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Examining the Impact of Tislelizumab Added to Chemotherapy on Health-Related Quality-of-Life Outcomes in Previously Untreated Patients With Nonsquamous Non–Small Cell Lung Cancer

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Purpose: This study assessed the effects of tislelizumab, a programmed cell death protein 1 inhibitor, in combination with chemotherapy versus chemotherapy alone as first-line treatment on health-related quality of life (HRQoL) in patients with advanced nonsquamous non–small cell lung cancer (nSQ-NSCLC).

Methods: Patients in this randomized, open-label, multicenter phase III study RATIONALE 304 (NCT03663205) with histologically confirmed stage IIIB/IV nSQ-NSCLC were randomized 2:1 to tislelizumab plus platinum-pemetrexed (arm T + PP) or platinum-pemetrexed alone (arm PP). Health-related QoL was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Lung Cancer. Key patient-reported outcome endpoints include mean score change from baseline at weeks 12 (during chemotherapy) and 18 (following chemotherapy) in the 30-item Quality of Life Questionnaire Core's global health status/quality of life (GHS/QoL) and time to deterioration in GHS/QoL.

Results: Three hundred thirty-two patients received at least 1 dose of study drug and completed at least 1 HRQoL assessment. Global health status/QoL score improved in arm T + PP at week 18 (between-group least square mean difference, 5.7; 95% confidence interval [CI], 1.0–10.5; $P = 0.018$). Patients in arm T + PP experienced greater reduction in coughing (−5.9; 95% CI, −11.6 to −0.1; $P = 0.044$), dyspnea (−3.8; 95% CI, −7.8 to 0.1; $P = 0.059$), chest pain (−6.2; 95% CI, −10.8 to −1.6; $P = 0.008$), and peripheral neuropathy (−2.6; 95% CI, −5.5 to 0.2; $P = 0.066$). Median time to deterioration in GHS/QoL was not achieved for either arm.

Discussion: The addition of tislelizumab to platinum-based chemotherapy was associated with improvements in nSQ-NSCLC patients' HRQoL as well as the important disease-specific symptoms of coughing, chest pain, and dyspnea.

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Key Words: Health-related quality of life, nonsquamous non–small cell lung cancer, patient-reported outcomes, programmed cell death protein 1 inhibitor

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Globally, there are approximately 2.1 million new lung cancer cases and 1.8 million deaths each year.[1] Lung cancer is the leading cause of cancer incidence and death, both globally and in China, where there were an estimated 733,300 new cases and 610,200 deaths in 2015.[2] Platinum-based regimens are the standard first-line therapy for Chinese patients with locally advanced/metastatic nonsquamous (nSQ) non–small cell lung cancer (NSCLC) without epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) mutations[3]; however, despite the available treatments, overall survival (OS) remains low for these patients.[4] In addition to their low OS rates, disease-related symptoms have a significant negative impact on patients' health-related quality of life (HRQoL).[5–8] Recent trials examining the clinical outcomes of treatment with immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1) or programmed death 1 ligand (PD-L1) as a monotherapy or in combination with chemotherapy have shown promising clinical results[9–11] and improvements in HRQoL in patients with nSQ-NSCLC.[12–14]

Tislelizumab is a humanized monoclonal antibody against PD-1,[4,15–17] which is under clinical development for the treatment of several solid tumor malignancies, including NSCLC.[4,16,18] RATIONALE 304 (NCT03663205) is a randomized, open-label, multicenter phase III clinical trial examining the efficacy and safety of tislelizumab plus platinum-pemetrexed (T + PP) chemotherapy versus platinum-pemetrexed (PP) alone in patients with previously untreated, locally advanced/metastatic nSQ-NSCLC without *EGFR* mutations or known *ALK* gene translocation.[19] After a median follow-up of 9.8 months, progression-free survival (PFS) was significantly longer in arm T + PP compared with arm PP (median PFS, 9.7 vs. 7.6 months; hazard ratio [HR], 0.645; 95% confidence interval [CI], 0.462–0.902; $P = 0.0044$). The objective response rate was also higher in arm T + PP (57.4%; 95% CI, 50.6–64.0) compared with arm PP (36.9%; 95% CI, 28.0–46.6). Furthermore, the incidence and frequency of observed adverse events (AEs) were similar between arms, and most AEs were mild or moderate in severity and were manageable.

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Health-related QoL was assessed using patient-reported outcomes (PROs) and were evaluated as a prespecified secondary objective in RATIONALE 304 to determine whether tislelizumab plus chemotherapy could improve HRQoL and lung cancer symptoms as well as delay the time to deterioration (TTD) in HRQoL compared with chemotherapy alone in patients with nSQ-NSCLC.

