TPS 515: A phase II study of agenT-797 (invariant natural killer T cells), botensilimab (Fc-enhanced CTLA-4 inhibitor) and balstilimab (anti-PD-1) in patients with advanced, refractory gastroesophageal adenocarcinoma

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BACKGROUND

Gastroesophageal (GE) cancer is the third most common cancer worldwide and the second leading cause of cancer-related mortality, with 1.3 million deaths annually.

Programmed death-1 (PD-1) inhibitors are approved in combination with chemotherapy for frontline treatment in patients with advanced disease, though most patients develop progression of their disease.

Second-line treatment is with ramucirumab (anti-vascular endothelial growth factor receptor-2 antibody) and paclitaxel for which median progression-free survival (PFS) is 4.4 months and the objective response rate (ORR) is 28%.[1]

AgenT-797: allogeneic invariant natural killer T cells

AgenT-797 is a cellular therapy product, composed of allogeneic human unmodified invariant natural killer T (iNKT) cells, isolated from mononuclear cell aphaeresis units from healthy donors and expanded ex vivo.

iNKT cells are a distinct lymphocyte subset, which induce direct cytotoxicity following T cell receptor (TCR) recognition of CD1d (cluster of differentiation 1d), a non-polymorphic major histocompatibility complex Class I relative that is characteristic among gastrointestinal tumors, including GE cancers. iNKT cells are also indirectly cytotoxic via up regulation of IL-12 expression and IFN-γ release, inducing dendritic cell maturation.

In a phase I trial of patients with PD-1 refractory disease, agenT-797, with a PD-1 inhibitor, was found to be safe and demonstrated activity in those with gastric cancer and other solid tumors.[2]

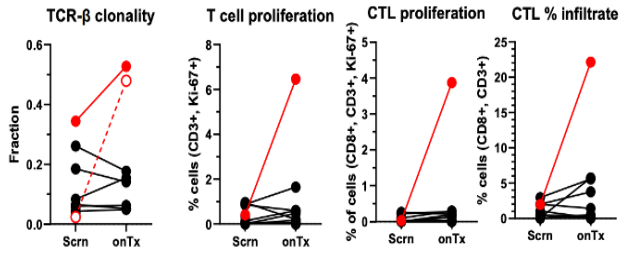


Figure 1 (left): A patient with gastric cancer (red) achieved a long-term, durable response and demonstrated significant T cell infiltration and expansion compared to non-responders.[2] The red dashed line denotes expansion of a single T cell clone.

Botensilimab: Fc-enhanced anti-CTLA-4 inhibitor

Botensilimab is a fully humanized, fragment crystallizable (Fc)-engineered immunoglobulin G1 anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody.

Increased Fc engagement induces high affinity binding to Fc gamma receptors located on immune cells, including antigen presenting cells (APCs) and NK cells, which in turn enhances antigen-specific T cell responses, while simultaneously targeting immunosuppressive regulatory T cells (Tregs). This results in increased T cell priming, expansion and memory formation, increased frequency of APCs, Treg depletion, as well as decreased complement mediated toxicity, compared to the first generation anti-CTLA-4 inhibitor, ipilimumab.

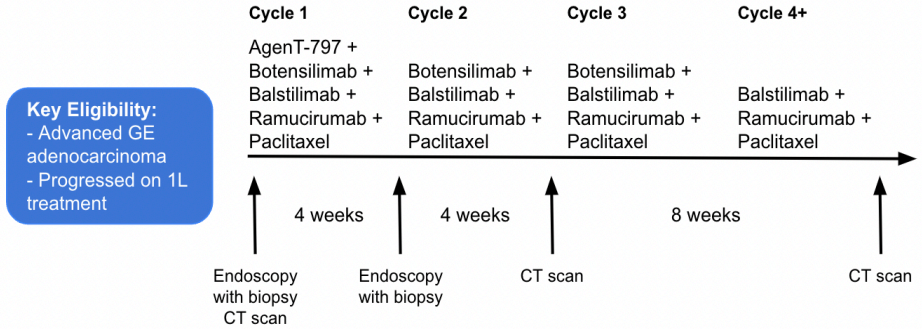
In a phase I study, botensilimab, with balstilimab (anti-PD-1), was found to be safe and demonstrated significant anti-tumor activity in heavily pre-treated patients with immunotherapy refractory disease and immunologically cold tumors.[3]

