

AACR Annual Meeting 2017 – Abstract #4606

Preclinical characterization of a novel fully human IgG1 anti-PD-L1 mAb CK-301.

Short Title:

CK-301, a novel anti-PD-L1 mAb

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Abstract:

Antibodies targeting Programmed Death-1 (PD-1), or its ligand, PD-L1, have demonstrated remarkable efficacy in subsets of cancer patients, with inhibition of the interaction between PD-1 on T-cells and PD-L1 on tumor cells leading to the recovery of anti-tumor immune response and immune-mediated eradication of tumors. However, not all patients respond to existing PD-1 and PD-L1 targeting agents and relapses to therapy still occur. Therefore, there exists a need to identify additional therapeutics and approaches to engage the immune system to enhance the efficacy of current anti-cancer therapies. Using phage and yeast display approaches, we have discovered and optimized a novel, fully human PD-L1 specific IgG1 antibody, CK-301, which exhibits sub-nanomolar binding affinity for PD-L1. CK-301 blocks binding of PD-L1 to both PD-1 and B7-1 in enzyme-linked immunosorbent assays (ELISA) and cell-based competition assays. Using an assay measuring inhibition of a nuclear factor of activated T-cells (NFAT) reporter caused by PD-L1 binding to PD-1, we demonstrate that CK-301 completely reverses reporter inhibition at concentration of less than 1 µg/ml, IC₅₀ of the dose response curve is 80ng/ml. CK-301 enhances IFN-gamma secretion in allogeneic mixed lymphocyte reaction (MLR) using primary human T-cells and immature dendritic cells. CK-301 can also trigger antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) mediated killing of PD-L1+ cell lines, including lymphoma cells. CK-301 has similar sub-nanomolar affinity for cynomolgus monkey PD-L1 as for human PD-L1, hence we chose *Macaca fascicularis* for pre-clinical toxicology and safety pharmacology studies. Single dose administration of CK-301 to monkeys up to the highest tested dose of 100 mg/kg was shown to be safe and demonstrated linear dose-dependent pharmacokinetic (PK) properties over the dose range from 1 to 100 mg/kg with a half-life of 15 days at 100 mg/kg. A first-in-human Phase 1 study of CK-301 is planned to commence in mid-2017.