RATIONALE 304: Tislelizumab Plus Chemotherapy Versus Chemotherapy Alone as First-line Treatment for Locally Advanced/Metastatic Nonsquamous Non-Small Cell Lung Cancer

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COI and Financial Disclosure Information

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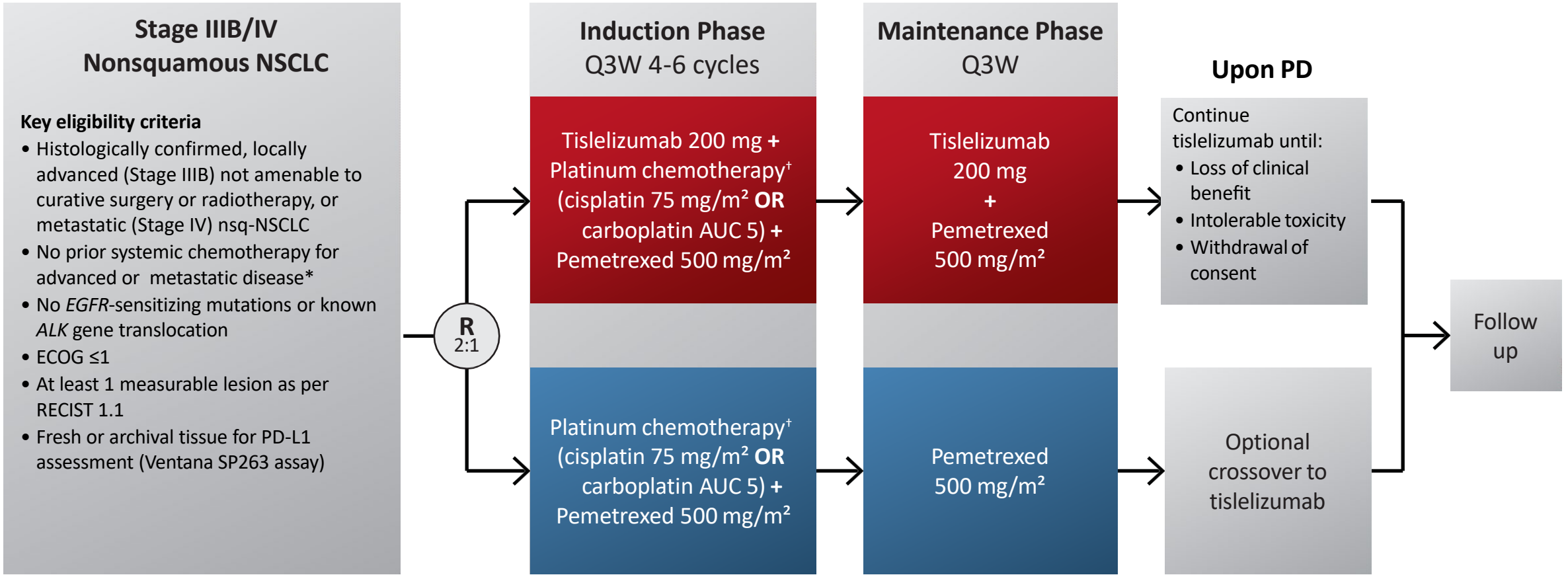
Introduction

- Recent global studies have examined whether better patient outcomes could be achieved using an anti-PD-(L)1 antibody in combination with chemotherapy[1,2]
- Tislelizumab is a humanized IgG4 monoclonal antibody that binds PD-1, currently being developed for the treatment of multiple human malignancies
- In three early phase studies (BGB-A317-001; BGB-A317-102; BGB-A317-206), tislelizumab, as a single agent and in combination with chemotherapy, was generally well tolerated and demonstrated encouraging antitumor activity in Asian and non-Asian populations with solid tumors, including advanced lung cancers[3-5]
- RATIONALE 304 is a Phase 3, open-label, multicenter, randomized study to evaluate the efficacy and safety of tislelizumab in combination with platinum (cisplatin or carboplatin) and pemetrexed compared with platinum and pemetrexed alone as first-line treatment in patients with Stage IIIB or IV non-squamous non-small cell lung cancer (nsq-NSCLC)

[1]Gandhi, et al. *N Engl J Med*. 2018;378(22):2078-2092; [2]West, et al. *Lancet Oncol*. 2019; 20(7):924-937; [3]Desai, et al. *J Immunother Cancer*. 2020;8(1):e000453; [4]Shen, et al. *J Immunother Cancer*. 2020;8(1):e000437; [5]Wang, et al. *Lung Cancer*. 2020; 147:259-268.

