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Tislelizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy as First-line Treatment of Advanced Gastric or Gastroesophageal Junction Adenocarcinoma: Final Analysis Results of the RATIONALE-305 Study

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DECLARATION OF INTERESTS

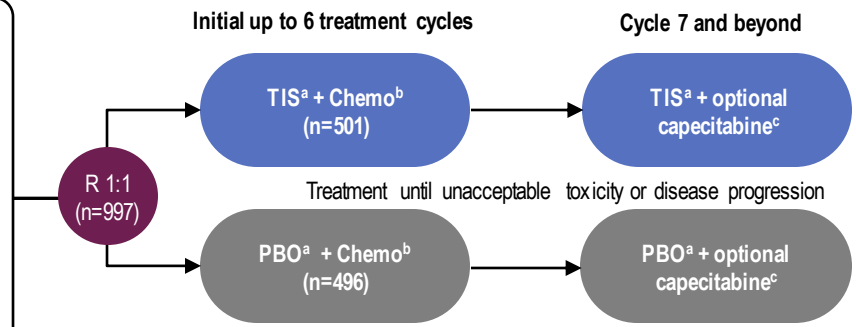
Rui-Hua Xu has received consulting fees from Hutchison, Hengrui, Junshi, Qilu, CPPC, Roche, Merck Serono; and has participated on data safety monitoring boards or advisory boards for Astellas, MSD, AstraZeneca, Junshi, Hengrui, BeiGene, Innovent, CPPC, and Keymed Bioscience.

Study Design

RATIONALE-305 - randomised, double-blind, global, phase 3 study

Inclusion criteria:

- Age ≥18 years
- Locally advanced unresectable or metastatic adenocarcinoma of stomach- / gastro-oesophageal junction
- No HER2-positive disease
- No prior systemic therapy for advanced disease
- At least one measurable or non-measurable lesion (RECIST v1.1)
- ECOG PS 0 or 1



Endpoints

- ***Primary endpoint:*** OS in PD-L1 score ≥5% [d] and ITT populations
- ***Secondary endpoints:*** PFS, ORR, DoR, DCR, CBR, HRQoL, and safety

Stratification

- Regions of enrolment
- Peritoneal metastasis
- PD-L1 expression score (≥5% vs <5%)[d]
- Investigator-chosen chemotherapy (XELOX or FP)

Statistical considerations

- Analysis of OS in the ITT population was to be performed after OS in the PD-L1 score ≥5% population had been demonstrated to be statistically significant favouring TIS + chemo
- Planned to enrol 980 patients: 87% power to detect HR 0.80 with 768 OS events in the ITT population (all randomised patients) at a one-sided alpha of 0.025
- Final analysis (cutoff date: 28 February 2023) based on 776 OS events (ITT)

[a] Tislelizumab 200 mg or placebo (day 1) Q3W.
[b] Oxaliplatin 130 mg/m² IV Q3W (day 1) and oral capecitabine 1000 mg/m² twice daily (days 1-14) Q3W (XELOX), or cisplatin 80 mg/m² IV Q3W (day 1) and 5-fluorouracil 800 mg/m²/day IV (days 1-5) Q3W (FP).
[c] Capecitabine as maintenance therapy was optional and only for XELOX-treated patients.
[d] PD-L1 score was determined using the VENTANA PD-L1 (SP263) assay by tumour area positivity (TAP) score.
Abbreviations: CBR, clinical benefit rate; Chemo, chemotherapy; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HRQoL, health-related quality of life; ITT, intent-to-treat; IV, intravenous; ORR, objective response rate; OS, overall survival; PBO, placebo; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; R, randomisation; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TIS, tislelizumab.

Baseline Characteristics (ITT Population)

