Neoadjuvant Tislelizumab (TIS) Plus Chemotherapy (CT) With Adjuvant TIS Versus Neoadjuvant Placebo (PBO) Plus CT With Adjuvant PBO in Resectable Non–Small Cell Lung Cancer (NSCLC): Patient-Reported Outcomes (PROs) in the RATIONALE-315 Trial

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Conclusions

Perioperative tislelizumab did not affect health-related quality of life (HRQoL) in patients with resectable NSCLC in either the neoadjuvant or adjuvant treatment phase

Patients in the tislelizumab arm reported improvements in the key symptoms of coughing and chest pain

Taken together, the event-free survival (EFS) and overall survival (OS) benefits combined with maintained or improved PROs support the use of perioperative tislelizumab plus neoadjuvant platinum-based CT for treatment-naïve patients with resectable stage II-IIIA NSCLC

Background

- The prognosis for patients with NSCLC is relatively poor with 5-year survival rates of 35% and 10%-15% for patients with stage II and stage IIIA disease, respectively[1]
- Symptoms associated with NSCLC also correspond with poor health-related quality of life (HRQoL)[2,3]
- In the pivotal phase 3 RATIONALE-315 trial (NCT04379635) of patients with resectable stage II-IIIA NSCLC, perioperative TIS plus neoadjuvant platinum-based CT led to a clinically meaningful and statistically significant benefit for EFS as well as an OS benefit trend compared with perioperative PBO plus neoadjuvant platinum-based CT
- The current analyses report the results for PROs from RATIONALE-315

Methods

Study Design and Patients

- The study included treatment-naïve patients with resectable stage II-IIIA NSCLC who were eligible for platinum-doublet CT and had no known epidermal growth factor receptor (*EGFR*) mutations or anaplastic large-cell lymphoma kinase (*ALK*) gene translocations (**Figure 1**)
  - Patients were randomized (1:1) to either 3-4 cycles of neoadjuvant TIS 200 mg or PBO (administered intravenously [IV] every 3 weeks) plus CT, followed by surgery and up to 8 cycles of adjuvant TIS 400 mg or PBO (IV every 6 weeks)

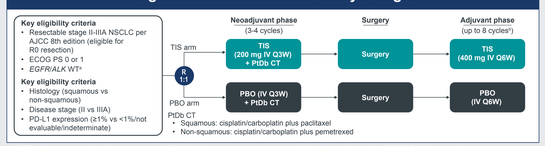
Assessments

- PROs were assessed at baseline (pre dose at Day 1 of Cycle 1) and key clinical cycles (Cycle 3 of the neoadjuvant phase and Cycles 3 and 7 of the adjuvant phase)
  - These key clinical cycles were prespecified as clinically justifiable for assessing the short-term and longer-term treatment effects in both arms
- The following key PRO endpoints were pre-selected based on their relevance to NSCLC and treatment side effects, as well as their use in previous studies[4-6]:
  - European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core 30 (QLQ-C30): global health status/ quality of life (GHS/QoL), physical functioning, and fatigue symptom scales
    - Higher scores on the GHS/QoL and physical functioning scales indicate better HRQoL or functioning, whereas a higher score on the fatigue symptom scale suggests worse symptoms
  - EORTC Quality of Life Questionnaire – Lung Cancer Module (QLQ-LC13): coughing, chest pain, and dyspnea
    - Higher scores on the QLQ-LC13 indicate worse symptoms or problems

Statistical Analyses

- Analyses were conducted using the data cutoff of August 21, 2023
- All HRQoL measures were summarized in the intent-to-treat analysis set and by overall phases and adjuvant phase, respectively
- Adjusted completion rates were defined as the number of patients who completed the questionnaires at each cycle divided by the number still on treatment
- Change from baseline in each key PRO endpoint to Cycle 3 (both neoadjuvant and adjuvant) and Cycle 7 (adjuvant) was analyzed using a constrained longitudinal data analysis model
  - 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 95% confidence interval (CI)
  - A clinically meaningful change was defined as a ≥5-point mean change from baseline[7-10]
- Time to deterioration (TDD) was defined as time to first onset of a ≥10-point[10] change in the worsening direction from baseline and confirmed by a subsequent worsening; the Kaplan-Meier method was used to estimate the deterioration curve in each group
  - The log-rank test and hazard ratio (HR) showed the magnitude of treatment effect

Figure 1. RATIONALE-315 Study Design



EGFR testing was mandatory for non-squamous NSCLC. †Adjuvant treatment was only administered to patients with an ECOG PS of 0 or 1 and adequate organ function for ≤8 cycles or until disease recurrence/progression, unacceptable adverse events, or death occurred, or until the patient and/or investigator decided to discontinue study treatment.
AJCC, American Joint Committee on Cancer; *ALK*, anaplastic large-cell lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group Performance Status; *EGFR*, epidermal growth factor receptor; IV, intravenous; NSCLC, non–small cell lung cancer; PBO, placebo; PD-L1, programmed death-ligand 1; PtDb CT, platinum-based doublet chemotherapy; Q3W, every 3 weeks; Q6W, every 6 weeks; R, randomized; R0, pathological complete resection of the primary tumor; TIS, tislelizumab; WT, wild type.

