ORIGINAL ARTICLE

Tislelizumab Versus Docetaxel in Patients With Previously Treated Advanced NSCLC (RATIONALE-303): A Phase 3, Open-Label, Randomized Controlled Trial

Caicun Zhou, MD,[a,*] Dingzhi Huang, MD,[b] Yun Fan, MD,[c] Xinmin Yu, MD,[c] Yunpeng Liu, MD,[d] Yongqian Shu, MD,[e] Zhiyong Ma, MD,[f] Ziping Wang, MD,[g] Ying Cheng, MD,[h] Jie Wang, MD,[i] Sheng Hu, MD,[j] Zhihua Liu, MD,[k] Elena Poddubskaya, MD,[l] Umut Disel, MD,[m] Andrey Akopov, MD,[n] Mikhail Dvorkin, MD,[o] Wenjuan Zheng, MD,[p] Yiyuan Ma, MD,[p] Yan Wang, MD,[p] Songzi Li, PhD,[q] Cunjing Yu, PhD,[p] Gareth Rivalland, MD[r]

[a]*Department of Medical Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, People's Republic of China*
[b]*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, People's Republic of China*
[c]*Department of Thoracic Medical Oncology, Cancer Hospital of University of Chinese Academy of Sciences and Zhejiang Cancer Hospital, Hangzhou, People's Republic of China*
[d]*The First Hospital of China Medical University, Shenyang, People's Republic of China*
[e]*Department of Oncology, Jiangsu Province Hospital, Nanjing, People's Republic of China*
[f]*The Affiliated Cancer Hospital of Zhengzhou University/Henan Cancer Hospital, Zhengzhou, People's Republic of China*
[g]*Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Thoracic Medical Oncology, Peking University Cancer Hospital and Institute, Beijing, People's Republic of China*
[h]*Department of Medical Thoracic Oncology, Jilin Cancer Hospital, Changchun, People's Republic of China*
[i]*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, People's Republic of China*
[j]*Hubei Cancer Hospital, Wuhan, People's Republic of China*
[k]*Jiangxi Cancer Hospital, Nanchang, People's Republic of China*
[l]*Clinical Center Vitamed and Sechenov University, Moscow, Russia*
[m]*Acibadem Health Group- Adana Acibadem Hospital/Medical Oncology, Adana, Turkey*
[n]*Pavlov First State Medical University, Saint-Petersburg, Russia*
[o]*BHI of Omsk Region Clinical Oncology Dispensary, Omsk, Russia*
[p]*BeiGene (Beijing) Co., Ltd., Beijing, People's Republic of China*
[q]*BeiGene USA, Inc., Emeryville, California*
[r]*Department of Cancer and Blood, Auckland City Hospital, Auckland, New Zealand*

Received 25 May 2022; revised 7 September 2022; accepted 15 September 2022
Available online - XXX

*Corresponding author.

Disclosure: Dr. Zhou has received payments or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Amoy Diagnostics, Boehringer Ingelheim, C-Stone, Hengrui, Innovent Biologics, Lilly China, LUYE Pharma, Merck Sharp & Dohme, Qilu, Roche, Sanofi, and TopAlliance Biosciences Inc.; and is on data safety monitoring boards or advisory boards for Hengrui, Innovent Biologics, Qilu, and TopAlliance Biosciences Inc. Dr. Rivalland has received funding (to individual) for advisory board participation from Merck Sharp & Dohme and a speaker honorarium from AstraZeneca. Drs. Zheng, Y. Ma, Y. Wang, Li, and C. Yu are employees of, and have received stocks from, BeiGene, Ltd. The remaining authors declare no conflict of interest.

Address for correspondence: Caicun Zhou, MD, Department of Medical Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai 200433, People's Republic of China. E-mail: caicunzhoudr@163.com

ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2022.09.217

ABSTRACT

Introduction: The phase 3 RATIONALE-303 trial (NCT03358875) investigated the efficacy and safety of tislelizumab versus docetaxel in pretreated patients with advanced NSCLC. Here, we report the efficacy and safety results and describe the exploratory biomarker analyses.

Methods: A total of 805 patients aged more than or equal to 18 years with locally advanced or metastatic squamous or nonsquamous NSCLC were randomized 2:1 to intravenous tislelizumab 200 mg or docetaxel 75 mg/m^2 every 3 weeks. Co-primary end points were overall survival (OS) in the intent-to-treat (ITT) and programmed death-ligand 1 (PD-L1) tumor cell expression greater than or equal to 25% populations. The exploratory biomarker analyses included PD-L1 expression, tumor mutation burden, and gene expression profile.

Results: At the prespecified interim analysis (August 10, 2020), the co-primary end point of OS in the ITT population was met, with a statistically significant and clinically meaningful improvement in OS with tislelizumab versus docetaxel (median 17.2 versus 11.9 mo, respectively; hazard ratio [HR] = 0.64, $p < 0.0001$). At the final analysis (July 15, 2021), the other co-primary end point of OS in the PD-L1 tumor cell greater than or equal to 25% population was further met (median 19.3 versus 11.5 mo, respectively; HR = 0.53, $p < 0.0001$), and OS continued to improve in the ITT population (median 16.9 versus 11.9 mo, respectively, HR = 0.66). Exploratory biomarker analyses revealed the potential association of *NOTCH1–4* mutations with improved tislelizumab efficacy for both OS and progression-free survival, whereas tissue tumor mutation burden correlated with progression-free survival benefit, but not OS benefit. No new safety signals were identified.

Conclusions: Tislelizumab was found to have a significantly improved and long-term clinical benefit in OS versus docetaxel in pretreated patients with advanced NSCLC, regardless of PD-L1 expression.

Keywords: Tislelizumab; Docetaxel; Non–small cell lung cancer; Randomized clinical trial

Introduction

Lung cancer is the leading cause of cancer mortality worldwide,[1] and NSCLC accounts for most lung cancers.[2,3]

Several global trials have revealed anti–PD-1 or anti-PD-L1 therapies to have efficacy and safety benefits versus chemotherapy in patients who have progressed after platinum-based chemotherapy.[4–8] Overall survival (OS) improvements of approximately 3 to 4 months compared with docetaxel have been achieved with anti–PD-1 or anti-PD-L1 monotherapy, although the median OS achieved in patients with pretreated, advanced NSCLC remains at approximately 9 to 13 months.[4–8]

Tislelizumab is an anti–PD-1 immunoglobulin G4 monoclonal antibody with high affinity for the PD-1 receptor and was engineered to eliminate the binding function to Fc gamma receptors and complement 1q.[9] Tislelizumab was found to have robust efficacy and a manageable safety profile across multiple tumor types.[10–14] The phase 3 RATIONALE-303 trial (NCT03358875) was conducted to evaluate the efficacy and safety of tislelizumab versus docetaxel in patients with locally advanced or metastatic NSCLC who had progressed after at least one previous platinum-based doublet regimen. Here, we report co-primary and secondary end points and describe post hoc exploratory biomarker analyses.

Materials and Methods

Patients

RATIONALE-303 is a global, open-label, randomized, phase 3 clinical trial conducted at 124 sites in 10 countries (Supplementary Fig. 1). The study was initially intended to enroll approximately 640 patients only in the People's Republic of China, and the enrollment was subsequently expanded to other countries, targeting approximately 800 patients in total, on the basis of a protocol amendment in February 2018. The trial was performed according to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines and approved by the relevant Institutional Review Board or Independent Ethics Committee for each study site. An Independent Data Monitoring Committee reviewed the efficacy and safety data. All patients provided written informed consent.

