IMPROVED IMMUNOLOGIC AND THERAPEUTIC ACTIVITY OF ANCHORED INTERLEUKIN (IL-12) IMMUNOTHERAPY IN COMBINATION WITH CYTOTOXIC CHEMOTHERAPY AND IMMUNE CHECKPOINT INHIBITOR IN A HEAD AND NECK CANCER MODEL

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Background Head and neck squamous cell carcinoma is a heterogeneous group of cancers associated with high rates of locoregional recurrence and metastatic disease despite chemoradiation therapy. These tumors have exhibited limited responses to immune checkpoint inhibitors. Murine ANK-101 is a novel anchored form of IL-12 that persists in the tumor microenvironment for up to 30 days without systemic toxicity. We tested the hypothesis that local IL-12 could potentiate the therapeutic response of chemotherapy or immune checkpoint blockade for head and neck cancers.

Methods In C57BL/6 mice, we used established murine oral carcinoma (MOC1) tumors as a model for non-HPV-related head and neck carcinoma with the treatments commencing when the tumors were 100–200 mm³. Treatment with cis-platinum (5 mg/kg, IP injection once weekly for three weeks), murine ANK-101 (5 ug IT), anti-PD-1 (200ug, IP once weekly for three weeks), or various combinations were evaluated. Tumors were measured by calipers and tumor size one week after last treatment was used for comparisons of tumor growth. Mice were also followed for survival. Tumor size was compared using Student’s t-test between groups and multiple comparisons utilized two-way ANOVA testing. Survival was calculated using the Kaplan-Meier method.

Results In the MOC1 model, anti-PD-1 and cis-platinum alone had no impact on tumor growth. ANK-101 alone, however, was associated with a significant delay in tumor growth. The combination of ANK-101 and platinum or ANK-101 and anti-PD-1 resulted in further delay in tumor growth. Triple therapy with ANK-101, chemotherapy, and anti-PD-1 did not provide additional treatment effect which was near maximal with two drug treatment. The combination of ANK-101 and chemotherapy or anti-PD-1 was also associated with a survival benefit. Increased CD8+ T cell recruitment to the tumor microenvironment was seen with ANK-101 treatment. Furthermore, ANK-101 treatment skewed the macrophage population from M2 to M1.

Conclusions Anchored IL-12 improves therapeutic responses to cis-platinum chemotherapy and immune checkpoint blockade in the murine PD-1-refractory MOC1 head and neck cancer model. These preliminary data demonstrate that combining local IL-12 with cytotoxic chemotherapy and/or immune checkpoint blockade merits investigation in other tumor models.

Ethics Approval All animal studies were performed according to approved NIH Intramural Animal Care and Use Committee protocol (LTIB-38). All mice were housed and maintained in accordance with the Association for Assessment and Accreditation of Laboratory Animal Care guidelines.

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