



# **NKTR-214 plus NKTR-262, a Scientifically-Guided Rational Combination Approach for Immune Oncology**

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**SVP, Biology and Preclinical Development**  
**Nektar Therapeutics**

**World Preclinical Congress, 2017**

# Nektar Therapeutics

San Francisco, CA



100,000-sq.ft.  
State-of-the-Art  
R&D Center

Huntsville, AL



114,000-sq.ft.  
Manufacturing  
Facility

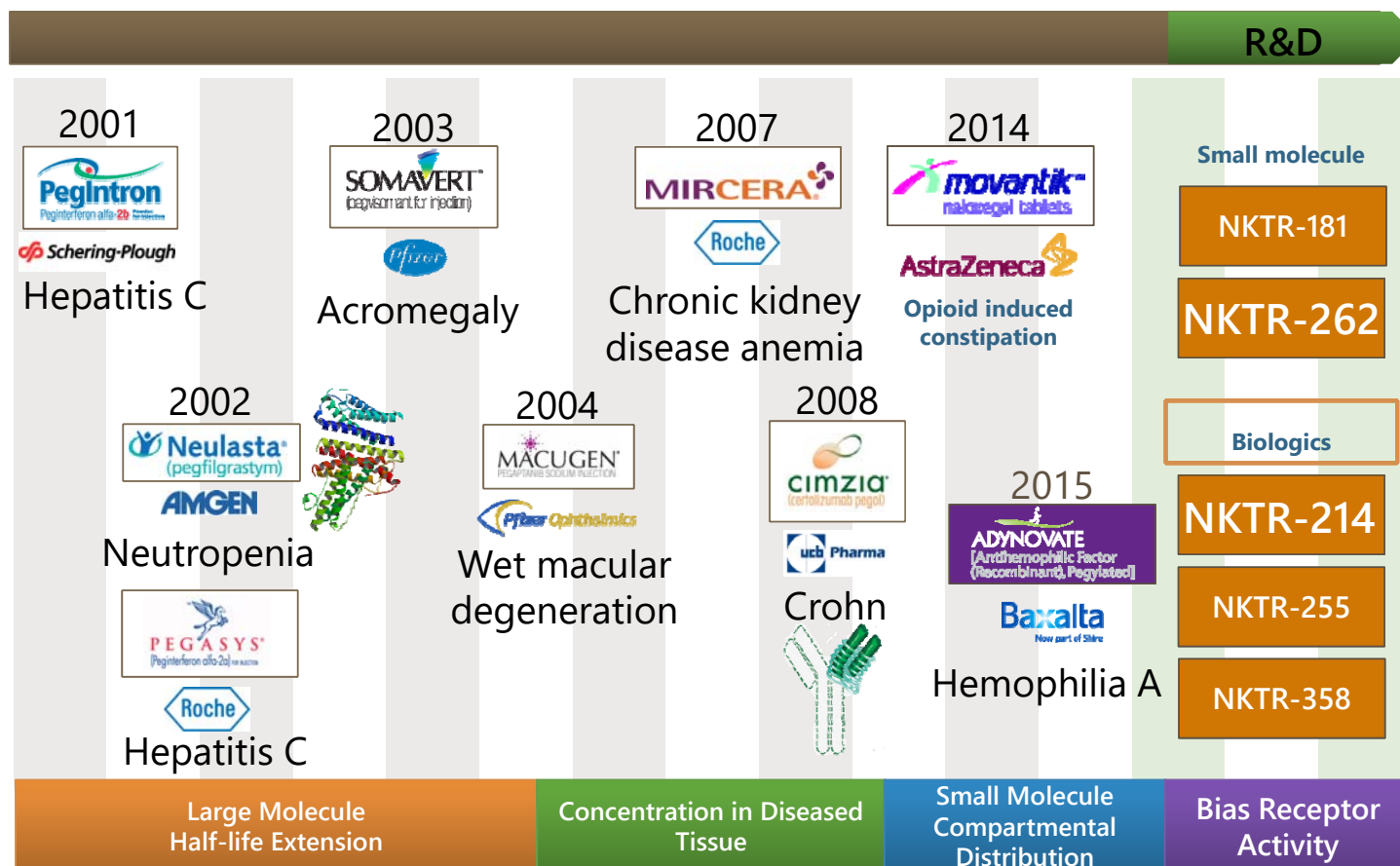
Hyderabad, India



88,000-sq.ft.  
R&D Support  
Facility

- ▶ **Biopharmaceutical company leveraging polymer conjugation technologies to develop new therapies in multiple disease areas**
- ▶ **Strong heritage of partnership with top biopharma companies**
- ▶ **~ 450 employees**
  - R&D Center and Headquarters in San Francisco, CA
  - Pharmaceutical Development & Manufacturing in Huntsville, AL
  - R&D support in Hyderabad, India

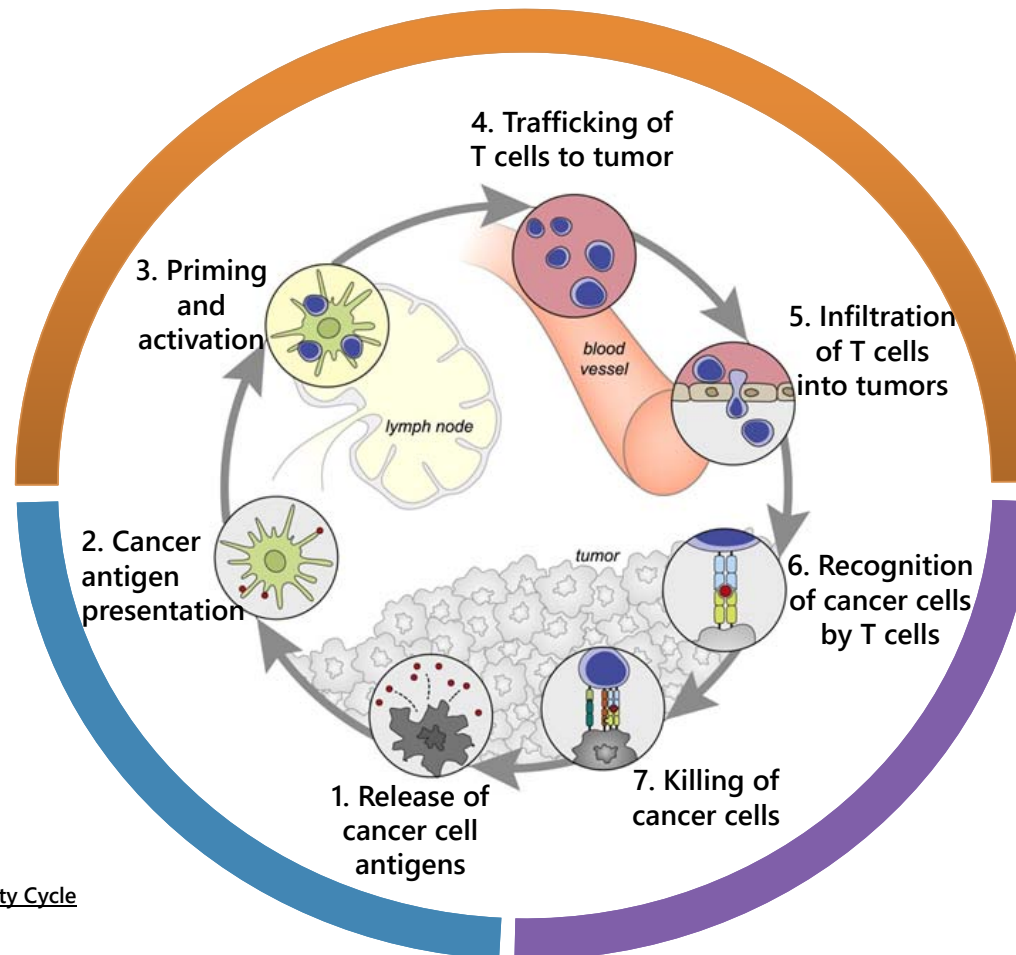
# Evolution of Nektar's Polymer Conjugation Technology



# Overview

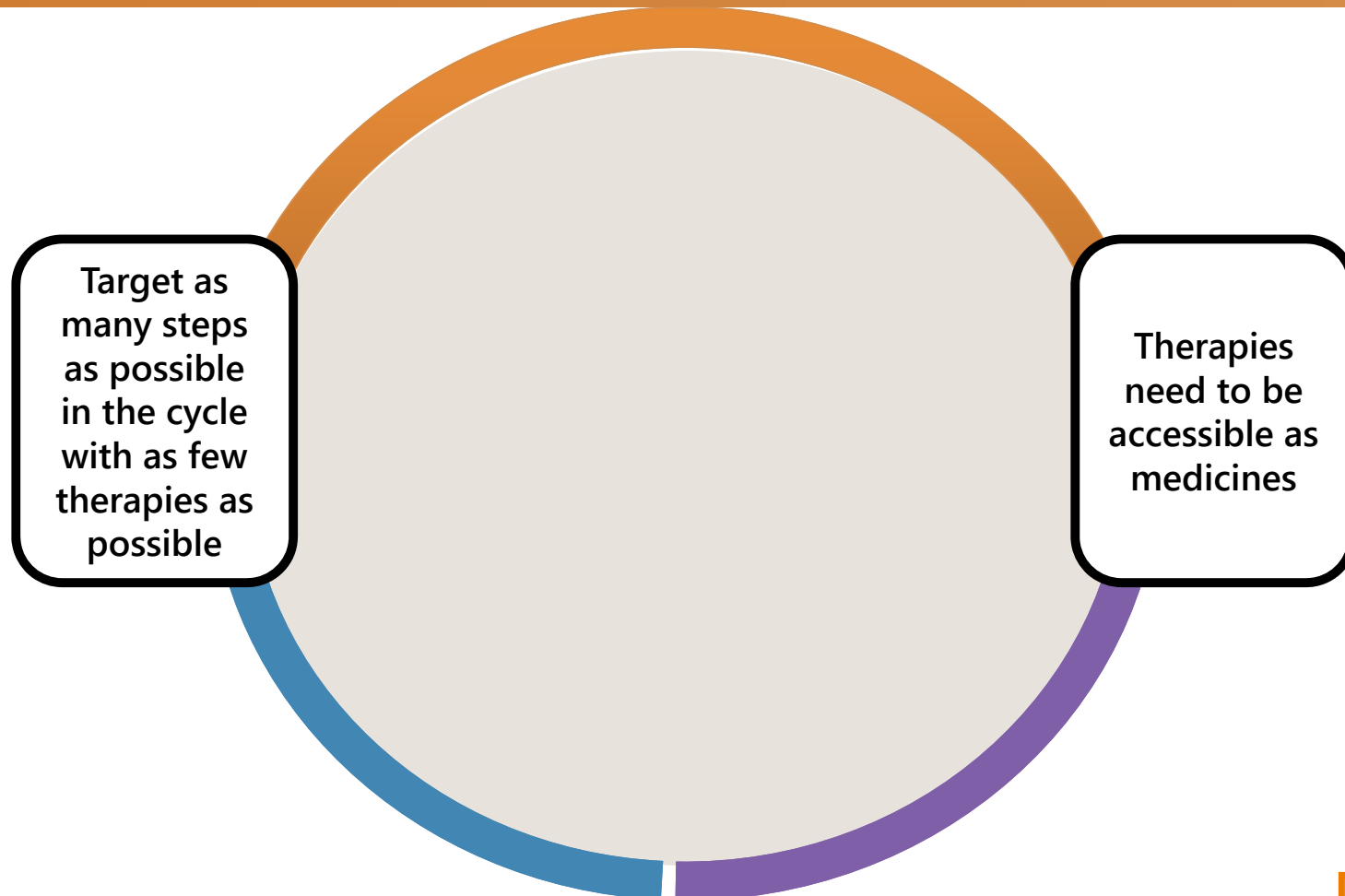
- ▶ An introduction to IO research at Nektar
- ▶ NKTR-214
  - CD122 biased agonist based on PEG-conjugation of IL-2
- ▶ NKTR-262
  - Intratumoral PEG-conjugated TLR7/8 agonist
- ▶ Combination of NKTR-262 + NKTR-214 for IO
  - Complementarity of non-overlapping innate + adaptive immune mechanisms

