INTRODUCTION

• Recombinant human IL-2 (rIL-2) is effective immunotherapy for metastatic melanoma and renal cell carcinoma with durable responses in ~ 15% of patients, but side effects limit its use
• IL-2 has pleiotropic immune modulatory effects which may limit its anti-tumor activity
• Binding to the heterotrimeric IL-2Rαβγ leads to expansion of suppressive Treg which antagonizes anti-tumor immunity
• NKTR-214 was engineered for biased immune-activating effects and for providing a sustained signal through the IL-2 receptor pathway
• The resulting design of NKTR-214 comprises recombinant human IL-2 i) chemically conjugated with multiple releasable chains of polyethylene glycol (PEG), ii) Slow release of PEG chains over time generates active PEG conjugated -2 metabolites of increasing biactivity, improving pharmacokinetics and tolerability. iii) Active NKTR-214 metabolites bind IL-2R activation towards IL-2 receptor

NKTR-214: Molecular design, prodrug and comparative tumor pharmacokinetics[1] NKTR-214 releases to an array of ‘daughter’ conjugated 5-2 species

RESULTS

Modeling of PEG chain release in vivo indicates that conjugated IL-2 derived from NKTR-214 occupies the IL-2Rγc with an AUC that is 90-fold greater than IL-2

Mobilization of lymphocytes from the periphery into the tumor is an important property of NKTR-214

CONCLUSIONS

• NKTR-214 activates the IL-2 pathway by slowly releasing the PEG chains over time, evolving into an array of IL-2 conjugates that occupy the IL-2Rγc with greater AUC than rIL-2
• In vivo, NKTR-214 and rIL-2 induce the release of bioactive IL-2 as well as the release of IL-2 metabolites. The release is enhanced in NKTR-214
• NKTR-214 activation of the IL-2Rγc appears to be important for mediating anti-tumor activity

REFERENCE