1078-TiP - Phase 1/2, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of SNS-101 (anti-VISTA) as Monotherapy and in Combination with Cemiplimab in Patients with Advanced Solid Tumors

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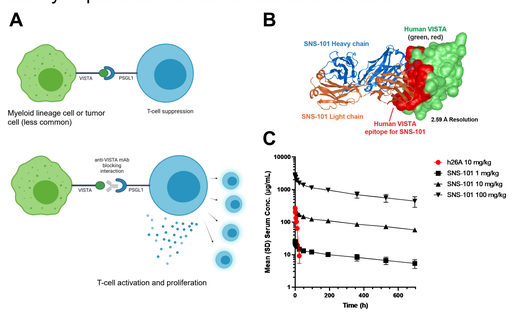
Background

SNS-101 is a novel monoclonal antibody, selectively targeting the active/protonated form of V-domain Ig suppressor of T-cell activation (VISTA) found at low pH in the tumor microenvironment (TME). SNS-101 binds to VISTA at pH 6.0 with high affinity and blocks the interaction between the T-cell checkpoint protein P-selectin glycoprotein ligand-1 (PSGL-1) and VISTA. Based on preclinical data, SNS-101, either as monotherapy or in combination with a programmed cell death protein-1 (PD-1) blocker, cemiplimab (cemi), is expected to exhibit an acceptable tolerability profile and demonstrate anti-tumor activity in patients with advanced solid tumors.



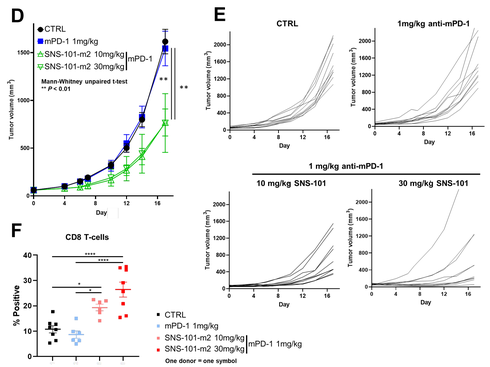


Figure 1. Mechanism of action of SNS-101. (**A**) SNS-101 blocks the VISTA:PSGL-1 interaction in the acidic TME, relieving anti-tumor T-cell suppression and promoting T cell activation and expansion. (**B**) Crystal structure of SNS-101 Fab:hVISTA complex. (**C**) SNS-101 displays linear elimination kinetics unlike a pH-independent anti-VISTA mAb 26A[3], which demonstrates rapid clearance. (**D-F**) SNS-101 enhances anti-PD-1 response and dose-dependently increases tumor-infiltrating CD8 T-cells in a syngeneic mouse model. (**D**) Mean tumor volumes, (**E**) spider plots and (**F**) tumor-infiltrating CD8+ T-cells are shown.

Study Design

- This is a first in human, open-label, multi-center, dose escalation and expansion study to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and efficacy of SNS-101, as monotherapy or in combination with cemi in patients with advanced solid tumors (NCT05864144).
- This study is being conducted in 3 parts:
  - **Part A (~25 pts):** Phase 1 Monotherapy Dose Escalation (SNS-101 alone)
  - **Part B (~24 pts):** Phase 1 Combination Dose Escalation (SNS-101 + cemi)
  - **Part C (~80 pts):** Phase 2 Expansion Cohorts (SNS-101 ± cemi)
- Dose escalation/de-escalation will proceed following the Bayesian Optimal Interval Design until the Maximum Tolerated Dose (MTD)/Recommended Phase 2 Dose (RP2D) is determined
- DLT period is 21 days for monotherapy and 22 days for combination
- Tumor imaging will be performed every 6 weeks
- All patients will receive SNS-101 ± cemi as intravenous infusion(s) every 3 weeks and may continue until confirmed progressive disease or unacceptable toxicity
- No pre-medications required

Key Inclusion Criteria

- Histologically or cytologically documented locally advanced, unresectable or metastatic solid tumor
- Refractory or intolerant to standard of care for advanced disease or not eligible for standard of care therapy
- Measurable disease
- ECOG performance status 0 or 1
- Life expectancy of ≥ 3 months
- Willing to provide pre-treatment (archival or fresh) and on-treatment tumor biopsy samples
- Adequate organ function
- Women of childbearing potential and fertile males with WOCBP partners must use highly effective contraception during the study and for 180 days after the study. Patients must agree not to donate eggs (ova, oocytes) or sperm during the study

Study Sites

- START San Antonio, San Antonio, TX
- START Mountain Region, West Valley City, UT
- NEXT Oncology, Dallas, Irving, TX

