Efficacy, Safety, and Health-Related Quality of Life From a Global Phase 3 Study of Tislelizumab as Second- or Third-Line Therapy for Patients With Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC): RATIONALE 303

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Background: Tislelizumab is an anti-PD-1 antibody engineered to minimize FcγR binding on macrophages, a mechanism of T-cell clearance and potential anti-PD-1 resistance. RATIONALE 303 (BGB-A317-303; NCT03358875) compared efficacy, safety, and health-related quality-of-life (HRQoL) of tislelizumab versus docetaxel in advanced NSCLC.

Methods: In this phase 3 study, patients without oncogenic driver mutations who failed ≥1 prior therapy (including platinum) were randomized 2:1 to tislelizumab 200 mg IV Q3W or docetaxel 75 mg/m^2 IV Q3W. Dual primary endpoints were OS in the ITT (OS_{ITT}) and PD-L1–positive (≥25% TC; Ventana SP263 PD-L1 Assay) analysis sets. A prespecified OS interim analysis was conducted after ≈426 deaths; superiority testing was conducted for OS_{ITT}. HRQoL was measured using QLQ-C30-GHS/QoL from EORTC-QLQ-C30 and lung cancer subscales from EORTC-QLQ-LC13.

Results: Patients (N=805) were randomized (n=535, tislelizumab; n=270, docetaxel). At 19-months median follow-up (reverse Kaplan-Meier estimation), median OS significantly improved with tislelizumab versus docetaxel in ITT (17.2 vs 11.9 months; HR=0.64; 95% CI:

0.53-0.78) and PD-L1–positive (HR=0.52; 95% CI: 0.38-0.71) analysis sets; PFS_{ITT}, ORR_{ITT}, and DoR_{ITT} also improved with tislelizumab (**Table**). Common any/grade ≥3 treatment-emergent AEs were anemia/pneumonia (tislelizumab) and alopecia/neutropenia (docetaxel). Treatment-related AEs leading to death occurred in 1.5% (tislelizumab) and 1.6% (docetaxel) of patients. GHS/QoL scores and fatigue rates improved relative to baseline in cycles 4 and 6 with tislelizumab versus docetaxel. Physical functioning domain score was stable with tislelizumab but decreased with docetaxel in cycles 4 and 6; significant differences between treatment arms emerged at cycle 6. With tislelizumab, EORTC-QLQ-LC13 index score, coughing, and peripheral neuropathy improved significantly at cycles 4 and 6 versus docetaxel; by cycle 6, dyspnea trended toward improvement.

Conclusions: Tislelizumab was tolerable and prolonged OS versus docetaxel regardless of histology or PD-L1 expression with improved PFS, ORR, and HRQoL measures (reduced lung cancer symptoms, fatigue, and improved physical functioning).

	ITT Analysis Set (N=805)			
	Arm A Tislelizumab (n=535)		**Arm B Docetaxel (n=270)**	
Efficacy				
Median OS, mo	**17.2**		**11.9**	
OS difference, mo	5.3			
HR (95% CI)[a]	0.64 (0.53-0.78)			
P-value[a,b]	**<0.0001**			
Median PFS, mo	**4.1**		**2.6**	
PFS difference, mo	1.5			
HR (95% CI)[a]	0.64 (0.53, 0.76)			
P-value[a,b]	<0.0001[c]			
ORR, n (%)	**117 (21.9)**		**19 (7.0)**	
ORR difference, %	14.9			
OR (95% CI)	3.71 (2.24, 6.14)			
P-value[d]	<0.0001[c]			
Median DoR, mo (95% CI)	**13.5 (8.5, 21.8)**		**6.2 (2.1, 7.2)**	
Adverse event profile				
AEs occurring in ≥15% of patients in either arm, n (%)	**All grade**	**Grade ≥3**	**All grade**	**Grade ≥3**
Anemia	152 (28.5)	18 (3.4)	112 (43.4)	16 (6.2)
Alanine aminotransferase increased	106 (19.9)	4 (0.7)	38 (14.7)	0
Cough	104 (19.5)	5 (0.9)	40 (15.5)	1 (0.4)
Aspartate aminotransferase increased	101 (18.9)	5 (0.9)	31 (12.0)	1 (0.4)
Appetite decreased	82 (15.4)	5 (0.9)	59 (22.9)	3 (1.2)
Weight decreased	81 (15.2)	4 (0.7)	26 (10.1)	0
Alopecia	5 (0.9)	0	122 (47.3)	2 (0.8)
Neutrophil count decreased	15 (2.8)	3 (0.6)	95 (36.8)	71 (27.5)
Neutropenia	9 (1.7)	3 (0.6)	81 (31.4)	72 (27.9)
White blood cell count decreased	20 (3.7)	1 (0.2)	74 (28.7)	47 (18.2)

Leukopenia	15 (2.8)	1 (0.2)	69 (26.7)	41 (15.9)
Asthenia	67 (12.5)	6 (1.1)	56 (21.7)	14 (5.4)
Constipation	65 (12.2)	0	42 (16.3)	0
Hypoalbuminemia	70 (13.1)	0	41 (15.9)	1 (0.4)
Nausea	59 (11.0)	0	41 (15.9)	1 (0.4)

[a]Stratified.
[b]One-sided log-rank test.
[c]Descriptive *P*-value.
[d]Cochran-Mantel-Haenszel.
Abbreviations: AE, adverse event; CI, confidence interval; DoR, duration of response; HR, hazard ratio; ITT, intent-to-treat; mo, months; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.