RATIONALE 304 Study (BGB-A317-304)



Stratification factors
- **Disease stage (IIIB vs IV)**
- **PD-L1 TC expression (<1% vs 1%-49% vs ≥50%)**

Primary endpoint: PFS_{IRC}
Secondary endpoints: ORR, DoR, OS, and safety profile

***** Patients with prior neoadjuvant or adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for non-metastatic disease must have experienced a disease-free interval of ≥6 months from the last dose of chemotherapy and/or radiotherapy prior to randomization.

† Investigator's choice.

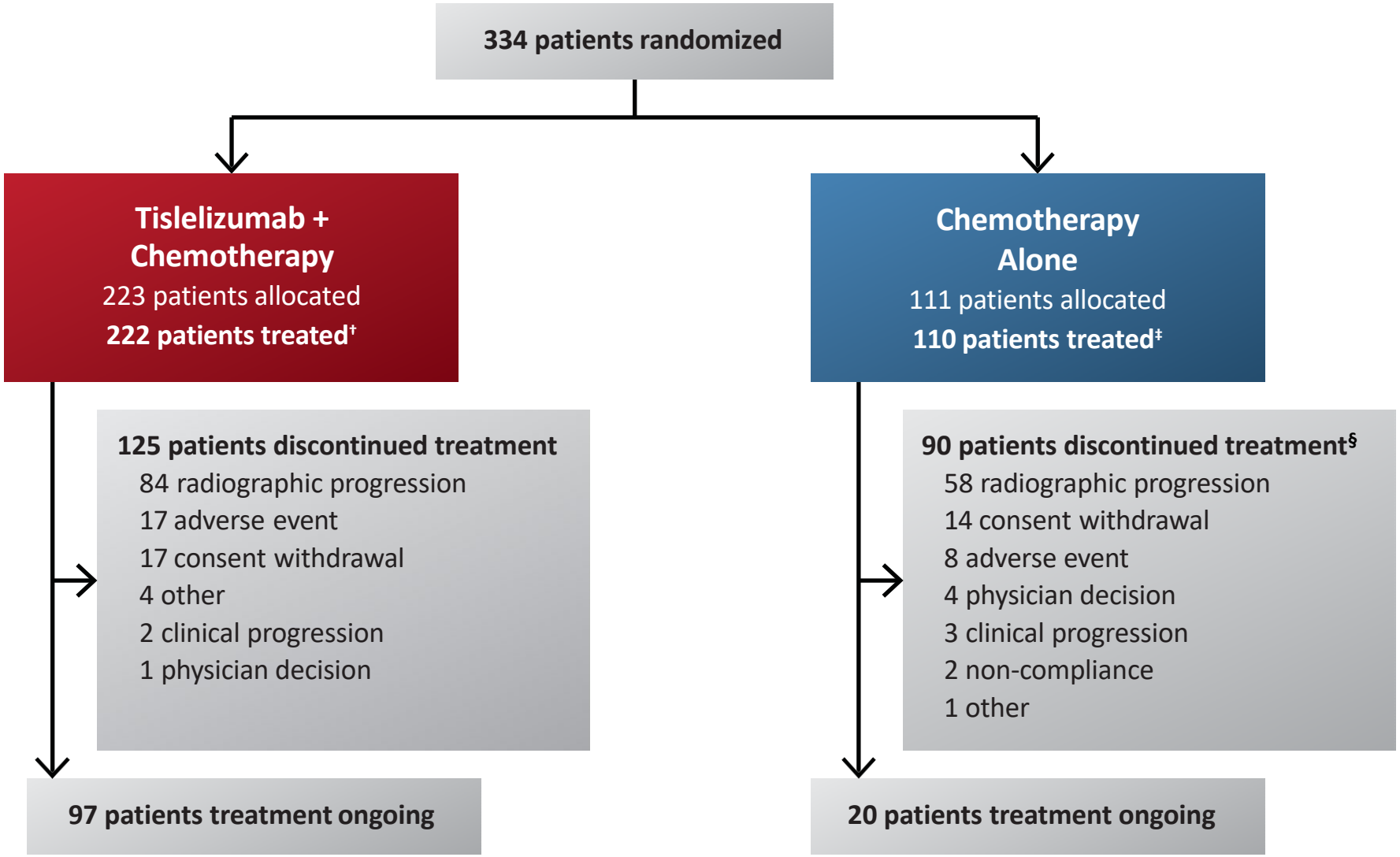
Abbreviations: DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; IRC, Independent Review Committee; nsq-NSCLC, nonsquamous non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; R, randomized; TC, tumor cell.

