Lessons from VISTA: New Strategies to Address an Important Immune Checkpoint

November 21, 2022

Guest Speaker:

Robert Schreiber, Ph.D.

Andrew M. and Jane M. Distinguished Professor of Pathology and Immunology; Professor, Molecular Microbiology; and Director of the Bursky Center for Human Immunology and Immunotherapy Programs at the Washington University School of Medicine. He is also co-leader of the Tumor Immunology Program of Washington University's Siteman Comprehensive Cancer Center, an Associate Director of the Scientific Advisory Board to the Cancer Research Institute and Co-editor-in-Chief of the journal Cancer Immunology Research. Schreiber obtained his PhD in Immunology/Biochemistry at the State University of New York in Buffalo, New York, and received his postdoctoral training at The Scripps Research Institute in La Jolla, California. Sensei IOAB Member.

Sensei Presenters:

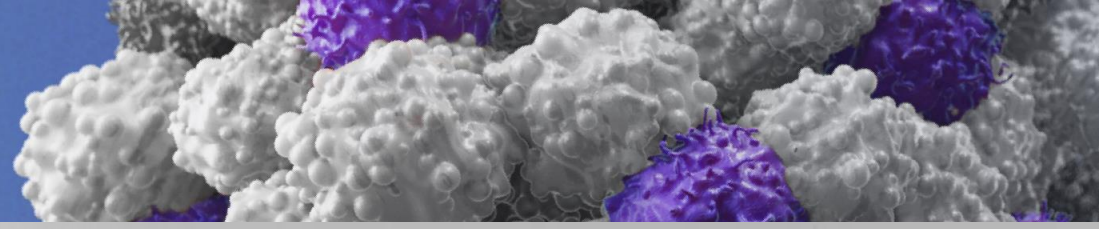
John Celebi
Chief Executive Officer

Dr. Robert Pierce
Chief R&D Officer

Dr. Ron Weitzman
Interim CMO

Dr. Edward van der Horst
SVP, TMAb Antibody Development

Disclaimer



This presentation has been prepared by Sensei Biotherapeutics, Inc. (the “Company,” "we," "us") and is made for informational purposes only. The information set forth herein does not purport to be complete or to contain all of the information you may desire. Statements contained herein are made as of the date of this presentation unless stated otherwise, and neither the delivery of this presentation at any time, nor any sale of securities, shall under any circumstances create an implication that the information contained herein is correct as of any time after such date or that information will be updated or revised to reflect information that subsequently becomes available or changes occurring after the date hereof.

This presentation contains estimates and other statistical data made by independent parties and by us relating to market shares and other data about our industry. This presentation also contains "forward-looking" statements as that term is defined in the Private Securities Litigation Reform Act of 1995 that are based on our management's beliefs and assumptions and on information currently available to management. These forward-looking statements include, without limitation, expectations regarding the development of our product candidates; the potential safety profile of our product candidates; the potential benefits of our product candidates; the availability of data from our preclinical studies; the timing of selection of product candidates; the timing of IND submissions to the FDA; expected clinical development timelines; and our belief that our existing cash and cash equivalents will be sufficient to fund our operations at least into the first quarter of 2025.

When used in this presentation, the words and phrases "designed to," "may," "believes," "intends," "seeks," "anticipates," "plans," "estimates," "expects," "should," "assumes," "continues," "could," "will," "future" and the negative of these or similar terms and phrases are intended to identify forward-looking statements. Forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. Risks and uncertainties that may cause actual results to differ materially include uncertainties inherent in the development of therapeutic product candidates, such as preclinical discovery and development, conduct of clinical trials and related regulatory requirements, our reliance on third parties over which we may not always have full control, and other risk and uncertainties that are described in our Quarterly Report on Form 10-Q filed with the SEC on November 8, 2022 and our other Periodic Reports filed with the SEC. Forward-looking statements represent our management's beliefs and assumptions only as of the date of this presentation and include all matters that are not historical facts. Our actual future results may be materially different from what we expect. Except as required by law, we assume no obligation to update these forward-looking statements publicly, or to update the reasons actual results could differ materially from those anticipated in the forward-looking statements, even if new information becomes available in the future.

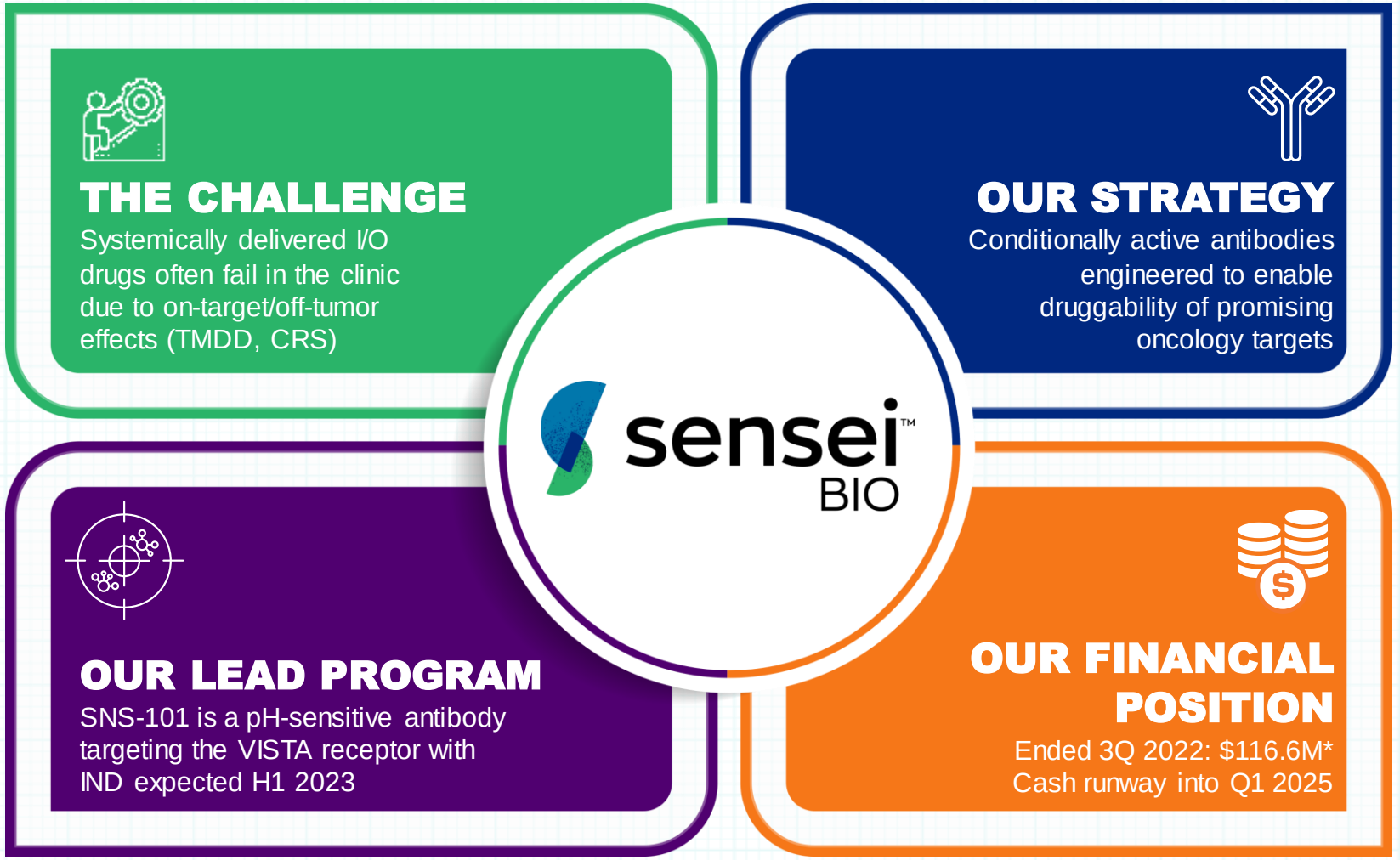
Certain information contained in this presentation relates to, or is based on, studies, publications, surveys and other data obtained from third-party sources and the Company's own internal estimates and research. While the Company believes these third-party sources to be reliable as of the date of this presentation, it has not independently verified, and makes no representation as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. In addition, all of the market data included in this presentation involves a number of assumptions and limitations, and there can be no guarantee as to the accuracy or reliability of such assumptions. Finally, while we believe our own internal research is reliable, such research has not been verified by any independent source.

sensei™ BIO

Agenda

John Celebi *President & Chief Executive Officer, Sensei Bio*	Welcome/TMAb Mission
Robert Schreiber, Ph.D. *Professor, Washington University School of Medicine* *Member, Sensei Immuno-Oncology Advisory Board*	VISTA Biology
Edward van der Horst, Ph.D. *SVP, TMAb Antibody Development, Sensei Bio*	SNS-101 Overview & Preclinical Data Review
Robert Pierce, M.D. *Chief R&D Officer, Sensio Bio* **Ron Weitzman, M.D.** *Interim Chief Medical Officer, Sensei Bio*	SNS-101 Translational Medicine & Clinical Development Plan
Neil Canavan *MD, KOL Network, LifeSci Advisors*	Fireside Chat

Engineered Selectivity to Extend the Reach of Immuno-oncology Agents



*Consists of cash, cash equivalents and marketable securities

Lack of Selectivity is a Major Obstacle to CI Innovation

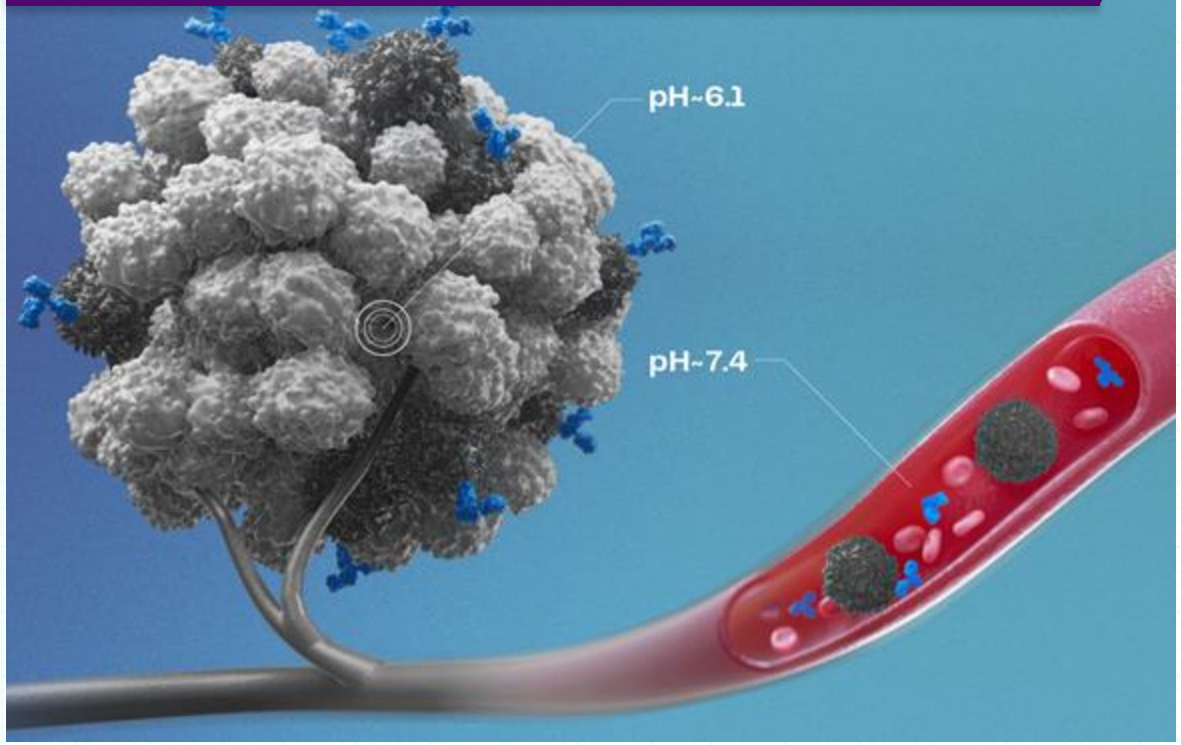
Industry Problem	Sensei's Solution
Conventional antibodies target immune checkpoints that are highly expressed in normal tissues, resulting in:	**Conditionally active antibodies are selectively targeted to the tumor microenvironment, potentially providing:**
Dose-limiting toxicities due to on-target/off-tumor action	Little or no toxicity due to selective on-target/on-tumor action
Pharmacological sink effect requires higher and more frequent dosing	Lower and less frequent doses by avoiding normal tissue binding
Suboptimal activity due to poor PK and dose-limiting toxicities	Powerful activity selectively focused on the tumor microenvironment

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

Robert Schreiber, Ph.D.

