

Tislelizumab Plus Platinum and Etoposide Versus Placebo Plus Platinum and Etoposide as First-Line Treatment for Extensive-Stage Small-Cell Lung Cancer: Patient-Reported Outcomes in the RATIONALE-312 Trial

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INTRODUCTION

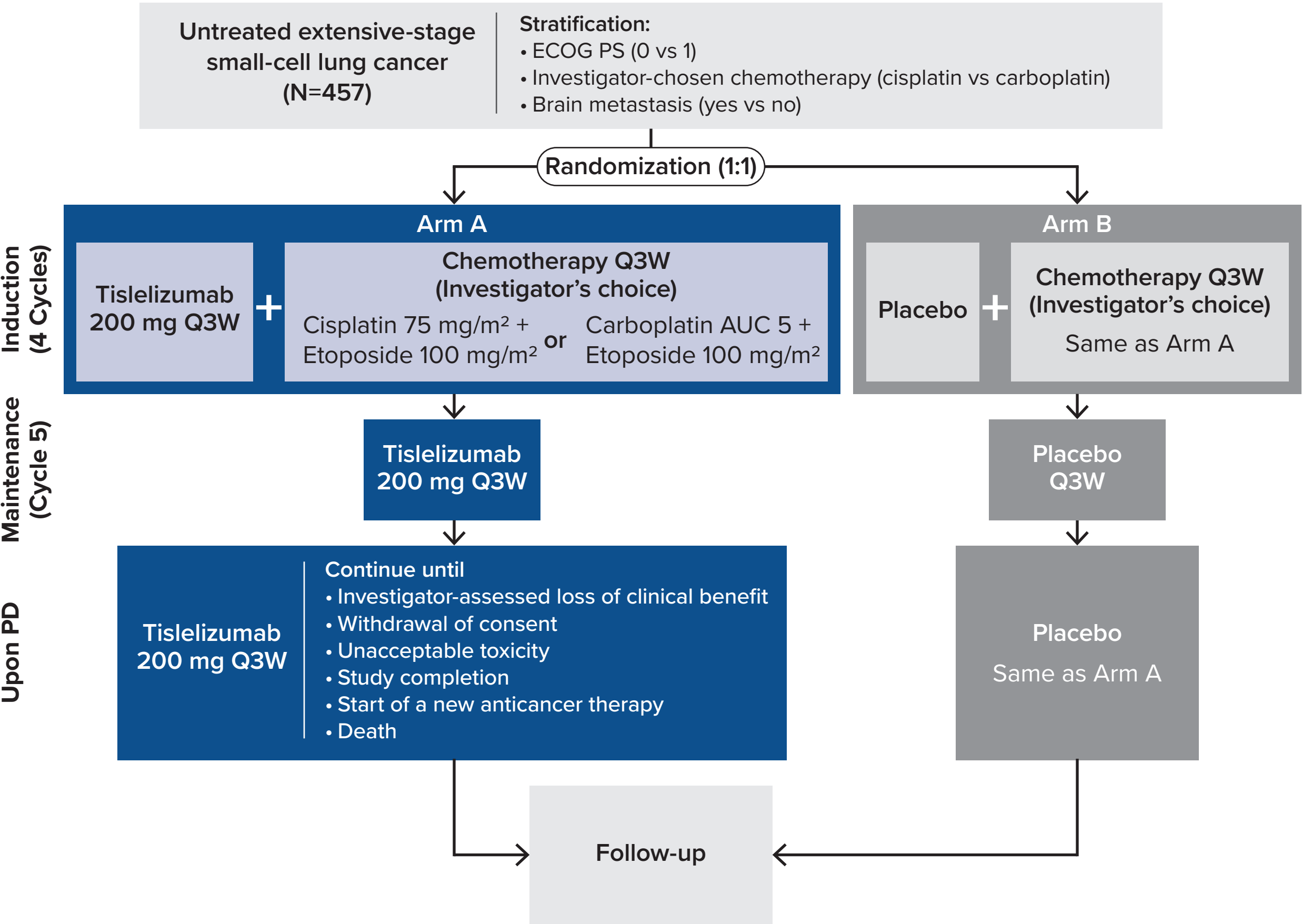
- Small-cell lung cancer (SCLC) accounts for 15% of lung cancers and is characterized by rapid progression and early metastasis, with 70% of cases diagnosed at an extensive stage (ES)
- Patients with ES-SCLC face a significant symptom burden and a notable decline in health-related quality of life (HRQoL)<sup>2</sup>
- In the phase 3 RATIONALE-312 trial (NCT04005716) of ES-SCLC patients, adding tislelizumab to chemotherapy (etoposide and a platinum agent) as first-line treatment significantly improved overall survival (OS) and progression-free survival (PFS) compared to placebo plus chemotherapy<sup>3</sup>
- The current analysis reports results for patient-reported outcomes (PROs) in patients treated with tislelizumab from the RATIONALE-312 study

