RATIONALE-303: Long-Term Outcomes With Tislelizumab in Previously Treated Advanced or Metastatic Non-Small Cell Lung Cancer

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CONCLUSIONS

- After an additional 30 months of follow-up since the final analysis, patients with previously treated locally advanced or metastatic non-small cell lung cancer (NSCLC) continued to experience clinically meaningful and durable survival benefits with tislelizumab compared with docetaxel
- Patients receiving tislelizumab had longer overall survival (OS) in both the intent-to-treat (ITT) and programmed death-ligand 1 (PD-L1) ≥25% populations, as well as prolonged progression-free survival (PFS), higher objective response rates (ORRs), more durable responses, and fewer grade ≥3 treatment-emergent adverse events (TEAEs) and treatment-related adverse events (TRAEs) than patients receiving docetaxel, despite longer treatment exposure
- Our findings continue to demonstrate tislelizumab as a treatment option for previously treated patients with locally advanced or metastatic NSCLC

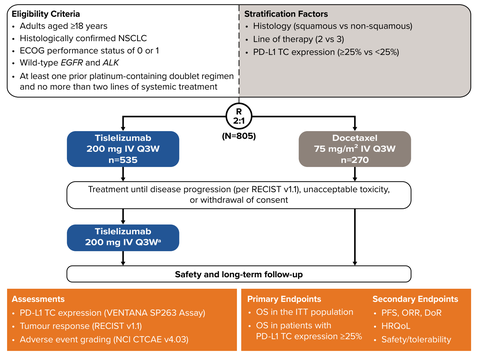
INTRODUCTION

- Tislelizumab has demonstrated improved OS in patients with locally advanced or metastatic NSCLC that progressed after platinum-based chemotherapy, compared with docetaxel[1]
- The RATIONALE-303 trial evaluated tislelizumab vs docetaxel in previously treated locally advanced or metastatic NSCLC.[1] The trial met both primary endpoints, demonstrating an OS benefit with tislelizumab vs docetaxel in the ITT population and in patients with PD-L1 tumour cell (TC) expression ≥25%
- Here, we report long-term efficacy and safety outcomes from the RATIONALE-303 trial, with an additional 30 months of follow-up since the final analysis

METHODS

- RATIONALE-303 (NCT03358875) was a global, open-label, randomised phase 3 trial comparing tislelizumab with docetaxel in patients with advanced or metastatic NSCLC who were previously treated with platinum-based chemotherapy (**Figure 1**)
- Time-to-event endpoints were estimated using Kaplan–Meier methodology, with the Brookmeyer and Crowley method used to estimate 95% confidence intervals (CIs) for median PFS, OS, and duration of response (DoR)
- ORR differences and odds ratios between treatment arms were calculated using the Cochran–Mantel–Haenszel chi-square test
- Hazard ratios (HRs) and associated 95% CIs were calculated using unstratified and stratified Cox models (histology, prior lines of therapy, and PD-L1 TC expression)

Figure 1. Study Design



[a]Optional treatment continuation at investigator's discretion.

Abbreviations: *ALK*, anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; HRQoL, health-related quality of life; IV, intravenously; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; Q3W, every 3 weeks; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours.

RESULTS

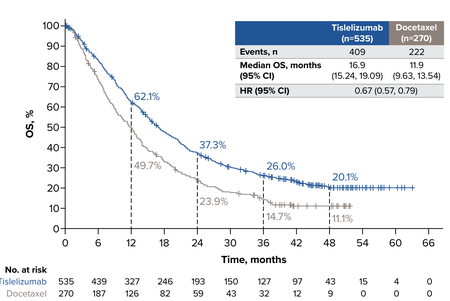
Patient Disposition and Baseline Characteristics

- A total of 805 patients were enrolled, of which 535 (66.5%) were randomised to receive tislelizumab, and 270 (33.5%) to receive docetaxel
  - Baseline characteristics were generally well balanced between treatment arms, with a median age of 61.0 years in both arms and predominantly male patients (77.8% tislelizumab; 76.3% docetaxel)
  - Histology was distributed as squamous (46.4% vs 45.2%) and non-squamous (53.6% vs 54.8%), with most patients receiving treatment as second-line therapy (84.7% vs 84.8%)
  - PD-L1 TC expression ≥25% was observed in 343 patients (42.6%) overall, with similar distribution between arms (42.4% tislelizumab; 43.0% docetaxel)
- At data cutoff for study closeout (January 18, 2024), median OS follow-up was 46.5 months (95% CI: 45.8, 47.1) for tislelizumab and 41.0 months (95% CI: 39.3, 44.0) for docetaxel
  - This updated analysis reflects an additional 30 months of follow-up since the final analysis
- Thirteen patients (tislelizumab, n=1; docetaxel, n=12) were included in the ITT population but excluded from the safety analysis set due to those patients not receiving study treatment

