NKTR-255 Exhibits Target Mediated Drug Disposition and Stimulates Proliferation of Cytotoxic Immune Cells in Cynomolgus Monkeys

Kavitha Bhasi, Palakshi Obalapur, Peiwen Kuo, Ping Zhang, Paul Sims, Takahiro Miyazaki, and Werner Rubas

Nektar Therapeutics, San Francisco, CA

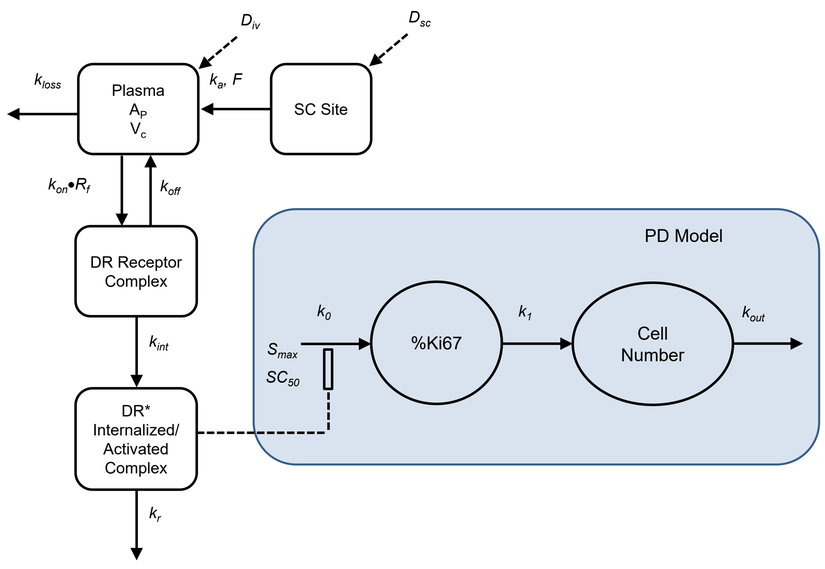
Introduction

- IL-15 is a cytokine that activates T cells and NK cells and has long been recognized for its potential as an immunotherapeutic agent for the treatment of cancer.
- Exploiting this potential has been challenging due to unfavorable pharmacokinetic properties requiring daily dosing.
- NKTR-255 is a polymer-modified IL-15 that shows sustained exposure relative to hrIL-15 while retaining potency and high affinity for IL-15Rα.
- Modeling was conducted to characterize the PK/PD of NKTR-255 in cynomolgus monkeys.

Methods

- To assess the PK/PD effects in monkeys, NKTR-255 was administered via intravenous (iv) and subcutaneous (sc) routes and whole blood was collected at specific time points.
- PK data was collected after seven iv doses ranging from 0.001-0.3 mg/kg and three sc doses ranging from 0.01-0.1 mg/kg. All NKTR-255 doses are expressed in IL-15 equivalents.
- NKTR-255 was quantified using ELISA-based plasma measurement.
- Flow cytometry was used to measure signaling proliferative status (Ki-67 expression) and absolute frequency of various lymphocyte subpopulations.
- Modeling was conducted using NONMEM 7; and first-order conditional estimation method with interaction (FOCEI) was implemented for all runs.

Schematic Representation of TMDD PK Model and Indirect-Response PD Model (Mager et al, 2003) for NKTR-255 Following IV and SC Administration



Equations Describing Target Mediated Drug Disposition (TMDD) PK Model and Indirect-Response Pharmacodynamics (PD) Model (Mager et al, 2003) for NKTR-255 Following IV and SC Administration

