Elucidating factors of therapeutic response to immunotherapy combined with neoadjuvant radiation therapy for rectal cancer

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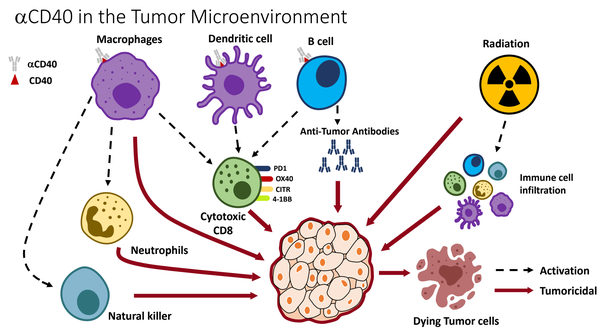
INNATE: anti-CD40, Sotigalimab, during neoadjuvant short course radiotherapy and chemotherapy

Background: Rectal Cancer

The Problem
- For those less than 50 years old, there is a 4x relative risk of developing rectal cancer if born in the 90's than if born in the 50's.
- Approximately 50% of patients with locally advanced disease recur within 3 years following standard-of-care-treatment
- Approved immunotherapies have shown little activity in colorectal cancer (CRC) outside of MMR-deficient subtypes

The Standard of Care
- Curative treatment involves radiation (RT), chemotherapy (CT), and surgery
- Total neoadjuvant therapy is a new standard, but there are multiple acceptable approaches and sequencing.
- The critical need: To develop new therapeutic approaches to improve survival

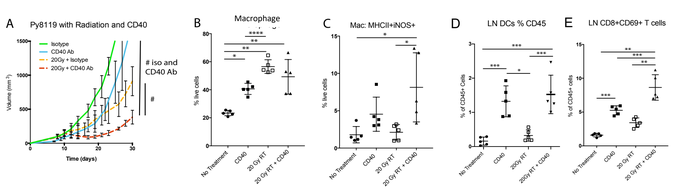
anti-CD40 Immunotherapy Opportunity



anti-CD40 can impact many players in the tumor microenvironment (TME) in combination with RT

The Drug
- Sotigalimab (APX005M): Agonistic anti-CD40 Ab with Fc mutation to enhance its potency and limit ADCC activity (*Filbert, Cancer Imm Immunother, 2021*)
- Potential activity in pancreatic cancer (*O'Hara, Lancet Oncology, 2021*)

RT + anti-CD40, a Promising Combination for Immunologically Unresponsive Tumors

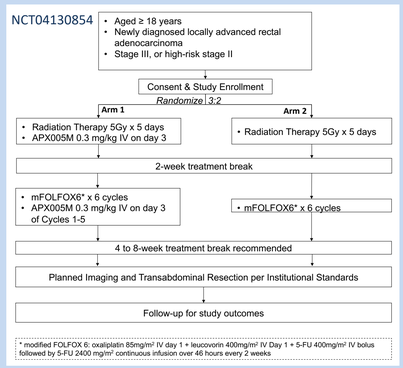


Aguilera et. al., Clin Cancer Res, 2020

Potential roles of CD40 in modulating RT responses in the TME. (A) RT and anti-CD40 better than either alone in immune resistant tumors (given day 10 and 100ug FGK4.5 q3days x4). After RT and anti-CD40: **(B)** greater macrophage ($CD11b^+F480^+$) infiltration, **(C)** greater inflammatory phenotype, **(D)** increased DCs ($CD11b^-CD11c^+MHCII^+$) in draining LN and **(E)** greater activated CD8 T cells.

Trial Design for Locally Advanced Rectal Cancer

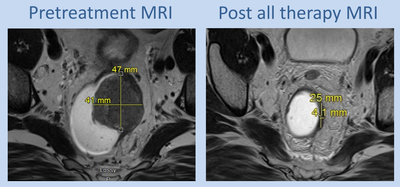
Design
- Stage III or high-risk stage II (<1cm to anal ring, cT4, 3mm MR fascia, no sphincter preservation, and vascular invasion)
- Randomized 3:2 with total accrual goal of 58 patients
- Standard short course RT 25Gy in 5 fractions
- 3 months of FOLFOX
- APX005M: 3rd day post RT and chemo cycles 1-5
- Avoid steroids in pre-med



Endpoints
- Primary: pCR (Null 20% and goal is 50% pCR)
- Secondary: safety, 3 yr OS, 3 yr DFS, toxicity

A patient in the Sotigalimab arm

Pretreatment MRI | Post all therapy MRI

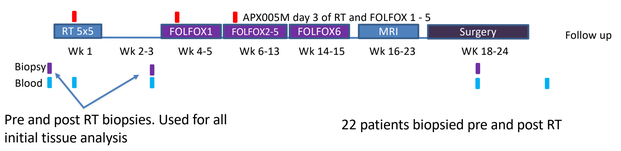


Updates
- Opened 6/2020 (UTSW)
- 3 centers open (UTSW, OHSU and Wake Forest)
- 25 enrolled
- Pending 7 centers
- 55% <50 yo

OHSU · Community Health Network · The University of Chicago Medicine · UTSouthwestern Medical Center · Wake Forest Baptist Health · The University of Arizona Cancer Center · VA · Moffitt Cancer Center

