RATIONALE-303: Post-Hoc Analysis of Tislelizumab Monotherapy in Previously Treated Non-Small Cell Lung Cancer With Metastases

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CONCLUSIONS

- The global pivotal study RATIONALE-303 reported survival benefits and a tolerable safety profile for tislelizumab monotherapy vs docetaxel as second-line or later treatment in previously treated patients with locally advanced or metastatic squamous or non-squamous non-small cell lung cancer (NSCLC)
- After an additional 30 months of follow-up since the final analysis, this post-hoc analysis demonstrated improvements in overall survival (OS) and investigator-assessed progression-free survival (PFS_{INV}) and objective response rate (ORR_{INV}) with tislelizumab monotherapy in patients with varying numbers of metastatic sites, including those with liver metastases
- No new safety signals were observed

INTRODUCTION

- NSCLC frequently metastasises, with liver metastases occurring in approximately 20% of patients with metastatic NSCLC[1]
- Liver metastases in NSCLC present unique challenges; they exhibit immune-privileged characteristics, leading to reduced antigen-specific CD8+ T-cells and immunosuppressive environments, which weaken antitumour immune responses[2-4]
- Liver metastases in NSCLC respond less favourably to chemotherapy, correlating with worse clinical outcomes and shorter survival[5]
- The final analysis of the global, open-label, randomised, multicentre phase 3 RATIONALE-303 trial (data cutoff: July 15, 2021) demonstrated superior OS with tislelizumab (anti-programmed cell death protein-1 antibody) vs docetaxel in patients with locally advanced or metastatic squamous or non-squamous NSCLC that progressed after platinum-based chemotherapy[6]
- Given the poor prognosis associated with liver metastases, we conducted a post-hoc subgroup analysis of RATIONALE-303 to evaluate tislelizumab's efficacy in patients with metastases, including liver metastases

METHODS

- This post-hoc analysis included patients with baseline metastases from the RATIONALE-303 trial (NCT03358875)
- Patients aged ≥18 years with histologically confirmed, previously treated locally advanced or metastatic squamous or non-squamous NSCLC were randomised (2:1) to receive tislelizumab 200 mg intravenously (IV) or docetaxel 75 mg/m^2 IV once every 3 weeks
- Efficacy (OS, PFS_{INV}, and ORR_{INV}) and safety outcomes were analysed based on the number of confirmed metastatic sites (locally advanced [ie, no metastatic sites], one or two metastatic sites, or three or more metastatic sites) and presence or absence of liver metastases at baseline
- Time-to-event endpoints were estimated using Kaplan–Meier methodology, with the Brookmeyer and Crowley method used to estimate the 95% confidence intervals (CIs) for median OS and PFS_{INV}. Hazard ratios (HRs) and associated 95% CIs were calculated using an unstratified Cox proportional hazards model

RESULTS

Demographics, Baseline Characteristics, and Tumour Characteristics

- Among the 805 randomised patients (tislelizumab, n=535; docetaxel, n=270), 688 (85.5%) had at least one metastatic site at baseline (tislelizumab, n=451; docetaxel, n=237) (**Table 1**)
- A total of 106 (13.2%) patients had liver metastases at baseline (tislelizumab, n=73; docetaxel, n=33) (**Table 2**)
- Patient demographics, baseline characteristics, and tumour characteristics for patients with and without metastases were similar between the tislelizumab and docetaxel arms

Table 1. Patient Demographics and Baseline Characteristics by Number of Confirmed Metastatic Sites at Baseline (ITT Population)

