A Bispecific SNIPER™ Demonstrates Preclinical Efficacy through the Selective Elimination of Tumor Tregs

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9th World Bispecific
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Outline

- Introduction to Invenra and the SNIPER™ technology
- Using SNIPER™ to target Tregs in the tumor
- *In vivo* validation and Immune profiling

About Invenra

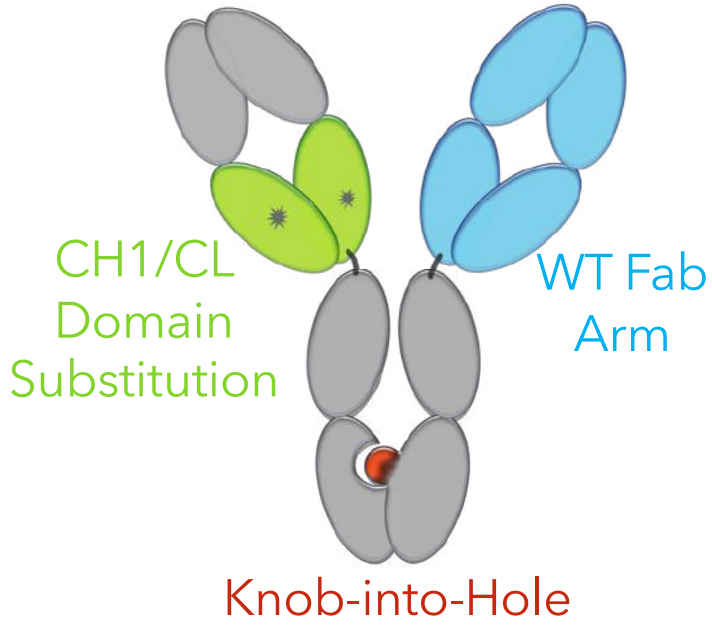
Broad capabilities in fully human monoclonal antibody, VHH and bispecific antibody discovery

Novel approaches for engaging the immune system and modulating the tumor microenvironment using our B-Body™ bispecific platform

Exploiting the platform to generate first-in-class therapeutics for our internal pipeline and strategic partners

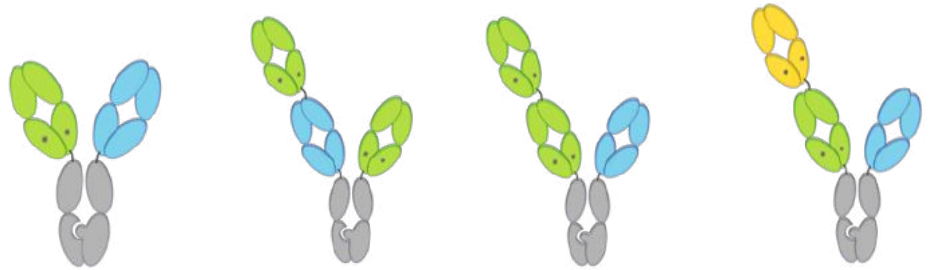
B-Body™ Platform Design

Plug-N-Play Variable Domains



Light chain mispairing is not detected – allows for efficient HT screening

Invenra's B-Body™ Family



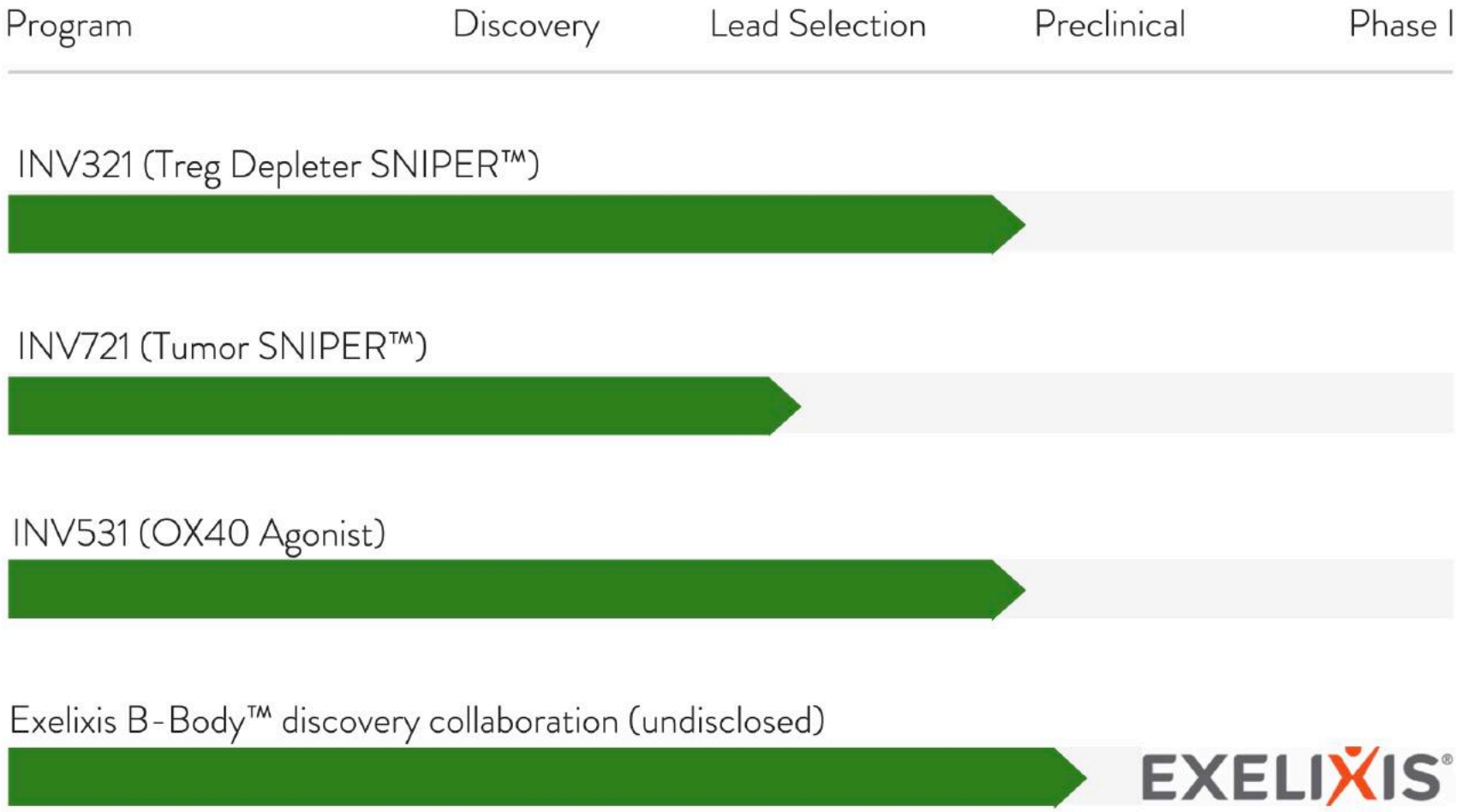
Bispecific 1x1 B-Body™

Bispecific 2x1 B-Body™

Trispecific 2x1 B-Body™

- Binding Specificity #1
- Binding Specificity #2
- Binding Specificity #3

Invenra's Internal Pipeline



Invenra has a differentiated asset pipeline

Antibody Specificity – A Double-Edged Sword

Antibodies have exquisite binding specificity for the drug target

- Selective binding can be achieved for a single amino acid or post translational changes
- A significant advantage over small molecule drugs

Unfortunately, the drug target is not always specifically expressed in the location of the disease

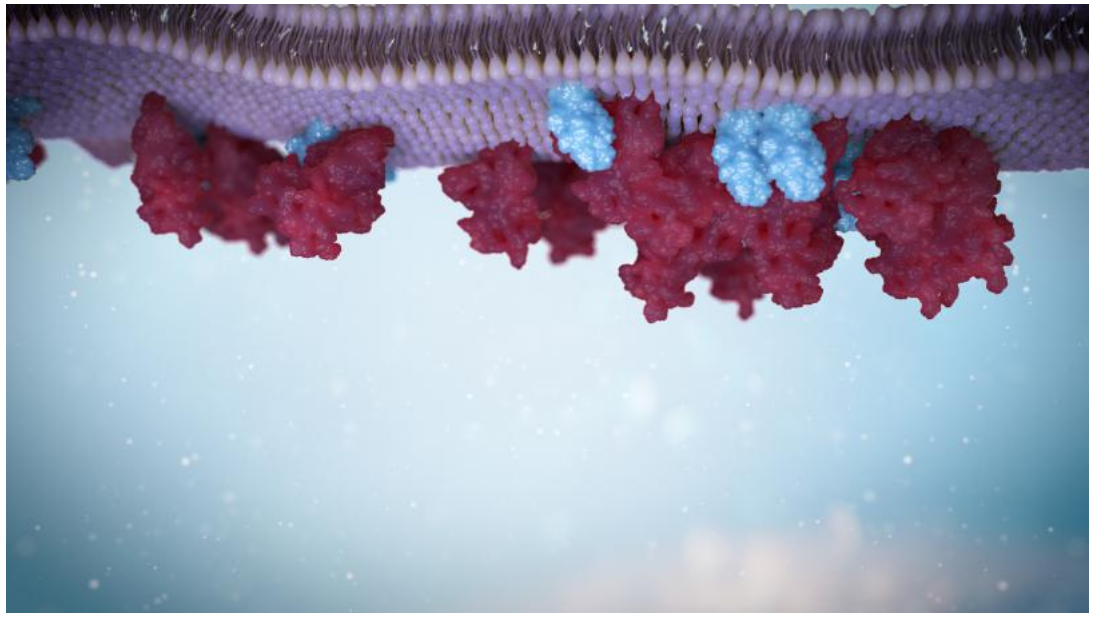
- Expression of the drug target in healthy tissue can result in toxicity or loss of efficacy
- Unwanted drug target expression can limit the potential therapeutic uses