References

1. Wilke H, Muro K, Van Cutsem E et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol. 2014 Oct;15(11):1224-35.
2. Hadfield MJ, Safran H, Purbhoo MA, Grossman JE, Buell JS, Carneiro BA. Overcoming resistance to programmed cell death protein 1 (PD-1) blockade with allogeneic invariant natural killer T-cells (iNKT). Oncogene. 2024 Mar;43(10):758-762.
3. Bullock AJ, Schlechter BL, Fakih MG et al. Botensilimab plus balstilimab in relapsed/refractory microsatellite stable metastatic colorectal cancer: a phase 1 trial. Nat Med. 2024 Sep;30(9):2558-2567.

METHODS

TRIAL SCHEMA: This is an investigator-initiated, single-arm phase II trial of agenT-797, botensilimab, and balstilimab, with ramucirumab and paclitaxel in patients with advanced GE adenocarcinoma who have received one prior line of therapy, performed at Memorial Sloan Kettering Cancer Center. NCT06251793.



Primary Endpoint:
Objective response rate

Secondary Endpoints:
Progression-free survival
Overall survival
Disease control rate
Duration of response
Safety and tolerability

Induction Cycle: Patients with a high disease burden, as determined by the treating investigator, will begin with all treatment components together. Patients with measurable disease may begin treatment with an induction cycle of agenT-797/botenslimiab/balstilimab, before addition of ramucirumab/paclitaxel with cycle 2, if deemed appropriate by the treating investigator. Patients with evaluable disease must be eligible to begin with an induction cycle and will begin treatment with agenT-797 alone prior to the addition of botensilimab/balstilimab/ramucirumab/paclitaxel with cycle 2.

Drug	Dose	Dose Frequency
AgenT-797	$1.4x10^7$ cells/kg	Day 1 of treatment, cycle one only
Botensilimab[1]	75 mg fixed dose	Day 1 of each 28-day cycle for three cycles
Balstilimab	240 mg fixed dose	Days 1 and 15 of each 28-day cycle
Ramucirumab	8 mg/kg	Days 1 and 15 of each 28-day cycle
Paclitaxel[2]	80 mg/m^2	Days 1, 8, and 15 of each 28-day cycle

Table 1 (Above): Drug dosing and frequency

[1]The starting dose of botensilimab is 75 mg on day 1 of a 28 day cycle for a total of three doses. Following treatment of the first 10 patients, a planned review of safety and outcomes will evaluate whether subsequent patients should be treated at dose level -1 (50 mg) based on frequency and severity of immune-related adverse events.

[2]Patients may be treated with 70 mg/m^2 if deemed necessary per treating physician's discretion.

Planned Correlative Studies

- Evaluate changes to TCR clonality on treatment in the peripheral blood and tissue
- Perform flow cytometric analysis on peripheral blood mononuclear cells at baseline and throughout treatment to define changes in composition and activation of lymphocyte subset populations
- Define evolution of changes in tumor microenvironment using RNA sequencing and multiplex immunofluorescence of serially collected pre- and on-treatment biopsies

Major Inclusion Criteria

- Metastatic or advanced unresectable esophageal, gastroesophageal junction, or gastric adenocarcinoma
- Disease progression on one prior line of therapy
- Measurable or evaluable disease as defined by RECIST v1.1 criteria. Patients with evaluable disease must be eligible to begin with an induction cycle
- Age 18 years or older
- Adequate organ function

Major Exclusion Criteria

- Previously received ramucirumab
- Received taxane based chemotherapy within 6 months of study enrollment
- Had a prior grade ≥3 immune related adverse event due to anti–PD-1, anti–PD-L1, anti–PD-L2, or anti-CTLA4 therapy at any time
- Active central nervous system metastases