METHODS

Study Design and Patients

- Eligible adult patients in China with previously untreated ES-SCLC were randomly assigned (1:1) to receive four cycles of intravenous (IV) tislelizumab 200 mg or placebo, in combination with etoposide and a platinum agent (cisplatin or carboplatin) as induction treatment, followed by tislelizumab 200 mg or placebo as maintenance (Figure 1)

Figure 1. RATIONALE-312 Study Design



Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; PD, progressive disease.

Assessments

- PROs were assessed at baseline (predose at Day 1 of Cycle 1), at every cycle through Cycle 4, then every other cycle thereafter until the end-of-treatment visit, and at the safety follow-up visit
- Key clinical Cycles 4 and 6 were prespecified based on their relevance to ES-SCLC and treatment side effects
  - European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core 30 (QLQ-C30): GHS/QoL and physical functioning scales
    - Higher scores on these scales reflect better HRQoL and physical functioning
  - EORTC Quality of Life Questionnaire Lung Cancer Module (QLQ-LC13): dyspnea, coughing, hemoptysis, dysphagia, chest pain, pain in arms and shoulders, and peripheral neuropathy symptoms
    - Higher scores on these scales indicate worse symptoms

Statistical Analyses

- The data cutoff date was April 19, 2023, and all randomized patients who completed the baseline and at least one postbaseline PRO questionnaire were included in the analyses
- Adjusted completion rates, defined as the ratio of number of patients who completed the questionnaires at each visit divided by the number still in treatment, were reported
- Change from baseline in each key PRO endpoint to Cycle 4 and Cycle 6 was analyzed using a linear mixed-effects model for repeated measures
  - The model included baseline score, stratification factors, treatment arm, visit, and treatment arm by visit interaction as fixed effects and visit as a repeated measure
  - Between-group comparisons were reported as differences in the least squares (LS) mean change from baseline, with corresponding 95% confidence intervals (CI) and nominal *P*-values
  - A clinically meaningful change was defined as a ≥5-point mean change from baseline<sup>4,5</sup>
- Time to deterioration (TTD) was defined as time to first onset of a ≥10-point change in the worsening direction from baseline with confirmation by a subsequent worsening in the following cycle
  - The hazard ratios showed the magnitude of treatment effect

RESULTS

- At the data cutoff date of April 19, 2023, a total of 457 patients were randomized (1:1) to receive tislelizumab (n=227) or placebo (n=230), combined with chemotherapy
- Patient demographics and baseline disease characteristics were generally balanced across treatment arms (Table 1)

