

# RATIONALE-305

1L GC/GEJC



# RATIONALE-305 Trial Design



## Phase 3

Global

**Study Identifier:**  
BGB-A317-305, NCT03777657

**Primary Endpoint:** OS in PD-L1+ (PD-L1 score  $\geq 5\%$ <sup>a</sup>) and ITT analysis set  
**Key Secondary Endpoints:** PFS, ORR, DoR, DCR, CBR, HRQoL, safety

### Key eligibility criteria

- Histologically confirmed GC/GEJC
- HER2/neu-negative disease
- Measurable disease
- ECOG PS  $\leq 1$
- No previous therapy for locally advanced unresectable or metastatic GC/GEJC<sup>b</sup>
- No prior therapy with drug specifically targeting T-cell co-stimulation or checkpoint pathways

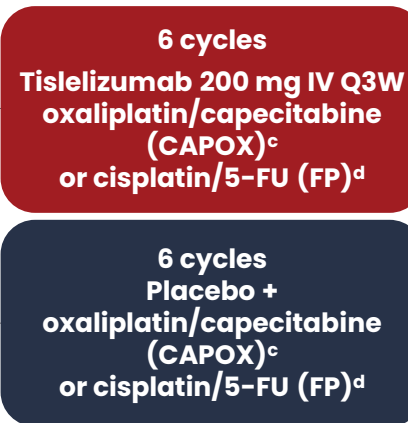
### Stratification factors

- Regions of enrollment
- Peritoneal metastasis
- PD-L1 score (PD-L1  $\geq 5\%$  vs  $< 5\%$ )
- Investigator's choice of chemo

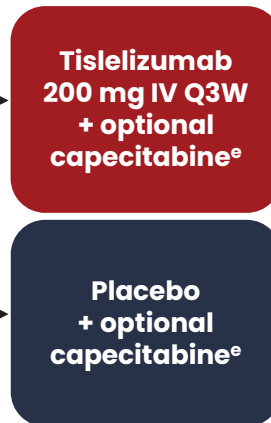
### Treatment

screening

R 1:1



### Maintenance



Treatment until unacceptable toxicity or disease progression

### Follow-up

Safety and survival

<sup>a</sup>PD-L1 score was determined using VENTANA SP263 assay; <sup>b</sup>Patients may have received prior neoadjuvant or adjuvant therapy as long as it was completed, and they have no recurrence or disease progression for at least 6 months; <sup>c</sup>Oxaliplatin 130 mg/m<sup>2</sup> Day 1 + capecitabine 1000 mg/m<sup>2</sup> BID Day 1-14, Q3W; <sup>d</sup>Cisplatin 80 mg/m<sup>2</sup> Day 1 + 5-FU 800 mg/m<sup>2</sup>/day CIV Day 1-5, Q3W. <sup>e</sup>Maintenance capecitabine was optional and was only permitted for patients who initially received CAPOX.

1L=1st line, 5-FU=5-fluorouracil, CBR=clinical benefit rate, DCR=disease control rate, DoR=duration of response, ECOG PS=Eastern Cooperative Oncology Group performance status, GC=gastric cancer, GEJC=gastroesophageal junction carcinoma, HER2=human epidermal growth factor receptor-2, HRQOL=health-related quality of life, ITT=intention-to-treat, IV=intravenous, ORR=objective response rate, OS=overall survival, PD-1=programmed cell death protein 1, PD-L1=programmed death-ligand 1, PFS=progression-free survival, Q3W=every 3 weeks, R=randomized, TTR=time to response.

Xu R-H et al. Oral presentation at ESMO 2023. Abstract LBA80; ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/NCT03777657>. Accessed October 9, 2025.

