RATIONALE-303: long-term outcomes with tislelizumab in previously treated advanced or metastatic non-small cell lung cancer

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ABSTRACT

Introduction: In the final analysis of RATIONALE-303 (NCT03358875), patients with locally advanced or metastatic squamous or non-squamous non-small cell lung cancer (NSCLC) who progressed after platinum-based chemotherapy experienced significantly improved overall survival (OS) with tislelizumab (an anti-programmed cell death protein-1 antibody) vs docetaxel. RATIONALE-303 met its dual primary endpoints of OS in the intent-to-treat (ITT) population and OS in patients with tumour cell programmed death-ligand 1 (PD-L1) expression of ≥25%. We present long-term efficacy outcomes with an additional 30-month follow-up since the final analysis.

Methods: RATIONALE-303 was a global, open-label, randomised, multicentre, phase 3 trial. Patients aged ≥18 years with histologically confirmed, locally advanced or metastatic (squamous or non-squamous) NSCLC who progressed on prior platinum-based chemotherapy were randomised (2:1) to receive intravenous tislelizumab 200 mg or docetaxel 75 mg/m^2 every 3 weeks. Co-primary endpoints were OS in the ITT population and PD-L1 ≥25% populations. Secondary endpoints were investigator-assessed progression-free survival (PFS_{INV}), objective response rate (ORR_{INV}), duration of response (DoR_{INV}), and safety.

Results: As of January 18, 2024, median follow-up for OS was 46.5 and 46.7 months for tislelizumab and 41.0 and 41.6 months for docetaxel in the ITT (tislelizumab, n=535; docetaxel, n=270) and PD-L1 ≥25% (tislelizumab, n=227; docetaxel, n=115) populations, respectively (by reverse Kaplan–Meier method). Tislelizumab-treated patients experienced sustained clinical benefit vs docetaxel (Table). Respective median OS was 16.9 vs 11.9 months (stratified HR=0.67; 95% CI: 0.57, 0.80; *P*<.0001) in the ITT population and 19.3 vs 11.5 months (stratified HR=0.52; 95% CI: 0.40, 0.68; *P*<.0001) in patients with PD-L1 ≥25%. In the ITT population, median PFS_{INV} was significantly higher with tislelizumab vs docetaxel (4.2 vs 2.6 months [HR=0.64; 95% CI: 0.54, 0.76; *P*<.0001]); ORR_{INV} (22.6% vs 7.8%) and median DoR_{INV} (13.5 vs 6.1 months) were also higher with tislelizumab vs docetaxel. Tislelizumab-treated patients experienced a lower incidence of grade ≥3 treatment-emergent adverse events (43.6% vs 74.8%) and treatment-related grade ≥3 events (16.1% vs 66.3%) vs docetaxel-treated patients. No new safety signals were identified.

Conclusion: After an additional 30 months' follow-up since the final analysis, previously treated patients with advanced or metastatic NSCLC in the ITT and PD-L1 ≥25% populations of RATIONALE-303 continued to experience a clinically meaningful improvement in OS with tislelizumab vs docetaxel. Tislelizumab-treated patients also had higher response rates, more durable responses, delayed disease progression, and a favourable safety profile compared with docetaxel. These results further support tislelizumab as a treatment option for this patient population.

Table. Efficacy Outcomes in the RATIONALE-303 Trial

	ITT Population		PD-L1 ≥25% Population	
	Tislelizumab (n=535)	**Docetaxel (n=270)**	**Tislelizumab (n=227)**	**Docetaxel (n=115)**
Median OS, months (95% CI)	16.9 (15.2, 19.1)	11.9 (9.6, 13.5)	19.3 (16.5, 22.6)	11.5 (8.2, 13.5)
Stratified HR (95% CI) *P* **value**	0.67[a] (0.57, 0.80) <.0001[a,c]		0.52[b] (0.40, 0.68) <.0001[b,c]	
12-month OS rate, % (95% CI)	62.1 (57.9, 66.1)	49.7 (43.5, 55.7)	67.4 (60.8, 73.1)	48.3 (38.5, 57.4)
24-month OS rate, % (95% CI)	37.3 (33.2, 41.5)	23.9 (18.8, 29.3)	42.7 (36.1, 49.1)	22.4 (15.0, 30.8)
36-month OS rate, % (95% CI)	26.0 (22.3, 29.9)	14.7 (10.6, 19.4)	32.5 (26.4, 38.7)	14.3 (8.3, 21.8)
48-month OS rate, % (95% CI)	20.1 (16.5, 23.9)	11.1 (7.5, 15.6)	26.1 (20.3, 32.2)	9.9 (5.0, 16.8)
60-month OS rate, % (95% CI)	20.1 (16.5, 23.9)	NE (NE, NE)	26.1 (20.3, 32.2)	NE (NE, NE)
Median PFS_{INV}, months (95% CI)	4.2 (3.9, 5.5)	2.6 (2.2, 3.8)	NR	NR
Stratified HR (95% CI) *P* **value**	0.64[a] (0.54, 0.76) <.0001[a,c]		NR	
ORR_{INV}, n (%)	121 (22.6)	21 (7.8)	85 (37.4)	9 (7.8)
Median DoR_{INV}, months (95% CI)	13.5 (8.5, 19.4)	6.1 (2.3, 7.2)	NR	NR

Data cutoff: Jan 18, 2024.

[a]Stratified by histology (squamous vs non-squamous), lines of therapy (second vs third), and PD-L1 expression (≥25% TC vs <25% TC). [b]Stratified by histology (squamous vs non-squamous) and lines of therapy (second vs third). [c]One-sided stratified log-rank test *P* value.

CI, confidence interval; DoR_{INV}, investigator-assessed duration of response; HR, hazard ratio; ITT, intent-to-treat; ORR_{INV}, investigator-assessed objective response rate; OS, overall survival; NR, not reported; PD-L1, programmed death-ligand 1; PFS_{INV}, investigator-assessed progression-free survival; TC, tumour cell.