Tislelizumab versus Docetaxel in Previously Treated Advanced Non-Small Cell Lung Cancer: Final Analysis of RATIONALE-303

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Abstract:

Introduction: In RATIONALE-303 (NCT03358875) tislelizumab significantly improved OS vs docetaxel in the ITT population at the interim analysis (IA), based upon which, tislelizumab was approved in China for treatment of advanced NSCLC patients with progressive disease after chemotherapy. Here, we report outcomes of the final analysis (FA) and *post hoc* biomarker analysis.

Methods: Patients ≥18 years with histologically confirmed, locally advanced or metastatic squamous or non-squamous NSCLC were randomized (2:1) to IV tislelizumab 200 mg or IV docetaxel 75 mg/m^2 every 3 weeks. Co-primary endpoints were OS in the ITT and PD-L1 TC ≥25% populations. The study had one planned IA only in the ITT population. The FA was conducted in the PD-L1 TC ≥25% population with secondary endpoints (PFS_{INV}, ORR_{INV}, DoR_{INV}) tested sequentially once superiority of OS in PD-L1 TC ≥25% population was demonstrated in the FA. Exploratory biomarker analyses included PD-L1 expression, tumor mutation burden (TMB), and gene expression profile.

Results: Between November 30, 2017 and April 8, 2020, 805 patients were randomized to tislelizumab (N=535) or docetaxel (N=270). The co-primary endpoint of OS (ITT) was met at IA (data cut-off August 10, 2020). At data cut-off (July 15, 2021), FA was conducted in the PD-L1 TC ≥25% population. Median follow-up times (reverse Kaplan-Meier

method) were 30.9 months for tislelizumab and 27.5 months for docetaxel. In ITT population, tislelizumab continued to improve OS vs docetaxel (median OS 16.9 months vs 11.9 months, respectively; HR=0.66). In PD-L1 TC ≥25% population, tislelizumab showed a statistically significant OS benefit vs docetaxel (median OS 19.3 months vs 11.5 months; HR=0.53; p<0.0001). A consistent OS benefit was observed for almost all pre-defined subgroups. The study also met secondary endpoints at this FA. In the *post hoc* biomarker analysis, the association of TMB and genetic alterations including single target gene mutation or pathway mutations with clinical outcomes was further explored. Compared with TMB which was correlated with PFS benefit for tislelizumab vs docetaxel but was not correlated to OS benefit, except at the highest cutoff (≥14 mut/Mb), *NOTCH1–4* mutations showed association with better tislelizumab efficacy, which was correlated with both PFS and OS benefit (**Table**). No new safety signals were identified.

Conclusion: Tislelizumab continued to improve OS vs docetaxel in pretreated advanced NSCLC regardless of PD-L1 expression at final analysis. Biomarker analysis implied the potential association of *NOTCH1–4* mutations with greater tislelizumab efficacy for both OS and PFS.

Table

	ITT population		**PD-L1 TC ≥25% population**		***NOTCH1–4* mut population**		***NOTCH1–4* WT population**	
	TIS (N=535)	**D (N=270)**	**TIS (N=227)**	**D (N=116)**	**TIS (N=26)**	**D (N=15)**	**TIS (N=218)**	**D (N=101)**
OS events, n (%) [IA]	365 (68.2) [275 (51.4)]	206 (76.3) [166 (61.5)]	141 (62.1)	87 (75.0)	13 (50.0)	13 (86.7)	152 (69.7)	79 (78.2)
Median OS (95% CI), mos [IA]	16.9 (15.2, 19.1) [17.2 (15.3, 20.0)]	11.9 (9.6, 13.5) [11.9 (10.2, 13.9)]	19.3 (16.5, 22.6)	11.5 (8.2, 13.5)	24.7 (14.2, NE)	7.7 (3.3, 14.3)	15.7 (13.9, 17.9)	12.9 (10.4, 14.9)
Stratified HR[‡] (95% CI) [IA]	0.66 (0.56, 0.79) p<0.0001*[†] [0.64 (0.53, 0.78) p<0.0001*]		0.53 (0.40, 0.70) p<0.0001*		0.22 (0.10, 0.49) p=0.0002*[†]		0.75 (0.57, 0.99) p=0.0390*[†]	

PFS_{INV} events, n (%)	451 (84.3)	208 (77.0)	177 (78.0)	94 (81.0)	14 (53.8)	14 (93.3)	187 (85.8)	83 (82.2)
Median PFS_{INV} (95% CI), mos	4.2 (3.9, 5.5)	2.6 (2.2, 3.8)	6.5 (6.2, 8.3)	2.4 (2.1, 4.1)	14.1 (6.2, NE)	2.6 (2.0, 4.1)	4.1 (2.2, 6.2)	3.3 (2.1, 4.1)
Stratified HR‡ (95% CI)	0.63 (0.53, 0.75)		0.37 (0.28, 0.49)		0.17 (0.08, 0.37)		0.72 (0.55, 0.95)	
ORR_{INV}, n (%)	121 (22.6)	19 (7.0)	85 (37.4)	8 (6.9)	-	-	-	-
Median DoR_{INV}, (95% CI), mos	13.5 (8.5, 19.6)	6.0 (2.1, 7.2)	11.9 (8.3, 19.6)	4.2 (0.6, 6.1)	-	-	-	-

IA data cut-off: August 10, 2020

FA data cut-off: July 15, 2021

**1-sided stratified log-rank test*

†Descriptive p value

‡Stratified by histology (squamous vs non-squamous) and lines of therapy (second vs third)

Abbreviations: CI, confidence intervals; D, docetaxel; DoR_{INV}, investigator-assessed duration of response; FA, final analysis; HR, hazard ratio; IA, interim analysis; ITT, intent-to-treat; IV, intravenous; mos, months; mut, mutation; NE, not estimable; NSCLC, non-small cell lung cancer; ORR_{INV}, investigator-assessed objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS_{INV}, investigator-assessed progression-free survival; TC, tumor cell; TIS, tislelizumab; vs, versus; WT, wild type