TISLELIZUMAB PLUS STANDARD CHEMOTHERAPY AND HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH ADVANCED SQUAMOUS NON-SMALL CELL LUNG CANCER

RATIONALE TRIAL PROGRAM

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BACKGROUND

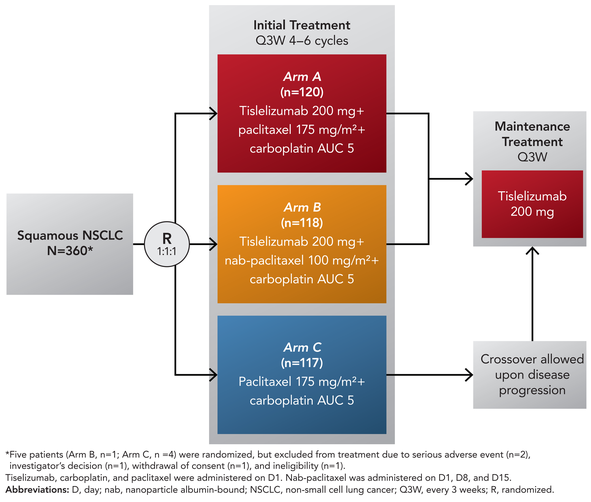
- Disease-related symptoms associated with advanced non-small cell lung cancer (NSCLC) may be associated with poor health-related quality of life (HRQoL)[1,2]
- A number of recent clinical trials have reported significant improvements in the HRQoL of patients with NSCLC treated with programmed cell death protein-1/programmed death ligand-1 (PD-[L]1)[3-5]
- The phase 3 RATIONALE 307 study (BGB-A317-307) examined the efficacy and safety of tislelizumab combined with either paclitaxel and carboplatin (*Arm A*) or nab-paclitaxel and carboplatin (*Arm B*) versus paclitaxel and carboplatin alone (*Arm C*) as first-line treatment for advanced squamous NSCLC[6]
  - After a median study follow-up of 8.6 months, tislelizumab plus chemotherapy demonstrated significantly improved progression-free survival (PFS) over chemotherapy alone
    - The hazard ratio (HR) for PFS was 0.524 (95% CI: 0.370-0.742; *P*=0.0001) for *Arm A* vs *Arm C*; the HR for PFS was 0.478 (0.336-0.679; *P*<0.0001) for *Arm B* vs *Arm C*
  - The incidence and frequency of observed adverse events (AEs) were similar between the three arms and most AEs were mild or moderate in severity and were manageable
    - The most commonly reported treatment-related AEs (TRAEs) associated with any study component were mainly hematologic in nature
- The objectives of this analysis included evaluation of HRQoL while patients received tislelizumab plus chemotherapy or chemotherapy alone

METHODS

Study Design, Patients, and Treatment

- RATIONALE 307 was a randomized, open-label, multicenter, phase 3 study conducted in China; the study design is detailed in Figure 1
- Patients were randomized 1:1:1 to receive tislelizumab combined with either paclitaxel and carboplatin (*Arm A*) or nab-paclitaxel and carboplatin (*Arm B*), or paclitaxel and carboplatin alone (*Arm C*)
- HRQoL was a secondary outcome that was measured using the EOTRC-QLQ-C30 (cancer-specific) and EORTC-QLQ-LC13 (lung cancer–specific module) patient-reported outcome (PRO) questionnaires

Figure 1: Study Design



*Five patients (Arm B, n=1; Arm C, n =4) were randomized, but excluded from treatment due to serious adverse event (n=2), investigator's decision (n=1), withdrawal of consent (n=1), and ineligibility (n=1).
Tislelizumab, carboplatin, and paclitaxel were administered on D1. Nab-paclitaxel was administered on D1, D8, and D15.
Abbreviations: D, day; nab, nanoparticle albumin-bound; NSCLC, non-small cell lung cancer; Q3W, every 3 weeks; R, randomized.