SNIPER™ bispecific antibodies can maintain highly specific binding while limiting that binding to the desired location

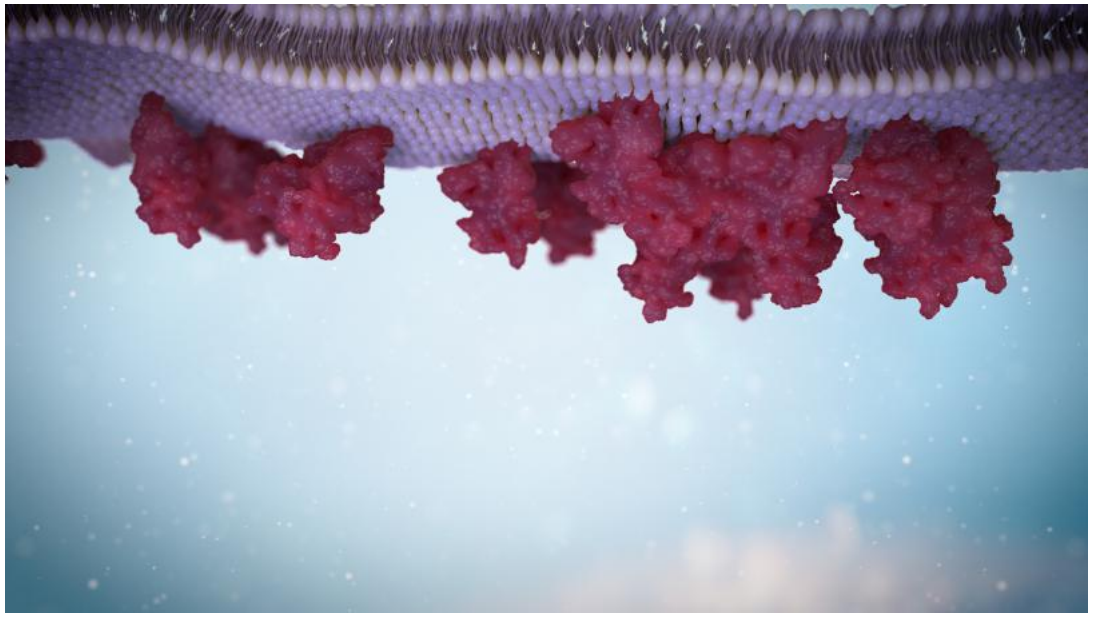
Highly Specific Antibodies Cannot Overcome Nonspecific Target Expression

Invenra's SNIPER™ Approach

Target Cell



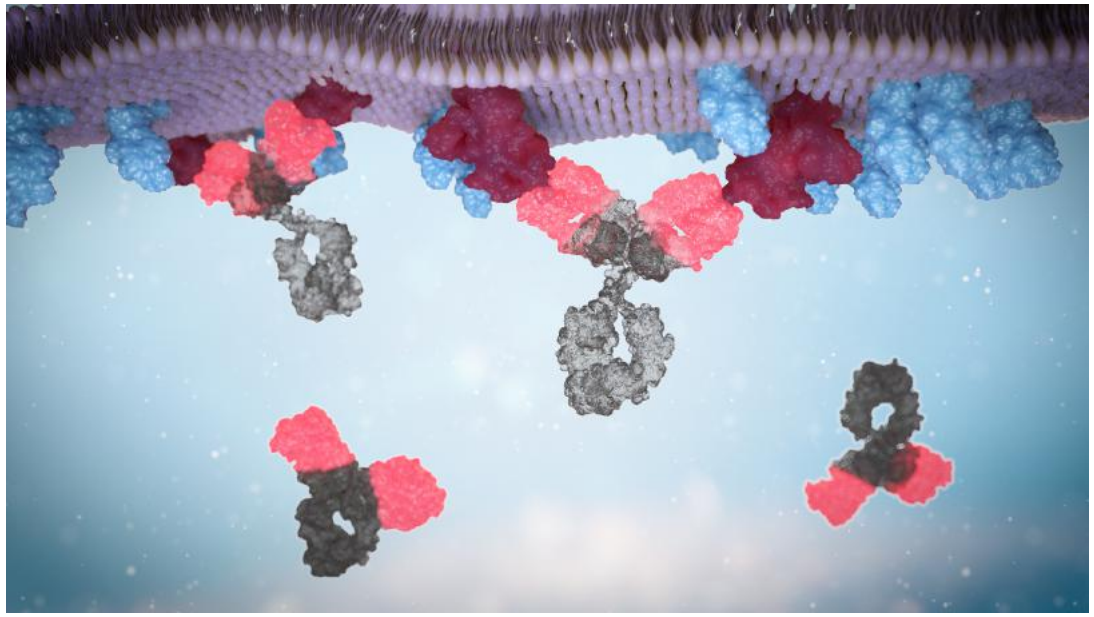
Non-Target Cell



Antibody therapies typically bind to targets found on multiple cell types (tumor *and* healthy).
The target expression profile directly contributes to efficacy and toxicity.

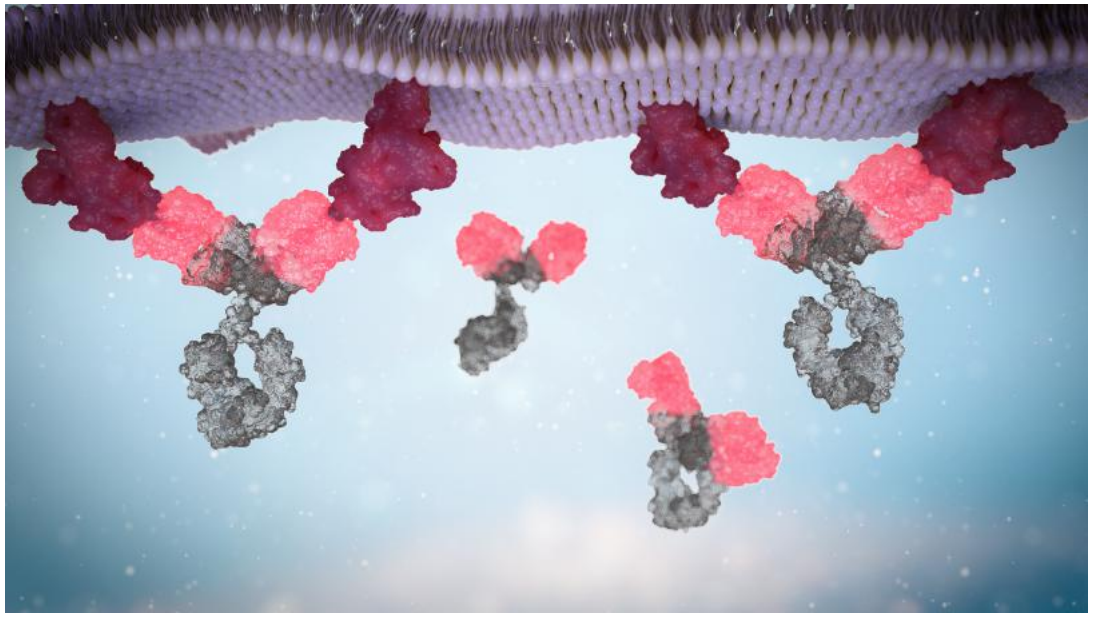
Monoclonal Antibodies bind both cells

Target Cell



Monoclonal antibodies can bind with high affinity to target cells to drive the desired biology (tumor reduction, immune activation, etc)

Non-Target Cell

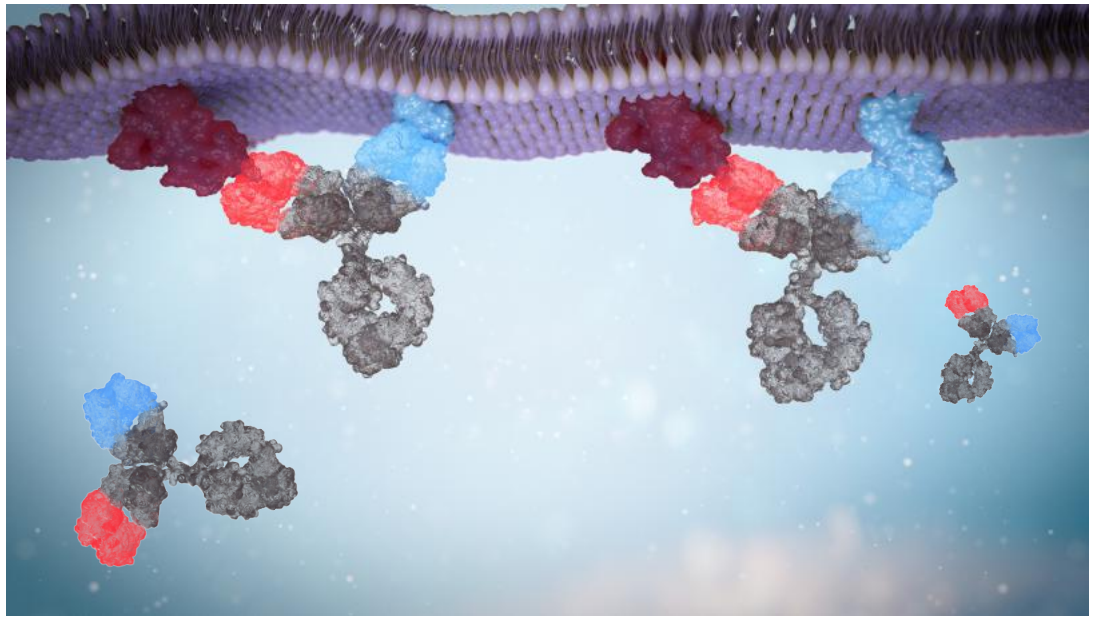


Monoclonal antibodies can bind with high affinity to non-target cells and cause unintended toxicities

