RATIONALE-303 Phase 3 tislelizumab vs docetaxel in previously treated advanced NSCLC: China subgroup analysis

Professor Yun Fan

Department of Thoracic Medical Oncology, Cancer Hospital of University of Chinese Academy of Sciences & Zhejiang Cancer Hospital, Hangzhou, China

Authors

Authors:

Y. Fan,[1] D. Huang,[2] Z. Ma,[3] X. Yu,[1] Y. Cheng,[4] Y. Ma,[5] Y. Wang,[5] Z. Pan,[5] C. Yu,[6] C. Zhou[6]

Affiliations:

[1]Department of Thoracic Medical Oncology, Cancer Hospital of University of Chinese Academy of Sciences & Zhejiang Cancer Hospital, Hangzhou, China, 310022; [2]Department of Thoracic Medical Oncology, Lung Cancer Diagnosis and Treatment Center, Key Laboratory of Cancer Prevention and Therapy, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin, China, 300060; [3]Department of Respiratory Medicine, Affiliated Cancer Hospital of Zhengzhou University/Henan Cancer Hospital, Zhengzhou, Henan, China, 450008; [4]Jilin Cancer Hospital, Jilin, China, 130021; [5]BeiGene (Beijing) Co., Ltd., Shanghai, China 200131; [6]Department of Medical Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, PR China, 200433

Corresponding author:

Prof Caicun Zhou, Department of Medical Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, PR China, 200433 (email: caicunzhoudr163.com).

Presenter DISCLOSURES

I do not have any financial relationships to disclose

Introduction

- Tislelizumab is an anti-PD-1 antibody designed to minimize FcγR binding on macrophages in order to abrogate antibody-dependent phagocytosis, a potential mechanism of resistance to anti-PD-1 therapy[1,2]
- In China, tislelizumab in combination with chemotherapy is approved for first-line treatment of advanced squamous NSCLC[3]
- RATIONALE-303 was a global, randomized, open-label, Phase 3 clinical study that compared the efficacy and safety of tislelizumab monotherapy vs docetaxel in patients with locally advanced or metastatic NSCLC, who had progressed on a prior platinum-containing chemotherapy regimen[4]
- The interim analysis of RATIONALE-303 demonstrated improved overall survival for tislelizumab vs docetaxel in the ITT and PD-L1 ≥ 25% populations, with a manageable safety profile[4]
- Here, we report the results of a subgroup analysis of Chinese patients from the RATIONALE-303 study

- **Scan QR code to view the primary results of the RATIONALE-303 study:**

ClinicalTrials.gov Identifier: NCT03358875

ITT, intent-to-treat; NSCLC, non-small cell lung cancer; OS, overall survival; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1

1. Qin S, et al. Future Oncol 2019;15:1811–22; 2. Zhang T, et al. Cancer Immunol Immunother 2018;67:1079–90; 3. BeiGene. Press Releases: China National Medical Products Administration Approves Tislelizumab in Combination with Chemotherapy in First-Line Advanced Squamous Non-Small Cell Lung Cancer. Available at: https://ir.beigene.com/news-releases/news-release-details/china-national-medical-products-administration-approves Accessed April 2021; 4. Zhou C, et al. Presented at: American Association for Cancer Research. April 10–15, 2021 and May 17–21, 2021

