STimulator of INterferon Genes (STING) Activation as an Immunogenic Therapy for Undifferentiated Pleomorphic Sarcoma

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INTRODUCTION:

Undifferentiated pleomorphic sarcoma (UPS) is one of the most common and aggressive soft tissue sarcomas (STS). Systemic therapies against UPS are lacking. The tumor microenvironment (TME) of many STS, including UPS are characteristically low in spontaneous tumor infiltrating lymphocytes (TILs) and enriched in immune suppressive cell types including myeloid derived suppressor cells and tumor associated macrophages. Activation of the STimulator of INterferon Genes (STING) pathway is an emerging immunotherapeutic strategy that can recruit TILs into the TME in murine models of carcinoma. In our murine model of UPS, intra-tumoral administrations of a murine-specific STING agonist, DMXAA, results in profound immune mediated tumor clearance in 50-75% of treated mice. To assess the clinical translation feasibility of this immunotherapeutic strategy, newly developed STING agonists effective against both the mouse and human STING receptors must be examined in UPS. The objective of this study is to evaluate the anti-tumor potential of three STING agonists that active against both murine and human STING receptors: ADU-S100 (CDN), MSA-2, and E7766 as monotherapies and in combination with immune checkpoint blockade (ICB) therapy in a murine model of UPS.

METHODS:

Immune competent mice were orthotopically engrafted with a syngeneic murine UPS cell line in the right hindlimb muscle. Once palpable, mice in the monotherapy groups were treated with a single intra-tumoral dose of 1) CDN (25µg - 500µg), 2) MSA-2 (18mg/kg), 3) E7766 (50µg - 150µg), or 4) DMXAA (18mg/kg). Mice who were treated in combination with ICB therapy received 8 doses of 250µg of monoclonal anti-PD1 in addition to a single dose of CDN, MSA-2, E7766, or DMXAA. Tumor volume measurements and tumor bioluminescence were measured over time. Any surviving mice were rechallenged with UPS in the contralateral limb. To delineate the immune profiles of STING treated UPS tumors, flow cytometry and Nanostring transcriptomics were completed 24hrs, 72hrs, and 1-week after STING monotherapy treatment.

RESULTS:

Unlike DMXAA, monotherapy with CDN or MSA-2 failed to eradicate UPS tumors, but an increased survival time was observed relative to control animals (Fig 1). Survival studies with E7766 have shown complete UPS clearance in 18-40% of E7766 treated mice (Fig 1). In total, 100% of the surviving E7766 and DMXAA treated mice completely rejected the rechallenge inoculation of UPS cells, suggesting adaptive immune protection was conferred against UPS (Fig 1). Flow cytometry and transcriptomic immune profiling of CDN, MSA-2, and DMXAA treated tumors at multiple timepoints post-treatment showed similar inflammatory changes and increased lymphocytic infiltration (Fig 2). STING + ICB therapy significantly improved survival outcomes in CDN+ICB treated tumors, as 14% of CDN+ICB treated mice completely eradicated their UPS tumors. In DMXAA monotherapy and DMXAA+ICB combination therapy, there were no significant differences in survival, as 50% of the monotherapy treated mice and 55% of the combination therapy treated mice survived (Fig 3). Unfortunately, there were no survivors in the MSA-2+ICB group, but survival was significantly extended compared to MSA-2 monotherapy (Fig 3). Additional flow cytometry and transcriptomics studies evaluating E7766 treated tumors are ongoing.

DISCUSSION AND CONCLUSION:

STING activation is a promising immunotherapeutic strategy for UPS. We have demonstrated that the human and murine compatible STING agonist, E7766, can be used to elicit immune mediated UPS clearance and adaptive immune protection against UPS rechallenge. Comparing the immune modulatory effects of CDN, MSA-2, DMXAA, and E7766 in the UPS TME will provide insight into differences between these drugs that allow some to be more efficacious than others in monotherapy and combination therapy contexts. Ultimately, this study demonstrates the potential opportunity for clinical translation of STING as an immunotherapy for STS which could significantly improve outcomes for this patient demographic.