MATERIALS AND METHODS

Study Design and Population

RATIONALE 304 (NCT03663205) is a randomized, open-label, multicenter phase III clinical trial conducted at 47 sites in China to assess the efficacy and safety of treatment with tislelizumab added to platinum-pemetrexed chemotherapy (arm T + PP) versus platinum-pemetrexed chemotherapy alone (arm PP).[19] Eligible patients were randomized 2:1 to arm T + PP or arm PP. Randomization was stratified by disease stage (IIIB vs. IV) and tumor cell PD-L1 membrane expression (<1% vs. 1%–49% vs. ≥50%).

Patients in arm T + PP received tislelizumab 200 mg plus platinum-based chemotherapy (carboplatin area under the curve 5 or cisplatin 75 mg/m^2 in combination with pemetrexed 500 mg/m^2) once every 3 weeks intravenously for 4 to 6 cycles (at investigator's discretion) during induction treatment, followed by maintenance tislelizumab plus pemetrexed treatment. Patients in arm PP received platinum-based chemotherapy (carboplatin area under the curve 5 or cisplatin 75 mg/m^2 in combination with pemetrexed 500 mg/m^2) once every 3 weeks for 4 to 6 cycles (at investigator's discretion) during induction treatment, followed by maintenance pemetrexed treatment.

Adult patients (aged 18–75 years) who were treatment-naive with histologically confirmed stage IIIB or IV nSQ-NSCLC, with at least 1 measurable lesion, were eligible for inclusion if they provided fresh or archival tumor tissues for PD-L1 expression analysis. Patients with mixed non–small cell histology tumors were eligible if the major histological component was nSQ. Patients must have had no prior systemic chemotherapy for advanced or metastatic disease, although prior neoadjuvant/adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for nonmetastatic disease was permitted with a disease-free interval of ≥6 months from the last dose of chemotherapy and/or radiotherapy prior to randomization. Exclusion criteria also included a known *EGFR*-sensitizing mutation or *ALK* gene translocation; prior treatment with EGFR inhibitors, ALK inhibitors, and/or therapies targeting PD-1/PD-L1; systemic immunosuppressive agents ≤14 days prior to randomization; a history of interstitial lung disease; or noninfectious pneumonitis.

The study was performed according to the ethical principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and the requirements of the public registration of clinical trials. Written informed consent was obtained prior to participation in the study.

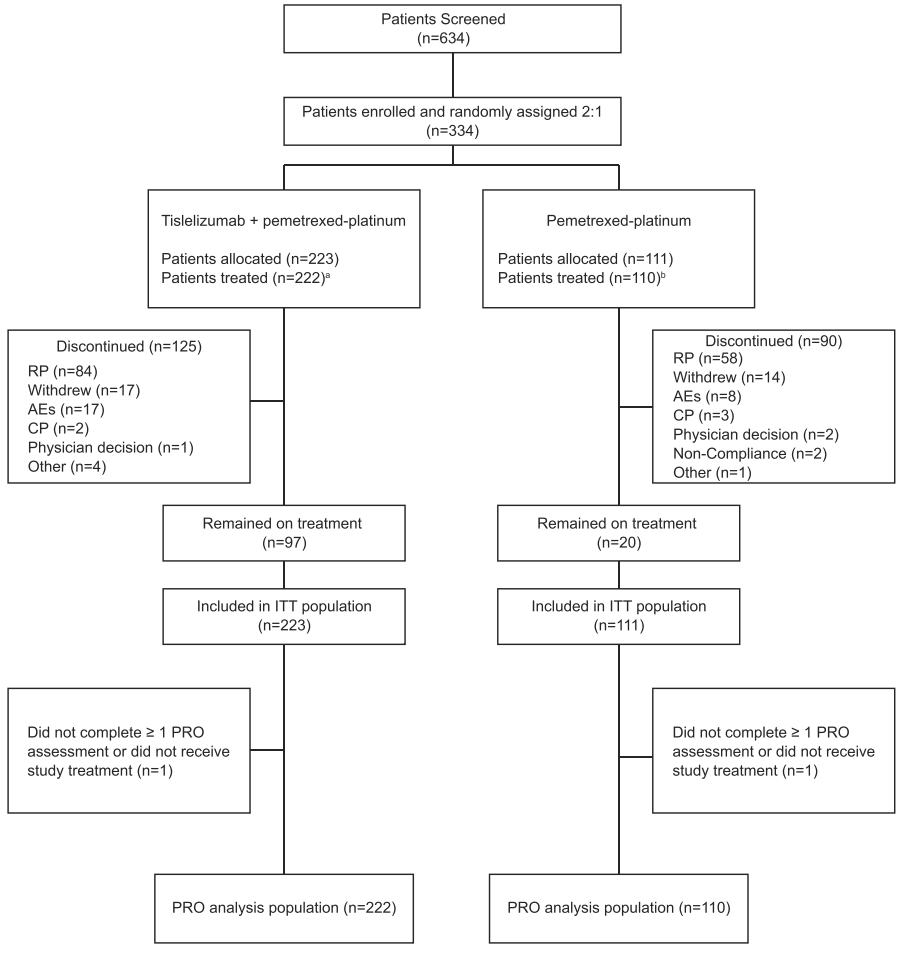

FIGURE 1. CONSORT diagram. Disposition of patients in the study. CP indicates clinical progression; ITT, intent-to-treat; RP, radiographic progression. [a]One patient randomized to combination therapy was not treated because inclusion criteria were not met. [b]One patient randomized to pemetrexed-platinum therapy was not treated owning to withdrawal of consent.

