD-L1 was ineffective. Anti-CCR8 was a potent combination partner with anti-PD-1 resulting in 30-50% complete tumor regressions in PD-1 resistant models.

Conclusions: Based on these preclinical data, JTX-1811, a high affinity CCR8-specific, human monoclonal antibody with anti-tumor ADCC activity, is being developed for selective depletion of tumor-infiltrating Tregs. JTX-1811 may be useful in PD-1 resistant settings and may restore the activity of PD-1 inhibitors in the setting of primary or acquired resistance to ICB.

SUMMARY

- Tumor infiltrating Treg (TITR) cells immunosuppress anti-tumor immunity in the TME
- CCR8 may be a superior target for TITR cells
- High expression in TITR cells
- Near absence in peripheral Treg cells
- Targeting CCR8 Treg cells may have single agent activity in PD-1 resistant setting and may restore PD-1 activity as a combination
- An antibody with enhanced ADCC may optimize the window for depletion of human TITR cells