AVA-NP-695 POTENTLY AND SELECTIVELY INHIBITS ENPP1 TO ACTIVATE STING PATHWAY AND ABROGATE TUMOR METASTASIS IN 4T1 BREAST CANCER SYNGENEIC MOUSE MODEL

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Background Innate immune modulators such as STING agonists have become attractive approaches to improve the efficacy of Immune Checkpoint Inhibitors (ICI) due to their ability to turn cold tumors hot. Owing to the modest clinical efficacy of STING agonists, there is a need for other approaches for activating the cGAS-STING pathway for cancer immunotherapy. One such approach is through the inhibition of the enzyme ENPP1, a negative regulator of the STING pathway which directly hydrolyses 2',5'-cGAMP. ENPP1 is overexpressed in several tumor cells like human astrocyte tumors and TNBC cells like 4T1 and MDA-MB-231, and plays a key role in tumor progression and block T cell infiltration in breast and lung cancer patients. ENPP1 not only abolishes the cGAS-STING mediated immune activation but also produces adenosine, an immune suppressor which promotes cell migration. AVA-NP-695 is a highly potent orally available ENPP1 inhibitor being developed for cancer immunotherapy.

Methods The inhibition potency of AVA-NP-695 was confirmed by enzymatic assays using various substrate like p-Nitrophenyl-5'-TMP, cGAMP and ATP. The efficacy of AVA-NP-695 was depicted in 4T1 Tumor bearing BALB/c mice as monotherapy and in combination with anti-PD-L1, Olaparib and Paclitaxel. Efficacy of AVA-NP-695 in combination with radiation (6.2Gy X 4) was also evaluated in ENPP1 overexpressing ANV5 tumors.

Results Herein, we demonstrate that AVA-NP-695, a selective and potent ENPP1 inhibitor showed no adverse effect at 1000mg/kg BID in 7 Day repeated dose in BALB/C mice, thereby demonstrating an excellent therapeutic window. Results from in vivo studies have shown superior tumor growth inhibition (TGI) and impact on tumor metastasis by AVA-NP-695 (6mg/kg BID) compared to Olaparib and Anti-PD1 in a syngeneic 4T1 breast cancer mouse model. Subsequently, combination of AVA-NP-695 with Anti-PD-L1, Olaparib and Paclitaxel and demonstrated encouraging combinatorial efficacy of AVA-NP-695 along with Paclitaxel. Monotherapeutic arm for Paclitaxel and AVA-NP-695 depicted 40% and 44% TGI respectively, however their combined treatment resulted in ~60% TGI. Additionally, the AVA-NP-695 treatment alone showed 50% enhanced mean survival time followed by 68%, 68% and 72% when given in combination with anti-PD-L1, Olaparib and Paclitaxel respectively. Finally, AVA-NP-695 showed complete tumor ablation of ANV5 ENPP1 overexpressed tumors when given in combination with radiation. Combination group showed significantly delayed recurrence compared to only radiotherapy.

Conclusions The potent anti-tumor efficacy of AVA-NP-695 both as monotherapy and combination along with its safety profile provides a strong rationale for the therapeutic potential of AVA-NP-695 against solids tumors, particularly breast cancer.