Results from RATIONALE-303: A global Phase 3 study of tislelizumab vs docetaxel as second- or third-line therapy for patients with locally advanced or metastatic NSCLC

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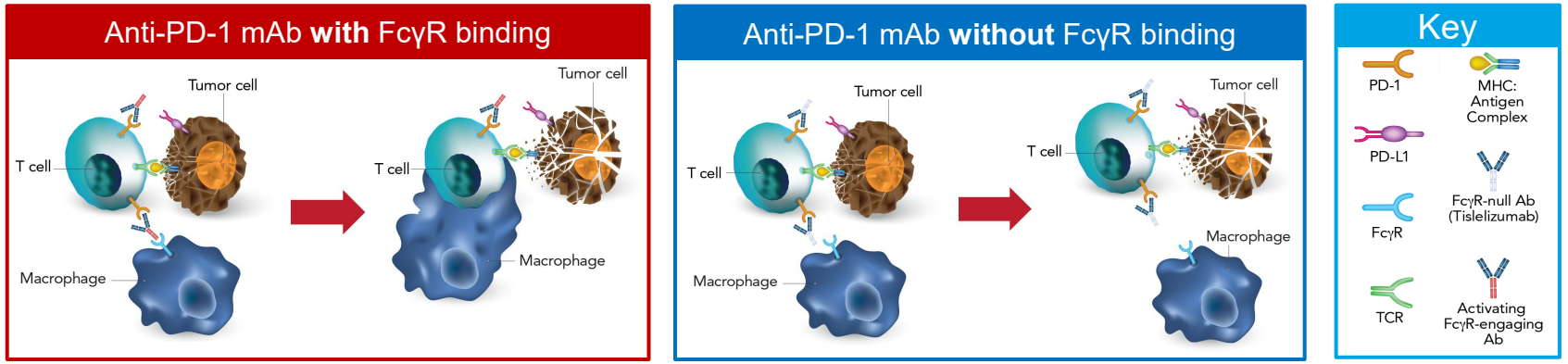
Disclosures

- Honoraria as a speaker:
  - Lilly China, Sanofi, BI, Roche, MSD, Qilu, Hengrui, Innovent Biologics, C-Stone, LUYE Pharma, TopAlliance Biosciences Inc., Amoy Diagnostics
- Advisor:
  - Innovent Biologics, Hengrui, Qilu, TopAlliance Biosciences Inc.

Background

Anti-PD-1/L1 therapies have been shown to improve OS by 2–4 months vs docetaxel in patients with locally advanced or metastatic 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, 2L+ tislelizumab demonstrated antitumor activity in multiple advanced solid tumors including NSCLC[8] and is approved for relapsed/refractory classical Hodgkin lymphoma, 2L treatment of locally advanced or metastatic urothelial carcinoma, 2L and 3L hepatocellular carcinoma and 1L treatment of advanced squamous and non-squamous NSCLC (in China)

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

1L, first-line; 2L, second-line; 3L, third-line; Ab, antibody; mAb, monoclonal antibody; MHC, major histocompatibility complex; NSCLC, non-small cell lung cancer; OS, overall survival; PD-1, programmed death protein-1; PD-L1, programmed cell ligand-1; TCR, T-cell receptor

1. Borghaei H, et al. N Engl J Med 2015;373:1627–39; 2. Brahmer J, et al. N Engl J Med 2015;373:123–35; 3. Herbst RS, et al. Lancet 2016;387:1540–50; 4. Rittmeyer A, et al. Lancet 2017;389:255–65;
5. Zhang T, et al. Cancer Immunol Immunother 2018:1079–90; 6. Dahan R, et al. Cancer Cell 2015;28:285–95; 7. Qin S, et al. Future Oncol 2019;15:1811–22; 8. Shen L, et al. J Immunother Cancer 2020;8:e000437corr1

Study design

A Phase 3, open-label, multicenter, randomized study (NCT03358875)

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

N=805

2:1 R

- **Tislelizumab 200 mg IV Q3W**
- **Docetaxel 75 mg/m^2 IV Q3W**

Treatment until unacceptable toxicity, disease progression, or withdrawal

Tislelizumab 200 mg IV Q3W*

Optional continued tislelizumab treatment

Safety and survival follow up

Stratification

- Histology (squamous vs non-squamous)
- Lines of therapy (2nd vs 3rd)
- PD-L1 status (< 25% vs ≥ 25% TC staining)

Dual primary endpoints

- OS in the ITT and PD-L1 ≥ 25% populations

Secondary endpoints

- ORR, DoR, PFS
- HRQoL and safety

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

*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

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; PD-L1, programmed death ligand-1 ; PFS, progression-free survival; Q3W, every 3 weeks; R, randomized; TC, tumor cell

