Background: Interferon gamma (IFNg) cytokine induces cellular antigen presentation and has great potential in cancer treatment through enhancement of tumor antigen specific cytotoxic T cell response. However, the unfavorable pharmacokinetics (PK) and the pleiotropy of native IFNg have limited its therapeutic potential. NKTR-288 is a polymer-conjugated IFNg mutein, designed to improve exposure by increasing hydrodynamic radius and reducing receptor and heparin binding affinity to provide optimized on-target pharmacodynamics (PD). Here, we report on the discovery of NKTR-288 and investigate its pharmacological properties.

Methods: Binding of NKTR-288 to interferon gamma receptor 1 (IFNGR1) and heparin was measured by surface plasmon resonance. The biological activity of NKTR-288 was measured by pSTAT1 induction in tumor cell lines and primary myeloid cells in vitro and in vivo. PK/PD was measured in nonhuman primates (NHP), and human xenograft mouse models. Antitumor efficacy and enhancement of checkpoint blockade was measured in the mouse syngeneic B16F10 tumor model using a mouse IFNg polymer conjugate as a surrogate for NKTR-288.

Results: NKTR-288 has increased hydrodynamic radius to slow renal clearance and binds to IFNGR1 and heparin with reduced affinity compared to recombinant IFNg1b, thereby reducing clearance due to target-mediated drug deposition. In vitro, NKTR-288 maintains the maximum potential (Emax) for pSTAT1 induction on target cells. In vivo, NKTR-288 shows durable exposure in tumor bearing mice (half-life [T½] 18.2 to 24.2 hr) and NHP (T½ 31.6 to 37.3 hr) and is well tolerated at pharmacologically active doses. NKTR-288 has a desirable PK/PD profile that can attain greater induction and duration of MHCI than can be achieved with the native cytokine. NKTR-288 also upregulates PD-L1 in tumor tissue supporting combination therapy with checkpoint inhibitors. In a syngeneic tumor model, a surrogate mouse conjugate exhibited significant antitumor efficacy (57% TGI), and increased efficacy when combined with anti-PD-1 (73% TGI) or anti-PD-L1 (68% TGI). Treatments were well tolerated and tumor growth inhibition was immune system mediated, requiring T cells.

Conclusions: NKTR-288 is a novel IFNGR agonist with optimized pharmacological properties for tolerable and sustained induction of tumor antigen presentation, potentially increasing tumor cytotoxic T cell response, immune infiltration, and TME modification. As evidence, a mouse surrogate conjugate demonstrated T cell-mediated anti-tumor activity, and enhanced checkpoint blockade efficacy in a low-MHCI “cold” tumor model. These results highlight the potential of NKTR-288 as a novel cytokine immunotherapy in cancer patients, with the potential to enhance PD-1/PD-L1 checkpoint blockade efficacy and broaden the responsive patient population.

Ethics Approval: Animal studies were performed under protocols approved by the Institutional Animal Care and Use Committee of Nektar Therapeutics and the Canadian Council on Animal Care. All studies met the ethical and humane criteria for transportation, housing, and care established by the US NIH guidelines or Canadian animal care regulators.