Supplemental Online Content

Wang J, Lu S, Yu X, et al. Tislelizumab plus chemotherapy vs chemotherapy alone as first-line treatment for advanced squamous non–small-cell lung cancer: a phase 3 randomized clinical trial. *JAMA Oncol*. Published online April 1, 2021. doi:10.1001/jamaoncol.2021.0366

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods.

Additional Inclusion/Exclusion Criteria

Inclusion Criteria:

- Patients had not received prior systemic therapy for advanced or metastatic disease.
- Prior neoadjuvant/adjuvant therapy or chemoradiation therapy with curative intent was allowed if there had been a disease-free interval ⩾6 months prior to randomization.

Exclusion Criteria:

- Patients had prior active malignancies ⩽2 years from study entry or locally recurring cancers that underwent curative treatment, not including non-small cell lung cancer.
- Patients had prior treatment with inhibitors of EGFR, ALK, and/or PD-1/L1 inhibitors.

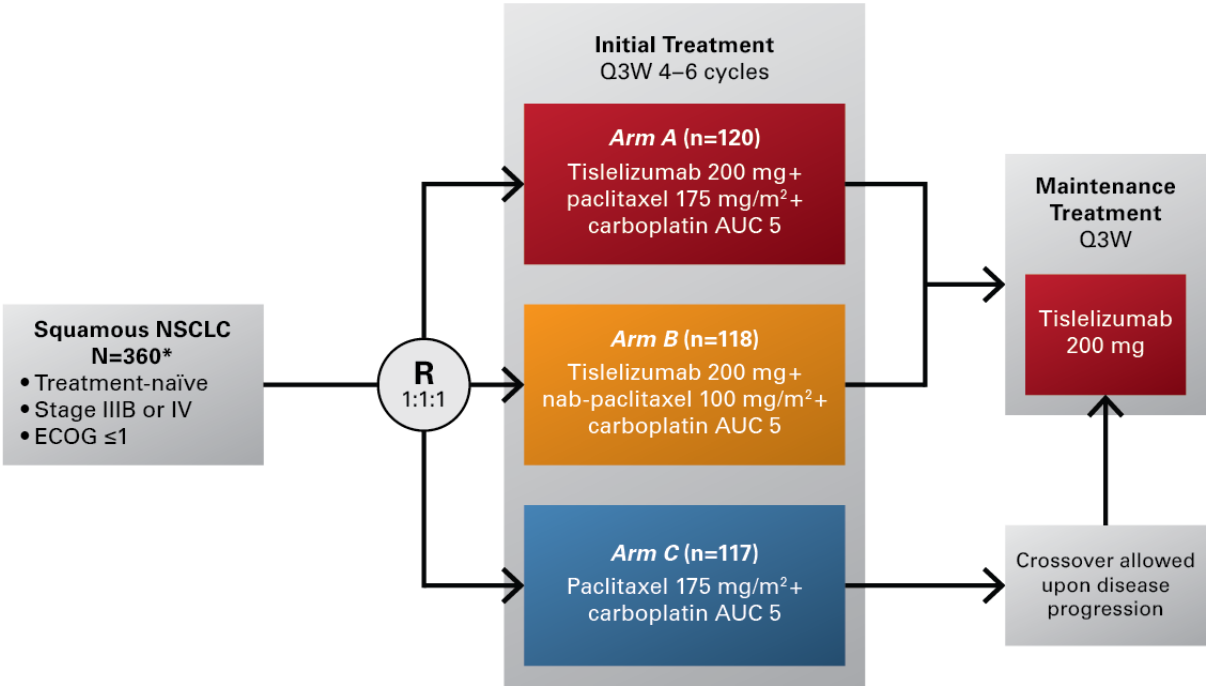
Endpoint Definitions

- Progression-free survival: Defined as the time from randomization to the first objectively documented disease progression per RECIST v1.1 or death from any cause, whichever occurs first.
- Overall survival: Time from the date of randomization to the date of death from any cause.
- Objective response rate: Complete response (CR) plus partial response (PR) per RECIST v1.1 criteria.
- Duration of response: Time from the first occurrence of a documented objective response to documented disease progression per RECIST v1.1 criteria or death by any cause, whichever occurs first.
- Disease control rate: CR plus PR plus stable disease (≥6 weeks).