- $\frac{dA_{P,iv}}{dt} = k_{off} \cdot DR_{iv} - \left(\frac{k_{on}}{V_c}\right) \cdot A_{P,iv} \cdot R_{f,iv} - k_{loss} \cdot A_{P,iv}\ , IC = IV\ Dose$ Eq.(1)
- $\frac{dA_{P,sc}}{dt} = k_a \cdot A_{sc} + k_{off} \cdot DR_{sc} - \left(\frac{k_{on}}{V_c}\right) \cdot A_{P,sc} \cdot R_{f,sc} - k_{loss} \cdot A_{P,sc}$ Eq.(2)
- $\frac{dDR_{ad}}{dt} = \left(\frac{k_{on}}{V_c}\right) \cdot A_{P,ad} \cdot R_{f,ad} - (k_{off} + k_{int}) \cdot DR_{ad}$ Eq.(3)
- $\frac{dA_{sc}}{dt} = -k_a \cdot A_{sc}\ ,\ IC = F \cdot SC\ Dose$ Eq.(4)
- $R_{f,ad} = R_{max} - DR_{ad}$ Eq.(5)
- $\frac{dDR^*_{ad}}{dt} = k_{int} \cdot DR_{ad} - k_r \cdot DR^*_{ad}$ Eq.(6)
- $\frac{dKi_{67}}{dt} = k_0 \cdot \left(1 + \frac{S_{max} \cdot DR^*_{ad}}{SC_{50} + DR^*_{ad}}\right) - k_1 \cdot Ki_{67}$ Eq.(7)
- $\frac{dT_1}{dt} = k_1 \cdot Ki_{67} - k_{out} \cdot CN$ Eq.(8)
- $k_0 = CN^0 \cdot k_{out}$ Eq.(9)
- $Ki^0_{67} = \frac{k_0}{k_1}$ Eq.(10)
- $S_{max} = \frac{E_{max}}{Ki^0_{67}} - 1$ Eq.(11)

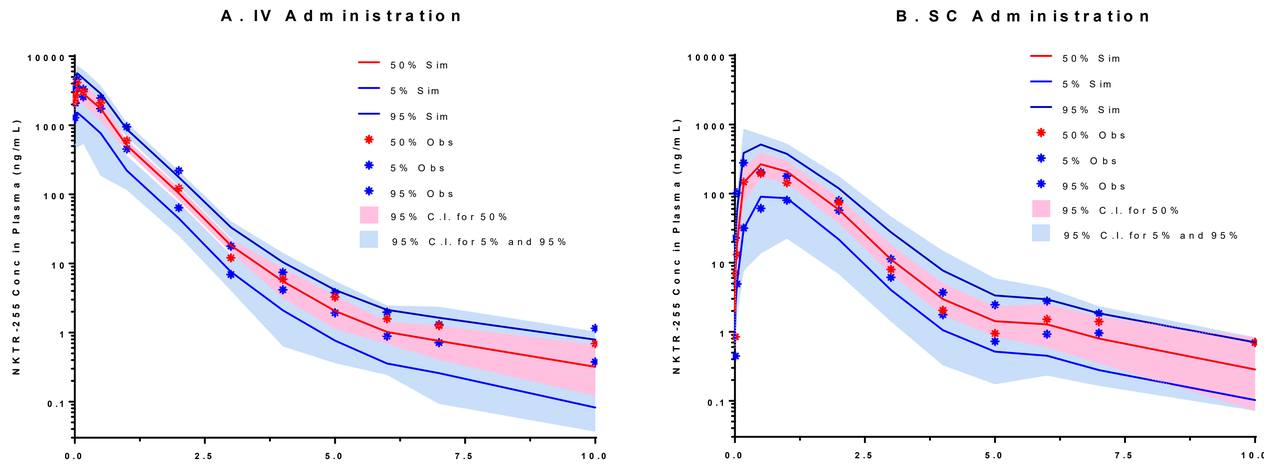
Abbreviations: A_P, V_c: amount of drug and volume of central compartment; D_{iv} and D_{sc}: doses for iv and sc administration (ad) routes; k_{on}, k_{off}, k_{int}: association, dissociation, internalization rate constants; k_{loss}: additional drug elimination pathways; k_a: absorption from sc dosing site to the central compartment; iv and sc: intravenous and subcutaneous administration (ad) routes; R_{max}: maximum receptor quantity; R_f: amount of free cell-surface receptors; DR_{ad}: drug-receptor complex; F: bioavailability; DR^*_{ad}: internalized/activated drug-receptor complex; k_r: loss of DR*; k_0: zero-order input rate for Ki-67; k_1: first-order loss rate for Ki-67 which also represents the input rate for cells; k_{out}: first-order loss rate for cells; Ki_{67}: %Ki-67; CN: Number of cells (CD8 T-cells and NK cells); S_{max}: maximum stimulation effect by drug; SC_{50}: drug concentration at 50% of maximum effect; E_{max}: maximum PD response for $\%Ki_{67}$; $Ki_{67}{}^0$,CN^0: baseline values for %Ki-67 and cell numbers, respectively