Eligible patients were adults (≥18 y of age) with histologically confirmed, locally advanced or metastatic squamous or nonsquamous NSCLC, regardless of level of tumor PD-L1 expression, who had progressive disease during or after at least one platinum-containing doublet regimen (no more than two previous systemic treatment lines for advanced or metastatic disease), and had Eastern Cooperative Oncology Group performance status of 0 or 1. Patients with treated, stable brain metastases were also eligible for inclusion. Patients who had received previous docetaxel treatment for metastatic disease or previous immune checkpoint inhibitor (ICI) therapies targeting PD-1, PD-L1, or CTLA-4, and patients with known *EGFR* mutation or *ALK* gene translocation were ineligible. A full listing of the eligibility criteria is

provided in the Supplementary Methods and the protocol in the Supplementary Appendices.

Study Design and Treatment

Patients were randomized (2:1) using an interactive web response technology system to receive open-label intravenous tislelizumab 200 mg every 3 weeks or docetaxel 75 mg/m^2 every 3 weeks until disease progression per Response Evaluation Criteria in Solid Tumors version 1.1, intolerable toxicity, or withdrawal of consent (Supplementary Fig. 1). Randomization was stratified by pathologic types (squamous versus nonsquamous), line of therapy (second line versus third line), and tumor cell PD-L1 expression ($<$25% versus $\geq$25%, as assessed by VENTANA SP263 immunohistochemistry assay). Crossover to tislelizumab was not permitted; at the investigators' discretion, patients could be treated beyond disease progression under protocol-defined conditions.

End Points and Assessments

The co-primary end points were OS both in the intent-to-treat (ITT) population, which included all randomized patients, and in a subset of patients with PD-L1 expression on greater than or equal to 25% of the tumor cells. Secondary efficacy end points included investigator-assessed progression-free survival (PFS), objective response rate (ORR), duration of response (DoR), and health-related quality of life (data not reported herein) in the ITT and PD-L1 greater than or equal to 25% populations and safety. Results of exploratory biomarker analyses which included PD-L1 expression, tumor mutational burden (TMB), and gene expression profile were evaluated in the biomarker-evaluable (BE) population which was defined as all randomized patients with assessable mutation data. Radiological tumor assessments were evaluated by the investigators as per Response Evaluation Criteria in Solid Tumors version 1.1 at baseline and every 9 weeks ($\pm$7 d) for the first 12 months and then every 12 weeks ($\pm$7 d) from year 2 onward. Safety was assessed in the safety population, which included all patients who received at least one dose of the study drug, during the treatment phase and safety follow-up phase (up to 30 d after the last study treatment or initiation of new anticancer therapy, whichever occurred first for any adverse event [AE]). Immune-mediated AEs were monitored for up to 90 days after the last dose of tislelizumab. Treatment-emergent AEs (TEAEs) were coded using Medical Dictionary for Regulatory Activities version 24.0 and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Patients were followed up for survival every 3 months ($\pm$14 d) after the safety follow-up visit. A complete list of all end points and methods used for biomarker analyses is provided in the Supplementary Appendix (page 11).

Biomarker Analyses

DNA sequencing was performed on formalin-fixed, paraffin-embedded samples using OncoScreen Plus 520 panel. Somatic variants on the exons of 520 genes were identified using an algorithm optimized for the assay.[15] Only nonsynonymous variants were included for downstream association analysis with efficacy. TMB was defined as the number of single-nucleotide variants and short insertion and deletion per megabase on the coding region.

Statistical Analyses

The Kaplan-Meier method was used to estimate medians and 95% confidence intervals (CIs) of OS, PFS, and DoR. The stratified log-rank test was used to evaluate OS difference between the treatment arms. A stratified Cox proportional hazards model with Efron's method of tie handling was used to determine hazard ratio (HR) and its 95% CI. Actual values of stratification factors for randomization were fitted as strata in the stratified analyses. The family-wise type I error rate is controlled at one-sided alpha level of 0.025 in all hypothesis tests of the above-mentioned primary and secondary end points. With a sample size of 800, the trial would have 87% power to reveal a HR for OS in the ITT population of 0.75 at one-sided alpha level of 0.02 (as calculated based on 560 events), whereas the remaining alpha was assigned to the OS test in the PD-L1 greater than or equal to 25% subgroup. The study had one planned interim analysis only in the ITT population when 426 events were observed. The final analysis of OS was planned to take place after 560 events were observed in the ITT population and 207 events were observed in the subgroup of patients with tumor PD-L1 greater than or equal to 25%. The hypotheses in the secondary end points were tested sequentially once superiority of OS in the PD-L1 greater than or equal to 25% subgroup was found in the final analysis (Supplementary Methods and Supplementary Fig. 2). Full statistical methods are provided in the Statistical Analysis Plan as an appendix to the Supplementary Materials. In the additional exploratory biomarker analysis, *NOTCH1–4* mutation status (mutant versus wild type) and its interaction with the treatment were added to the stratified Cox proportional hazards model to explore the association of *NOTCH1–4* mutations with tislelizumab efficacy.

