NKTR-358: A Selective Regulatory T Cell Inducing Agent for the Treatment of Autoimmune and Inflammatory Diseases

Jonathan Zalevsky
SVP Research & CSO
Nektar Therapeutics
Introduction

- A progressive imbalance of regulatory T cells (Tregs) relative to conventional T cells (Tcon) is shared by many autoimmune diseases
- Enhanced sensitivity of Tregs to IL-2 supports use of low-dose IL-2 therapy
  - Low-dose IL-2 therapy hampered by poor pharmacokinetics, AEs, short-lived effects
  - Magnitude of Treg mobilization ultimately limited by elicitation of Tcon
  - Clinical benefit demonstrated in GVHD, psoriasis, SLE and other indications
NKTR-358

• Preferential increase in number and activity of Tregs, minimal action on non-Tregs
  — Potential first-in-class therapeutic for direct manipulation of Tregs
• Biotherapeutic born from Nektar’s extensive development experience with IL-2 and polymer conjugation
• Utilizes the FDA-approved aldesleukin sequence
• Monthly or twice monthly self-administered subcutaneous product for the treatment of autoimmune, chronic inflammatory, and allergy indications

Nektar and Eli Lilly entered into a co-development agreement for NKTR-358 in August 2017
NKTR-358 was Discovered by In Vivo Screening

C57Bl/6

IL-2
qdx5
SC

Conjugate
Single dose
SC

Assess immune cell populations in blood using flow cytometry

Fold change in Treg populations over time for different dosages of NKTR-358:
- Green square: NKTR-358, 0.3 mg/kg
- Blue square: NKTR-358, 0.1 mg/kg
- Red square: NKTR-358, 0.03 mg/kg

Fold change in Treg populations over time for different dosages of IL-2:
- Purple square: IL-2, 0.1 mg/kg qdx5
- Green square: IL-2, 0.3 mg/kg qdx5
- Violet square: IL-2, 1 mg/kg qdx5

Time (Days):
0 2 4 6 8 10 12 14

Fold change in Treg (mean ± SEM):
NKTR-358 has Attenuated Affinity to IL-2 Receptors

- PEG-conjugation reduces binding affinity of NKTR-358 relative to IL-2
- Relative to IL-2, NKTR-358 has:
  - Lower binding affinity to IL-2Rβ
  - Different binding bias for IL-2Rα & IL-2Rβ
NKTR-358 Favors Activation of Treg Over Tcon

For IL-2:
- Red dots represent Treg.
- Blue squares represent NK cells.
- Green triangles represent CD8 cells.

For NKTR-358:
- Red dots represent Treg.
- Blue squares represent NK cells.
- Green triangles represent CD8 cells.

The graphs show the concentration (ng/mL, log scale) on the x-axis and pSTAT5 MFI on the y-axis.
NKTR-358 Promotes Selective Treg Activation

**CD8 T cells**

- % of total cells
- Days post dose

**CD4 Treg, CD25 MFI**

- Mean Fluorescence Intensity
- Days post dose

**Ki67+ Treg**

- % Ki67+ (percent)
- Days post dose

**NK cells**

- % of total cells
- Days post dose

**CD4 Treg, FoxP3 MFI**

- Mean Fluorescence Intensity
- Days post dose

**ICOS+ Treg**

- % ICOS+ (percent)
- Days post dose

Legend:
- 0.3 mg/kg
- 0.1 mg/kg
- 0.03 mg/kg
- Vehicle
NKTR-358 Promotes Treg Suppressive Function

Vehicle, d1

Vehicle, d4

0.3 mg/kg, d1

0.3 mg/kg, d4

% Proliferating Cells (Mean ± SEM)

Days post dose

1:2 Treg:Tcon

Vehicle

0.3 mg/kg
NKTR-358 Suppresses Inflammation in Mouse DTH

- Sensitization KLH, flank
- Elicitation KLH, ear
- Measure ear

Day 0 NKTR-3 s.c. q3d; CsA qd

Δ ear thickness (mm x 10^-2, mean ± SEM)