Results (Executive Summary)

- PK parameter estimates for elimination of NKTR-255 from central compartment (k_{loss}), receptor binding (k_{on} and k_{off}) and internalization (k_{int}) rates are 0.0641 hr^{-1}, 1.25 $nM^{-1}hr^{-1}$, 0.136 hr^{-1}, and 0.0094 hr^{-1}, respectively.
- PD parameter estimates were independent of dosing route and shows that NKTR-255 stimulates proliferation of NK cells more potently than CD8 T cells by a factor of ~10-fold with potency (SC_{50}) of 0.0252 nmol/kg and 0.24 nmol/kg, respectively, in cynomolgus monkeys.

Results

Prediction-Corrected Visual Predictive Check Plots for NKTR-255 PK Following: A) IV and B) SC Administration in Monkeys

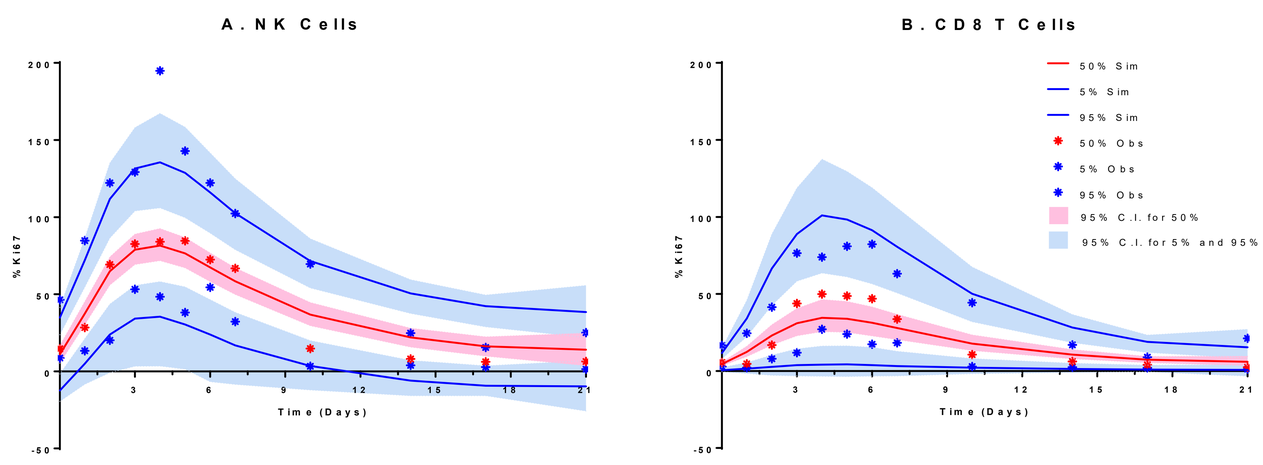


PK Parameter Estimates Following IV and SC Administration of NKTR-255 in Monkeys

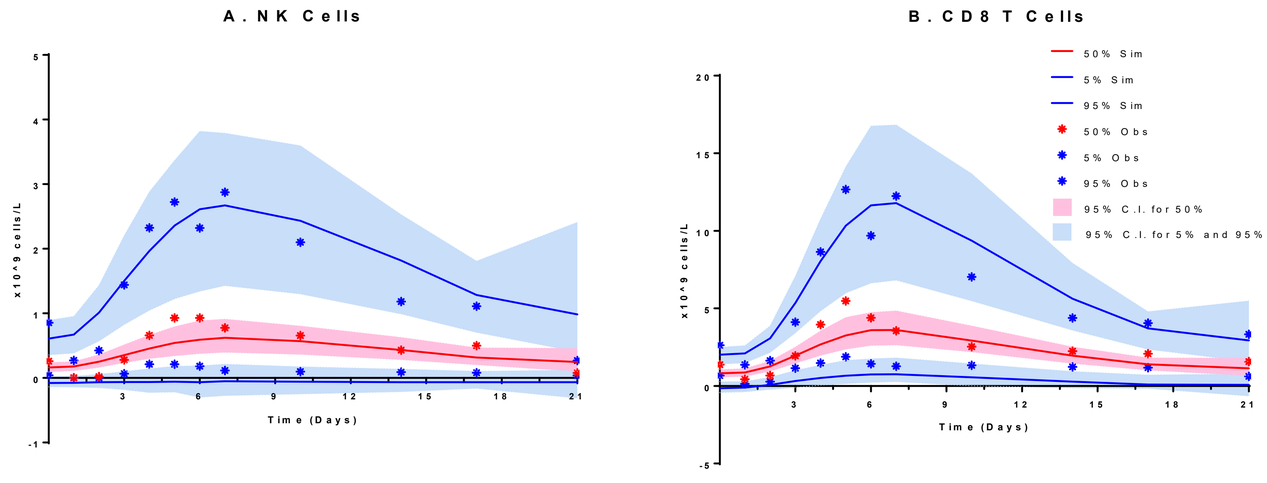
PK Parameter (units)	Estimate	%RSE (of Estimate)	IIV	%RSE (of IIV)
k_{loss} (hr^{-1})	0.0641	2	--	--
k_{on} ($nM^{-1}hr^{-1}$)	1.25	25	--	--
k_{off} (hr^{-1})	0.136	13	--	--
k_{int} (hr^{-1})	0.0094	17	0.168	54
R_{max} (nmol/kg)	0.196	17	--	--
V_c (mL/kg)	37	4	--	--
k_a (hr^{-1})	0.0988	15	0.148	47
F	0.657	14	0.0906	60
Proportional error constant	0.117	10	--	

k_{loss}: additional drug elimination pathways; k_{on}, k_{off}, k_{int}: association, dissociation, internalization rate constants; R_{max}: maximum receptor quantity; V_c: volume of central compartment; k_a: absorption from sc dosing site to the central compartment; F: bioavailability; IIV: inter-individual variability; RSE: relative standard error

