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Annual Congress

STAR-221: A phase 3 study of first-line domvanalimab, zimberelimab, and chemotherapy vs nivolumab + chemotherapy in advanced *HER2*-negative gastric, gastroesophageal junction, or esophageal adenocarcinoma

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Declaration of Interests

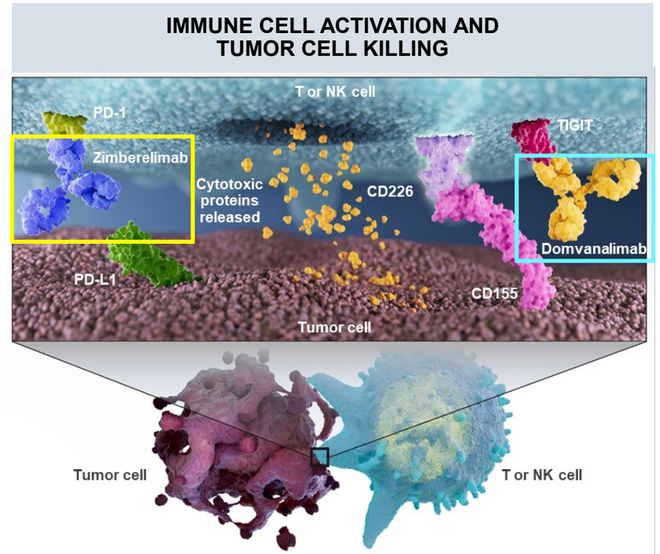
Sun Young Rha reported,

Grants or contracts for other studies from ABL Bio, Amgen, Arcus Biosciences, Astellas Pharma, AstraZeneca, BeOne, Bold Therapeutics, Celltrion, Daiichi Sankyo, DongA, Eisai, Henlius, Ipsen, Jazz, Merck KGaA, Merck Sharp and Dohme, Ono Pharmaceutical, Pfizer, and Taiho Pharmaceutical

Consulting, steering committee and advisory board for Amgen, AstraZeneca, Astellas Pharma, Arcus Biosciences, BeOne, Celltrion, Daiichi Sankyo, Gilead, Henlius, Indivumed, LG Chem, Eisai, Merck, MSD, Takeda, Toray

Introduction

- The addition of anti–PD-1 antibodies to chemo has improved survival outcomes in advanced gastroesophageal adenocarcinoma[1–3]
- However, clinical outcomes remain poor, with median overall survival of 13–15 months[2–4]; thus, more effective first-line treatment options are needed
- TIGIT is an inhibitory immune checkpoint expressed on activated T cells and natural killer cells, and plays a critical role in limiting immunity against tumors[5]
- The dual blockade of TIGIT and PD-1 using domvanalimab (dom; Fc-silent, anti-TIGIT) and zimberelimab (zim; anti–PD-1) with chemo showed activity in the phase 2 EDGE-Gastric A1 trial[6]
- We report the results of STAR-221, a phase 3 study of first-line dom + zim + chemo in patients with advanced *HER2*-negative GC/GEJC/EAC



1. Janjigian YY, et al. *Lancet.* 2021;398:27-40. 2. Rha SY, et al. *Lancet Oncol.* 2023;24:1181-95. 3. Qiu M-Z, et al. *BMJ.* 2024;385:e078876. 4. Janjigian YY, et al. *J Clin Oncol.* 2024;42:2012-20. 5. Chauvin J-M and Zarour HM. *J Immunother Cancer.* 2020;8:e000957. 6. Janjigian YY, et al. *Nat Med.* 2025;31:4274-80.

Chemo, chemotherapy; EAC, esophageal adenocarcinoma; GC, gastric cancer; GEJC, gastroesophageal junction carcinoma; *HER2*, human epidermal growth factor receptor 2; PD-1, programmed cell death protein 1; TIGIT, T-cell immunoreceptor with immunoglobulin and ITIM (immunoreceptor tyrosine-based inhibitory motif) domains.

Study Design

➢ **Global randomized phase 3 trial of dom + zim + chemo vs nivolumab + chemotherapy as 1st line treatment in HER2 - AGC**

Key eligibility criteria

- Age ≥ 18 years
- Histologically confirmed diagnosis of locally advanced unresectable or metastatic GC/GEJC/EAC
- ECOG PS 0–1
- Measurable disease per RECIST v1.1
- *HER2*-negative tumor
- No prior systemic treatment for locally advanced unresectable or metastatic GC/GEJC/EAC

N = 1040

R 1:1

Dom + Zim + chemo

Dom (1600 mg) + zim (480 mg) Q4W + FOLFOX Q2W
or
Dom (1200 mg) + zim (360 mg) Q3W + CAPOX Q3W

Nivo + chemo

Nivo (240 mg) Q2W + FOLFOX Q2W
or
Nivo (360 mg) Q3W + CAPOX Q3W

Until unacceptable toxicity, loss to follow-up, disease progression, study withdrawal, sponsor closure of study, or death

Endpoints

Primary:
- OS

Key secondary:
- PFS
- TTD by FACT-Ga

Other secondary:
- ORR
- DOR
- Safety

Primary and key secondary endpoints assessed in the following analysis populations:
- *ITT*
- *PD-L1–high (TAP ≥ 5%)*
- *PD-L1–positive (TAP ≥ 1%)*

Stratification factors

- **PD-L1 expression:** TAP ≥ 5% vs TAP < 5%
- **ECOG PS:** 0 vs 1
- **Region:** Asia vs Canada/EU5/US vs rest of world

STAR-221 aimed to evaluate the efficacy and safety of dom + zim + chemo as first-line treatment in patients with *HER2*-negative advanced gastroesophageal adenocarcinoma

CAPOX, capecitabine and oxaliplatin; chemo, chemotherapy; dom, domvanalimab; DOR, duration of response; EAC, esophageal adenocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EU5, European Union 5; FACT-Ga, Functional Assessment of Cancer Therapy – Gastric; FOLFOX, oxaliplatin, leucovorin, fluorouracil; GC, gastric cancer; GEJC, gastroesophageal junction carcinoma; *HER2*, human epidermal growth factor receptor 2; ITT, intent-to-treat; nivo, nivolumab; OS, overall survival; ORR, objective response rate; PD-L1, programmed death ligand 1; PFS, progression-free survival; Q2/3/4W, every 2/3/4 weeks; R, randomized; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TAP, tumor area positivity; TTD, time to first deterioration; US, United States; zim, zimberelimab.

