

# Conditionally Active Antibodies for Immuno-oncology

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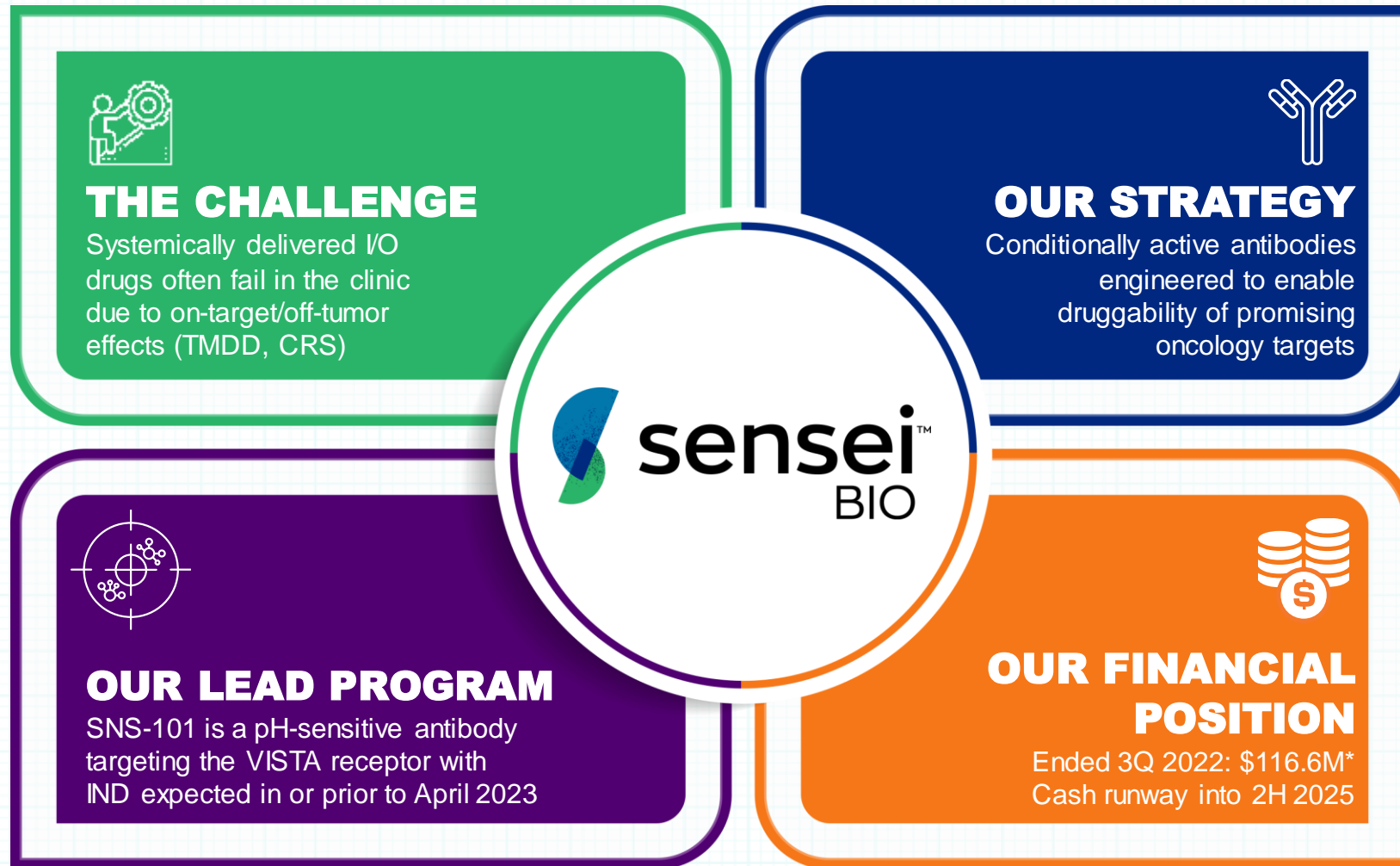
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# Engineered Selectivity to Extend the Reach of Immuno-oncology Agents



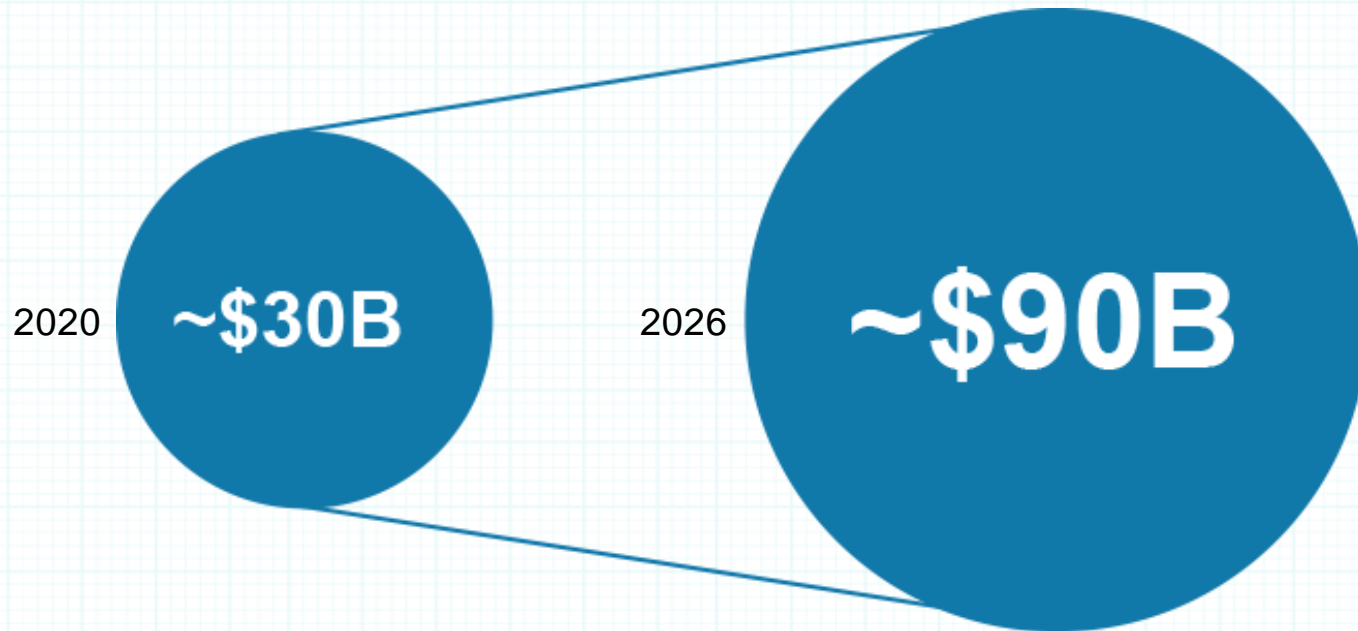
# Innovative Pipeline of IO Drugs with Broad Commercial Potential

Program (Target)	Indication	Discovery	IND-enabling	Phase 1 / 2 Clinical
SNS-101* (VISTA)	Solid Tumors			
SNS-102 (VSIG4)	Solid Tumors			
SNS-103 (ENTPDase1/CD39)	Solid Tumors			

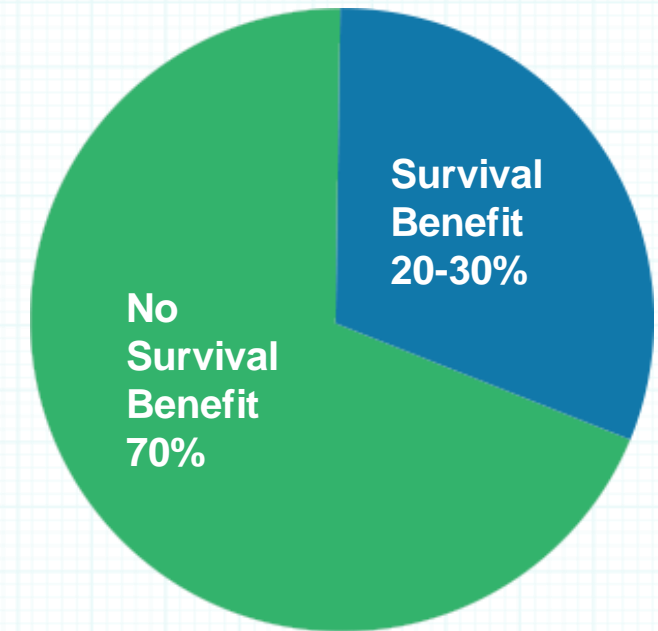
**REGENERON** \*Sensei has entered into a clinical supply agreement with Regeneron supporting the planned evaluation of SNS-101 in combination with Regeneron's anti-PD-1 therapy Libtayo® (cemiplimab) in a Phase 1/2 clinical trial in solid tumors.

# The Modern-Day Challenge in Immuno-Oncology

The PD-1/PD-L1 market is big and growing fast<sup>1</sup>



PD-1/PD-L1 monotherapy does not benefit 70% of patients<sup>2</sup>



# Lack of Selectivity is a Major Obstacle to CI Innovation

Industry Problem	Sensei's Solution
<p><b>Conventional antibodies target immune checkpoints that are highly expressed in normal tissues, resulting in:</b></p> <ul style="list-style-type: none"><li>Dose-limiting toxicities due to on-target/off-tumor action</li><li>Pharmacological sink effect requires higher and more frequent dosing</li><li>Suboptimal activity due to poor PK and dose-limiting toxicities</li></ul>	<p><b>Conditionally active antibodies are selectively targeted to the tumor microenvironment, potentially providing:</b></p> <ul style="list-style-type: none"><li>Little or no toxicity due to selective on-target/on-tumor action</li><li>Lower and less frequent doses by avoiding normal tissue binding</li><li>Powerful activity selectively focused on the tumor microenvironment</li></ul>

Only one new checkpoint inhibitor has been approved since the original CTLA-4 and PD-1/PD-L1 group

