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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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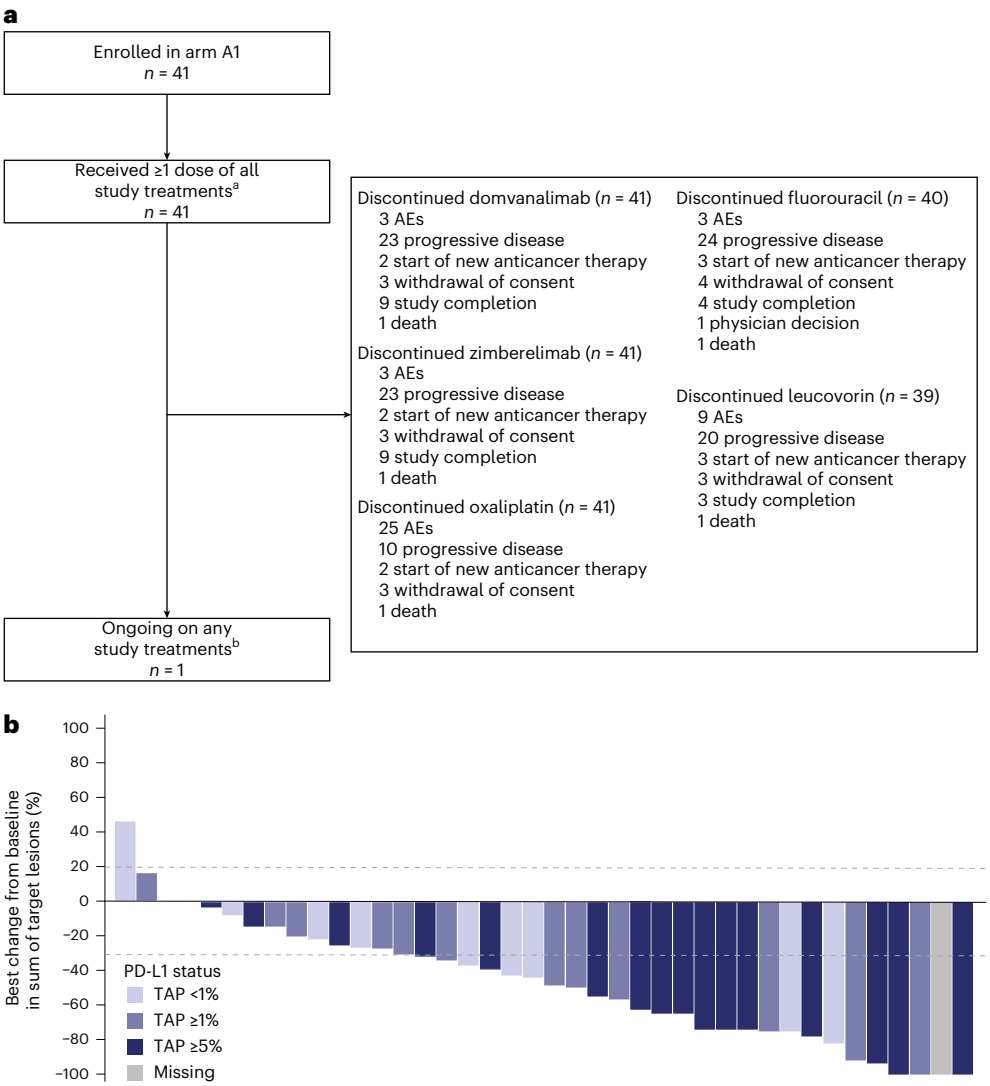

Fig. 1 | Trial profile and clinical response. a,**b**, Patient dispositions (**a**) and best percent change from baseline in sum of target lesions in patients with confirmed response (**b**). [a]One patient did not receive leucovorin owing to institutional standard practice, but they did receive all other assigned study treatments. [b]One patient is ongoing on leucovorin and fluorouracil but has discontinued domvanalimab and zimberelimab due to completion of the 2-year maximum treatment duration. The dashed reference lines indicate a 20% increase or 30% decrease from baseline in the sum of target lesions.

The addition of programmed cell death protein 1 (PD-1) inhibitors to chemotherapy has reshaped first-line treatment for metastatic gastroesophageal cancer, expanding therapeutic options and improving outcomes[1,2]. However, durable benefit remains limited, with a median overall survival (OS) of approximately 14 months[3–6] and only about 17% of patients living beyond 3 years[7], highlighting the need for strategies that can further extend and deepen benefit.

T cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT) is an inhibitory checkpoint expressed on activated T cells and natural killer cells across multiple cancer types[8]. TIGIT suppresses T cell activation by outcompeting the activating receptor CD226 for the shared ligand CD155 (ref. 9). TIGIT expression correlates with PD-1, particularly in tumor-infiltrating T cells[10], and the two pathways have distinct, nonredundant roles in regulating antitumor immunity[11]. Anti-TIGIT agents demonstrate promising antitumor activity across solid tumors when combined with anti-PD-1 therapies, with and without chemotherapy[8,10,12].

Domvanalimab is an anti-TIGIT monoclonal antibody that, when combined with anti-PD-1 therapy, enhances immune cell activation compared with anti-PD-1 alone[13]. Domvanalimab is engineered to be Fc silent to avoid inducing antibody-dependent cellular cytotoxicity (ADCC), thereby preserving peripheral regulatory T cells (Tregs) that are critical for maintaining immune homeostasis[14]. This Fc-silent design may reduce autoimmune toxicities and immune-mediated side effects relative to Fc-enabled anti-TIGIT antibodies[14]. Zimberelimab, a fully human anti-PD-1 monoclonal antibody with high affinity binding for PD-1 (ref. 15), has demonstrated safety and efficacy across multiple tumor types[13,16,17].

Chemotherapy can prime the tumor microenvironment by enhancing antigen release, increasing immune cell infiltration and reducing immunosuppressive cell populations[18]. In preclinical studies, chemotherapy followed by dual checkpoint blockade with domvanalimab and zimberelimab potentiated a robust and durable antitumor immune response[14,19]. In two phase 2 trials in patients with advanced non-small cell lung cancer, first-line treatment with domvanalimab and zimberelimab demonstrated improved outcomes versus zimberelimab[13] and versus zimberelimab or chemotherapy[20]. Building on this rationale, we report results from arm A1 of the phase 2 EDGE-Gastric study (NCT05329766) of domvanalimab and zimberelimab in combination with oxaliplatin, leucovorin and fluorouracil (FOLFOX) as first-line treatment for patients with locally advanced unresectable or metastatic *HER2*-negative gastric (GC), gastroesophageal junction (GEJC) or esophageal adenocarcinoma (EAC).