Tumor Assessments and Screening for PD-L1 Expression

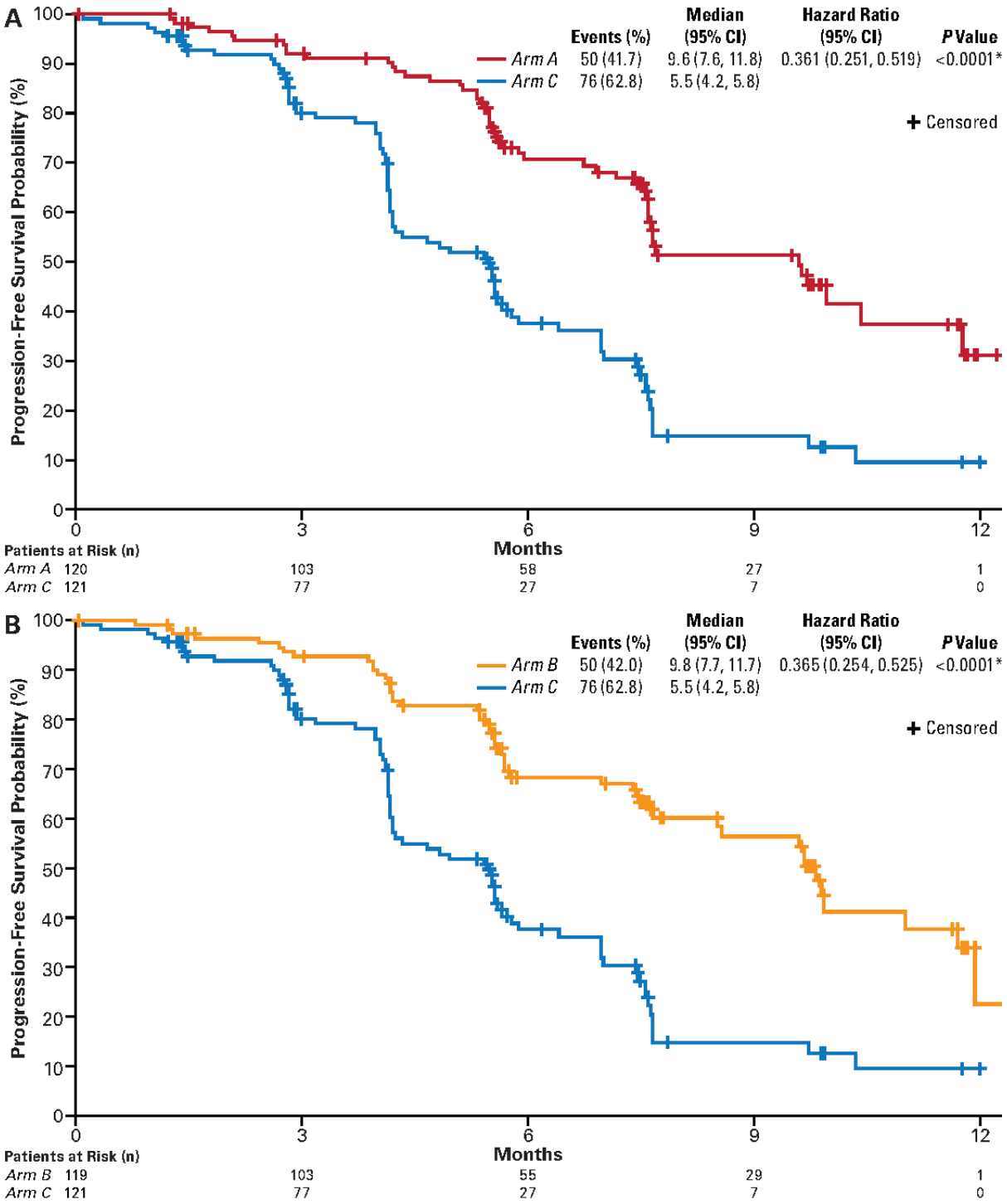
Tumor assessments and radiographic imaging by MRI or CT were performed every 6 weeks during the first 6 months, every 9 weeks for the remainder of the first year, and every 12 weeks thereafter. Tumor cell PD-L1 membrane staining was assessed during screening with the VENTANA PD-L1 (SP263) assay at a central laboratory.

eFigure 1. Study design



Target accrual was 342 patients, with 114 patients planned per arm.
*A total of 360 patients were randomized; 5 patients (n=1 [*B*]; n=4 [*C*]) did not receive study treatment.
Tislelizumab, carboplatin, and paclitaxel were administered on D1.
Nab-paclitaxel was administered on D1, D8, and D15.
Abbreviations: D, day; ECOG, Eastern Cooperative Oncology Group; nab, nanoparticle albumin-bound; NSCLC, non-small cell lung cancer; Q3W, every 3 weeks; R, randomized.

