Adv Ther (2026) 43:165–183
https://doi.org/10.1007/s12325-025-03415-0

ORIGINAL RESEARCH

Tislelizumab + Chemotherapy in Gastric Cancer: Long-Term RATIONALE-305 Randomized Trial Follow-up

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Received: August 13, 2025 / Accepted: October 21, 2025 / Published online: November 18, 2025

ABSTRACT

Introduction: Tislelizumab + chemotherapy has shown promising results as first-line treatment for advanced gastric/gastroesophageal junction adenocarcinoma (GC/GEJC). We present long-term safety and efficacy outcomes from the RATIONALE-305 trial after 3 years of follow-up, focusing on the intent-to-treat (ITT) population and subgroups based on programmed death ligand-1 (PD-L1) expression.

Methods: RATIONALE-305, a randomized, double-blind, placebo-controlled, phase 3 trial conducted across 146 centers in Asia, Europe, and North America (December 2018–February 2024), enrolled 997 adults with human epidermal growth factor receptor 2–negative advanced GC/GEJC, randomized 1:1 to receive tislelizumab + chemotherapy or placebo + chemotherapy. The primary endpoint was overall survival (OS) in patients with PD-L1 Tumor Area Positivity (TAP) score ≥ 5% and the ITT population. Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), safety, and tolerability. At 3-year follow-up, 959 (96.2%) patients had discontinued or completed

Tao Sheng: At time of study in Biostatistics.

Prior Presentation: Data from this manuscript were previously presented in part at The European Society for Medical Oncology (ESMO) Gastrointestinal Cancers Congress 2024 (June 26–29, 2024, Munich, Germany) and at ESMO Congress 2024, September 13–17, 2024, Barcelona, Spain.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12325-025-03415-0.

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treatment. The minimum follow-up duration was 36.6 months.

***Results*:** In all randomized patients ($n=997$), 69.4% male and 30.6% female, tislelizumab + chemotherapy improved OS versus placebo + chemotherapy [15.0 months (95% CI 13.6–16.5) vs. 12.9 months (95% CI 12.1–14.1); stratified hazard ratio (HR) 0.79]. Investigator-assessed PFS was also improved [6.9 months (95% CI 5.7–7.2) vs. 6.2 months (95% CI 5.6–6.9); stratified HR 0.79]. The ORR was higher with tislelizumab + chemotherapy. In patients with a PD-L1 TAP score ≥ 5% [$n=546$ (54.8%)], similar OS and PFS benefits were observed compared to the ITT population. OS was 16.4 (95% CI 13.6–19.1) months versus 12.8 (95% CI 12.0–14.5) months, stratified HR 0.71 for tislelizumab + chemotherapy versus placebo + chemotherapy, respectively. PFS was 7.2 (95% CI 5.8–8.4) months versus 5.9 (95% CI, 5.6–7.0) months, stratified HR 0.69. No new safety signals were identified.

***Conclusion*:** Results from RATIONALE-305 continued to show durable and improved efficacy outcomes with tislelizumab + chemotherapy versus placebo + chemotherapy at 3 years in advanced GC/GEJC, supporting PD-L1 as a potential prognostic biomarker.

***Trial Registration*:** ClinicalTrials.gov Identifier: NCT03777657.

Keywords: Chemotherapy; Gastroesophageal junction adenocarcinoma; Overall survival; PD-L1 expression; Progression-free survival; Tislelizumab; Gastric adenocarcinoma

Key Summary Points

Why carry out this study?
Advanced gastric and gastroesophageal junction adenocarcinomas (GC/GEJC) have poor prognosis and limited treatment options, highlighting the need for more effective therapies
This study aimed to evaluate the long-term efficacy and safety of adding tislelizumab to standard chemotherapy in patients with advanced GC/GEJC
What was learned from the study?
After 3 years of follow-up, patients receiving tislelizumab + chemotherapy had longer overall survival and progression-free survival than those receiving chemotherapy alone, with a more pronounced difference observed in patients with programmed death ligand 1 (PD-L1) ≥ 5% by Tumor Area Positivity score

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The study demonstrated that tislelizumab + chemotherapy is a promising first-line treatment option for advanced GC/GEJC, with a manageable safety profile and improved patient-reported outcomes

These findings indicate that tislelizumab + chemotherapy can improve survival and reduce symptom burden in patients with GC/GEJC and support the potential use of PD-L1 expression as a predictive biomarker for treatment response, which may help guide personalized treatment decisions in the future

INTRODUCTION

With the advent of chemotherapy combinations with immune checkpoint inhibitors in the past decade, there has been substantial improvement in the treatment of advanced human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction adenocarcinoma (GC/GEJC) compared with preexisting therapies [1–6]. First-line treatment modalities combining chemotherapy and programmed cell death 1 (PD-1) inhibitors have demonstrated improved efficacy and survival outcomes in this population, leading to their approval in several countries [7–13]. Accordingly, in the phase 3 RATIONALE-305 trial in patients with advanced GC/GEJC, tislelizumab (a PD-1 inhibitor) plus chemotherapy demonstrated statistically significant overall survival (OS) benefit versus chemotherapy alone as first-line therapy in both patients with a programmed death ligand 1 (PD-L1) score ≥ 5% and the intent-to-treat (ITT) population (regardless of PD-L1 status) [5]. At final analysis (minimum follow-up, 24.6 months; data cutoff, February 28, 2023), median OS for tislelizumab + chemotherapy versus chemotherapy alone was 16.4 versus 12.8 months in patients with PD-L1 Tumor Area Positivity (TAP) score ≥ 5% [hazard ratio (HR) 0.71 (95% confidence interval [CI] 0.58–0.86)] and 15.0 versus 12.9 months in the ITT population [HR 0.80 (95% CI 0.70–0.92); $p = 0.001$]. Treatment was effective in all patient subgroups, including those in Asia versus Europe or North America, as well as those with peritoneal, liver, and metastatic disease. Based on these results, the US Food and Drug Administration approved tislelizumab + chemotherapy for first-line treatment of GC/GEJC in patients with PD-L1 ≥ 1% tumor expression in December 2024.

Patients with higher PD-L1 expression have demonstrated comparatively more benefit from immunotherapies across a variety of tumor types, including GC/GEJC [3, 4, 6, 14]. In advanced GC/GEJC, PD-L1 expression measured by combined positive score (CPS), a cell counting-based method, has shown predictive value in clinical response to checkpoint inhibitors [4]. Analytical concordance between the TAP score (a visual estimation method) and CPS demonstrated that these methods are comparable measures of PD-L1 expression in tislelizumab-treated patients with GC/GEJC or esophageal squamous cell carcinoma [15].

We report long-term safety and efficacy at a minimum follow-up of 3 years from the RATIONALE-305 trial evaluating tislelizumab + chemotherapy as first-line treatment in advanced GC/GEJC in both patients with a PD-L1 TAP score ≥ 5% and the ITT population, with additional analyses of OS and progression-free survival (PFS) outcomes based on PD-L1 CPS ≥ 5, prevalence by PD-L1 expression at multiple cutoffs, and patient-reported outcomes (PROs).

METHODS

Study Design

RATIONALE-305 was a randomized, double-blind, global, phase 3 trial in adults aged ≥ 18 years with previously untreated locally advanced unresectable or metastatic HER2-negative GC/GEJC. The trial design and patient eligibility criteria have been reported in detail previously and are also described in the Supplementary Material [5]. The trial was conducted in compliance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki, and it was approved by the relevant institutional

review board/independent ethics committee for each study site. Written informed consent was obtained before study participation.

Patients continued treatment until disease progression or unacceptable toxicity. After 2 years of study treatment, if a complete response, partial response, or stable disease was achieved, treatment could be stopped based on the investigator's evaluation of a patient's clinical benefit and risk.

Endpoints and Assessments

Study endpoints and assessments have been described previously [5]. In summary, the primary endpoint was OS in patients with PD-L1 TAP score ≥ 5% and in the ITT population. Secondary endpoints (assessed by investigators) included PFS, confirmed objective response rate (ORR), disease control rate, clinical benefit rate, time to response, and duration of response (DoR), evaluated in patients with a PD-L1 TAP score ≥ 5% and in all randomized patients; these were assessed as post hoc analyses in patients who remained progression free at 3 years. Safety and tolerability were assessed in patients who received at least one dose of study treatment. PROs were assessed in all randomized patients (Supplementary Material).

Statistical Analysis

The statistical methodology for RATIONALE-305 has been reported previously [5]. Briefly, ~ 384 deaths in patients with PD-L1 TAP score ≥ 5% and ~ 768 deaths in all randomized patients at final analysis were estimated to provide 80% and 87% power, respectively, for superiority testing at a one-sided significance level of 0.025. Efficacy analyses were conducted in patients with PD-L1 TAP score ≥ 5% and in all randomized patients, with OS and PFS evaluated using a stratified log-rank test. A Cox proportional hazard regression model was used to estimate OS and PFS HRs and associated two-sided 95% CIs. The median and cumulative probabilities of time-to-event endpoints were estimated using the Kaplan-Meier method. OS was assessed in prespecified subgroups by PD-L1 expression status using TAP score, region, and baseline characteristics. ORR along with Clopper-Pearson two-sided 95% CIs were calculated and compared between treatment arms. Analyses performed at 3-year follow-up are considered descriptive. Time to deterioration (TTD) was estimated based on Kaplan-Meier method. All statistical analyses were conducted using SAS® version 9.4 (SAS Institute, Cary, NC, USA) or higher.

