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Biomarker Analysis From a Phase II Study of AgenT-797 (invariant natural killer T cells) with Botensilimab (Fc-enhanced CTLA-4 inhibitor) and Balstilimab (anti-PD-1) in PD-1 Refractory Gastroesophageal Cancer

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Disclosure Information

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Background

- **PD-1 inhibitors**, combined with chemotherapy, are approved for frontline treatment of advanced gastroesophageal cancer, but most patients develop disease progression[1-3]. Standard second-line therapy with ramucirumab (anti-VEGF) and paclitaxel has poor outcomes[4].

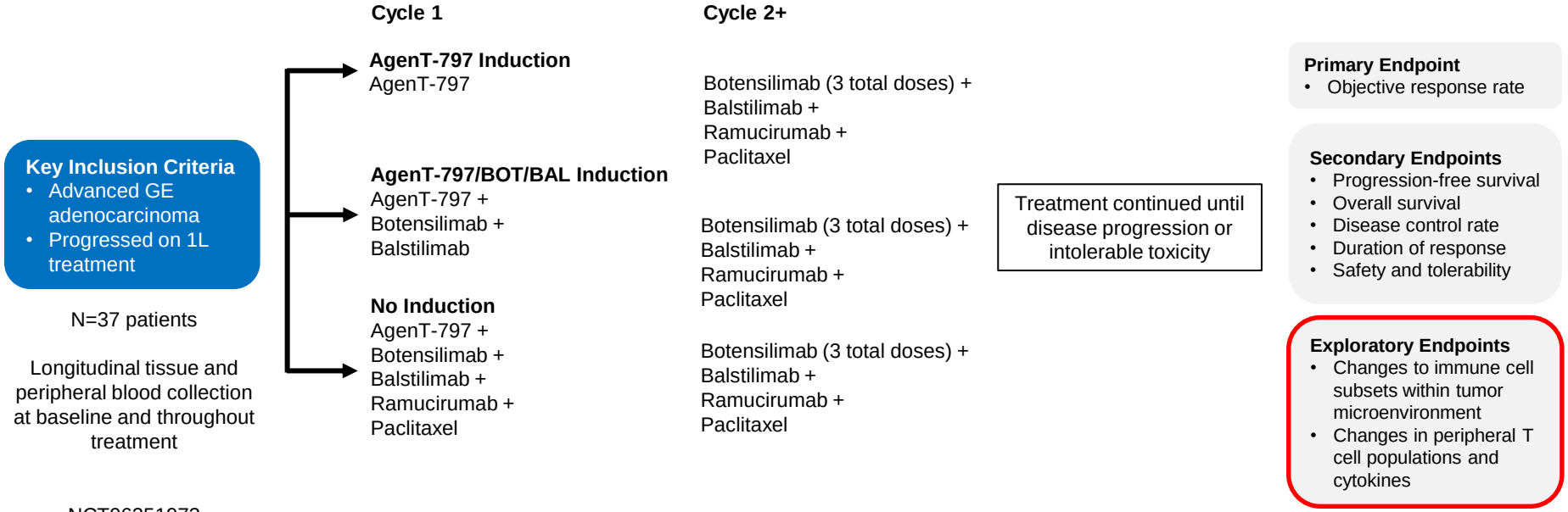
- **AgenT-797** is an allogeneic iNKT cell therapy inducing direct cytotoxicity via CD1d recognition and indirect effects through IL-12 and IFN-γ upregulation. In a phase I trial of patients with PD-1 refractory tumors, AgenT-797 + PD-1 inhibitors showed activity in gastric cancer and other solid tumors[5].

- **Botensilimab**, an Fc-engineered anti-CTLA-4 antibody**,** enhances T cell priming, activation, and memory while depleting regulatory T cells. In a phase I trial of patients with heavily pre-treated, immunotherapy-refractory disease or immunologically cold tumors, botensilimab + balstilimab (anti-PD-1) demonstrated significant efficacy[6].

