Translational Pharmacology and First-in-Human Dose Projections for Cancer Immunotherapy Drugs: Case Study of MOXR0916 (Anti-OX40 Antibody)

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Outline

• First-in-Human dose selection approaches
• Cancer immunotherapy and OX40 biology
• *In vitro* and *in vivo* effects of MOXR0916
• MOXR0916 Pharmacokinetics and Target occupancy
• First-in-human dose projection strategy
• Summary
First-in-Human dose selection

NOAEL- No Observable Adverse Effect Level

- “the highest dose level that does not produce a significant increase in adverse effects in comparison to the control group” – FDA
- Can be based on clinical pathology markers, histopathology or other on/off target observations
- Human equivalent dose (HED) calculated using appropriate scaling factors
- A safety factor (>10 fold) applied

MABEL- Minimum anticipated biological effect level

- Calculating FIH dose from concentrations that is anticipated to produce minimal biological/pharmacological response
- Relevant pharmacological and biological information (mechanism of action, species-specific target binding affinity and target expression and distribution) are considered
- MABEL can be determined from in vitro or dose ranging in vivo studies
- Can utilize mechanistic PK/PD models to determine dose selection
First-in-Human dose selection: comparison of different approaches

- NOAEL- or HNSTD-based
  Defined from toxicity studies

- Effects
  - PAD-based
  - MABEL-based
  - MPAD

- Clinical Dose or Exposure
  - Therapeutic Range
  - Toxicity
Cancer-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 tumors (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)

Immuno-suppression

αCTLA4
αVEGF
aPD-1/PD-L1
aCTLA4-ADCC

Chen & Mellman (2013) Immunity
OX40 Function: Promote Antigen Dependent Effector T cell Activation and Treg Cell Inhibition

OX40: positive regulator targeting two steps in the cancer immunity cycle

Costimulates T cell response to antigen (CD4>CD8)

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4. Trafficking of T cells to tumors (CTLs)
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6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (Immune and cancer cells)

Inhibit / reduce Tregs

αOX40

Chen & Mellman (2013) Immunity
MOXR0916 is a humanized IgG1 monoclonal antibody drug candidate that targets OX40, and currently is being tested in a Phase I clinical trial.

MOXR0916 functions as an agonist antibody, which results in activation rather than blockade, of the OX40 signaling pathway upon receptor binding.

MOXR0916 is hypothesized to promote antitumor immunity through 2 distinct mechanisms: activation and proliferation of Teff and inhibition of Treg function.

- In preclinical models, anti-OX40 treatment also results in reduction of Treg cells.

- In vitro, the co-stimulatory effects of MOXR0916 were abrogated when the antibody was engineered to prevent Fc receptor binding.
MOXR0916 enhances Teff cell activation and proliferation, and suppresses Treg activity in *in vitro* T cell cultures.
In vivo studies with anti-mouse OX40 (PRO307205)

- All *in vivo* efficacy studies were performed with an anti-muOX40 murine IgG2a surrogate molecule PRO307205 as MOXR0916 does not cross-react with murine OX40.

- MOXR0916 has approximately 8-fold higher affinity for human OX40 than PRO307205 for murine OX40.

- Dose ranging studies with single and multiple doses were performed in multiple tumor models to assess:
  - Efficacy
  - PD biomarker response in tumor and periphery

- EMT6 (syngeneic orthotopic breast cancer model) is the workhorse *in vivo* mouse tumor model.
Anti-mouse OX40, PRO307205, demonstrates a spectrum of activity including durable responses

~200 mm³ tumors, treated 10 mg/kg, 2x/week for 3 weeks
*In vivo* efficacy studies of PRO307205 treatment in EMT6 model show trend of dose response

Tumor growth kinetics in individual animals from one representative efficacy study

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Survival analysis

% Survival

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% of complete response

Mean±SD calculated based on 5 dose ranging efficacy studies
PRO307205 induces dose dependent MOA associated PD modulation in blood and tumors

All data shown from EMT6, similar trend in PD modulation observed in multiple tumor models
Mouse PK summary for MOXR0916 and PRO307205

- Linear, dose proportional PK for MOXR0916 in non-tumor bearing scid mouse
- Clearance of PRO307205 was found to be faster compared to MOXR0916
MOXR0916 cynomolgus monkey PK/PD

- MOXR0916 binds human and cyno OX40 with equivalent affinity
- PK is as expected for typical IgG1 and dose proportional
  - Projected human CL = 2.5 ml/d/kg, $t_{1/2} \sim 3$ wk
- ATAs detected in all animals in the 0.5 mg/kg and 5 mg/kg (but not 30 mg/kg) dose groups, with loss of exposure and receptor occupancy
- No significant activation or proliferation of peripheral T cells
- No significant reduction in absolute peripheral T cell counts
Cyno tox study (NOAEL) and in vitro cytokine release assay
- OX40 is transiently expressed only on activated T cells
- Healthy cynos/unstimulated PBMCs will have negligible activated T cells (lack of relevant antigens)

In vitro studies of T cell proliferation and cytokine production (MABEL)
- Artificially sensitive because pre-stimulation with anti-CD3 required to upregulate OX40

Receptor occupancy (MABEL)
- Relationship between peripheral RO and efficacy/toxicity not established because of variability in mouse studies and lack of antigen stimulation in cynos

Anti-OX40 in mouse tumor model provides the only measurement of pharmacological activity in vivo (MPAD)
- PD effects were observed in mouse tumor model at doses ≥ 0.1 mg/kg
- 0.1 mg/kg projects to a human starting dose of 0.002 mg/kg (~200 mcg flat dose)
  - Scaling of PK: adjust for 6 fold difference in clearance
  - Adjust for 8.2 fold difference in potency
Summary

• MOXR0916 is a humanized agonist anti-OX40 monoclonal antibody in development for the treatment of solid tumors.

• Both *in vitro* and *in vivo* studies support the dual mechanism of action (MOA) that differentiates MOXR0916 from and complements the MOAs of other immunotherapies.

• MOXR0916 demonstrated typical pharmacokinetics for an IgG1 in mouse and cynomolgus monkeys, with a typical half-life and dose-proportional exposure.

• Quantitative data from pharmacology, PK and PD were used for predicting relevant activity and doses of MOXR0916 for testing in clinical trials.