VISTA Biology

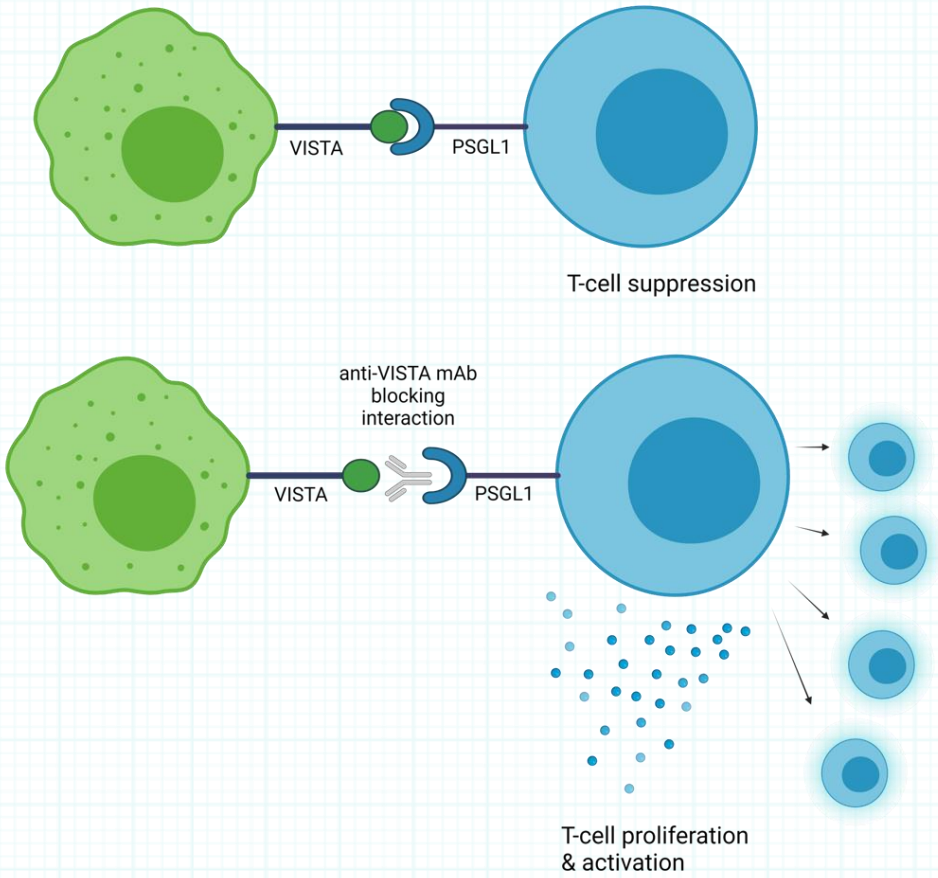
VISTA (B7-H5) is recognized an important immune checkpoint and B7 family member that is expressed on myeloid cells, a hub of immunosuppressive activity, and is activated via binding to its receptor on T-cells (PSGL-1) at sub-physiologic pH

sensei BIO

VISTA: A promising immune checkpoint target expressed predominantly on myeloid cells

- VISTA (V-domain Ig-containing Suppressor of T cell Activation VISTA), also known as B7-H5 or PD-1H is a B7 family member protein with homology to PD-L1
- VISTA suppresses T cell activation[1]
- Highly expressed on myeloid cells including macrophages and neutrophils; NK cells, T-regs and exhausted T cells have been reported to express VISTA[2]
- VISTA expression appears to be upregulated by hypoxia with a HIF1α site identified in VISTA's promoter
- Inhibition of VISTA may "convert" myeloid cells to a proinflammatory/immune activating state; VISTA may "reverse signal" and play a role in enforcing myeloid immunosuppressive program
- Excellent therapeutic combinability with CTLA-4 or PD-1/PD-L1 T cell checkpoints[3]

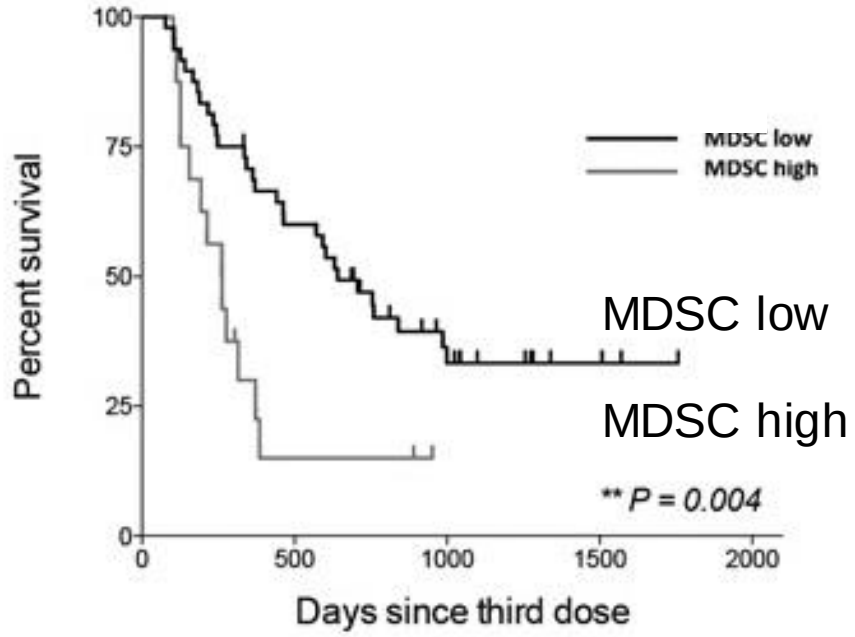
VISTA is a Negative Regulator of T cell Function



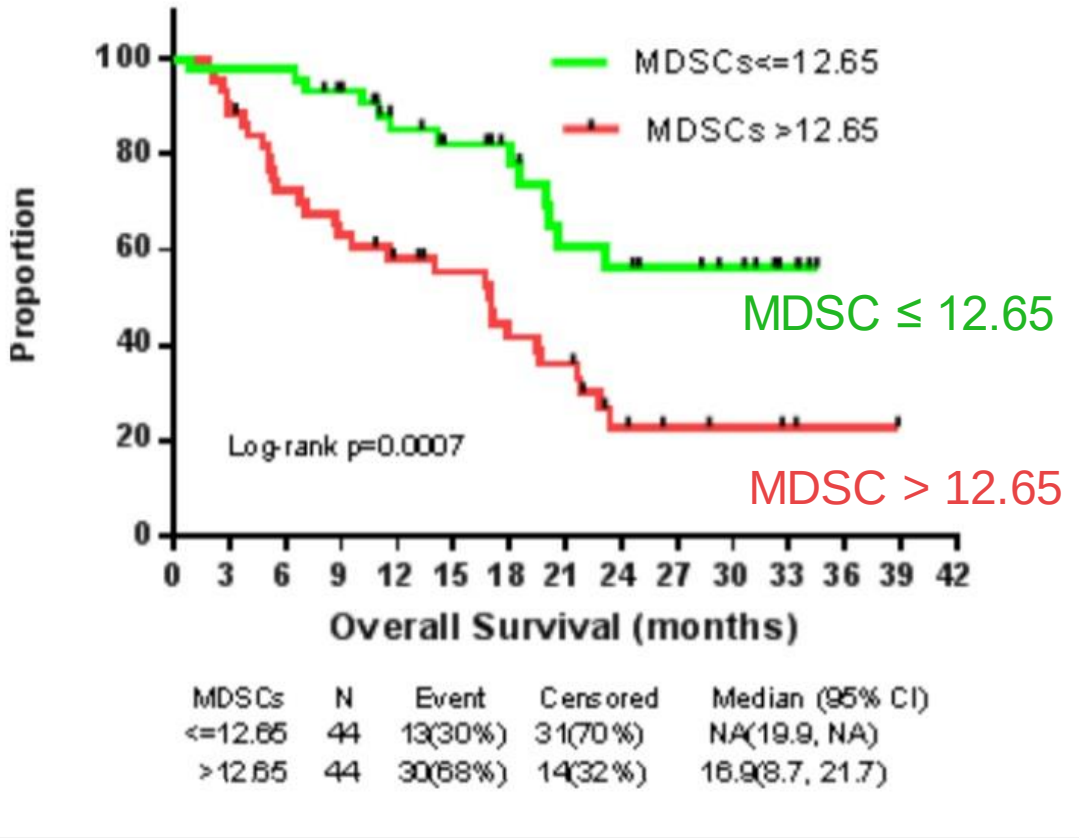
1 Wang et al, *JEM*, 2011
2 Lines et al. *Cancer research* vol. 74,7 (2014)
3 Gao et al. *Nature medicine* vol. 23,5 (2017)

Patients with High Circulating Myeloid Cells Have Shown Lower Overall Survival When Treated with Checkpoint Blockade

Ipilimumab-treated Melanoma Patients



Nivolumab-treated Melanoma Patients



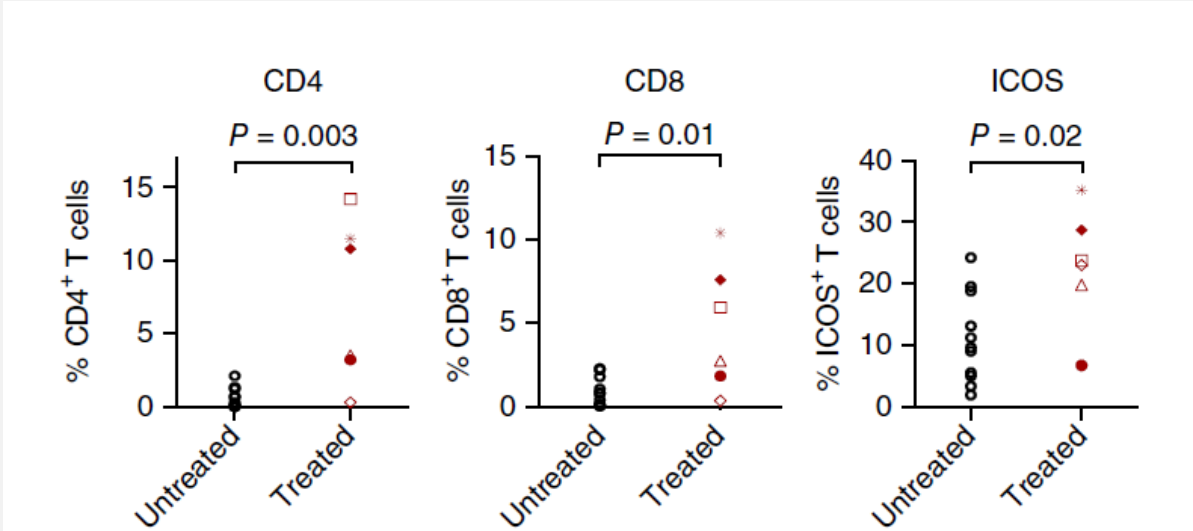
sensei BIO

Kitano et al., *Cancer Immunol Res*. 2012
Weber et al., Cancer Immunol Res. 2016

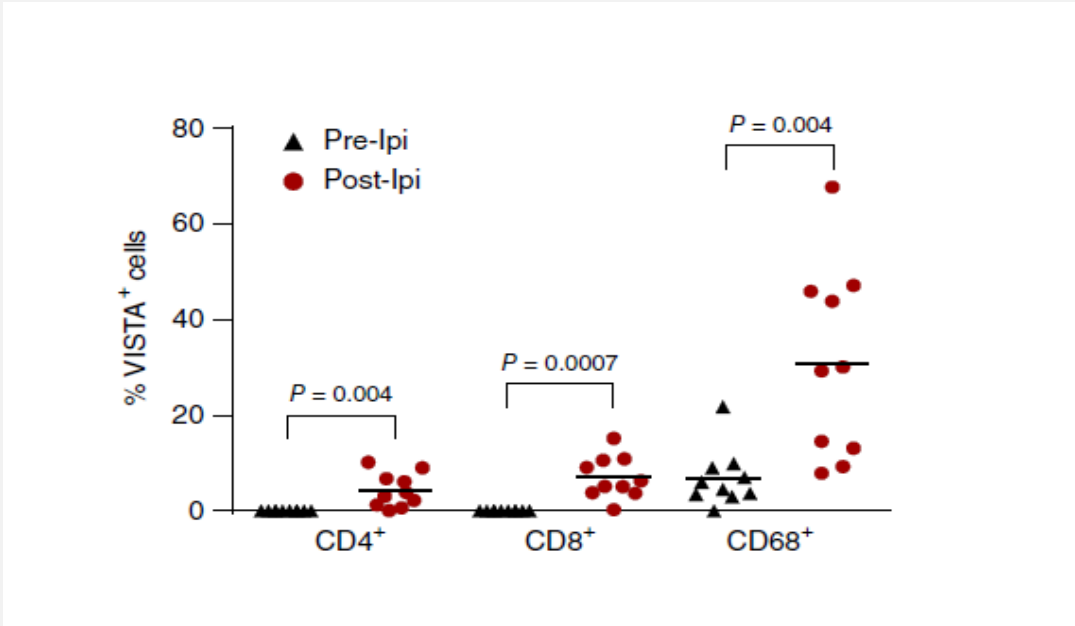
VISTA Checkpoint May Be an Important Resistance Mechanism to Checkpoint Blockade

Can targeting VISTA augment T-cell checkpoint blockade in refractory tumors?

Prostate Immune Cell Infiltrates Increase Following Ipilumimab Treatment



VISTA Increases on Prostate Immune Cell Infiltrates Following Ipilumimab Treatment

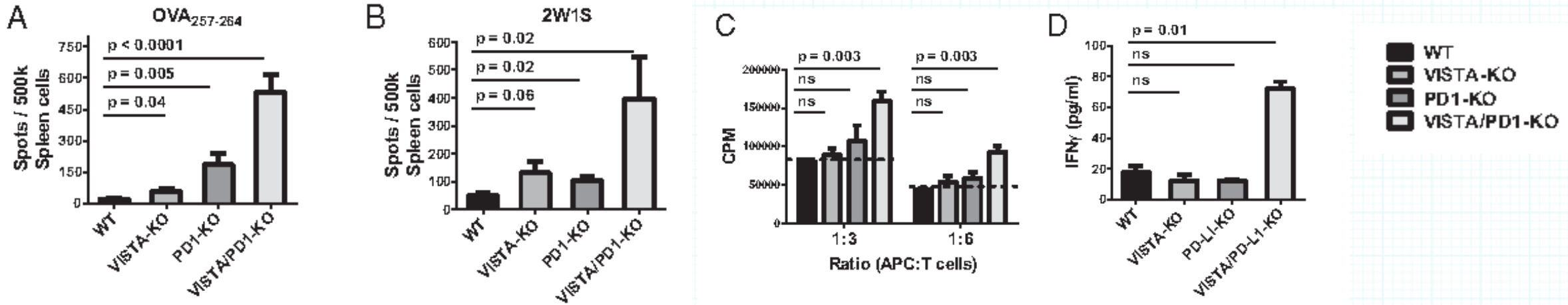


Gao et al., Nat Med. 2017

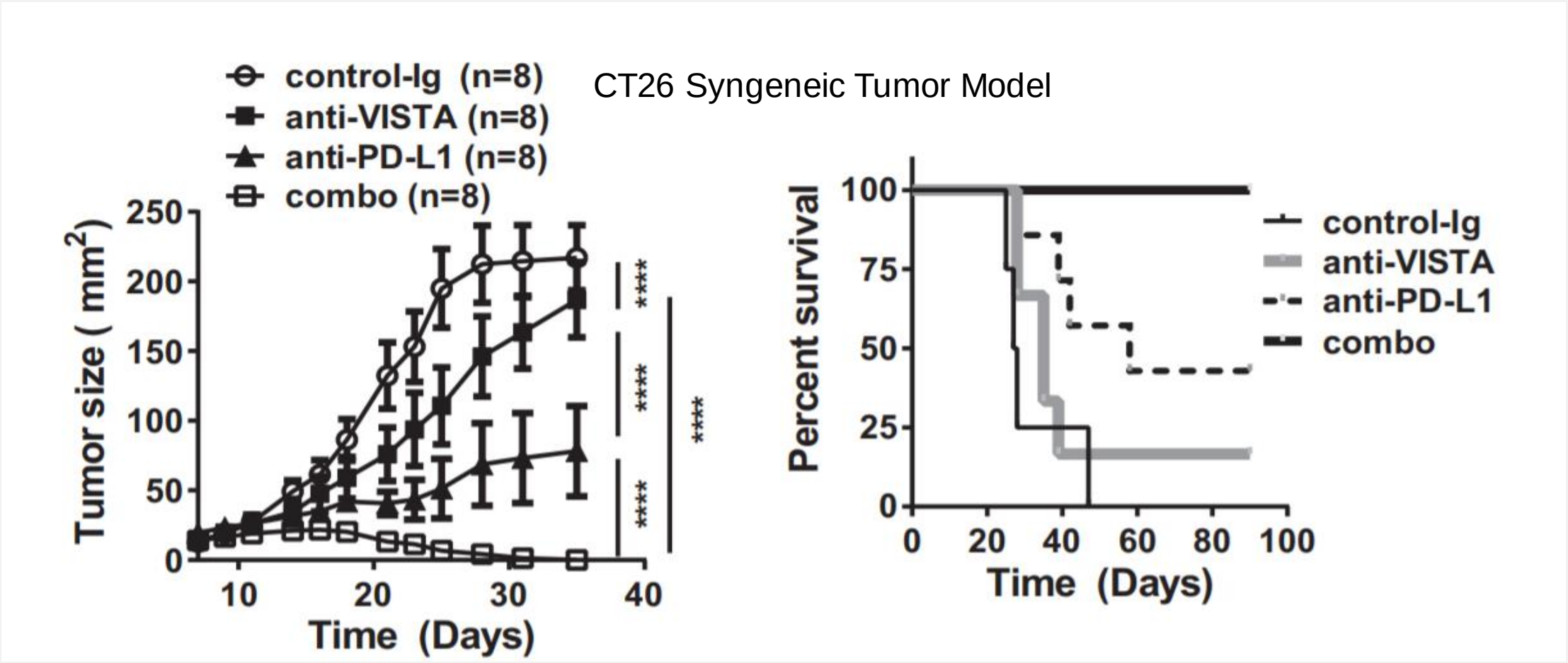
Blocking PD-1 and VISTA together leads to a synergistic increase in antigen-specific T cell responses in Vaccine Models