Table 1. Demographic and Clinical Characteristics

Demographic/Characteristic	Tislelizumab + Chemotherapy (n=227)	Placebo + Chemotherapy (n=230)
Age, y, n (%)		
Median (IQR)	63 (56-66)	62 (56-67)
<65 y	138 (61)	149 (65)
≥65 y	89 (39)	81 (35)
Sex, n (%)		
Male	186 (82)	186 (81)
Female	41 (18)	44 (19)
ECOG performance status, n (%)		
0	35 (15)	34 (15)
1	192 (85)	196 (85)
Smoking status, n (%)		
Never	53 (23)	59 (26)
Current	151 (67)	135 (59)
Former	23 (10)	36 (16)
AJCC stage at study entry <sup>a,b</sup> , n (%)		
IIIA	4 (2)	2 (1)
IIIB	16 (7)	27 (12)
IV	207 (91)	201 (87)
Number of metastatic sites <sup>c</sup> , n (%)		
1	2 (<1)	2 (<1)
2	42 (19)	64 (28)
≥3	183 (81)	164 (71)
Liver metastasis, n (%)		
Yes	64 (28)	59 (26)
No	163 (72)	171 (74)
Brain metastasis, n (%)		
Yes	1 (<1)	4 (2)
No	226 (>99)	226 (98)
Baseline LDH, n (%)		
≤ULN	114 (50)	109 (47)
>ULN	113 (50)	121 (53)
Choice of platinum, n (%)		
Carboplatin	180 (79)	181 (79)
Cisplatin	47 (21)	49 (21)

Note: The data cutoff was April 19, 2023. Data are n (%) unless stated otherwise.

<sup>a</sup>Study entry was the date of randomization.

<sup>b</sup>On the basis of AJCC Staging Manual Seventh Edition.

<sup>c</sup>A patient could have multiple metastatic sites.

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; LDH, lactate dehydrogenase; ULN, upper limit of normal.