# The Immunity Cycle and Multiple Points of Intervention for I-O Therapies

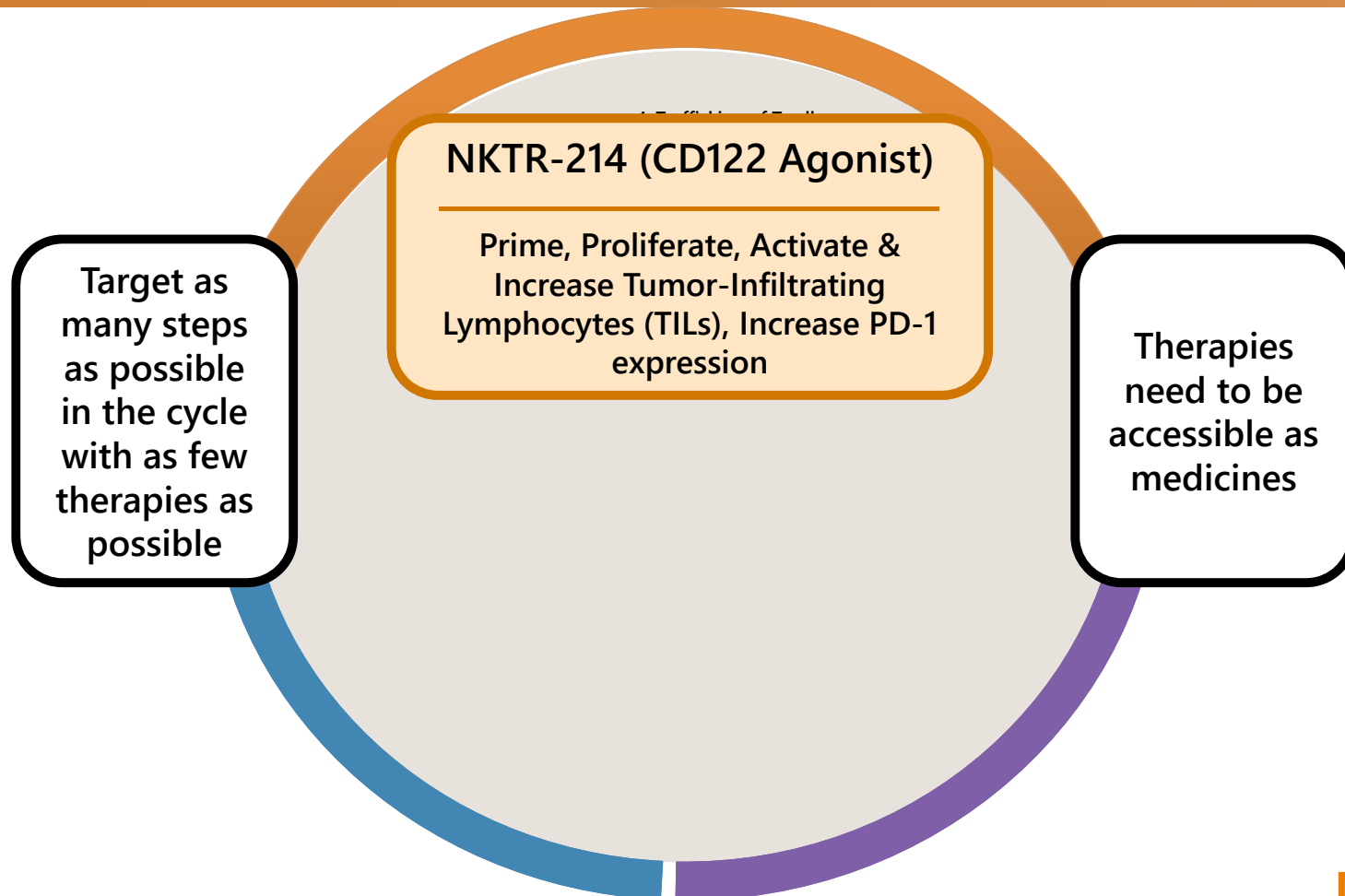


Source:  
[Oncology Meets Immunology: The Cancer-Immunity Cycle](#)  
Chen and Mellman  
Immunity, Volume 39, Issue 1, 1 - 10

# Nektar's Immuno-Oncology Strategy to Create Therapies that Cover the Immunity Cycle

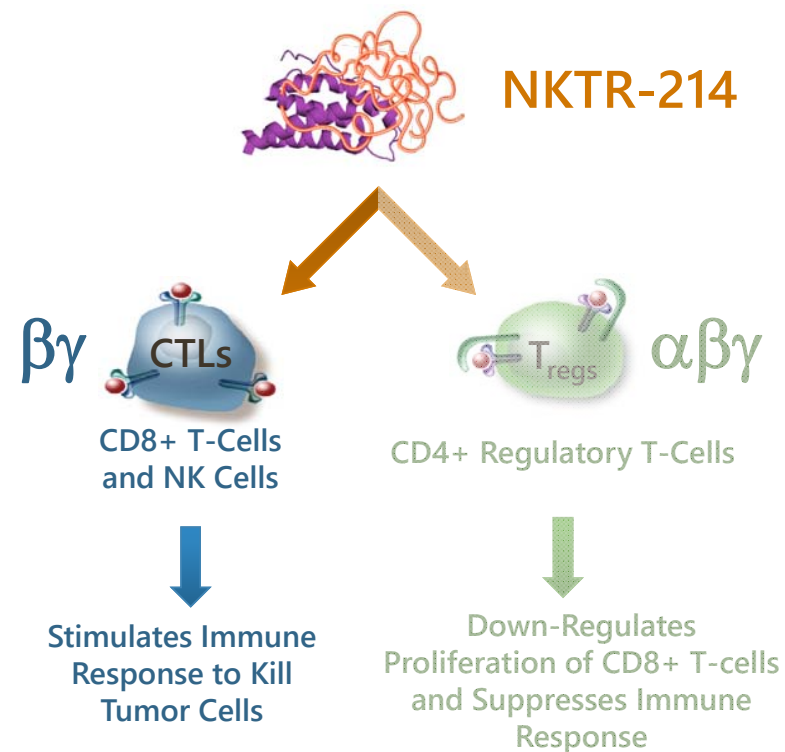


# Nektar's Immuno-Oncology Strategy to Create Therapies that Cover the Immunity Cycle



# NKTR-214: Biasing Action to CD 122, or IL-2R Beta, to Stimulate T-Cell Production

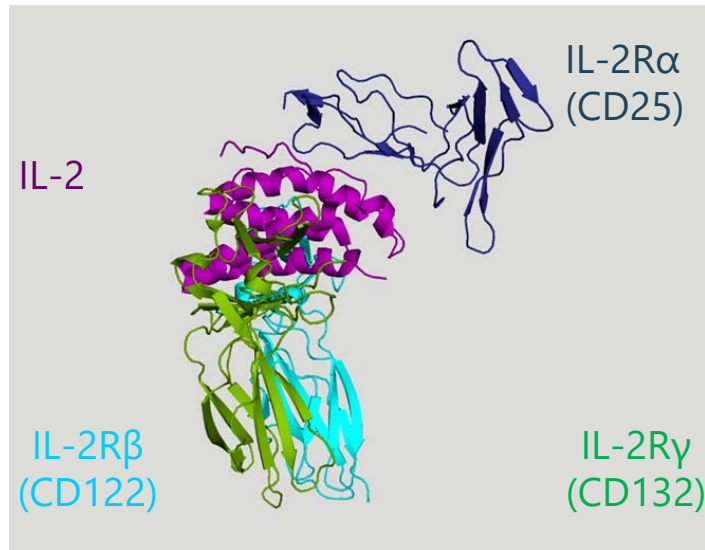
- ▶ Biases signaling to favor the CD122 Receptor (IL-2R $\beta\gamma$  complex)
- ▶ Eliminates over-activation of IL-2 pathway that results in serious safety issues
- ▶ Achieves antibody-like dosing schedule in outpatient setting





# NKTR-214 Is A CD122-biased Cytokine, Designed To Improve Efficacy And Mitigate Toxicity of the IL-2 Pathway

Structural model of IL-2 docked with IL-2R $\alpha\beta\gamma$

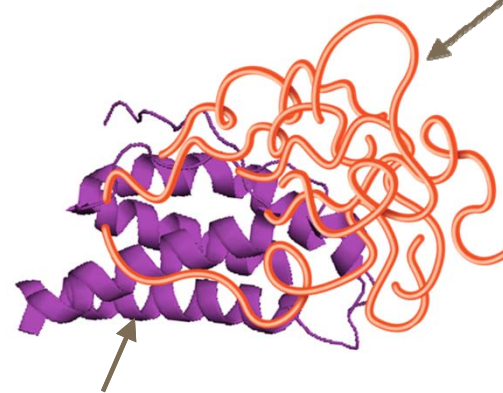


IL-2: purple  
IL-2R $\beta$ : cyan

IL-2R $\alpha$ : blue  
IL-2R $\gamma$ : green

NKTR-214

High molecular weight hydrolyzable polymers located at strategic sites



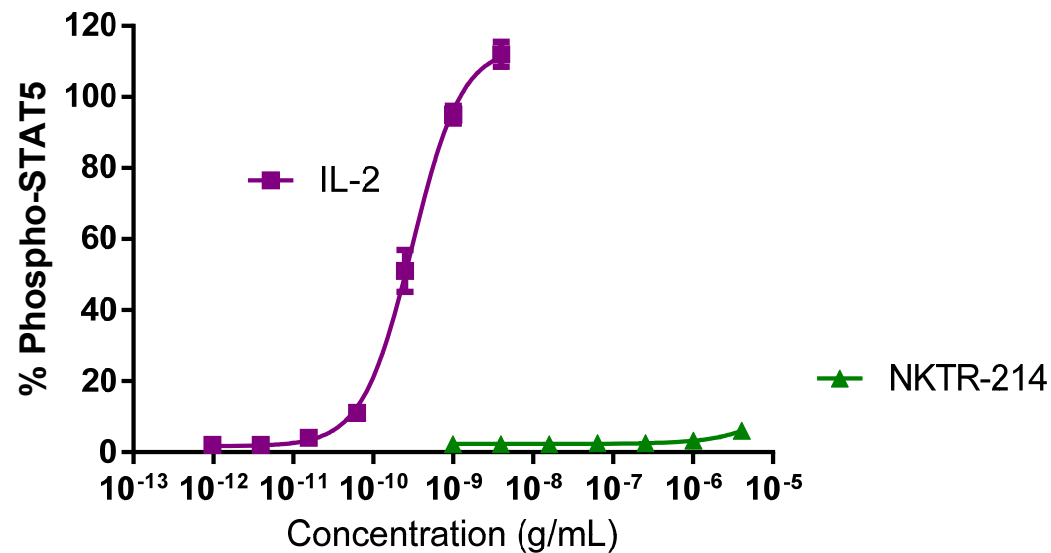
IL-2 cytokine core

- rhIL-2, same amino acid sequence as clinically validated molecule (aldesleukin)

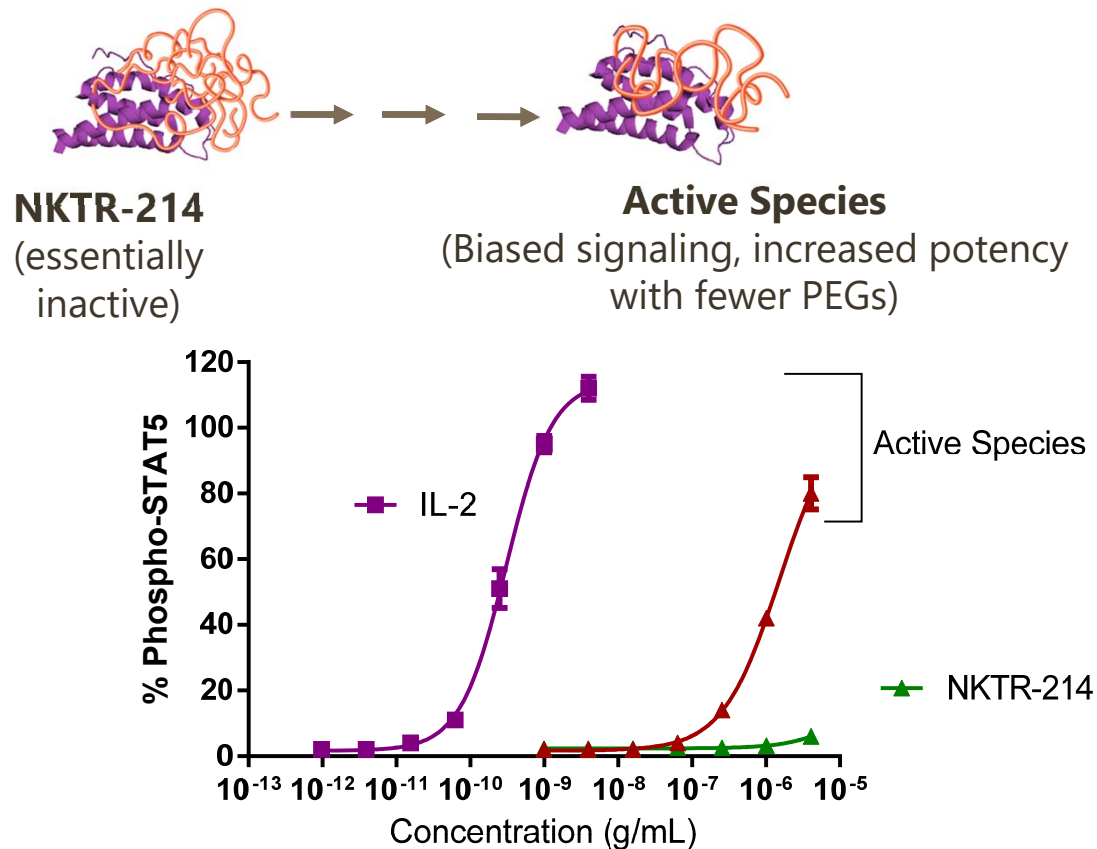
# NKTR-214: Biased Signaling And Prodrug Design To Improve Risk/Benefit Profile



