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Domvanalimab, Zimberelimab, and FOLFOX in First-Line Advanced Gastric, Gastroesophageal Junction, or Esophageal Adenocarcinoma: 26-Month Update From EDGE-Gastric, Arm A1

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Disclosures

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Background

- First-line treatment for patients with metastatic gastroesophageal cancer has evolved to include PD-1 inhibitors plus chemotherapy, but durable benefit remains limited[1–3]
- Dual blockade of TIGIT and PD-1 may enhance antitumor immunity in advanced gastroesophageal cancers
- Here, we present long-term results from Arm A1 of the phase 2 EDGE-Gastric study (NCT05329766) evaluating first-line domvanalimab (anti-TIGIT), zimberelimab (anti–PD-1), and FOLFOX in advanced *HER2*-negative GC/GEJC/EAC

EDGE-Gastric, Arm A1 Study Design

Key Eligibility Criteria
- First-line locally advanced unresectable or metastatic GC/GEJC/EAC
- Measurable disease per RECIST v1.1
- ECOG 0–1
- Known *HER2*-positive tumors excluded
- Irrespective of PD-L1 levels

N = 41

Domvanalimab 1600 mg Q4W
Zimberelimab 480 mg Q4W
FOLFOX Q2W

Treatment continues until PD or unacceptable toxicity

Scanning interval: Q6W through week 48 or end of treatment and Q12W thereafter

Primary Endpoints
- Safety
- Investigator ORR

Secondary Endpoints
- Efficacy by PD-L1 (OS, PFS, DCR,[a] DOR)
- PK and biomarker data

At the 03 March 2025 data cutoff, the median study follow-up was 26.4 months

BOR, best overall response; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; FOLFOX, oxaliplatin 85 mg/m^2 IV, leucovorin 400 mg/m^2 IV, fluorouracil 400 mg/m^2 IV bolus + 2400 mg/m^2 continuous 46-48-hour IV infusion; GC/GEJC/EAC, gastric, gastroesophageal junction, or esophageal adenocarcinoma; *HER2*, human epidermal growth factor receptor 2; IV, intravenous; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PK, pharmacokinetics; Q2W, every 2 weeks; Q4W, every 4 weeks; Q6W, every 6 weeks; Q12W, every 12 weeks; TIGIT, T-cell immunoreceptor with immunoglobulin and ITIM domain.

[a]DCR was defined as the percentage of patients with a confirmed BOR of complete response, partial response, or stable disease.

1. Janjigian YY, et al. *Lancet*. 2021;398:27–40. 2. Rha SY, et al. *Lancet Oncol*. 2023;24:1181–1195. 3. Janjigian YY, et al. *J Clin Oncol*. 2024;42:2012–2020.

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Baseline Characteristics

	Arm A1 N = 41, n (%)
Age, years, mean (range)	62 (30–82)
Sex	
Female	17 (42)
Country	
South Korea	19 (46)
United States/France	22 (54)
ECOG PS 1	25 (61)
Histologically confirmed diagnosis	
Gastric adenocarcinoma	26 (63)
GEJ adenocarcinoma	5 (12)
Esophageal adenocarcinoma	10 (24)

	Arm A1 N = 41, n (%)
Current disease status	
Locally advanced unresectable disease	2 (5)
Metastatic disease	39 (95)
Liver metastases	12 (29)
Peritoneal metastases	18 (44)
TAP category[a]	
TAP ≥ 5%	16 (39)
TAP ≥ 1%	29 (71)
TAP < 1%	11 (27)
Microsatellite instability status[b]	
High	1 (2)
Low/stable	35 (85)

ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; PD-L1, programmed cell death ligand 1; TAP, tumor area positivity.

[a]Evaluated at central laboratory. One patient had no tissue available for central laboratory evaluation of PD-L1 expression; local lab results showed the patient's tumor was PD-L1 low according to 22C3 assay.

[b]5 (12%) patients had unknown microsatellite instability status.

