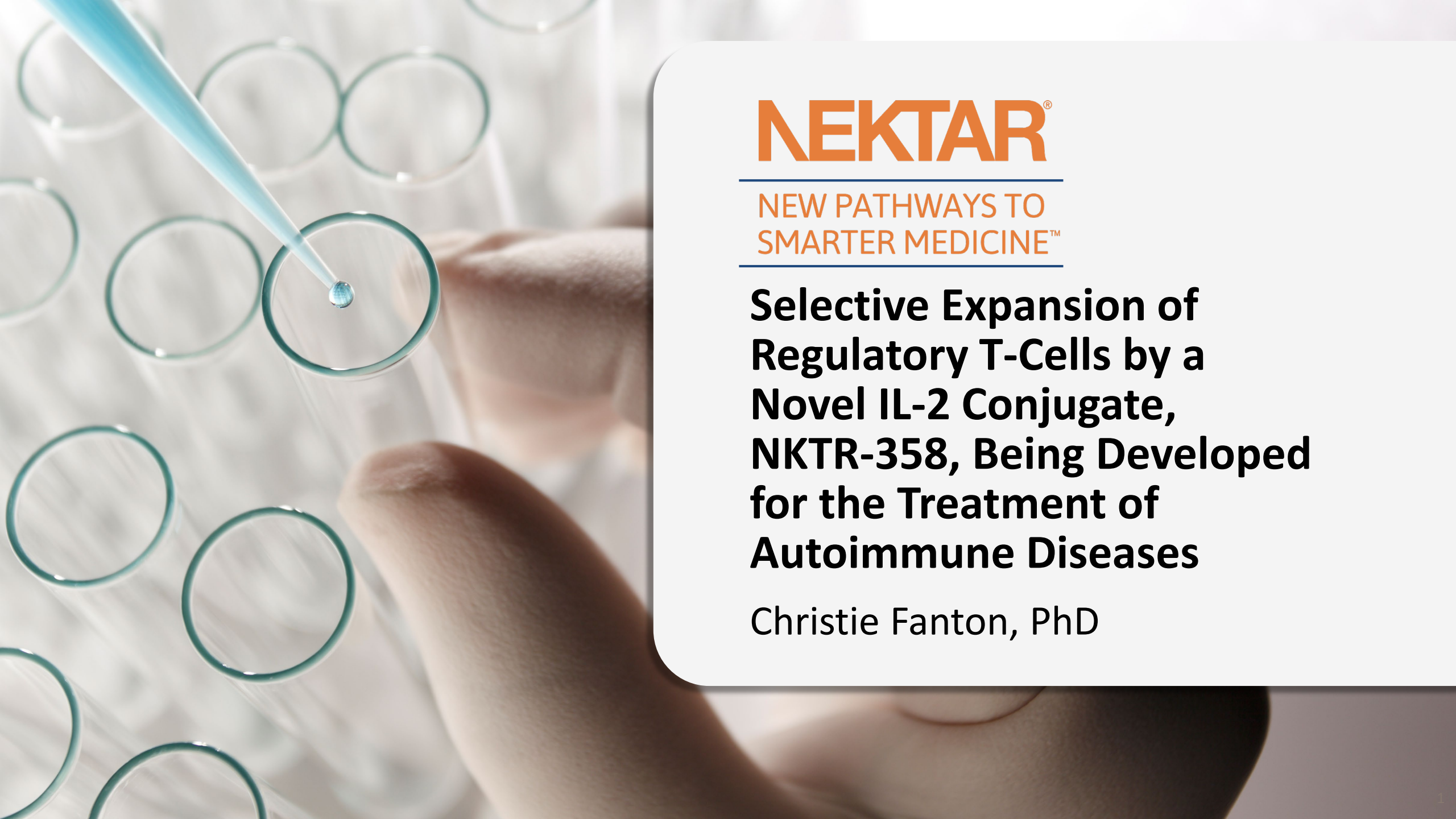

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NEW PATHWAYS TO SMARTER MEDICINE™

Selective Expansion of Regulatory T-Cells by a Novel IL-2 Conjugate, NKTR-358, Being Developed for the Treatment of Autoimmune Diseases

Christie Fanton, PhD

Presenter Disclosure Information

Christie Fanton, PhD
Nektar Therapeutics

The following relationships exist related to this presenter:

- C. Fanton is an employee of Nektar Therapeutics and owns shares of the company

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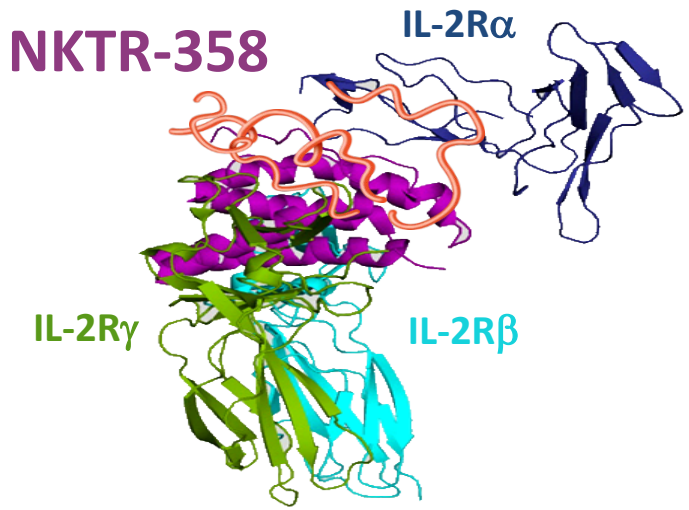
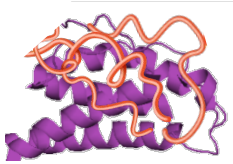
Lilly

NKTR-358: PEG-conjugated rhIL-2 Selectively Induces Regulatory T Cells (Tregs) and Their Suppressive Activity



PEG-conjugation:

- Stable covalent conjugation to rhIL-2 (aldesleukin sequence)
- Increases half life (vs IL-2)
- Alters binding profile of NKTR-358 (relative to IL-2) with lower binding affinity to IL-2Rβ and different binding bias for IL-2Rα & IL-2Rβ
- Imparts selectivity for effect on Tregs over Tcons (vs IL-2)



NKTR-358

Selectively Expands T-Reg Cells

βγ

CD8+ T-Cells and NK Cells

Stimulates Immune Response to Kill Tumor Cells

αβγ

CD4+ Regulatory T-Cells

Down-Regulates Proliferation of conventional T-cells

Stimulated Tregs with potential for long term control of immune response

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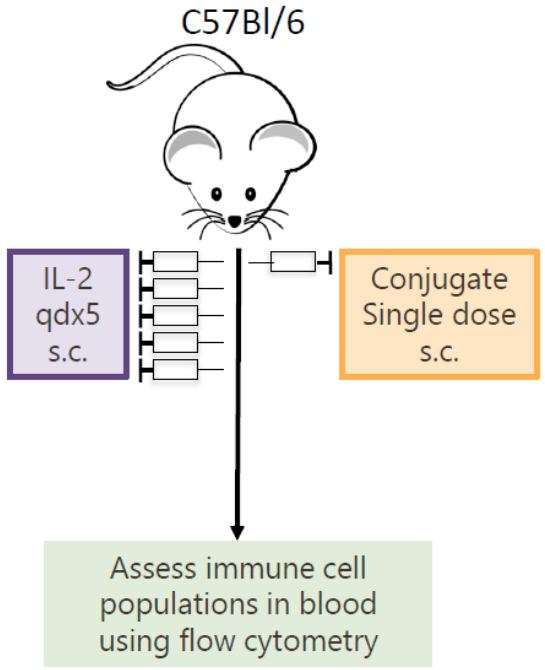
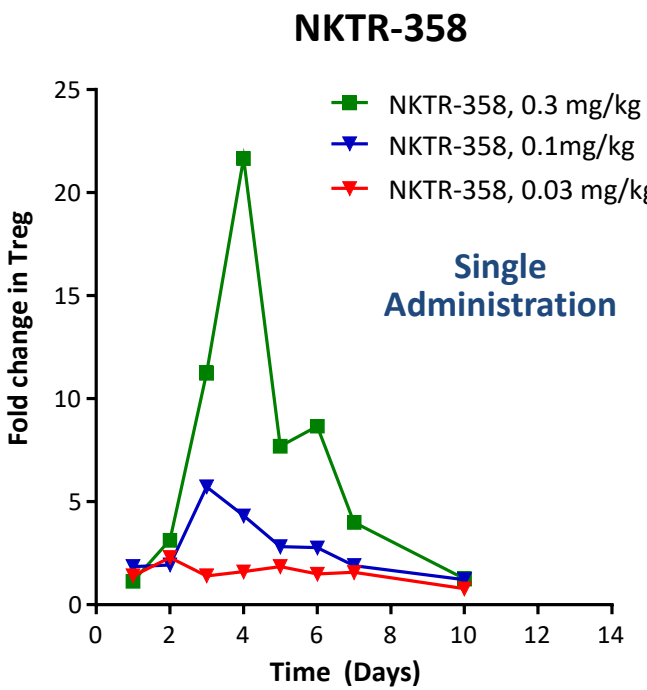
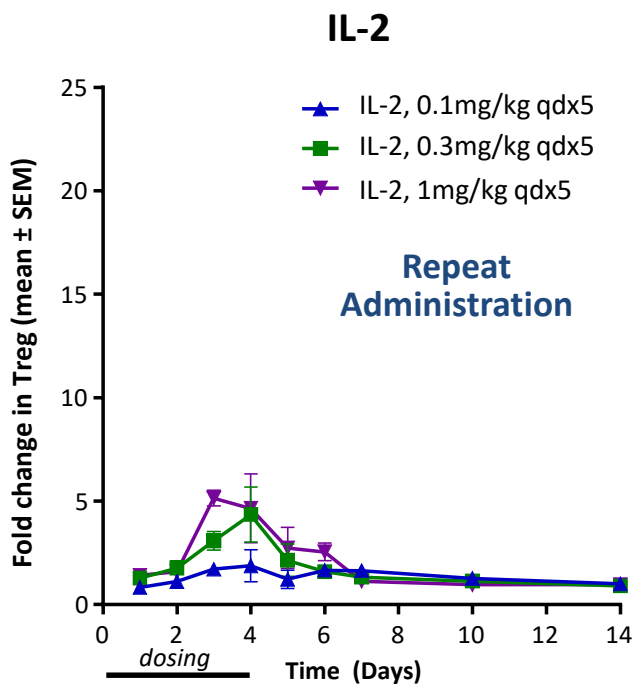
Comparison of NKTR-358 and IL-2 by *In Vivo* Screening