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Table 1 | Baseline demographics and clinical characteristics

Characteristic	Overall N=41
Median age in years (range)	62 (30–82)
Sex, *n* (%)	
Female	17 (41)
Male	24 (59)
Country, *n* (%)	
South Korea	19 (46)
USA/France	22 (54)
Race, *n* (%)	
Asian	21 (51)
White	14 (34)
Not reported	6 (15)
ECOG PS, *n* (%)	
0	16 (39)
1	25 (61)
Histologically confirmed diagnosis, *n* (%)	
GC adenocarcinoma	26 (63)
GEJC adenocarcinoma	5 (12)
EAC	10 (24)
Clinical tumor stage at study entry, *n* (%)	
III	2 (5)
IVA	10 (24)
IVB	29 (71)
Current disease status, *n* (%)	
Locally advanced unresectable	2 (5)
Metastatic	39 (95)
Liver metastases, *n* (%)	12 (29)
Peritoneal metastases, *n* (%)	18 (44)
Microsatellite instability status, *n* (%)	
High	1 (2)
Low	4 (10)
Stable	31 (76)
Unknown	5 (12)
EBV mutation status, *n* (%)	
No	17 (42)
Unknown	24 (59)
Prior systemic therapy, *n* (%)	9 (22)
Prior radiotherapy, *n* (%)	5 (12)

Percentages may not total 100% due to rounding. EBV, Epstein–Barr virus.

Table 2 | Tumor response

Parameter	Overall N=41[a]	TAP≥1% n=29	TAP≥5% n=16	TAP<1% n=11
ORR, rate (*n*) (90% CI)	59% (24) (44.5–71.6%)	62% (18) (45.1–77.1%)	69% (11) (45.2–86.8%)	46% (5) (20.0–72.9%)
BOR, *n* (%)				
Complete response	3 (7%)	2 (7%)	1 (6%)	0
Partial response	21 (51%)	16 (55%)	10 (63%)	5 (46%)
Stable disease	14 (34%)	10 (35%)	5 (31%)	4 (36%)
Progressive disease	2 (5%)	1 (3%)	0	1 (9%)
No postbaseline scan	1 (2%)	0	0	1 (9%)
DCR, rate (*n*)	93% (38)	97% (28)	100% (16)	82% (9)
DOR in months, median (90% CI)[b]	12.4 (10.2–15.4)	12.4 (10.2–15.9)	15.4 (10.9–21.0)	4.4 (2.7–NE)

[a]One patient had no tissue available for central laboratory evaluation of PD-L1 expression; local laboratory results showed the patient's tumor was PD-L1 low according to the 22C3 assay. [b]Estimated using the Kaplan–Meier method. CIs were calculated based on the log–log transformation.

Results

Study population and patient disposition

Between 30 August 2022 and 3 March 2023, 41 patients were enrolled across 20 sites (including hospitals, academic medical centers and clinical research units) in the USA, France and South Korea (Fig. 1a). No data were excluded from the arm A1 analyses. This study included both male and female human participants ($n = 24$ male and $n = 17$ female) aged 30–82 years.

Twenty-six (63%) patients had gastric adenocarcinoma, 29 (71%) patients were programmed cell death ligand 1 (PD-L1) positive (tumor area positivity (TAP) score ≥1%), 16 (39%) patients were TAP ≥5% and 11 (27%) patients were TAP <1%; there was one patient with known MSI-H status (Table 1). There was correlation between TAP score and combined positivity score (CPS) ($r = 0.83$, $P < 0.0001$). The overall percent agreement was 76% for TAP ≥5% versus CPS ≥5 and 87% for TAP≥1% versus CPS ≥1 (Extended Data Fig. 1).

At data cutoff (3 March 2025), median study follow-up was 26.4 months. All patients received at least one dose of each study drug except one, who did not receive leucovorin per institutional practice. Median duration of treatment exposure was 49.4 weeks (range <1–117 weeks).

Efficacy

The confirmed objective response rate (ORR) was 59% (90% confidence interval (CI) 44.5–71.6%), including 3 complete responses (7%) and 21 partial responses (51%) (Fig. 1b and Table 2). The disease control rate (DCR) was 93%. The median duration of response (DOR) was 12.4 months (90% CI 10.2–15.4 months) among the 24 patients with confirmed response.

Tumor responses were higher in TAP ≥1% and TAP ≥5% subgroups: ORR was 62% (90% CI 45.1–77.1%) and 69% (90% CI 45.2–86.8%), respectively, with DCR of 97% and 100%, respectively. Median DOR was 12.4 months (90% CI 10.2–15.9 months) and 15.4 months (90% CI 10.9–21.0 months), respectively. Tumor response was lower in patients with TAP <1%, with ORR of 46% (90% CI 20.0–72.9%).

Median progression-free survival (PFS) was 12.9 months (90% CI 9.8–14.6 months), with a 24-month PFS rate of 26% (90% CI 14.8–38.5%) (Fig. 2a). By PD-L1 status, median PFS was 13.2 months (90% CI 11.3–15.2 months) in TAP ≥1%, 14.5 months (90% CI 11.3 months to not estimable (NE)) in TAP ≥5% and 6.8 months (90% CI 3.0–13.8 months) in TAP <1% (Fig. 2b,c).

Median OS was 26.7 months (90% CI 18.4 months–NE), with a 24-month OS rate of 50% (90% CI 36.3–62.6%) (Fig. 3a). Median OS was 26.7 months (90% CI 19.5 months–NE) in TAP ≥1%, not reached (90% CI 17.4 months–NE) in TAP ≥5% and 18.4 months (90% CI 12.2 months–NE) in TAP <1% (Fig. 3b,c). Corresponding 24-month OS rates were 54% (90% CI 37.3–67.7%), 56% (90% CI 33.9–73.6%) and 33% (90% CI 10.8–58.1%), respectively.