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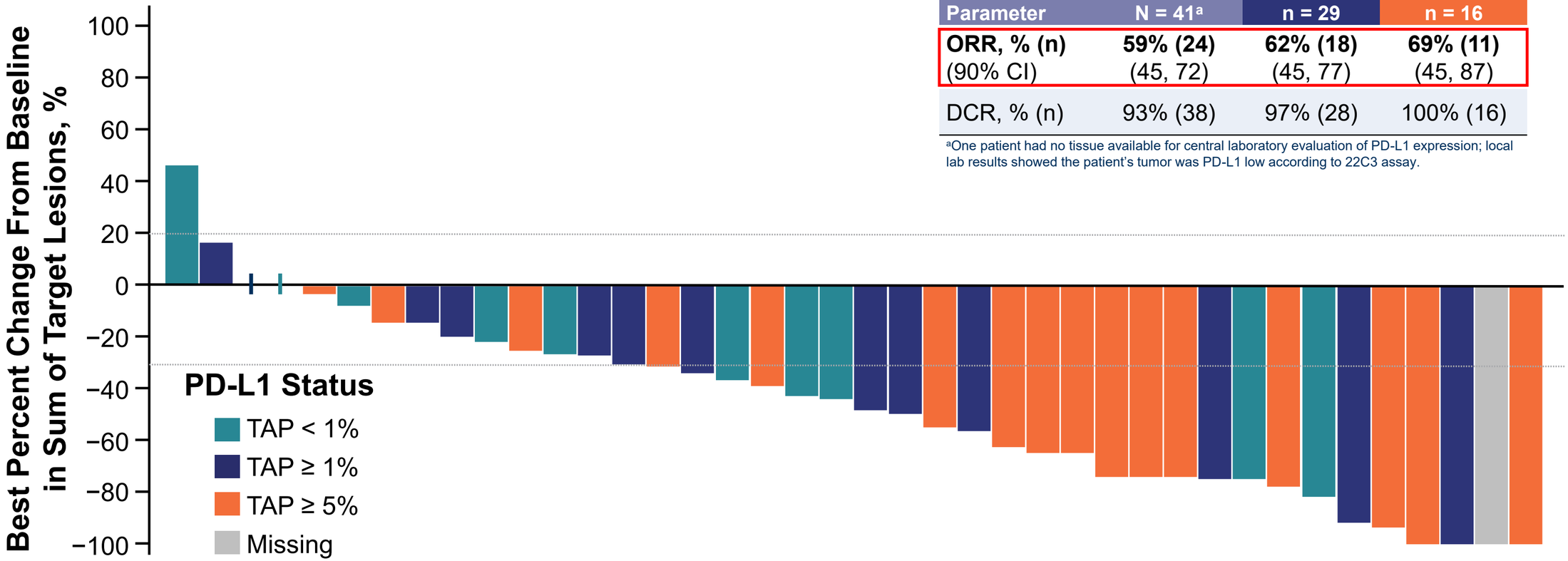
Clinical Response

Parameter	Overall N = 41[a]	TAP ≥ 1% n = 29	TAP ≥ 5% n = 16
ORR, % (n) (90% CI)	**59% (24)** (45, 72)	**62% (18)** (45, 77)	**69% (11)** (45, 87)
DCR, % (n)	93% (38)	97% (28)	100% (16)

[a]One patient had no tissue available for central laboratory evaluation of PD-L1 expression; local lab results showed the patient's tumor was PD-L1 low according to 22C3 assay.



DCR, disease control rate; ORR, objective response rate, PD-L1, programmed cell death ligand 1; TAP, tumor area positivity.
Dashed reference lines indicate a 20% increase or 30% decrease from baseline in the sum of target lesions.

