228 ANTAGONISTIC PH-SELECTIVE VISTA ANTIBODY SNS-101 POTENTIATES ANTI-PD-1/PD-L1-INDUCED ANTI-TUMOR IMMUNITY

[1]Thomas Thisted, [1]Arnab Mukherjee, [1]Kanam Malhotra, [1]Zuzana Biesova, [1]Yuliya Kleschenko, [1]Zhi-Gang Jiang, [1]Anokhi Cifuentes, [2]Nadthakarn Boland, [2]Nels Nielson, [1]Edward van der Horst*. [1]*Sensei Biotherapeutics Inc., Rockville, MD, USA*; [2]*Adimab LLC., Lebanon, NH, USA*

Background Immunotherapies, especially immune checkpoint inhibitors, have become a cornerstone of cancer treatment. Remarkable clinical responses have been observed blocking the programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) axis across a spectrum of indications. However, innate and/or acquired resistance to anti-PD-1 blockade remains a major challenge. V-domain Ig suppressor of T-cell activation (VISTA) is a B7-family member, which promotes T-cell and myeloid quiescence and represents a promising target, particularly in combination with anti-PD-1/PD-L1 treatment. Recently, the interaction of VISTA with its receptor PSGL-1 was demonstrated to be significantly enhanced by the acidic tumor microenvironment (TME). As VISTA is highly expressed on myeloid cells, including those in the blood, antibodies binding VISTA at physiological pH 7.4 could result in rapid elimination from circulation through targeted-mediated drug disposition, making efficacious drug occupancy levels difficult to reach and potentially narrowing the therapeutic window. An antibody engineered to selectively bind and block VISTA at low pH in the TME may therefore be an ideal drug candidate.

Methods In this study, fully human anti-VISTA antibodies were generated through pH-selective enrichment strategies of a yeast-based display library comprising highly diverse synthetic immune repertoires. The 'parental' antibodies have been extensively characterized using in vitro flow-cytometry, surface-plasmon resonance (SPR) and PSGL-1/VISTA inhibition assays in primary human CD4 and CD8 T-cells at pH 6.0 and pH 7.4. Eight parental antibodies were identified and tested for combinatorial efficacy with anti-PD-1 in vivo in human VISTA knock-in mice inoculated with syngeneic MC-38 tumors. These antibodies underwent further optimization for enhanced binding affinity at pH 6.0 and decreased binding at pH 7.4. 'Progeny' antibody ranking was based on the same in vitro and in vivo characterization as parental antibodies.

Results Eighty four parental antibodies were initially discovered. Flow-cytometry and SPR analysis revealed candidates displaying pH-dependent binding to endogenously expressed native VISTA on cells, and a PSGL-1/VISTA inhibition assay at pH 6.0 was run to identify and rank potent interface blockers. Eight candidate antibodies were tested in an in vivo intervention study in combination with anti-murine PD-1 demonstrating varied combinatorial efficacy with a subset leading to superior tumor rejection. Characterization of optimized progeny antibodies led to identification of anti-VISTA antibody SNS-101.

Conclusions Enrichment of highly diverse antibody libraries led to the identification of a pH-selective inhibitory anti-VISTA antibody SNS-101, which exerts excellent combinability with anti-PD-1 leading to superior anti-tumor activity in a mouse model.

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