Statistical Considerations

- **Primary endpoint:** Progression-free survival (PFS) as assessed by an independent review committee (IRC) per RECIST v1.1
- **Planned enrollment:** 320 patients
- **Overall alpha for study: one-sided alpha=0.025**
  - Study had 85% power to show hazard ratio (HR) for PFS_{IRC} of 0.65 in intent-to-treat (ITT) population
  - Protocol specified one interim analysis for ITT population
- **Interim analysis reviewed by independent data monitoring committee**
  - Planned to occur after ~153 (71%) PFS events per independent review committee (IRC) observed in ITT population
  - Data cutoff date: 23 Jan 2020
  - Median follow-up: 9.8 months
  - Observed number of PFS per IRC events: 159 (74%)
  - One-sided alpha level*: 0.0092

*Adjusted based on the observed number of events using O'Brien-Fleming method.

Disposition



† One patient randomized to combination therapy was not treated because inclusion criteria was not met.
‡ One patient randomized to chemotherapy alone was not treated due to withdrawal of consent.
§ A total of 26 patients crossed over to receive tislelizumab.

Data cut-off: 23 Jan 2020

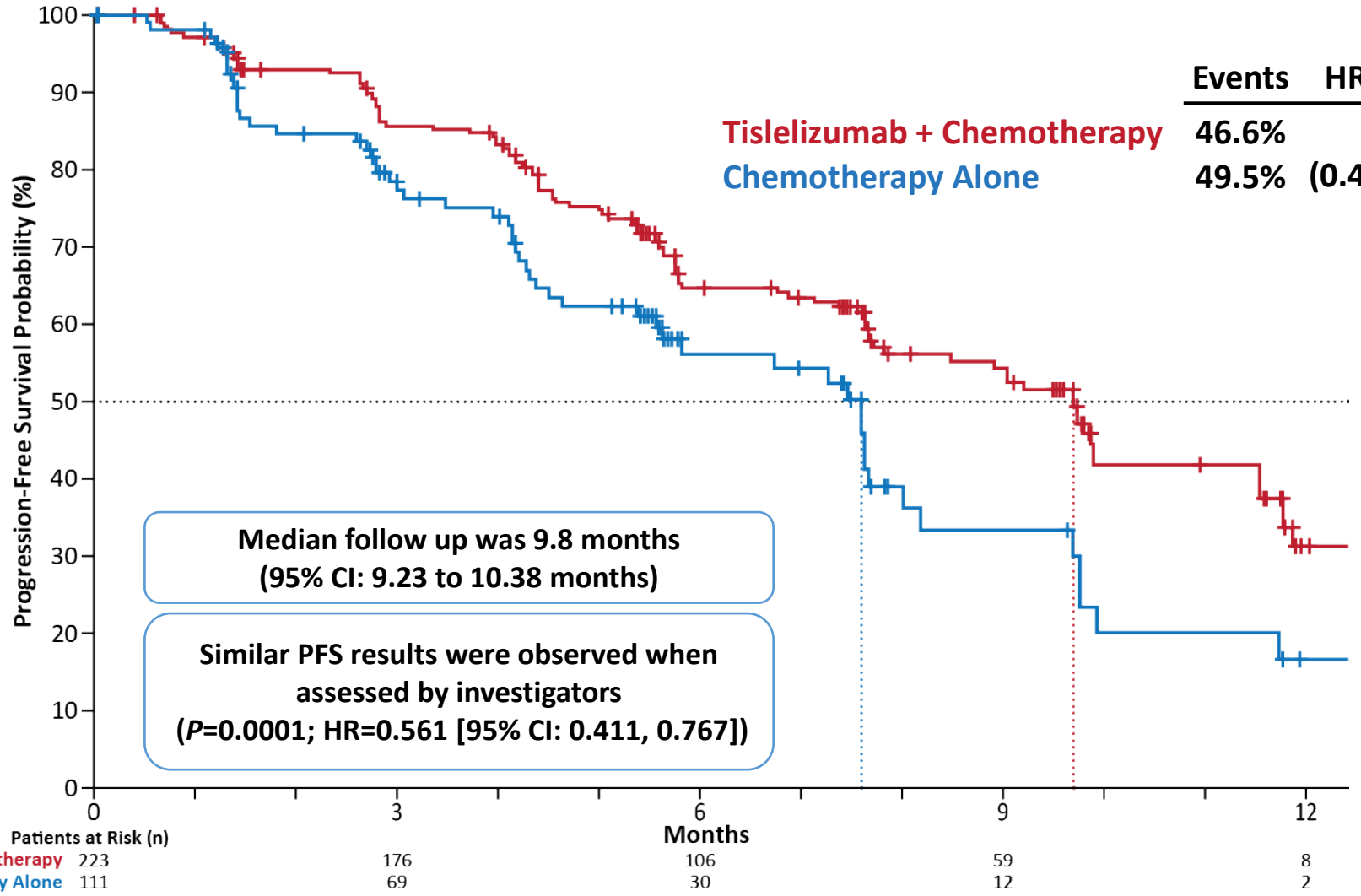
Demographics and Baseline Disease Characteristics (ITT Population)

