First-Line Tislelizumab Plus Chemotherapy in Gastric/Gastroesophageal Junction Cancer: RATIONALE-305 Asian Subgroup

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Declaration of Interests

- **Hidekazu Hirano** has received grants from Amgen, Astellas, Bristol Myers Squibb, Chugai Pharmaceutical, Daiichi Sankyo, Eisai, Incyte, Janssen Pharmaceuticals, Merck Biopharma, MSD, Novartis, Ono Pharmaceutical, Pfizer, Seagen, and Taiho Pharmaceutical; and has received payment or honoraria from Nichi-Iko, Novartis, Ono Pharmaceutical, Taiho Pharmaceutical, and Teijin Pharma
- **Rui-Hua Xu** has no interests to disclose

Introduction

- Gastric cancer (GC) is one of the leading causes of cancer-related deaths worldwide; Asia has a notably higher incidence and mortality rate of GC, and the disease is of particular concern in China, South Korea, and Japan[1,2-4]
- Prior to the introduction of immunotherapy, platinum plus fluoropyrimidine chemotherapy was the standard first-line therapy for advanced GC/gastroesophageal junction cancer (GEJC), with median overall survival (OS) of less than 12 months[5-7]
- The RATIONALE-305 study met its primary endpoint, showing significant improvement in OS with tislelizumab plus chemotherapy vs placebo plus chemotherapy in the PD-L1 ≥5% population at interim analysis, and in the intent-to-treat (ITT) population at final analysis, with favorable progression-free survival[8,9]
- Overall, results of the final analysis supported tislelizumab plus chemotherapy as a potential first-line treatment option for patients with advanced GC/GEJC[8]
- Here, we present results from the Asian patient subgroup of the RATIONALE-305 study at final analysis
- **Scan QR code to view the primary results of the RATIONALE-305 study**

ClinicalTrials.gov Identifier: NCT03777657.

Abbreviation: PD-L1, programmed death-ligand 1.

1. Sung H, et al. *CA Cancer J Clin*. 2021;71(3):209-249; 2. Shin WS, et al. *Cancers (Basel)*. 2023;15(9):2639; 3. Yan X, et al. *Chin J Cancer Res*. 2023;35(2):81-91; 4. Sekiguchi M, et al. *Digestion*. 2022;103(1):22-28; 5. Cheng J, et al. *Ther Adv Med Oncol*. 2019;11:1758835919877726; 6. Lordick F, et al. *Ann Oncol*. 2022;33(10):1005-1020; 7. Catenacci DV, et al. *Oncologist*. 2021;26(10):e1704-1729; 8. Xu RH, et al. *Ann Oncol*. 2023; 34(suppl_2):S1320-1321; 9. Moehler MH, et al. *J Clin Oncol*. 2023;41(suppl 4):286.

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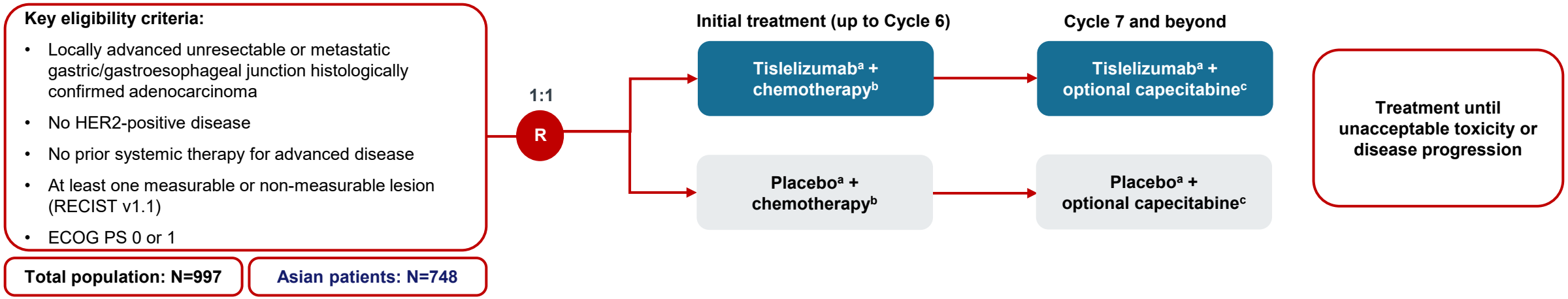
Study Design and Patient Population