Study Population

- Adult patients (aged 18-75 years) with histologically confirmed locally advanced or metastatic squamous NSCLC, with at least one measurable lesion, were eligible for inclusion if they provided fresh or archival tumor tissues for PD-L1 expression analysis
  - Patients must have had no prior systemic therapy for advanced or metastatic disease
  - Prior neoadjuvant/adjuvant therapy or chemoradiation therapy was allowed if completed ≥6 months prior to randomization
- Patients with a known *EGFR*-sensitizing mutation or *ALK* gene translocation, or prior treatment with EGFR inhibitors, ALK inhibitors, and/or therapies targeting PD-(L)1 were ineligible

HRQoL Assessments and Endpoints

- The EORTC QLQ-C30 and QLQ-LC13 questionnaires were administrated at baseline, at every other cycle through Cycle 13, then every four cycles thereafter, and at the end of treatment; questionnaires were completed prior to any clinical activities during site visits
- For the current analysis, data from baseline to Cycle 5 (Week 12) only, were used to account for direct comparisons between *Arms A* and *B* (chemotherapy combination) and *Arm C* (chemotherapy only)
- Compliance and completion were summarized by treatment group and visit
- Analyses included health status and lung cancer–specific symptoms:
  - QLQ-C30: Global health status
  - QLQ-LC13: Coughing, dysphagia, dyspnea, hemoptysis, pain in arms and shoulders, pain in chest, and peripheral neuropathy

Statistical Analysis

- The analysis population was comprised of all randomized patients who received at least one dose of study drug and completed at least one HRQoL assessment
- Changes from baseline were evaluated at prespecified Weeks 6 and 12 to allow for sufficient response to enable a comparison of scores between groups
- Least square (LS) mean score change from baseline to Week 6 (Cycle 3) and Week 12 (Cycle 5) were assessed using a constrained longitudinal data analysis model, with the PRO score as the response variable, and treatment by study visit interaction and stratification factor for randomization as covariates, based on the missing at random assumption
- *P*-values were two-sided and nominal, without multiple adjustment
- Analyses were conducted using the data cutoff of December 6, 2019 (median follow-up of 8.6 months)

RESULTS

Patient Characteristics

- Demographics and baseline characteristics were well balanced across all arms (Table 1)

Table 1: Demographics and Baseline Characteristics

ITT Population		*Arm A* Tislelizumab + PC (n=120)	*Arm B* Tislelizumab + nab-PC (n=119)	*Arm C* PC (n=121)
Median age, years (range)		60 (41-74)	63 (38-74)	62 (34-74)
Age group, n (%)	<65	81 (67.5)	67 (56.3)	85 (70.2)
	≥65	39 (32.5)	52 (43.7)	36 (29.8)
Sex, n (%)	Male	107 (89.2)	112 (94.1)	111 (91.7)
	Female	13 (10.8)	7 (5.9)	10 (8.3)
Tobacco use, n (%)	Former	72 (60.0)	86 (72.3)	71 (58.7)
	Current	24 (20.0)	21 (17.6)	27 (22.3)
	Never	24 (20.0)	12 (10.1)	23 (19.0)
ECOG status, n (%)	0	31 (25.8)	22 (18.5)	32 (26.4)
	1	89 (74.2)	97 (81.5)	89 (73.6)
Solid tumor stage, n (%)	Stage IIIB	38 (31.7)	40 (33.6)	44 (36.4)
	Stage IV	82 (68.3)	79 (66.4)	77 (63.6)
PD-L1 % expression on tumor cells, n (%)	<1%[a]	48 (40.0)	47 (39.5)	49 (40.5)
	1-49%	30 (25.0)	30 (25.2)	31 (25.6)
	≥50%	42 (35.0)	42 (35.3)	41 (33.9)
Confirmed distant metastatic site(s)[b], n (%)	Bone	24 (20.0)	16 (13.4)	21 (17.4)
	Liver	15 (12.5)	15 (12.6)	14 (11.6)
	Brain	2 (1.7)	3 (2.5)	1 (0.8)

[a]Patients with non-evaluable tumor samples were included in the <1% PD-L1 expression tumor cell subgroup.
[b]A patient was counted only once within each category but may be counted in multiple categories.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; nab, nanoparticle albumin-bound; PC, paclitaxel and carboplatin; PD-L1, programmed death ligand-1.