Statistical considerations

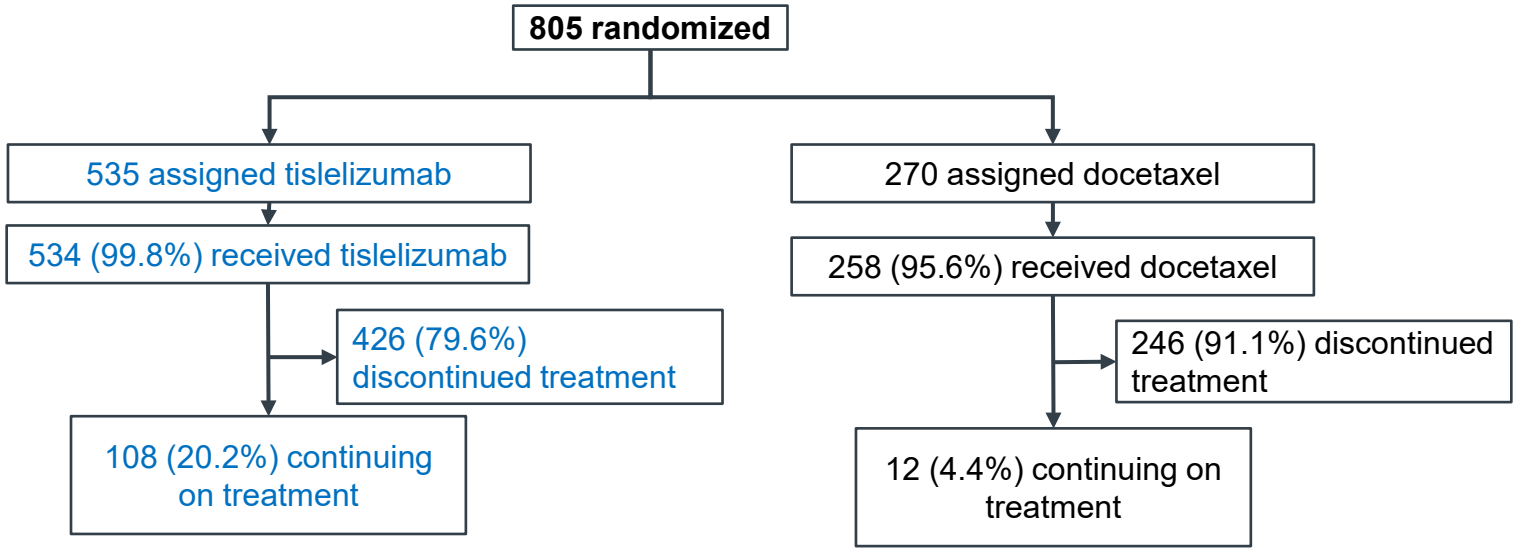
- Primary endpoints: OS in the ITT population and in the PD-L1 ≥ 25% population
- Planned enrolment: ~800 patients
- Overall alpha for the study: one-sided α 0.025
  - 560 death events will provide approximately 87% power to detect an OS HR (tislelizumab/docetaxel) of 0.75 with a one-sided alpha of 0.02 in the ITT
  - 207 death events in the PD-L1 ≥ 25% population will 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 will be 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
  - Pre-specified 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: 10th August 2020
  - Observed number of death events: 441 (54.8%)
  - One-sided alpha level: α 0.0120 for ITT (based on the observed number of death events)

HR, hazard ratio; ITT, intent-to-treat; PD-L1, programmed death ligand-1; OS, overall survival

Patient disposition



Patients, n (%)	Tislelizumab (N=535)	Docetaxel (N=270)
Patients discontinued from study	287 (53.6)	184 (68.1)
Patients remaining on study	248 (46.4)	86 (31.9)
Patients receiving tislelizumab treatment beyond radiographic progressive disease	144 (26.9)	–
Patients receiving any subsequent anticancer therapy	266 (49.7)	169 (62.6)
Immunotherapy	31 (5.8)	53 (19.6)

