NKTR-255: an IL-15-based therapeutic with optimized biological activity and anti-tumor efficacy

Peter Kirk1, Murali Addepalli1, Thomas Chang1, Ping Zhang1, Marina Konakova1, Katsunobu Hagihara1, Steven Pai3, Laurie VanderVeen1, Palakshi Obalapur1, Peiwen Kuo1, Phi Quach1, Mekhala Maiti1, Christie Fanton1, Takahiro Miyazaki1, Poorna Chandra1, Arunasree Lanka1, Ravi Nutakki1, Lawrence Fong4, Deborah Charych1, Jonathan Zalevsky1, Peter Kirk1, Murali Addepalli1, Thomas Chang1, Ping Zhang1, Marina Konakova1, Katsunobu Hagihara1, Steven Pai3, Laurie VanderVeen1, Palakshi Obalapur1, Peiwen Kuo1, Phi Quach1, Mekhala Maiti1, Christie Fanton1, Takahiro Miyazaki1, Poorna Chandra1, Arunasree Lanka1, Ravi Nutakki1, Lawrence Fong4, Deborah Charych1, Jonathan Zalevsky1

1Nektar Therapeutics, San Francisco, California; 2Helen Diller Family Comprehensive Cancer Center, UCSF, San Francisco, California

Introduction

Interleukin-15 has been identified as a promising candidate for use as an immuno-oncology therapeutic, but the native cytokine has poor drug-like properties. NKTR-255 is a novel immunotherapeutic agent consisting of polymer-engineered IL-15 designed to optimally engage the IL-15 receptor complex and provide durable pathway activation in vivo. Here we show that NKTR-255 has greatly improved plasma and tumor exposure relative to IL-15, induces NK and CD8 T-cell activation and proliferation, and has single-agent efficacy in syngeneic tumor models.

Results

NKTR-255 binds to IL-15Rs

NKTR-255 is bioactive, with sub-nanomolar EC50

Compared to IL-15, NKTR-255 has greatly improved plasma and tumor exposure

NKTR-255 induces NK cell proliferation and activation

NKTR-255 induces sustained signaling in lymphocytes in vivo

NKTR-255 treatment results in reduced tumor growth rate, an increase in the CD8:Treg ratio in spleen and tumor, and an increase in the frequency of IFNγ/TNFα+ CD8 T-cells

NKTR-255 reduces tumor burden in CT-26 and B16F10 lung metastasis models

Discussion

NKTR-255 treatment results in sustained IL-15 activity, which induces CD8 T-cell and NK cell activation and proliferation, and produces long-lived immunophenotypic changes in tumor-bearing mice. The design of NKTR-255 enables a potential drug-like therapeutic strategy for accessing IL-15-based immunotherapy.