Immune-checkpoint proteins VISTA and PD-1 nonredundantly regulate murine T-cell responses

Jun Liu[a,b], Ying Yuan[a,1], Wenna Chen[a], Juan Putra[c], Arief A. Suriawinata[c], Austin D. Schenk[d], Halli E. Miller[a], Indira Guleria[e], Richard J. Barth[d], Yina H. Huang[c], and Li Wang[a,2]



VISTA Blockade Synergizes With PD-1/L-1 Pathway Inhibition in a Tumor Model



Liu J. et al. *PNAS* 2015

Why Has VISTA Been a Difficult Target?

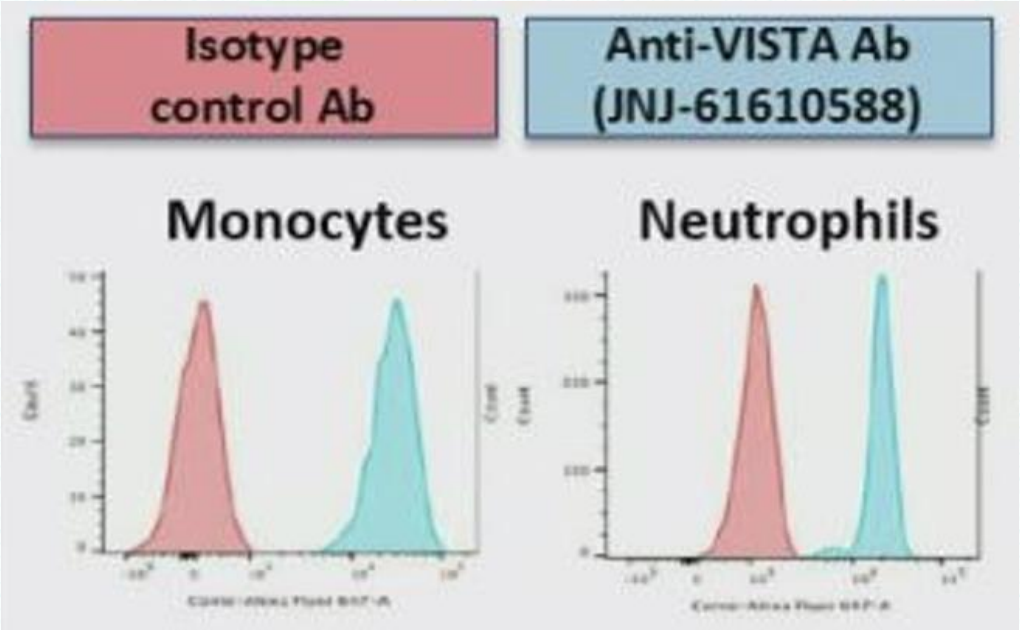
Development of successful drugs targeting VISTA inhibition had been stymied in the past due to two major factors:

- **Strong constitutive expression of VISTA on neutrophils and monocytes in the blood**
  - Binding of drugs to VISTA+ cells in the blood at physiologic pH results in target-mediated drug disposition (TMDD) and clearance
  - Binding of mAbs to cells in blood can lead to cellular activation and cytokine release syndrome (CRS), particularly Fc-competent IgG1 antibodies
  - JNJ 61610588, an Fc-competent IgG1 monoclonal antibody, was the first anti-VISTA mAb was tested in the clinic (Phase 1, advanced solid tumors)
    - TMDD was pronounced and CRS was noted at subtherapeutic doses, including a grade 3 CRS at 0.3 mg/kg[1]
    - Development was halted by JNJ; this antibody is now licensed to Curis and renamed CI-8893
- **Lack of clarity on the identity of the critical counter-receptor responsible for T cell suppression**
  - Putative interaction partners included VISTA itself (homotypic interaction), VSIG-3, VSIG-8, Syndecan-2, LRIG-1 and PSGL-1
  - Unclear how to select the right "inhibitor" if you don't know what interaction needs to be blocked
  - From an immunological perspective, PSGL-1 makes sense as it had been previously demonstrated to act as a T cell checkpoint, strongly suppressing T cell activation, concomitantly increasing PD-1 expression and exhaustion

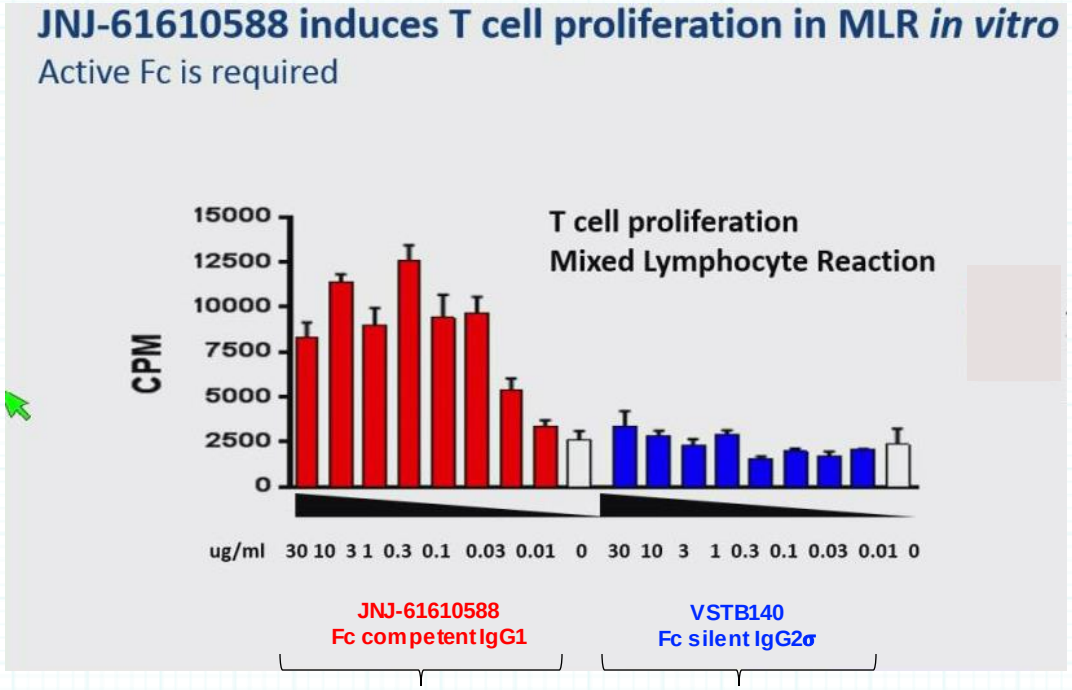
[1]CA-4948 & CI-8993 Clinical Data Update, *January 2022 (Curis corporate presentation)*

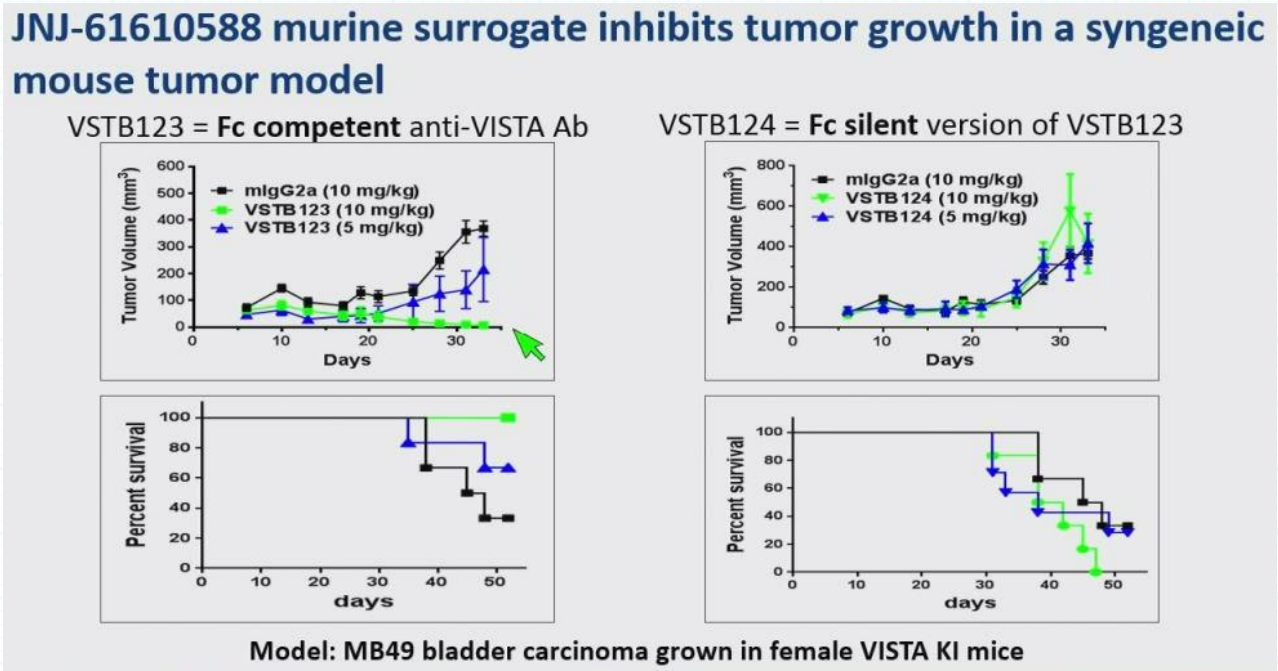
VISTA is Expressed at High Levels on Human Monocytes and Neutrophils

Flow Cytometry Analysis of VISTA Expression on Normal Human Peripheral Immune Cells



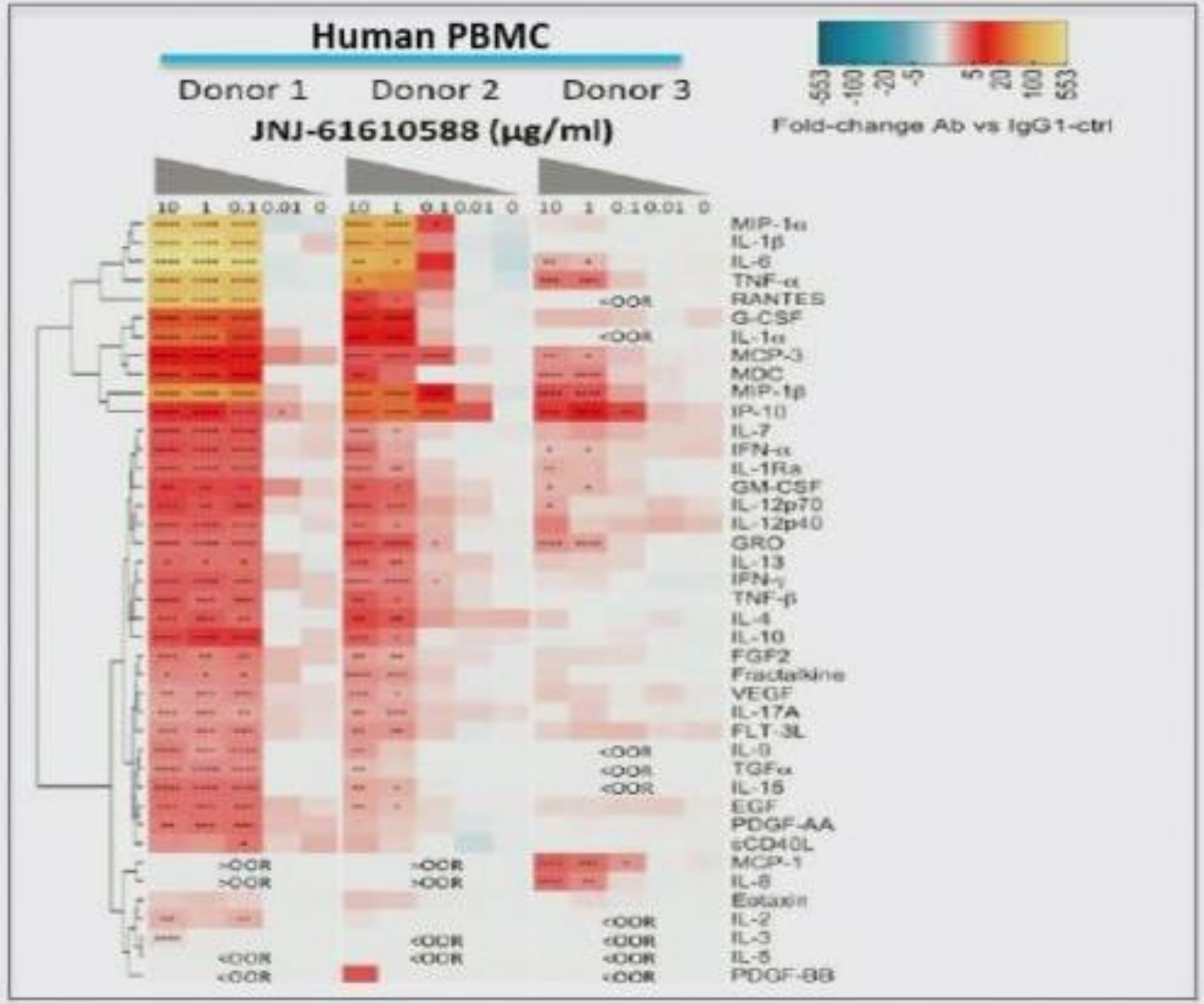
Fc-competent Framework is Required for Optimal Activity of Anti-VISTA Monoclonal Antibodies