# Baseline Demographics and Disease Characteristics

	Tislelizumab + chemo (n=501)	Placebo + chemo (n=496)
<b>Median age (range), years</b>	60.0 (23.0–86.0)	61.0 (25.0–86.0)
<b>Male, n (%)</b>	346 (69.1)	346 (69.8)
<b>Region, n (%)</b>		
Asia*	376 (75.0)	372 (75.0)
Europe/North America	125 (25.0)	124 (25.0)
<b>ECOG PS 1, n (%)</b>	332 (66.3)	342 (69.0)
<b>Primary tumour location, n (%)</b>		
Stomach	405 (80.8)	395 (79.6)
GEJ	96 (19.2)	100 (20.2) <sup>†</sup>
<b>Metastatic disease, n (%)</b>	494 (98.6)	490 (98.8)
<b>Peritoneal metastasis, n (%)</b>	220 (43.9)	214 (43.1)
<b>Prior adjuvant/neoadjuvant treatment, n (%)</b>	107 (21.4)	100 (20.2)
<b>PD-L1 score, n (%)</b>		
<5%	227 (45.3)	224 (45.2)
≥5%	274 (54.7)	272 (54.8)
<b>Investigator-chosen chemotherapy, n (%)</b>		
Oxaliplatin/capecitabine	466 (93.0)	465 (93.8)
Cisplatin/5-fluorouracil	35 (7.0)	31 (6.3)

Data cutoff: 28 February 2023.

Minimum study follow-up time (defined as from the date of last patient randomized to the data cutoff): 24.6 months. Median study follow-up duration (defined as from randomization to data cutoff, death, or study discontinuation due to other reasons, whichever came first for all patients) was 13.2 months (IQR 7.1–24.6).

\*Asia comprises China (including Taiwan), Japan, and South Korea. <sup>†</sup>The diagnosis of one patient was updated from gastric adenocarcinoma to be pancreatic cancer after randomization and the patient remained in the ITT population.

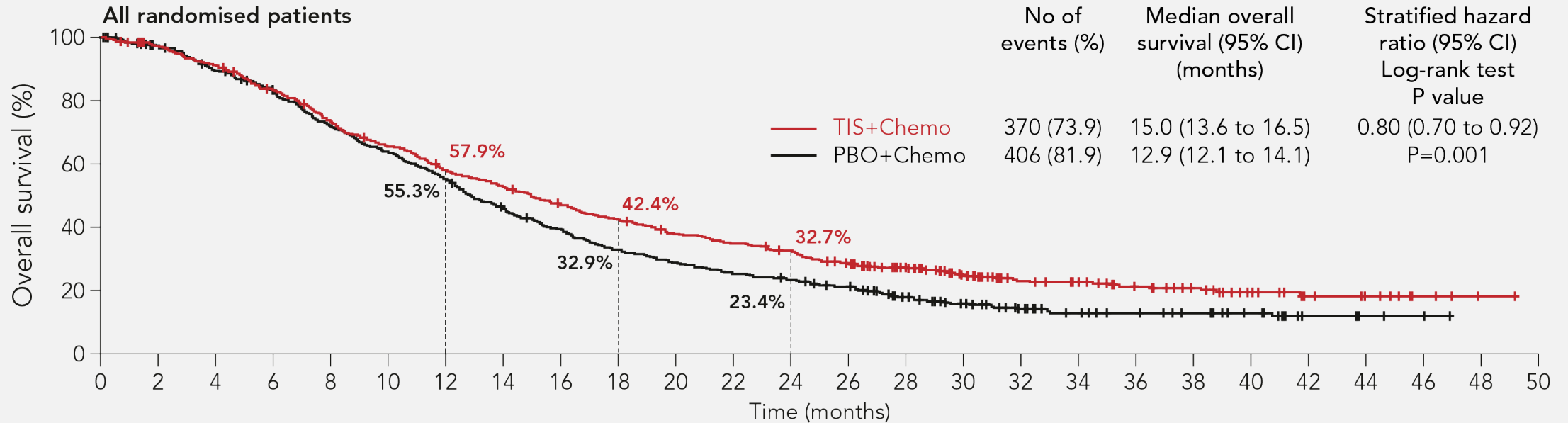
1L=1st line, Chemo=chemotherapy, ECOG PS=Eastern Cooperative Oncology Group performance status, GC=gastric cancer, GEJ=gastro-esophageal junction, IQR=interquartile range, ITT=intent-to-treat, PD-L1=programmed death-ligand 1.

Qiu M-Z et al. *BMJ*. 2024;385:e078876.

# Primary Endpoint: OS in ITT Population



Tislelizumab + chemo as first-line treatment of advanced GC/GEJC demonstrated a statistically significant and clinically meaningful improvement in OS over placebo + chemo in the ITT population at the **final analysis**



No at Risk

TIS+Chemo	501	477	445	404	355	316	278	254	226	202	179	165	152	130	107	77	59	53	43	31	22	13	10	4	1	0
PBO+Chemo	496	472	431	398	344	304	264	218	186	155	136	119	109	96	73	52	39	29	25	20	15	6	3	2	0	0

Data cutoff: 28 February 2023.

