第25届全国临床肿瘤学大会
暨2022年CSCO学术年会
2022年9月21日–25日 中国·厦门

Tislelizumab versus Docetaxel in Previously Treated Advanced Non-Small Cell Lung Cancer (NSCLC): Final Analysis of RATIONALE-303

Caicun Zhou[1]*, Dingzhi Huang[2], Yun Fan[3], Xinmin Yu[3], Yunpeng Liu[4], 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], Andrey Akopov[14], Mikhail Dvorkin[15], Yan Wang[16], Songzi Li[17], Cunjing Yu[16], Gareth Rivalland[18]

*[1]Department of Medical Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, 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]Department of Thoracic Medical Oncology, Cancer Hospital of University of Chinese Academy of Sciences & Zhejiang Cancer Hospital, Hangzhou, China; [4]The First Hospital of China Medical University, Shenyang, China; [5]Department of Oncology, Jiangsu Province Hospital, Nanjing, China; [6]The Affiliated Cancer Hospital of Zhengzhou University/Henan Cancer Hospital, Zhengzhou, China; [7]Department of Thoracic Medical Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China; [8]Department of Medical Thoracic Oncology, Jilin Cancer Hospital, Changchun, China; [9]Department of Medical Oncology, State Key Laboratory of Molecular Oncology, National Cancer Centre/National Clinical Research Centre 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]Clinical Center Vitamed and Sechenov University, Moscow, Russia; [13]Acibadem Health Group - Adana Acibadem Hospital/Medical Oncology, Adana, Turkey; [14]Pavlov First State Medical University, Saint-Petersburg, Russia; [15]BHI of Omsk Region Clinical Oncology Dispensary, Omsk, Russia; [16]BeiGene (Beijing) Co., Ltd., Beijing, China; [17]BeiGene, Ltd., Ridgefield Park, NJ, USA; [18]Department of Cancer and Blood, Auckland City Hospital, Auckland, New Zealand. *Presenting author*

Conclusions

- **Tislelizumab continued to improve overall survival (OS) vs docetaxel in patients with pretreated advanced NSCLC at final analysis**
- **Exploratory biomarker analysis showed a potential association of *NOTCH1-4* mutations with greater tislelizumab efficacy for both OS and progression-free survival (PFS)**
- **In the final analysis, no new safety signals were identified in the tislelizumab arm after 11 months of additional follow-up**
- **Tislelizumab treatment maintained a favorable safety profile compared with docetaxel, with fewer ≥Grade 3 TEAEs**