Data cut-off: August 10, 2020

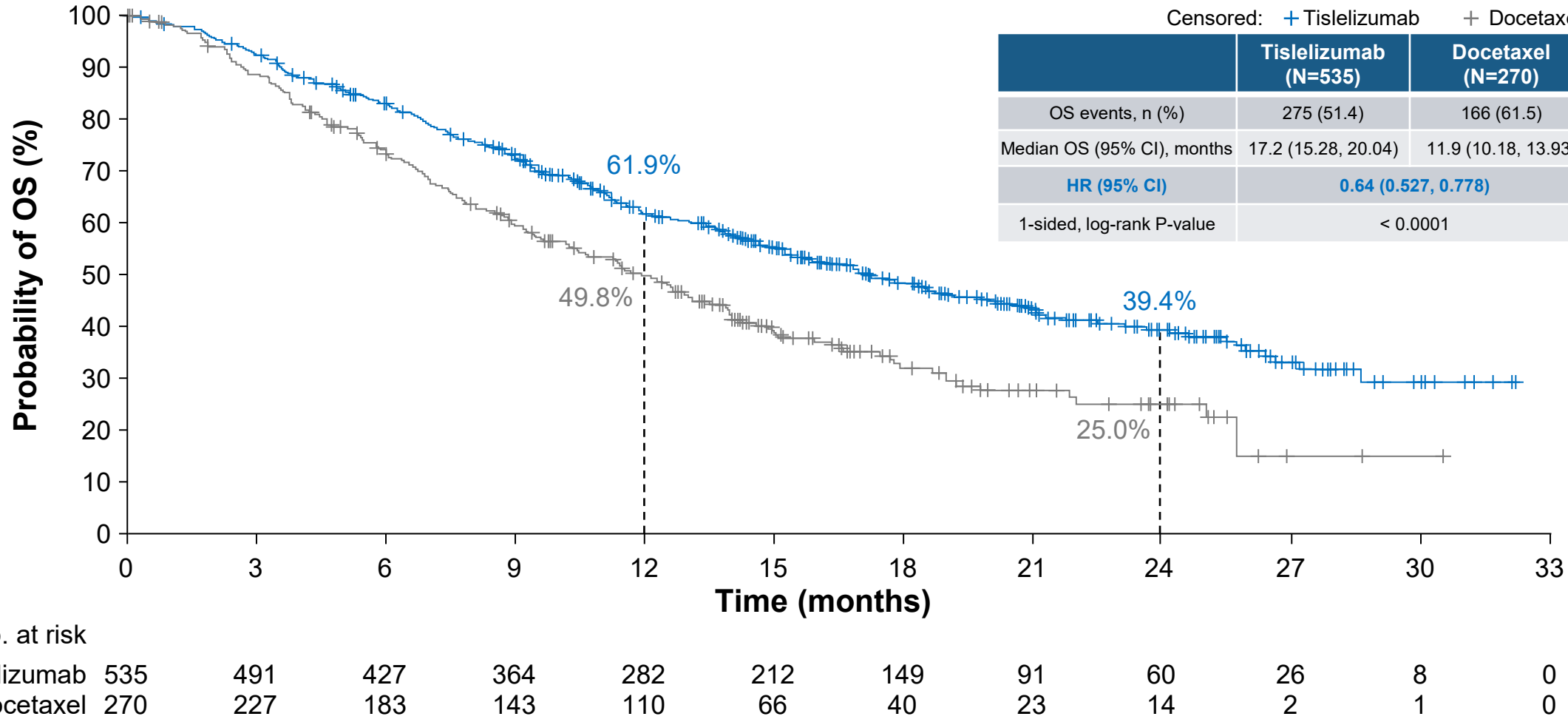
Baseline demographics and characteristics

	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)
Sex, n (%)		
Male	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)

	Tislelizumab (N=535)	Docetaxel (N=270)
***EGFR* mutation, n (%)**		
Wild type	339 (63.4)	183 (67.8)
Unknown	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 (%)		
Yes	39 (7.3)	18 (6.7)
Liver metastasis, n (%)		
Yes	73 (13.6)	33 (12.2)

Data cut-off: August 10, 2020
ALK, anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; PD-L1, programmed death ligand-1

Primary endpoint: Overall survival (ITT)



	Tislelizumab (N=535)	Docetaxel (N=270)
OS events, n (%)	275 (51.4)	166 (61.5)
Median OS (95% CI), months	17.2 (15.28, 20.04)	11.9 (10.18, 13.93)
HR (95% CI)	**0.64 (0.527, 0.778)**	
1-sided, log-rank P-value	< 0.0001	

No. at risk

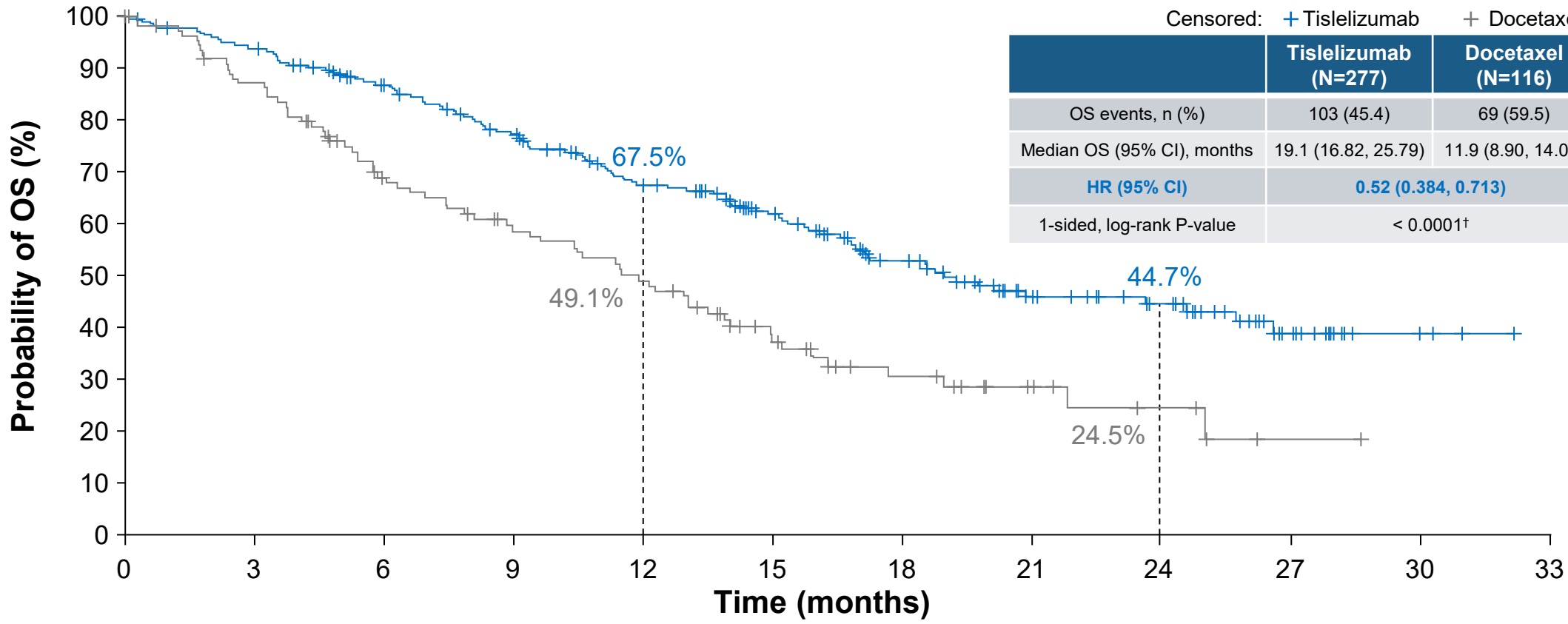
Tislelizumab	535	491	427	364	282	212	149	91	60	26	8	0
Docetaxel	270	227	183	143	110	66	40	23	14	2	1	0

