INNATE: Immunotherapy during neoadjuvant therapy for rectal cancer to elucidate local and systemic therapeutic responses

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A Phase II Randomized Multi-center Trial with and without sotigalimab (APX005M), a CD40 Antibody

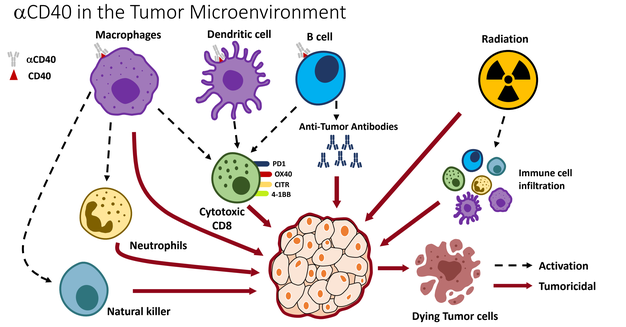
Background: Rectal Cancer

The Problem
- There is a 4x relative risk of developing rectal cancer for those <50 years old compared to 40 years ago
- 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 sequence and approach to CT and RT acceptable
- The critical need: To develop new therapeutic approaches to improve survival

αCD40 Immunotherapy Opportunity

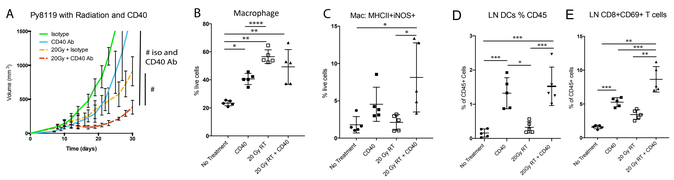
αCD40 in the Tumor Microenvironment



αCD40 can impact may players in the tumor microenvironment (TME) in combination with RT.

The Drug
- APX005M: Agonistic αCD40 Ab with FC mutation to enhance its agonistic potency and limit ADCC activity (*Filbert, Cancer Imm Immunother, 2021*)
- Potential activity in pancreatic cancer (*O'Hara, Lancet Oncology, 2021*)

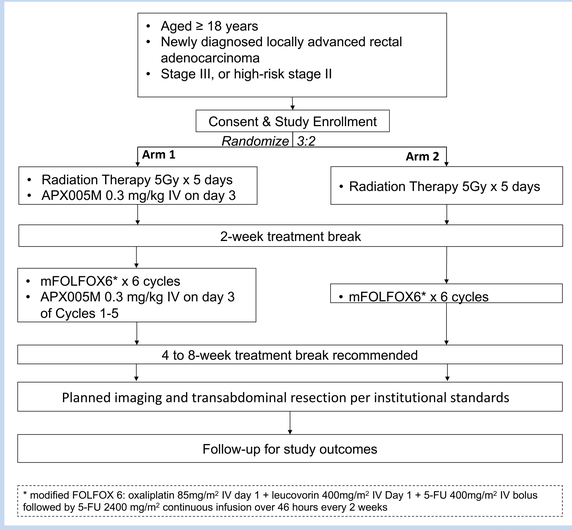
RT and αCD40, a Promising Combination



Aguilera et. al., Clin Cancer Res, 2020

Potential roles of CD40 in modulating RT responses in the TME. A. RT and αCD40 better than either alone in immune resistant tumors (given day 10 and 100ug FGK4.5 q3days x4). **B.** Greater macrophage ($CD11b^+F480^+$) infiltration after RT and **(C)** greater inflammatory phenotype. **D.** Increased DCs ($CD11b^-CD11c^+MHCII^+$) in draining LN with αCD40 and **(E)** greater activated CD8 T cells.