Changes in each PRO from baseline to cycles 4 and 6 were analyzed using a mixed model for repeated measures (MMRM); differences in the least-squares mean change (95% CI) between the arms from baseline to key clinical cycles 4 and 6 were assessed, and between-group *p* values were two-sided and nominal, without multiplicity adjustment. Least-squares mean changes (95% CI) were measured and reported. Changes in PRO of 5 to > 10 points were defined as "small," 10 to 20 as "moderate," and > 20 as "large;" a meaningful difference was defined as ≥ 5 points [16].

RESULTS

Patient Disposition and Characteristics

Baseline and disease characteristics in the ITT population have been reported previously and are summarized here briefly [5]. Among 997 patients included, 692 (69.4%) were male, 305 (30.6%) were female, 748 (75.0%) were Asian [including Chinese (51.9%), Korean (13.0%), and Japanese (10.1%)], and 223 (22.4%) were white; median (IQR) age was 61.0 (53.0–67.0) years. Data cutoff for 3-year survival follow-up was February 28, 2024. Minimum study follow-up duration (defined as time from randomization date of last enrolled patient to data cutoff) was 36.6 months. Of 501 patients randomized to tislelizumab + chemotherapy, 498 (99.4%) of whom were treated, 23 (4.6%) were still on therapy and 475 (94.8%) had discontinued or completed treatment (see Fig. S1 in

the Supplementary Material). After study treatment discontinuation, 273 (54.5%) received subsequent anticancer therapies (Table S1 in the Supplementary Material). Of 496 patients randomized to placebo + chemotherapy, 494 (99.6%) of whom were treated, 10 (2.0%) were still on therapy, and 484 (97.6%) had discontinued or completed treatment; after study treatment discontinuation, 300 (60.5%) received subsequent anticancer therapies. Median duration of exposure was 5.9 months (minimum, maximum: 0.1, 59.0) for tislelizumab + chemotherapy and 5.7 months (0.3, 48.7) for placebo + chemotherapy.

PD-L1 Subgroup Prevalence

Of 997 patients randomized (tislelizumab + chemotherapy, $n = 501$; placebo + chemotherapy, $n = 496$), 997 had evaluable TAP scores and 974 had evaluable post hoc CPS results (Table S2 in the Supplementary Material). A PD-L1 TAP score ≥ 5% was reported in 546 patients (54.8% of ITT population), of whom 274 were randomized to tislelizumab + chemotherapy and 272 were randomized to placebo + chemotherapy. Prevalence of PD-L1 subgroups was comparable across arms by TAP score or CPS at different thresholds.

Overall Survival

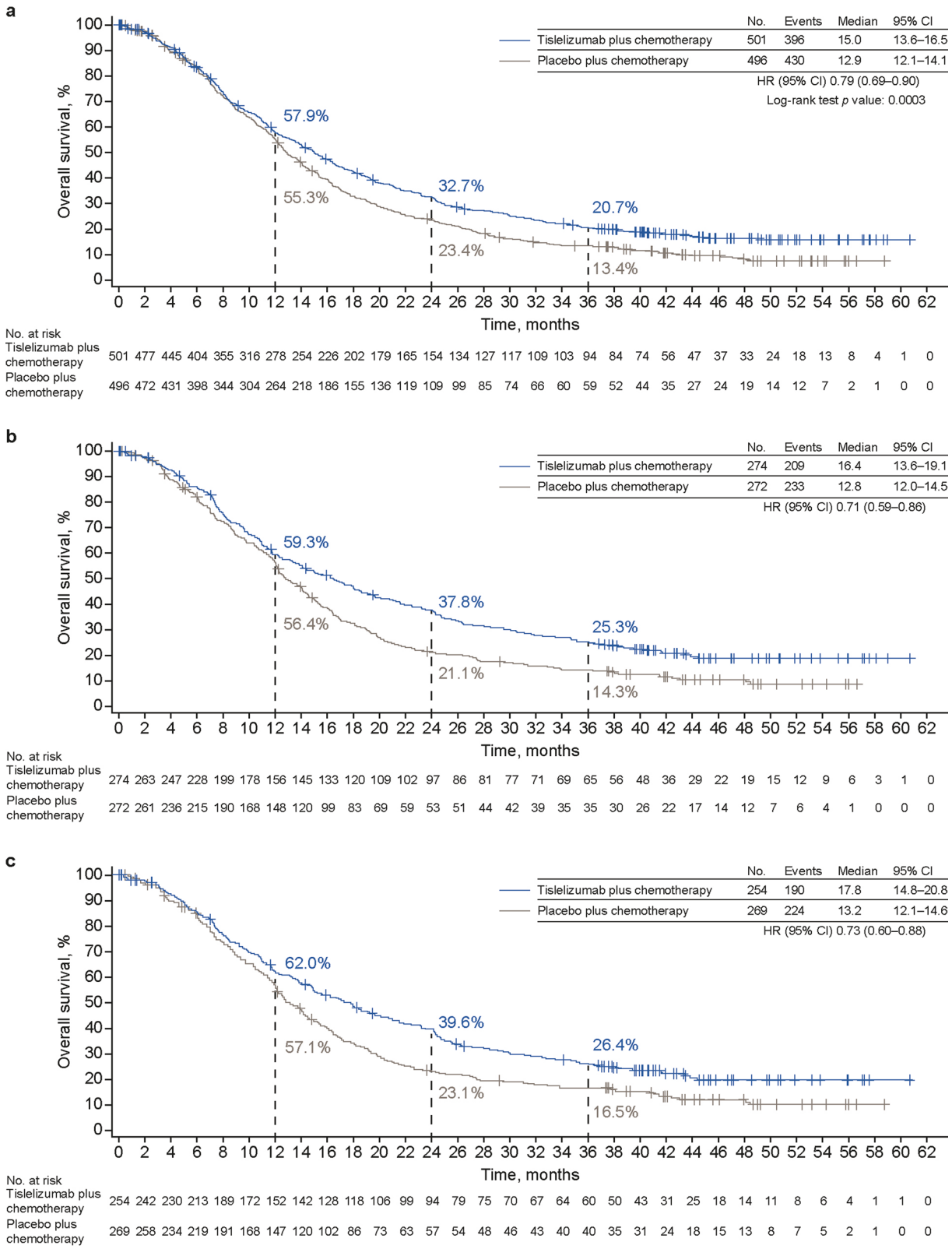
At 3-year follow-up, improvements were maintained with tislelizumab + chemotherapy versus placebo + chemotherapy for OS [median OS, 15.0 months (95% CI 13.6–16.5) vs. 12.9 months (95% CI 12.1–14.1), respectively; stratified HR 0.79 (95% CI 0.69–0.90)] in all randomized patients (Fig. 1a). In the tislelizumab + chemotherapy arm versus the placebo + chemotherapy arm, the 36-month OS rate was 20.7% (95% CI 17.1–24.4) versus 13.4% (95% CI 10.5–16.6), respectively. Unstratified HRs for OS results improved in the tislelizumab + chemotherapy arm versus the placebo + chemotherapy arm across multiple prespecified subgroups in all randomized patients (Fig. 2a).

Similar to the ITT population, OS benefit was observed in patients with PD-L1 TAP score ≥ 5%, with separation of Kaplan-Meier curves in favor of tislelizumab + chemotherapy (Fig. 1b); median OS (95% CI) for the tislelizumab + chemotherapy arm versus the placebo + chemotherapy arm was 16.4 (13.6–19.1) months versus 12.8 (12.0–14.5) months [stratified HR 0.71 (95% CI 0.59–0.86)]. Kaplan-Meier curves revealed clinically meaningful OS results that were similar between those defined by a PD-L1 TAP score ≥ 5% and CPS ≥ 5 (Fig. 1b, c). In the tislelizumab + chemotherapy arm versus the placebo + chemotherapy arm, the 36-month OS rates in patients with PD-L1 TAP score ≥ 5% were 25.3% (95% CI 20.2–30.7) versus 14.3% (95% CI 10.3–18.8), respectively. Unstratified HRs for OS in both arms across multiple prespecified subgroups in patients with PD-L1 TAP score ≥ 5% are shown in Fig. 2b.

Progression-Free Survival

Similar to OS results, investigator-assessed PFS was also improved in the tislelizumab + chemotherapy arm versus the placebo + chemotherapy arm in all randomized patients [stratified HR 0.79 (95% CI 0.68–0.91)] (Fig. 3a). Additionally, stratified HRs for PFS results improved in the tislelizumab + chemotherapy arm versus the placebo + chemotherapy arm across multiple prespecified subgroups in all randomized patients (Fig. 4a).

