Randomized Phase 3 Study of Tislelizumab Plus Chemotherapy Versus Chemotherapy Alone as First-Line Treatment for Advanced Nonsquamous Non-Small Cell Lung Cancer: RATIONALE-304 Updated Analysis

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Conclusions

In this updated analysis of RATIONALE-304, tislelizumab plus platinum-based chemotherapy as first-line treatment for advanced non-squamous NSCLC continued to demonstrate a clinically meaningful PFS benefit, higher ORR, and longer DoR versus platinum-based chemotherapy alone, and was generally well tolerated, 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 nonsquamous (nsq) non-small cell lung cancer (NSCLC), interim results from the open-label, multicenter, randomized, phase 3 RATIONALE-304 trial (NCT03663205) demonstrated significantly prolonged progression-free survival (PFS) and an improved tumor response rate 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-304

Methods

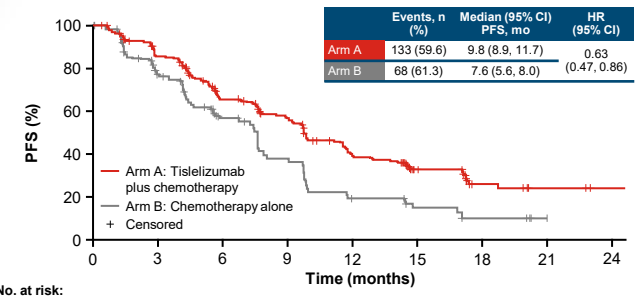
- Patients aged 18-75 years with treatment-naive, stage IIIB (not amenable to curative surgery/radiotherapy) or stage IV nsq-NSCLC were enrolled[3]
- Patients were randomized (2:1) to open-label
  - **Arm A**: Tislelizumab 200 mg intravenously every 3 weeks plus platinum-based chemotherapy for 4-6 cycles, followed by maintenance tislelizumab plus pemetrexed; or
  - **Arm B**: Platinum-based chemotherapy alone for 4-6 cycles, followed by maintenance pemetrexed[3]
- **Primary endpoint:** PFS, assessed by independent review committee (IRC) 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:** overall survival (OS), IRC-assessed objective response rate (ORR; by Response Evaluation Criteria in Solid Tumors version 1.1) and duration of response (DoR), and safety[3]
- Scan the QR code for full methodology from the previously published interim analysis

Results

Patient Disposition and Baseline Characteristics

- Between July 23, 2018, and July 31, 2019, 334 patients were randomized to Arm A (n=223) or Arm B (n=111)[3]
- Demographics and baseline characteristics were well balanced between arms[3]
  - Overall, median age was 61 years, most patients were male (74.0%), and most had stage IV disease at baseline (81.7%)
  - Tumor cell programmed death-ligand 1 (PD-L1) membrane expression was <1% or unevaluable in 43.1% of patients, 1-49% in 24.0%, and ≥50% in 32.9%

Figure 1. IRC-Assessed PFS (ITT Analysis Set)



Data cutoff: October 26, 2020. ITT analysis set included all randomized patients. Arm A: Tislelizumab plus platinum-based chemotherapy and pemetrexed; Arm B: Platinum-based chemotherapy and pemetrexed. Median PFS estimated using Kaplan-Meier methodology with 95% CIs constructed using the Brookmeyer and Crowley method. HR 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; mo, months; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

- At the FA cutoff date (October 26, 2020)
  - Median study follow-up was 16.1 months (range: 0.0-27.2); 6.3 additional months compared with the interim analysis[3]
  - More patients remained on assigned treatment in Arm A (24.2%) than Arm B (5.4%)

Efficacy

PFS

- The study met its primary objective of prolonging IRC-assessed PFS in the tislelizumab plus chemotherapy arm (Arm A) versus chemotherapy alone (Arm B) at the interim analysis[3]
- The PFS improvement in Arm A versus Arm B remained consistent at the FA cutoff date (October 26, 2020); PFS hazard ratio (HR) 0.63 (95% confidence interval [CI]: 0.47, 0.86) (**Figure 1**)
- PFS benefit was observed in all PD-L1 expression subgroups (**Table 1**)

