IL12 Fc-fusions engineered for reduced potency and extended half-life exhibit strong anti-tumor activity and improved therapeutic index compared to wild-type IL12 agents

Interleukin-12 (IL12) is a heterodimeric proinflammatory cytokine that induces differentiation of Th1 cells, increased proliferation and cytokotoxicity of T and NK cells, and may aid in myeloid remodeling. Stimulation with IL12 leads to production of IFNγ and IFNγ. These immune-stimulating aspects of IL12 are promising for cancer treatment and may help to convert immunosuppressed “cold” tumors into inflamed “hot” tumors. Preclinical studies in mice revealed that IL12 can have a dramatic effect on shrinking syngeneic tumors; however, clinical studies in humans have resulted in severe toxicity and a small therapeutic window, limiting potential clinical use.

Introduction

Potential reduced IL12-Fc have superior exposure due to slower receptor-mediated clearance and improved PK, and more sustained PD. Potency-reduced IL12-Fc cause extended margination of NK and T cells, with greater systemic activation and increased tumor infiltration. Potency-reduced IL12-Fc are efficacious as single-agent and in combination with anti-PD-1 in a huCD34 MCF7 tumor model.

IL12-Fc were engineered for reduced in vitro potency

Potency-reduced IL12-Fc have substantially improved PK, PD, and therapeutic index in non-human primates

Potency-reduced surrogate mIL12-Fc are highly efficacious, have superior intratumor PD, and are better tolerated than WT-mIL12-Fc in a CT26 tumor model

Lead candidate XmAb662 is efficacious as a single-agent and in combination with anti-PD1 in a huCD34 MCF7 tumor model

Summary

- IL12 heterodimeric Fc-fusions (IL12-Fc) were engineered with a reduced potency IL12 to improve therapeutic index compared to therapeutics using native (wild-type) IL12.
- Potency-reduced IL12-Fc demonstrate significant anti-tumor activity in mice concurrent with activation and proliferation of CD8 T cells and tumor-selective IFNγ production.
- Potency-reduced IL12-Fc have improved therapeutic index, improved PK, and more sustained PD compared to IL12-Fc in non-human primates.
- These results support clinical testing of lead candidate XmAb662 as a potential novel and better-tolerated IL12 cytokine therapy in cancer patients.