Tislelizumab versus docetaxel in previously treated advanced non-small cell lung cancer (NSCLC): Final analysis of RATIONALE-303

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Conclusions

Tislelizumab continued to improve OS vs docetaxel in patients with pretreated advanced NSCLC at final analysis.

Exploratory biomarker analysis showed a potential association of *NOTCH1-4* mutations with greater tislelizumab efficacy for both OS and PFS.

In the final analysis, no new safety signals were identified in the tislelizumab arm after 11 months of additional follow-up.

Tislelizumab treatment maintained a favorable safety profile compared with docetaxel, with fewer ≥grade 3 TEAEs.

Background

Anti-programmed cell death protein 1/death-ligand 1 (PD-[L]1) therapies have improved overall survival (OS) by 3-4 months vs docetaxel in patients with advanced NSCLC who progressed after platinum-based chemotherapy.[1-4]

Tislelizumab is a monoclonal antibody with high binding affinity to the PD-1 receptor, which was specifically engineered to minimize Fcγ receptor binding on macrophages.[5,6]

In RATIONALE-303, tislelizumab significantly prolonged OS vs docetaxel in the intent-to-treat (ITT) population at the interim analysis (IA) (data cutoff: August 10, 2020),[7] leading to its approval in China for patients with advanced NSCLC whose disease progressed after chemotherapy.[8]

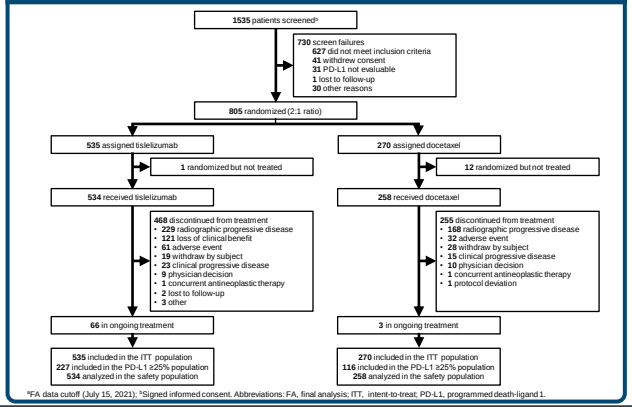
Here, we report the outcomes of the final analysis and post hoc exploratory biomarker analysis.

(Clinicaltrials.gov: NCT03358875)

Methods

- Patients ≥18 years with histologically confirmed, locally advanced or metastatic squamous or nonsquamous NSCLC were randomized (2:1) to tislelizumab 200 mg intravenously (IV) or docetaxel 75 mg/m^2 IV every 3 weeks
- Co-primary endpoints were OS in the ITT and PD-L1 tumor cell (TC) ≥25% populations. The study had one planned IA only in the ITT population. The final analysis (FA) for efficacy was conducted in the ITT population and PD-L1 ≥25% population
- Exploratory biomarker analyses included PD-L1 expression, tumor mutational burden (TMB), and gene expression profile

Figure 1. CONSORT diagram (final analysis)[a]

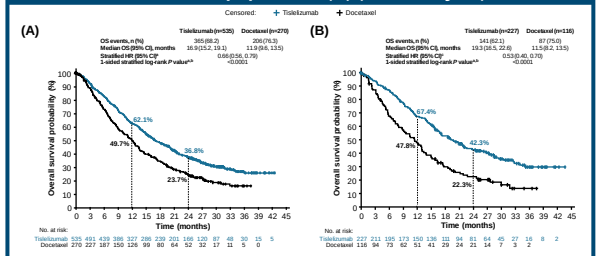


[a]FA data cutoff (July 15, 2021); [b]Signed informed consent. Abbreviations: FA, final analysis; ITT, intent-to-treat; PD-L1, programmed death-ligand 1.

Results

- Between November 2017 and April 2020, 805 patients were randomized to tislelizumab (n=535) or docetaxel (n=270) (**Figure 1**)
- At FA data cutoff (July 15, 2021), median follow-up times were 16.0 months for tislelizumab and 10.7 months for docetaxel in the ITT population
- Baseline demographics and disease characteristics were representative of the target population and were well balanced between both arms, including PD-L1 expression and histology[7]
- The co-primary endpoint of OS in the ITT population was met at the IA. **Figure 2A** is a descriptive update of this endpoint; the OS data at FA are consistent with the OS IA data[7]
- The other co-primary endpoint of OS in the PD-L1 TC ≥25% population was met at the FA (**Figure 2B**)

Figure 2. OS in the ITT population (A), and PD-L1 ≥25% population (B) (final analysis)



Data cutoff: July 15, 2021. [a]Stratified by histology (squamous vs nonsquamous), line of therapy (second vs third), and TC PD-L1 expression (<25% vs ≥25%); [b]P value is descriptive; [c]Stratified by histology (squamous vs nonsquamous) and line of therapy (second vs third). Abbreviations: HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; PD-L1, programmed death-ligand 1; TC, tumor cell.