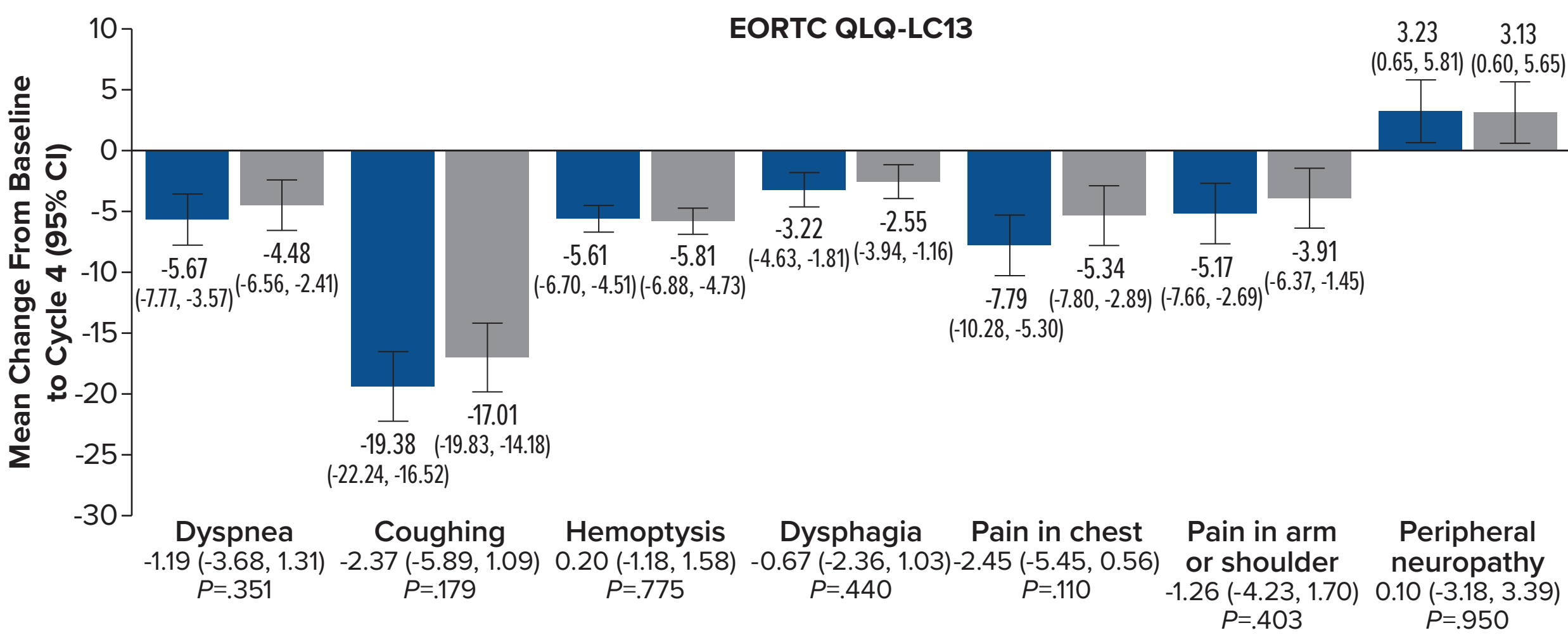
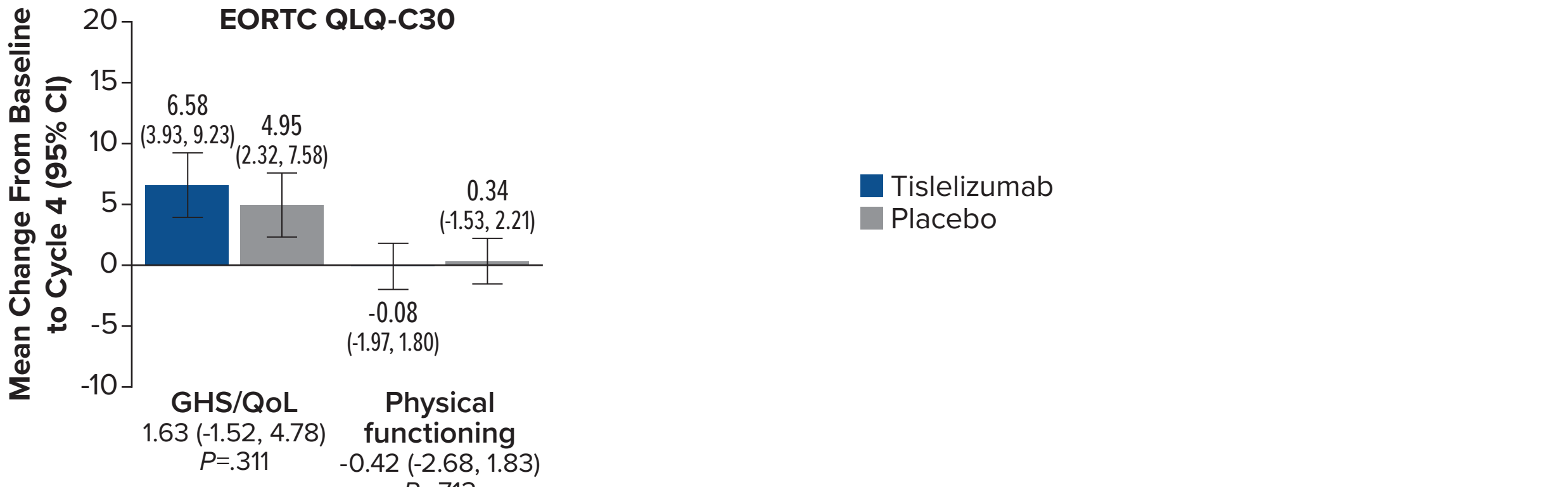
Adjusted Completion Rates

- The adjusted completion rates were 100% and consistent across treatment arms at each assessment timepoint