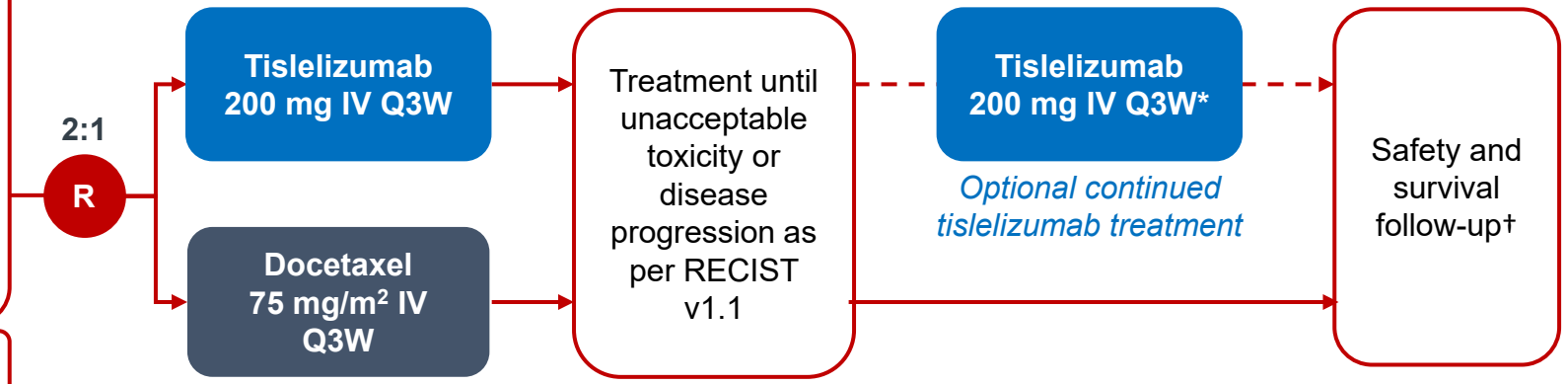
Study design and patient population

Key eligibility criteria:

- Locally advanced or metastatic NSCLC
- Recurrence or progression during or after platinum-based doublet chemotherapy
- ≤ 2 lines of prior systemic treatment
- No known EGFR mutation or ALK fusion oncogene

Total population: N=805

Chinese patients: n=641



Stratification

- Histology (squamous vs non-squamous)
- Line of therapy (second vs third)
- PD-L1 status (< 25% vs ≥ 25% TC staining)

Endpoints

- **Dual primary endpoints:** OS in the ITT and PD-L1 ≥ 25% populations
- **Secondary endpoints:**
  - ORR, DoR, and PFS
  - HRQoL and safety

PD-L1 ≥ 25% population included all patients with ≥ 25% of TCs with PD-L1 membrane staining (assessed by Ventana SP263 assay)

*Patients receiving tislelizumab will be permitted to continue tislelizumab treatment beyond radio-imaging progression per RECIST v1.1 if clinical benefit is seen in the absence of symptomatic deterioration and unacceptable toxicity per investigator's discretion; †Survival follow-up was applicable to patients who discontinued treatment for reasons other that disease progression or death

ALK, anaplastic lymphoma kinase; DoR, duration of response; EGFR, epidermal growth factor receptor; HRQoL, health-related quality of life; ITT, intent-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; RECIST, Response Evaluation Criteria in Solid Tumors; TC, tumor cell