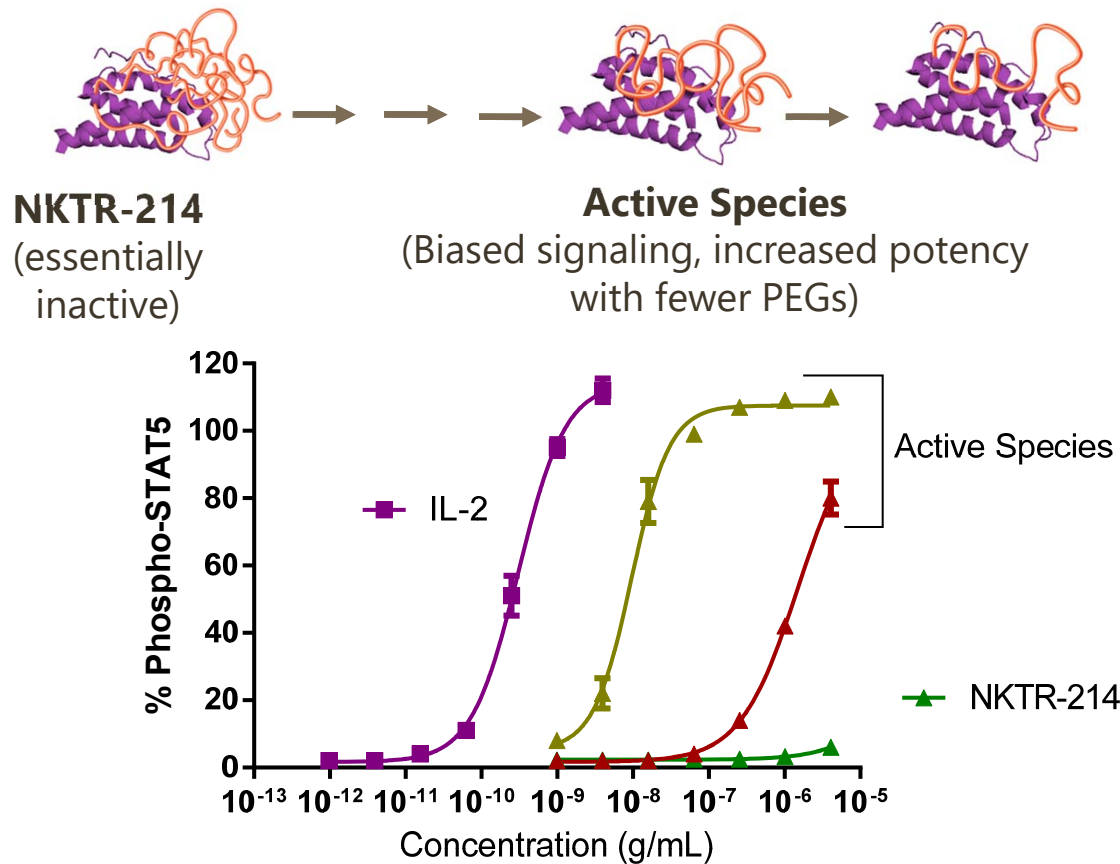
**NKTR-214**  
(essentially inactive)



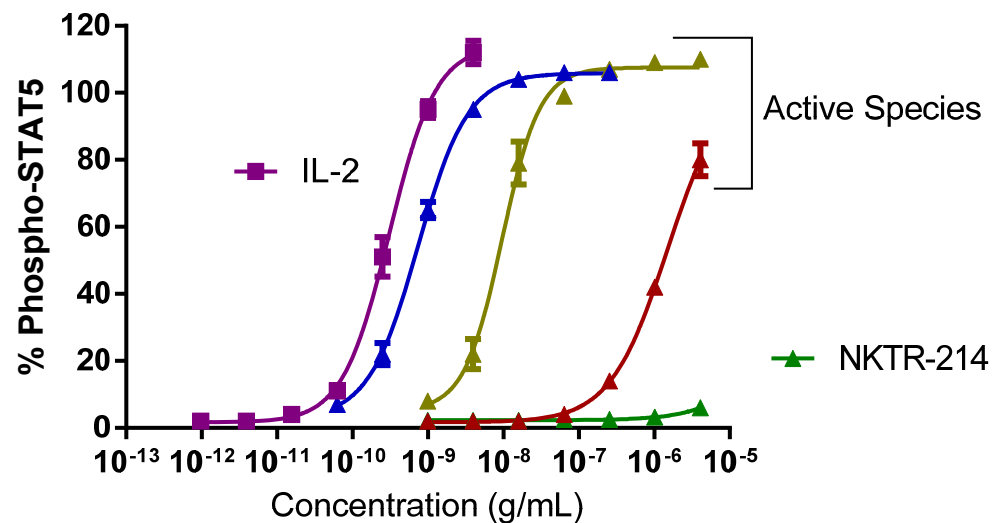
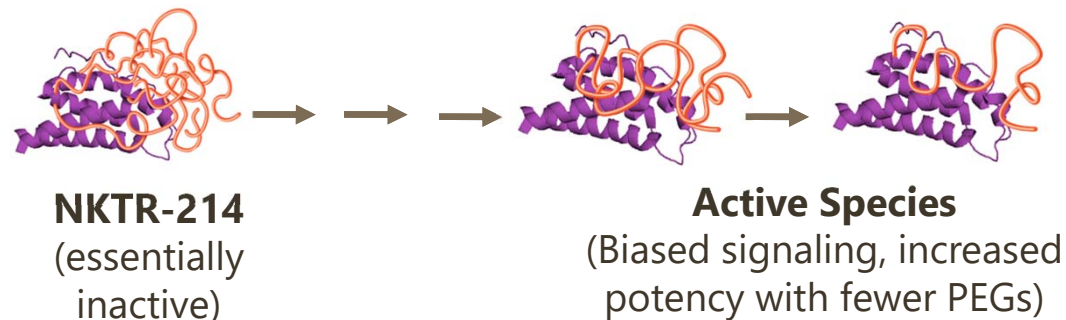
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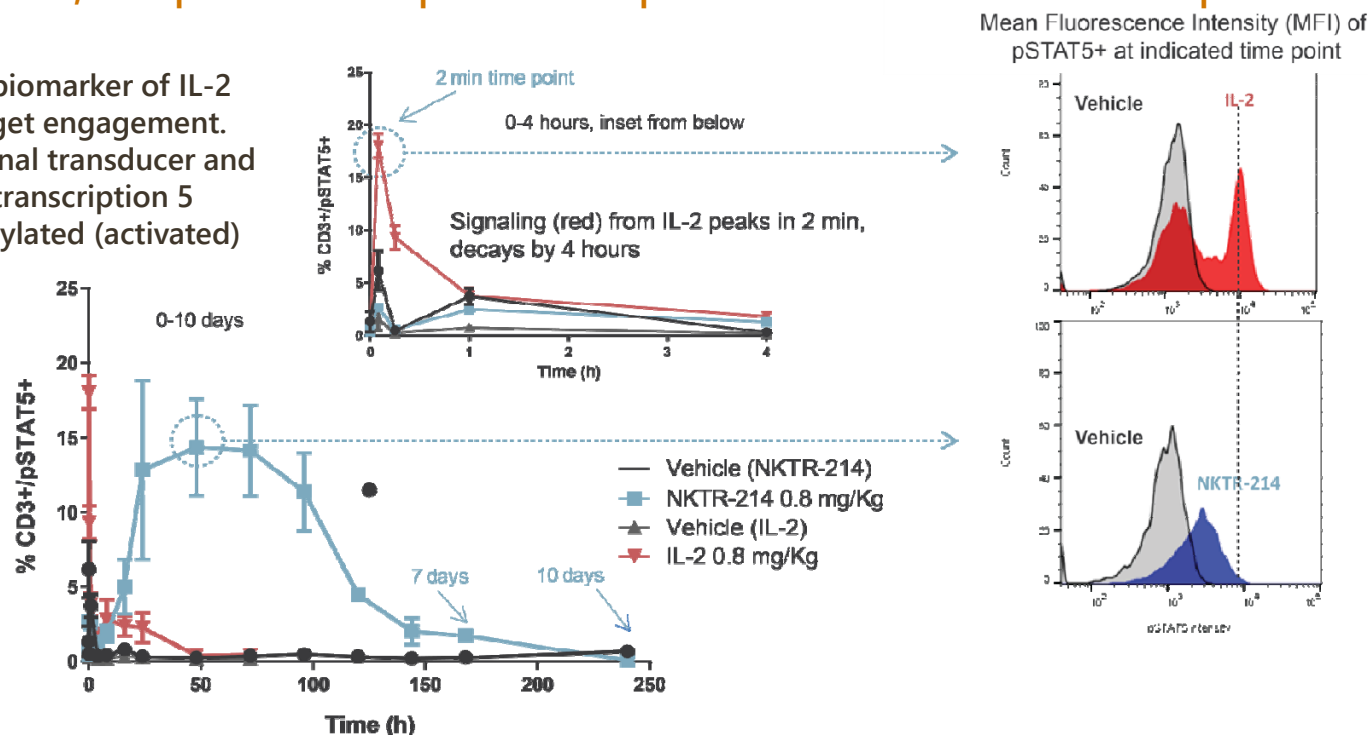
# NKTR-214: Biased Signaling And Prodrug Design To Improve Risk/Benefit Profile



# NKTR-214 Mechanism of Action Delivers a Controlled and Biased Signal to the IL-2 Pathway

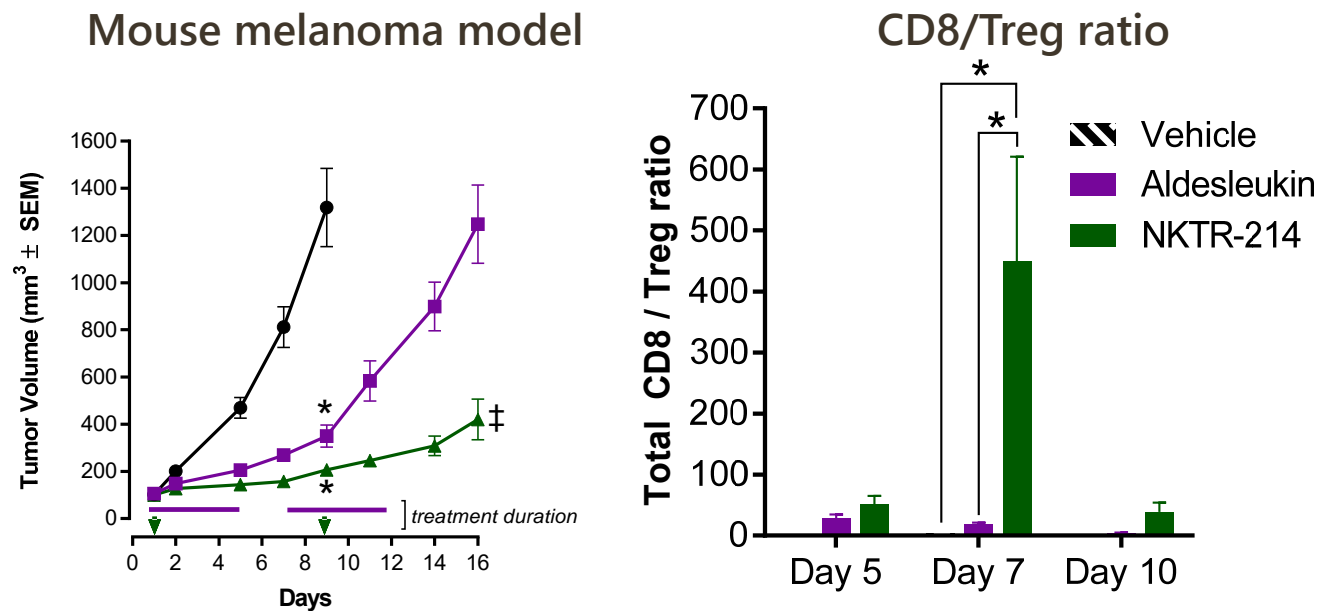
In mice, a single dose of NKTR-214 gradually builds and sustains pSTAT5 levels through seven days post-dose. In contrast, IL-2 produces a rapid burst of pSTAT that declines four hours post-dose.

pSTAT5 is a biomarker of IL-2 receptor target engagement.  
pSTAT5= signal transducer and activator of transcription 5  
p=phosphorylated (activated)



