1063 IMMUNE CORRELATES WITH RESPONSE IN PATIENTS WITH METASTATIC SOLID TUMORS TREATED WITH A TUMOR TARGETING IMMUNOCYTOKINE NHS-IL12

[1]Stephanie C Pitts*, [1]Nicole J Toney, [2]Margaret E Gatti-Mays, [1]Nicholas P Tschernia, [1]Julius Strauss, [1]James L Gulley, [1]Jeffrey Schlom, [3]Renee N Donahue. [1]*National Cancer Institute, Bethesda, MD, USA*; [2]*The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA*; [3]*National Cancer Institute, Center for Immuno-Oncology, Bethesda, MD, USA*

Background NHS-IL12 (now designated PDS0301) is a tumor-targeting immunocytokine targeting DNA/histones in necrotic areas of the tumor microenvironment. NHS-IL12 has shown promising results in preclinical studies as a monotherapy and in combination with other anti-cancer therapies such as the HDAC inhibitor Entinostat. The first-in-human clinical trial (NCT01417546) administered NHS-IL12 as a monotherapy subcutaneously in patients every-four weeks (Q4W), with a maximum tolerated dose of 16.8 mcg/kg and was expanded to include a high-exposure cohort consisting of bi-weekly treatment (Q2W) at two dose levels: 12.0 mcg/kg and 16.8 mcg/kg. Here, we present on immune correlates in peripheral blood to determine the impact of the dose level and schedule of NHS-IL12 on immune activation and evaluate immune correlates of clinical response.

Methods Serum, peripheral blood mononuclear cells (PBMC), and complete blood counts were collected from patients in the Q2W cohort (receiving 12.0 mcg/kg or 16.8 mcg/kg) and Q4W cohort (receiving 16.8 mcg/kg) throughout NHS-IL12 treatment. Serum levels of cytokines/soluble factors were evaluated by ELISA and Mesoscale assays, and PBMCs were assessed for 158 immune cell subsets by multicolor flow cytometry. New assays to detect soluble NK ligands (B7-H6, MICA, MICB), and more extensively characterize the association between NK lytic activity and phenotype were developed in healthy donor samples.

Results Higher levels of immune activation were seen with a dose of 16.8 mcg/kg versus 12.0 mcg/kg NHS-IL12 in patients in the high-exposure cohort, as evidenced by greater increases in serum IFNγ, TNFα, and soluble PD-1, and greater increases in frequencies of peripheral ki67$^+$ mature natural killer (NK), CD8$^+$ T, and NKT cells. Greater immune activation was also seen in the Q2W versus Q4W cohort, as demonstrated by greater increases in pro-inflammatory serum analytes, ki67$^+$ CD8$^+$ T, NK, and NKT cells, intermediate monocytes, and a greater decrease in CD73$^+$ T cells. Specific immune analytes at baseline including lower levels of monocytes and plasmacytoid dendritic cells, and greater increases after treatment in refined NK cell subsets and refined and total CD8$^+$ T cells, associated with improved clinical outcome. New assays to interrogate the functional role of NK cells were developed and will be applied in immune correlative studies of NHS-IL12.

Conclusions These findings demonstrate enhanced immune activation of both NK and T cells with higher dose levels and more frequent dosing of NHS-IL12. These findings may help to guide future schedule and dosing regimens of clinical studies of NHS-IL12 as monotherapy and in combination therapies.

Ethics Approval All subjects gave written informed consent. Study protocol (NCT01417546) was approved by the NIH's IRB, and conducted in accordance with institutional and federal guidelines.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.1063