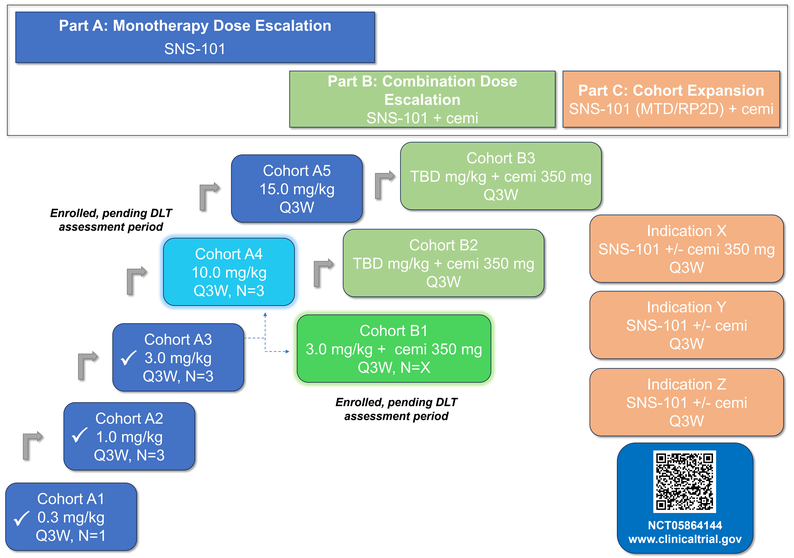


Figure 2. Dose escalation schematic for monotherapy and combination therapy.

Biomarker Plan

Pharmacokinetics and Safety
Blood, serum
- SNS-101 PK/exposure in blood
- Anti-SNS-101 antibody detection (ADA)
- Cytokine panel: IFN-γ, IL-10, IL-8, IL-6, TNF-α, CCL-5

Immunophenotyping
Blood, PBMCs
- Comprehensive T-cell phenotyping by multi-dimensional flow cytometry

Pharmacodynamic / Response
FFPE tissue, Whole blood, Cell-free plasma
- HLA typing
- TCR / BCR repertoire analysis
- Mutation identification / TMB / Neoantigen prediction
- MSI status
- ctDNA tracking

Spatial Imaging
FFPE tissue
- Multiplex CODEX imaging with custom 53-plex panel
- Cellular phenotyping
- Immune cell infiltration and interactions, neighborhood analysis

Study Objectives

Primary	• Safety & Tolerability • MTD/RP2D
Secondary	• PK (C_{max}, AUC, CL, $t_{1/2}$) • Immunogenicity (ADA) • Anti-tumor activity (ORR, DoR, DCR, PFS)
Exploratory	• PD biomarkers • TME phenotypes

C_{max}, maximum serum concentration; AUC, area under the curve; CL, clearance; $t_{1/2}$, half-life; ORR, overall response rate; DoR, duration of response; DCR, disease control rate; PFS, progression free survival

SUMMARY

Key Features of SNS-101

- SNS-101 is a pH-selective, high-affinity, cynomolgus monkey cross-reactive IgG1 with excellent biophysical and biochemical properties
- VISTA:SNS-101 co-crystal structure demonstrates SNS-101 directly blocks the pH-dependent interaction between VISTA and PSGL-1, as well as interactions with other putative receptors, relieving anti-tumor T-cell suppression and promoting T-cell activation and expansion
- SNS-101 exhibits linear elimination kinetics in non-human primates, overcoming PK limitations observed with other anti-VISTA antibodies
- SNS-101 demonstrates significant enhancement of anti-tumor effects in combination with anti-PD-1 antibodies in association with an increase in CD8+ T-cells

Status of Trial in Progress

- Monotherapy Cohorts A1 (0.3 mg/kg) to A3 (3.0 mg/kg) have completed without DLT; Cohort A4 (10 mg/kg) has been enrolled
- Combination Cohort B1 (3mg/kg SNS-101 + 350 mg cemi) has been enrolled
- Anticipate initial monotherapy PK and safety data in Q4 2023 and topline data in 2024
- Anticipate initial combination PK and safety data in Q1 2024

References

1. Lines JL, et al. Cancer Immunol Res. 2014; 6:510-517.
2. Johnston RJ, et al. Nature 2019; 574:565–570.
3. Thisted T, et al. JITC 2022; 10.

Acknowledgements

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Disclosures

K.P., J.C. and S.S. have no conflict of interests. F.D.S. and E.H.vdH are employees at Sensei Biotherapeutics.

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