Safety

All patients experienced at least one treatment-emergent adverse event (TEAE) (Table 3), most commonly nausea (59%) and a decrease in neutrophil count (44%) (Supplementary Table 1). Grade ≥3 TEAEs occurred in 30 (73%) patients, including neutrophil count decrease

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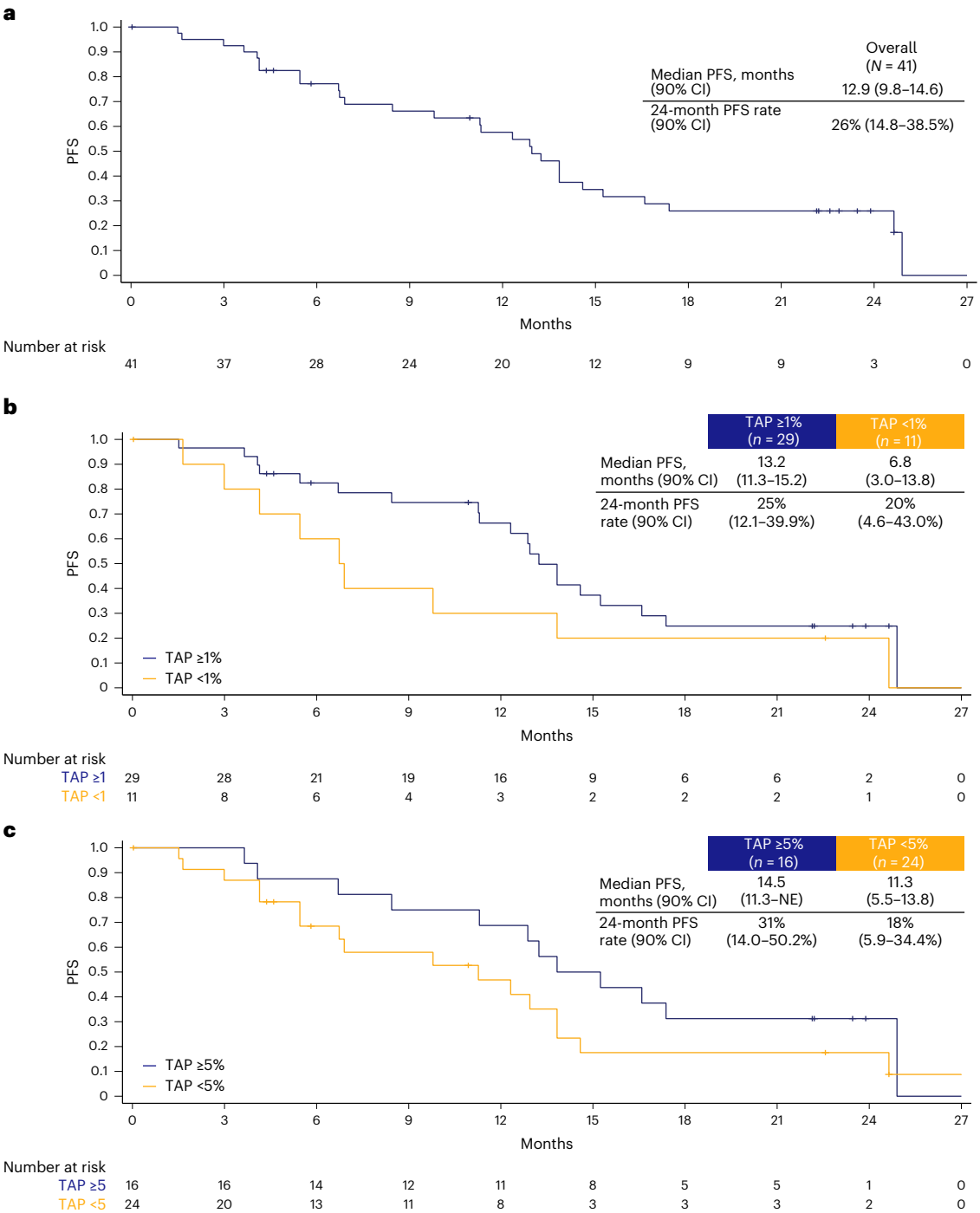

Fig. 2 | Kaplan-Meier estimates of PFS. a–**c**, PFS in all treated patients (**a**), in patients who were TAP ≥1% and TAP <1% (**b**) and in patients who were TAP ≥5% and TAP <5% (**c**). One patient had no tissue available for central laboratory evaluation of PD-L1 expression; local laboratory results showed the patient's tumor was PD-L1 low according to the 22C3 assay.

(37%), anemia (17%) and neutropenia (15%) (Supplementary Table 2). Grade ≥3 TEAEs attributed to domvanalimab and/or zimberelimab were reported in seven (17%) patients.

TEAEs leading to discontinuation of domvanalimab and/or zimberelimab were reported in four (10%) patients. The discontinuation of domvanalimab and/or zimberelimab was due to one event each of grade 2 blood alkaline phosphatase increased, grade 2 anxiety, grade 3 peripheral neuropathy and grade 3 ileus. Serious TEAEs were reported in 15 (37%) patients, none related to domvanalimab or zimberelimab. TEAEs that led to death occurred in one (2%) patient; the event term was listed as 'death' and was assessed as related to disease progression, not related to any study treatment.

Immune-related TEAEs were reported in 11 (27%) patients, including 9 (22%) related to domvanalimab and/or zimberelimab. The most common were hypothyroidism (12%), adrenal insufficiency (5%) and pneumonitis (5%). No grade ≥3 immune-mediated TEAEs were reported.