		Tislelizumab + Chemotherapy (n=223)	Chemotherapy Alone (n=111)
Median age, years (range)		60 (27, 75)	61 (25, 74)
Sex, n (%)	Male	168 (75.3)	79 (71.2)
Smoking status, n (%)	Current/former	147 (65.9)	66 (59.5)
	Never	76 (34.1)	45 (40.5)
ECOG performance status, n (%)	0	54 (24.2)	24 (21.6)
	1	169 (75.8)	87 (78.4)
Disease stage, n (%)	IIIB	40 (17.9)	21 (18.9)
	IV	183 (82.1)	90 (81.1)
Location of distant metastases, n (%)[a]	Liver	20 (9.0)	17 (15.3)
	Brain	11 (4.9)	7 (6.3)
PD-L1 expression in TC, n (%)	<1%[b]	96 (43.0)	48 (43.2)
	≥ 1%	127 (57.0)	63 (56.7)
	1-49%	53 (23.8)	27 (24.3)
	≥50%	74 (33.2)	36 (32.4)
***ALK* rearrangement status, n (%)**	Negative	166 (74.4)	79 (71.2)
	Unknown	57 (25.6)	32 (28.8)
***EGFR* mutation status, n (%)**	Negative	218 (97.8)	109 (98.2)
	Positive/unknown[c]	5 (2.2)	2 (1.8)

[a] Patients were counted only once within each category but could have been counted in multiple categories.
[b] Includes patients with unevaluable PD-L1 expression (n=5).
[c] Includes patients with *EGFR* sensitizing mutant or indeterminate status that were identified via tissue-based test; reported as major protocol deviations.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; PD-L1, programmed death-ligand 1; TC, tumor cell.

Data cut-off: 23 Jan 2020

Progression-Free Survival as Assessed by IRC (ITT Population)



	Events	HR (95% CI)	Log-rank one-sided *P**
Tislelizumab + Chemotherapy	46.6%	0.645 (0.462, 0.902)	0.0044
Chemotherapy Alone	49.5%		

Median PFS (95%CI)
9.7 months (7.7, 11.5)
7.6 months (5.6, 8.0)

Median follow up was 9.8 months (95% CI: 9.23 to 10.38 months)

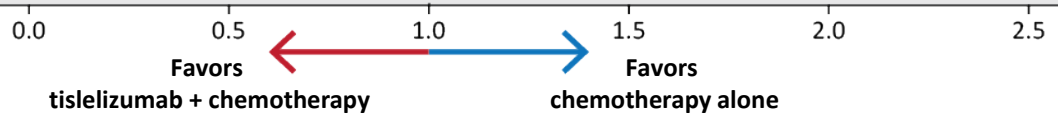
Similar PFS results were observed when assessed by investigators (*P*=0.0001; HR=0.561 [95% CI: 0.411, 0.767])

* Stratified by disease stage and PD-L1 expression.
Abbreviations: CI, confidence interval; HR, hazard ratio; IRC, independent review committee; ITT, intent-to-treat; PFS, progression-free survival.