Statistical Analysis Plan and Patient Disposition

Statistical analysis plan

Overall study: 1-sided α = 0.025

Primary endpoint: $OS_{PD\text{-}L1\text{–}high}$ (α = 0.02[a])

Primary endpoint: OS_{ITT} (α = 0.005[a])

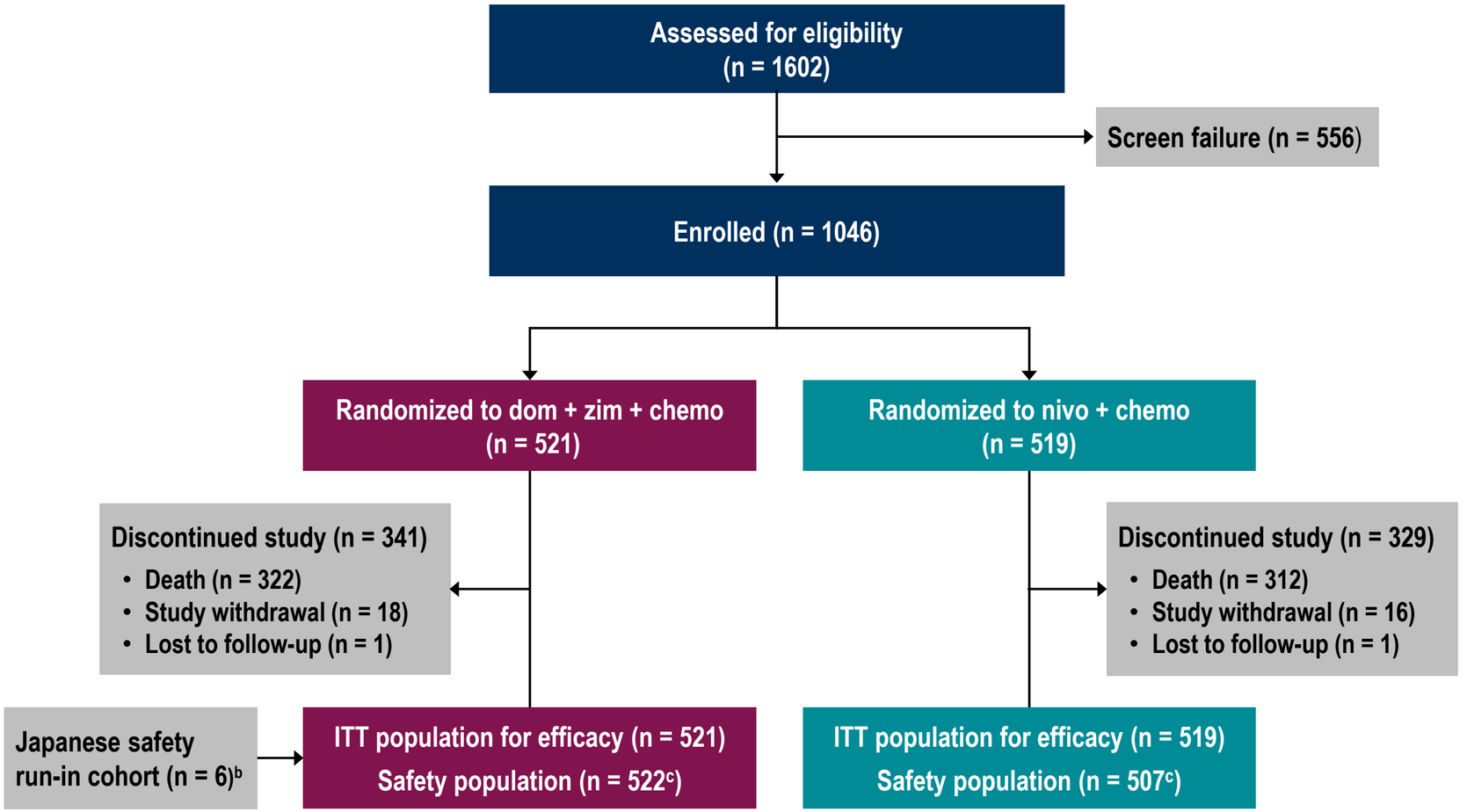
Primary endpoint: $OS_{PD\text{-}L1\text{–}positive}$ (α = 0[a])

If all OS endpoints are statistically significant, pass α = 0.025 to PFS

Secondary endpoint: PFS tested using same alpha allocation and testing procedure as OS

If all PFS endpoints are statistically significant, pass α = 0.025 to TTD

Secondary endpoint: TTD tested using same alpha allocation and testing procedure as PFS



[a]Alphas were pre-allocated and passed among the endpoints depending on the testing results. [b]Included in the safety population for the dom + zim + chemo arm. [c]Patients randomized and never dosed (n = 5, dom + zim + chemo; n = 12, nivo + chemo). Chemo, chemotherapy; dom, domvanalimab; ITT, intent-to-treat; nivo, nivolumab; OS, overall survival; OS_{ITT}, OS in the ITT population; $OS_{PD\text{-}L1\text{–}high}$, OS in the PD-L1–high (TAP ≥ 5%) population; $OS_{PD\text{-}L1\text{–}positive}$, OS in the PD-L1–positive (TAP ≥ 1%) population; PD-L1, programmed death ligand 1; PFS, progression-free survival; TAP, tumor area positivity; TTD, time to first deterioration; zim, zimberelimab.

Demographics and Baseline Characteristics

Characteristics	ITT		PD-L1–high (TAP ≥ 5%)		PD-L1–positive (TAP ≥ 1%)	
	Dom + zim + chemo (n = 521)	Nivo + chemo (n = 519)	Dom + zim + chemo (n = 250)	Nivo + chemo (n = 251)	Dom + zim + chemo (n = 413)	Nivo + chemo (n = 419)
Median age (range), years	62 (24–89)	63 (23–86)	63 (28–87)	63 (23–82)	62 (24–87)	63 (23–86)
Sex, male	356 (68)	357 (69)	171 (68)	184 (73)	280 (68)	294 (70)
Race						
Asian	133 (26)	132 (25)	59 (24)	61 (24)	104 (25)	103 (25)
Black or African American	14 (3)	6 (1)	8 (3)	5 (2)	13 (3)	6 (1)
White	287 (55)	297 (57)	127 (51)	141 (56)	219 (53)	236 (56)
Other/not specified[a]	87 (17)	84 (16)	56 (22)	44 (18)	77 (19)	74 (18)
Region						
Asia	129 (25)	129 (25)	58 (23)	59 (24)	102 (25)	100 (24)
Canada/EU5/US	125 (24)	122 (24)	58 (23)	57 (23)	100 (24)	100 (24)
Rest of world	267 (51)	268 (52)	134 (54)	135 (54)	211 (51)	219 (52)
ECOG PS 0 or 1	520 (> 99)	518 (> 99)	250 (100)	250 (> 99)	413 (100)	418 (> 99)
PD-L1 status[b]						
PD-L1–negative (TAP < 1%)	105 (20)	99 (19)	–	–	–	–
PD-L1–positive (TAP ≥ 1%)	413 (79)	419 (81)	–	–	–	–
PD-L1–high (TAP ≥ 5%)	250 (48)	251 (48)	–	–	–	–
Histologically confirmed diagnosis						
GC	386 (74)	375 (72)	186 (74)	178 (71)	294 (71)	297 (71)
GEJC	90 (17)	91 (18)	43 (17)	50 (20)	80 (19)	80 (19)
EAC	45 (9)	53 (10)	21 (8)	23 (9)	39 (9)	42 (10)
Disease stage – metastatic	498 (96)	498 (96)	236 (94)	245 (98)	395 (96)	406 (97)
Prior surgery received – yes	91 (17)	87 (17)	39 (16)	36 (14)	60 (15)	59 (14)
Chemotherapy regimen received						
FOLFOX	354 (68)	350 (67)	179 (72)	170 (68)	282 (68)	284 (68)
CAPOX	162 (31)	157 (30)	71 (28)	75 (30)	128 (31)	124 (30)

All values are n (%) unless otherwise indicated. [a]Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiracial, not reported, and unknown. [b]PD-L1 was assessed using the VENTANA PD-L1 (SP263) Companion Diagnostic assay. Samples were scored using TAP, defined as the total percentage of the tumor area covered by tumor cells with PD-L1 membrane staining at any intensity and tumor-associated immune cells with PD-L1 staining at any intensity.[1]