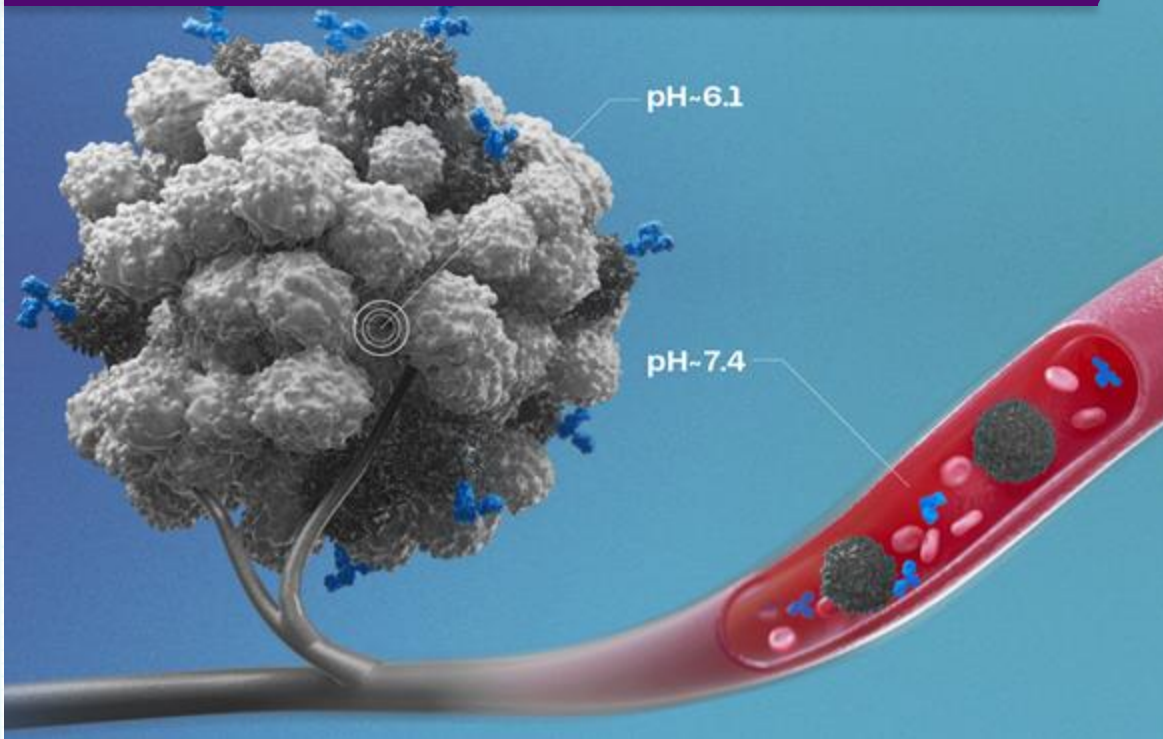




# pH-sensitive Antibodies Have Potential to Selectively Bind Their Targets in the Low-pH Tumor Microenvironment

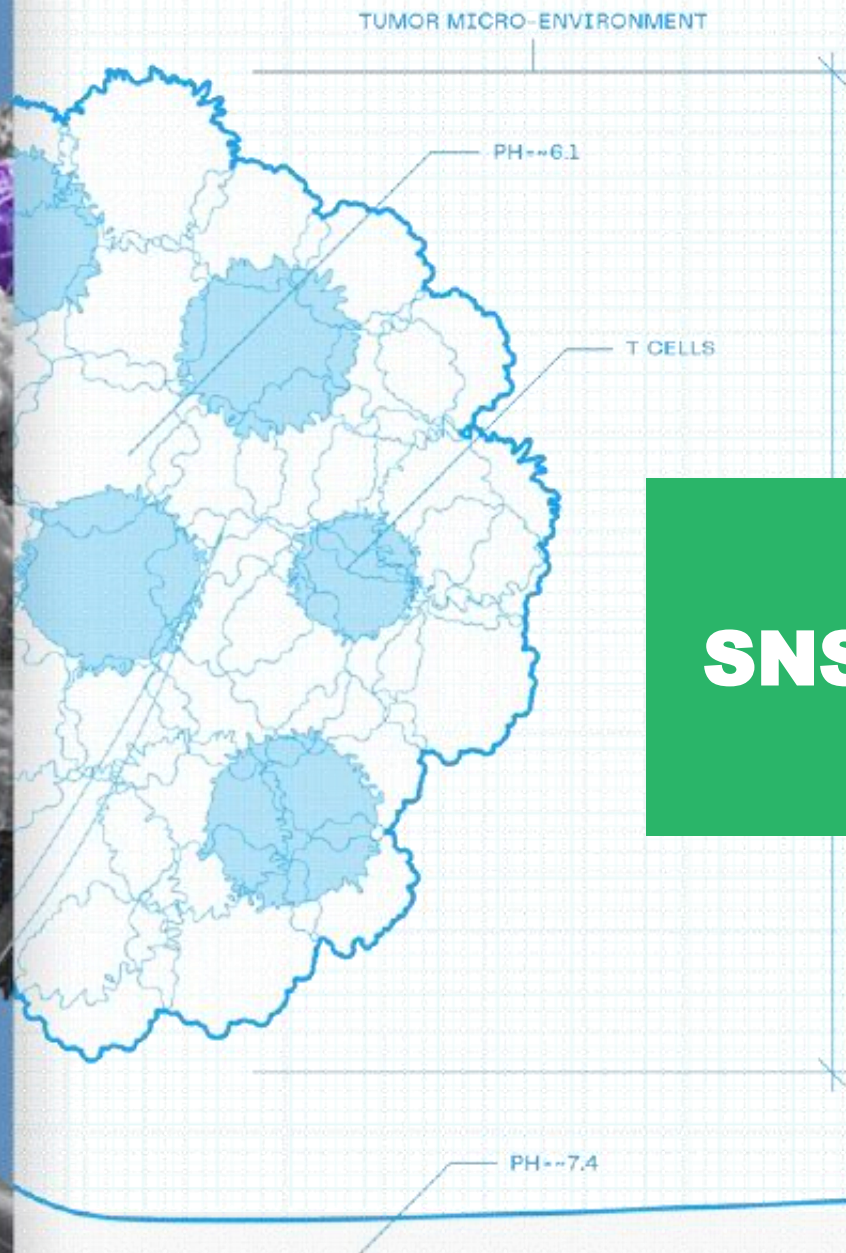
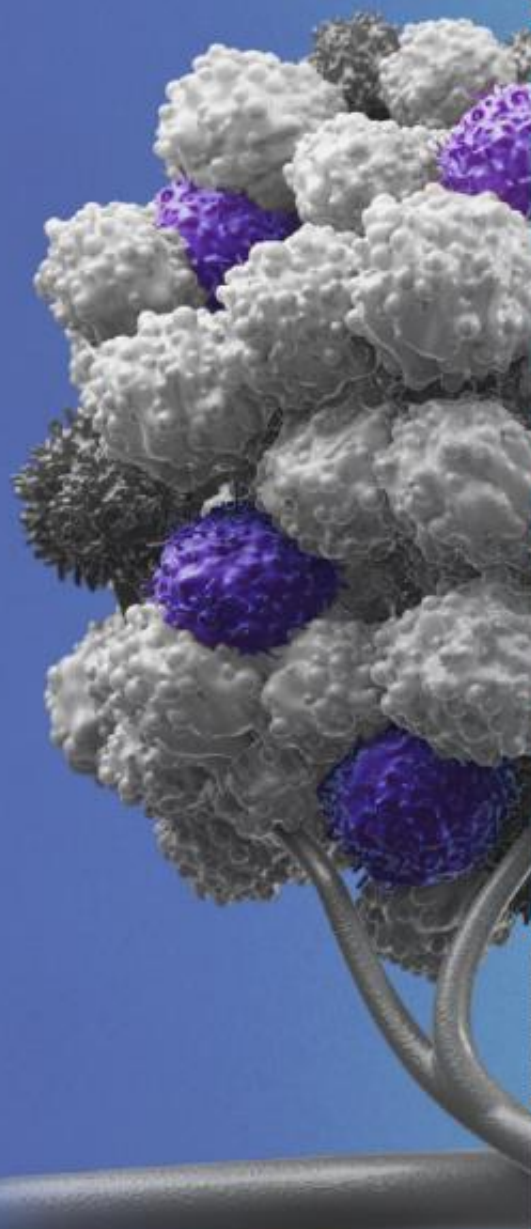
## TMAb Platform

The tumor microenvironment of pH ~6 is lower than physiological pH of 7.4



Sensei's technology identifies pH-sensitive antibodies designed to bind only at the tumor

- Exploits the tumor microenvironment using pH-selective properties
- Intended to alleviate undesirable properties:
  - Dose-limiting toxicities due to on-target/off-tumor binding
  - Higher and more frequent dosing due to poor pharmacokinetics (Target-mediated Drug Disposition (TMDD))
- Bolsters specific activities
- Goal is to unlock previously undruggable immune targets