eFigure 2. Progression-free survival by investigator

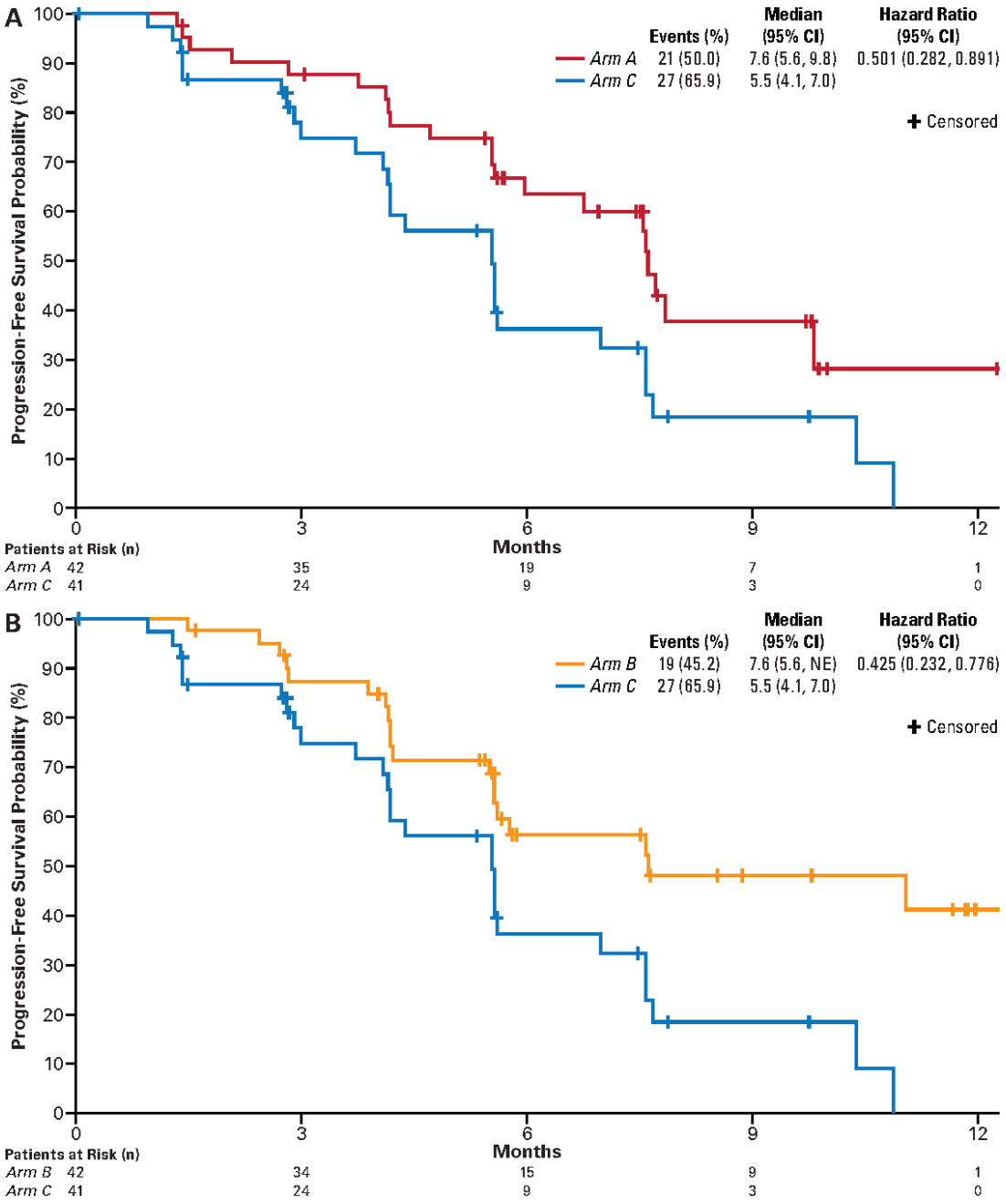


Arm A versus *Arm C* (A) and *Arm B* versus *Arm C* (B).

*Descriptive *P*-value.

