**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 CDP, the TRLR 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 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 agonists and cross-present antigens more effectively than plasmacytoid 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 DCs. While pDCs are high expressors of TLR9, responsive to CpG, myeloid DCs.

**Preclinical Data**

Flt3L was injected intra-tumor (IT) or intraperitoneal (IP). Tumor, spleen or draining lymph nodes were assessed at 72h for influx of CD11c+ dendritic cells.

**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 target the 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.

**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.

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.