Stratification factors

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

Endpoints

- **Primary endpoint:** OS in PD-L1 score ≥5% and ITT populations
- **Secondary endpoints:** progression-free survival (PFS), objective response rate (ORR), duration of response (DoR), and safety

- Of 997 randomized patients, 748 (tislelizumab with chemotherapy: n=376; placebo with chemotherapy: n=372) were enrolled from Asia; of whom 403 had a PD-L1 score of ≥5%
- The Asian subgroup comprised patients from China (including Taiwan), Japan, and South Korea
- As of data cutoff of final analysis (February 28, 2023), median study follow-up in the Asian subgroup was 14.5 months (range: 0.1-50.1) and minimum study follow-up in this subgroup was 24.6 months

[a]Tislelizumab 200 mg or placebo Q3W (day 1). [b]Oxaliplatin 130 mg/m² IV (day 1) and oral capecitabine 1000 mg/m² twice daily (14 consecutive days from day 1) Q3W (XELOX), or cisplatin 80 mg/m² IV (day 1) and FP 800 mg/m²/day IV (days 1-5) Q3W. [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 tumor area positivity score.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; FP, 5-fluorouracil; HER2, human epidermal growth factor receptor 2; ITT, intent-to-treat; IV, intravenous; OS, overall survival; PD-L1, programmed death-ligand 1; Q3W, once every 3 weeks; R, randomized; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

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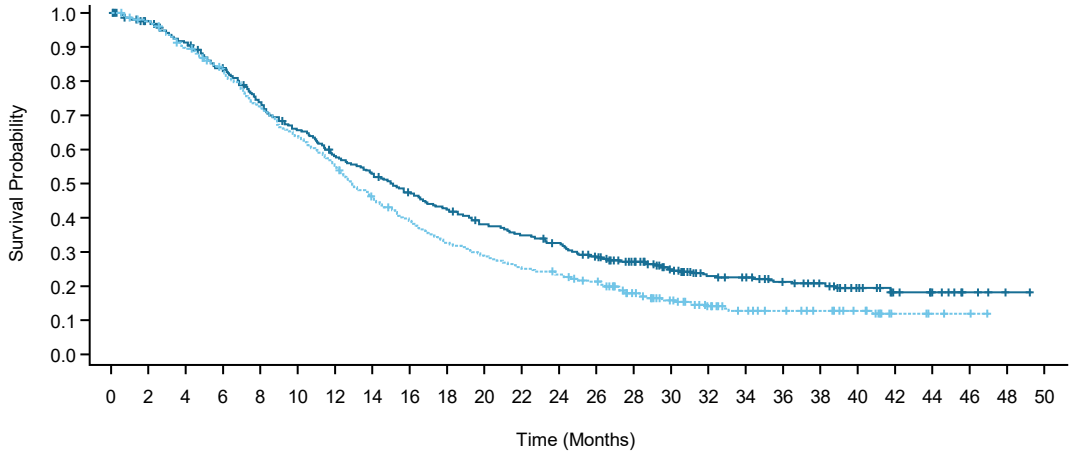
OS: Overall Population

ITT Population at Final Analysis[1]

	Events, n (%)	Median OS (95% CI), Months[a]	HR (95% CI)[a] *P* value[b]
TIS + chemo (n=501)	370 (73.9)	15.0 (13.6, 16.5)	0.80 (0.70, 0.92)
PBO + chemo (n=496)	406 (81.9)	12.9 (12.1, 14.1)	0.0011

