A phase 1/2 study of safety, tolerability, and pharmacokinetics of SNS-101, a pH-sensitive anti-VISTA mAb, as monotherapy and in combination with cemiplimab in patients with advanced solid tumors

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BACKGROUND

- VISTA (V-domain Ig suppressor of T-cell activation) is a significant emerging immuno-oncology target. Despite the therapeutic potential of VISTA inhibition demonstrated in preclinical studies [1], clinical development of anti-VISTA antibodies has been challenging due to dose-limiting on-target cytokine release at sub-therapeutic doses and target mediated drug disposition (TMDD) [2].
- SNS-101 is a fully human IgG1 monoclonal antibody designed to selectively disrupt the VISTA:PSGL-1 immune checkpoint in the acidic tumor microenvironment. Preclinical data demonstrate the potential of SNS-101 to exhibit favorable safety and tolerability profiles and promote anti-tumor activity as monotherapy or in combination with PD-1 blockade [3-5].

STUDY DESCRIPTION

- 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 cemiplimab (cemi) in patients with advanced solid tumors (NCT05864144).
- Patients must have histologically or cytologically documented locally advanced, unresectable or metastatic solid tumor, be refractory or intolerant to standard of care for advanced disease or not eligible for standard of care therapy, have measurable disease, and an ECOG Performance Status of 0 or 1.
- This study is being conducted in 3 parts:
  - **Part A:** Phase 1 Monotherapy Dose Escalation (SNS-101 alone)
  - **Part B:** Phase 1 Combination Dose Escalation (SNS-101 + cemi)
  - **Part C:** 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

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

References

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3. Thisted, T. *et al.* Antagonistic pH-selective VISTA antibody SNS-101 potentiates anti-PD-1/PD-L1-induced anti-tumor immunity. In Proceedings of the SITC Annual Meeting 2021, Washington D.C., 2021.
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TRIAL DESIGN

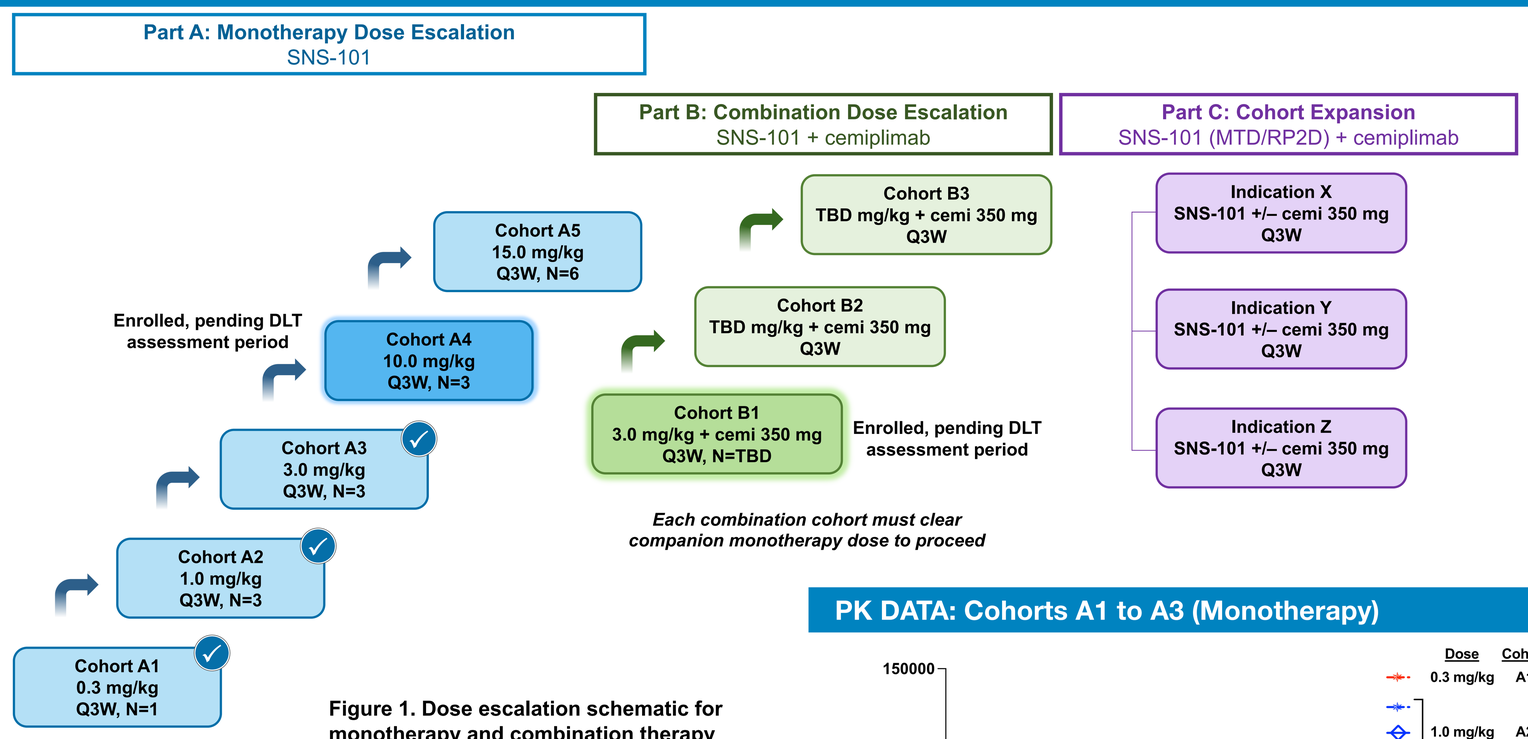

Figure 1. Dose escalation schematic for monotherapy and combination therapy

STUDY DISPOSITION

- As of 10/3/2023, a total of 13 patients have been enrolled across Parts A and B
- Part A/monotherapy: 10 patients have been enrolled across 4 dose levels (Cohorts A1 to A4)
- Part B/combination: 3 patients have been enrolled at the first dose level (Cohort B1)