Infusion-related reactions were reported in 12 (29%) patients, including three (7%) related to domvanalimab and/or zimberelimab. Infusion-related reactions reported in more than one patient by

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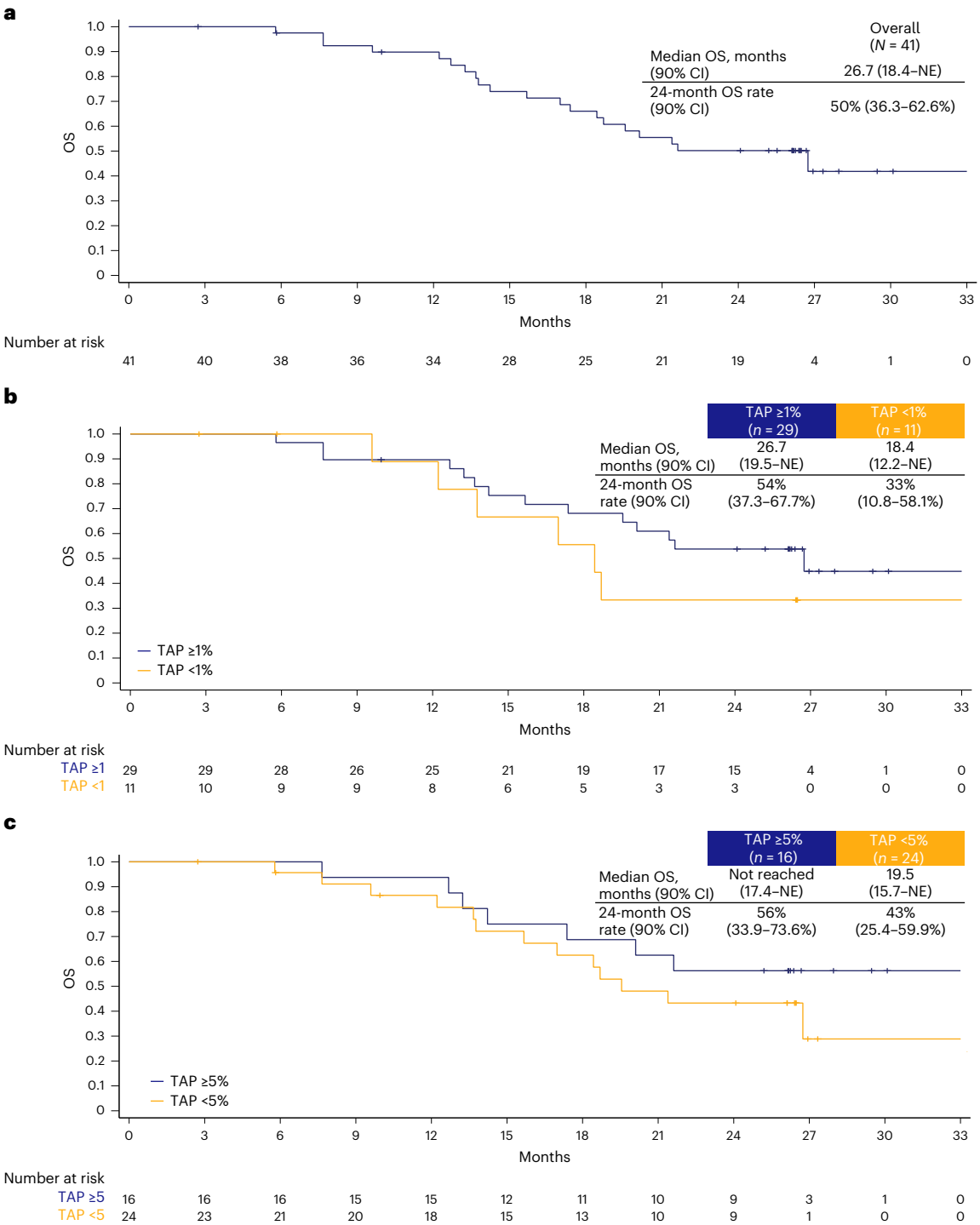

Fig. 3 | Kaplan-Meier estimates of OS. a–**c**, OS in all treated patients (**a**), in patients who were TAP ≥1% and TAP <1% (**b**) and in patients who were TAP ≥5% and TAP <5% (**c**). One patient had no tissue available for central laboratory evaluation of PD-L1 expression; local laboratory results showed the patient's tumor was PD-L1 low according to the 22C3 assay.

preferred term were pyrexia (17%) and infusion-related reaction (7%). One grade 3 event (dyspnea) led to oxaliplatin discontinuation without further dose modifications.

Discussion

In the multicenter, international EDGE-Gastric study arm A1, we demonstrate durable disease control and long-term survival with dual TIGIT and PD-1 blockade using domvanalimab and zimberelimab plus FOLFOX as first-line therapy for advanced *HER2*-negative GC/GEJC/EAC. After a median study follow-up of 26.4 months, outcomes were encouraging, with an ORR of 59%, median DOR of 12.4 months, median PFS of 12.9 months and median OS of 26.7 months. Clinical activity was observed across PD-L1 subgroups. The safety profile was similar to that expected for anti-PD-1 therapy plus platinum-based chemotherapy[1,3,4]. These observations are being further investigated in the ongoing, randomized, phase 3 STAR-221 trial (NCT05568095), comparing domvanalimab, zimberelimab and chemotherapy with nivolumab and chemotherapy[21].

Table 3 | Safety summary

AE, *n* (%)	Patients *N*=41
Any TEAEs	41 (100)
Related to domvanalimab and/or zimberelimab	32 (78)
Grade ≥3 TEAEs	30 (73)
Related to domvanalimab and/or zimberelimab	7 (17)
Serious TEAEs	15 (37)
Related to domvanalimab and/or zimberelimab	0
TEAEs leading to death	1 (2)[a]
TEAEs leading to dose modification/interruption of any study drug	35 (85)
Of domvanalimab and/or zimberelimab	20 (49)
TEAEs leading to discontinuation of any study drug	27 (66)
Of domvanalimab and/or zimberelimab	4 (10)
Immune-related TEAEs	11 (27)
Related to domvanalimab and/or zimberelimab	9 (22)
Most common (>1 patient)	
Hypothyroidism	5 (12)
Adrenal insufficiency	2 (5)
Pneumonitis	2 (5)
Infusion-related reactions	12 (29)
Related to domvanalimab and/or zimberelimab	3 (7)
Most common (>1 patient)	
Pyrexia	7 (17)
Infusion-related reaction	3 (7)

[a]Not related to any study treatment. Patients who experienced multiple TEAEs of the same type were counted only once. In the assessment of TEAE severity, patients were counted once at the highest severity reported at each level of summarization.