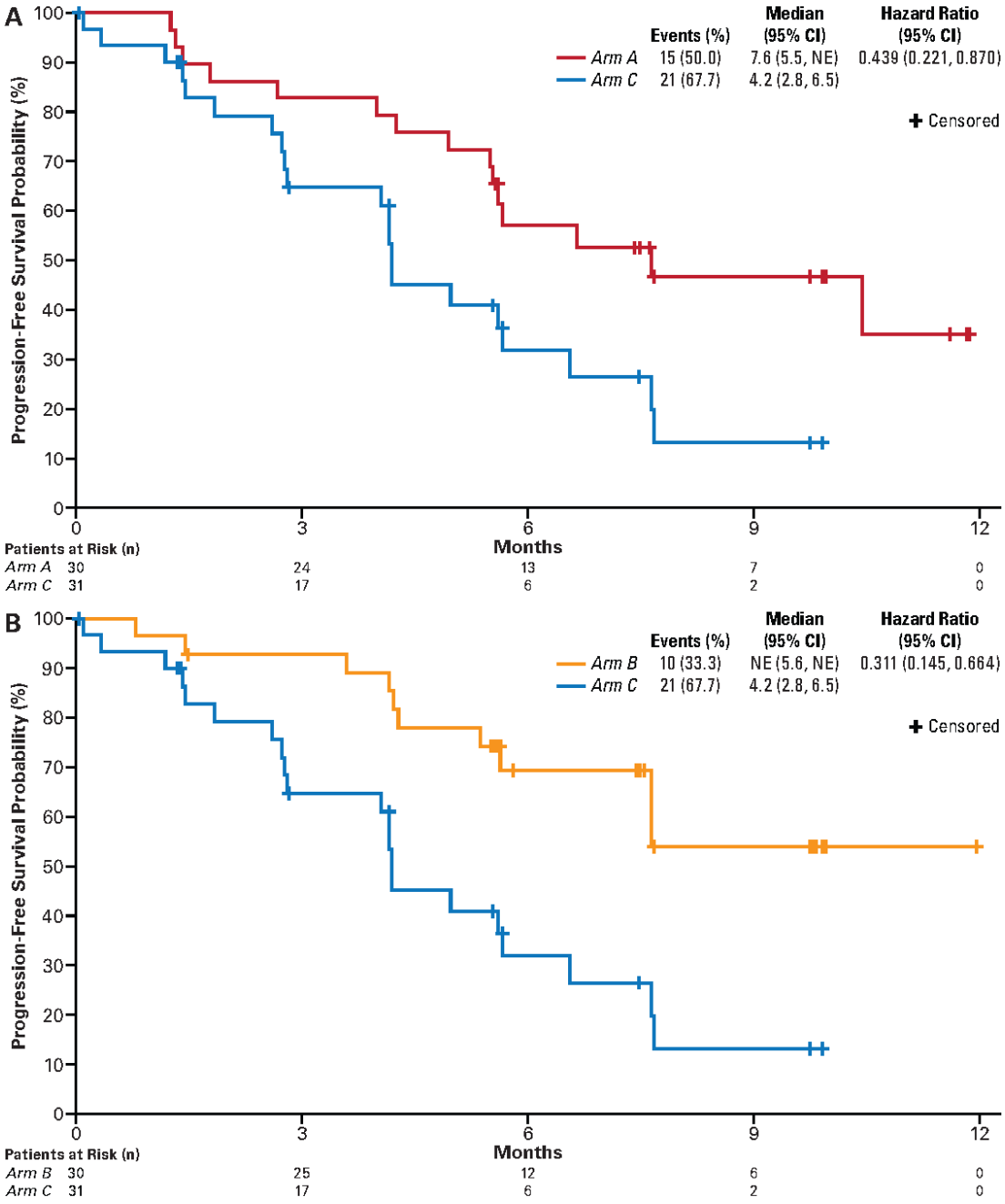
Abbreviation: CI, confidence interval.

eFigure 3. Progression-free survival by Independent Review Committee in patients with ⩾50% tumor cell PD-L1 expression



