EXAMINING THE IMPACT OF TISLELIZUMAB ADDED TO PLATINUM-DOUBLET CHEMOTHERAPY ON HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH NONSQUAMOUS NSCLC

RATIONALE TRIAL PROGRAM

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BACKGROUND

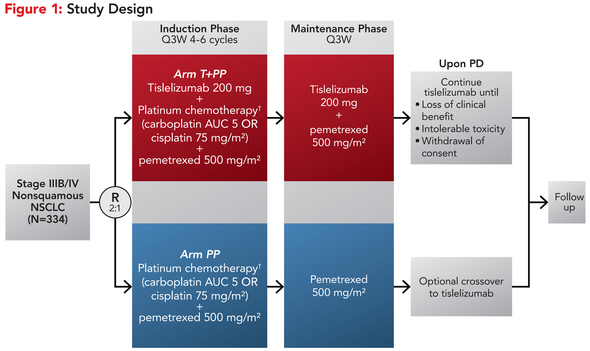
- Disease-related symptoms associated with advanced non-small cell lung cancer (NSCLC) may be associated with poor health-related quality of life (HRQoL)[1,2]
- A number of recent clinical trials have reported significant improvements in the HRQoL of NCSLC patients treated with programmed cell death protein-1/programmed death-ligand 1 (PD-1/PD-L1)[3-5]
- RATIONALE 304 (BGB-A317-304) is a phase 3, open-label, multicenter trial examining the efficacy and safety of tislelizumab (BGB-A317) added to platinum-pemetrexed (*Arm T+PP*) versus platinum-pemetrexed alone (*Arm PP*) as first-line treatment in patients with stage IIIB or IV nonsquamous NSCLC[6]
  - After a median study follow-up of 8.6 months, tislelizumab plus platinum-pemetrexed showed significantly improved progression-free survival (PFS) over platinum-pemetrexed alone
    - The hazard ratio (HR) for PFS was 0.645 (95% CI: 0.462-0.902; *P*=0.0044) for *Arm T+PP* vs *Arm PP*
  - 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
- The patient-reported outcome (PRO) objective of the current analysis is to evaluate HRQoL in patients within the RATIONALE 304 trial

METHODS

Study Design, Patients, and Treatment

- RATIONALE 304 is a randomized, open-label, multicenter, phase 3 study conducted in China; the study design is detailed in Figure 1
- Patients with nonsquamous NSCLC without *EGFR* mutations or known *ALK* gene translocation, and have not received prior systemic chemotherapy, were randomized 2:1 to *Arm T+PP* or *Arm PP*
- HRQoL was a secondary outcome that was measured via PRO questionnaires using the EORTC-QLQ-C30 (cancer-specific) and EORTC-QLQ-LC13 (lung cancer–specific module)

Figure 1: Study Design



†Investigator's choice.
Abbreviations: NSCLC, non-small cell lung cancer; PD, progressive disease; Q3W, every 3 weeks; R, randomized.

Study Population

- Adult patients (aged 18-75 years) with histologically confirmed locally advanced or metastatic nonsquamous 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 with mixed non-small cell histology tumors were eligible if the major histological component was nonsquamous
  - Patients must have had no prior systemic chemotherapy 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-1/PD-L1, or systemic immunosuppressive agents ≤14 days prior to randomization, a history of interstitial lung disease, or noninfectious pneumonitis were ineligible

HRQoL Assessments and Endpoints

- 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
- Compliance and completion were summarized by treatment group and visit
  - Compliance was defined as the proportion of patients who completed ≥1 HRQoL assessment among those who were expected to complete the questionnaire at each clinic visit
  - Completion was defined as the proportion of patients who completed ≥1 HRQoL assessment at each visit
- Analyses included health status and lung cancer–specific symptoms:
  - QLQ-C30: Global health status, physical functioning, and fatigue
  - QLQ-LC13: Coughing, dysphagia, dyspnea, hemoptysis, pain in arms and shoulders, chest pain, and peripheral neuropathy
  - Changes from baseline were evaluated primarily at prespecified Weeks 12 and 18 to allow for sufficient response to enable a comparison of scores between groups

