Background VISTA (V-domain Ig suppressor of T-cell activation) is a negative checkpoint regulator (NCR), highly expressed on myeloid cells.\(^1\) PSGL-1 on T-cells has been identified as a novel NCR that limits survival and promotes T-cell exhaustion.\(^2\) Recently, VISTA was reported to bind PSGL-1 and suppress T-cell activity exclusively under acidic conditions (\(~\text{pH 6 in lymph nodes or the tumor microenvironment}\)\(^3\), \(^4\)). Although VISTA inhibition demonstrated excellent therapeutic combinatorial with other modalities targeting NCRs (e.g., CTLA-4, PD-1/PD-L1),\(^5\) clinical development of anti-VISTA antibodies has been challenging due to: 1) high clearance via target-mediated drug disposition (TMDD) by VISTA+ neutrophils and monocytes at physiologic pH; and 2) cellular activation and cytokine release syndrome (CRS) at sub-therapeutic doses by engagement of VISTA in the blood.\(^6\)

We developed SNS-101, a human monoclonal IgG1 antibody specific for the protonated, active form of VISTA, which is designed to disrupt the immunosuppressive VISTA:PSGL-1 interaction, avoid TMDD and mitigate potential CRS.

Methods The binding potential of SNS-101 to VISTA+ cells was determined in human and non-human primate (NHP) whole-blood by flow cytometry. The effect of SNS-101 on human monocytes and T-cells was evaluated \(\text{in vivo}\) in human CD34+ cord blood cell reconstituted BGRSF mice, which develop both human lymphoid and myeloid compartments. The pharmacokinetic (PK) profile was assessed in NHPs. Anti-tumor efficacy was assessed in VISTA-KI mice implanted with the syngeneic tumor model, MC38, and tumor-infiltrating T-cells were analyzed by flow cytometry.

Results SNS-101 did not bind to human or NHP VISTA+ monocytes, neutrophils and natural killer cells. In humanized BGRSF mice, SNS-101 induced significant expansion of CD4 and CD8 central memory (CCR7+CD45RA-), and naïve (CCR7+CD45RA+) CD8 T-cells, respectively, but had no significant impact on monocyte activation. PK studies in NHPs showed linear elimination kinetics. Conversely, a non-pH-sensitive antibody bound VISTA+ immune cells, induced monocyte activation followed by a decrease in cell numbers and was rapidly cleared in NHPs. Anti-tumor efficacy studies in MC-38 demonstrate that SNS-101 enhanced anti-PD-1 response and dose-dependently increased tumor-infiltrating CD8 T-cells.

Conclusions Our results demonstrate that SNS-101 exhibits linear elimination kinetics in NHPs, overcoming TMDD-induced PK limitations observed with other anti-VISTA antibodies. Importantly, SNS-101 induced expansion of naïve and memory T-cell phenotypes \(\text{in vivo}\) without activation or depletion of monocytes, differentiating it from non-pH-selective VISTA antibodies. In the MC-38 syngeneic tumor model, SNS-101 demonstrated significant enhancement of anti-tumor effects in combination with anti-PD-1 antibodies through an increase in CD8+ T-cells.

REFERENCES