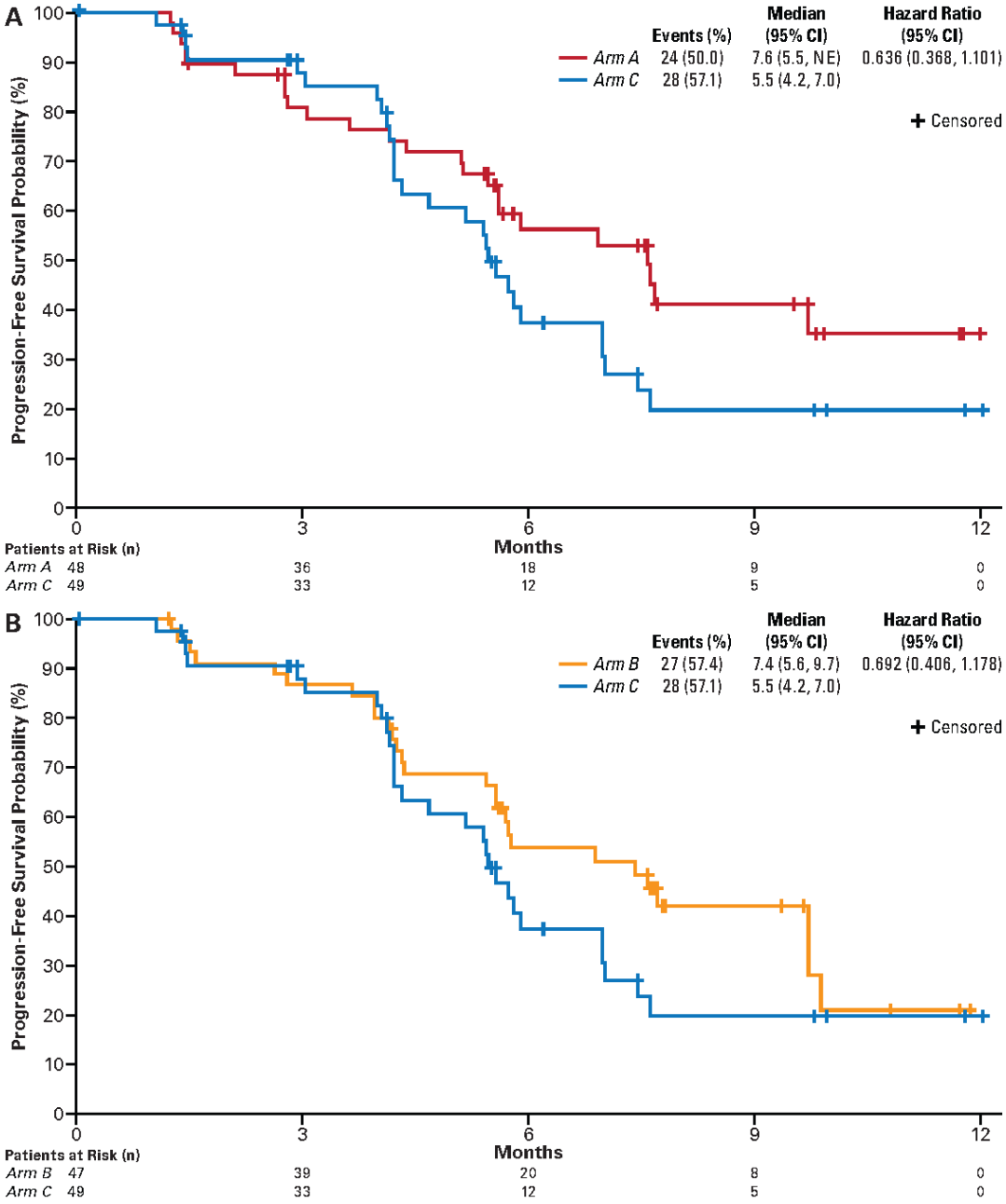
Arm A versus *Arm C* (A) and *Arm B* versus *Arm C* (B).
Abbreviations: CI, confidence interval; NE, not evaluable; PD-L1, programmed death-ligand 1.

eFigure 4. Progression-free survival by Independent Review Committee in patients with 1-49% tumor cell PD-L1 expression



Arm A versus *Arm C* (A) and *Arm B* versus *Arm C* (B).
Abbreviations: CI, confidence interval; NE, not evaluable; PD-L1, programmed death-ligand 1.

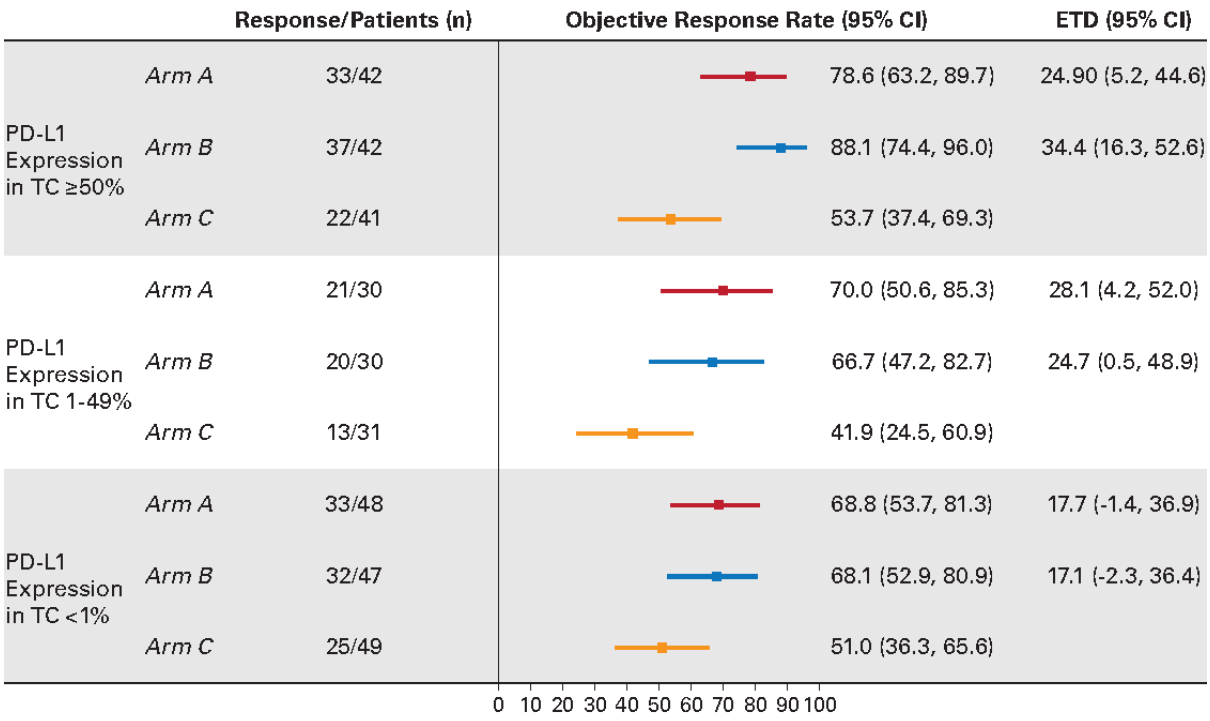
eFigure 5. Progression-free survival by Independent Review Committee in patients with <1% tumor cell PD-L1 expression



