Randomized Phase 3 Study of Tislelizumab Plus Chemotherapy Versus Chemotherapy Alone as First-Line Treatment for Advanced Squamous Non-Small Cell Lung Cancer: RATIONALE-307 Updated Analysis

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Conclusions

In this updated analysis of the RATIONALE-307 trial, addition of tislelizumab to platinum-based chemotherapy as first-line treatment for advanced squamous NSCLC continued to demonstrate a clinically meaningful PFS benefit, higher ORR, and longer DoR versus platinum-based chemotherapy alone, and had a manageable safety profile, with no new safety signals identified.

Background

Tislelizumab, a monoclonal antibody with high affinity and binding specificity for programmed cell death protein 1, was specifically engineered to minimize Fcγ receptor binding on macrophages.[1,2]

In patients with advanced squamous (sq) non-small cell lung cancer (NSCLC), interim results from the phase 3 RATIONALE-307 trial (NCT03594747) demonstrated significantly prolonged progression-free survival (PFS) and improved tumor response rates with first-line tislelizumab plus platinum-based chemotherapy versus platinum-based chemotherapy alone.[3]

Here, we report updated results from the final analysis (FA) of RATIONALE-307, including longer follow-up. In addition, the effect of subsequent treatment after disease progression on overall survival (OS) results is explored.

Methods

- Adults with treatment-naïve, stage IIIB (not amenable to curative surgery/ radiotherapy) or stage IV sq-NSCLC were enrolled[3]
- Patients were randomized (1:1:1) to open-label
  - **Arm A**: Tislelizumab 200 mg intravenously (IV) every 3 weeks (Q3W) plus 4-6 cycles of paclitaxel and carboplatin;
  - **Arm B**: Tislelizumab 200 mg IV Q3W plus 4-6 cycles of *nab*-paclitaxel and carboplatin; or
  - **Arm C**: 4-6 cycles of paclitaxel and carboplatin[3]
- **Primary endpoint:** Independent review committee (IRC)-assessed PFS in the intent-to-treat (ITT) analysis set
  - As the primary endpoint was met and statistical significance achieved at the interim analysis,[3] no formal statistical testing was conducted at the FA
- **Secondary endpoints included:** OS, IRC-assessed objective response rate (ORR) and duration of response (DoR), and safety[3]
- Scan QR code for full methodology from the previously published interim analysis

Results

Patient Disposition and Baseline Characteristics

- Between July 30, 2018, and September 30, 2020, 360 patients were randomized to Arm A (n=120), Arm B (n=119), or Arm C (n=121)[3]
- Demographics and baseline characteristics were well balanced between arms[3]
  - Overall, median age was 62 years, most patients were male (91.7%), and most had stage IV disease at baseline (66.1%)
  - Tumor cell programmed death-ligand 1 (PD-L1) membrane expression was unevaluable in 1.7% of patients, <1% in 38.3%, 1-49% in 25.3%, and ≥50% in 34.7%
- At the FA cutoff (September 30, 2020)
  - Median study follow-up was 18.7 months (95% confidence interval [CI]: 18.0, 20.0); 10.1 additional months compared with the interim analysis[3]
  - Overall, 25.8% of patients in Arm A and 28.6% in Arm B remained on their assigned treatment; patients in Arm C had finished study treatment after 4-6 cycles

Efficacy

PFS

- The study met its primary objective of prolonging PFS per IRC in Arms A and B versus Arm C at the interim analysis.[3] The improvement in median PFS in Arms A and B versus Arm C remained consistent at the FA cutoff (**Figure 1**)
- PFS benefits in Arms A and B versus Arm C, respectively, were largely consistent and significant across PD-L1 expression subgroups (**Table 1**)

ORR

- ORR (95% CI) was higher in Arms A (74.2% [65.4, 81.7]) and B (73.9% [65.1, 81.6]) than Arm C (47.9% [38.8, 57.2]); complete response rates were 5.8%, 6.7%, and 0.8%, respectively, accompanied by longer median DoR (95% CI): 8.4 months (5.0, 15.8), 8.6 months (7.1, 12.5), and 4.3 months (2.9, 5.4), respectively
- ORR benefit was also seen in Arms A and B versus Arm C across all PD-L1 expression subgroups (**Table 1**)