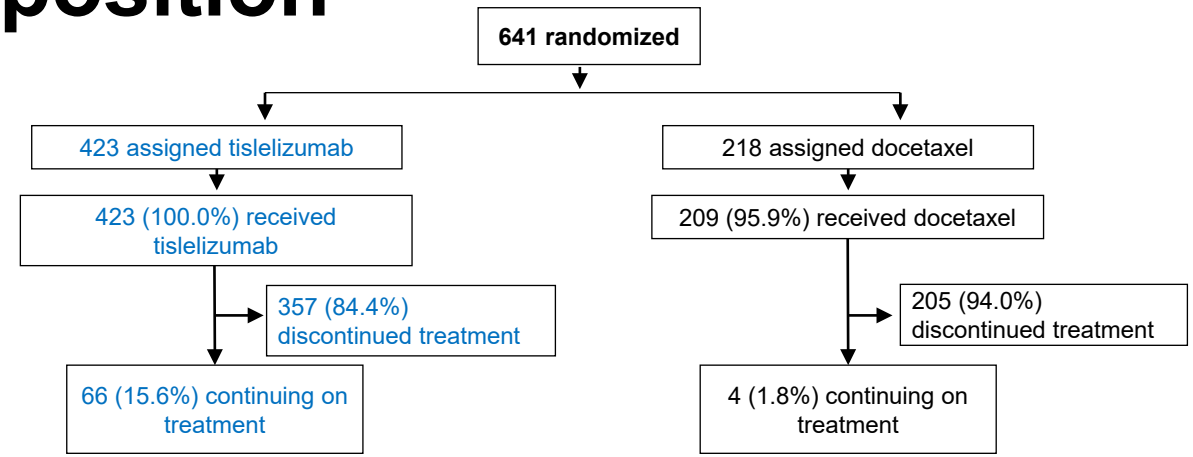
Randomization and study follow-up

- Between November 30, 2017, and April 8, 2020, 641 Chinese patients were randomized to receive tislelizumab (n=423) or docetaxel (n=218)
- The median age was 61.0 years, and 507 (79.1%) patients were male. The majority of patients were former or current smokers (66.9%), and 33.1% never smoked. A total of 85.3% of patients had metastatic disease at randomization
- At data cut-off on August 10, 2020, 70 (10.9%) patients remained on treatment
- Median follow-up* was 15.1 months for tislelizumab and 10.7 months for docetaxel

Data cut-off: August 10, 2020

*Study follow-up time is defined as the time from the randomization date to date of death or end of study date (whichever occurs first) for patients discontinued from the study or the database cut-off date for ongoing patients

Patient disposition



Characteristic	Tislelizumab (n=423)	Docetaxel (n=218)
Patients randomized, N (%)	**423 (100.0)**	**218 (100.0)**
Patients discontinued from study, n (%)	243 (57.4)	159 (72.9)
Patients remaining on study, n (%)	180 (42.6)	59 (27.1)
Patients receiving tislelizumab treatment beyond radiographic progressive disease, n (%)	109 (25.8)	-
Patients receiving any subsequent anticancer therapy, n (%)	242 (57.2)	149 (68.3)
Immunotherapy, n (%)	29 (6.9)	47 (21.6)

Data cut-off: August 10, 2020
Data shown are from the intent-to treat Chinese subpopulation

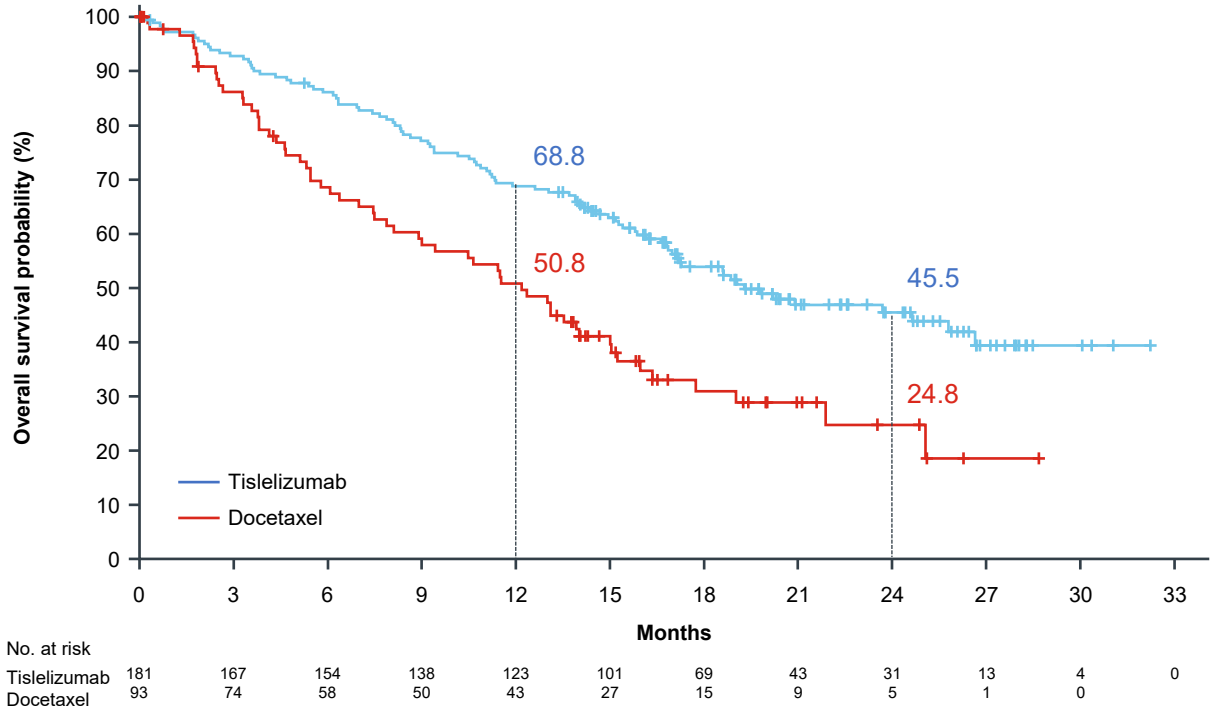
Demographics and baseline characteristics