Prediction-Corrected Visual Predictive Check Plots for NKTR-255 PD for %Ki-67 for: A) NK and B) CD-8 T Cells



Prediction-Corrected Visual Predictive Check Plots for NKTR-255 PD for Number of Cells for: A) NK and B) CD-8 T Cells



PD Parameter Estimates Following IV and SC Administration of NKTR-255 in Monkeys

PD Parameter (units)	NK Cells		CD8 T Cells	
	Estimate (%RSE)	IIV (%RSE)	Estimate (%RSE)	IIV (%RSE)
k_r (hr^{-1})	0.0425 (6)	--	0.0192 (21)	0.3 (44)
E_{max} (%)	100 (fix)	0.00593 (66)	100 (fix)	0.0366 (115)
SC_{50} (nmol/kg)	0.0252 (14)	0.0816 (61)	0.24 (22)	--
$Ki_{67}{}^0$ (%)	18.8 (6)	--	6.1 (16)	0.114 (56)
k_1 (hr^{-1})	0.0313 (8)	--	0.018 (16)	--
CN^0 ($x10^9$ cells/L)	0.178 (18)	0.596 (23)	0.648 (19)	0.139 (62)
Proportional error constant	--	--	0.574 (4)	--
Additive error (%)	16.8 (5)	--	--	--
Proportional error constant	0.65 (8)	--	0.321 (18)	--
Additive error ($x10^9$ cells/L)	0.156 (18)	--	0.706 (28)	--

k_r: loss of DR*; E_{max}: maximum PD response for $\%Ki_{67}$; SC_{50}: drug concentration at 50% of maximum effect; k_1: first-order loss rate for %Ki-67; $Ki_{67}{}^0$,CN^0: baseline values for %Ki-67 and cell numbers, respectively

Conclusions

- NKTR-255 displays TMDD PK disposition. Similarly to hrIL-15, NKTR-255 stimulates the proliferation of NK cells more potently than the CD8 T-cells in cynomolgus monkeys.
- The model parameters along with the in-vitro potency values will be used to predict MABEL dose selection in first-in-man clinical studies.

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