Monoclonal Antibodies Can't Distinguish Target vs Healthy Cell Expression

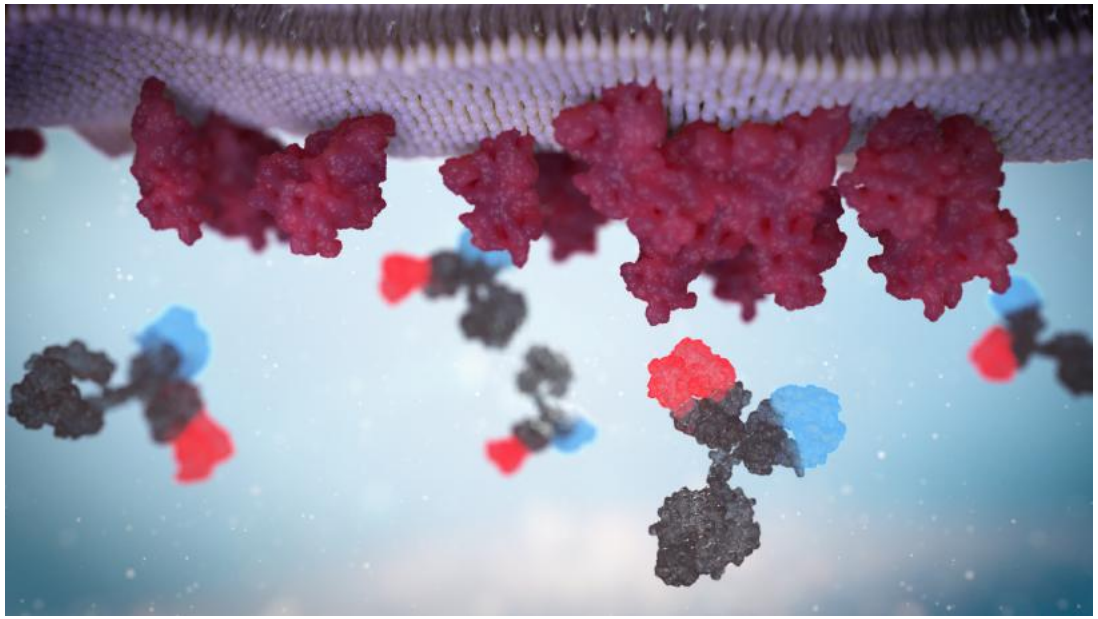
Invenra's SNIPER™ binds only tumor

Target Cell



Invenra's SNIPERs™ are designed such that binding to two targets with low monovalent affinity, but high avidity is required for specificity and efficacy

Non-Target Cell

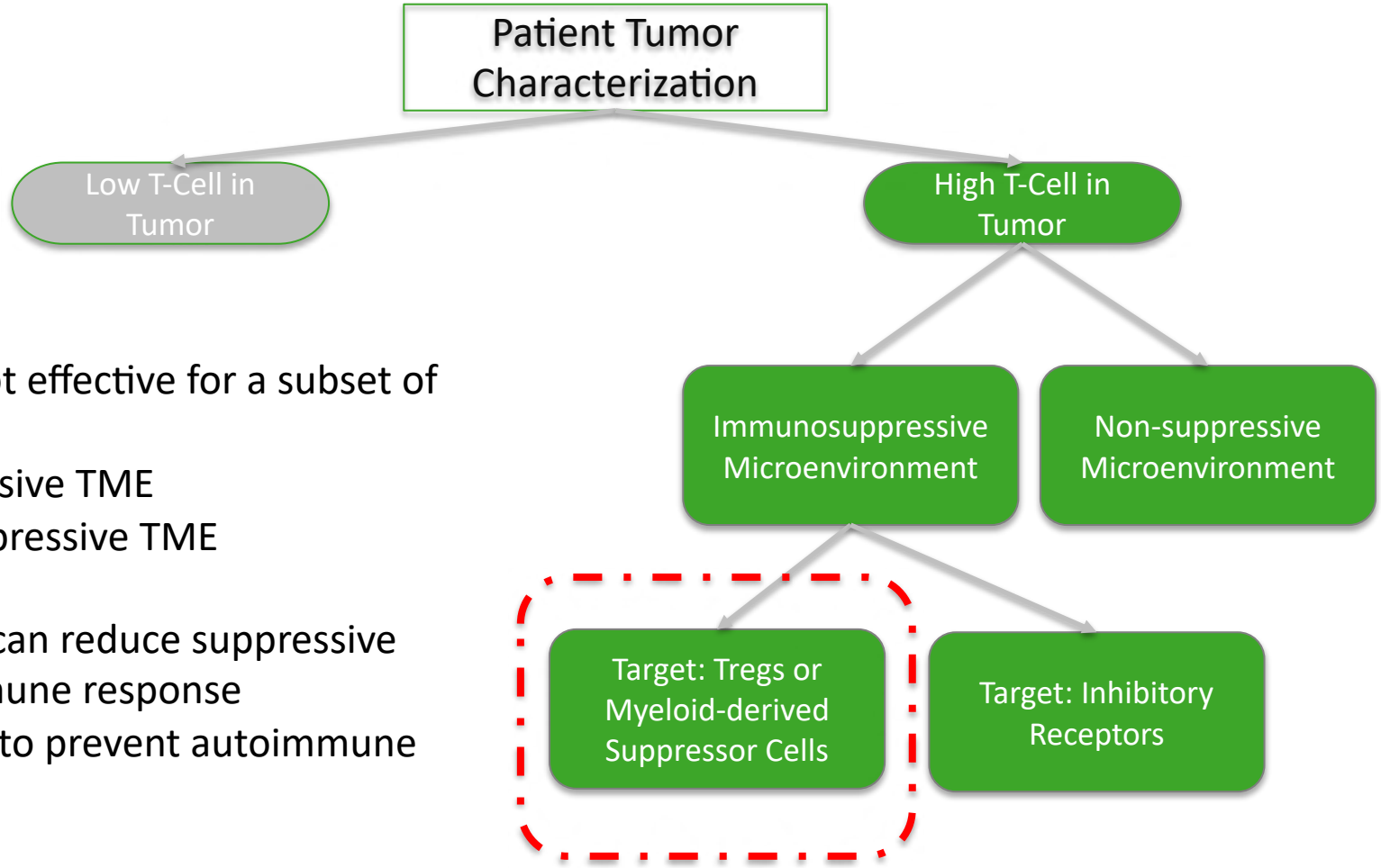


Invenra's SNIPERs™ minimize binding to non-target cells and significantly reduce unwanted toxicity.

The SNIPER™ Approach Can Delivery Better Tissue Specificity

INV321: Tumor Specific Treg Depleter

The Need for Treg Depletion



- Current I-O therapies are not effective for a subset of patients
  - Tumors have a suppressive TME
  - Therapy induces a suppressive TME

- Elimination of Tumor Tregs can reduce suppressive TME and rebalance the immune response
- Avoid global Treg depletion to prevent autoimmune disease

Treg Depletion in the Tumor may Improve I-O Therapies

The Challenge for Treg Depletion using Monoclonal Antibodies

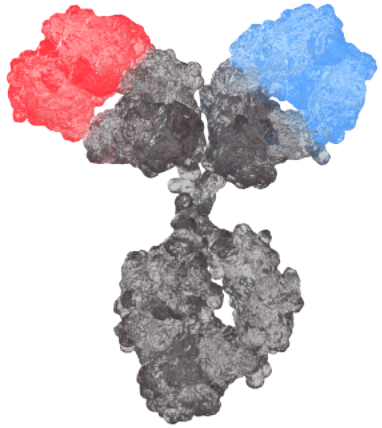
- Typical monoclonal antibody approaches use high affinity binding to target Tregs
  - Target expression is usually higher on Tregs than on other immune cell populations
  - Target-specific biology (ligand blocking, agonism, etc) could enhance efficacy
- What are the challenges with monoclonal approaches?
  - Risk depletion of other immune cells needed for activity/safety because target is not exclusively found on Tumor Tregs
  - Target-specific biology may change depending on cell-type (reduce efficacy or increase toxicity)

Exploring the Clinical Performance of Potential Treg Depleters

Common Treg Targets	Clinical Efficacy	Effect on Peripheral Immune Cells	Clinical Toxicity
CTLA-4	Yes	No Depletion	Autoimmunity
CCR4	TBD	Depletion of Peripheral Tregs	Severe Skin Tox
OX40	No	TBD	No
GITR	No	No Depletion	No
CD25	TBD	Depletion of Peripheral Tregs	Immune Disorders
CCR8	TBD	TBD	TBD