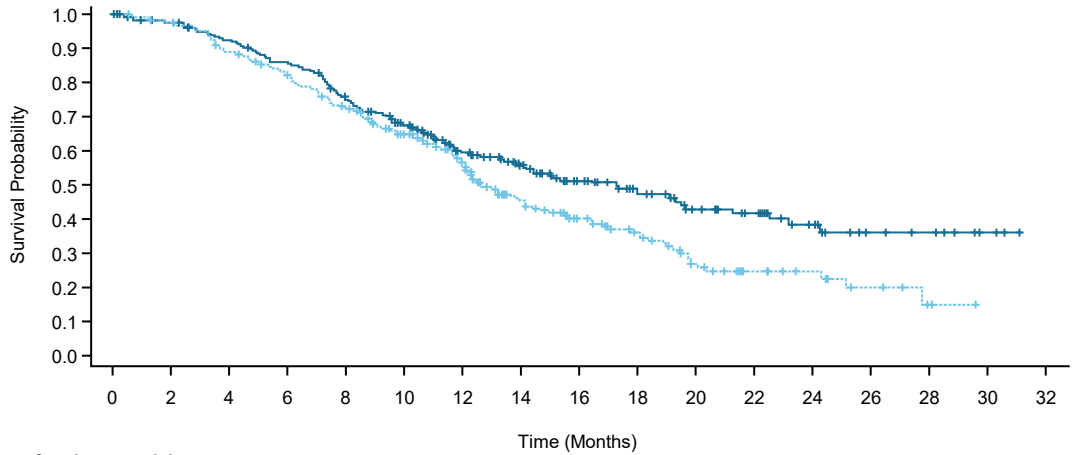


Number of patients at risk:

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 at Interim Analysis[2]

	Events, n (%)	Median OS (95% CI), Months[c]	HR (95% CI)[c] *P* value[b]
TIS + chemo (n=274)	130 (47.4)	17.2 (13.9, 21.3)	0.74 (0.59, 0.94)
PBO + chemo (n=272)	161 (59.2)	12.6 (12.0, 14.4)	0.0056



Number of patients at risk:

TIS + chemo	274	262	246	227	196	167	122	93	70	52	38	30	19	11	9	3	0
PBO + chemo	272	261	237	215	189	156	118	80	57	44	26	16	12	6	2	0	0

Improved OS differences of 2.1 and 4.6 months in favor of tislelizumab plus chemotherapy vs placebo plus chemotherapy were observed in the overall ITT and PD-L1 score ≥5% populations at final and interim analysis, respectively[2]

[a]Cox regression model was stratified by regions (east Asia vs rest of the world), PD-L1 expression, and presence of peritoneal metastasis. [b]*P*-values are one-sided and based on the stratified log-rank test.
[c]Cox regression model was stratified by regions (east Asia vs rest of the world) and presence of peritoneal metastasis.

Abbreviations: Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; PBO, placebo; PD-L1, programmed death-ligand 1; TIS, tislelizumab.

1. Xu RH, et al. *Ann Oncol.* 2023; 34(suppl_2):S1320-1321; 2. Moehler MH, et al. *J Clin Oncol* 2023;41(suppl 4):286.

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Demographics and Baseline Characteristics

	Asian Subgroup ITT Population		Overall ITT Population	
	TIS + Chemo (n=376)	PBO + Chemo (n=372)	TIS + Chemo (n=501)	PBO + Chemo (n=496)
Age - median (range), years	59.0 (23.0-86.0)	61.0 (25.0-83.0)	60.0 (23.0-86.0)	61.0 (25.0-86.0)
Sex - male, n (%)	258 (68.6)	261 (70.2)	346 (69.1)	346 (69.8)
ECOG PS, n (%)				
0	120 (31.9)	102 (27.4)	169 (33.7)	154 (31.0)
1	256 (68.1)	270 (72.6)	332 (66.3)	342 (69.0)
Primary tumor location, n (%)[a]				
Stomach	329 (87.5)	319 (85.8)	405 (80.8)	395 (79.6)
GEJ	47 (12.5)	52 (14.0)	96 (19.2)	100 (20.2)
PD-L1 TAP score, n (%)				
≥5%	202 (53.7)	201 (54.0)	274 (54.7)	272 (54.8)
<5%	174 (46.3)	171 (46.0)	227 (45.3)	224 (45.2)
Metastatic disease, n (%)	373 (99.2)	369 (99.2)	494 (98.6)	490 (98.8)
Peritoneal metastasis, n (%)	165 (43.9)	160 (43.0)	220 (43.9)	214 (43.1)
Investigator-chosen chemo, n (%)				
Oxaliplatin/capecitabine	370 (98.4)	367 (98.7)	466 (93.0)	465 (93.8)
Cisplatin/5-fluorouracil	6 (1.6)	5 (1.3)	35 (7.0)	31 (6.3)

Data cutoff: February 28, 2023.

[a]The diagnosis of one patient was updated from gastric adenocarcinoma to be pancreatic cancer after randomization and the patient remained in the ITT population.

