Tislelizumab versus docetaxel in patients with previously treated advanced squamous (sq) non-small cell lung cancer (NSCLC): Subanalysis from Phase 3 RATIONALE-303 randomized clinical study

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Abstract No: CT554

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[1–3]

The multicenter, randomized, open-label, Phase 3 RATIONALE-303 study (NCT03358875) investigated the efficacy and safety of tislelizumab vs docetaxel in patients with squamous (sq) or non-squamous (non-sq) 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[4]

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 sq NSCLC in RATIONALE-303

Methods

The study design has been described previously[4] 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 (sq vs non-sq), 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 sq histology

Results

Patient disposition

In total, 248 patients were randomized to tislelizumab and 122 patients to docetaxel (the sq 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**)

Conclusions

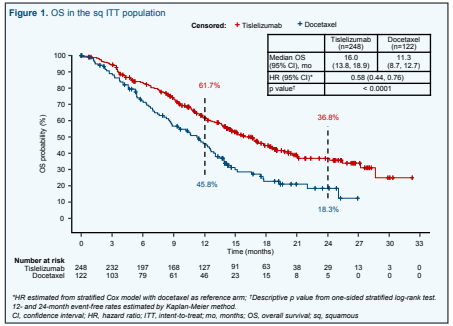
- In this RATIONALE-303 trial subanalysis among patients with sq locally advanced or metastatic NSCLC previously treated with platinum-based chemotherapy:
  - Tislelizumab **prolonged OS** vs docetaxel in patients with sq NSCLC
  - Tislelizumab **improved PFS and ORR, and prolonged DoR** vs docetaxel in patients with sq 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**[4]

Table 1. Baseline demographics and disease characteristics in the sq 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)

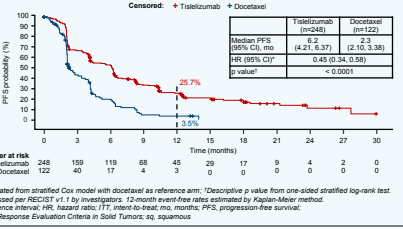
*Tumor cells with PD-L1 membrane staining assessed via the VENTANA SP263 assay.
ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intent-to-treat; PD-L1, programmed death-ligand 1; sq, squamous

Figure 1. OS in the sq ITT population



*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; sq, squamous

Figure 2. PFS in the sq ITT population



*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; sq, squamous

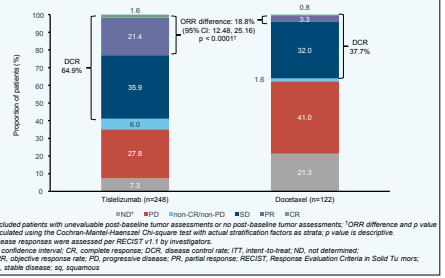
Efficacy: Response rates

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**)

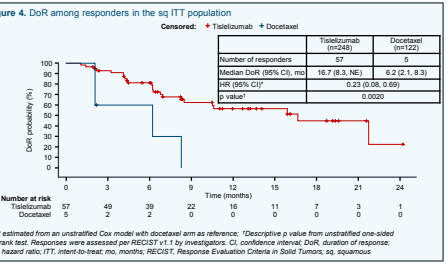
Median DoR was prolonged with tislelizumab (16.7 months [95% CI: 8.3, not-estimable) vs docetaxel (6.2 months [95% CI: 2.1, 8.3]) (**Figure 4**)

Figure 3. Disease response in the sq 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 Tu mors; SD, stable disease; sq, squamous

Figure 4. DoR among responders in the sq ITT population



*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; sq, squamous

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 sq 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 (ve rsion 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 Ca ncer Institute Common Terminology Criteria for Adverse Events; sq, squamous; TEAE, treatment-emergent adverse event

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Acknowledgments

This study was sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Victor ia Dagwell, MSc, of Ashfield MedComms, an Ashfield Health company, and was funded by BeiGene, Ltd.

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