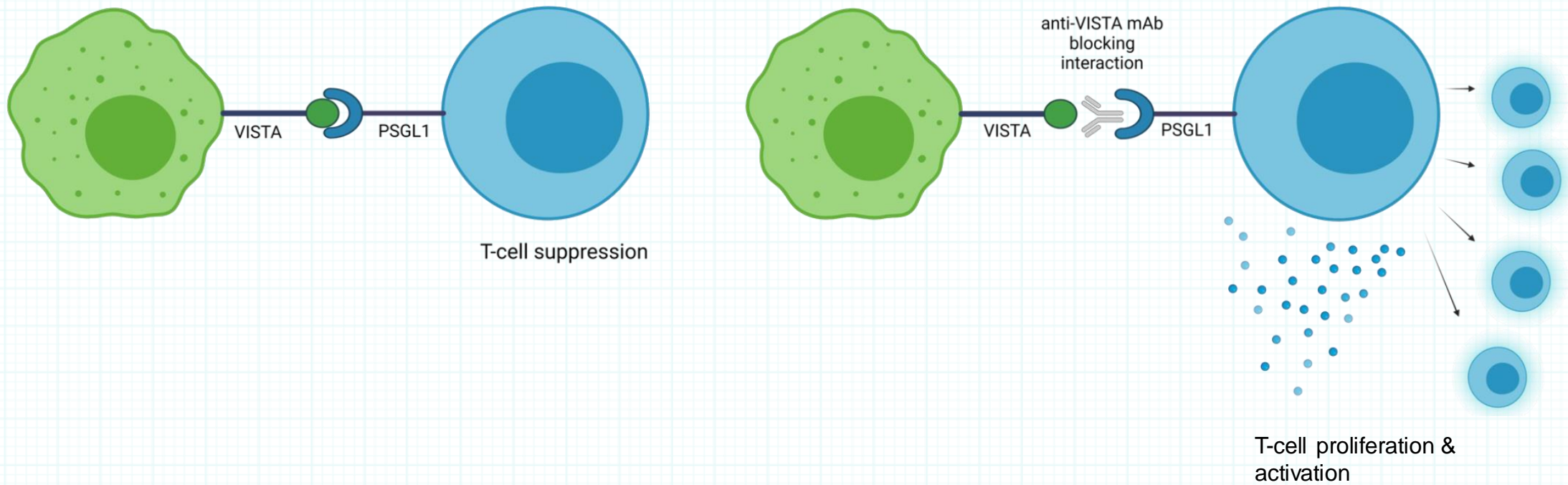


**SNS-101**

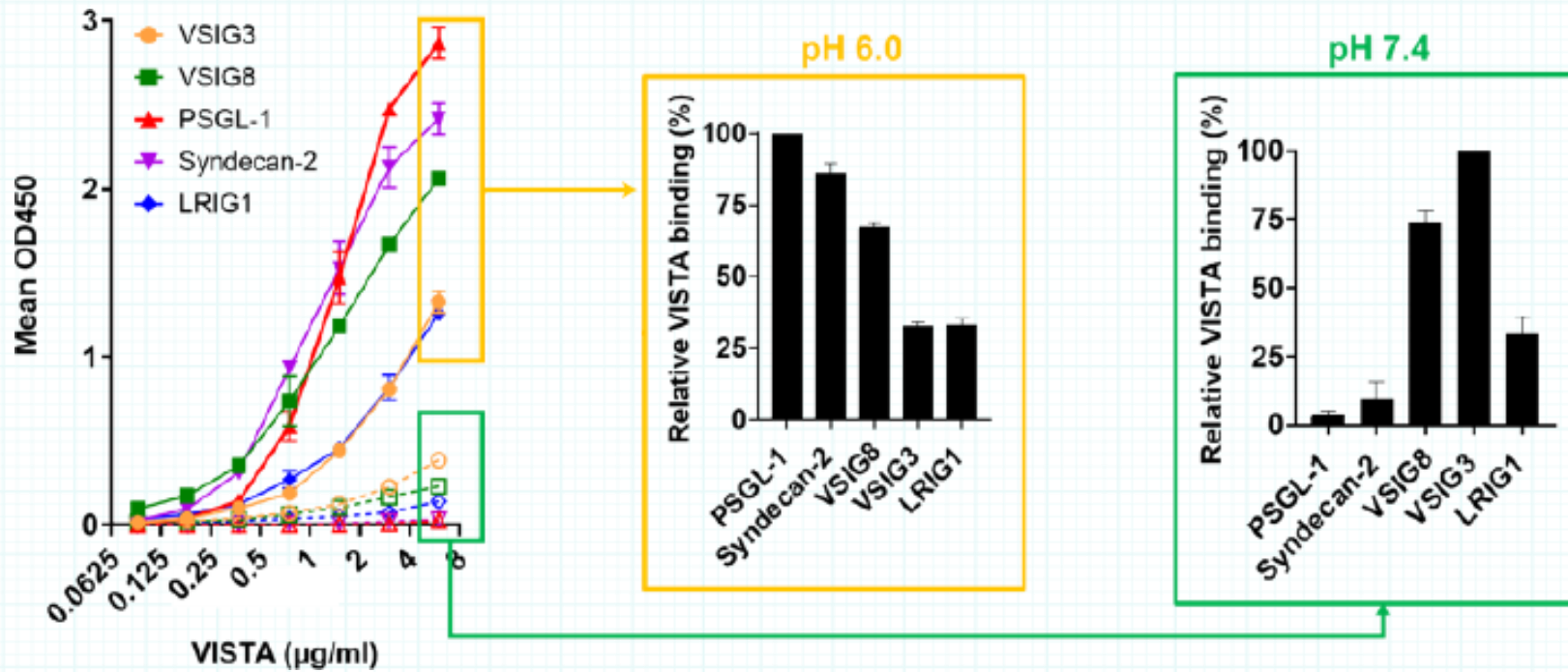


# VISTA: A Potent T cell Checkpoint Extensively Expressed on Myeloid Cells<sup>1</sup>

VISTA is a B7 family member that suppresses T cell function



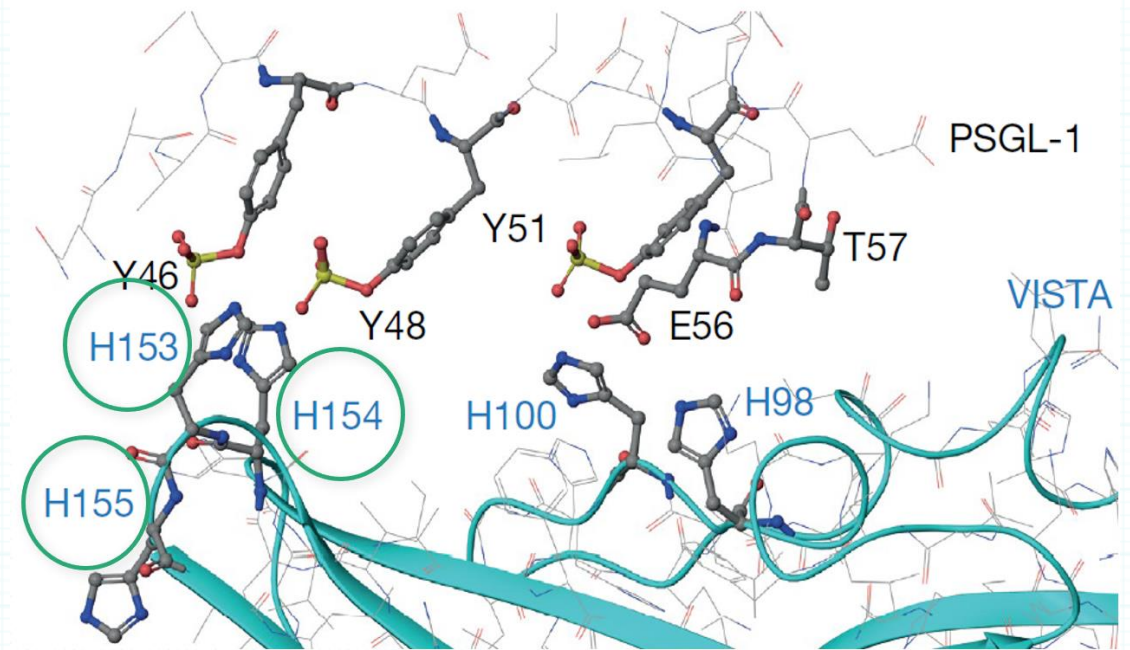
# The VISTA:PSGL-1 Interaction is Selective for low pH



# VISTA Checkpoint is Activated at the Low pH of the Tumor Microenvironment

VISTA extracellular domain is uniquely rich in histidines<sup>1</sup>

Protonated VISTA histidines are required for  
PSGL-1 binding<sup>1</sup>





# SNS-101: Selectively Targeting VISTA with a pH-sensitive Antibody

## Key features


- Selectivity for Active VISTA<sup>pH6</sup> over VISTA<sup>pH7.4</sup>
- Designed to block VISTA's interaction with PSGL-1 and all other T-cell receptors at pH 6.0
- IgG1 format
- Active Fc

	pH 6.0	pH 7.4
Monovalent Affinity (K <sub>D</sub> ) [nM]	0.218	132 (~No binding)

## Development milestones

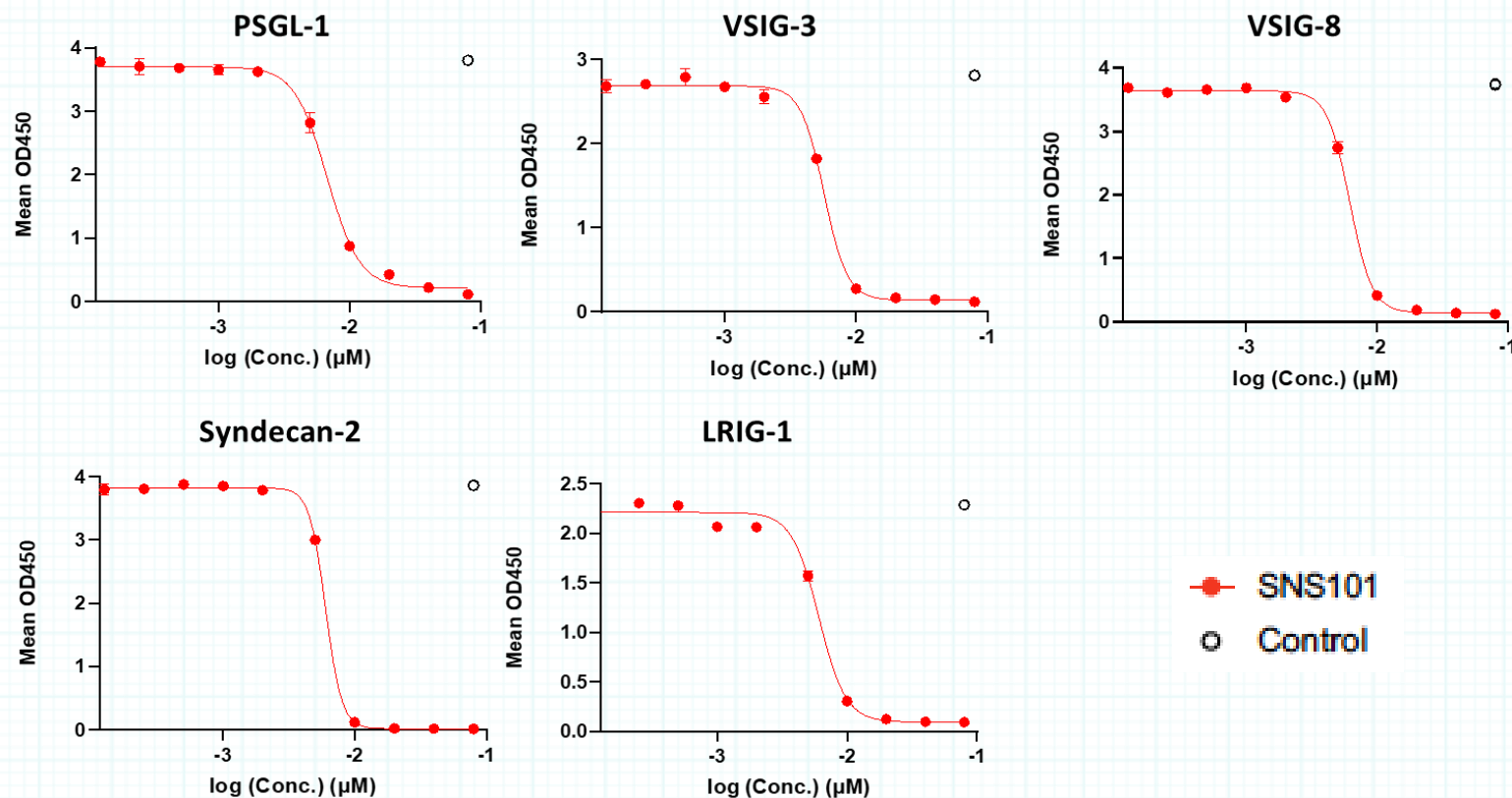
- Multi-dose Non-Human Primate (NHP) PK & Toxicology data in 1H 2023
- IND submission expected in or prior to April 2023

# SNS-101 Is a Fully Differentiated Anti-VISTA Antibody

	SNS-101 	CI-8993; JNJ-61610588 (J&J/Curis)	K01401-020; W0180 (Pierre Fabre)	HMBD-002 (Hummingbird)	KVA12.1 (Kineta)	VISTA.18 (BMS)	(PMC-309) Pharm Abcine
Inhibit PSGL-1 Binding	✓	✓	✓	✗	✓	✓	✓
pH Sensitive Binding	✓	✗	✗	✗	✗	✓	✗
Fc Active	✓ (IgG1)	✓ (IgG1)	N/A	✗	✓ (IgG1)	✗ (IgG4)	✓ (IgG1)
Stage	Preclinical	Phase 1	Phase 1	Phase 1	Phase 1	Preclinical	Preclinical