Characteristic	Tislelizumab (n=423)	Docetaxel (n=218)
Median age (range), years	60.0 (28–79)	61.0 (32–76)
Patients aged < 65 years, n (%)	301 (71.2)	151 (69.3)
Sex, n (%)		
Male	336 (79.4)	171 (78.4)
Female	87 (20.6)	47 (21.6)
ECOG performance status, n (%)		
0	83 (19.6)	34 (15.6)
1	340 (80.4)	184 (84.4)
Smoking status, n (%)		
Never	139 (32.9)	73 (33.5)
Current	30 (7.1)	10 (4.6)
Former	254 (60.0)	135 (61.9)
PD-L1 expression, n (%)		
≥ 25%	181 (42.8)	93 (42.7)
< 25%	242 (57.2)	125 (57.3)
Histology, n (%)		
Squamous	191 (45.2)	95 (43.6)
Non-squamous	232 (54.8)	123 (56.4)

Characteristic	Tislelizumab (n=423)	Docetaxel (n=218)
EGFR mutation, n (%)		
Wild type	265 (62.6)	148 (67.9)
Mutant	1 (0.2)	0 (0.0)
Unknown	157 (37.1)	70 (32.1)
ALK rearrangement, n (%)		
Wild type	211 (49.9)	111 (50.9)
Translocated	0 (0.0)	0 (0.0)
Unknown	212 (50.1)	107 (49.1)
Prior therapy, n (%)		
Second	359 (84.9)	187 (85.8)
Third	64 (15.1)	31 (14.2)
Disease stage at study entry*, n (%)		
Locally advanced	69 (16.3)	25 (11.5)
Metastatic	354 (83.7)	193 (88.5)
Brain metastasis, n (%)		
Yes	34 (8.0)	17 (7.8)
No	389 (92.0)	201 (92.2)
Liver metastasis, n (%)		
Yes	52 (12.3)	27 (12.4)
No	371 (87.7)	191 (87.6)

Data cut-off: August 10, 2020
Data shown are from the intent-to treat Chinese subpopulation; *Study entry date referred to as randomization date
ALK, anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; PD-L1, programmed death ligand-1

Overall survival in patients with PD-L1 expression ≥ 25%



	Tislelizumab (n=181)	Docetaxel (n=93)
Events (% of patients)	91 (50.3)	59 (63.4)
Median OS (95% CI), months*	19.3 (16.82–26.64)	12.2 (8.11–15.01)
HR (95% CI)†	0.52 (0.374–0.728)	
P-value‡	< 0.0001	

Tislelizumab showed clinically meaningful improvements in OS compared with docetaxel in Chinese patients with PD-L1 expression ≥ 25%

