A Comparison of Tislelizumab Plus Chemotherapy vs Programmed Cell Death Protein-1 (PD-1) Inhibitor Monotherapy in First-Line Non-Squamous Non-Small Cell Lung Cancer (NSCLC) Patients With Programmed Cell Death-Ligand 1 (PD-L1) ≥50%

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CONCLUSION

- In patients with locally advanced/metastatic first-line non-squamous NSCLC with PD-L1 ≥50%, tislelizumab plus chemotherapy may have a more favorable risk-benefit than PD-1 inhibitor (PD-1i) monotherapy, regardless of gender, smoking status, or PD-L1 expression level
- This exploratory analysis further supports the use of tislelizumab plus chemotherapy as a first-line treatment in patients with advanced or metastatic non-squamous NSCLC with PD-L1 ≥50%

INTRODUCTION

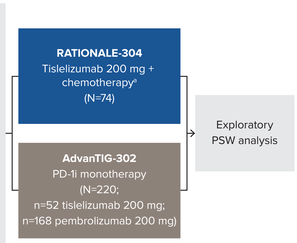
- Anti-PD-1/PD-L1 monoclonal antibodies (mAbs) with or without chemotherapy are approved first-line therapies for metastatic/locally advanced NSCLC
  - Tislelizumab is an anti-PD-1 mAb approved in China and Europe in combination with chemotherapy for squamous/non-squamous NSCLC[1,2]
  - There are no head-to-head studies comparing tislelizumab plus chemotherapy to anti-PD-1/PD-L1 mAbs alone in locally advanced/metastatic first-line non-squamous NSCLC with PD-L1 ≥50%
- RATIONALE-304 was a phase 3 trial in China of first-line tislelizumab plus chemotherapy versus chemotherapy in patients with locally advanced or metastatic non-squamous NSCLC (NCT03663205)[3]
  - Tislelizumab plus chemotherapy was associated with clinically meaningful improvement in progression-free survival (PFS) assessed by the independent review committee (IRC) and overall survival (OS) compared with chemotherapy in patients with PD-L1 ≥50%[4]
- AdvanTIG-302 was a phase 3, international trial investigating first-line ociperlimab plus tislelizumab, pembrolizumab alone, and tislelizumab alone, in locally advanced/recurrent or metastatic NSCLC patients with PD-L1 tumor cells ≥50% (NCT04746924)[5]
- This retrospective exploratory analysis is the first to examine the risk-benefit of tislelizumab plus chemotherapy vs PD-1i monotherapy with tislelizumab or pembrolizumab in this patient population

METHODS

Trial Design

- Patients with locally advanced/metastatic first-line non-squamous NSCLC with PD-L1 ≥50% and no actionable mutations who received tislelizumab plus chemotherapy in the phase 3 RATIONALE-304 trial or PD-1i monotherapy (tislelizumab or pembrolizumab) in the phase 3 AdvanTIG-302 trial were compared (**Figure 1**)

Figure 1. Study Design



[a]Chemotherapy: pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2 (or carboplatin AUC 5).
Abbreviations: *ALK*, anaplastic lymphoma kinase; AUC, area under the curve; *EGFR*, epidermal growth factor receptor; PSW, propensity score weighting.

Analysis and Statistical Methods

- Exploratory propensity score weighting (PSW) analyses were performed to estimate average treatment effect on the treated (ATT) to allow simplified reproduction of a randomized trial by adjusting for clinically relevant baseline demographics and disease characteristics between RATIONALE-304 and AdvanTIG-302, and reducing the confounding effects of these factors
  - OS, PFS, and overall response rate (ORR) were evaluated for all patients, and by sex, smoking status, and PD-L1 subgroups
  - Unweighted safety was reported

RESULTS

Baseline Characteristics and Patient Disposition

- As of the data cutoff dates of April 26, 2023, for RATIONALE-304 and May 30, 2025, for AdvanTIG-302, 294 patients were included (N=74, RATIONALE-304; N=220, AdvanTIG-302 [n=52 tislelizumab, n=168 pembrolizumab])
- Baseline characteristics are shown in **Table 1**
  - For smokers, no patients who received tislelizumab plus chemotherapy and 17.5% of patients who received PD-1i monotherapy were female; for non-smokers, a total of 77.4% who received tislelizumab plus chemotherapy and 65.4% who received PD-1i monotherapy were female

Table 1. Baseline characteristics

	Tislelizumab plus chemotherapy (N=74)	PD-1i monotherapy (N=220)
Age group, %		
≥65 years	35.1	55.0
<65 years	64.9	45.0
Sex, %		
Female	32.4	23.2
Male	67.6	76.8
ECOG PS, %		
0	18.9	30.5
1	81.1	69.5
Brain metastases, %	9.5	20.5
Liver metastases, %	10.8	10.9
Smoking status, %		
Current	18.9	23.6
Former	39.2	64.5
Never	41.9	11.8

PD-1i monotherapy consisted of tislelizumab or pembrolizumab.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intent-to-treat.

