ASCO® Gastrointestinal Cancers Symposium

RATIONALE-305: Phase 3 Study of Tislelizumab + Chemotherapy vs Placebo + Chemotherapy as First-line Treatment of Advanced Gastric or Gastroesophageal Junction Adenocarcinoma

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Background

- Gastric cancer is the fifth most common cancer globally[1] and is more prevalent in Eastern Asia[2]
- The prognosis for patients with advanced unresectable or metastatic gastric cancer or gastroesophageal junction adenocarcinoma (GC/GEJC) treated with standard-of-care chemotherapy (chemo) remains unsatisfying[3]
- The addition of anti-programmed cell death protein 1 (PD-1) antibodies to chemo demonstrated improved survival,[4] and nivolumab plus chemo has been approved as first-line (1L) treatment in GC/GEJC in many countries/regions for patients with different PD-L1 expression[5-7]
- **Tislelizumab (TIS)** is an anti-PD-1 monoclonal antibody engineered to minimize binding to FcγR on macrophages.[8] In a phase 2 study, 1L TIS plus chemo demonstrated durable antitumor activity in GC/GEJC patients[9]
- RATIONALE-305 assessed the efficacy and safety of 1L TIS or placebo plus investigator's choice of chemo in unresectable, locally advanced or metastatic GC/GEJC
- We report results from the interim analysis performed in the PD-L1+ patient population

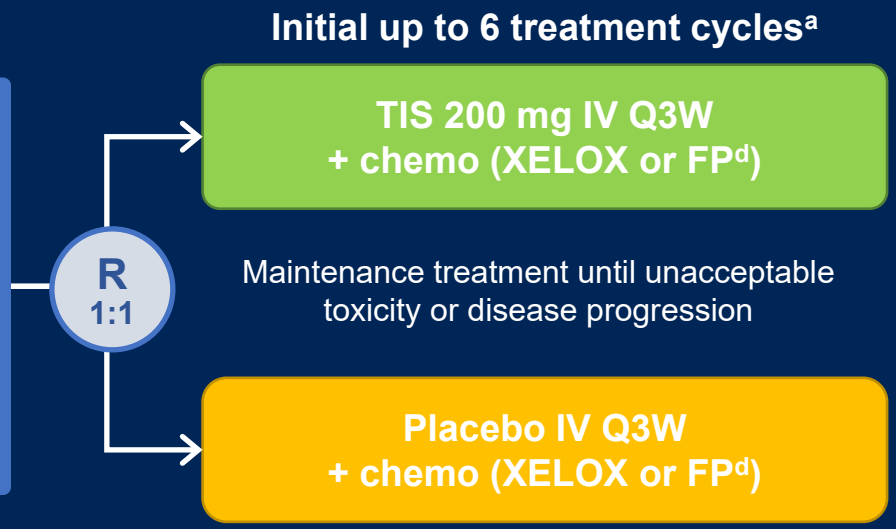
1. Global Cancer Observatory: Cancer Today, Lyon, France: International Agency for Research on Cancer. Available at: https://gco.iarc.fr/today/data/factsheets/cancers/39-All-cancers-fact-sheet.pdf; 2. WHO International Agency for Research on Cancer. Oesophagus. GLOBOCAN 2020b. Available at: https://gco.iarc.fr/today/data/factsheets/populations/160-china-fact-sheets.pdf; 3. Patel and Cecchini. *Curr Treat Options Oncol*. 2020;21(9):70; 4. Janjigian Y, et al. *Lancet*. 2021;398:27-40; 5. US Food and Drug Administration. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nivolumab-combination-chemotherapy-metastatic-gastric-cancer-and-esophageal; 6. PPF. Available at: https://www.ppf.eu/insights/biotech-market/september-2021-review-of-news-from-the-most-innovative-therapeutic-areas-and-the/opdivo-approved-as-first-immunotherapy-for-first-line-advanced-gastric-cancer-in; 7. Bristol Myers Squibb Press Release. Available at: https://news.bms.com/news/corporate-financial/2021/Bristol-Myers-Squibb-Receives-European-Commission-Approval-for-Opdivo-nivolumab--Chemotherapy-for-Patients-with-HER2-Negative-Advanced-or-Metastatic-Gastric-Gastroesophageal-Junction-or-Esophageal-Adenocarcinoma-/default.aspx; 8. Zhang T, et al. *Cancer Immunol Immunother*. 2018;67:1079-1090; 9. Xu J, et al. *Clin. Cancer Res.* 2020;26:4542-4250.