Abbreviations: Chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; ITT, intent-to-treat; PBO, placebo; PD-L1, programmed death-ligand 1; TAP, tumor area positivity; TIS, tislelizumab.

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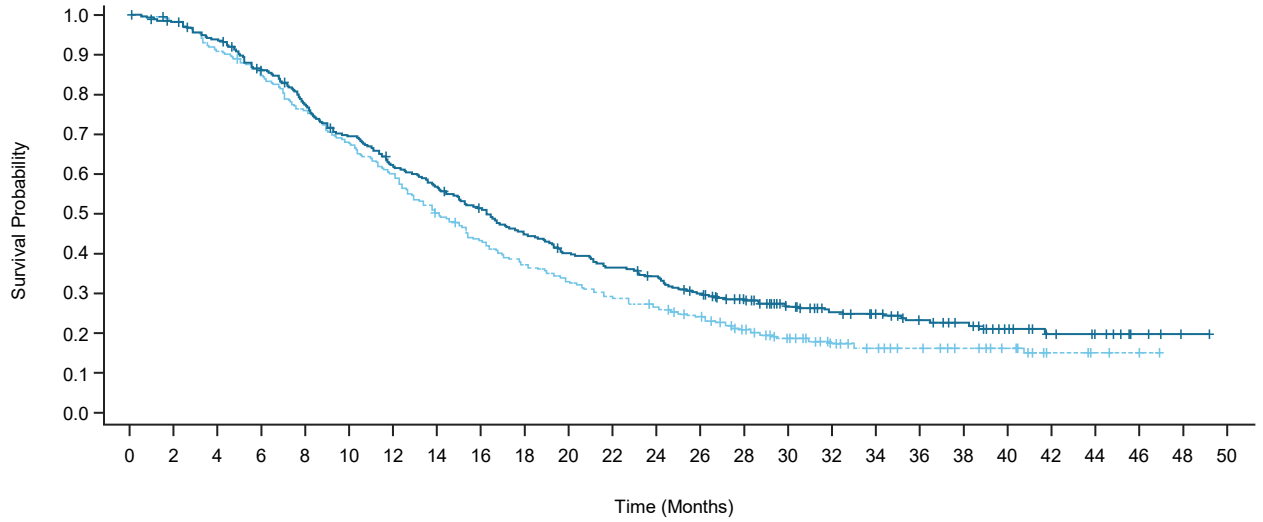
OS: Asian Subgroup (ITT Population)



Number of patients at risk:

TIS + chemo	376	363	346	316	282	252	224	205	184	160	142	130	120	103	86	64	54	48	38	30	21	13	10	4	1	0
PBO + chemo	372	361	333	312	275	246	217	182	156	134	118	104	94	83	64	47	36	28	24	20	15	6	3	2	0	0

	Events, n (%)	Median OS (95% CI), Months[a]	HR (95% CI)[a]
TIS + chemo (n=376)	274 (72.9)	16.4 (14.4, 18.0)	0.83 (0.70, 0.97)
PBO + chemo (n=372)	298 (80.1)	14.1 (12.8, 15.4)	

An improvement in OS was observed with tislelizumab plus chemotherapy vs placebo plus chemotherapy in the ITT population

Data cutoff: February 28, 2023.

[a]HR and 95% CIs were estimated from an unstratified Cox regression model including treatment as a covariate.

Abbreviations: Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; PBO, placebo; TIS, tislelizumab.

