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, 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). 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.

Methods This is a first-in-human, open-label, multi-center, dose escalation and expansion study to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics and efficacy of SNS-101 as monotherapy or in combination with cemiplimab in patients with advanced solid tumors (NCT05864144). The study is being conducted in 3 parts: Part A: Phase 1 (P1) Monotherapy Dose Escalation (SNS-101 alone); Part B: P1 Combination Dose Escalation (SNS-101 + cemiplimab); Part C: Phase 2 (P2) Expansion Cohorts (SNS-101 ± cemiplimab). Patients will receive SNS-101 ± cemiplimab as intravenous infusion(s) every 3 weeks and may continue until confirmed progressive disease or unacceptable toxicity. Dose escalation follows the Bayesian Optimal Interval Design until the Maximum Tolerated Dose (MTD)/Recommended Phase 2 Dose (RP2D) is determined. Primary objectives include safety, tolerability and RP2D/MTD (P1), and evaluation of anti-tumor activity (P2). Safety and tolerability assessments include monitoring of dose limiting toxicities (DLTs) and adverse events (AEs), PK, anti-drug antibodies and inflammatory cytokine release. Tumor imaging and T-cell immunophenotyping are being utilized to monitor responses.

Results As of August 31, 2023, 7 patients were enrolled in Part A across three dosing cohorts (0.3 mg/kg, 1 mg/kg and 3 mg/kg). No DLTs or CRS events were noted. Nine AEs (8/9 Grade 1–2) have been reported in 5 patients. One Grade 5 AE related to disease progression and not to the treatment was observed. One AE, dermatitis acneiform, is considered treatment-related. Infusions have not required premedications. PK results show high concordance with preclinical modeling data, demonstrating dose-proportional exposure, linear elimination kinetics, and suggesting the absence of TMDD.

Conclusions SNS-101 has been well tolerated and effectively dosed ≥ 10-fold higher than first-generation VISTA targeting antibodies. Preliminary clinical data support our hypothesis that pH-sensitive targeting of VISTA with SNS-101 may overcome safety and tolerability challenges encountered with non-pH-selective anti-VISTA antibodies. Updated data from ongoing cohorts will be presented.

Trial Registration NCT05864144 (Start May 2023, Est. Close June 2027)

ClinicalTrials.gov, Trial #NCT02671955.