SNS-101, a highly pH-selective VISTA:PSGL-1 inhibitory antibody, potentiates anti-PD-1 sensitivity, expands memory T-cells and enhances tumor infiltration of CD8 T-cells

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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 (~pH 6 in lymph nodes or the tumor microenvironment) [3, 4]. Although VISTA inhibition demonstrated excellent therapeutic combinability 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

- Binding potential of SNS-101 to VISTA$^+$ cells was determined in human and non-human primate (NHP) whole-blood by flow cytometry
- Effect of SNS-101 on human monocytes and T-cells was evaluated *in vivo* in human CD34$^+$ cord blood cell reconstituted BRGSF mice, which develop both human lymphoid and myeloid compartments
- Pharmacokinetic (PK) profile was assessed in NHPs
- Anti-tumor efficacy was assessed in VISTA-KI mice implanted with the syngeneic tumor model, MC38
- Tumor-infiltrating T-cells were analyzed by flow cytometry
- SNS-101 was compared to two clinical stage, non-pH-selective anti-VISTA antibodies by grafting variable regions onto a human IgG1 framework: 1) JNJ (JNJ-61610588 [7] (now CI-8993)) or 2) h26A (26A [8])

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RESULTS

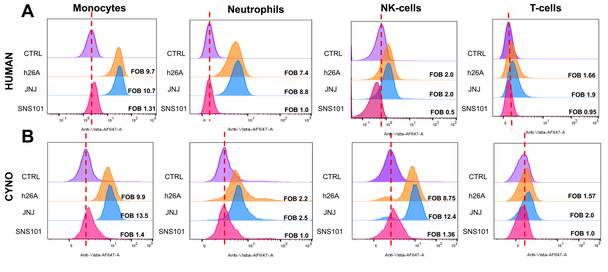


Figure 1. SNS-101 does not bind to human or NHP VISTA$^+$ monocytes, neutrophils and natural killer cells. The non-pH-sensitive antibodies JNJ and h26A bind to VISTA$^+$ immune cells. AF-647-labeled SNS-101, JNJ, h26A and hIgG1 isotype control (CTRL) were used to interrogate (**A**) human and (**B**) cynomolgus monkey monocytes, neutrophils, NK-cells and T-cells by flowcytometry. FOB = Fold over background.

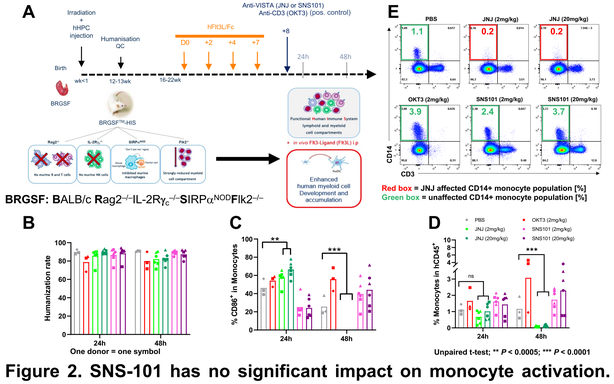


Figure 2. SNS-101 has no significant impact on monocyte activation. (**A**) BRGSF-HIS mice (reconstituted functional **h**uman **i**mmune **s**ystem) were generated as previously described [9]. (**B**) BRGSF-HIS mice were quality controlled by assessing human CD45$^+$ cells in spleen. Mice were sacrificed at 24h and 48h and immune cell proportions in spleen were evaluated by flow cytometry. Non-pH-sensitive antibody JNJ induces (**C**) monocyte activation (CD86$^+$) followed by (**D**) a decrease in monocyte proportions (CD45$^+$). (**E**) Representative dot plot at 48h post-treatment shows JNJ-induced decrease in CD14$^+$ monocytes.