Study Design

Randomized, double-blind, global phase 3 study

Key eligibility criteria:

- Histologically confirmed GC/GEJC
- Exclude patients with HER2-positive tumors
- No previous therapy for unresectable, locally advanced or metastatic GC/GEJC



Primary endpoints

OS in PD-L1+ (PD-L1 score ≥5%[b]) and ITT analysis set

Secondary endpoints[c]

PFS, ORR, DoR, DCR, CBR, TTR, HRQoL, safety

Stratification

- Region of enrolment
- Peritoneal metastasis
- PD-L1 score (PD-L1 ≥5% vs <5%[b])
- Investigator's choice of chemo

Statistical considerations:

- If OS in the PD-L1+ analysis set is statistically significant, OS in the ITT analysis set is tested hierarchically
- An interim analysis was performed based on 291 actual observed events for the PD-L1+ analysis set, and the updated one-sided *P* value boundary was 0.0092

[a]Investigator's choice of doublet regimen (XELOX or FP) is administered up to 6 cycles; capecitabine as optional maintenance therapy only for XELOX regimen may be administered until disease progression, intolerable toxicity, or another treatment discontinuation criterion was met. Tislelizumab (or placebo) was administered until disease progression, intolerable toxicity, or another treatment discontinuation criterion was met.

[b]PD-L1 score was determined using VENTANA SP263 assay.

[c]All tumor response assessments were performed by investigator per RECIST v1.1.

[d]XELOX: Oxaliplatin 130 mg/m² Day 1 + capecitabine 1000 mg/m² BID Day 1-14, Q3W; FP: Cisplatin 80 mg/m² Day 1 + 5-FU 800 mg/m2/day CIV Day 1-5, Q3W.

Baseline Characteristics in the PD-L1+ Analysis Set

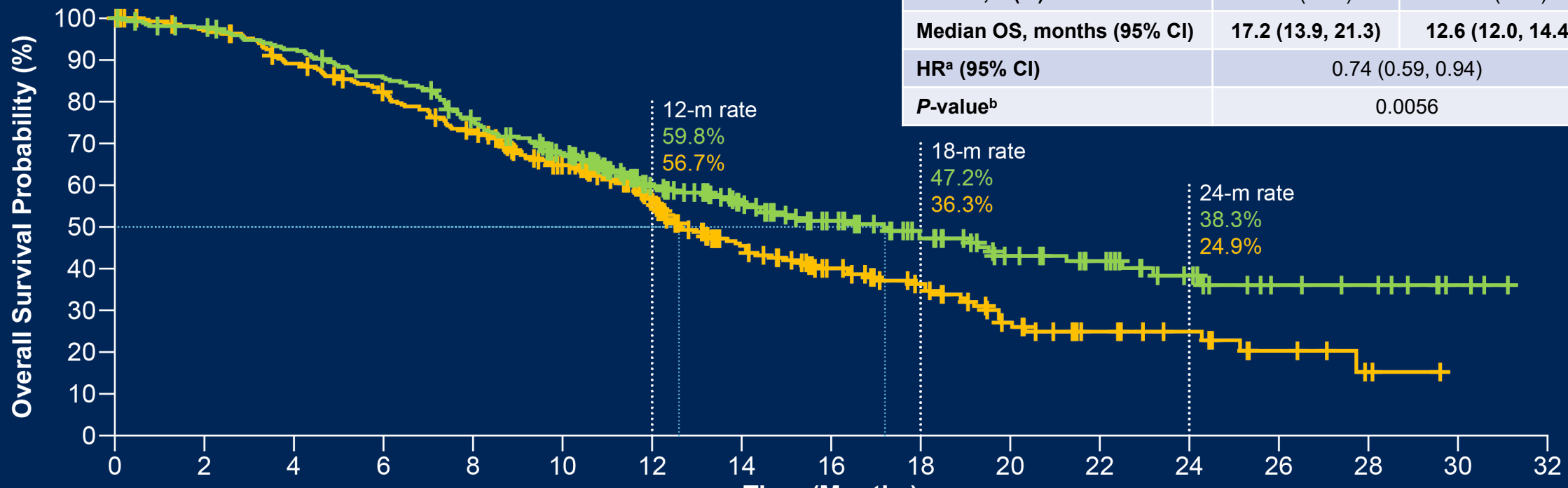
		TIS + Chemo (n=274)	Placebo + Chemo (n=272)
Median age, years (range)		61.0 (23.0-83.0)	62.0 (30.0-84.0)
Male sex, % (n)		70.4 (193)	73.9 (201)
Region, % (n)	**East Asia[a]**	73.7 (202)	73.9 (201)
	Rest of world[b]	26.3 (72)	26.1 (71)
ECOG PS, % (n)	**0**	35.8 (98)	31.6 (86)
	1	64.2 (176)	68.4 (186)
Primary location, % (n)	**Stomach**	81.4 (223)	78.7 (214)
	GEJC	18.6 (51)	21.3 (58)
Investigator-chosen chemo, % (n)	**XELOX**	92.7 (254)	93.4 (254)
	FP	7.3 (20)	6.6 (18)
Metastatic diseases, % (n)		98.5 (270)	98.5 (268)
Peritoneal metastasis, % (n)		41.2 (113)	40.1 (109)
Prior adjuvant/neoadjuvant treatment, % (n)		13.5 (37)	14.0 (38)