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
- Least square (LS) mean score change from baseline to Week 12 (Cycle 5) and Week 18 (Cycle 7) 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 January 23, 2020 (median follow-up of 9.8 months)

RESULTS

Patient Characteristics

- Baseline characteristics were comparable across the two treatment arms and were representative of the target patient population (Table 1)

Table 1: Demographics and Baseline Characteristics

ITT Population		*Arm T+PP* N=223	*Arm PP* N=111
Median age, years (range)		60 (27-75)	61 (25-74)
Age group, n (%)	<65	163 (73.1)	74 (66.7)
	≥65	60 (26.9)	37 (33.3)
Sex, n (%)	Male	168 (75.3)	79 (71.2)
	Female	55 (24.7)	32 (28.8)
Smoking status, n (%)	Current	32 (14.3)	13 (11.7)
	Former	115 (51.6)	53 (47.7)
	Never	76 (34.1)	45 (40.5)
ECOG performance status, n (%)	0	54 (24.2)	24 (21.6)
	1	169 (75.8)	87 (78.4)
Disease stage, n (%)	Stage IIIB	40 (17.9)	21 (18.9)
	Stage IV	183 (82.1)	90 (81.1)
PD-L1 expression in tumor cells, n (%)	<1%[a]	96 (43.0)	48 (43.2)
	1-49%	53 (23.8)	27 (24.3)
	≥50%	74 (33.2)	36 (32.4)
EGFR-sensitizing mutation status, n (%)	Negative	218 (97.8)	109 (98.2)
	Positive or unknown[b]	5 (2.2)	2 (1.8)
ALK rearrangement status, n (%)	Negative	166 (74.4)	79 (71.2)
	Unknown	57 (25.6)	32 (28.8)
Location of distant metastases[c], n (%)	Bone	75 (33.6)	41 (36.9)
	Liver	20 (9.0)	17 (15.3)
	Brain	11 (4.9)	7 (6.3)

[a]Five patients with unevaluable PD-L1 status were included in PD-L1 <1% category.
[b]Includes patients with *EGFR*-sensitizing mutations that were identified via tissue-based test, reported as major protocol deviations.
[c]Patients were counted once within each category but may have been counted in multiple categories.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; PD-L1, programmed death-ligand 1; PP, platinum-pemetrexed; T, tislelizumab.

Completion and Compliance Rates for HRQoL Assessments

- The analysis population included 332 patients: 222 in *Arm T+PP* and 110 in *Arm PP*
- Compliance with the QLQ-C30 and QLQ-LC13 questionnaires was similar among both groups at Week 12 and Week 18 and remained at ≥95% at both timepoints (Table 2)

Table 2: Completion and Compliance Rates for HRQoL Assessments

Analysis Population			*Arm T+PP* N=222	*Arm PP* N=110
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)
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)

Data presented as n (%).
Abbreviations: HRQoL, health-related quality of life; PP, platinum-pemetrexed; T, tislelizumab.

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

- GHS/QoL improved in *Arm T+PP* at Weeks 12 and 18 and worsened compared to baseline in *Arm PP* at both timepoints
- There was significant difference in LS mean change from baseline to Week 18 between arms in GHS/QoL (Table 3)

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

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

[a]Number of patients who completed EORTC QLQ-C30 GHS/QoL at the noted timepoint.
[b]Number of patients in analysis population.
[c]Based on cLDA model with EORTC QLQ-C30 GHS/QoL scores as response variable, treatment by study visit interaction, and stratification factors for randomization as covariates
[d]*P*-values are two-sided and nominal.
Abbreviations: CI, confidence interval; cLDA, constrained longitudinal data analysis; GHS, Global Health Status; LS, least square; PP, platinum-pemetrexed; QoL, quality of life; SD, standard deviation; T, tislelizumab.