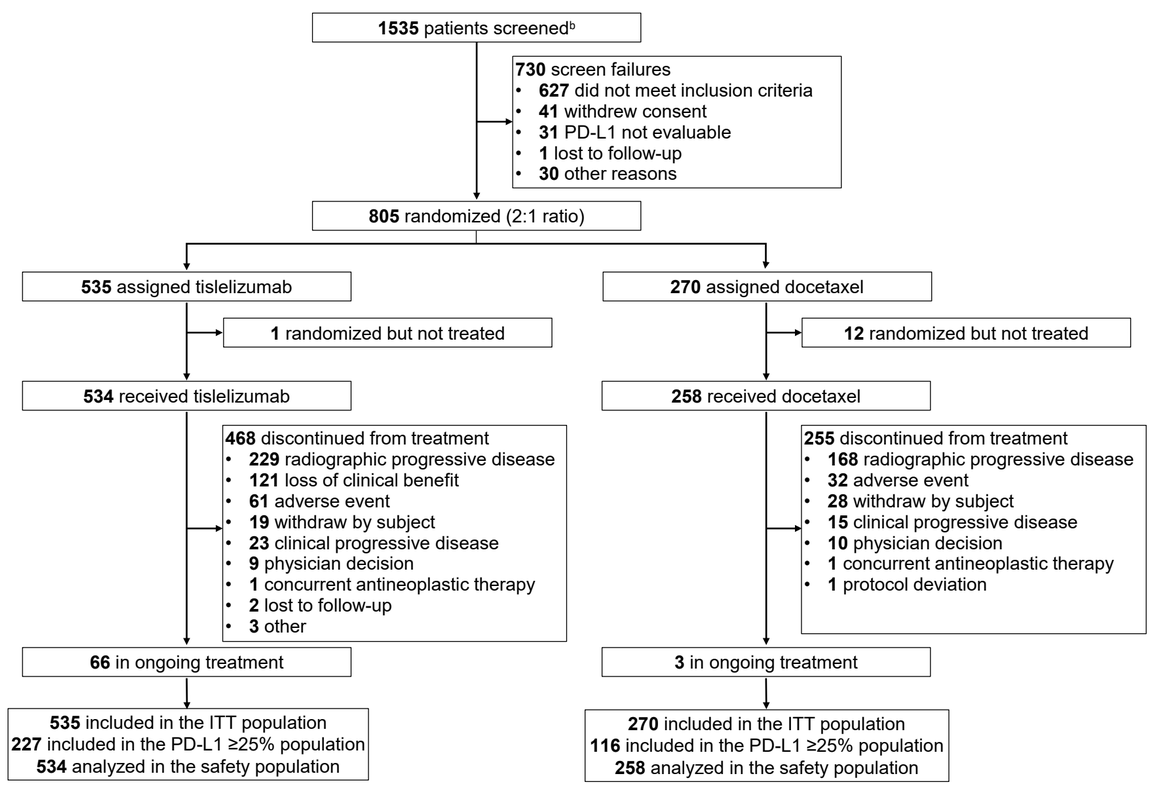
Background

- Anti-programmed cell death protein 1/death-ligand 1 (PD-[L]1) therapies have improved OS by 3-4 months vs docetaxel in patients with advanced NSCLC who progressed after platinum-based chemotherapy[1-4]
- Tislelizumab is a monoclonal antibody with high binding affinity to the PD-1 receptor, which was specifically engineered to minimize Fcγ receptor binding on macrophages[5,6]
- In RATIONALE-303, tislelizumab significantly prolonged OS vs docetaxel in the intent-to-treat (ITT) population at the interim analysis (IA) (data cutoff: August 10, 2020),[7] leading to its approval in China for patients with advanced NSCLC whose disease progressed after chemotherapy[8]
- Here, we report the outcomes of the final analysis and post hoc exploratory biomarker analysis (Clinicaltrials.gov: NCT03358875)

Methods

- Patients ≥18 years with histologically confirmed, locally advanced or metastatic squamous or nonsquamous NSCLC were randomized (2:1) to tislelizumab 200 mg intravenously (IV) or docetaxel 75 mg/m^2 IV every 3 weeks
- Co-primary endpoints were OS in the ITT and PD-L1 tumor cell (TC) ≥25% populations. The study had one planned IA only in the ITT population. The final analysis (FA) for efficacy was conducted in the ITT population and PD-L1 ≥25% population
- Exploratory biomarker analyses included PD-L1 expression, tumor mutational burden (TMB), and gene expression profile

Figure 1. CONSORT diagram (final analysis)[a]