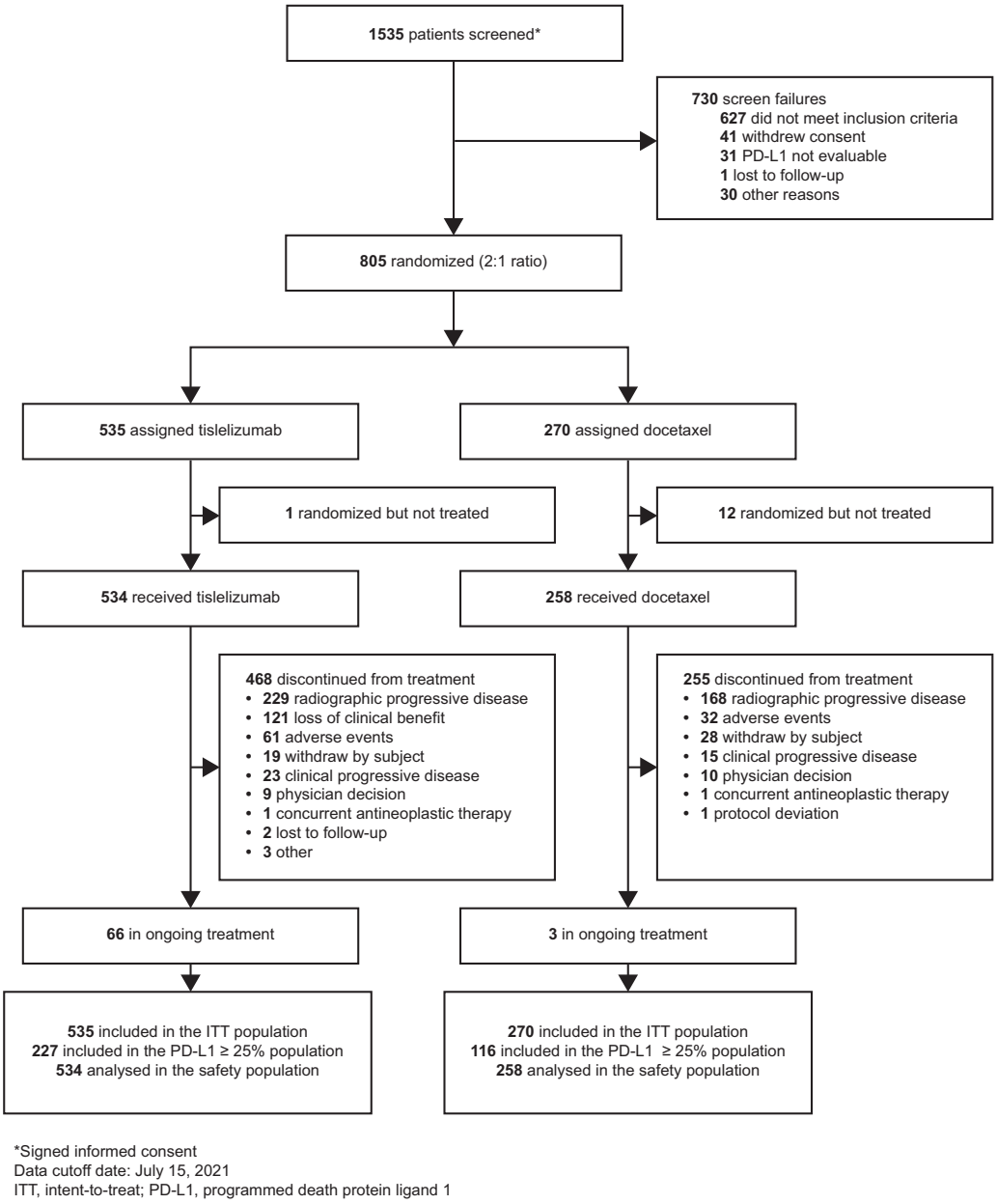

Figure 1. CONSORT diagram (final analysis). ITT, intent-to-treat; PD-L1, programmed death-ligand 1.

Results

Patients and Treatment

Between November 2017 and April 2020, a total of 1535 patients were screened and 805 patients meeting the eligibility criteria were randomized into the tislelizumab (n = 535) and docetaxel (n = 270) treatment arms (Fig. 1). A total of 13 patients (one in the tislelizumab arm and 12 in the docetaxel arm) were randomized but did not receive the study treatment and were included in the ITT population, but not in the safety population. At the data cutoff for the final analysis (July 15, 2021), median study follow-up time was 16.0 months (range: 0.3–43.5 mo) for tislelizumab and 10.7 months (range: 0.03–38.3 mo) for docetaxel.

The baseline demographic and disease characteristics of the patients were representative of the target population and were well balanced between those receiving tislelizumab and docetaxel, including PD-L1 expression and pathologic type (Table 1). In the ITT population (all randomized patients), the median age was 61.0 years, 641 patients (79.6%) were enrolled in the People's Republic of China, and 343 patients (42.6%) had tumors with PD-L1 expression level at or above the VENTANA SP263 immunohistochemistry assay 25% cutoff. The baseline demographic and disease characteristics of the

Table 1. Baseline Demographic and Disease Characteristics (ITT Population)

Baseline Characteristics	Tislelizumab (n = 535)	Docetaxel (n = 270)
Median age, y (range)	61.0 (28-88)	61.0 (32-81)
Patients aged <65 y, n (%)	364 (68.0)	180 (66.7)
Sex, n (%)		
Male	416 (77.8)	206 (76.3)
Female	119 (22.2)	64 (23.7)
Race, n (%)		
Asian	424 (79.3)	219 (81.1)
White	93 (17.4)	44 (16.3)
Other	18 (3.4)	7 (2.6)
Region, n (%)		
People's Republic of China	423 (79.1)	218 (80.7)
Rest of world	112 (20.9)	52 (19.3)
ECOG performance status, n (%)		
0	116 (21.7)	50 (18.5)
1	419 (78.3)	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% TC	308 (57.6)	154 (57.0)
≥25% TC	227 (42.4)	116 (43.0)
Pathologic type, n (%)		
Squamous	248 (46.4)	122 (45.2)
Nonsquamous	287 (53.6)	148 (54.8)
Current line of therapy, n (%)		
Second	453 (84.7)	229 (84.8)
Third	82 (15.3)	41 (15.2)
Disease stage,[a] n (%)		
Locally advanced	84 (15.7)	33 (12.2)
Metastatic	451 (84.3)	237 (87.8)
Confirmed distant metastatic site(s), n (%)		
Bone	166 (31.0)	79 (29.3)
Liver	73 (13.6)	33 (12.2)
Brain	39 (7.3)	18 (6.7)

Note: ITT population included all randomized patients. Data cutoff: July 15, 2021.
[a]At study entry (randomization).
ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; PD-L1, programmed death-ligand 1; TC, tumor cell.

BE population, which included 244 patients in the tislelizumab arm and 116 patients in the docetaxel arm (44.7% of the ITT population), were generally consistent with the ITT population (Supplementary Table 1).

At the data cutoff for the final analysis, 153 patients (28.6%) in the tislelizumab arm and 45 patients (16.7%) in the docetaxel arm remained in the study and 66 patients (12.3%) in the tislelizumab arm and three (1.1%) in the docetaxel arm remained on the treatment (Fig. 1). Patient disposition at the interim analysis is also summarized in Supplementary Figure 3. Poststudy anticancer therapy was received by 297 patients (55.5%) and 179 patients (66.3%) in the tislelizumab and docetaxel arms, respectively, most often chemotherapy or protein kinase inhibitors. In the docetaxel arm, 55 patients (20.4%) received poststudy immunotherapy after discontinuation from docetaxel treatment compared with 40 patients (7.5%) in the tislelizumab arm (Supplementary Fig. 4).

Efficacy

The prespecified interim analysis was performed when 441 OS events were observed in the ITT population (data cutoff: August 10, 2020). OS in the ITT population was tested at one-sided α of 0.012 as determined on the basis of the Hwang-Shih-DeCani spending function with γ parameter of -2. In the interim analysis, there was a statistically significant and clinically meaningful OS benefit in the tislelizumab arm versus the docetaxel arm in the ITT population (median OS 17.2 mo [95% CI: 15.3–20.0] versus 11.9 mo [95% CI: 10.2–13.9], respectively; HR 0.64 [95% CI: 0.53–0.78]; $p < 0.0001$ [Supplementary Fig. 5*A*]). Median OS was also longer with tislelizumab compared with docetaxel in the PD-L1 greater than or equal to 25% population at the interim analysis (median OS = 19.1 mo [95% CI: 16.8–25.8] versus 11.9 mo [95% CI: 8.9–14.0], respectively; HR = 0.52 [95% CI: 0.38–0.71] [Supplementary Fig. 5*B*]). The

