Enhanced cancer vaccine effectiveness with NKTR-214, a CD122 biased cytokine
Nektar Therapeutics

► Biopharmaceutical company leveraging polymer conjugation technologies to develop new therapies in multiple disease areas

► Strong heritage of partnership with top biopharma companies

► ~ 500 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**: PegIntron (Merck) for Hepatitis C
- **2002**: Neulasta (Amgen) for Neutropenia
- **2003**: Somavert (Pfizer) for Acromegaly
- **2004**: Macugen (Bausch + Lomb) for Wet macular degeneration
- **2007**: Mircera (Roche) for Chronic kidney disease anemia
- **2014**: Movantik (AstraZeneca) for Opioid induced constipation
- **2015**: Adynovate (Amgen) for Hemophilia A

- **Small molecule**
  - NKTR-181
  - NKTR-262
  - NKTR-214
  - NKTR-255
  - NKTR-358

- **Large Molecule**
  - Half-life Extension
  - Concentration in Diseased Tissue
  - Small Molecule Compartmental Distribution
  - Bias Receptor Activity
**Focus of Nektar Pipeline**

**Immuno-oncology**

- **Target the innate and adaptive immune system**
  
  - **NKTR-214** (Co-Develop and Co-Promote) - CD122-Biased Agonist
    - Multiple Solid Tumors
    - *In Phase 1/2 Trials*
  
  - **NKTR-262** (Wholly-Owned) - TLR 7/8 Agonist
    - Multiple Solid Tumors
    - *Phase 1 study opened for recruitment Q1 2018*
  
  - **NKTR-255** (Wholly-Owned) - IL-15 Receptor Agonist
    - *IND 2019*

**Immunology**

- **Harness the immune system to fight autoimmune disease**
  
  - **NKTR-358** (Co-Promote) - T Regulatory Cell Stimulator
    - Lupus
    - Crohn’s Disease
    - Rheumatoid Arthritis
    - Psoriasis
    - *In Phase 1 Studies:*
      - SAD ongoing
      - MAD in Lupus patients
        - Initiated April 2018

**Chronic Pain**

- **Potentially to help prevent the abuse and addiction**
  
  - **NKTR-181** (Wholly-Owned) - New Opioid Agonist Molecule
    - Pain relief without the high levels of euphoria that can lead to abuse and addiction with standard opioids
    - Chronic low back pain in opioid-naïve adult patients
    - *NDA Submitted Q2 2018*
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**
NKTR-214: Prodrug design to improve Risk/Benefit Profile

NKTR-214 is a prodrug that is inactive which generates biased IL-2 with increased potency

NKTR-214 increases the quality and quantity of the T cell response in tumor bearing mice

> 400-fold increased ratio of CD8 to Treg cells
NKTR-214 drives greater T cell expansion and clonality in a murine tumor model along with check point inhibitors

Langowski, J., et al., AACR 2016, ABS 558
Deepening of Responses Over Time

SITC 2017 (Data Cut: Nov 2, 2017)

26/36 (72%) Reduction in Target Lesions

ASCO 2018 (Data Cut: May 29, 2018)

30/37 (81%) Reduction in Target Lesions

* Best overall response is PD (SD for target lesions, PD per non-target lesions)
# Best overall response is SD (PR for target lesions, PD per new lesion at confirmatory scan)
+ Best overall response is PR (CR for target lesions, non-target lesions still present)

Data are shown for patients with post-baseline scans that included assessment of target lesions.
NKTR-214: A robust CD8 T cell activator that shows promising clinical activity

- NKTR-214 is a CD122 biased agonist that stimulates IL-2 receptor pathway
- NKTR-214 demonstrates single agent activity and shows synergistic activity with checkpoint inhibitors in tumor models
  - Enhances CD8 T cells and decreases T regs and provides a favorable immune milieu
  - Expands T cells and induces greater clonality when combined with anti-PD-1 demonstrating antigen specific expansion
- NKTR-214 in combination with nivolumab showed encouraging anti-tumor activity with notable ORR in PD-L1 negative patients
- Ongoing enrollment in PIVOT-02 continuing for additional tumor types in I-O naïve and refractory settings
Phases of Immune response that need attention during a cancer vaccine design

Conventional vaccine (prophylactic)
- Priming Phase
- Expansion Phase
- Effector Phase
- Memory Phase