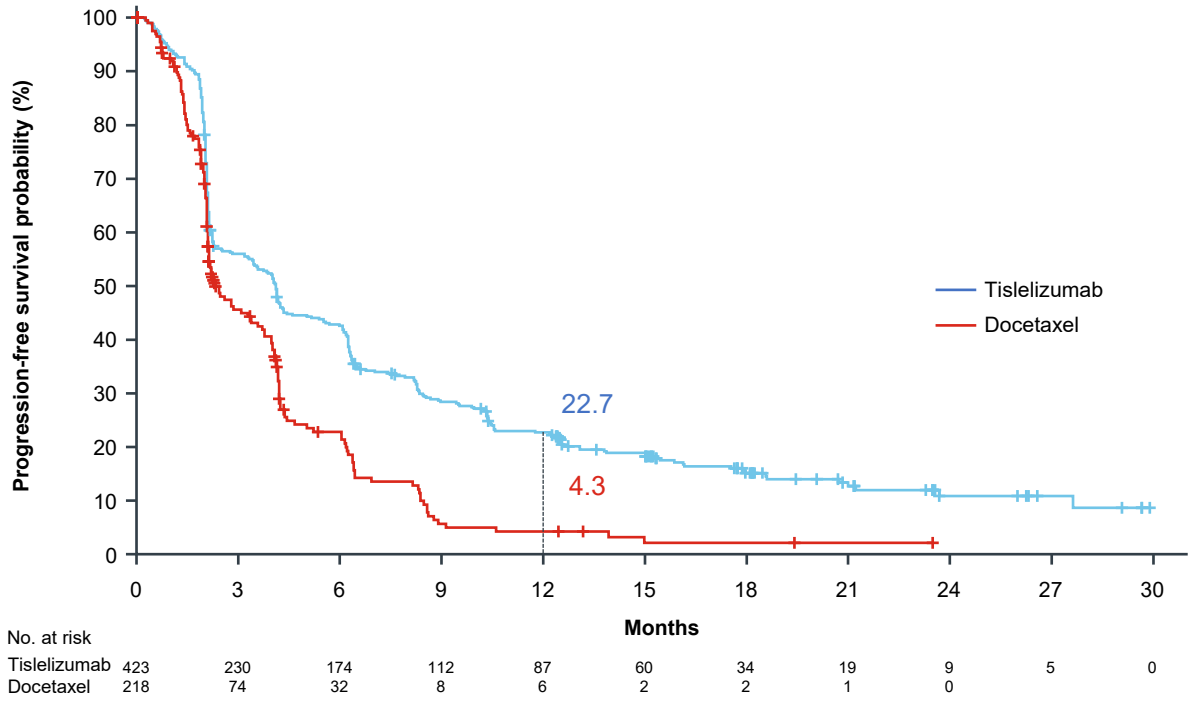
Data cut-off: August 10, 2020

Data shown are from the intent-to treat Chinese subpopulation; + on KM curves correspond to censored values

*Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley; †Stratified by stratification factors: histology (squamous vs non-squamous), lines of therapy (second vs third); ‡One-sided p-value was estimated from stratified log-rank test.

CI, confidence interval; HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand-1

Progression-free survival



	Tislelizumab (n=423)	Docetaxel (n=218)
Events (% of patients)	347 (82.0)	165 (75.7)
Median PFS (95% CI), months*	4.1 (3.42–4.34)	2.3 (2.14–3.58)
HR (95% CI)†	0.61 (0.501–0.741)	
P-value‡	< 0.0001	

Tislelizumab showed clinically meaningful improvements in PFS compared with docetaxel in Chinese patients

Data cut-off: August 10, 2020

Data shown are from the intent-to treat Chinese subpopulation; + on KM curves correspond to censored values

*Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. Data for patients without disease progression or death at the time of analysis, or those who received new anticancer therapy or were lost to follow-up were censored; †Stratified by stratification factors: histology (squamous vs non-squamous), lines of therapy (second vs third), and PD-L1 expression (≥25% TC vs <25% TC). ‡One-sided p-value was estimated from stratified log-rank test

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival

Disease response and duration of response*

	Tislelizumab (n=423)	Docetaxel (n=218)
ORR, % (95% CI)	21.5 (17.69–25.74)	5.5 (2.88–9.42)
Best overall response, n (%)		
Complete response	7 (1.7)	0 (0.0)
Partial response	84 (19.9)	12 (5.5)
Stable disease	123 (29.1)	73 (33.5)
Non-complete response/non-progressive disease†	19 (4.5)	3 (1.4)
Progressive disease	160 (37.8)	88 (40.4)
Could not be determined‡	30 (7.1)	42 (19.3)
Median DoR (95% CI), months§	13.5 (8.54–21.78)	4.2 (0.56–6.24)
HR (95% CI)	0.24 (0.113–0.493)	

Tislelizumab was associated with a greater ORR and a more durable tumor response vs docetaxel in Chinese patients