Completion and Compliance Rates for HRQoL Assessments

- The analysis population included 355 patients: 120 in *Arm A*, 118 in *Arm B*, and 117 in *Arm C*
- Compliance with the QLQ-C30 and QLQ-LC13 questionnaires were similar among groups at Week 6 and Week 12 and remained at ≥95% at both time points (Table 2)

Table 2: Completion and Compliance Rates for HRQoL Assessments

Analysis Population			*Arm A* Tislelizumab + PC (n=120)	*Arm B* Tislelizumab + nab-PC (n=118)	*Arm C* PC (n=117)
QLQ-C30	Baseline		120 (100.0)	117 (99.2)	117 (100.0)
	Week 6	Completion	107 (89.2)	106 (89.8)	103 (88.0)
		Compliance	107/109 (98.2)	106/108 (98.1)	103/104 (99.0)
	Week 12	Completion	96 (80.0)	92 (78.0)	59 (50.4)
		Compliance	96/98 (98.0)	92/95 (96.8)	59/61 (96.7)
QLQ-LC13	Baseline		120 (100.0)	117 (99.2)	117 (100.0)
	Week 6	Completion	107 (89.2)	106 (89.8)	103 (88.0)
		Compliance	107/109 (98.2)	106/108 (98.1)	103/104 (99.0)
	Week 12	Completion	96 (80.0)	92 (78.0)	59 (50.4)
		Compliance	96/98 (98.0)	92/95 (96.8)	59/61 (96.7)

Data presented as n (%).
Completion was defined as the proportion of patients who completed ≥1 HRQoL assessment.
Compliance was defined as the proportion of patients who completed ≥1 HRQoL assessment over those who were expected to complete the questionnaire at each clinic visit.
Abbreviations: HRQoL, health-related quality of life; nab, nanoparticle albumin-bound; PC, paclitaxel and carboplatin.

Change From Baseline in EORTC QLQ-C30 Global Health Status (GHS)/QoL Score

- There was no significant difference in LS mean score change from baseline to Week 6 or Week 12 in the tislelizumab plus chemotherapy arms versus the chemotherapy only arm (*Arm A* vs *Arm C*, *Arm B* vs *Arm C*) in GHS/QoL (Table 3)

Table 3: Changes From Baseline in EORTC QLQ-C30 GHS/QoL Score

Analysis Population		*Arm A* Tislelizumab + PC (n=120)	*Arm B* Tislelizumab + nab-PC (n=118)	*Arm C* PC (n=117)
Baseline	Mean score (SD)	66.6 (22.13)	65.7 (19.93)	66.5 (20.10)
Week 6	Mean score (SD)	68.5 (20.65)	69.5 (20.38)	68.2 (19.31)
	LS mean change from baseline (95% CI)	2.1 (-1.4, 5.6)	3.7 (0.2, 7.1)	1.6 (-1.9, 5.1)
	Difference in LS mean (95% CI)	0.5 (-4.2, 5.2)	2.1 (-2.6, 6.8)	
	P-value	0.8330	0.3842	
Week 12	Mean score (SD)	70.6 (19.64)	70.6 (20.36)	67.7 (17.99)
	LS mean change from baseline (95% CI)	3.8 (-0.2, 7.8)	3.8 (-0.2, 7.8)	0.4 (-4.4, 5.2)
	Difference in LS mean (95% CI)	3.4 (-2.4, 9.2)	3.4 (-2.5, 9.3)	
	P-value	0.2536	0.2541	

Abbreviations: CI, confidence interval; GHS, Global Health Status; LS, least square; nab, nanoparticle albumin-bound; PC, paclitaxel and carboplatin; QoL, quality of life; SD, standard deviation.

Change From Baseline in EORTC QLQ-LC13 Subscales (Table 4)

- Coughing as a symptom of NSCLC continued to improve over time for *Arms A* and *B*; patients in *Arms A* and *B* experienced a larger reduction in coughing at Weeks 6 and 12 compared with patients in *Arm C*
- Patients in *Arms A* and *B* experienced a reduction in dyspnea while over the course of chemotherapy treatment, patients in *Arm C* experienced an increase in dyspnea
- Patients in all three arms experienced a reduction in hemoptysis, with larger reductions observed in *Arms A* and *B*
- Peripheral neuropathy increased in all three arms; however, *Arm B* had the smallest increase
- All three arms provided comparable pain relief, including pain in the arm or shoulder and pain in the chest

