REGN5458

Name: REGN5458
Synonyms: REGN 5458
Indication: Multiple myeloma
Company: Regeneron Pharmaceuticals

REGN5458, a human bispecific antibody that binds to BCMA and CD3. In vitro, REGN5458 efficiently activates T cells and induces polyclonal T cell killing of myeloma cell lines with a range of BCMA cell-surface densities, and also induces cytotoxicity of primary human plasma cells. Similar to gamma-sectretase inhibitors, incubation of myeloma cell lines with REGN5458 increased surface levels of BCMA. In xenogenic studies, after BCMAhigh NCI-H929 and BCMAlow MOLP-8 MM cells were co-implanted with PBMC and grown subcutaneously in immunodeficient NOD/SCID/L2Rgamma-deficient (NSG) mice, REGN5458 doses as low as 0.4 mg/kg significantly suppressed the growth of both tumors. Using aggressive, systemic xenogenic tumor models, in which NSG mice were engrafted with PBMC and intravenously injected with BCMAhigh OPM-2 cells or BCMAlow MOLP-8 cells expressing luciferase, REGN5458 reduced tumor burden and suppressed tumor growth at doses as low as 0.4 mg/kg.

In immunocompetent mice genetically engineered to express human CD3, REGN5458 inhibited the growth of syngeneic murine tumors expressing human BCMA at doses as low as 0.04 mg/kg. Finally, as REGN5458 binds to cynomolgus CD3 and BCMA and mediates cytotoxicity of primary cynomolgus plasma cells, the pharmacology of REGN5458 was evaluated in cynomolgus monkeys. REGN5458 administration was well-tolerated, resulting in a mild inflammatory response characterized by transiently increased CRP and serum cytokines.

Importantly, REGN5458 treatment led to the depletion of BCMA+ plasma cells in the bone marrow, demonstrating cytotoxic activity in non-human primates.
The anti-tumor efficacy of REGN5458 was compared to BCMA-specific CAR T cells using 2nd generation CAR lentiviral constructs containing a single-chain variable fragment binding domain from REGN5458's BCMA binding arm and 4-1BB and CD3z signaling domains. Human PBMC-derived T cells were transduced to express this CAR and expanded.

Both REGN5458 and the BCMA CAR T cells demonstrated similar targeted cytotoxicity of myeloma cell lines and primary patient blasts in vitro, and were capable of clearing established systemic OPM-2-luciferase myeloma tumors in NSG mice, but with different kinetics: treatment with REGN5458 resulted in rapid clearance of tumors within 4 days, whereas treatment with BCMA CAR T cells allowed tumors to continue to grow for 10-14 days following injection before rapidly inducing tumor clearance. Thus, REGN5458 exerts its therapeutic effect rapidly after injection, using effector T cells that are already in place. In contrast, BCMA CAR T cells require time to traffic to the tumor site and expand, before exerting anti-tumor effects.
Collectively, these data demonstrate the potent pre-clinical anti-tumor activity of REGN5458 that is comparable to that of CAR T cells, and provide a strong rationale for clinical testing of REGN5458 in patients with MM.