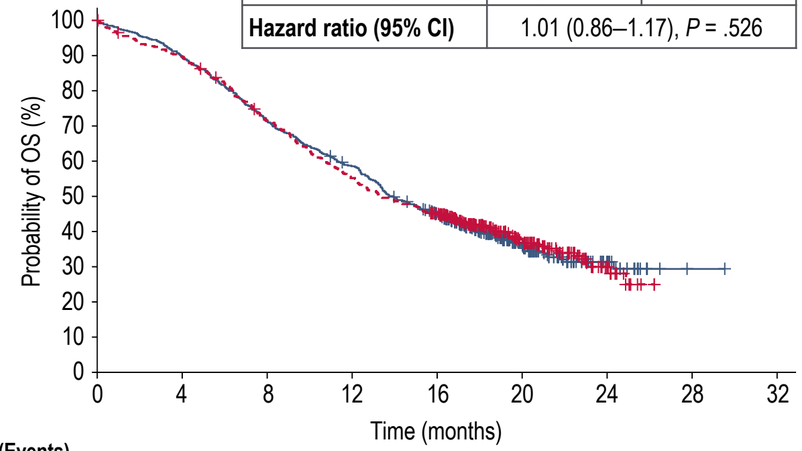
1. Liu C, et al. *Diagn Pathol*. 2023;18:48.

CAPOX, capecitabine and oxaliplatin; chemo, chemotherapy; dom, domvanalimab; EAC, esophageal adenocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EU5, European Union 5; FOLFOX, oxaliplatin, leucovorin, fluorouracil; GC, gastric cancer; GEJC, gastroesophageal junction carcinoma; ITT, intent-to-treat; nivo, nivolumab; PD-L1, programmed death ligand 1; TAP, tumor area positivity; US, United States; zim, zimberelimab.

Overall Survival

ITT Population

	Dom + zim + chemo	Nivo + chemo
mOS, months (95% CI)	14.0 (13.1–15.7)	13.4 (12.3–15.4)
Hazard ratio (95% CI)	1.01 (0.86–1.17), *P* = .526	

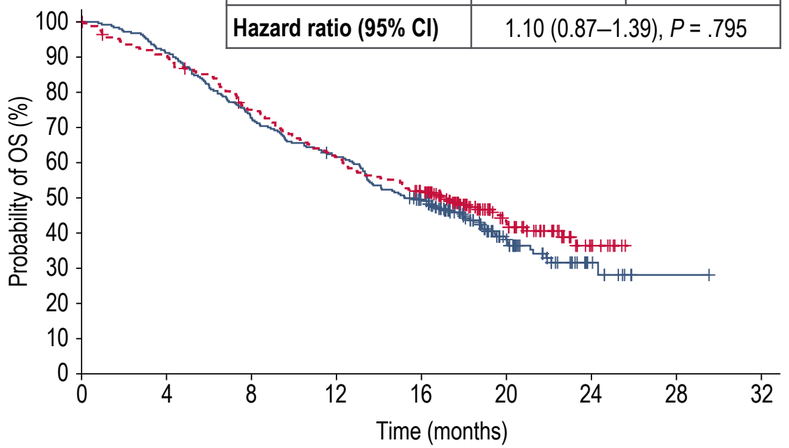


N at Risk (Events)

Dom + zim + chemo	521 (0)	469 (52)	374 (147)	304 (215)	221 (286)	91 (320)	21 (329)	1 (330)	0 (330)
Nivo + chemo	519 (0)	466 (51)	368 (146)	284 (230)	222 (283)	90 (310)	17 (320)	0 (322)	

PD-L1–high (TAP ≥ 5%)

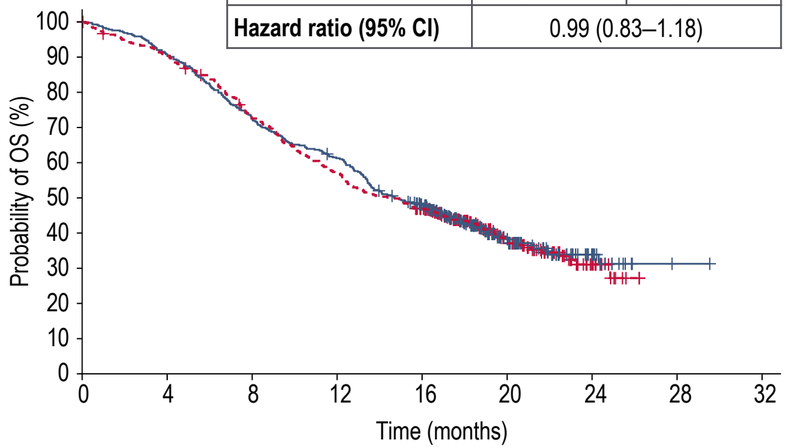
	Dom + zim + chemo	Nivo + chemo
mOS, months (95% CI)	15.2 (13.4–18.3)	17.2 (13.3–19.9)
Hazard ratio (95% CI)	1.10 (0.87–1.39), *P* = .795	



Dom + zim + chemo	250 (0)	228 (22)	182 (68)	153 (96)	117 (126)	45 (146)	10 (152)	1 (153)	0 (153)
Nivo + chemo	251 (0)	225 (24)	184 (63)	151 (96)	123 (119)	49 (134)	9 (138)	0 (138)	

PD-L1–positive (TAP ≥ 1%)

	Dom + zim + chemo	Nivo + chemo
mOS, months (95% CI)	14.7 (13.4–17.1)	14.7 (12.3–16.9)
Hazard ratio (95% CI)	0.99 (0.83–1.18)	



Dom + zim + chemo	413 (0)	375 (38)	300 (113)	252 (160)	186 (214)	70 (243)	17 (249)	1 (250)	0 (250)
Nivo + chemo	419 (0)	378 (39)	300 (114)	235 (179)	186 (220)	73 (245)	15 (253)	0 (254)	

- There was no OS benefit with dom + zim + chemo versus nivo + chemo in any of the 3 analysis populations
- Per testing procedure, statistical significance for OS was not assessed in the PD-L1–positive population

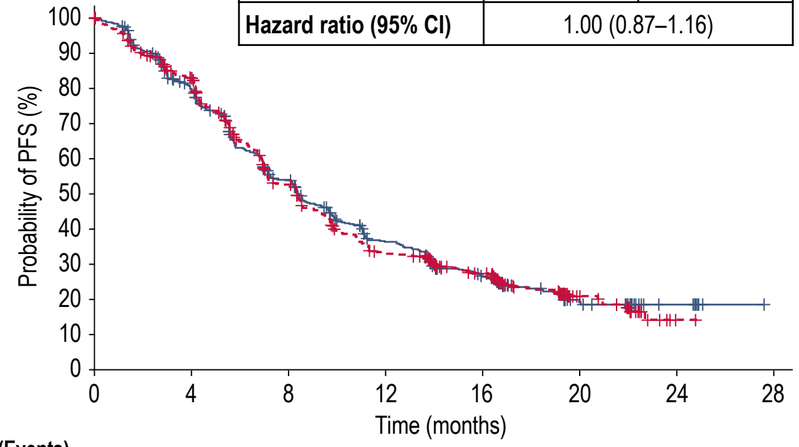
Median OS follow-up (ITT population): dom + zim + chemo, 13.7 months; nivo + chemo, 13.2 months

Chemo, chemotherapy; CI, confidence interval; dom, domvanalimab; ITT, intent-to-treat; mOS, median overall survival; nivo, nivolumab; OS, overall survival; PD-L1, programmed death ligand 1; TAP, tumor area positivity; zim, zimberelimab.