Data cut-off: August 10, 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

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival

Primary endpoint: Overall survival (PD-L1 ≥ 25%)*



	Tislelizumab (N=277)	Docetaxel (N=116)
OS events, n (%)	103 (45.4)	69 (59.5)
Median OS (95% CI), months	19.1 (16.82, 25.79)	11.9 (8.90, 14.03)
HR (95% CI)	**0.52 (0.384, 0.713)**	
1-sided, log-rank P-value	< 0.0001†	

No. at risk

Tislelizumab	227	211	183	157	128	101	69	43	31	13	4	0
Docetaxel	116	94	69	56	46	28	16	9	5	1	0	

Data cut-off: August 10, 2020

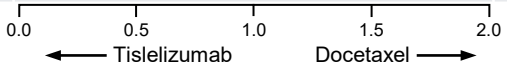
*PD-L1 ≥ 25% population included all patients with ≥ 25% of TCs with PD-L1 membrane staining (assessed via Ventana SP263 assay); †Descriptive P-value; One-sided P-value was estimated from stratified log-rank test. Hazard ratio was estimated from stratified Cox model with docetaxel group as reference group. Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley

CI, confidence interval; HR, hazard ratio; OS, overall survival

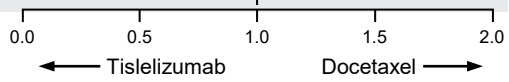
Overall survival (ITT): Subgroup analysis

Overall survival subgroup analysis (ITT)

Subgroup	No. of Events / No. of Patients	HR for death (95% CI)
Overall	441/805	0.64 (0.53–0.78)
Age		
< 65 years	300/544	0.61 (0.48, 0.77)
≥ 65 years	141/261	0.71 (0.50, 0.99)
Sex, n (%)		
Male	347/622	0.56 (0.45, 0.70)
Female	94/183	1.07 (0.69, 1.67)
Race, n (%)		
Asian	379/643	0.62 (0.51, 0.77)
White	49/138	0.61 (0.34, 1.08)
ECOG PS		
0	75/165	0.93 (0.56, 1.55)
1	366/640	0.60 (0.49, 0.74)
Smoking status		
Current/former	312/561	0.59 (0.47, 0.74)
Never	129/244	0.80 (0.56, 1.15)
PD-L1 expression in TC		
< 25% TC	269/462	0.74 (0.58, 0.95)
≥ 25% TC	172/343	0.52 (0.38, 0.71)
< 1% TC	178/319	0.74 (0.54, 1.00)
≥ 1% TC	263/486	0.58 (0.46, 0.75)
< 10% TC	235/410	0.69 (0.53, 0.90)
≥ 10% TC	206/395	0.59 (0.44, 0.78)
< 50% TC	326/561	0.68 (0.54, 0.85)
≥ 50% TC	115/244	0.55 (0.38, 0.80)