Data cut-off: 23 Jan 2020

Progression-Free Survival per IRC in Key Subgroups (ITT Population)

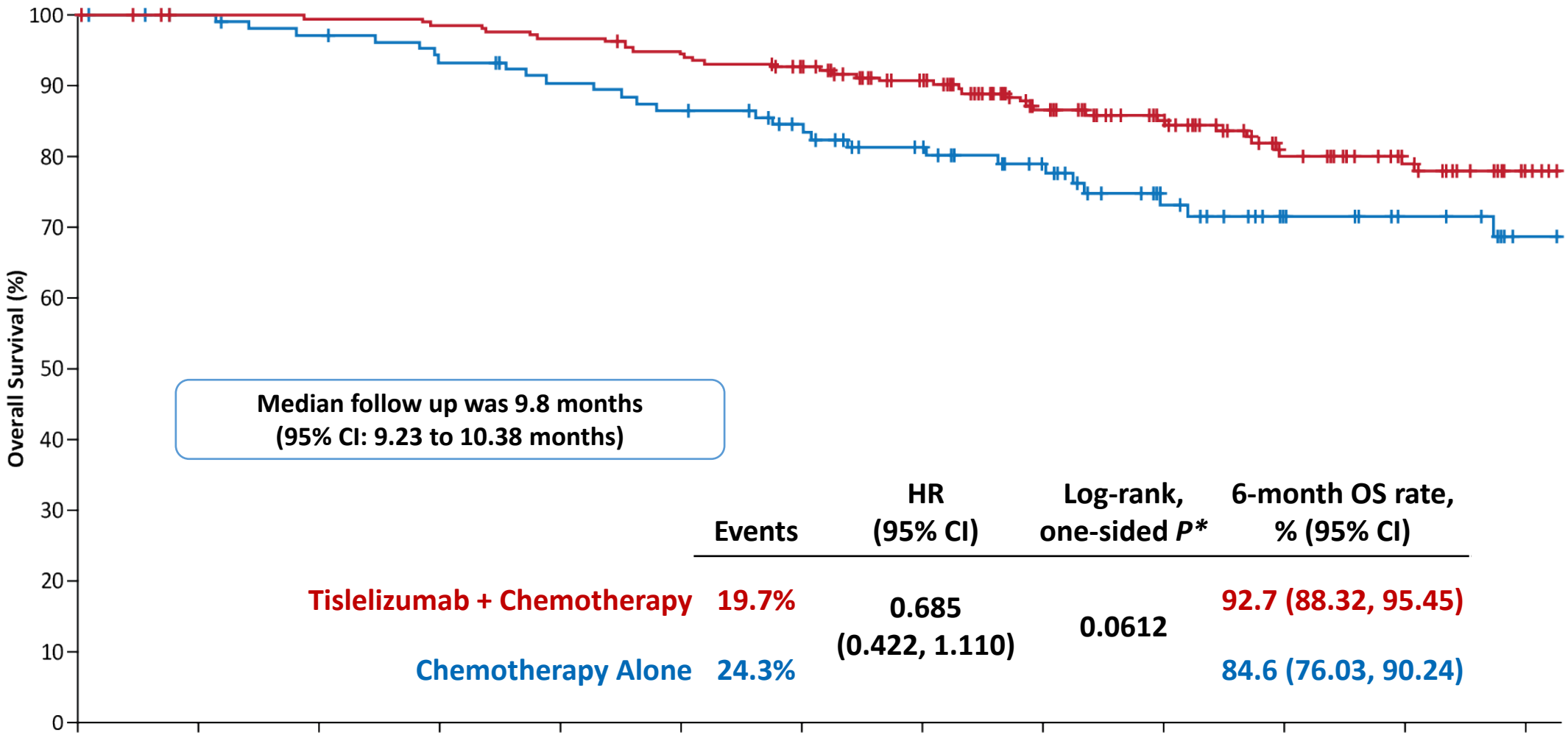
		Events/Patients (n)	HR (95% CI)
Overall		159/334	0.645 (0.462, 0.902)
Age	<65 years	112/237	0.606 (0.403, 0.911)
	≥65 years	47/97	0.727 (0.407, 1.297)
Sex	Female	43/87	0.946 (0.487, 1.840)
	Male	116/247	0.538 (0.367, 0.789)
ECOG Performance Status	0	34/78	0.834 (0.386, 1.800)
	1	125/256	0.601 (0.416, 0.868)
Smoking Status	Never	56/121	1.075 (0.596, 1.940)
	Current or Former	103/213	0.466 (0.311, 0.697)
Disease Stage	IIIB	30/61	0.664 (0.319, 1.379)
	IV	129/273	0.632 (0.436, 0.917)
Liver Metastasis	Yes	21/37	0.370 (0.153, 0.898)
	No	138/297	0.729 (0.505, 1.052)
PD-L1 Expression in TC	<1%	78/144	0.758 (0.469, 1.224)
	≥1%	81/190	0.549 (0.347, 0.869)
	1-49%	36/80	1.058 (0.507, 2.209)
	≥50%	45/110	0.308 (0.167, 0.567)
ALK Rearrangement	Negative	119/245	0.636 (0.434, 0.930)
	Unknown	40/89	0.669 (0.345, 1.297)



Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IRC, independent review committee; ITT, intent-to-treat; PD-L1, programmed death-ligand 1; TC, tumor cell.

Data cut-off: 23 Jan 2020

Overall Survival (ITT Population)



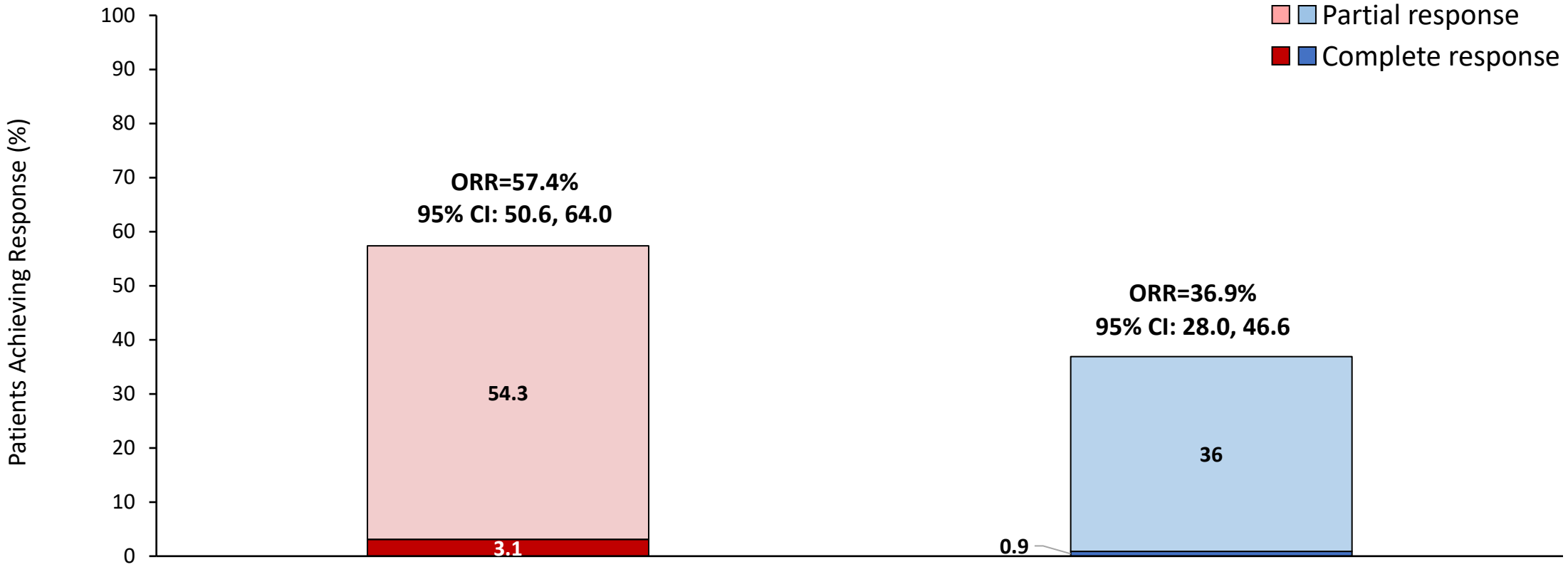
	Events	HR (95% CI)	Log-rank, one-sided *P**	6-month OS rate, % (95% CI)
Tislelizumab + Chemotherapy	19.7%	0.685 (0.422, 1.110)	0.0612	92.7 (88.32, 95.45)
Chemotherapy Alone	24.3%			84.6 (76.03, 90.24)

* Stratified by disease stage and PD-L1 expression.