C57BL/6 mice were treated with either one dose of NKTR-214 (blue) or aldesleukin (red); blood samples were collected at various time points post-dose. pSTAT5 in peripheral blood CD3+ T cells was assessed using flow cytometry. Top graph is an inset showing the 0-4 hour time period. Bottom graph shows the full 10 day time course of the experiment. Histograms on right depict pSTAT5 MFI for IL-2 (red) and NKTR-214 (blue)

# NKTR-214 Increases The Quality And Quantity Of The T-cell Response in Mice



> 400-fold increased ratio of CD8 to Treg cells

B16F10 melanoma, C57Bl/6 mice; N=9-12/group

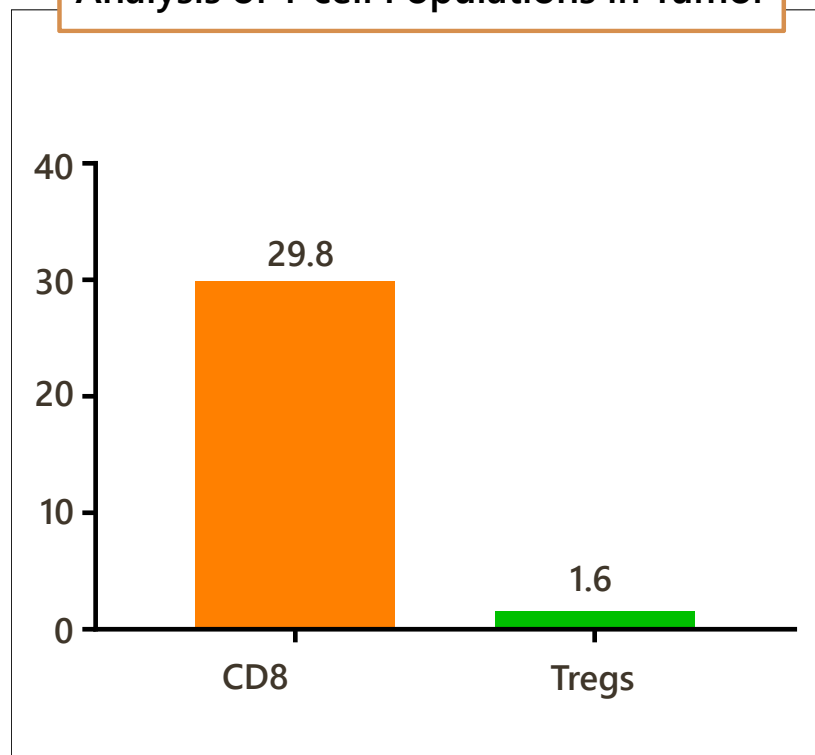
NKTR-214, 2mg/kg i.v. q9dx3; Aldesleukin, 3mg/kg i.p. bidx5, 2 cycles

\*,  $p < 0.05$ , ANOVA with Tukey's post-test (left) or Log-Rank (right) w.r.t. vehicle

‡,  $p < 0.05$ , Student's T-test (left) or Log-Rank (right) w.r.t. Aldesleukin

# NKTR-214 Selectively Grows T Cells, NK Cells in Tumor Microenvironment in Cancer Patients

Analysis of T cell Populations in Tumor



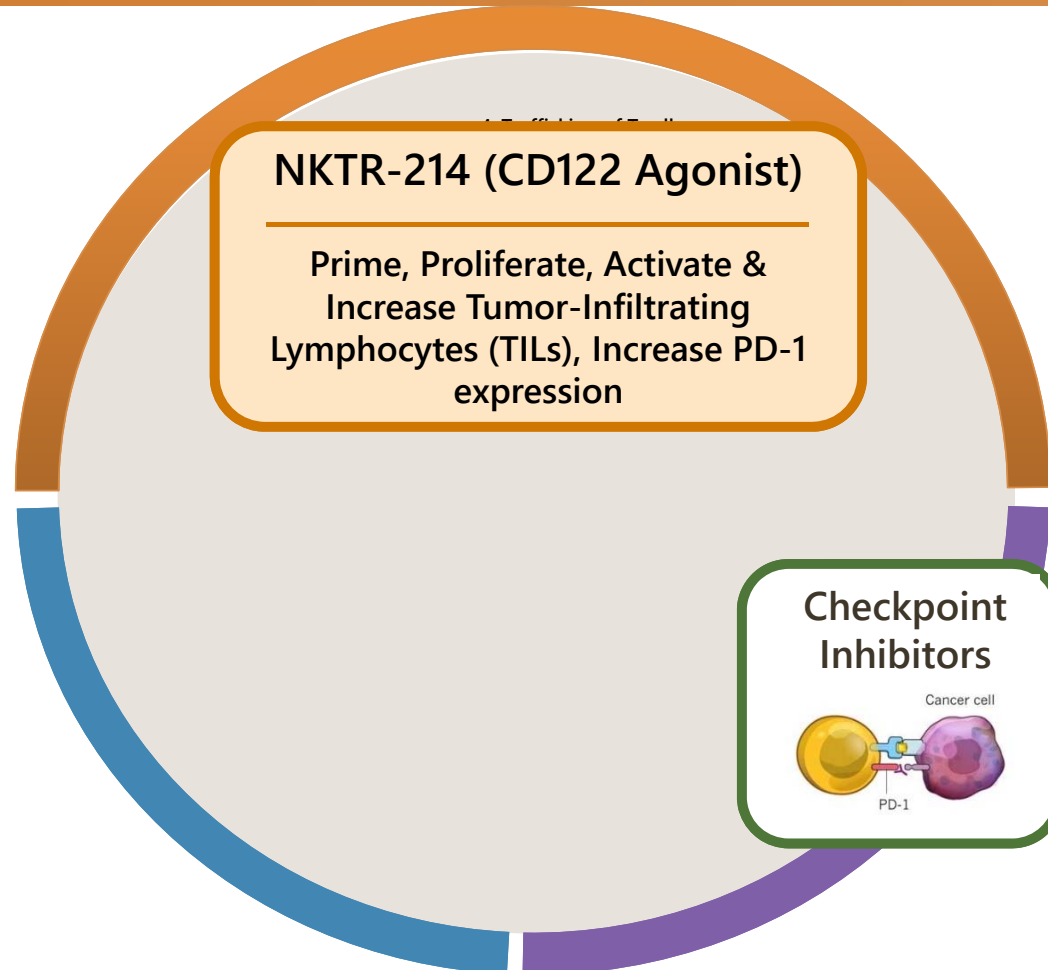
Fold change expressed as Week 3 / predose  
Shown are results from N=10 patients

## NKTR-214 drives immune activation in the tumor

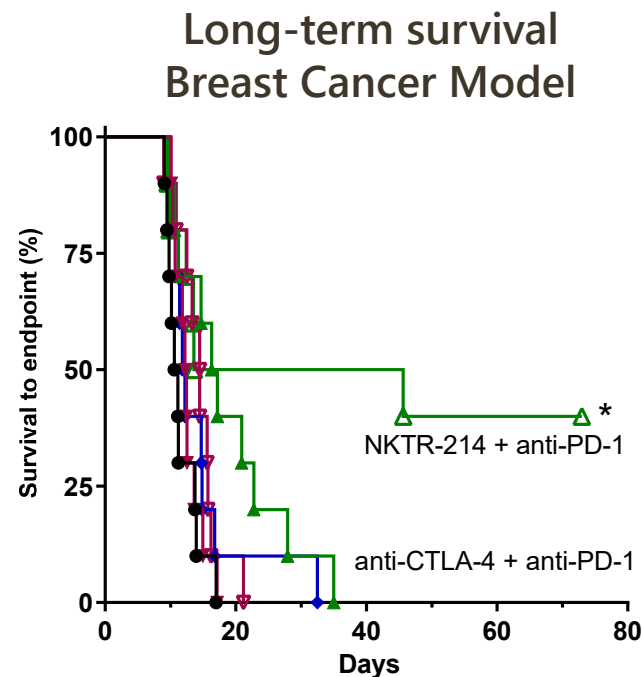
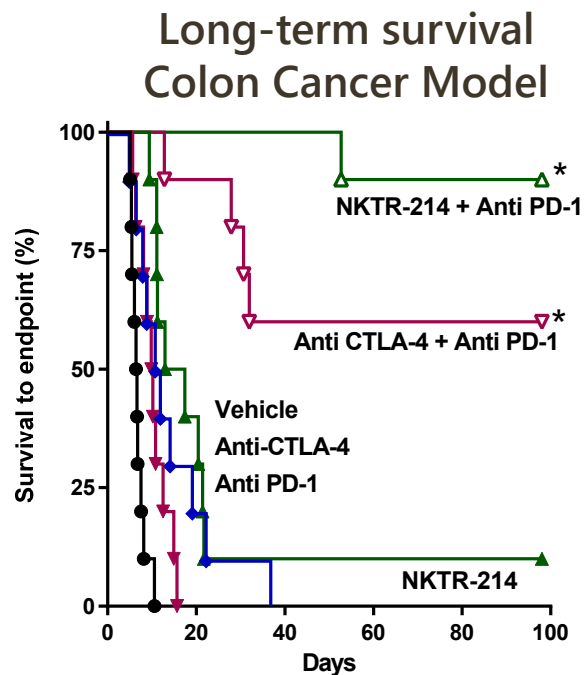
- Increase in total T cells, NK and CD8 T cells
- No increase in Tregs
- Increase in PD-1 positive CD8 T cells
- Increase in newly proliferating CD8 T cells
- Activation and expression of anti-tumor genes
- Change in T cell clonality in the tumor



# Nektar's Immuno-Oncology Strategy to Create Therapies that Cover the Immunity Cycle



# NKTR-214: Combination With Anti-PD-1 Consistently Produces Durable Responses in Mice

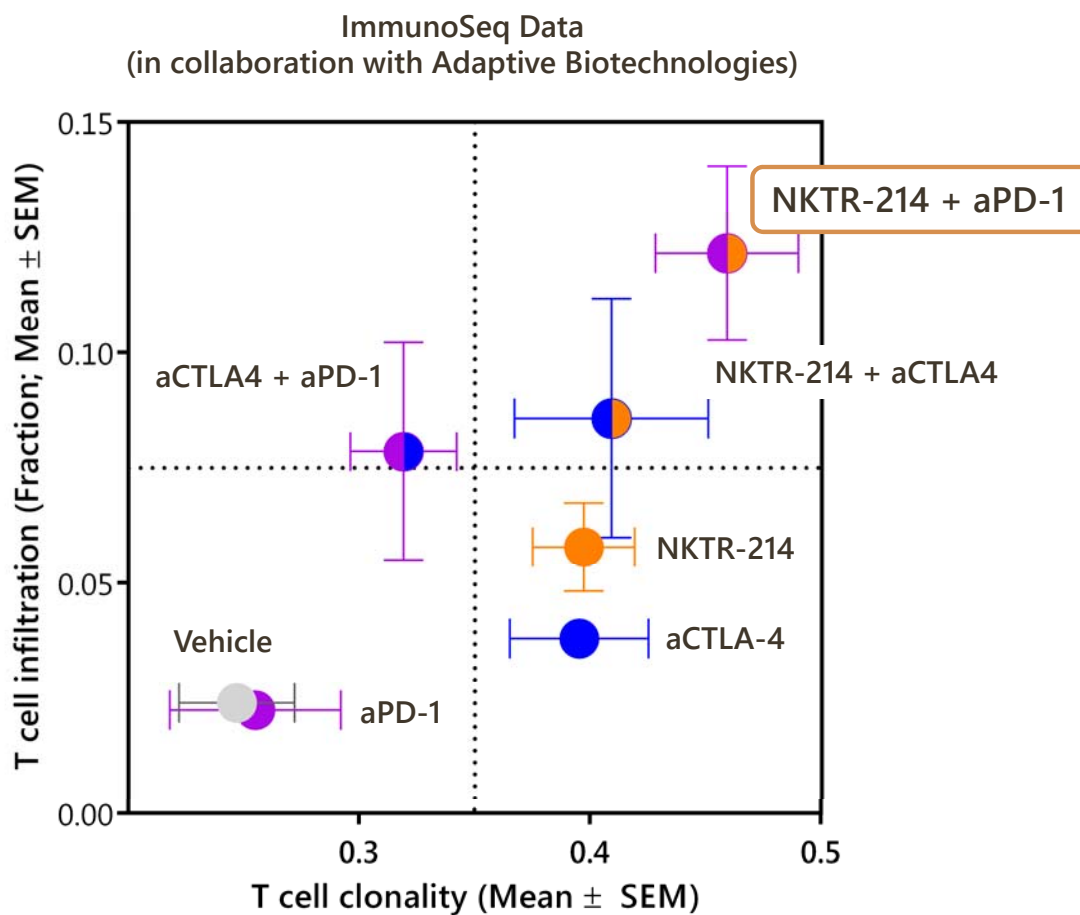
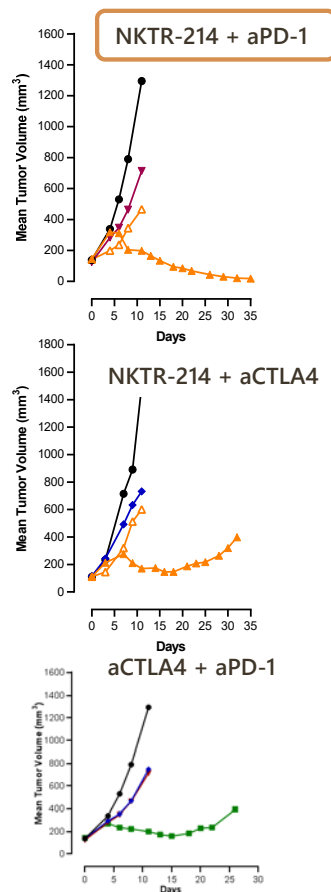