Change From Baseline to Cycle 4

- Changes from baseline in GHS/QoL did not differ between the two arms at Cycle 4 (Figure 2)
  - Clinically meaningful improvement was observed in the tislelizumab arm at Cycle 4, while the change in the placebo arm fell slightly below the clinically meaningful threshold
- Physical functioning scores were maintained at Cycle 4 in both arms, with no LS mean treatment difference from baseline observed between arms
- Changes from baseline in disease-specific symptoms of coughing, hemoptysis, and chest pain did not differ between the two arms at Cycle 4 (Figure 2)
  - Clinically meaningful improvements were observed for coughing, hemoptysis, and chest pain in both arms
- The tislelizumab arm demonstrated clinically meaningful improvements in dyspnea and arm or shoulder pain, whereas the placebo arm did not reach the clinically meaningful threshold (Figure 2)

Figure 2. Bar Plot of Least Squares Mean Changes From Baseline to Cycle 4

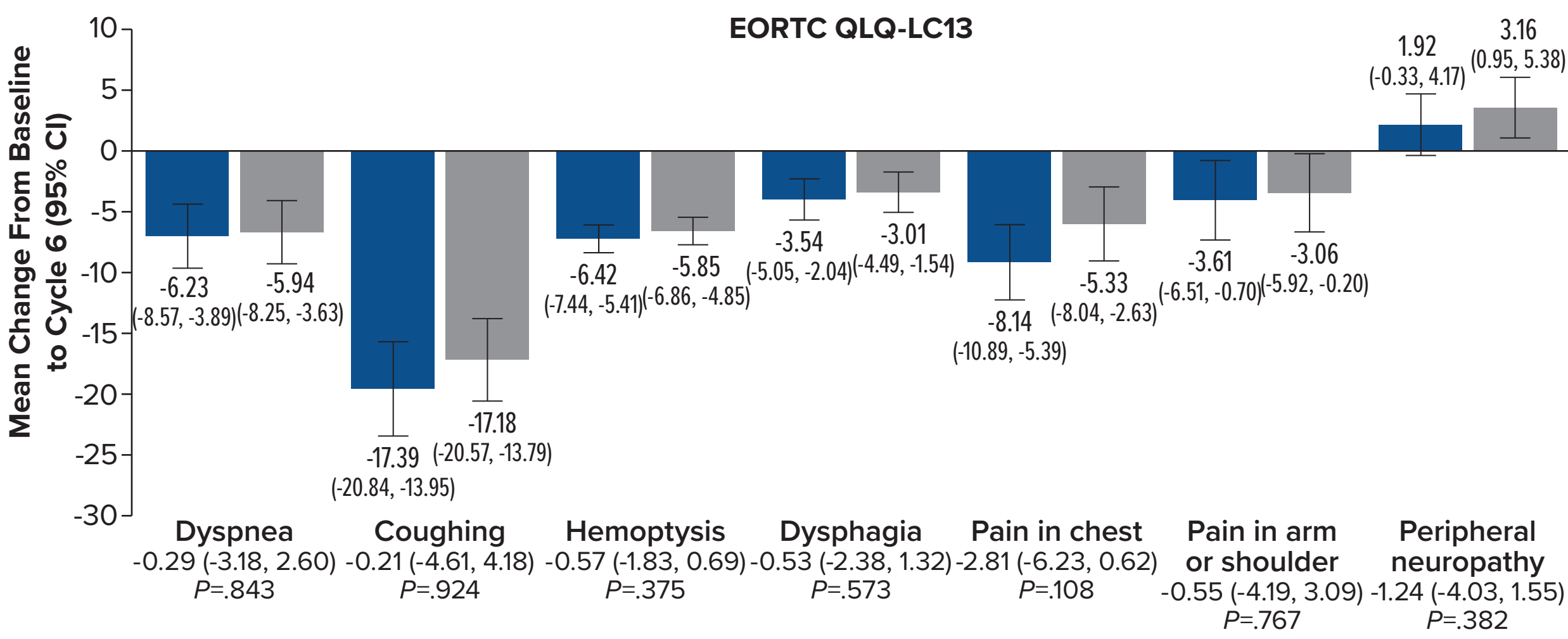
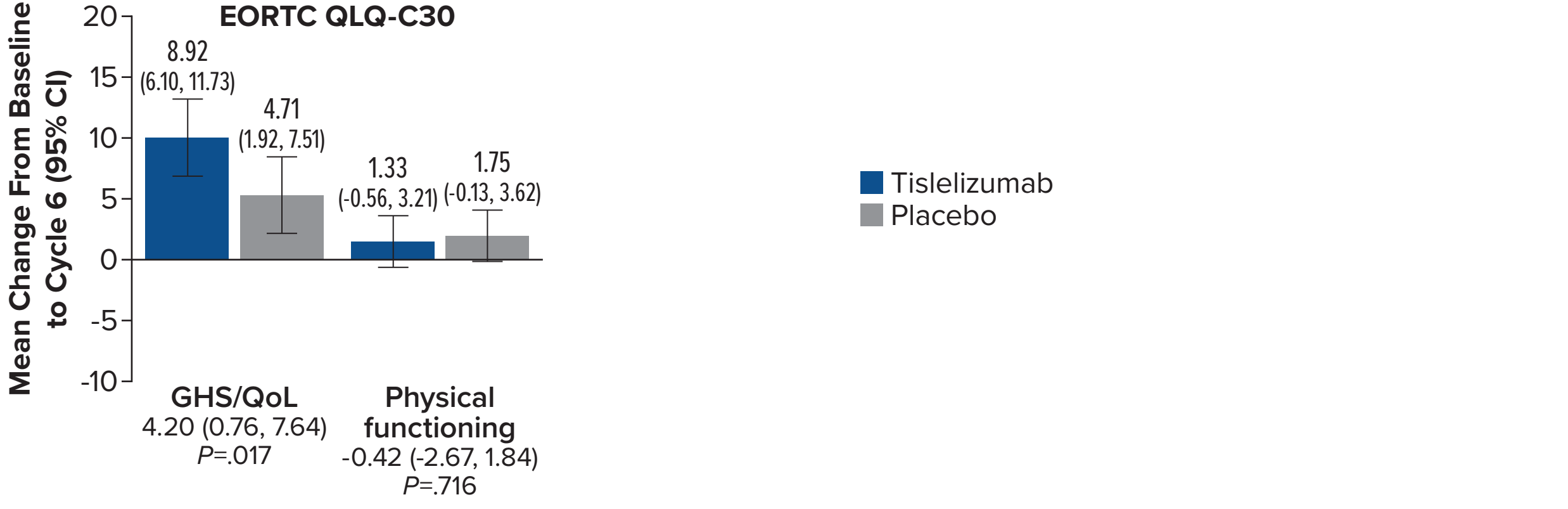