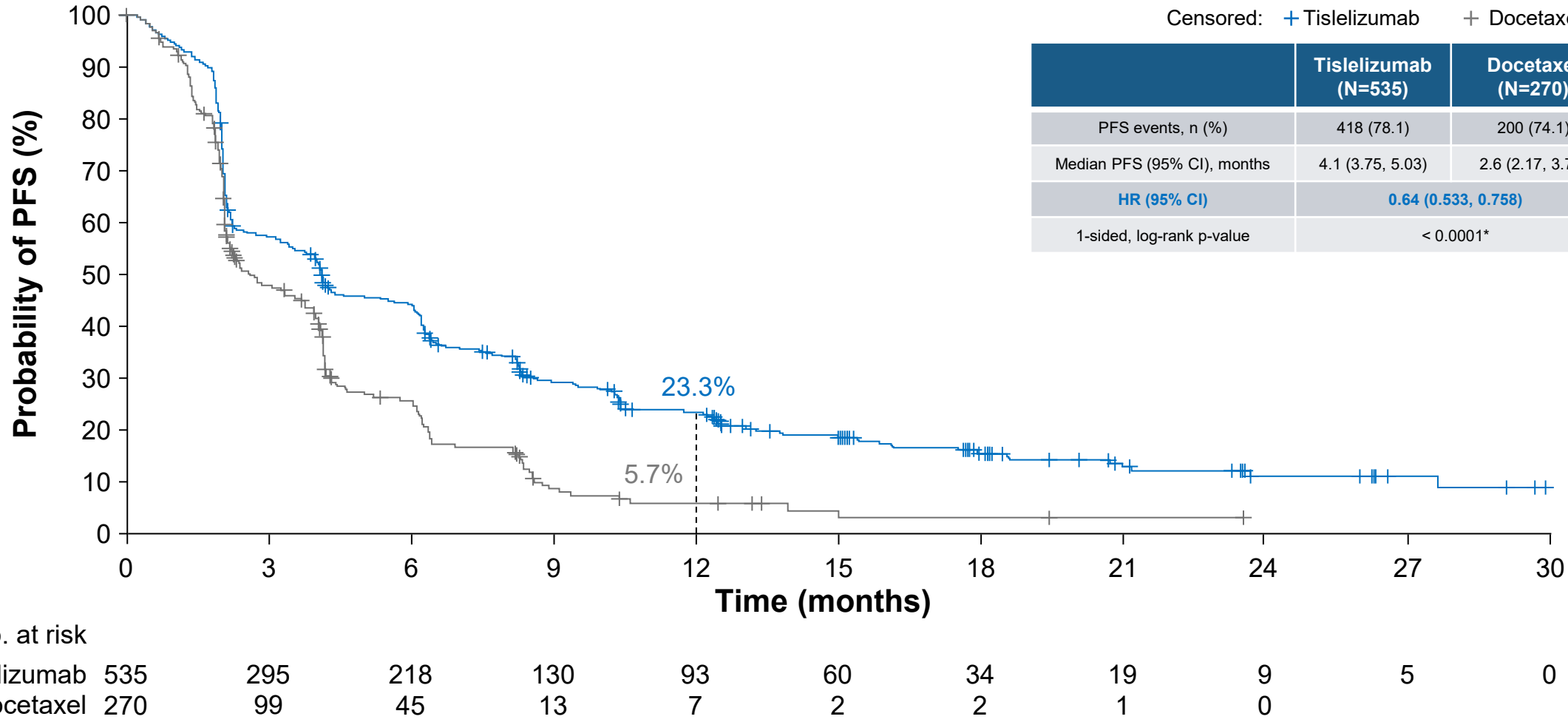
Subgroup	No. of Events / No. of Patients	HR for death (95% CI)
Histology		
Non-squamous	226/435	0.71 (0.54, 0.93)
Squamous	215/370	0.57 (0.43, 0.75)
***EGFR* mutation at baseline**		
Wild type	273/522	0.67 (0.53, 0.86)
Unknown	168/282	0.59 (0.43, 0.80)
***ALK* rearrangement at baseline**		
Wild type	200/371	0.69 (0.51, 0.92)
Unknown	241/434	0.61 (0.47, 0.79)
Line of therapy		
Second	370/682	0.62 (0.50, 0.76)
Third	71/123	0.80 (0.49, 1.32)
Disease Stage		
Locally advanced	55/117	0.56 (0.31, 1.00)
Metastatic	386/688	0.66 (0.54, 0.81)
Brain metastases at baseline		
Yes	35/57	0.96 (0.47, 1.96)
No	406/748	0.62 (0.51, 0.76)
Liver metastases at baseline		
Yes	66/106	0.46 (0.280–0.771)
No	375/699	0.66 (0.538–0.820)



A consistent overall survival benefit was observed for tislelizumab vs docetaxel for almost all studied subgroups

Data cut-off: August 10, 2020
HR and 95% CI were estimated from unstratified Cox model with docetaxel group as reference group
ALK, anaplastic lymphoma kinase; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance score; EGFR, epidermal growth factor receptor; ITT, intent-to-treat; OS, overall survival; PD-L1, programmed death ligand-1; TC, tumor cell

Secondary endpoint: Progression-free survival (ITT)



	Tislelizumab (N=535)	Docetaxel (N=270)
PFS events, n (%)	418 (78.1)	200 (74.1)
Median PFS (95% CI), months	4.1 (3.75, 5.03)	2.6 (2.17, 3.78)
HR (95% CI)	0.64 (0.533, 0.758)	
1-sided, log-rank p-value	< 0.0001*	