TABLE 1. Completion and Compliance Rates for HRQoL Assessments

	Arm T + PP (n = 222), n (%)	Arm PP (n = 110), n (%)
QLQ-C30		
Baseline	222 (100.0)	110 (100.0)
Week 12		
Completion	174 (78.4)	73 (66.4)
Compliance	174/176 (98.9)	73/74 (98.6)
Week 18		
Completion	150 (67.6)	54 (49.1)
Compliance	150/151 (99.3)	54/54 (100.0)
Week 24		
Completion	130 (58.6)	33 (30.0)
Compliance	130/130 (100.0)	33/33 (100.0)
Week 30		
Completion	93 (41.9)	23 (20.9)
Compliance	93/95 (97.9)	23/23 (100.0)
Week 36		
Completion	59 (26.6)	10 (9.1)
Compliance	59/60 (98.3)	10/10 (100.0)
QLQ-LC13		
Baseline	222 (100.0)	110 (100.0)
Week 12		
Completion	174 (78.4)	73 (66.4)
Compliance	174/176 (98.9)	73/74 (98.6)
Week 18		
Completion	150 (67.6)	54 (49.1)
Compliance	150/151 (99.3)	54/54 (100.0)
Week 24		
Completion	130 (58.6)	33 (30.0)
Compliance	130/130 (100.0)	33/33 (100.0)
Week 30		
Completion	93 (41.9)	23 (20.9)
Compliance	93/95 (97.9)	23/23 (100.0)
Week 36		
Completion	59 (26.6)	10 (9.1)
Compliance	59/60 (98.3)	10/10 (100.0)

HRQoL Endpoints

Health-related QoL was the secondary endpoint outcome assessed via 2 validated PRO instruments: the European Organization for Research and Treatment of Cancer 30-item Quality of Life Core Questionnaire (QLQ-C30)[20] and the European Organization for Research and Treatment of Cancer 13-item Quality of Life Questionnaire–Lung Cancer (QLQ-LC13).[21]

The QLQ-C30 is a validated instrument used to assess the HRQoL of cancer patients overall[20] and includes a global health status/quality of life (GHS/QoL) scale, 5 functional scales (physical, role, emotional, cognitive, and social functioning), 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 symptom single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial impact).[22] The GHS/QoL scale items are rated using a 7-point scale (anchored at "very poor" and "excellent"), whereas the remaining items are rated using a 4-point scale ("not at all," "a little," "quite a bit," "very much"). The current analyses focused on the 2-item GHS/QoL scale.

The QLQ-LC13 was developed in parallel with the QLQ-C30 and field tested together in lung cancer patients receiving treatment with chemotherapy and/or radiotherapy[21]; the QLQ-LC13 includes a symptom scale (dyspnea) and 9 symptom single items (coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, hemoptysis, pain in chest, pain in arm or shoulder, and pain in other parts). These items are rated using a Likert scale from 1 ("not at all") to 4 ("very much"). The current analyses focused on the main lung cancer symptom scales of coughing, dysphagia, dyspnea, hemoptysis, chest pain, pain in arm or shoulder, and peripheral neuropathy.

The QLQ-C30 and QLQ-LC13 were assessed at baseline, at every other cycle through cycle 13, then every 4 cycles thereafter, and at the end of treatment. Questionnaires were completed prior to any clinical activities during on-study site visits.

Key PRO endpoints were assessed via mean score change from baseline to week 12 and week 18, and TTD was measured via the QLQ-C30 GHS/QoL. The PRO endpoints assessment included mean score changes from baseline at weeks 12 and 18 in the QLQ-LC13 subscales of coughing, dysphagia, dyspnea, hemoptysis, chest pain, pain in arm or shoulder, and peripheral neuropathy. These time points were selected to represent times during (week 12) and after (week 18) chemotherapy treatment to minimize data loss due to disease progression or death.

Statistical Analyses

For the study primary endpoint analyses, the study had 85% power to detect an HR of 0.65 for disease progression or death, with a 1-sided α of 0.025 (based on 215 PFS events). Statistical methods for the primary analyses have been described

TABLE 2. Change From Baseline in QLQ-C30 GHS/QoL Scale Scores

	Arm T + PP	Arm PP
Baseline		
Mean score (SD)	n = 222*	n = 110*
	67.9 (19.98)	68.5 (16.87)
Week 12		
Mean score (SD)	n = 174*	n = 73*
	69.1 (19.67)	65.5 (16.22)
LS mean change from baseline (95% CI)†	n = 222‡	n = 110‡
	0.9 (−2.0 to 3.8)	−3.0 (−7.3 to 1.2)
Difference in LS mean (95% CI)†	3.9 (−0.9 to 8.7)	
P§	0.1069	
Week 18		
Mean score (SD)	n = 150*	n = 54*
	71.9 (17.82)	67.0 (16.10)
LS mean change from baseline (SD)†	n = 222‡	n = 110‡
	2.8 (0.0 to 5.6)	−2.9 (−7.1 to 1.3)
Difference in LS mean (95% CI)†	5.7 (1.0 to 10.5)	
P§	0.0183	

*Number of patients who completed QLQ-C30 GHS/QoL at the noted time point.

