Efficacy, Safety, and Health-Related Quality of Life From a Global Phase 3 Study of Tislelizumab as Second- or Third-Line Therapy for Patients With Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC): RATIONALE 303

Caicun Zhou[1], Dingzhi Huang[2], Xinmin Yu[3], Yunpeng Liu[4], Yun Fan[3], Yongqian Shu[5], Zhiyong Ma[6], Ziping Wang[7], Ying Cheng[8], Jie Wang[9], Sheng Hu[10], Zhihua Liu[11], Elena Poddubskaya[12], Umut Disel[13], Audrey Akopov[14], Yiyuan Ma[15], Yan Wang[15], Songzi Li[16], Cunjing Yu[15], Gisoo Barnes[16], Boxiong Tang[16], Gareth Rivalland[17]

[1]Shanghai Pulmonary Hospital, Shanghai, China; [2]Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; [3]Zhejiang Cancer Hospital, Hangzhou, China; [4]The First Hospital of China Medical University, Shenyang, China; [5]Jiangsu Province Hospital, Nanjing, China; [6]Henan Cancer Hospital, Zhengzhou, China; [7]Peking University Cancer Hospital & Institute, Beijing, China; [8]Jilin Cancer Hospital, Changchun, China; [9]State Key Laboratory of Molecular Oncology, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [10]Hubei Cancer Hospital, Wuhan, China; [11]Jiangxi Cancer Hospital, Nanchang, China; [12]VitaMed LLC., Moscow, Russia; [13]Acibadem Adana Hospital, Adana, Turkey; [14]Pavlov First Saint Petersburg State Medical University, Saint Petersburg, Russia; [15]BeiGene (Beijing) Co., Ltd., Beijing, China; [16]Beigene Ltd., San Mateo, CA, USA; [17]Auckland City Hospital, Auckland, New Zealand

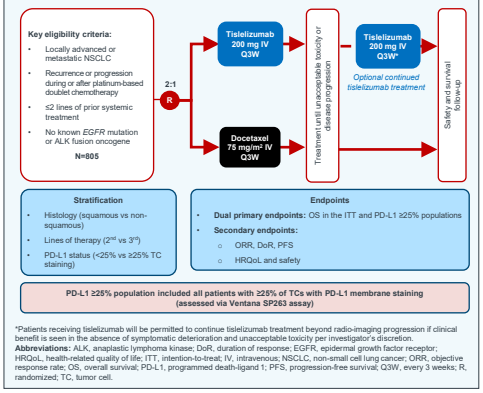
Background

- Anti-PD-1/L1 therapies have improved overall survival (OS) by 2-4 months vs docetaxel in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with disease progression after initial platinum-based chemotherapy[1-4]
- Tislelizumab is an anti-PD-1 antibody engineered to minimize FcγR binding on macrophages, a mechanism of T-cell clearance and potential anti-PD-1 resistance[5-7]
- In a phase 1/2 study, tislelizumab demonstrated antitumor activity in multiple advanced solid tumors including NSCLC[8]
- The phase 3 RATIONALE 303 study was initiated to investigate the efficacy and safety of tislelizumab vs docetaxel in patients with NSCLC who had progressed on a prior platinum-containing regimen (**Figure 1**)

Methods

Study Design

Figure 1. Study Design of RATIONALE 303 (NCT03358875), a Phase 3, Open-Label, Multicenter, Randomized Study



*Patients receiving tislelizumab will be permitted to continue tislelizumab treatment beyond radio-imaging progression if clinical benefit is seen in the absence of symptomatic deterioration and unacceptable toxicity per investigator's discretion.
Abbreviations: ALK, anaplastic lymphoma kinase; DoR, duration of response; EGFR, epidermal growth factor receptor; HRQoL, health-related quality of life; ITT, intention-to-treat; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; R, randomized; TC, tumor cell.

Statistical Considerations

- Overall alpha for the study: one-sided alpha of 0.025
  - 560 death events provide approximately 87% power to detect an OS hazard ratio (HR) (tislelizumab/docetaxel) of 0.75 with a one-sided alpha of 0.02 in the intention-to-treat (ITT) population
  - 207 death events in the PD-L1 ≥25% population provide approximately 86% power to detect an OS HR of 0.60 with a one-sided alpha of 0.007
- A sequential testing with alpha splitting approach was implemented
- Interim analysis (reviewed by independent data monitoring committee)
  - For the purposes of the interim analysis, formal OS superiority testing was conducted only in the ITT
  - Prespecified to be conducted after ~426 death events occurred (76% of planned events) using Hwang-Shih-DeCani spending function with γ parameter of -2
- Interim analysis at data cut-off date: 10 August 2020
  - Observed number of death events: 441 (54.8%)
  - One-sided alpha level of 0.0120 for ITT (based on the observed number of death events)
- Patient-reported outcomes (PROs) were collected at every treatment cycle to the end of treatment
  - Descriptive analyses were performed on all the domains and single items

