Tislelizumab Combined With Chemotherapy as First-line Therapy for Locally Advanced or Metastatic Non-squamous Non-small Cell Lung Cancer (nsq-NSCLC): Programmed Death-Ligand 1 (PD-L1) Expression ≥50% Subgroup Analysis of the Randomized, Phase 3 RATIONALE-304 Trial

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Conclusions

In patients with advanced nsq-NSCLC and tumor PD-L1 expression ≥50%, first-line tislelizumab plus chemotherapy demonstrated clinically meaningful improvements in progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and duration of response (DoR) and a manageable safety profile compared with chemotherapy alone.

Long-term follow-up data demonstrated durable clinical improvement with tislelizumab plus chemotherapy.

These findings support tislelizumab plus chemotherapy as a treatment option in first-line nsq-NSCLC patients with high PD-L1 expression.

Background

Lung cancer remains a leading cause of cancer-related mortality worldwide.[1] In advanced NSCLC, approximately 22%-30% of patients exhibit high PD-L1 expression (defined as ≥50% of tumor cells expressing PD-L1).[2,3] Higher PD-L1 expression levels in some tumor types have been associated with improved responses to immune checkpoint inhibitors.[4]

The phase 3 RATIONALE-304 trial (NCT03663205) demonstrated that first-line tislelizumab (BGB-A317, an anti-programmed death-1 inhibitor) plus chemotherapy improved efficacy outcomes compared with chemotherapy alone in Chinese patients with advanced nsq-NSCLC.[5] This exploratory analysis specifically examines the outcomes in patients from RATIONALE-304 whose tumors exhibited high PD-L1 expression (≥50%).

Methods

- Patients aged 18-75 years with treatment-naive, stage IIIB (not amenable to curative surgery/radiotherapy) or stage IV nsq-NSCLC were enrolled[6]
- Patients were randomized (2:1) to open-label:
  - Tislelizumab 200 mg intravenously every 3 weeks plus platinum-based chemotherapy for 4-6 cycles, followed by maintenance tislelizumab plus pemetrexed; or
  - Platinum-based chemotherapy alone for 4-6 cycles, followed by maintenance pemetrexed
- Endpoints in the PD-L1 ≥50% population:
  - Primary: PFS assessed by independent review committee (IRC)
  - Secondary: OS, ORR assessed by IRC using Response Evaluation Criteria in Solid Tumors version 1.1, DoR, and safety
- PD-L1 expression was assessed during screening using the VENTANA PD-L1 (SP263) Assay (Roche Diagnostics, Indianapolis, IN, USA) at a central laboratory

Results

Patient Disposition and Baseline Characteristics

- Of 334 randomized patients, 110 (32.9%) had PD-L1 expression ≥50% (tislelizumab plus chemotherapy: n=74; chemotherapy alone: n=36)
- Baseline patient characteristics were similar between arms and consistent with the ITT population[5]; median age was 62 years, 71.8% were male, and 81.8% had stage IV disease
- Median study follow-up was 16.5 months (data cutoff: October 26, 2020) and 23.4 months (updated OS analysis; data cutoff: April 26, 2023)
- Subsequent systemic therapy was received by 36.5% (27/74) of patients in the tislelizumab plus chemotherapy arm vs 66.7% (24/36) in the chemotherapy alone arm, with 8.1% (6/74) and 41.7% (15/36) receiving subsequent immunotherapy, respectively; 36.1% (13/36) patients from the chemotherapy alone arm crossed over to tislelizumab
- Treatment discontinuation occurred in 60.8% (45/74) of patients in the tislelizumab plus chemotherapy arm and 97.2% (35/36) in the chemotherapy alone arm