Data cutoff: October 08, 2021. Median follow up was 15.9 months in the TIS + chemo arm and 16.8 months in the placebo + chemo arm.
In the ITT population, 54.7% of patients in the TIS + chemo arm and 54.8% of patients in the placebo + chemo arm had a PD-L1 score of ≥5% and were included in the PD-L1+ analysis set.
[a]East Asia includes China (including Taiwan), Japan, and South Korea; [b]Rest of world includes US and EU.

Overall Survival (OS)

TIS plus chemo demonstrated statistically significant improvement in OS vs placebo plus chemo

	TIS + Chemo	Placebo + Chemo
Events, n (%)	130 (47.4)	161 (59.2)
Median OS, months (95% CI)	**17.2 (13.9, 21.3)**	**12.6 (12.0, 14.4)**
HR[a] (95% CI)	0.74 (0.59, 0.94)	
***P*-value[b]**	0.0056	



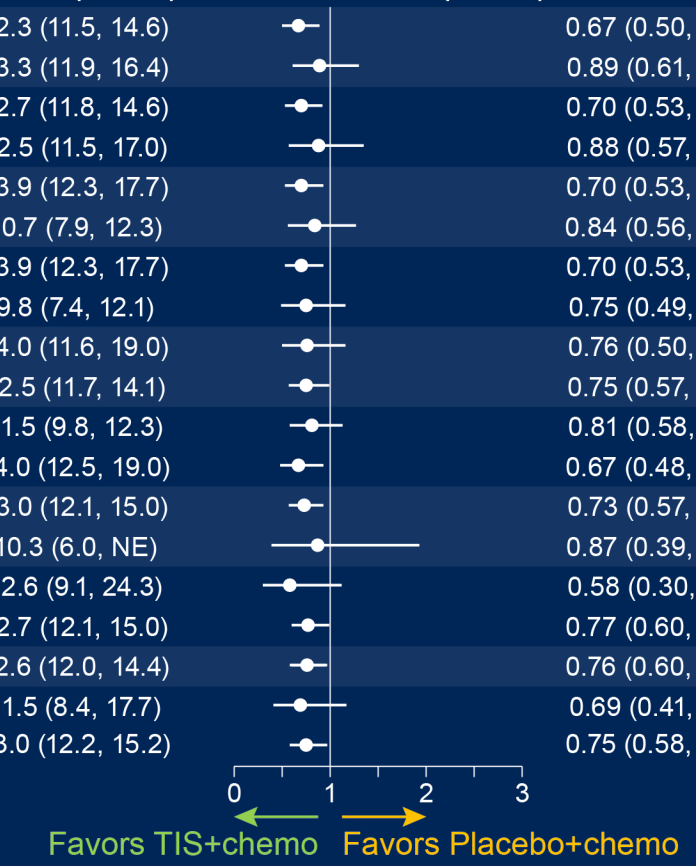
Number at Risk																
TIS+chemo	274	262	246	227	196	167	122	93	70	52	38	30	19	11	9	3	0
Placebo+chemo	272	261	237	215	189	156	118	80	57	44	26	16	12	6	2	0	0

[a]Primary OS analysis: Stratified by regions (east Asia vs rest of the world) and presence of peritoneal metastasis. [b]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.

