1341 CD27 AN EMERGING IMMUNO-ONCOLOGY TARGET AT THE CROSS-ROADS OF INNATE AND ADAPTIVE ANTI-TUMOR IMMUNE RESPONSES

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Background CD27 is a member of the TNF-Receptor superfamily expressed on CD4+ and CD8+ T cells, on NK and NKT cells and on B cells. It promotes T cell co-activation, proliferation, clonal expansion and differentiation into antigen specific cytotoxic and memory T cells after stimulation with its ligand CD70. Its stimulatory signal is mediated via the NFkB pathway, but also via the phosphatidylinositol 3 kinase and the protein kinase B. Moreover, CD27 signaling influences the innate immune response via a direct activation of NK cells and a subsequent secretion of interferon-gamma (IFN-γ). CD27 plays a central role in immunological responses and by promoting T cell and NK cell activation it contributes to anti-tumor immunity. Previous studies have demonstrated tumor growth inhibition with anti-CD27 agonistic monoclonal antibodies in different mice models for solid and hematological tumors. This mechanism of action can be partly explained by the recruitment of IFN-γ producing CD8+ T cells within the tumor. CD27 is a promising target for antitumor therapy.

Methods Kineta has generated a library of 147 fully human anti-CD27 monoclonal antibodies after immunization of Trianni mice.

Results From this library, a lead candidate with strong agonistic proprieties has been selected. This anti-CD27 antibody originates from a unique clade after alignment of the variable heavy chains. Kineta's lead candidate demonstrates selectivity and cross-reactivity with Non-Human Primate (NHP)-CD27 but not with the mouse-CD27. It also induces strong NFkB signaling in a Jurkat T cell-reporter, either soluble or cross-linked. It also induces T cell proliferation and secretion of pro-inflammatory cytokines in vitro. This T cell activation occurs only in the presence of a TCR engagement preventing future risks of spontaneous activation of naïve T cells *in vivo*. Our lead antibody also induces direct activation of NK cells demonstrated by the expression of CD69 on their surface. We have evaluated the anti-tumor properties of our lead antibody as a single agent in vivo in human CD27 Knock-In (KI) mice. Our anti-CD27 candidate induces a significant anti-tumor activity in the EG7 thymoma model. We have also demonstrated the anti-tumor efficacy of this lead candidate in Raji cells implanted in Scid mice. Preliminary experiments performed in human CD27 KI mice have demonstrated a long half-life of our antibody at different concentrations.

Conclusions Epitope characterization, NHP pharmacokinetic analysis and additional in vivo studies of our lead anti-CD27 antibody in different tumor models use as a single agent and in combination with different check-point inhibitors are ongoing.

http://dx.doi.org/10.1136/jitc-2022-SITC2022.1341