Results

- The intent-to-treat population consisted of 453 patients randomized to receive TIS (n=226) or PBO (n=227)
- Patient demographics and baseline disease characteristics were generally balanced across treatment arms (**Table 1**)

Table 1. Patient Demographics and Clinical Characteristics

	TIS Arm (n=226)	PBO Arm (n=227)
Age		
Median (IQR), years	62.0 (57.0-67.0)	63.0 (56.0-68.0)
≥65 years, n (%)	83 (37)	98 (43)
Sex, n (%)		
Male	205 (91)	205 (90)
Female	21 (9)	22 (10)
Asian race, n (%)	226 (100)	227 (100)
ECOG performance status, n (%)		
0	142 (63)	154 (68)
1	83 (37)	73 (32)
Smoking status, n (%)		
Current	43 (19)	52 (23)
Former	150 (66)	138 (61)
Never	33 (15)	37 (16)
Disease stage, n (%)		
II	92 (41)	91 (40)
IIIA	132 (58)	133 (59)
Histology, n (%)		
Squamous	179 (79)	175 (77)
Non-squamous	45 (20)	50 (22)
Other	2 (1)	2 (1)

ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; PBO, placebo; TIS, tislelizumab.

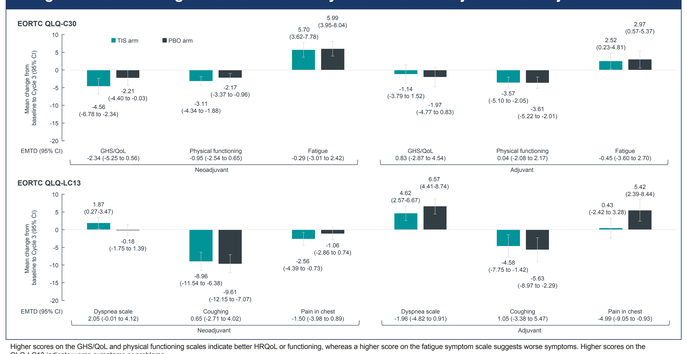
Adjusted Completion Rates

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

Change From Baseline to Cycle 3 (Neoadjuvant and Adjuvant Phases)

- The difference between the treatment arms in change from baseline to adjuvant Cycle 3 for chest pain was clinically meaningful (mean difference, -4.99 [95% CI, -9.05 to -0.93]). The level of chest pain was maintained from baseline at the adjuvant phase for the TIS arm, while patients in the PBO arm reached clinically worsening levels (5.42 [95% CI, 2.39-8.44]). The changes from baseline for other PRO endpoints were similar between the treatment arms (**Figure 2**)
- Patients in the TIS and PBO arms experienced clinically meaningful improvements in LS mean change from baseline to neoadjuvant Cycle 3 for coughing (mean change from baseline, -8.96 [95% CI, -11.54 to -6.38] for TIS and -9.61 [95% CI, -12.15 to -7.07] for PBO)

Figure 2. Mean Change From Baseline to Cycle 3 in the Neoadjuvant and Adjuvant Phases

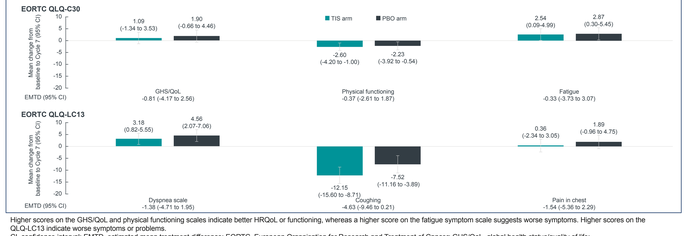


Higher scores on the GHS/QoL and physical functioning scales indicate better HRQoL or functioning, whereas a higher score on the fatigue symptom scale suggests worse symptoms. Higher scores on the QLQ-LC13 indicate worse symptoms or problems.
CI, confidence interval; EMTD, estimated mean treatment difference; EORTC, European Organisation for Research and Treatment of Cancer; GHS/QoL, global health status/quality of life; HRQoL, health-related quality of life; PBO, placebo; QLQ-C30, *Quality of Life Questionnaire – Core 30*; QLQ-LC13, Quality of Life Questionnaire – Lung Cancer Module; TIS, tislelizumab.