†Based on a constrained longitudinal data analysis model with QLQ-C30 GHS/QoL scores as response variable, treatment × study visit interaction, and stratification factors for randomization as covariates.

‡Number of patients in analysis population.

§*P* values are 2-sided and nominal.

TABLE 3. Change From Baseline in QLQ-LC13 Subscales

Subscale		Arm T + PP		Arm PP	
Coughing	Baseline				
	Mean score (SD)	n = 222*	31.4 (26.36)	n = 110*	28.2 (22.21)
	Week 12				
	Mean score (SD)	n = 174*	17.4 (19.53)	n = 73*	17.4 (19.53)
	LS mean change from baseline (95% CI)†	n = 222‡	13.0 (−16.6 to −9.4)	n = 110‡	−10.8 (−15.7 to −5.9)
	Difference in LS mean (95% CI)†		−2.2 (−7.4 to 3.1)		
	P§		0.4161		
	Week 18				
	Mean score (SD)	n = 150*	14.0 (18.63)	n = 54*	18.5 (20.13)
	LS mean change from baseline (SD)†	n = 222‡	−15.6 (−19.2 to −12.0)	n = 110‡	−9.8 (−15.1 to −4.5)
	Difference in LS mean (95% CI)†		−5.9 (−11.6 to −0.1)		
	P§		0.0444		
Dysphagia	Baseline				
	Mean score (SD)	n = 222*	3.0 (11.03)	n = 110*	2.7 (9.18)
	Week 12				
	Mean score (SD)	n = 174*	2.7 (9.09)	n = 73*	2.7 (9.22)
	LS mean change from baseline (95% CI)†	n = 222‡	−0.1 (−1.6 to 1.3)	n = 110‡	0.0 (−2.0 to 2.1)
	Difference in LS mean (95% CI)†		−0.2 (−2.5 to 2.1)		
	P§		0.8855		
	Week 18				
	Mean score (SD)	n = 150*	1.6 (7.05)	n = 54*	2.5 (8.81)
	LS mean change from baseline (SD)†	n = 222‡	−1.1 (−2.6 to 0.4)	n = 110‡	−0.5 (−2.7 to 1.7)
	Difference in LS mean (95% CI)†		−0.6 (−3.0 to 1.7)		
	P§		0.6021		
Dyspnea	Baseline				
	Mean score (SD)	n = 222*	18.6 (17.38)	n = 110*	15.6 (12.61)
	Week 12				
	Mean score (SD)	n = 174*	16.3 (13.28)	n = 73*	16.0 (11.86)
	LS mean change from baseline (95% CI)†	n = 222‡	−1.4 (−3.5 to 0.6)	n = 110‡	−0.3 (−3.2 to 2.6)
	Difference in LS mean (95% CI)†		−1.2 (−4.4 to 2.1)		
	P§		0.4807		
	Week 18				
	Mean score (SD)	n = 150*	15.3 (14.94)	n = 54*	18.3 (13.68)
	LS mean change from baseline (SD)†	n = 222‡	−1.6 (−3.9 to 0.6)	n = 110‡	2.2 (−1.3 to 5.7)
	Difference in LS mean (95% CI)†		−3.8 (−7.8 to 0.1)		
	P§		0.0585		
Hemoptysis	Baseline				
	Mean score (SD)	n = 222*	5.3 (12.17)	n = 110*	7.0 (14.35)
	Week 12				
	Mean score (SD)	n = 174*	2.1 (8.14)	n = 73*	1.8 (7.64)
	LS mean change from baseline (95% CI)†	n = 222‡	−3.6 (−5.3 to −2.0)	n = 110‡	−4.0 (−6.2 to −1.9)
	Difference in LS mean (95% CI)†		0.4 (−1.7 to 2.6)		
	P§		0.6997		
	Week 18				
	Mean score (SD)	n = 150*	1.1 (6.00)	n = 54*	1.9 (7.71)
	LS mean change from baseline (SD)†	n = 222‡	−4.6 (−6.3 to −3.0)	n = 110‡	−4.0 (−6.2 to −1.8)
	Difference in LS mean (95% CI)†		−0.7 (−2.7 to 1.4)		
	P§		0.5318		