Log-rank and Cox regression models were stratified by regions (Asia vs Europe/North America), PD-L1 expression (ITT population analysis only), and presence of peritoneal metastasis. P-values are one-sided and based on the stratified log-rank test. P-value boundary

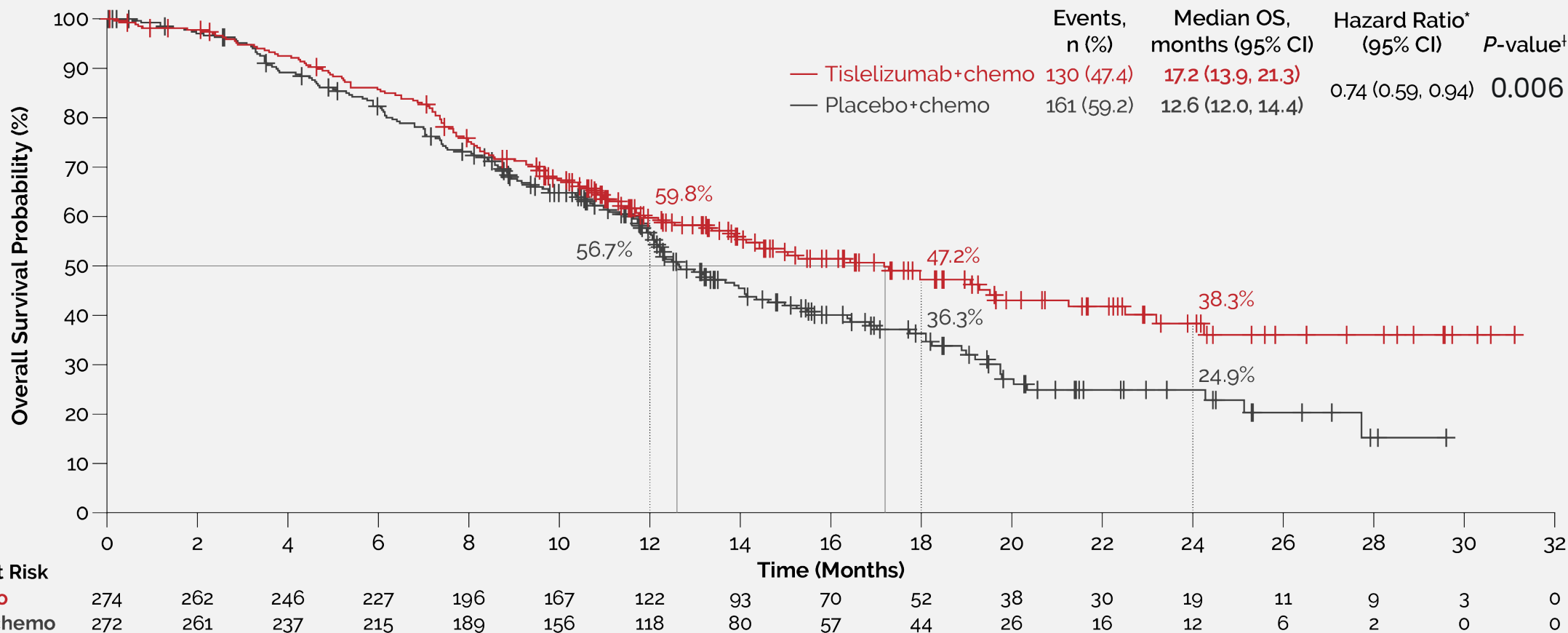
at final analysis is 0.0226. Medians were estimated by the Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. OS rates were estimated by the Kaplan-Meier method.

1L=1st line, Chemo=chemotherapy, CI=confidence interval, GC/GJEC=gastric or gastro-esophageal junction adenocarcinoma, HR=hazard ratio, ITT=intent-to-treat, OS=overall survival, PBO=placebo, PD-L1=programmed death-ligand 1, TIS=tislelizumab.

Qiu M-Z et al. *BMJ*. 2024;385:e078876.

