

## 371 ANALYSIS OF CHANGES IN PLASMA CYTOKINE LEVELS IN RESPONSE TO IL-12 THERAPY IN THREE CLINICAL TRIALS

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**Background** The ability of IL-12 to stimulate NK and T cell anti-tumor activity has made it an attractive candidate for overcoming immunosuppressive tumor microenvironments. Our group has demonstrated in pre-clinical models that IL-12 will enhance IgG receptor-mediated NK cell responses to antibody-coated tumor cells and conducted three studies where IL-12 was used in combination with an anti-tumor monoclonal antibody. These were OSU-9968, Phase 1 study of IL-12 + trastuzumab; OSU-1067, Phase 1 study of IL-12 + trastuzumab + paclitaxel in HER2-positive cancers and OSU-11010, Phase I/II study of IL-12 + cexutumimab in head and neck cancer.<sup>1-3</sup> Cytokine levels were measured in patients with varying responses in an effort to better characterize IL-12-induced immunity.

**Methods** Plasma cytokine levels in 21 patients across 3 studies were measured at baseline and at 4 time points after IL-12 administration. 2 patients had complete responses, 1 had a partial response, 9 patients had stable disease > 60 days and 9 had progressive disease. A combination of 7 U-PLEX, V-PLEX, and R-PLEX Human Biomarker Assays (Meso Scale Discovery) were performed to monitor levels of 23 cytokines: GM-CSF, IFN-gamma, IL-10, IL-8, IP-10, MCP-1, MDC, MIP-1alpha, MIP-1β, TNF-alpha, IL-15, IL-18, MCP-2, MIG, IL-13, IL-17, IL-1β, IL-4, IL-5, IL-6, IL-1alpha, TGFβ, VEGF. Student's t-test on GraphPad Prism 9.0.0 was used for statistical analyses.

**Results** Nine cytokines were significantly upregulated following IL-12 therapy. IFN-gamma levels increased from a mean of 27.42 pg/mL at baseline to 1764 pg/mL after IL-12 treatment (p=0.0246). GM-CSF, TNF-alpha and IL-10 also increased following IL-12 therapy (p=0.0199, 0.0004, 0.0003). Several chemotactic factors including MCP-1, MDC, MIP-1alpha, and MIP-1β increased from means of 483.1 pg/mL to 695.7 pg/mL, 3112 pg/mL to 4305 pg/mL, 62.44 pg/mL to 130.3 pg/mL and 263.1 to 487.4 pg/mL, respectively (p-values all < 0.013). Levels of IL-18 increased from a baseline mean of 2059 pg/mL to 3952 pg/mL (p=0.0003). Several cytokines were also differentially induced across response groups with MCP-1 and GM-CSF increased in responding patients (p=0.02, p=0.04) and IL-10, MIP-1β and IL-6 increased in progressive disease patients (p=0.02, p=0.01, p=0.03).

**Conclusions** The ability to detect significant changes in cytokines as a result of IL-12 therapy across three separate clinical trials supports the broad effects of IL-12 on NK cells and other immune compartments. The additional differential effect in responders vs. progressive disease patients indicates that these cytokines likely affect patient outcome and will be further evaluated as possible markers of response.

### REFERENCES

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**Ethics Approval** These studies were approved by the Human Institutional Review Board at The Ohio State University Medical Center; approval numbers 99H0185, 1999C0326 and 2011c0019, respectively.

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