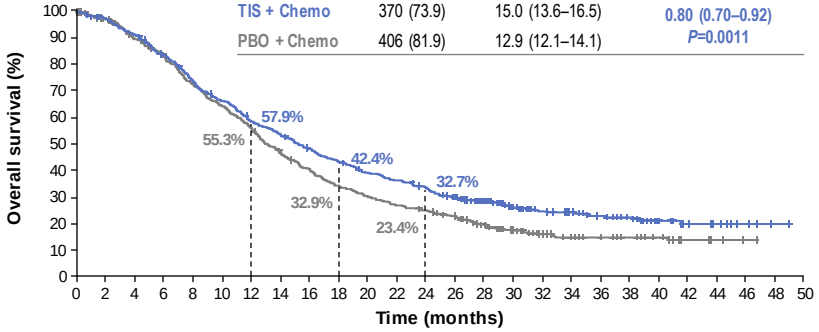
	TIS + Chemo (n=501)	PBO + Chemo (n=496)
Median age, years (range)	60.0 (23.0-86.0)	61.0 (25.0-86.0)
Male sex	346 (69.1)	346 (69.8)
Region		
Asia[a]	376 (75.0)	372 (75.0)
Europe/North America	125 (25.0)	124 (25.0)
ECOG PS 1	332 (66.3)	342 (69.0)
Primary tumour location		
Stomach	405 (80.8)	395 (79.6)
GEJ	96 (19.2)	100 (20.2)[b]
Metastatic disease	494 (98.6)	490 (98.8)
Peritoneal metastasis	220 (43.9)	214 (43.1)
Prior adjuvant/neoadjuvant treatment	107 (21.4)	100 (20.2)
PD-L1 score		
<5%	227 (45.3)	224 (45.2)
≥5%	274 (54.7)	272 (54.8)
Investigator-chosen chemotherapy		
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 randomised to the data cutoff): 24.6 months.
Median study follow-up duration (defined as from randomisation 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).
All data are n (%) unless otherwise stated. [a]Asia comprises China (including Taiwan), Japan, and South Korea. [b]The diagnosis of one patient was updated from gastric adenocarcinoma to be pancreatic cancer after randomisation and the patient remained in the ITT population.
Abbreviations: Chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastro-oesophageal junction; IQR, interquartile range; ITT, intent-to-treat; PD-L1, programmed death-ligand 1; PBO, placebo; TIS, tislelizumab.

Overall Survival

ITT Population

	Events, n (%)	Median OS (95% CI), Months	Stratified[a] HR (95% CI) Log-Rank Test *P*-value
TIS + Chemo	370 (73.9)	15.0 (13.6–16.5)	0.80 (0.70–0.92) *P*=0.0011
PBO + Chemo	406 (81.9)	12.9 (12.1–14.1)	

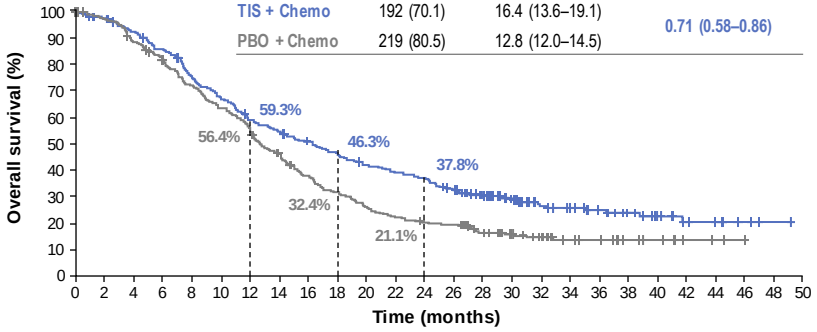


Number of patients at risk

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

PD-L1 Score ≥5% Population

	Events, n (%)	Median OS (95% CI), Months	Stratified[a] HR (95% CI)
TIS + Chemo	192 (70.1)	16.4 (13.6–19.1)	0.71 (0.58–0.86)
PBO + Chemo	219 (80.5)	12.8 (12.0–14.5)	



Number of patients at risk

TIS + Chemo	274	263	247	228	199	178	156	145	133	120	109	102	97	84	68	50	38	34	27	19	14	9	7	3	1	0
PBO + Chemo	272	261	236	215	190	168	148	120	99	83	69	59	53	51	39	29	23	16	14	9	7	3	2	1	0	0

- TIS + Chemo as first-line treatment of advanced GC/GEJC demonstrated a statistically significant and clinically meaningful improvement in OS over PBO + Chemo in the ITT population at the final analysis
- Updated OS results in the PD-L1 score ≥5% population remained consistent with those observed at the interim analysis (HR 0.74 [95%CI 0.59–0.94] *P*=0.0056) after an additional 17 months of follow-up, showing a clinically meaningful improvement in OS

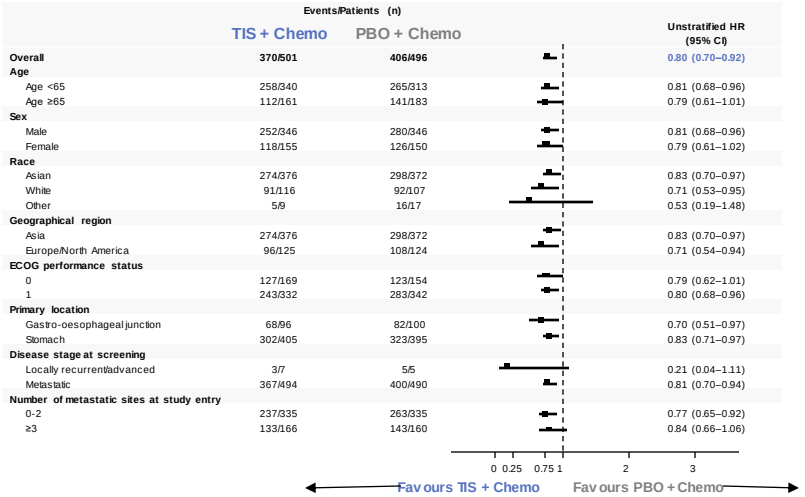
Data cutoff: 28 February 2023.