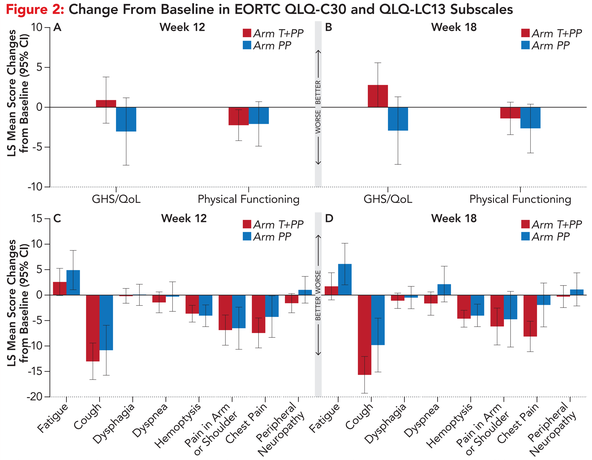
CONCLUSIONS

- The addition of tislelizumab to platinum-pemetrexed was associated with improvements in HRQoL compared to platinum-pemetrexed alone in patients with previously untreated stage IIIB or IV nonsquamous NSCLC
- Compared to platinum-pemetrexed alone, patients receiving tislelizumab experienced significant improvements in global health status in disease-specific symptoms such as coughing, pain, and, in particular, dyspnea; these patients also experienced less fatigue and decline in physical functioning at Week 18
  - Patients had less peripheral neuropathy in *Arm T+PP*
- The main limitation of this study was the open-label study design and the limited follow-up time in assessing HRQoL
  - The completion rate of the QLQ-C30 at Week 12 is markedly lower in *Arm PP* 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 304 trial, support the risk-benefit ratio for tislelizumab in combination with platinum-pemetrexed, and demonstrate that this combination is favorable compared to platinum-pemetrexed alone as first-line treatment of patients with nonsquamous NSCLC

Change From Baseline in EORTC QLQ-C30 and QLQ-LC13 Subscales

- At Week 18, LS mean score changes from baseline were more favorable in *Arm T+PP* than in *Arm PP* for QLQ-C30 and LC13 subscales (Figure 2B, 2D); notably, symptom scale scores for dyspnea improved in *Arm T+PP* and worsened in *Arm PP* (Figure 2D)
  - Similar patterns were observed in pain symptoms (chest pain and pain in arms and shoulders), coughing, and peripheral neuropathy when *Arm T+PP* showed more improvements than their counterparts
- Patients in *Arm T+PP* and *Arm PP* experienced a decline in physical functioning and increase in fatigue though the changes were greater in *Arm PP*, particularly at Week 18

Figure 2: Change From Baseline in EORTC QLQ-C30 and QLQ-LC13 Subscales



Abbreviations: CI, confidence interval; GHS, Global Health Status; LS, least square; PP, platinum-pemetrexed; QoL, quality of life; T, tislelizumab.

REFERENCES

1. Iyer S, Taylor-Stokes G, Roughley A. *Lung Cancer.* 2013;81(2):288-293.
2. Iyer S, Roughley A, Rider A, Taylor-Stokes G. *Support Care Cancer.* 2014;22(1):181-187.
3. Garassino MC, Gadgeel S, Esteban E, et al. *Lancet Oncol.* 2020;21(3):387-397.
4. Steffen McLouth LE, Lycan TW, Jr., Levine BJ, et al. *Clin Lung Cancer.* 2020;21(3):255-263.
5. Park R, Shaw JW, Korn A, McAuliffe J. *J Cancer Surviv.* 2020;14:363-376.
6. Lu S, Yu Y, Yu X, et al. Tislelizumab plus chemotherapy versus chemotherapy alone as first-line treatment for locally advanced/metastatic nonsquamous NSCLC. Poster presented at: European Society of Medical Oncology; September 19-21, 2020; Virtual Congress.

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