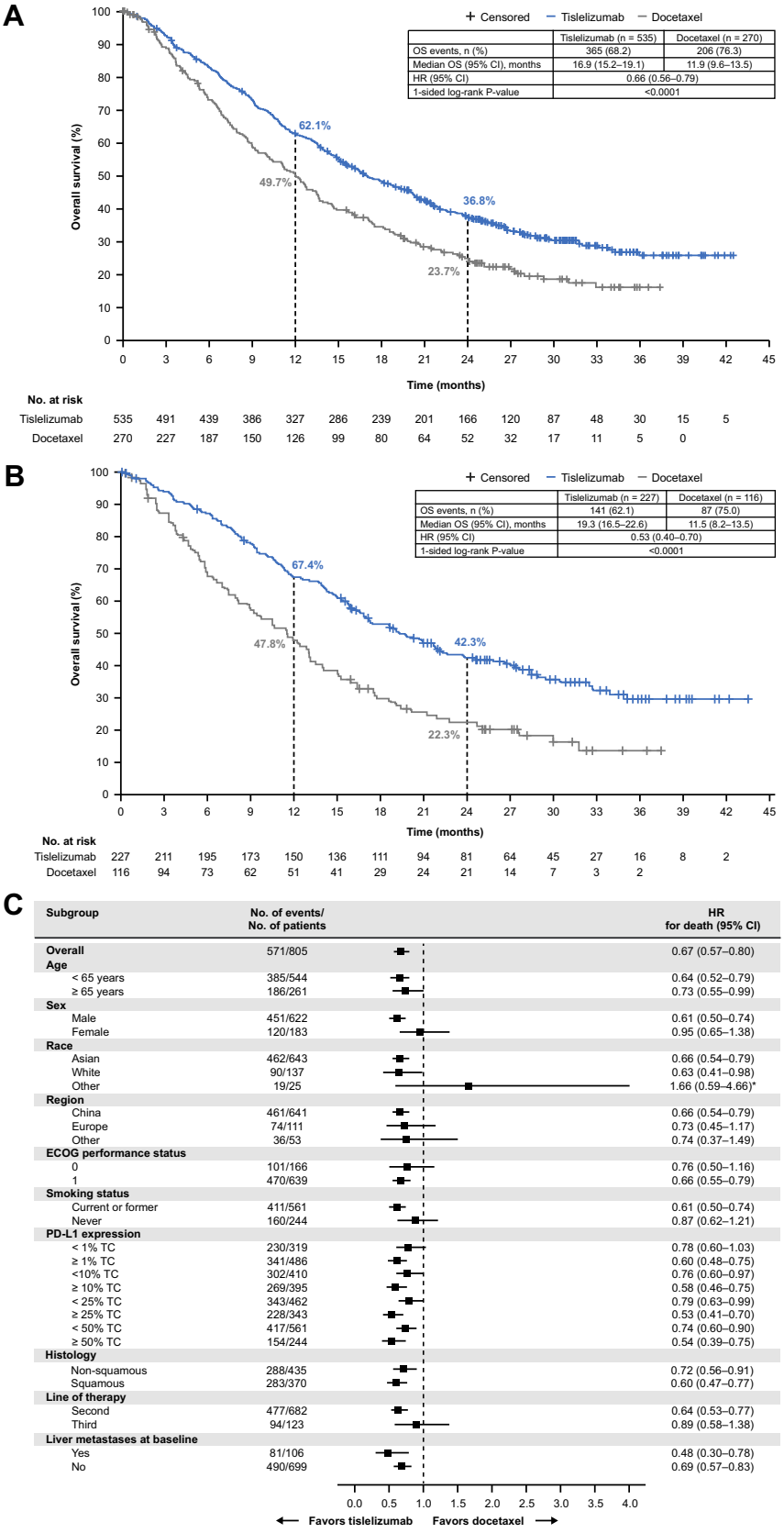

Figure 2. Kaplan–Meier analysis of OS in the ITT population (*A*), PD-L1 greater than or equal to 25% population (*B*), and treatment effects on OS, according to subgroup (ITT population**) (*C*) (final analysis). *The confidence interval of this subgroup is not illustrated completely due to space limit. **ITT population included all randomized patients. For one patient in

Independent Data Monitoring Committee evaluated that the median OS was significantly longer and more clinically meaningful with tislelizumab compared with docetaxel in the ITT population and recommended continuation of the trial to formally test the other co-primary end point of OS in the PD-L1 greater than or equal to 25% population at the final analysis.

At the final analysis data cutoff of July 15, 2021, there were 571 and 228 OS events in the ITT population and PD-L1 greater than or equal to 25% population, respectively. In the ITT population, tislelizumab continued to have OS benefit versus docetaxel (median OS = 16.9 mo [95% CI: 15.2–19.1] versus 11.9 mo [95% CI: 9.6–13.5], respectively; HR = 0.66 [95% CI: 0.56–0.79] [Fig. 2*A*]). OS rates for tislelizumab versus docetaxel at 12 and 24 months in the ITT population were 62.1% versus 49.7% and 36.8% versus 23.7%, respectively. As OS in the ITT population was met at the predefined interim analysis, the final analysis was carried out in the PD-L1 greater than or equal to 25% population at alpha of 0.025. In the PD-L1 greater than or equal to 25% population, tislelizumab had a statistically significant and clinically meaningful OS benefit versus docetaxel (median OS = 19.3 mo [95% CI: 16.5–22.6] versus 11.5 mo [95% CI: 8.2–13.5]; HR = 0.53 [95% CI: 0.40–0.70], $p < 0.0001$). OS rates for tislelizumab versus docetaxel at 12 and 24 months in the PD-L1 greater than or equal to 25% population were 67.4% and 47.8% versus 42.3% and 22.3%, respectively (Fig. 2*B*). In the PD-L1 less than 25% population, median OS for tislelizumab was 15.2 months (95% CI: 13.2–17.6) versus 12.3 months (95% CI: 9.3–14.3) for docetaxel (HR = 0.77 [95% CI: 0.62–0.96]). OS rates for tislelizumab versus docetaxel at 12 and 24 months in the PD-L1 less than 25% population were 58.3% versus 51.1% and 32.8% versus 24.7%, respectively.

A consistent OS benefit was observed for tislelizumab versus docetaxel for most studied subgroups in the ITT population, including at all levels of PD-L1 expression, different histologies, and patients with liver metastases at baseline. Similar OS benefit was observed in Asian and White patients (Fig. 2*C*).

The benefit of tislelizumab treatment was also supported by other key secondary end points, including PFS (HR = 0.63 [95% CI: 0.53–0.75; $p < 0.0001$] [Supplementary Fig. 6] and 0.37 [95% CI: 0.28–0.49, $p < 0.0001$] in the ITT and PD-L1 greater than or equal to 25% populations [data not found herein], respectively). Higher ORR and longer DoR were noted in the tislelizumab arm versus the docetaxel arm in the ITT population (ORR = 22.6% [95% CI: 19.1–26.4] versus 7.1% [95% CI: 4.3–10.8], respectively [$p < 0.0001$]; median DoR = 13.5 [95% CI: 8.5–19.6] versus 6.0 [95% CI: 2.1–7.2] mo, respectively) and in the PD-L1 greater than or equal to 25% population (ORR = 37.4% [95% CI: 31.3–44.1] versus 6.9% [95% CI: 3.0–13.1], respectively [$p < 0.0001$]; median DoR = 11.9 [95% CI: 8.3–19.6] versus 4.2 [95% CI: 0.6–6.1] mo, respectively). ORR and DCR in the ITT population are found in Supplementary Figure 7 and DoR in the ITT population is found in Supplementary Figure 8. In patients who experienced progressive disease, the change in tumor burden over time in the tislelizumab arm and the docetaxel arm is found in Supplementary Figure 9.

Efficacy in the BE Population. In the biomarker analysis, the association of TMB and genetic alterations at baseline, including single target gene mutation or pathway mutations, with clinical outcomes was explored. Tissue TMB was correlated with PFS benefit for tislelizumab versus docetaxel but was not correlated with OS benefit, except at the highest cutoff (≥14 mutations/megabase) (Supplementary Fig. 10). Nevertheless, among tested single target gene mutation or pathway mutations, *NOTCH1–4* mutation was correlated with improved PFS and OS benefits for tislelizumab.