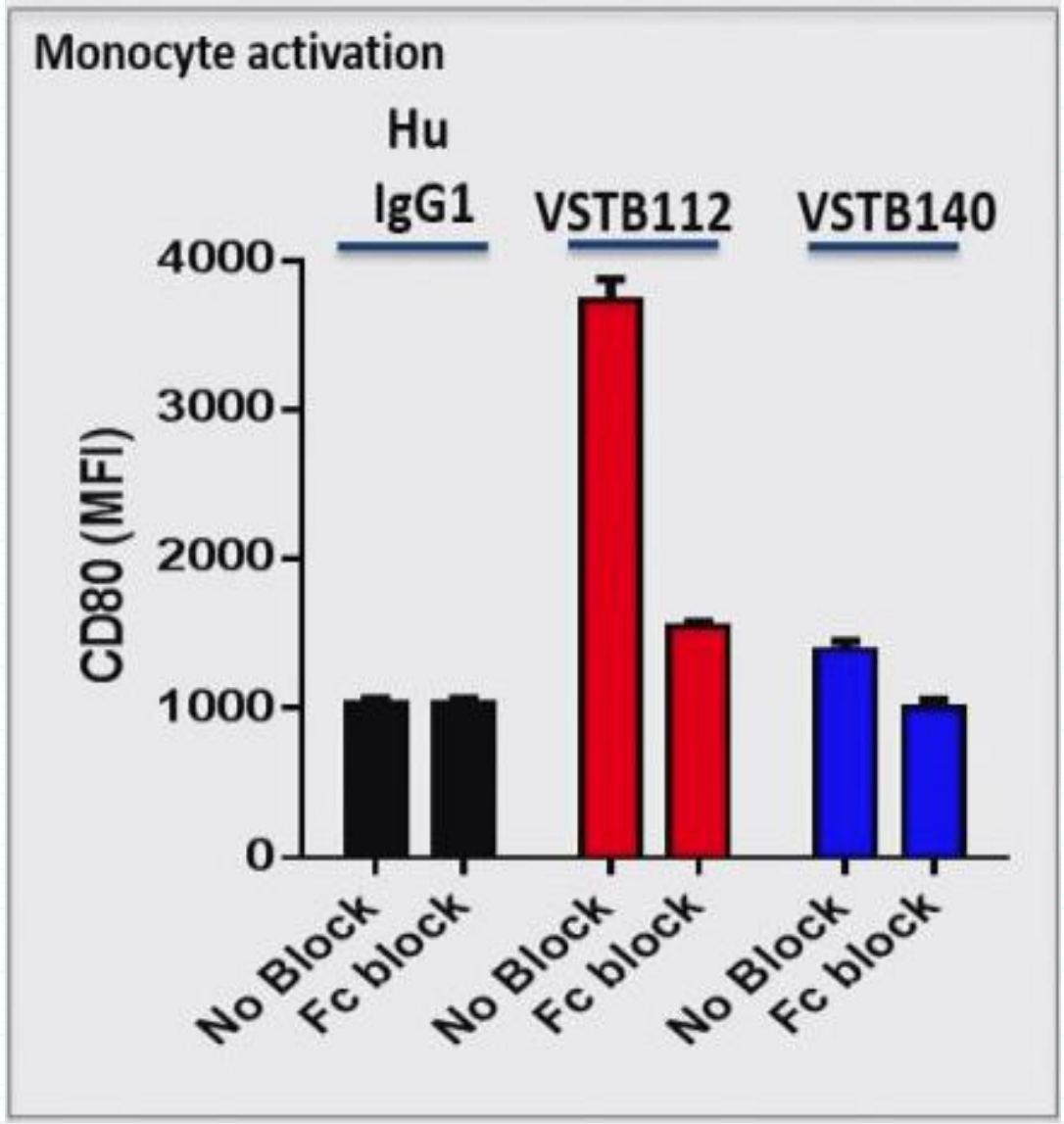




Combination of on-target/off-tumor binding to neutrophils and monocytes in the blood and Fc-mediated myeloid activation likely caused CRS seen with JNJ 61610588 in Phase 1 study

JNJ-61610588 or surrogate induced monocyte activation and cytokine release requires FC receptor cross-linking

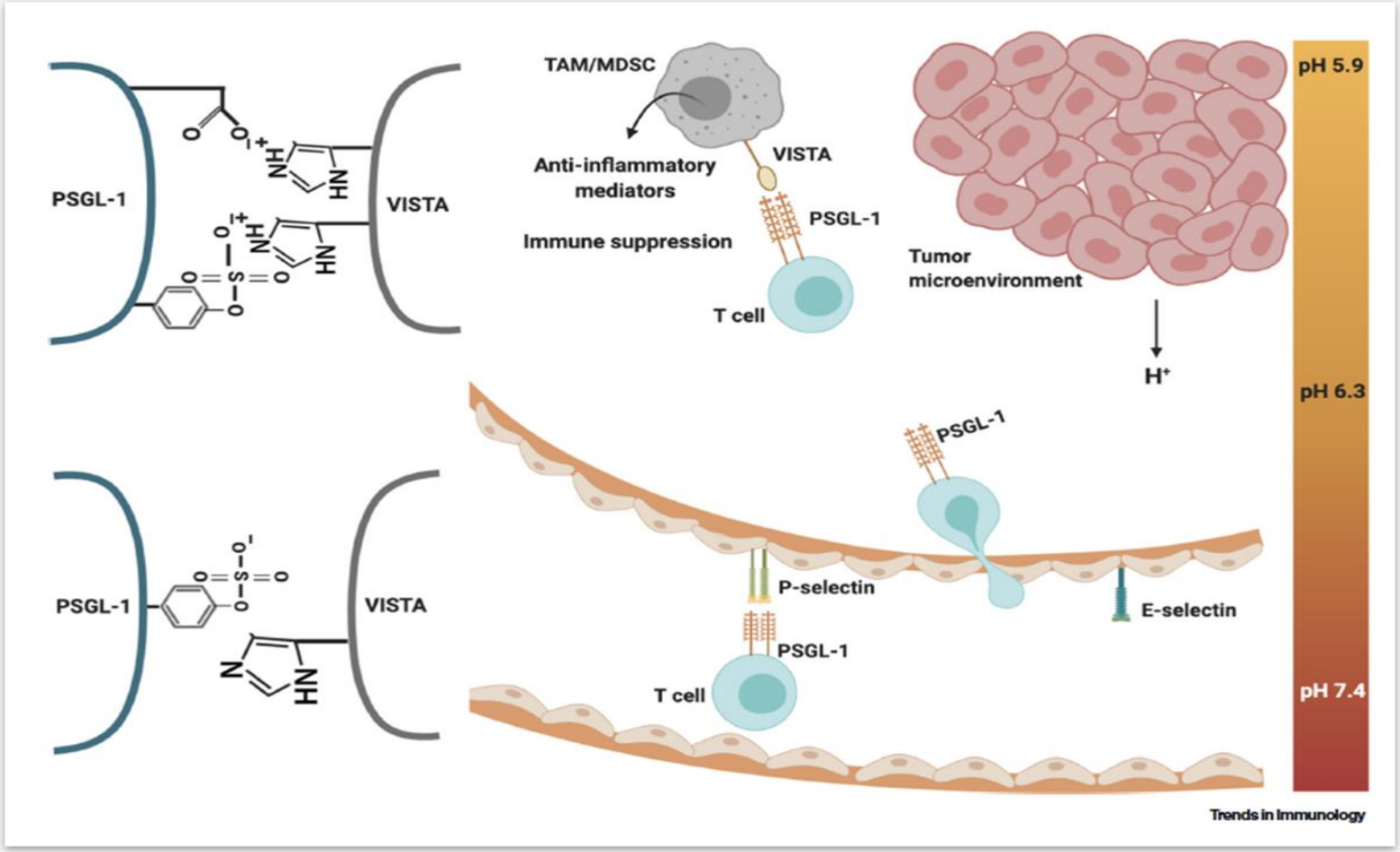




VISTA binding to the PSGL-1, inhibitory T cell receptor, is pH dependent

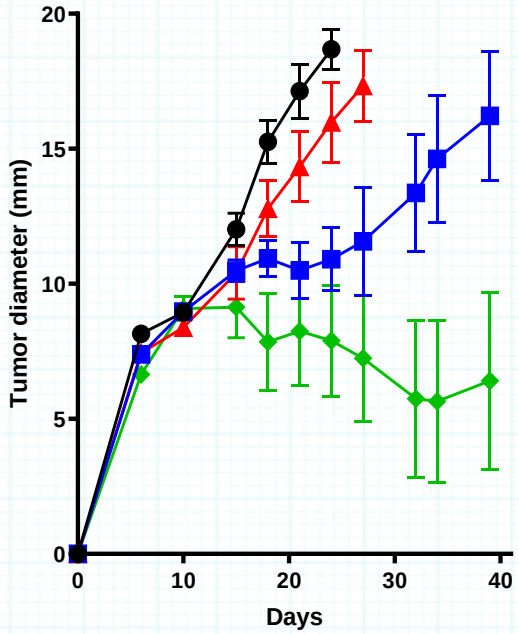
Active VISTA

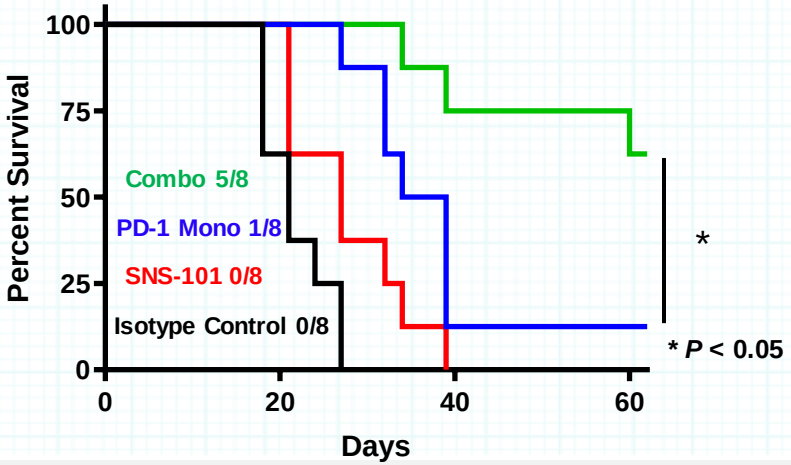
Inactive VISTA

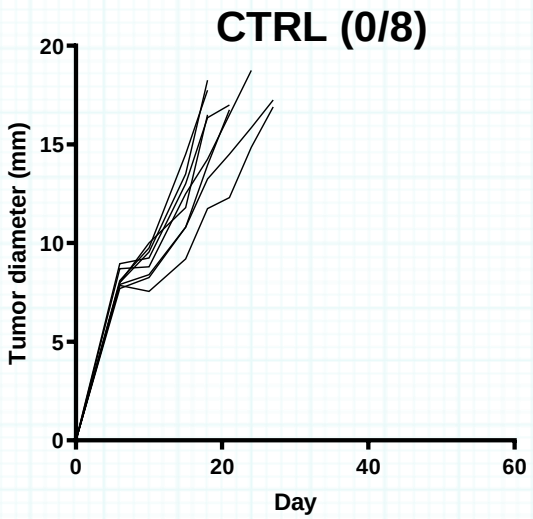


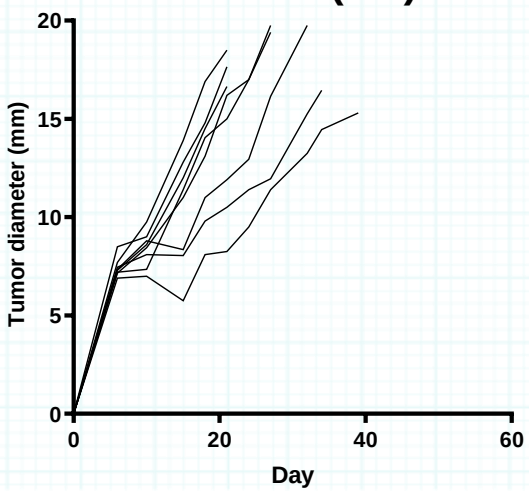
Adapted from Gao et al. *Nature medicine* vol. 23,5 (2017)

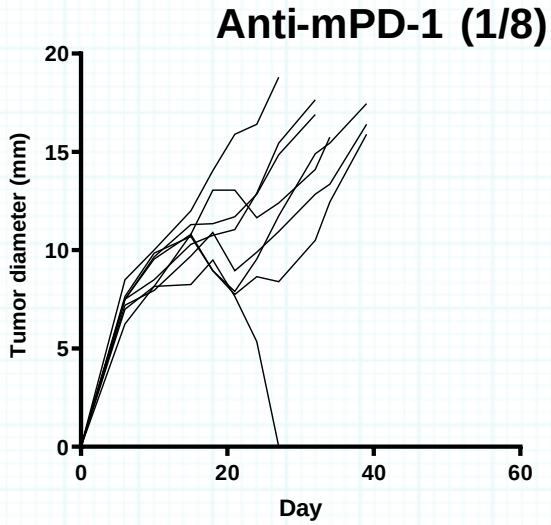
SNS-101 Re-sensitized Anti-PD-1 Insensitive Sarcomas Tumors in 1956 Model in Human VISTA Knock-in Mice

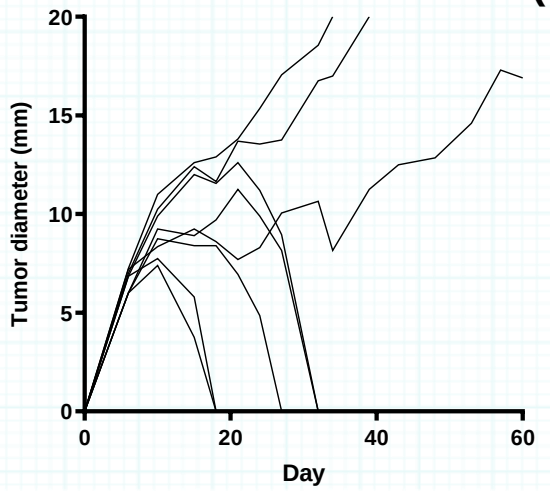












sensei BIO

Courtesy of Bob Schreiber/Wash U

VISTA Biology – Summary
Why VISTA Has Been Difficult to Drug Historically

- VISTA is expressed at high levels on monocytes and neutrophils
  - Binding to cells in the blood leads to sub-optimal PK due to target-mediated clearance and on-target/off-tumor toxicity (CRS)
- Engagement of FcgR may be a prerequisite for optimal activity of anti-VISTA antibodies
  - Fc silent antibodies are not effective at T cell proliferation ex vivo or anti-tumor activity in vivo despite picomolar binding affinity to VISTA
  - CRS likely due to binding to blood monocytes and neutrophils, resulting in FcgR-mediated activation
- BUT the VISTA checkpoint itself is only "ON", when VISTA is protonated under low pH conditions and capable of binding PSGL-1
- Opportunity to develop an antibody with high selectivity for the active/protonated form of VISTA versus the inactive form of VISTA in the blood.
  - Johnston, et al (BMS), demonstrated feasibility of this approach
  - Sensei has developed a conditionally-active, pH-dependent antibody (SNS-101)

Edward van der Horst, Ph.D.