Arm A versus *Arm C* (A) and *Arm B* versus *Arm C* (B).

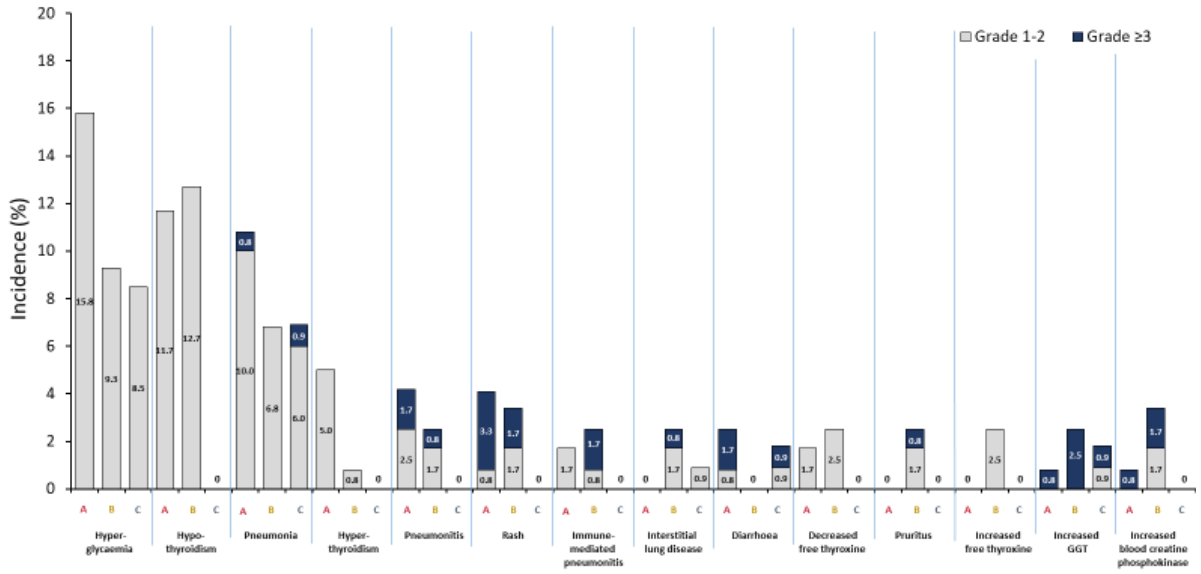
Abbreviations: CI, confidence interval; NE, not evaluable; PD-L1, programmed death-ligand 1.

eFigure 6. Objective response rate by PD-L1 expression as assessed by Independent Review Committee



Abbreviations: CI, confidence interval; ETD, estimated treatment difference; PD-L1, programmed death-ligand 1; TC, tumor cell.

eFigure 7. Potential immune-mediated AEs by preferred term occurring in >2 patients across treatment arms



Potential 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.

Arm A: Tislelizumab + PC.

Arm B: Tislelizumab + nab-PC.

Arm C: PC alone.

Abbreviations: AEs, adverse events; GGT, ɣ-glutamyltransferase; nab, nanoparticle albumin-bound; PC, paclitaxel and carboplatin.

eTable 1. Tislelizumab Treatment Exposure

	Arm A **Tislelizumab + Paclitaxel + Carboplatin (n=120)**	***Arm B*** **Tislelizumab + nab-Paclitaxel + Carboplatin (n=118)**	***Arm C*** **Paclitaxel + Carboplatin (n=117)**
Tislelizumab relative dose intensity[a]			
Median (range)	97.7 (64-108)	91.3 (55-100)	NA
Number of cycles received with tislelizumab			
Median (range)	10 (1-20)	10 (1-19)	NA
1-4 cycle, n (%)	23 (19.2)	20 (16.9)	NA
5-8 cycles, n (%)	16 (13.3)	26 (22.0)	NA
9-12 cycles, n (%)	49 (40.8)	44 (37.3)	NA
>12 cycles, n (%)	32 (26.7)	28 (23.7)	NA