Kaplan-Meier analyses of OS and PFS in the BE population according to *NOTCH1–4* mutation status are depicted in Figure 3. Tislelizumab treatment had a greater OS benefit for patients with *NOTCH1–4* mutation than wild type, compared with the docetaxel arm. At the final analysis data cutoff of July 15, 2021, median OS for patients with *NOTCH1–4* mutations was 24.7 months in the tislelizumab arm (95% CI: 14.2–not estimable) versus 7.7 months in the docetaxel arm (95% CI: 3.3–14.3; HR = 0.22 [95% CI: 0.10–0.49]; $p = 0.0002$). Patients with *NOTCH* wild type also benefited from tislelizumab treatment with median OS of 15.7 months (95% CI: 13.9–17.9) versus 12.9 months in the docetaxel arm (95% CI: 10.4–14.9; HR = 0.75 [95% CI: 0.57–0.99]; $p = 0.0390$) (Fig. 3*A*).

Similarly, patients with *NOTCH1–4* mutations had relatively better PFS benefit from tislelizumab treatment than patients carrying *NOTCH* wild type. Median PFS with tislelizumab was 14.1 months (95% CI: 6.2–not estimable) versus 2.6 months in the docetaxel arm (95%

the docetaxel arm, the month and day of death date are missing. This patient was censored at last known alive date in the OS analysis. One-sided *p* values were estimated from stratified log-rank test. HRs were 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. Data cutoff: July 15, 2021. CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; PD-L1, programmed death-ligand 1; TC, tumor cell.

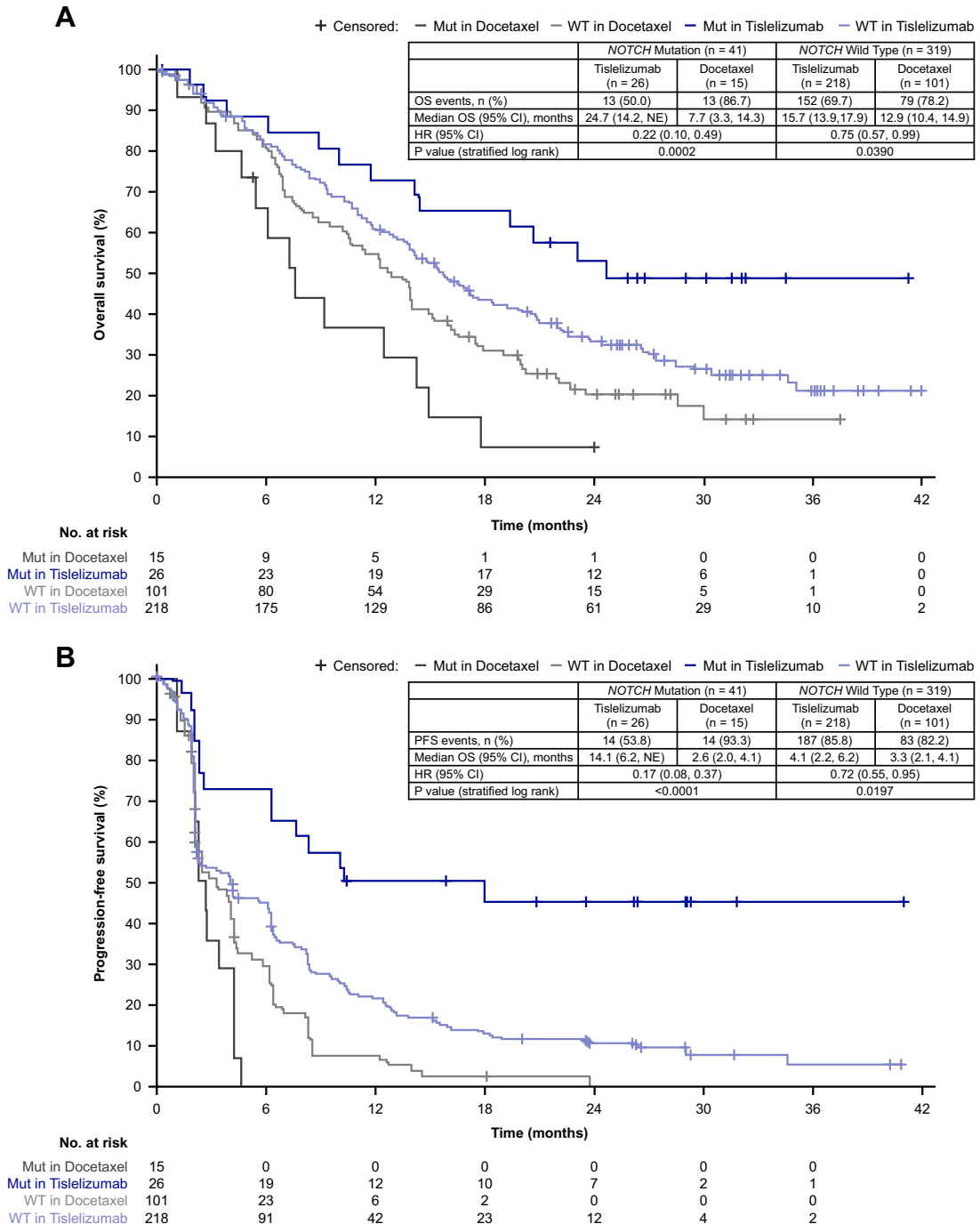

Figure 3. Kaplan-Meier analysis of OS (*A*) and PFS (*B*) (BE population*) according to *NOTCH* mutation status (final analysis). *BE population included all randomized patients with assessable mutation data. HRs were estimated from stratified Cox model with docetaxel group as reference group. Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. Data cutoff: July 15, 2021. The *p* values are descriptive. BE, biomarker evaluable; CI, confidence interval; HR, hazard ratio; Mut, mutation; NE, not estimable; OS, overall survival; PFS, progression-free survival; WT, wild type.

CI: 2.0–4.1) for patients with *NOTCH1–4* mutations (HR = 0.17 [95% CI: 0.08–0.37], $p < 0.0001$). Median PFS with tislelizumab was 4.1 months (95% CI: 2.2–6.2) versus 3.3 months in the docetaxel arm (95% CI: 2.1–4.1) for patients carrying *NOTCH* wild type (HR = 0.72 [95% CI: 0.55–0.95]; $p = 0.0197$) (Fig. 3*B*).

