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## PRELIMINARY RESULTS OF A PILOT STUDY OF INTRATUMORAL INJECTION OF AUTOLOGOUS DENDRITIC CELLS AFTER HIGH-DOSE CONFORMAL EXTERNAL BEAM RADIOTHERAPY IN UNRESECTABLE PRIMARY LIVER CANCERS

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**Background** Survival outcomes for patients with unresectable primary liver tumors (hepatocellular carcinoma [HCC] and intrahepatic cholangiocarcinoma [iCCA]) remain dismal, despite available locoregional and systemic treatment options. This pilot study aims to evaluate the safety and tolerability of intratumorally delivered autologous dendritic cell (DC) vaccine after external beam radiotherapy (EBRT) in unresectable HCC and iCCA. We hypothesize that *in situ* DC-mediated tumor vaccination via radiation-induced immunogenic cell death, will elicit tumor-specific immunity and improve clinical outcomes. **Methods** Enrolled subjects undergo leukapheresis for DC manufacturing prior to EBRT administration as per standard of care for unresectable localized HCC/iCCA. After EBRT, 7 monthly ultrasound-guided intratumoral injections of mature DC (30-60 million cells) are administered (figure 1). An adjuvant booster (Pevnar vaccine) is given with the first 3 injections. The primary endpoint is the incidence of significant toxicity, and secondary endpoints include objective response rate (ORR) and survival. Pre/post-treatment peripheral blood samples are collected for immune correlative studies, including multiparametric flow cytometry and single-cell RNA sequencing.

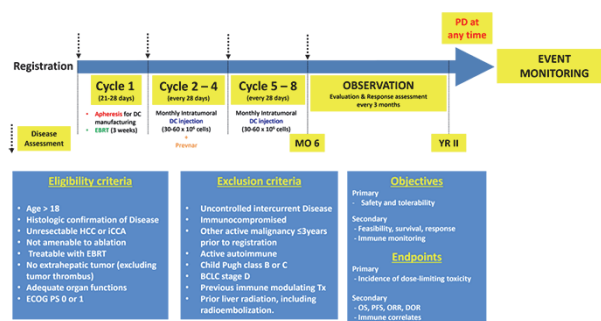
**Results** As of July 28, 2022, eight subjects have enrolled (5 HCC; 3 iCCA) with five (3 HCC; 2 iCCA) having completed the protocol and three (2 HCC; 1 iCCA) currently in active phase. DC manufacturing success has been 100% and the maximal dose of  $60 \times 10^6$  DC appears to be tolerated without autoimmunity or grade  $\geq 3$  adverse events (AEs), with the exception of one subject with grade 3 hyperbilirubinemia. The most common AEs include limited injection site pain and nausea. Early response data from the five subjects who have completed the protocol is encouraging with ORR of 60% ( $n=3$ , all partial response). One responder with iCCA has an ongoing response at 2 years (figure 2), and another HCC subject had stable disease for over one year. Preliminary cellular immunophenotyping and T cell receptor (TCR) clonotyping/profiling has revealed both the emergence of new TCR clones and expansion of existing TCR clones, including clones with tumor reactive and cytotoxic profile, suggesting this combination could enhance tumor reactive cytotoxic T cell response (figure 3). However, many of the TCR clones also have early exhaustion signal with upregulation of multiple checkpoint receptors. Thus, incorporating immune checkpoint inhibition (ICI) may help further enhance the cytotoxic functions of these TCR clones.

**Conclusions** Despite being preliminary, data from subjects treated to date suggest a favorable safety profile, encouraging signs of efficacy and induction of tumor-specific immunity which could be further enhanced by the addition of ICI.

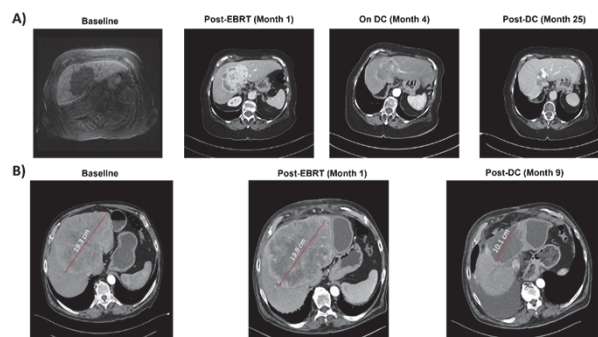
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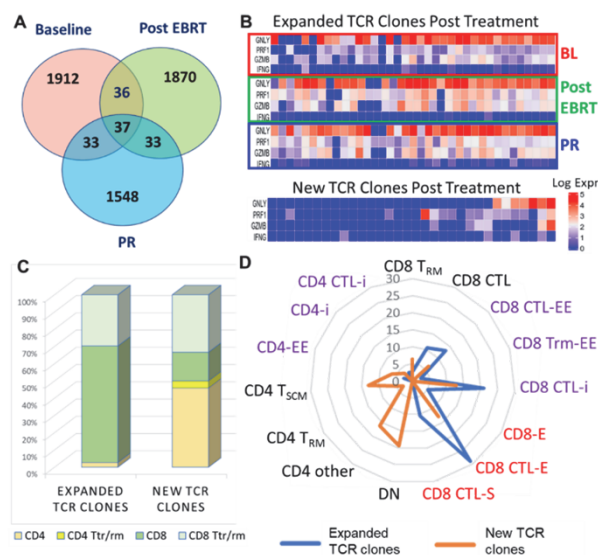
Ethics Approval This study was approved by the Mayo Clinic Ethics & Institutional Review Board (IRB# 16-0096335).



Abstract 689 Figure 1 NCT03942328 study schema.



Abstract 689 Figure 2 Representative images of treated patients. Patients with iCCA (A) and HCC (B) treated with EBRT and intratumoral DC injection on NCT03942328 study. Reduction in tumor size, corresponding to partial response is seen and is ongoing at 25 months and 9 months post-enrollment, respectively.



Abstract 689 Figure 3 TCR repertoire changes with EBRT and DC. (A) The number of unique and shared TCR clones from baseline (BL) to post-EBRT and after DC, at the time of partial response (PR) are shown.

(B) Heatmap of for TCR clones' RNA expression are show here for cytotoxic functions: GNLY, PRF1, GZMB; and for cytokine IFNG. Most of the TCR clones that are expanded with treatment have increased expression for cytotoxicity and IFNG (top 3 panels). In contrast, few new TCR clones post treatment have cytotoxic or IFNG expression (bottom panel). (C) While majority of the expanded clones are CD8, new TCR clones post-treatment are both CD4 and CD8, with a much smaller percentage having tissue/tumor origin. (D) Majority of the expanded TCR clones post- treatment have inhibited (-I, one or more checkpoints expressed), early exhausted (-EE), exhausted (-E) or senescent (-S) transcriptome. In contrast, new TCR clones post treatment have more stem memory and tissue derived resident memory profile.

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