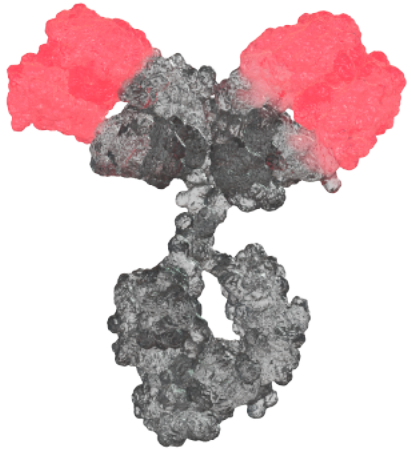
Benefits of the SNIPER™ Approach

SNIPER™ Approach



Specificity | Treg Depletion | Target Specific MOA | Efficacy | Low Tox

Monoclonal Approach



Specificity | Treg Depletion | Target Specific MOA | Efficacy | Low Tox

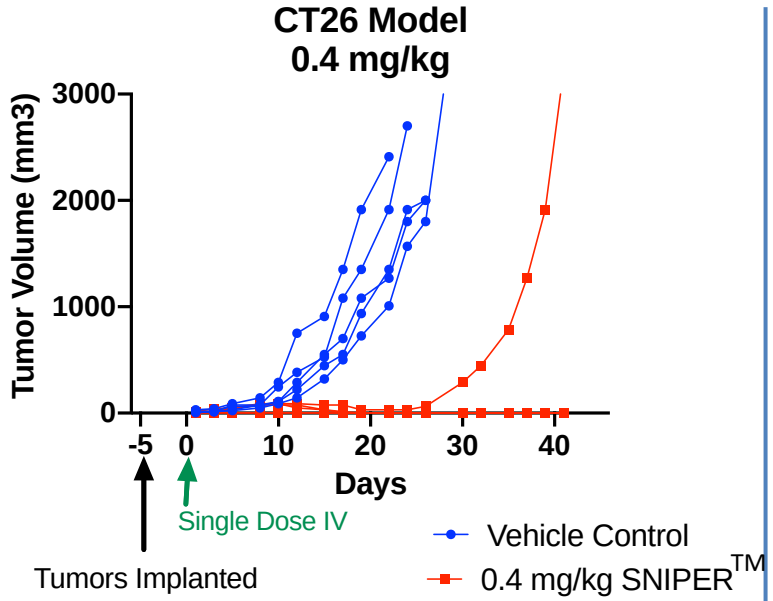
The SNIPER™ Approach can Increase Efficacy and Reduce Toxicity Risk

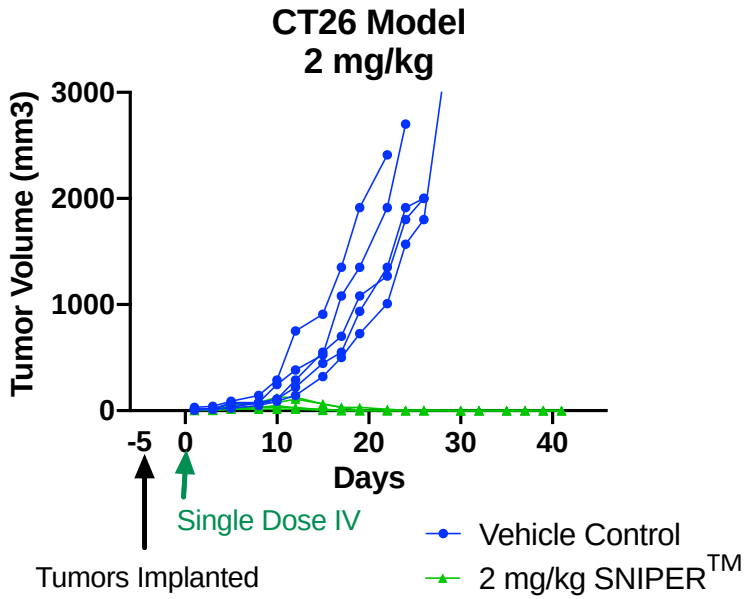
SNIPER™ Design Strategy

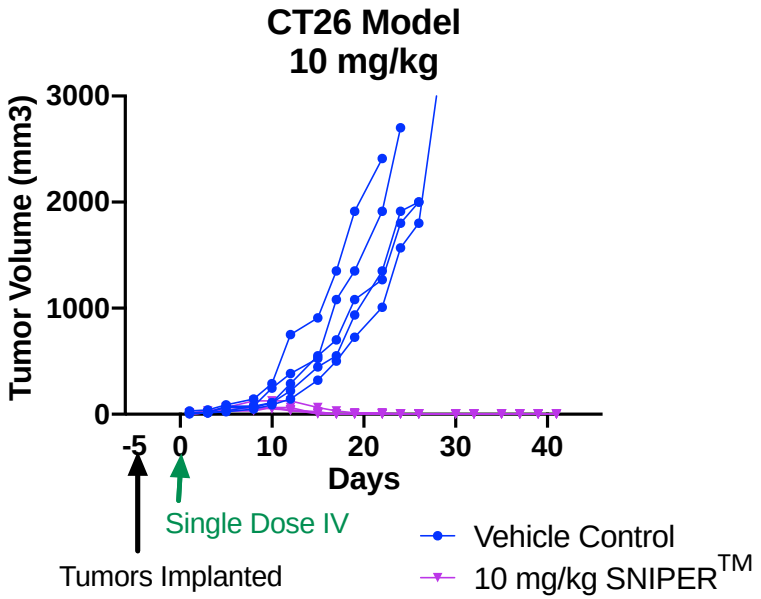
- A surrogate SNIPER™ was designed for proof-of-concept studies in murine tumor models
  - Weak monovalent affinity to two targets overexpressed on Tregs in the TME
  - Strong avidity requires presence of Target 1 **AND** Target 2
  - Target 1 and 2 ligands blocked only during avid binding

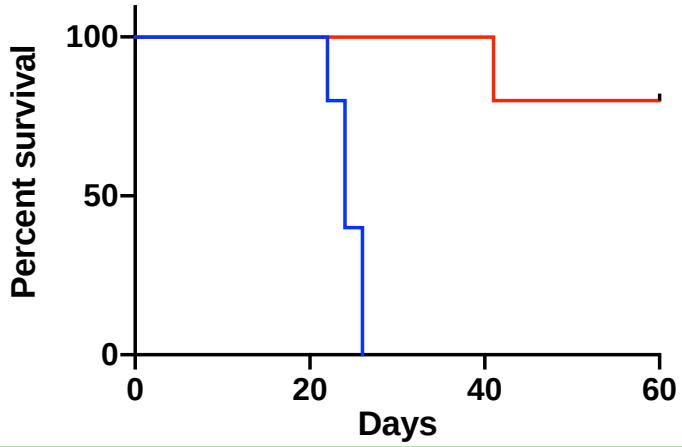
- Mouse surrogate used to guide design of human lead program (currently in cell line development)

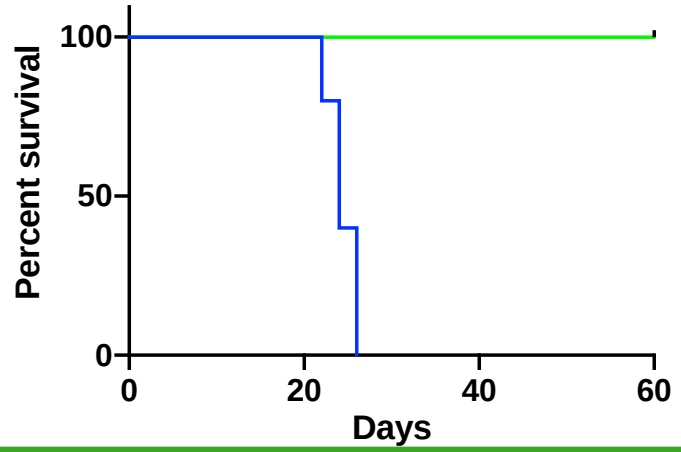
Single Dose of Invenra SNIPER™ Cures 14/15 mice in CT26 Syngeneic Model

