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Tislelizumab versus Docetaxel in Patients with Previously Treated Advanced Squamous Non-Small Cell Lung Cancer: Sub-Analysis from Phase 3 RATIONALE-303 Randomized Clinical Study

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Conclusions

- In this RATIONALE-303 trial subanalysis among patients with squamous locally advanced or metastatic NSCLC previously treated with platinum-based chemotherapy:
  - Tislelizumab **prolonged OS** vs docetaxel in patients with squamous NSCLC
  - Tislelizumab **improved PFS** and **ORR**, and **prolonged DoR** vs docetaxel in patients with squamous NSCLC
  - **Tislelizumab had a generally tolerable and manageable safety profile**, in line with the profile of other PD-1/L1 inhibitors, with a lower incidence of ≥ Grade 3 TEAEs vs docetaxel
- Results were generally **consistent with those in the overall ITT population**[1]

Background

- Tislelizumab is a humanized anti-programmed cell death protein 1 (PD-1) immunoglobin G4 variant monoclonal antibody with high affinity to PD-1, and was engineered to eliminate the binding function to Fc gamma receptors, in order to minimize antibody-dependent cellular phagocytosis, and complement-dependent cytotoxicity to T cells[2-4]
- The multicenter, randomized, open-label, Phase 3 RATIONALE-303 study (NCT03358875) investigated the efficacy and safety of tislelizumab vs docetaxel in patients with squamous or non-squamous locally advanced or metastatic NSCLC with progression during/after platinum-based chemotherapy
  - In a predefined interim analysis in the overall intent-to-treat (ITT) population, tislelizumab was found to significantly improve overall survival (OS) vs docetaxel (Median OS: 17.2 vs 11.9 months, respectively; hazard ratio [HR]=0.64 [95% confidence interval {CI}: 0.53, 0.78]; $p < 0.0001$), with a manageable safety profile[1]
- Given disease characteristics, standard of care, and prognosis differ between subtypes of NSCLC,[5] the present analysis investigated the efficacy and safety of tislelizumab vs docetaxel among the subgroup of patients with squamous NSCLC in RATIONALE-303

Methods

- The study design has been described previously[1] and is summarized below (scan QR code to read full study methods):
  - In total, 805 patients with histologically confirmed, advanced NSCLC with progressive disease during/after platinum-based chemotherapy and with≥ 1 platinum-containing regimen, but ≤ 2 prior lines of systemic therapy were randomized (2:1) to tislelizumab 200 mg intravenously (IV) or docetaxel 75 mg/m^2 IV every 3 weeks until disease progression, intolerable toxicity, or withdrawal
  - Randomization stratification factors were histology (squamous vs non-squamous), current line of therapy (2nd vs 3rd) and programmed death-ligand 1 (PD-L1) expression (≥ 25% vs < 25% of tumor cells [TC] with PD-L1 membrane staining assessed via the VENTANA SP263 assay)
  - The primary endpoint was OS assessed in two analysis sets: the ITT population and PD-L1 TC ≥ 25% population
  - For this interim analysis, only OS in the ITT population was formally tested
  - Secondary endpoints included investigator (INV)-assessed objective response rate (ORR), duration of response (DoR), progression-free survival (PFS), and safety and tolerability
  - Exploratory endpoints included INV-assessed disease control rate (DCR), clinical benefit rate, and biomarker, pharmacokinetics, and immunogenicity analysis
  - An interim analysis was prespecified after 426 deaths (76% of planned events), and was ultimately conducted after 441 deaths had occurred (data cutoff: August 10, 2020)
- In the subanalysis reported herein, efficacy and safety were assessed in the 370 randomized patients who had squamous histology

Results

Patient disposition

- In total, 248 patients were randomized to tislelizumab and 122 patients to docetaxel(the squamous ITT population)
- Baseline characteristics were balanced between arms (**Table 1**), and broadly similar to the overall ITT population[4]
- At the data cutoff date (August 10, 2020):
  - Median follow-up was 19.0 months (95% CI: 17.5, 20.9) in the tislelizumab treatment arm and 19.3 months (95% CI: 14.4, 21.0) in the docetaxel treatment arm