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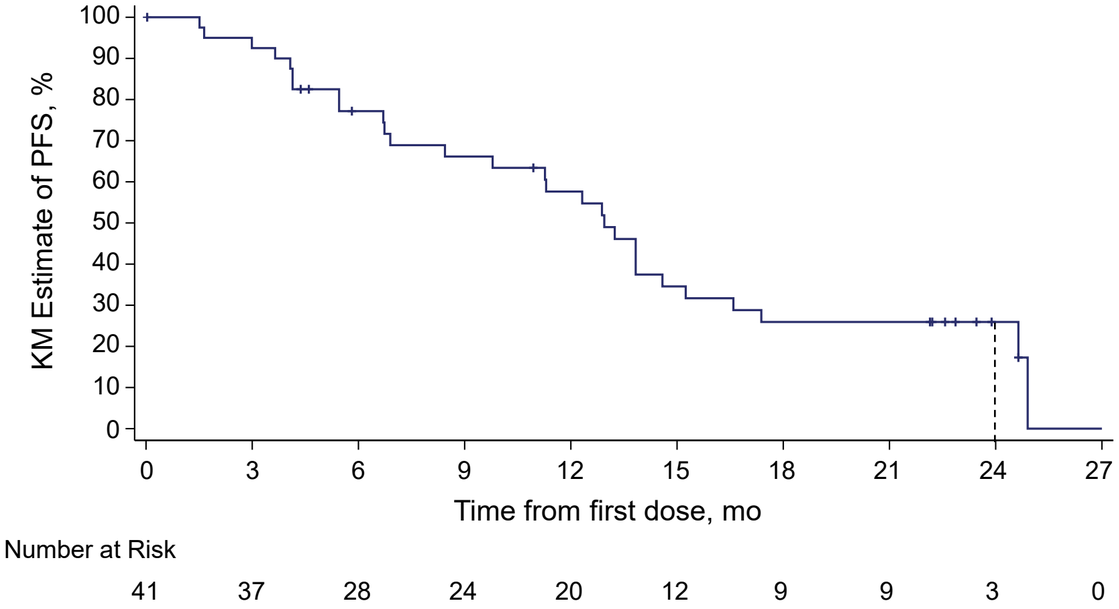
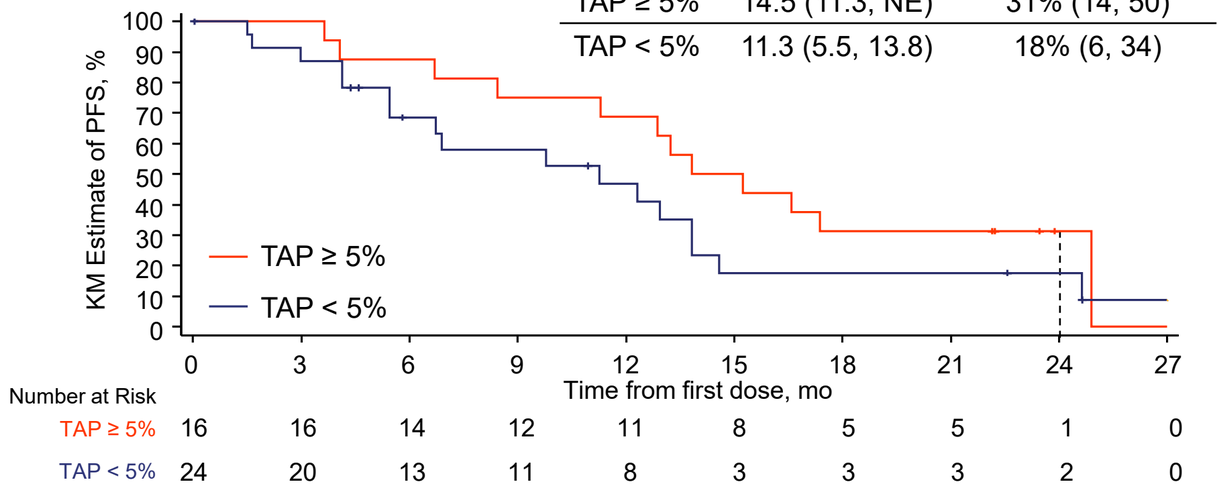
Progression-Free Survival

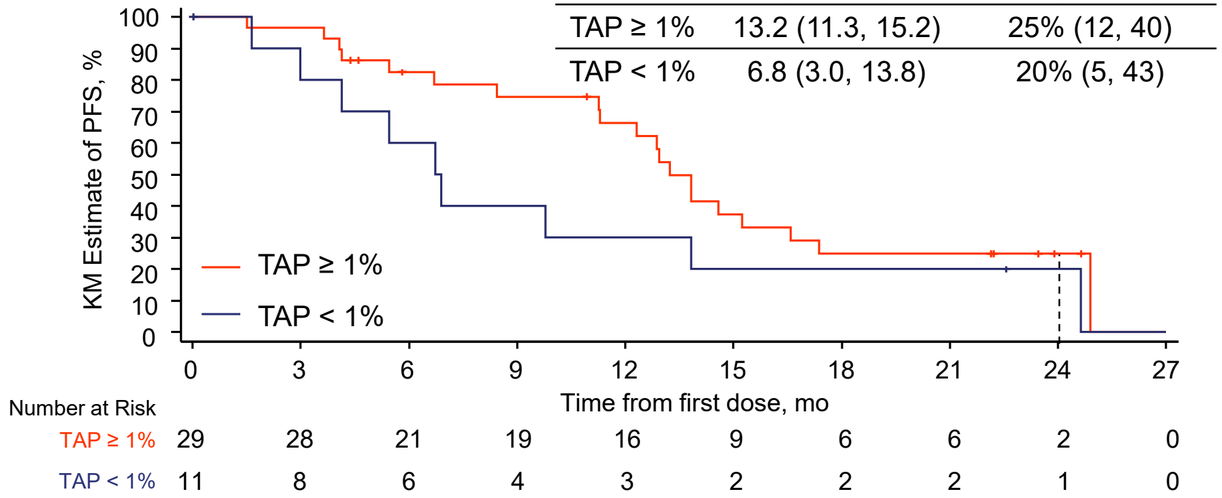
	Median PFS, mo (90% CI)	24-mo PFS rate, % (90% CI)
Overall	12.9 (9.8, 14.6)	26% (15, 39)