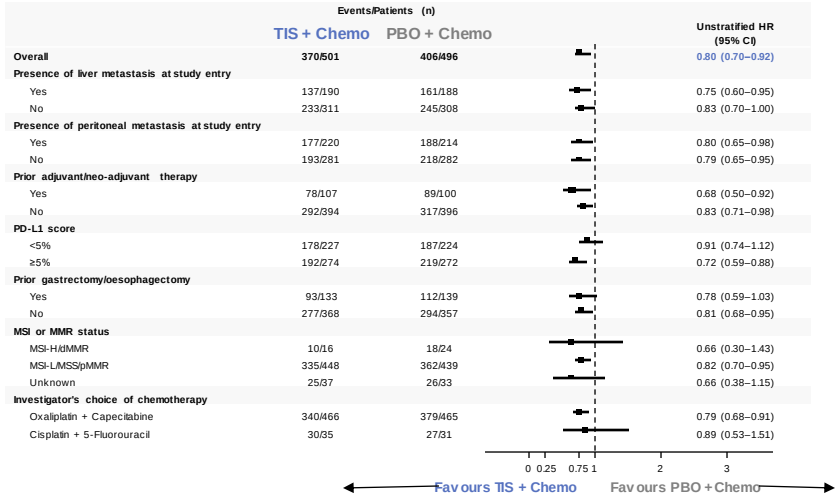
[a] Log-rank and Cox regression models were stratified by regions (Asia vs Europe/North America), PD-L1 expression (ITT population analysis only), and presence of peritoneal metastasis. *P*-values are one-sided and based on the stratified log-rank test. *P*-value boundary at final analysis is 0.0226.

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.

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

Overall Survival: Subgroup Analysis (ITT Population)





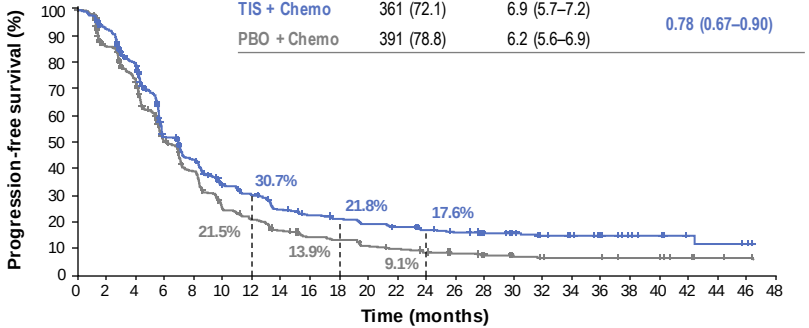
OS benefit of TIS + chemo was observed across multiple patient subgroups

Data cutoff: 28 February 2023.
Hazard ratios and their 95% CI were estimated from an unstratified Cox regression model including treatment as covariate. The race subcategory 'Other' includes Not Reported, Unknown and Other.
Abbreviations: Chemo, chemotherapy; dMMR, deficient mismatch repair; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MSI-L/H, microsatellite instability low/high; MSS, microsatellite stable; PBO, placebo; PD-L1, programmed death-ligand 1; pMMR, proficient mismatch repair; TIS, tislelizumab

Progression-Free Survival and Tumour Responses (ITT Population)

Progression-Free Survival

	Events, n (%)	Median PFS (95% CI), Months	Stratified[a] HR (95% CI)
TIS + Chemo	361 (72.1)	6.9 (5.7–7.2)	0.78 (0.67–0.90)
PBO + Chemo	391 (78.8)	6.2 (5.6–6.9)	