PFS benefit was observed in patients with PD-L1 TAP score ≥ 5%, with separation of Kaplan-Meier curves in favor of tislelizumab + chemotherapy (Fig. 3b). Median PFS (95% CI) favored patients treated with tislelizumab + chemotherapy versus placebo + chemotherapy in patients with PD-L1 TAP score ≥ 5% [7.2 (5.8–8.4) months vs. 5.9 (5.6–7.0) months]. Similar PFS outcomes were observed in patients with PD-L1 CPS ≥ 5 (Fig. 3b, c). Stratified HRs for PFS results in both arms across multiple prespecified subgroups in patients with PD-L1 TAP score ≥ 5% are reported in Fig. 4b.


a
Overall survival, %
Time, months
No. Events Median 95% CI
Tislelizumab plus chemotherapy 501 396 15.0 13.6–16.5
Placebo plus chemotherapy 496 430 12.9 12.1–14.1
HR (95% CI) 0.79 (0.69–0.90)
Log-rank test p value: 0.0003
57.9%
55.3%
32.7%
23.4%
20.7%
13.4%
No. at risk
Tislelizumab plus chemotherapy 501 477 445 404 355 316 278 254 226 202 179 165 154 134 127 117 109 103 94 84 74 56 47 37 33 24 18 13 8 4 1 0
Placebo plus chemotherapy 496 472 431 398 344 304 264 218 186 155 136 119 109 99 85 74 66 60 59 52 44 35 27 24 19 14 12 7 2 1 0 0
b
Overall survival, %
Time, months
No. Events Median 95% CI
Tislelizumab plus chemotherapy 274 209 16.4 13.6–19.1
Placebo plus chemotherapy 272 233 12.8 12.0–14.5
HR (95% CI) 0.71 (0.59–0.86)
59.3%
56.4%
37.8%
21.1%
25.3%
14.3%
No. at risk
Tislelizumab plus chemotherapy 274 263 247 228 199 178 156 145 133 120 109 102 97 86 81 77 71 69 65 56 48 36 29 22 19 15 12 9 6 3 1 0
Placebo plus chemotherapy 272 261 236 215 190 168 148 120 99 83 69 59 53 51 44 42 39 35 35 30 26 22 17 14 12 7 6 4 1 0 0 0
c
Overall survival, %
Time, months
No. Events Median 95% CI
Tislelizumab plus chemotherapy 254 190 17.8 14.8–20.8
Placebo plus chemotherapy 269 224 13.2 12.1–14.6
HR (95% CI) 0.73 (0.60–0.88)
62.0%
57.1%
39.6%
23.1%
26.4%
16.5%
No. at risk
Tislelizumab plus chemotherapy 254 242 230 213 189 172 152 142 128 118 106 99 94 79 75 70 67 64 60 50 43 31 25 18 14 11 8 6 4 1 1 0
Placebo plus chemotherapy 269 258 234 219 191 168 147 120 102 86 73 63 57 54 48 46 43 40 40 35 31 24 18 15 13 8 7 5 2 1 0 0

◂**Fig. 1** Kaplan-Meier estimates of overall survival in **a** the ITT population[a], in **b** patients with a PD-L1 TAP score of ≥ 5%, and in **c** patients with a PD-L1 CPS of ≥ 5. Both log-rank and Cox regression models were stratified by region (East Asia vs. rest of the world), PD-L1 expression, and presence of peritoneal metastasis. [a]The *p* value is one-sided and is based on the stratified log-rank test. *HR* hazard ratio, *ITT* intent to treat, *PD-L1* programmed death ligand 1, *TAP* Tumor Area Positivity

Response Assessment in the ITT Population and PD-L1 TAP Score ≥ 5% Population

A summary of antitumor activity in the ITT population and the PD-L1 TAP score ≥ 5% population is provided in Table S3 (Supplementary Material). Briefly, 47.3% (237/501) of patients treated with tislelizumab + chemotherapy versus 40.5% (201/496) treated with placebo + chemotherapy achieved an investigator-assessed ORR with an odds ratio (OR) of 1.33 (95% CI 1.03–1.72) in the ITT population. Similar activity was seen in the population with PD-L1 TAP score ≥ 5%. OR for ORR in both arms across multiple prespecified subgroups in patients with PD-L1 TAP score ≥ 5% are reported in Fig. S2 (Supplementary Material). Additionally, tislelizumab + chemotherapy demonstrated longer DoR with tislelizumab + chemotherapy than with placebo + chemotherapy in both the ITT population (8.6 vs. 7.2 months) and the population with PD-L1 TAP score ≥ 5% (10.0 vs. 6.9 months) (Fig. S3 in the Supplementary Material).

Response Assessment in Patients Who Remained Progression Free at 3 Years

A total of 70 patients (tislelizumab + chemotherapy, $n = 50$; placebo + chemotherapy, $n = 20$) remained progression free at 3 years. Disease history and baseline characteristics of these patients are described in Table S4 (Supplementary Material). The patients who remained progression free at 3 years had fewer (0–2) metastatic sites at study entry (80.0% vs. 67.2%), a lower incidence of peritoneal metastases (24.3% vs. 43.5%), and more moderately differentiated tumors (34.3% vs. 19.9%) than the ITT population ($p < 0.05$). These patients exhibited a longer DoR compared with the ITT population, regardless of whether they received tislelizumab + chemotherapy (not reached vs. 8.6 months) or placebo + chemotherapy (not reached vs. 7.2 months) (Fig. S4 in the Supplementary Material). A total of 92.0% (46/50) of patients treated with tislelizumab + chemotherapy versus 85.0% (17/20) treated with placebo + chemotherapy achieved an investigator-assessed ORR, with an OR of 1.57 (95% CI 0.32–7.79) (Table S5 in the Supplementary Material).

Patient-Reported Outcomes

TTD analyses in the ITT population showed significantly lower risk of clinically meaningful worsening in the tislelizumab + chemotherapy arm for global health status/quality of life (GHS/QoL) [HR (95% CI) 0.77 (0.60–0.98)], physical functioning [0.72 (0.57–0.92)], overall GE/GEJC symptom index [0.64 (0.45–0.92)], pain/discomfort [0.74 (0.58–0.96)], and upper gastrointestinal symptoms [0.73 (0.56–0.95)] (Table S6 in the Supplementary Material). The MMRM analysis of the least-squares mean difference (95% CI) between the arms to cycle 6 also confirmed better outcomes in the tislelizumab + chemotherapy arms for GHS/QoL [2.52 (0.29–4.74); $p = 0.03$], physical functioning [2.46 (0.49–4.43); $p = 0.01$], and fatigue [–3.01 (–5.78 to –0.24); $p = 0.03$], and overall symptom [–1.62 (–3.12 to –0.12); $p = 0.03$]. The improvements in pain/discomfort symptoms from baseline to cycles 4 and 6 in the tislelizumab + chemotherapy arm were small but clinically meaningful [–5.97 (–7.56 to –4.38)] (Fig. S5 in the Supplementary Material).

Safety in the ITT Population

Treatment-related adverse events (TRAEs) were reported in 483 (97.0%) of 498 patients in the tislelizumab + chemotherapy arm and in 476 (96.4%) of 494 patients in the placebo + chemotherapy arm (Table S7 in the Supplementary Material). Grade ≥ 3 TRAEs were reported in 269 (54.0%) patients in the tislelizumab + chemotherapy arm and in 246 (49.8%) patients in the placebo + chemotherapy arm of the overall

a

Subgroup	Event/Total: Tislelizumab plus chemotherapy	Event/Total: Placebo plus chemotherapy	Median (95% CI): Tislelizumab plus chemotherapy	Median (95% CI): Placebo plus chemotherapy	HR (95% CI)
Age					
< 65 years	271/340	279/313	15.3 (13.1–16.7)	12.5 (11.4–14.1)	0.79 (0.67–0.93)
≥ 65 years	125/161	151/183	14.3 (11.8–18.4)	13.7 (12.3–15.0)	0.80 (0.63–1.01)
Sex					
Male	269/346	297/346	15.0 (13.1–16.7)	13.2 (12.2–14.5)	0.79 (0.67–0.93)
Female	127/155	133/150	14.9 (11.7–19.1)	12.3 (10.7–14.7)	0.79 (0.62–1.01)
Region					
China (including Taiwan)	202/259	230/257	15.7 (13.9–18.4)	13.0 (11.9–14.3)	0.74 (0.62–0.90)
Japan and South Korea	86/117	90/115	16.9 (13.6–21.3)	18.1 (14.6–22.4)	0.91 (0.68–1.23)
ROW	108/125	110/124	11.0 (8.4–13.9)	10.5 (8.1–12.1)	0.73 (0.56–0.96)
Region group					
East Asia	288/376	320/372	16.4 (14.4–18.0)	14.1 (12.8–15.4)	0.79 (0.68–0.93)
ROW	108/125	110/124	11.0 (8.4–13.9)	10.5 (8.1–12.1)	0.73 (0.56–0.96)
Race					
Asian	288/376	320/372	16.4 (14.4–18.0)	14.1 (12.8–15.4)	0.79 (0.68–0.93)
White	101/116	94/107	11.0 (8.5–13.9)	9.8 (7.6–11.7)	0.74 (0.56–0.98)
Other	7/9	16/17	7.4 (0.7–NE)	13.5 (7.0–17.5)	0.48 (0.17–1.38)
ECOG performance status					
0	139/169	134/154	16.7 (13.6–19.2)	14.2 (12.1–16.1)	0.77 (0.61–0.98)
1	257/332	296/342	14.1 (12.2–16.0)	12.6 (11.5–13.7)	0.80 (0.67–0.94)
MSI or MMR status					
MSI-H/dMMR	11/16	18/24	17.2 (6.9–41.6)	13.5 (6.1–21.1)	0.69 (0.33–1.47)
MSI-L/MSS/pMMR	355/448	385/439	15.0 (13.5–16.6)	12.9 (12.2–14.1)	0.80 (0.69–0.92)
Unknown	30/37	27/33	14.8 (7.8–30.0)	11.3 (6.0–17.5)	0.71 (0.42–1.19)
Presence of peritoneal metastasis					
Yes	184/220	196/214	12.3 (10.6–14.3)	11.8 (10.5–13.0)	0.78 (0.64–0.96)
No	212/281	234/282	17.3 (15.0–20.3)	14.0 (12.6–16.0)	0.79 (0.65–0.95)
Liver metastasis					
Yes	150/190	165/188	13.9 (11.4–15.6)	12.9 (10.9–14.5)	0.77 (0.62–0.96)
No	246/311	265/308	16.0 (13.6–18.0)	12.9 (11.9–14.4)	0.80 (0.67–0.95)
Investigator's choice of chemotherapy					
Oxaliplatin + capecitabine	364/466	402/465	15.3 (13.9–16.9)	13.0 (12.2–14.2)	0.78 (0.68–0.90)
Cisplatin + 5-fluorouracil	32/35	28/31	9.6 (7.0–15.1)	9.8 (6.8–16.1)	0.88 (0.53–1.47)
PD-L1 expression					
PD-L1 score < 5%	187/227	197/224	14.1 (11.9–15.6)	12.9 (11.3–14.7)	0.89 (0.73–1.09)
PD-L1 score ≥ 5%	209/274	233/272	16.4 (13.6–19.1)	12.8 (12.0–14.5)	0.72 (0.60–0.87)
Prior adjuvant/neoadjuvant therapy					
Yes	82/107	92/100	17.5 (13.9–21.1)	13.8 (12.0–15.5)	0.67 (0.49–0.90)
No	314/394	338/396	14.3 (12.3–16.0)	12.6 (11.8–14.1)	0.83 (0.71–0.96)
Disease stage at screening					
Locally recurrent/advanced	3/7	5/5	NR (7.0–NE)	12.6 (2.9–NE)	0.21 (0.04–1.11)
Metastatic	393/494	424/490	14.9 (13.4–16.4)	12.9 (12.1–14.1)	0.80 (0.70–0.92)
Primary location					
Gastroesophageal junction	76/96	87/100	15.6 (12.2–19.7)	10.8 (9.1–13.1)	0.72 (0.53–0.99)
Stomach	320/405	342/395	14.9 (12.8–16.6)	13.3 (12.5–14.5)	0.81 (0.69–0.94)
Measurability					
Measurable	373/471	418/479	14.9 (13.1–16.4)	12.7 (12.0–13.9)	0.78 (0.68–0.90)
Nonmeasurable	23/30	12/17	19.0 (11.7–23.2)	22.0 (11.5–39.3)	1.20 (0.60–2.42)
Prior gastrectomy/esophagectomy					
Yes	97/133	120/139	17.6 (15.1–20.3)	14.6 (12.8–16.4)	0.75 (0.57–0.97)
No	299/368	310/357	14.1 (11.7–15.6)	12.4 (11.5–13.7)	0.81 (0.69–0.94)
Number of metastatic sites at baseline					
0–2	256/335	284/335	18.0 (15.9–20.3)	14.3 (12.8–15.8)	0.75 (0.63–0.89)
≥ 3	140/166	146/160	10.8 (8.5–12.2)	10.0 (8.6–11.9)	0.86 (0.68–1.08)