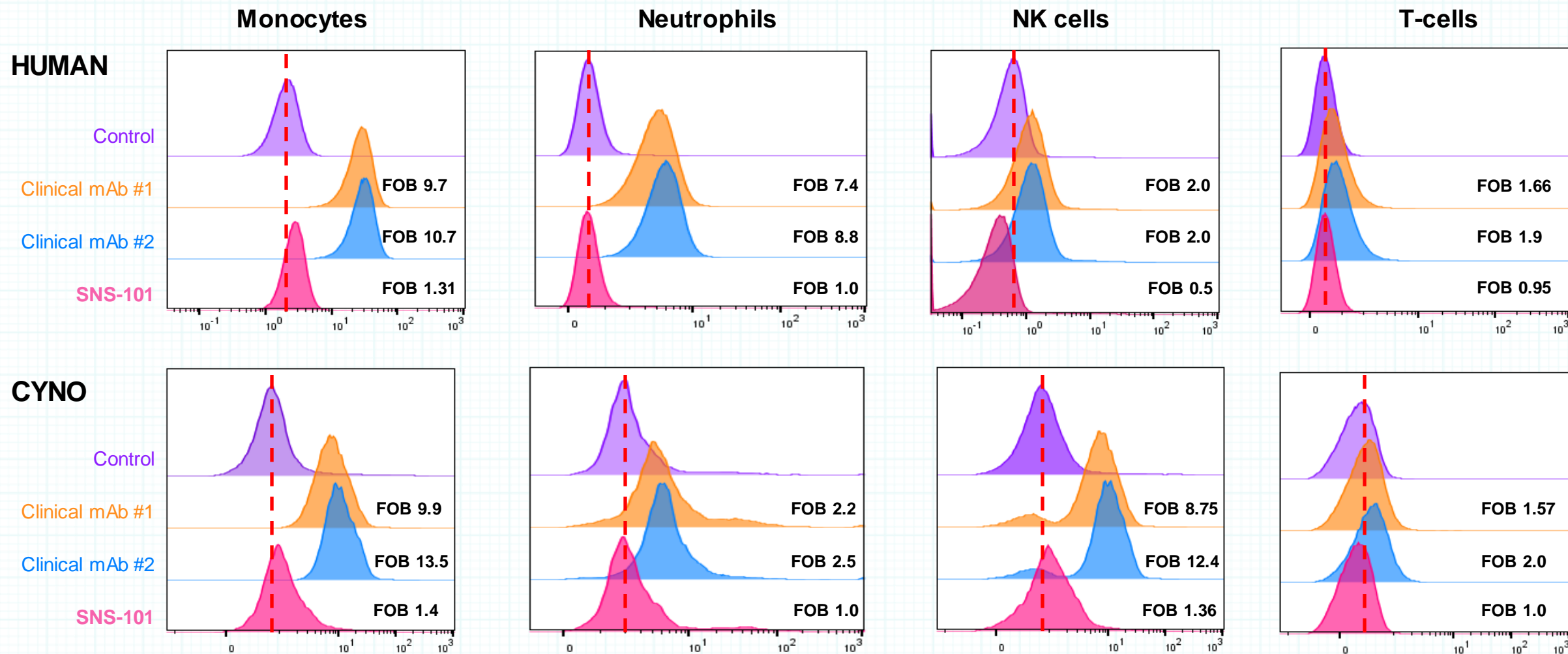
# SNS-101 Strongly Inhibits the VISTA:PSGL-1 Interaction And All Other Potential Binding Partners at pH 6.0 in *In Vitro* Assay

Receptor	IC50 [nM]
PSGL-1	7
VSIG3	6
VSIG8	6
Syndecan-2	6
LRIG1	6

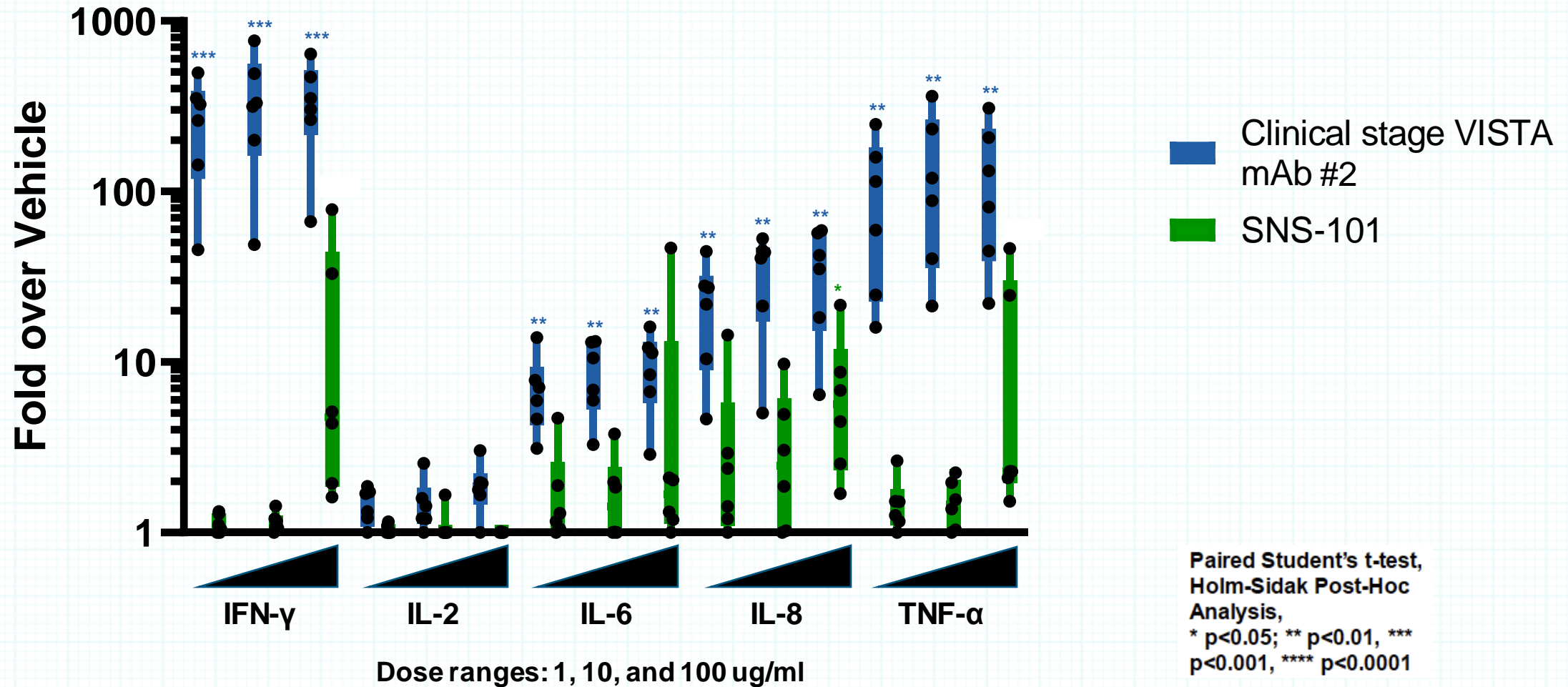




# No Significant Binding of SNS-101 to Monocytes, Neutrophils, NK Cells and T-cells in Whole blood at Physiological pH

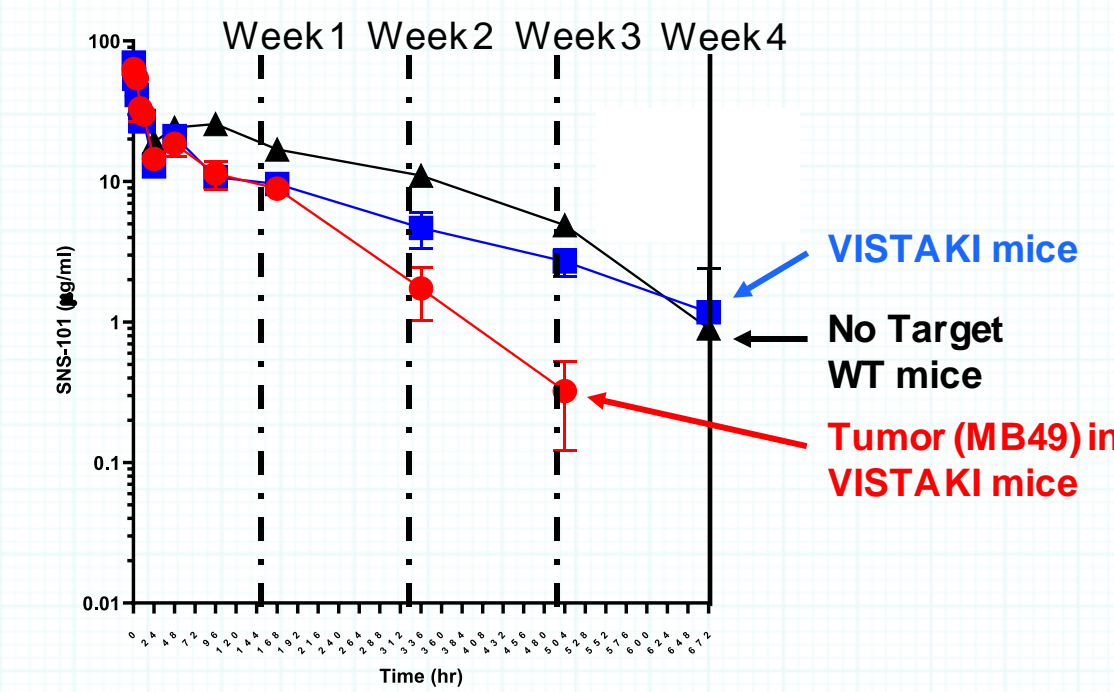


# SNS-101 Induced Substantially Lower Cytokine Release in Whole-blood Assay at Neutral pH Compared to pH-independent VISTA Antibody



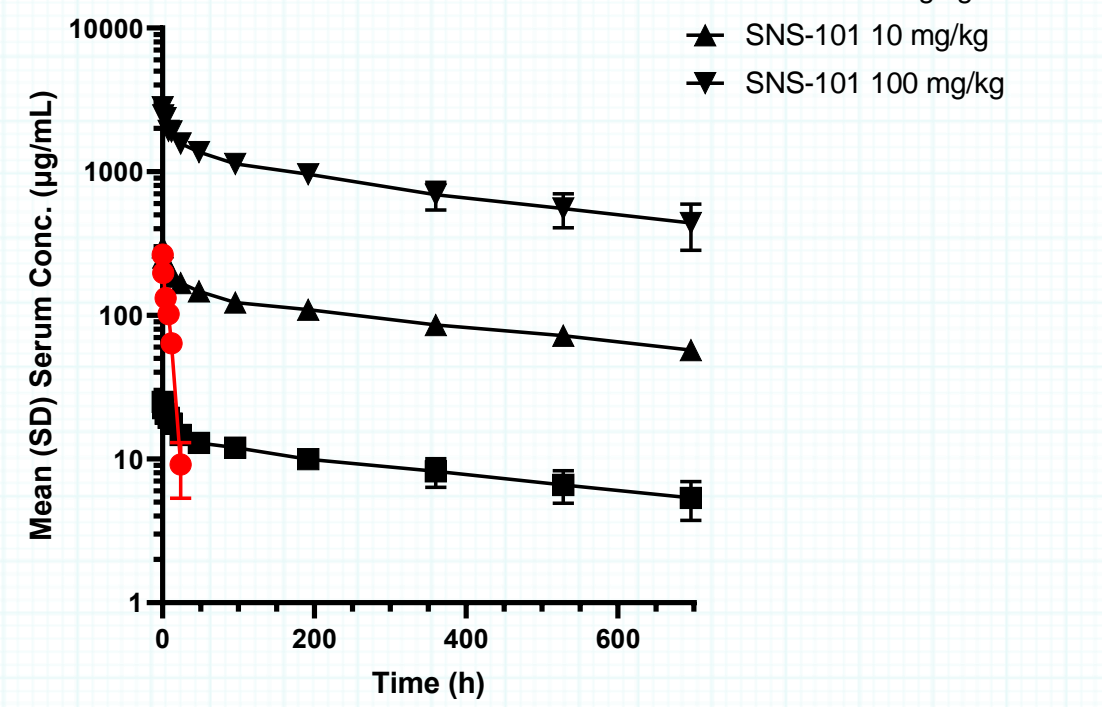
# SNS-101 Has Displayed a Favorable Single-dose PK Profile in Preclinical Studies - *No Significant TMDD in Human VISTA KI Mice or Non-human Primates*

Pharmacokinetics of Single Dose 5 mg/kg SNS-101 in VISTA Knock-in Mice



Demonstrated a long mean residence time in the blood, indicating a lack of significant target-mediated drug disposition (TMDD) and clearance in non-malignant tissues