**NKTR-214 + anti-PD-1 is superior to anti-CTLA-4 + anti-PD-1**

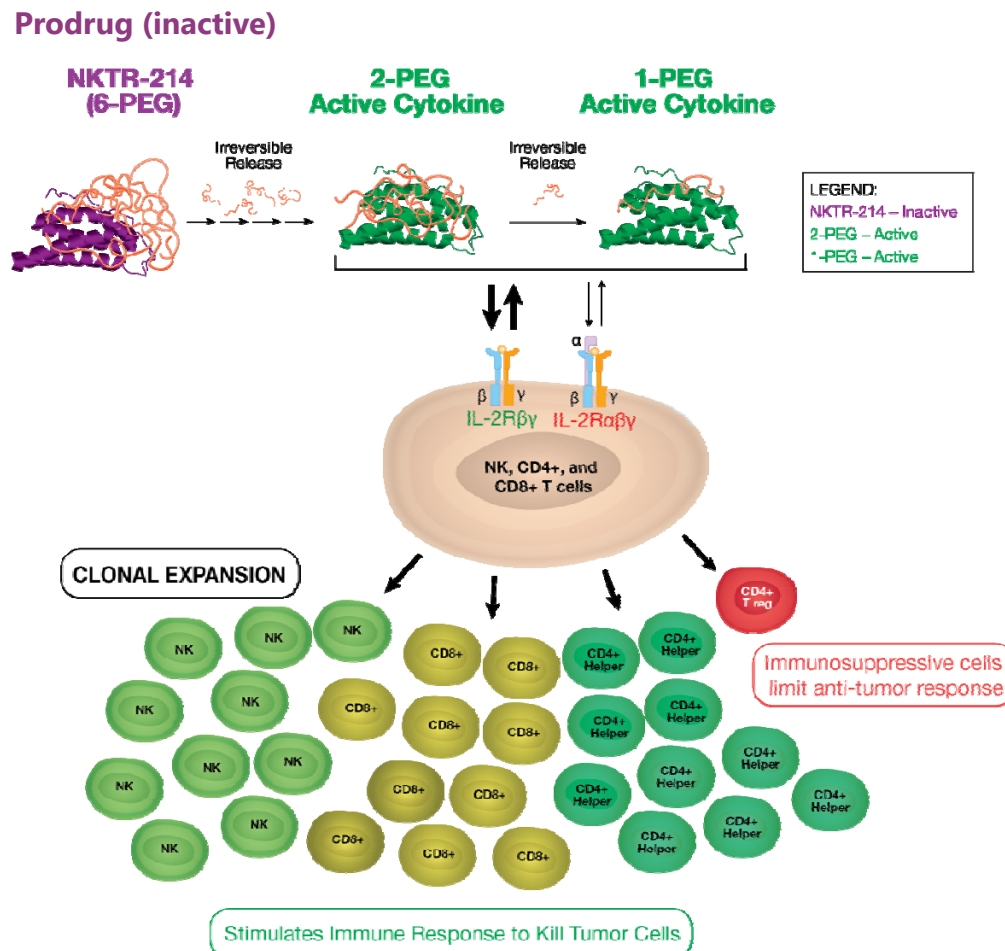
CT26 colon carcinoma, Balb/c mice, N=10/group  
 Anti-CTLA-4, 100µg i.p., twice-weekly; Anti-PD-1, 200µg i.p., twice weekly  
 NKTR-214, 0.8mg/kg i.v. q9dx3  
 \*,  $p < 0.05$ , ANOVA with Tukey's post-test (left) or Log-Rank (right) w.r.t. vehicle

EMT6 breast carcinoma, Balb/c mice, N=10/group  
 Anti-CTLA-4, 100µg i.p., twice-weekly; Anti-PD-1, 200µg i.p., twice weekly  
 NKTR-214, 0.8mg/kg i.v. q9dx3  
 \*,  $p < 0.05$ , ANOVA with Tukey's post-test (left) or Log-Rank (right) w.r.t. vehicle

# NKTR-214 Drives Greater T-cell Expansion And T-Cell Clonality in Mice

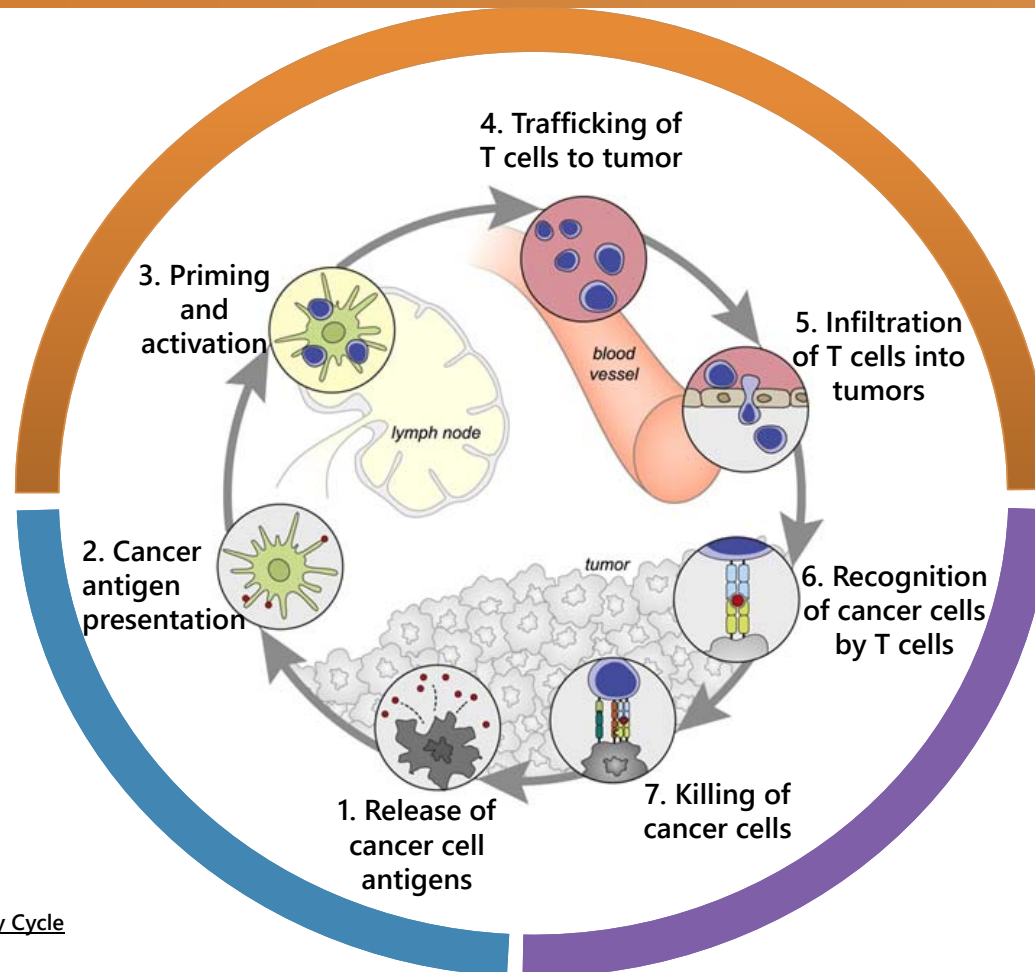


# Harnessing the IL-2 Pathway the Right Way to Increase TILs



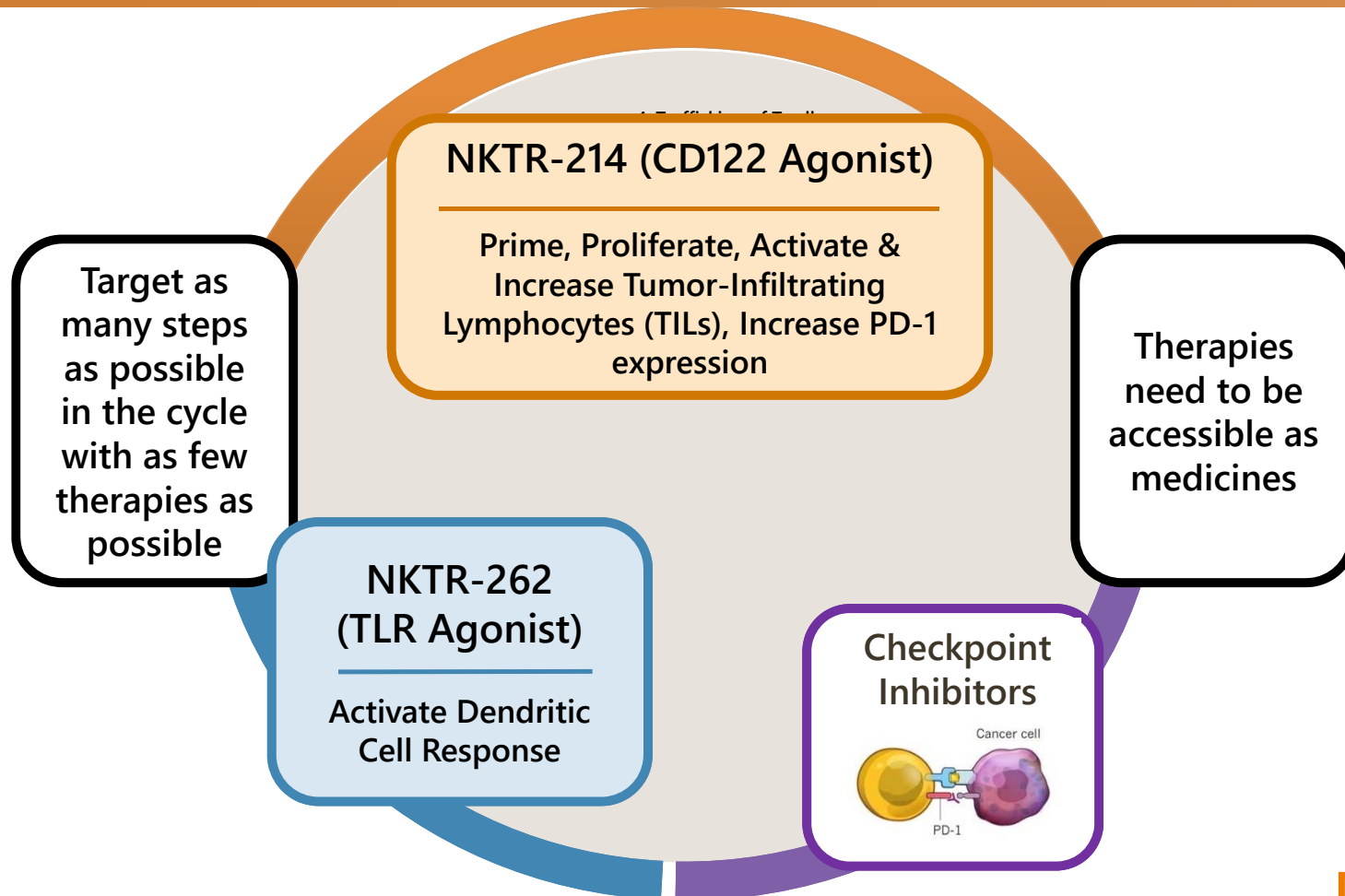
- ▶ Prodrug design to enable safe, outpatient dosing Q2w or Q3w
- ▶ Active cytokine species bias signaling through the heterodimeric IL-2 receptor pathway (IL-2R $\beta\gamma$ )
- ▶ Biased and sustained signaling to preferentially activate and expand effector CD8+ T and NK cells over Tregs in the tumor microenvironment