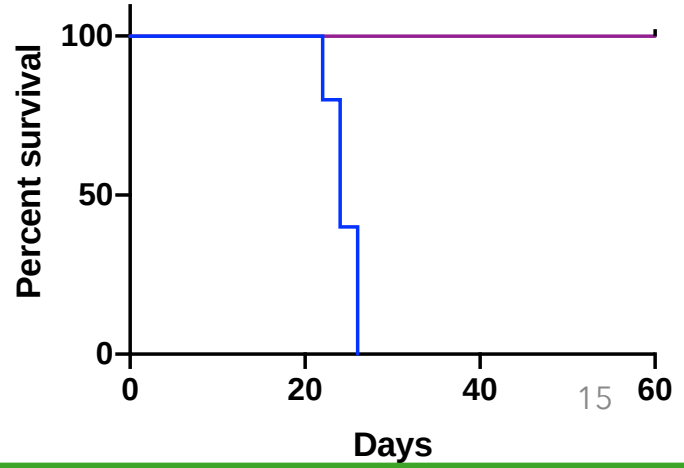






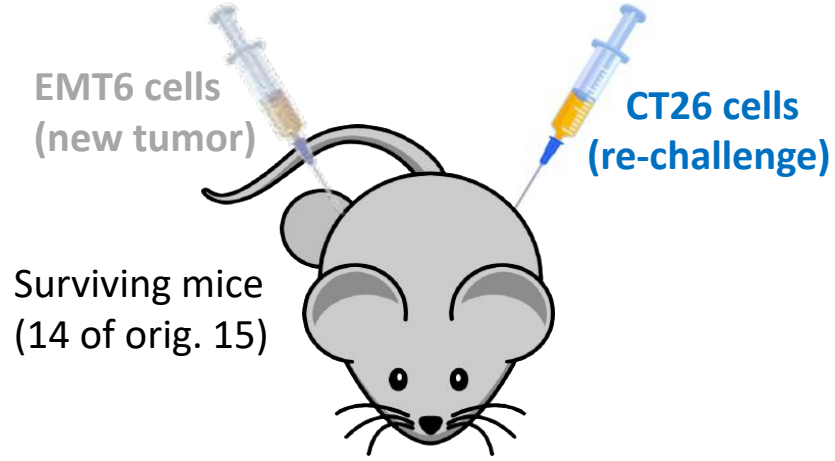


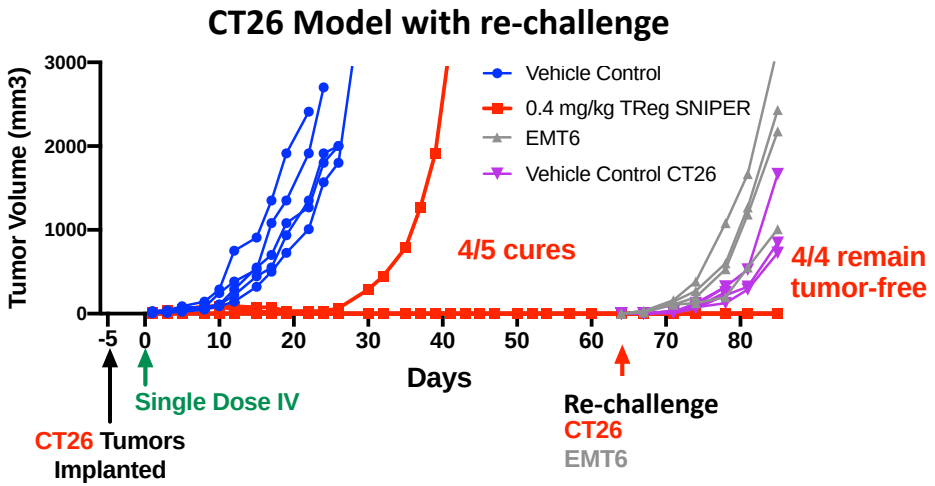


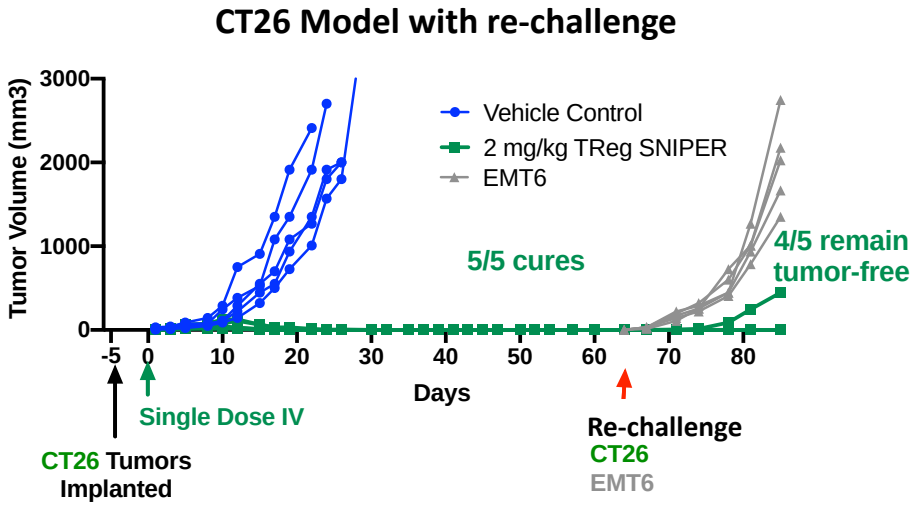


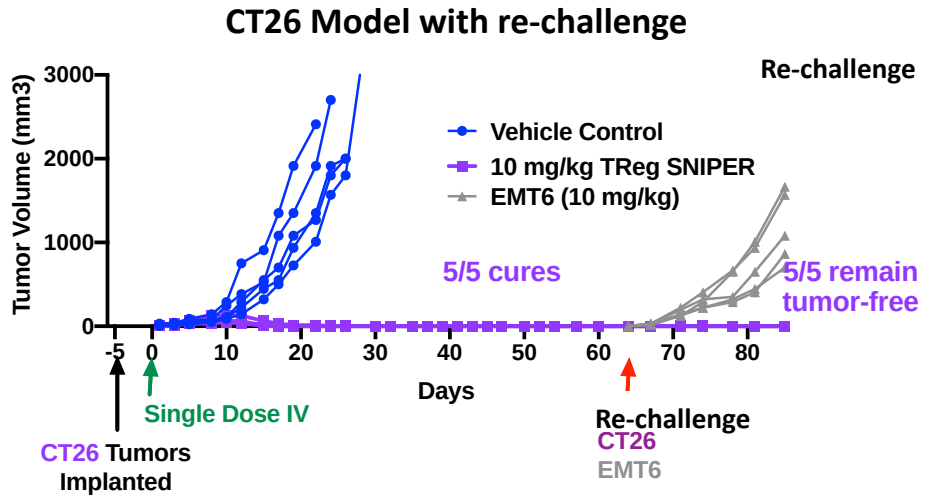
Effective at low dose without repeat dosing