# Primary Endpoint: OS in PD-L1+ (PD-L1 score $\geq 5\%$ )

At the **pre-specified interim analysis**, tislelizumab plus chemotherapy demonstrated statistically significant and clinically meaningful improvement in OS versus placebo plus chemotherapy in patients with PD-L1-positive GC/GEJC



Data cutoff: October 08, 2021.

\*Primary OS analysis: Stratified by regions (east Asia vs rest of the world) and presence of peritoneal metastasis. †One-sided stratified log-rank test. 116 (42.3%) patients and 147 (54.0%) patients in tislelizumab plus chemotherapy arm and placebo plus chemotherapy arm received subsequent anticancer systemic therapies, respectively. Of those, 19 (6.9%) patients and 38 (14.0%) patients received immunotherapy.

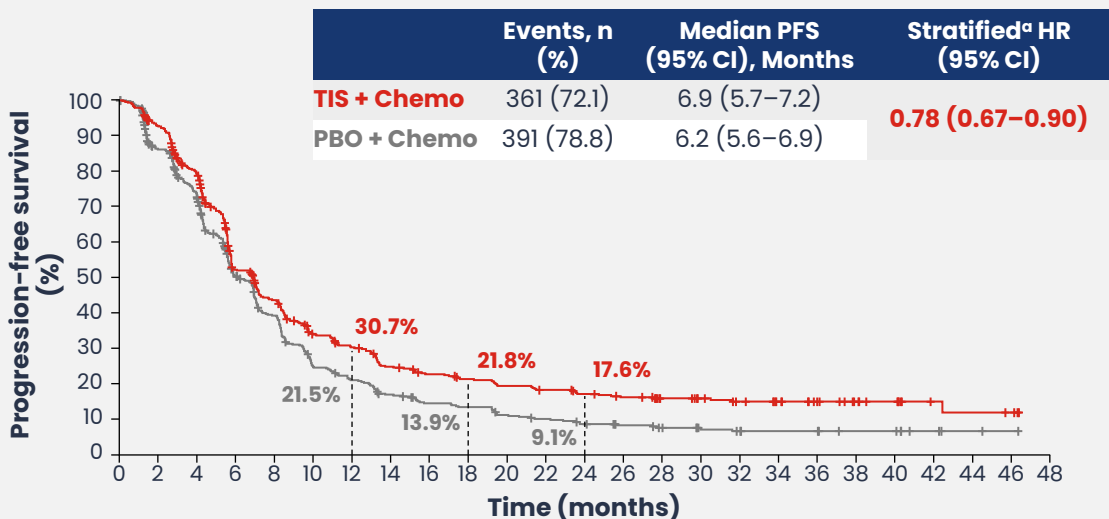
1L=1st line, CI=confidence interval, GC=gastric cancer, GEJC=gastroesophageal junction carcinoma, HR=hazard ratio, OS=overall survival, m=month

Qiu M-Z, et al. BMJ 2024; 385:e078876.

# Progression-Free Survival and Tumor Response (ITT)

Tislelizumab + chemo was associated with improved PFS, higher ORR and a more durable response vs placebo + chemo<sup>1</sup>

