INTRATUMORAL ELECTROPORATION OF PLASMAID-ENCODED IL-12 AND MEMBRANE-BOUND ANTI-CD3 INCREASES TUMOR IMMUNITY AND IMPROVES TUMOR CLONE ELIMINATION

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Poster No: LB-390

Abstract

Intratumoral (iT) delivery of plasmid-blend IL-12 and anti-CD3 immunomodulatory vectors via electroporation (EP) collectively referred to as T-ImoVec (anti-CD3) and iT-ImoVec (anti-CD3 + IL-12), engendering robust anti-tumor responses with minimal toxicity in preclinical and clinical studies. Our previous clinical data from melanoma patients treated with iT anti-CD3 identified a treatment-related increase in infiltrating T cells and cytokine production in tumor as a significant increase in the BIRMs score of patients with a clinical benefit, suggesting that iT-ImoVec (anti-CD3 + IL-12) delivers robust immune responses, as observed in patients with melanoma and other tumor types. Moreover, our previous study demonstrated that iT-ImoVec (anti-CD3) induced higher CD8+ T cell responses compared to iT-ImoVec (anti-CD3 + IL-12), in tumor samples analyzed by fluorescence-activated cell sorting (FACS) and RNA sequencing, indicating that iT-ImoVec (anti-CD3 + IL-12) elicits enhanced T cell responses. Here, using immuno-histological imaging of the tumor microenvironment (TME), we have demonstrated that iT-ImoVec (anti-CD3 + IL-12)-treated mice exhibited significantly increased expression levels of CD4+ T cells (FoxP3+, FoxP3–) in tumor microenvironment (TME), suggesting that iT-ImoVec (anti-CD3 + IL-12) delivers robust immune responses, as observed in patients with melanoma and other tumor types. In this preclinical study, we expected that patients with early-stage melanoma treated with iT-ImoVec (anti-CD3 + IL-12) demonstrated significantly increased expression levels of CD4+ T cells (FoxP3+, FoxP3–) in tumor, as observed in patients with melanoma and other tumor types. Here, we report the results of a randomized phase I clinical trial in 10 early-stage melanoma patients treated with iT-ImoVec (anti-CD3 + IL-12) and iT-ImoVec (anti-CD3), respectively. The results indicate that iT-ImoVec (anti-CD3 + IL-12) treatment delivered significantly higher CD4+ T cell responses compared to iT-ImoVec (anti-CD3) treatment, as assessed by FACS and RNA sequencing. Collectively, these data support the clinical use of iT-ImoVec (anti-CD3 + IL-12) for the treatment of patients with melanoma and other advanced solid tumors.

Multiclonic P2A-linked plasmid IL-12 and membrane-bound anti-CD3 construct is functional when expressed in vitro and in vivo

For the following graphs:

Combination of IL-12 and TCR stimulation yield T cell proliferation and effector cytokines from both regulatory and naive T cells

Transcriptomic analysis suggests membrane-bound anti-CD3 augments critical anti-tumor immune pathways triggered by TAVO

Membrane-bound anti-CD3 scFv augments local and systemic TAVO anti-tumor immunity in a metastatic breast tumor model

Summary and Conclusion

- Combination of iT-ImoVec (anti-CD3) and iT-ImoVec (anti-CD3 + IL-12) resulted in increased numbers of effector and effector memory T cells and activated T cells in peripheral blood.
- Intratumoral treatment with iT-ImoVec (anti-CD3 + IL-12) demonstrated significant increases in antigen-specific cytotoxicity and corresponding reduction in metastatic (untreated) tumor burden.
- Combination of iT-12 and membrane-bound anti-CD3 scFv induced an effective functional restoration of TILs isolated from a melanoma patient progressing on anti-PD1-TNF.