1522 REVITALIZING SYSTEMIC IMMUNE RESPONSES IN PROGRESSIVE NSCLC USING FLT3L AND SBRT

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Background Fms-like tyrosine kinase 3 ligand (FLT3L) is a potent hematopoietic growth factor that mobilizes stem cells and increases the number of circulating dendritic cells (DCs) in blood and organs. In a murine lung adenocarcinoma model, FLT3L had modest activity as monotherapy but demonstrated synergy when combined with high-dose radiotherapy.[1] Clinical trials have demonstrated that FLT3L is safe but has minimal activity in cancer patients. We performed a prospective trial for patients with advanced non-small cell lung cancer (NSCLC) to evaluate the immune correlates of combining FLT3L with stereotactic body radiotherapy (SBRT).

Methods Twenty-nine subjects were enrolled between October 2016 and January 2020 in a Phase II clinical, and all subjects failed at least one previous round of treatment (median 3 lines, range 1 to 5). Subcutaneous CDX-301 (75 µg/kg) was administered daily for five days with concomitant treatment of SBRT (figure 1). To identify immune cell signatures of response, we developed two high dimensional flow cytometry panels measuring 31 unique subsets found in peripheral blood mononuclear cells (PBMCs) and performed multiplex proteomic analysis measuring 92 different proteins at baseline, 2 weeks, 4 weeks, and 8 weeks post treatment.

Results In our trial, 55% of patients achieved progression free survival four months (PSF4) after treatment with 31% of the patients achieving abscopal responses. SBRT and CDX-301 induced significant increases in the myeloid compartment, including subsets of monocytes, myeloid-derived suppressor cells (MDSCs) and DCs (figure 2). Within the DC compartment, we found heterogeneity, with FceR1-expressing DC2 and DC3 being the most responsive to treatment. Despite the strong responses from DCs and MDSCs to SBRT and CDX-301, cellular responses returned to baseline 8 weeks post treatment. Notably, the treatment induced greater co-expression of HLADR and Ki67 on CD4 T cells than CD8 T cells. In abscopal responders, CD4 T cell phenotype continued to evolve over a longer time period with concomitant increases of Th1-like CD4 T cells, IL21, and DC1 over 4 weeks (figure 3).

Conclusions CDX-301 and SBRT emerge as a compelling approach to reactivate the immune system that has facilitated the progression of NSCLC. Patients with abscopal responses exhibit distinct cellular responses to FLT3L and SBRT that align with the emerging significance of DC1 and CD4 T cells. This sustained Type 1 response over 4 weeks in abscopal responders independent of high grade adverse events, indicating a unique therapeutic axis to harness systemic immunity against metastatic lesions in NSCLC.

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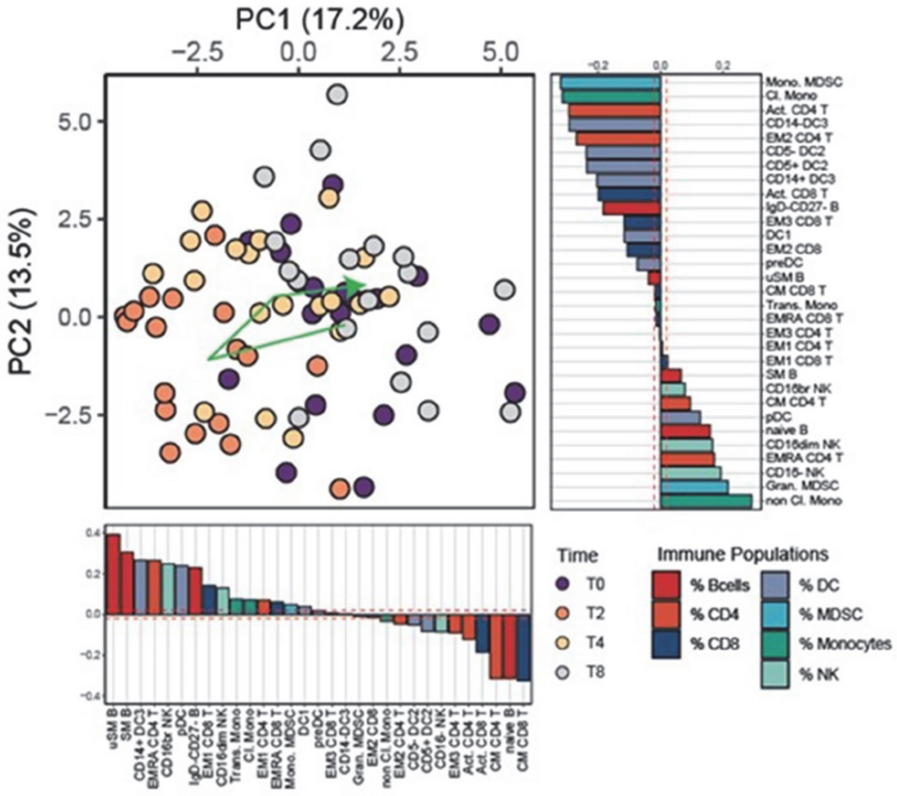
REFERENCE