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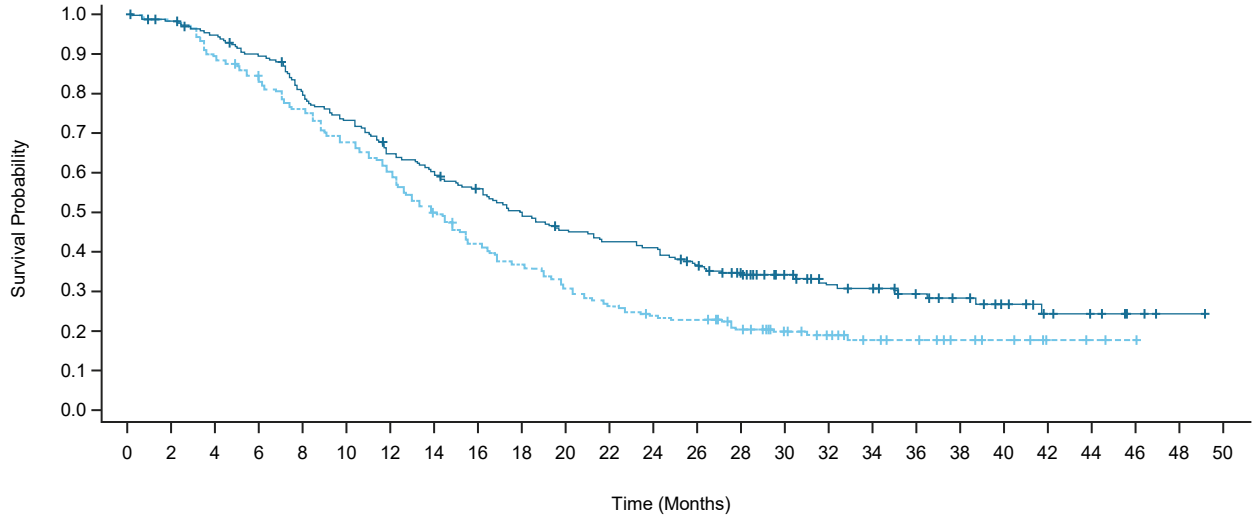
OS: Asian Subgroup (PD-L1 Score ≥5% Population)



Number of patients at risk:

TIS + chemo	202	196	188	176	156	143	126	117	107	94	86	81	78	68	56	43	35	31	24	19	14	9	7	3	1	0
PBO + chemo	201	195	177	165	149	133	119	97	81	71	60	51	45	43	35	26	21	15	13	9	7	3	2	1	0	0

	Events, n (%)	Median OS (95% CI), Months[a]	HR (95% CI)[a]
TIS + chemo (n=202)	135 (66.8)	18.0 (15.0, 21.6)	0.71 (0.56, 0.89)
PBO + chemo (n=201)	157 (78.1)	14.0 (12.3, 15.5)	

An improvement in OS was also observed with tislelizumab plus chemotherapy vs placebo plus chemotherapy in the PD-L1 score ≥5% population

Data cutoff: February 28, 2023.

[a]HR and 95% CIs were estimated from an unstratified Cox regression model including treatment as a covariate.

Abbreviations: Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; OS, overall survival; PBO, placebo; PD-L1, programmed death-ligand 1; TIS, tislelizumab.

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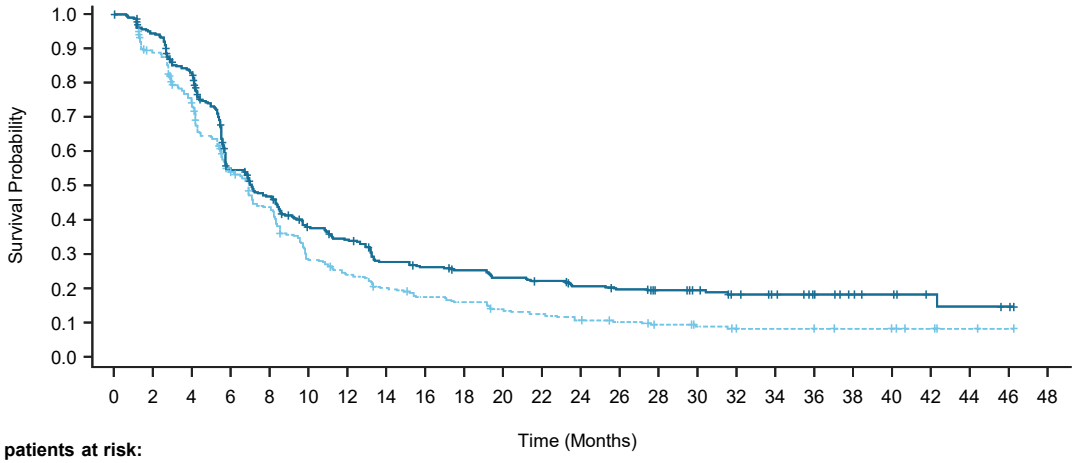
PFS: Asian Subgroup

ITT Population

	Events, n (%)	Median PFS (95% CI), Months	HR (95% CI)[a]
TIS + chemo (n=376)	266 (70.7)	7.1 (5.8, 8.3)	0.76 (0.64, 0.90)
PBO + chemo (n=372)	293 (78.8)	6.9 (5.8, 7.2)	