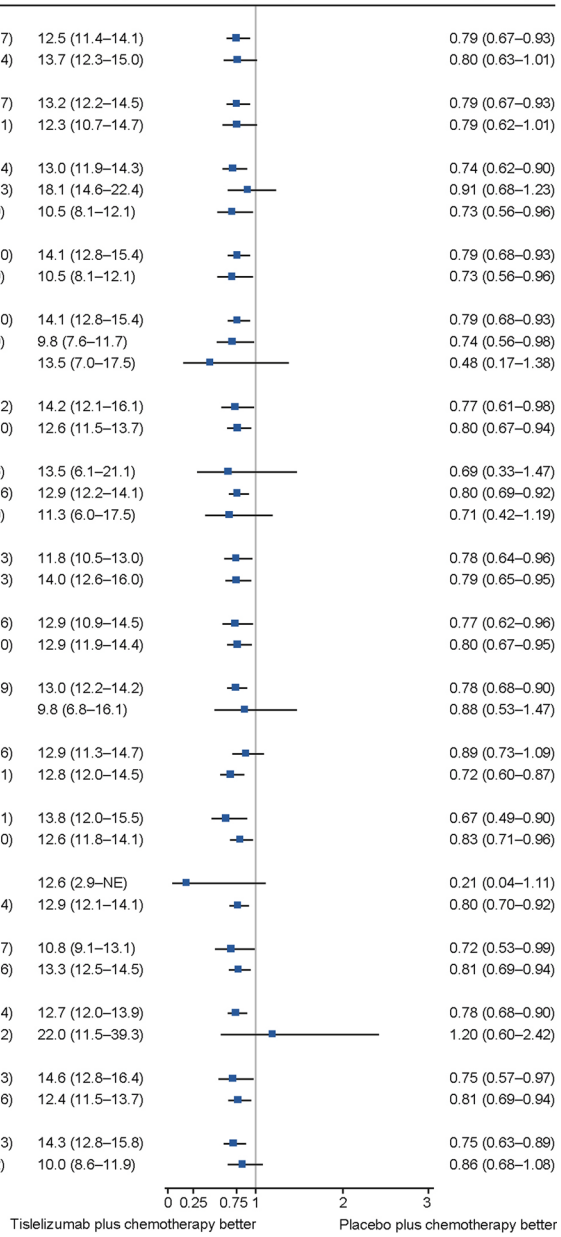


Fig. 2 Prespecified subgroup analysis of overall survival in **a** the ITT population and **b** the population with TAP score ≥ 5%. Data cutoff, February 28, 2024. Any subset with < 10 patients is not shown. Medians were estimated by the Kaplan-Meier method, with 95% CIs estimated using the method of Brookmeyer and Crowley using log-log transformation. HRs and 95% CIs were estimated from an unstratified Cox regression model including treatment as a covariate. The race subcategory "Other" includes not reported, unknown, and other. The range of the x-axis for HR is 0 to 3; some extreme values > 3 are not shown in the plot. *CI* confidence interval, *dMMR* mismatch repair deficient, *ECOG* Eastern Cooperative Oncology Group, *HR* hazard ratio, *ITT* intent to treat, *MSI-H/L* microsatellite instability-high/low, *MSS* microsatellite stable, *NE* not estimable, *NR* not reached, *PD-L1* programmed death ligand 1, *pMMR* mismatch repair proficient, *ROW* rest of the world, *TAP* Tumor Area Positivity

