TPS 4206

STAR-221: A Randomized, Open-Label, Multicenter, Phase 3 Trial of Domvanalimab, Zimberelimab, and Chemotherapy Versus Nivolumab and Chemotherapy in Previously Untreated, Locally Advanced Unresectable or Metastatic Gastric, Gastroesophageal Junction, and Esophageal Adenocarcinoma

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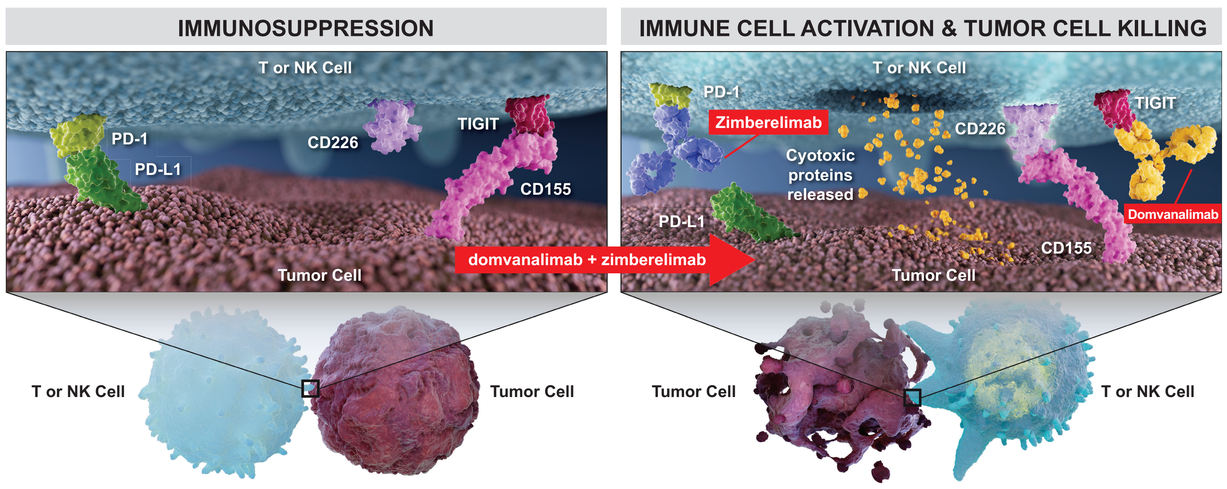
BACKGROUND

- Gastric, gastroesophageal junction (GEJ), and esophageal cancers are major contributors to the global cancer burden, with gastric and esophageal cancers representing the fifth and seventh most frequently diagnosed cancers, respectively[1]
  - The long-term prognosis for patients with metastatic gastric, GEJ, and esophageal cancer is still poor but is steadily improving as a result of recently-approved therapies, with the 5-year survival rate now at 21% for esophageal cancer and 33% for gastric cancer[2-4]
- Current first-line treatment for patients with gastric, GEJ, and esophageal cancer consists of chemotherapy with FOLFOX (oxaliplatin, leucovorin, and fluorouracil) or CAPOX (capecitabine and oxaliplatin), with or without the addition of a programmed cell death/ligand protein 1 (PD-L1) inhibitor[2,4]
  - Adding PD-L1 inhibitors to standard chemotherapy has improved outcomes in patients with unresectable or metastatic gastric, GEJ, and esophageal adenocarcinomas, particularly in patients with human epidermal growth factor receptor 2 (HER2)-negative disease and high PD-L1 expression[5,6]

Investigational Therapies

- Domvanalimab (AB154) is an Fc-silent, humanized, immunoglobulin G1 (IgG1) monoclonal antibody that blocks the binding of the checkpoint receptor T cell immunoglobulin and ITIM domain (TIGIT) to its ligand CD155[7]
- This reduces the inhibition of T cells and natural killer (NK) cells, promoting antitumor activity[8] (**Figure 1**)
  - As domvanalimab is Fc-silent, it does not stimulate antibody-dependent cellular cytotoxicity (ADCC)-mediated destruction of TIGIT-bearing immune cells
- Zimberelimab (AB122) is a fully human, IgG4 monoclonal antibody that binds PD-1 on T cells and NK cells, preventing PD-L1-mediated immunosuppressive effects and resulting in enhanced tumor cell death[9,10]
- Prior studies have demonstrated that combination therapy with anti-PD-[L]1 and anti-TIGIT is safe, tolerable, and has promising activity in patients with gastric, GEJ, and esophageal cancers[11]
- ARC-21 (EDGE-Gastric, NCT05329766) is an ongoing phase 2 study investigating the safety and efficacy of various combinations of domvanalimab and zimberelimab in patients with gastric, GEJ, and esophageal adenocarcinoma[12]

Figure 1. Checkpoint Inhibition and the TIGIT Pathway



NK, natural killer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; TIGIT, T cell Immunoglobulin and ITIM domain.