Single NKTR-358 administration in mouse leads to superior Treg induction compared to multiple IL-2 administrations

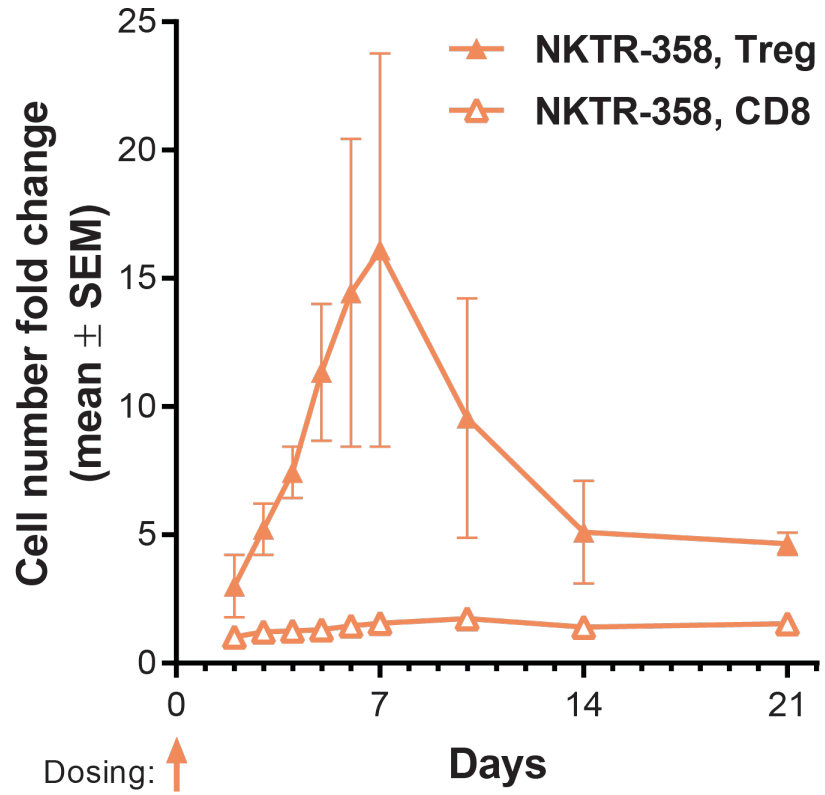


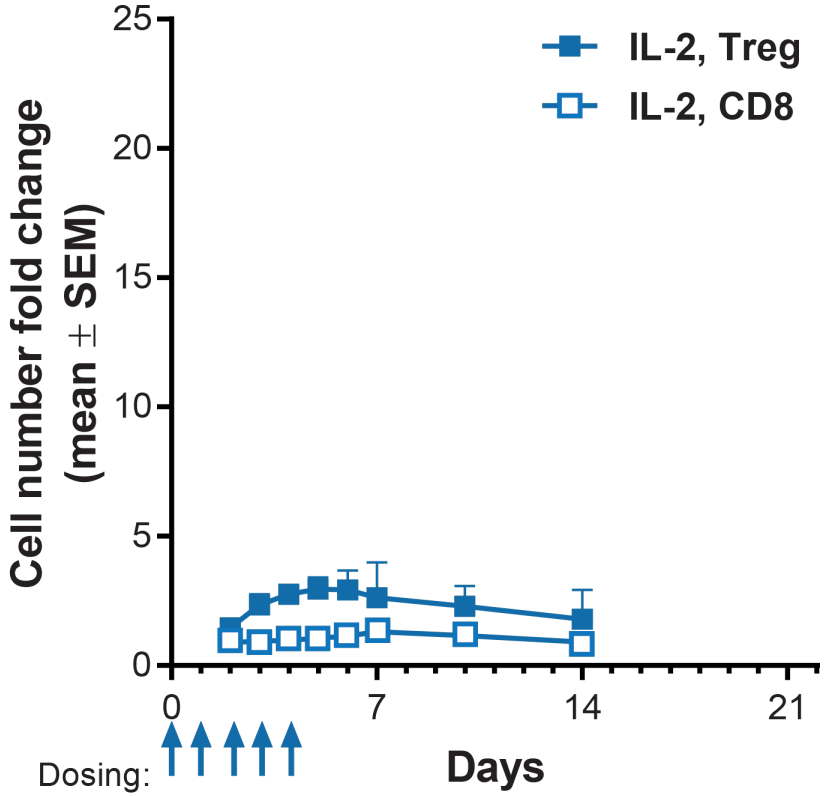




Source: 13th Annual World Congress on Inflammation 2017, Langowski et. al.

NKTR-358 Preferentially Expands Tregs in non-Human Primates



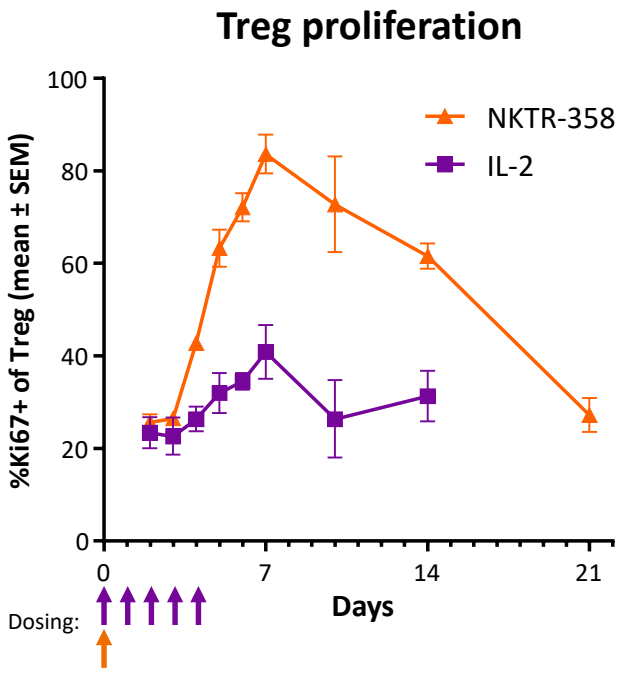


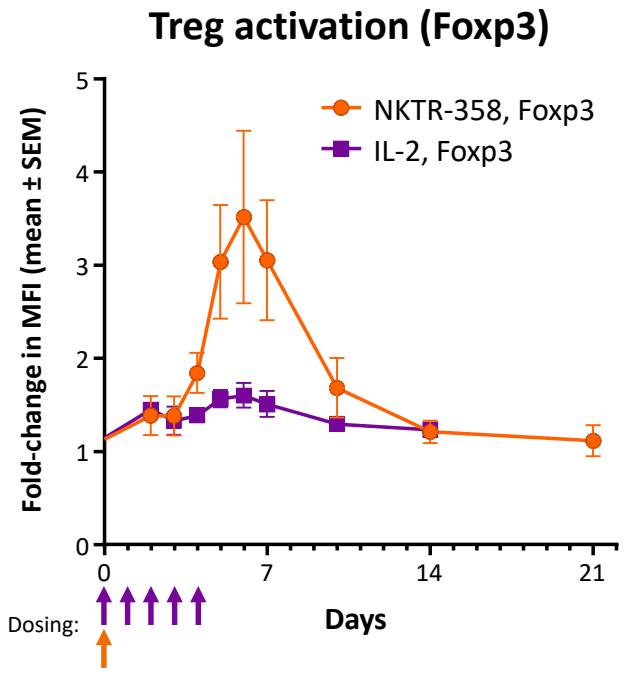
Cynomolgus monkeys administered:

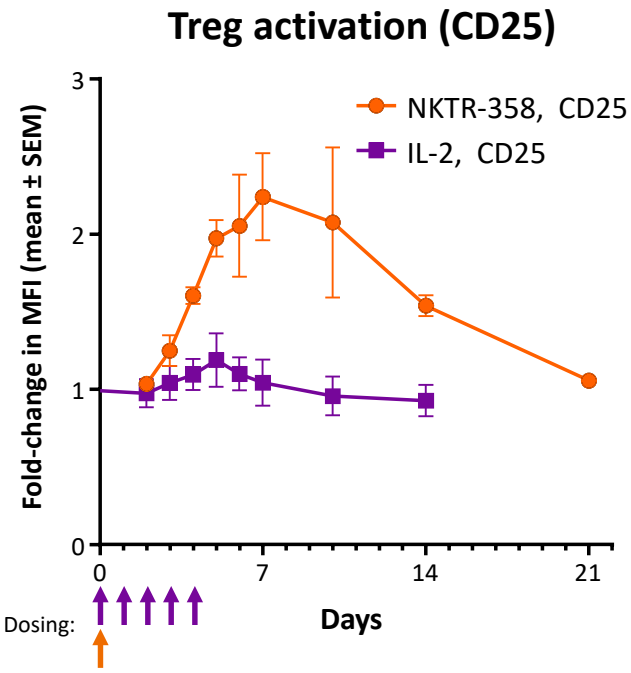
- NKTR-358 (25 µg/kg) single dose, or,
- Recombinant human IL-2 (5 µg/kg) daily on 5 consecutive days

Source: 13th Annual World Congress on Inflammation 2017, Langowski et. al.