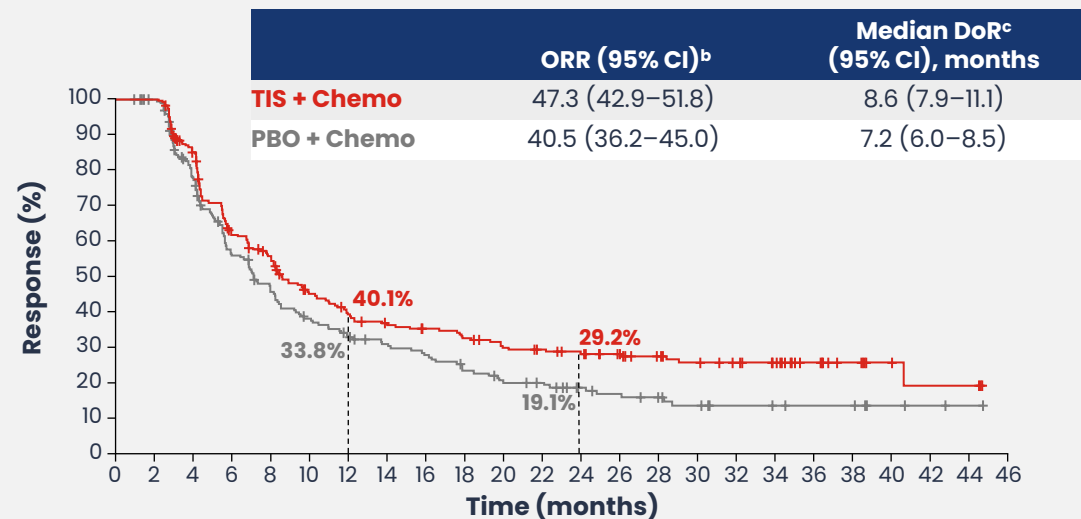
## Progression-Free Survival



Number of patients at risk

<b>TIS + Chemo</b>	501	434	361	226	184	136	120	97	86	79	72	67	60	55	41	37	32	27	21	16	12	5	4	3	0
<b>PBO + Chemo</b>	496	399	327	211	161	100	85	67	55	51	42	37	31	26	21	16	13	11	10	8	7	4	2	1	0

## Tumor Response



Number of patients at risk

<b>TIS + Chemo</b>	237	234	192	138	120	94	81	73	68	64	59	52	49	44	35	30	28	24	14	10	5	3	3	0
<b>PBO + Chemo</b>	201	193	146	101	84	66	57	50	46	39	32	29	23	19	17	12	9	9	7	7	4	2	1	0

Improvements in OS, PFS, and DoR with TIS plus CT vs PBO plus CT were maintained at 3-year follow-up<sup>2</sup>

Data cutoff: 28 February 2023.

Confirmed tumour responses assessed by investigators as per RECIST version 1.1.

<sup>a</sup>Cox regression model stratified by regions (Asia vs Europe/North America), PD-L1 expression and presence of peritoneal metastasis; <sup>b</sup>Exact Clopper-Pearson two-sided confidence interval; <sup>c</sup>Among patients who achieved a confirmed CR or PR only

Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. PFS rates were estimated by Kaplan-Meier method.

1L=1st line, Chemo=chemotherapy, CI=confidence interval, DoR=duration of response, GC=gastric cancer, GEJC=gastroesophageal junction carcinoma, HR=hazard ratio, ITT=intent-to-treat, ORR=objective response rate, PBO=placebo, PFS=progression-free survival, RECIST=Response Evaluation Criteria in Solid Tumors, TIS=tislelizumab.

1. Qiu M-Z, et al. *BMJ*. 2024;385:e078876; 2. Cruz-Correa M et al. Poster Presentation at ESMO 2024;1437P.

# Safety Summary



Tislelizumab + chemo had a manageable safety profile.

The most common TRAEs were consistent with the known safety profiles of the individual study treatment components.

n (%)	Tislelizumab + chemo (n=498)	Placebo + chemo (n=494)
<b>Any TRAE</b>	483 (97.0)	476 (96.4)
<b>Grade ≥3 TRAEs</b>	269 (54.0)	246 (49.8)
<b>Serious TRAEs</b>	113 (22.7)	72 (14.6)
<b>TRAEs leading to treatment discontinuation</b>	83 (16.7)	40 (8.1)
<b>TRAEs leading to dose modification</b>	381 (76.5)	375 (75.9)
<b>TRAEs leading to death<sup>a</sup></b>	6 (1.2) <sup>b</sup>	2 (0.4) <sup>c</sup>

3-year follow up (minimum follow up, 36.6 months).

<sup>a</sup>Excludes death due to disease progression. <sup>b</sup>Death (n=4), colitis (n=1), sepsis (n=1), subdural haematoma (n=1). <sup>c</sup>Pneumonia (n=2).

1L=1st line, AE=adverse event, Chemo=chemotherapy, GC=gastric cancer, GEJC=gastroesophageal junction carcinoma, PBO=placebo, TIS=tislelizumab, TRAE=treatment-related adverse event.

Cruz-Correa M et al. Poster Presentation at ESMO 2024;1437P.