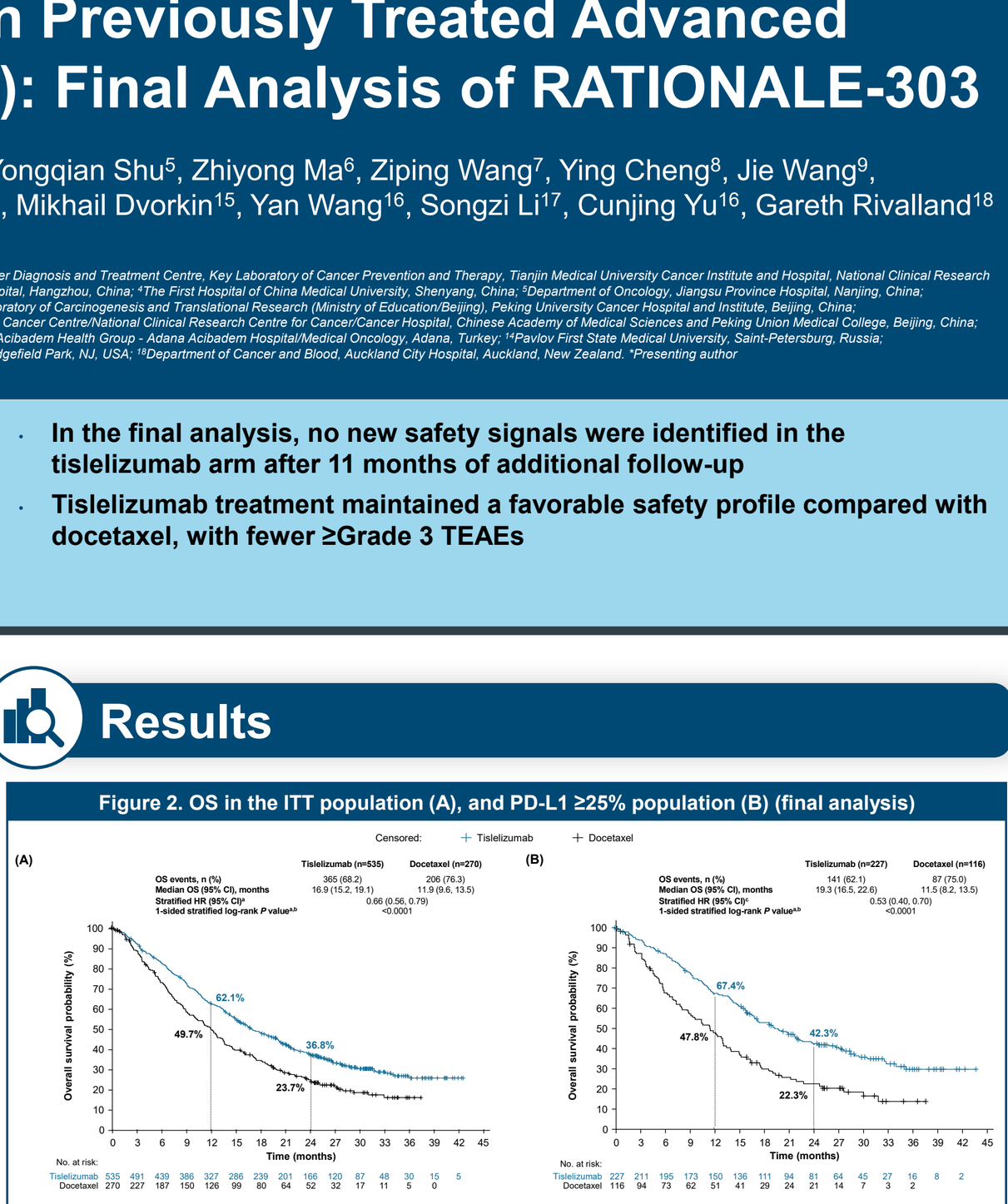
[a]FA data cutoff (July 15, 2021); [b]Signed informed consent. Abbreviations: FA, final analysis; ITT, intent-to-treat; PD-L1, programmed death-ligand 1.

Results

- Between November 2017 and April 2020, 805 patients were randomized to tislelizumab (n=535) or docetaxel (n=270) (**Figure 1**)
- At FA data cutoff (July 15, 2021), median follow-up times were 16.0 months for tislelizumab and 10.7 months for docetaxel in the ITT population
- Baseline demographics and disease characteristics were representative of the target population and were well balanced between both arms, including PD-L1 expression and histology[7]
- The co-primary endpoint of OS in the ITT population was met at the IA. **Figure 2A** is a descriptive update of this endpoint; the OS data at FA are consistent with the OS IA data[7]
- The other co-primary endpoint of OS in the PD-L1 TC ≥25% population was met at the FA (**Figure 2B**)

Results

Figure 2. OS in the ITT population (A), and PD-L1 ≥25% population (B) (final analysis)



Data cutoff: July 15, 2021. [a]Stratified by histology (squamous vs nonsquamous), line of therapy (second vs third), and TC PD-L1 expression (<25% vs ≥25%); [b]*P* value is descriptive; [c]Stratified by histology (squamous vs nonsquamous) and line of therapy (second vs third). Abbreviations: HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; PD-L1, programmed death-ligand 1; TC, tumor cell.