NKTR-358 Promotes Greater Treg Proliferation and Activation than IL-2 in non-Human Primates





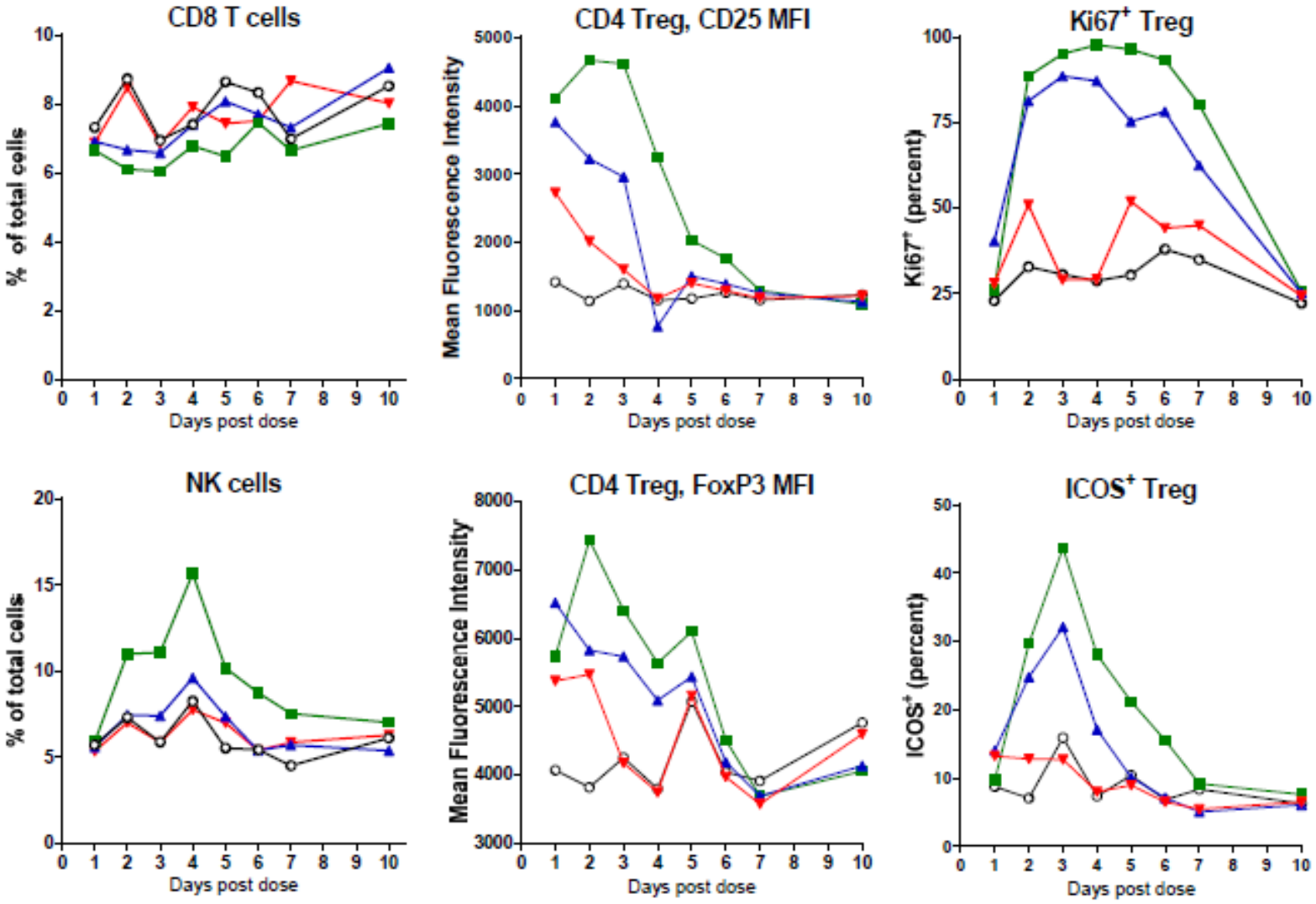


Cynomolgus monkey: 1M + 1F

- 25µg/kg : NKTR-358 single dose vs. qdx5 for IL-2

Source: 13th Annual World Congress on Inflammation 2017, Langowski et. al.

NKTR-358 Promotes Selective Treg Proliferation and Activation In Vivo



- Single dose NKTR-358 SC
- Induction of proliferation and activation markers
  - Helios, GITR, CTLA-4, CD39, CD73, OX40, and PD-1 (not shown)
  - Similar effect in blood and spleen (not shown)

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Source: 2017 American College of Rheumatology Annual Meeting, Langowski et. al.

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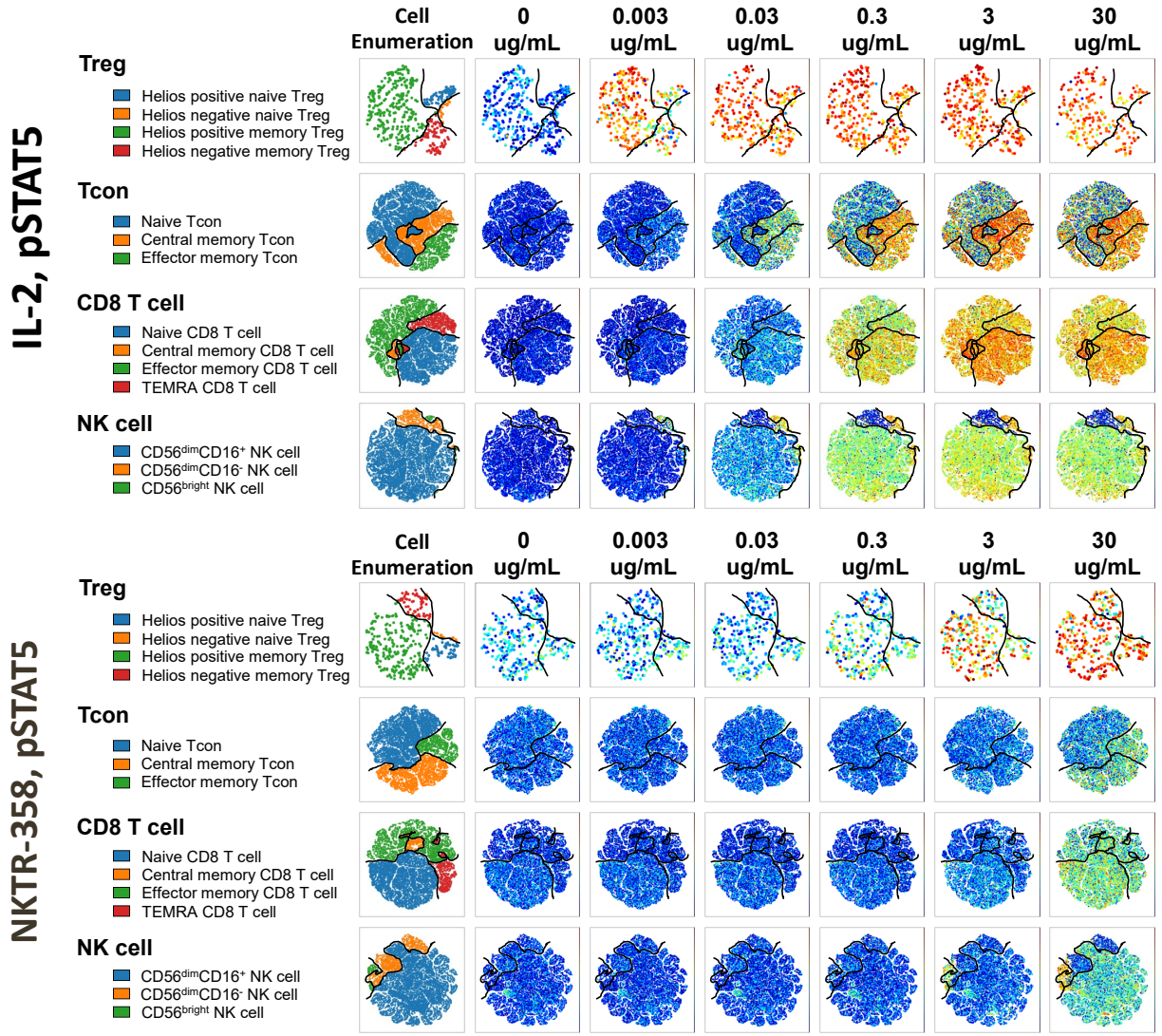
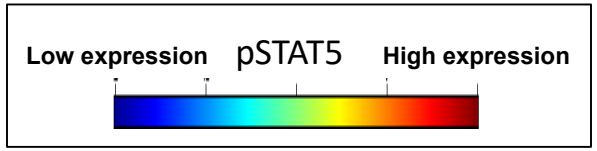
NKTR-358 Favors Activation of Tregs Over Other Subsets



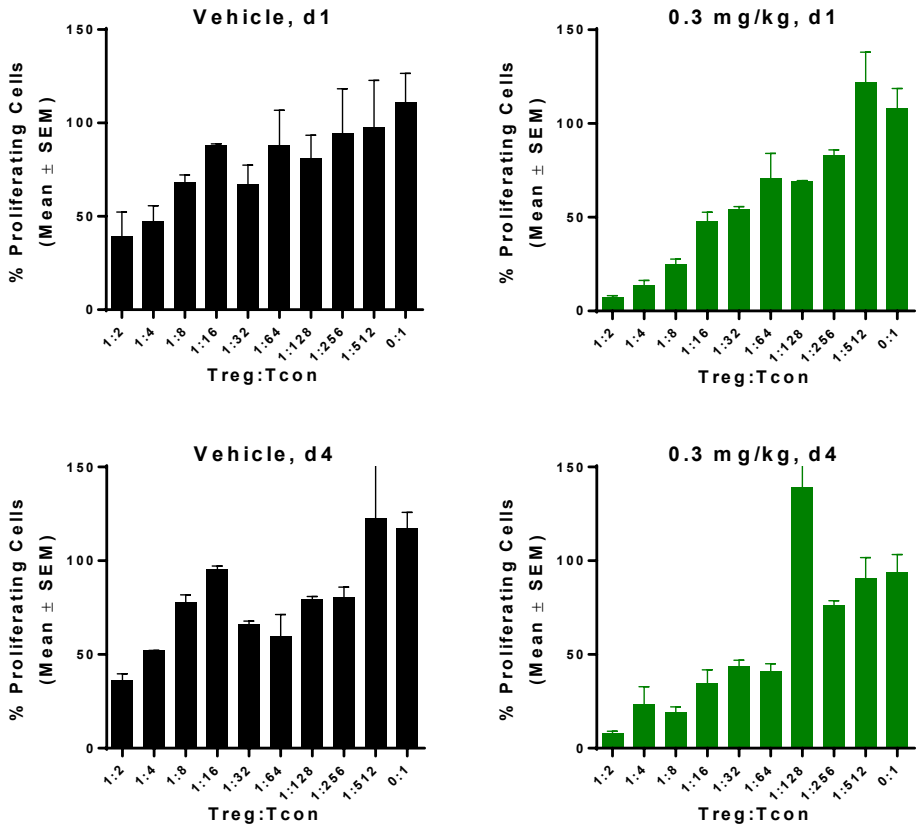
- Healthy human PBMCs
  - IL-2 or NKTR-358 for 15 min
  - Analysis by CyTOF
- IL-2 and NKTR-358 had primary effect on pSTAT5
  - No effect on pAKT, pERK, pS6, and pSTAT3 (save IL-2 on CD56+++ NK)