Progression-Free Survival

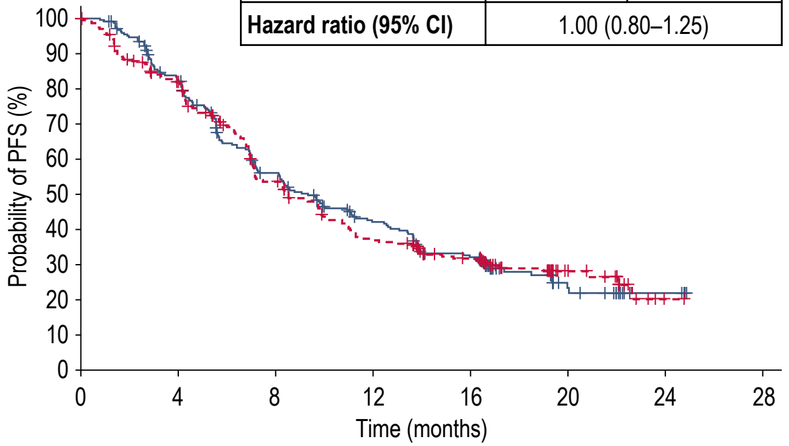
ITT Population

	Dom + zim + chemo	Nivo + chemo
mPFS, months (95% CI)	8.4 (7.3–9.6)	8.3 (7.2–9.0)
Hazard ratio (95% CI)	1.00 (0.87–1.16)	



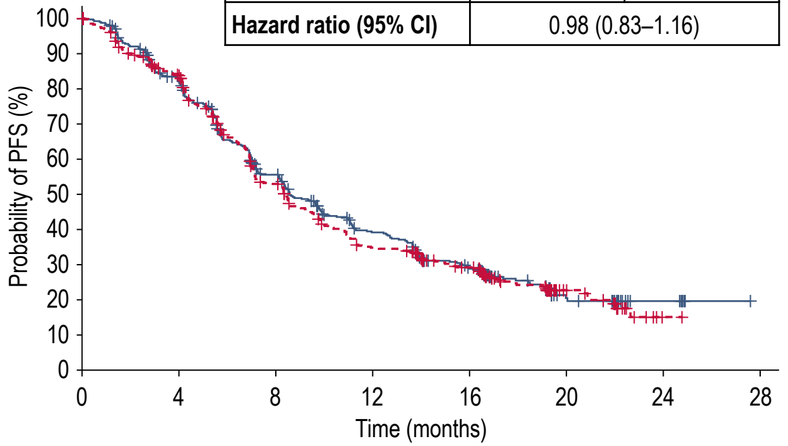
PD-L1–high (TAP ≥ 5%)

	Dom + zim + chemo	Nivo + chemo
mPFS, months (95% CI)	9.3 (7.3–11.2)	8.5 (7.1–10.2)
Hazard ratio (95% CI)	1.00 (0.80–1.25)	



PD-L1–positive (TAP ≥ 1%)

	Dom + zim + chemo	Nivo + chemo
mPFS, months (95% CI)	8.6 (8.1–9.9)	8.4 (7.1–9.4)
Hazard ratio (95% CI)	0.98 (0.83–1.16)	



N at Risk (Events)

Dom + zim + chemo	521 (0)	392 (101)	250 (225)	156 (304)	100 (345)	28 (363)	8 (364)	0 (364)
Nivo + chemo	519 (0)	403 (85)	240 (227)	143 (315)	99 (337)	28 (355)	1 (361)	0 (361)

Dom + zim + chemo	250 (0)	196 (42)	124 (103)	86 (133)	59 (153)	16 (163)	4 (164)	0 (164)
Nivo + chemo	251 (0)	190 (43)	117 (106)	77 (141)	56 (151)	19 (156)	1 (159)	0 (159)

Dom + zim + chemo	413 (0)	320 (71)	203 (172)	133 (230)	87 (264)	24 (280)	7 (281)	0 (281)
Nivo + chemo	419 (0)	326 (65)	194 (181)	122 (246)	86 (264)	26 (279)	1 (285)	0 (285)

- There was no PFS benefit with dom + zim + chemo versus nivo + chemo in any of the 3 analysis populations
- Per testing procedure, statistical significance was not assessed for PFS

Chemo, chemotherapy; CI, confidence interval; dom, domvanalimab; ITT, intent-to-treat; mPFS, median progression-free survival; nivo, nivolumab; PD-L1, programmed death ligand 1; PFS, progression-free survival; TAP, tumor area positivity; zim, zimberelimab.

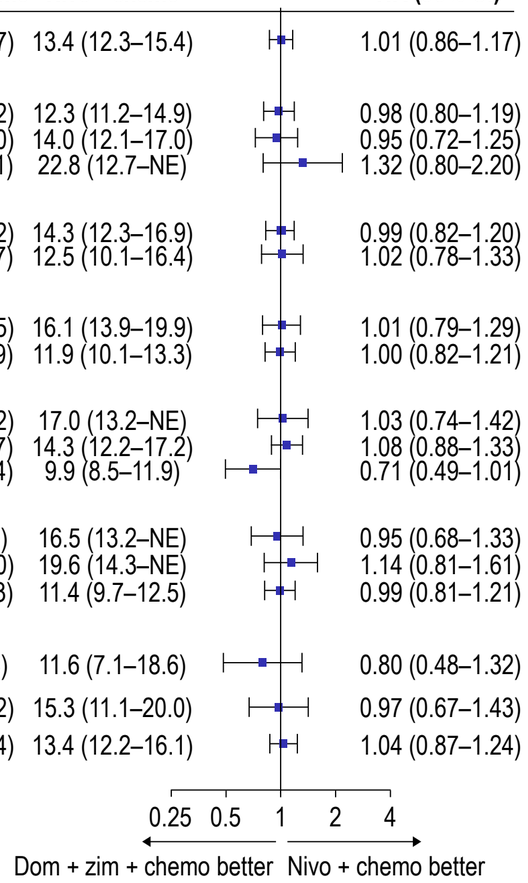
Objective Response Rate and Duration of Response