Change From Baseline to Cycle 7 (Adjuvant Phase)

- The worsening in dyspnea experienced by the PBO arm was near the clinically meaningful threshold (4.56 [95% CI, 2.07- 7.06]) (**Figure 3**)
- The TIS arm experienced a greater level of clinically meaningful improvement in adjuvant Cycle 7 for coughing (-12.15 [95% CI, -15.60 to -8.71]) than PBO with the difference reaching close to the clinically meaningful threshold (-4.63 [95% CI, -9.46 to 0.21)]
- The levels of chest pain were maintained in both arms

Figure 3. Mean Change From Baseline to Cycle 7 in the Adjuvant Phase



Higher scores on the GHS/QoL and physical functioning scales indicate better HRQoL or functioning, whereas a higher score on the fatigue symptom scale suggests worse symptoms. Higher scores on the QLQ-LC13 indicate worse symptoms or problems.
CI, confidence interval; EMTD, estimated mean treatment difference; EORTC, European Organisation for Research and Treatment of Cancer; GHS/QoL, global health status/quality of life; HRQoL, health-related quality of life; PBO, placebo; QLQ-C30, *Quality of Life Questionnaire – Core 30*; QLQ-LC13, Quality of Life Questionnaire – Lung Cancer Module; TIS, tislelizumab.

Time to Deterioration

- TTD analysis showed that patients in the TIS arm were at lower risk of worsening chest pain compared with those in the PBO arm (HR, 0.59 [95% CI, 0.38-0.91]) (**Table 2**)
- Risk of worsening was similar between the treatment arms for all other PRO endpoints

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

		TIS Arm (n=226)	PBO Arm (n=227)
EORTC QLQ-C30 GHS/QoL	Number of patients		
	Worsened, n (%)	79 (35.0)	73 (32.2)
	Censored, n (%)	147 (65.0)	154 (67.8)
	Median time to deterioration (95% CI),* months	30.2 (30.2-NE)	NR (NE-NE)
	Stratified HR (95% CI)†	0.98 (0.71-1.35)	
	Stratified log-rank test *P* value‡	0.4477	
Physical functioning	Number of patients		
	Worsened, n (%)	63 (27.9)	60 (26.4)
	Censored, n (%)	163 (72.1)	167 (73.6)
	Median time to deterioration (95% CI),* months	NR (20.4-NE)	NR (NE-NE)
	Stratified HR (95% CI)†	0.93 (0.65-1.33)	
	Stratified log-rank test *P* value‡	0.3480	
Fatigue	Number of patients		
	Worsened, n (%)	104 (46.0)	101 (44.5)
	Censored, n (%)	122 (54.0)	126 (55.5)
	Median time to deterioration (95% CI),* months	11.2 (7.6-NE)	6.2 (4.6-NE)
	Stratified HR (95% CI)†	0.86 (0.65-1.13)	
	Stratified log-rank test *P* value‡	0.1353	
EORTC QLQ-LC13 Dysphagia	Number of patients		
	Worsened, n (%)	105 (46.5)	111 (48.9)
	Censored, n (%)	121 (53.5)	116 (51.1)
	Median time to deterioration (95% CI),* months	7.5 (4.8-NE)	5.1 (4.4-6.8)
	Stratified HR (95% CI)†	0.87 (0.66-1.14)	
	Stratified log-rank test *P* value‡	0.1514	
Coughing	Number of patients		
	Worsened, n (%)	40 (17.7)	34 (15.0)
	Censored, n (%)	186 (82.3)	193 (85.0)
	Median time to deterioration (95% CI),* months	NR (NE-NE)	NR (NE-NE)
	Stratified HR (95% CI)†	1.14 (0.72-1.81)	
	Stratified log-rank test *P* value‡	0.7175	
Chest pain	Number of patients		
	Worsened, n (%)	35 (15.5)	49 (21.6)
	Censored, n (%)	191 (84.5)	178 (78.4)
	Median time to deterioration (95% CI),* months	NR (NE-NE)	NR (NE-NE)
	Stratified HR (95% CI)†	0.59 (0.38-0.91)	
	Stratified log-rank test *P* value‡	0.0079	

Time to deterioration is defined as the time from randomization to the first occurrence of a decrease of <10 scores in GHS/QoL and physical functioning, and an increase of ≥10 scores in QLQ-C30 symptom scale scores (fatigue) and QLQ-LC13 symptom scale scores (dysphagia, coughing, chest pain).
A deterioration is not counted as an event if a subsequent improvement returned the overall worsening from baseline to <10 points.
If a patient does not have an event (10% deterioration), they are censored at their last clinic visit at which HRQoL is measured.
*Estimates are based on Kaplan-Meier method. †Hazard ratio was based on Cox regression model stratified by histology (squamous vs non-squamous), disease stage (stage II vs stage IIIA), and PD-L1 expression (<1%, not evaluable, or indeterminate vs ≥1%) from interactive response technology. ‡The descriptive 1-sided *P* value was calculated using a log-rank test stratified by histology (squamous vs non-squamous), disease stage (stage II vs stage IIIA), and PD-L1 expression (<1%, not evaluable, or indeterminate vs ≥1%) from interactive response technology.
CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; GHS/QoL, global health status/quality of life; HR, hazard ratio; HRQoL, health-related quality of life; NE, not estimable; NR, not reached; PBO, placebo; PD-L1, programmed death-ligand 1; QLQ-C30, Quality of Life

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