OS Subgroup Analysis in PD-L1+ Analysis Set

Improvement in OS was observed across prespecified subgroups

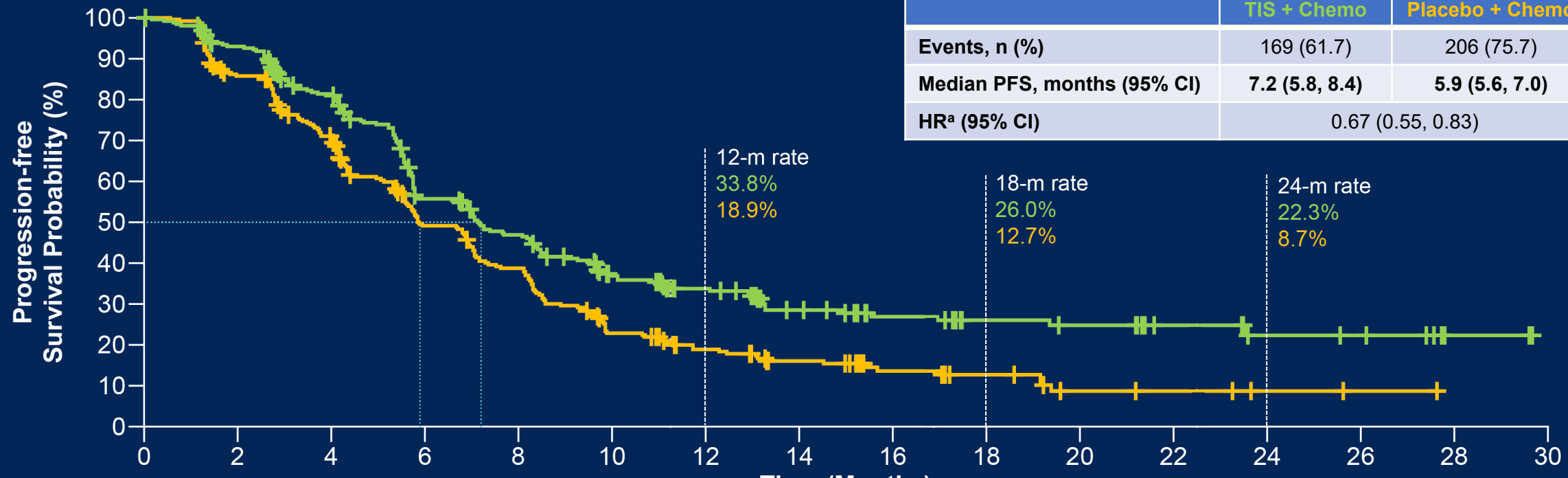
Subgroup		TIS+chemo Event/Total	Placebo+chemo Event/Total	TIS+chemo Median (95% CI)	Placebo+chemo Median (95% CI)	HR (95% CI)
Age	<65	81/175	98/157	19.3 (13.9, 24.2)	12.3 (11.5, 14.6)	0.67 (0.50, 0.89)
	≥65	49/99	63/115	14.1 (11.4, 23.2)	13.3 (11.9, 16.4)	0.89 (0.61, 1.30)
Gender	Male	87/193	121/201	18.0 (13.4, NE)	12.7 (11.8, 14.6)	0.70 (0.53, 0.92)
	Female	43/81	40/71	15.3 (10.4, 22.5)	12.5 (11.5, 17.0)	0.88 (0.57, 1.35)
Region	East Asia	88/202	113/201	19.3 (15.0, NE)	13.9 (12.3, 17.7)	0.70 (0.53, 0.93)
	Rest of World	42/72	48/71	10.2 (7.5, 15.0)	10.7 (7.9, 12.3)	0.84 (0.56, 1.27)
Race	Asian	88/202	113/201	19.3 (15.0, NE)	13.9 (12.3, 17.7)	0.70 (0.53, 0.93)
	White	38/64	45/62	10.2 (8.2, 15.0)	9.8 (7.4, 12.1)	0.75 (0.49, 1.16)
ECOG Performance Score	0	44/98	44/86	18.0 (12.2, NE)	14.0 (11.6, 19.0)	0.76 (0.50, 1.16)
	1	86/176	117/186	15.0 (13.3, 19.6)	12.5 (11.7, 14.1)	0.75 (0.57, 0.99)
Presence of Peritoneal Metastasis	Yes	68/113	74/109	11.7 (9.6, 14.1)	11.5 (9.8, 12.3)	0.81 (0.58, 1.13)
	No	62/161	87/163	23.2 (18.0, NE)	14.0 (12.5, 19.0)	0.67 (0.48, 0.93)
Investigator's Choice of Chemotherapy	Oxaliplatin+Capecitabine	118/254	149/254	18.0 (14.1, 22.5)	13.0 (12.1, 15.0)	0.73 (0.57, 0.93)
	Cisplatin+5-Fluorouracil	12/20	12/18	9.8 (6.1, NE)	10.3 (6.0, NE)	0.87 (0.39, 1.93)
Prior Adjuvant/ Neo-Adjuvant Therapy	Yes	15/37	22/38	21.3 (11.4, NE)	12.6 (9.1, 24.3)	0.58 (0.30, 1.12)
	No	115/237	139/234	16.4 (13.3, 19.6)	12.7 (12.1, 15.0)	0.77 (0.60, 0.99)
Disease Stage at Screening	Metastatic	130/270	159/268	16.4 (13.8, 19.6)	12.6 (12.0, 14.4)	0.76 (0.60, 0.95)
Primary Location	Gastro-Esophogeal Junction	24/51	35/58	18.0 (11.5, 21.3)	11.5 (8.4, 17.7)	0.69 (0.41, 1.17)
	Stomach	106/223	126/214	17.2 (13.8, 24.2)	13.0 (12.2, 15.2)	0.75 (0.58, 0.97)



