Initial results from a first in human Phase 1 study of SNS-101 (pH-selective anti-VISTA antibody) alone or in combination with cemiplimab in patients with advanced solid tumors

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Introduction

Checkpoint Inhibitor Background:
- Immune checkpoint inhibitors targeting PD-1 and CTLA-4 have significantly advanced cancer therapy.
- Broad tissue expression leads to safety risks, reducing efficacy and narrowing therapeutic windows[1].

VISTA Checkpoint Overview:
- V-domain immunoglobulin suppressor of T-cell activation (VISTA) is an immune checkpoint on myelomonocytic cells.
- VISTA suppresses T-cell function, aiding tumor immune evasion[2, 3].
- Interacts pH-dependently with T-cell receptor PSGL-1 in the acidic tumor microenvironment (TME).

Challenges with Anti-VISTA Antibodies:
- Prior anti-VISTA antibodies faced issues with cellular activation, cytokine release syndrome (CRS) at sub-therapeutic doses, and target-mediated drug disposition (TMDD) by VISTA-positive neutrophils and monocytes at physiological pH[4, 5].

Development of SNS-101:
- SNS-101 is a pH-sensitive, fully human monoclonal antibody (mAB) targeting VISTA.
- Selectively binds and blocks VISTA in acidic TME, enhancing tumor-specific accumulation.
- Designed to reduce off-target effects, improving tolerability and efficacy of VISTA-targeting immunotherapy[3].

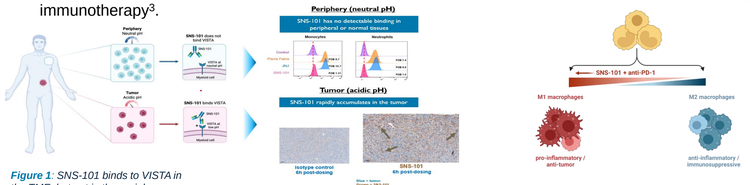


Figure 1: SNS-101 binds to VISTA in the TME, but not in the periphery

Methods

- First in human, Ph 1/2 open label, multicenter, dose escalation/expansion study of SNS-101 +/- cemiplimab (cemi) in patients with advanced solid tumors with primary (unfavorable candidates for immunotherapy) or acquired PD-1 therapy resistance (progressed on prior anti-PD-1 therapy), and who have received and failed or were intolerant to standard of care for advanced disease or not candidates for standard of care therapy, with an ECOG 0 or 1.
- Enrolled patients represented a broad range of tumor types to determine safety and tolerability as quickly as possible.
- SNS-101 +/- cemi was given as an IV infusion once every 3 wks. Patients were not routinely prophylaxed for CRS.
- **Primary endpoints:** Evaluate safety and tolerability of SNS-101 +/- cemi and establish MTD/RP2D.
- **Secondary endpoints:** Determine PK profile, assess immunogenicity and evaluate preliminary anti-tumor activity.

Results

- Dose escalation enrollment completed with 16 patients in the monotherapy arm and 18 patients in the combination arm.
- Patients cleared all planned dosing cohorts of SNS-101 +/- cemi with no dose limiting toxicities (DLT) observed (Figure 2).

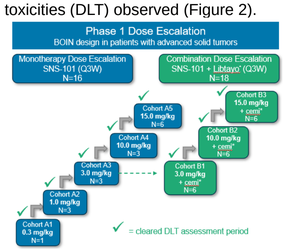


Figure 2: Clinical trial protocol schema

**Sarcoma: Leiomyosarcoma, Ewing Sarcoma, PEComa, Hemangiopericytoma (mono) and Leiomyosarcoma and Desmoplastic small round cell (combo)*
***Other Tumor Types: Small cell lung carcinoma, Gallbladder, Adenocystic carcinoma maxillary sinus, and mediastinal carcinoma (mono) and Ovarian, Duodenal, granulosa cell tumor (germ cell)*

Monotherapy arm: 75% males with median age of 61.5 (min 35, max 79), 88% white, 6% Asian, 6% not reported and 63% with ECOG 1.
Combination arm: 61% males with median age of 62 (min 33, max 81), 77% white, 11% African American, 6% Asian, 6% not reported and 78% with ECOG 1.