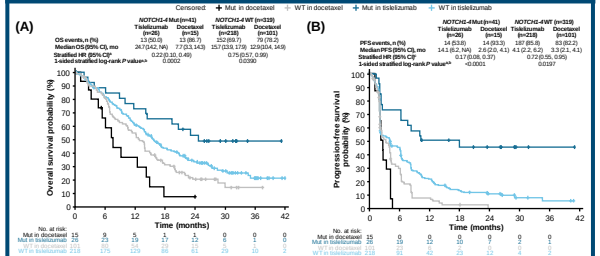
- Results for key secondary endpoints are shown in **Table 1**

Table 1. Secondary efficacy endpoints (final analysis)

	ITT population[a]		PD-L1 TC ≥25% population[b]	
	Tislelizumab (n=535)	Docetaxel (n=270)	Tislelizumab (n=227)	Docetaxel (n=116)
Median PFS (95% CI), mo[c]	4.2 (3.9, 5.5)	2.6 (2.2, 3.8)	6.5 (6.2, 8.3)	2.4 (2.1, 4.1)
Stratified HR (95% CI)	0.63 (0.53, 0.75)		0.37 (0.28, 0.49)	
ORR, n (%)[c]	121 (22.6)	19 (7.0)	85 (37.4)	8 (6.9)
Median DoR, (95% CI), mo[c]	13.5 (8.5, 19.6)	6.0 (2.1, 7.2)	11.9 (8.3, 19.6)	4.2 (0.6, 6.1)

Data cutoff: July 15, 2021. [a]Stratified by histology (squamous vs nonsquamous), line of therapy (second vs third), and TC PD-L1 expression (<25% vs ≥25%); [b]Stratified by histology (squamous vs nonsquamous) and line of therapy (second vs third); [c]Investigator assessed. Abbreviations: CI, confidence interval; DoR, duration of response; HR, hazard ratio; ITT, intent-to-treat; mo, months; ORR, objective response rate; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TC, tumor cell.

Figure 3. OS (A) and PFS (B) in the BEP according to *NOTCH1-4* mutation status (final analysis)



Data cutoff: July 15, 2021. [a]Stratified by histology (squamous vs nonsquamous), line of therapy (second vs third), and TC PD-L1 expression (<25% vs ≥25%); [b]P value is descriptive; [c]Stratified by histology (squamous vs nonsquamous) and line of therapy (second vs third). Abbreviations: BEP, biomarker-evaluable population; HR, hazard ratio; ITT, intent-to-treat; mo, months; Mut, mutation; NA, not applicable; OS, overall survival; PFS, progression-free survival; WT, wild type.

Biomarker analysis

- In this post hoc biomarker analysis, *NOTCH1-4* mutations showed a potential association with better tislelizumab efficacy, which was correlated with both OS and PFS benefit (**Figure 3**)
- Tissue TMB was correlated with PFS benefit for tislelizumab vs docetaxel but was not correlated with OS benefit, except at the highest cutoff (≥14 mutations/megabase) (data not shown)

Safety

- No new safety signals were identified (**Table 2**). Fewer ≥grade 3 TEAEs were reported in the tislelizumab arm than in the docetaxel arm (42.1% vs 74.8%, respectively)

Table 2. TEAEs occurring in ≥15% of patients[a] (safety population[b])

	Tislelizumab (n=534)		Docetaxel (n=258)	
n (%)	**Any grade**	**≥Grade 3**	**Any grade**	**≥Grade 3**
Patients with at least one TEAE				
Any TEAE	517 (96.8)	225 (42.1)	254 (98.4)	193 (74.8)
ALT increased	110 (20.6)	5 (0.9)	39 (15.1)	0 (0)
AST increased	104 (19.5)	5 (0.9)	32 (12.4)	1 (0.4)
Weight decreased	86 (16.1)	4 (0.7)	30 (11.6)	0 (0.0)
Cough	114 (21.3)	5 (0.9)	40 (15.5)	1 (0.4)
Anemia	156 (29.2)	18 (3.4)	115 (44.6)	18 (7.0)
Decreased appetite	88 (16.5)	5 (0.9)	62 (24.0)	3 (1.2)

Data cutoff: July 15, 2021. [a]In the tislelizumab arm; [b]Safety population included all patients receiving at least one dose of study drug. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

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Poster recording