# Treatment-Related Adverse Events With an Incidence $\geq 10\%$

n (%)	Tislelizumab + Chemo (n=498)				Placebo + Chemo (n=494)			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
<b>Nausea</b>	215 (43)	231 (46)	26 (5)	11 (2)	230 (47)	217 (44)	25 (5)	4 (<1)
<b>Decreased appetite</b>	224 (45)	13 (3)	0 (0)	0 (0)	223 (45)	9 (2)	0 (0)	0 (0)
<b>Decreased platelet count</b>	168 (34)	14 (3)	0 (0)	0 (0)	169 (34)	16 (3)	0 (0)	0 (0)
<b>Decreased neutrophil count</b>	118 (24)	41 (8)	15 (3)	0 (0)	126 (26)	46 (9)	11 (2)	0 (0)
<b>Vomiting</b>	109 (22)	54 (11)	5 (1)	0 (0)	103 (21)	53 (11)	4 (<1)	0 (0)
<b>Anemia</b>	150 (30)	11 (2)	0 (0)	0 (0)	150 (30)	12 (2)	0 (0)	0 (0)
<b>Increased aspartate aminotransferase</b>	133 (27)	25 (5)	0 (0)	0 (0)	126 (26)	35 (7)	2 (<1)	0 (0)
<b>Decreased white blood cell count</b>	132 (27)	12 (2)	1 (<1)	0 (0)	133 (27)	4 (<1)	0 (0)	0 (0)
<b>Increased alanine aminotransferase</b>	104 (21)	14 (3)	1 (<1)	0 (0)	126 (26)	8 (2)	0 (0)	0 (0)
<b>Diarrhea</b>	105 (21)	8 (2)	0 (0)	0 (0)	93 (19)	4 (<1)	0 (0)	0 (0)
<b>Peripheral sensory neuropathy</b>	99 (20)	12 (2)	0 (0)	0 (0)	115 (23)	11 (2)	0 (0)	0 (0)
<b>PPES</b>	105 (21)	1 (<1)	0 (0)	0 (0)	113 (23)	3 (<1)	0 (0)	0 (0)
<b>Asthenia</b>	80 (16)	15 (3)	0 (0)	0 (0)	83 (17)	10 (2)	0 (0)	0 (0)
<b>Fatigue</b>	66 (13)	10 (2)	0 (0)	0 (0)	64 (13)	7 (1)	0 (0)	0 (0)
<b>Neutropenia</b>	66 (13)	9 (2)	0 (0)	0 (0)	55 (11)	6 (1)	0 (0)	0 (0)
<b>Hypoesthesia</b>	41 (8)	32 (6)	1 (<1)	0 (0)	46 (9)	32 (7)	2 (<1)	0 (0)
<b>Increased blood bilirubin</b>	68 (14)	1 (<1)	0 (0)	0 (0)	67 (14)	0 (0)	0 (0)	0 (0)
<b>Thrombocytopenia</b>	54 (11)	6 (1)	1 (<1)	0 (0)	55 (11)	3 (<1)	0 (0)	0 (0)
<b>Decreased weight</b>	45 (9)	14 (3)	1 (<1)	0 (0)	42 (9)	12 (2)	2 (<1)	0 (0)
<b>Hypothyroidism</b>	58 (12)	0 (0)	0 (0)	0 (0)	53 (11)	0 (0)	0 (0)	0 (0)

Data cutoff: February 28, 2023.

Data are shown for all grade incidence of  $\geq 10\%$  in either treatment arm. Treatment-related adverse events are sorted by decreasing frequency for all grade events in the tislelizumab plus chemotherapy arm. Patients with two or more adverse events in the same preferred term are counted only once for that preferred term. Adverse events were graded based on National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 and coded using Medical Dictionary for Regulatory Activities version 24.0.

1L=1st line, AE=adverse event, Chemo=chemotherapy, GC=gastric cancer, GEJC=gastroesophageal junction carcinoma, PBO=placebo, PPES=Palmar-plantar erythrodysesthesia syndrome, TIS=tislelizumab, TRAE=treatment-related adverse event.

Qiu M-Z et al. *BMJ*. 2024;385:e078876.

# Patient Baseline Characteristics (ITT Analysis Set)

## RATIONALE-305: North American/European Subgroup

- Of 997 patients enrolled in the study, 249 (25.0%) were included in the EU/NA patient subgroup analysis
- Patient baseline characteristics were generally balanced between treatment arms
- At data cutoff, minimum follow-up in the overall population was 24.6 months for tislelizumab plus chemotherapy and 25.0 months for placebo plus chemotherapy