ADVERSE EVENTS

A total of 11 AEs have been reported in 5 patients

- There have been no DLTs, CRS or imAEs observed
- All AEs have been Grade 1 or 2, except one Grade 5 SAE (bronchial obstruction)
- One SAE (bronchial obstruction) leading to death was reported. It was not considered related to SNS-101, and was attributed to disease progression
- One AE (Grade 2 dermatitis acneiform) was considered related to SNS-101 (1.0 mg/kg)

AE, adverse event; DLT, dose-limiting toxicity; CRS, Cytokine Release Syndrome; imAE, immune-mediated adverse event; SAE, serious adverse event

CYTOKINE DATA: Cohorts A1 to A3 (Monotherapy)

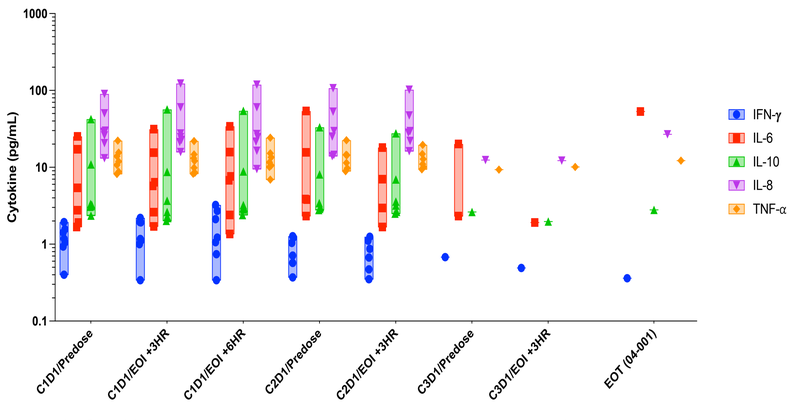

Figure 2. Cytokine analysis. Blood samples were taken pre-dose, 3 hours post-infusion and 6 hours post infusion at C1D1, and pre- and 3hr-post thereafter. Serum was assayed for indicated cytokines using a platform (MSD) that has been validated for clinical sample analysis.

- No significant changes in key inflammatory cytokines
- Data is consistent with lack of observed CRS to date at all dose levels and with SNS-101 ex vivo whole blood analysis[5]

PK DATA: Cohorts A1 to A3 (Monotherapy)

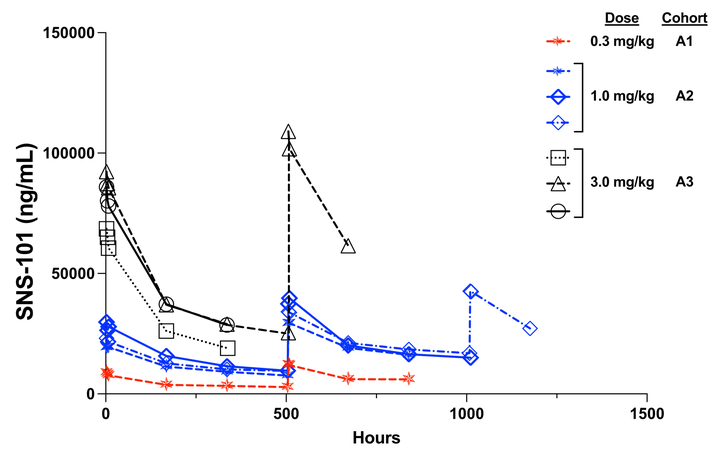

Figure 3. Pharmacokinetic analysis. Blood samples were taken pre-dose, EOI, 3 and 6 hours post-infusion at C1D1; pre-dose, EOI and 3 hours post-infusion at C2D1 and C3D1; pre-dose C4D1 thereafter; and pre-dose at C1D8, C1D15, C2D8, C2D15, C3D8 and C3D15.

- Dose-proportional exposure is consistent with lack of TMDD
- No notable accumulation with repeat dosing
- Data is consistent with linear PK observed in pre-clinical studies

CONCLUSIONS

- SNS-101 displays an acceptable risk/benefit profile and has been effectively dosed ≥ 10-fold higher than first-generation VISTA targeting antibodies
- Preliminary clinical data support the hypothesis that pH-sensitive targeting of VISTA with SNS-101 may overcome safety and tolerability challenges encountered with non-pH-selective anti-VISTA antibodies

ACKNOWLEDGEMENTS

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Trial Registration NCT05864144

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.

Ethics Approval
This study was conducted in accordance with the Declaration of Helsinki ethical principles, guidelines for Good Clinical Practice, and requirements of public registration of clinical trials. The protocol, the informed consent form and other written materials provided to participants, and any other relevant study documentation was approved by the Institutional Review Board associated with each clinical site with enrolled patients. Written informed Consent was obtained from each subject at enrollment.