Tislelizumab Versus Docetaxel in Previously Treated Advanced Non-Small Cell Lung Cancer: Final Analysis of RATIONALE-303

Authors: 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]

Affiliations: [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, New Jersey, USA; [18]Department of Cancer and Blood, Auckland City Hospital, Auckland, New Zealand

Objectives: In RATIONALE-303 (NCT03358875) tislelizumab significantly improved overall survival (OS) versus docetaxel in the intent-to-treat (ITT) population at the interim analysis (IA), based upon which tislelizumab was approved in China for treatment of advanced non-small cell lung cancer (NSCLC) patients with progressive disease after chemotherapy. Here, we report outcomes of the final analysis (FA) and post hoc biomarker analysis.

Methods: Patients ≥18 years with histologically confirmed, locally advanced or metastatic squamous or nonsquamous NSCLC were randomized (2:1) to intravenous (IV) tislelizumab 200 mg or IV docetaxel 75 mg/m^2 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 FA was conducted in the PD-L1 TC ≥25% population with secondary endpoints (investigator-assessed progression-free survival [PFS], objective response rate, and duration of response) tested sequentially once superiority of OS in the PD-L1 TC ≥25% population was demonstrated in the FA. Exploratory biomarker analyses included PD-L1 expression, tumor mutational burden (TMB), and gene expression profile.

Results: Between November 30, 2017, and April 8, 2020, 805 patients were randomized to tislelizumab (N=535) or docetaxel (N=270). The co-primary endpoint of OS (ITT) was met at IA (data cut-off August 10, 2020). At data cut-off

(July 15, 2021), FA was conducted in the PD-L1 TC ≥25% population. Median follow-up times (reverse Kaplan-Meier method) were 30.9 months for tislelizumab and 27.5 months for docetaxel. In the ITT population, tislelizumab continued to improve OS versus docetaxel (median OS 16.9 months vs 11.9 months, respectively; hazard ratio [HR]=0.66). In the PD-L1 TC ≥25% population, tislelizumab showed a statistically significant OS benefit versus docetaxel (median OS 19.3 months vs 11.5 months; HR=0.53; *P*<0.0001). A consistent OS benefit was observed for almost all pre-defined subgroups. The study also met secondary endpoints at this FA. In the post hoc biomarker analysis, the association of TMB and genetic alterations including single-target gene mutation or pathway mutations with clinical outcomes was further explored. Compared with TMB, which was correlated with PFS benefit for tislelizumab versus docetaxel but was not correlated to OS benefit, except at the highest cutoff (≥14 mut/Mb), *NOTCH1–4* mutations showed association with better tislelizumab efficacy, which was correlated with both PFS and OS benefit (**Table**). No new safety signals were identified.

Conclusions: Tislelizumab continued to improve OS versus docetaxel in pretreated advanced NSCLC regardless of PD-L1 expression at final analysis. Biomarker analysis implied the potential association of *NOTCH1–4* mutations with greater tislelizumab efficacy for both OS and PFS.

Table

	ITT Population		**PD-L1 TC ≥25% Population**		***NOTCH1–4* Mut Population**		***NOTCH1–4* WT Population**	
	TIS (N=535)	**D (N=270)**	**TIS (N=227)**	**D (N=116)**	**TIS (N=26)**	**D (N=15)**	**TIS (N=218)**	**D (N=101)**
OS events, n (%) [IA]	365 (68.2) [275 (51.4)]	206 (76.3) [166 (61.5)]	141 (62.1)	87 (75.0)	13 (50.0)	13 (86.7)	152 (69.7)	79 (78.2)
Median OS (95% CI), months [IA]	16.9 (15.2, 19.1) [17.2 (15.3, 20.0)]	11.9 (9.6, 13.5) [11.9 (10.2, 13.9)]	19.3 (16.5, 22.6)	11.5 (8.2, 13.5)	24.7 (14.2, NE)	7.7 (3.3, 14.3)	15.7 (13.9, 17.9)	12.9 (10.4, 14.9)
Stratified HR[c] (95% CI) [IA]	0.66 (0.56, 0.79) *P*<0.0001[a,b] [0.64 (0.53, 0.78) *P*<0.0001[a]]		0.53 (0.40, 0.70) *P*<0.0001[a]		0.22 (0.10, 0.49) *P*=0.0002[a,b]		0.75 (0.57, 0.99) *P*=0.0390[a,b]	

PFS_{INV} events, n (%)	451 (84.3)	208 (77.0)	177 (78.0)	94 (81.0)	14 (53.8)	14 (93.3)	187 (85.8)	83 (82.2)
Median PFS_{INV} (95% CI), months	4.2 (3.9, 5.5)	2.6 (2.2, 3.8)	6.5 (6.2, 8.3)	2.4 (2.1, 4.1)	14.1 (6.2, NE)	2.6 (2.0, 4.1)	4.1 (2.2, 6.2)	3.3 (2.1, 4.1)
Stratified HR[c] (95% CI)	0.63 (0.53, 0.75)		0.37 (0.28, 0.49)		0.17 (0.08, 0.37)		0.72 (0.55, 0.95)	
ORR_{INV}, n (%)	121 (22.6)	19 (7.0)	85 (37.4)	8 (6.9)	-	-	-	-
Median DoR_{INV}, (95% CI), months	13.5 (8.5, 19.6)	6.0 (2.1, 7.2)	11.9 (8.3, 19.6)	4.2 (0.6, 6.1)	-	-	-	-

IA data cut-off: August 10, 2020.

FA data cut-off: July 15, 2021.

[a] 1-sided stratified log-rank test.

[b] Descriptive *P*-value.

[c] Stratified by histology (squamous vs nonsquamous) and lines of therapy (second vs third).

Abbreviations: CI, confidence intervals; D, docetaxel; DoR_{INV}, investigator-assessed duration of response; FA, final analysis; HR, hazard ratio; IA, interim analysis; ITT, intent-to-treat; mut, mutation; NE, not estimable; ORR_{INV}, investigator-assessed objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS_{INV}, investigator-assessed progression-free survival; TC, tumor cell; TIS, tislelizumab; WT, wild type.