	Locally Advanced (No Metastatic Sites)		One or Two Metastatic Sites		Three or More Metastatic Sites	
	Tislelizumab (n=84)	Docetaxel (n=33)	Tislelizumab (n=328)	Docetaxel (n=172)	Tislelizumab (n=123)	Docetaxel (n=65)
Median age (range), years	63.0 (29.0-79.0)	62.0 (50.0-77.0)	61.0 (29.0-88.0)	62.0 (33.0-80.0)	61.0 (39.0-78.0)	59.0 (40.0-81.0)
Male, n (%)	74 (88.1)	28 (84.8)	253 (77.1)	136 (79.1)	89 (72.4)	42 (64.6)
Region, n (%)						
China	69 (82.1)	25 (75.8)	266 (81.1)	139 (80.8)	88 (71.5)	54 (83.1)
Rest of the world	15 (17.9)	8 (24.2)	62 (18.9)	33 (18.2)	35 (28.5)	11 (16.9)
Histologic subtype, n (%)						
Squamous	57 (67.9)	23 (69.7)	149 (45.3)	78 (45.3)	42 (34.1)	21 (32.3)
Non-squamous	27 (32.1)	10 (30.3)	179 (54.6)	94 (54.7)	81 (65.9)	44 (67.7)
Confirmed distant metastatic site(s), n (%)						
Bone	1 (1.2)	0	85 (25.9)	37 (21.5)	80 (65.0)	42 (64.6)
Liver	0	0	31 (9.5)	11 (6.4)	42 (34.1)	22 (33.8)
Brain	0	0	16 (4.9)	12 (7.0)	23 (18.7)	6 (9.2)

Abbreviation: ITT, intent-to-treat.

Table 2. Patient Demographics and Baseline Characteristics in Patients With or Without Liver Metastases at Baseline (ITT Population)

	With Liver Metastases		Without Liver Metastases	
	Tislelizumab (n=73)	Docetaxel (n=33)	Tislelizumab (n=462)	Docetaxel (n=237)
Median age (range), years	59.0 (29.0-84.0)	62.0 (40.0-81.0)	61.0 (29.0-88.0)	62.0 (33.0-80.0)
Male, n (%)	51 (69.9)	23 (69.7)	365 (79.0)	183 (77.2)
Region, n (%)				
China	52 (71.2)	27 (81.8)	371 (80.3)	191 (80.6)
Rest of the world	21 (28.8)	6 (18.2)	91 (19.7)	46 (19.4)
Histologic subtype, n (%)				
Squamous	35 (47.9)	14 (42.4)	213 (46.1)	108 (45.6)
Non-squamous	38 (52.1)	19 (57.6)	249 (53.9)	129 (54.4)
Confirmed distant metastatic site(s), n (%)				
Bone	39 (53.4)	20 (60.6)	127 (27.5)	59 (24.9)
Liver	73 (100.0)	33 (100.0)	0	0
Brain	8 (11.0)	4 (12.1)	31 (6.7)	14 (5.9)

Efficacy

- As of January 18, 2024, median study follow-up was 16.6 months for tislelizumab and 10.7 months for docetaxel, with a minimum study follow-up time of 45.3 months
- Consistent clinical benefits were observed in patients treated with tislelizumab vs docetaxel, regardless of the number of metastatic sites at baseline (**Table 3**)
  - Sustained OS benefit (**Figure 1**)
  - Consistently improved PFS_{INV} benefit (**Figure 2**)
  - Higher ORR_{INV}

Table 3. Efficacy Outcomes by Number of Confirmed Metastatic Sites at Baseline (ITT Population)

	Locally Advanced (No Metastatic Sites)		One or Two Metastatic Sites		Three or More Metastatic Sites	
	Tislelizumab (n=84)	Docetaxel (n=33)	Tislelizumab (n=328)	Docetaxel (n=172)	Tislelizumab (n=123)	Docetaxel (n=65)
Median OS, months (95% CI)	24.5 (20.7, 29.5)	14.9 (12.6, 19.3)	17.5 (15.8, 20.0)	12.7 (9.7, 15.2)	11.2 (7.6, 12.9)	7.8 (5.8, 10.5)
HR (95% CI)	0.52 (0.33, 0.83)		0.71 (0.57, 0.87)		0.68 (0.49, 0.94)	
Median PFS_{INV}, months (95% CI)	8.3 (5.5, 13.1)	3.7 (2.1, 6.9)	4.2 (3.6, 6.2)	2.6 (2.1, 4.0)	2.3 (2.1, 4.0)	2.2 (1.9, 4.0)
HR (95% CI)	0.58 (0.35, 0.96)		0.62 (0.50, 0.76)		0.65 (0.46, 0.92)	
ORR_{INV}, n (%)	26 (31.0)	4 (12.1)	73 (22.3)	15 (8.7)	22 (17.9)	2 (3.1)
95% CI	21.3, 42.0	3.4, 28.2	17.9, 27.2	5.0, 14.0	11.6, 25.8	0.4, 10.7