# The Immunity Cycle and Multiple Points of Intervention for I-O Therapies



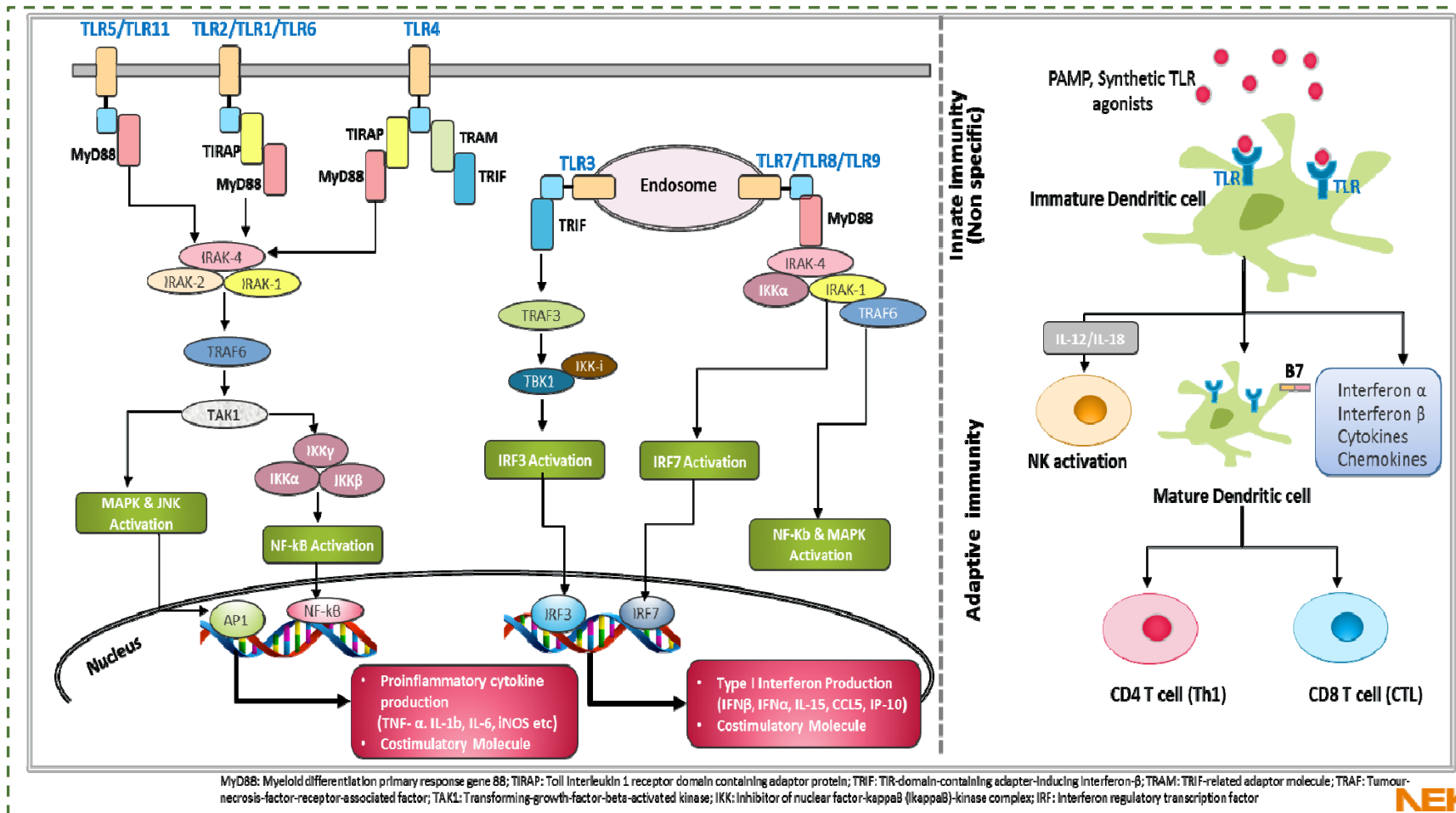
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# Nektar's Immuno-Oncology Strategy to Create Therapies that Cover the Immunity Cycle

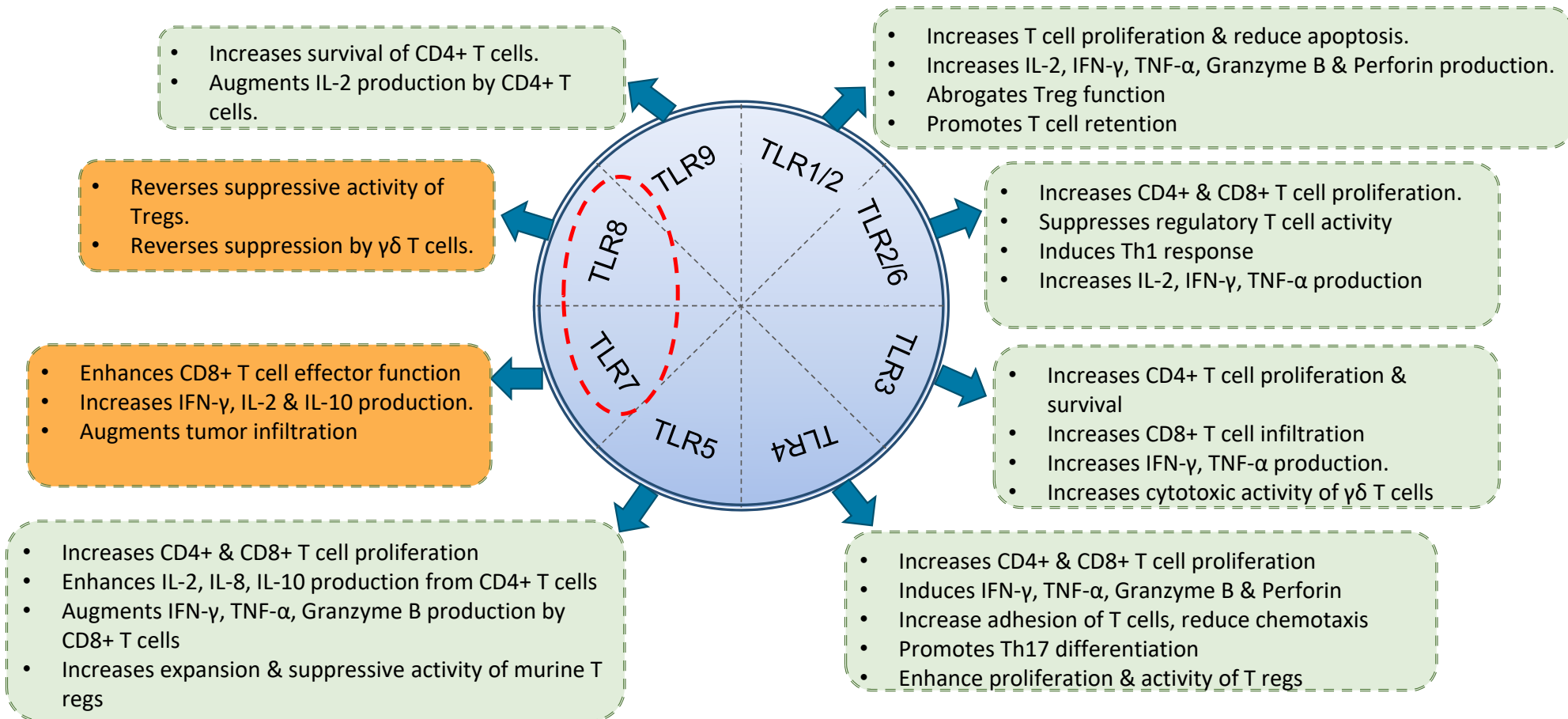


# TLRs Signaling:

## Innate Immune Activation and the Linkage to the Adaptive Immune Response



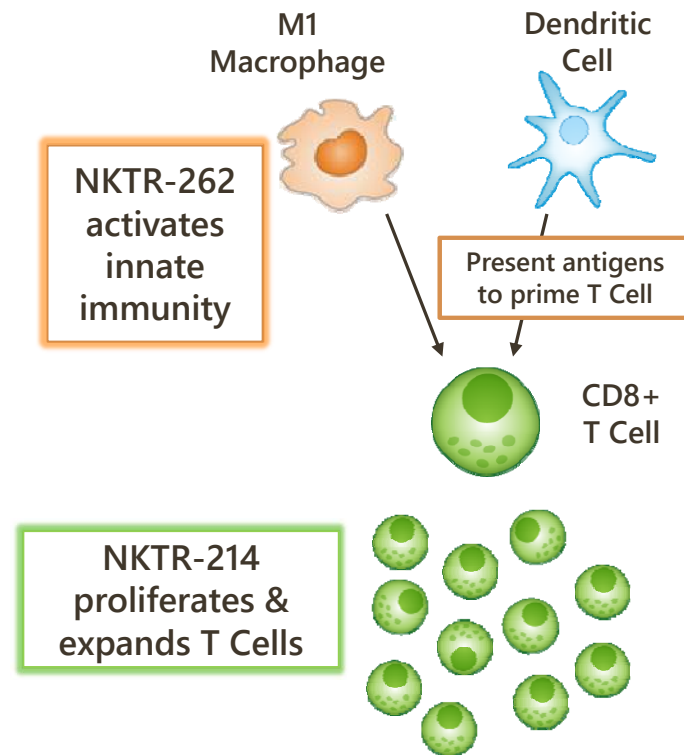
# Effects of TLR Engagement on Different T Cell Subsets



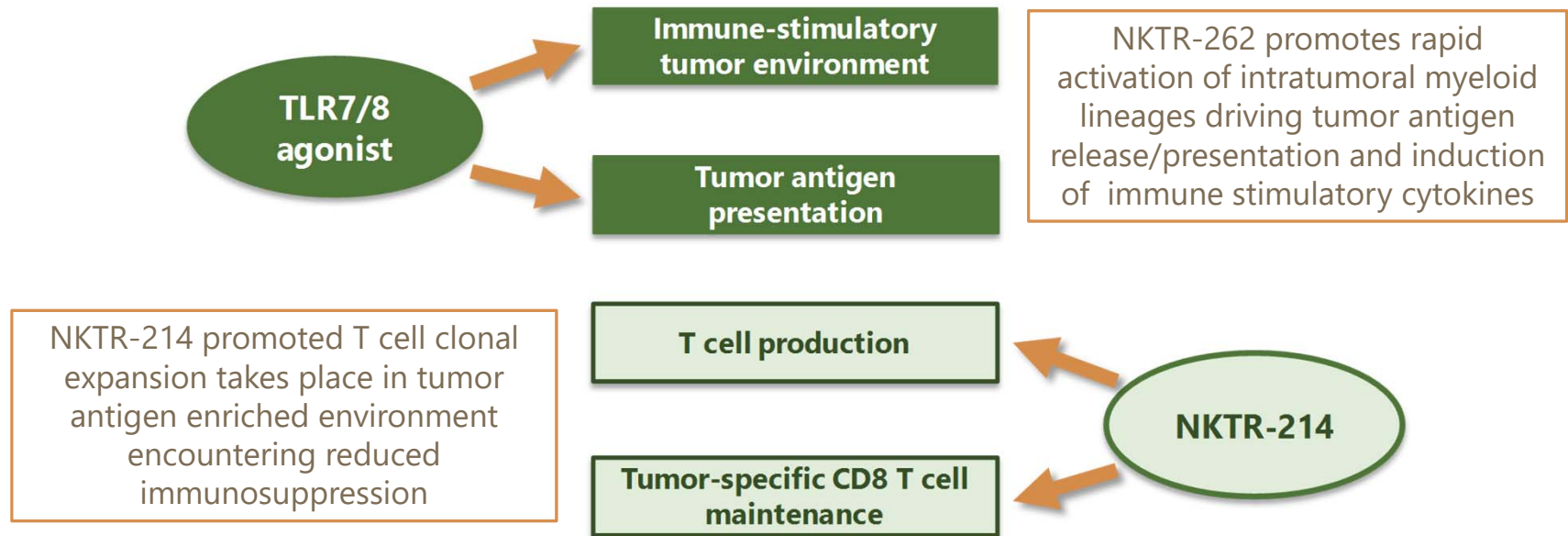


# NKTR-262: Adding a Unique Intratumoral TLR Agonist to Nektar's Immuno-Oncology Portfolio

- ▶ TLR agonists activate innate immunity, myeloid cell response and increase tumor antigen presentation
  - Overcomes tumor-suppressing micro-environment by mimicking local infection
- ▶ Nektar technology optimizes specific abscopal effect in tumors without systemic exposure of TLR agonist
- ▶ NKTR-262 designed to be highly synergistic with NKTR-214
- ▶ NKTR-262 with NKTR-214 represent a novel, wholly-owned combination regimen in immuno-oncology



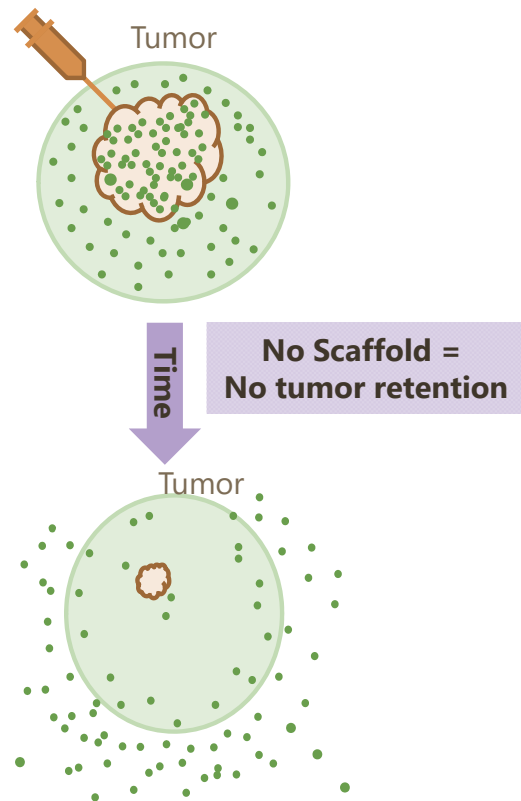
# Comprehensive Activation of the Anti-Tumor Immune Cascade by NKTR-262 + NKTR-214







