**AIM:** Intratumoral (IT) electroporation (EP) of plasmid IL-12 promotes systemic anti-tumor immunity and is being evaluated in Phase 2 trials. In patients (pts) with advanced melanoma (MEL) treated with IL-12 EP, regression of non-injected lesions was seen in 4/19 pts in the Phase I study and 13/21 pts in the ongoing Phase 2 study. This study explores systemic efficacy and immune correlates in clinical samples and in a bilateral MEL model, utilizing the poorly immunogenic B16 cell line, to test the hypothesis that intratumoral IL-12 EP can enhance tumor immunogenicity.

**METHODS:** Pre- and post-treatment biopsies and blood were collected from MEL trial pts. A B16 2-tumor MEL model was developed in mice. Tumors treated with IL-12 EP were compared to untreated tumors in the same animal. mRNA was evaluated by NanoString and leukocyte populations by IHC and flow cytometry.

**RESULTS:** Analyses of clinical samples indicated a doubling of NK cells in the treated tumor as well as increased frequency in activated NK cells in circulation. In the B16 model, complete regression was seen in 20/20 treated tumors at post-treatment day 7 and 4/10 untreated tumors at day 18 or 22. Regression in untreated tumors was accompanied by a TIL infiltrate and transcriptional profile consistent with increased NK, CD8, CD4 and Tregs. In addition, the infiltrate was associated with increased mRNA for PD-1, PD-L1, IFNg and IFNg-inducible genes involved in antigen presentation and processing.

**CONCLUSIONS:** IL-12 EP results in regression of untreated lesions in pts and mice. Analysis of IL-12 EP-treated tumors showed a pattern consistent with NK cell infiltration, IFNg expression and upregulation of IFNg-driven genes, including ones involved in antigen processing and presentation. In mice, where untreated tumors were systematically analyzed, a TIL infiltrate and transcriptional IFNg program was identified consistent with enhanced B16 immunogenicity. This model provides insights into the immune reactions in both the electroporated tumor and in untreated lesions. Although preliminary, data from the B16 model and IL-12-treated pts support the hypothesis that augmentation of immunogenicity is a component of IL-12’s systemic anti-tumor effects.

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