	Median PFS, mo (90% CI)	24-mo PFS rate, % (90% CI)
TAP ≥ 5%	14.5 (11.3, NE)	31% (14, 50)
TAP < 5%	11.3 (5.5, 13.8)	18% (6, 34)



	Median PFS, mo (90% CI)	24-mo PFS rate, % (90% CI)
TAP ≥ 1%	13.2 (11.3, 15.2)	25% (12, 40)
TAP < 1%	6.8 (3.0, 13.8)	20% (5, 43)



KM, Kaplan-Meier; mo, months; NE, not estimable; PFS, progression-free survival; TAP, tumor area positivity.

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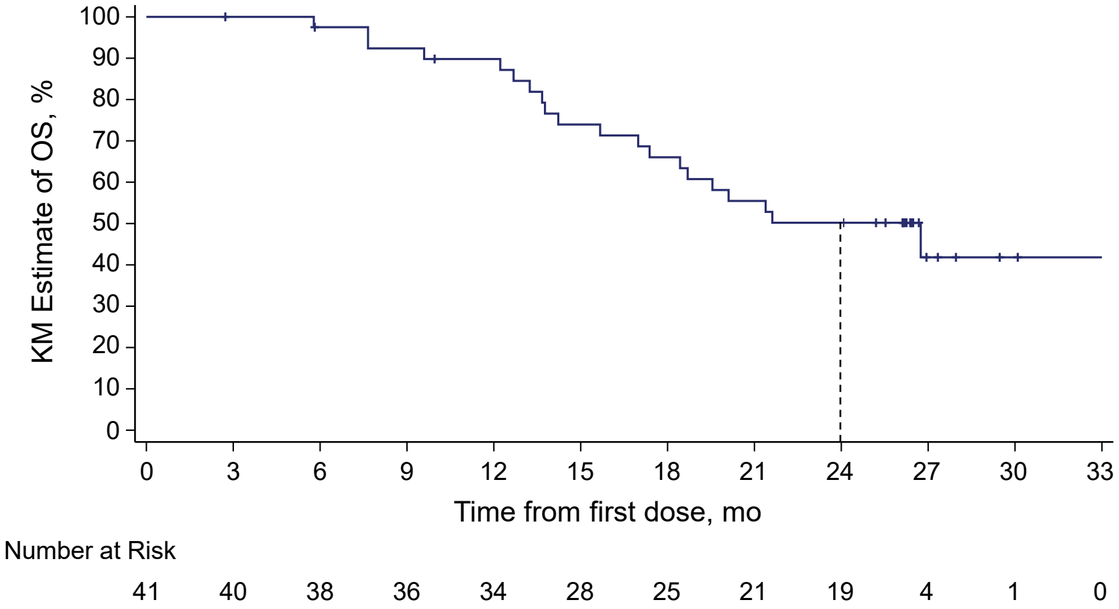
Overall Survival