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TABLE 3. *(Continued)*

Subscale		Arm T + PP		Arm PP	
Pain in arm or shoulder	Baseline				
	Mean score (SD)	n = 222*	17.0 (22.14)	n = 110*	14.2 (21.87)
	Week 12				
	Mean score (SD)	n = 174*	9.4 (17.78)	n = 73*	8.2 (15.50)
	LS mean change from baseline (95% CI)†	n = 222‡	−6.9 (−9.9 to −3.9)	n = 110‡	−6.5 (−10.6 to −2.4)
	Difference in LS mean (95% CI)†		−0.4 (−4.9 to 4.1)		
	P§		0.8679		
	Week 18				
	Mean score (SD)	n = 150*	9.3 (19.36)	n = 54*	9.9 (21.11)
	LS mean change from baseline (SD)†	n = 222‡	−6.1 (−9.8 to −2.5)	n = 110‡	−4.7 (−10.2 to 0.7)
	Difference in LS mean (95% CI)†		−1.4 (−7.4 to 4.6)		
	P§		0.6391		
Chest pain	Baseline				
	Mean score (SD)	n = 222*	16.7 (22.37)	n = 110*	18.8 (23.26)
	Week 12				
	Mean score (SD)	n = 174*	9.2 (16.95)	n = 73*	12.8 (17.24)
	LS mean change from baseline (95% CI)†	n = 222‡	−7.4 (−10.4 to −4.5)	n = 110‡	−4.2 (−8.3 to −0.2)
	Difference in LS mean (95% CI)†		−3.2 (−7.6 to 1.2)		
	P§		0.1562		
	Week 18				
	Mean score (SD)	n = 150*	7.6 (14.00)	n = 54*	15.4 (19.11)
	LS mean change from baseline (SD)†	n = 222‡	−8.1 (−11.1 to −5.1)	n = 110‡	−1.9 (−6.2 to 2.4)
	Difference in LS mean (95% CI)†		−6.2 (−10.8 to −1.6)		
	P§		0.0082		
Peripheral neuropathy	Baseline				
	Mean score (SD)	n = 222*	5.3 (14.79)	n = 110*	2.7 (9.18)
	Week 12				
	Mean score (SD)	n = 174*	2.9 (10.04)	n = 73*	5.0 (12.01)
	LS mean change from baseline (95% CI)†	n = 222‡	−1.6 (−3.5 to 0.3)	n = 110‡	1.1 (−1.5 to 3.7)
	Difference in LS mean (95% CI)‡		−2.6 (−5.5 to 0.2)		
	P§		0.0667		
	Week 18				
	Mean score (SD)	n = 150*	4.2 (11.12)	n = 54*	4.9 (11.95)
	LS mean change from baseline (SD)†	n = 222‡	−0.3 (−2.4 to 1.9)	n = 110‡	1.1 (−2.1 to 4.4)
	Difference in LS mean (95% CI)†		−1.4 (−4.9 to 2.1)		
	P§		0.4287		

*Number of patients who completed the QLQ-LC13 subscale at the noted time point.

†Based on a constrained longitudinal data analysis model with the QLQ-LC13 subscale as the response variable, treatment × study visit interaction, and stratification factors for randomization as covariates.

‡Number of patients in the analysis population.

§*P* values are 2-sided and nominal.

previously.[19] No power calculation for PROs was conducted; *P* values for these analyses are nominal, and all are 2-sided without adjustment for multiplicity.

Patient-reported outcome analyses included all randomized patients who received at least 1 dose of study drug and completed at least 1 HRQoL assessment. Upon investigator-assessed progressive disease, patients would be optional to receive subsequent therapy, so HRQoL assessments up to investigator-assessed progressive disease were included. Patients were considered to have completed at least 1 PRO assessment if they completed at least 1 item on a PRO instrument. Compliance with the PRO assessments was defined as the proportion of patients who completed at least 1 item among those expected to complete the questionnaire (i.e., those who had not discontinued and had a scheduled study visit). Evaluation of mean change from baseline to weeks 12 and 18 in the PRO instrument score was based on a constrained longitudinal data analysis model, with the PRO score as the response variable and treatment, study visit, treatment × study visit interaction, and randomization stratification factors (PD-L1 expression in tumor cell and disease stage) as covariates, based on the missing at random assumption. Between-group comparisons were reported as differences in the least square (LS) mean change from baseline with the 95% CI and nominal *P* value.

Time to deterioration in the GHS/QoL score was defined as time to first onset of ≥10-point decrease from baseline with confirmation by a decrease in the subsequent cycle. The Kaplan-Meier method was used to estimate the deterioration curve in each group; a stratified Cox model with Efron's method of tie handling was used to assess between-group differences. The QLQ-C30 and QLQ-LC13 scores were standardized to a scale ranging from 0 to

100 by linear transformation. For GHS/QoL, higher scores indicate a higher (better) level of function, whereas for the symptom scales, higher scores indicate a higher (worse) severity of symptoms.

