INBRX-106: a novel hexavalent anti-OX40 agonist for the treatment of solid tumors

September 30, 2021
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Four differentiated clinical programs

**INBRX-101**
AAT-Fc fusion protein
- Potential for first meaningful advancement for patients in 35 years
- Estimated ~$2B+ market size
- Initial Phase 1 data late this year
- Registration study could start in late 2022

**INBRX-109**
Tetravalent DR5 agonist
- Single agent activity in chondrosarcoma and mesothelioma
- Potential rapid path to approval in chondrosarcoma, registration study initiated
- First combination cohorts: mesothelioma, pancreatic adenocarcinoma and Ewing sarcoma with data in H1 2022

**INBRX-106**
Hexavalent OX40 agonist
- Potential across numerous tumors, including cold tumors
- Strong mechanistic rationale for PD-1 combination
- Key data readouts in combination expansion cohorts in 2H 2022

**INBRX-105**
PD-L1 x 4-1BB tetravalent conditional agonist
- Potential across all PD-L1 expressing tumors
- 4-1BB agonism is clinically validated
- Strong mechanistic rationale for PD-1 combination
- Key data readouts in combination expansion cohorts in 2H 2022
Overview

1. Background
2. Non-clinical data
3. Clinical biomarker data
4. Conclusions
OX40 (CD134) Overview

- OX40 is a member of the TNF receptor superfamily
- Expressed on memory and regulatory T cells and is inducibly upregulated on activated T cells
- Ligation of OX40 costimulates effector T cell activity
- Expression significantly increased in tumor microenvironment

[Link: https://www.creative-diagnostics.com/ox40-ox40l-signaling-pathway.htm]
**OX40 agonism**

- Ligands are cell surface trimers
- Trimerization is usually the minimal activation cluster
- Agonism of OX40 drives NF-κB signaling
- Higher order clusters mediate stronger and more potent activation of NF-κB
- Bivalent Abs are poor OX40 agonists
INBRX-106 is a best-in-class OX40 agonist

INBRX-106 incorporates all known attributes for optimal OX40 agonism
- Increased valency and effector enabled Fc domain have both been empirically shown to promote activity
- Lack of ligand blocking activity may provide APC activation and natural cellular crosstalk

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### INBRX-106: Therapeutic Concept

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| Achieve robust NF-κB signaling | • Optimize valency to promote target clustering  
• 6 OX40 binding domains per molecule |
| Enable FcR-dependent clustering | • Utilize a wild-type Fc format |
| Retain natural crosstalk | • Do not block ligand |

*Diagram showing the structure of OX40: sdAb with Fc and 129kDa*
Valency drives OX40 agonism in *in vitro* assays

- Suboptimal CD3 stimulation can be enhanced through OX40 agonism
- INBRX-106 outperformed bivalent OX40 agonist
OX40 agonism exhibits a bell-shaped dose response relationship

- The highest optimally active dose corresponds to full receptor occupancy in both species
- Excess soluble drug leads to less than hexameric receptor engagement
OX40 engagement causes downmodulation of OX40 on primary T cells *in vitro.*

**Mouse OX40 downmodulation**

![Mouse OX40 downmodulation graph](image)

**Human OX40 downmodulation**

![Human OX40 downmodulation graph](image)
Multivalent OX40 exhibits a bell shaped dose response curve and causes rapid loss of cell surface receptor

- An INBRX-106-like molecule achieves robust activity at low doses in mouse tumor models
- OX40 loss happens very fast and is a PD biomarker of target engagement
Criteria for Single Agent RP2D Selection

1. Robust OX40 downregulation at end of infusion, as a measure of productive target engagement

2. Pharmacokinetic profile that allows for periodic agonism of OX40

3. Demonstration of peripheral pharmacodynamics (memory CD4$^+$ T cell activation and proliferation)

4. Demonstration of clinical benefit (patient enrollment-dependent)

RP2D is anticipated to be quite low based on potency, desired periodic agonism and early signs of activity
Phase 1 INBRX-106 single-agent study overview

PART 1: Dose escalation
INBRX-106 single-agent
Locally advanced or metastatic solid tumors

3+3 design
Q3W dosing interval

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PART 2: Dose expansion
INBRX 106 single-agent
At selected RP2D

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Criteria for RP2D Selection:

1. Robust OX40 downregulation at end of infusion, as a measure of productive target engagement

• Doses between 0.001 and 3.0 mg/kg induce target downmodulation at EOI
Criteria for RP2D Selection:

2. Pharmacokinetic profile that allows for periodic agonism of OX40

- Doses between 0.001 and 0.1 mg/kg allow for repeated target engagement on a Q3W schedule
Criteria for RP2D Selection:

3. Demonstration of peripheral pharmacodynamics (memory CD4⁺ T cell activation and proliferation)

• Doses between 0.1 and 1.0 mg/kg induce greatest proliferation of a CD4 memory T cell population
Criteria for RP2D Selection:

3. Demonstration of peripheral pharmacodynamics (memory CD4\(^+\) T cell activation and proliferation)

• Doses between 0.01 and 1.0 mg/kg induce most robust peripheral memory T-cell activation
Criteria for Single Agent RP2D Selection

1. Robust OX40 downregulation at end of infusion, as a measure of productive target engagement

2. Pharmacokinetic profile that allows for periodic agonism of OX40

3. Demonstration of peripheral pharmacodynamics (memory CD4⁺ T cell activation and proliferation)

4. Demonstration of clinical benefit (patient enrollment-dependent)

0.0003  0.001  0.003  0.01  0.03  0.1  0.3  1.0  3.0
Conclusions

• Hexavalent engagement of OX40:
  - Provides superior co-stimulation to T cells
  - Enhances T-cell functionality; additional benefit of combination with PD1 blockade

• OX40 biology presents unique challenges for selecting the appropriate clinical dosing strategy
  - Rapid target downmodulation
  - Bell-shaped dose response relationship

• Integration of preclinical and clinical biomarker and bioanalytical data sets to understand optimal dose and schedule of INBRX-106
Our patients mean everything

We would like to express our appreciation for the patients who have previously participated or are currently enrolled in our clinical trials. We recognize the valuable time and effort you have committed to our research efforts, the contributions of which are essential to our success in finding new and effective treatments against cancer and rare diseases. Your contributions will help others as a result of the knowledge gained from your participation.

THANK YOU