Figure 1. Kaplan–Meier Analysis of OS by Number of Confirmed Metastatic Sites at Baseline (ITT Population)

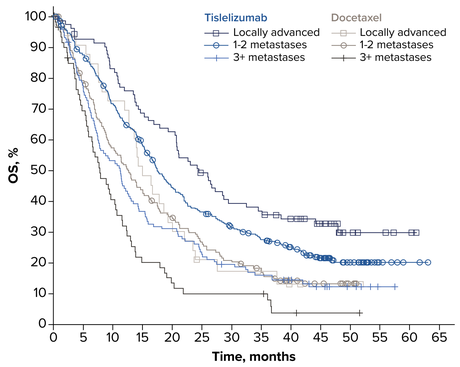
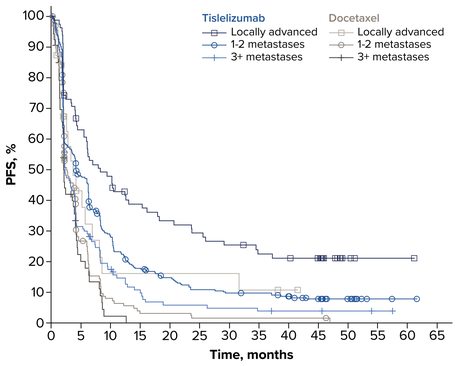


Figure 2. Kaplan–Meier Analysis of PFS by Number of Confirmed Metastatic Sites at Baseline (ITT Population)



- Consistent clinical benefits were maintained in patients treated with tislelizumab, with or without liver metastases at baseline, vs docetaxel (**Table 4**)
  - Sustained OS benefit (**Figure 3**)
  - Maintained PFS_{INV} benefit (**Figure 4**)
  - Higher ORR_{INV}

Table 4. Efficacy Outcomes in Patients With or Without Liver Metastases at Baseline (ITT Population)

	With Liver Metastases		Without Liver Metastases	
	Tislelizumab (n=73)	Docetaxel (n=33)	Tislelizumab (n=462)	Docetaxel (n=237)
Median OS, months (95% CI)	13.4 (7.9, 17.3)	6.8 (4.1, 7.8)	17.6 (15.8, 20.4)	12.9 (11.3, 14.0)
HR (95% CI)	0.48 (0.30, 0.78)		0.69 (0.58, 0.82)	
Median PFS_{INV}, months (95% CI)	2.1 (2.0, 4.0)	2.0 (1.8, 4.0)	4.3 (4.1, 6.2)	2.9 (2.3, 4.0)
HR (95% CI)	0.53 (0.33, 0.85)		0.62 (0.52, 0.74)	
ORR_{INV}, n (%)	11 (15.1)	2 (6.1)	110 (23.8)	19 (8.0)
95% CI	7.8, 25.4	0.7, 20.2	20.0, 28.0	4.9, 12.2

Figure 3. Kaplan–Meier Analysis of OS in Patients With or Without Liver Metastases at Baseline (ITT Population)