Additional descriptive analyses were conducted for weeks 24, 30, and 36, examining mean changes from baseline for the QLQ-C30 GHS/QoL mean score, as well as the specific QLQ-C30 and QLQ-LC13 subscales included in this study.

RESULTS

A total of 334 patients (223 in arm T + PP and 111 in arm PP) were randomized between July 23, 2018, and July 31, 2019 (Fig. 1). The demographics and clinical characteristics were generally balanced across the 2 treatment arms and were representative of the target patient population (Supplemental Digital Content, http://links.lww.com/PPO/A36). As of data cutoff of January 23, 2020, the median length of follow-up was 9.8 months (95% CI, 9.2–10.4 months).

Completion and Compliance Rates

The HRQoL analysis population included 332 patients: 222 in arm T + PP and 110 in arm PP. The proportion of patients who completed the QLQ-C30 and QLQ-LC13 was lower at week 18 than at baseline or week 12, partly because of patients missing from the analysis by design (i.e., because they had discontinued treatment as a result of disease progression, AE, withdrawn consent, physician decision, or other; Table 1). At baseline, 222 (100%) of 222 patients in arm T + PP and 110 (100%) of 110 patients in arm PP were compliant with QLQ-C30; at week 12, 174 (98.9%) of 176 and 73 (98.6%) of 74 patients, respectively, were compliant, and at week 18, 150 (99.3%) of 151 and 54 (100%) of 54 patients, respectively, were compliant. Compliance with QLQ-LC13 was similar (Table 1). Compliance was higher than completion at all time points in both groups because the population for assessment of completion included all patients at each time point, whereas the compliance was assessed for patients expected to complete at each time point.

Change From Baseline at Weeks 12 and 18

QLQ-C30 GHS/QoL Scale

Baseline GHS/QoL mean scores were similar between groups (Table 2). Relative to baseline, scores at week 12 were maintained in both arm T + PP (LS mean change: 0.9 point; 95% CI,−2.0 to 3.8 increase) and arm PP (−3.0 point; 95% CI, −7.3 to 1.2 decrease; Table 2), with a between-group LS mean difference of 3.9 (95% CI, −0.9 to 8.7; $P = 0.1069$). At week 18, GHS/QoL score was improved by 2.8 points (95% CI, 0.0–5.6) in arm T + PP, whereas it had worsened by −2.9 points (95% CI, −7.1 to 1.3) in arm PP, with a between-group LS mean difference of 5.7 (95% CI, 1.0–10.5; $P = 0.0183$).

QLQ-LC13 Subscales

For the QLQ-C30 and QLQ-LC13 subscales, LS mean score changes from baseline to week 18 were generally more favorable in arm T + PP than in arm PP (Table 3). At week 12, the reduction in coughing was similar in arm T + PP (LS mean change = −13.0; 95% CI, −16.6 to −9.4) and arm PP (LS mean change = −10.8; 95% CI, −15.7 to −5.9), with a between-group LS mean difference of −2.2 (95% CI, −7.4 to 3.1; $P = 0.4161$). However, at week 18, the reduction in coughing in arm T + PP (LS mean change = −15.6; 95% CI, −19.2 to −12.0) was greater than arm PP (LS mean change = −9.8; 95% CI, −15.1 to −4.5), with a between-group LS mean difference of −5.9 (95% CI, −11.6 to −0.1; $P = 0.044$). Change in dysphagia from baseline was also similar in the 2 arms at week 12 (between-group LS mean difference = −0.2; 95% CI, −2.5 to 2.1; $P = 0.8855$) and week 18 (between-group LS mean difference = −0.6; 95% CI, −3.0 to 1.7; $P = 0.6021$). Change in dyspnea from baseline was similar in the 2 arms at week 12 (between-group LS mean difference = −1.2; 95% CI, −4.4 to 2.1; $P = 0.4807$) and week 18 (between-group LS mean difference = −3.8; 95% CI, −7.8 to 0.1; $P = 0.0585$). However, at week 18, arm T + PP experienced a reduction from baseline in dyspnea (LS mean change = −1.6; 95% CI, −3.9 to 0.6), whereas arm PP experienced an increase (LS mean change = 2.2; 95% CI, −1.3 to −5.7).

Change in hemoptysis from baseline was similar in the 2 arms at week 12 (between-group LS mean difference = 0.4; 95% CI, −1.7 to 2.6; $P = 0.6997$) and week 18 (between-group LS mean difference = −0.7; 95% CI, −2.7 to 1.4; $P = 0.5318$). Change in pain in arm or shoulder from baseline was similar in the 2 arms at week 12 (between-group LS mean difference = −0.4; 95% CI, −4.9 to 4.1; $P = 0.8679$) and week 18 (between-group LS mean difference = −1.4; 95% CI, −7.4 to 4.6; $P = 0.6391$). For chest pain, the 2 arms experienced a similar decline from baseline (between-group LS mean difference of −3.2; 95% CI, −7.6 to 1.2; $P = 0.1562$). At week 18, the change from baseline for arm T + PP (LS mean change = −8.1; 95% CI, −11.1 to −5.1) was greater than arm PP (LS mean change = −1.9; 95% CI, −6.2 to 2.4), with a between-group LS mean difference of −6.2 (95% CI, −10.8 to −1.6; $P = 0.0082$). Peripheral neuropathy declined at week 12 for arm T + PP (LS mean change = −1.6; 95% CI,