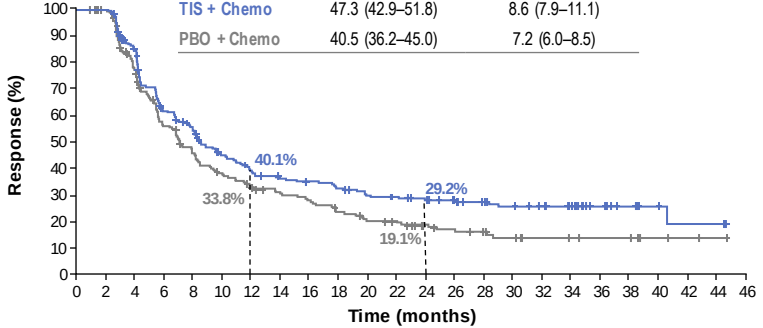


Number of patients at risk

TIS + Chemo	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
PBO + Chemo	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

Tumour Response

	ORR (95% CI)[b]	Median DoR[c] (95% CI), months
TIS + Chemo	47.3 (42.9–51.8)	8.6 (7.9–11.1)
PBO + Chemo	40.5 (36.2–45.0)	7.2 (6.0–8.5)



Number of patients at risk

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

TIS + Chemo was associated with improved PFS, higher ORR and a more durable response vs PBO + Chemo

Data cutoff: 28 February 2023. Confirmed tumour responses assessed by investigators as per RECIST version 1.1.

[a] Cox regression model stratified by regions (Asia vs Europe/North America), PD-L1 expression and presence of peritoneal metastasis.

[b] Exact Clopper-Pearson two-sided confidence interval.

[c] 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.

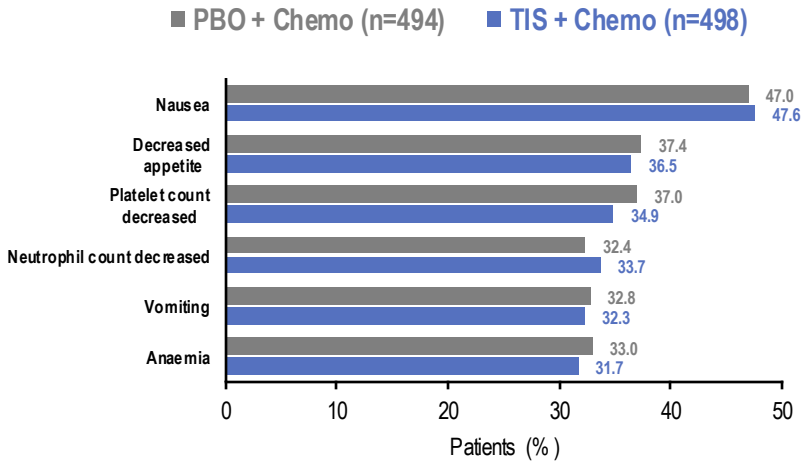
Abbreviations: Chemo, chemotherapy; CI, confidence interval; DoR, duration of response; HR, hazard ratio; ITT, intent-to-treat; ORR, objective response rate; PBO, placebo; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TIS, tislelizumab.

Safety Summary (Safety Population)

Summary of AE Incidence

n (%)	TIS + Chemo (n=498)	PBO + Chemo (n=494)
Any TRAE	483 (97.0)	476 (96.4)
Grade ≥3 TRAEs	268 (53.8)	246 (49.8)
Serious TRAEs	113 (22.7)	72 (14.6)
Any immune-mediated AE	154 (30.9)	58 (11.7)
TRAEs leading to treatment discontinuation	80 (16.1)	40 (8.1)
TRAEs leading to death[a]	6 (1.2)	2 (0.4)

TRAEs of Any Grade with Incidence ≥ 30%



- TIS + Chemo had a manageable safety profile
- The most common TRAEs were consistent with the known safety profiles of the individual study treatment components

Data cutoff: 28 February 2023.
[a] Excluding death due to disease under study.
Abbreviations: AE, adverse event; Chemo, chemotherapy; PBO, placebo; TIS, tislelizumab; TRAE, treatment-related adverse event.

Conclusion

TIS + Chemo produced a statistically significant and clinically meaningful improvement in OS vs PBO + Chemo as first-line treatment in patients with advanced or metastatic GC/GEJC (ITT population)

- Median OS 15.0 months (95% CI 13.6-16.5) vs 12.9 months (95% CI 12.1-14.1), respectively
- Stratified HR 0.80 (95% CI 0.70-0.92; *P*=0.0011)

TIS + Chemo continued to demonstrate clinically meaningful improvement in OS in patients with PD-L1 score ≥5% with longer follow-up at the final analysis

- Median OS 16.4 months (95% CI 13.6-19.1) vs 12.8 months (95% CI 12.0-14.5), respectively
- Stratified HR 0.71 (95% CI 0.58-0.86)

The safety profile of TIS + Chemo was manageable, with no new safety signals identified

These data suggest that TIS + Chemo presents a potential new first-line treatment option for patients with advanced GC/GEJC

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