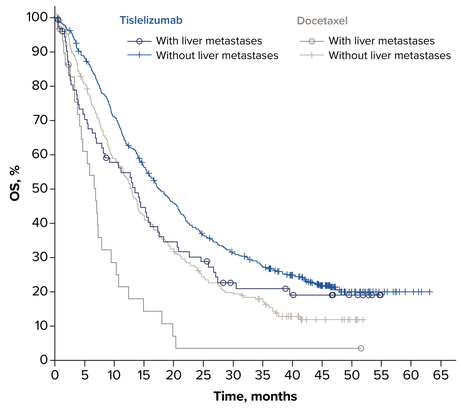
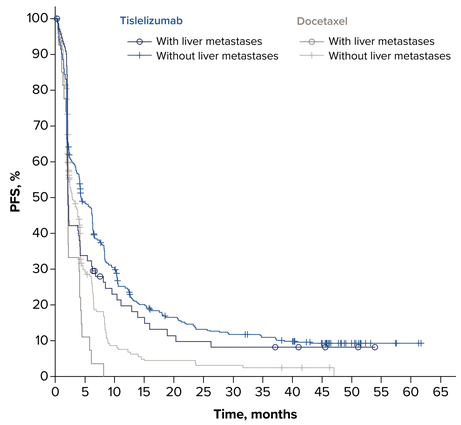


Figure 4. Kaplan–Meier Analysis of PFS in Patients With or Without Liver Metastases at Baseline (ITT Population)



Safety/Tolerability Profile

- Safety outcomes were consistent with the known safety profiles of tislelizumab and docetaxel
- Tislelizumab demonstrated a tolerable and acceptable safety profile across all subgroups (**Tables 5** and **6**)

Table 5. Safety Outcomes by Number of Confirmed Metastatic Sites at Baseline (Safety Population)

	Locally Advanced (No Metastatic Sites)		One or Two Metastatic Sites		Three or More Metastatic Sites	
n (%)	Tislelizumab (n=84)	Docetaxel (n=33)	Tislelizumab (n=327)	Docetaxel (n=165)	Tislelizumab (n=123)	Docetaxel (n=60)
Patients with ≥1 TEAEs	83 (98.8)	33 (100.0)	316 (96.6)	163 (98.8)	119 (96.7)	58 (96.7)
Patients with ≥1 TRAEs	71 (84.5)	32 (97.0)	248 (75.8)	156 (94.5)	85 (69.1)	54 (90.0)
Serious TEAEs	21 (25.0)	12 (36.4)	119 (36.4)	48 (29.1)	52 (42.3)	24 (40.0)
TEAEs leading to death	1 (1.2)	2 (6.1)	22 (6.7)	5 (3.0)	12 (9.8)	5 (8.3)
TEAEs leading to treatment discontinuation	9 (10.7)	8 (24.2)	41 (12.5)	17 (10.3)	17 (13.8)	9 (15.0)
Patients with any imAEs	33 (39.3)	1 (3.0)	118 (36.1)	5 (3.0)	35 (28.5)	3 (5.0)

Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. imAEs were determined using a programmatic algorithmic approach and based on a defined list of preferred terms, without manual medical adjudication.
Abbreviations: imAE, immune-mediated adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Table 6. Safety Outcomes in Patients With or Without Liver Metastases at Baseline (Safety Population)

	With Liver Metastases		Without Liver Metastases	
n (%)	Tislelizumab (n=72)	Docetaxel (n=29)	Tislelizumab (n=462)	Docetaxel (n=229)
Patients with ≥1 TEAEs	69 (95.8)	28 (96.6)	449 (97.2)	226 (98.7)
Patients with ≥1 TRAEs	53 (73.6)	26 (89.7)	351 (76.0)	216 (94.3)
Serious TEAEs	30 (41.7)	11 (37.9)	162 (35.1)	73 (31.9)
TEAEs leading to death	6 (8.3)	2 (6.9)	29 (6.3)	10 (4.4)
TEAEs leading to treatment discontinuation	10 (13.9)	3 (10.3)	57 (12.3)	31 (13.5)
Patients with any imAEs	21 (29.2)	2 (6.9)	165 (35.7)	7 (3.1)

Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. imAEs were determined using a programmatic algorithmic approach and based on a defined list of preferred terms, without manual medical adjudication.

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DISCLOSURES

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