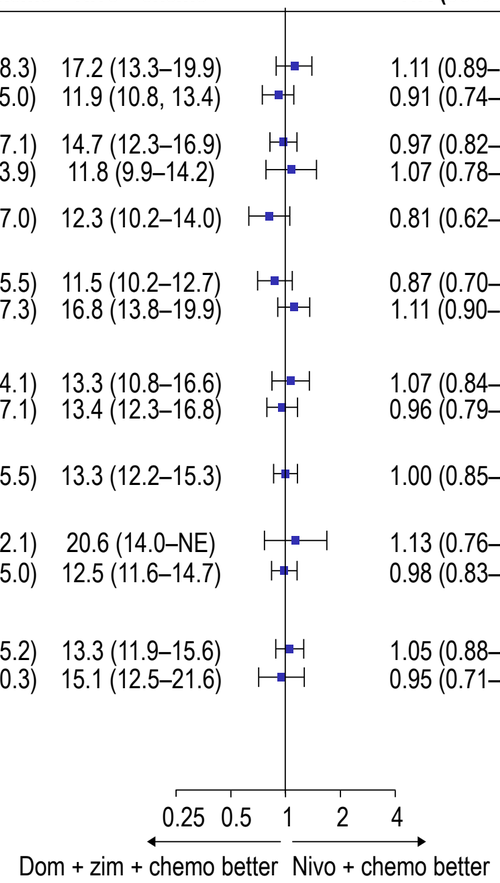
	ITT		PD-L1–high (TAP ≥ 5%)		PD-L1–positive (TAP ≥ 1%)	
	Dom + zim + chemo (n = 521)	Nivo + chemo (n = 519)	Dom + zim + chemo (n = 250)	Nivo + chemo (n = 251)	Dom + zim + chemo (n = 413)	Nivo + chemo (n = 419)
ORR, n (%)	284 (55)	291 (56)	147 (59)	148 (59)	242 (59)	239 (57)
95% CI	50.1–58.8	51.7–60.4	52.4–65.0	52.6–65.1	53.7–63.4	52.1–61.8
CR, n (%)[a]	17 (3)	19 (4)	13 (5)	11 (4)	15 (4)	14 (3)
PR, n (%)[a]	267 (51)	272 (52)	134 (54)	137 (55)	227 (55)	225 (54)
SD, n (%)	180 (35)	160 (31)	87 (35)	67 (27)	132 (32)	127 (30)
PD, (%)	29 (6)	23 (4)	7 (3)	16 (6)	20 (5)	19 (5)
NE, n (%)[b]	28 (5)	45 (9)	9 (4)	20 (8)	19 (5)	34 (8)
Median DOR (95% CI), mo	10.5 (9.5–12.4)	9.5 (8.1–11.2)	12.1 (9.8–15.2)	11.1 (8.6–19.3)	11.0 (9.7–13.6)	9.6 (8.1–12.4)

[a]Confirmed response assessed according to RECIST v1.1. [b]Includes responses that are NE or NA. Chemo, chemotherapy; CI, confidence interval; CR, complete response; dom, domvanalimab; DOR, duration of response; ITT, intent-to-treat; NA, not assessed; NE, not evaluable; nivo, nivolumab; ORR, objective response rate; PD, progressive disease; PD-L1, programmed death ligand 1; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; TAP, tumor area positivity; zim, zimberelimab.

Overall Survival – Subgroup Analysis (ITT)

Subgroup	n	Median OS, months (95% CI) Dom + zim + chemo	Nivo + chemo	HR (95% CI)
Overall	1040	14.0 (13.1–15.7)	13.4 (12.3–15.4)	1.01 (0.86–1.17)
Age group				
< 65 years	594	13.7 (12.6–15.2)	12.3 (11.2–14.9)	0.98 (0.80–1.19)
≥ 65 to 75 years	327	14.6 (12.2–18.0)	14.0 (12.1–17.0)	0.95 (0.72–1.25)
≥ 75 years	119	16.3 (11.3–22.1)	22.8 (12.7–NE)	1.32 (0.80–2.20)
Sex				
Male	713	14.6 (13.3–16.2)	14.3 (12.3–16.9)	0.99 (0.82–1.20)
Female	327	12.9 (11.2–16.7)	12.5 (10.1–16.4)	1.02 (0.78–1.33)
ECOG PS at randomization				
0	452	16.8 (14.0–19.5)	16.1 (13.9–19.9)	1.01 (0.79–1.29)
1	587	12.6 (11.1–13.9)	11.9 (10.1–13.3)	1.00 (0.82–1.21)
Race				
Asian	265	16.7 (13.7–20.2)	17.0 (13.2–NE)	1.03 (0.74–1.42)
White	584	13.4 (11.3–15.7)	14.3 (12.2–17.2)	1.08 (0.88–1.33)
Other	171	13.4 (11.5–16.4)	9.9 (8.5–11.9)	0.71 (0.49–1.01)
Geographic region of enrollment				
Asia	258	17.6 (14.1–NE)	16.5 (13.2–NE)	0.95 (0.68–1.33)
Canada/EU5/US	247	16.8 (13.6–21.0)	19.6 (14.3–NE)	1.14 (0.81–1.61)
Rest of world	535	11.8 (10.0–13.3)	11.4 (9.7–12.5)	0.99 (0.81–1.21)
Histologically confirmed diagnosis				
Esophageal adenocarcinoma	98	16.4 (6.7–21.3)	11.6 (7.1–18.6)	0.80 (0.48–1.32)
Gastroesophageal junction adenocarcinoma	181	14.7 (12.4–20.2)	15.3 (11.1–20.0)	0.97 (0.67–1.43)
Gastric adenocarcinoma	761	13.6 (12.7–15.4)	13.4 (12.2–16.1)	1.04 (0.87–1.24)
PD-L1 expression				
PD-L1–high (TAP ≥ 5%)	501	15.2 (13.4–18.3)	17.2 (13.3–19.9)	1.11 (0.89–1.40)
PD-L1–low (TAP < 5%)	539	13.2 (11.6–15.0)	11.9 (10.8, 13.4)	0.91 (0.74–1.12)
PD-L1–positive (TAP ≥ 1%)	832	14.7 (13.4–17.1)	14.7 (12.3–16.9)	0.97 (0.82–1.16)
PD-L1–negative (TAP < 1%)	204	11.2 (10.1–13.9)	11.8 (9.9–14.2)	1.07 (0.78–1.49)
TAP ≥ 1% and TAP < 5%	337	13.7 (12.4–17.0)	12.3 (10.2–14.0)	0.81 (0.62–1.06)
Peritoneal metastasis at baseline				
Yes	436	13.5 (12.3–15.5)	11.5 (10.2–12.7)	0.87 (0.70–1.10)
No	604	14.4 (13.1–17.3)	16.8 (13.8–19.9)	1.11 (0.90–1.37)
Liver metastasis at baseline				
Yes	399	13.1 (10.9–14.1)	13.3 (10.8–16.6)	1.07 (0.84–1.36)
No	641	15.4 (13.3–17.1)	13.4 (12.3–16.8)	0.96 (0.79–1.17)
Disease stage at baseline				
Metastatic	996	13.9 (13.1–15.5)	13.3 (12.2–15.3)	1.00 (0.85–1.17)
Prior anticancer surgery				
Yes	178	16.7 (13.6–22.1)	20.6 (14.0–NE)	1.13 (0.76–1.69)
No	862	13.4 (12.4–15.0)	12.5 (11.6–14.7)	0.98 (0.83–1.16)
Actual chemotherapy received				
FOLFOX	704	13.5 (12.6–15.2)	13.3 (11.9–15.6)	1.05 (0.88–1.26)
CAPOX	319	16.7 (12.8–20.3)	15.1 (12.5–21.6)	0.95 (0.71–1.27)





CAPOX, capecitabine and oxaliplatin; chemo, chemotherapy; CI, confidence interval; dom, domvanalimab; ECOG PS, Eastern Cooperative Oncology Group performance status; EU5, European Union 5; FOLFOX, oxaliplatin, leucovorin, fluorouracil; HR, hazard ratio; ITT, intent-to-treat; NE, not estimable; nivo, nivolumab; OS, overall survival; PD-L1, programmed death ligand 1; TAP, tumor area positivity; US, United States; zim, zimberelimab.