Data cut-off: August 10, 2020
Data shown are from the intent-to treat Chinese subpopulation
*Investigator assessed per RECIST v1.1; †Defined as persistence of one or more nontarget lesions and/or maintenance of tumor marker level above the normal limits; ‡Included patients who had post-baseline tumor assessments, none of which were evaluable; or patients who had no post-baseline tumor assessments due to death, withdrawal of consent, loss to follow-up, or any other reasons; §Median was estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley
CI, confidence interval; DoR, duration of response; HR, hazard ratio; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid tumors

Overall safety profile*

	Tislelizumab (n=423) n (%)	Docetaxel (n=209) n (%)
Mean duration of exposure, weeks (SD)	34.0 (32.08)	13.4 (13.50)
Mean number of treatment cycles (SD)	10.9 (10.08)	4.4 (4.33)
Patients with at least one TEAE[†]	409 (96.7)	206 (98.6)
Treatment-related TEAE	321 (75.9)	195 (93.3)
≥ Grade 3 TEAEs	165 (39.0)	157 (75.1)
Treatment-related TEAEs of ≥ Grade 3	64 (15.1)	140 (67.0)
Serious TEAEs	144 (34.0)	66 (31.6)
Treatment-related serious TEAEs	59 (13.9)	47 (22.5)
TEAEs leading to death	22 (5.2)	9 (4.3)
Treatment-related TEAE leading to death	7 (1.7)	3 (1.4)
TEAEs leading to permanent treatment discontinuation	41 (9.7)	26 (12.4)
Treatment-related TEAE leading to permanent treatment discontinuation	28 (6.6)	21 (10.0)

The safety profile of tislelizumab in Chinese patients was consistent with the overall patient population[1]

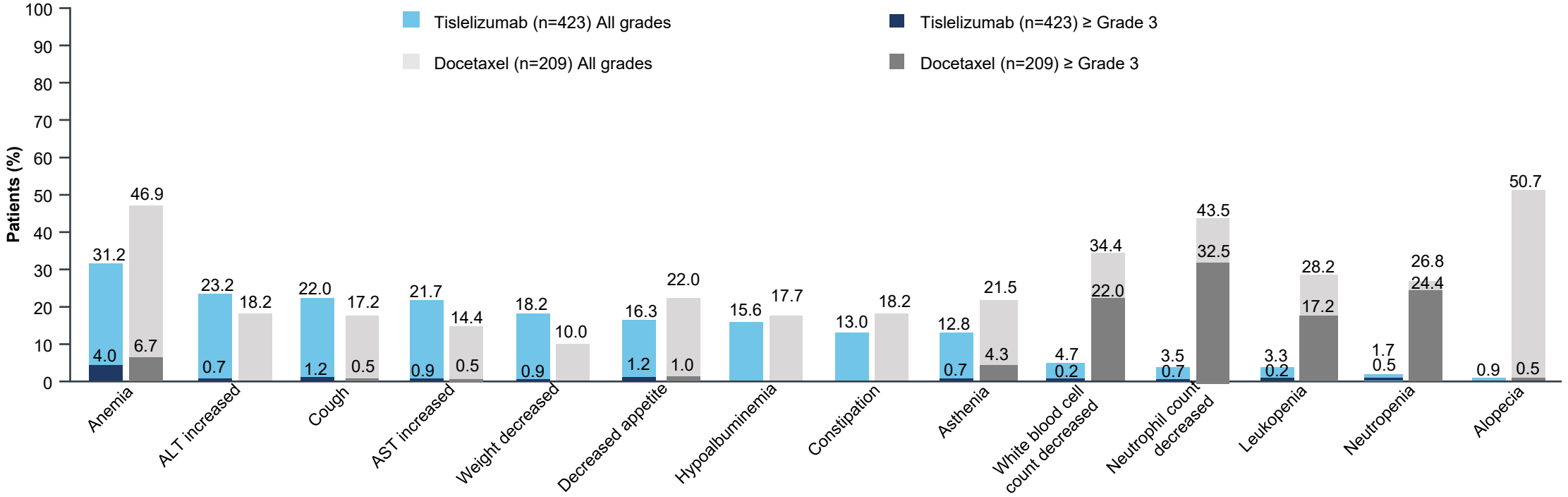
Data cut-off: August 10, 2020

*Data shown are from the safety analysis set, which included all randomized patients who received at least 1 dose of any study drug; [†]A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pre-treatment) on or after the first dose of study drug up to 30 days following study drug discontinuation or initiation of new anticancer therapy