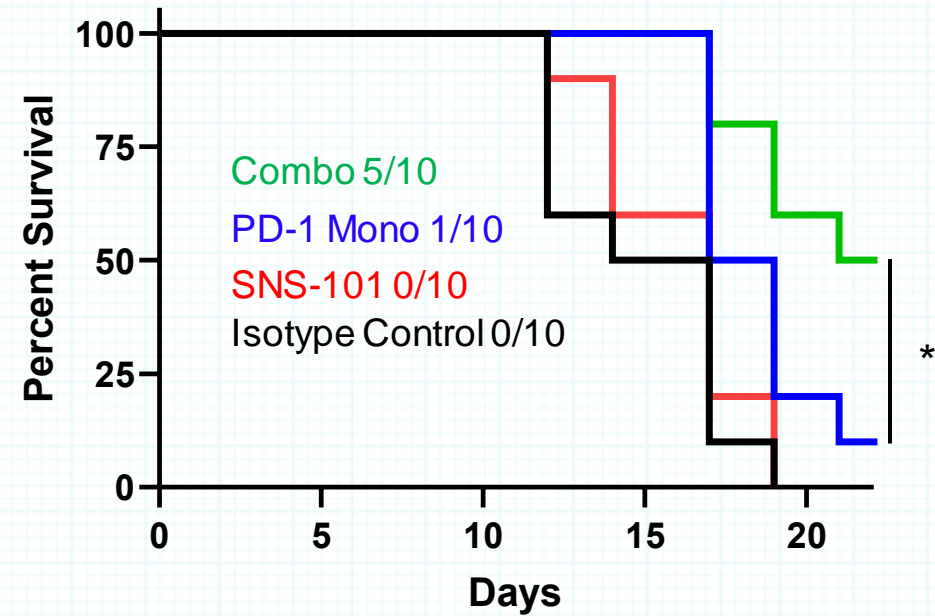
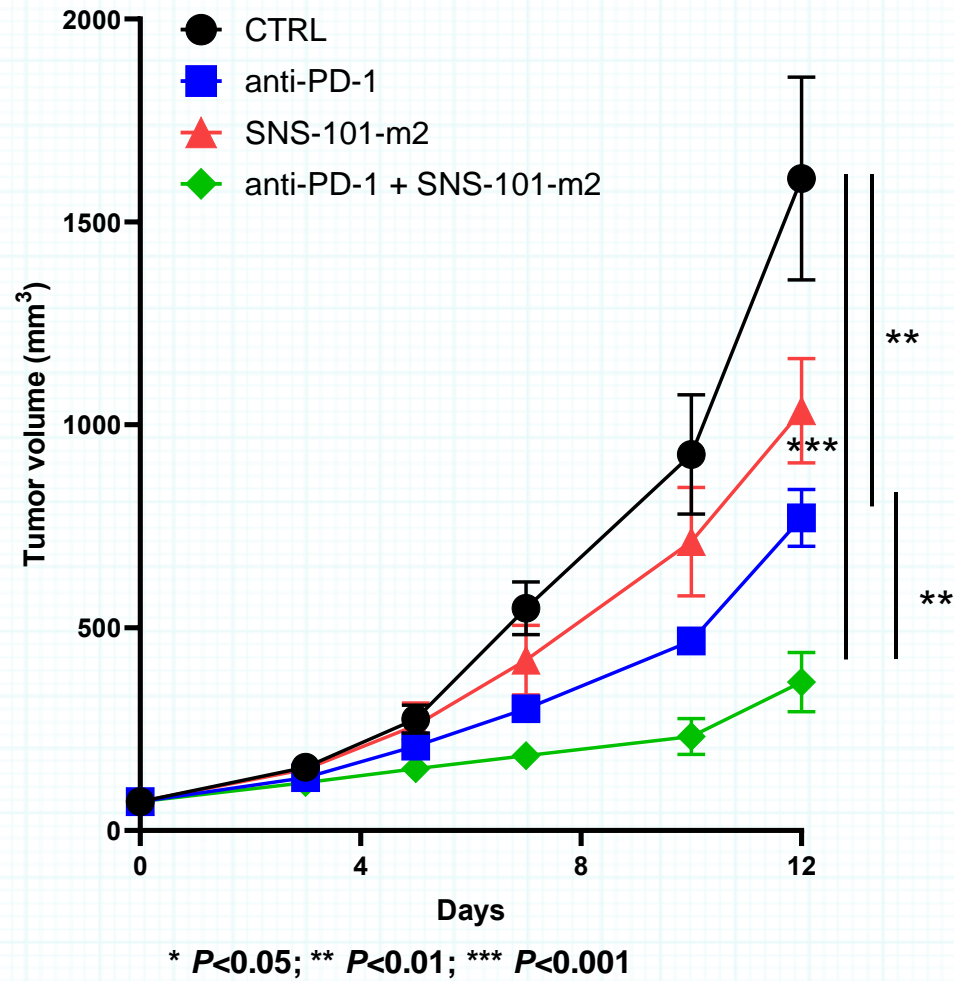
Pharmacokinetics of Single Dose SNS-101 in Cyno monkeys



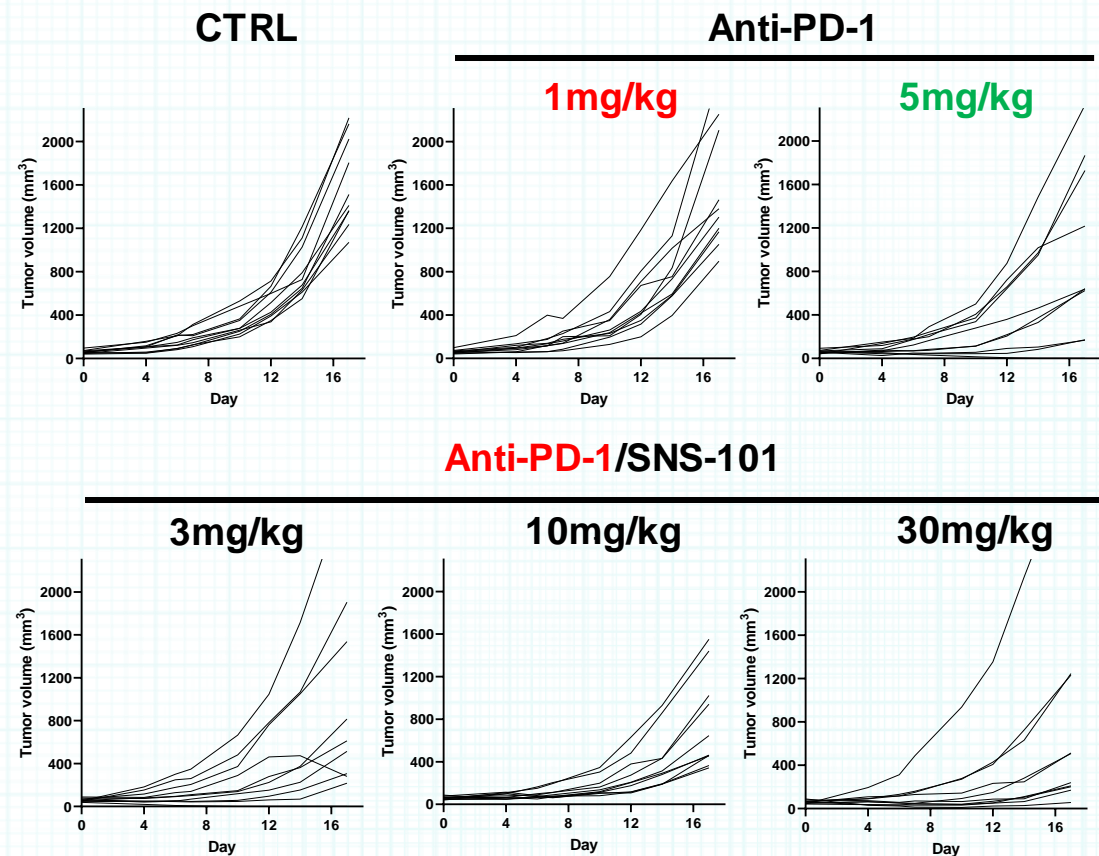
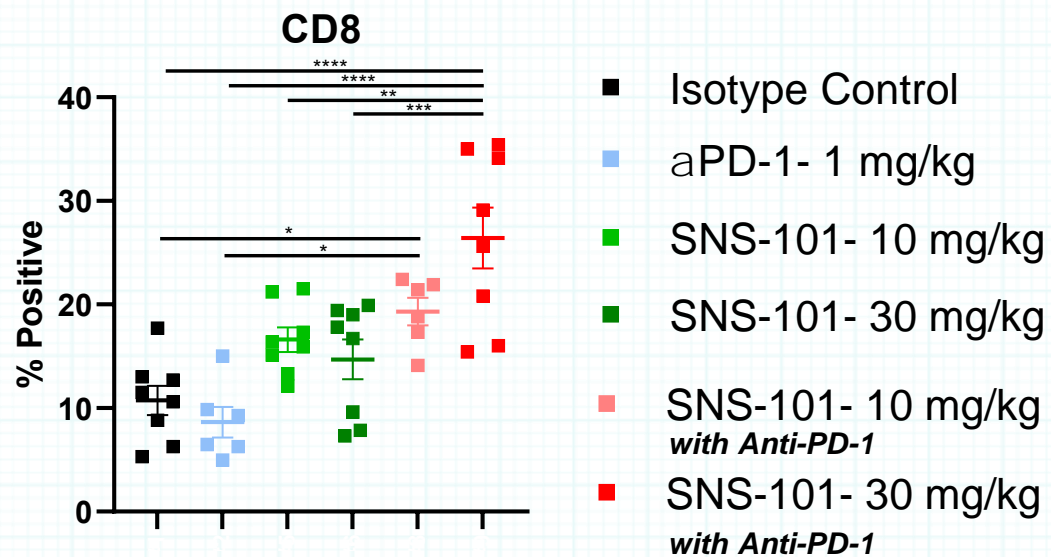
SNS-101 displays linear elimination kinetics unlike a pH-independent anti-VISTA mAb, which demonstrates TMDD and rapid clearance



