The Selective Elimination of Tumor Tregs by a Bispecific SNIPER Antibody Delivers a Strong Anti-Tumor Activity

Bryan Glaser, PhD
April 27, 2021
Biologics Europe: Online
Invenra’s Guiding Strategy in Oncology

• “For decades, new treatments for advanced cancer were considered successful if they could slow the cancer’s growth and extend survival a few months. For all children with cancer, and for most adults with cancer, we should aim for more than a few months. Our goal must remain eliminating all cancer in these patients and preventing cancer from ever coming back.”

Paul Sondel MD, PhD
Pediatric Oncologist and Immunotherapy Researcher
University of Wisconsin Carbone Cancer Center
We Believe All Three of These Lines Should be Pursued To Cure Late-Stage Metastatic Disease
### Two Preclinical Oncology Programs

- **Program**: INV721
  - **Line of Attack**: Immunogenic Cell Death
  - **Progress**: Discovery → Lead Selection → Preclinical
  - **Phase 1**: Not yet

- **Program**: INV321
  - **Line of Attack**: Eliminate Suppressive Tregs
  - **Progress**: Discovery → Lead Selection → Preclinical
  - **Phase 1**: Not yet

- **Pipeline assets are focused on the three lines of attack**

- **Asset qualities**:
  - Large standalone value
  - Synergy with each other
  - Can be building blocks for other Invenra Technologies
INV321
A Tumor Selective Treg SNIPER
The Need for Targeted Treg Depletion

• Tumors can have a suppressive tumor microenvironment (TME) that limit Current IO therapies

• Monoclonal antibody challenges:
  • High affinity non-specific binding, toxicity
  • Depletion of other needed immune cells
  • Target-specific biology can change depending on cell type

• Depletion of tumor Tregs with bispecifics can:
  • Reduce suppressive TME and rebalance the immune response
  • Avoid global Treg depletion to prevent autoimmune disease
  • Improve the efficacy of IO therapies
INV321: A SNIPER™ Bispecific with Best-in-Class Potential

• Typical monoclonal antibody approaches use high affinity binding to target Tregs
  • Target expression is typically higher on Tregs than other immune cell populations
  • Target-specific biology (ligand blocking, agonism, etc.) could enhance efficacy

• Treg targets are often not exclusively found on one immune cell type

• Our SNIPER approach has comprehensively analyzed current Treg depletion targets
  • Screened primary cancer patient samples vis flow cytometry to identify promising double-positive target pairs
  • Comprehensively defined two targets of interest and confirmed biology in murine and human systems
  • Produced and tested 100s of B-Bodies™ to identify combinations of binding arms that achieve desired selectivity for tumor Tregs

• Have advanced INV321 through *in vitro* and *in vivo* testing against these 2 targets
The Invenra SNIPER™ Approach to Enhancing Specificity

- Bispecifics designed with weak monovalent affinity to each target, but strong avidity to the combination
- Maximizes specificity and efficacy
- Minimizes binding to non-target cells significantly reducing possible side effects/toxicity
- Can better direct ADCC, ADC, radionuclides, or T-cells to targeted cells while avoiding healthy cells

**BENEFITS**
- On-disease specificity
- Multiple MOAs
- Increased therapeutic window

**LIABILITIES**
- Limited MOA
- On-target efficacy, but off-target toxicities
A Single Dose of INV321 Eliminated Most Tumors

- Strong avidity requires presence of Target 1 AND Target 2
- Target 1 and Target 2 ligands blocked only during avid binding
INV321: CT26 Rechallenge

INV321 Stimulates a Strong Immune Response and Immune Memory
INV321: Treg Depletion in CT26 Efficacy Models

INV321 in CT26 Murine Model

2 mg/kg (single dose, IV)

Tumor ~ 100 mm³ at dosing

INV321 Specifically Depletes Tregs in the Tumor and not the Blood
Comparing INV321 to Anti-CTLA-4 in a RENCA Tumor Model

INV321 is more Potent than 9D9 in a RENCA Tumor Model

INV321 has Similar Efficacy to CTLA-4 Therapies

D0 – RENCA i.d.
D9 – Abs i.v. (mg/kg)
INV321 (Hu IgG1)
9D9 (mu IgG2b)
Randomized ~ 40 mm³
Tumor Immunophenotyping: Day 12 Post Dosing

SNIPER™ Increases the Ratio of CD8/Treg in the Tumor

Note: No significant changes observed in the periphery

Tregs: FoxP3$^{+}$CD127$^{lo}$ & Effectors: CD44$^{hi}$CD62L$^{lo}$

INV321 Specifically Eliminates Tumor Tregs and Increase Effector T-cells
INV321: Promising Proof-of-Concept Established

- Multiple MOAs
  - Enhanced ADCC (antibody-dependent cell-mediated cytotoxicity)
  - Specific disruption of two target-ligand interactions
  - May alter surface expression of targets through induced degradation

- Significant market opportunities in broad oncology indications
  - Primary focus on SCLC; secondary on non-small cell lung cancer, melanoma and head & neck cancers
  - Single agent activity
  - Suitable for combinations
    - PD-1/PD-L1
    - T cell-redirecting bispecifics
    - CAR-T therapeutics
Invenra’s Path to the Clinic

**Pipeline**

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**Indications**

- Phase Ib: Combination with RT in relapsed SCLC

**Additional Indications:** NSCLC, Melanoma, Head and Neck

**Combinations:** Anti-PD1/PD-L1, Car-T, T-cell redirecting bispecifics
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