1360 TREATMENT WITH A NOVEL HEXAVALENT OX40 AGONIST REMODELS THE TUMOR MICROENVIRONMENT TO FAVOR ANTI-TUMOR IMMUNITY IN MICE

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Background T cell costimulation through tumor necrosis factor receptors, such as OX40 (CD134), provides critical survival and differentiation signals. Although OX40 agonists were tested in early-phase clinical trials, their therapeutic efficacy was limited, necessitating the development of more effective agents. To address this, novel bivalent or hexameric anti-mouse OX40 agonists (cx-82 and INBRX-106m, respectively) were developed that potently enhance T cell activation. We investigated differences in the mechanisms of action between bivalent and hexavalent OX40 agonists. We hypothesized that INBRX-106m, through increased receptor clustering, provides stronger costimulatory signals to enhance anti-tumor immunity.
Methods Tumor-bearing mice (CT26, MCA-205) received control (IgG), anti-OX40 monoclonal antibody (clone OX86), bivalent OX40 agonist (cx-82), or hexavalent OX40 agonist (INBRX-106m). T cell activation status in blood, lymph nodes (LN), and tumor was determined by flow cytometry 7 days later. Tumor growth and survival were also determined. Data represent 1–2 experiments (n=5/group) and were analyzed by 1-way ANOVA (phenotypes) or Log-rank test (survival). $CD45^+$ cells were sorted for transcriptomic analysis using single-cell RNA-seq (10x Genomics).
Results INBRX-106m treatment significantly improved tumor regression and survival compared to control and anti-OX40 (OX86) ($p<0.001$). Furthermore, a trend towards improved survival was observed with INBRX-106m compared to cx-82. INBRX-106m also induced increased T cell proliferation (Ki-67; LN) as compared to bivalent anti-OX40 agents. INBRX-106m treatment led to decreased PD-1 expression in $CD4^+$ Treg ($p=0.0015$), $CD4^+$ Teff, $CD8^+$, and NK cell populations (LN). By day 7, there were no significant differences in $CD4^+$ Treg or Teff frequencies (LN); however, INBRX-106m-treated $CD4^+$ Teff cells retained higher proliferative capacity (Ki-67; $p=0.0029$). TIL analysis demonstrated enhanced $CD8^+$ T cell infiltration with decreased CD62L, suggesting increased effector differentiation following INBRX-106m. Finally, scRNA-seq analysis revealed marked changes in T cell and antigen presenting cell (APC) subsets post-INBRX-106m as compared to bivalent anti-OX40 agents.
Conclusions OX40 agonist therapy with INBRX-106m significantly improved tumor regression, overall survival, and T cell activation/differentiation in multiple preclinical tumor models in comparison to anti-OX40 (OX86) and cx-82. Flow cytometry and transcriptomic analysis indicated that INBRX-106m uniquely remodels the tumor microenvironment to promote anti-tumor immunity through alterations in T cell and APC differentiation. Additional studies are underway to validate these findings. A clinical trial with the human hexavalent OX40 antibody (INBRX-106) as a monotherapy and in combination with pembrolizumab (anti-PD-1) for patients with locally advanced or metastatic solid tumors is currently ongoing (NCT04198766).
Ethics Approval Experimental procedures were performed according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals and in accordance with the Earle A. Chiles Research Institute (EACRI) Institutional Animal Care and Use Committee (Animal Welfare Assurance No. A3913–01).

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