Efficacy: OS

- Tislelizumab improved OS vs docetaxel (HR, 0.58 [95% CI: 0.44; 0.76]; $p < 0.0001$) (**Figure 1**)
- Median OS was longer with tislelizumab (16.0 months [95% CI: 13.8, 18.9]) vs docetaxel (11.3 months [95% CI: 8.7, 12.7])

Efficacy: PFS

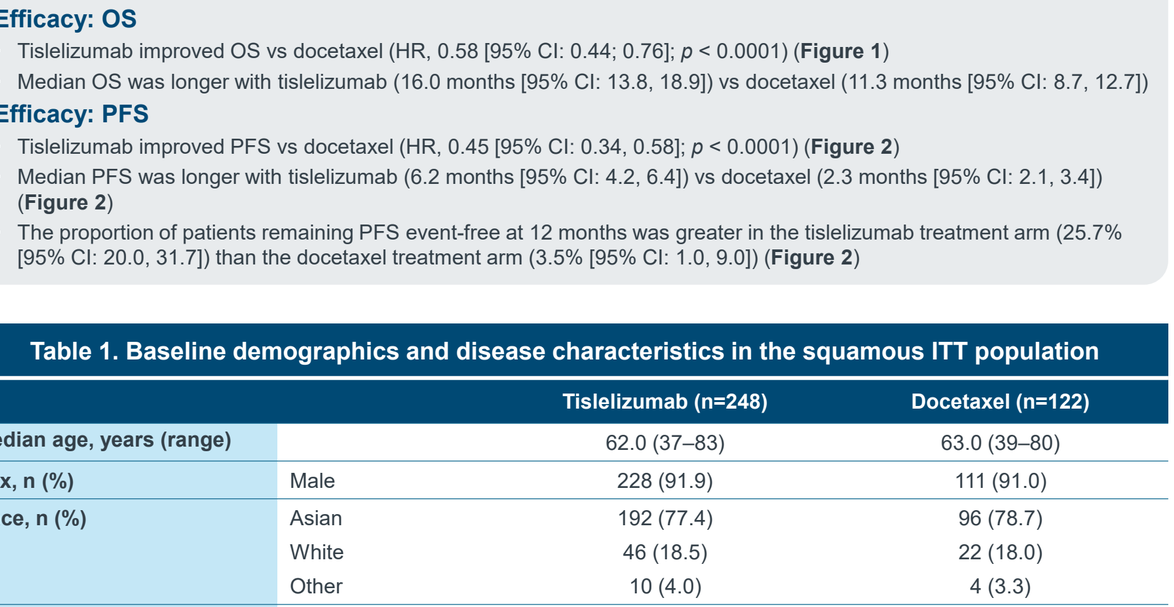
- Tislelizumab improved PFS vs docetaxel (HR, 0.45 [95% CI: 0.34, 0.58]; $p < 0.0001$) (**Figure 2**)
- Median PFS was longer with tislelizumab (6.2 months [95% CI: 4.2, 6.4]) vs docetaxel (2.3 months [95% CI: 2.1, 3.4]) (**Figure 2**)
- The proportion of patients remaining PFS event-free at 12 months was greater in the tislelizumab treatment arm (25.7% [95% CI: 20.0, 31.7]) than the docetaxel treatment arm (3.5% [95% CI: 1.0, 9.0]) (**Figure 2**)

Table 1. Baseline demographics and disease characteristics in the squamous ITT population