Safety Summary

	Dom + zim + chemo[a] (n = 522)	Nivo + chemo (n = 507)
Median treatment duration (range), months	7.5 (0.1–25.9)	7.1 (0–25.1)
All-grade AEs	512 (98)	494 (97)
Grade 3–4 AEs	331 (63)	321 (63)
All-grade serious AEs	197 (38)	207 (41)
All-grade AEs leading to death	32 (6)	39 (8)
All-grade AEs leading to interruption of any study drug	380 (73)	392 (77)
AEs leading to interruption of dom, zim, or nivo	318 (61)	332 (65)
All-grade AEs leading to discontinuation of any study drug	253 (48)	236 (47)
AEs leading to discontinuation of dom, zim, or nivo	40 (8)	42 (8)
All-grade infusion-related reactions	80 (15)	138 (27)
All-grade immune-mediated AEs	116 (22)	122 (24)

All values are n (%) unless otherwise specified. [a]The safety analysis population included 6 patients from the Japanese safety run-in cohort.
AE, adverse event; chemo, chemotherapy; dom, domvanalimab; nivo, nivolumab; zim, zimberelimab.

Immune-Mediated Adverse Events and Infusion-Related Reactions

	Dom + zim + chemo[a] (n = 522)		Nivo + chemo (n = 507)	
Treatment-emergent adverse events, n (%)	**Any grade**	**Grade 3–4**	**Any grade**	**Grade 3–4**
Immune-mediated adverse event[b]	116 (22)	35 (7)	122 (24)	33 (7)
Most common (> 5 patients in any treatment group)				
Hypothyroidism	51 (10)	1 (< 1)	42 (8)	1 (< 1)
Pneumonitis	19 (4)	2 (< 1)	36 (7)	9 (2)
Hyperthyroidism	17 (3)	0	19 (4)	0 (0)
Colitis	12 (2)	5 (1)	6 (1)	3 (1)
Adrenal insufficiency	7 (1)	2 (< 1)	5 (1)	0
Immune-mediated enterocolitis	7 (1)	4 (1)	1 (< 1)	1 (< 1)
Immune-mediated hepatitis	2 (< 1)	2 (< 1)	7 (1)	6 (1)
Hepatitis	1 (< 1)	1 (< 1)	7 (1)	3 (1)
Infusion-related reactions[c]	80 (15)	15 (3)	138 (27)	15 (3)
Most common (> 5 patients in any treatment group)				
Infusion related reaction	25 (5)	4 (1)	37 (7)	0
Pyrexia	18 (3)	3 (1)	44 (9)	1 (< 1)
Abdominal pain	13 (2)	0	8 (2)	2 (< 1)
Chills	9 (2)	0	14 (3)	0
Hypersensitivity	6 (1)	2 (< 1)	11 (2)	2 (< 1)
Back pain	6 (1)	0	7 (1)	1 (< 1)
Dyspnea	6 (1)	2 (< 1)	5 (1)	0
Rash	4 (1)	0	13 (3)	1 (< 1)
Pruritus	3 (1)	0	19 (4)	0
Drug hypersensitivity	3 (1)	1 (< 1)	8 (2)	5 (1)
Hypotension	1 (< 1)	0	7 (1)	1 (< 1)

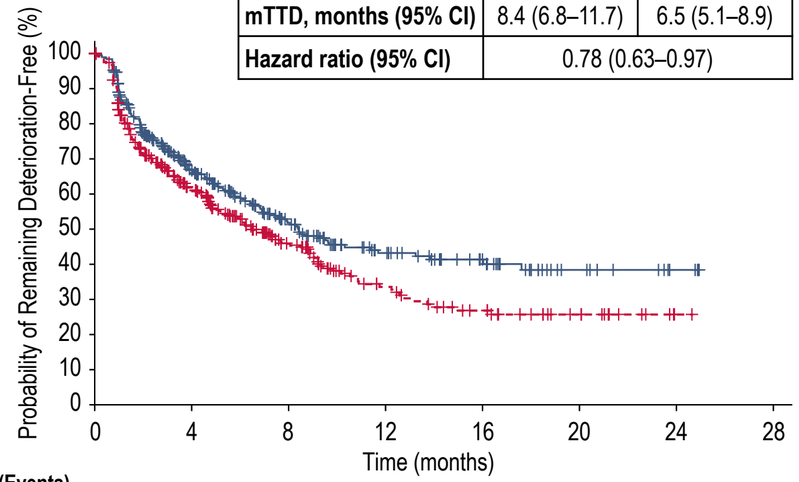
[a]The safety analysis population included 6 patients from the Japanese safety run-in cohort. [b]AEs of any grade in the custom PD-1 immune-related AE search list (search name, "PD-1 Immune-related adverse events") except for the preferred terms contained in the search list with search name "PD-1 Skin toxicities" where only grade ≥ 3 AEs were included. [c]AEs in the custom IRR search list (search name, "PD-1 Infusion Related Reactions") that occurred within 24 hours of the end of a study drug infusion administration and the event was 2 days or less in duration.

AE, adverse event; chemo, chemotherapy; dom, domvanalimab; IRR, infusion-related reaction; nivo, nivolumab; PD-1, programmed cell death protein 1; zim, zimberelimab.

Time to First Deterioration in HRQoL by FACT-Ga

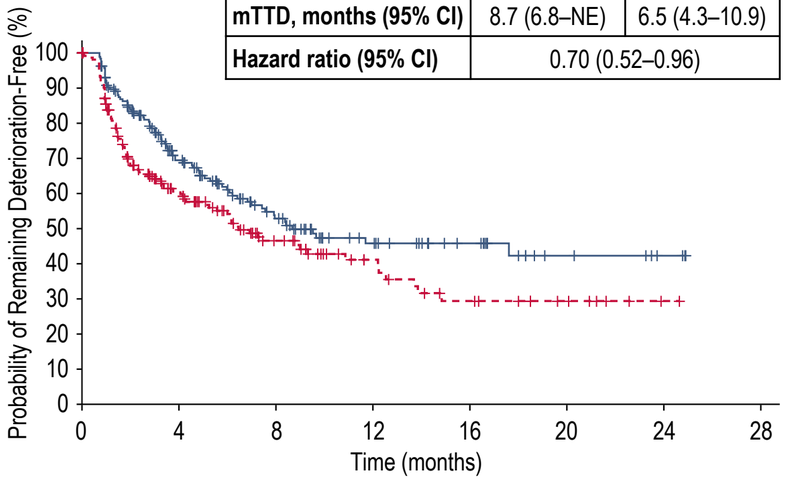
ITT Population

	Dom + zim + chemo	Nivo + chemo
mTTD, months (95% CI)	8.4 (6.8–11.7)	6.5 (5.1–8.9)
Hazard ratio (95% CI)	0.78 (0.63–0.97)	



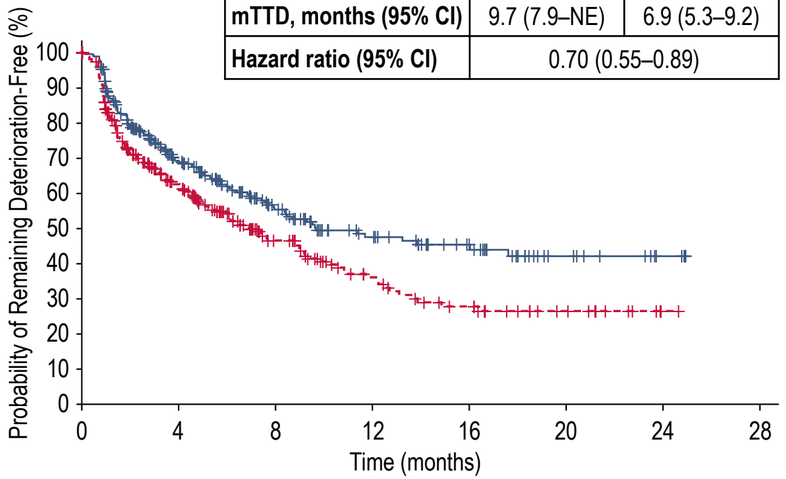
PD-L1–high (TAP ≥ 5%)

