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

Ying Cheng*,[1] Dingzhi Huang,[2] Zhiyong Ma,[3] Yun Fan,[4] Jie Wang,[5] Xinmin Yu,[4] Mikhail Dvorkin,[6] Gareth Rivalland,[7] Yiyuan Ma,[8] Yan Wang,[8] Yan Ma,[8] Caicun Zhou[9]

[1]Department of Medical Thoracic Oncology, Jilin Cancer Hospital, Changchun, China; [2]Department of Thoracic Medical Oncology, Lung Cancer Diagnosis and Treatment Centre, Key Laboratory of Cancer Prevention and Therapy, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Centre for Cancer, Tianjin, China; [3]The Affiliated Cancer Hospital of Zhengzhou University/Henan Cancer Hospital, Zhengzhou, China; [4]Department of Thoracic Medical Oncology, Cancer Hospital of University of Chinese Academy of Sciences & Zhejiang Cancer Hospital, Hangzhou, China; [5]State Key Laboratory of Molecular Oncology, Department of Medical Oncology, National Cancer Centre/National Clinical Research Centre for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [6]BHI of Omsk Region Clinical Oncology Dispensary, Omsk, Russia; [7]Department of Cancer and Blood, Auckland City Hospital, Auckland, New Zealand; [8]BeiGene (Beijing) Co., Ltd., Beijing, China; [9]Department of Medical Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China. *Presenting author

Abstract No: CT553

Background

- Tislelizumab is a humanized immunoglobin G4 programmed cell death protein 1 (PD-1) inhibitor monoclonal antibody with high affinity and binding specificity for PD-1, and was engineered 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-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 non-sq disease 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 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 435 randomized patients who had non-sq histology

Results

Patient disposition

- Patient 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 20.0 months (95% CI: 18.3, 20.0) in the tislelizumab treatment arm and 16.7 months (95% CI: 15.2, 19.8) in the docetaxel treatment arm

Efficacy: OS

- Tislelizumab improved OS vs docetaxel (HR=0.71 [95% CI: 0.54; 0.93]; p=0.0064) (**Figure 1**)
  - Median OS was longer with tislelizumab (18.6 months [95% CI: 15.4, 23.2]) vs docetaxel (13.8 months [95% CI: 9.4, 17.9])

Efficacy: PFS

- Treatment with tislelizumab resulted in a numerical improvement in PFS vs docetaxel (HR=0.84 [95% CI: 0.66, 1.06]; p=0.0686) (**Figure 2**)
  - While median PFS was similar with tislelizumab (2.5 months [95% CI: 2.1, 4.0]) and docetaxel (3.6 months [95% CI: 2.2, 4.1), the proportion of patients remaining PFS event-free at 12 months was higher in the tislelizumab treatment arm than the docetaxel arm (21.3% vs 7.5%, respectively) (**Figure 2**)

Conclusions

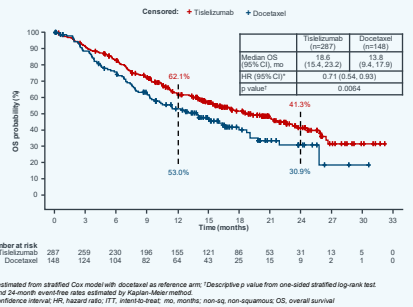
- In this RATIONALE-303 trial subanalysis among patients with non-sq locally advanced or metastatic NSCLC previously treated with platinum-based chemotherapy:
  - Tislelizumab **prolonged OS** vs docetaxel in patients with non-sq NSCLC
  - Tislelizumab **improved PFS rate at 12 months and ORR, and prolonged DoR** vs docetaxel in patients with non-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 non-sq ITT population

		Tislelizumab (n=287)	Docetaxel (n=148)
Median age, years (range)		59.0 (28–88)	60.0 (32–81)
Sex, n (%)	Male	188 (65.5)	95 (64.2)
Race, n (%)	Asian	232 (80.8)	123 (83.1)
	White	48 (16.7)	22 (14.9)
	Other	7 (2.4)	3 (2.0)
Smoking status, n (%)	Never	128 (44.6)	68 (45.9)
	Current/former	159 (55.4)	80 (54.1)
PD-L1 expression, n (%)*	≥ 25%	113 (39.4)	60 (40.5)
	< 25%	174 (60.6)	88 (59.5)
Line of therapy, n (%)	Second	243 (84.7)	127 (85.8)
	Third	44 (15.3)	21 (14.2)
ECOG PS, n (%)	0	69 (24.0)	31 (20.9)
	1	218 (76.0)	117 (79.1)
Disease stage, n (%)	Locally advanced	26 (9.1)	10 (6.8)
	Metastatic	261 (90.9)	138 (93.2)

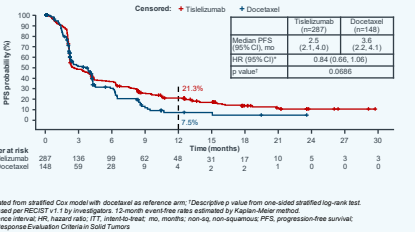
*Tumor cells with PD-L1 membrane staining assessed via the VENTANA SP263 assay.
ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intent-to-treat; non-sq, non-squamous; PD-L1, programmed death-ligand 1

Figure 1. OS in the non-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; non-sq, non-squamous; OS, overall survival

