841 LBL-019, A NOVEL TNFR2 AGONIST ANTIBODY, SHOWS POTENT ANTI-TUMOR EFFICACY THROUGH PREFERENTIALLY ACTIVATING CD8+ T CELLS AND ALLEVIATING THE SUPPRESSIVE EFFECT OF TREG CELLS

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Background Tumor necrosis factor receptor-2 (TNFR2), representing co-stimulatory and survival signaling, is selectively expressed on immune cells, especially Treg and memory T cells, promoting both Tregs and cytotoxic T cells proliferation. Due to the paradoxical functions, two types of TNFR2 antibodies are under development: depletion or agonistic antibody. The depletion antibodies eliminate TNFR2+ Tregs and MDSC through ADCC or CDC, while the agonistic antibodies activate and expand cytotoxic T cells to inhibit tumors. Here, we report a novel TNFR2 agonistic antibody, LBL-019, which preferentially activates CD8+ T cells compared to CD4+ T cells, and in addition, can alleviate the suppressive effect of Treg cells.

Methods A diverse panel of antibodies against TNFR2 was screened and developed using mouse hybridoma technology. Robust in vitro assessments of candidates, including TNFR2 binding, TNF-α blockade, NF-κB report gene and cell functional assays validated and identified LBL-019 as the lead therapeutic candidate. In vivo, efficacy of LBL-019 and its combination with PD-1 antibody was evaluated in MC38 tumor models.

Results LBL-019 is a human/cyno cross-reactive TNFR2 antibody that binds TNFR2 with high affinity and specificity and recognizes a unique epitope in the CRD1 domain of TNFR2; LBL-019 is a potent agonist and blocks the TNFR2-TNF-α interaction in cell-based ligand binding assays and activating downstream NF-κB signal independent of TNF-α. LBL-019 plays anti-tumor efficacy through two distinct mechanisms. Firstly, it preferentially stimulated a 200% expansion of CD8 T cells compared to a 30% increase in CD4+ T cells, triggered the release of IFN-γ and up-regulated the expression of activation maker such as CD25, PD-1, and 41BB, depending on Fc crosslinking. Secondly, LBL-019 could alleviate the inhibitory effects of Treg cells on CD4/CD8 T cells, thereby promoting T cell proliferation and activation. Moreover, the combinational efficacy of LBL-019 with anti-PD1 has been demonstrated in vitro and in vivo, inhibiting tumor growth in the MC38 tumor model (TGI=80%).

Conclusions LBL-019 is a potent TNFR2 agonistic antibody. It effectively activated TNFR2 downstream signaling independent of TNF-α. By preferentially co-stimulating CD8+ T cells, LBL-019 promoted cytotoxic T cells proliferation and activation, and counteracted the immunosuppressive function of Tregs cells. The in-vitro and in-vivo anti-tumor activity of LBL-019 was evaluated both as a monotherapy and in combination with an anti-PD-1 antibody. The results demonstrate potent anti-tumor efficacy, supporting the advancement of LBL-019 in clinical development for the treatment of various human tumors.

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