Cancer Immuno-editing
- Elimination
- Equilibrium
- Escape

Cancer Vaccine (therapeutic)
- Priming Phase
- Expansion Phase
- Effector Phase

Sequelae of immune events
Cancer vaccine forms an integral part of the treatment protocol

Escape
Deploy **Checkpoint inhibitors** to prevent tumor cells from escaping immune system

Priming Phase
Stimulate patient's immune system against tumor antigens

Expansion Phase
NKTR-214 plays a critical role in this Phase

Effector Phase
Ellicit direct or indirect immune response leading to **tumor cell death**
Melanoma vaccine model to study NKTR-214

Murine model for cancer vaccine evaluation

- Pmel-1 T cells with TCR genes that target B16 melanoma antigen gp100
- Adoptive transfer of Pmel-1 T cells + peptide vaccination in B16F10 transplanted tumor model
- IL-2 seem to be essential for driving the Pmel-1 response against the B16F10 tumors
- NKTR-214 was evaluated in this model and compared with Aldesleukin (recombinant IL-2)
- Vaccine = gp100 peptide + anti-CD40 + TLR-7 agonist
- NKTR-214 demonstrated more effective efficacy than Aldesleukin to delay tumor growth

Collaboration with Meenu Sharma, Willem Overwijk, MD Anderson Cancer Center

Zalevsky, J. SMI cancer vaccine, 2017. oral presentation
NKTR-214 induced sustained expansion of Pmel-1 T cells and reduced T regs in the tumor milieu

Zalevsky, J. SMI cancer vaccine, 2017. oral presentation
Proof of concept study with Nouscom neo antigen vaccine and NKTR-214

Neoantigen from Nouscom

- Nouscom generated a CT26 tumor based vaccine GAd-CT26-20 encoding 20 top scoring neo antigens after Next Gen Sequencing of CT26 tumors
- Utilize CT26 mouse model which has high neoantigen load
- Demonstrates partial response to checkpoint inhibitors
- Single injection of GAd-CT26-20 vaccine induced T cells against 5 neo antigens in both CD4 and CD8 T cell compartment
- Assessment of NKTR-214 with GAd-CT26-20 vaccine conducted in the model
NKTR-214 dramatically improves efficacy of Nouscom GAd-CT26-20 vaccine

D’Alise, AM. Et al., Keystone PEV, 2018. Abstract Poster
Vaccine and NKTR-214 broadens the immune responses to non-immunogenic peptides

T cell response measured with pool of vaccine
- Pool 5 immunogenic peptide
- Pool 15 not immunogenic neo-epitopes

D’Alise, AM. Et al., Keystone PEV, 2018. Abstract Poster
Combination of GAd-CT26-20 vaccine with anti-PD-1 and NKTR-214 is curative in established tumor setting in mice

**Vaccine:**
- GAd day 0, 5x10^8 vp
- MVA 20ep scr, day 28 10^7 pfu

**NKTR-214:** d6, d14, d22, 36, 43, 46(iv)

**Results:**
- **Vaccine:**
  - 4/9 Responses (44%)
  - 2 CR, 2 PR
- **Vaccine + NKTR-214:**
  - 8/9 Responses (89%)
  - 4 CR, 4 PR
- **Vaccine + anti-PD-1 + NKTR-214:**
  - 6/6 Responses (100%)
  - 6 CR

**CR** = complete response
**PR** = partial response (>40% tumor shrinkage)

D’Alise, AM. et al., Keystone PEV, 2018. Abstract Poster
Summary and Conclusions

► NKTR-214 in combination with gp100 peptide vaccine enhanced anti-tumor efficacy and delayed tumor growth in a melanoma mouse model
  ▪ Addition of NKTR-214 drove enhanced Pmel-1 T cell expansion
  ▪ NKTR-214 decreased the T reg load in the tumor
  ▪ NKTR-214 performed substantially better than aldesleukin to stably maintain high effector/T reg ratio in the tumor

► NKTR-214 in combination with GAd-NOUS-20 neoantigen dramatically improved anti-tumor efficacy in a CT26 mouse model
  ▪ 93% CR compared to single agent (6% for Gad-NOUS-20 and 26% for NKTR-214)
  ▪ NKTR-214 potentiated CD4 and CD8 T cell responses to immunogenic and non immunogenic epitopes
  ▪ Triple combination of vaccine, anti-PD-1 and NKTR-214 cured established tumors

► Vaccibody announces clinical collaboration agreement with Nektar Therapeutics
  ▪ Evaluate VB10.NEO and NKTR-214 in patients with squamous cell carcinoma of H&N