In Situ Vaccine for Low-Grade Lymphoma: Combination of Intratumoral Flt3L and Poly-ICLC With Low-Dose Radiotherapy.

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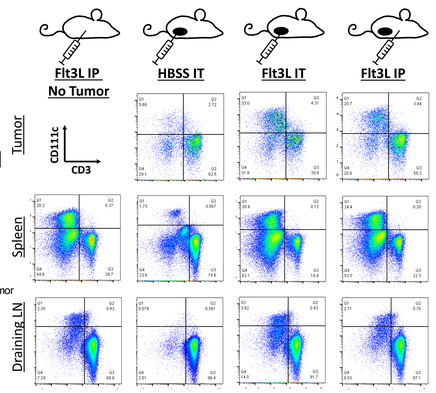
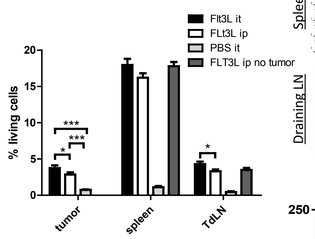
Background

Lymphomas are the 5th most common cancer in the United States, 40% of these cases are indolent non-Hodgkin's lymphoma (iNHL) and are incurable with standard therapy. In a previous trial of *in situ* vaccination in iNHLs, in which intratumoral CpG, the TLR9 agonist, was combined with low dose radiation to induce a systemic immune response against tumor, induction of tumor-specific CD8 T cell responses and durable clinical remissions of patients' untreated sites of disease was seen in some patients. One limitation in this previous trial may have been the scarcity of intratumoral dendritic cells (DC) and the suppressive tumor microenvironment. DC are uniquely able to endocytose dying (e.g. irradiated) tumor cells for cross-presentation to anti-tumor CD8 T cells. In this new iteration of *in situ* vaccine, Flt3L is added as a priming step to increase the presence of intratumoral DCs ahead of vaccination. FMS-like tyrosine kinase 3 ligand (Flt3L) induced tumor leukocyte infiltration and regression in lymphoma tumors in pre-clinical trials, and CDX-301- a formulation of Flt3L - was shown to mobilize BDCA-1 and BDCA-3 myeloid DC subsets in an early phase trial. These DC subsets respond to several TLR agonists and cross-present antigens more effectively than plasmacytoid DCs. While pDCs are high expressors of TLR9, responsive to CpG, myeloid dendritic cells express a wider array of TLRs, including high levels of TLR3.

Preclinical Data

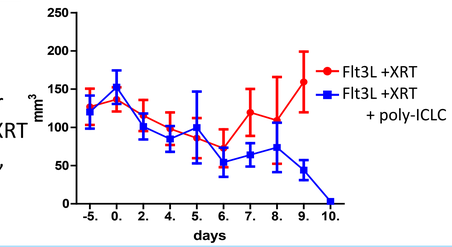
Flt3L was injected intra-tumor (IT) or intraperitoneal (IP). Tumor, spleen or draining lymph nodes were assessed at 72h for influx of CD111c$^+$ dendritic cells.





Initial murine trial

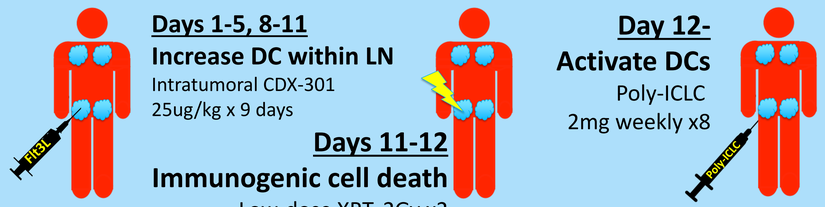
A20 subQ pretreated for 9 days with Flt3L, local XRT on d0 (1 day after Flt3L), poly-ICLC on d0-4.

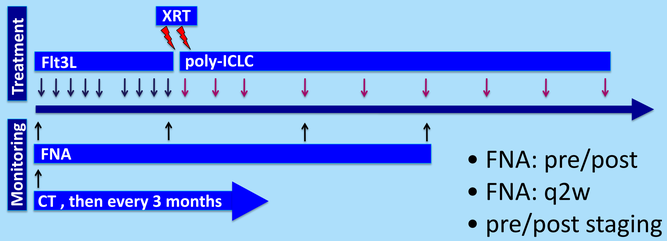


The study protocol and all amendments were approved by the institutional review board at The Mount Sinai Hospital and the study was conducted in accordance with the provisions of the Declaration of Helsinki.

