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

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Nektar Therapeutics

- 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

- **2001**
  - Hepatitis C
  - **Peglntron** by Schering-Plough
- **2002**
  - Neutropenia
  - **Neulasta** by Amgen
- **2003**
  - Acromegaly
  - **SOMAVERT** by Pfizer
- **2004**
  - Wet macular degeneration
  - **MACugen** by Pfizer
- **2007**
  - Chronic kidney disease anemia
  - **MIRCERA** by Roche
- **2008**
  - Crohn’s
  - **Cimzia** by UCB Pharma
- **2014**
  - Opioid induced constipation
  - **Movantik** by AstraZeneca
- **2015**
  - Hemophilia A
  - **Advocate** by AbbVie

**Small molecule**
- NKTR-181
- NKTR-262

**Biologics**
- NKTR-214
- NKTR-255
- NKTR-358

**R&D**
- Large Molecule Half-life Extension
- Concentration in Diseased Tissue
- Small Molecule Compartmental Distribution
- Bias Receptor Activity

**NKTR**
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

1. Release of cancer cell antigens
2. Cancer antigen presentation
3. Priming and activation
4. Trafficking of T cells to tumor
5. Infiltration of T cells into tumors
6. Recognition of cancer cells by T cells
7. Killing of cancer cells

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

1. Release of cancer cell antigens (cancer cell death)
2. Cancer antigen presentation (dendritic cells/APCs)
3. Priming and activation (APCs & T cells)
4. Trafficking of T cells to tumor (CTLs)
5. Infiltration of T cells into tumors (CTLs, endothelial cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (immune and cancer cells)

Therapies need to be accessible as medicines
Target as many steps as possible in the cycle with as few therapies as possible
Nektar’s Immuno-Oncology Strategy to Create Therapies that Cover the Immunity Cycle

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 NKTR-214 (CD122 Agonist)
Prime, Proliferate, Activate & Increase Tumor-Infiltrating Lymphocytes (TILs), Increase PD-1 expression

Target as many steps as possible in the cycle with as few therapies as possible
Therapies need to be accessible as medicines
NKTR-214: Biasing Action to CD 122, or IL-2R Beta, to Stimulate T-Cell Production

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

NKTR-214

βγ

CTLs

CD8+ T-Cells

and NK Cells

Stimulates Immune Response to Kill Tumor Cells

αβγ

Tregs

CD4+ Regulatory T-Cells

Down-Regulates Proliferation of CD8+ T-cells and Suppresses Immune Response
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-2Rαβγ**

- IL-2: purple
- IL-2Rβ: cyan
- IL-2Rα: blue
- IL-2Rγ: green

**IL-2 cytokine core**

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

**NKTR-214**

- High molecular weight hydrolyzable polymers located at strategic sites
NKTR-214: Biased Signaling And Prodrug Design To Improve Risk/Benefit Profile

NKTR-214 (essentially inactive)

% Phospho-STAT5

Concentration (g/mL)

IL-2

NKTR-214

Charych, D., et al. AACR 2013, Abstract #482
NKTR-214: Biased Signaling And Prodrug Design To Improve Risk/Benefit Profile

NKTR-214 (essentially inactive)

Active Species (Biased signaling, increased potency with fewer PEGs)

% Phospho-STAT5

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Charych, D., et al. AACR 2013, Abstract #482
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).

Charych, D., et al. AACR 2013, Abstract #482
NKTR-214 Increases The Quality And Quantity Of The T-cell Response in Mice

Mouse melanoma model

CD8/Treg ratio

> 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

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

Analysis of T cell Populations in Tumor

Fold change expressed as Week 3 / predose
Shown are results from N=10 patients
Nektar’s Immuno-Oncology Strategy to Create Therapies that Cover the Immunity Cycle

** NKTR-214 (CD122 Agonist) **
Prime, Proliferate, Activate & Increase Tumor-Infiltrating Lymphocytes (TILs), Increase PD-1 expression
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-2Rβγ)
- **Biased and sustained** signaling to preferentially activate and expand effector CD8+ T and NK cells over Tregs in the tumor microenvironment
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NKTR-214 (CD122 Agonist)
- Prime, Proliferate, Activate & Increase Tumor-Infiltrating Lymphocytes (TILs), Increase PD-1 expression

NKTR-262 (TLR Agonist)
- Activate Dendritic Cell Response

Checkpoint Inhibitors

Therapies need to be accessible as medicines

Target as many steps as possible in the cycle with as few therapies as possible
TLRs Signaling:
Innate Immune Activation and the Linkage to the Adaptive Immune Response
Effects of TLR Engagement on Different T Cell Subsets

- Increases CD4+ T cell proliferation & survival
- Augments IL-2 production by CD4+ T cells
- Reverses suppressive activity of Tregs.
- Reverses suppression by γδ T cells.
- Enhances CD8+ T cell effector function
- Increases IFN-γ, IL-2 & IL-10 production.
- Augments tumor infiltration
- Increases CD4+ & CD8+ T cell proliferation
- Enhances IL-2, IL-8, IL-10 production from CD4+ T cells
- Augments IFN-γ, TNF-α, Granzyme B production by CD8+ T cells
- Increases expansion & suppressive activity of murine T regs
- Increases CD4+ & CD8+ T cell proliferation & survival
- Increases CD8+ T cell infiltration
- Increases IFN-γ, TNF-α production.
- Increases cytotoxic activity of γδ T cells
- Increases CD4+ & CD8+ T cell proliferation
- Induces IFN-γ, TNF-α, Granzyme B & Perforin
- Increase adhesion of T cells, reduce chemotaxis
- Promotes Th17 differentiation
- Enhance proliferation & activity of T regs
- Increases T cell proliferation & reduce apoptosis.
- Increases IL-2, IFN-γ, TNF-α, Granzyme B & Perforin production.
- Abrogates Treg function
- Promotes T cell retention
- Increases CD4+ & CD8+ T cell proliferation
- Suppresses regulatory T cell activity
- Induces Th1 response
- Increases IL-2, IFN-γ, TNF-α production
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 microenvironment 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

TLR7/8 agonist promotes rapid activation of intratumoral myeloid lineages driving tumor antigen release/presentation and induction of immune stimulatory cytokines.

NKTR-262 promotes rapid activation of intratumoral myeloid lineages driving tumor antigen release/presentation and induction of immune stimulatory cytokines.

NKTR-214 promoted T cell clonal expansion takes place in tumor antigen enriched environment encountering reduced immunosuppression.

T cell production and maintenance are enhanced by NKTR-214.

Systemic tumor eradication is achieved through combination treatment, which 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

- **No Scaffold = No tumor retention**
- **PEG-Scaffold = Tumor retention**

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

Combination of TLR Agonist + NKTR-214

Promotes Immune Activation

Overcomes Immune Suppression

Vehicle
NKTR 214
TLR
Combo

% CD8 T Cells

% CD11c/CD8 Dendritic Cells

% Neutrophils

% Tregs

% Macrophages

% Monocytes
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