1.Janjigian et al Lancet 2021; 2.Rha et al Lancet Oncol 2023; 3.Janjigian et al Lancet 2023; 4.Wilke et al Lancet Oncol 2014; 5.Hadfield MJ et al Oncogene 2024; 6.Bullock AJ et al Nat Med 2024

Methods: Trial Schema

- Investigator-initiated phase II study of agenT-797, botensilimab, and balstilimab in combination with ramucirumab and paclitaxel in refractory gastroesophageal cancer



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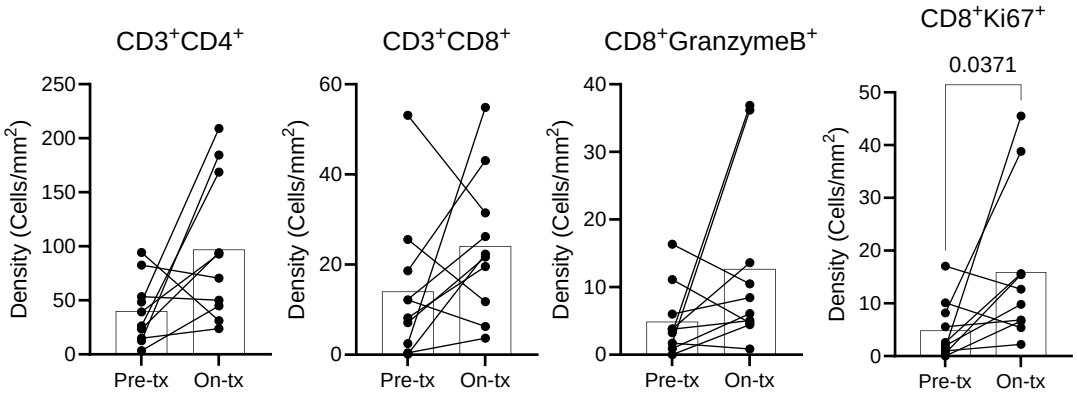
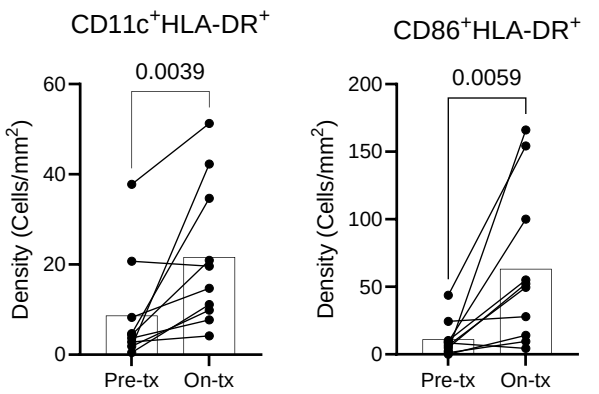
Baseline Clinical Characteristics

Characteristics	Number of Patients (N = 15)
Median age (IQR), years	63 (39-73)
Male Female	11 (73%) 4 (27%)
Esophageal / GEJ Gastric	11 (73%) 4 (27%)
Number metastatic sites 1 ≥ 2	 5 (33%) 10 (67%)
Liver metastases Peritoneal metastases	9 (60%) 5 (33%)
Frontline Treatment: PD-1 + Chemotherapy PD-1 + Trastuzumab + Chemotherapy PD-1 + TKI + Chemotherapy PD-1 + TIGIT + Chemotherapy PD-1 + CLDN Ab + Chemotherapy PD-1 + FGFR2 Ab/Placebo + Chemotherapy	 8 (53%) 2 (13%) 2 (13%) 1 (7%) 1 (7%) 1 (7%)
Induction Treatment: AgenT-797 cells alone AgenT-797 / Botensilimab / Balstilimab No induction	 2 (13%) 5 (33%) 8 (53%)