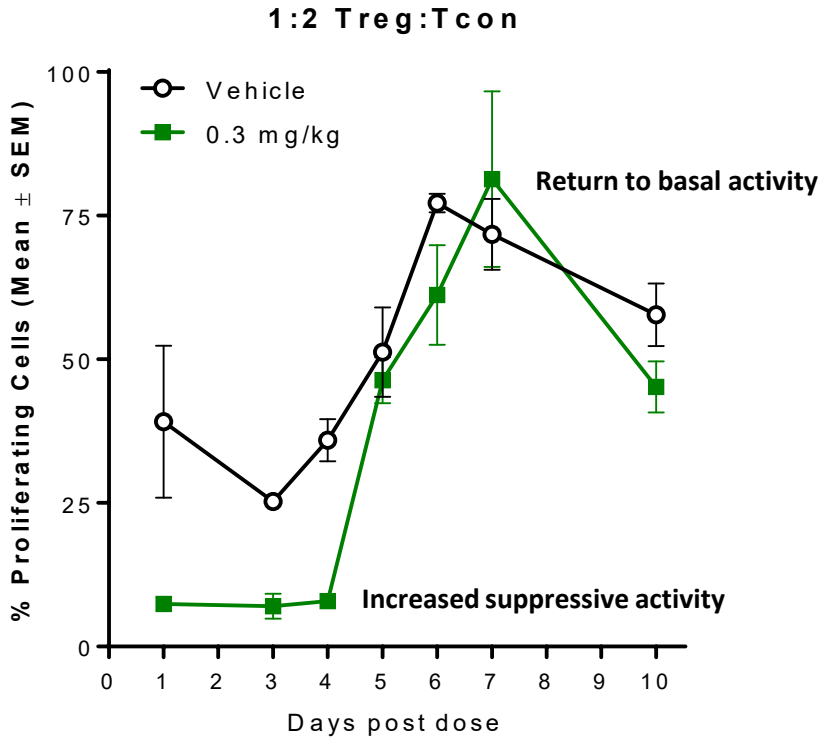


Source: T Reg Summit 2018 – T Reg Directed Therapy for Auto-Immune Disorders; Zalevsky, J, "NKTR-358: A Selective Regulatory T Cell Inducing Agent for the Treatment of Autoimmune and Inflammatory Diseases"

NKTR-358 Increases Treg Suppressive Activity

In vivo / Ex vivo T suppressor assay in mice



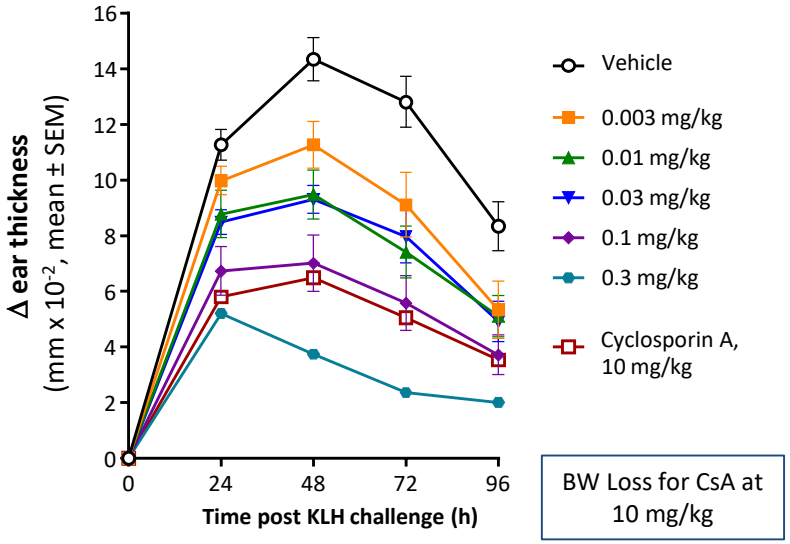


Source: 2017 American College of Rheumatology Annual Meeting, Langowski et. al.

NKTR-358 Suppresses Antigen-Driven Inflammation

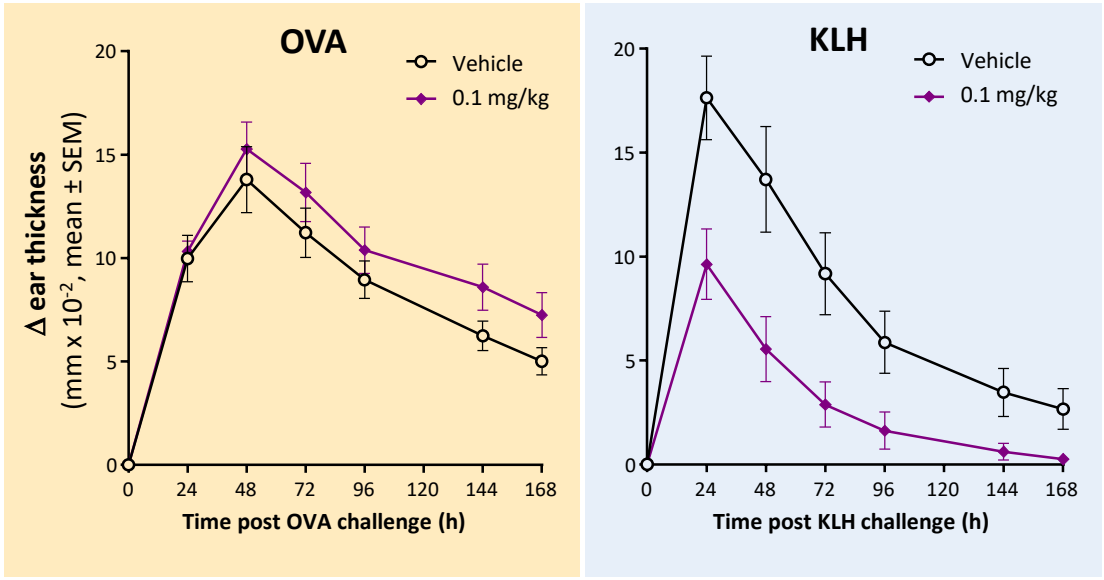
Effect is durable and antigen-specific

Primary efficacy



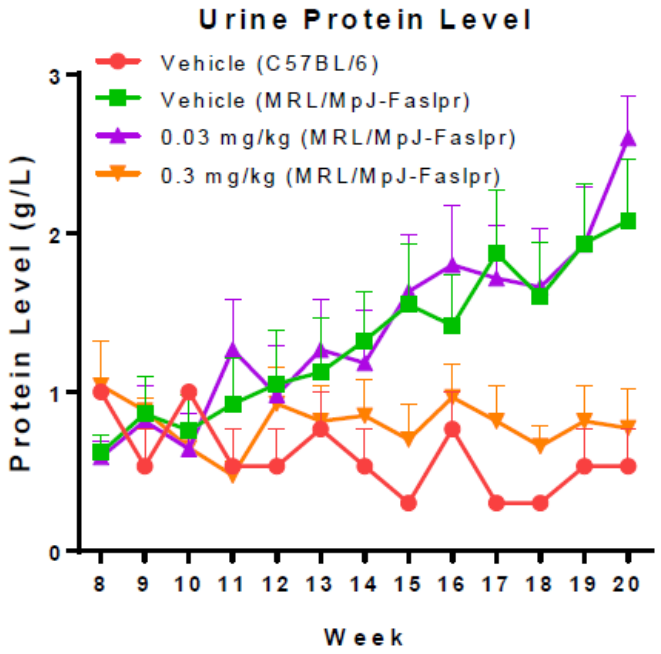
BW Loss for CsA at 10 mg/kg

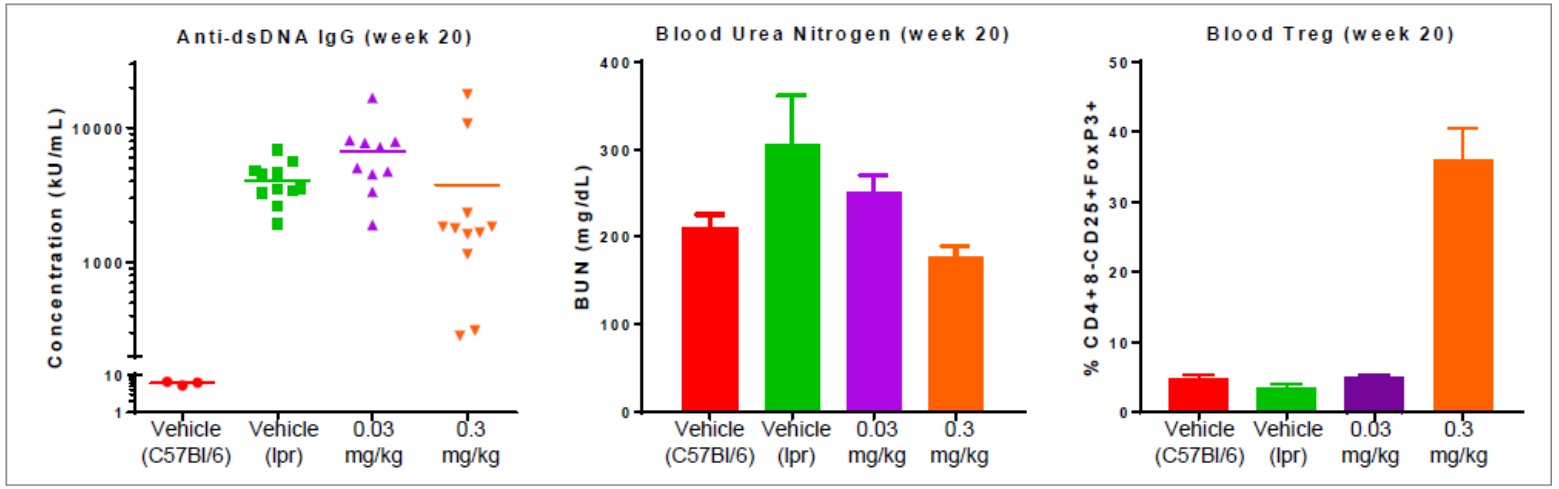
Rechallenge : Antigen-specific Treg memory



Source: 2017 American College of Rheumatology Annual Meeting, Langowski et. al.