Efficacy

- At the final analysis, tislelizumab plus chemotherapy improved PFS_{IRC} vs chemotherapy alone (median PFS_{IRC} 14.6 vs 4.6 months; stratified HR=0.31; 95% CI: 0.18, 0.55) in the PD-L1 ≥50% population (**Figure 1A**)
  - PFS_{IRC} benefit for tislelizumab plus chemotherapy was consistent across various patient subgroups (**Figure 1B**)
- Tislelizumab plus chemotherapy showed higher confirmed ORR_{IRC} (70.3% vs 30.6%), greater complete response (CR) rate (9.5% vs 0%), and longer DoR (not estimable [NE] vs 8.5 months) vs chemotherapy alone (**Table 1**)
- OS was improved with tislelizumab plus chemotherapy vs chemotherapy alone (**Table 1**):
  - Final analysis: median OS was NE vs 13.1 months (HR=0.39; 95% CI: 0.22, 0.71)
  - Updated analysis (with an additional 6.9 months of median follow-up): median OS was 41.9 vs 13.1 months (HR=0.38; 95% CI: 0.24, 0.63) (**Figure 2A**)
  - OS results from subgroup analyses were variable due to limited sample sizes (**Figure 2B**)
- Patients with long-term tislelizumab treatment (≥35 cycles, n=22) demonstrated 100% ORR_{IRC} (36.4% CR), median DoR NE (95% CI: 29.6 months, NE), and 4-year OS rate of 90.5% (95% CI: 67.0, 97.5); 63.6% remained progression-free without subsequent therapy

Table 1. Secondary Efficacy Endpoints (PD-L1 ≥50% Population)

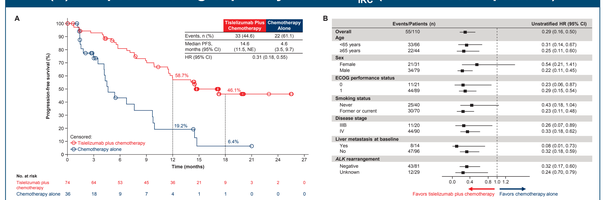
	Tislelizumab Plus Chemotherapy (n=74)	Chemotherapy Alone (n=36)	HR (95% CI)
ORR_{IRC}[1] % (95% CI)[a]	70.3 (58.5, 80.3)	30.6 (16.3, 48.1)	-
ORR difference, % (95% CI)[b]	39.5 (21.2, 57.9)		-
Median DoR, months (95% CI)[c]	NE (13.2, NE)	8.5 (3.3, NE)	0.32 (0.13, 0.82)
Median OS (final analysis), months (95% CI)[c]	NE (NE, NE)	13.1 (5.6, NE)	0.39 (0.22, 0.71)[d]
Median OS (updated analysis), months (95% CI)[c,e]	41.9 (24.1, NE)	13.1 (5.6, 19.4)	0.38 (0.24, 0.63)

Data cutoff: October 26, 2020. The chemotherapy alone arm was the reference group.

[a] 95% CI for ORR was calculated using the Clopper–Pearson method. [b] ORR difference was calculated using the Cochran–Mantel–Haenszel chi-square test with actual stratification factors as strata. [c] Medians were estimated by Kaplan–Meier methodology, with 95% CIs estimated using the method of Brookmeyer and Crowley. [d] HR and 95% CI were calculated using a Cox proportional-hazards model stratified by stage IIIB vs IV disease. [e] Updated OS analysis data cutoff: April 26, 2023.

Abbreviations: CI, confidence interval; DoR, duration of response; HR, hazard ratio; NE, not evaluable; ORR_{IRC}, objective response rate by independent review committee; OS, overall survival; PD-L1, programmed death-ligand 1.

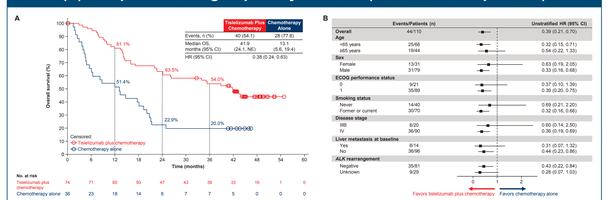
Figure 1. (A) Kaplan–Meier Curves of PFS_{IRC} and (B) Prespecified Subgroup Analysis of PFS_{IRC} (PD-L1 ≥50% Population)



Data cutoff: October 26, 2020. (A) HRs and associated 95% CIs were calculated using a Cox proportional-hazards model stratified by stage IIIB vs IV disease. (B) HRs and associated 95% CIs were calculated using an unstratified Cox proportional-hazards model.