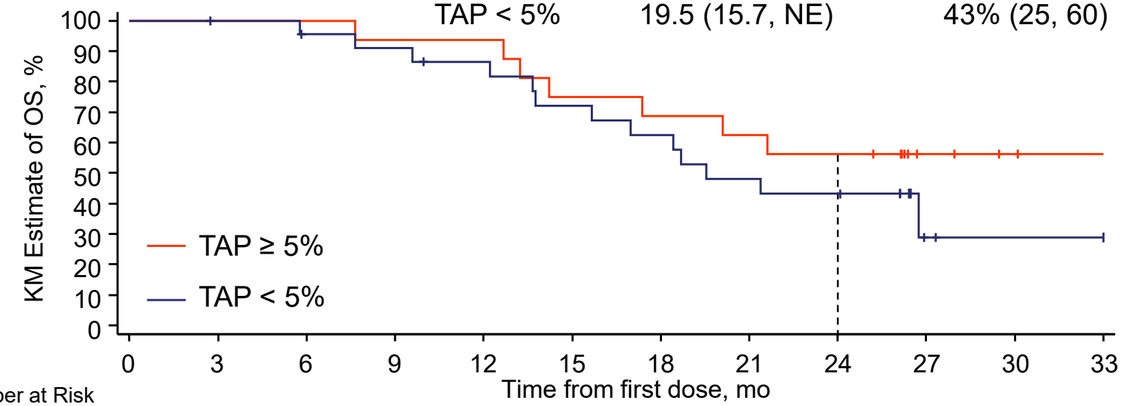
	Median OS, mo (90% CI)	24-mo OS rate, % (90% CI)
Overall	26.7 (18.4, NE)	50% (36, 63)



Number at Risk

	41	40	38	36	34	28	25	21	19	4	1	0

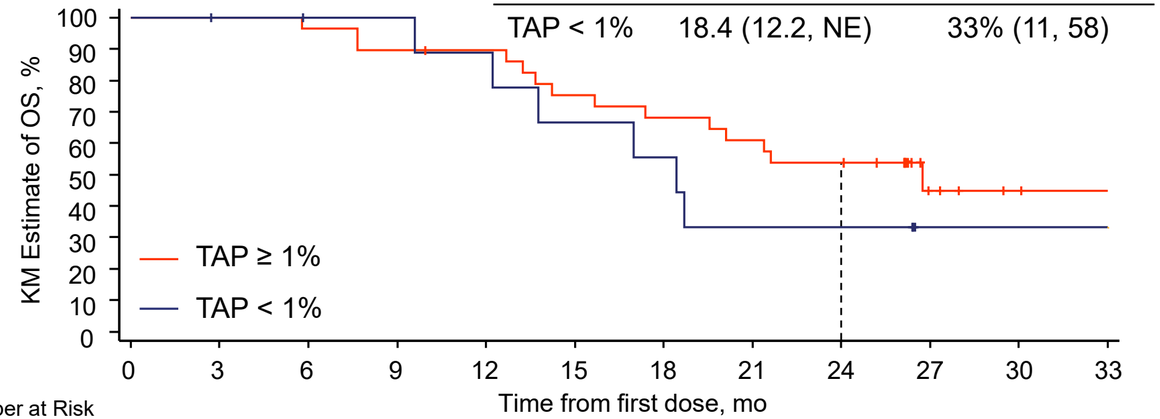
	Median OS, mo (90% CI)	24-mo OS rate, % (90% CI)
TAP ≥ 5%	Not reached (17.4, NE)	56% (34, 74)
TAP < 5%	19.5 (15.7, NE)	43% (25, 60)



Number at Risk

TAP ≥ 5%	16	16	16	15	15	12	11	10	9	3	1	0
TAP < 5%	24	23	21	20	18	15	13	10	9	1	0	0

	Median OS, mo (90% CI)	24-mo OS rate, % (90% CI)
TAP ≥ 1%	26.7 (19.5, NE)	54% (37, 68)
TAP < 1%	18.4 (12.2, NE)	33% (11, 58)



Number at Risk

TAP ≥ 1%	29	29	28	26	25	21	19	17	15	4	1	0
TAP < 1%	11	10	9	9	8	6	5	3	3	0	0	0

KM, Kaplan-Meier; mo, months; NE, not estimable; OS, overall survival; TAP, tumor area positivity.

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Overall Safety Summary

	Arm A1 N = 41, n (%)
Any TEAEs	41 (100)
Related to dom/zim	32 (78)
Grade ≥ 3 TEAEs	30 (73)
Related to dom/zim	7 (17)
Serious TEAEs	15 (37)
Related to dom/zim	0
TEAEs leading to discontinuation of any study drug	27 (66)
TEAEs leading to discontinuation of dom/zim	4 (10)
TEAEs leading to dose modification/interruption of any study drug	35 (85)
TEAEs leading to death	1 (2)[a]

Immune-Related TEAEs[b]	Arm A1 N = 41, n (%)
Any	11 (27)
Reported in > 1 patient	
Hypothyroidism	5 (12)
Adrenal insufficiency	2 (5)
Pneumonitis	2 (5)
Grade ≥ 3	0

Infusion-Related Reactions[c]	Arm A1 N = 41, n (%)
Any	12 (29)
Related to dom/zim	3 (7)
Reported in > 1 patient	
Pyrexia	7 (17)
Infusion-related reaction	3 (7)
Grade ≥ 3	1 (2)[d]

AE, adverse event; dom, domvanalimab; PD-1, programmed cell death protein 1; TEAEs, treatment-emergent AEs; zim, zimberelimab.

