SINGAPORE 2023 ESMO ASIA

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

Ken Kato reports:

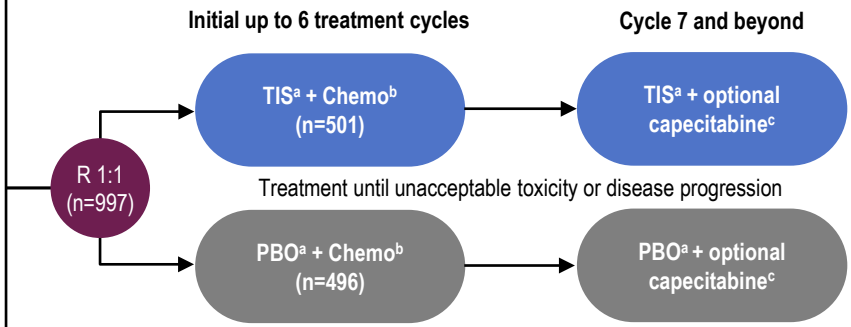
- Speaker's bureau: Bristol-Myers Squibb, MSD, Ono
- Research grants: Ono
- Principal Investigator: AstraZeneca, Bayer, BeiGene, Bristol-Myers Squibb, MSD, Ono
- Advisory role: AstraZeneca, Bayer, BeiGene, Bristol-Myers Squibb, MSD, Ono, Seagen, Servier

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: February 28, 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 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; TAP, tumour area positivity; TIS, tislelizumab.

Baseline Characteristics (ITT Population)

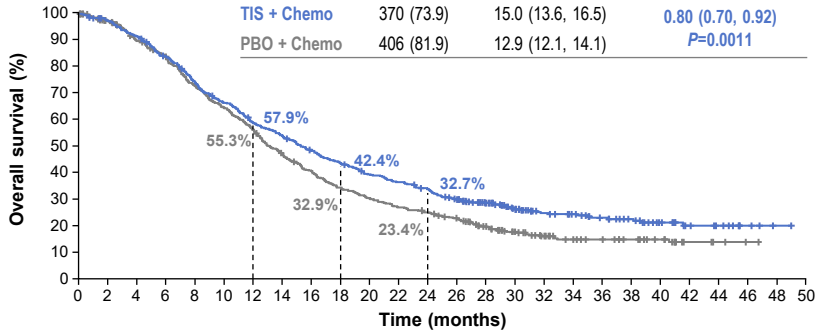
	TIS + Chemo (n=501)	PBO + Chemo (n=496)
Median age, years (range)	60.0 (23.0-86.0)	61.0 (25.0-86.0)
Male sex	346 (69.1)	346 (69.8)
Region		
Asia[a]	376 (75.0)	372 (75.0)
Europe/North America	125 (25.0)	124 (25.0)
ECOG PS 1	332 (66.3)	342 (69.0)
Primary tumour location		
Stomach	405 (80.8)	395 (79.6)
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: February 28, 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 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)	

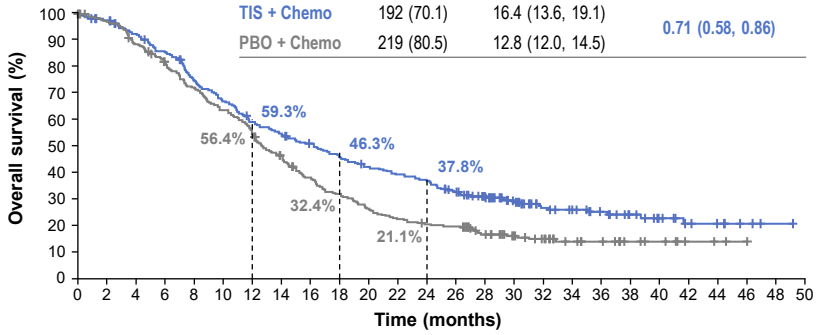


Number of patients at risk

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

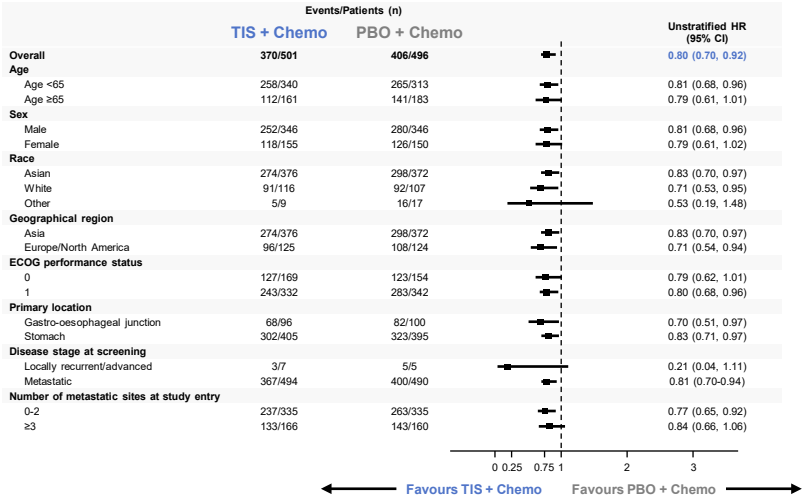
Data cutoff: February 28, 2023.