	Dom + zim + chemo	Nivo + chemo
mTTD, months (95% CI)	8.7 (6.8–NE)	6.5 (4.3–10.9)
Hazard ratio (95% CI)	0.70 (0.52–0.96)	



PD-L1–positive (TAP ≥ 1%)

	Dom + zim + chemo	Nivo + chemo
mTTD, months (95% CI)	9.7 (7.9–NE)	6.9 (5.3–9.2)
Hazard ratio (95% CI)	0.70 (0.55–0.89)	



N at Risk (Events)

Dom + zim + chemo	521 (0)	188 (114)	99 (150)	53 (164)	33 (166)	12 (168)	4 (168)	0 (168)
Nivo + chemo	519 (0)	186 (137)	85 (177)	42 (196)	26 (204)	13 (205)	1 (205)	0 (205)

Dom + zim + chemo	250 (0)	100 (52)	55 (72)	30 (78)	18 (78)	7 (79)	3 (79)	0 (79)
Nivo + chemo	251 (0)	82 (68)	41 (84)	22 (88)	13 (94)	7 (94)	1 (94)	0 (94)

Dom + zim + chemo	413 (0)	156 (84)	84 (110)	49 (120)	32 (122)	12 (124)	4 (124)	0 (124)
Nivo + chemo	419 (0)	150 (110)	68 (141)	37 (154)	23 (162)	11 (163)	1 (163)	0 (163)

Per testing procedure, statistical significance was not assessed for TTD

Chemo, chemotherapy; CI, confidence interval; dom, domvanalimab; FACT-Ga, Functional Assessment of Cancer Therapy – Gastric; HRQoL, health-related quality of life; ITT, intent-to-treat; mTTD, median time to first deterioration; NE, not estimable; nivo, nivolumab; PD-L1, programmed death ligand 1; TAP, tumor area positivity; TTD, time to first deterioration; zim, zimberelimab.

Conclusions

- Dom + zim + chemo did not improve OS in comparison with nivo + chemo in any of the 3 analysis populations (ITT, PD-L1–high, or PD-L1–positive)
- The safety profile of dom + zim + chemo was consistent with the known safety profile of anti–PD-(L)1 + chemo, and the safety profile was similar in both study arms
  - No new safety concerns were identified from the dom + zim + chemo combination
  - These findings suggest that safety did not contribute to the lack of any additional clinical benefit with dom + zim + chemo compared with nivo + chemo
- TTD by FACT-Ga was numerically longer with dom + zim + chemo than with nivo + chemo across all 3 analysis populations, but statistical significance was not assessed for TTD per the testing procedure
- In this study, there was no clear analysis population with particular benefit from the dom + zim + chemo combination for patients with advanced gastroesophageal adenocarcinoma

Chemo, chemotherapy; dom, domvanalimab; FACT-Ga, Functional Assessment of Cancer Therapy – Gastric; ITT, intent-to-treat; nivo, nivolumab; OS, overall survival; PD-1, programmed cell death protein 1; PD-(L)1, PD-1 and PD-L1; PD-L1, programmed death ligand 1; TTD, time to first deterioration; zim, zimberelimab.

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Annual Congress

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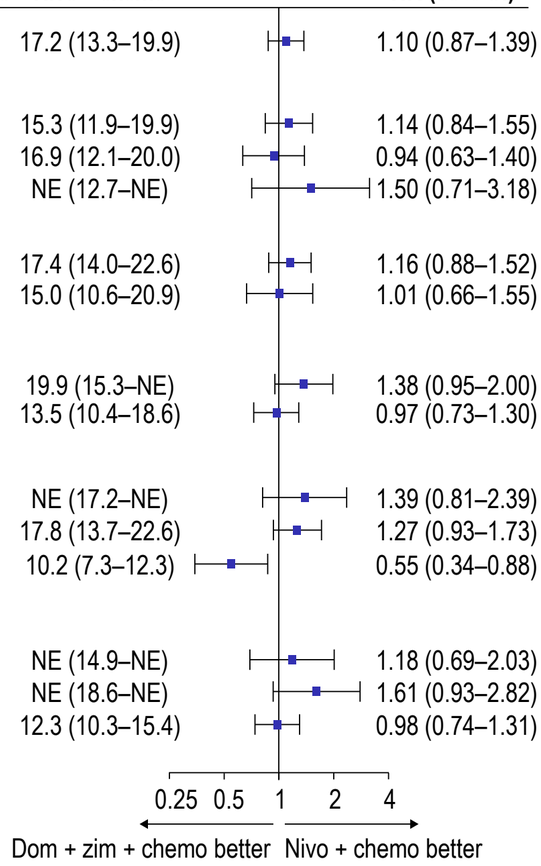
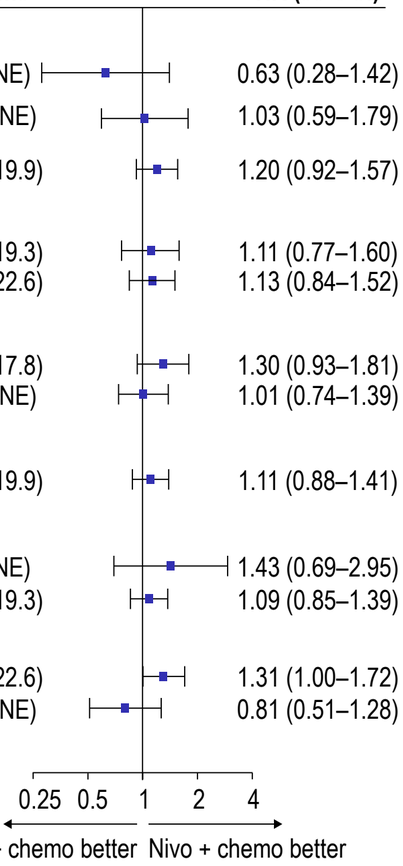
Backup

Overall Survival – Subgroup Analysis (PD-L1–High)

Subgroup	n	Median OS, months (95% CI): Dom + zim + chemo	Median OS, months (95% CI): Nivo + chemo	HR (95% CI)
Overall	501	15.2 (13.4–18.3)	17.2 (13.3–19.9)	1.10 (0.87–1.39)
Age group				
< 65 years	269	14.1 (12.6–18.0)	15.3 (11.9–19.9)	1.14 (0.84–1.55)
≥ 65 to 75 years	168	16.4 (13.1–21.1)	16.9 (12.1–20.0)	0.94 (0.63–1.40)
≥ 75 years	64	22.1 (10.5–NE)	NE (12.7–NE)	1.50 (0.71–3.18)
Sex				
Male	355	15.2 (13.4–18.8)	17.4 (14.0–22.6)	1.16 (0.88–1.52)
Female	146	16.7 (11.5–20.0)	15.0 (10.6–20.9)	1.01 (0.66–1.55)
ECOG PS at randomization				
0	209	17.3 (13.5–20.0)	19.9 (15.3–NE)	1.38 (0.95–2.00)
1	292	13.7 (11.6–18.3)	13.5 (10.4–18.6)	0.97 (0.73–1.30)
Race				
Asian	120	19.1 (13.7–NE)	NE (17.2–NE)	1.39 (0.81–2.39)
White	268	14.6 (9.4–18.7)	17.8 (13.7–22.6)	1.27 (0.93–1.73)
Other	100	14.6 (12.8–19.4)	10.2 (7.3–12.3)	0.55 (0.34–0.88)
Geographic region of enrollment				
Asia	117	19.5 (14.7–NE)	NE (14.9–NE)	1.18 (0.69–2.03)
Canada/EU5/US	115	18.0 (13.4–24.3)	NE (18.6–NE)	1.61 (0.93–2.82)
Rest of world	269	13.2 (10.5–15.7)	12.3 (10.3–15.4)	0.98 (0.74–1.31)