Domvanalimab is an Fc-silent anti-TIGIT antibody, which may confer a differentiated safety profile compared with Fc-enabled designs. Fc-enabled anti-TIGIT antibodies can trigger ADCC, depleting activated T cells and Tregs in the tumor microenvironment and/or circulation[14]. While these effects may enhance immunity in some contexts, they can also reduce the pool of activated effector T cells and increase the risk of immune-mediated toxicities[22,23]. By contrast, the Fc-silent anti-TIGIT antibody domvanalimab preserves peripheral Tregs critical for maintaining immune homeostasis and is not associated with increased ADCC, which may mitigate autoimmune toxicities and provide durable antitumor activity when combined with PD-1 inhibition[14,19,23].

Results from the EDGE-Gastric study arm A1 compare favorably with established first-line regimens of chemotherapy plus anti-PD-1 agents. Across pivotal phase 3 trials with nivolumab, pembrolizumab and tislelizumab, ORRs were 47–60%, median PFS was less than 8 months and median OS was 15 months or less[1,3,4]. By contrast, EDGE-Gastric arm A1 achieved a median PFS exceeding 12 months and a median OS approaching 27 months, suggesting that dual TIGIT and PD-1 blockade may extend the benefit of immunotherapy beyond current standards.

The findings are consistent with other early phase trials of anti-TIGIT, anti-PD-1 and chemotherapy in patients with advanced *HER2*-negative GC/GEJC, such as the phase 1b AdvanTIG-105 study and the phase 2 GEMINI-Gastric study, which reported ORRs of 53–57% overall and ~63% in patients who were PD-L1 high[24,25]. Together, these data suggest that patients who are PD-L1 high may derive particular benefit from TIGIT inhibition added to PD-1 blockade. These were small, early phase studies, and the combination of anti-TIGIT, anti-PD-1 and chemotherapy is being explored further in the ongoing phase 3 STAR-221 trial.

EDGE-Gastric is a proof-of-concept, open-label phase 2 study, with limitations related to sample size, study design and assay heterogeneity. FOLFOX was selected as the chemotherapy regimen in the EDGE-Gastric study arm A1 as it was widely regarded as a standard of care for patients with gastroesophageal cancer at the time of study design. It was not possible to determine the contribution of components of domvanalimab, zimberelimab and FOLFOX in arm A1, but the efficacy outcomes with the combination therapy exceed expectations from the existing data for standard of care, with a manageable toxicity profile.

In the EDGE-Gastric study, PD-L1 status was assessed by the VENTANA PD-L1 (SP263) assay with TAP score, which was recently used to support the approval of tislelizumab for the treatment of advanced PD-L1-positive GC/GEJC adenocarcinoma by the US Food and Drug Administration[3,26]. We observed concordance between the VENTANA SP263 assay with TAP scoring at ≥1% and ≥5% cutoffs, and the Dako PharmDx 28-8 PD-L1 assay with CPS scoring. This aligns with studies in GC that have shown high concordance in PD-L1 testing between three major PD-L1 assays (28-8, 22C3 and SP263) with TAP (≥1% and ≥5%) and CPS (≥1 and ≥5) scoring[27–29]. However, there are potential sources of variability for the concordance rate from sources other than the scoring algorithms. Namely, the EDGE-Gastric study employed multiple pathologists, and the same pathologist was not requested to perform both SP263 and 28-8 evaluations for each patient. Previous research has shown high interobserver variability of CPS scoring[30]. The 28-8 assay was performed retrospectively, and although serial sections adjacent to those used for the SP263 assay were taken, tissue sample heterogeneity cannot be ruled out as a potential source of variability.

Domvanalimab, zimberelimab and FOLFOX achieved durable responses and long-term survival with manageable toxicity in patients with previously untreated advanced *HER2*-negative gastroesophageal cancer. The Fc-silent design of domvanalimab may further optimize the therapeutic window by balancing efficacy with safety in the context of PD-1 blockade and chemotherapy. These findings provide the rationale for continued investigation of domvanalimab, zimberelimab and chemotherapy in advanced GC/GEJC/EAC in the ongoing phase 3 STAR-221 trial.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-025-04022-w.

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Methods

Study design

EDGE-Gastric (NCT05329766) is an ongoing, phase 2, open-label, multicenter clinical 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) (Extended Data Fig. 2). Cohort A comprises two nonrandomized (A1 and A2) and two randomized arms (A3 and A4). In arm A1, presented here, patients with no prior systemic treatment for locally advanced or metastatic GC/GEJC/EAC received intravenously administered domvanalimab 1,600 mg and zimberelimab 480 mg once every 4 weeks with FOLFOX (oxaliplatin 85 mg m^{-2}, leucovorin 400 mg m^{-2}, fluorouracil 400 mg m^{-2} on day 1 and fluorouracil 2,400 mg m^{-2} on days 1 and 2 (continuous 46–48-h infusion)) once every 2 weeks. The study is open label, so investigators were not blinded to the allocation of enrolled patients. EDGE-Gastric (NCT05329766) was registered on 8 April 2022 with ClinicalTrials.gov, https://clinicaltrials.gov/study/NCT05329766. Additional details are provided in the study protocol (online only).

Patients

Eligible patients were aged ≥18 years, had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, and had not received previous systemic treatment for locally advanced or metastatic disease. Patients with known *HER2*-positive status and patients with untreated, symptomatic or actively progressing central nervous system brain metastases were excluded. Complete eligibility criteria are presented in Supplementary Table 3.

Sex was recorded as a binary variable based on self-reported biological characteristics. Gender identity was not collected or analyzed in this study. No analyses stratified by sex were conducted.

Ethics approval and consent

The study was conducted in full conformance with the Declaration of Helsinki, the Council for International Organizations of Medical Sciences International Ethical Guidelines, institutional review board regulations and all other applicable local regulations. The study protocol was approved by the local ethics committee at each site (Supplementary Table 4). All patients provided written informed consent before any study procedures; patients were not compensated monetarily for participation in this trial.