SNS-101 Overview & Preclinical Data

sensei BIO

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

Key features

- Selectivity for Active VISTA^{pH6} over VISTA$^{pH7.4}$
- 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_D) [nM]	0.218	132 (~No binding)

Development milestones

- Preclinical PK, safety and efficacy data presented at conferences throughout 2022
- IND submission planned for 1H23

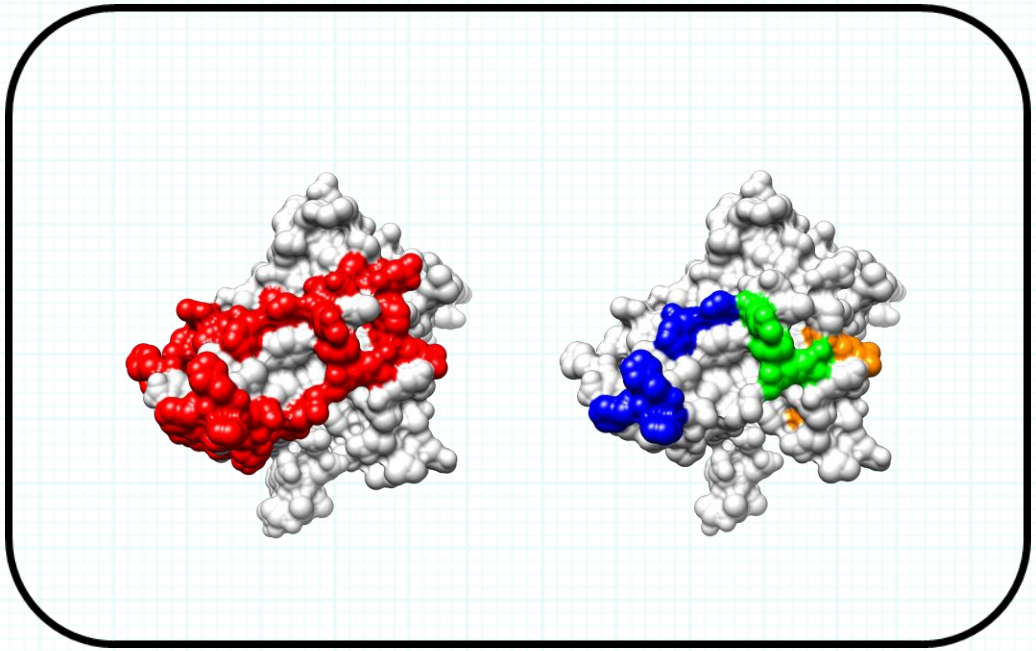
SNS-101 Is a Fully Differentiated Anti-VISTA Antibody

	SNS-101 (sensei BIO)	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	Preclinical	Preclinical	Preclinical

Johnston et al., Nature 2019; Kineta website; Snyder et al, AACR Annual Meeting 2016; Pierre Fabre website; Hummingbird website; Thakkar et al, J of Immunother Cancer, 2022; PharmAbcine website

SNS-101 Blocks PSGL-1:VISTA Protein Interface

SNS-101

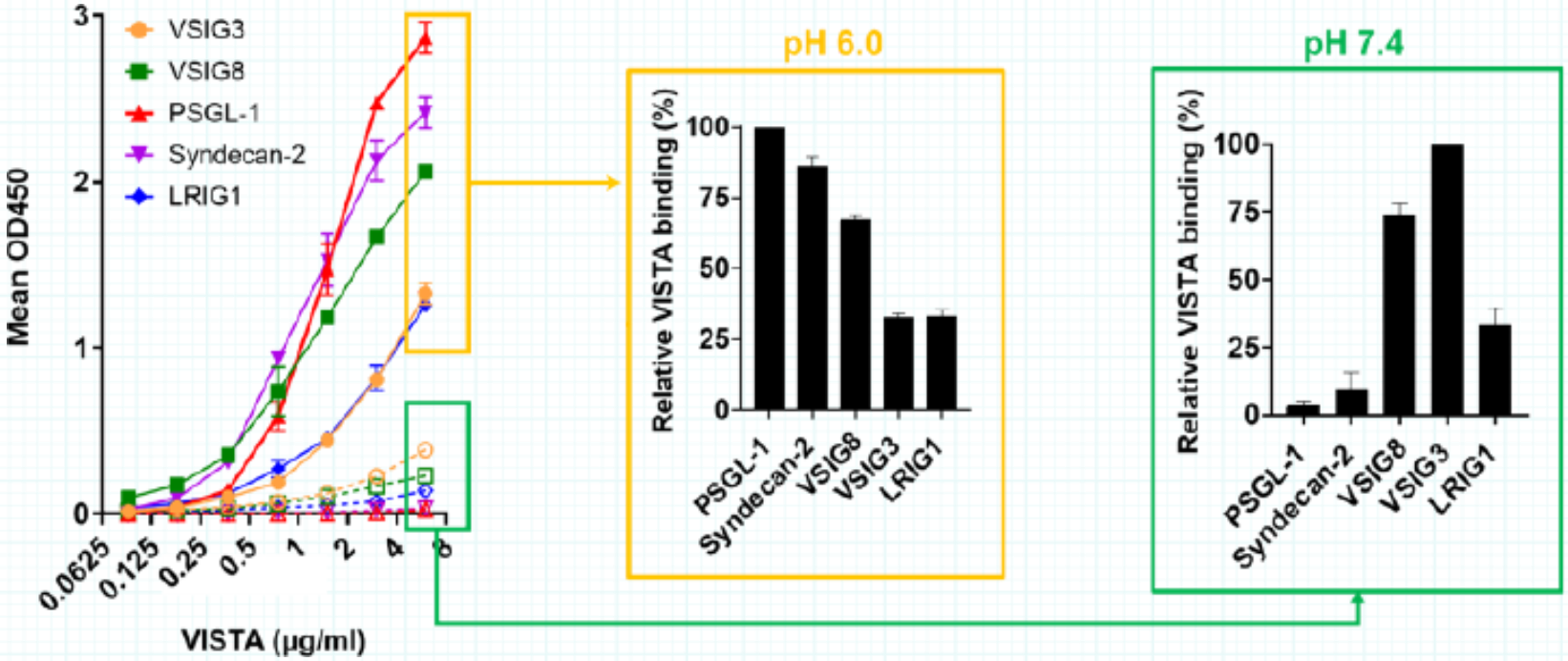


PSGL-1, VSIG-3, and LRIG-1

- VISTA's extracellular domain is uniquely rich in histidines[1]
- Histidines are protonated at low pH enabling VISTA to distinguish the active (acidic pH) and inactive (neutral pH) PSGL-1 binding interface

1. Johnston et al., Nature 2019

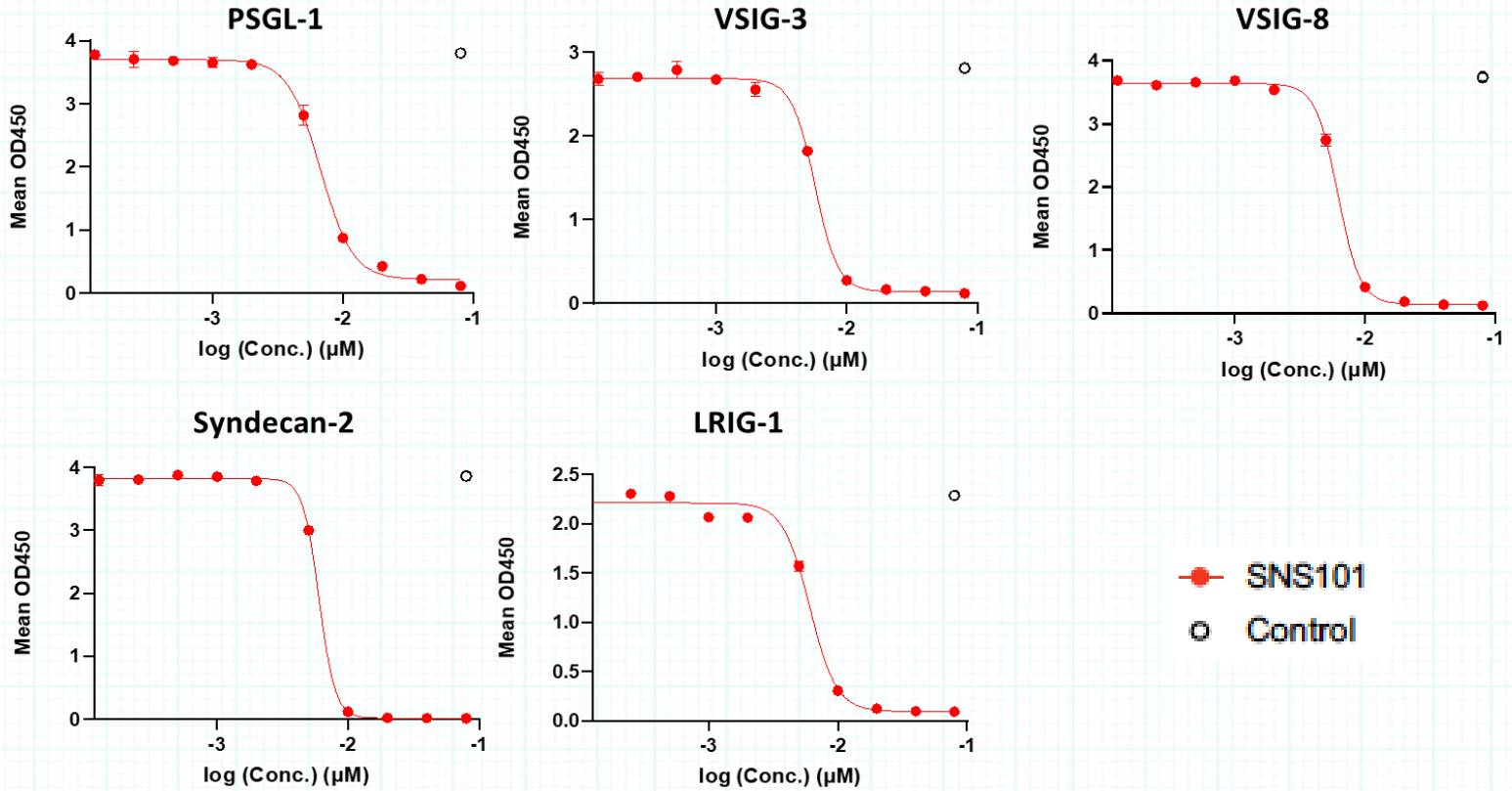
The VISTA:PSGL-1 Interaction is Selective for low pH



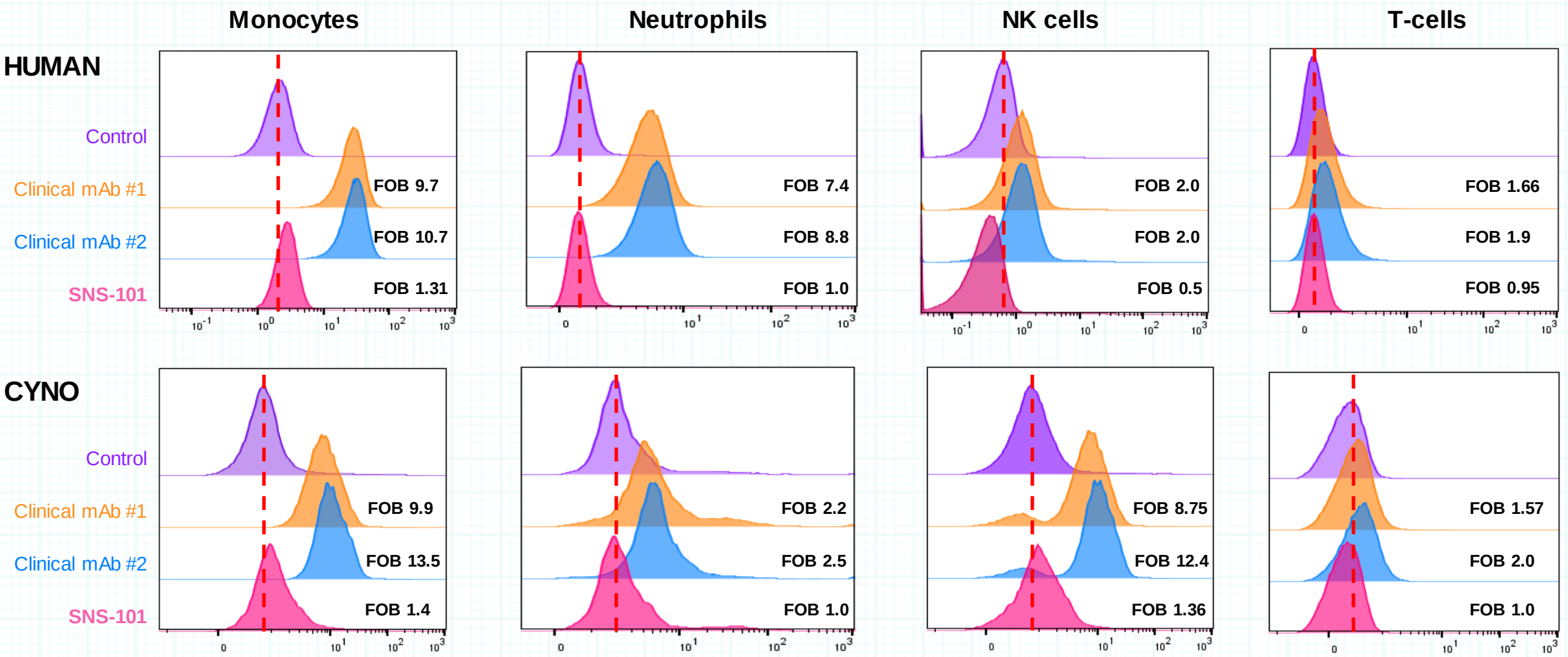
Data are based on *in vitro* assay.