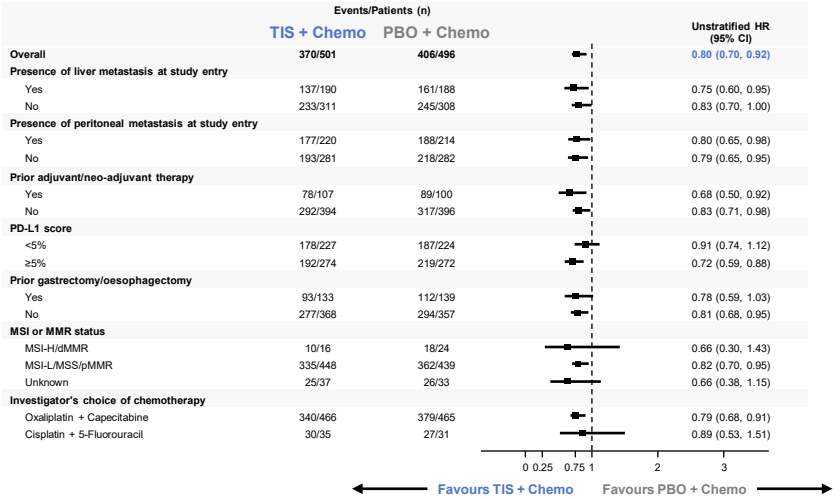
[a]Log-rank and Cox regression models were stratified by region (Asia vs Europe/North America), PD-L1 expression (ITT population analysis only), and presence of peritoneal metastasis. *P*-values are one-sided and based on the stratified log-rank test. *P*-value boundary at final analysis is 0.0226.

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)





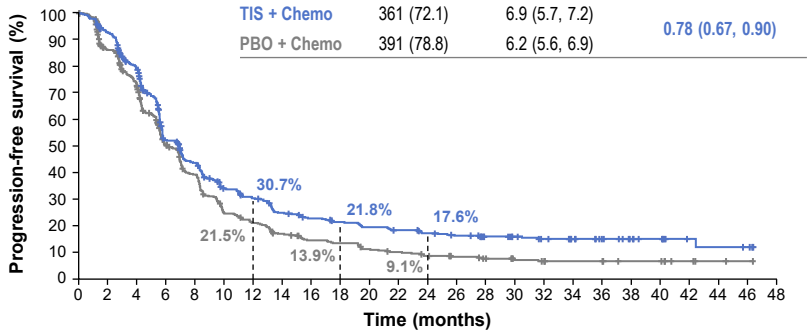
OS benefit of TIS + chemo was observed across multiple patient subgroups

Data cutoff: February 28, 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; CI, confidence interval; dMMR, deficient mismatch repair; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intent-to-treat; 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)	

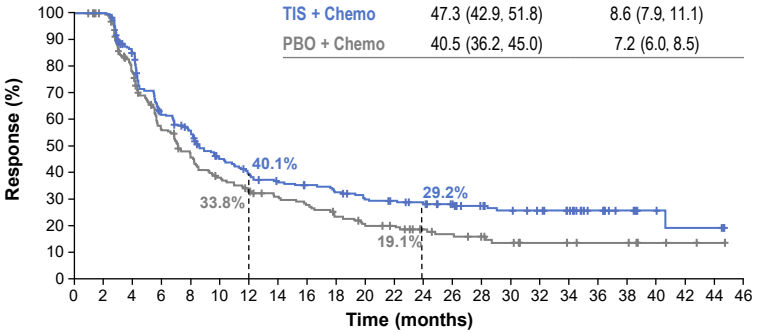


Number of patients at risk

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

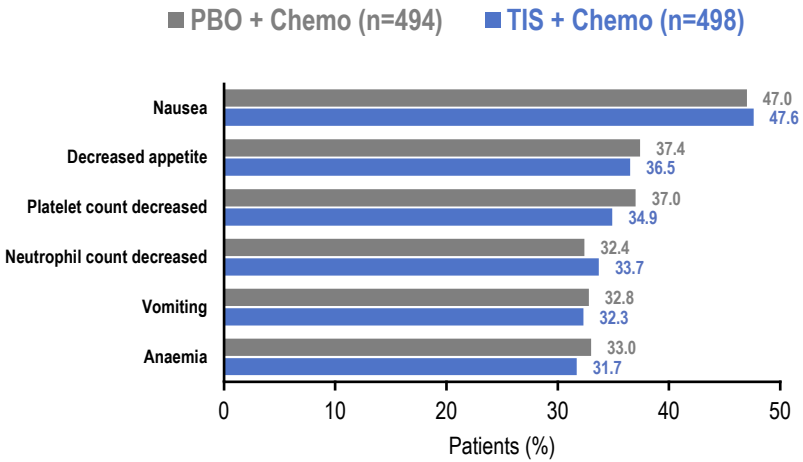
Data cutoff: February 28, 2023. Confirmed tumour responses assessed by investigators as per RECIST version 1.1.
[a]Cox regression model stratified by region (Asia vs Europe/North America), PD-L1 expression and presence of peritoneal metastasis.
[b]Exact Clopper-Pearson two-sided confidence interval.
[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; CR, complete response; DoR, duration of response; HR, hazard ratio; ITT, intent-to-treat; ORR, objective response rate; PBO, placebo; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response; 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: February 28, 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

Acknowledgments: We as authors would like to thank the patients and their families for their study participation and the global investigators and site personnel for their support during the conduct of this important trial. This study was sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Simon Lancaster, BSc, of Ashfield MedComms, an Inizio company, and was funded by BeiGene, Ltd.

Abbreviations: Chemo, chemotherapy; CI, confidence interval; ESMO, European Society for Medical Oncology; FPN, Final Publication Number; 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.