TNFRSF25 Agonists for Immuno-Oncology

Non-Confidential Presentation
Introduction to Pelican

- **TNFRSF25** is a potential best-in-class T cell co-stimulator due to its preferential specificity to ‘memory’ CD8+ T cells that are most potent in tumor killing
- **PTX-35**, the lead compound, is a humanized TNFRSF25 agonist antibody with an IND filing expected in approximately 15 months
- Pre-clinical studies with the murine precursor to PTX-35 show advantages over competing T cell co-stimulator programs based on CD8+ T cell specificity
- Pelican is the only company with a disclosed program targeting TNFRSF25 for use in immuno-oncology (I/O) with a broad, pioneering intellectual property estate
- Pelican awarded a $15.2M grant from CPRIT (Cancer Prevention Research Institute of Texas) to develop PTX-35 through a comprehensive 70-patient first-in-man Phase 1a/b/c clinical trial
Importance of CD8+ T cells and T cell costimulation

• Both, reversal of immune suppression (checkpoint inhibitors) in the tumor microenvironment and boosting of the effector arm (costimulation of CD8+ T-cells) are important.

• T cell costimulators could complement checkpoint inhibitors as combination therapies are required to improve patient responses.

T cell costimulatory therapy, when combined with checkpoint inhibitors could significantly improve clinical responses for a broader range of patients that are currently non-responsive to checkpoint inhibitors.
TNFRSF25 as a Novel I/O Combination Target

- TNFRSF25 is the most recently discovered T cell costimulator, and is a rapidly emerging target

- Pelican is the only company developing TNFRSF25 agonist antibodies for I/O

“Although TNFRSF25 is chromosomally localized with 4-1BB, OX40, GITR and CD27, sequence analysis suggests that TNFRSF25 is relatively divergent or perhaps ancestral...Thus we might expect that therapeutics directed against this pathway will have unique activity.”

-Gordon Freeman et al

Summary of TNFRSF25 Functions

- **Costimulation**
- **Proliferation**
- **Transient inhibition** of suppression

**Shared with GITR & OX40**

**TNFRSF25 Specific**

**Shared with OX40**
Properties of TNFRSF25 as a Novel T Cell Costimulator

TNFRSF25 is a potent T cell co-stimulator with potential advantages over the competition

• TNFRSF25 agonism leads to antigen-experienced ‘memory’ T cells (both CD4+ and CD8+) that are instrumental in tumor eradication
• Contrasting with other T cell costimulators, TNFRSF25 agonism leads to a more pronounced ‘memory’ CD8+ cytotoxic T cell activation - the cells most crucial in tumor eradication
• TNFRSF25 signaling in T cells is dependent upon prior engagement of the T cell receptor (TCR), implying antigen specific T cell proliferation
• Pre-clinical studies with TNFRSF25 agonist mAb have demonstrated potent anti-tumor metrics:
  ➢ antigen driven T cell proliferation
  ➢ increased effector cytokine production
  ➢ Increased effector immune function
  ➢ Increased survival in a B16-F10 melanoma and CT26 colon carcinoma
Expression of T cell Costimulators

- Compared to other T cell costimulators, TNFRSF25 is preferentially expressed on CD8+ T cells

TNFRSF25 is preferentially expressed by human CD8+ T cells (red = high expression)

Genomics Institute of the Novartis Research Foundation
Su et al. PNAS 2004:101(16);6062-7
Preferential CD8+ T cell Induction

Pre-clinical Studies with murine agonist antibody shows preferential CD8+ T cell Induction; differentiation from other T cell costimulators

- The frequency of antigen-specific memory CD4+ or memory CD8+ T cells were examined following treatment of mice with a vaccine alone, or in combination with OX40 (OX86) or TNFRSF25 (4C12) antibodies

![Diagram showing TCR Vβ5 and TCR Va2 distribution with 4C12 and OX86](image)

- TNFRSF25 preferentially ‘boosts’ CD8+ T cell immunity, whereas OX40 is preferential to CD4+ T cells