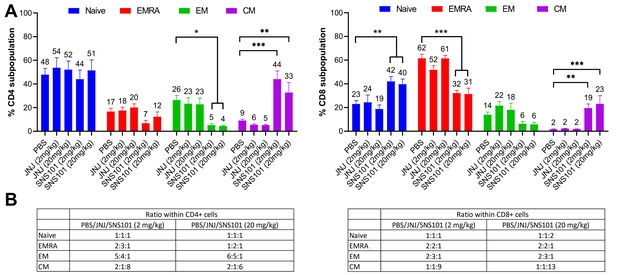
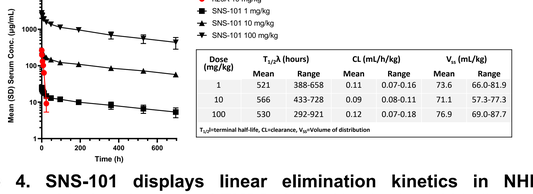


Figure 3. SNS-101 induces significant expansion of CD4 and CD8 T-cell subsets. (**A**) SNS-101 increases central memory (CCR7$^+$CD45RA$^-$) of CD4 and CD8, and naïve (CCR7$^+$CD45RA$^+$) CD8 T-cells. (**B**) Ratio of immune subsets within CD4 and CD8 T-cells relative to treatment. (**C**) Representative contour plot of (**A**) 24h post-treatment.



Dose (mg/kg)	$T_{1/2}$λ (hours)		CL (mL/h/kg)		V_{ss} (mL/kg)	
	Mean	Range	Mean	Range	Mean	Range
1	521	388-658	0.11	0.07-0.16	73.6	66.0-81.9
10	566	433-728	0.09	0.08-0.11	71.1	57.3-77.3
100	530	292-921	0.12	0.07-0.18	76.9	69.0-87.7

$T_{1/2}$λ=terminal half-life, CL=clearance, V_{ss}=Volume of distribution

Figure 4. SNS-101 displays linear elimination kinetics in NHPs consistent with the absence of TMDD. Non-pH-selective h26A displayed pronounced TMDD and was below limit of quantitation at 48h. SNS-101 (1, 10, and 100 mg/kg) and h26A (10 mg/kg) were administered to groups of monkeys (n=4; 2/sex) once via intravenous infusion for 1 hour. Table, PK Parameters of SNS-101.

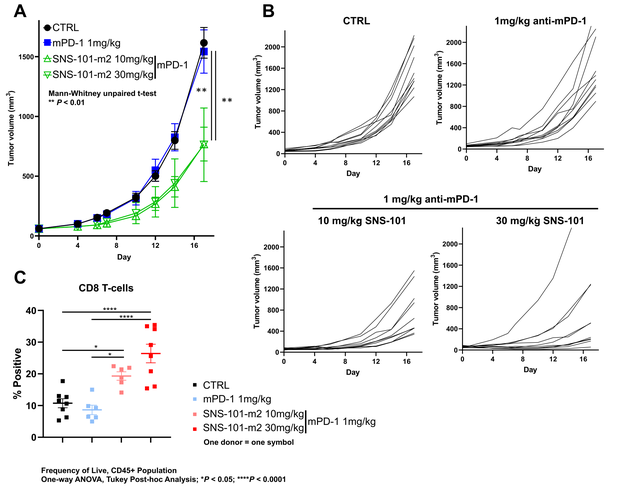


Figure 5. SNS-101 enhances anti-PD-1 response and dose-dependently increases tumor-infiltrating CD8 T-cells. (**A**) Mean tumor volumes, (**B**) spider plots and (**C**) tumor-infiltrating CD8 T-cells are shown. 1 x 10^6 MC-38 were implanted into female VISTA-KI mice. Mice were randomized (n=10/cohort) once tumor volumes reached ~60-80 mm^3 and received IP injections every 3 days for 2 weeks as indicated. At Day 17 post-treatment, single cell suspensions were generated from tumor extracts through physical and enzymatic dissociation. Frequency of CD8+ cells was determined in the singlet, live, CD45$^+$ population by analytical flow cytometry analysis.

CONCLUSIONS

- SNS-101 exhibited 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 *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 in association with an increase in CD8$^+$ T-cells