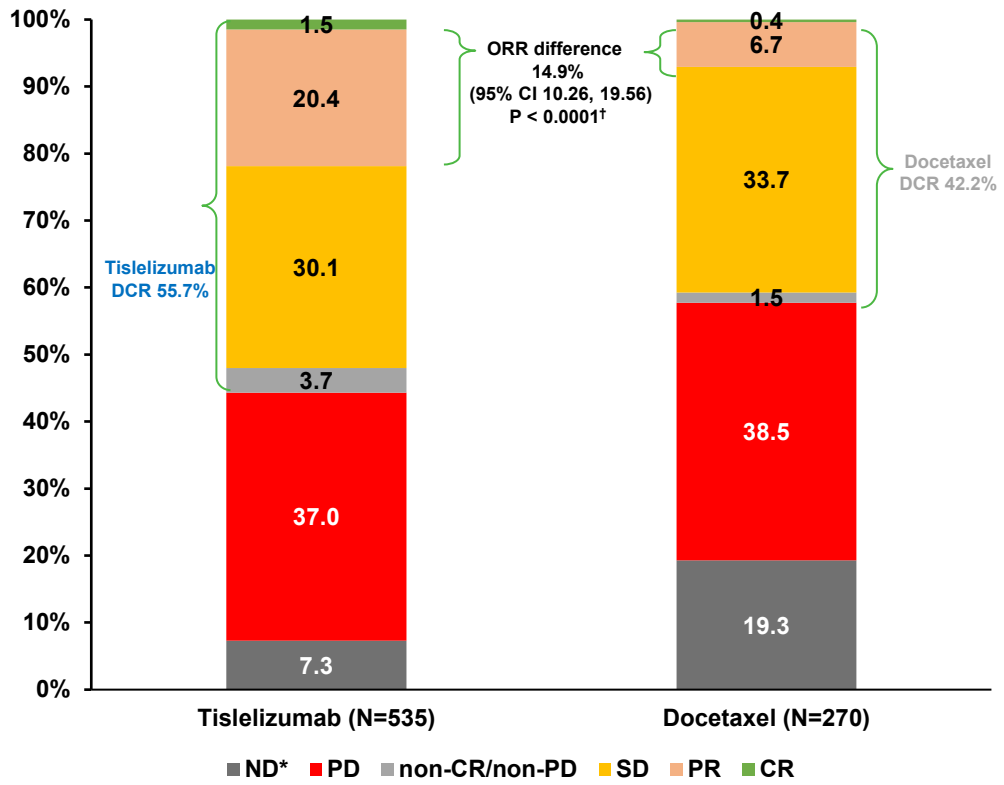
Data cut-off: August 10, 2020

*Descriptive P-value; 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

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; PFS, progression-free survival

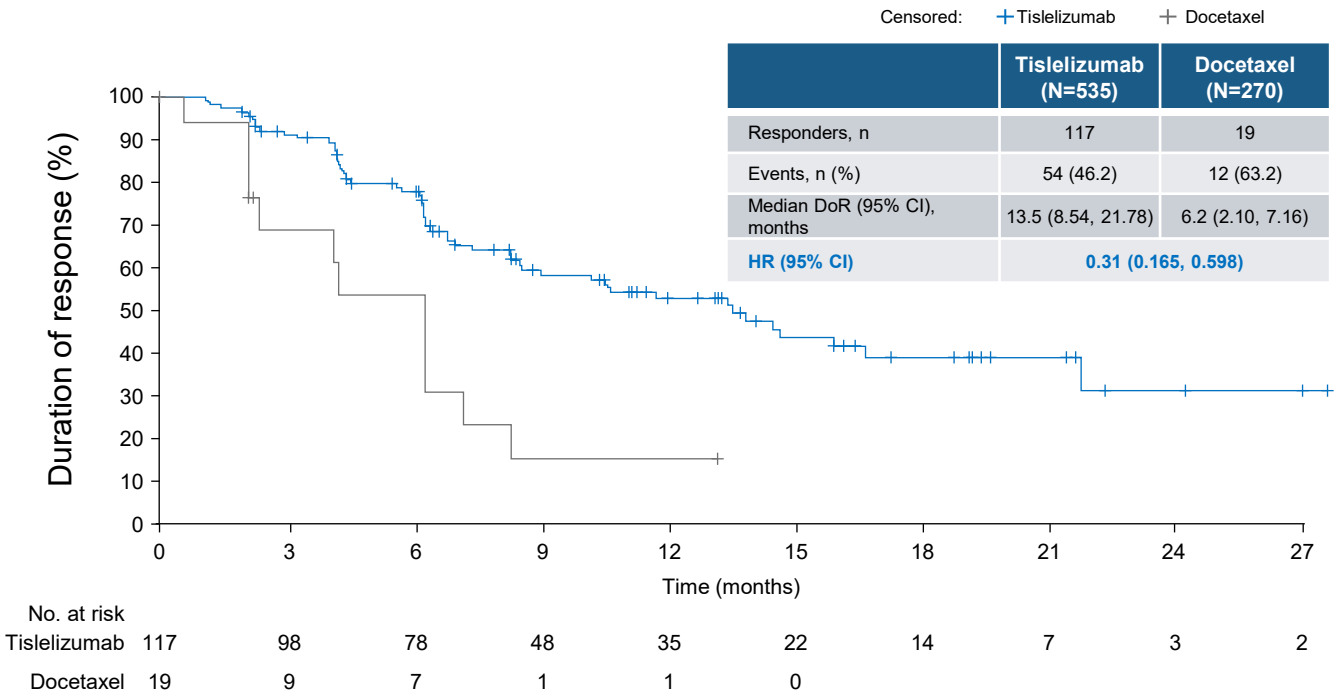
Secondary endpoint: Disease response (ITT)

Investigator-assessed disease response per RECIST v1.1



*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; ORR differences and ORs between arms were calculated using the Cochran-Mantel-Haenszel Chi-square test with actual stratification factors as strata

Duration of response



	Tislelizumab (N=535)	Docetaxel (N=270)
Responders, n	117	19
Events, n (%)	54 (46.2)	12 (63.2)
Median DoR (95% CI), months	13.5 (8.54, 21.78)	6.2 (2.10, 7.16)
HR (95% CI)	0.31 (0.165, 0.598)	