AE, adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event

1. Zhou C, et al. Presented at: American Association for Cancer Research. April 10–15, 2021 and May 17–21, 2021

TEAEs occurring in ≥ 15% of patients in either treatment group*†



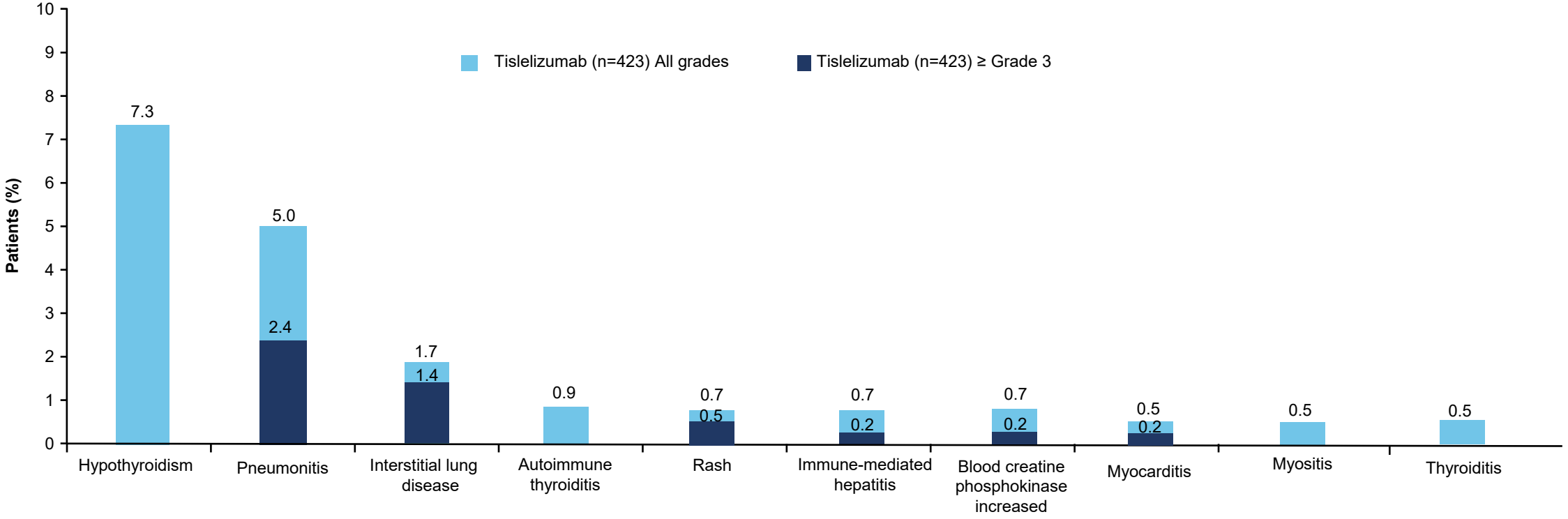
Data cut-off: August 10, 2020

*Data shown are from the safety analysis set, which included all randomized patients who received at least 1 dose of any study drug; †A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pre-treatment) on or after the first dose of study drug up to 30 days following study drug discontinuation or initiation of new anticancer therapy

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event

The most commonly reported TEAEs were anemia, ALT increased, and cough in the tislelizumab arm, and alopecia, anemia, and neutrophil count decreased in the docetaxel arm