13/14 mice rejected re-challenge



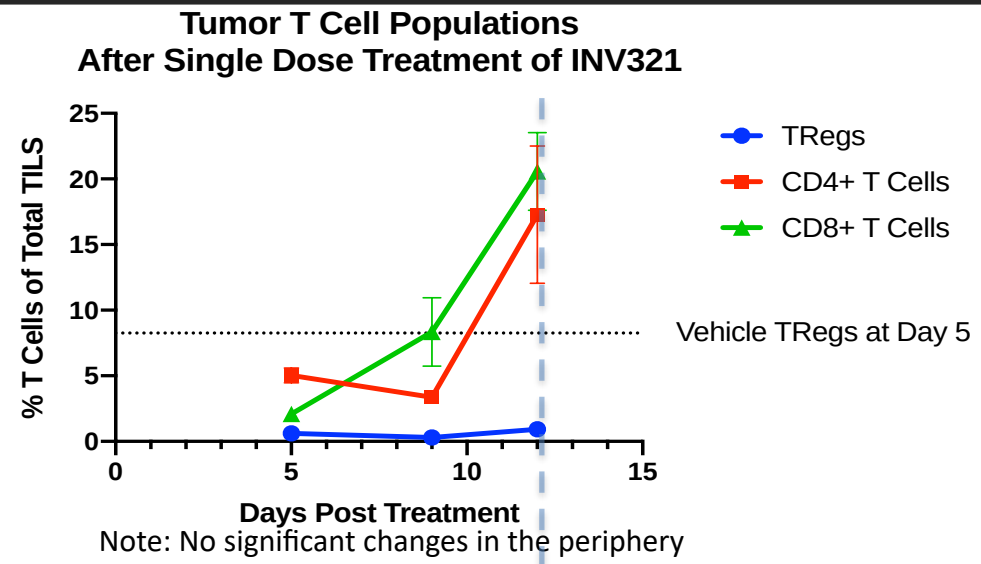




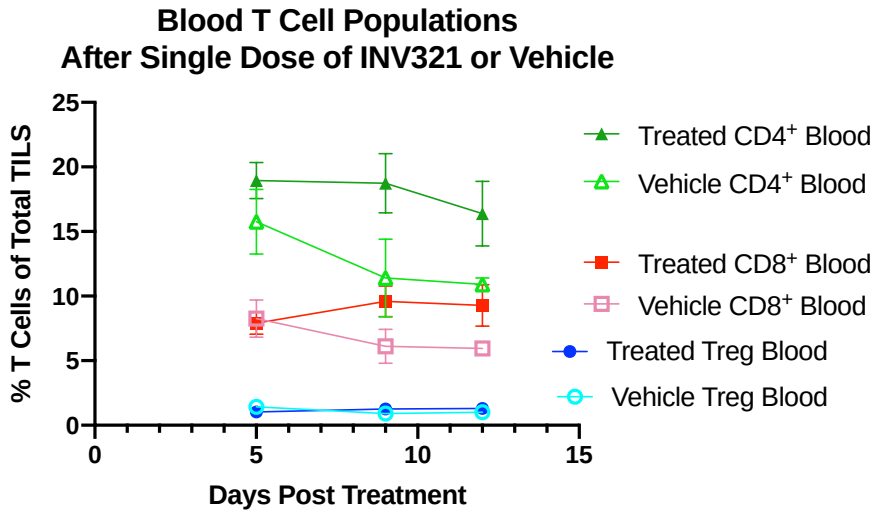


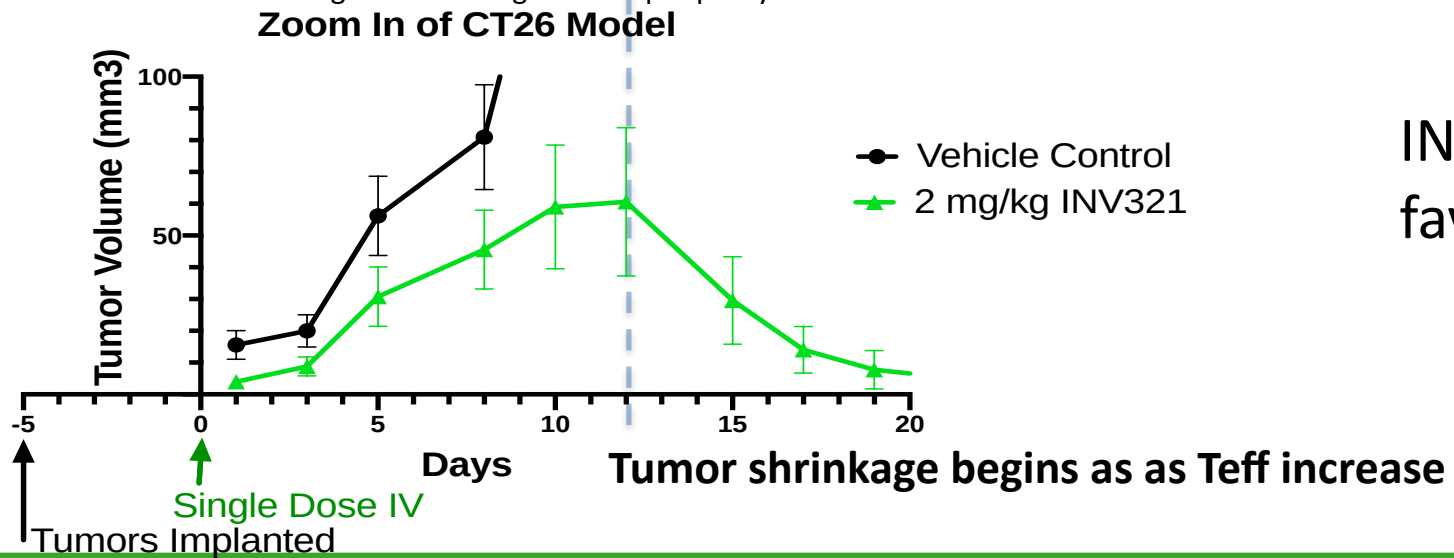
Immune Memory is Stimulated

Remodeling the TME Reduces Tumor Growth



Note: No significant changes in the periphery





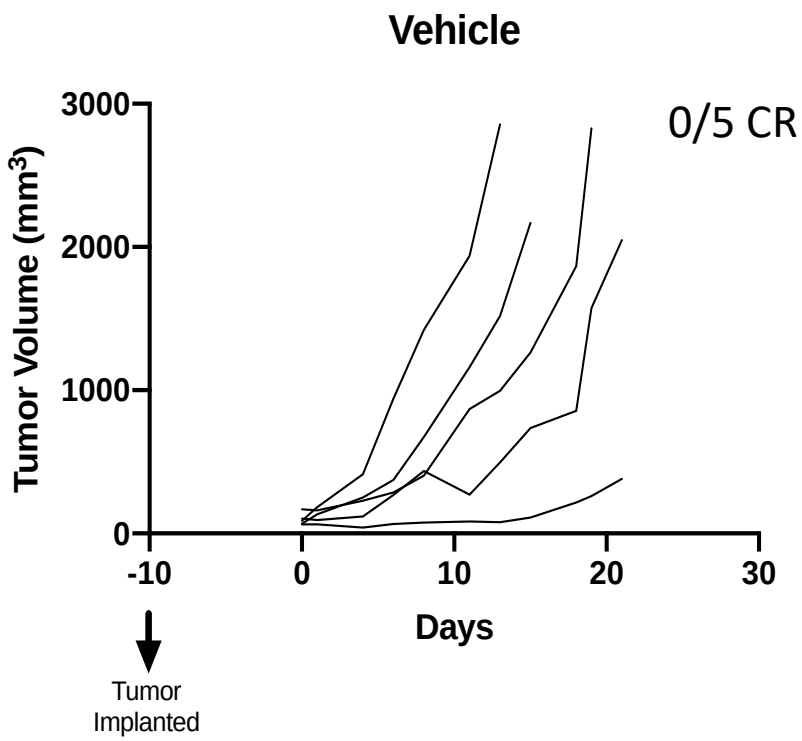
Tumor shrinkage begins as as Teff increase

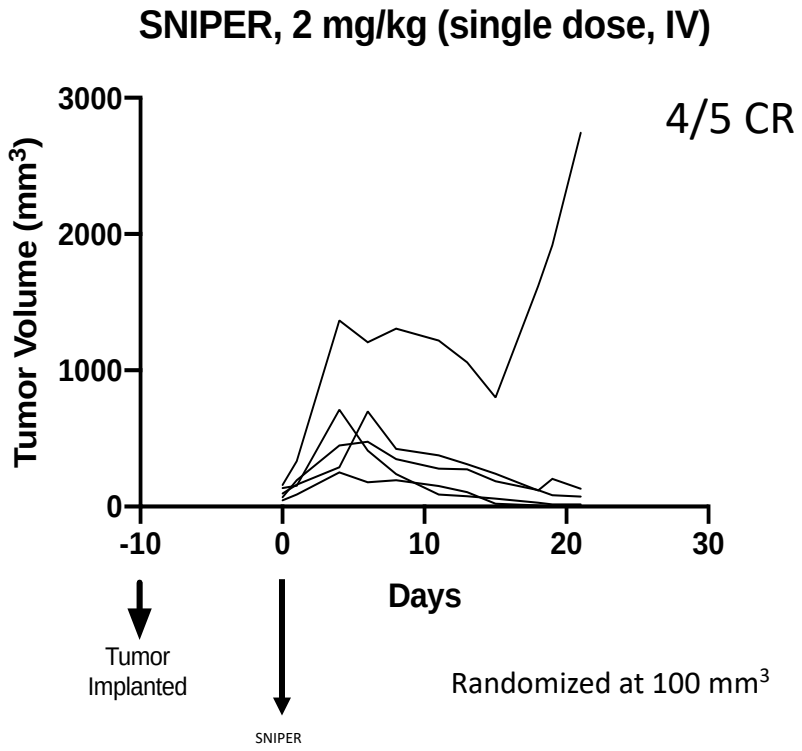
INV321 can remodel the TME to be favorable for T-cells and T-cell Therapies

- Potential for combination with T-cell redirecting bispecifics
- Potential for combination with Immune cell therapies

Single Dose of INV321 Reduces Tumor Tregs and Enhances T-cells

INV321 Efficacy in CT26 Tumors > 100 mm^3





INV321 Has Efficacy in Tumors Greater than 100 mm^3

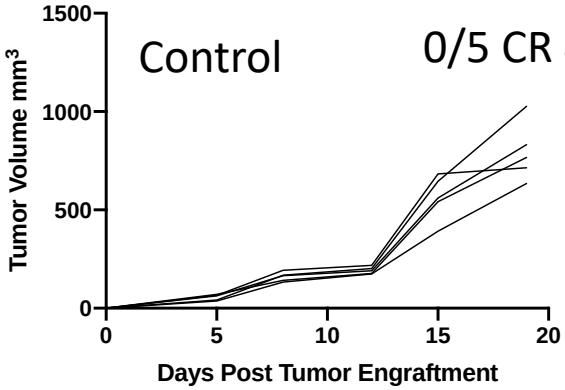
Comparison of Treg Depleting Antibodies

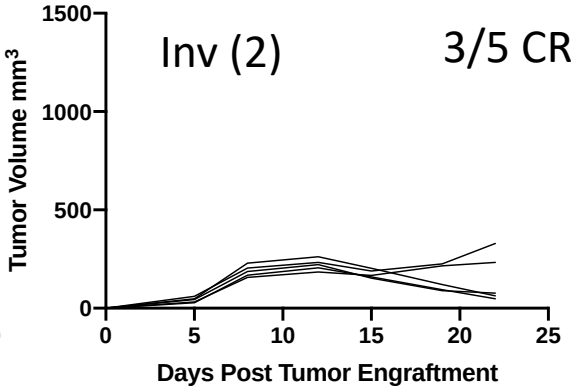
Goal: Compare the activity of putative Treg depleting antibodies in head-to-head comparisons with the INV321 surrogate.