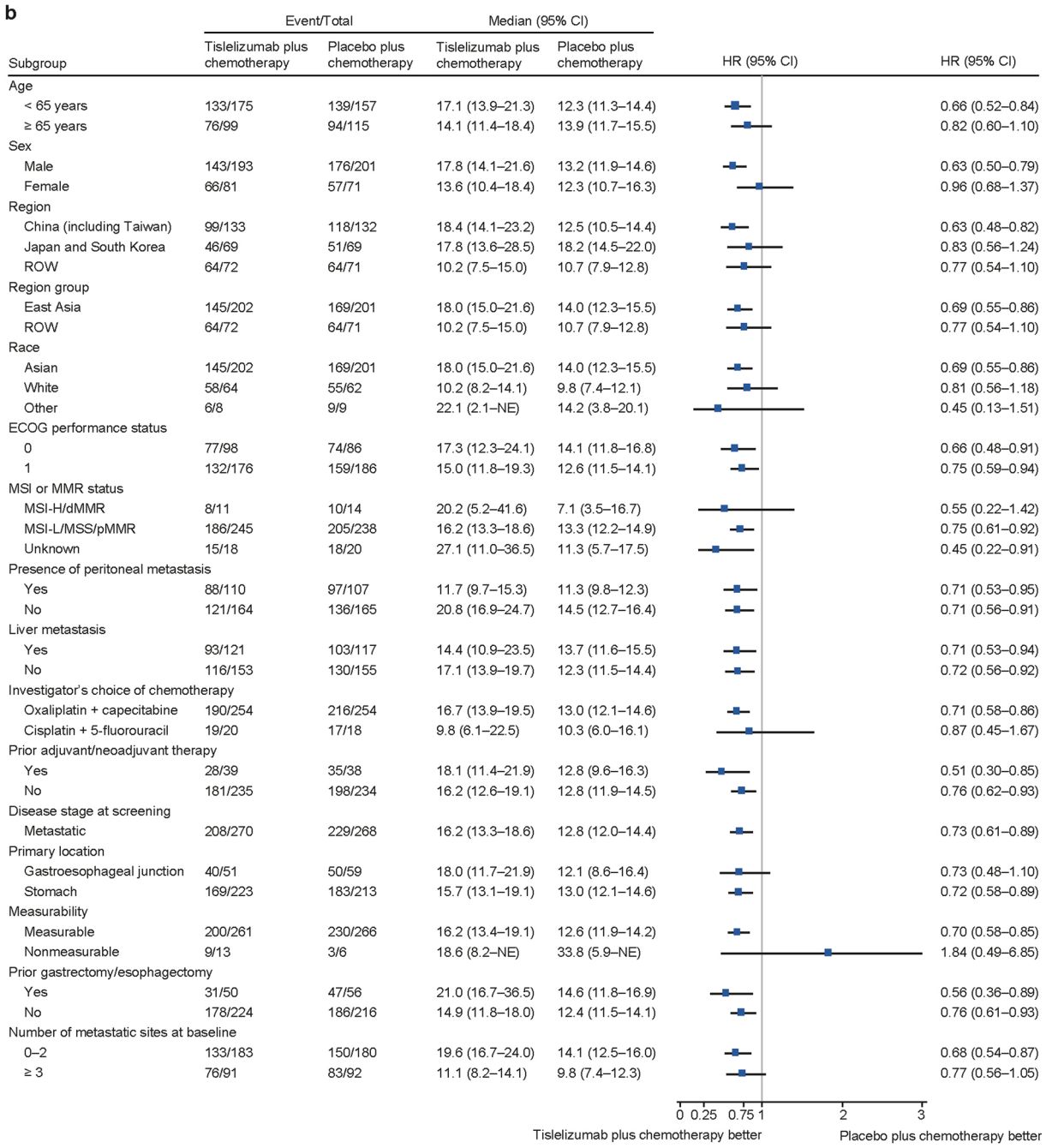
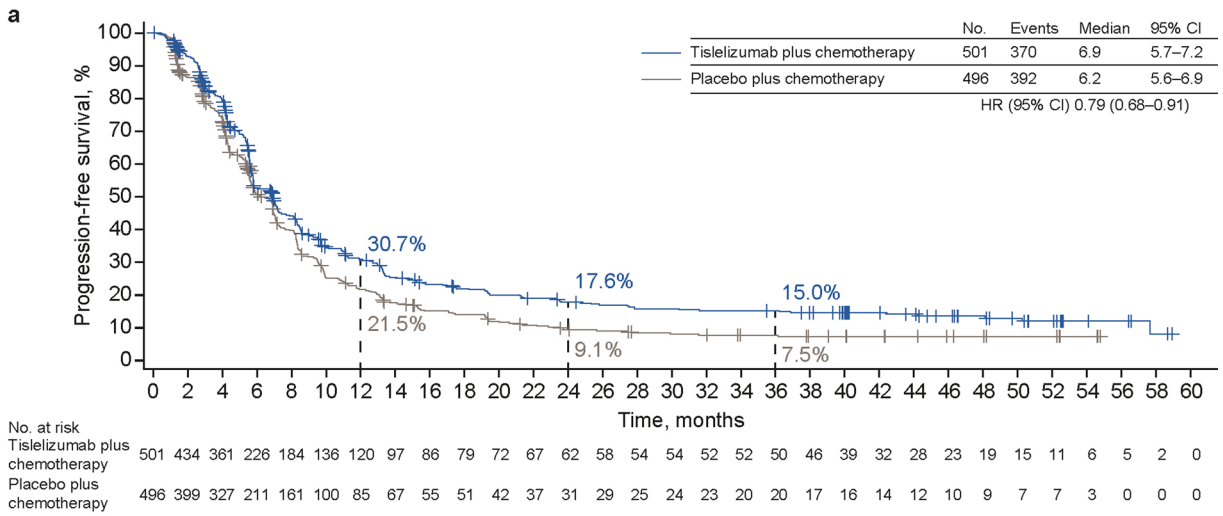
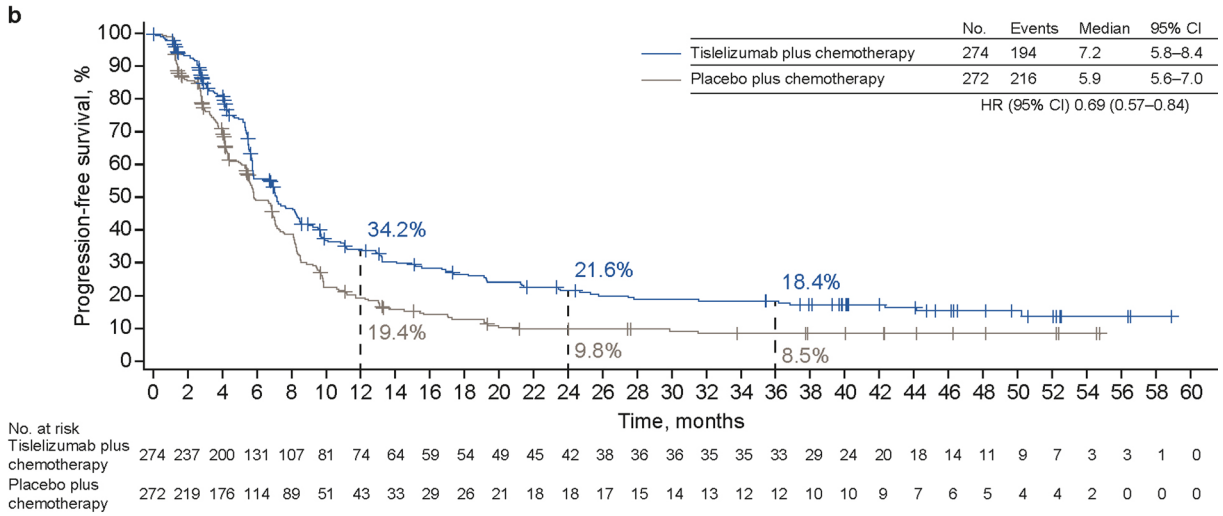
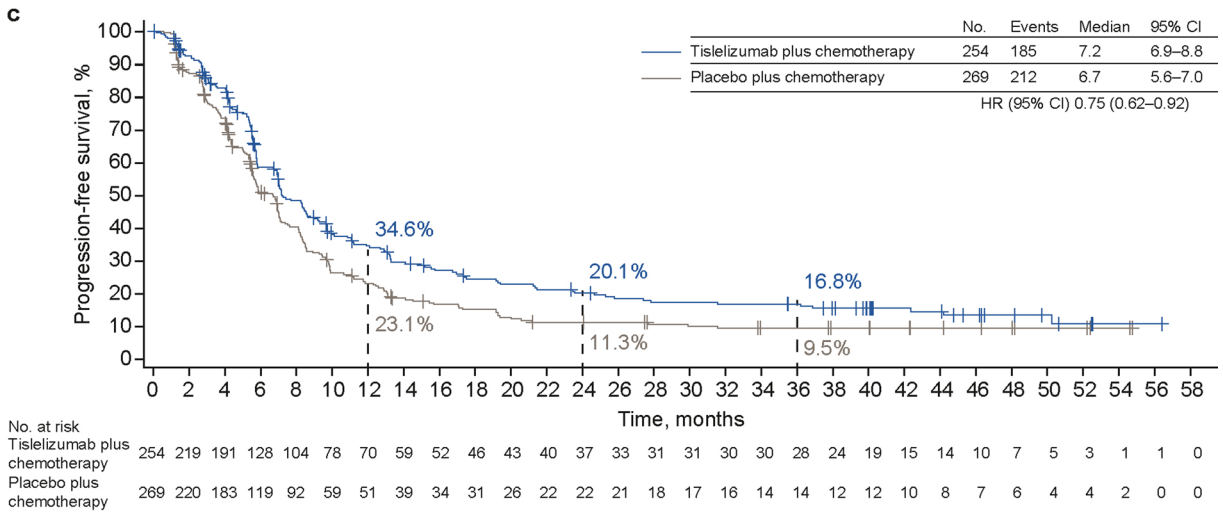


Fig. 2 continued

ITT population (Table S7 in the Supplementary Material). The most common grade ≥ 3 TRAEs were decreased neutrophil count and decreased platelet count (Table 1). Serious TRAEs occurred in 113 (22.7%) patients in the tislelizumab + chemotherapy arm versus 72 (14.6%) patients in the placebo + chemotherapy arm (Table S7 in the Supplementary Material), with decreased platelet count, pneumonia, and vomiting the most commonly reported. TRAEs were also common in those who remained progression free at 3 years (Table S8 in the Supplementary


a
Progression-free survival, %
Time, months
No. Events Median 95% CI
Tislelizumab plus chemotherapy 501 370 6.9 5.7–7.2
Placebo plus chemotherapy 496 392 6.2 5.6–6.9
HR (95% CI) 0.79 (0.68–0.91)
30.7%
21.5%
17.6%
9.1%
15.0%
7.5%
No. at risk
Tislelizumab plus chemotherapy 501 434 361 226 184 136 120 97 86 79 72 67 62 58 54 54 52 52 50 46 39 32 28 23 19 15 11 6 5 2 0
Placebo plus chemotherapy 496 399 327 211 161 100 85 67 55 51 42 37 31 29 25 24 23 20 20 17 16 14 12 10 9 7 7 3 0 0 0


b
Progression-free survival, %
Time, months
No. Events Median 95% CI
Tislelizumab plus chemotherapy 274 194 7.2 5.8–8.4
Placebo plus chemotherapy 272 216 5.9 5.6–7.0
HR (95% CI) 0.69 (0.57–0.84)
34.2%
19.4%
21.6%
9.8%
18.4%
8.5%
No. at risk
Tislelizumab plus chemotherapy 274 237 200 131 107 81 74 64 59 54 49 45 42 38 36 36 35 35 33 29 24 20 18 14 11 9 7 3 3 1 0
Placebo plus chemotherapy 272 219 176 114 89 51 43 33 29 26 21 18 18 17 15 14 13 12 12 10 10 9 7 6 5 4 4 2 0 0 0


c
Progression-free survival, %
Time, months
No. Events Median 95% CI
Tislelizumab plus chemotherapy 254 185 7.2 6.9–8.8
Placebo plus chemotherapy 269 212 6.7 5.6–7.0
HR (95% CI) 0.75 (0.62–0.92)
34.6%
23.1%
20.1%
11.3%
16.8%
9.5%
No. at risk
Tislelizumab plus chemotherapy 254 219 191 128 104 78 70 59 52 46 43 40 37 33 31 31 30 30 28 24 19 15 14 10 7 5 3 1 1 0
Placebo plus chemotherapy 269 220 183 119 92 59 51 39 34 31 26 22 22 21 18 17 16 14 14 12 12 10 8 7 6 4 4 2 0 0

◂**Fig. 3** Kaplan-Meier estimates of progression-free survival in **a** the ITT population, in **b** patients with a PD-L1 TAP score of ≥ 5%, and in **c** patients with a PD-L1 CPS of ≥ 5. The Cox regression model was stratified by region (East Asia vs. rest of the world), PD-L1 expression, and presence of peritoneal metastasis. *HR* hazard ratio, *ITT* intent to treat, *PD-L1* programmed death ligand 1, *TAP* Tumor Area Positivity

Material). Of these patients, 20% experienced serious TRAEs. None of the patients who were progression free experienced TRAEs leading to death. A higher percentage of patients remaining progression free required dose modifications because of TRAEs compared with the overall ITT population (Tables S7 and S8 in the Supplementary Material).