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

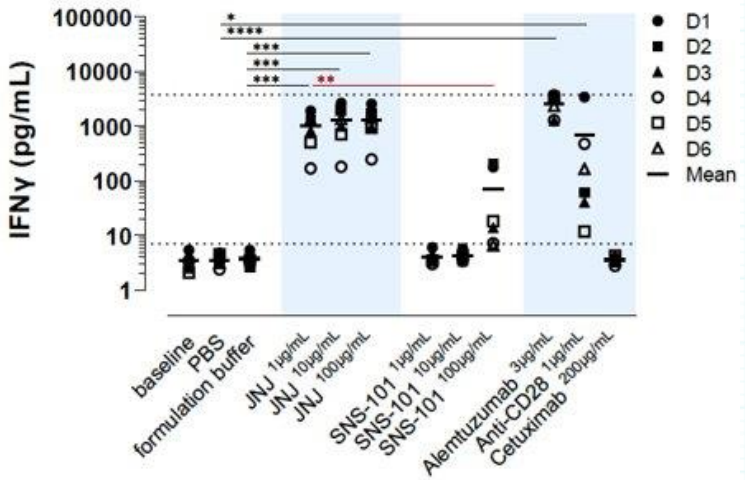


No Significant Binding of SNS-101 to Monocytes, Neutrophils, NK Cells and T-cells in Whole blood at Physiological pH

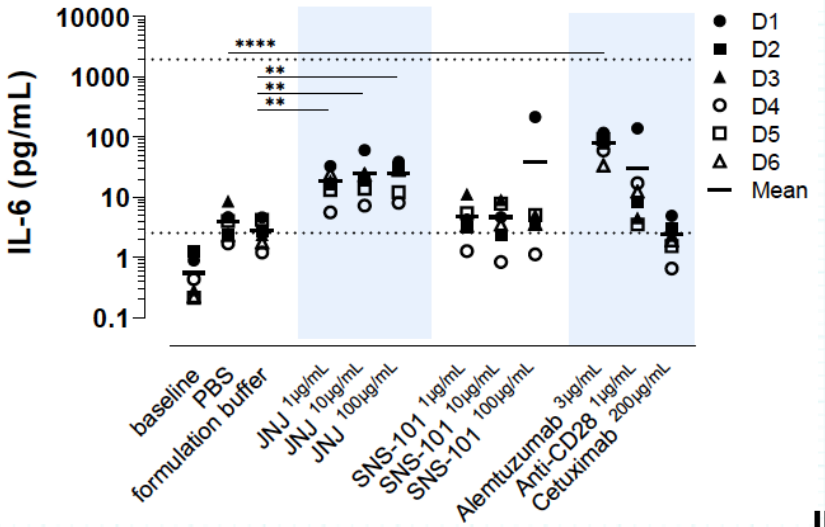


SNS-101 Induced Substantially Lower Cytokine Release in Whole-blood Assay at Neutral pH Compared to pH-independent VISTA Antibody

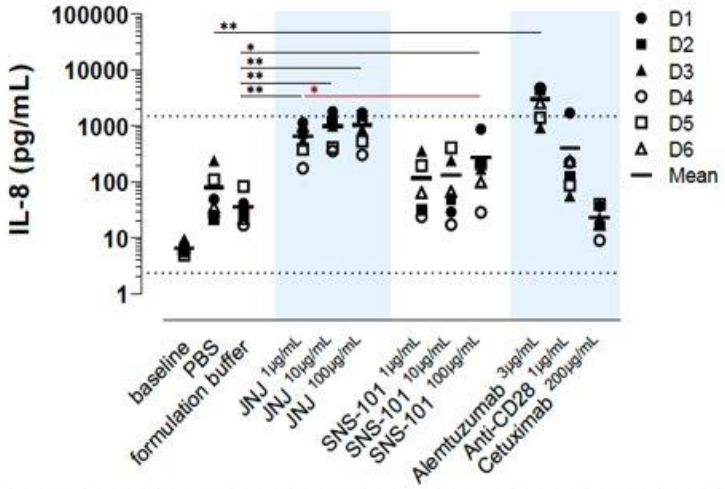
IFN-γ



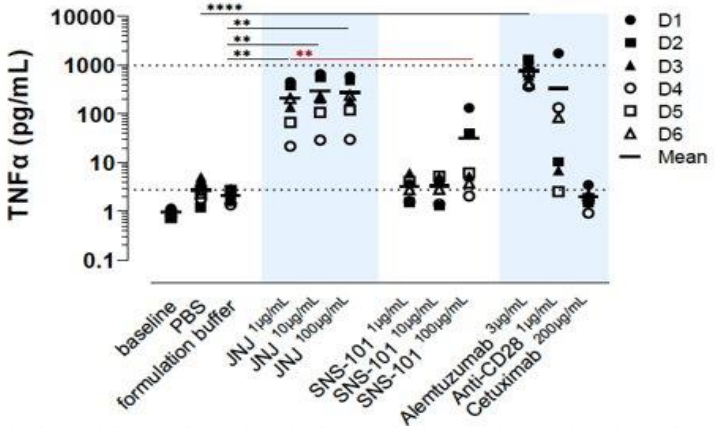
IL-6



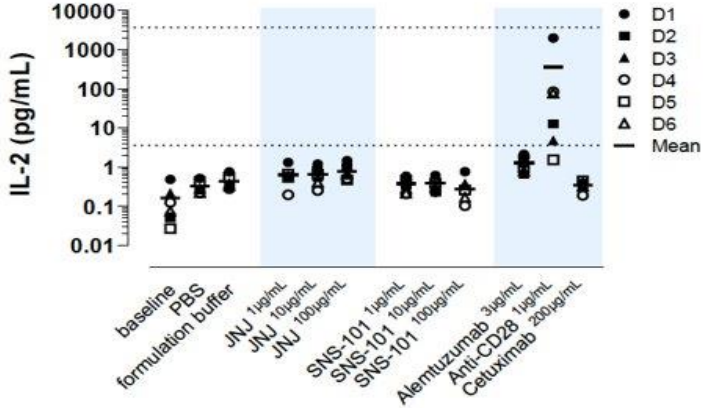
IL-8



TNF-α



IL-2

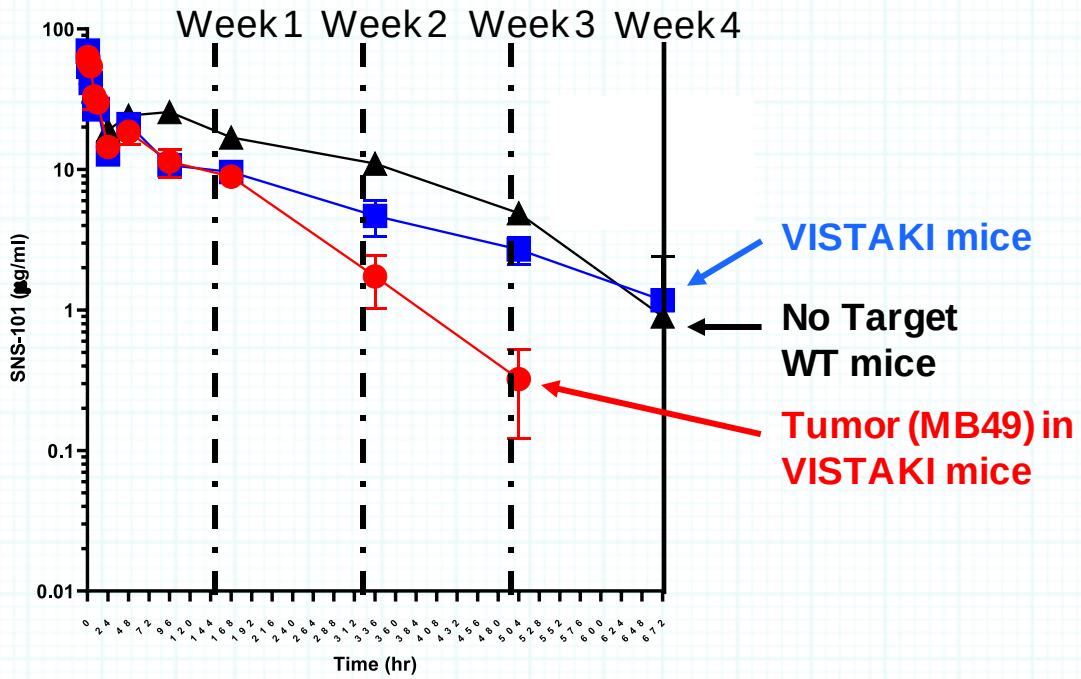


Paired Student's t-test, Holm-Sidak Post-Hoc Analysis,
*** p<0.05; ** p<0.01, *** p<0.001, **** p<0.0001**

sensei BIO

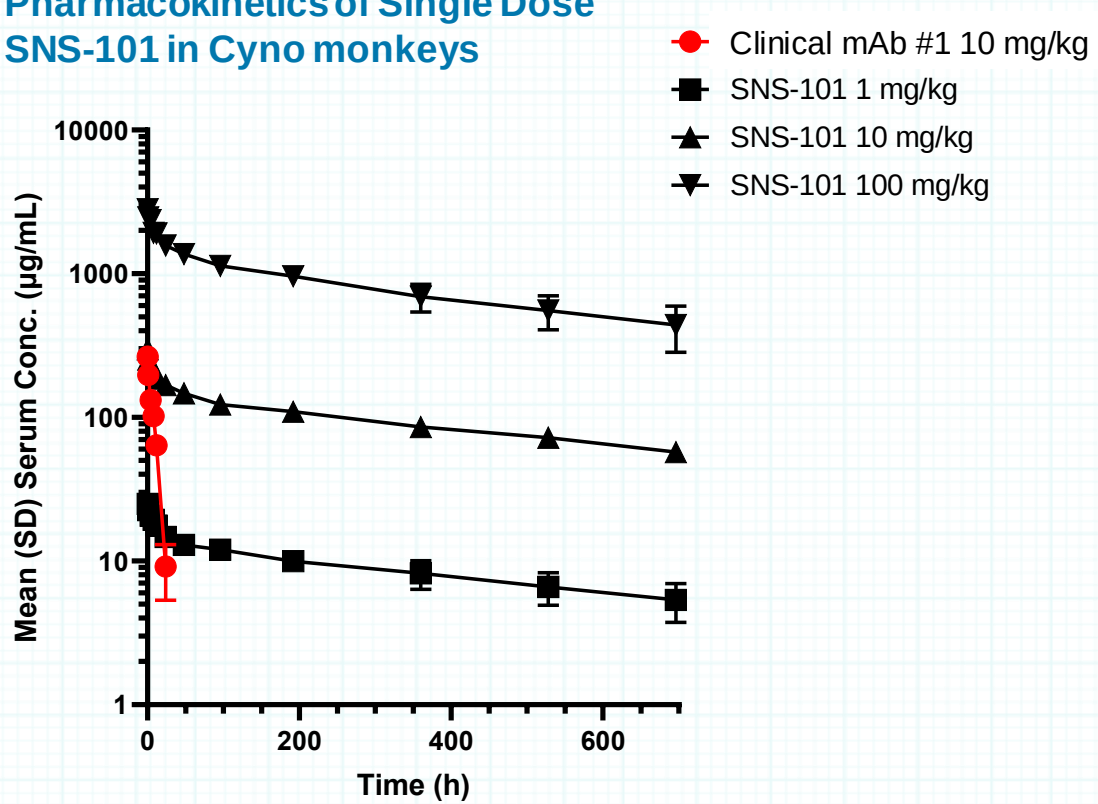
SNS-101 Has Displayed a Favorable Single-dose PK Profile in Preclinical Studies - *No Significant TMDD in Human VISTA KI Mice or Cyno Monkeys*

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



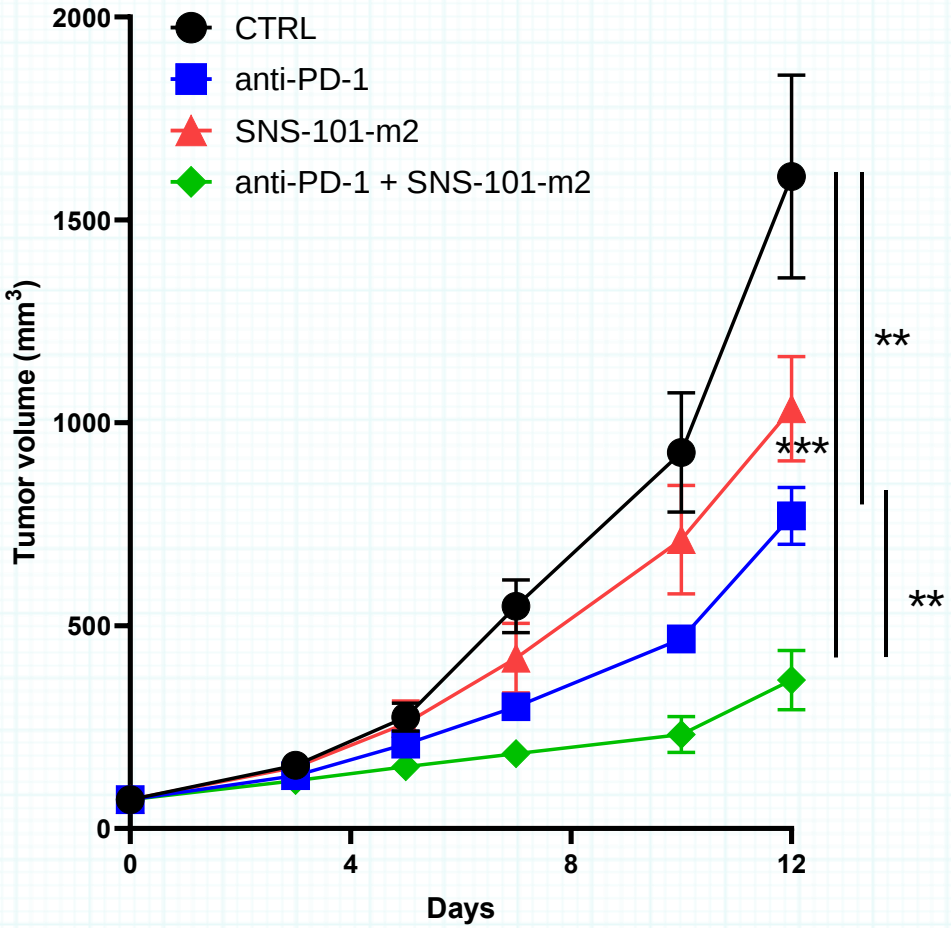
Demonstrated a long mean residence time in the blood, indicating a lack of significant target-mediated drug disposition (TMDD) and clearance in non-malignant tissues