- Vehicle
- 0.003 mg/kg
- 0.01 mg/kg
- 0.03 mg/kg
- 0.1 mg/kg
- 0.3 mg/kg
- Cyclosporin A, 10 mg/kg

Time post KLH challenge (h)
NKTR-358 Promotes Treg Infiltration in Mouse DTH

Time post-KLH challenge

\[ ^* p < 0.05, \quad ^{****} p < 0.0001 \text{ vs Vehicle w.r.t. same timepoint} \]
One-way ANOVA (Bonferroni’s post-test)

\[ ^\sharp p < 0.001, \text{ unpaired t-test vs Vehicle w.r.t. same timepoint} \]
Combination of NKTR-358 + Anti-Inflammatory: Synergy of Non-Overlapping MOAs
NKTR-358 Promotes Antigen-Specific Treg Memory

**Sensitization**
- KLH, flank

**Elicitation**
- KLH, ear

Measure ear

Day 0

Day 5

3 – 4 weeks, no treatment

NKTR-358 s.c. q3d; CsA qd

---

**Primary efficacy**

- OVA
- KLH

**Rechallenge: Antigen-specific Treg memory**

- Vehicle
- 0.003 mg/kg
- 0.01 mg/kg
- 0.03 mg/kg
- 0.1 mg/kg
- 0.3 mg/kg
- Cyclosporin A, 10 mg/kg

**Time post KLH challenge (h)**

0 24 48 72 96

**Time post OVA challenge (h)**

0 24 48 72 96 120 144 168

**Time post KLH challenge (h)**

0 24 48 72 96 120 144 168

**Ear thickness (mm x 10^-2, mean ± SEM)**

0 2 4 6 8 10 12 14 16

0 5 10 15 20
NKTR-358 Efficacy in OVA-Induced Food Allergy in Mice

Clinical Score

MCPT1

Anti-OVA IgE

Sensitization
OVA + adjuvant, i.p.

Challenge
OVA, oral

Clinical score
Serum MCPT1, IgE

Day 0
Day 16
Day 28

NKTR-358 or CsA

OVA
OVA + CsA 10 mg/kg
OVA + NKTR-358 0.1 mg/kg

naive 'control'

NEKTAR

Lilly
NKTR-358 Efficacy in Mouse 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
**Preferential and Sustained Treg Expansion in NHP**

### Treg, CD8 in blood

- **NKTR-358, Treg**
- **IL-2, Treg**

### Treg activation

- **Treg proliferation (Ki67)**
- **Treg activation (CD25)**

Cynomolgus monkey: 1M + 1F

25µg/kg: NKTR-358 single dose vs. qdx5 for IL-2
NKTR-358 Suppresses Inflammation in Monkey DTH

CHS: Cutaneous Hypersensitivity
TT: Tetanus Toxoid

Arrows: NKTR-358 s.c., 0.003 & 0.015 mg/kg q2w
*p < 0.05 vs CHS, ANOVA
Development Status of NKTR-358

• Phase I Single Ascending Dose trial initiated March 2017
  – Primary readouts are Treg mobilization and activity, Treg/Tcon selectivity ratio, PK and safety
  – Goal is to establish a range of dose levels to be advanced into a clinical trial in patients with SLE

• Phase I Multiple Ascending Dose trial in SLE Patients Q2 2018

• Nektar and Lilly plan multiple indications in Phase II
Summary of NKTR-358

• NKTR-358 is an immune-regulatory cytokine drug being developed by Nektar and Lilly that induces profound Treg effects
  – Greater magnitude of total Treg cell increase than IL-2
  – Highly selective for Tregs with limited effects on non-Treg cells
  – Increased Treg suppressive capacity and induction of long-lived Treg memory
  – Prolonged activation and proliferation of Treg in higher species

• Clinical development ongoing for the treatment of autoimmune and chronic inflammatory indications