Neoadjuvant CD40 agonism remodels the tumor immune microenvironment in locally advanced esophageal/gastroesophageal junction cancer

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Abstract #: 1361

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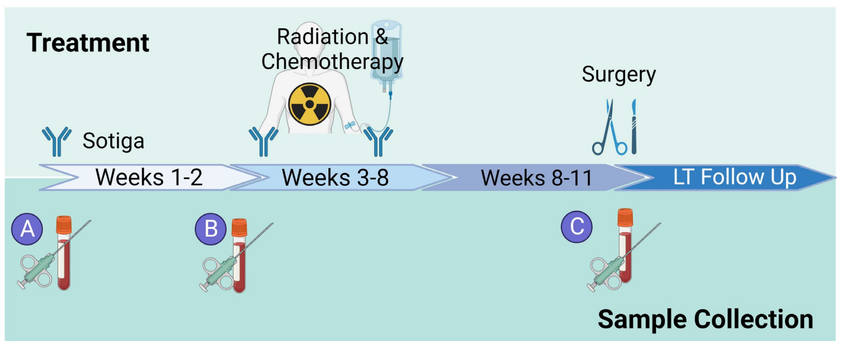
BACKGROUND AND RATIONALE

Neoadjuvant chemoradiation (CRT) followed by surgical resection is the standard of care for patients with locally advanced esophageal/ gastroesophageal junction (E/GEJ) cancer. A pathologic complete response (pCR) at surgery is associated with improved survival outcomes. Sotigalimab (sotiga) is a potent CD40 agonist mAb capable of inducing and expanding anti-tumor immune responses [1].

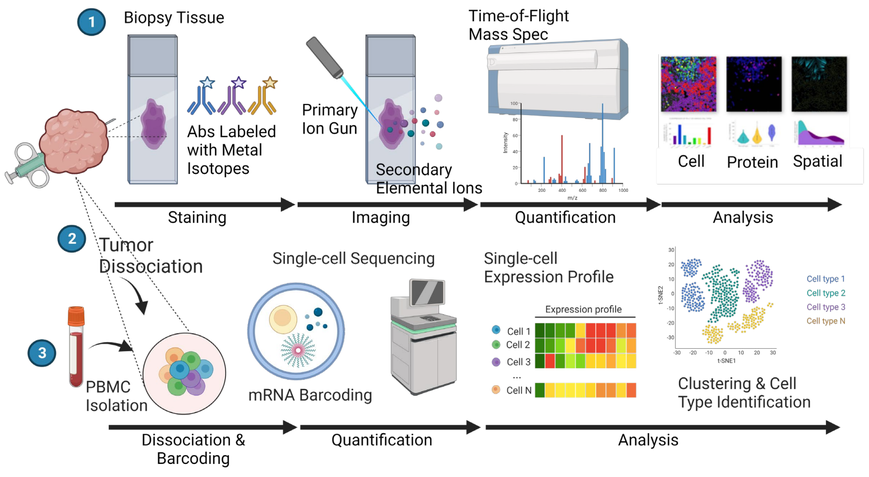
In a phase II clinical trial of sotiga combined with neoadjuvant CRT in patients with locally advanced E/GEJ cancer, we saw pathologic complete responses (pCR) in 38% of patients [2]. Here, deep immune profiling was performed on samples from the circulation and tumor microenvironment (TME) from a subset of patients to gain insight into the mechanism of action of sotiga.

STUDY PROTOCOL



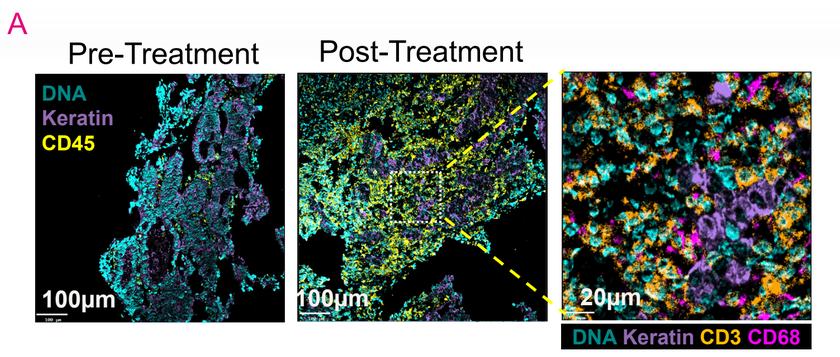
This study reports on data from an initial cohort of patients from a larger study [2]. Blood samples (PBMC) were collected before (A) and after treatment (B), and after surgery (N=6). Paired tumor biopsies were collected before (A) and after (B) sotiga treatment (N=4). When available, tumor samples were collected from surgical specimens (C).