Progression-Free Survival in the PD-L1+ Analysis Set

TIS plus chemo improved PFS over placebo plus chemo

	TIS + Chemo	Placebo + Chemo
Events, n (%)	169 (61.7)	206 (75.7)
Median PFS, months (95% CI)	**7.2 (5.8, 8.4)**	**5.9 (5.6, 7.0)**
HR[a] (95% CI)	0.67 (0.55, 0.83)	



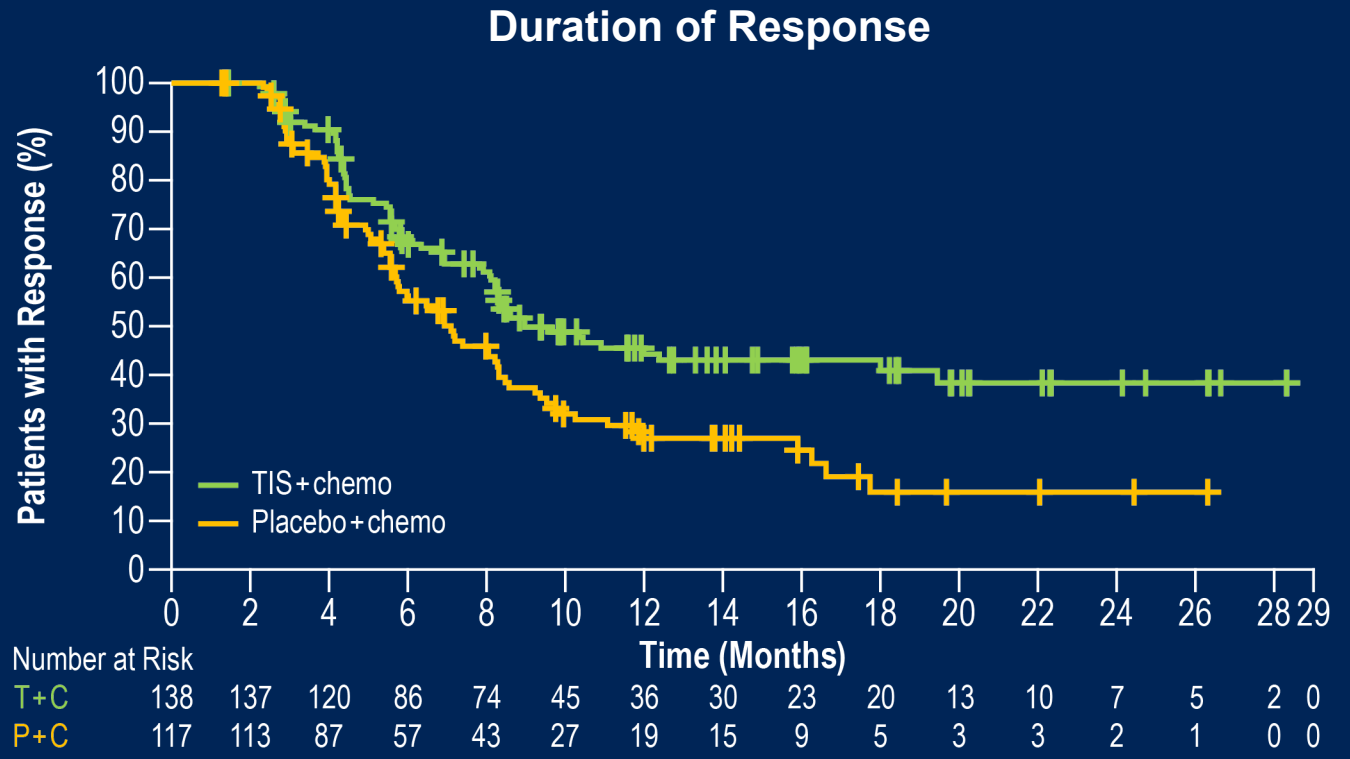
Number at Risk															
TIS+chemo	274	236	199	130	106	74	57	40	31	21	19	12	8	7	2	0
Placebo+chemo	272	219	176	114	89	50	35	25	15	11	5	4	2	1	0	0

[a]Stratified by regions (east Asia versus rest of the world) and presence of peritoneal metastasis.