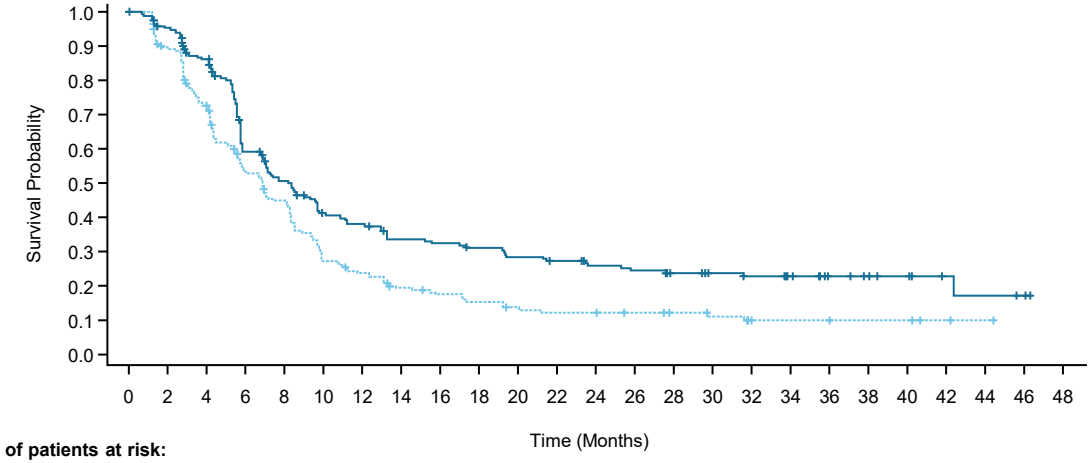


Number of patients at risk:

TIS + chemo	376	334	285	180	149	115	103	81	76	71	65	61	54	51	40	37	32	27	21	16	12	5	4	3	0
PBO + chemo	372	308	251	171	136	87	73	59	49	45	38	34	29	25	21	16	13	11	10	8	7	4	2	1	0

PD-L1 Score ≥5% Population

	Events, n (%)	Median PFS (95% CI), Months	HR (95% CI)[a]
TIS + chemo (n=202)	134 (66.3)	8.2 (6.9, 9.7)	0.67 (0.53, 0.84)
PBO + chemo (n=201)	157 (78.1)	6.8 (5.6, 8.1)	



Number of patients at risk:

TIS + chemo	202	179	157	104	86	67	62	53	51	48	44	41	36	34	27	24	22	18	13	11	8	4	3	2	0
PBO + chemo	201	167	133	91	76	46	39	30	26	23	19	17	17	15	13	10	7	6	5	4	4	2	1	0	0

Improved PFS was observed with tislelizumab plus chemotherapy vs placebo plus chemotherapy in the ITT and PD-L1 score ≥5% populations

Data cutoff: February 28, 2023.

[a]HR was based on an unstratified Cox regression model.

Abbreviations: Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; PBO, placebo; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TIS, tislelizumab.

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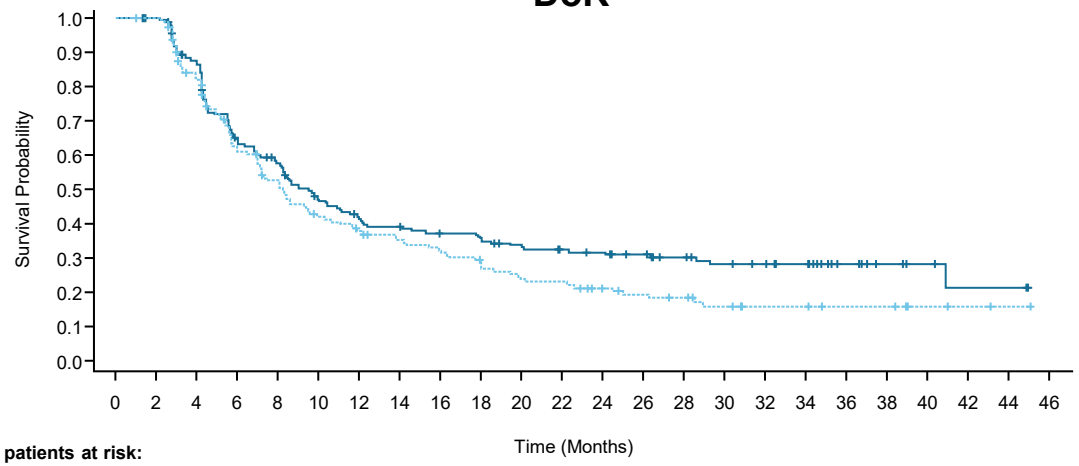
Disease Response & Duration of Response: Asian Subgroup

