1357 CD27 IS A NEW PROMISING T CELL CO-STIMULATORY TARGET FOR THE CANCER IMMUNOTHERAPY – DEVELOPMENT AND SELECTION OF A LEAD ANTI-CD27 AGONIST ANTIBODY

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Background Members of the tumor necrosis factor receptor superfamily (TNFRSF) are key co-stimulators of T cells. CD27, a member of the TNFRSF, is expressed only on the surface of lymphocytes, including naive and activated CD4+ and CD8+ T cells as well as NK cells. It enhances T cell activation, proliferation, and differentiation of effector and memory T cells after stimulation with its ligand, CD70. The costimulatory signal of CD27 is mediated via the NFkB pathway but also via the phosphatidylinositol 3 kinase and the protein kinase B pathways. CD27 signaling also influences the innate immune response via direct activation of NK cells and subsequent secretion of interferon-gamma (IFNg). Several published preclinical studies demonstrated that anti-CD27 agonistic monoclonal antibodies can promote T-cell activation and antitumor immunity making CD27 an attractive cancer immunotherapy target.

Methods Here we describe the characterization, preclinical development, and selection of our anti-CD27 fully human monoclonal antibody (mAb) lead candidate. We selected this candidate from a library of 147 anti-CD27 mAbs generated after immunization of humanized Trianni® mice with soluble human CD27 extracellular domain (hCD27-ECD).

Results Anti-CD27 mAbs were tested in an accelerated stability study and showed excellent stability parameters for up to 7 days at 4 and 37°C in commonly used formulation buffers. The selected agonist anti-CD27 mAb demonstrated high affinity binding to both human and cynomolgus monkey CD27 and not to mouse CD27. It also demonstrated high specificity against CD27 with no cross-reactivity detected against other members of the TNFRSF. This lead candidate did not block the binding of CD27 natural ligand, CD70 and induced strong NFkB-mediated CD27 signaling in the absence or presence of cross-linking by Fc gamma receptors or secondary cross-linking antibodies. Moreover, this anti-CD27 mAb mediated NFkB activation is significantly potentiated by the addition of a sub-optimal amount of soluble CD70. The anti-CD27 lead mAb induced T cell proliferation and secretion of pro-inflammatory cytokines only in the presence of sub-optimal TCR stimulation *in vitro* using primary human T cells. It also activated NK cells demonstrated by CD69 expression induction. The anti-CD27 mAb lead candidate showed extended serum half-life in hCD27-KI mice. It also demonstrated a significant antitumor effect as a single agent in human CD27-Knockin mice (hCD27-KI) subcutaneously implanted with MC38 or in NOD-SCID mice subcutaneously implanted with Raji.

Conclusions These preclinical results establish that the selected anti-CD27 mAb is a promising drug candidate and we are actively pursuing its development.

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