IL-12 MRNA MONOTHERAPY IS EFFECTIVE IN MURINE TUMORS RESISTANT TO CHECKPOINT INHIBITION

Sreevidya Santha, Jayalakshmi Lakshipathi, Man Li, Yuping Qian, Nadia Luшибi, Katerina Politi, Marcus Rosenberg, lim Eyles*, Viswanathan Muthusamy. Yale School of Medicine, New Haven, CT, USA; AstraZeneca, Cambridge, Cambridgeshire, UK

Background Interleukin-12 (IL-12) is a potent activator of anti-tumor immunity, but its use as a systemic therapy is limited due to toxicity. MEDI1191 comprises recombinant IL-12 mRNA formulated in lipid nanoparticles for intratumoral (IT) injection resulting in high expression of the cytokine in the immediate tumor microenvironment (TME). This novel drug is tolerated and efficacious in a preclinical setting, and has entered Phase 1 of Clinical Development (NCT03439280).

Methods We hypothesized that because IL-12 can directly activate effector T-cells and Natural Killer (NK) cells, MEDI1191 may be effective in tumors resistant to checkpoint inhibitor therapy due to defects within antigen presentation pathways. To test this, we used two MHC class I negative syngeneic allograft models, YUMMER 1.7 melanoma and MC38 colorectal carcinoma, both of which were engineered by CRISPR knock out of the beta-2 microglobulin gene (B2m KO). Tumor bearing mice were treated with a single IT injection of mIL12 mRNA or multiple systemic injections of a murine anti-PD-L1 antibody.

Results Therapy with checkpoint inhibitors, as expected, had no significant tumor growth inhibiting effect on the B2m KO tumors in contrast to durable complete responses observed following a single IT injection of mIL12 mRNA (without concomitant anti-PD-L1 treatment). All (10/10) the mIL12 mRNA treated mice bearing YUMMER 1.7 B2m KO tumors and 7/10 mice with MC38 B2m KO tumors had complete responses and were resistant to rechallenge with a second implantation of the same tumor cells. IT injection of mIL-12 mRNA resulted in marked upregulation of several immune activating and chemoattractant cytokines associated with a TH1 phenotype. Significant changes were observed within the TME, characterized by an increased infiltration of T cells and altered phenotype of tumor residing macrophages.

Conclusions Our results support the hypothesis that IT IL-12 mRNA therapy can beneficially re-profile the TME and may benefit human cancer patients who have developed resistance to checkpoint inhibitors.

Acknowledgements We acknowledge Moderna Inc. for kindly providing the mIL12 mRNA.

REFERENCES

http://dx.doi.org/10.1136/jitc-2023-SITC2023.1069