Increased Immune Cell Infiltration

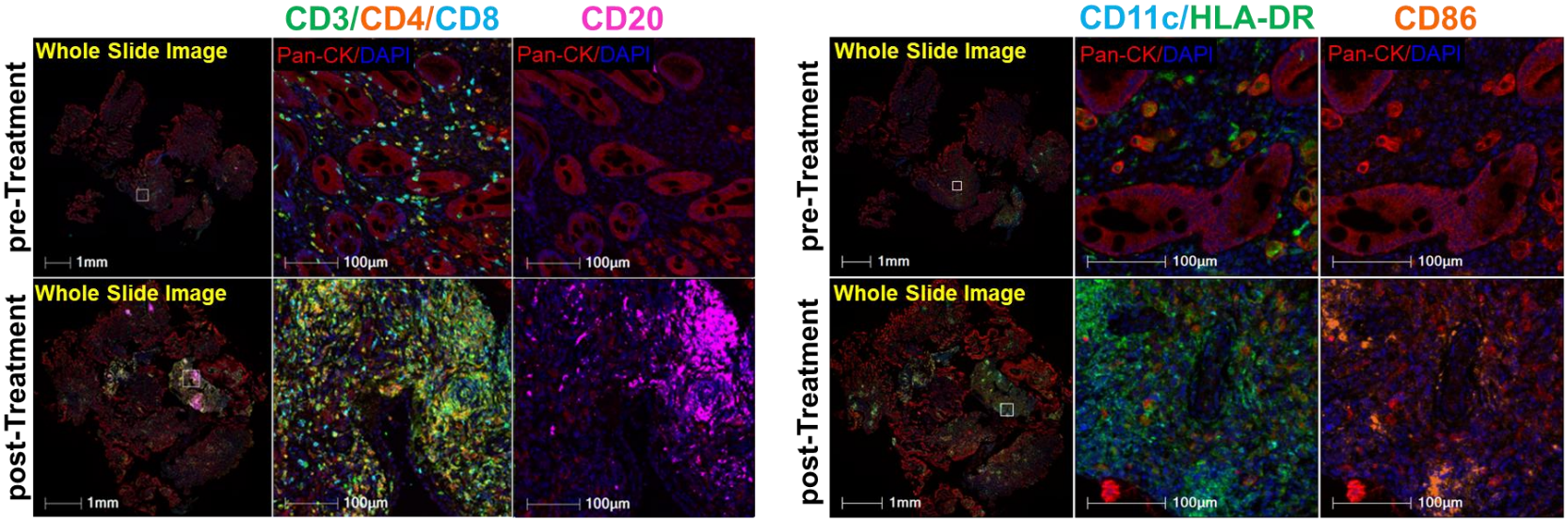
- Tumor immune infiltration and activation of cytotoxic T cells
- Enhanced antigen presenting activity within tumor