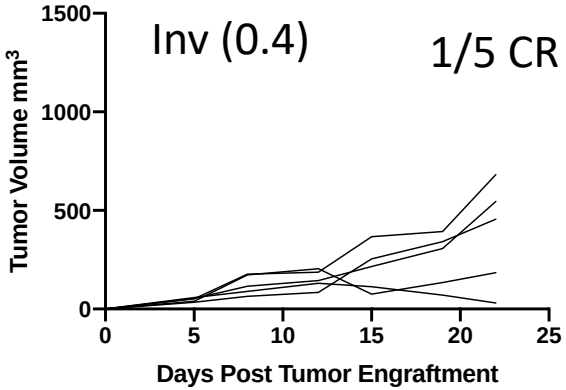
- Preliminary experiments compared SNIPER™ (huIgG$_1$) to Anti-CTLA4 (muIgG2b)
- Final comparisons will strive to compare all formats in muIgG$_{2a}$ to maximize depletion potential
  - Examine anti-tumor effect and immune profiling
  - Studies will not capture toxicity

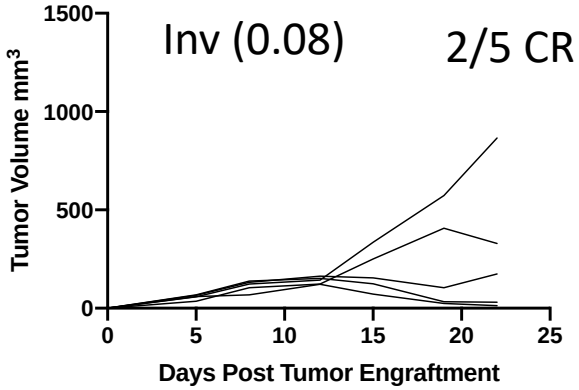
Comparison Study	Status
CTLA-4	Ongoing
CCR4	In Planning
OX40	In Planning
GITR	In Planning
CD25	In Planning
CCR8	In Planning

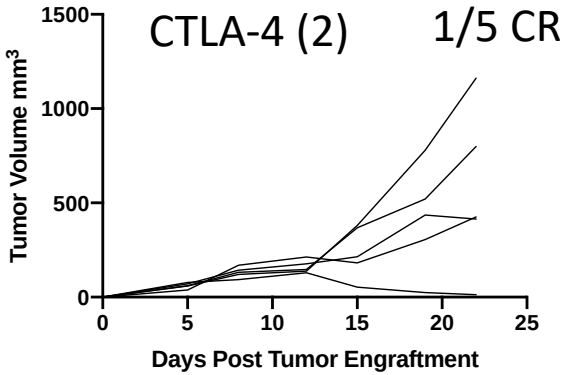
Comparing INV321 to Anti-CTLA-4 in a CT26 Tumor Model

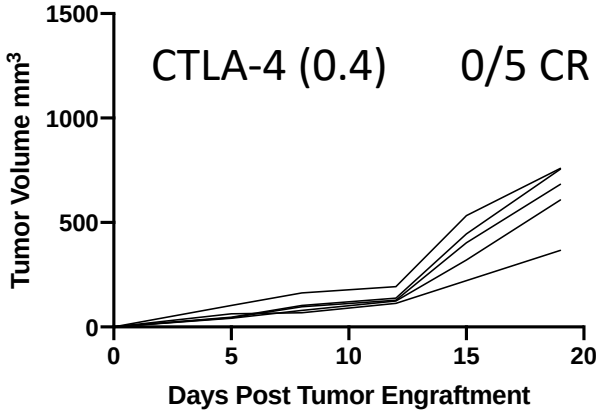


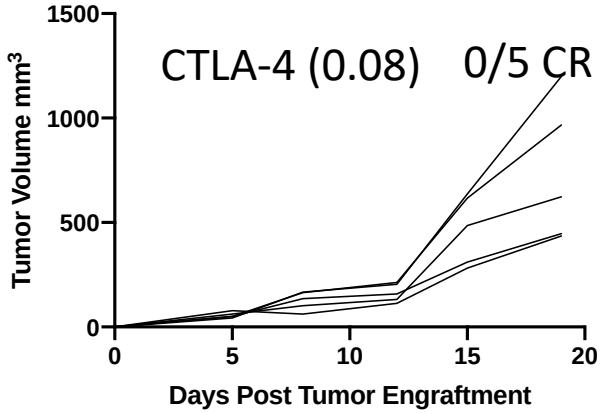












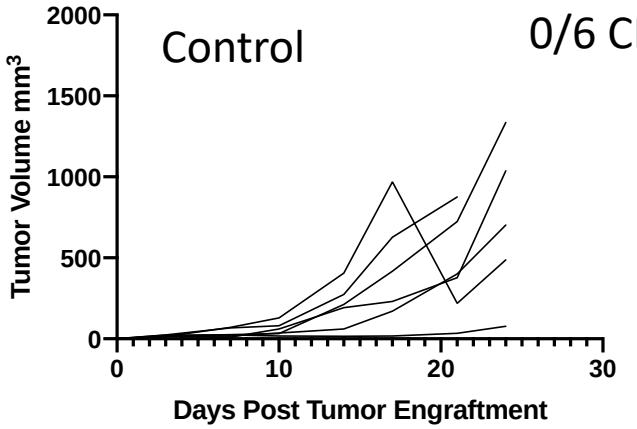
d. 0 - CT26 i.d.
d. 5 - Abs (mg/kg)

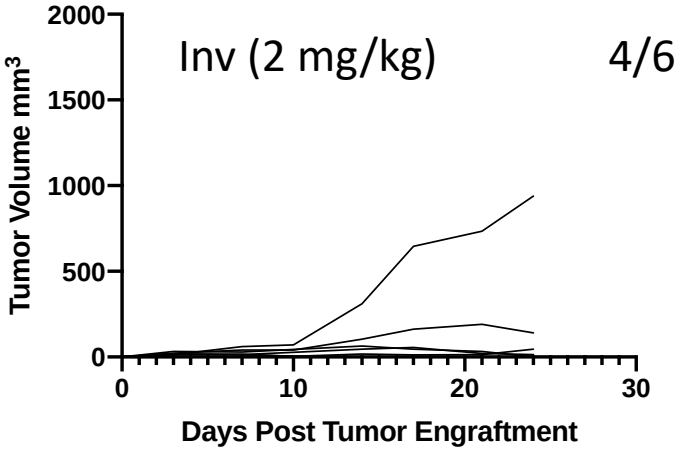
INV321 (Hu IgG_1)
9D9 (mu IgG_{2b})

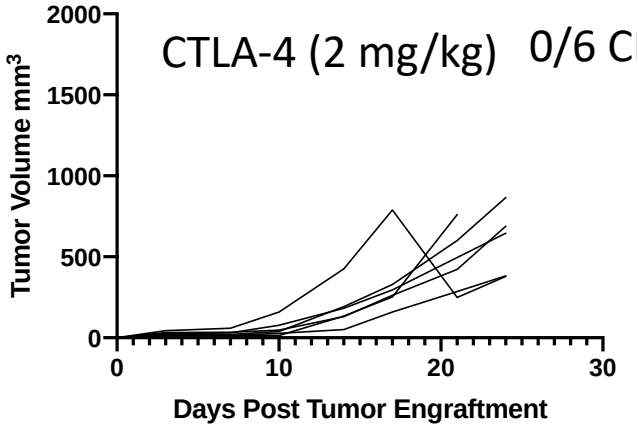
Randomized ~ 40 mm^3

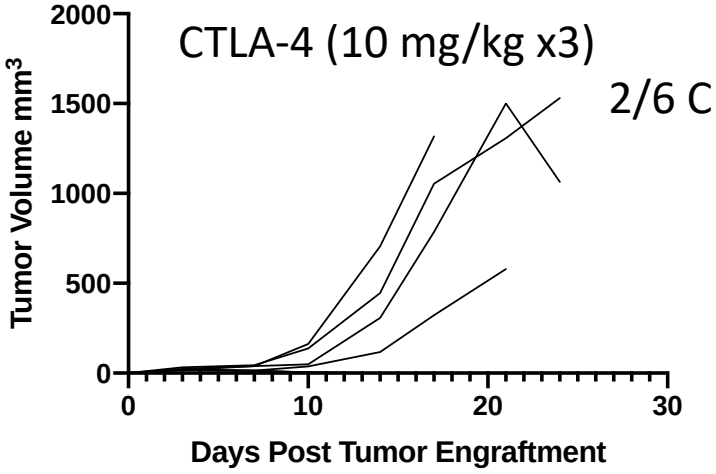
INV321 is more Potent than 9D9 in a CT26 Tumor Model

Comparing INV321 to Anti-CTLA-4 in a RENCA Tumor Model









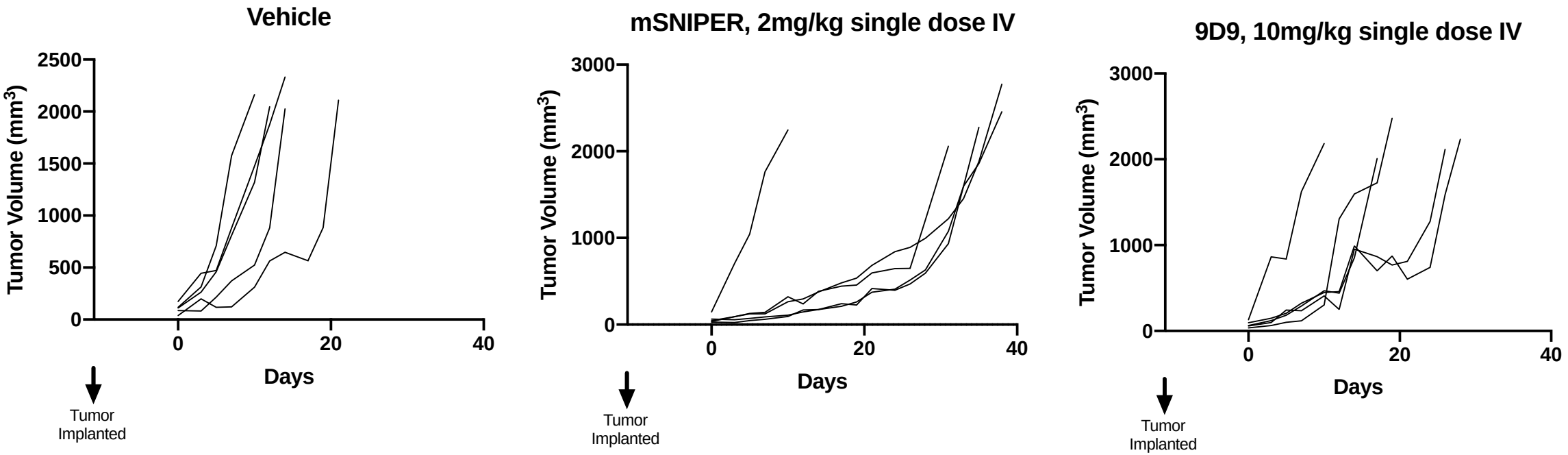
D0 – RENCA i.d.
D9 – Abs i.v. (mg/kg)