HRQoL Assessments and Endpoints

- Health-related quality of life (HRQoL) endpoints included the global health status (GHS)/QoL, physical functioning, and fatigue domains of the EORTC QLQ-C30 and the QLQ-LC13's index score and most relevant lung cancer symptoms (eg, dyspnea, coughing, peripheral neuropathy, pain in chest, pain in arms/shoulders, hemoptysis)
  - Endpoint selection criteria was based on the descriptive analysis and previously published studies
- For GHS/QoL and physical functioning domain, higher scores indicate a higher (better) function; for fatigue domain and symptom scales, higher scores indicate higher (worse) symptom severity
- Least square mean score change from baseline to Cycle 4 and Cycle 6 were assessed using a constrained longitudinal data analysis model with the PRO score as the response variable, and treatment by study visit interaction and stratification factors for randomization as covariates, based on the missing at random assumption

Patient Characteristics

- As of 10 August 2020, 805 patients were randomized (tislelizumab, n=535; docetaxel, n=270)
- At the time of data cut-off, 248 patients (46.4%) receiving tislelizumab and 86 patients (31.9%) receiving docetaxel remained in the study
- Patient demographics and baseline disease characteristics were well balanced across arms (**Table 1**)
- Median OS was longer in patients treated with tislelizumab compared with patients treated with docetaxel (17.2 vs 11.9 months, respectively) (**Figure 2**)
- Longer OS for those treated with tislelizumab was also demonstrated among patients with high PD-L1 expression (**Figure 3**)
- Median progression-free survival (PFS) was 4.1 and 2.6 months in the tislelizumab and docetaxel groups, respectively (**Figure 4**)
- The difference in objective response rate (ORR) between arms was 14.9% and favored tislelizumab over docetaxel (**Figure 5**)
- Median duration of response (DoR) was 13.5 months and 6.2 months for patients receiving tislelizumab and docetaxel, respectively
- Compared with docetaxel, tislelizumab was associated with a notably lower incidence of grade ≥3 adverse events (AEs) (**Table 2**)
- The most commonly reported treatment-emergent AEs (TEAEs) were anemia (tislelizumab arm) and alopecia (docetaxel arm) (**Figure 6**)
- The most common grade ≥3 TEAE was neutropenia in the docetaxel arm (27.9% vs 0.6% with tislelizumab) (**Figure 6**)
- Among patients receiving tislelizumab, the most common immune-mediated TEAE was hypothyroidism (**Figure 7**)
- Treatment-related AEs leading to death occurred in 1.5% (tislelizumab) and 1.6% (docetaxel) of patients (**Table 2**)

Conclusions

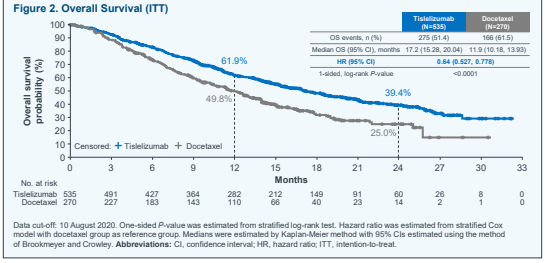
- Tislelizumab monotherapy in second- and third-line NSCLC
  - Significantly prolonged OS in the ITT population
  - Significantly prolonged OS in the PD-L1 ≥25% population
- Tislelizumab prolonged PFS, improved ORR, and prolonged DoR vs docetaxel
- Tislelizumab had a tolerable and manageable safety profile consistent with other PD-1/L1 inhibitors, with a lower incidence of grade ≥3 AEs than docetaxel
- Patients treated with tislelizumab reported improved HRQoL measures (reduced lung cancer symptoms, fatigue, and improved physical functioning) vs docetaxel