Increased Immune Cell Infiltration

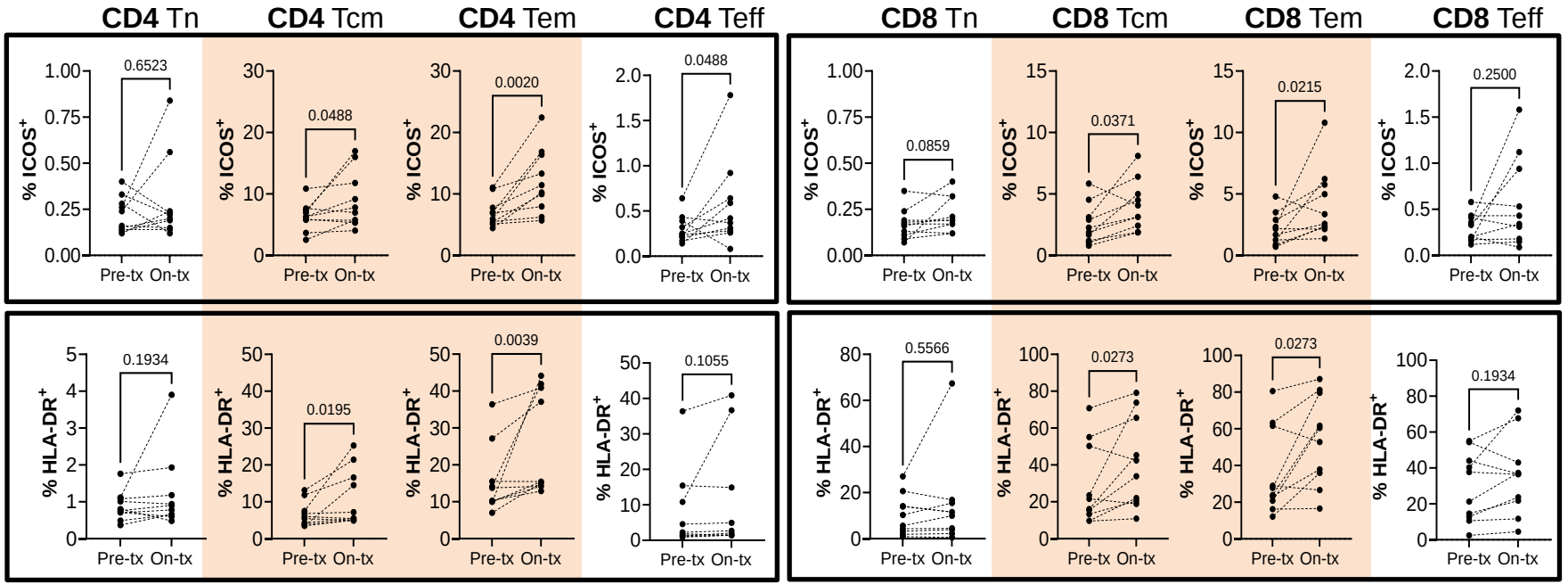
- Tumor immune infiltration and formation of tertiary lymphoid structures (TLS)
- Enhanced antigen presenting activity within tumor