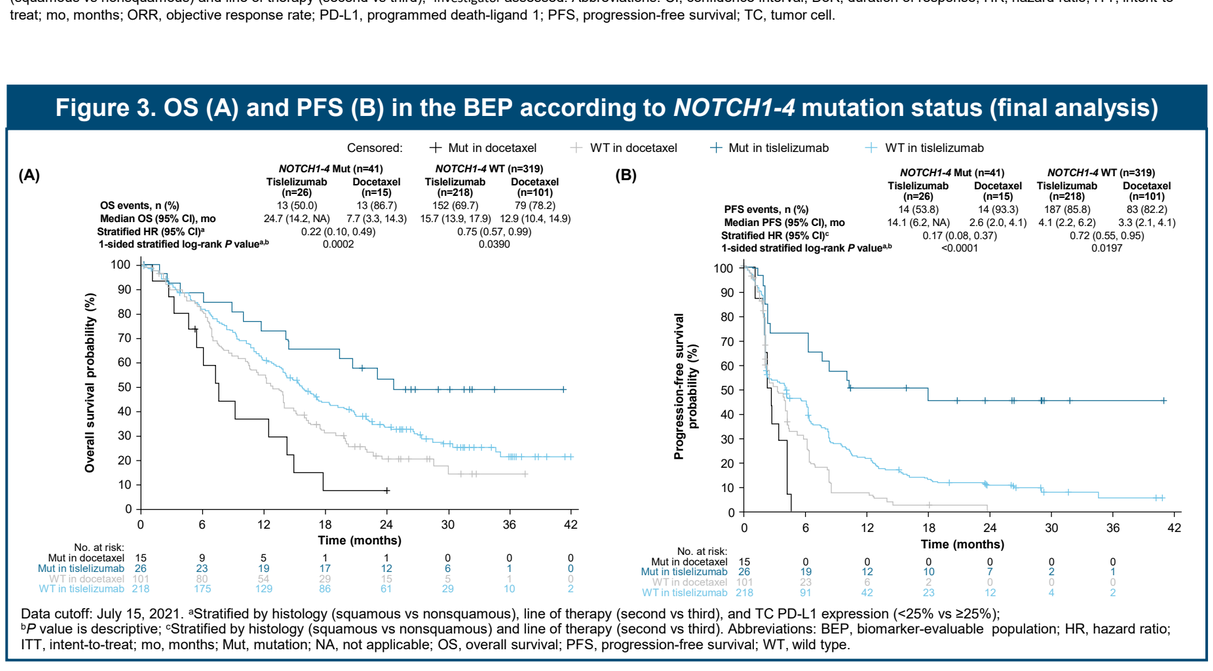
- Results for key secondary endpoints are shown in **Table 1**

Table 1. Secondary efficacy endpoints (final analysis)

	ITT population[a]		PD-L1 TC ≥25% population[b]	
	Tislelizumab (n=535)	Docetaxel (n=270)	Tislelizumab (n=227)	Docetaxel (n=116)
Median PFS (95% CI), mo[c]	4.2 (3.9, 5.5)	2.6 (2.2, 3.8)	6.5 (6.2, 8.3)	2.4 (2.1, 4.1)
Stratified HR (95% CI)	0.63 (0.53, 0.75)		0.37 (0.28, 0.49)	
ORR, n (%)[c]	121 (22.6)	19 (7.0)	85 (37.4)	8 (6.9)
Median DoR, (95% CI), mo[c]	13.5 (8.5, 19.6)	6.0 (2.1, 7.2)	11.9 (8.3, 19.6)	4.2 (0.6, 6.1)

Data cutoff: July 15, 2021. [a]Stratified by histology (squamous vs nonsquamous), line of therapy (second vs third), and TC PD-L1 expression (<25% vs ≥25%); [b]Stratified by histology (squamous vs nonsquamous) and line of therapy (second vs third); [c]Investigator assessed. Abbreviations: CI, confidence interval; DoR, duration of response; HR, hazard ratio; ITT, intent-to-treat; mo, months; ORR, objective response rate; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TC, tumor cell.

