AVA-NP-695, A POTENT AND SELECTIVE ENPP1 INHIBITOR, DEMONSTRATES STRONG ANTI-TUMOR EFFICACY AS MONOTHERAPY AND IN COMBINATION WITH RADIATION

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Background STING agonists have become an attractive immunomodulatory approach to activate the cGAS-STING pathway for turning cold tumors hot and thereby improving the efficacy of Immune Checkpoint Inhibitors (ICI). However, considering their modest clinical efficacy, there is a substantial need for other approaches to activating the cGAS-STING pathway for cancer immunotherapy. Inhibition of the enzyme ENPP1, a negative regulator of the cGAS-STING pathway is one such approach. ENPP1 hydrolyses 2’3’-cGAMP (endogenous STING agonist) and negatively regulates STING dependent immune activation. Several tumors like human astrocyte tumors and TNBC like 4T1 and MDA-MB-231 have high ENPP1 expression which plays a key role in tumor progression and blocks T cell infiltration. 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 small molecule ENPP1 inhibitor being developed for cancer immunotherapy.

Methods Inhibition potencies of AVA-NP-695 were confirmed by enzymatic assays using substrates like p-Nitrophenyl-5’-TMP, 2’3’-cGAMP and ATP. The efficacy of AVA-NP-695 was demonstrated 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 was also evaluated in ENPP1 overexpressing breast tumors. Finally, combination of PSMA-RLT with AVA-NP-695 was evaluated for treating prostate cancer.

Results We demonstrate that AVA-NP-695, a selective and potent small molecule ENPP1 inhibitor showed no adverse effects at 1000 mg/kg BID in 14 day repeated dose toxicity 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 metastasis by AVA-NP-695 (6 mg/kg BID) compared to Olaparib and Anti-PD1 in a syngeneic 4T1 breast cancer mouse model. Subsequently, combination of AVA-NP-695 with Anti-PD1, Olaparib and Paclitaxel 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, combination of AVA-NP-695 with radiation (Fractionated dose and Targeted Radionuclide) demonstrated substantial tumor growth reduction across various tumor models.

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.

Ethics Approval All animal studies involved obtained the prerequisite ethics committee(s) approval.