	SNS-101 n=16	SNS-101 + cemi n=18
Prior lines metastatic therapy		
Median	2	2.5
Min, Max	0, 7	1,7
Prior PD-1/PDL-1 YES%		
% YES	8 (50)	4 (22)
Cancer Type, n (%)		
Responsive to PD-1 monotherapy (e.g. "hot" tumors)	3 (19)	2 (11)
Head and Neck	2	0
Kidney	1	2
Unresponsive to PD-1 monotherapy (e.g. "cold" tumors)	13 (81)	16 (89)
MSS Colon	4	7
MSS Endometrial	0	1
Esophageal	1	0
Pancreatic	0	3
Sarcoma*	4	2
Other**	4	3

Table 1: Treatment history and cancer type of enrolled patients

Results (continued)

Primary Endpoints Were Achieved

Safety and Tolerability:
- SNS-101 monotherapy and in combination with cemi was well-tolerated with no dose-limiting toxicities observed (Table 2).
- Most common adverse events: fatigue (n=5), cough (n=4), and rash maculo-papular, pleural effusion and pyrexia (n=3, each).
- **Monotherapy:**
  - 13/16 patients (81%) experienced at least one TEAE, majority of AEs being Grade 1 or 2.
  - One patient experienced Grade 1 cytokine release syndrome (CRS) at 15 mg/kg SNS-101.
- **Combination therapy:**
  - 14/18 patients (78%) experienced at least TEAE, with the majority of AEs Grade 1 or 2.
  - One patient experienced Grade 1 CRS at 15 mg/kg SNS-101 plus cemi.
  - Four patients experienced immune-mediated events:
    - Grade 3 diabetic ketoacidosis at 3 mg/kg SNS-101 plus cemi
    - Grade 2 rash maculo-papular at 3 mg/kg SNS-101 plus cemi
    - Two patients with elevated liver enzymes both at 10 mg/kg SNS-101 + cemi (one with Grade 3 ALT/Grade 1 AST and one with Grade 3 ALT/AST)
- No significant changes to key cytokine levels across all cohorts (Figure 3).

	SNS-101 n=16 (%)	SNS-101 + cemi n=18 (%)
At least 1 TEAE	13 (81)	14 (78)
At least 1 SAE	1 (6)	8 (44)
≥Grade 3 TEAE	2 (13)	8 (44)
At least 1 TEAE leading to discontinuation	1* (6)	1# (5)
DLTs	0	0
AESI	1 (6)	5 (28)
Immune-mediated	0	4 (22)
CRS	1 (6)	1 (6)

Table 2: Summary of Adverse Events

**One patient experienced an SAE, Grade 5 bronchial obstruction, that resulted in death; related to disease progression, not to SNS-101*
 # One patient discontinued due to immune-mediated AEs of Grade 3 AST and ALT

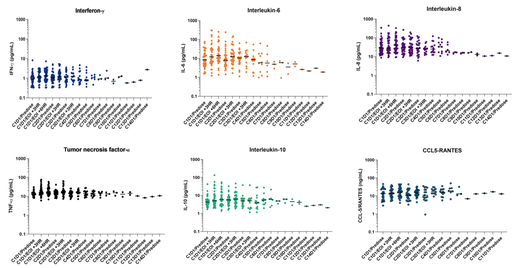


Figure 3: Summary of cytokine levels

Secondary Endpoints

Pharmacologically favorable PK properties:
- SNS-101 exhibited linear elimination profile of a mAb consistent with lack of TMDD irrespective of combination with cemi.
- Dose-proportional increases in exposure.
- Supports Q3W dosing.

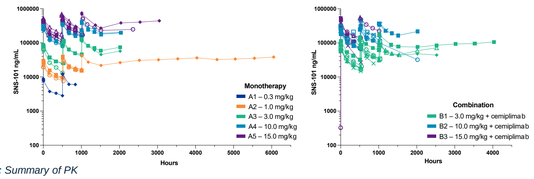
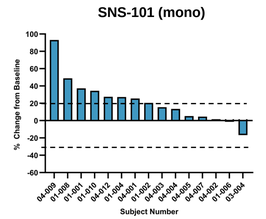


Figure 4: Summary of PK



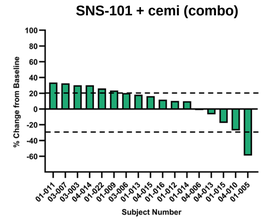


Figure 5: Best overall change in size of tumor target lesions in subjects with at least one follow-up scan. Dashed lines indicate progression >=+20%) or partial response (-30%).

Monotherapy:
- 7 patients achieved stable disease as best overall response.
- 2 patients have prolonged stable disease, currently on treatment out to 42+ weeks and 24+ weeks.
- One pembrolizumab-resistant HPV+ H&N patient at 15 mg/kg SNS-101 had tumor regression of 17%; discontinued at Week 12 due to PD.

Combination therapy:
- 1 MSS endometrial patient at 3 mg/kg + cemi had confirmed PR (59% decrease); ongoing 30+ weeks.
- 1 MSS colon patient at 3 mg/kg + cemi had tumor regression of 27%; discontinued at Week 18 due to PD.
- 1 RCC pt at 10 mg/kg + cemi had tumor regression of 18%; discontinued due to immune-mediated toxicity.

Exploratory

- Dose-dependent changes in specific T-cell populations indicate potential SNS-101-related pharmacological effect.
- Phenotypic shift of circulating (antigen experienced) effector T-cells toward increased peripheral homing and effector function (TEMRA).