Figure 3. OS (A) and PFS (B) in the BEP according to *NOTCH1-4* mutation status (final analysis)



Data cutoff: July 15, 2021. [a]Stratified by histology (squamous vs nonsquamous), line of therapy (second vs third), and TC PD-L1 expression (<25% vs ≥25%); [b]*P* value is descriptive; [c]Stratified by histology (squamous vs nonsquamous) and line of therapy (second vs third). Abbreviations: BEP, biomarker-evaluable population; HR, hazard ratio; ITT, intent-to-treat; mo, months; Mut, mutation; NA, not applicable; OS, overall survival; PFS, progression-free survival; WT, wild type.

Biomarker analysis

- In this post hoc biomarker analysis, *NOTCH1-4* mutations showed a potential association with better tislelizumab efficacy, which was correlated with both OS and PFS benefit (**Figure 3**)
- Tissue TMB was correlated with PFS benefit for tislelizumab vs docetaxel but was not correlated with OS benefit, except at the highest cutoff (≥14 mutations/megabase) (data not shown)

Safety

- No new safety signals were identified (**Table 2**). Fewer ≥Grade 3 TEAEs were reported in the tislelizumab arm than in the docetaxel arm (42.1% vs 74.8%, respectively)

Table 2. TEAEs occurring in ≥15% of patients[a] (safety population[b])

	Tislelizumab (n=534)		Docetaxel (n=258)	
n (%)	**Any grade**	**≥Grade 3**	**Any grade**	**≥Grade 3**
Patients with at least one TEAE				
Any TEAE	517 (96.8)	225 (42.1)	254 (98.4)	193 (74.8)
ALT increased	110 (20.6)	5 (0.9)	39 (15.1)	0 (0)
AST increased	104 (19.5)	5 (0.9)	32 (12.4)	1 (0.4)
Weight decreased	86 (16.1)	4 (0.7)	30 (11.6)	0 (0.0)
Cough	114 (21.3)	5 (0.9)	40 (15.5)	1 (0.4)
Anemia	156 (29.2)	18 (3.4)	115 (44.6)	18 (7.0)
Decreased appetite	88 (16.5)	5 (0.9)	62 (24.0)	3 (1.2)

Data cutoff: July 15, 2021. [a]In the tislelizumab arm; [b]Safety population included all patients receiving at least one dose of study drug. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

References

1. Borghaei H, et al. *N Engl J Med*. 2015;373:1627-1639.
2. Brahmer J, et al. *N Engl J Med*. 2015;373:123-135.
3. Herbst RS, et al. *Lancet*. 2016;387:1540-1550.
4. Rittmeyer A, et al. *Lancet*. 2017;389:255-265.
5. Zhang T, et al. *Cancer Immunol Immunother*. 2018;67:1079-1090.
6. Dahan R, et al. *Cancer Cell*. 2015;28:285-295.
7. Zhou C, et al. AACR 2021; oral presentation.
8. BeiGene. China NMPA approves tislelizumab as second- or third-line treatment for patients with locally advanced or metastatic non-small cell lung cancer. Available at: https://ir.beigene.com/news-details/?id=3e337eaa-a5f6-4368-95e0-3e0d35a71254. Accessed July 2022.

Acknowledgments

This study was sponsored by BeiGene, Ltd. Editorial support was provided by Medical Expressions and funded by BeiGene.

Disclosures

CZ 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, MSD, 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. **GR** has received funding (to individual) for advisory board participation from MSD (Australia) and a speaker honorarium from AstraZeneca. **YW**, **SL**, and **CY** are employees of, and have received stocks from, BeiGene, Ltd. All other authors have declared no competing interests.

***Correspondence:**
caicunzhoudr@163.com (Caicun Zhou)