		Tislelizumab (n=248)	Docetaxel (n=122)
Median age, years (range)		62.0 (37–83)	63.0 (39–80)
Sex, n (%)	Male	228 (91.9)	111 (91.0)
Race, n (%)	Asian	192 (77.4)	96 (78.7)
	White	46 (18.5)	22 (18.0)
	Other	10 (4.0)	4 (3.3)
Smoking status, n (%)	Never	34 (13.7)	14 (11.5)
	Current/former	214 (86.3)	108 (88.5)
PD-L1 expression, n (%)*	≥ 25%	114 (46.0)	56 (45.9)
	< 25%	134 (54.0)	66 (54.1)
Line of therapy, n (%)	Second	210 (84.7)	102 (83.6)
	Third	38 (15.3)	20 (16.4)
ECOG PS, n (%)	0	46 (18.5)	19 (15.6)
	1	202 (81.5)	103 (84.4)
Disease stage, n (%)	Locally advanced	57 (23.0)	24 (19.7)
	Metastatic	191 (77.0)	98 (80.3)

*Tumor cells with PD-L1 membrane staining assessed via the VENTANA SP263 assay.
ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intent-to-treat; PD-L1, programmed death-ligand 1.

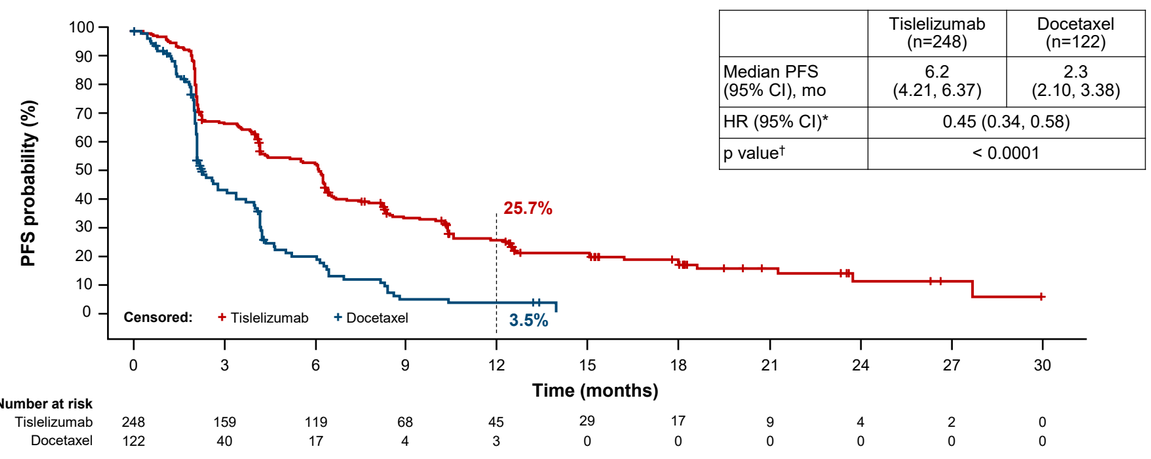
Figure 1. OS in the squamous ITT population



	Tislelizumab (n=248)	Docetaxel (n=122)
Median OS (95% CI), mo	16.0 (13.8, 18.9)	11.3 (8.7, 12.7)
HR (95% CI)*	0.58 (0.44, 0.76)	
p value†	< 0.0001	

*HR estimated from stratified Cox model with docetaxel as reference arm; †Descriptive p value from one-sided stratified log-rank test. 12- and 24-month event-free rates estimated by Kaplan-Meier method.
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, months; OS, overall survival.