Procedures

Lesions were assessed at screening and every 6 weeks thereafter through week 48 or end of treatment (whichever occurred first), then every 12 weeks thereafter until disease progression, initiation of a subsequent anticancer therapy, loss to follow-up, withdrawal of consent, study termination or death—whichever occurred first. Treatment was continued until disease progression, unacceptable toxicities, initiation of a subsequent anticancer therapy, physician or patient decision to withdraw, completion of a maximum treatment duration of 2 years or death—whichever occurred first. With the patient's agreement, investigators could continue treatment beyond initial disease progression at their discretion based on the patient's risk–benefit profile. Patients who experienced unacceptable toxicity, symptomatic deterioration due to disease progression or confirmed disease progression were discontinued from study treatment.

Tumor tissue was evaluated for PD-L1 expression at a central laboratory. Tumor samples were stained using the VENTANA PD-L1 (SP263) companion diagnostics assay (Roche Diagnostics). The VENTANA PD-L1 (SP263) assay is approved in the USA as a companion diagnostic to determine PD-L1 expression at a ≥1% tumor cell cutoff in patients with non-small cell lung cancer. Pathologists assessed PD-L1 expression in tumor cells and tumor-associated immune cells using the TAP score. The TAP score is defined as the total percentage of the tumor area (tumor and any desmoplastic stroma) covered by tumor cells with membranous PD-L1 staining at any intensity and tumor-associated immune cells with PD-L1 staining at any intensity, according to visual estimation. As previously published, TAP scores of ≥1% and ≥5% were used as cutoffs[31]. Patients with TAP score ≥1% were considered PD-L1 positive and <1% were considered PD-L1 negative. Patients with TAP score ≥5% were considered PD-L1 high and <5% were considered PD-L1 low. In the assessment of concordance between the SP263 assay with TAP score and the 28-8 assay with CPS, the 28-8 assay was performed retrospectively on serial sections to minimize effects from tissue heterogeneity.

Endpoints and assessments

The dual primary endpoints of safety and investigator-assessed ORR were evaluated in patients who enrolled and received any study treatment (treated analysis population). ORR was defined as the percentage of patients with a confirmed best overall response (BOR) of complete response or partial response, per RECIST v1.1. Patients who discontinued before completing postbaseline tumor assessments were considered nonresponders.

Secondary endpoints were OS, PFS, DCR and DOR overall and by PD-L1 expression, as well as ORR by PD-L1 expression. OS was defined as the time from first dose until death due to any cause. PFS was defined as the time from first dose until first documentation of progressive disease or death due to any cause. DCR was defined as the percentage of patients with a confirmed BOR of complete response, partial response or stable disease. DOR was defined as the time from date of initial response (complete response or partial response) until the date of first documented disease progression or death due to any cause (in confirmed responders only).

Adverse events (AEs) were assessed in the treated analysis population and coded using the Medical Dictionary for Regulatory Affairs v25.0. Severity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Investigators assessed whether an AE was related to study treatment. Infusion-related reactions were defined as AEs that occurred ≤1 day after the end of study drug infusion administration (within 24 h if time was 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, pruritus or rash). Immune-related AEs were defined as all AEs of any grade in the custom PD-1 immune-related AE search list, except for preferred terms containing "PD-1 skin toxicities", for which only grade ≥3 AEs were included.

Statistical analysis

The EDGE-Gastric study was prespecified to include three cohorts (A, B and C) and cohort A was prespecified to include four arms (A1–A4) (Extended Data Fig. 2). All cohorts and arms have a prespecified enrollment plan and statistical design. The planned enrollment in arm A1 was approximately 40 patients, of which approximately 50% would have PD-L1 high expression. The sample size justification was based on an estimation framework, and the study was designed for descriptive statistical analysis rather than formal statistical hypothesis testing with Type I error and power considerations.

Median OS, median PFS, median DOR, PFS rate at 24 months and OS rate at 24 months were estimated using the Kaplan–Meier method. For PFS, OS and DOR, the 90% CI was based on the log–log transformation of the corresponding survival function. Exact binomial Clopper–Pearson 90% CIs were constructed for ORR. The median duration of study follow-up was calculated as the time from cycle 1, day 1, until the data cutoff date, regardless of events or dropout. Statistical analyses were performed using SAS software, version 9.4.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Arcus Biosciences is committed to responsible sharing of data from clinical trials sponsored by Arcus Biosciences. Summary and de-identified individual participant data as well as other trial information (protocols, statistical analysis plans and clinical study reports) may be available upon request. Arcus will continue to protect the privacy of our clinical trial participants. Requests for data from any qualified researcher who engages in rigorous, independent scientific research will be considered if the clinical trial data are not part of an ongoing or planned regulatory submission. Original data will be available for 12 months, beginning 3 months after approval of the study drug for use in patients or a new indication. For information on the process or to submit a request, see https://trials.arcusbio.com/our-transparency-policy.

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Author contributions

Y.Y.J.: conceptualization, data curation, formal analysis, funding, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing—original draft, writing—review and editing. D.-Y.O.: conceptualization, investigation, project administration, resources, software, supervision, validation, writing—original draft, writing—review and editing. M.P.: investigation, supervision, writing—review and editing. Z.A.W.: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, writing—original draft, writing—review and editing. S.P.: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing—original draft, writing—review and editing. S.N.: conceptualization, data curation, formal analysis, investigation, methodology, validation, visualization, writing—review and editing. A.D.P.: data curation, investigation, project administration, supervision, validation, writing—review and editing. A.T.: project administration, resources, supervision, visualization, writing—review and editing. D.O.K.: formal analysis, supervision, validation, visualization, writing—review and editing. E.A.R.S.: conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, visualization, writing—original draft, writing—review and editing. S.Y.R.: conceptualization, investigation, methodology, project administration, resources, supervision, validation, visualization, writing—original draft, writing—review and editing.