Efficacy

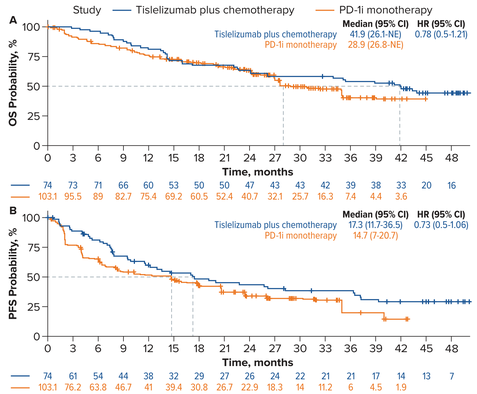
- Overall, the addition of chemotherapy to tislelizumab suggested improved overall efficacy compared with PD-1i monotherapy (**Table 2**), including a trend for improved OS and PFS (**Figure 2**); this trend was also demonstrated in patients regardless of smoking status or gender (**Figures 3A-3C/4A-4C**)
  - Tislelizumab plus chemotherapy may also provide improved efficacy compared with PD-1i monotherapy in male patients (median OS [95% CI]: 41.9 [24.2-not estimable (NE)] for tislelizumab plus chemotherapy vs NR [31.0-NE] months for PD-1i monotherapy; HR [95% CI]: 0.92 [0.55-1.55]; median PFS [95% CI]: 20.0 [12.2-39.4] for tislelizumab plus chemotherapy vs 12.4 [8.0-30.4] months for PD-1i monotherapy; HR [95% CI]: 0.78 [0.50-1.21]; data not shown)
- Tislelizumab plus chemotherapy may also provide improved efficacy compared with PD-1i monotherapy in patients with PD-L1 50-89% (**Figures 3D/4D**)
  - Tislelizumab plus chemotherapy may also provide improved efficacy compared with PD-1i monotherapy in patients with PD-L1 ≥90% (median OS [95% CI]: 41.9 [14.5-NE] for tislelizumab plus chemotherapy vs 28.9 [26.8-NE] months for PD-1i monotherapy; HR [95% CI]: 0.99 [0.54-1.82]; data not shown) but further investigation is required

Table 2. Efficacy Data

Endpoint	Unweighted	After PSW
OS		
HR (95% CI)	0.90 (0.61-1.35)	0.78 (0.50-1.21)
RMST difference (95% CI)[a]	0.74 (−2.75-4.23)	2.15 (−1.5-5.81)
Tau, months[a]	39.1	
PFS		
HR (95% CI)	0.83 (0.59-1.17)	0.73 (0.50-1.06)
ORR, % (95% CI)		
Tislelizumab + chemotherapy	70.3 (59.8-80.7)	70.3 (59.8-80.7)
PD-1i monotherapy	56.4 (45.0-67.7)	50.8 (41.2-60.5)
Risk difference	13.9 (1.5-26.3)	19.4 (5.2-33.6)

PD-1i monotherapy consisted of tislelizumab or pembrolizumab. [a]RMST provides an estimate of the average survival time up to a predefined "restriction time" (denoted by Tau). RMST at time Tau can be interpreted as the average of each patient's survival time truncated at Tau. RMST at time Tau means the mean survival time for those patients whose survival time ≤ Tau. From Kaplan–Meier curve, RMST is the area under the survival curves upon the restricted time.
Abbreviations: RMST, restricted mean survival time.

Figure 2. Kaplan–Meier curve for OS (A) and PFS (B) in patients who received tislelizumab plus chemotherapy compared with PD-1i monotherapy using the ATT weighted Cox model



Dashed lines correspond to median OS or PFS.

Figure 3. Kaplan–Meier curve for OS in smokers (A), non-smokers (B), females (C), and patients with PD-L1 50-89% (D) who received tislelizumab plus chemotherapy compared with PD-1i monotherapy using the ATT weighted Cox model