Figure 2. PFS in the squamous ITT population



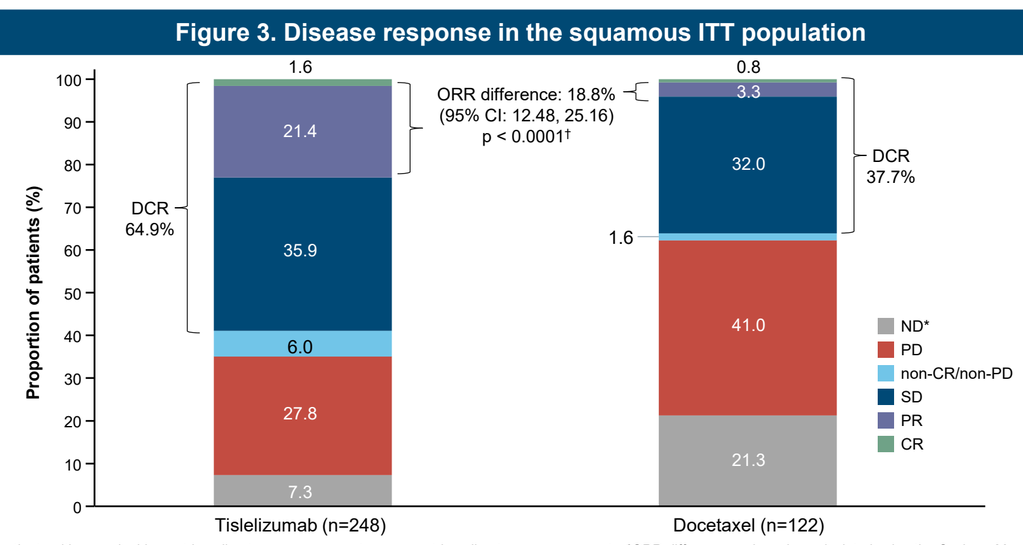
	Tislelizumab (n=248)	Docetaxel (n=122)
Median PFS (95% CI), mo	6.2 (4.21, 6.37)	2.3 (2.10, 3.38)
HR (95% CI)*	0.45 (0.34, 0.58)	
p value†	< 0.0001	

*HR estimated from stratified Cox model with docetaxel as reference arm; †Descriptive p value from one-sided stratified log-rank test. PFS assessed per RECIST v1.1 by investigators. 12-month event-free rates estimated by Kaplan-Meier method.
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, months; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Efficacy: Response rates

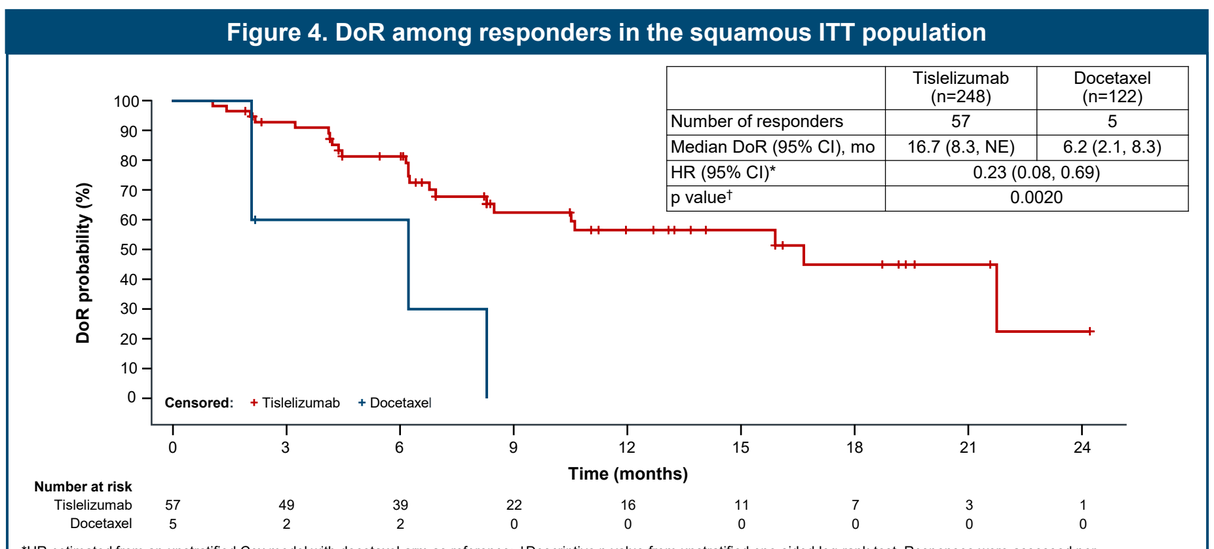
- ORR was greater with tislelizumab (23.0%) than docetaxel (4.1%) (**Figure 3**)
- DCR (an exploratory endpoint) was greater with tislelizumab (64.9%) vs docetaxel (37.7%) (**Figure 3**)
- Median DoR was prolonged with tislelizumab (16.7 months [95% CI: 8.3, not-estimable) vs docetaxel (6.2 months [95% CI: 2.1, 8.3]) (**Figure 4**)