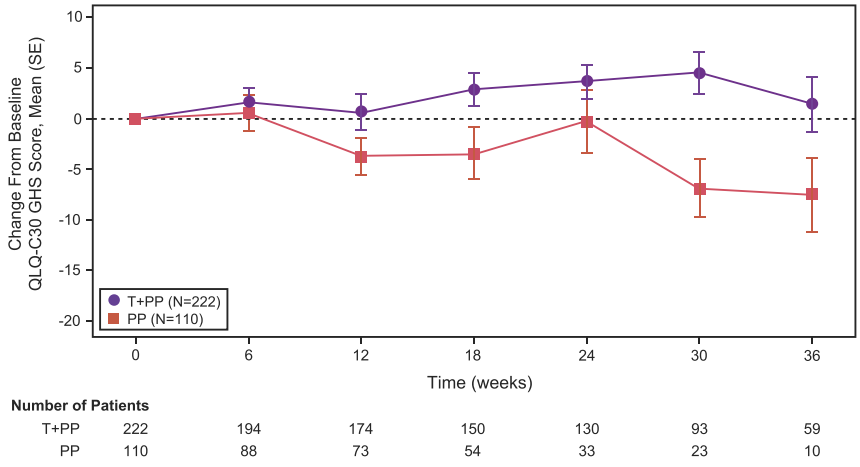

FIGURE 2. Mean change from baseline in QLQ-C30 GHS/QoL scale scores.

TABLE 4. Observed and Change From Baseline for QLQ-LC13 Subscales at Weeks 24, 30, and 36

		Arm T + PP (n = 222)		Arm PP (n = 110)	
		Observed	**Change From Baseline**	**Observed**	**Change From Baseline**
Coughing	Week 24				
	n	130	130	33	33
	Mean (SD)	15.1 (18.61)	−15.4 (26.30)	14.1 (20.46)	−9.1 (29.19)
	Week 30				
	n	93	93	23	23
	Mean (SD)	14.7 (20.54)	−17.6 (27.62)	15.9 (19.77)	−11.6 (31.15)
	Week 36				
	n	59	59	10	10
	Mean (SD)	13.0 (20.55)	−18.1 (29.89)	16.7 (17.57)	−10.0 (16.10)
Dysphagia	Week 24				
	n	130	130	33	33
	Mean (SD)	1.8 (7.55)	−1.0 (13.08)	4.0 (11.05)	1.0 (10.15)
	Week 30				
	n	93	93	23	23
	Mean (SD)	2.2 (8.23)	−0.4 (13.45)	2.9 (9.60)	0.0 (14.21)
	Week 36				
	n	59	59	10	10
	Mean (SD)	1.1 (6.08)	−0.6 (9.77)	0.0 (0.00)	−6.7 (14.05)
Dyspnea	Week 24				
	n	130	130	33	33
	Mean (SD)	13.8 (13.42)	−2.8 (16.68)	16.2 (14.19)	1.3 (15.15)
	Week 30				
	n	93	93	23	23
	Mean (SD)	12.8 (12.47)	−4.8 (16.90)	16.9 (11.05)	4.3 (11.96)
	Week 36				
	n	59	59	10	10
	Mean (SD)	13.9 (12.82)	−3.4 (17.78)	16.7 (9.44)	−1.1 (3.51)
Hemoptysis	Week 24				
	n	130	130	33	33
	Mean (SD)	1.3 (6.44)	−4.1 (12.46)	2.0 (8.08)	−4.0 (13.84)
	Week 30				
	n	93	93	23	23
	Mean (SD)	1.8 (7.56)	−4.3 (13.21)	2.9 (13.90)	−4.3 (20.85)
	Week 36				
	n	59	59	10	10
	Mean (SD)	1.7 (7.39)	−4.5 (11.51)	0.0 (0.00)	−3.3 (10.54)
Pain in arm or shoulder	Week 24				
	n	130	130	33	33
	Mean (SD)	8.7 (16.89)	−9.0 (24.48)	9.1 (15.08)	0.0 (20.41)
	Week 30				
	n	93	93	23	23
	Mean (SD)	7.5 (15.64)	−8.6 (22.47)	8.7 (14.97)	0.0 (17.41)
	Week 36				
	n	59	59	10	10
	Mean (SD)	8.5 (15.89)	−6.8 (25.36)	10.0 (16.10)	3.3 (18.92)