Higher scores on the GHS/QoL and physical functioning scales indicate better HRQoL, or functioning. Higher scores on the QLQ-LC13 indicate worse symptoms or problems. Abbreviations: CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; GHS/QoL, global health status/quality of life; HRQoL, health-related quality of life; QLQ-C30, Quality of Life Questionnaire-Core 30; QLQ-LC13, Quality of Life Questionnaire-Lung Cancer Module.

Change From Baseline to Cycle 6

- For GHS/QoL, the LS mean treatment difference between the arms was statistically significant, with the tislelizumab arm demonstrating a clinically meaningful improvement compared to the placebo arm at Cycle 6 (Figure 3)
- Physical functioning scores continued to be maintained at Cycle 6 in both arms, with no LS mean treatment difference between arms observed
- At Cycle 6, both the tislelizumab and placebo arms maintained clinically meaningful improvements in coughing, hemoptysis, and chest pain
- Change from baseline in dyspnea did not differ between the two arms at Cycles 6
  - Both arms showed clinically meaningful improvement in dyspnea symptoms

Figure 3. Bar Plot of Least Squares Mean Change From Baseline to Cycle 6



Higher scores on the GHS/QoL and physical functioning scales indicate better HRQoL, or functioning. Higher scores on the QLQ-LC13 indicate worse symptoms or problems. Abbreviations: CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; GHS/QoL, global health status/quality of life; HRQoL, health-related quality of life; QLQ-C30, Quality of Life Questionnaire-Core 30; QLQ-LC13, Quality of Life Questionnaire-Lung Cancer Module.