	EU/NA Patient Subgroup		
	TIS + Chemo (n=125)	PBO + Chemo (n=124)	Total (n=249)
<b>Median age, years (range)</b>	61.0 (23.0-83.0)	62.5 (30.0-86.0)	62.0 (23.0-86.0)
<b>Male, n (%)</b>	88 (70.4)	85 (68.5)	173 (69.5)
<b>ECOG PS, n (%)</b>			
0	49 (39.2)	52 (41.9)	101 (40.6)
1	76 (60.8)	72 (58.1)	148 (59.4)
<b>Primary tumor location, n (%)</b>			
Stomach	76 (60.8)	76 (61.3)	152 (61.0)
GEJ	49 (39.2)	48 (38.7)	97 (39.0)
<b>Metastatic disease,<sup>a</sup> n (%)</b>	121 (96.8)	121 (97.6)	242 (97.2)
<b>Peritoneal metastasis, n (%)</b>	55 (44.0)	54 (43.5)	109 (43.8)
<b>Prior adjuvant/neoadjuvant treatment, n (%)</b>	23 (18.4)	17 (13.7)	40 (16.1)
<b>PD-L1 score, n (%)</b>			
<5%	53 (42.4)	53 (42.7)	106 (42.6)
≥5%	72 (57.6)	71 (57.3)	143 (57.4)

Data cutoff: February 28, 2023.

<sup>a</sup>Disease stage rating at screening was based on American Joint Committee on Cancer TNM Staging Classification for Carcinoma of the Stomach and for Carcinoma of the Esophagus and Esophagogastric Junction (8th ed., 2017). Chemo=chemotherapy, ECOG PS=Eastern Cooperative Oncology Group performance status, EU=European, GEJ=gastroesophageal junction, NA=North American, PBO=placebo, PD-L1=programmed death-ligand 1, TIS=tislelizumab. Arkenau T, et al. Poster Presentation at ASCO-GI 2024; Poster 330.

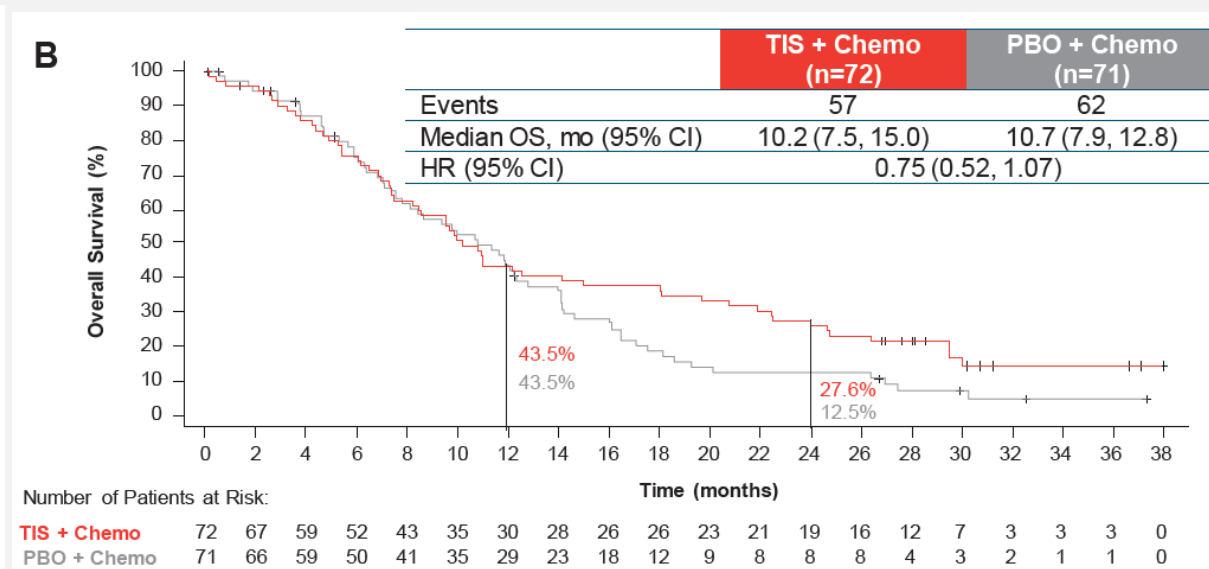
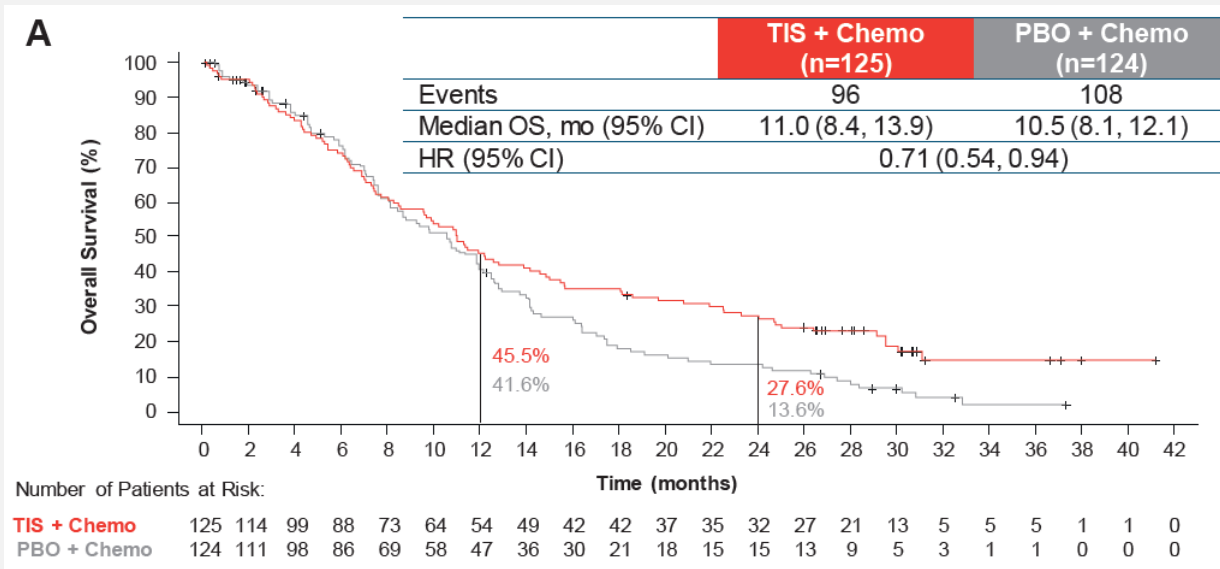
# Overall Survival