**Systemic tumor eradication**

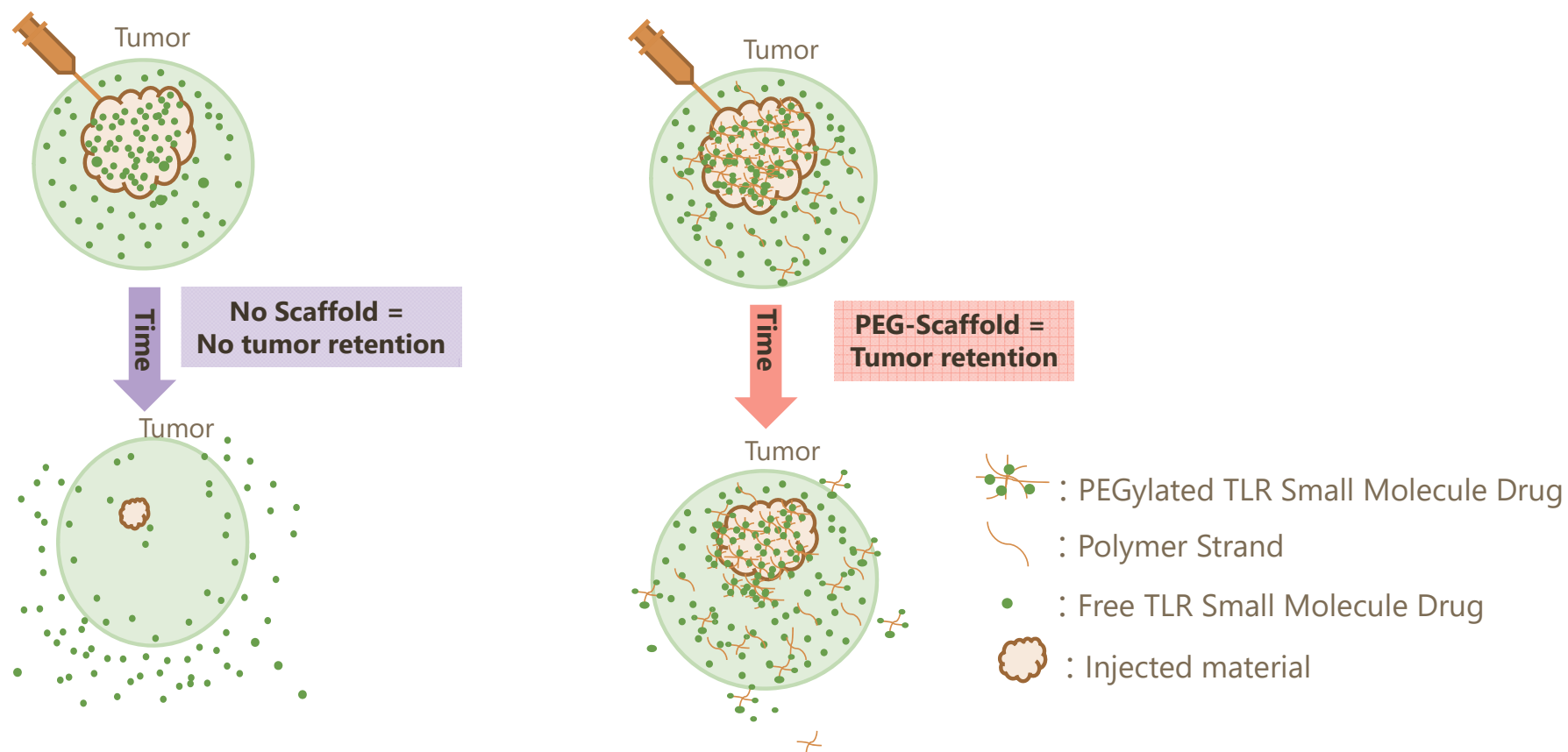
Combination treatment enhances tumor specific CD8 T cell immune surveillance leading to systemic tumor clearance

# Our Strategy: PEGylation Will Keep Scaffold in Tumor And Reduces Systemic Exposure

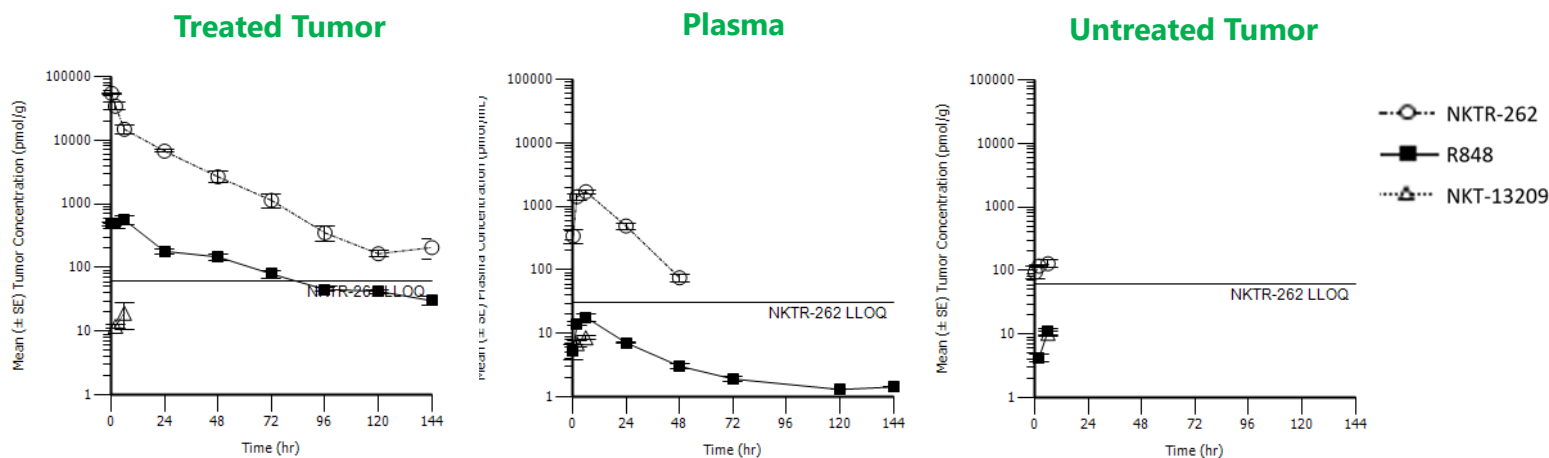


-  : PEGylated TLR Small Molecule Drug
-  : Polymer Strand
-  : Free TLR Small Molecule Drug
-  : Injected material

# Our Strategy: PEGylation Will Keep Scaffold in Tumor And Reduces Systemic Exposure

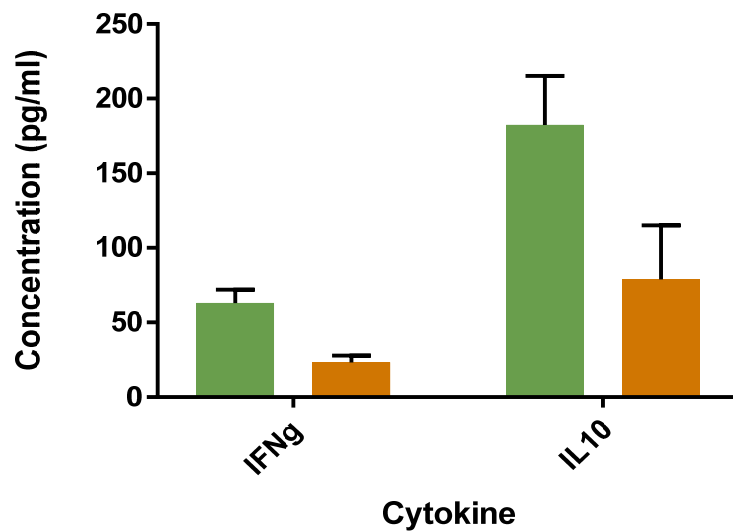


# NKTR-262 Prolonged Exposure of a TLR 7/8 Small Molecule in the Tumor With Minimal Exposure in Mouse Plasma

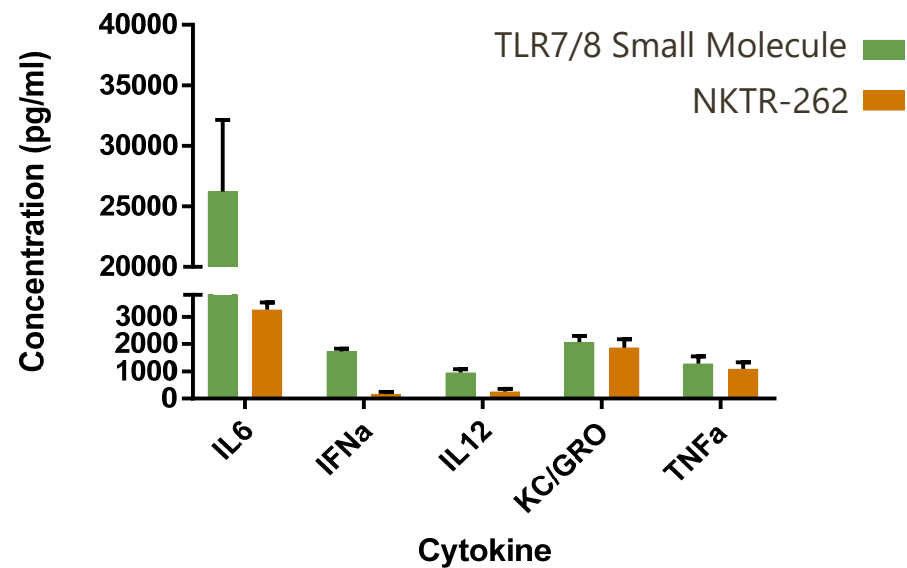


There was a delay in distribution of NKTR-262 from treated tumor to plasma.