Figure 2. PFS in the non-sq ITT population

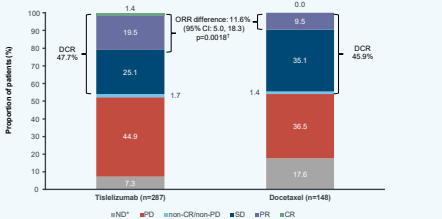


*HR estimated from stratified Cox model with docetaxel as reference arm; †Descriptive p value from one-sided stratified log-rank test.
PFS assessed per RECIST v1.1 by investigators. 12-month event-free rates estimated by Kaplan-Meier method.
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat;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

Efficacy: Response rates

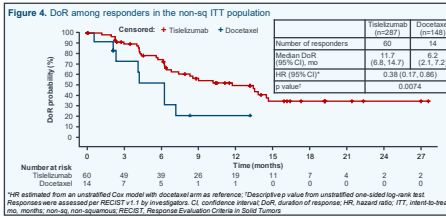
- ORR was greater with tislelizumab (20.9%) than docetaxel (9.5%) (**Figure 3**)
- DCR (an exploratory endpoint) was similar in the two treatment arms (**Figure 3**)
- Median DoR was prolonged with tislelizumab (11.7 months [95% CI: 6.8, 14.7]) vs docetaxel (6.2 months [95% CI: 2.1, 7.2]) (**Figure 4**)

Figure 3. Disease response in the non-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; non-sq, non-squamous; 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 non-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; non-sq, non-squamous; RECIST, Response Evaluation Criteria in Solid Tumors

Safety

- Fewer patients experienced ≥ Grade 3 treatment-emergent adverse events (TEAEs) with tislelizumab (39.0%) than docetaxel (70.9%) (**Table 2**)
  - The most commonly reported ≥ Grade 3 TEAEs were anemia for tislelizumab (3.8% vs 4.3% with docetaxel) and neutropenia for docetaxel (52.5% vs 1.4% with tislelizumab) (**Table 2**)
  - Treatment-related ≥ Grade 3 TEAEs occurred in 42 (14.6%) patients in the tislelizumab treatment arm and 85 (60.3%) patients in the docetaxel treatment arm (**Table 2**)
  - The incidence of TEAEs leading to death was low in both arms (**Table 2**), though slightly higher in the tislelizumab arm due to longer treatment exposure (median duration of exposure was 18.1 weeks in the tislelizumab arm vs 9.3 weeks in the docetaxel arm). In the exposure-adjusted analysis of the full safety analysis set, tislelizumab demonstrated a lower exposure-adjusted event rate for TEAEs leading to death compared with docetaxel (0.8 vs 1.3, respectively)

Table 2. Summary of TEAE incidence in the non-sq safety analysis population*

Patients, n (%)	Tislelizumab (n=287)		Docetaxel (n=141)	
Any TEAE	274 (95.5)		138 (97.9)	
Treatment related	198 (69.0)		131 (92.9)	
≥ Grade 3 TEAE	112 (39.0)		100 (70.9)	
Treatment related	42 (14.6)		85 (60.3)	
Serious TEAE	101 (35.2)		38 (27.0)	
≥ Grade 3	81 (28.2)		35 (24.8)	
Treatment related	37 (12.9)		25 (17.7)	
TEAE leading to death†	19 (6.6)		5 (3.5)	
Treatment related	4 (1.4)		2 (1.4)	
TEAE leading to permanent treatment discontinuation	27 (9.4)		14 (9.9)	
Treatment related	13 (4.5)		9 (6.4)	
Immune-mediated TEAE	51 (17.8)		NA	
TEAEs reported in ≥ 15% (all grades) of patients in either arm	All grades	≥ Grade 3	All grades	≥ Grade 3
Anemia	76 (26.5)	11 (3.8)	56 (39.7)	6 (4.3)
AST increased	64 (22.3)	5 (1.7)	18 (12.8)	0 (0)
ALT increased	63 (22.0)	4 (1.4)	24 (17.0)	0 (0)
Cough	59 (20.6)	4 (1.4)	25 (17.7)	0 (0)
Weight decreased	44 (15.3)	2 (0.7)	13 (9.2)	0 (0)
Decreased appetite	41 (14.3)	3 (1.0)	26 (18.4)	0 (0)
Hypoalbuminemia	37 (12.9)	0 (0)	23 (16.3)	0 (0)
Nausea	37 (12.9)	0 (0)	22 (15.6)	0 (0)
Constipation	31 (10.8)	0 (0)	22 (15.6)	0 (0)
Asthenia	29 (10.1)	1 (0.3)	29 (20.6)	8 (5.7)
Neutropenia‡	15 (5.2)	4 (1.4)	97 (68.8)	74 (52.5)
Leukopenia‡	14 (4.9)	0 (0)	80 (56.7)	48 (34.0)
Alopecia	0 (0)	0 (0)	70 (49.6)	2 (1.4)

*The safety analysis population included all patients receiving any dose of study drug. AE grades were based on NCI CTCAE (v4.03); †The majority of TEAEs leading to death were assessed as not related to study treatment by investigators; ‡Includes neutropenia and neutrophil count decreased; §Includes leukopenia and white blood cell 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

References

1. Zhang T, et al. Cancer Immunol Immunother 2018:1079–90
2. Dahan R, et al. Cancer Cell 2015;28:285–95
3. Hong Y, et al. FEBS Open Bio 2021;11:782–92
4. Zhou C, et al. Cancer Res 2021;81 (Abs CT039) [presented at AACR 2021]
5. Planchard D, et al. Ann Oncol 2018;29:iv192–237

Acknowledgments

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

Author contact details: jl.cheng@163.com (Ying Cheng)