[a]Not related to any study treatment.

[b]Immune-related AEs were reported by the investigator and defined using a custom PD-1 immune-related AE search list. The list included all AEs regardless of grade, except for preferred terms containing "PD-1 skin toxicities," which were included only if they were grade ≥ 3.

[c]Infusion-related reactions were reported by the investigator and defined as AEs that occurred ≤ 1 day after the end of study drug infusion administration (within 24 hours if time is available), were ≤ 2 days in duration, and were in the custom AE preferred term search list (infusion-related reaction, pyrexia, chills, rigors, hypotension, dyspnea, wheezing, urticaria, flushing, back pain, abdominal pain, drug hypersensitivity, anaphylactic reaction, hypersensitivity, type 1 hypersensitivity, pruritis, and rash).

[d]There was 1 grade 3 event (dyspnea) that led to oxaliplatin discontinuation without further dose modifications.

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Conclusions

- **First-line DOM (anti-TIGIT), ZIM (anti–PD-1), and FOLFOX** showed encouraging efficacy results in advanced gastric, gastroesophageal junction, or esophageal adenocarcinoma with **median PFS of 12.9 months, and median OS of 26.7 months**
- Safety profile was consistent with anti–PD-1 plus platinum-based chemotherapy
- The phase 3 STAR-221 trial (NCT05568095) comparing first-line domvanalimab, zimberelimab, and chemotherapy to nivolumab and chemotherapy is ongoing

FOLFOX, oxaliplatin 85 mg/m^2 IV, leucovorin 400 mg/m^2 IV, fluorouracil 400 mg/m^2 IV bolus + 2400 mg/m^2 continuous 46-48-hour IV infusion; IV, intravenous; PD-1, programmed cell death protein 1; TIGIT, T-cell immunoreceptor with immunoglobulin and ITIM domain.

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Domvanalimab and zimberelimab in advanced gastric, gastroesophageal junction or esophageal cancer: a phase 2 trial

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Dual inhibition of T cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT) and programmed cell death protein 1 (PD-1) may enhance antitumor immunity in advanced gastroesophageal cancers. Here we report the EDGE-Gastric study, an ongoing, multicenter, international, phase 2 study with three cohorts, one in the first-line setting (cohort A) and two in the second-line or greater setting (cohorts B and C). Cohort A comprises four arms: two nonrandomized (A1 and A2) and two randomized (A3 and A4). In arm A1, presented here, dual blockade of TIGIT and PD-1 with domvanalimab (Fc-silent anti-TIGIT) and zimberelimab (anti-PD-1) plus oxaliplatin, leucovorin, fluorouracil (FOLFOX) was evaluated in patients with previously untreated advanced *HER2*-negative gastric, gastroesophageal junction or esophageal adenocarcinoma. Among 41 treated patients, the confirmed objective response rate was 59% (90% confidence interval (CI) 44.5–71.6%), median progression-free survival was 12.9 months (90% CI 9.8–14.6 months) and median overall survival was 26.7 months (90% CI 18.4 months to not estimable (NE)). In patients with tumor area positivity ≥1% (PD-L1 positive) and tumor area positivity ≥5% (PD-L1 high), respectively, the objective response rate was 62% (90% CI 45.1–77.1%) and 69% (90% CI 45.2–86.8%), median progression-free survival was 13.2 months (90% CI 11.3–15.2 months) and 14.5 months (90% CI 11.3 months–NE), and median overall survival was 26.7 months (90% CI 19.5 months–NE) and not reached (90% CI 17.4 months–NE). Immune-related adverse events were reported in 27% of patients; the safety profile was consistent with that reported for anti-PD-1 plus platinum-based chemotherapy. Dual TIGIT and PD-1 blockade with domvanalimab and zimberelimab plus chemotherapy demonstrated encouraging efficacy, and the regimen is being evaluated in the phase 3 STAR-221 trial. ClinicalTrials.gov identifier: NCT05329766.

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