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TABLE 4. *(Continued)*

		Arm T + PP (n = 222)		Arm PP (n = 110)	
Chest pain	Week 24				
	n	130	130	33	33
	Mean (SD)	7.7 (14.10)	−6.9 (21.84)	14.1 (22.10)	−2.0 (18.52)
	Week 30				
	n	93	93	33	33
	Mean (SD)	6.5 (14.12)	−9.0 (21.50)	13.0 (19.43)	−1.4 (12.22)
	Week 36				
	n	59	59	10	10
	Mean (SD)	6.2 (14.48)	−10.2 (23.37)	6.7 (14.05)	−3.3 (10.54)
Peripheral neuropathy	Week 24				
	n	130	130	33	33
	Mean (SD)	3.6 (10.37)	−1.3 (15.75)	6.1 (13.06)	5.1 (14.72)
	Week 30				
	n	93	93	33	33
	Mean (SD)	3.6 (10.38)	−0.7 (13.88)	5.8 (16.37)	4.3 (18.27)
	Week 36				
	n	59	59	10	10
	Mean (SD)	5.6 (14.05)	0.6 (20.98)	10.0 (22.50)	6.7 (26.29)

−3.5 to 0.3) and increased for arm PP (LS mean change = 1.1; 95% CI, −1.5 to 3.7) with a between-group LS mean difference of −2.6 (95% CI, −5.5 to 0.2; $P = 0.0667$). At week 18, there was no difference between the 2 arms (between-group LS mean difference = −1.4; 95% CI, −4.9 to 2.1; $P = 0.4287$).

Time to Deterioration

Median TTD in the QLQ-C30 GHS/QoL mean score was not reached in either arm. Deterioration in the GHS/QoL mean score occurred in 37 patients (18.9%) in arm T + PP and 22 patients (22.2%) in arm PP.

Descriptive Long-term Follow-up (Weeks 24, 30, 36)

Mean QLQ-C30 GHS/QoL scores improved from baseline to week 36 in arm T + PP (Fig. 2) and remained above baseline, whereas those in arm PP remained below the baseline. The 13-item Quality of Life Questionnaire–Lung Cancer subscale means and change from baseline for weeks 24, 30, and 36 are provided in Table 4. Both arms experienced declines in coughing and chest pain at weeks 24, 30, and 36; however, the reduction observed in arm T + PP was numerically larger than that of arm PP. Arm T + PP experienced a reduction in dyspnea symptoms at each of the follow-up periods whereas arm PP experienced more symptoms, on average, at weeks 24 and 30. Arm or shoulder pain declined, on average, across all follow-up weeks for arm T + PP while remaining at baseline levels or increasing (week 36) in arm PP. Arm T + PP experienced little change from baseline in peripheral neuropathy, whereas increases were observed in arm PP.

DISCUSSION

The addition of tislelizumab to platinum-pemetrexed was associated with improvements in HRQoL compared with platinum-pemetrexed alone in patients with previously untreated stage IIIB or IV nSQ-NSCLC in the RATIONALE 304. Compared with platinum-pemetrexed alone, patients receiving tislelizumab experienced clinically meaningful improvements in the QLQ-C30 GHS/QoL scale at week 18, as well as the disease-specific symptoms of coughing, chest pain, peripheral neuropathy, and dyspnea; these patients also experienced less fatigue and decline in physical functioning at week 18 (following chemotherapy). Time to deterioration in GHS/QoL was not reached for either arm. Furthermore, descriptive results suggested that improvements in the QLQ-C30 GHS/QoL scale extended through week 24, and gains were observed as late as 36 weeks. Long-term improvements were also observed for the disease-specific symptom subscales of the QLQ-LC13.

As PD-1/PD-L1 inhibitors gain market access authorization for first-line treatment in NSCLC with corresponding changes in the therapeutic guidelines, new health economic evaluations will be required to account for these changes and ensure patient access. There is also a lack of long-term clinical data for immunotherapy in NSCLC; as such, long-term follow-up that includes HRQoL outcomes will be critically important to understand the results for future clinical practice. Of note, the QLQ-LC13 module for assessing HRQoL in lung cancer patients is being updated to include new items related to the adverse effects of targeted therapies and surgery; future research should evaluate updated PROs.[23]

Although the results of this study are encouraging, they should be considered alongside the following limitations. First, the current study was an open-label design and had limited follow-up time in assessing change in patients' HRQoL. Second, the completion rate of the QLQ-C30 at week 12 is markedly lower in arm PP and may have contributed to the lack of an effect in GHS. Lastly, minimal clinical difference was not calculated for this specific population and without sensitivity analysis, and TTD threshold was based on standard 10-point worsening.

Overall, HRQoL was improved in first-line patients receiving tislelizumab and platinum-pemetrexed compared with patients receiving platinum-pemetrexed alone. These HRQoL data, together with the efficacy and safety results from the RATIONALE 304 trial, support the favorable risk-benefit ratio for tislelizumab in combination with platinum-pemetrexed and demonstrate that this combination is favorable compared with platinum-pemetrexed alone as first-line treatment of patients with nSQ-NSCLC.

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