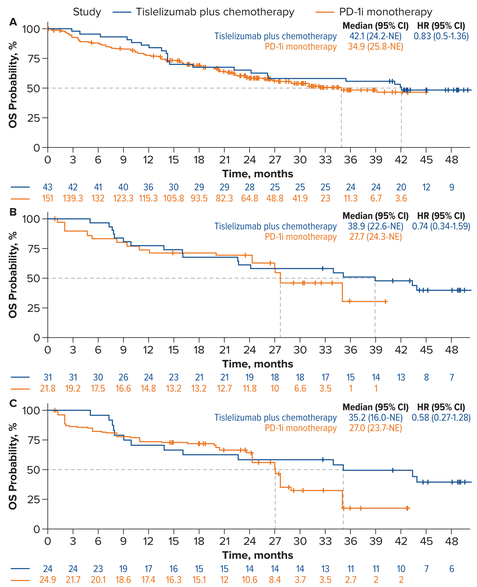
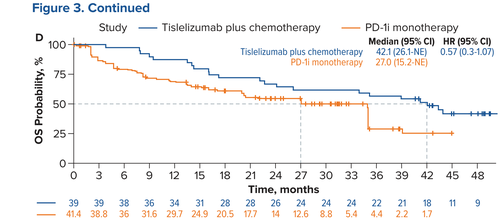
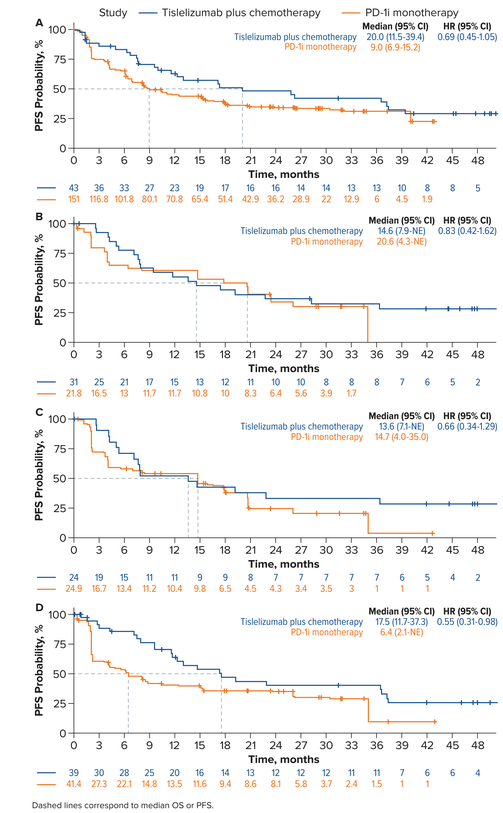


Figure 3. Continued



Dashed lines correspond to median OS or PFS.

Figure 4. Kaplan–Meier curve for PFS in smokers (A), non-smokers (B), females (C), and patients with PD-L1 50-89% (D) who received tislelizumab plus chemotherapy compared with PD-1i monotherapy using the ATT weighted Cox model



Dashed lines correspond to median OS or PFS.

Safety and Tolerability

- Treatment-related treatment-emergent adverse events (TEAEs) occurred in the majority of patients who received tislelizumab plus chemotherapy or PD-1i monotherapy (**Table 3**)
  - Tislelizumab plus chemotherapy was associated with a higher cumulative incidence of treatment-related TEAEs than PD-1i monotherapy (**Table 3**)
- Grade ≥3 immune-mediated adverse events (imAEs) occurred in 10.8% of patients who received tislelizumab plus chemotherapy and 11.9% of patients who received PD-1i monotherapy (**Table 3**)

Table 3. Overall Safety Summary

	Tislelizumab plus chemotherapy (N=74)	PD-1i monotherapy (N=219)[a]
Any TEAE, n (%)	74 (100)	212 (96.8)
Grade ≥3	59 (79.7)	120 (54.8)
Serious	37 (50.0)	96 (43.8)
Leading to death	5 (6.8)	12 (5.5)
Leading to treatment discontinuation	28 (37.8)	40 (18.3)
Any treatment-related TEAE, n (%)	74 (100)	174 (79.5)
Grade ≥3	50 (67.6)	43 (19.6)
Serious	18 (24.3)	30 (13.7)
Leading to death	1 (1.4)	2 (0.9)
Leading to treatment discontinuation	26 (35.1)	28 (12.8)
Any tislelizumab- or pembrolizumab-related TEAE, n (%)	64 (86.5)	174 (79.5)
Grade ≥3	24 (32.4)	42 (19.2)
Serious	12 (16.2)	29 (13.2)
Leading to death	1 (1.4)	2 (0.9)
Leading to treatment discontinuation	17 (23.0)	28 (12.8)
Any chemotherapy-related TEAE, n (%)	74 (100)	NA
Grade ≥3	48 (64.9)	NA
Serious	13 (17.6)	NA
Leading to death	0 (0)	NA
Leading to treatment discontinuation	20 (27.0)	NA
Any imAE, n (%)	32 (43.2)	99 (45.2)
Grade ≥3	8 (10.8)	26 (11.9)

PD-1i monotherapy consisted of tislelizumab or pembrolizumab.
[a]One enrolled patient did not receive treatment and was removed from the safety analysis set.
Abbreviation: NA, not applicable.

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