Table 1. Demographics and Baseline Characteristics

	Tislelizumab (N=535)	Docetaxel (N=270)
Median age, years (range)	61.0 (28-88)	61.0 (32-81)
Patients aged < 65 years, n (%)	364 (68.0)	180 (66.7)
Male, n (%)	416 (77.8)	206 (76.3)
Race, n (%)		
Asian	424 (79.3)	219 (81.1)
White	94 (17.6)	44 (16.3)
ECOG performance status, n (%)		
0	115 (21.5)	50 (18.5)
1	420 (78.5)	220 (81.5)
Smoking status, n (%)		
Never	162 (30.3)	82 (30.4)
Current/former	373 (69.7)	188 (69.6)
PD-L1 expression, n (%)		
≥ 25%	227 (42.4)	116 (43.0)
< 25%	308 (57.6)	154 (57.0)
Histology, n (%)		
Squamous	248 (46.4)	122 (45.2)
Non-squamous	287 (53.6)	148 (54.8)
Unknown *EGFR* mutation, n (%)	195 (36.4)	87 (32.2)
ALK rearrangement, n (%)		
Wild type	241 (45.0)	130 (48.1)
Unknown	294 (55.0)	140 (51.9)
Current line of therapy, n (%)		
Second	453 (84.7)	229 (84.8)
Third	82 (15.3)	41 (15.2)
Disease stage, n (%)		
Locally advanced	83 (15.5)	34 (12.6)
Metastatic	452 (84.5)	236 (87.4)
Brain metastasis, n (%)	39 (7.3)	18 (6.7)
Liver metastasis, n (%)	73 (13.6)	33 (12.2)

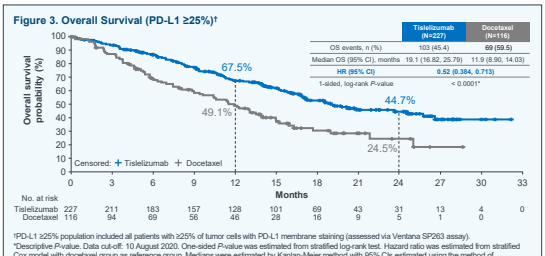
Abbreviations: ALK, anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; PD-L1, programmed death-ligand 1

Figure 2. Overall Survival (ITT)



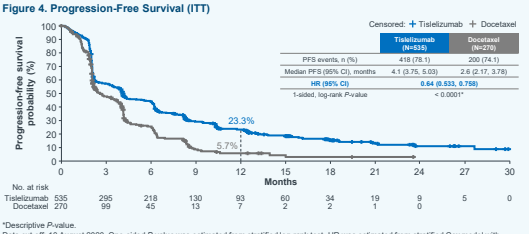
Data cut-off: 10 August 2020. One-sided *P*-value was estimated from stratified log-rank test. Hazard ratio was estimated from stratified Cox model with docetaxel group as reference group. Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. **Abbreviations:** CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat.

Figure 3. Overall Survival (PD-L1 ≥25%)†



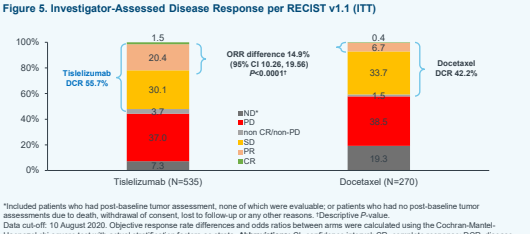
†PD-L1 ≥25% population included all patients with ≥25% of tumor cells with PD-L1 membrane staining (assessed via Ventana SP263 assay).
*Descriptive *P*-value. Data cut-off: 10 August 2020. One-sided *P*-value was estimated from stratified log-rank test. Hazard ratio was estimated from stratified Cox model with docetaxel group as reference group. Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. **Abbreviations:** CI, confidence interval; HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand 1.

Figure 4. Progression-Free Survival (ITT)



*Descriptive *P*-value.
Data cut-off: 10 August 2020. One-sided *P*-value was estimated from stratified log-rank test. HR was estimated from stratified Cox model with docetaxel group as reference group. Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. **Abbreviations:** CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; PFS, progression-free survival.

Figure 5. Investigator-Assessed Disease Response per RECIST v1.1 (ITT)



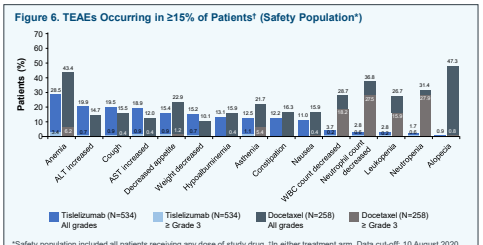
*Included patients who had post-baseline tumor assessment, none of which were evaluable; or patients who had no post-baseline tumor assessments due to death, withdrawal of consent, lost to follow-up or any other reasons. †Descriptive *P*-value.
Data cut-off: 10 August 2020. Objective response rate differences and odds ratios between arms were calculated using the Cochran-Mantel-Haenszel chi-square test with actual stratification factors as strata. **Abbreviations:** CI, confidence interval; CR, complete response; DCR, disease control rate; ITT, intention-to-treat ND, could not be determined; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Table 2. Overall Safety Profile (Safety Analysis Set*)