Pharmacokinetics of Single Dose SNS-101 in Cyno monkeys

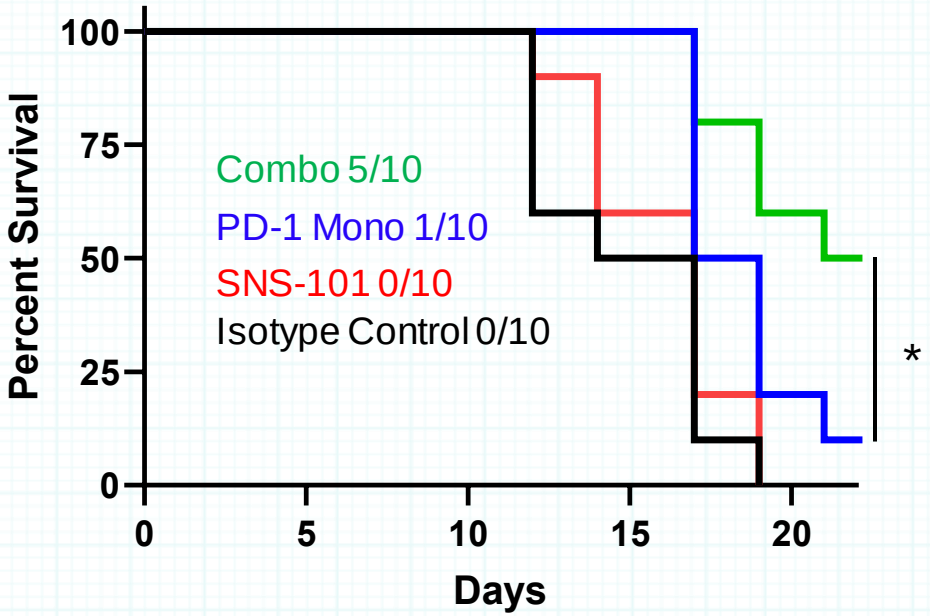


SNS-101 displays linear elimination kinetics unlike a pH-independent anti-VISTA mAb, which demonstrates TMDD and rapid clearance

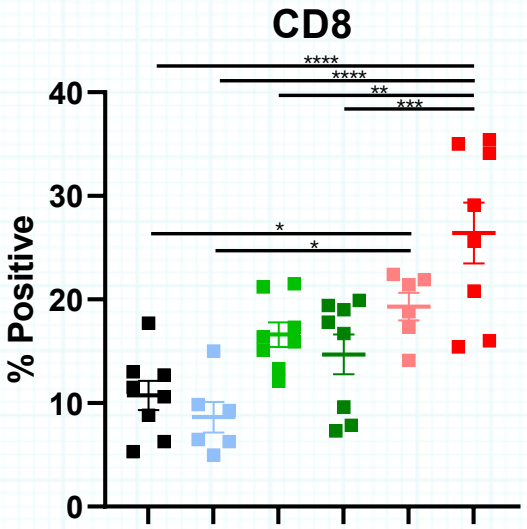
SNS-101 Demonstrated Strong Combinatorial Activity with Anti-PD-1 in MC38 Model in Human VISTA Knock-in Mice



* *P*<0.05; ** *P*<0.01; *** *P*<0.001

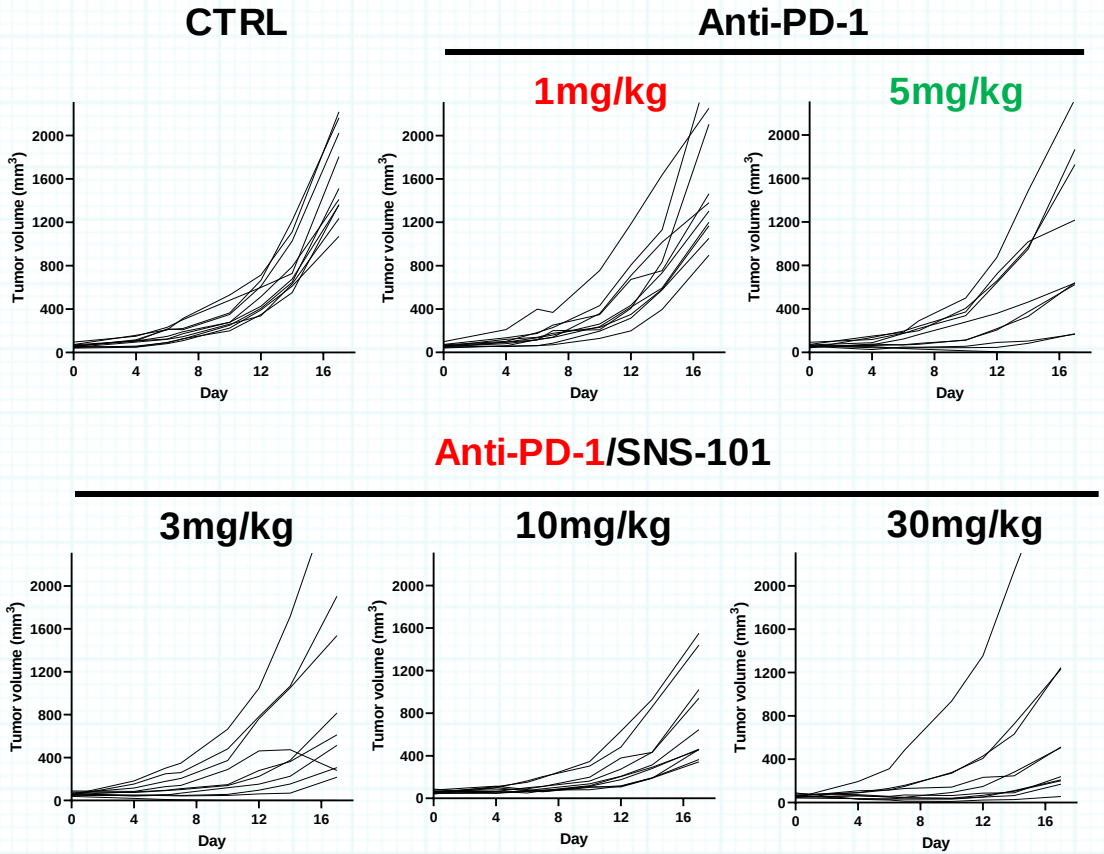


SNS-101 Demonstrated Increased CD8 T-cells in Combination With Anti-PD-1 in MC38 Tumors *In Vivo*



- Isotype Control
- aPD-1- 1 mg/kg
- SNS-101- 10 mg/kg
- SNS-101- 30 mg/kg
- SNS-101- 10 mg/kg ***with Anti-PD-1***
- SNS-101- 30 mg/kg ***with Anti-PD-1***

Frequency of Live, CD45+ Population
One-way ANOVA, Tukey Post-Hoc Analysis,
* p<0.05; ** p<0.01, *** p<0.001, **** p<0.0001



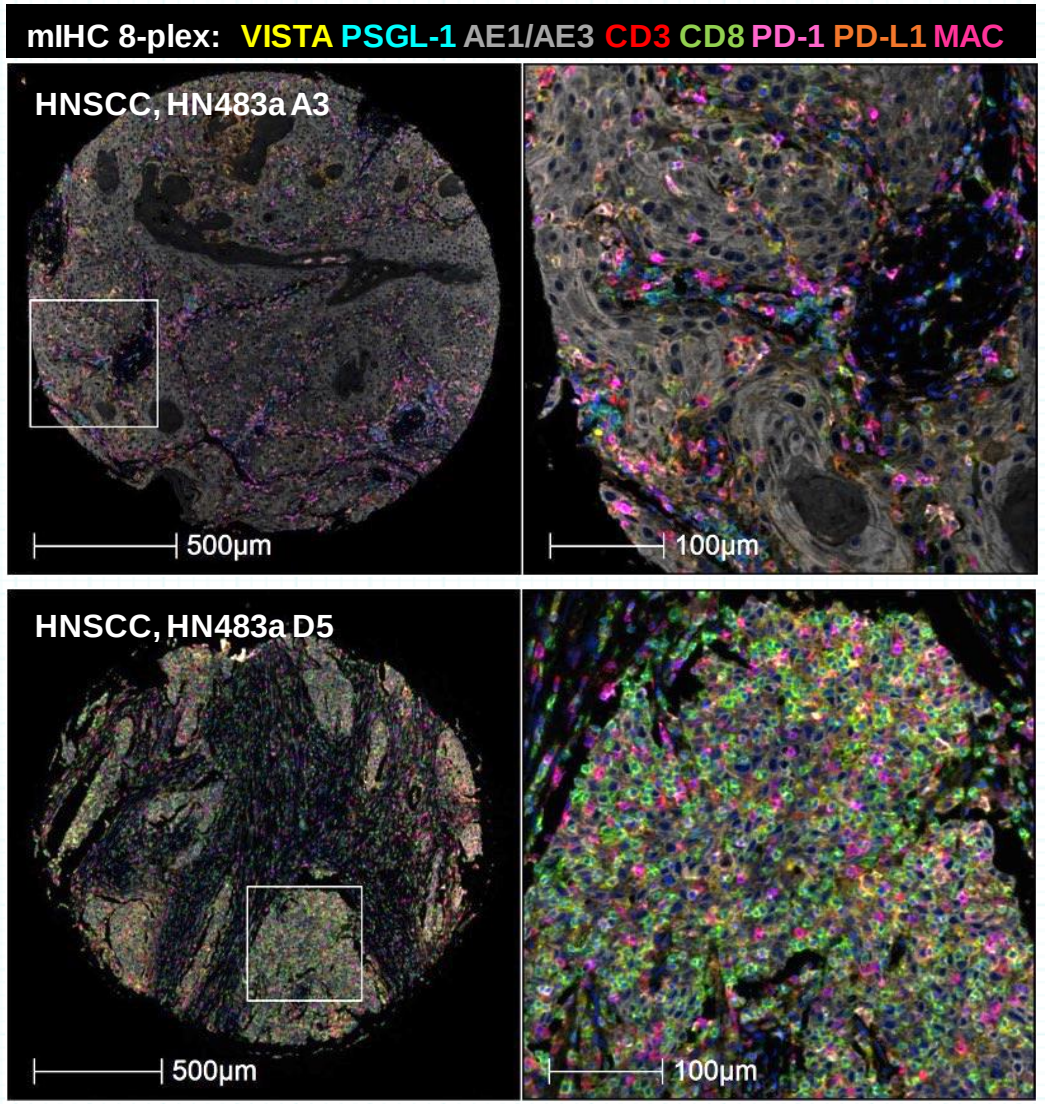
Robert Pierce, M.D. & Ron Weitzman, M.D.

SNS-101 Translational Medicine & Clinical Development Plan

sensei BIO

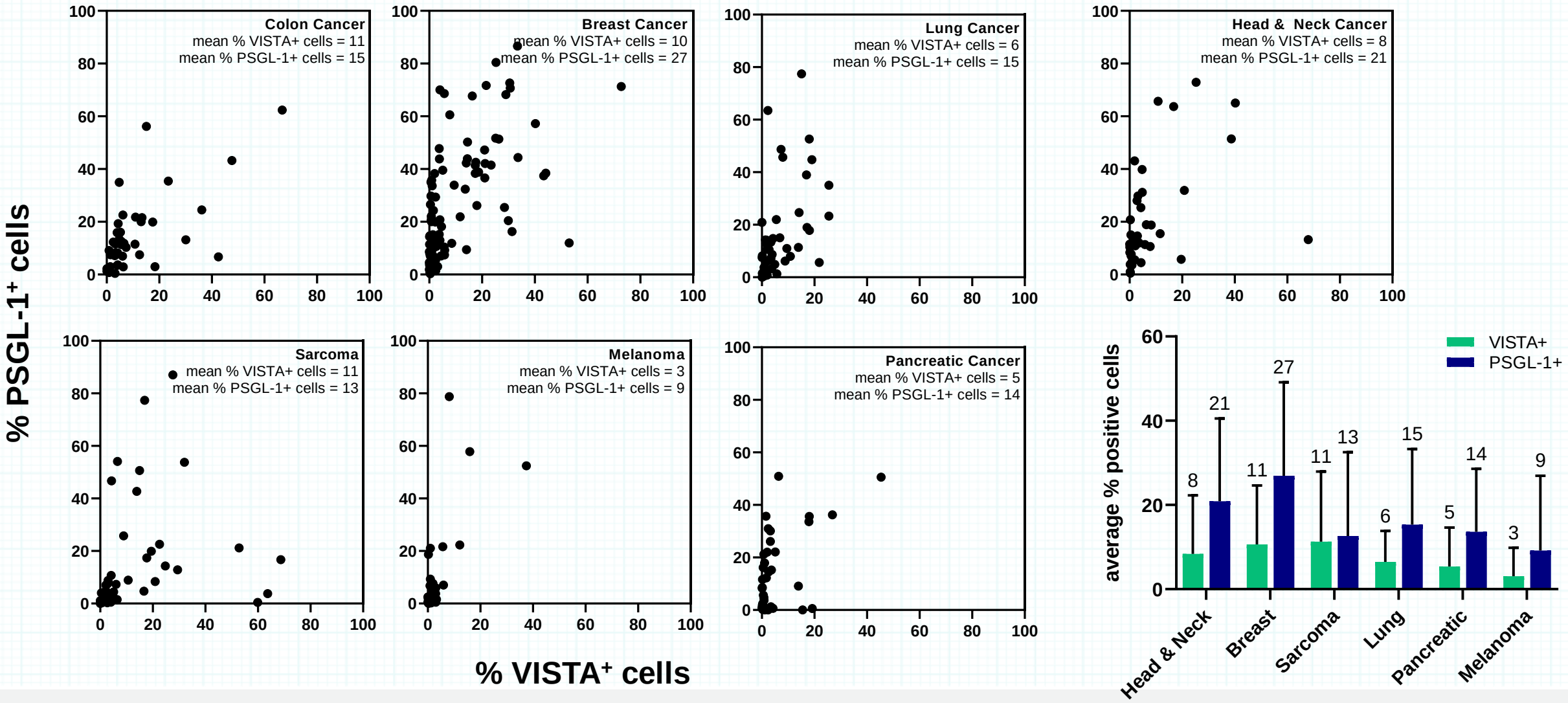
Multiplex IHC Enables Spatial Mapping of VISTA in the TME