CONCLUSIONS

- The RATIONALE-312 trial demonstrated that patients with ES-SCLC who received first-line treatment with tislelizumab plus chemotherapy maintained or improved patient-reported symptoms compared with those who received placebo plus investigator's choice of chemotherapy
- Improvement in GHS/QoL was significantly greater in the tislelizumab arm compared to the placebo arm, with the tislelizumab arm achieving a clinically meaningful benefit at Cycle 6
- Clinically meaningful improvements in the disease-specific symptoms of coughing, hemoptysis, chest pain, and dyspnea were observed in both treatment arms at Cycle 6
- These PRO data, together with previously reported efficacy and safety data, support the use of tislelizumab plus chemotherapy as a first-line treatment option for patients with ES-SCLC

Time to Deterioration

- Only 16-26% of patients in both arms experienced a deterioration event, and TTD analysis showed that tislelizumab plus chemotherapy did not increase the risk of clinically meaningful worsening of physical functioning, coughing, or chest pain (Table 2)

Table 2. Analyses of Time to Deterioration for EORTC QLQ-C30 and QLQ-LC13

		Tislelizumab + Chemotherapy (n=227)	Placebo + Chemotherapy (n=229)
EORTC QLQ-C30	Physical functioning		
	Worsened, n (%)	59 (26.0)	59 (25.8)
	Censored, n (%)	168 (74.0)	170 (74.2)
	Time to clinically meaningful worsening, <sup>a</sup> median (months) (95% CI)	NR (20.5, NE)	NR (10.3, NE)
EORTC QLQ-LC13	Coughing		
	Worsened, n (%)	37 (16.3)	48 (21.0)
	Censored, n (%)	190 (83.7)	181 (79.0)
	Time to clinically meaningful worsening, <sup>a</sup> median (months) (95% CI)	NR (NE, NE)	NR (NE, NE)
EORTC QLQ-LC13	Pain in chest		
	Worsened, n (%)	44 (19.4)	60 (26.2)
	Censored, n (%)	183 (80.6)	169 (73.8)
	Time to clinically meaningful worsening, <sup>a</sup> median (months) (95% CI)	NR (NE, NE)	NR (NE, NE)
EORTC QLQ-LC13	Pain in chest		
	Worsened, n (%)	44 (19.4)	60 (26.2)
	Censored, n (%)	183 (80.6)	169 (73.8)
	Time to clinically meaningful worsening, <sup>a</sup> median (months) (95% CI)	NR (NE, NE)	NR (NE, NE)
EORTC QLQ-LC13	Pain in chest		
	Worsened, n (%)	44 (19.4)	60 (26.2)
	Censored, n (%)	183 (80.6)	169 (73.8)
	Time to clinically meaningful worsening, <sup>a</sup> median (months) (95% CI)	NR (NE, NE)	NR (NE, NE)

Time to deterioration is defined as the time from randomization to first 10-point (or greater) decrease/increase, or death, as measured by the subscale indicated. If a patient does not have an event (death or deterioration), they are censored at their last clinic visit at which corresponding score is measured.

<sup>a</sup>Estimates are based on Kaplan-Meier method.

<sup>b</sup>Hazard ratio was based on unstratified Cox regression model including treatment as covariate.

Abbreviations: CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; GHS/QoL, global health status/quality of life; HR, hazard ratio; NE, not estimable; NR, not reached.

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DISCLOSURES

TQ, CC, GB, BB: Employees of BeiGene and report stock or other ownership; YC: No disclosures.

ACKNOWLEDGMENTS

This study was funded by BeiGene, Ltd. BeiGene, US, Inc. has changed its name to BeOne Medicines USA, Inc. This change comes ahead of the anticipated global rebranding to BeOne Medicines Ltd.