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

Data cut-off: 23 Jan 2020

Disease Response per IRC (ITT Population)



	Tislelizumab + Chemotherapy (n=223)	Chemotherapy Alone (n=111)
Disease Control Rate, % (95% CI)	89.2 (84.4, 93.0)	81.1 (72.5, 87.9)
Duration of Response, median (95% CI), months	8.5 (6.80, 10.58)	6.0 (4.99, NE)

Abbreviations: CI, confidence interval; IRC, independent review committee; ITT, intent-to-treat; ORR, objective response rate.

Data cut-off: 23 Jan 2020

Treatment Exposure and Overview of TEAEs (Safety Population)

	Tislelizumab + Chemotherapy (n=222)	Chemotherapy Alone (n=110)
Treatment cycles, median (range)		
Tislelizumab	10 (1, 25)	NA
Pemetrexed	9 (1, 24)	6.5 (1, 18)
Carboplatin	4 (1, 6)	4 (1, 6)
Cisplatin	4 (1, 6)	4 (2, 6)
TEAEs, n (%)		
Any grade	222 (100)	109 (99.1)
Grade ≥3	150 (67.6)	59 (53.6)
Serious AEs	74 (33.3)	23 (20.9)
Leading to permanent discontinuation	57 (25.7)	10 (9.1)
Leading to treatment modification	149 (67.1)	57 (51.8)
Leading to death	7 (3.2)	2 (1.8)

Abbreviations: AEs, adverse events; NA, not applicable; TEAEs, treatment-emergent adverse events.

Data cut-off: 23 Jan 2020

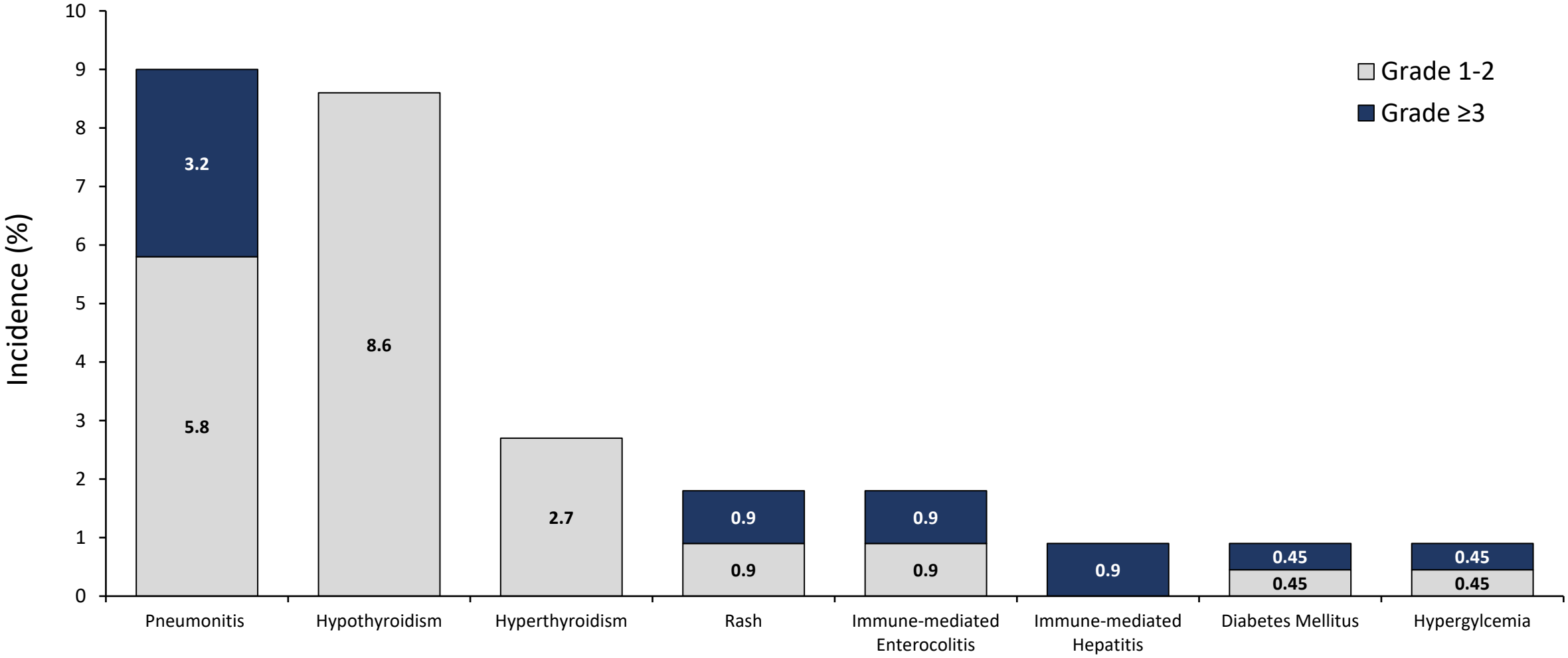
Most Common Treatment-Related AEs Occurring in ≥20% of Patients in the Safety Population