ITT Population

	ORR, % (95% CI)[a,b]	Median DoR (95% CI), Months[c]
TIS + chemo (n=376)	51.1 (45.9, 56.2)	9.5 (8.1, 11.5)
PBO + chemo (n=372)	43.5 (38.4, 48.8)	8.2 (6.9, 9.9)

DoR



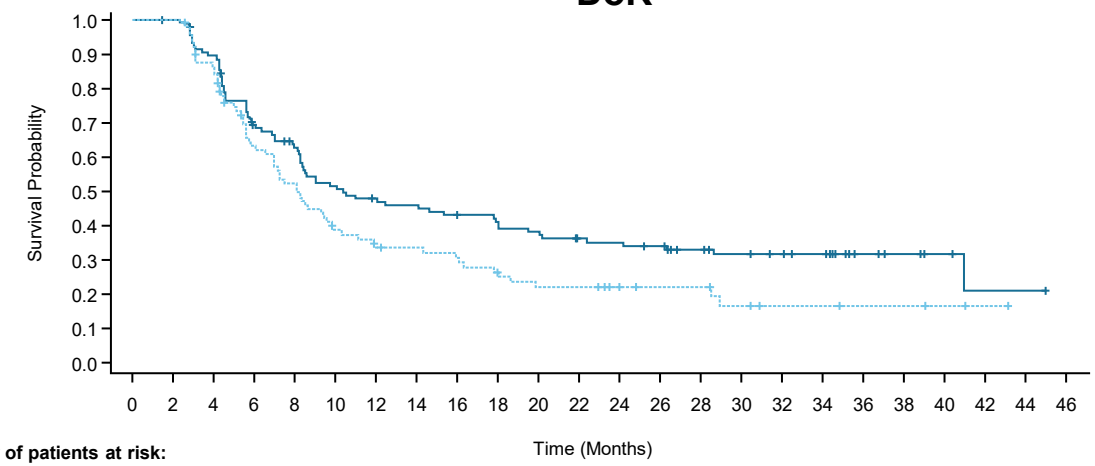
Number of patients at risk:

TIS + chemo	192	190	160	116	101	81	70	65	61	58	53	48	46	41	34	30	28	24	14	10	5	3	3	0
PBO + chemo	162	156	124	88	74	58	51	46	42	36	30	29	23	19	17	12	9	9	7	7	4	2	1	0

PD-L1 Score ≥5% Population

	ORR, % (95% CI)[a,b]	Median DoR (95% CI), Months[d]
TIS + chemo (n=202)	56.9 (49.8, 63.9)	10.3 (8.2, 18.0)
PBO + chemo (n=201)	45.3 (38.3, 52.4)	8.0 (6.5, 9.9)

DoR



Number of patients at risk:

TIS + chemo	115	114	102	76	67	55	49	48	44	41	39	34	33	31	25	22	20	17	9	7	4	2	2	0
PBO + chemo	91	89	72	51	42	30	25	24	22	17	15	15	11	10	10	6	4	4	3	3	2	1	0	0

Tislelizumab plus chemotherapy showed a favorable ORR and DoR compared with placebo plus chemotherapy in the ITT and PD-L1 score ≥5% populations

Data cutoff: February 28, 2023.

[a]ORR was calculated using the unstratified Cochran-Mantel-Haenszel method. [b]ORR is defined as the proportion of patients with a confirmed complete response or partial response. [c]DoR analysis performed on 192 patients in the TIS + chemo arm and 162 patients in the PBO + chemo arm. [d]DoR analysis performed on 115 patients in the TIS + chemo arm and 91 patients in the PBO + chemo arm.

Abbreviations: Chemo, chemotherapy; CI, confidence interval; DoR, duration of response; ITT, intent-to-treat; ORR, objective response rate; PBO, placebo; PD-L1, programmed death-ligand 1; TIS, tislelizumab.