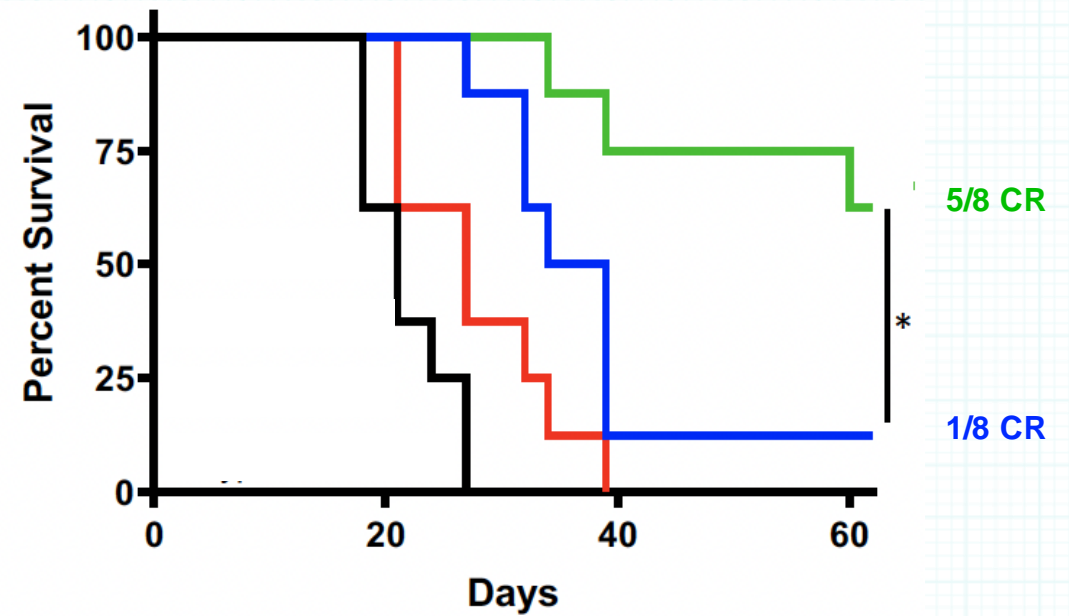
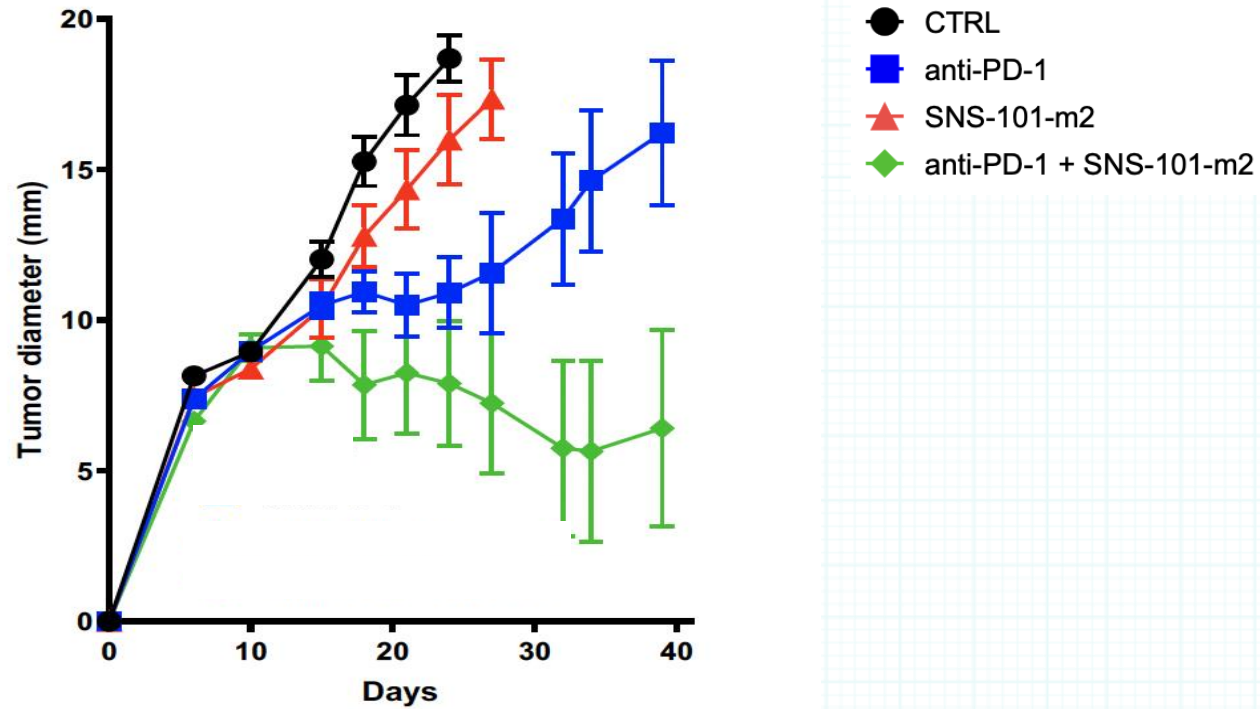
# SNS-101 with Anti-PD-1 Demonstrated Strong Combinatorial Anti-tumor Activity in MC38 Model in Human VISTA Knock-in Mice



# SNS-101 Increased CD8 T-cells in Combination With Anti-PD-1 in MC38 Tumors *In Vivo*



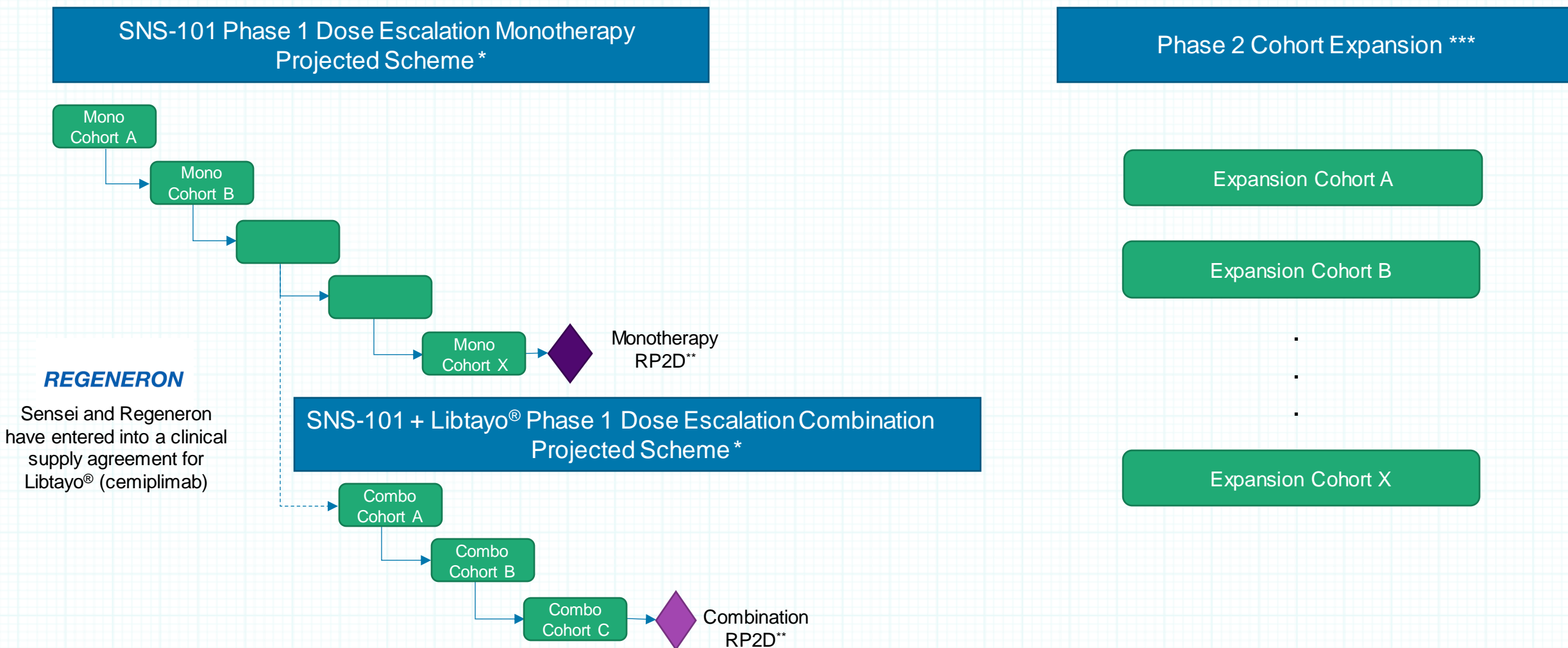
# SNS-101 Re-sensitized Anti-PD-1 Insensitive Sarcoma Tumors in Human VISTA Knock-in Mice

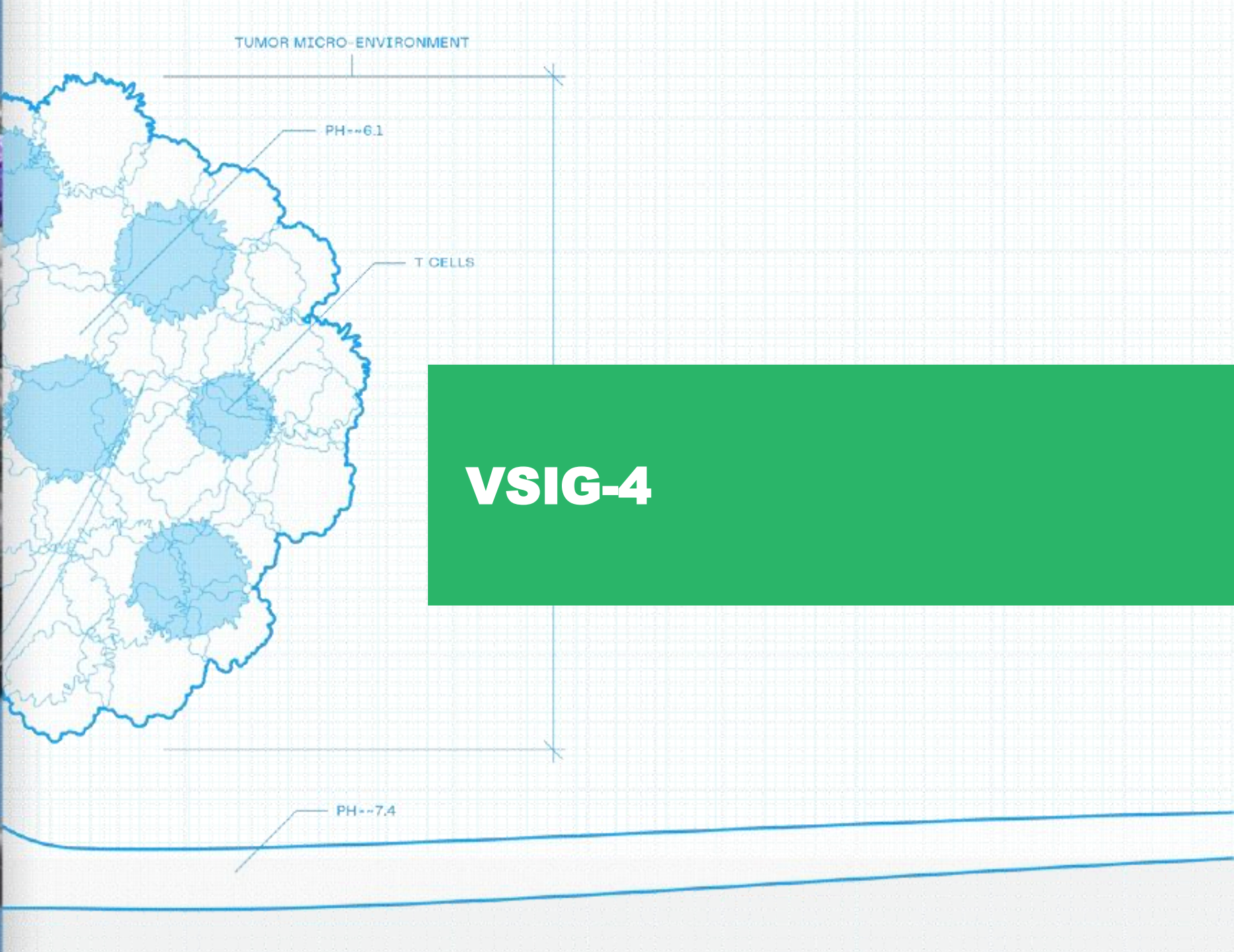
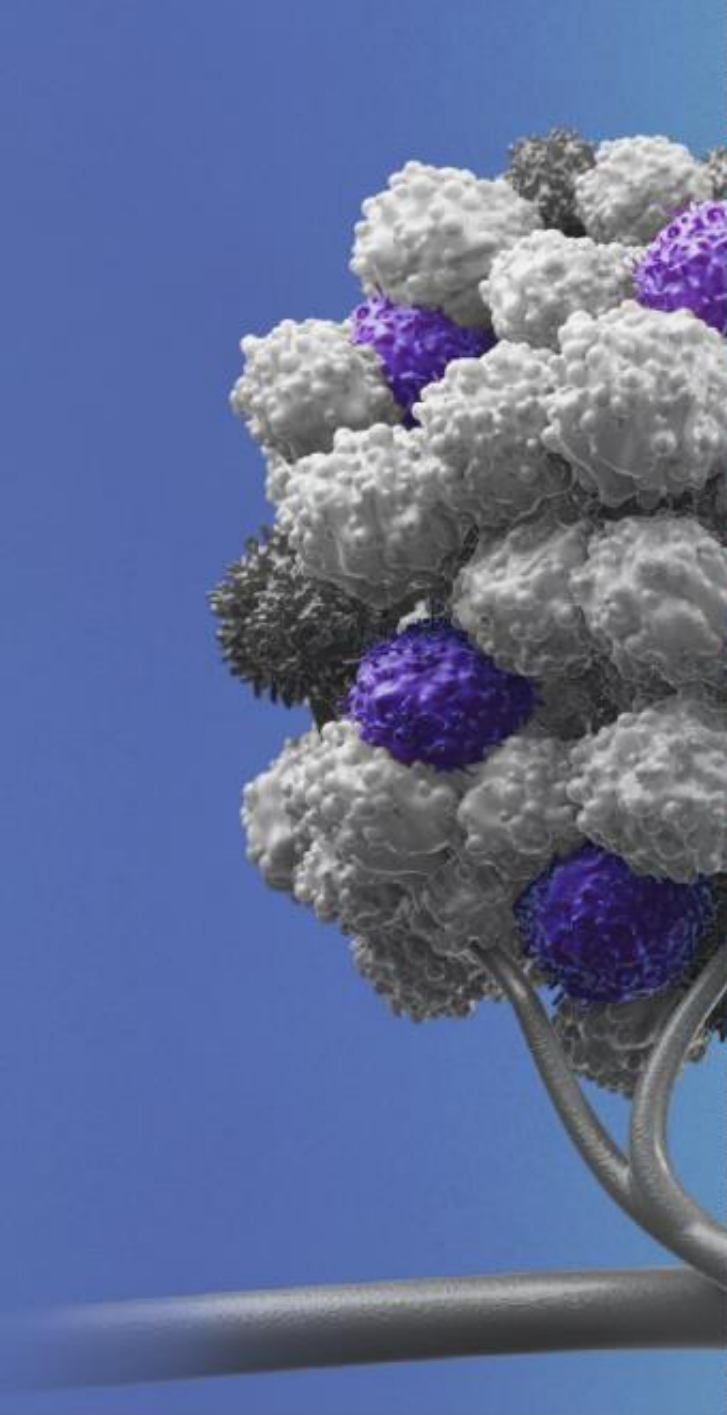