Antitumor Response in the PD-L1+ Analysis Set

TIS plus chemo was associated with a numerically higher ORR and more durable response vs placebo plus chemo

	TIS + Chemo (n=274)	Placebo + Chemo (n=272)
ORR[a], % (95% CI[b])	**50.4** (44.3, 56.4)	**43.0** (37.1, 49.1)
Best overall response, % (n)		
CR	**3.3** (9)	**1.8** (5)
PR	**47.1** (129)	**41.2** (112)
SD[c]	**38.0** (104)	**40.1** (109)
PD	**4.4** (12)	**11.8** (32)
Undetermined[d]	**7.3** (20)	**5.1** (14)
Disease control rate, % (95% CI[a])	**88.3** (83.9, 91.9)	**83.1** (78.1, 87.3)
Median DoR, months (95% CI)	**9.0** (8.2, 19.4)	**7.1** (5.7, 8.3)



[a]ORR is defined as the percentage of patients with confirmed CR/PR.
[b]Exact Clopper-Pearson 2-sided confidence interval.
[c]SD includes non-CR and non-PD.
[d]Best overall response of 'undetermined' included patients who had postbaseline tumor assessment, none of which were evaluable; or patients who had no postbaseline tumor assessments due to death, withdrawal of consent, lost to follow up, or any other reasons.

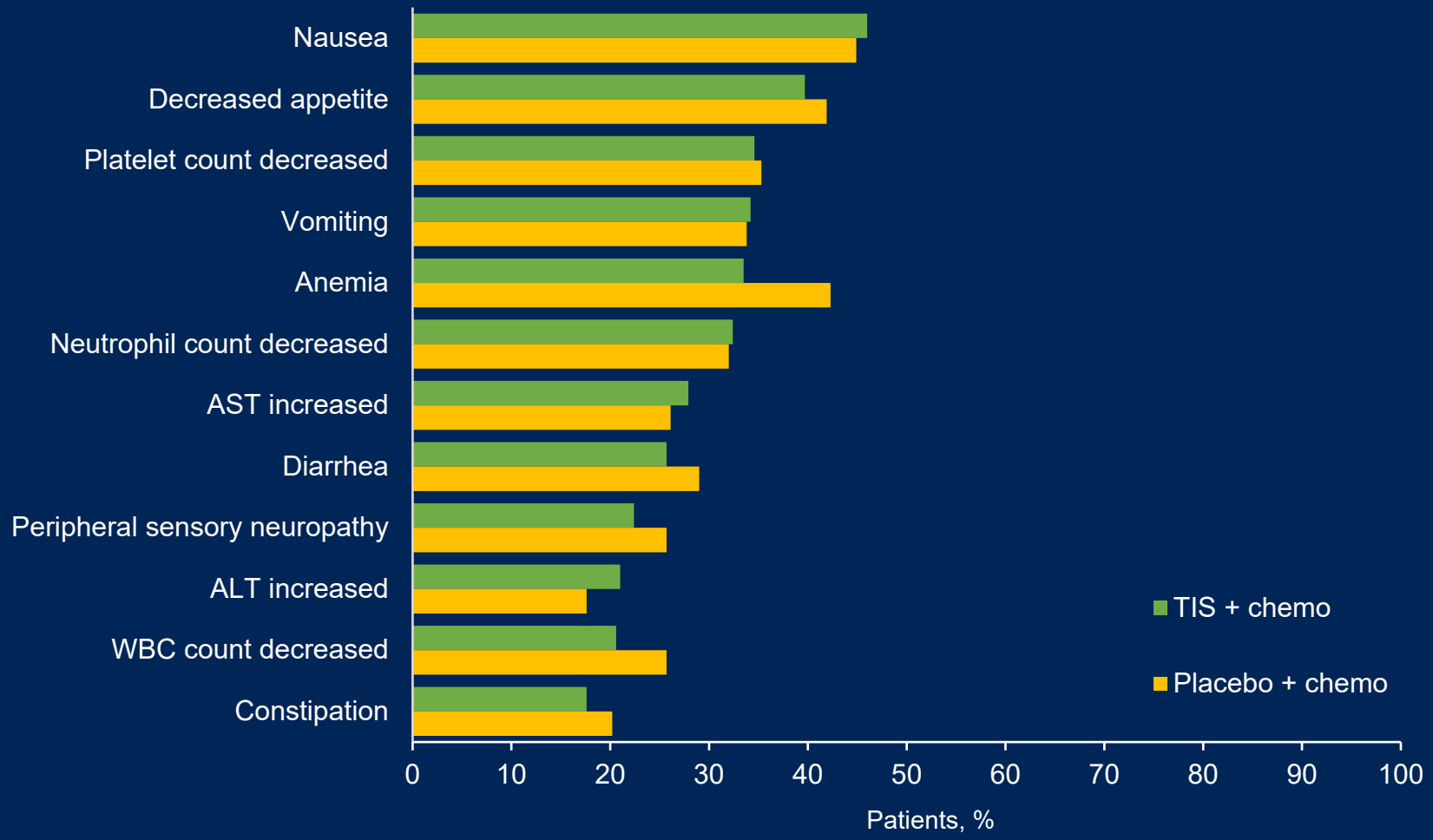
Safety Summary

TIS plus chemo had a manageable safety profile in patients with unresectable, locally advanced or metastatic GC/GEJC