One-sided P-value was estimated from unstratified log-rank test. Hazard ratio was estimated from unstratified 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 cut-off: August 10, 2020
CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; HR, hazard ratio; ITT, intent-to-treat; ND, could not be determined; OR, odds ratio; ORR, objective response rate; PD, disease progression; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumors; SD, stable disease

Overall safety

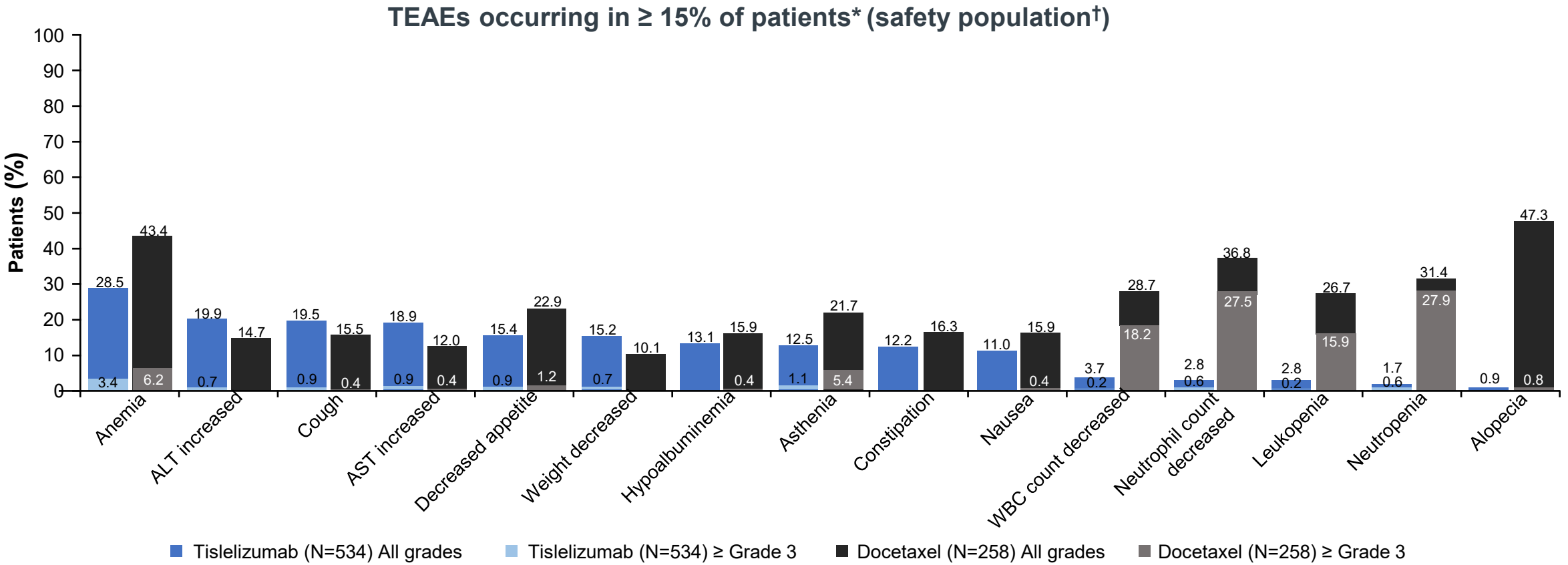
Overall safety profile (safety analysis set*)

	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)

Compared with docetaxel, tislelizumab was associated with a notably lower incidence of ≥ Grade 3 AEs