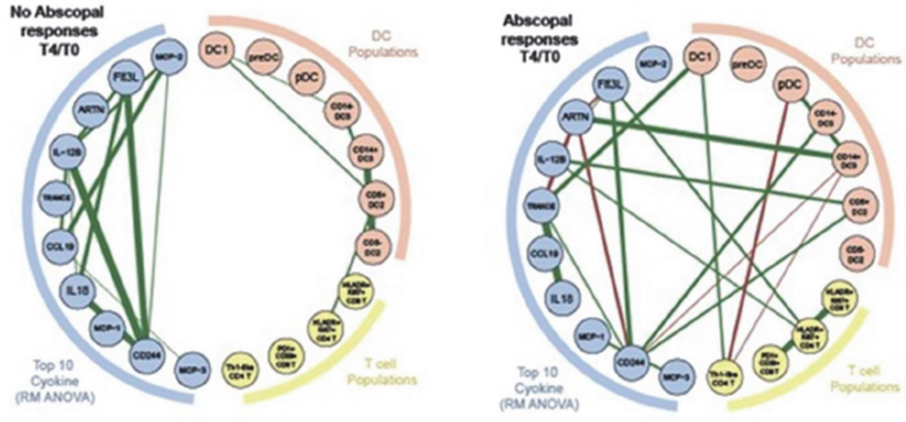
1. Chakravarty PC. Flt3-ligand administration after radiation therapy prolongs survival in a murine model of metastatic lung cancer. *Cancer Res.*1999;**59**;6028–32.

Ethics Approval This study (2015–5267) was approved by the Albert Einstein College of Medicine IRB on 9/30/2015. All participants provided informed consent

Abstract 1522 Figure 1 Trial scheme



Abstract 1522 Figure 2 Patient level PCA using aggregated flow cytometry data representing 31 unique immune populations. Each point is colored by timepoint with the green arrow representing the mean of PC1 and PC2 at each timepoint. Variable contributions for the PC1 axis (right) and PC2 axis (bottom) are ranked by magnitude and direction of contribution and colored by parent population



Abstract 1522 Figure 3 Spearman rank correlations of the fold change from T4 to T0 (baseline) in DC1, preDC, pDC, CD14-DC3, CD14+DC3, CD5 +DC2, CDS- DC2, Th1-like CD4 T cells (CXCR5+), exhausted CD8 T cells (PD1+CD39+), activated CD4 T cells (HLADR+Ki67+), activated CD8 T cells (HLADR+Ki67+), and the top 10 cytokines from that are changing the most with time. Nodes are colored by associated group (cytokine, T cells, and DCs). Green edges represent positive correlations and red edges represent negative correlations. Correlations >0.7 for inclusion in correlation network

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