Category, % (n)	TIS + Chemo (n=272)	Placebo + Chemo (n=272)
Median duration of tislelizumab/placebo treatment, weeks (range)	27.9 (0.6-135.3)	24.4 (2.3-128.6)
Any TEAE	99.6 (271)	97.8 (266)
Treatment-related	97.1 (264)	96.0 (261)
TEAE at grade ≥3	64.7 (176)	62.9 (171)
Treatment-related	52.6 (143)	48.5 (132)
Serious TEAE	42.3 (115)	36.8 (100)
Treatment-related	25.7 (70)	16.5 (45)
TEAE leading to discontinuation	22.4 (61)	12.1 (33)
TEAE leading to discontinuation of TIS/placebo	14.3 (39)	6.6 (18)
TEAE leading to discontinuation of any chemo component	19.9 (54)	11.4 (31)
TEAE leading to death	8.8 (24)	7.7 (21)
Treatment-related	2.2 (6)	0.7 (2)

For each row category, a patient with two or more adverse events in that category was counted only once. AE grades were evaluated based on National Cancer Institute–Common Terminology Criteria for Adverse Events (version 5.0). AE terms were coded using Medical Dictionary for Drug Regulatory Affairs version 24.0.

Treatment-Emergent Adverse Events (TEAEs) Reported in ≥20% of Patients



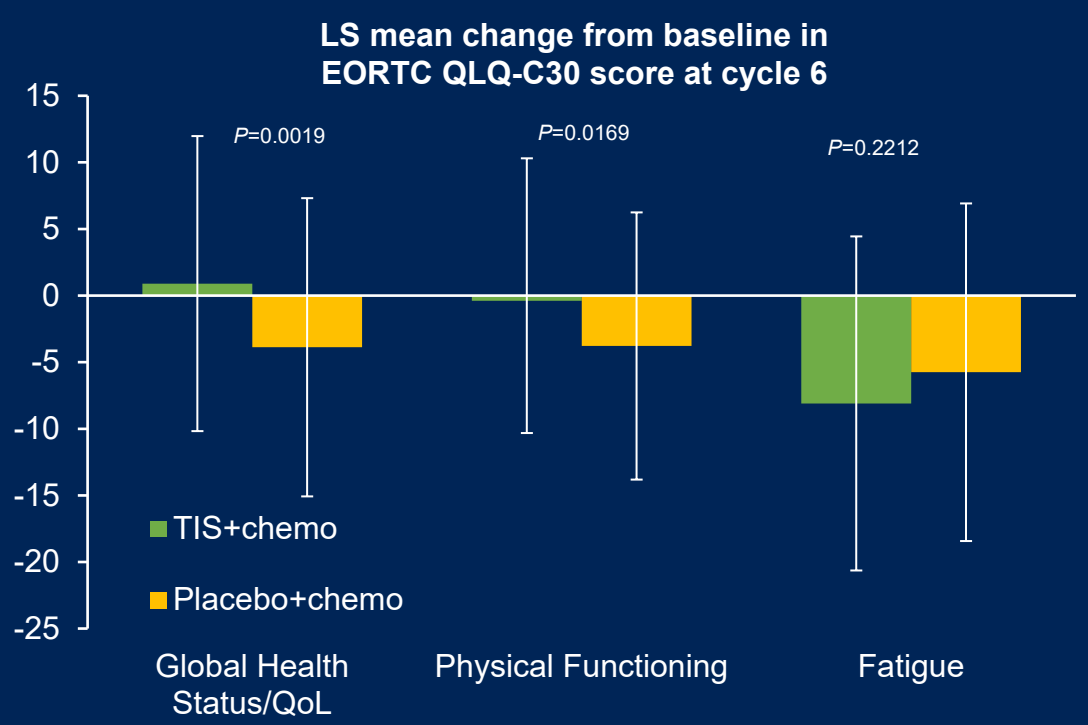
The profile of TEAEs with tislelizumab plus chemo was consistent with the known profile of each treatment agent, with no new safety signals identified