Safety

The safety population encompassed all patients receiving any dose of the study drug and included 534 patients in the tislelizumab arm and 258 in the docetaxel arm. At the final analysis data cutoff of July 15, 2021 (after the additional 11-mo follow-up period beyond the interim analysis), median duration of exposure was 24.0 weeks (range: 1–188 wk) in the tislelizumab arm and 9.1 weeks (range: 1–154 wk) in the docetaxel arm. The median number of treatment cycles was 8.0 (range: 1–62 cycles) in the tislelizumab arm versus 3.0 (range: 1–50 cycles) in the docetaxel arm. Overall, with more than two times longer median duration of exposure to treatment, patients in the tislelizumab arm generally experienced a

Table 2. TEAEs and TRAEs Occurring in Greater Than or Equal to 10% of Patients (Safety Population)

Preferred Term	Tislelizumab (n = 534)		Docetaxel (n = 258)	
TEAEs occurring in ≥10% of patients,[a] n (%)	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Anemia	156 (29.2)	18 (3.4)	115 (44.6)	18 (7.0)
Cough	114 (21.3)	5 (0.9)	40 (15.5)	1 (0.4)
ALT increased	110 (20.6)	5 (0.9)	39 (15.1)	0 (0.0)
AST increased	104 (19.5)	5 (0.9)	32 (12.4)	1 (0.4)
Decreased appetite	88 (16.5)	5 (0.9)	62 (24.0)	3 (1.2)
Weight decreased	86 (16.1)	4 (0.7)	30 (11.6)	0 (0.0)
Hypoalbuminemia	76 (14.2)	1 (0.2)	40 (15.5)	1 (0.4)
Asthenia	75 (14.0)	7 (1.3)	58 (22.5)	14 (5.4)
Constipation	73 (13.7)	0 (0.0)	43 (16.7)	0 (0.0)
Pneumonia	71 (13.3)	40 (7.5)	36 (14.0)	24 (9.3)
Arthralgia	68 (12.7)	1 (0.2)	24 (9.3)	1 (0.4)
Dyspnea	67 (12.5)	11 (2.1)	36 (14.0)	7 (2.7)
Hypothyroidism	62 (11.6)	0 (0.0)	2 (0.8)	0 (0.0)
Pyrexia	61 (11.4)	2 (0.4)	26 (10.1)	0 (0.0)
Nausea	61 (11.4)	0 (0.0)	43 (16.7)	1 (0.4)
Hemoptysis	59 (11.0)	6 (1.1)	22 (8.5)	3 (1.2)
Hyperglycemia	55 (10.3)	8 (1.5)	29 (11.2)	3 (1.2)
Hyponatremia	52 (9.7)	10 (1.9)	29 (11.2)	11 (4.3)
Diarrhea	40 (7.5)	4 (0.7)	35 (13.6)	5 (1.9)
Insomnia	33 (6.2)	1 (0.2)	26 (10.1)	0 (0.0)
White blood cell count decreased	20 (3.7)	1 (0.2)	74 (28.7)	47 (18.2)
Leukopenia	17 (3.2)	1 (0.2)	73 (28.3)	41 (15.9)
Neutrophil count decreased	16 (3.0)	3 (0.6)	95 (36.8)	71 (27.5)
Neutropenia	10 (1.9)	3 (0.6)	81 (31.4)	72 (27.9)
Alopecia	7 (1.3)	0 (0.0)	126 (48.8)	2 (0.8)
Febrile neutropenia	0 (0.0)	0 (0.0)	33 (12.8)	33 (12.8)
TRAEs occurring in ≥10% of patients,[a] n (%)	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
ALT increased	91 (17.0)	5 (0.9)	34 (13.2)	0 (0.0)
AST increased	81 (15.2)	4 (0.7)	30 (11.6)	1 (0.4)
Anemia	60 (11.2)	5 (0.9)	97 (37.6)	13 (5.0)
Hypothyroidism	60 (11.2)	0 (0.0)	0 (0.0)	0 (0.0)
Asthenia	40 (7.5)	1 (0.2)	46 (17.8)	10 (3.9)
Decreased appetite	33 (6.2)	1 (0.2)	50 (19.4)	2 (0.8)
Nausea	31 (5.8)	0 (0.0)	34 (13.2)	1 (0.4)
Diarrhea	19 (3.6)	2 (0.4)	29 (11.2)	5 (1.9)
White blood cell count decreased	13 (2.4)	1 (0.2)	73 (28.3)	46 (17.8)
Constipation	13 (2.4)	0 (0.0)	26 (10.1)	0 (0.0)
Leukopenia	13 (2.4)	0 (0.0)	71 (27.5)	40 (15.5)
Neutrophil count decreased	9 (1.7)	1 (0.2)	93 (36.0)	70 (27.1)
Neutropenia	5 (0.9)	0 (0.0)	78 (30.2)	70 (27.1)
Alopecia	4 (0.7)	0 (0.0)	123 (47.7)	2 (0.8)
Febrile neutropenia	0 (0.0)	0 (0.0)	33 (12.8)	33 (12.8)

Note: Safety population included all patients receiving any dose of the study drug. Data cutoff: July 15, 2021.

[a]In either treatment arm.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

lower incidence of TEAEs compared with those in the docetaxel arm. As of July 15, 2021, data cutoff, 96.8% of patients in the tislelizumab arm and 98.4% of patients in the docetaxel arm had experienced at least one TEAE (any grade and any cause) (Supplementary Table 2). Fewer patients reported TEAEs of grade greater than or equal to 3 in the tislelizumab arm than in the docetaxel arm (42.1% versus 74.8%, respectively) (Supplementary Table 2). Treatment-related AEs (TRAEs) were lower in severity and occurred in a lower proportion of patients in the tislelizumab arm than in the docetaxel arm (74.9% versus 93.8% of patients had TRAEs of any grade and 15.7% versus 66.3% of patients had TRAEs of grade $\geq$ 3, respectively) (Supplementary Table 2). TEAEs and TRAEs occurring in greater than or equal to 10% of patients are summarized in Table 2. TEAEs leading to death occurred in 6.4% of patients in the tislelizumab arm and 4.7% in the docetaxel arm. Eight deaths (1.5%) in the tislelizumab arm and four deaths (1.6%) in the docetaxel arm were considered to be treatment related (Supplementary Table 2). The incidence of immune-mediated TEAEs of all grades in the tislelizumab arm was 18.9%, with hypothyroidism (7.9%), pneumonitis and immune-mediated lung disease (4.5%) being the most often occurring events (Supplementary Fig. 11).

Discussion

The phase 3 RATIONALE-303 study met both the coprimary end points of OS in the ITT and PD-L1 greater than or equal to 25% populations. At the interim analysis, the risk of death was reduced by 36% in the tislelizumab arm compared with the docetaxel arm in the ITT population. On the basis of this statistically significant and clinically relevant improvement in OS, tislelizumab was approved in the People's Republic of China for the treatment of patients with advanced NSCLC with disease progression while receiving, or after, platinum-based chemotherapy. The final analysis was carried out in the PD-L1 greater than or equal to 25% population and revealed a statistically significant improvement in OS with tislelizumab compared with docetaxel in the PD-L1 greater than or equal to 25% population with HR of 0.53. At this final analysis, after the additional 11 months of follow-up beyond the interim analysis, OS benefit continued to be found in the tislelizumab arm compared with the docetaxel arm in the ITT population (OS HR = 0.66). A consistent OS benefit was observed for tislelizumab versus docetaxel in most of the studied subgroups in the ITT population, including at all levels of PD-L1 expression, different histologies, and in patients with liver metastases, which have been reported to be associated with worse prognosis and lower benefit from PD-1/PD-L1 monotherapy.[16–18] Similar efficacy benefits were observed in Asian and White patients. In addition, tislelizumab improved PFS versus docetaxel with HRs of 0.37 and 0.63 in the PD-L1 greater than or equal to 25% and ITT populations, respectively.