	Tislelizumab (N=534)	Docetaxel (N=258)
Mean duration of exposure, weeks (SD)	32.6 (29.70)	14.5 (13.84)
Mean number of treatment cycles (SD)	10.5 (9.37)	4.7 (4.49)
Any TEAE, n (%)	509 (95.3)	254 (98.4)
Treatment-related	390 (73.0)	242 (93.8)
Grade ≥3 TEAE	206 (38.6)	193 (74.8)
Treatment-related	77 (14.4)	171 (66.3)
Serious TEAE	174 (32.6)	83 (32.2)
Grade ≥3	138 (25.8)	76 (29.5)
Treatment-related	67 (12.5)	59 (22.9)
TEAE leading to death	32 (6.0)	11 (4.3)
Treatment-related	8 (1.5)	4 (1.6)
TEAE leading to permanent treatment discontinuation	56 (10.5)	32 (12.4)
Treatment-related	32 (6.0)	25 (9.7)

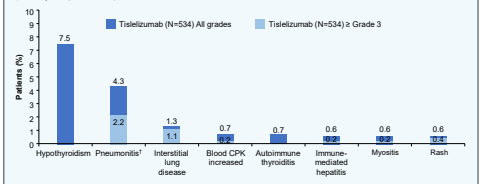
*Safety analysis set included all patients receiving any dose of study drug. Data cut-off: 10 August 2020. Adverse event grades were evaluated based on NCI-CTCAE (version 4.03). **Abbreviations:** SD, standard deviation; TEAE, treatment-emergent adverse event.

Figure 6. TEAEs Occurring in ≥15% of Patients† (Safety Population*)



*Safety population included all patients receiving any dose of study drug. †In either treatment arm. Data cut-off: 10 August 2020. Adverse event grades were evaluated based on NCI-CTCAE (version 4.03). **Abbreviations:** ALT, alanine transaminase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event; WBC, white blood cell.

Figure 7. Immune-Mediated TEAEs Occurring in ≥0.5% of Tislelizumab-Treated Patients (Safety Population*)

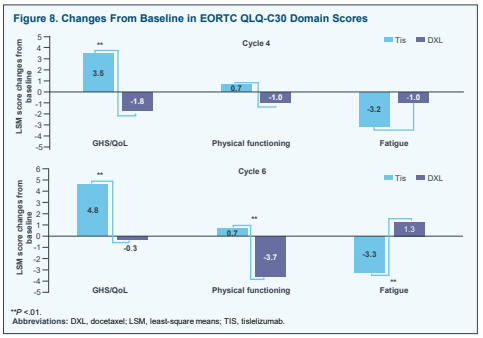


*Safety population included all patients receiving any dose of study drug. †Combined pneumonitis and immune-mediated pneumonitis. Data cut-off: 10 August 2020. Adverse events grades were evaluated based on NCI-CTCAE (version 4.03). **Abbreviations:** CPK, creatine phosphokinase; TEAE, treatment-emergent adverse event.

Results

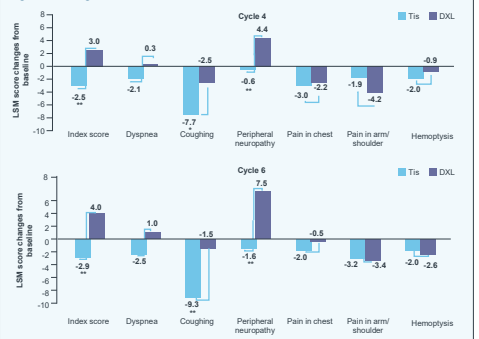
- Patients in the tislelizumab arm experienced improvements in GHS/QoL and fatigue in Cycles 4 and 6 compared with the docetaxel arm (**Figure 8**)
- The physical functioning domain score was stable with tislelizumab but decreased with docetaxel in Cycles 4 and 6; significant differences between treatment arms emerged at Cycle 6
- Patients treated with tislelizumab had a significantly improved EORTC QLQ-LC13 index score (overall symptomatology), coughing, and peripheral neuropathy vs the docetaxel arm at Cycles 4 and 6 (**Figure 9**)
  - By Cycle 6, dyspnea was trending toward significant improvement with tislelizumab
- The difference in pain measures (chest; arms/shoulders) and hemoptysis were not significant between treatment arms

Figure 8. Changes From Baseline in EORTC QLQ-C30 Domain Scores



**P<.01.
Abbreviations: DXL, docetaxel; LSM, least-square means; TIS, tislelizumab.

Figure 9. Changes From Baseline in EORTC QLQ-LC13 Scores



Abbreviations: DXL, docetaxel; LSM, least-square means; TIS, tislelizumab.

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For questions/comments about this presentation please contact Yiyuan Ma at: yiyuan.ma@beigene.com