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

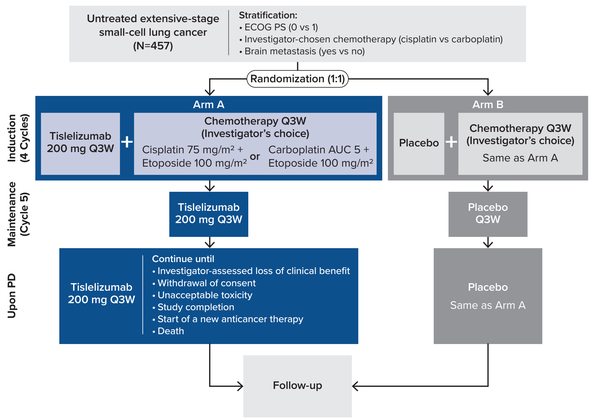
- Small-cell lung cancer (SCLC) accounts for 15% of lung cancers and is characterized by rapid progression and early metastasis, with 70% of cases diagnosed at an extensive stage (ES)[1]
- Patients with ES-SCLC face a significant symptom burden and a notable decline in health-related quality of life (HRQoL)[2]
- 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[3]
- 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[4-6]
- Time to deterioration (TDD) 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[a,b], n (%)		
IIIA	4 (2)	2 (1)
IIIB	16 (7)	27 (12)
IV	207 (91)	201 (87)
Number of metastatic sites[c], 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.
[a]Study entry was the date of randomization.
[b]On the basis of AJCC Staging Manual Seventh Edition.
[c]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.

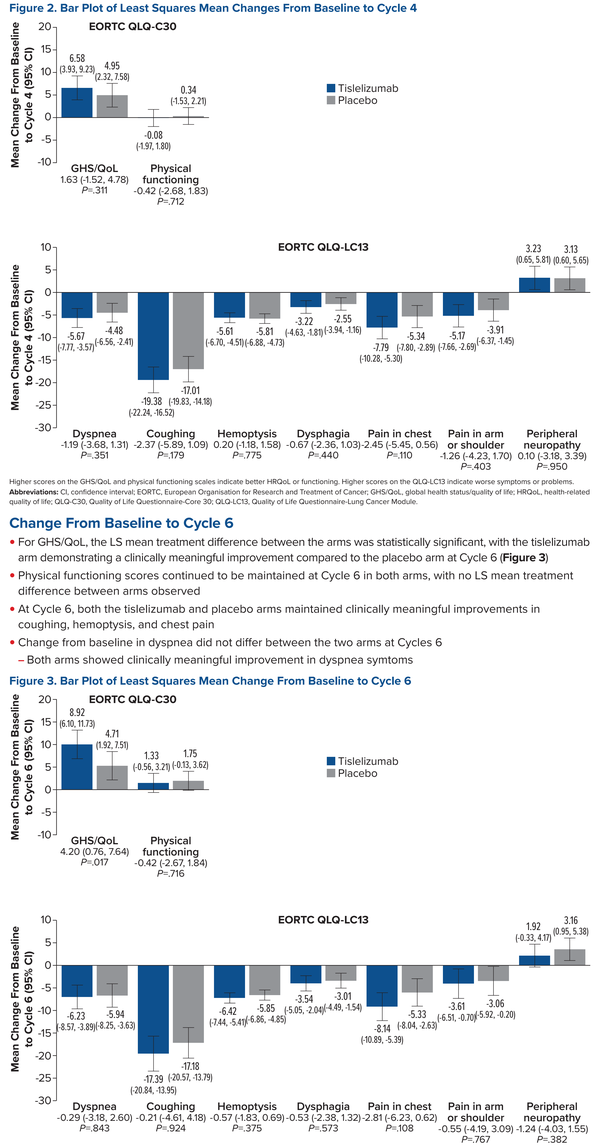
Adjusted Completion Rates

- 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 symtoms

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,[a] median (months) (95% CI)	NR (20.5, NE)	NR (10.3, NE)
		Unstratified HR (95% CI)[b]	0.92 (0.642, 1.330)	–
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,[a] median (months) (95% CI)	NR (NE, NE)	NR (NE, NE)
		Unstratified HR (95% CI)[b]	0.73 (0.473, 1.123)	–
	Pain in chest	Worsened, n (%)	44 (19.4)	60 (26.2)
		Censored, n (%)	183 (80.6)	169 (73.8)
		Time to clinically meaningful worsening,[a] median (months) (95% CI)	NR (NE, NE)	NR (NE, NE)
		Unstratified HR (95% CI)[b]	0.72 (0.485, 1.057)	–

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.
[a]Estimates are based on Kaplan-Meier method.
[b]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.

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