METHODS



1. Biopsy samples were analyzed by IonPath using multiplex ion beam imaging (MIBI).
2. Tumor samples were also dissociated and scRNAseq and TCR sequencing were performed using the 10X Genomics platform.
3. PBMCs were isolated from whole blood, scRNAseq and TCR sequencing were performed using the 10X Genomics platform.

RESULTS



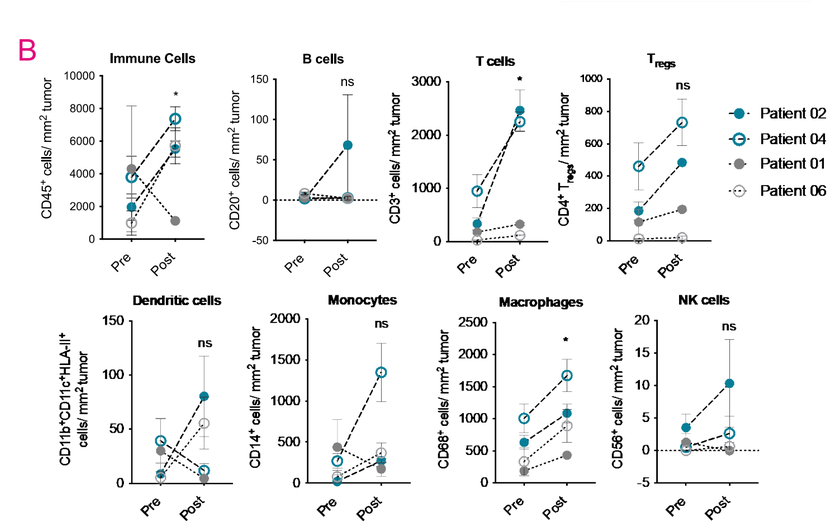


Figure 1. Treatment with sotiga increases immune infiltration into the TME, including T cells and myeloid cells. **A.** Representative images of MIBI analyses of immune cells (CD45+, yellow), T cells (CD3+, orange) and myeloid cells (CD68+, magenta) of pre- and post-treatment biopsies from Patient 04. **B.** The density of each immune cell type per tumor area (n=4).

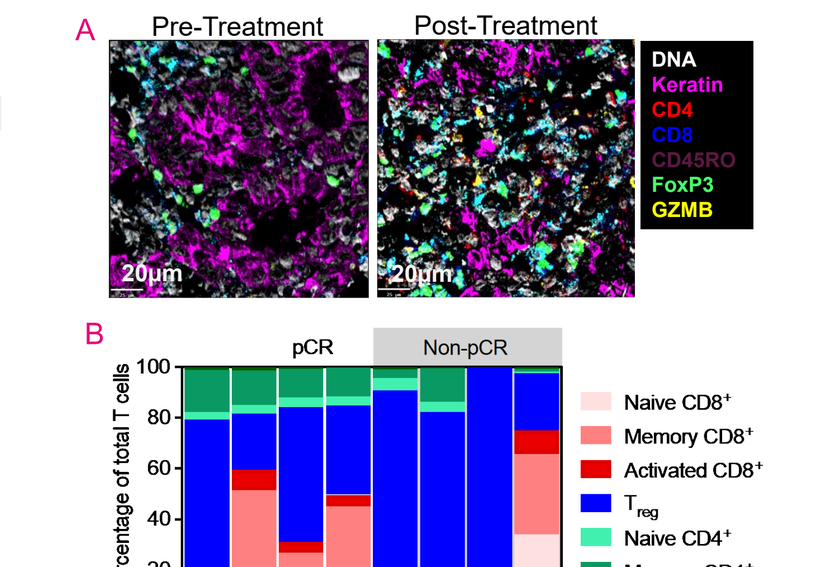


Figure 2. Tumor-infiltrating myeloid cells are activated post-sotiga. A. Representative images of MIBI analyses of DCs (CD11b+, CD11c+, HLA-II+, white arrow; CD86+ activated DCs) of pre- and post-treatment biopsies from Patient 04. **B.** Quantification of DC and DC-subtype density. **C.** Expression of activation markers CD86 and HLA-II on DCs.

Figure 3. Sotiga induces an activated T cell infiltrate and reduces Tregs in tumors. A. Representative images of MIBI analyses of T cells (CD45RO-, naïve; CD45RO+, memory; granzyme B+, activated; FoxP3+, Treg) of pre- and post-treatment biopsies from Patient 04. **B.** Quantification of proportions of T cell subsets in the TME.