Our results, with median OS exceeding 16 months (ITT population) with tislelizumab treatment, are encouraging for this patient population. Prolongation of median OS by 7.8 and 5.0 months in the tislelizumab arms versus docetaxel (for the PD-L1 $\geq$ 25% and ITT populations, respectively) compared favorably with historical anti–PD-1 anti-PD-L1 treatment in second- or third-line NSCLC clinical trials.[4–7,19] It has been suggested that a high frequency of poststudy use of ICIs in the control arm might affect OS outcomes.[8] In our study, the frequency of poststudy use of immunotherapy (20.4% in the docetaxel arm versus 7.5% in the tislelizumab arm) is higher than that in previous trials in this setting; nevertheless, a marked OS benefit was still observed in the tislelizumab arm. The availability of more options for poststudy anticancer therapy than ever before could be an important factor leading to a longer median OS for both arms than previously reported. Among these poststudy therapies, some anticancer drugs have been approved on the basis of survival benefit in third-line NSCLC therapy. In addition, the early separation of the Kaplan-Meier OS curves in the first 3 months observed here suggests that tislelizumab may be associated with a lower rate of hyperprogressive disease, fast progression, and early mortality; these early events can affect the shape of the Kaplan–Meier OS curves during the first 3 to 6 months of treatment.[20–22] Molecular interactions between ICI antibodies and macrophages by means of Fc receptors have been proposed as a mechanism for hyperprogressive disease in NSCLC after PD-1 or PD-L1 blockade.[23] Given the property of tislelizumab to minimize Fc gamma receptor binding on macrophages,[9] it may therefore be associated with lower rates of hyperprogressive disease and other early events.

In the exploratory biomarker analysis, we observed that tissue TMB was correlated with PFS, but not OS benefit, for tislelizumab versus docetaxel. Similar outcomes have been observed with blood TMB, for example, the BFAST trial revealed no survival benefit of atezolizumab monotherapy as first-line treatment of metastatic NSCLC in patients with high blood TMB versus chemotherapy.[24] Although TMB can be a useful prognostic indicator for patients receiving treatment with ICIs, there is currently only limited evidence for a predictive role in this context.[24–26] In addition, tissue TMB was available for only 45% of patients in this study which underlines the practical difficulties in TMB testing in routine clinical practice.[25] Given that TMB focuses on the number of mutations in the tumor genome, which may include mutations that exert influences on the clinical outcome in different directions, single target gene mutations and

pathway mutations were further explored. Patients with *NOTCH1–4* mutation had greater benefit of tislelizumab versus chemotherapy than patients with wild-type *NOTCH1–4* for both PFS and OS. The NOTCH pathway, a highly conserved signaling system, is regulated by short-range cell–cell interactions between NOTCH receptor (NOTCH1–4) and ligands and plays a critical role in tissue homeostasis, fetal development, and organogenesis. It has been suggested that *NOTCH* mutation in NSCLC may be dominated by inhibitory function as revealed by the pattern of mutational loci in NSCLC on the basis of data in the Catalogue of Somatic Mutations in Cancer database.[27,28] *NOTCH* mutation was also reported to be associated with an activated immune microenvironment, including infiltration of M1 macrophages and antigen processing by means of degradation in the proteasome, which may partially explain the underlying mechanism of *NOTCH* mutation in association with better immunotherapeutic outcomes.[27,29] Moreover, in contrast to the findings in the tislelizumab arm, patients with *NOTCH* mutation had lower benefit from docetaxel treatment than those with wild-type *NOTCH*. Owing to the small numbers of patients with *NOTCH* mutation in this study, the relationship between *NOTCH1–4* mutation status and the efficacy of ICIs need to be explored further.

In the final analysis, no new safety signals were identified for tislelizumab after 11 months of additional follow-up. Tislelizumab treatment maintained a favorable safety profile compared with docetaxel, with a lower proportion of patients experiencing grade greater than or equal to 3 TEAEs. This was consistent with other anti–PD-1 or anti-PD-L1 trials in previously treated patients.[4–8,19] The incidence and nature of immune-mediated TEAEs with tislelizumab were consistent with previous anti–PD-1 or anti-PD-L1 trials in this setting.[4–8,19]

In recent years, addition of immunotherapy to platinum-based doublet chemotherapy has become the new standard of care in NSCLC first-line treatment,[30,31] although access to first-line immunotherapy can still be limited in certain countries or regions. Moreover, for patients with nonsquamous NSCLC, the addition of first-line bevacizumab to carboplatin/paclitaxel produced comparable efficacy to current anti–PD-1 or anti-PD-L1 antibody plus chemotherapy and continues to be an alternative first-line treatment.[32] Therefore, we believe that there is still a substantial proportion of patients with NSCLC who remain immunotherapy naive after receiving first-line treatment or who either do not have access to first-line immunotherapy or else do not receive it.

Limitations

The study was initially intended to enroll approximately 640 patients only in the People's Republic of China, but the enrollment was subsequently expanded to other countries. Therefore, patients from outside of the People's Republic of China had a relatively shorter duration of follow-up than the Chinese patients. The use of an open-label design may have influenced investigator assessments such as PFS and response which were secondary or exploratory end points. Regulatory approvals for nivolumab in this treatment setting started to be obtained in some of the participating countries at the time of trial accrual, but patient access is very limited. Therefore, docetaxel remained an often used standard therapy option in second- and third-line NSCLC treatment. In line with other second-/third-line NSCLC treatment trials,[4–8,19,33] our study retained this often available standard therapy, without permitting crossover, in the control arm in compliance with the ethical principles listed in ICH E10, but it was a limitation of the study design. In addition, the limited proportion of patients (45%) with tissue TMB available and small numbers of patients with *NOTCH* mutation were also a limitation, which may lead to bias and preclude a firm conclusion, so further investigation in larger cohorts is needed.

In conclusion, tislelizumab had a marked improved and long-term clinical benefit in OS, PFS, ORR, and DoR than docetaxel in patients with locally advanced or metastatic NSCLC who progressed on or after platinum-based chemotherapy, regardless of tumor PD-L1 expression or pathologic type. Tislelizumab had sustained tolerability with a favorable safety profile compared with docetaxel. Tislelizumab represents an additional treatment option for patients with NSCLC who do not receive ICIs in first line (e.g., owing to limited access to this class of medication or selection of a platinum-based doublet plus bevacizumab as first-line treatment). *NOTCH1–4* mutation may be a potential biomarker for predicting the improved efficacy of tislelizumab monotherapy worthy of further validation in a randomized prospective trial.

CRediT Authorship Contribution Statement

Caicun Zhou: Conceptualization, Methodology, Supervision, Investigation, Writing—review and editing.

Dingzhi Huang, Ziping Wang, Xinmin Yu, Yunpeng Liu, Yongqian Shu, Sheng Hu, Zhihua Liu, Gareth Rivalland: Investigation, Writing—review and editing.

Yun Fan, Zhiyong Ma, Ying Cheng, Jie Wang: Supervision, Investigation, Writing—review and editing.

Elena Poddubskaya, Umut Disel, Andrey Akopov, Mikhail Dvorkin: Investigation, Writing—review and editing.

Wenjuan Zheng: Project administration, Writing—review and editing.

Yiyuan Ma: Conceptualization, Methodology, Project administration, Writing—review and editing.

Yan Wang: Project administration, Writing—review and editing.

Songzi Li: Data curation, Formal analysis, Writing—review and editing.

Cunjing Yu: Project administration, Investigation, Writing—review and editing.

Data Availability

On request, and subject to certain criteria, conditions, and exceptions, BeiGene, Ltd., will provide access to individual deidentified participant data from BeiGene-sponsored global interventional clinical studies conducted for medicines (1) for indications that have been approved or (2) in programs that have been terminated. BeiGene will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data requests may be submitted to DataDisclosure@beigene.com.