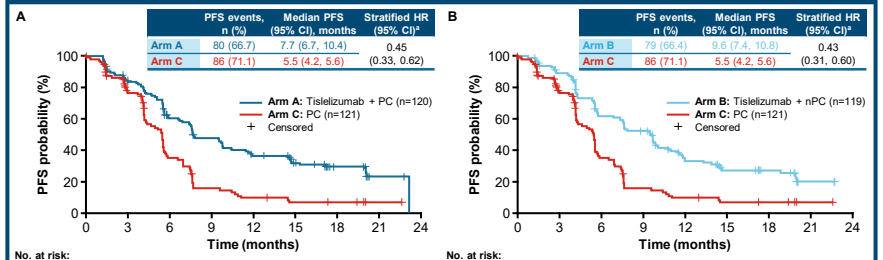
OS

- OS hazard ratios (HRs) for Arms A and B versus Arm C at the latest OS data cutoff (July 15, 2022 [ad-hoc analysis]) are displayed in **Table 2**. RATIONALE-307 was designed to demonstrate PFS superiority and met its primary objective; the study was not designed with a sufficient power and sample size to test for OS. OS assessment can be confounded by voluntary withdrawal and loss to follow-up, and effective subsequent lines of therapy, including in-trial crossover[4]
- As of the July 15, 2022, cutoff, a high proportion of patients in Arm C received subsequent immunotherapy (63.6% [77/121]), of whom 92.2% (71/77) crossed over to tislelizumab. In contrast, fewer patients in Arm A (15.0% [18/120]) and Arm B (10.9% [13/119]) received subsequent treatment with immunotherapy
- Among patients from Arm C who crossed over to tislelizumab, median time from last dose of chemotherapy to subsequent tislelizumab was 10.3 weeks (minimum time to crossover, 0.1 weeks)
- A supportive analysis was conducted to adjust for the potential impact of in-study crossover using a two-stage model[5] (**Table 2**). The reductions in HRs seen with the supportive analysis suggest the OS benefit for tislelizumab in combination with chemotherapy versus chemotherapy alone may have been partially obscured by in-study crossover

Safety

- Tislelizumab plus chemotherapy (Arms A and B) was tolerable; no new safety signals were identified at the FA compared with the interim analysis[3,6]

Figure 1. IRC-Assessed PFS for Arms A and C (A) and Arms B and C (B) (ITT Analysis Set)



Data cutoff: September 30, 2020. ITT analysis set included all randomized patients. Median PFS estimated using Kaplan-Meier methodology with 95% CIs constructed using the Brookmeyer and Crowley method. [a]HRs and 95% CIs estimated using a stratified Cox proportional hazard model with Efron's method of tie handling, with the treatment arm as covariate, and disease stage and PD-L1 tumor cell expression as stratification factors. **Abbreviations:** CI, confidence interval; HR, hazard ratio; IRC, independent review committee; ITT, intent-to-treat; nPC, *nab*-paclitaxel and carboplatin; PC, paclitaxel and carboplatin; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

Table 1. IRC-Assessed Efficacy Outcomes by PD-L1 Expression Subgroup

	Arm A	Arm B	Arm C	HR (95% CI) Arm A vs C	HR (95% CI) Arm B vs C
Median PFS, months (95% CI)					
PD-L1 <1%	7.6 (5.6, 14.7)	7.6 (5.6, 9.9)	5.5 (4.2, 7.0)	0.55 (0.34, 0.91)	0.66 (0.41, 1.07)
PD-L1 1-49%	10.4 (5.5, 20.0)	10.1 (7.4, 12.0)	5.0 (2.8, 6.5)	0.40 (0.21, 0.76)	0.40 (0.22, 0.74)
PD-L1 ≥50%	7.7 (6.0, 9.8)	9.7 (5.6, NE)	5.5 (4.1, 7.0)	0.44 (0.26, 0.75)	0.33 (0.18, 0.59)
ORR (95% CI)					
PD-L1 <1%	70.8% (55.9, 83.0)	68.1% (52.9, 80.9)	49.0 (34.4, 63.7)	-	-
PD-L1 1-49%	70.0% (50.6, 85.3)	66.7% (47.2, 82.7)	38.7% (21.8, 57.8)	-	-
PD-L1 ≥50%	81.0% (65.9, 91.4)	85.7 (71.5, 94.6)	53.7 (37.4, 69.3)	-	-

Data cutoff: September 30, 2020. Arm A: Tislelizumab plus PC; Arm B: Tislelizumab plus nPC; Arm C: PC alone. ITT analysis set, including all randomized patients.
Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; NE, not estimable; nPC, *nab*-paclitaxel and carboplatin; ORR, overall response rate; PC, paclitaxel and carboplatin; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

Table 2. OS Analyses (ITT Analysis Set)

	Median OS, months (95% CI)			HR (95% CI) Arm A vs C	HR (95% CI) Arm B vs C
	Arm A	Arm B	Arm C		
ITT analysis[a]	26.1 (19.0, 33.8)	23.3 (18.8, 26.4)	19.4 (16.0, 23.4)	0.69 (0.50, 0.95)	0.84 (0.61, 1.14)
Two-stage model[b]	26.1 (19.0, 33.8)	23.3 (18.8, 26.4)	14.0 (11.7, 17.5)	0.53 (0.38, 0.75)	0.60 (0.43, 0.83)

Data cut-off: July 15, 2022 (ad-hoc analysis). Arm A: Tislelizumab plus PC; Arm B: Tislelizumab plus nPC; Arm C: PC alone. ITT analysis set included all randomized patients. [a]Median (95% CI) follow-up: Arm A, 39.8 (39.1, 41.4) months; Arm B, 40.5 (39.0, 42.6) months; Arm C, 39.5 (38.8, 42.0) months. [b]Median (95% CI) follow-up: Arm A, 39.8 (39.1, 41.4) months; Arm B, 40.5 (39.0, 42.6) months; Arm C, 24.3 (23.2, 25.8) months. **Abbreviations:** CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; nPC, *nab*-paclitaxel and carboplatin; OS, overall survival; PC, paclitaxel and carboplatin.

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Disclosures

Dr **Jie Wang** declares no potential conflict of interest.

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