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

Most common TEAEs

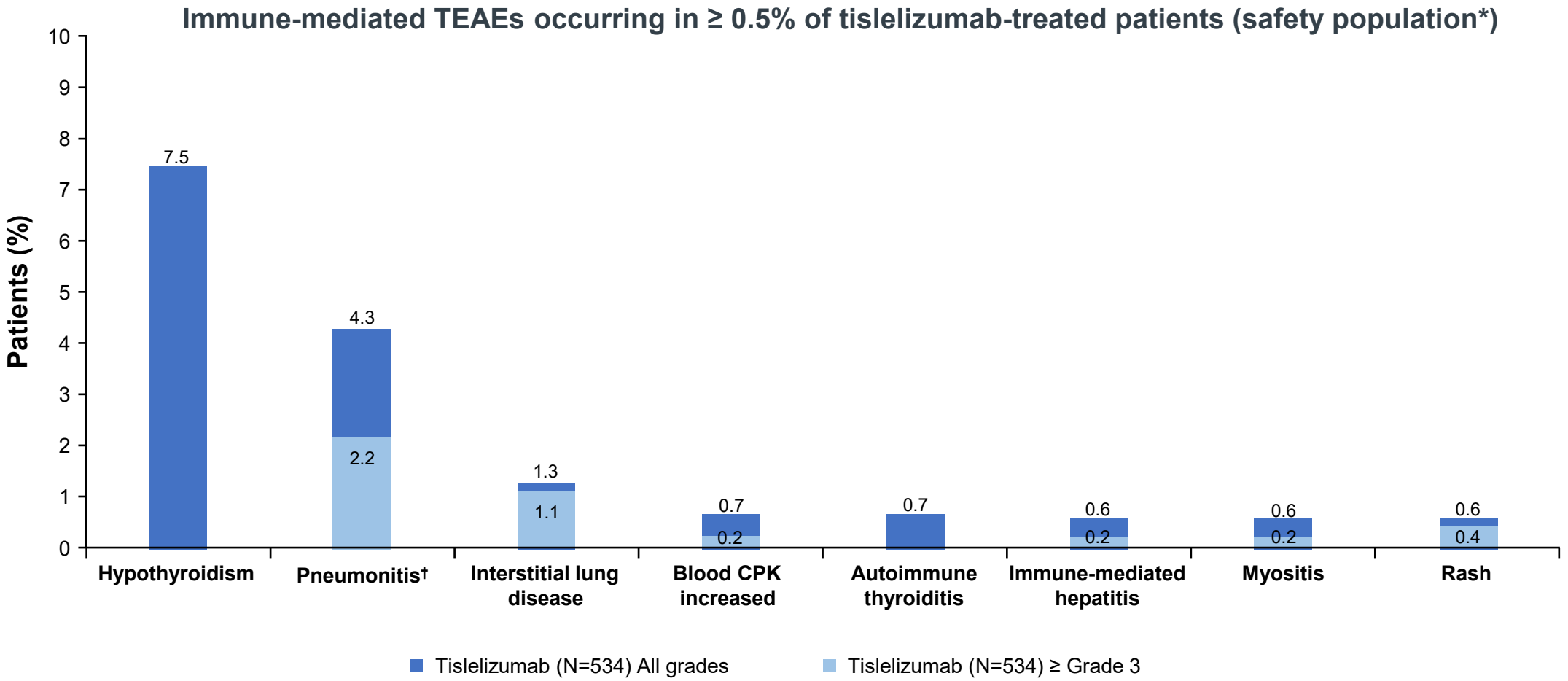


The most commonly reported TEAEs were anemia (tislelizumab arm) and alopecia (docetaxel arm)

The most common ≥ Grade 3 TEAE was neutropenia in the docetaxel arm in 27.9% of patients vs 0.6% with tislelizumab

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

Immune-mediated TEAEs



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

Summary

- 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 showed consistent benefit over docetaxel across all PD-L1 expression subgroups
- Tislelizumab prolonged PFS, improved ORR and prolonged DoR versus 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

*PD-L1 ≥ 25% population included all patients with ≥ 25% of TCs with PD-L1 membrane staining (assessed via Ventana SP263 assay)
AE, adverse events; DoR, duration of response; ITT, intent-to-treat; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PD-1, programmed death protein-1; PD-L1, programmed cell ligand-1

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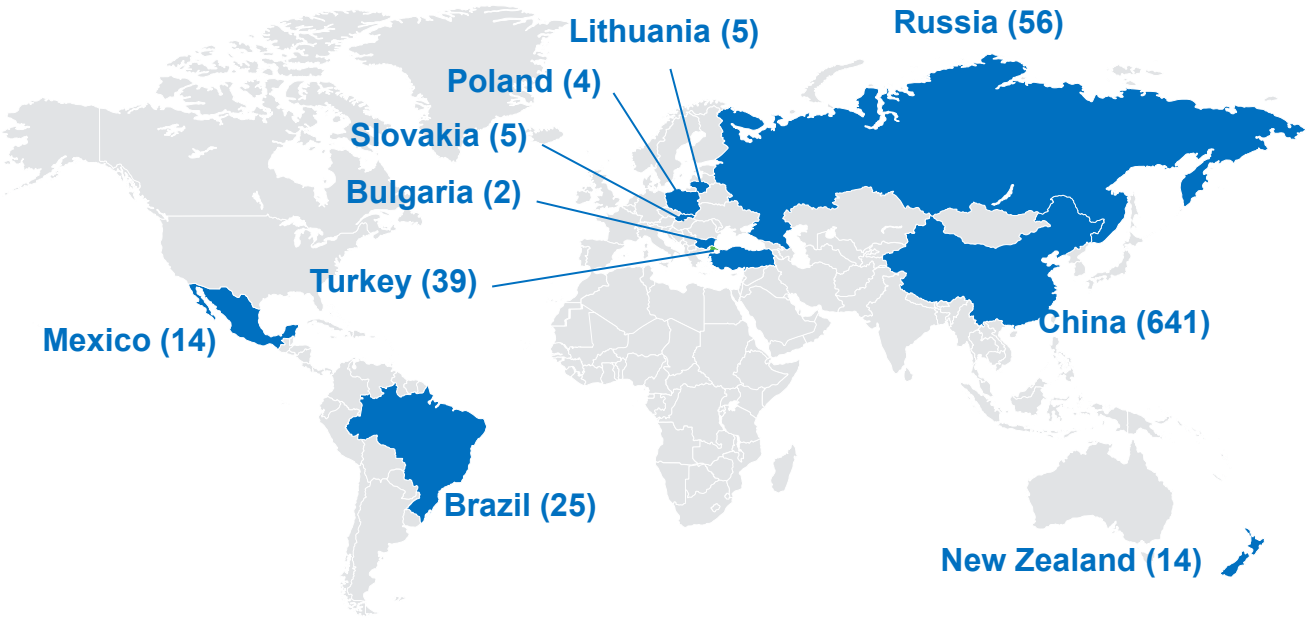

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