- Quantification of VISTA and PSGL-1 Expression
- Spatially resolve VISTA^{+} and PSGL-1^{+} within the broader immune-relevant context of the TME
- Spatial resolution of VISTA, PSGL-1 and other candidate immune checkpoints within the TME may reflect critical cell-cell interactions and inhibitory nodes
- VISTA/PSGL-1 **proximity** may reflect engagement of VISTA checkpoint and high probability of response to SNS-101



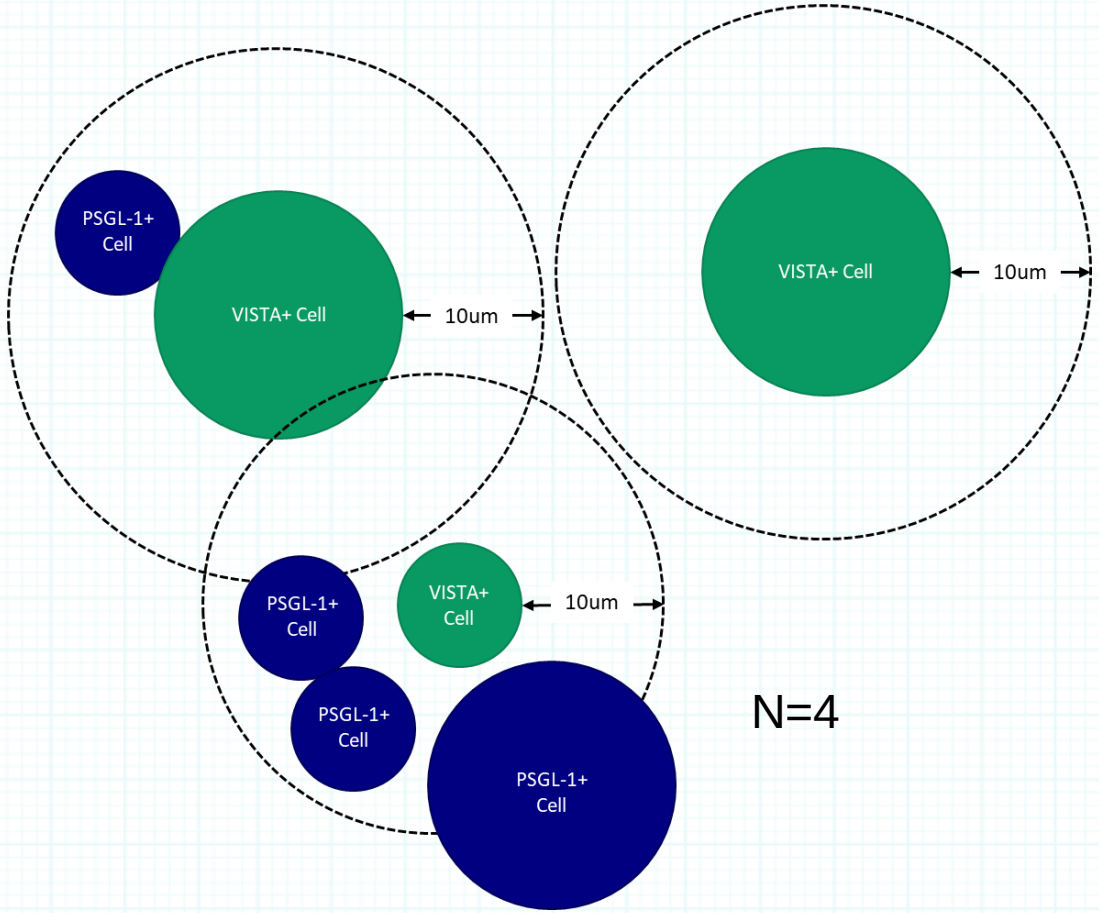
sensei BIO

Quantitative Multiplex Immunohistochemistry Enables Stratification of Tumors with High Expression of VISTA and/or PSGL-1



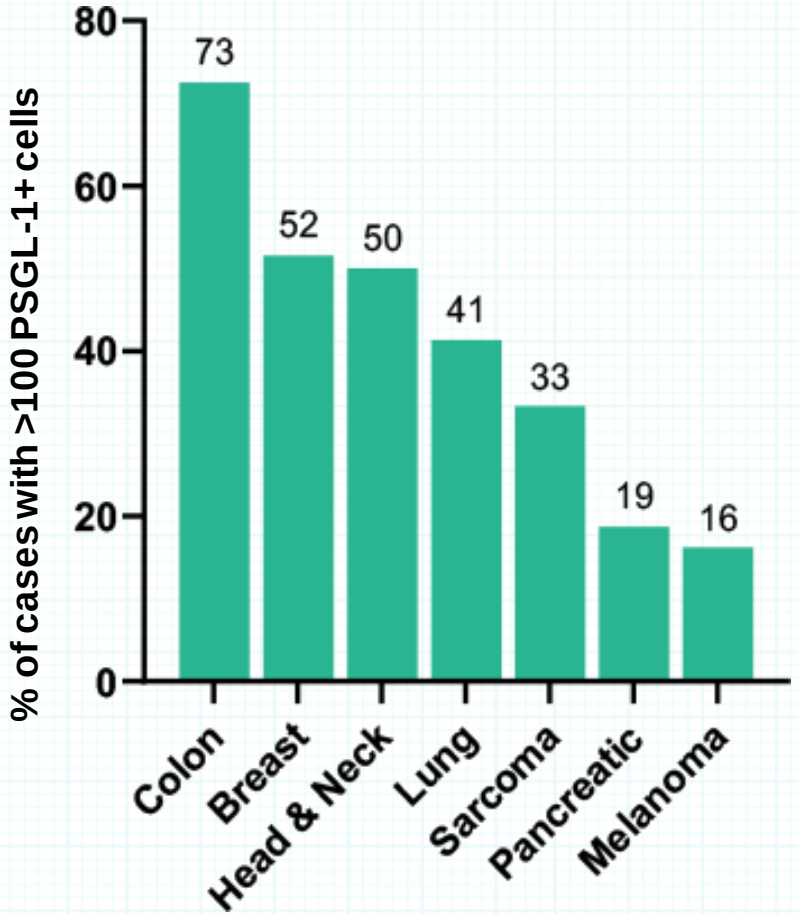
High VISTA/PSGL-1 Proximity Scores in CRC, Breast, HNSCC and Lung

How we measure spatial proximity



N=4

Stratification of tumor types based on mIHC analysis of TMAs



SNS-101: Approach for Phase 2 Cohort Identification to Help Identify and Prioritize High Probability-of-Success Expansion Cohorts

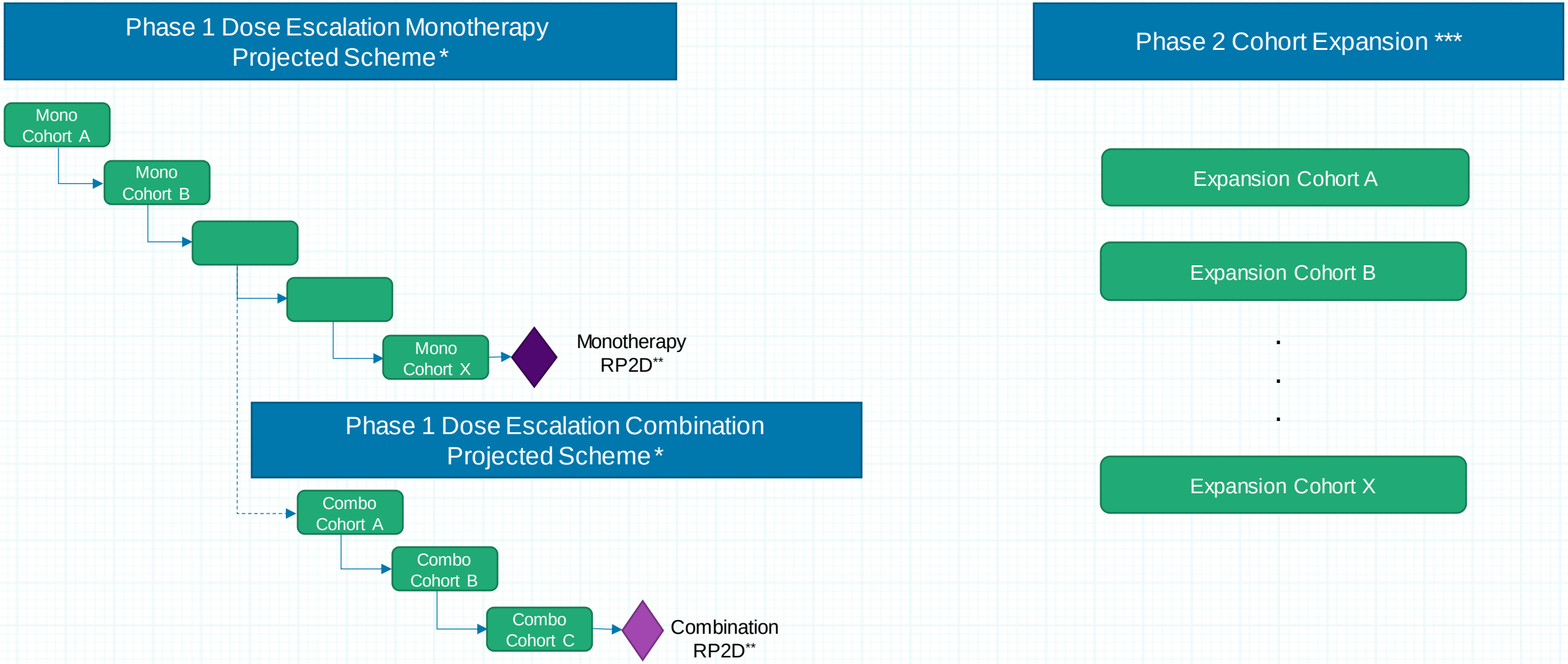
I. Multiplex immunohistochemistry on patient tumor TMAs using 8-plex assay (VISTA, PSGL-1, PD-L1, PD-1, CD3, CD8, macrophage cocktail (CD68+CD163), tumor marker (pancytokeratin)

- Expression analysis of VISTA, PSGL-1, PD-1, PD-L1 in broader immune context
- Proximity analysis (VISTA/PSGL-1 and PD-L1/PD-1)
- Frequency of VISTA^{+} tumor cells across tumor types
- Distribution of VISTA, PSGL-1 and Proximity Indices across TME phenotypes (e.g. inflamed, immune-excluded, immune-ignored)
- Acquisition of well-curated, clinical samples with ICI treatment history and outcomes
- Is VISTA/VISTA-PSGL-1 proximity upregulated in PD-1 non-responders?

II. Multiplex IHC and scRNAseq on multiple preclinical tumor models

- Does VISTA/PSGL-1 proximity correlate with response to SNS-101?
- Other potential biomarkers of VISTA/PSGL-1 checkpoint engagement?

Preliminary SNS-101 Phase 1/2 Study Schematic



* Phase 1/2 study design is preliminary and subject to change, including based on feedback from the FDA following submission of IND.

** RP2D = Recommended Phase 2 Dose

*** Tumor types, indication and samples size to be determined based on findings from dose-escalation phase and emerging scientific data; cohorts may run concurrently.

SNS-101 Responder Hypothesis based on SNS-101 Preclinical and Translational Data

SNS-101 Preclinical/Translational Strengths	Potential Clinical Direction
• SNS-101 demonstrated strong combinatorial activity with anti-PD-1 in MC38 model in human VISTA-KI mice • In-vivo efficacy profile in combination with PD-1 showed increase tumor-infiltrating CD8 T-cells	• **Boosting αPD-1 response in Inflamed/Immunogenic tumor types**: • *Current Plan*: checkpoint inhibitor naïve patients with inflamed solid tumors (e.g., HNSCC), who are responsive to αPD-1 treatment, would receive combination treatment of SNS-101 + αPD-1 and be assessed for a boost in anti-tumor activity
• Immunohistochemistry (IHC) staining VISTA/PSGL-1 proximity assay suggests tumors with high VISTA/PSGL-1 proximity signal Include CRC, Breast, NSCLC and HNSCC	• **Inducing a response in inflamed, but typically αPD-1 non-responsive tumors** (e.g., MSS colon, HR^+ breast) with combination of SNS-101 and αPD-1
• SNS-101 and PD-1 blockade led to enhanced tumor regression in syngeneic 1956 tumors implanted in VISTA-KI mice	• ***Bona fide* αPD-1 refractory patients (e.g., NSCLC):** Does treatment with combination treatment of SNS-101 + αPD-1 overcome resistance?

Fireside Chat with Neil Canavan

sensei™ BIO

Question & Answer Session

sensei™ BIO

VISTA Science Symposium

November 21, 2022

Guest Speaker:

Robert Schreiber, Ph.D.

Andrew M. and Jane M. Distinguished Professor of Pathology and Immunology; Professor, Molecular Microbiology; and Director of the Bursky Center for Human Immunology and Immunotherapy Programs at the Washington University School of Medicine. He is also co-leader of the Tumor Immunology Program of Washington University's Siteman Comprehensive Cancer Center, an Associate Director of the Scientific Advisory Board to the Cancer Research Institute and Co-editor-in-Chief of the journal Cancer Immunology Research. Schreiber obtained his PhD in Immunology/Biochemistry at the State University of New York in Buffalo, New York, and received his postdoctoral training at The Scripps Research Institute in La Jolla, California. Sensei IOAB Member.

Sensei Presenters:

John Celebi
Chief Executive Officer

Dr. Robert Pierce
Chief R&D Officer

Ron Weitzman
Interim CMO

Dr. Edward van der Horst
SVP, TMAb Antibody Development