In all, 157 (31.5%) patients in the tislelizumab + chemotherapy arm versus 58 (11.7%) in the placebo + chemotherapy arm experienced immune-mediated adverse events, with 38 (7.6%) versus 10 (2.0%) patients, respectively, experiencing grade 3 or higher events (Table S9 in the Supplementary Material). A comprehensive summary of safety events, including immune-mediated adverse events, is provided in Table S9 (in the Supplementary Material).

DISCUSSION

After 3 years of follow-up, tislelizumab + chemotherapy as first-line treatment for advanced GC/GEJC continued to demonstrate clinically meaningful improvement in OS and PFS over placebo + chemotherapy in patients with PD-L1 TAP score ≥ 5% and in the ITT population. OS and PFS rates at 36 months were notably higher with tislelizumab + chemotherapy than with placebo + chemotherapy in the ITT population (20.7% vs. 13.4% and 15.0% vs. 7.5%, respectively). Updated OS and PFS results in the population with PD-L1 TAP score ≥ 5% at 36.6 months' minimum follow-up remained consistent with those observed at final analysis [stratified HR for OS 0.71 (95% CI 0.58–0.86); stratified HR for PFS 0.68 (95% CI 0.56–0.83)] after an additional 12.0 months of follow-up, showing sustained improvement in OS [5]. Additionally, patients who remained progression free at 3 years were more prevalent in the tislelizumab + chemotherapy population, exhibited distinct characteristics, and had longer DoR than the ITT population, with a higher ORR in the tislelizumab + chemotherapy arm compared with placebo + chemotherapy. PRO outcomes for TTD analysis showed that patients receiving tislelizumab + chemotherapy were at lower risks of clinical worsening for the Quality of Life Questionnaire-Core 30 (QLQ-C30) key endpoints of GHS/QoL [HR (95% CI) 0.77 (0.60–0.98)] and physical functioning [0.72 (0.57–0.92)] and for the QLQ–Stomach (QLQ-STO22) key endpoints of pain/discomfort [HR 0.74 (95% CI 0.58–0.96)] and upper gastrointestinal symptoms [0.73 (0.56–0.95)]. Results based on the MMRM analysis showed that patients receiving tislelizumab + chemotherapy experienced clinically meaningful improvements in pain/discomfort at both cycle 4 and cycle 6. Additionally, tislelizumab + chemotherapy had a manageable safety profile, with no new safety signals.

OS outcomes of RATIONALE-305 are consistent with those of other long-term phase 3 trials evaluating first-line anti–PD-1 antibody + chemotherapy combinations for advanced GC/GEJC, including CheckMate 649 (nivolumab + chemotherapy), KEYNOTE-859 (pembrolizumab + chemotherapy), and ORIENT-16 (sintilimab + chemotherapy); in these trials, the improved HR for OS observed in the ITT population was comparatively greater in patients with higher expression of PD-L1 [3, 4, 17]. Additionally, 36-month OS rates in CheckMate 649 were 17% with nivolumab + chemotherapy versus 10% with chemotherapy alone in the ITT population [3]. In our analysis, 36-month OS rates were 20.7% with tislelizumab + chemotherapy versus 13.4% with placebo + chemotherapy (Fig. 1). One important distinction between the trials is that in CheckMate 649, very few patients in the nivolumab + chemotherapy arm (2%) received subsequent immunotherapy [18], whereas more patients in the tislelizumab + chemotherapy arm (13%) received subsequent immunotherapy in RATIONALE-305. Recent data from CheckMate 649 showed a 60-month OS rate (12%) that is similar to the 36-month OS rate

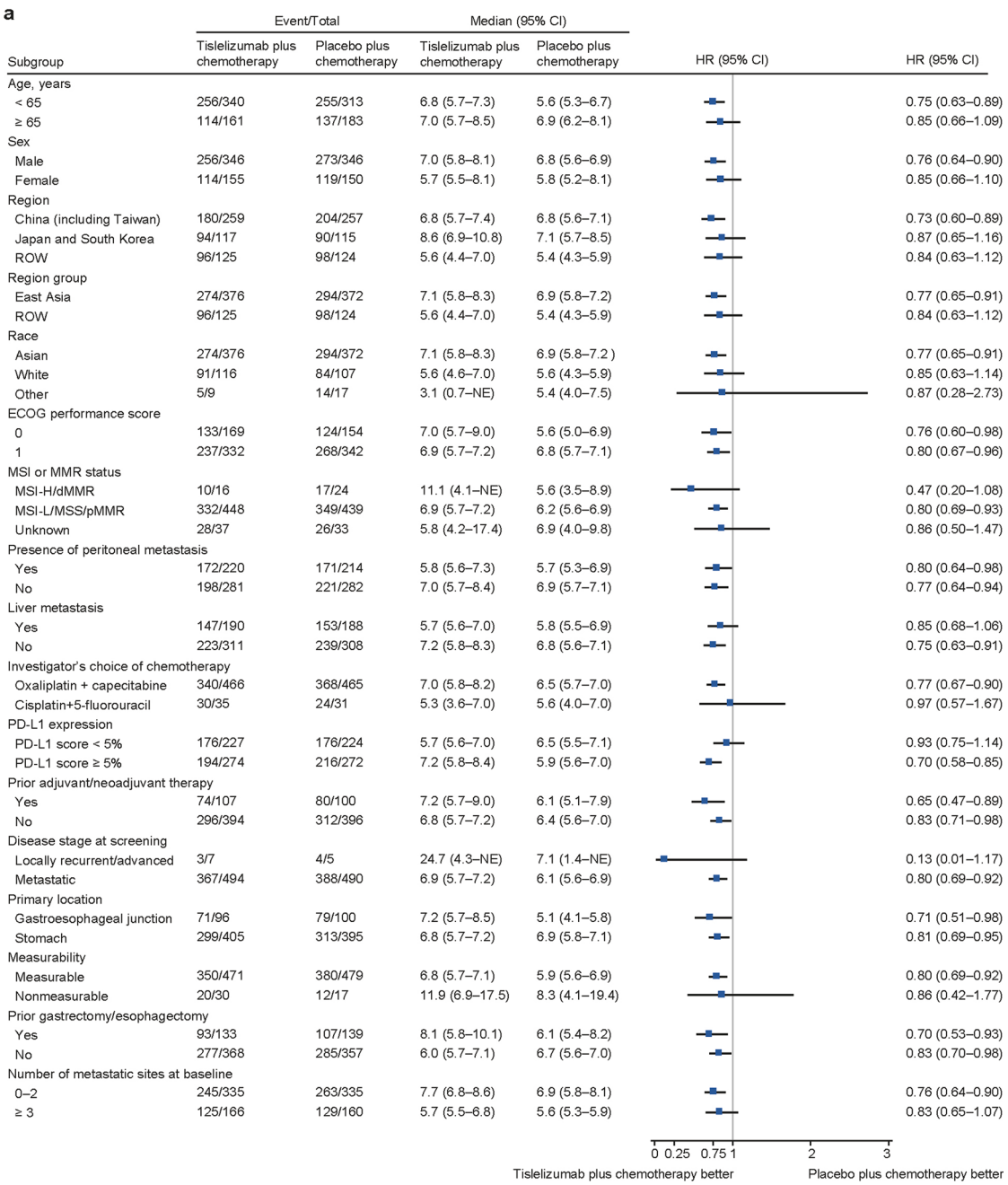


Fig. 4 Prespecified subgroup analysis of progression-free survival in **a** the ITT population and **b** the population with TAP score ≥ 5%. Data cutoff, February 28, 2024. Any subset with < 10 patients is not shown. Medians were estimated by the Kaplan-Meier method, with 95% CIs estimated using the method of Brookmeyer and Crowley using log-log transformation. HRs and 95% CIs were estimated from an unstratified Cox regression model including treatment as a covariate. The race subcategory "Other" includes not reported, unknown, and other. The range of the x-axis for HR is 0 to 3; some extreme values > 3 are not shown in the plot. *CI* confidence interval, *dMMR* mismatch repair deficient, *ECOG* Eastern Cooperative Oncology Group, *HR* hazard ratio, *ITT* intent to treat, *MSI-H/L* microsatellite instability-high/low, *MSS* microsatellite stable, *PD-L1* programmed death ligand 1, *pMMR* mismatch repair proficient, *ROW* rest of the world, *TAP* Tumor Area Positivity