RESULTS CONTINUED

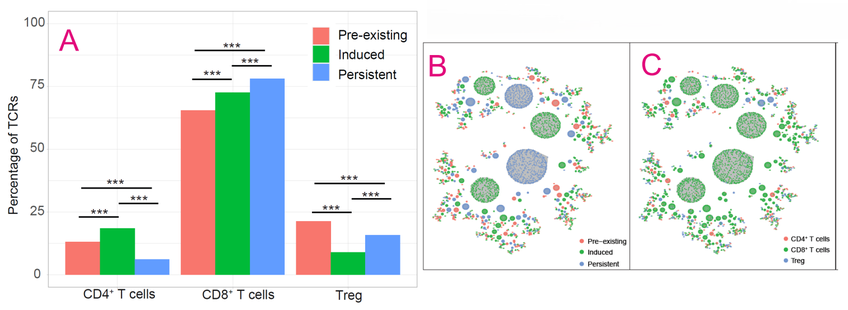


Figure 4. Single-cell immune repertoire analysis demonstrates induction of CD8⁺ T cell clones post-sotiga. **A.** Quantitative & **B&C.** network analysis of TCR by T cell sub-type in all T cells (A – TME, B&C – PBMCs and TME) (A&B; Pre-existing – before sotiga - pink, Induced – only present after sotiga - green, Persistent – present pre and post - blue). **B.** Analysis by timepoint. **C.** Analysis by subtype (CD4⁺ T cells- pink, CD8⁺ T cells- green, Tregs- blue).

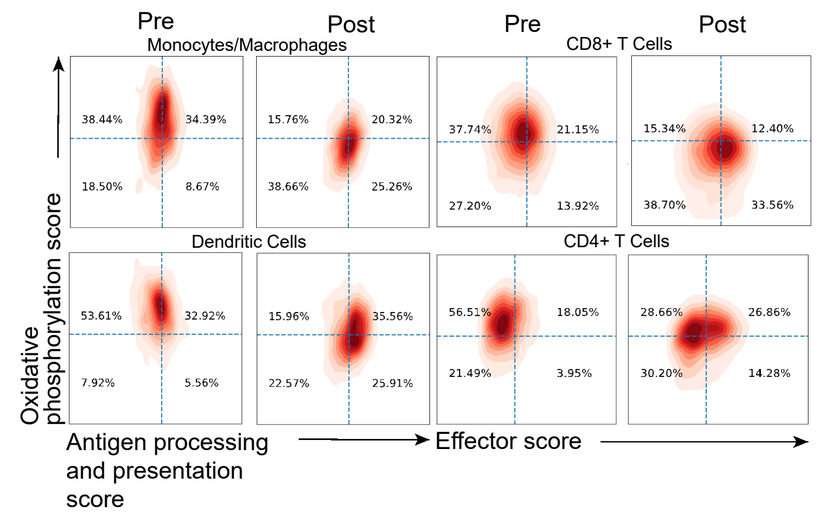
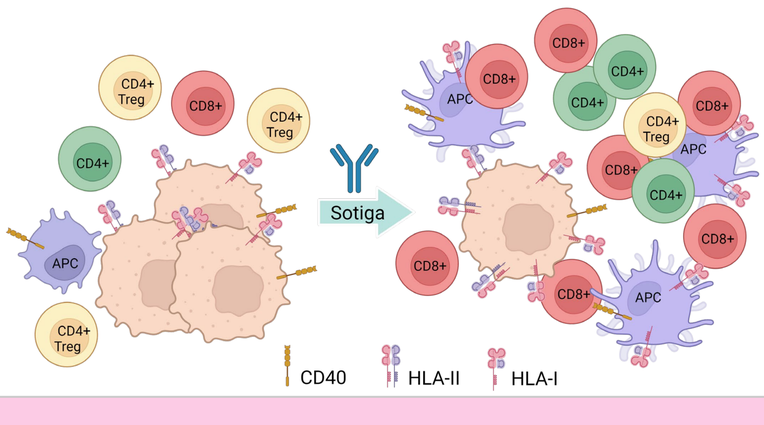


Figure 5. Sotiga induces effector function (x-axis) in association with downregulation of oxidative phosphorylation (y-axis) in monocytes/macrophages, DCs, CD8⁺ and non-Treg CD4⁺ T cells in the TME. scRNAseq analysis was used to calculate scores for metabolic and functional phenotypes based on gene expression in individual cells pre- and post-sotiga treatment. Scores for cells from the TME were then plotted for individual cells in dot-plot analysis.

CONCLUSION



Treatment with sotiga induced the activation of antigen presentation leading to the downstream generation of novel T cell clonotypes, enhanced T cell activation, and altered immune cell metabolism.

- This is the first demonstration that single-agent systemic sotiga can induce significant inflammatory responses in the TME.
- The conversion of “cold” tumors to “hot”, a key mechanism of sotiga, is the foundation of immunotherapy.

REFERENCES

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2. Ko A, et al. A Multicenter Phase 2 Study of Sotigalimab (CD40 Agonist) in Combination with Neoadjuvant Chemoradiation for Resectable Esophageal and GEJ) Cancers. ESMO Annual Conference; 2022.