STING ACTIVATION IN SARCOMA: ASSESSING TRANSLATIONAL THERAPEUTIC STRATEGIES

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Background Undifferentiated pleomorphic sarcoma (UPS) is a highly aggressive and metastatic soft tissue sarcoma that is resistant to most conventional systemic therapies and immunotherapies. Activation of the STimulator of INterferon Genes (STING) pathway is an emerging immunotherapeutic strategy that can be used to recruit effector lymphocytes into the TME to induce tumour eradication. In a murine model of UPS, we have demonstrated that intra-tumoural (i.t.) administrations of a murine-specific STING agonist, DMXAA, results in profound immune mediated tumour clearance. The objective of this study is to evaluate the anti-tumour potential of three STING agonists that can activate both murine and human STING receptors as monotherapies and in combination with immune checkpoint blockade (ICB) therapy in a murine model of UPS to assess translational feasibility.

Methods Immune competent mice were orthotopically engrafted with a syngeneic murine UPS cell line in the hindlimb muscle. UPS bearing mice in the monotherapy groups were treated with a single i.t. dose of 1) CDN, 2) MSA-2, 3) E7766 or 4) DMXAA. Mice treated in combination with ICB therapy received monoclonal anti-PD1 in addition to a single dose of CDN, MSA-2, or DMXAA. Tumour volume measurements and bioluminescence were measured over time. Surviving mice were re-challenged with UPS in the contralateral limb. Flow cytometry and 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 tumours. Survival studies with E7766 have shown UPS clearance in 18-40% of E7766 treated mice. 100% of the surviving E7766 and DMXAA treated mice completely rejected the re-challenge inoculation of UPS cells. Immune profiling of CDN, MSA-2, and DMXAA treated tumours at multiple timepoints post-treatment showed similar inflammatory changes and increased lymphocytic infiltration. STING+ICB therapy significantly improved survival outcomes in CDN+ICB treated tumours, as 14% of CDN+ICB treated mice eradicated their UPS tumours. In DMXAA monotherapy and DMXAA+ICB combination therapy, there were no significant differences in survival. Unfortunately, there were no survivors in the MSA-2+ICB group, but survival was significantly extended compared to MSA-2 monotherapy.

Conclusions 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 re-challenge. Ultimately, this study demonstrates the potential opportunity for clinical translation of STING as an immunotherapy for UPS which could significantly improve outcomes for this patient demographic.

REFERENCES