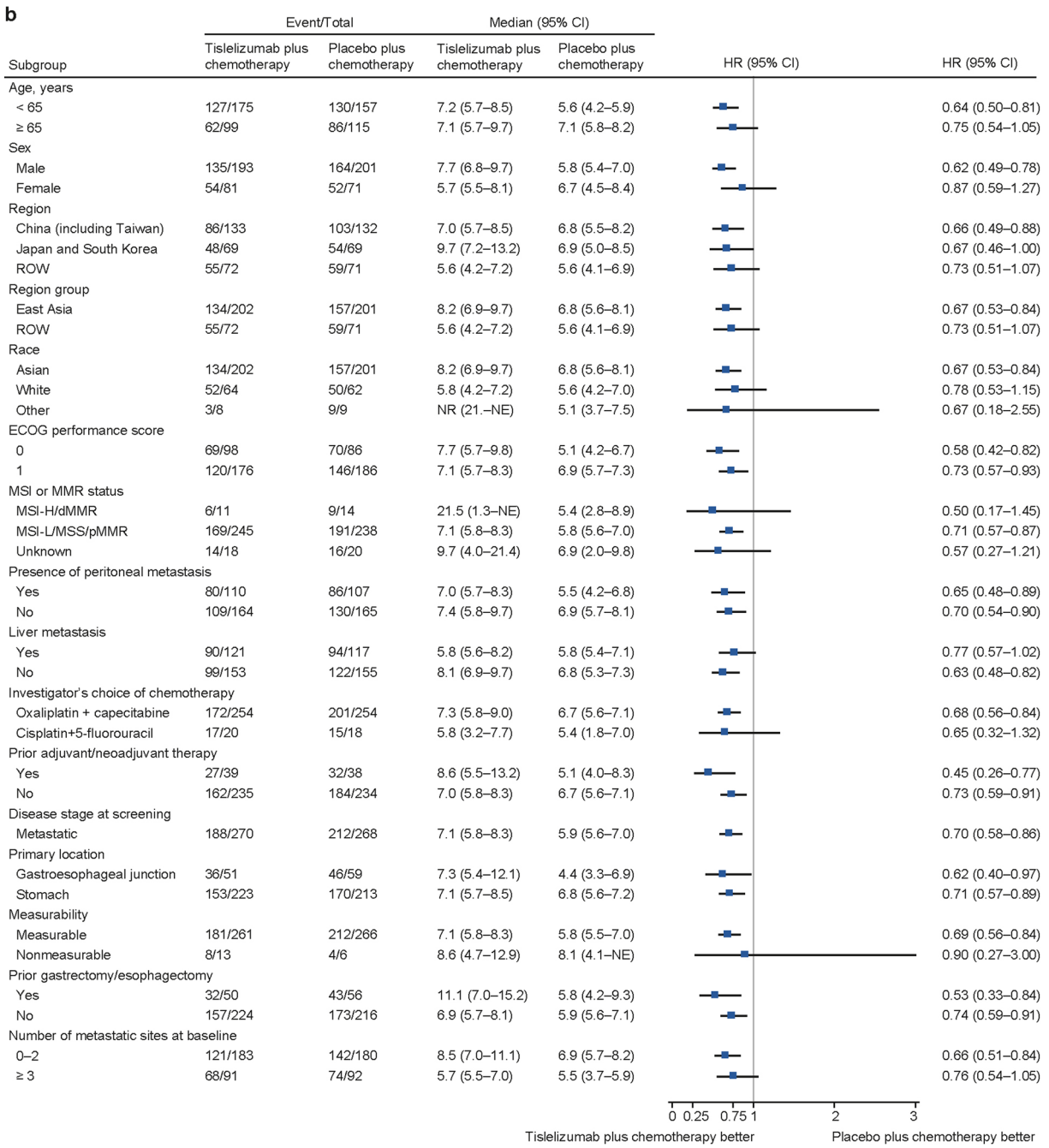


Fig. 4 continued

(17%), suggesting that for some PD-1 inhibitors combined with chemotherapy, there may be a trend toward sustained long-term survival in this patient population [3, 19]. However, it is important to note the limitations of cross-trial comparisons—in this case, the significant differences between CheckMate 649 and RATIONALE-305 in terms of enrolling patients with poor prognosis. While 43.5% of patients in RATIONALE-305 had peritoneal disease [5], only 23.8% of patients in CheckMate 649 had this condition [3]. Additionally, compared with

Table 1 Treatment-related adverse events with an incidence of ≥ 10% by preferred term and worst grade (safety population)

	Tislelizumab + chemotherapy (*n* = 498)		Placebo + chemotherapy (*n* = 494)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Any event	483 (97.0)	269 (54.0)	476 (96.4)	246 (49.8)
Nausea	237 (47.6)	13 (2.6)	232 (47.0)	9 (1.8)
Decreased appetite	185 (37.1)	14 (2.8)	185 (37.4)	16 (3.2)
Platelet count decreased	175 (35.1)	56 (11.2)	183 (37.0)	57 (11.5)
Neutrophil count decreased	169 (33.9)	59 (11.8)	160 (32.4)	57 (11.5)
Vomiting	162 (32.5)	11 (2.2)	163 (33.0)	12 (2.4)
Anemia	159 (31.9)	25 (5.0)	163 (33.0)	37 (7.5)
Aspartate aminotransferase increased	147 (29.5)	13 (2.6)	137 (27.7)	4 (0.8)
White blood cell count decreased	120 (24.1)	15 (3.0)	135 (27.3)	8 (1.6)
Alanine aminotransferase increased	115 (23.1)	8 (1.6)	97 (19.6)	4 (0.8)
Diarrhea	112 (22.5)	13 (2.6)	126 (25.5)	11 (2.2)
Peripheral sensory neuropathy	106 (21.3)	0	116 (23.5)	0
Palmar-plantar erythrodysesthesia syndrome	96 (19.3)	15 (3.0)	93 (18.8)	10 (2.0)
Asthenia	76 (15.3)	10 (2.0)	72 (14.6)	7 (1.4)
Fatigue	76 (15.3)	9 (1.8)	61 (12.3)	6 (1.2)
Neutropenia	74 (14.9)	33 (6.6)	80 (16.2)	34 (6.9)
Hypoesthesia	69 (13.9)	0	67 (13.6)	0
Blood bilirubin increased	61 (12.2)	7 (1.4)	59 (11.9)	3 (0.6)
Thrombocytopenia	60 (12.0)	14 (2.8)	55 (11.1)	14 (2.8)
Weight decreased	59 (11.8)	0	53 (10.7)	0
Hypothyroidism	56 (11.2)	0	13 (2.6)	0

Data cutoff, February 28, 2024. Data are for patients, *n* (%) by worst grade of event. Data are shown for all-grade events with incidence of ≥ 10% in either treatment arm. Treatment-related adverse events are sorted by decreasing frequency for all-grade events in the tislelizumab + 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

CheckMate 649, RATIONALE-305 enrolled fewer patients with ECOG 0 (32.4% vs 42.0%), more Asian patients (75.0% vs 23.7%), and more patients who had received previous surgery (27.3% vs 21.3%) [3, 5].

Prespecified and post hoc subgroup analyses showed improvements in OS and PFS with tislelizumab + chemotherapy treatment for a variety of subgroups. In patients with PD-L1 TAP scores ≥ 5%, OS and PFS were prolonged in the tislelizumab +

chemotherapy arm over the placebo + chemotherapy arm, consistent with the results observed at a matched CPS cutoff ≥ 5 and in the overall study population. Comparable outcomes observed at matched thresholds (5% vs. 5) in this study are consistent with significant agreement and concordance, which have been demonstrated previously between the TAP score and CPS in patients treated with tislelizumab with GC/GEJC or esophageal squamous cell carcinoma [15]. Additionally, peritoneal disease was a stratification factor unique to RATIONALE-305. Both OS and PFS benefits were observed with tislelizumab + chemotherapy in patients with peritoneal disease.

The PRO results in this study add to the emerging literature on the effectiveness of immunotherapies in advanced GC/GEJC [20, 21]. This study was designed with several methodological strengths that enhance the reliability of the PRO findings, including using both general cancer- and gastric cancer-specific modules to capture patients' experience during clinical visits, and predefining and assessing PRO burden and treatment impact with QLQ-C30 and QLQ-STO22 before data unblinding. Significant descriptive *p* values were observed in least-squares mean treatment differences (95% CI) for the tislelizumab + chemotherapy arm in pain/discomfort and upper gastrointestinal symptoms, which are the most burdensome symptoms experienced by this patient population [22]. By using validated oncology-specific measures, we found early and sustained symptom improvements that aligned with patients' perceived wellbeing.

These results, in combination with demonstrated efficacy benefit and a manageable safety profile, further support tislelizumab + chemotherapy as a new first-line treatment option for advanced GC/GEJC and emphasize the potential role of PD-L1 expression as a prognostic biomarker for treatment response to tislelizumab + chemotherapy in this population.

Limitations

The trial design allowed investigators to choose the platinum partner for the chemotherapy backbone and was permissive to maintenance tislelizumab or tislelizumab + capecitabine. These provisions are common in contemporary trials [4], but future efforts can delineate the implications of maintenance tislelizumab with or without chemotherapy on outcomes in this population. Additionally, to extend the antitumor benefit beyond first-line treatment, maintenance tislelizumab may have been increasingly utilized during the 3-year follow-up to ensure optimal continuum of care [23]. As we do not have exact data on how often chemotherapy was reduced and discontinued from our trial, further cumulative tislelizumab data from upper gastrointestinal cancer trials are needed to determine the proportion of patients who stayed on treatment for a longer duration with tislelizumab alone and potentially improved PROs, as shown for several tumor types, including GC/GEJC [24].

CONCLUSION

After a minimum 3-year follow-up, tislelizumab + chemotherapy as first-line treatment for GC/GEJC continued to demonstrate clinically meaningful improvements in OS, PFS, ORR, and DoR compared with placebo + chemotherapy in the ITT population and the PD-L1 subgroups, with consistently positive PRO results and no new safety signals. These results, along with previous results from the RATIONALE-305 final analysis in all randomized patients, support tislelizumab + chemotherapy as a first-line treatment option for advanced HER2-negative GC/GEJC.

ACKNOWLEDGEMENTS

We thank the investigators, the site support staff, and especially the patients for participating in this study. We also thank Gisoo Barnes, PhD, and Bryant Barnes, BS, of BeOne Medicines, Ltd., who provided their expertise on PROs. This study was sponsored by BeOne Medicines, Ltd.

Medical Writing/Editorial Assistance. Medical writing support was provided by Erika

Young, PharmD, of Parexel, with funding provided by BeOne Medicines, Ltd.