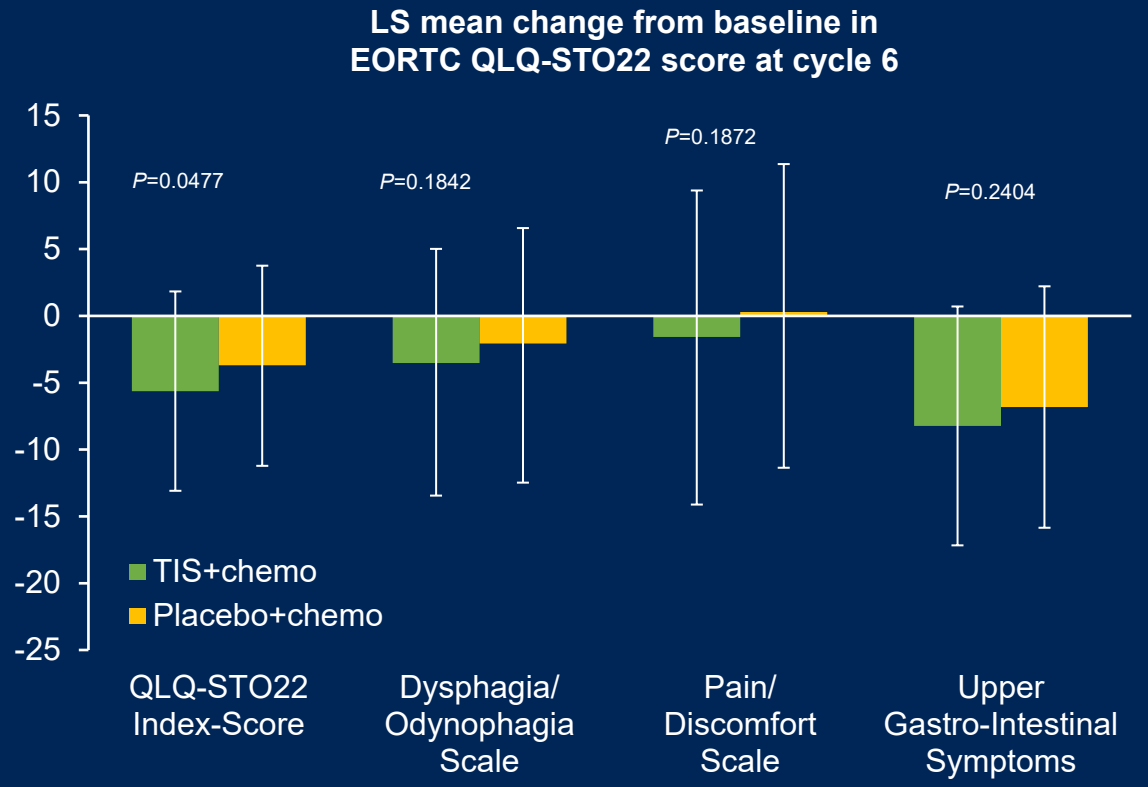
Patients with multiple events for a given preferred term were counted only once at the worst severity for the preferred term. AE grades were evaluated based on National Cancer Institute–Common Terminology Criteria for Adverse Events (version 5.0). AE terms were coded using Medical Dictionary for Drug Regulatory Affairs version 24.0.

Health-Related Quality of Life

Addition of TIS to chemo not only did not worsen HRQoL, but suggested better HRQoL as indicated by:

- **Maintenance of Global Health Status/QoL, physical functioning, and greater reduction in general stomach cancer symptoms**
- **There was also a trend towards reduction in fatigue, pain/discomfort and upper gastrointestinal symptoms with TIS plus chemo**





Higher scores in global health status and physical function and lower scores in symptom scales represents better outcomes. *P*-values are nominal.

Conclusions

- TIS plus chemo demonstrated statistically significant and clinically meaningful improvement in OS versus placebo plus chemo in patients with PD-L1-positive GC/GEJC
  - Median OS: 17.2 vs 12.6 months; HR 0.74 (95% CI 0.59, 0.94); *P*=0.0056
- The OS benefit with TIS plus chemo was accompanied by improvements in PFS, DoR, and ORR compared with placebo plus chemotherapy
- TIS plus chemo had a manageable safety profile in patients with unresectable, locally advanced or metastatic GC/GEJC, with no new safety signals identified
- Better HRQoL was generally observed in patients treated with TIS plus chemo than in patients treated with placebo plus chemo

RATIONALE-305 results offer tislelizumab plus chemotherapy as a new 1L treatment option for patients with PD-L1-positive unresectable, locally advanced or metastatic GC/GEJC

The study continues to be double-blinded towards OS final analysis in the ITT population, results of which will be presented later this year

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