NKTR-358 Is Efficacious in a Mouse Model of SLE





- NKTR-358 demonstrated dose-dependent efficacy on multiple parameters in mouse SLE
- 0.3 mg/kg (q3d, week 8-20) reduces urine protein and blood urea nitrogen to naïve mouse parameters
- Efficacy is consistent with Treg elevation

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Source: T Reg Summit 2018 – T Reg Directed Therapy for Auto-Immune Disorders; Zalevsky, J, "NKTR-358: A Selective Regulatory T Cell Inducing Agent for the Treatment of Autoimmune and Inflammatory Diseases"

Lilly

NKTR-358: Single Ascending Dose Study Objectives

Assess the effects of subcutaneous administration of single-ascending doses of NKTR-358 in healthy volunteers on:

Primary

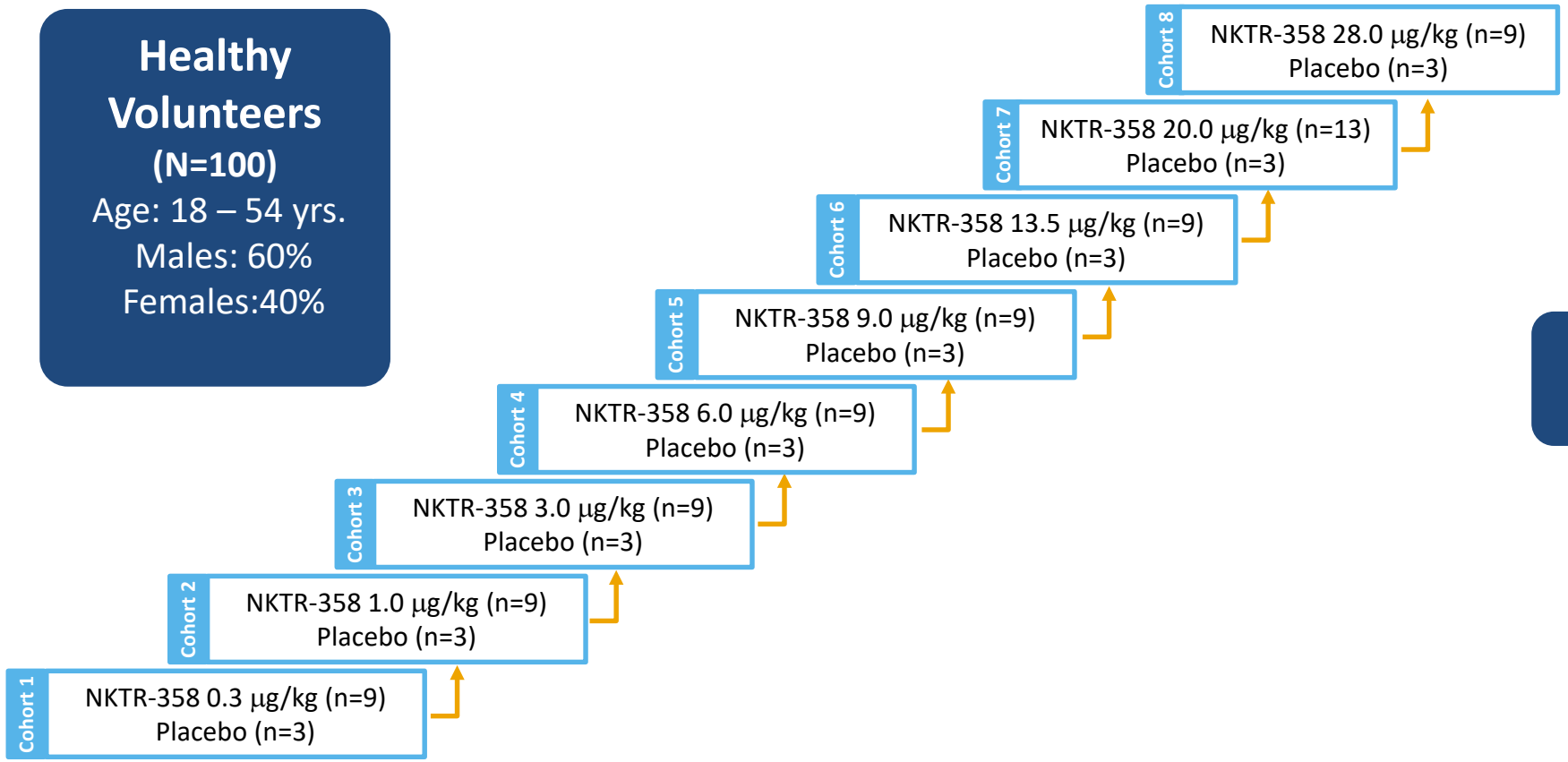
- Safety and tolerability in subjects as evaluated by:
  - Adverse events
  - Vital signs
  - Clinical safety lab results
  - Cytokine levels

Secondary

- Time course and extent of changes in the numbers and activity of Tregs, Tcons, and NK cells and subsets
- Pharmacokinetics (PK) of NKTR-358
- Other immunological effects: cytokine levels, peripheral blood cell populations, serum proteins and gene expression

Study Design: Randomized Double-blind Study of Subcutaneous Single Ascending Doses of NKTR-358 in Healthy Volunteers

Healthy Volunteers
(N=100)
Age: 18 – 54 yrs.
Males: 60%
Females:40%



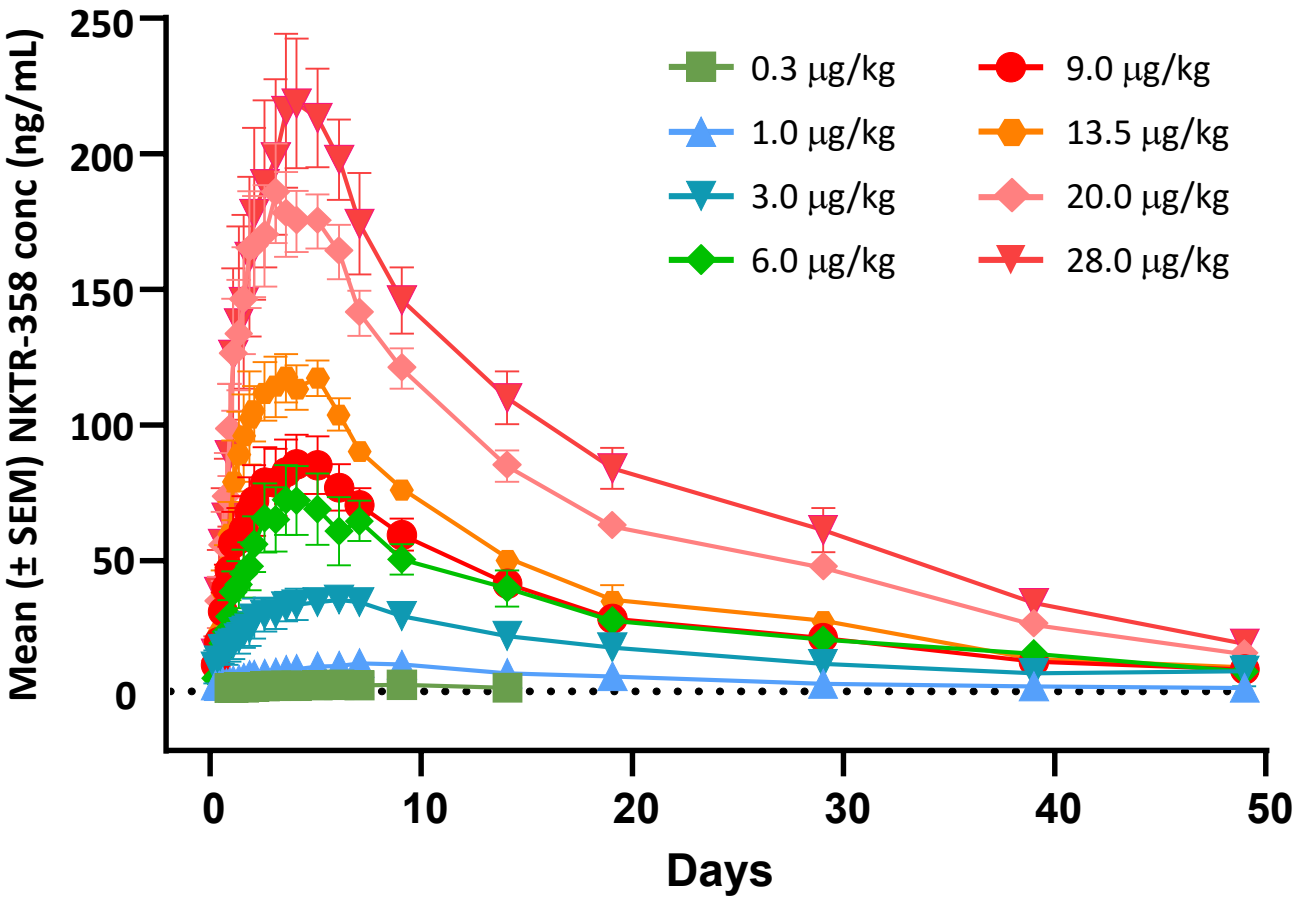
Each cohort followed for 50 days

Study Enrolled and Follow-up Complete

NKTR-358 SAD Study Results: NKTR-358 Was Safe and Well-Tolerated in Healthy Volunteers

- No dose-limiting toxicities, deaths, or AEs leading to study discontinuation
- No clinically significant vital sign, ECG, or physical examination abnormalities
- Adverse events primarily limited to mild or moderate (Grade 1 or 2) injection site reactions
- 4 subjects experienced Grade 1 mild events of headache
- 1 subject at the highest dose tested (28.0 µg/kg) experienced mild (Grade 1) signs and symptoms of vomiting, diarrhea, anorexia, tachycardia, and myalgia attributed to elevated cytokine levels
- No anti-drug antibodies detected

NKTR-358 Concentration Curves Indicate Dose Proportional Pharmacokinetics



- NKTR-358 Cmax and AUC values exhibited a dose proportional increase
- NKTR-358 concentrations reached maximum levels in 5-7 days
- NKTR-358 has an estimated elimination half-life of 8-11 days
  - half-life of IL-2 in human serum is ~5-7 minutes

