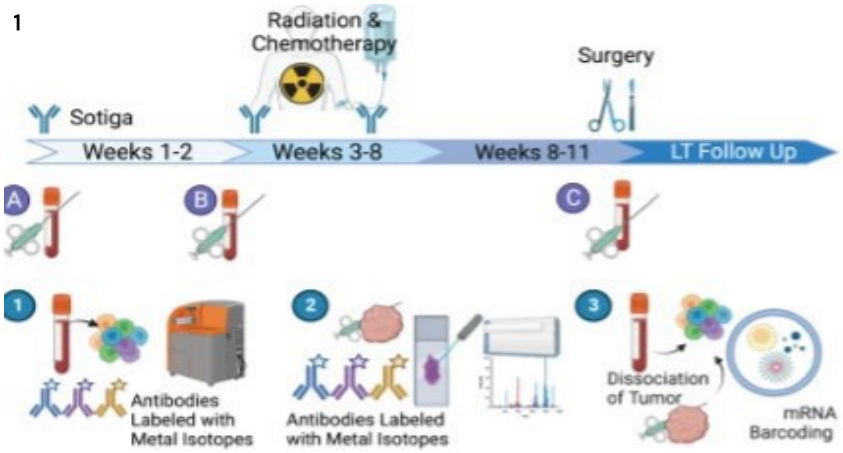
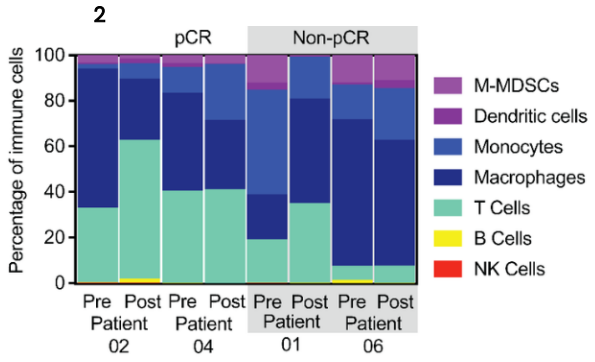
Case Study

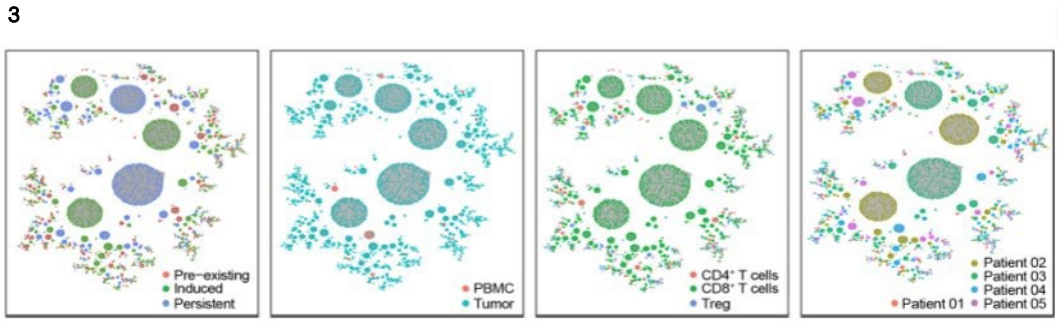
Mapping the Tumor Microenvironment: Sotigalimab's Role in Remodeling Immune Responses

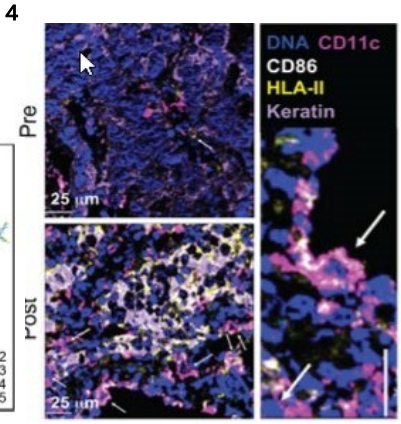
Publications continue to underscore the transformative impact of immune checkpoint inhibitors, which have significantly extended survival rates across various cancers. However, a persistent challenge remains in that many tumors develop resistance mechanisms that compromise the effectiveness of cancer immunotherapies. To address this challenge, researchers have developed monoclonal antibodies (mAbs) that act as agonists to immunostimulatory molecules. Among these targets, CD40, a receptor expressed on antigen-presenting cells (APCs), has shown considerable promise in enhancing antitumor responses.

The intricate and dynamic nature of immune interactions within the tumor microenvironment posed significant challenges for Pyxis Oncology's researchers, as traditional methods were inadequate for capturing the spatially organized immune responses. To address this, cutting-edge analytical methods would be essential to gain deeper insights into sotigalimab's (an agonistic anti-CD40 monoclonal antibody) potential to enhance cancer treatment outcomes.









1) Patients were treated with sotigalimab at the initiation of the study (a), at the beginning of week 3 (b) and at week 8 (c). Chemotherapy and radiation were initiated after the second dose of sotigalimab (b). Tissue biopsies and blood samples were collected at timepoints pre-treatment, at week 3, and at surgery. Blood samples were used to assess changes to the peripheral immune system using CyTOF (1) and scRNAseq (3). Fixed tissue samples were sectioned, stained, and analyzed using MIBI (2). The tumor tissue was also dissociated into a single-cell suspension and analyzed by scRNAseq (3). 2) MIBI analysis depicts changes in cell density and upregulation of activation markers for DCs in the TME. 3) Network plot of T cell clones (paired alpha and beta chain) with cluster details (newly induced, persistent, or pre-existing clones; blood or tumor compartment; T cell type) or patient identity overlaid. 4) Images from MIBI analysis from samples taken pre- and post-sotigalimab treatment.