\*  $p < 0.05$



# Preliminary SNS-101 Phase 1/2 Study Schematic



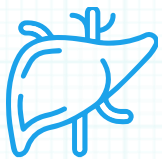
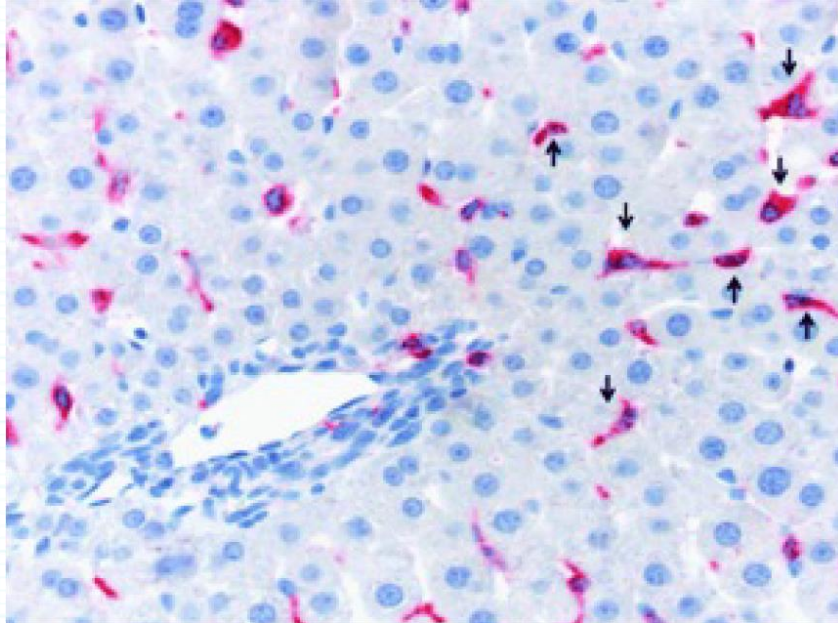


**VSIG-4**



# VSIG4 is an Immunosuppressive Receptor with On-Target, Off-Tumor Challenges

## Tissue macrophages (Kupffer cells) in liver

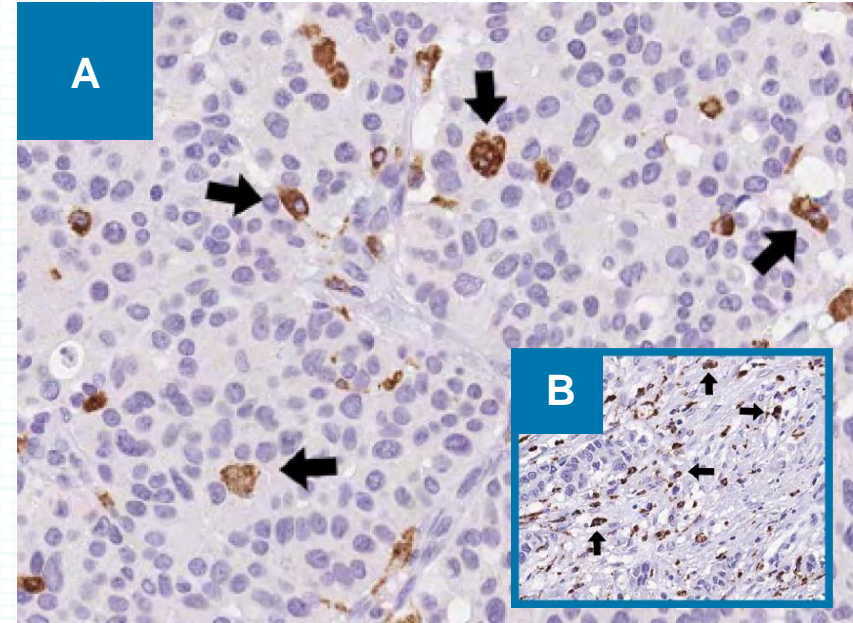


### In the liver, VSIG-4 ...

Is expressed on Kupffer cells

Appears to drive significant target-mediated drug disposition (TMDD) and clearance

## Tumor-associated macrophages in tumor and stroma (inset)



### In the tumor microenvironment, VSIG-4 ...

Correlates with immunosuppressive "M2" macrophage infiltration

Inhibits T cell activation

Promotes tumor growth based on data from a syngeneic Lewis lung carcinoma model in knockout mice



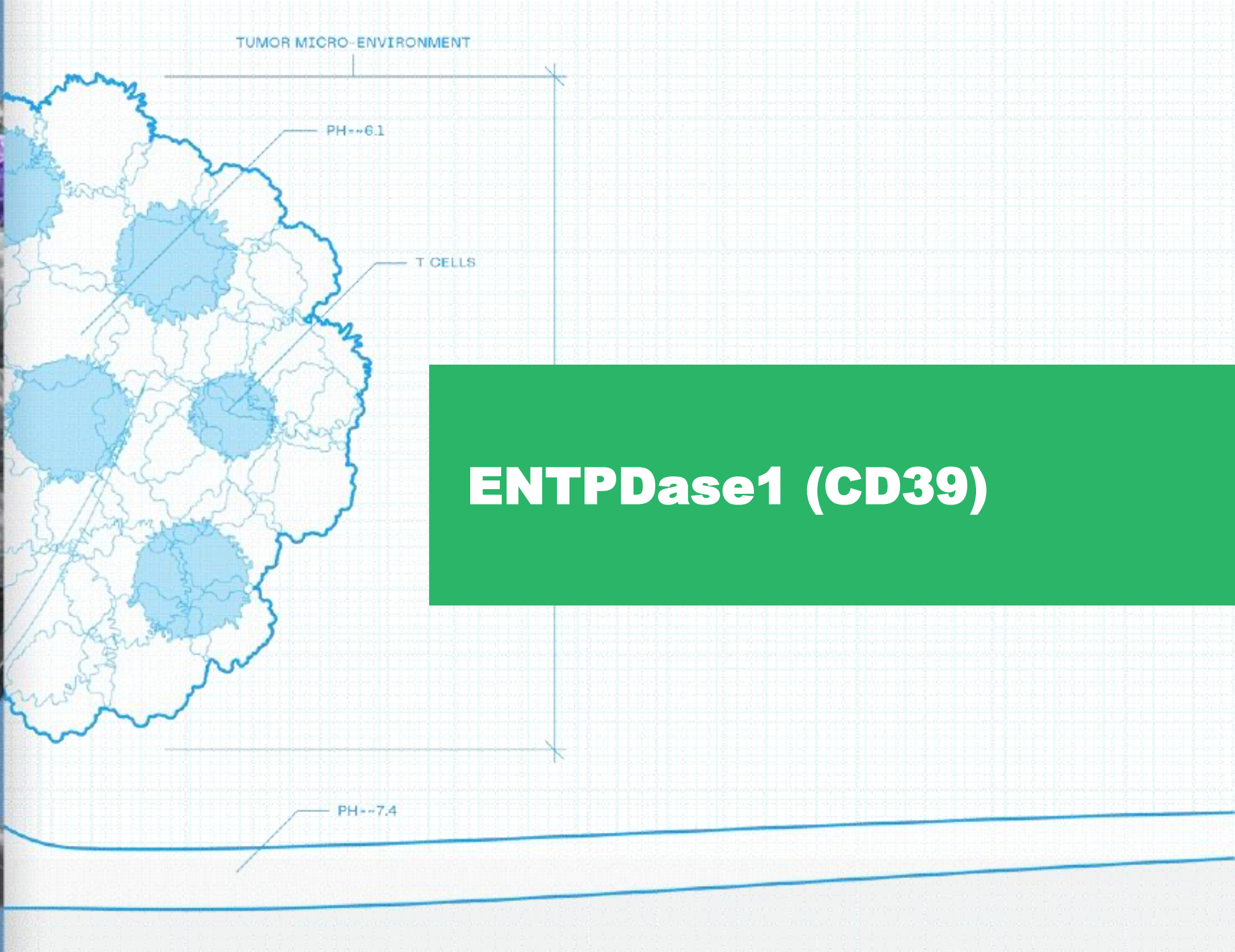
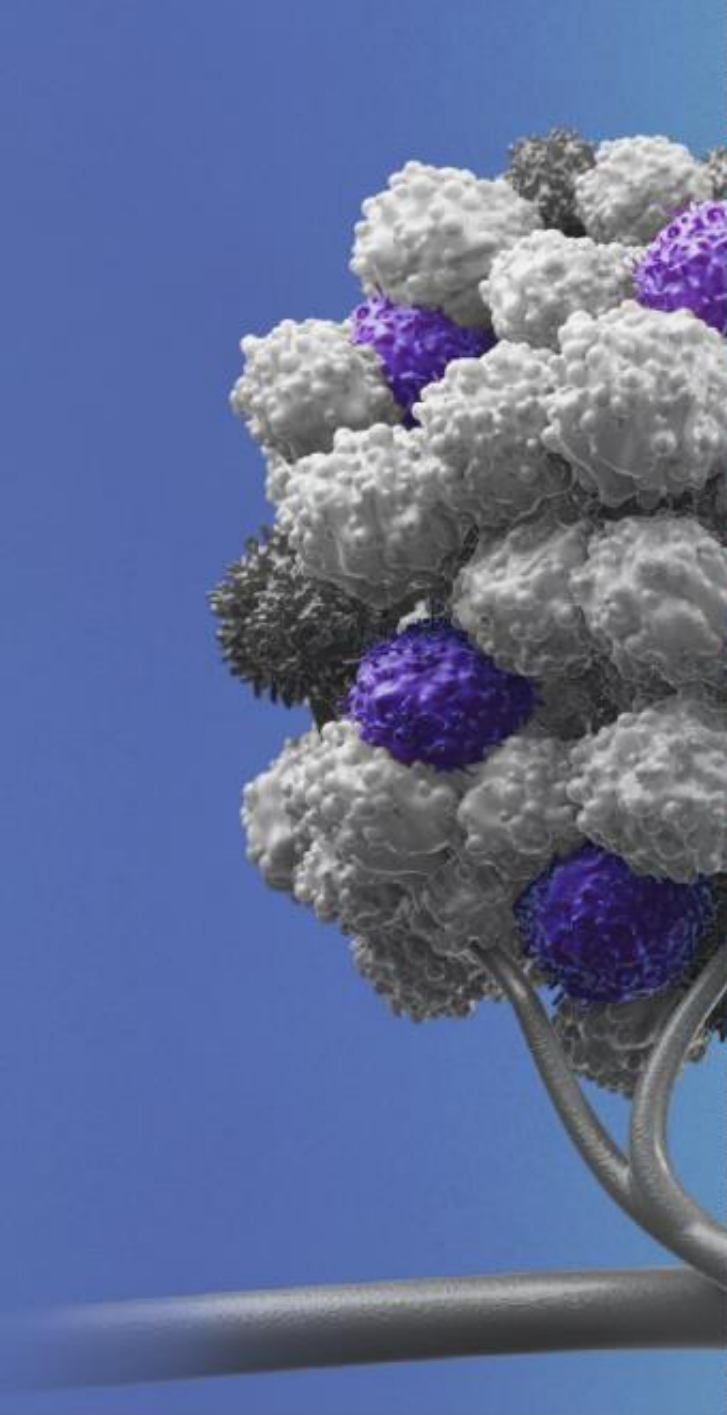
# Sensei Has Identified pH-sensitive VSIG4 Antibodies