Efficacy Outcomes

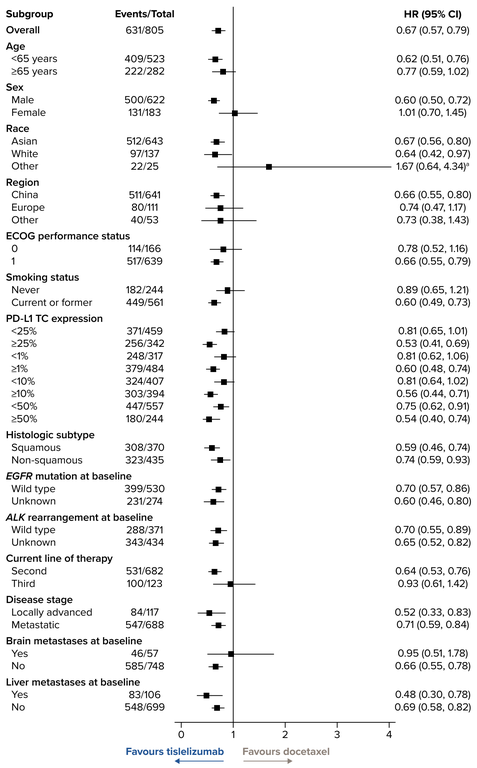
- The OS benefit of tislelizumab compared with docetaxel was maintained relative to the final analysis[1] in both the ITT population and the PD-L1 TC expression ≥25% subgroup
  - In the ITT population, median OS was 16.9 vs 11.9 months (HR=0.67; 95% CI: 0.57, 0.79) (**Figure 2A**)
  - In the PD-L1 TC expression ≥25% subgroup, median OS was 19.3 vs 11.5 months (HR=0.52; 95% CI: 0.40, 0.68) (**Figure 2B**)
- In both populations, OS rates at 12, 24, 36, and 48 months were consistently higher in the tislelizumab arm compared with the docetaxel arm

Figure 2. Kaplan–Meier Analysis of OS in (A) the ITT Population and (B) the PD-L1 TC Expression ≥25% Subgroup



- Tislelizumab demonstrated an OS benefit across most prespecified subgroups, including different PD-L1 TC expression levels, histologic subtypes, and lines of therapy (**Figure 3**)

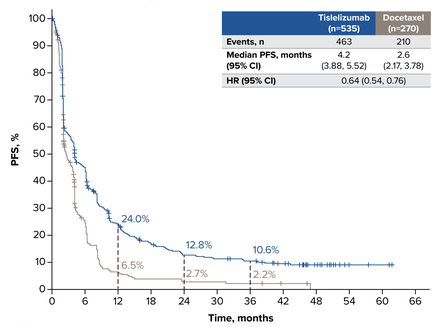
Figure 3. Forest Plot of OS Across Prespecified Subgroups (ITT Population)[a]



[a]For 1 patient in the docetaxel arm, the month and day of death date are missing, therefore, this patient was censored at the last known alive date in the OS analysis.

- In the ITT population, median PFS was 4.2 months with tislelizumab vs 2.6 months with docetaxel (HR=0.64; 95% CI: 0.54, 0.76) (**Figure 4**)
- PFS rates at 12, 24, and 36 months were also higher with tislelizumab vs docetaxel

Figure 4. Kaplan–Meier Analysis of PFS in the ITT Population



- The ORR in the ITT population was higher in the tislelizumab arm compared with the docetaxel arm (**Table 1**)
- In the PD-L1 TC expression ≥25% subgroup, ORR was higher in the tislelizumab arm (37.4%) vs the docetaxel arm (7.8%)
- Disease control rate (DCR) in the ITT population was higher with tislelizumab vs with docetaxel
- Median DoR in the ITT population was longer for tislelizumab compared with docetaxel