## RATIONALE-305: North American/European Subgroup

- In the EU/NA subgroup, tislelizumab plus chemotherapy improved OS compared with placebo plus chemotherapy in the ITT analysis set (the HR results for OS in this subgroup should be interpreted with caution)
- OS rates at 24 months were higher with tislelizumab plus chemotherapy vs placebo plus chemotherapy in the ITT analysis set (27.6% vs 13.6%) and PD-L1+ analysis set (27.6% vs 12.5%)

### OS in the Eu/NA Patient Subgroup in the (A) ITT Analysis Set and (B) PD-L1+ Analysis Set



Data cutoff: February 28, 2023.

Chemo=chemotherapy, CI=confidence interval, EU=European, HR=hazard ratio, ITT=intent-to-treat, NA=North American, OS=overall survival, PD-L1=programmed death-ligand 1

Arkenau T, et al. Poster Presentation at ASCO-GI 2024; Poster 330.

# Safety



## RATIONALE-305: North American/European Subgroup

- Incidences of grade  $\geq 3$  TRAEs (48.8% vs 49.2%) and TRAEs leading to death (1.6% vs 0.8%) were similar between arms, while more patients discontinued treatment (13.0% vs 5.6%) due to TRAEs with tislelizumab plus chemotherapy vs placebo plus chemotherapy, respectively
- Overall, the safety profile of tislelizumab plus chemotherapy was manageable in patients with locally advanced, unresectable, or metastatic GC/GEJC in the EU/NA subgroup

	EU/NA Patient Subgroup	
	TIS + Chemo (n=123)	PBO + Chemo (n=124)
TRAE of any grade, n (%)	117 (95.1)	116 (93.5)
TRAE of grade $\geq 3$ , n (%)	60 (48.8)	61 (49.2)
TRAE leading to discontinuation, <sup>a</sup> n (%)	16 (13.0)	7 (5.6)
TRAE leading to death, n (%)	2 (1.6)	1 (0.8)

Data cutoff: February 28, 2023.

<sup>a</sup>Discontinuation of any treatment component.

Chemo=chemotherapy, EU/NA=European/North American, PBO=placebo, TIS=tislelizumab, TRAE=treatment-related treatment-emergent adverse event.

Arkenau T, et al. Poster Presentation at ASCO-GI 2024; Poster 330.