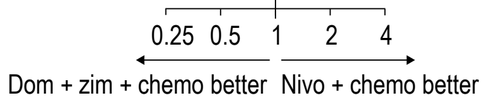
Subgroup	n	Median OS, months (95% CI): Dom + zim + chemo	Median OS, months (95% CI): Nivo + chemo	HR (95% CI)
Histologically confirmed diagnosis				
Esophageal adenocarcinoma	44	20.0 (16.1–NE)	12.3 (6.4–NE)	0.63 (0.28–1.42)
Gastroesophageal junction adenocarcinoma	93	16.7 (10.5–NE)	20.0 (10.7–NE)	1.03 (0.59–1.79)
Gastric adenocarcinoma	364	14.1 (12.8–18.0)	17.2 (13.3–19.9)	1.20 (0.92–1.57)
Peritoneal metastasis at baseline				
Yes	185	13.6 (11.2–18.0)	12.9 (10.7–19.3)	1.11 (0.77–1.60)
No	316	16.4 (13.4–19.4)	19.4 (15.1–22.6)	1.13 (0.84–1.52)
Liver metastasis at baseline				
Yes	211	13.1 (9.5–14.1)	15.1 (10.8–17.8)	1.30 (0.93–1.81)
No	290	19.4 (15.7–21.9)	19.9 (12.9–NE)	1.01 (0.74–1.39)
Disease stage at baseline				
Metastatic	481	15.2 (13.4–18.7)	16.9 (13.3–19.9)	1.11 (0.88–1.41)
Prior anticancer surgery				
Yes	75	22.1 (13.4–NE)	NE (17.4–NE)	1.43 (0.69–2.95)
No	426	14.7 (12.7–18.0)	15.1 (12.3–19.3)	1.09 (0.85–1.39)
Actual chemotherapy received				
FOLFOX	349	14.1 (12.8–16.6)	17.3 (13.3–22.6)	1.31 (1.00–1.72)
CAPOX	146	19.5 (13.3–NE)	18.2 (10.6–NE)	0.81 (0.51–1.28)



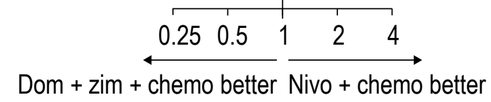
CAPOX, capecitabine and oxaliplatin; chemo, chemotherapy; CI, confidence interval; dom, domvanalimab; ECOG PS, Eastern Cooperative Oncology Group performance status; EU5, European Union 5; FOLFOX, oxaliplatin, leucovorin, fluorouracil; HR, hazard ratio; NE, not estimable; nivo, nivolumab; OS, overall survival; PD-L1, programmed death ligand 1; US, United States; zim, zimberelimab.

Overall Survival – Subgroup Analysis (PD-L1–Positive)

Subgroup	n	Median OS, months (95% CI): Dom + zim + chemo	Median OS, months (95% CI): Nivo + chemo	HR (95% CI)
Overall	832	14.7 (13.4–17.1)	14.7 (12.3–16.9)	0.99 (0.83–1.18)
Age group				
< 65 years	467	13.7 (12.6–16.2)	12.3 (10.9–15.3)	0.96 (0.76–1.20)
≥ 65 to 75 years	269	17.3 (13.3–20.0)	15.6 (12.5–18.6)	0.90 (0.66–1.22)
≥ 75 years	96	16.7 (12.3–NE)	22.8 (12.7–NE)	1.24 (0.69–2.23)
Sex				
Male	574	14.7 (13.4–17.7)	15.1 (12.5–17.4)	0.98 (0.79–1.21)
Female	258	13.6 (12.1–18.0)	12.7 (10.1–19.4)	0.97 (0.71–1.32)
ECOG PS at randomization				
0	359	17.3 (14.6–20.0)	16.6 (14.9–20.6)	1.04 (0.79–1.38)
1	473	13.3 (11.6–15.7)	12.5 (10.4–15.1)	0.94 (0.75–1.18)
Race				
Asian	207	17.6 (14.4–NE)	19.6 (15.1–NE)	1.09 (0.74–1.60)
White	455	14.0 (12.3–17.1)	15.3 (12.2–18.5)	1.05 (0.83–1.32)
Other	151	13.4 (12.1–17.8)	10.0 (8.3–12.1)	0.64 (0.44–0.94)
Geographic region of enrollment				
Asia	202	19.5 (14.7–NE)	18.7 (13.8–NE)	0.96 (0.65–1.42)
Canada/EU5/US	200	16.8 (13.5–21.3)	20.6 (16.1–NE)	1.27 (0.86–1.88)
Rest of world	430	12.7 (10.2–14.1)	11.4 (9.3–12.7)	0.90 (0.72–1.13)



Subgroup	n	Median OS, months (95% CI): Dom + zim + chemo	Median OS, months (95% CI): Nivo + chemo	HR (95% CI)
Histologically confirmed diagnosis				
Esophageal adenocarcinoma	81	16.4 (6.7–21.3)	12.3 (6.8–20.6)	0.86 (0.49–1.51)
Gastroesophageal junction adenocarcinoma	160	14.7 (11.6–NE)	15.3 (11.2–22.6)	0.97 (0.64–1.46)
Gastric adenocarcinoma	591	14.6 (13.2–17.1)	14.0 (12.3–17.2)	0.99 (0.81–1.22)
Peritoneal metastasis at baseline				
Yes	328	13.6 (12.4–16.6)	11.9 (10.2–13.2)	0.86 (0.66–1.12)
No	504	16.2 (13.4–18.8)	16.9 (14.4–20.0)	1.07 (0.85–1.35)
Liver metastasis at baseline				
Yes	342	13.4 (11.2–14.9)	13.7 (10.8–16.9)	1.05 (0.81–1.37)
No	490	16.8 (14.0–20.0)	15.1 (12.3–19.4)	0.92 (0.73–1.16)
Disease stage at baseline				
Metastatic	801	14.7 (13.4–17.1)	14.0 (12.3–16.9)	0.97 (0.81–1.16)
Prior anticancer surgery				
Yes	119	18.7 (13.2–NE)	22.8 (15.1–NE)	1.21 (0.72–2.02)
No	713	14.1 (13.1–16.7)	13.2 (11.8–15.4)	0.95 (0.79–1.14)
Actual chemotherapy received				
FOLFOX	566	14.0 (13.0–16.2)	13.8 (11.9–16.9)	1.05 (0.85–1.29)
CAPOX	252	19.4 (13.6–NE)	18.2 (12.7–22.8)	0.89 (0.63–1.25)



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