Competing interests

Y.Y.J. reports stock and other ownership interests with Inspirna; reports honoraria from Astellas Pharma, AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Master Clinician Alliance, Michael J. Hennessy Associates, Merck, Peerview and Research to Practice; reports consulting or advisory role with AbbVie, AmerisourceBergen, Arcus Biosciences, AskGene Pharma, Astellas Pharma, AstraZeneca, Basilea Pharmaceutical, Bayer, Bristol Myers Squibb, Daiichi Sankyo, Geneos, GlaxoSmithKline, Guardant Health, Imedex, Imugene, Jazz Pharmaceuticals, Lilly, Lynx Health, Merck, Merck Serono, Mersana, Michael J. Hennessy Associates, Paradigm, Peerview, Pfizer, Phanes Therapeutics, Research to Practice, Rgenix, Seagen, Silverback Therapeutics and Zymeworks; reports research funding (to the institution) from Arcus Biosciences, AstraZeneca, Bayer, Bristol Myers Squibb, Cycle for Survival, Fred's Team, Genentech/Roche, Lilly, Rgenix, Transcenta and United States Department of Defense; reports travel, accommodations, and expenses from Bristol Myers Squibb Japan and Merck; and reports other relationship with Axis Medical Education, Clinical Care Options and Research to Practice. D.-Y.O. reports consulting or advisory role with Arcus Biosciences, ASLAN Pharmaceuticals, AstraZeneca, Basilea, Bayer, BeiGene, Celgene, Genentech/Roche, Halozyme, IQVIA, Novartis, Merck Serono, Taiho Pharmaceutical, Turning Point Therapeutics, Yuhan and Zymeworks; and reports research funding from Array BioPharma, AstraZeneca, BeiGene, Handok, Lilly, MSD, Novartis and Servier. M.P. reports honoraria from Castle Biosciences; reports consulting or advisory role (paid to the institution) with AstraZeneca, Bayer, CytomX Therapeutics, Daiichi Sankyo, Ipsen, Novartis, Pfizer and Seagen; and reports research funding (to the institution) from 1200 Pharma, Arcus Biosciences, Astellas Pharma, BeiGene, BioNTech, Bristol Myers Squibb, Codiak Biosciences, CytomX Therapeutics, Eisai, Gilead Sciences, Gritstone Bio, HiberCell, Immune-Onc Therapeutics, Leap Therapeutics, OncXerna Therapeutics, Panbela Therapeutics, Revolution Medicines, SQZ Biotechnology, Surface Oncology, Translational Genomics Research Institute, TransThera Sciences (Nanjing) Inc. and ZielBio. Z.A.W. reports consulting or advisory role with Alligator Bioscience, Amgen, Arcus Biosciences, Astellas Pharma, AstraZeneca, Bayer, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Ipsen, Janssen, Jazz, Lilly, Merck, Merck KGaA, Novartis, Pfizer, PureTech, Revolution Medicine, Roche/Genentech and Seagen; reports travel/accommodations/expenses from Amgen, Bayer, Lilly and Merck; and reports research funding from Arcus Biosciences, Bristol Myers Squibb, Merck, Novartis, Pfizer and Plexxikon. S.P., S.N., A.D.P., A.T. and E.A.R.S. are employees of Arcus Biosciences, Inc. and may own stock and/or stock options. D.O.K. is an employee of Gilead Sciences, Inc. and owns stock in Gilead Sciences. S.Y.R. reports research funding and grants (to the institution) for conducting clinical trials from ABLBIO, ALX Oncology, AMGEN, Arcus Biosciences, Astellas Pharma, AstraZeneca, BeiGene, Boehringer Ingelheim, Bold Therapeutics, Daiichi Sankyo, Eisai, Ipsen, Leap Therapeutics, Macrogenics, Merck KGaA, Merck Sharp and Dohme, Ono Pharmaceutical, Pfizer, Seagen, Taiho Pharmaceutical, Toray, YH Corp and Zymeworks; reports consulting fees from Indivumed and LG Biochem; reports personal fees/honoraria from Amgen, Astellas, Bristol Myers Squibb/Ono, Daiichi Sankyo, Eisai and Merck Sharp and Dohme; and reports participation on data safety monitoring boards or advisory boards for Amgen, Astellas, AstraZeneca, Daiichi Sankyo and Toray.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-025-04022-w.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41591-025-04022-w.

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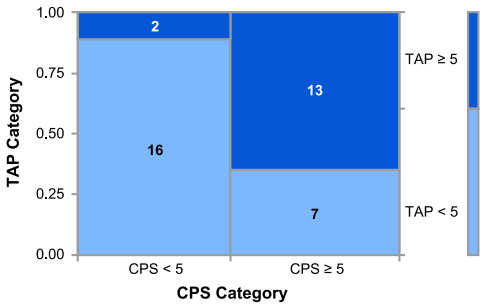
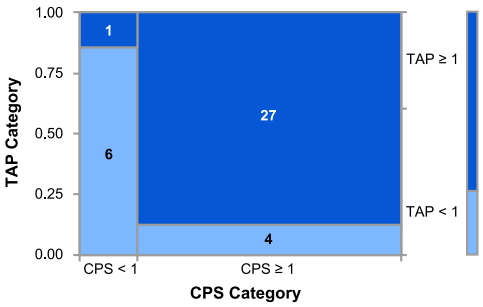


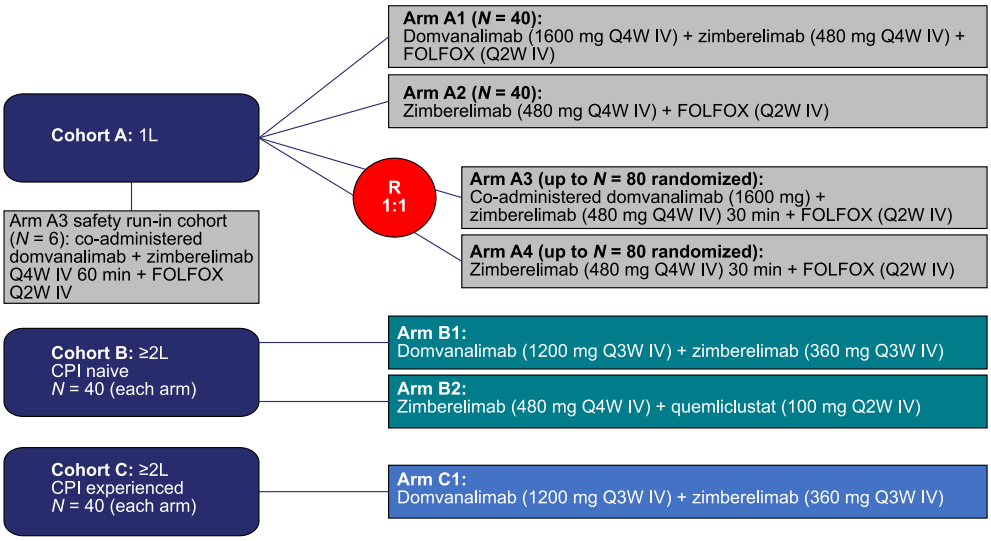
SP263 TAP 5%	28-8 CPS5 High	Low	Total	Agreement	%
High	13	2	15	Positive	65
Low	7	16	23	Negative	89
Total	20	18	38	Overall	76