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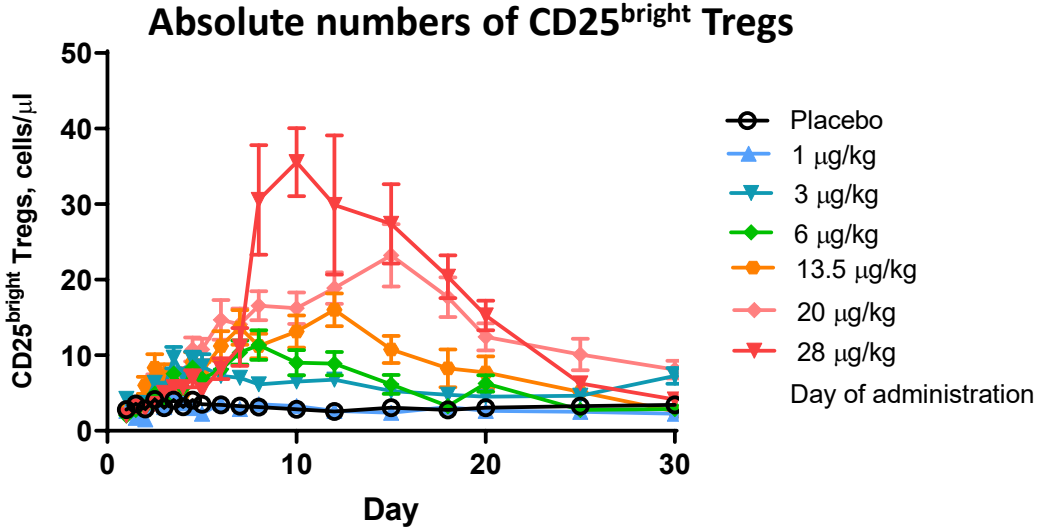
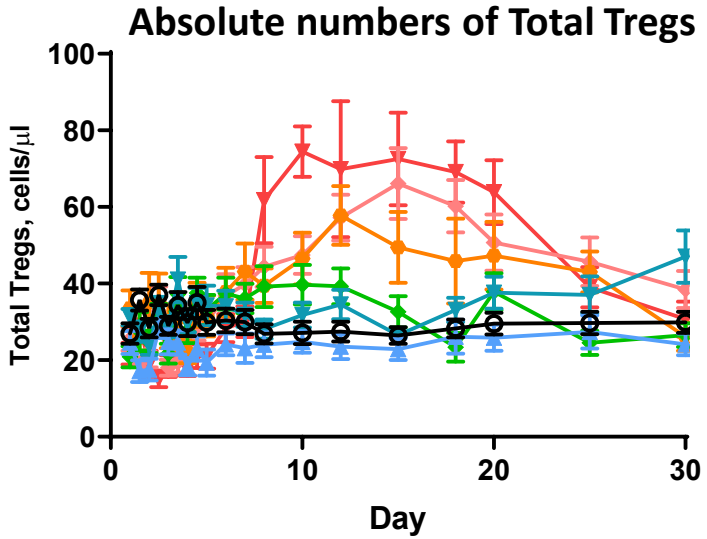
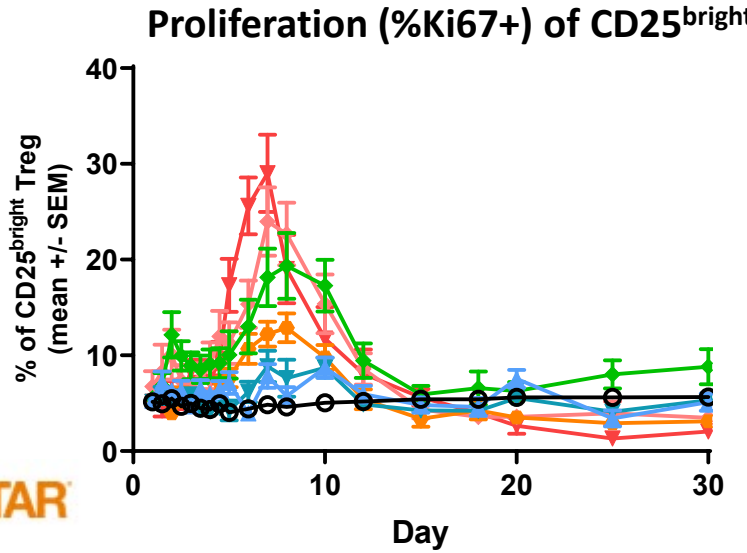
NKTR-358 Leads to Sustained, Dose-dependent Increases in Numbers and Proliferation (%Ki67+) of Total and CD25^{bright} Tregs







At 28 µg/kg NKTR-358:

- 3.5-fold mean peak increase (above predose levels) in numbers of total Tregs and 17-fold mean peak increase in numbers of CD25^{bright} Tregs, suggesting a large increase in most suppressive Treg population
- Treg levels peak at Days 10-12 and do not return to baseline until Days 20-25 following administration
- 6-fold mean increase in Ki67+ CD25^{bright} Tregs above predose value

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Not all cohorts are shown for clarity

Source: 2019 American College of Rheumatology Annual Meeting, Fanton et. al.

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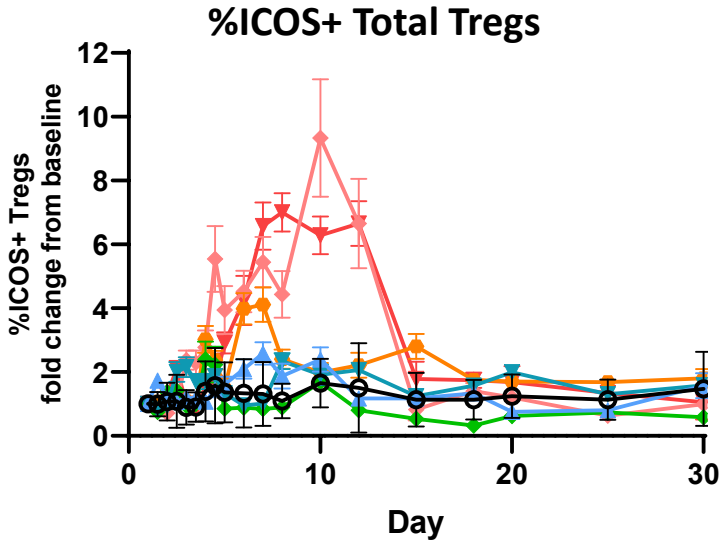
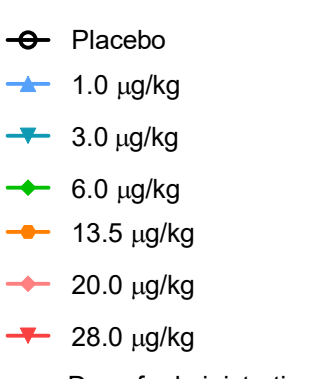
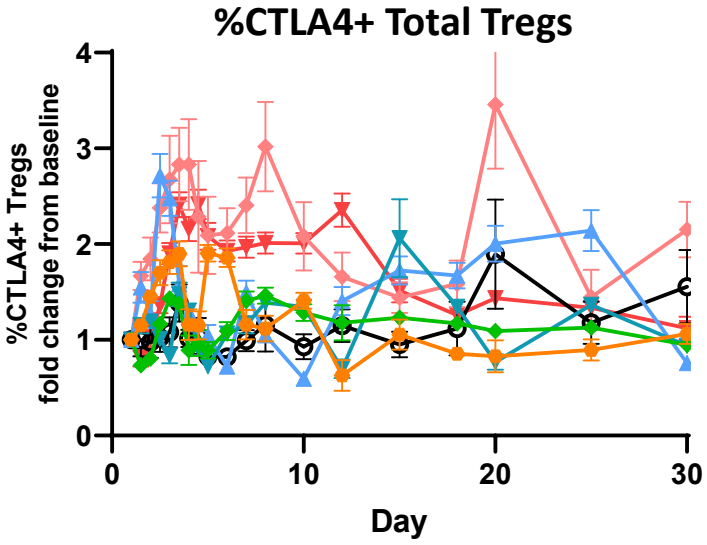
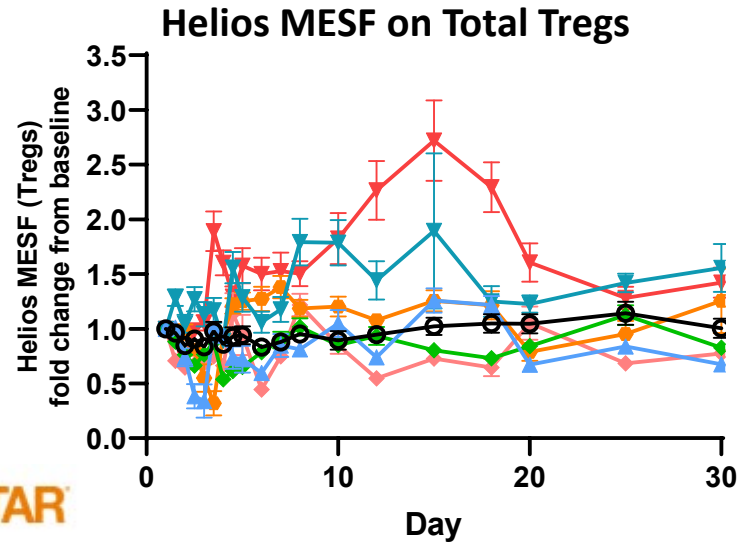
NKTR-358 Increases Expression of Treg Activation Markers









- Sustained increase in percentage of Treg activation markers CTLA4+ and ICOS+ at 20 and 28 µg/kg NKTR-358
- Increase in Helios expression (MESF) on Total Tregs at highest dose of NKTR-358

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Not all cohorts are shown for clarity

Source: 2019 American College of Rheumatology Annual Meeting, Fanton et. al.

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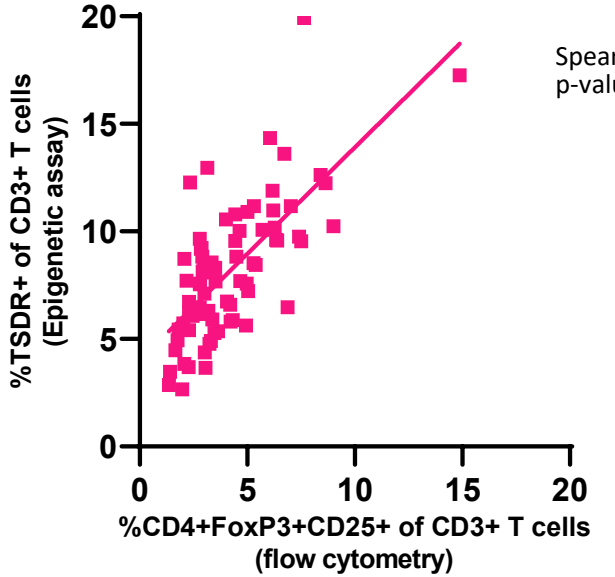
Identification of NKTR-358-induced Tregs Supported by Correlation with Demethylation Status of FoxP3 Gene

Correlation of % Total Tregs Across Assays at 28 μg/kg



Spearman r = 0.647 (n=76)
p-value <0.0001

Each data point represents an individual blood sample from 9 NKTR-358-treated subjects where data was available for both flow cytometry and demethylation assays

- Constitutive FoxP3 expression in Tregs is regulated at the epigenetic level by demethylation of TSDR in the FoxP3 gene, and an epigenetically active (demethylated) FoxP3 gene is observed solely in Tregs and not in activated, conventional (non-Treg) CD4+ T cells
- After 28 μg/kg NKT-358 administration, a significant correlation is observed between NKTR-358-induced Tregs identified by flow cytometry and Tregs identified by epigenetic analysis (% demethylation of FoxP3 TSDR)

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Source: 2019 American College of Rheumatology Annual Meeting, Fanton et. al.