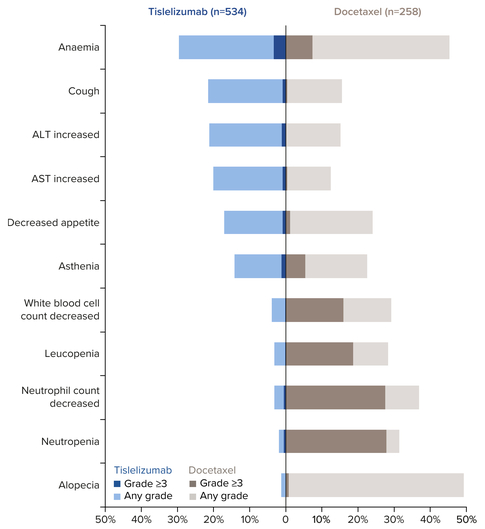
Table 1. Investigator-Assessed Disease Response per RECIST v1.1 (ITT Population)

	Tislelizumab (n=535)	Docetaxel (n=270)
ORR, n (%)	121 (22.6)	21 (7.8)
95% CI	19.1, 26.4	4.9, 11.6
DCR, n (%)	298 (55.7)	114 (42.2)
95% CI	51.4, 60.0	36.3, 48.4
DoR (median), months (95% CI)	13.5 (8.5, 19.4)	6.1 (2.3, 7.2)

Safety/Tolerability Profile

- In the tislelizumab arm, 534 (99.8%) patients received treatment, and the median treatment duration was ~5.5 months (range: ~0.2-63.2)
- In the docetaxel arm, 258 (95.6%) patients received treatment, and the median treatment duration was ~2.1 months (range: ~0.2-48.3)
- Despite longer treatment exposure with tislelizumab, patients experienced a lower rate of grade ≥3 TEAEs compared with docetaxel (43.6% vs 74.8%) (**Figure 5**)

Figure 5. Incidence of TEAEs Occurring in ≥20% of Patients (Safety Population)



Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

- The incidence of any-grade, grade ≥3, and serious TRAEs and discontinuations due to TRAEs was lower with tislelizumab vs docetaxel (**Table 2**)

Table 2. Safety Summary (Safety Population)

TRAE Summary	Tislelizumab (n=534)	Docetaxel (n=258)
Patients with ≥1 TRAEs, n (%)	404 (75.7)	242 (93.8)
Grade ≥3 TRAEs	86 (16.1)	171 (66.3)
Serious TRAEs	76 (14.2)	59 (22.9)
Grade ≥3 serious TRAEs	56 (10.5)	56 (21.7)
TRAEs leading to death, n (%)	8 (1.5)	4 (1.6)
TRAEs leading to any treatment discontinuation, n (%)	38 (7.1)	26 (10.1)
TRAEs leading to treatment modification,[a] n (%)	76 (14.2)	81 (31.4)
Patients with infusion-related reactions, n (%)	5 (0.9)	9 (3.5)
Patients with any imAEs,[b] n (%)	186 (34.8)	9 (3.5)

Adverse events were classified based on Medical Dictionary for Regulatory Activities v24.0 and graded according to NCI CTCAE v4.03. Patients with multiple events for a given preferred term were counted only once at the maximum grade for the preferred term.

[a]Treatment modification for tislelizumab included dose interruption, dose delay, and infusion rate decrease; treatment modification for docetaxel included dose interruption, dose delay, infusion rate decrease, and dose reduction.

[b]imAEs were determined using a predefined programmatic algorithmic approach and were based on a list of preferred terms, without manual medical adjudication.

- No new safety signals were observed with the extended follow-up
  - The most frequently reported any-grade TRAEs with tislelizumab (in ≥10% of patients) were alanine aminotransferase increased (17.4%), aspartate aminotransferase increased (16.1%), hypothyroidism (12.0%), and anaemia (11.6%)
- Overall, 34.8% of patients treated with tislelizumab experienced immune-mediated adverse events (imAEs), most of which were grade 1/2 in severity
  - The three most frequently reported imAEs with tislelizumab were hypothyroidism (13.7%), skin reactions (9.9%), and pneumonitis (9.0%)

REFERENCES

1. Zhou C, et al. *J Thorac Oncol.* 2023;18:93-105.

DISCLOSURES

CZ: Consulting fees from Innovent Biologics, Hengrui, Qilu, and TopAlliance Biosciences; Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Lilly China, Sanofi, Boehringer Ingelheim, Roche, Merck Sharp & Dohme, Qilu, Hengrui, Innovent Biologics, Alice, C-Stone, LUYE Pharma, TopAlliance Biosciences, Amoy Diagnostics, and AnHeart. **YW, YB, WZ:** Employment with BeOne Medicines, Ltd. **KN:** Employment with and stock ownership in BeOne Medicines, Ltd. **YF, ZM, PRMM:** No disclosures.

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