Author Contributions. Do-Youn Oh, Markus Moehler, and Yaling Xu had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the acquisition of data. *Concept and design:* Marcia Cruz-Correa, Silu Yang, and Markus Moehler. *Acquisition, analysis, or interpretation of data:* Marcia Cruz-Correa, Do-Youn Oh, Ken Kato, Josep Tabernero, Yuxian Bai, Jianhua Shi, Keun-Wook Lee, Hidekazu Hirano, David Spigel, Lucjan Wyrwicz, Roberto Pazo Cid, Antonio Cubillo Gracián, Yaling Xu, Tao Sheng, Silu Yang, Rui Hua Xu, Markus Moehler. *Drafting of the manuscript:* All authors. *Critical review of the manuscript for important intellectual content:* All authors. *Statistical analysis:* Tao Sheng.

Funding. Open Access funding enabled and organized by Projekt DEAL. This study was funded by BeOne, Ltd. The funder had a role in study design, data collection, data analysis, data interpretation, and writing of the clinical study report, provided medical writing support for this publication, and funded the journal's Rapid Service and Open Access fees. The clinical researchers were independent from the funder, and all authors had access to all relevant aggregated study data and provided final approval for the decision to submit the manuscript for publication. All authors take responsibility for the integrity of the data and the accuracy of the data analysis. The study protocol was developed by BeOne, Ltd., in collaboration with the study investigators. BeOne, Ltd., was also involved in data collection, analysis, and interpretation of results. Statistical analyses were performed by statisticians at BeOne, Ltd.

Data Availability. BeOne Medicines voluntarily shares anonymous data on completed studies responsibly and provides qualified scientific and medical researchers access to anonymous data and supporting clinical trial documentation for clinical trials in dossiers for medicines and indications after submission and approval in the United States, China, and Europe. Clinical trials supporting subsequent local approvals, new indications, or combination products are eligible for sharing once corresponding regulatory approvals are achieved. BeOne Medicines shares data only when permitted by applicable data privacy and security laws and regulations. In addition, data can only be shared when it is feasible to do so without compromising the privacy of study participants. Qualified researchers may submit data requests/research proposals for BeOne Medicines review and consideration through BeOne Medicines' clinical trial webpage at https://beonemedicines.com/science/clinical-trials/.

Declarations

Conflict of Interest. Marcia Cruz Correa has received grants or contracts from BeOne Medicines, Ltd., AbbVie, Genentech, Taiho, Seagen, Bristol Myers Squibb, Merck, Pfizer, Janssen, Mirati, Tempus, Huyabio, Regeneron, and Delfi; has received patents from Johns Hopkins University; and owns stock options in the Pan American Center for Oncology Trials. Do-Youn Oh has received honoraria from AstraZeneca, Novartis, Array Biopharma, Lilly, Servier, BeOne Medicines, Ltd., MSD, and Handok, and has participated on data safety monitoring boards or advisory boards for AstraZeneca, Novartis, Genentech Roche, Merck Serono, Bayer, Taiho, Aslan, Halozyme, Zymeworks, Celgene, Basilea, BeOne Medicines, Ltd., Yunan, Arcus Biosciences, Turning Point Therapeutics, IQVIA, and MSD Oncology. Ken Kato has received consulting fees from AstraZeneca, Bayer, BeOne Medicines, Ltd., Bristol Myers Squibb, Janssen, Merck Bio, Merck & Co., Novartis, Ono, and Roche; has received payment for expert testimony from Bristol Myers Squibb and Ono; and has participated on data safety monitoring boards or advisory boards for Bristol Myers Squibb, Chugai, Merck & Co., and Ono. Josep Tabernero owns stocks in Oniria Therapeutics; has received honoraria from Imedex/HMP, Medscape Education, MJH Life Sciences, and PeerView Institute for Medical Education and Physicians Education; and has received

consulting fees from Array Biopharma, AstraZeneca, Bayer, Boehringer Ingelheim, Cardiff Oncology, Chugai, Daiichi Sankyo, F. Hoffmann-La Roche Ltd, Genentech, HalioDX SAS, Hutchison MediPharma International, Ikena Oncology, Inspirna Inc, IQVIA, Lilly, Menarini, Merck Serono, Merus, MSD, Mirati, NeoPhore, Novartis, Ona Therapeutics, Orion Biotechnology, Peptomyc, Pfizer, Pierre Fabre, Samsung Bioepis, Sanofi, Scandion Oncology, Scorpion Therapeutics, Seattle Genetics, Servier, Sotio Biotech, Taiho, TheraMyc, and Tolremo Therapeutics. Yuxian Bai reports no conflicts of interest. Jianhua Shi reports no conflicts of interest. Keun-Wook Lee has received grants or contracts from BeOne Medicines, Ltd., AstraZeneca, Ono Pharmaceutical, Merck Sharp & Dohme, Merck KGaA, Roche, Pfizer, Leap Therapeutics, ALX Oncology, Zymeworks, Astellas, MacroGenics, Amgen, Seagen, Bolt Therapeutics, Trishula Therapeutics, Oncologie, Pharmacyclics, MedPacto, Green Cross Corp, ABLBIO, Y-BIOLOGICS, Daiichi Sankyo, Taiho, InventisBio, Elevar Therapeutics, Metafines, Idience, Genome & Company, and Exelixis. Hidekazu Hirano has received research grants from BeOne Medicines, Ltd., Taiho, Seagen, Amgen, ALX Oncology, and Bristol Myers Squibb, and reports speaker honorarium from Bristol Myers Squibb, Taiho, Novartis, NICHI IKO, Teijin Pharma, and Ono Pharmaceutical. David Spigel reports grants from Genentech/Roche, Novartis, Celgene, Bristol Myers Squibb, Lilly, AstraZeneca, University of Texas of SW Medical Center-Simmons Cancer Center, Merck, G1 Therapeutics, Neon Therapeutics, Nektar, Celldex, Clovis Oncology, Daiichi Sankyo, Astellas Pharma, GRAIL, Transgene, Aeglea Biotherapeutics, Ipsen, BIND Therapeutics, Eisai, ImClone Systems, Janssen Oncology, MedImmune, Agios, GlaxoSmithKline, Tesaro, Cyteir Therapeutics, Novocure, Elevation Oncology, Calithera Biosciences, Arcus Biosciences, Arrys Therapeutics, Bayer, BeOne Medicines, Ltd., Blueprint Medicine, Boehringer Ingelheim, Hutchison MediPharma, Incyte, Kronos Bio, Loxo Oncology, MacroGenics, Molecular Templates, Pure Tech Health, Razor Genomics, Repare Therapeutics, Rgenix, Tizona Therapeutics, Verastem, BioNTech, AbbVie, Amgen, Anheart Therapeutics, Ascendis Pharma, Endeavor BioMedicines, Erasca, Faeth Therapeutics, Fujifilm, Gilead Sciences, Jazz Pharmaceuticals, Lyell Immunopharma, Millennium, Moderna Therapeutics, Monte Rosa Therapeutics, Peloton Therapeutics, Shenzhen Chipscreen Biosciences, Stemline Therapeutics, Synthekine, Taiho Oncology, Tango Therapeutics, Tarveda Therapeutics, Zai Lab, Apollomics, Strata Oncology, and Asher Biotherapeutics; and has received consulting fees from Genentech/Roche, Novartis, Bristol Myers Squibb, AstraZeneca, GlaxoSmithKline, Molecular Templates, Jazz Pharmaceuticals, Sanofi-Aventis, Regeneron, Lilly, BeOne Medicines, Ltd., Ipsen, Monte Rosa Therapeutics, AbbVie, Lyell Immunopharma, and Novocure. Lucjan Wyrwicz has received honoraria from AstraZeneca, BeOne Medicines, Ltd., Bristol Myers Squibb, MSD, Roche, and Servier; has acted as a committee member for Bristol Myers Squibb and Servier; and owns stocks with BeOne Medicines, Ltd. Roberto Pazo Cid has received honoraria from Roche, Astellas, Bristol Myers Squibb, Ipsen, Celgene, and Eisai; has received support for attending meetings and/or travel from Roche, Servier, Lilly, and Bristol Myers Squibb; and has participated on data safety monitoring boards or advisory boards for AstraZeneca, Roche, and Ipsen. Antonio Cubillo Gracián reports no conflicts of interest. Yaling Xu reports no conflicts of interest. Tao Sheng is an employee of Vera Therapeutics, Inc., and reports stocks and previous employment with BeOne Medicines, Ltd. Silu Yang reports employment with BeOne Medicines, Ltd. Rui Hua Xu reports no conflicts of interest. Markus Moehler reports consulting or advisory roles for Bayer, MSD, Merck Serono, Amgen, Taiho, Pfizer, Roche, Lilly, Servier, BeOne Medicines, Ltd., Bristol Myers Squibb, AstraZeneca, Astellas, Dragonfly, and Novartis; reports honoraria from Amgen, Roche/Genentech, Merck Serono, MSD Oncology, Bristol Myers Squibb, AstraZeneca/MedImmune, Servier, Pierre Fabre, Sanofi, Transcenta, Daiichi Sankyo, Astellas, and Nordic; has received grant or research funding from Amgen, Leap Therapeutics, Merck Serono, and MSD; and reports other renumeration from AIO, Amgen, Merck Serono, Roche, Bayer, ASCO, German Cancer Society, MSD, ESMO, BeOne Medicines, Ltd., and EORTC.

Ethical Approval. The RATIONALE-305 trial protocol was approved by the relevant institutional review boards and independent ethics committees for each study site. The study was conducted in compliance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki of 1964. All patients provided written informed consent before participating in the study.

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