Trial Design for Locally Advanced Rectal Cancer



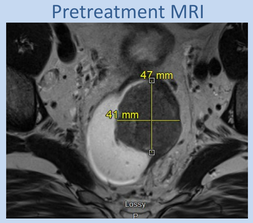
NCT04130854

Design
- Stage III or high-risk stage II <1cm from anal ring, bulky cT4/within 3mm MR fascia, not a candidate for sphincter preservation, and EMVI
- Randomized 3:2 with total accrual goal of 58 patients
  - With or without APX005M
- Short course RT
- 3 months of FOLFOX chemotherapy
- APX005M: 3rd day RT and chemo cycles 1-5

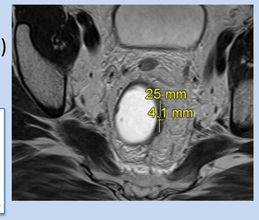
Endpoints
- Primary: pCR (Null 20% and goal is 50% pCR)
- Secondary: 3 yr OS, 3 yr DFS, toxicity

Updates
- Opened 6/2020 (UTSW)
- 3 centers open (UTSW, OHSU and Wake Forest)
- 17 enrolled as of 10/15/2021
- Pending 7 centers

Pretreatment MRI



Post-treatment MRI

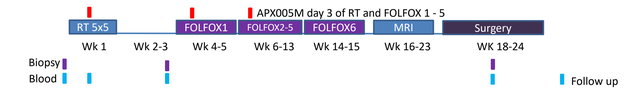


OHSU · Community Health Network · The University of Chicago Medicine · UTSouthwestern Medical Center · Wake Forest Baptist Health · The University of Arizona Cancer Center · VA · Moffitt Cancer Center

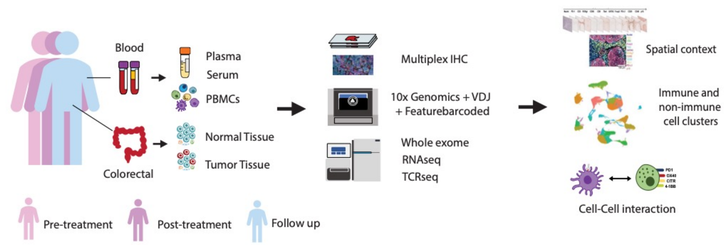
Arm	Age (range) 55% < 50 yo	Enrolled	Received planned tx	Completed surgery
APX005M	27-65	10	10	6
Standard	40-75	7	7	3 (1 progressed)

Elucidating Local and Systemic Responses

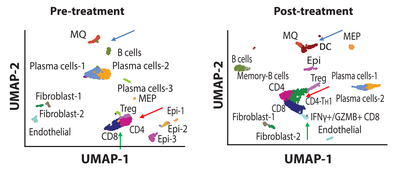
Treatment timeline



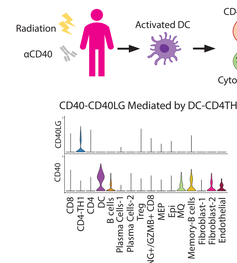
Tissue analysis plan



TME Pre and post therapy suggests immune response (early data)

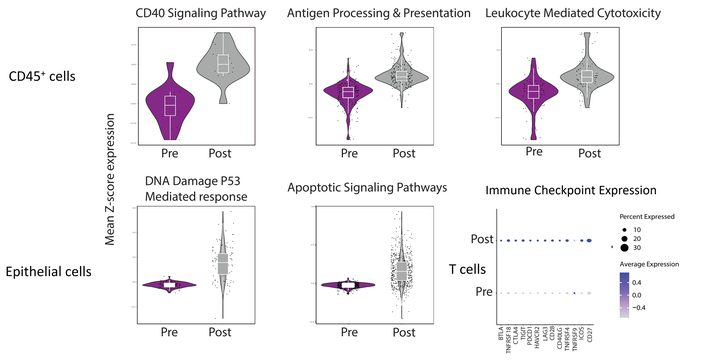


- There were no DCs, CD4-TH1, or CD8-IFN$^+$/GZMB$^+$ pretreatment
- After treatment there was an induction of each cell subtype
- Transcriptomic changes across many cell subtypes
- 1 patient treated with APX005M



- CD4-TH1 expressed CD40LG
- DCs highest expressors of CD40

Antitumor immune responses to αCD40 and RT (early data)



1 patient, 10x Genomics scRNAseq cell subset analysis

Summary:
- Rectal neoadjuvant approach: Excellent platform to test new RT immunotherapy combinations
- Results from clinical and tissue analysis of INNATE trial pending

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