INV321 (Hu IgG_1)
9D9 (mu IgG_{2b})

Randomized ~ 40 mm^3

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

RENCA Large Tumor Model: SNIPER™ vs 9D9



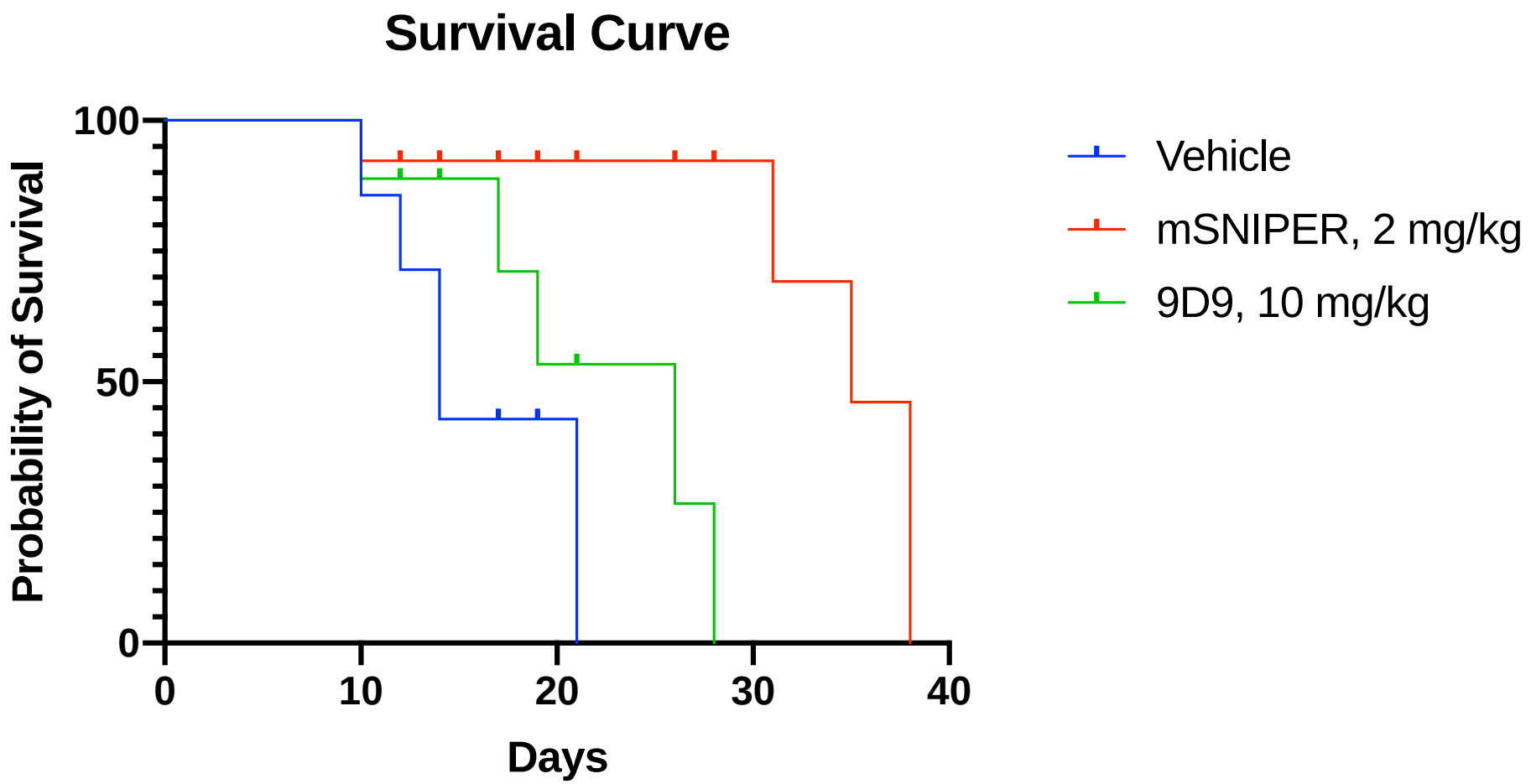
INV321 (Hu IgG_1)
9D9 (mu IgG_{2b})

Mice were randomized and dosed IV 10 days after implantation (Tumors ~ 75 mm^3)

n=6

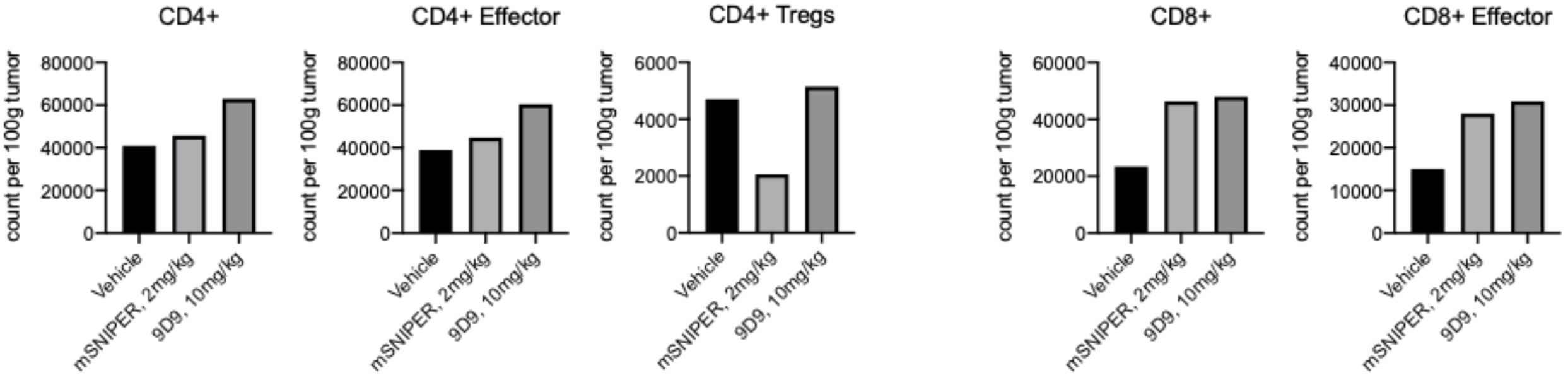
Large Tumors had Increased Resistance to Single Agent Therapy

RENCA Large Tumor Model: SNIPER™ vs 9D9



SNIPER™ Increased Survival Time Compared to 9D9

Tumor Immunophenotyping: Day 7 Post Dosing

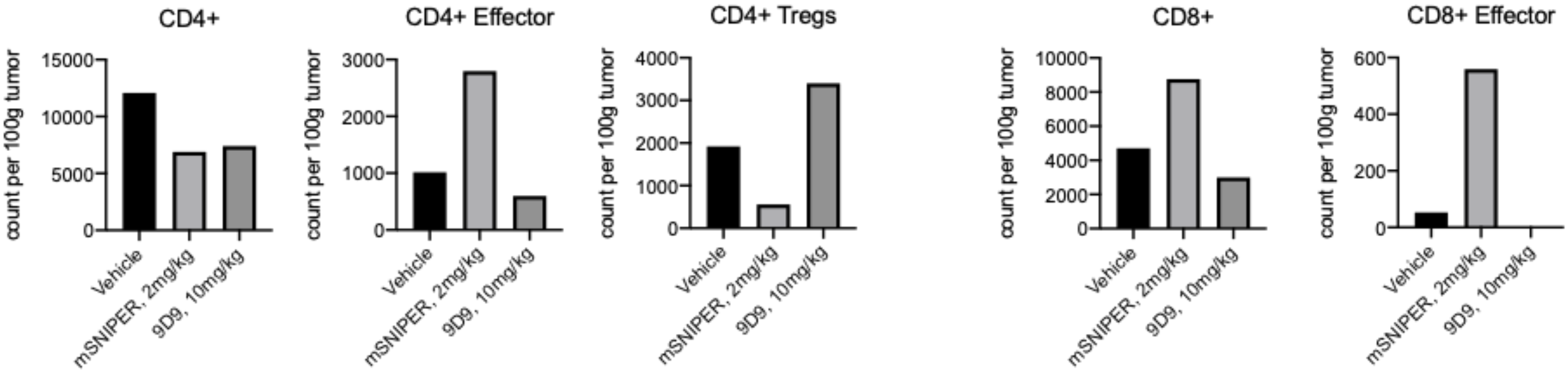


Tregs: FoxP3^{+}CD127^{lo} & Effectors: CD44^{hi}CD62L^{lo}

Note: No significant changes observed in the periphery

SNIPER™ Depleted Tregs in Tumor Better than 9D9

Tumor Immunophenotyping: Day 12 Post Dosing



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

Note: No significant changes observed in the periphery

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

SNIPER™ Lead Summary: ready for development

- Next Steps:
  - Additional efficacy studies
    - Combination studies using more challenging syngeneic models
    - Continue exploring comparison to monoclonal Treg Depleting antibodies
  - Human Lead Development
    - Cyno PK/PD Study
    - Cell line development

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The Invenra Team

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