SP263 TAP 1%	28-8 CPS1 High	Low	Total	Agreement	%
High	27	1	28	Positive	87
Low	4	6	12	Negative	86
Total	31	7	38	Overall	87

Extended Data Fig. 1 | Concordance between SP263 assay with TAP score and 28-8 assay with CPS. PD-L1 expression levels observed using the VENTANA SP263 assay with TAP scoring at ≥1% and ≥5% cutoffs and the Dako PharmDx 28-8 PD-L1 assay with CPS scoring. CPS, combined positivity score; TAP, tumor area positivity.

https://doi.org/10.1038/s41591-025-04022-w



Extended Data Fig. 2 | EDGE-Gastric study design. 1 L, first line; 2 L, second line; CPI, checkpoint inhibitor; FOLFOX, oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, fluorouracil 400 mg/m^2 on day 1 and fluorouracil 2400 mg/m^2 on days 1 and 2 (continuous 46–48-hour infusion); IV, intravenous; min, minute; Q2W, once every 2 weeks; Q3W, once every 3 weeks; Q4W, once every 4 weeks; R, randomized.

nature portfolio

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☒	☐ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐ A description of all covariates tested
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☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☒	☐ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	n/a
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Datasets for the clinical trial were prepared using standards from Clinical Data Interchange Consortium Study Data Tabulation Model implementation for human clinical trials and Analysis Dataset Model.
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Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Table 1 report breakdown by sex (female and male) of the patients. No sex-based analyses were performed because there is no evidence to suggest that sex would impact on efficacy.
Reporting on race, ethnicity, or other socially relevant groupings	Race and/or ethnicity were determined and classified based on self-report.
Population characteristics	The EDGE-Gastric study, Arm A1 was conducted at 20 sites in the United States, France, and Korea. Patients were aged ≥ 18 years, had an ECOG performance status of 0 or 1, and had not received previous systemic treatment for locally advanced or metastatic disease. Complete eligibility criteria are shown in Supplementary Table 1. Demographic and baseline disease characteristics are shown in Table 1.
Recruitment	The EDGE-Gastric study, Arm A1 was recruited at 20 clinical sites in the United States, France, and Korea. Participants were recruited by investigators at each participating study site. Recruiting bias is not expected to be higher on this study than on other clinical trials of similar phase and size, and is not anticipated to substantially impact results.
Ethics oversight	No central IRB or ethics committee was used. At each site, the study was conducted in adherence to the requirements of 21 Code of Federal Regulations, International Council for Harmonization guidelines, institutional review board regulations and all other applicable local regulations. The protocol was approved by the local ethics committee at each site (Supplementary Table 4). All patients provided written informed consent; patients were not compensated monetarily for their participation in this trial. This study was conducted in full conformance with the International Council for Harmonization E6 guideline for Good Clinical Practice and the consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, and applicable laws and regulations. The study was conducted in the United States under a US Investigational New Drug application and complied with US Food and Drug Administration regulations, including all applicable local, state and federal laws.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	The EDGE-Gastric study was a proof-of-concept, open-label, phase 2 study. As such, the sample size justification was based on an estimation framework, and the study was designed for descriptive statistical analysis rather than formal statistical hypothesis testing with Type I error and power considerations. The planned sample size was approximately 40 participants, depending on the toxicities observed, of which approximately 50% would have PD-L1-high expression.
Data exclusions	No data were excluded from the Arm A1 analyses. Inclusion/exclusion criteria are described in the methods and in Supplementary Table 1. The goal of the study was to assess the safety and tolerability of domvanalimab, zimberelimab, and FOLFOX combination therapy in patients with advanced gastric cancer, gastroesophageal junction cancer, or esophageal adenocarcinoma.
Replication	This was a clinical trial. No replication was performed.
Randomization	All participants were centrally assigned to study treatment using an Interactive Voice/Web Response System. Directions and log in/contact information for the Interactive Voice/Web Response System were provided to each site.
Blinding	This is an open-label trial; therefore, the sponsor, investigator, and patient know the study treatment administered.

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Materials & experimental systems

n/a	Involved in the study
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☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	EDGE-Gastric (NCT05329766) was registered on April 8, 2022 with ClinicalTrials.gov, https://clinicaltrials.gov/study/NCT05329766.
Study protocol	The redacted protocol and the statistical analysis plan are provided in the supplemental materials.
Data collection	The EDGE-Gastric study, Arm A1 enrolled patients between June 10, 2022, and February 7, 2025. The EDGE-Gastric study, Arm A1 was recruited at 21 clinical sites (including hospitals, academic medical centers, and clinical research units) in the United States, France, and Korea.
Outcomes	The protocol-specified co-primary objectives were safety and investigator-assessed ORR evaluated in patients who enrolled and received any study treatment (treated analysis population). ORR was defined as the percentage of patients with a confirmed best overall response (BOR) of complete response (CR) or partial response (PR) per RECIST v1.1. Patients who discontinued before completing postbaseline tumor assessments were considered nonresponders. Secondary endpoints were OS, PFS, disease control rate (DCR) and duration of response (DOR) overall and by PD-L1 expression, as well as ORR by PD-L1 expression. OS was defined as the time from first dose until death due to any cause. PFS was defined as the time from first dose until first documentation of progressive disease or death due to any cause. DCR was defined as the percentage of patients with a confirmed BOR of CR, PR or stable disease. DOR was defined as the time from date of initial response (CR or PR) until the date of first documented disease progression or death due to any cause (in confirmed responders only). Tumor response was assessed by investigators using RECIST v1.1. Safety data included type, incidence, seriousness, causality and severity of TEAEs and serious adverse events, as assessed by investigators according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.035. Adverse events were coded using the MedDRA v25.0.

Plants

Seed stocks	n/a
Novel plant genotypes	n/a
Authentication	n/a