	Tislelizumab + Chemotherapy (n=222)		Chemotherapy Alone (n=110)	
Preferred term	**Grade 1-2**	**Grade ≥3**	**Grade 1-2**	**Grade ≥3**
Anemia[1]	151 (68.0)	30 (13.5)	71 (64.5)	11 (10.0)
Leukopenia[2]	135 (60.8)	48 (21.6)	65 (59.1)	16 (14.5)
Thrombocytopenia[3]	112 (50.5)	43 (19.4)	55 (50.0)	15 (13.6)
Nausea	94 (42.3)	1 (0.5)	43 (39.1)	1 (0.9)
ALT increased	92 (41.4)	8 (3.6)	45 (40.9)	3 (2.7)
AST increased	86 (38.7)	4 (1.8)	49 (44.5)	0 (0.0)
Neutropenia[4]	83 (37.4)	99 (44.6)	42 (38.2)	39 (35.5)
Fatigue[5]	74 (33.3)	3 (1.4)	35 (31.8)	1 (0.9)
Decreased appetite	63 (28.4)	3 (1.4)	28 (25.5)	1 (0.9)
Vomiting	55 (24.8)	1 (0.5)	23 (20.9)	1 (0.9)

Data presented as n (%).
1. Anemia included: reports of anemia, haemoglobin decreased, and red blood cell count decreased.
2. Leukopenia included: reports of white blood cell count decreased, and leukopenia.
3. Thrombocytopenia included: reports of platelet count decreased and thrombocytopenia.
4. Neutropenia included: reports of neutrophil count decreased and neutropenia.
5. Fatigue included: asthenia, fatigue, and malaise.
Abbreviations: AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Data cut-off: 23 Jan 2020

Immune-Mediated AEs by Preferred Term Occurring in ≥2 Patients in Tislelizumab + Chemotherapy group



Immune-mediated AEs were selected from a group of preferred terms, regardless of whether the investigator attributed the event to a trial regimen or considered the event to be immune related.

Abbreviations: AEs, adverse events.

Data cut-off: 23 Jan 2020

Summary and Future Directions

- The addition of tislelizumab resulted in significantly improved PFS as assessed by an IRC (9.7 vs 7.6 months; *P*=0.0044, HR=0.645 [95% CI: 0.462, 0.902]) as well as higher ORR and longer DoR than chemotherapy alone in Chinese patients with advanced nsq-NSCLC
- Tislelizumab in combination with platinum and pemetrexed was generally well tolerated
  - No new safety signals were identified with the addition of tislelizumab to standard chemotherapy
- The results from this pivotal phase 3 study support tislelizumab in combination with platinum and pemetrexed as a potential new standard first-line treatment for advanced nsq-NSCLC

Abbreviations: CI, confidence interval; DoR, duration of response; HR, hazard ratio; IRC, independent review committee; nsq-NSCLC, nonsquamous non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival.

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