Abbreviations: ALK, anaplastic lymphoma kinase; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IRC, independent review committee; NE, not estimable; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

Figure 2. (A) Kaplan–Meier Curves of OS and (B) Prespecified Subgroup Analysis of OS (PD-L1 ≥50% Population)



(A) Data cutoff: April 26, 2023. HRs and associated 95% CIs were estimated from an unstratified Cox proportional-hazards model with the chemotherapy alone arm as a reference group. Event-free rates were estimated by Kaplan–Meier method with 95% CIs estimated using the Greenwood's formula. (B) Data cutoff: October 26, 2020. HRs and associated 95% CIs were calculated using an unstratified Cox proportional-hazards model.

Abbreviations: ALK, anaplastic lymphoma kinase; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; NE, not estimable; OS, overall survival; PD-L1, programmed death-ligand 1.

Safety

- The incidences of grade ≥3 treatment-emergent adverse events (TEAEs) (75.7% vs 48.6%) and serious TEAEs (43.2% vs 28.6%) were higher in the tislelizumab plus chemotherapy arm compared with the chemotherapy alone arm (**Table 2**)
- The most frequently reported grade ≥3 TEAEs in both arms were neutropenia, thrombocytopenia, leukopenia, and anemia
- Immune-mediated adverse events (imAEs) of all grades were reported in 39.2% of patients in the tislelizumab plus chemotherapy arm vs 5.7% in the chemotherapy alone arm (**Table 2**)
- The most frequently reported grade ≥3 imAEs in the tislelizumab plus chemotherapy arm were pneumonitis, endocrinopathies (diabetes mellitus), and myocarditis/pericarditis

Table 2. Summary of TEAEs (PD-L1 ≥50% Population; Safety Analysis Set)

	Tislelizumab Plus Chemotherapy (n=74)	Chemotherapy Alone (n=35)
Patients with ≥1 TEAE, n (%)	74 (100.0)	35 (100.0)
Grade ≥3	56 (75.7)	17 (48.6)
Serious	32 (43.2)	10 (28.6)
Leading to death	3 (4.1)	1 (2.9)
Patients with ≥1 TEAE leading to discontinuation, n (%)	21 (28.4)	2 (5.7)
Patients with ≥1 TEAE leading to treatment modification,[a,b] n (%)	61 (82.4)	20 (57.1)
Patients with ≥1 imAE, n (%)	29 (39.2)	2 (5.7)
Grade ≥3	7 (9.5)	1 (2.9)

Data cutoff: October 26, 2020. The safety analysis set includes all enrolled patients who received ≥1 dose of study drug. Adverse event grades were evaluated based on National Cancer Institute – Common Terminology Criteria for Adverse Events (version 5.0).

[a] Treatment modification of tislelizumab included dose delay, infusion interruption, and infusion rate decrease. [b] Treatment modification of chemotherapy included dose reduction, infusion interruption, dose delay, and infusion rate decrease.

Abbreviations: imAE, immune-mediated adverse event; PD-L1, programmed death-ligand 1; TEAE, treatment-emergent adverse event.

References

1. Sung H, et al. *CA Cancer J Clin*. 2021;71:209-249.
2. Dietel M, et al. *Lung Cancer*. 2019;134:174-179.
3. Skov BG, et al. *Mod Pathol*. 2020;33:109-117.
4. Tang Q, et al. *Front Immunol*. 2022;13:964442.
5. Lu S, et al. *ESMO Open*. 2024;9:103728.
6. Lu S, et al. *J Thorac Oncol*. 2021;16:1512-1522.

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Disclosures

Yan Yu reports no conflicts of interest.

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