pH-Sensitive VSIG4 Parental Antibodies Selected for Further Optimization

- Sensei has:
  - Identified 8 parental antibodies for further optimization;
  - Identified novel VSIG4 receptors on primary T-cells by Hi-Res proteomics, which are currently in verification stage;
  - Identified pH-sensitive antibodies highlighting the potential breadth of the TMAb platform
- Plan to select product candidate in 2023

Antibody Reference #	Ratio of pH Selectivity (6.0 vs 7.4)	Blockage of Immobilized VSIG4-T-cell Inhibition	Blockage of Cellular VSIG4-T-cell Inhibition
1	1	+	+
2	7	+	+
3	1	+	+
4	3	+	+
5	3	+/-	+
6	25	+	+
7	1	+	+
8	2	-	+

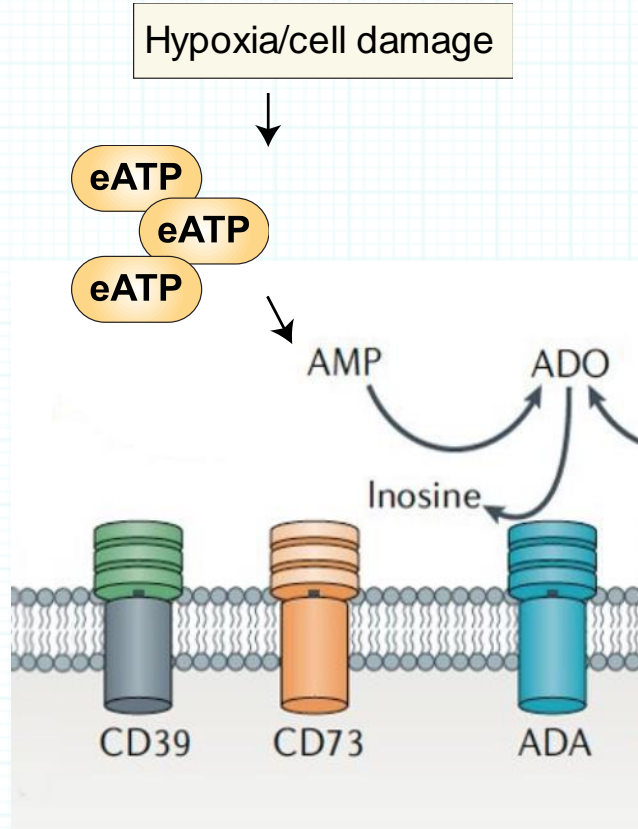
\* Ratio assessed by flow cytometry on VSIG4 overexpressing cells



**ENTPDase1 (CD39)**



# ENTPDase1 (CD39) is the Rate Limiting Enzyme in the Production of Immunosuppressive Adenosine



- Primary function is conversion of extracellular ATP / ADP to adenosine, which exerts immunosuppressive properties through binding to A2a/A2b receptors
- Expressed on various immune cells in both tumors and normal tissues
- Development of a TMAb antibody has potential for improved safety and PK profile compared to competitor CD39 mAbs





# Sensei Has Identified pH-sensitive ENTPDase1 (CD39) Antibodies

- Identified 8 pH-sensitive parental antibodies for lead optimization
- Plan to select lead product candidate in 2023

**pH-Sensitive CD39 Parental Antibodies  
Selected for Further Optimization**

Antibody Reference #	Ratio of pH Selectivity (6.0 vs 7.4)
1	1
2	6
3	4
4	5
5	18
6	1
7	1
8	1

# Expected Program Milestones



## **SNS-101 (anti-VISTA)**

- 1H 2023: Multi-dose Non-Human Primate (NHP) PK & Toxicology data
- In or Prior to April 2023: IND filing



## **SNS-102 (anti-VSIG4)**

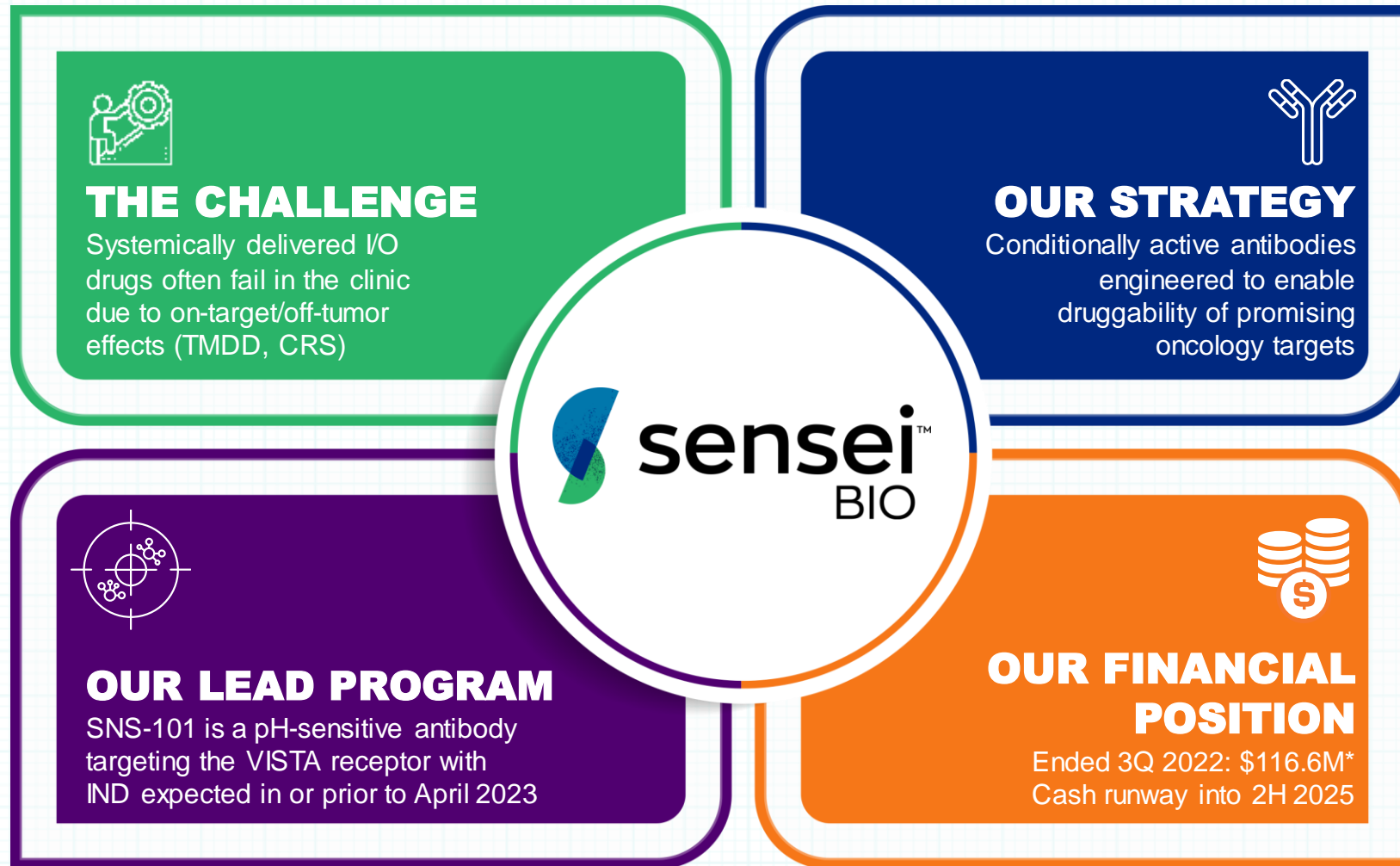
- 2023: Select product candidate



## **SNS-103 (anti-ENTPDase1/CD39)**

- 2023: Select product candidate

# Engineered Selectivity to Extend the Reach of Immuno-oncology Agents





# Proven Team With Deep Experience



**John Celebi, MBA**  
President and CEO



**Erin Colgan**  
Chief Financial Officer



**Patrick Gallagher**  
Chief Business Officer

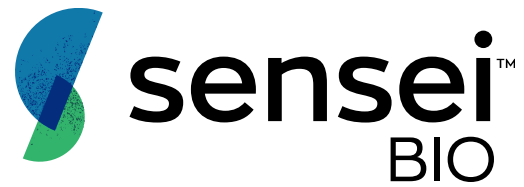


**Edward van der Horst, Ph.D.**  
Chief Scientific Officer



**Christopher Gerry, J.D.**  
VP, General Counsel





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**HQ:** 451 D St, Unit 710 , Boston, MA 02210 / **MD:** 1405 Research Blvd, Suite 125, Rockville, MD 20850

**[senseibio.com](https://senseibio.com)**

# Appendix

## *References for Slide 23*

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