[a]Relative dose intensity was defined as the ratio of the actual dose intensity (mg/cycle) and the planned dose intensity (mg/cycle).
Abbreviations: NA, not applicable; nab, nanoparticle albumin-bound.

eTable 2. Chemotherapy Treatment Exposure

	Arm A Tislelizumab + Paclitaxel + Carboplatin (n=120)		Arm B Tislelizumab + nab-Paclitaxel + Carboplatin (n=118)		*Arm C* Paclitaxel + Carboplatin (n=117)	
	Paclitaxel	Carboplatin	nab-Paclitaxel	Carboplatin	Paclitaxel	Carboplatin
Relative dose intensity (%) per patient[a]						
Median (range)	94.83 (62.2, 104.2)	94.81 (63.5, 110.1)	55.07 (23.3, 80.0)	82.56 (47.0, 105.9)	97.67 (62.1, 105.5)	96.68 (51.7, 123.0)
Duration of exposure, weeks						
Median (range)	15.07 (3.0, 24.3)	15.07 (3.0, 24.3)	14.00 (3.0, 24.9)	14.00 (3.0, 24.9)	13.43 (0.3, 22.4)	13.43 (0.3, 26.1)
Number of cycles received						
Median (range)	4.5 (1, 6)	4.5 (1, 6)	4.0 (1, 6)	4.0 (1, 6)	4.0 (1, 6)	4.0 (1, 6)
1 cycle, n (%)	7 (5.8)	7 (5.8)	9 (7.6)	9 (7.6)	7 (6.0)	7 (6.0)
2 cycles, n (%)	10 (8.3)	9 (7.5)	5 (4.2)	5 (4.2)	7 (6.0)	7 (6.0)
3 cycles, n (%)	4 (3.3)	4 (3.3)	18 (15.3)	18 (15.3)	8 (6.8)	8 (6.8)
4 cycles, n (%)	39 (32.5)	40 (33.3)	49 (41.5)	52 (44.1)	38 (32.5)	38 (32.5)
>4 cycles, n (%)	60 (50)	60 (50)	37 (31.4)	34 (28.8)	57 (48.7)	57 (48.7)

[a]Relative dose intensity was defined as the ratio of the actual dose intensity (mg/cycle) and the planned dose intensity (mg/cycle).
Abbreviation: nab, nanoparticle albumin-bound.

eTable 3. Progression-Free Survival by Disease Stage per RECIST version 1.1 by Independent Review Committee in ITT Analysis Set

	Stage IIIB	Stage IV
Tislelizumab plus PC versus PC alone		
Median Tislelizumab plus PC (95% CI)	9.8 (5.95, NE)	7.6 (5.59, 7.82)
Median PFS PC alone (95% CI)	5.6 (4.17, 7.43)	5.2 (4.17, 5.59)
PFS HR (95% CI)	0.402 (0.215, 0.750)	0.570 (0.376, 0.862)
Tislelizumab plus nab-PC versus PC alone		
Median PFS Tislelizumab plus nab-PC (95% CI)	11.0 (7.56, NE)	7.4 (5.59, 9.86)
Median PFS PC alone (95% CI)	5.6 (4.17, 7.43)	5.2 (4.17, 5.59)
PFS HR (95% CI)	0.372 (0.202, 0.686)	0.537 (0.350, 0.824)

Abbreviations: CI, confidence interval; ITT, intent-to-treat; nab, nanoparticle albumin-bound; nab-PC, nab-paclitaxel plus carboplatin; PC, paclitaxel plus carboplatin; RECIST, Response Evaluation Criteria in Solid Tumors.

eTable 4. Progression-Free Survival by PD-L1 Expression per RECIST version 1.1 by Independent Review Committee in ITT Analysis Set

	PD-L1 <1%	PD-L1 ≥1%
Tislelizumab plus PC versus PC alone		
Median PFS Tislelizumab plus PC (95% CI)	7.6 (5.45, NE)	7.6 (5.95, 10.41)
Median PFS in PC alone (95% CI)	5.5 (4.21, 6.97)	5.0 (4.14, 5.59)
PFS HR (95% CI)	0.636 (0.368, 1.101)	0.453 (0.293, 0.703)
Tislelizumab plus nab-PC versus PC alone		
Median PFS in Tislelizumab plus nab-PC (95% CI)	7.4 (5.55, 9.69)	11.0 (5.75, NE)
Median PFS in PC alone (95% CI)	5.5 (4.21, 6.97)	5.0 (4.14, 5.59)
PFS HR (95% CI)	0.692 (0.406, 1.178)	0.367 (0.229, 0.588)

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; nab, nanoparticle albumin-bound; nab-PC, nab-paclitaxel plus carboplatin; PC, paclitaxel plus carboplatin; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

eTable 5. Biomarker Interaction Analysis for PD-L1 at Cutoff of 1% TC per RECIST version 1.1 by Independent Review Committee in ITT Analysis Set