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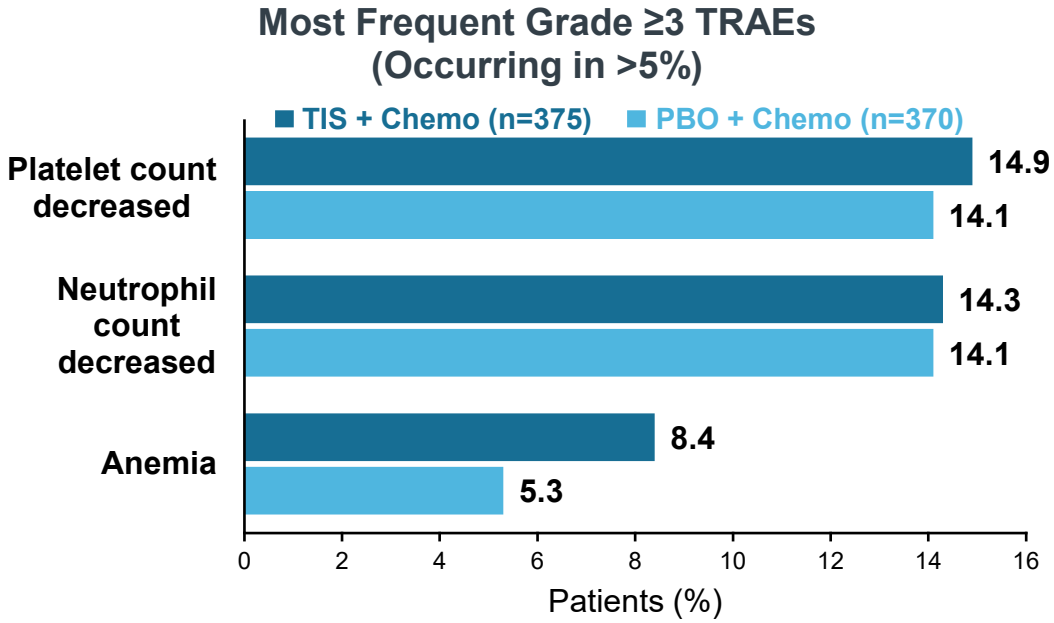
Safety Summary: Asian Subgroup (Safety Analysis Population)

	Tislelizumab + Chemotherapy (n=375)	Placebo + Chemotherapy (n=370)
Patients with at least one TRAE	366 (97.6)	360 (97.3)
Grade ≥3 TRAEs	208 (55.5)	185 (50.0)
Serious TRAEs	97 (25.9)	55 (14.9)
TRAE leading to death	9 (2.4)	3 (0.8)
TRAE leading to treatment discontinuation	64 (17.1)	33 (8.9)



No new safety signals with tislelizumab plus chemotherapy were identified in the Asian subgroup

Data cutoff: February 28, 2023. Data are n (%).

Abbreviations: Chemo, chemotherapy; PBO, placebo; TIS, tislelizumab; TRAE, treatment-related adverse event.

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Conclusions

- In Asian patients in the RATIONALE-305 study
  - **Tislelizumab plus chemotherapy showed an improvement** in OS vs placebo plus chemotherapy in both the ITT and PD-L1 score ≥5% populations
  - Additionally, tislelizumab plus chemotherapy demonstrated **improved PFS, favorable response rates** and **more durable antitumor responses** versus placebo plus chemotherapy
  - Tislelizumab plus chemotherapy also showed a **manageable safety profile,** with **no new safety signals identified**
- The efficacy and safety results in the Asian patient subgroup were consistent with the results in the overall study population, suggesting this combination may be a first-line treatment option for Asian patients with advanced GC/GEJC[1]

Abbreviations: GC/GEJC, gastric/gastroesophageal junction cancer; ITT, intent-to-treat; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

1. Xu RH, et al. *Ann Oncol.* 2023; 34(suppl_2):S1320-1321.

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Acknowledgments

- The authors would like to thank the patients and their families for their participation in the study, and the global investigators and site personnel for their support during the conduct of this important trial

- This study is sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Gemma Walker, BSc, of Ashfield MedComms, an Inizio company, and was funded by BeiGene, Ltd.

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