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

	Arm A	Arm B	HR (95% CI) Arm A vs B
Median PFS, months (95% CI)			
PD-L1 <1%	7.6 (5.4, 9.7)	7.6 (4.3, 7.9)	0.81 (0.52, 1.25)
PD-L1 1-49%	9.7 (6.9, 11.7)	9.7 (5.6, 16.8)	0.90 (0.49, 1.63)
PD-L1 ≥50%	14.6 (11.5, NE)	4.6 (3.5, 9.7)	0.29 (0.16, 0.50)
ORR (95% CI)			
PD-L1 <1%	43.8% (33.6, 54.3)	27.1% (15.3, 41.8)	-
PD-L1 1-49%	62.3% (47.9, 75.2)	44.4% (25.5, 64.7)	-
PD-L1 ≥50%	73.0% (61.4, 82.6)	41.7% (25.5, 59.2)	-

Data cutoff: October 26, 2020. Arm A: Tislelizumab plus platinum-based chemotherapy and pemetrexed; Arm B: Platinum-based chemotherapy and pemetrexed. ITT analysis set, including all randomized patients. **Abbreviations:** CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; NE, not estimable; ORR, overall response rate; 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 B
	Arm A	Arm B	
ITT analysis[a]	21.6 (17.9, 26.0)	20.1 (14.9, 28.1)	0.85 (0.63, 1.14)
Two-stage model[4,b]	21.6 (17.9, 26.0)	14.9 (13.3, 21.1)	0.68 (0.50, 0.92)

Data cutoff: July 15, 2022 (ad-hoc analysis). Arm A: Tislelizumab plus platinum-based chemotherapy and pemetrexed; Arm B: Platinum-based chemotherapy and pemetrexed. ITT analysis set included all randomized patients. [a]Median (95% CI) follow-up: Arm A, 38.8 (38.1, 40.1) months; Arm B, 38.6 (36.0, 40.6) months. [b]Median (95% CI) follow-up: Arm A, 38.8 (38.1, 40.1) months; Arm B, 20.0 (14.2, 36.0) months. **Abbreviations:** CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival.

ORR

- ORR was higher in Arm A (57.8%; 95% CI: 51.1, 64.4) versus Arm B (36.0%; 95% CI: 27.1, 45.7); complete response rates were 4.9% versus 1.8%, respectively, accompanied by longer median DoR (10.6 months [95% CI: 8.4, 15.8] versus 6.9 months [95% CI: 5.0, 10.6], respectively)
- The ORR benefit in Arm A was consistently seen across all PD-L1 expression subgroups (**Table 1**)

OS

- OS HRs for Arm A versus Arm B at the latest OS data cutoff (July 15, 2022 [ad-hoc analysis]) are displayed in **Table 2**
- RATIONALE-304 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[5]
- As of the July 15, 2022, cutoff, subsequent immunotherapy after disease progression was received by 52.3% (58/111) of patients in Arm B (72.4% of whom [42/58] crossed over to tislelizumab) and by 10.8% (24/223) of patients in Arm A
- Of the patients from Arm B who crossed over to tislelizumab:
  - 26/42 (61.9%) crossed over within one cycle
  - Median time from last dose of chemotherapy to subsequent tislelizumab was 2.6 weeks (minimum time to crossover, 0.1 weeks)
- The reduction in HR in the two-stage supportive analysis[4] suggests the OS benefit for tislelizumab in combination with chemotherapy may have been partially obscured by in-study crossover

Safety

- The tislelizumab plus chemotherapy combination (Arm A) was tolerable; no new safety signals were identified at the FA compared with the interim analysis[3]

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Disclosures

Dr **Shun Lu** declares the following conflicts of interest: AstraZeneca, BeiGene, BMS, GenomiCare, Hansoh, Heng Rui, Hutchison MediPharma, Menarini, Mirati Therapeutics Inc., Novartis, Pfizer, Roche, Yuhan Corporation, and ZaiLab.

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