4C12 = TNFRSF25 Agonist mAb
OX86 = OX40 Agonist mAb

Schreiber et al. J Immunol 2012;189(7);3311-8
Comparative Anti-Tumor Activity

TNFRSF25 agonism with murine agonist mAb shows increased survival compared to agonism of other costimulators

- Comparative activity of OX40, GITR, 4-1BB and TNFRSF25 agonist mAbs in a long-established (9-day) B16-F10 melanoma model

Schreiber T. et al. SITC 2014
Comparative CD8+ T cell Potency – TNFRSF25 Stand out
Major Highlights from Pre-clinical Studies

- mAb to TNFRSF25, drives the development of **antigen-specific CD8+ T cells** (this effect mimics TLIA, the natural monogamous ligand of TNFRSF25)

- mAb to TNFRSF25 results in costimulation and expansion of antigen-experienced memory T cells, both CD4+ and CD8+; notable is a significantly enhanced effect on **memory CD8+ T cells**, the cell type most potent in tumor eradication

- Costimulation occurs only in the context of **TCR recognition of antigen**

- TNFRSF25 appears to have **superior activity** in stimulating memory CD8+ cells relative to OX40, 4-1BB and GITR

- Agonism with TNFRSF25 mAb leads to increases in **effector cytokine** and **effector immune function**, and increases survival in mouse models

- In mouse melanoma models, TNFRSF25 mAb results in increased survival compared to agonism of OX40, GITR, 4-1BB with respective agonist mAbs
Completed and Ongoing Steps in PTX-35 Development

**IND Enabling Studies are Planned Under CPRIT Award**

- ✓ Lead Antibody Generation
- ✓ Humanization
- ✓ Sequence Analysis
- ✓ Functional Analysis
- ✓ Affinity Measurement
- ✓ Competition with TL1A for Binding
- ✓ Epitope Mapping
- ✓ Backup mAb Generation
- ✓ Affinity maturation
  - ➢ Biophysical Characterization
  - ➢ Cell Line Development
- • GMP Manufacturing
- • IND Enabling Tox Package

- ✓ Completed
- ➢ Ongoing
- • Planned
## CPRIT Funded Preliminary Phase 1 Design

### Accelerated Titration Cohort

**Phase Ia**
- Population: Confirmed solid tumor with ≥1 measurable lesion refractory to standard therapy
- Biomarker driven PD endpoint: Proliferation of antigen-specific CD8+ T cells in the peripheral blood 5 days post treatment
- **N = 1** patient per cohort
- Starting dose defined in NHP
- 100% dose increase per patient
- PD defined as above
- Proceed to Ib when a single DLT or 2 grade 2 events are observed

**Phase Ib**
- 3 + 3 Design
- Starting dose (MABEL) defined in Phase Ia
- 40% dose increase per group
- PD defined as above
- MTD determined by maximum dose at which <1 DLT occurs in the 6 patient cohort

### Expansion Cohort

**Phase Ic**
- Population: Confirmed solid tumor (no more than 3 tumor types) with ≥1 measurable lesion refractory to standard therapy OR in combination with I/O SOC (for example Opdivo or Keytruda)
- ~30 patients enrolled
- Therapeutic dose defined in Phase Ib
- PD defined as in Phase Ia and Phase Ib
- PK/PD interactions monitored for combination therapy
- Preliminary assessment of efficacy in refined tumor indication
Summary

• TNFRSF25 is a potential best-in-class T cell costimulator due to its preferential specificity to ‘memory’ CD8+ T cells that are most potent in tumor killing

• Pelican is the only company with a disclosed program targeting TNFRSF25 for use in immuno-oncology with a broad, pioneering intellectual property estate

• PTX-35, the lead compound, is a humanized TNFRSF25 agonist antibody with an IND filing expected in 18 months or so

• Pre-clinical studies completed with the murine precursor to PTX-35 show advantages over competing T cell costimulator programs based on CD8+ T cell specificity

• Pelican awarded a $15.2M grant from CPRIT (Cancer Prevention Research Institute of Texas) to develop PTX-35 through a comprehensive 70-patient first-in-man Phase 1 clinical trial
Thank you for your consideration.