CONCLUSIONS

- The addition of tislelizumab to paclitaxel + carboplatin or nab-paclitaxel + carboplatin maintained or improved HRQoL compared with paclitaxel + carboplatin alone in patients with previously untreated advanced squamous NSCLC in the RATIONALE 307 study
- Compared with chemotherapy alone, patients receiving tislelizumab in combination with chemotherapy experienced an improvement in symptoms associated with NSCLC including coughing, dyspnea, and hemoptysis
  - Patients had less peripheral neuropathy in *Arm B*
- The main limitation of this study was the open-label study design and the limited follow-up time in assessing HRQoL in patients treated with paclitaxel + carboplatin after completion of chemotherapy
  - The completion rate of the QLQ-C30 at Week 12 is markedly lower in *Arm C* and may have contributed to the lack of significance in global health status
- These HRQoL data, together with the efficacy and safety results from the RATIONALE 307 trial, demonstrate a favorable risk-benefit ratio of tislelizumab in combination with carboplatin and paclitaxel or nab-paclitaxel, as first-line treatment of patients with squamous NSCLC

Table 4: Change From Baseline in EORTC QLQ-LC13 Subscales

Analysis Population		*Arm A* Tislelizumab + PC (n=120)		*Arm B* Tislelizumab + nab-PC (n=118)		*Arm C* PC (n=117)	
		Observed	Change from baseline	Observed	Change from baseline	Observed	Change from baseline
Coughing	Baseline	40.3 (25.16)		37.3 (24.43)		34.8 (21.17)	
	Week 6	26.2 (21.97)	-14.0 (25.09)	26.1 (21.08)	-11.6 (30.18)	23.0 (20.89)	-12.3 (22.86)
	Week 12	20.1 (22.93)	-20.1 (29.21)	26.4 (22.93)	-12.7 (33.82)	26.6 (22.13)	-7.3 (23.22)
Dysphagia	Baseline	4.7 (15.15)		5.7 (13.34)		5.1 (14.92)	
	Week 6	5.3 (17.82)	0.9 (18.00)	4.7 (11.67)	-1.6 (14.09)	4.9 (15.06)	0.3 (15.12)
	Week 12	4.5 (16.49)	0.0 (19.35)	4.0 (13.84)	-2.9 (18.26)	6.2 (14.48)	1.7 (15.69)
Dyspnea	Baseline	20.7 (17.81)		19.4 (19.09)		20.6 (17.58)	
	Week 6	18.2 (14.67)	-1.5 (17.80)	17.6 (16.65)	-2.4 (20.69)	19.5 (14.96)	-1.1 (15.60)
	Week 12	16.7 (14.51)	-1.9 (18.14)	18.2 (15.15)	-1.8 (19.92)	18.6 (13.28)	2.4 (15.17)
Hemoptysis	Baseline	11.9 (19.23)		13.7 (20.60)		9.1 (16.16)	
	Week 6	4.0 (11.86)	-7.5 (19.05)	4.7 (12.55)	-9.4 (24.24)	5.2 (12.13)	-3.9 (18.85)
	Week 12	2.4 (9.96)	-9.4 (19.77)	5.4 (16.59)	-9.4 (26.76)	5.6 (14.05)	-2.3 (19.44)
Pain in arm or shoulder	Baseline	13.3 (21.35)		12.8 (20.46)		13.7 (23.22)	
	Week 6	15.0 (21.10)	2.8 (23.40)	8.8 (14.77)	-4.1 (20.93)	11.3 (18.99)	-1.0 (26.59)
	Week 12	11.8 (19.33)	-0.3 (24.42)	8.7 (17.73)	-5.1 (20.93)	9.0 (19.41)	1.1 (23.95)
Pain in chest	Baseline	19.4 (22.70)		17.1 (22.58)		21.4 (22.09)	
	Week 6	12.1 (20.16)	-5.9 (27.02)	9.1 (14.93)	-7.5 (24.47)	13.6 (20.04)	-6.8 (22.07)
	Week 12	12.5 (19.50)	-5.9 (23.69)	11.2 (18.01)	-5.8 (21.32)	10.7 (16.88)	-5.6 (24.09)
Peripheral neuropathy	Baseline	6.1 (17.81)		4.8 (11.80)		6.6 (17.09)	
	Week 6	16.2 (26.84)	10.9 (29.24)	11.6 (22.56)	6.6 (20.79)	15.2 (25.04)	8.7 (25.12)
	Week 12	19.8 (27.18)	14.6 (28.54)	14.9 (23.37)	9.4 (22.82)	23.7 (31.59)	20.3 (29.70)

Data presented as mean (SD).
Abbreviations: nab, nanoparticle albumin-bound; PC, paclitaxel and carboplatin; SD, standard deviation.

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