Immune-mediated TEAEs occurring in ≥ 0.5% of tislelizumab-treated patients*†

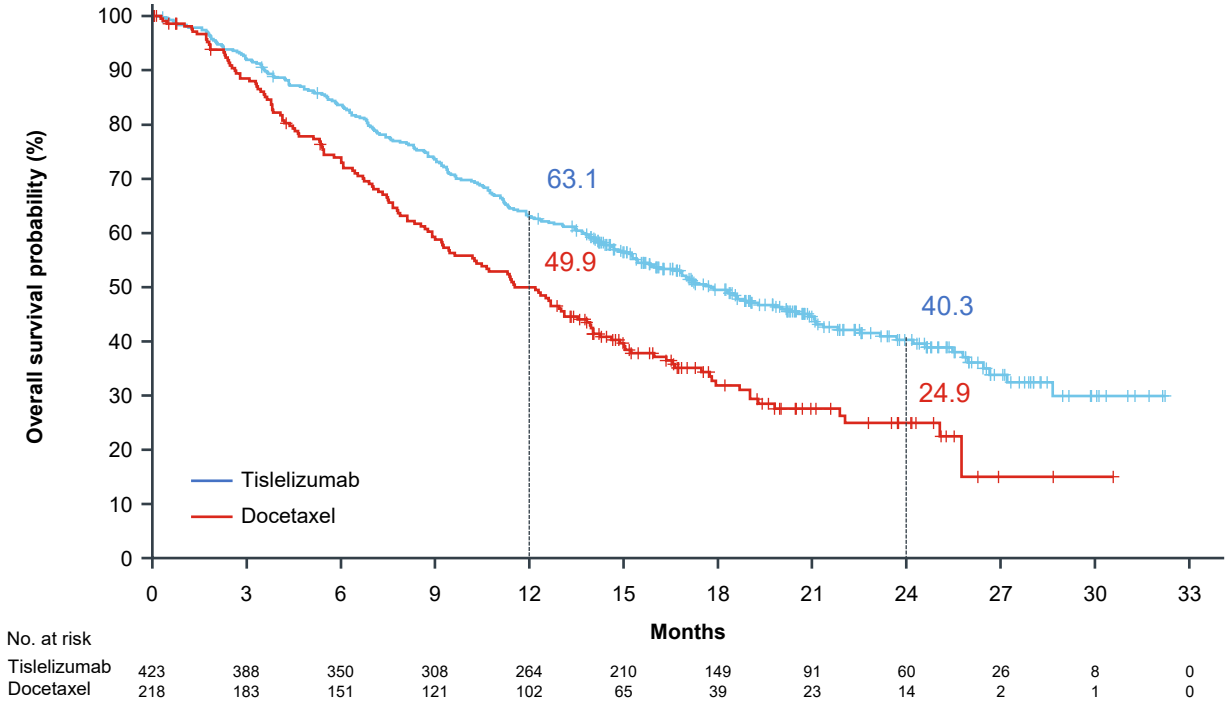


Data cut-off: August 10, 2020

*Data shown are from the safety analysis set, which included all randomized patients who received at least 1 dose of any study drug; †A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pre-treatment) on or after the first dose of study drug up to 30 days following study drug discontinuation or initiation of new anticancer therapy

AE, adverse event; TEAE, treatment-emergent adverse event

Overall survival



	Tislelizumab (n=423)	Docetaxel (n=218)
Events (% of patients)	235 (55.6)	144 (66.1)
Median OS (95% CI), months*	17.8 (15.44–20.90)	11.5 (9.43–13.93)
HR (95% CI)†	0.62 (0.500–0.761)	
P-value‡	< 0.0001	

Tislelizumab showed clinically meaningful improvements in OS compared with docetaxel in Chinese patients

Data cut-off: August 10, 2020
Data shown are from the intent-to treat Chinese subpopulation; + on KM curves correspond to censored values
*Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley; †Stratified by stratification factors: histology (squamous vs non-squamous), lines of therapy (second vs third), and PD-L1 expression (≥ 25% TC vs < 25% TC). ‡One-sided p-value was estimated from stratified log-rank test
CI, confidence interval; HR, hazard ratio; OS, overall survival

Conclusions

- Consistent with the overall population, tislelizumab demonstrated clinically meaningful improvements in OS, PFS, DoR and ORR, vs docetaxel in second- and third-line NSCLC Chinese patients
- Tislelizumab showed consistent benefit over docetaxel in Chinese patients with PD-L1 expression ≥ 25%
- Tislelizumab had a tolerable and manageable safety profile consistent with other PD-1/L1 inhibitors, with a smaller proportion of patients experiencing ≥ Grade 3 treatment-related TEAEs vs docetaxel

DoR, duration of response; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand-1; PFS, progression-free survival; TEAE, treatment-emergent adverse event

Acknowledgements

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