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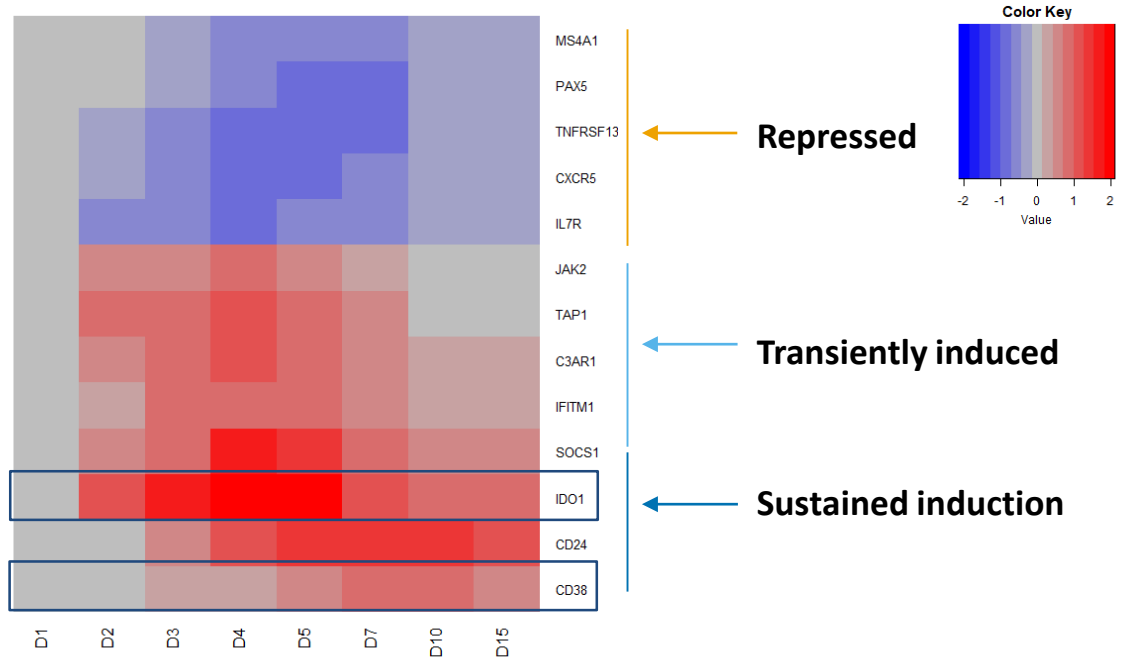
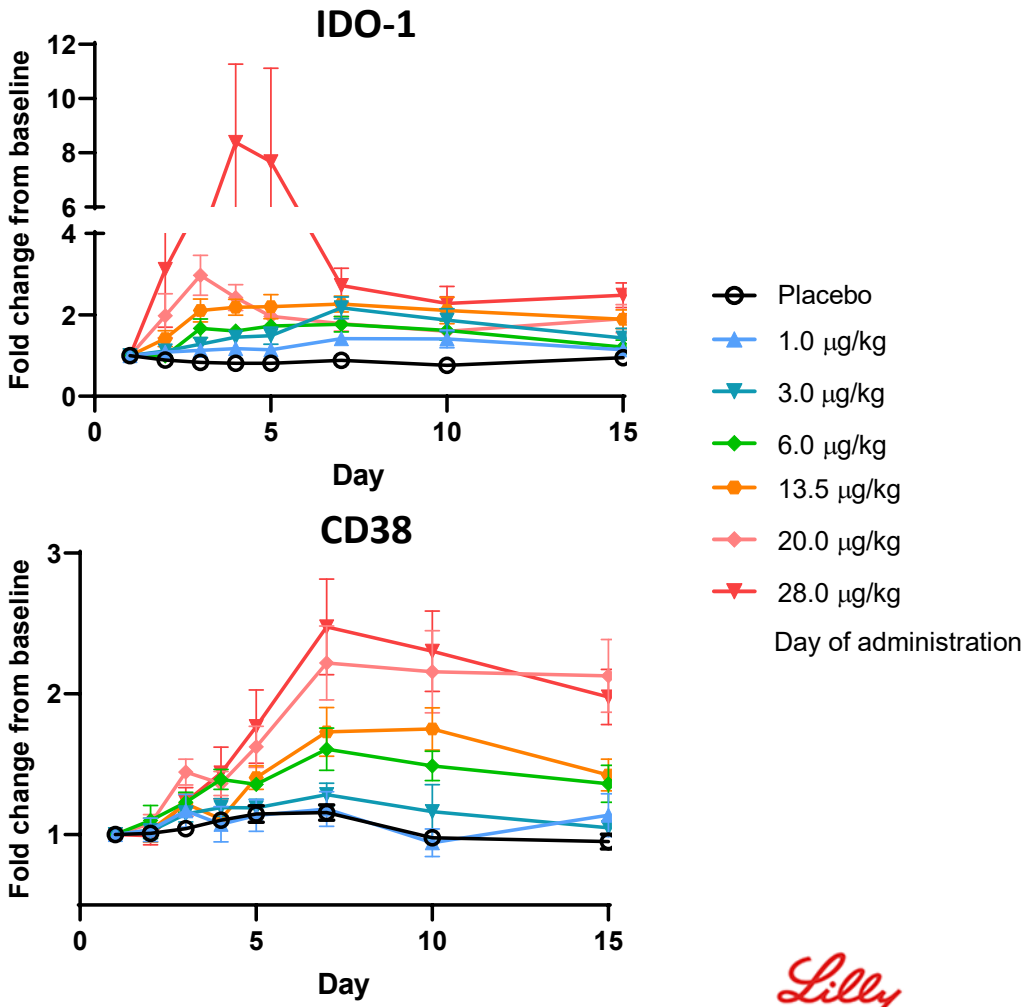
Genes Associated with Treg Regulation Show Correlation with Treg Induction

Pattern of Differential Expression of 13 Correlated Genes at 28 μg/kg



- Increase in number and magnitude of differentially expressed genes in response to NKTR-358 administration observed
- NKTR-358-dependent differential expression of 13 genes significantly correlated with induction of Tregs as measured by flow cytometry ($p<0.05$)

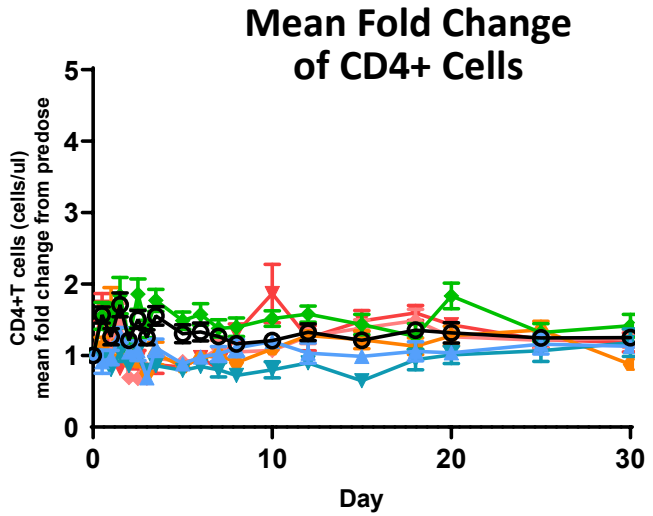
Dose Dependent Changes in 2 Genes Correlated with Treg Induction

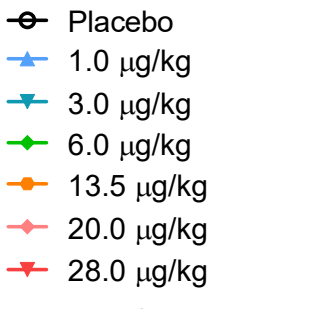


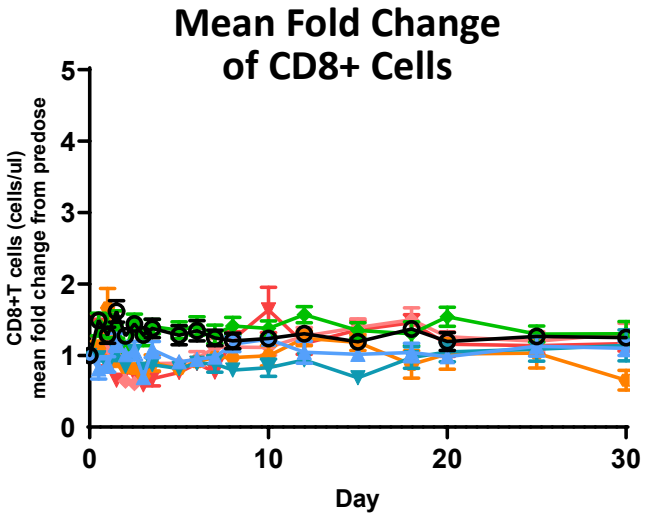
Not all cohorts are shown for clarity

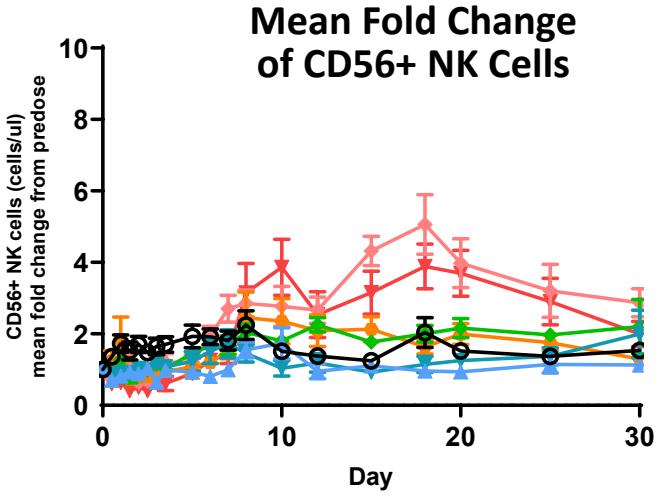
Source: 2019 American College of Rheumatology Annual Meeting, Fanton et. al.