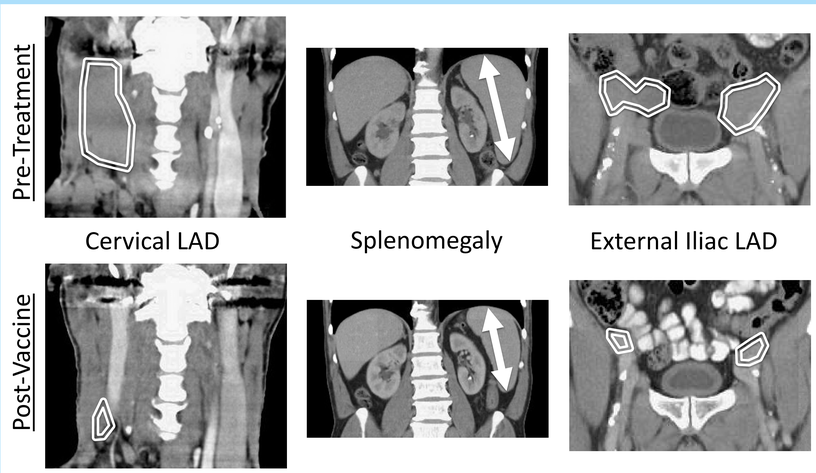
Trial Design

This Phase I/II trial tests the hypothesis that this novel *in situ* vaccination will induce clinical remissions at distant (untreated) tumor sites in two cohorts of patients with either previously untreated or relapsed/refractory iNHL (n=15 per group). Intratumoral CDX-301 25ug/kg is injected into a palpable lymph node for 9 days, followed 2Gy local radiotherapy on day 9 and 10 to the target lymph node. On day 10, following radiation therapy, intratumoral poly-ICLC 2mg is injected to activate local DCs. Poly-ICLC 2mg is then injected on day 14, day 17 (1 week after initial dose) and weekly thereafter for a total of 9 treatments over 8 weeks. Response is assessed with CT scans every three months as per the Revised Response Criteria for Malignant Lymphoma, also known as the Cheson criteria, and leukemic phase of lymphoma monitored by peripheral blood flow cytometry. For information: NCT01976585.



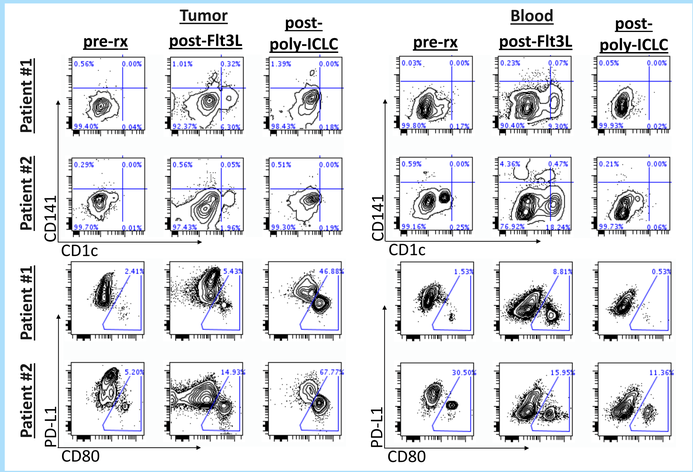


- FNA: pre/post
- FNA: q2w
- pre/post staging (such as below)



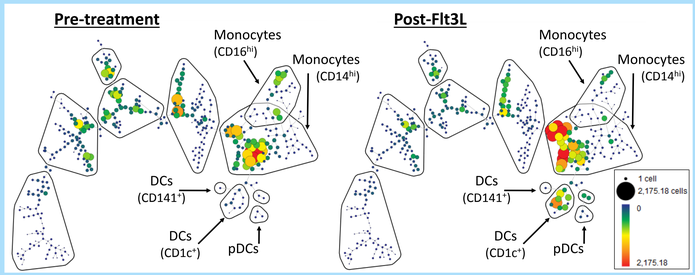
Correlative studies

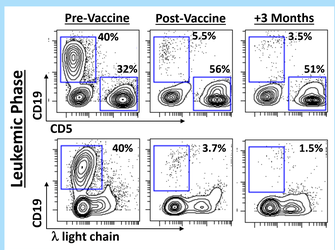
PBMCs and excisional LN are obtained before the initiation of the trial, and whole blood and FNAs are obtained every 2 weeks to monitor the inflammatory response to the vaccine. Sample studies confirming cellular response to vaccine regimen are shown below.



Correlative studies

Flow cytometry and CyTOF demonstrating the ability of Flt3L to induce influx of DCs as seen in mice. CD1c (BDCA1$^+$) and CD141 (BDCA3$^+$) DCs hone to treated tumors following treatment with Flt3L (upper top panels) and T cells attain a mature (PD-L1^{lo} CD80^{hi}) phenotype. Similar influx of DC subsets, primarily CD1c+ DCs is documented by CyTOF (below left). Lower right demonstrates resolution of leukemic phase disease in one patient





Accrual started in January, 2014 and is ongoing. 12 patients have been enrolled including 8 untreated patients and 4 with relapsed/refractory disease. We are actively enrolling patients in the trial. Interim analysis planned following the first 15 patients.

Mount Sinai *The Tisch Cancer Institute*