MEDI1191 (IL-12 MRNA) INDUCES PERIPHERAL AND INTRATUMORAL IMMUNOSTIMULATORY EFFECT IN PATIENTS WITH CUTANEOUS OR SUBCUTANEOUS (C/SC) LESIONS

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Background MEDI1191 is an investigational therapy composed of mRNA encoding bioactive interleukin-12 (IL-12p70) in a lipid nanoparticle optimized for intratumoral injection. We hypothesized that intratumoral injection of MEDI1191 will reprogram the immunosuppressed tumor microenvironment (TME) and increase cytotoxic T-cell recruitment, proliferation and activation.

Methods In an ongoing phase 1 dose escalation study (NCT03946800), patients with C/SC lesions received 0.1-12µg MEDI1191 sequentially (Part 1A) or concurrently (Part 1B) with intravenous durvalumab (1300 mg). Clinical samples were collected to monitor changes in peripheral cytokines, circulating tumor (ct) DNA, peripheral and tumoral gene signatures and T cell infiltration. Results Peripheral blood cytokine analysis revealed increased serum IL-12 levels in 27/29 (93%) patients post first injection and was associated with ≥2-fold increase in serum IFN-γ in 24/29 (83%) patients. The IFN-inducible chemokines (CXCL9, CXCL10 and CXCL11) in periphery were detected at the protein and transcriptomic levels. In 11 patients whose blood samples underwent bulk RNA sequencing, markers of activated peripheral T cells were detectable over time with increased mean fold change of GZMB, IFNG and IL12RB1 gene expression in patients with partial response (PR, n=1) or stable disease (SD, n=5) patients. Pre-treatment expression of the genes encoding key mediators of cytotoxic T-cell function were potential predictors of response as observed by significantly higher expressions of peripheral IL12RB1 and IFNG genes at baseline in PR/SD patients. Using immunohistochemistry (IHC), we observed ≥ 2-fold increase in CD8 T cells (8/17, 47%) and Ki-67+CD3+ T-cells (7/17, 41%) in tumor biopsies 15 days post first injection. Patients with increased intratumoral CD8 T cells by IHC and RNA sequencing showed higher tumoral GZMB and IFNG gene expression. In 9 patients with evaluable tumor biopsies at baseline and post-treatment, we observed an increase in antitumor gene signatures, including activated CD8 (7/9, 78%), activated NK (7/9, 78%), M1 macrophages (7/9, 78%) and IFN-γ signaling (8/9, 89%). Consistent with IL-12’s role as a central mediator of Th1 cell development, we observed an increase in Th1 signature and STAT4 gene (6/9, 67%). Analysis of ctDNA in plasma of 17 patients demonstrated >50% reduction in mutant allele frequency in 2/3 patients who developed PR.

Conclusions Intratumoral injection of MEDI1191 induces pharmacodynamic changes within the TME such as increase in activated T cell infiltration and upregulation of anti-tumor gene signatures. There was an associated immunomodulatory effect in the periphery, including elevated IL-12, IFN-γ and activated T-cells.

Trial Registration NCT03946800

REFERENCE


Ethics Approval The IRB/IEC responsible for each site reviewed and approved the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the subjects. Institutional Review Boards, Mount Sinai Health System, New York (Board Number 19-00279).