Induction: agenT-797+BOT/BAL

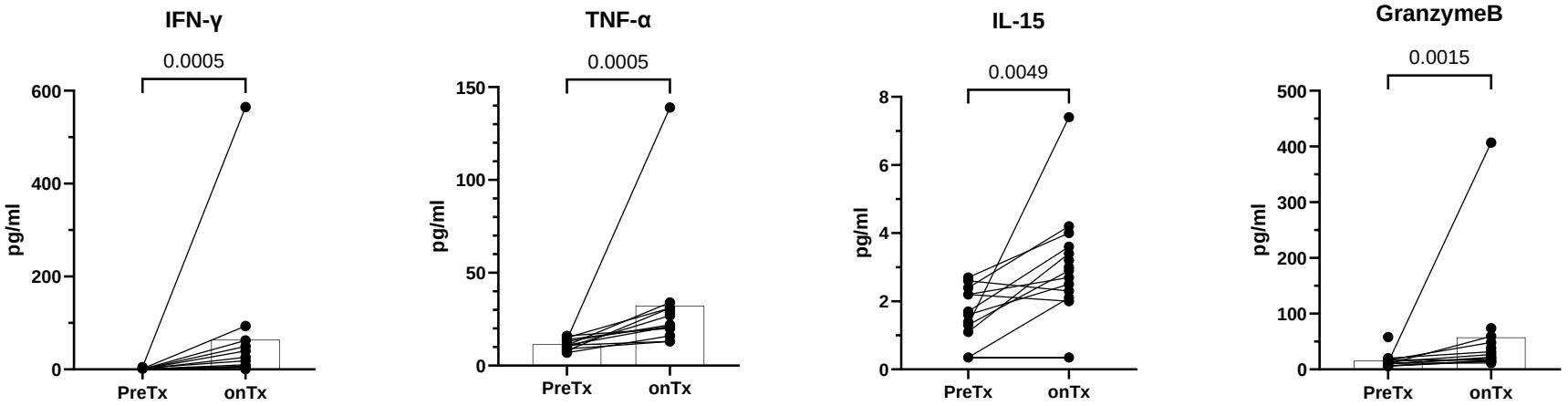
T cell Activation in Peripheral Blood

- Activation of central and effector memory T cells



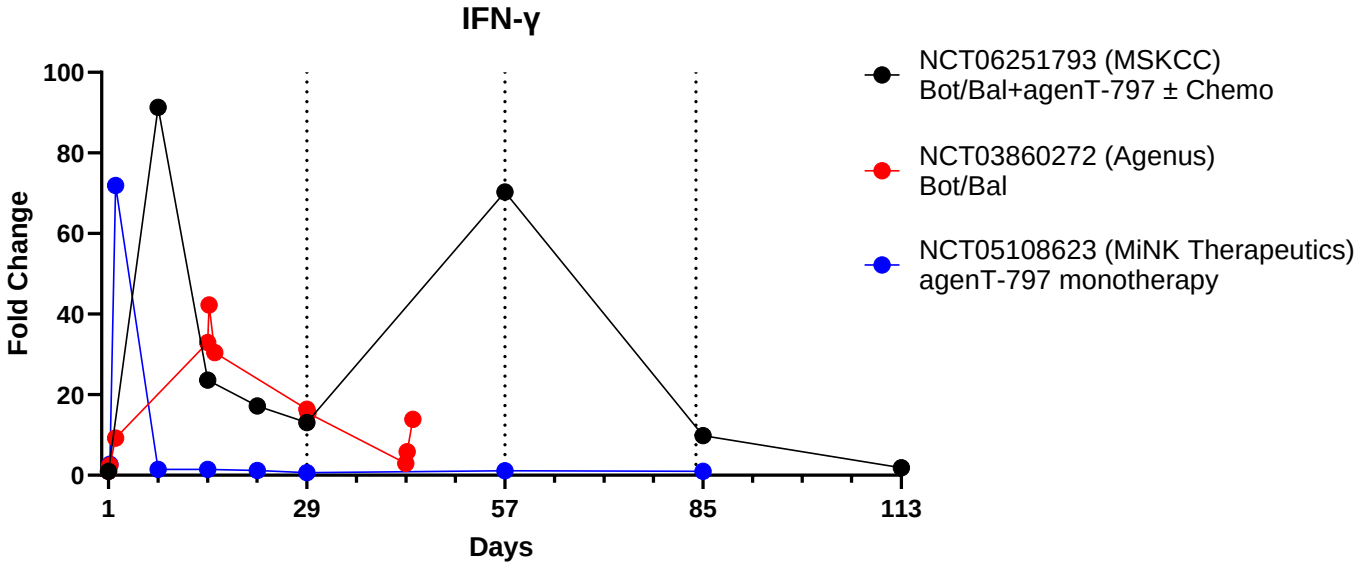
Increase in Peripheral Immune Activation

- Proinflammatory biomarkers indicating increased activity of cytotoxic lymphocytes



Sustained Increase of IFN-γ

- Pronounced IFN-γ response with agenT-797/BOT/BAL combination than was seen with BOT/BAL alone
- Prolonged IFN-γ response than was seen with agenT-797 monotherapy
- Secondary IFN-γ response observed upon BOT/BAL re-dosing



Key Takeaways and Future Directions

- The combination of agenT-797, botensilimab, and balstilimab with ramucirumab and paclitaxel induces immune modulation in patients with PD-1 refractory gastroesophageal cancer. This is characterized by:
  - Tumor infiltration of T cells and antigen presenting cells
  - Activation of central and effector memory T cells
  - Elevated levels of pro-inflammatory cytokines, specifically IFN-γ, in peripheral blood
- Additional biomarker analyses in process, including T cell receptor sequencing of tissue and matched peripheral blood samples
- Continued patient enrollment onto the study is underway

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