Figure 3. Disease response in the squamous ITT population



*Included patients with unevaluable post-baseline tumor assessments or no post-baseline tumor assessments; †ORR difference and p value calculated using the Cochran-Mantel-Haenszel Chi-square test with actual stratification factors as strata; p value is descriptive. Disease responses were assessed per RECIST v1.1 by investigators.
CI, confidence interval; CR, complete response; DCR, disease control rate; ITT, intent-to-treat; ND, not determined; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Figure 4. DoR among responders in the squamous ITT population



	Tislelizumab (n=248)	Docetaxel (n=122)
Number of responders	57	5
Median DoR (95% CI), mo	16.7 (8.3, NE)	6.2 (2.1, 8.3)
HR (95% CI)*	0.23 (0.08, 0.69)	
p value†	0.0020	

*HR estimated from an unstratified Cox model with docetaxel arm as reference; †Descriptive p value from unstratified one-sided log-rank test. Responses were assessed per RECIST v1.1 by investigators.
CI, confidence interval; DoR, duration of response; HR, hazard ratio; ITT, intent-to-treat; mo, months; RECIST, Response Evaluation Criteria in Solid Tumors.

Safety

- Fewer patients experienced ≥ Grade 3 treatment-emergent adverse events (TEAEs) with tislelizumab (38.1%) than docetaxel (79.5%) (**Table 2**)
  - Treatment-related ≥ Grade 3 TEAEs occurred in 35 (14.2%) patients in the tislelizumab treatment arm and 86 (73.5%) patients in the docetaxel treatment arm (**Table 2**)
  - The most commonly reported ≥ Grade 3 TEAE was pneumonia for tislelizumab (8.9%) and neutropenia (including neutropenia and neutrophil count decreased) and leukopenia (including leukopenia and white blood cell count decrease) for docetaxel (59.0% and 34.2%, respectively) (**Table 2**)

Table 2. Summary of TEAE incidence in the squamous safety analysis population*

Patients, n (%)	Tislelizumab (n=247)		Docetaxel (n=117)	
Any TEAE	235 (95.1)		116 (99.1)	
Treatment related	192 (77.7)		111 (94.9)	
≥ Grade 3 TEAE	94 (38.1)		93 (79.5)	
Treatment related	35 (14.2)		86 (73.5)	
Serious TEAE	73 (29.6)		45 (38.5)	
≥ Grade 3	57 (23.1)		41 (35.0)	
Treatment related	30 (12.1)		34 (29.1)	
TEAE leading to death	13 (5.3)		6 (5.1)	
Treatment related	4 (1.6)		2 (1.7)	
TEAE leading to permanent treatment discontinuation	29 (11.7)		18 (15.4)	
Treatment related	19 (7.7)		16 (13.7)	
Immune-mediated TEAE	43 (17.4)		NA	
TEAEs reported in ≥ 15% of patients (all grades) in either arm	**All grades**	**≥ Grade 3**	**All grades**	**≥ Grade 3**
Anemia	76 (30.8)	7 (2.8)	56 (47.9)	10 (8.5)
Decreased appetite	41 (16.6)	2 (0.8)	33 (28.2)	3 (2.6)
Asthenia	38 (15.4)	5 (2.0)	27 (23.1)	6 (5.1)
Pneumonia	31 (12.6)	22 (8.9)	19 (16.2)	11 (9.4)
Leukopenia†	21 (8.5)	2 (0.8)	63 (53.8)	40 (34.2)
Neutropenia‡	9 (3.6)	2 (0.8)	79 (67.5)	69 (59.0)
Alopecia	5 (2.0)	0 (0)	52 (44.4)	0 (0)

*The safety analysis population included all patients receiving any dose of study drug. AE grades were based on NCI CTCAE (version 4.03); †Includes leukopenia and white blood cell count decreased; ‡Includes neutropenia and neutrophil count decreased.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NA, not applicable; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.

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