KNOCKDOWN OF VISTA PROTEIN USING ANTISENSE OLGONUCLEOTIDES PROMOTES SUPERIOR ANTI-TUMOR IMMUNITY COMPARED TO ANTIBODY BLOCKADE

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Background VISTA is an immunosuppressive checkpoint that can be expressed by a diverse array of immune cells, including CD4+ and CD8+ T cells, natural killer cells, macrophages, dendritic cells (DCs) and neutrophils. VISTA expression is specifically upregulated on tumor infiltrating myeloid cells such as DCs, tumor associated macrophages (TAMs) and myeloid derived suppressor cells (MDSCs). Previous studies showed that antibody blockade of VISTA could reduce tumor growth in multiple melanoma models and enhance T cell responses within the tumor microenvironment (TME). Antibody blockade of VISTA, however, may be sub-optimal therapeutic solution as VISTA has been shown to co-localize with a recycling endosomal protein that contributes to its rapid turnover on and off the cell surface. Also, VISTA blockade in non-myeloid tissues has the potential to cause dose-limiting toxicities.

Methods We used a series of VISTA anti-sense oligonucleotides (ASO) to downregulate VISTA protein expression. Generation 2.5 Ionis ASO have minimal off-target inflammatory activity and are efficiently taken up by myeloid cells when delivered unformulated. We implanted C57Bl/6J mice with 1.5x10^5 B16-Ova melanoma cells subcutaneously on the flank and treated with anti-mouse VISTA antibody 13F3 for five injections or daily VISTA ASO over three weeks. Flow cytometry was performed to determine VISTA expression levels on TAMs, DC, and MDSCs. Tumor growth and survival were followed until tumor volume endpoints were reached.

Results Flow cytometric analysis confirmed ASO-mediated VISTA knockdown across the tumor myeloid compartment. Our results indicate that VISTA ASO regressed pre-implanted B16-OVA tumors and cured 40% of mice compared to minimal benefit with the 13F3 antibody. Overall, we observed a decrease in tumor growth and improved survival with VISTA ASO treatment compared to 13F3. VISTA ASO was well-tolerated at efficacious doses.

Conclusions Together, these data suggest VISTA expression in tumor myeloid stroma can be effectively downregulated using anti-sense oligonucleotides. Therapeutic approaches that reduce VISTA protein (e.g. VISTA ASOs) may provide superior efficacy and reduced off-target toxicity due to lack of ASO accessibility compared with monoclonal antibody-based approaches.

REFERENCES

Ethics Approval All animal studies were approved by the MD Anderson Cancer Center Institutional Animal Care and Use Committee (Houston, Texas, USA) under protocol 00001378-RN00/1.