- **MIBI** (Multiplexed Ion Beam Imaging) technology enabled:

- **Immune Profiling and Spatial Insights**: provided a detailed spatial and quantitative analysis of immune cells, revealing how sotigalimab reshaped immune interactions within the TME.

- **Spatial Organization Insights**: helped researchers visualize the spatial organization and activation status of immune cells.

- **Biomarker Discovery**: identified potential biomarkers for personalized cancer therapy that resulted from the high-resolution mapping of the immunological changes.

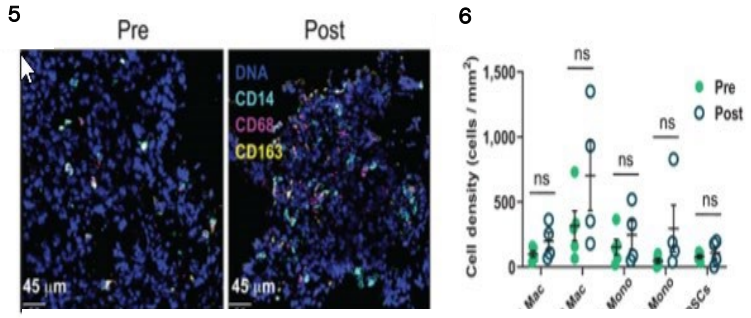
- **Understanding TME Dynamics**: and enabled the exploration of how sotigalimab transitioned the tumor microenvironment from an immune-suppressive state to an inflammatory, anticancer environment, enhancing antitumor immune responses.

Conclusion

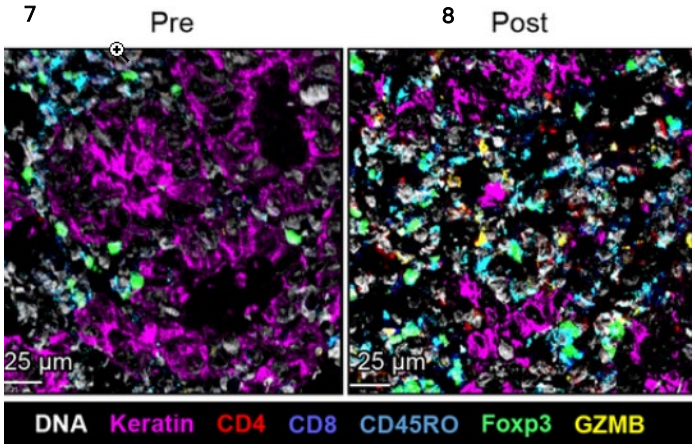
The research team employed state-of-the-art imaging technologies and high-dimensional single-cell analysis to precisely map how sotigalimab altered the tumor immune microenvironment. Their findings revealed that sotigalimab enhanced antigen presentation, primed new T cell clones, and reduced regulatory T cells, thereby contributing to a more effective antitumor immune response. The study provides valuable insights into the complex dynamics of the tumor immune microenvironment and underscores the critical role that spatially resolved, high-dimensional data plays in helping researchers understand and optimize cancer immunotherapies.

Reference

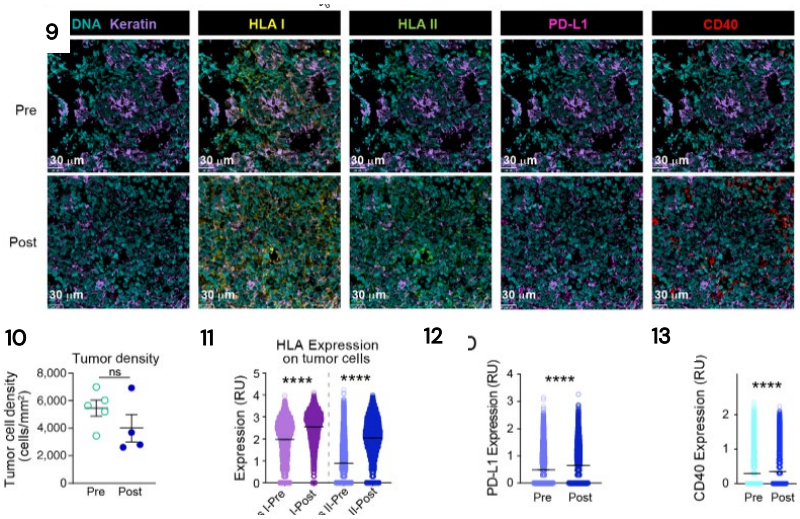
Neoadjuvant CD40 Agonism Remodels the Tumor Immune Microenvironment in Locally Advanced Esophageal/Gastroesophageal Junction Cancer.
Soto, M.; Cancer Research communications (2024) Jan 25;4(1):200-212
DOI: https://doi.org/10.1158/2767-9764.CRC-23-0550



Visualization (E) and quantification (F) of monocyte, macrophage, and MDSC subsets



7) Visualization and 8) quantification of monocyte, macrophage, and MDSC subsets



Sotigalimab results in immunomodulation and apoptosis of tumor cells. **9,** Tumor cells in the TME were characterized using MIBI analysis of keratin, HLA-I, HLA-II, PD-L1, and CD40 (representative image: patient 04). **10,** Quantification of tumor cell density by MIBI (pre $n = 5$, post $n = 4$). **11–13,** Expression of the phenotypic markers was also quantified in the MIBI analysis for HLA I and II (C), PD-L1 (D), and CD40 (E; pre $n = 5$, post $n = 4$).

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