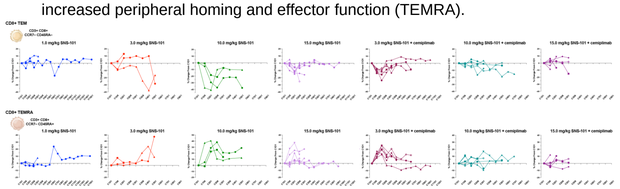


Figure 8: Pharmacodynamic Analysis T-cell Phenotyping: Monotherapy & Combination Cohorts CD8+ T effector memory & T effector memory RA

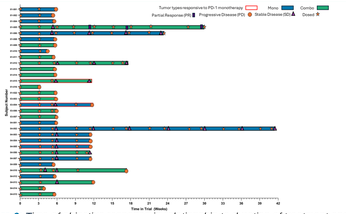


Figure 6: Time of objective response in relationship to duration of treatment and time of treatment cessation in subjects with at least one follow-up scan.

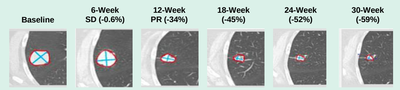
I/O-naïve MSS Endometrial Cancer with PR 3.0 mg/kg SNS-101 + cemi (Patient 01-005):

68 yo female with endometrial carcinoma, dx Dec 2020, ECOG 0
- ER/PR positive, HER negative; PD-1/PD-L1: not tested

Prior Treatment/Surgery
- Total laparoscopic hysterectomy with bilateral salpingo-oophorectomy, and additional sentinel lymph node dissection, Dec 2020
- Paclitaxel/Carboplatin (adjuvant setting), Feb 2021 to Aug 2021
- Anastrozole (metastatic setting), Aug 2023 to Sep 2023

Adverse Events
- Grade 3 diabetic ketoacidosis 4 days after Cycle 3 infusions, related to SNS-101 and cemi, AESI (immune-mediated) and SAE (hospitalization)
- Patient recovered and maintained on Insulin and continued study therapy

Tumor Assessments



I/O-naïve MSS Colon Cancer 3.0 mg/kg SNS-101 + cemi (Patient 04-010):

62 yo male with colon cancer; dx Jan 2017, ECOG 1
- PD-1/PD-L1: Negative

Prior Treatment/Surgery
- Received 7 prior lines of therapy in the metastatic setting with the last 3 therapies investigational

Adverse Events
- Grade 2 dry skin, related to SNS-101, not related to cemi
- Grade 2 rash maculo-papular, related to SNS-101 and cemi, AESI (immune-mediated), resolved after treatment with prednisone
- Grade 2 pruritis, related to SNS-101 and cemi

Tumor Assessments
- 6-Week Scans: Stable Disease (19% decrease)
- 12-Week Scans: Stable Disease (27% decrease)
- 18-Week Scans: Progressive Disease (23% increase from nadir)

Conclusions and Future Directions

- SNS-101 is a pH dependent VISTA targeting mAb that has demonstrated promising early clinical data consistent with its mechanism of action, including:
  - An absence of severe cytokine release syndrome at pharmacologically relevant dose levels
  - An absence of target mediated drug disposition and a half-life compatible with Q3W dosing
  - Dose-dependent shift in circulating (antigen experienced) effector T-cells toward increased peripheral homing and effector function (TEMRA)
  - Both the monotherapy and SNS-101 + cemiplimab combination are well tolerated in a population of advanced, refractory solid tumors
  - Preliminary signs of encouraging clinical activity in combination with cemiplimab in patients with microsatellite stable disease (CRC and Endometrial)
- Dose expansion cohorts are underway in both monotherapy (MSS CRC) and combination therapy (MSS CRC, NSCLC, H&N, Melanoma)

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REFERENCES

1. Postow, M. A., Sidlow, R. & Hellmann, M. D. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. N Engl J Med. e 378, 158–168 (2018).
2. Yuan, L., Tatineni, J., Mahoney, K. M. & Freeman, G. J. VISTA: A Mediator of Quiescence and a Promising Target in Cancer Immunotherapy. Trends Immunol. 42, 209–227 (2021).
3. Thisted, T. et al. VISTA checkpoint inhibition by pH-selective antibody SNS-101 with optimized safety and pharmacokinetic profiles enhances PD-1 response. Nat Commun 15, 2917 (2024).
4. Wu, C., Cao, X. & Zhang, X. VISTA inhibitors in cancer immunotherapy: a short perspective on recent progresses. RSC Med. Chem., 12, 1672-1679 (2021).
5. Huang, X. et al. VISTA: An immune regulatory protein checking tumor and immune cells in cancer immunotherapy. J Hematol Oncol 13, 83 (2020).