# Reduced Plasma Cytokine Induction with NKTR-262 Compared to Dose-Matched Free TLR7/8 Small Molecule

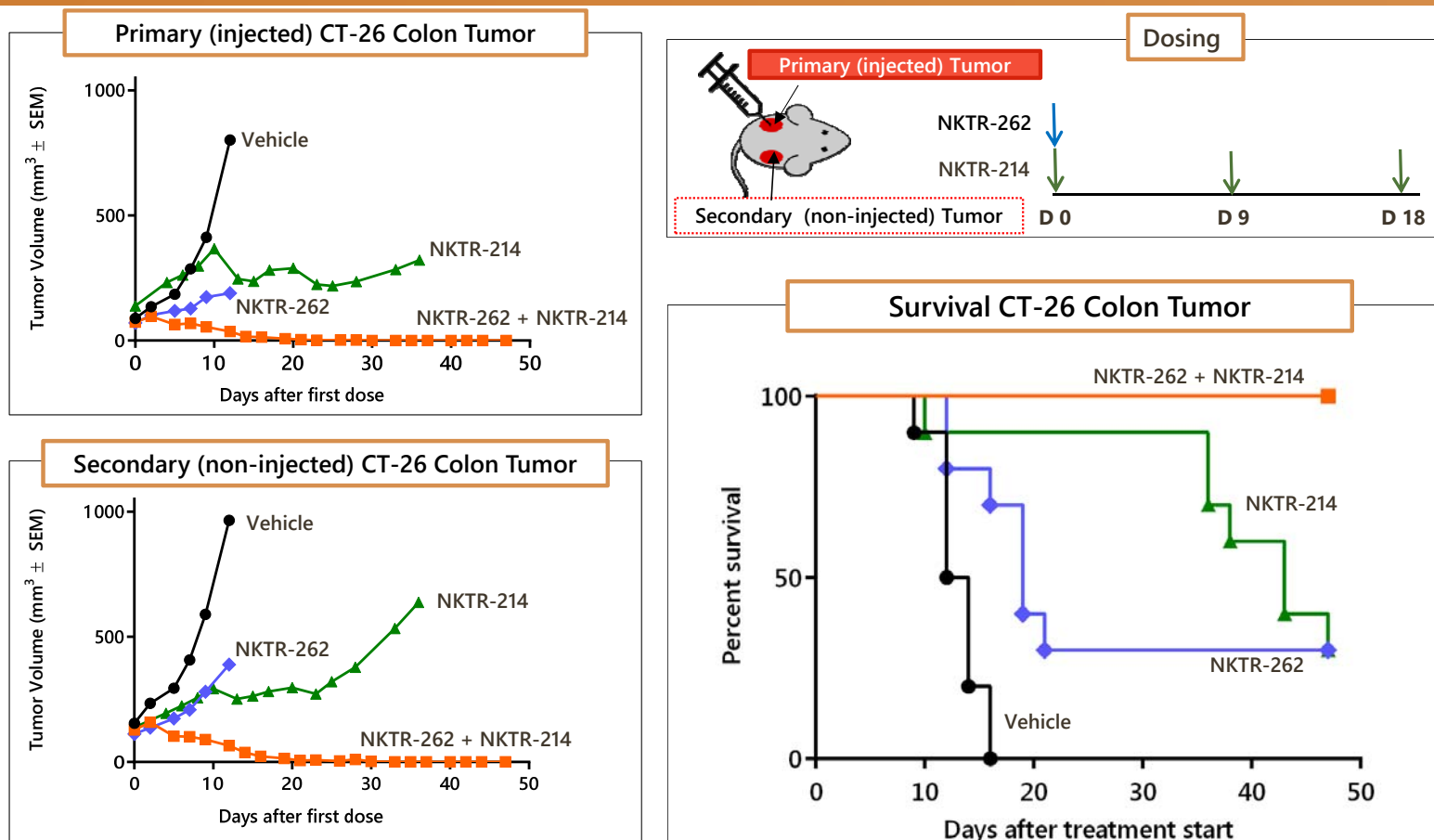


Peak of cytokine production at 6hrs post-dose



Peak of cytokine production at 2hrs post-dose

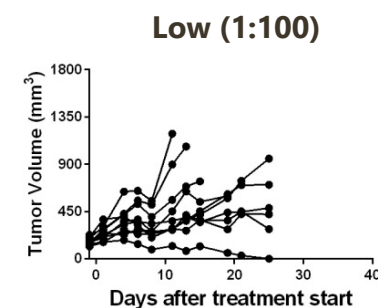
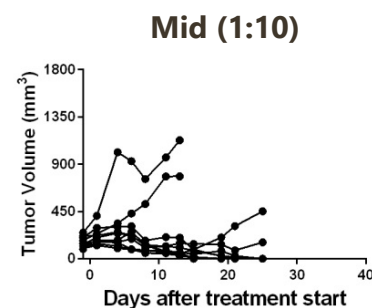
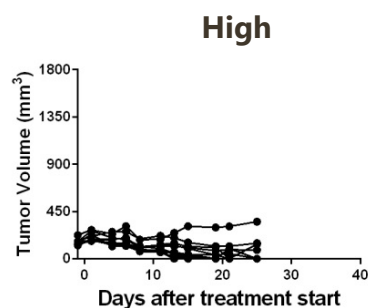
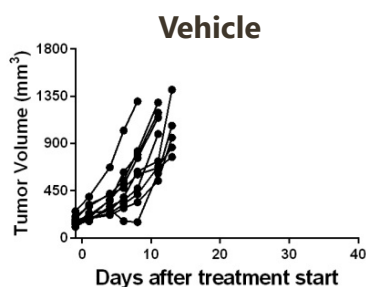
# Complete Regression and Abscopal Effect with Combination of NKTR-262 and NKTR-214 in Mice



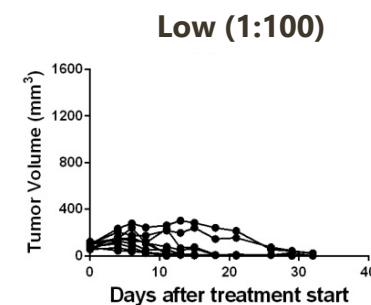
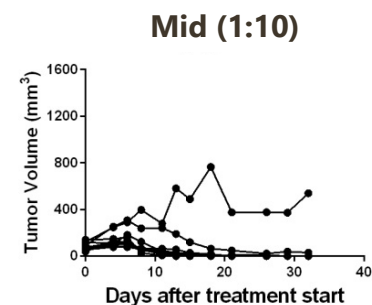
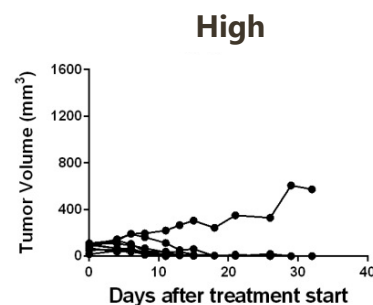
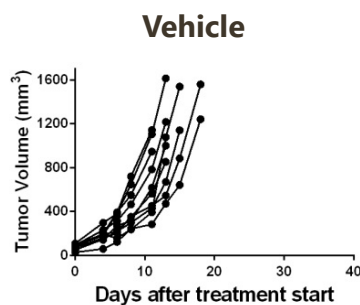
NKTR-262 40 µg in 40 µL volume given in a single IT dose, NKTR-214 0.8 mg/kg q9dx3 IV; N=10 per group

# 100% Cure Rate of Treated Tumors With NKTR-262 at Low Dose in Combination With NKTR-214 in Mice

TLR7/8



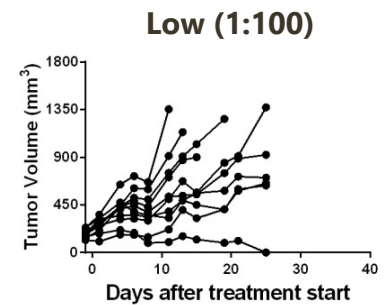
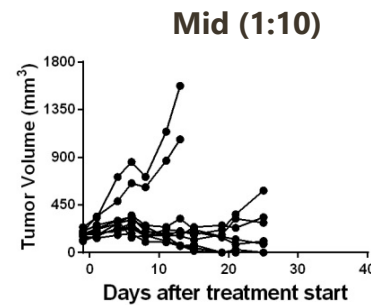
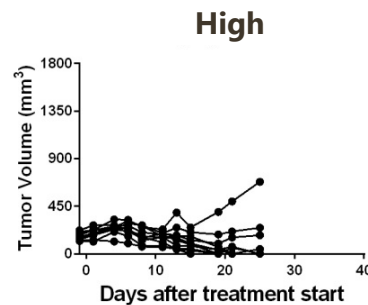
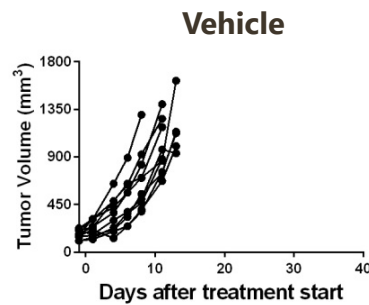
NKTR-262



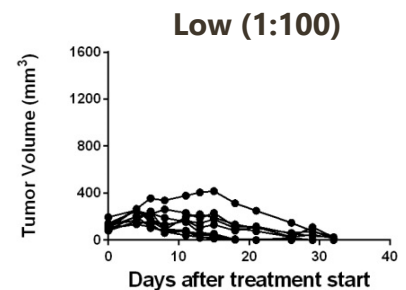
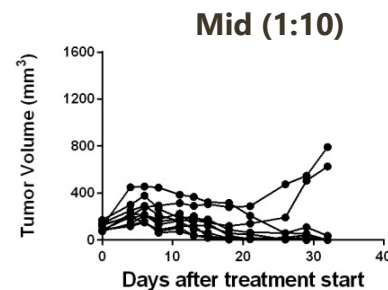
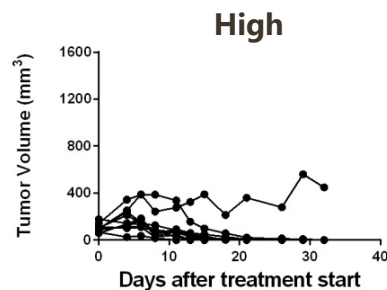
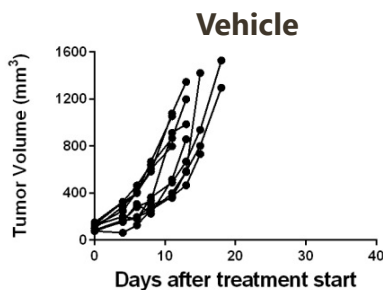


# 100% Abscopal Effect With NKTR-262 at Low Dose in Combination With NKTR-214 in Mice

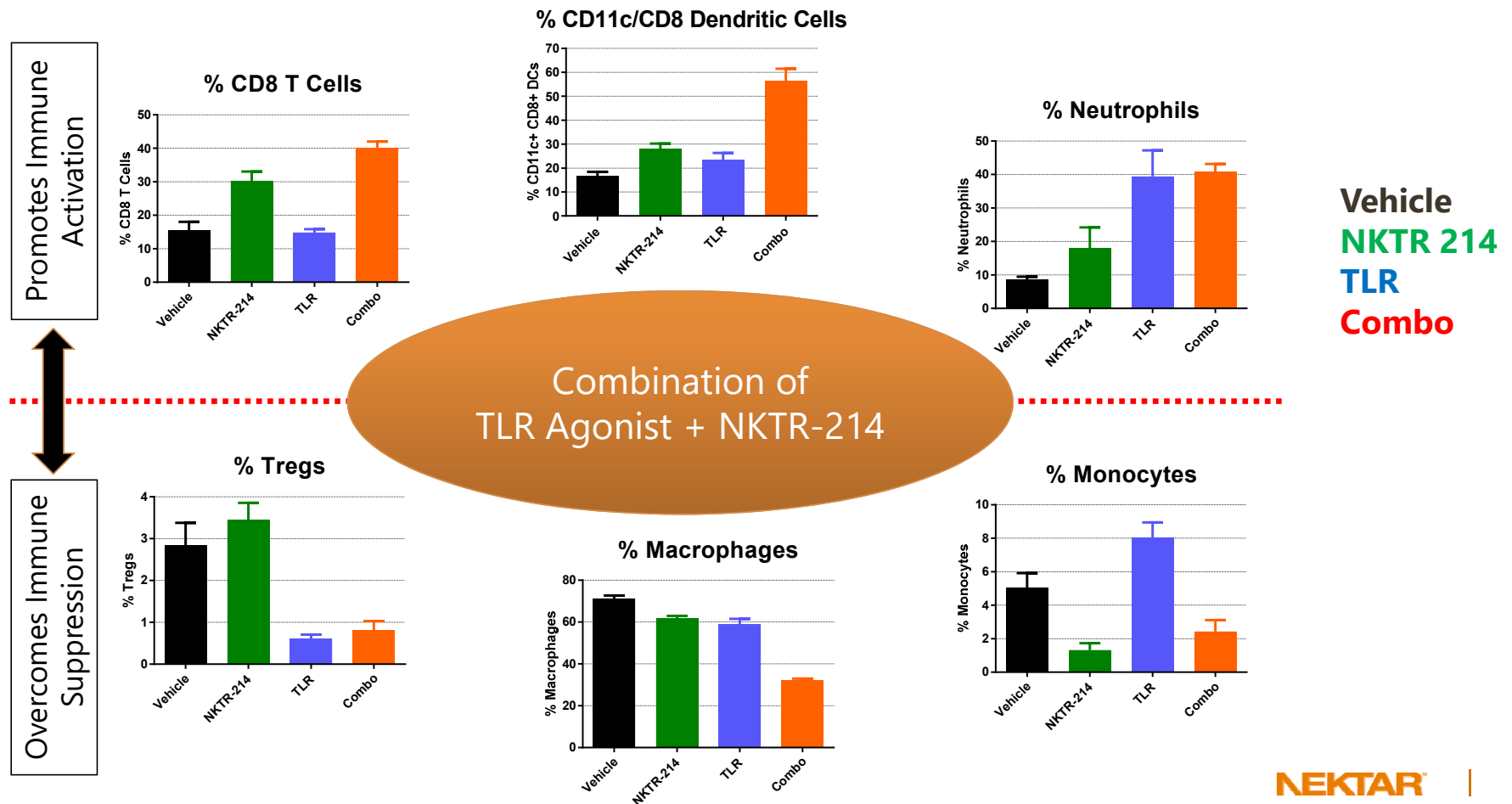
TLR7/8



NKTR-262



# TLR Agonist + NKTR-214: A Comprehensive Mechanism for Immune Therapy



# Summary of NKTR-262: PEG-Conjugated TLR7/8 Agonist

- ▶ PEG conjugate of a small molecule TLR7/8 agonist
  - Complex and structurally novel molecule
  - 4-arm PEG molecule to which four small molecules are attached via hydrolysable glycine linker
- ▶ Designed to have optimized pharmacokinetic (PK), pharmacodynamic (PD), safety and efficacy properties superior to conventional small molecules
- ▶ NKTR-262 provides sustained exposure of TLR7/8 in the tumor with minimal extratumoral exposure for better tolerability in preclinical studies
- ▶ Non-overlapping MOA with NKTR-214
  - **Combination optimally engages the immune system** to generate a highly effective IO therapy
- ▶ Single intratumoral NKTR-262 + systemic NKTR-214 produced **complete abscopal effect** in preclinical studies