Studying Therapeutic Response in Tumors

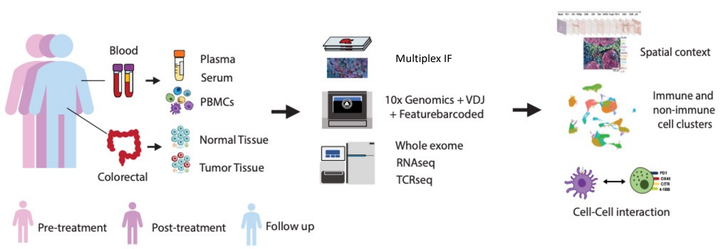
Treatment timeline



Pre and post RT biopsies. Used for all initial tissue analysis

22 patients biopsied pre and post RT

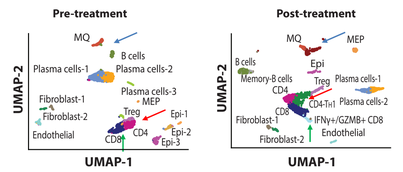
Tissue analysis plan

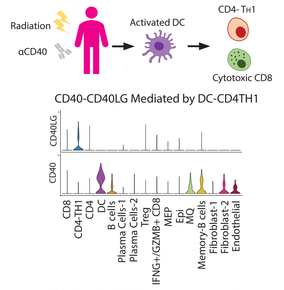


Plan for thorough tissue analysis… Biopsies: single cell RNAseq with feature barcodes and T/BCR seq. Whole exome sequencing. Bulk RNAseq. TCRseq when indicated. Mulitplexed immunofluorescence with the CODEX system. **Blood:** similar opportunity will be in conjunction with tissue analysis.

Elucidating Local and Systemic Responses

TME Pre and post Sotigalimab suggests adaptive immune response

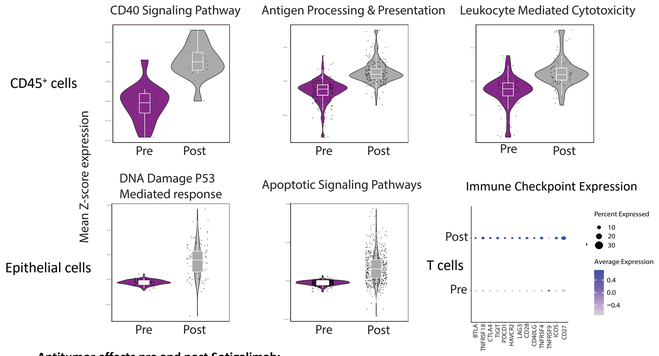




In one patient pre and post Sotigalimab:
- 10x Genomics scRNAseq
- There were no DCs, CD4-TH1, or CD8-IFN⁺/GZMB⁺ pretreatment
- After treatment there was an induction of each cell subtype
- Transcriptomic changes across many cell subtypes observed
- Full data integration with other patients pending

CD40 and CD40LG expression by cell type
- CD4-TH1 expressed CD40LG
- DCs highest expressors of CD40

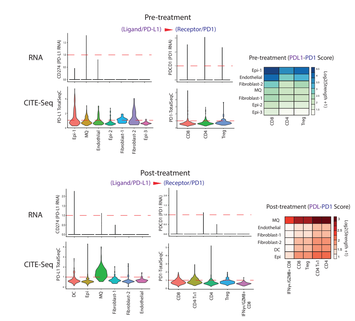
Antitumor immune responses to anti-CD40 and RT



Antitumor effects pre and post Sotigalimab:
- One patient, 10x Genomics scRNAseq cell subset comparison
- Compared CD45⁺ cells, epithelial cells, and immune checkpoints in T cells

PD-L1 is induced in macrophages

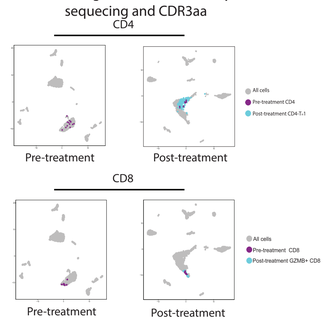
CITE-seq is indispensable for cell interaction network



Surface proteome allows critical perspective: RNA vs CITEseq
- Upper: PD-L1 and PD-1 pre-treatment shows epithelial cells and fibroblasts express the most PD-L1
- Lower: Post-treatment shows induction of PD-L1 on macrophages and PD1 on each lymphocyte subset

Tracked T cell clones were activated

Track the origin of CD4 and CD8 by VDJ sequecing and CDR3aa



TCRseq shows T cell dynamics
- Upper CD4 TCR seq and lower is CD8 TCR seq
- For CD4 there were TCR clones that were identified in the post treatment CD4-TH1 subpopulation with new clones
- For CD8 the same story about post treatment in GZMB⁺ cells

Summary:
- Rectal neoadjuvant approach: Excellent platform to test new RT immunotherapy combinations
- Combination of Sotigalimab with radiation and chemotherapy enhanced immune and inflammatory responses in the TME and converted cold tumor to hot.
- Tissue analysis of biopsy specimen allows greater understanding of therapeutic effects and mechanism of action of Sotigalimab in combination with chemotherapy and radiotherapy
- Currently analyzing 14 patients pre and post RT for first large assessment.

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