Acknowledgments

Financial support for this study was provided by BeiGene, Ltd. BeiGene, Ltd., had a role in the study design, data collection, data analysis, and data interpretation. Funding for medical writing support was provided by BeiGene. The authors had full access to all data in the study and had final responsibility for the decision to submit for publication. The authors thank the investigators, Steering Committee members, Rafal Dziadziuszko, MD, Gilberto de Castro Jr., MD, patients, and site personnel who made this study possible. Third-party medical writing assistance under the direction of the authors was provided by Simon Lancaster, BSc, of Ashfield MedComms, an Inizio company, and was funded by BeiGene, Ltd. This study was sponsored by BeiGene, Ltd.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2022.09.217.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209-249.
2. Howlader N, Noone AM, Krapcho M, et al. *SEER Cancer Statistics Review, 1975-2017*. Bethesda, MD: National Cancer Institute; 2020.
3. Carlisle JW, Ramalingam SS. A banner year for immunotherapy and targeted therapy. *Nat Rev Clin Oncol*. 2019;16:79-80.
4. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. 2015;373:1627-1639.
5. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med*. 2015;373:123-135.
6. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. 2016;387:1540-1550.
7. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet*. 2017;389:255-265.
8. Barlesi F, Vansteenkiste J, Spigel D, et al. Avelumab versus docetaxel in patients with platinum-treated advanced non-small-cell lung cancer (JAVELIN Lung 200): an open-label, randomised, phase 3 study. *Lancet Oncol*. 2018;19:1468-1479.
9. Zhang T, Song X, Xu L, et al. The binding of an anti-PD-1 antibody to FcγRI has a profound impact on its biological functions. *Cancer Immunol Immunother*. 2018;67:1079-1090.
10. Xu J, Bai Y, Xu N, et al. Tislelizumab plus chemotherapy as first-line treatment for advanced esophageal squamous cell carcinoma and gastric/gastroesophageal junction adenocarcinoma. *Clin Cancer Res*. 2020;26:4542-4550.
11. Ye D, Liu J, Zhou A, et al. Tislelizumab in Asian patients with previously treated locally advanced or metastatic urothelial carcinoma. *Cancer Sci*. 2021;112:305-313.
12. Wang Z, Zhao J, Ma Z, et al. A phase 2 study of tislelizumab in combination with platinum-based chemotherapy as first-line treatment for advanced lung cancer in Chinese patients. *Lung Cancer*. 2020;147:259-268.
13. Lu S, Wang J, Yu Y, et al. Tislelizumab plus chemotherapy as first-line treatment for locally advanced or metastatic nonsquamous NSCLC (RATIONALE 304): a randomized phase 3 trial. *J Thorac Oncol*. 2021;16:1512-1522.
14. Wang J, Lu S, Yu X, et al. Tislelizumab plus chemotherapy vs chemotherapy alone as first-line treatment for advanced squamous non-small cell lung cancer: a phase 3 randomized clinical trial. *JAMA Oncol*. 2021;7:709-717.
15. Tang Y, Li Y, Wang W, et al. Tumor mutation burden derived from small next generation sequencing targeted gene panel as an initial screening method. *Transl Lung Cancer Res*. 2020;9:71-81.
16. Tumeh PC, Hellmann MD, Hamid O, et al. Liver metastasis and treatment outcome with anti-PD-1 monoclonal antibody in patients with melanoma and NSCLC. *Cancer Immunol Res*. 2017;5:417-424.
17. Paz-Ares LG, Shen K, Higgs BW, et al. Association of liver metastases (LM) with survival in NSCLC patients treated with durvalumab (D) in two independent clinical trials. *J Clin Oncol*. 2017;35(suppl 15):3038-3038.
18. Pillai RN, Kamphorst AO, Owonikoko TK, et al. Liver metastases and sensitivity to checkpoint inhibition in patients with non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2016;34(suppl 15):e20665-e20665.

19. Wu YL, Lu S, Cheng Y, et al. Nivolumab versus docetaxel in a predominantly Chinese patient population with previously treated advanced NSCLC: CheckMate 078 randomized phase III clinical trial. *J Thorac Oncol*. 2019;14:867–875.
20. Ferrara R, Mezquita L, Texier M, et al. Hyperprogressive disease in patients with advanced non-small cell lung cancer treated with PD-1/PD-L1 inhibitors or with single-agent chemotherapy. *JAMA Oncol*. 2018;4:1543–1552.
21. Ferrara R, Mezquita L, Texier M, et al. Comparison of fast-progression, hyperprogressive disease, and early deaths in advanced non-small-cell lung cancer treated with PD-1/PD-L1 inhibitors or chemotherapy. *JCO Precis Oncol*. 2020;4:829–840.
22. Gandara D, Reck M, Moro-Sibilot D, et al. Fast progression in non-small cell lung cancer: results from the randomized phase III OAK study evaluating second-line atezolizumab versus docetaxel. *J Immunother Cancer*. 2021;9:e001882.
23. Lo Russo G, Moro M, Sommariva M, et al. Antibody-Fc/FcR interaction on macrophages as a mechanism for hyperprogressive disease in non-small cell lung cancer subsequent to PD-1/PD-L1 blockade. *Clin Cancer Res*. 2019;25:989–999.
24. Dziadziuszko R, Peters S, Gadgeel SM, et al. 12810 - Atezolizumab (atezo) vs platinum-based chemo in blood-based tumour mutational burden-positive (bTMB+) patients (pts) with first-line (1L) advanced/metastatic (m)NSCLC: results of the Blood First Assay Screening Trial (BFAST) phase III cohort C. *Ann Oncol*. 2021;32:S950–S951.
25. Dall'Olio FG, Marabelle A, Caramella C, et al. Tumour burden and efficacy of immune-checkpoint inhibitors. *Nat Rev Clin Oncol*. 2022;19:75–90.
26. Sha D, Jin Z, Budczies J, Kluck K, Stenzinger A, Sinicrope FA. Tumor mutational burden as a predictive biomarker in solid tumors. *Cancer Discov*. 2020;10:1808–1825.
27. Zhang K, Hong X, Song Z, et al. Identification of deleterious *NOTCH* mutation as novel predictor to efficacious immunotherapy in NSCLC. *Clin Cancer Res*. 2020;26:3649–3661.
28. Catalogue of Somatic Mutations in Cancer (COSMIC). Database. https://cancer.sanger.ac.uk/cosmic. Accessed May 10, 2022.
29. Long J, Wang D, Yang X, et al. Identification of NOTCH4 mutation as a response biomarker for immune checkpoint inhibitor therapy. *BMC Med*. 2021;19:154.
30. Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28(suppl 4):iv1–iv21.
31. Planchard D, Popat S, Kerr K, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up. https://www.esmo.org/content/download/347819/6934778/1/ESMO-CPG-mNSCLC-15SEPT2020.pdf. Accessed April 2, 2021.
32. Zhou C, Wu YL, Chen G, et al. BEYOND: a randomized, double-blind, placebo-controlled, multicenter, phase III study of first-line carboplatin/paclitaxel plus bevacizumab or placebo in Chinese patients with advanced or recurrent nonsquamous non-small-cell lung cancer. *J Clin Oncol*. 2015;33:2197–2204.
33. Zhou C, Caglevic C, Zhou J, et al. KEYNOTE-033: phase 3 study of pembrolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (NSCLC). *Ann Oncol*. 2017;28(suppl 10):X143.