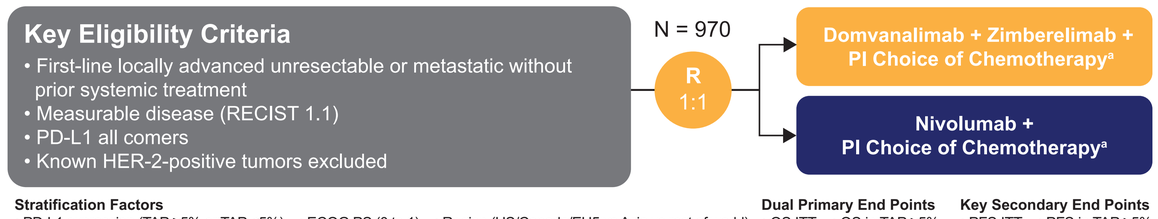
Study Objective

- STAR-221 will investigate whether adding domvanalimab (anti-TIGIT) to the combination of anti-PD-1 therapy and chemotherapy provides additional clinical benefit to patients with locally advanced unresectable or metastatic gastric, GEJ, and esophageal adenocarcinoma

Study Design

- STAR-221 (NCT05568095) is a global, multicenter, randomized, open-label, phase 3 study (**Figure 2**)
- Approximately 970 patients will be randomized 1:1 to Arm A and Arm B
- Patients randomized to Arm A will receive either:
  - Combination therapy with domvanalimab 1600 mg and zimberelimab 480 mg, administered intravenously every 4 weeks, in addition to FOLFOX chemotherapy every 2 weeks or
  - Combination therapy with domvanalimab 1200 mg and zimberelimab 360 mg, administered intravenously every 3 weeks, in addition to CAPOX chemotherapy every 3 weeks
- Patients randomized to Arm B will receive either:
  - Nivolumab 240 mg, administered intravenously every 2 weeks, and FOLFOX chemotherapy every 2 weeks or
  - Nivolumab 360 mg, administered intravenously every 3 weeks, and CAPOX chemotherapy every 3 weeks
- Patients will receive treatment until death, unacceptable toxicity, loss to follow-up, disease progression, withdrawal from the study, or study termination
- Randomization will be stratified by PD-L1 expression (tumor area positivity [TAP] ≥5% vs TAP <5%), Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1) and geographic region (US, Canada, and Europe vs Asia vs rest of world)

Figure 2. STAR-221 Study Design



CAPOX, apecitabine and oxaliplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFOX, oxaliplatin, leucovorin, and fluorouracil; HER2, human epidermal growth factor receptor 2; ITT, intent-to-treat; OS, overall survival; PD-L1, programmed cell death/ligand protein 1; PFS, progression-free survival; PI, primary investigator; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors, TAP, tumor area positivity.
[a]Investigator choice of chemotherapy: FOLFOX or CAPOX.

METHODS

Patient Population

- Eligible patients are adults with histologically confirmed, locally advanced unresectable or metastatic gastric, GEJ, or esophageal adenocarcinoma
- Key inclusion and exclusion criteria are shown in **Table 1**

Table 1. Key Inclusion and Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Histologically confirmed, locally advanced unresectable or metastatic gastric, GEJ, or esophageal adenocarcinoma • ≥1 measurable lesion(s) per RECIST v1.1 • ECOG performance status of 0-1	• Known HER2-positive tumor(s) • Prior systemic treatment for locally advanced unresectable or metastatic gastric, GEJ, or esophageal adenocarcinoma

ECOG, Eastern Cooperative Oncology Group; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; RECIST, Response Evaluation Criteria in Solid Tumors.

Outcomes and End Points

- Patients will undergo imaging to assess disease response every 6 weeks for 48 weeks, and then once every 12 weeks
- All participants who discontinue study intervention for reasons other than disease progression (eg, adverse events) will continue tumor assessments every 12 weeks (±7 days)
- Key study end points are listed in **Table 2**

Table 2. Key Study End Points

Primary Efficacy End Points	Secondary Efficacy End Points	Safety End Points
• Overall survival in the full ITT population • Overall survival in patients with high PD-L1 expression	• Progression-free survival (ITT and PD-L1 high) • Objective response rate (ITT and PD-L1 high) • Duration of response (ITT and PD-L1 high)	• Incidence and severity of adverse events and serious adverse events • Clinically meaningful trends in safety parameters

ITT, intent-to-treat; PD-L1, programmed cell death/ligand protein 1; RECIST, Response Evaluation Criteria in Solid Tumors.
Efficacy end points will be assessed by the investigator according to RECIST 1.1.

- The primary and secondary end points will be assessed in the intent-to-treat (ITT) population, defined as all randomized participants, as well as in the subset of patients with high PD-L1 expression (TAP ≥5%)
- Safety end points will be assessed in the safety-evaluable population, defined as all participants who received ≥1 dose of any study treatment

Status

- The study is currently open for enrollment in the United States

REFERENCES

1. Bray F et al. *CA Cancer J Clin.* 2018;68:394-424.
2. NCCN Clinical Practice Guidelines in Oncology. Esophageal and Esophagogastric Junction Cancers, Version 2.2023, *J Natl Compr Cancer Netw.* 2023;21:393-422.
3. NCCN Clinical Practice Guidelines in Oncology. Gastric Cancer, Version 2.2022, *J Natl Compr Cancer Netw.* 2022;20:167-192.
4. Siegel RL et al. *CA Cancer J Clin.* 2023;73:17-48.
5. Sun JM et al. *Lancet.* 2021;398:759-771. Erratum in: *Lancet.* 2021;398:1874.
6. Janjigian YY et al. *Lancet.* 2021;398:27-40.
7. Le Mercier I et al. *Front Immunol.* 2015;6:1-15.
8. Martinet L Smyth MJ. *Nat Rev Immunol.* 2015;15:243-254.
9. Markam A. *Drugs.* 2021;81:2063-2068.
10. Yi M et al. *Mol Cancer.* 2022;21:28.
11. Wainberg Z et al. *Ann Oncol.* 2021;32(Suppl 3):S227-S228.
12. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT05329766.

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