NKTR-358: No Changes in Numbers of Tcon Cells and Low-level Increases in Numbers of CD56+ NK Cells







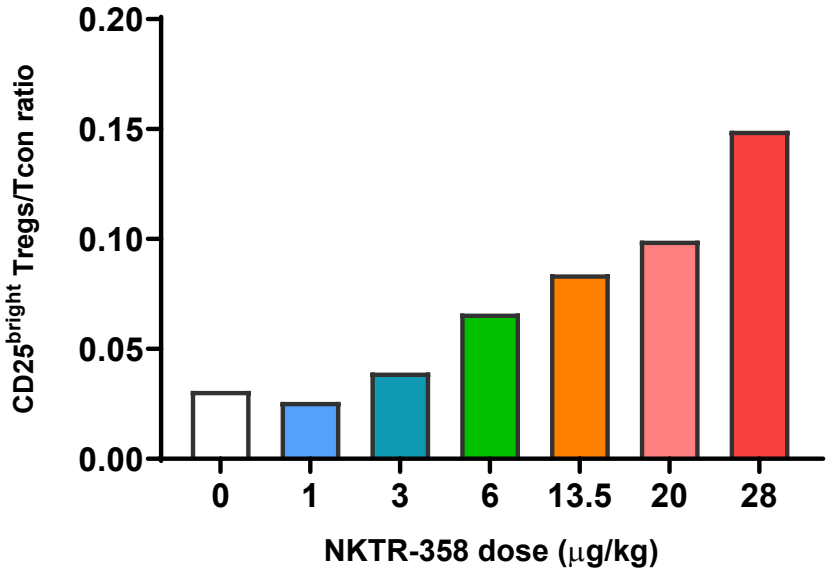


Not all cohorts are shown for clarity

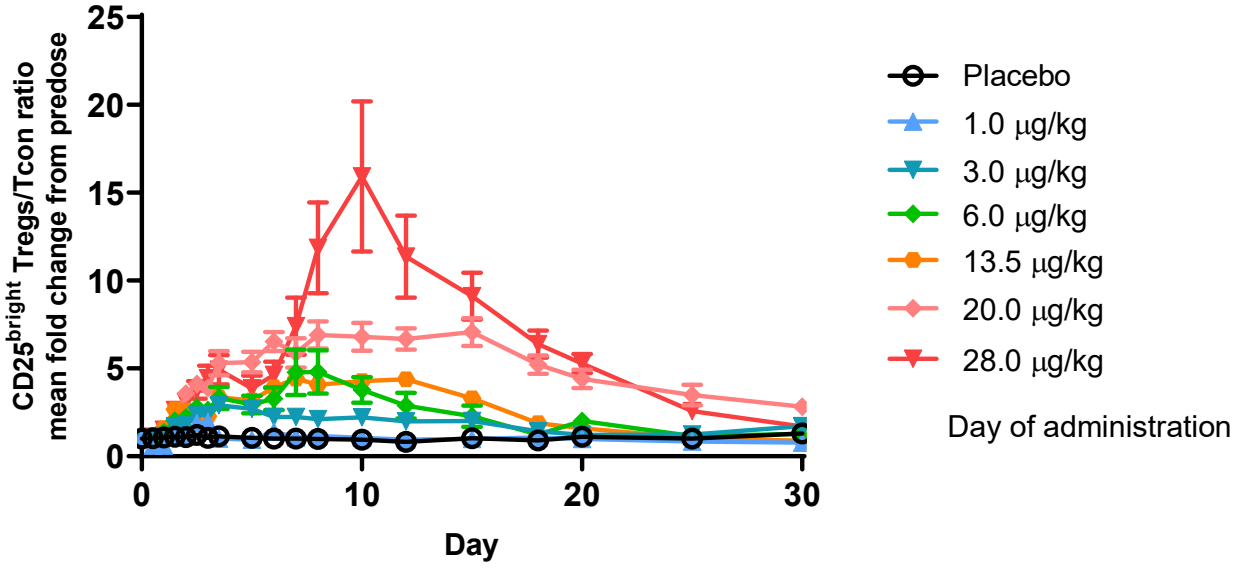
Source: 2019 American College of Rheumatology Annual Meeting, Fanton et. al.

NKTR-358 Selectively Induces Tregs in a Dose-Dependent Manner

Median Peak Effect of CD25^{bright} Treg/Tcon Ratio



Mean Fold Change in CD25^{bright} Tregs/Tcon Cell Ratio



NKTR-358 administration leads to 15-fold increase in mean peak Treg: Tcon ratio over baseline at 28 µg/kg.

In this analysis Tcon cells are defined as CD8+ Tcells; Not all cohorts are shown for clarity

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Source: 2019 American College of Rheumatology Annual Meeting, Fanton et. al.

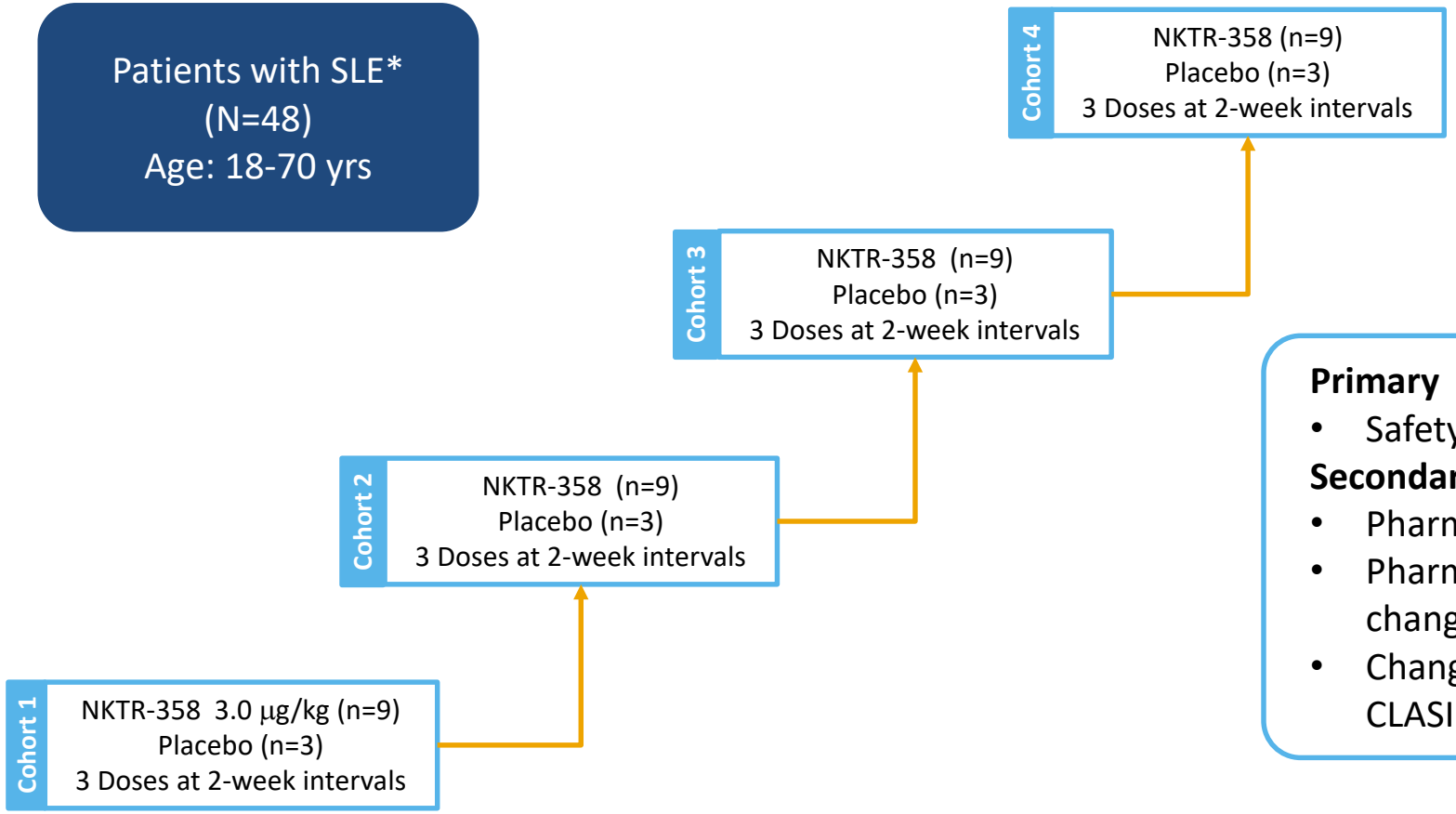
Lilly

NKTR-358 SAD Study: Conclusions

- Safe and well tolerated in this first in human study
- Dose proportional pharmacokinetics and prolonged exposure with a half-life of 8-11 days
- Marked and selective dose-dependent expansion of numbers of Treg cells, as demonstrated by flow cytometric and epigenetic analyses
- The induction of Tregs is selective, with no measurable changes in numbers and percentages of CD4+ and CD8+ Tcons at all doses and low-level increases of NK cell numbers at highest doses tested
- Tregs induced by NKTR-358 are activated, as measured by flow cytometry and RNA expression analyses
- Data provide strong support for studying NKTR-358 in autoimmune and inflammatory diseases
- NKTR-358 is currently being studied in a multiple ascending dose clinical trial in patients with SLE and additional studies in other inflammatory diseases are ongoing or planned

Ongoing Phase 1b Study of Subcutaneous Multiple Ascending Doses of NKTR-358 in Patients With SLE

Patients with SLE*
(N=48)
Age: 18-70 yrs



Each cohort followed for 79 days

Primary

- Safety and tolerability of NKTR-358

Secondary

- Pharmacokinetics of NKTR-358
- Pharmacodynamics: Time course and extent of changes in Tregs, Tcons, NK cells and cytokines
- Change in Disease Activity based on SLEDAI and CLASI scores

*Diagnosis of adult SLE according to 1997 ACR criteria for at least 6 months

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