	PD-L1 ≥1%	PD-L1 <1%	PD-L1 ≥1%: PD-L1 <1% Ratio	*P*-Value
Tislelizumab plus PC versus PC alone				
Progression-free survival, HR (95% CI)	0.449 (0.290, 0.695)	0.621 (0.358, 1.075)	0.723 (0.358, 1.458)	0.3651
Objective response rate, OR (95% CI)	3.372 (1.648, 6.901)	2.196 (0.950, 5.073)	1.536 (0.512, 4.605)	0.4438
Tislelizumab plus nab-PC versus PC alone				
Progression-free survival, HR (95% CI)	0.361 (0.227, 0.576)	0.689 (0.404, 1.174)	0.525 (0.258, 1.065)	0.0743
Objective response rate, OR (95% CI)	4.145 (1.980, 8.677)	2.099 (0.910, 4.843)	1.975 (0.649, 6.012)	0.231

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; nab, nanoparticle albumin-bound; nab-PC, nab-paclitaxel plus carboplatin; OR, odds ratio; PC, paclitaxel plus carboplatin; PD-L1, programmed death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; TC, tumor cell.

eTable 6. Overall Summary of Treatment-Emergent Adverse Events

	Arm A **Tislelizumab + Paclitaxel + Carboplatin (n=120)**	***Arm B*** **Tislelizumab + nab-Paclitaxel Carboplatin (n=118)**	***Arm C*** **Paclitaxel + Carboplatin (n=117)**
Patients with ⩾1 TEAE	120 (100.0)	117 (99.2)	117 (100.0)
Grade ⩾3 TEAE	106 (88.3)	102 (86.4)	98 (83.8)
Serious TEAE	44 (36.7)	45 (38.1)	29 (24.8)
TEAE leading to death	4 (3.3)	5 (4.2)	5 (4.3)
TEAEs leading to discontinuation			
Any study treatment component	15 (12.5)	35 (29.7)	18 (15.4)
Tislelizumab	12 (10.0)	12 (10.1)	NA
Paclitaxel	9 (7.5)	NA	17 (14.5)
nab-paclitaxel	NA	28 (23.7)	NA
Carboplatin	9 (7.5)	27 (22.9)	17 (14.5)
TEAEs leading to dose modification or treatment delays			
Tislelizumab	53 (44.2)	93 (78.8)	NA
Paclitaxel	63 (52.5)	NA	47 (40.2)
nab-paclitaxel	NA	108 (91.5)	NA
Carboplatin	63 (52.5)	93 (78.7)	44 (37.6)

Data presented as n (%).
Abbreviations: NA, not applicable; nab, nanoparticle albumin-bound; TEAE, treatment-emergent adverse event.

eTable 7. Incidence of Treatment-Related Adverse Events Occurring in ≥15% of Patients

Preferred Term	*Arm A* Tislelizumab + Paclitaxel + Carboplatin (n=120)		*Arm B* Tislelizumab + nab-Paclitaxel + Carboplatin (n=118)		*Arm C* Paclitaxel + Carboplatin (n=117)	
	All Grades, n (%)	Grade ≥3, n (%)	All Grades, n (%)	Grade ≥3, n (%)	All Grades, n (%)	Grade ≥3, n (%)
Patients with ≥1 TRAE	**119 (99.2)**	**103 (85.8)**	**117 (99.2)**	**99 (83.9)**	**117 (100.0)**	**94 (80.3)**
Anemia	99 (82.5)	6 (5.0)	104 (88.1)	24 (20.3)	87 (74.4)	11 (9.4)
Alopecia	77 (64.2)	0	81 (68.6)	0	72 (61.5)	0
Decreased neutrophil count	75 (62.5)	62 (51.7)	72 (61.0)	54 (45.8)	68 (58.1)	53 (45.3)
Decreased white blood cell count	63 (52.5)	26 (21.7)	68 (57.6)	32 (27.1)	62 (53.0)	28 (23.9)
Leukopenia	57 (47.5)	19 (15.8)	66 (55.9)	30 (25.4)	56 (47.9)	21 (17.9)
Neutropenia	51 (42.5)	40 (33.3)	50 (42.4)	32 (27.1)	55 (47.0)	47 (40.2)
Decreased appetite	50 (41.7)	1 (0.8)	49 (41.5)	1 (0.8)	35 (29.9)	1 (0.9)
Increased ALT	48 (40.0)	2 (1.7)	40 (33.9)	2 (1.7)	27 (23.1)	0
Decreased platelet count	40 (33.3)	5 (4.2)	52 (44.1)	16 (13.6)	28 (23.9)	2 (1.7)
Increased AST	39 (32.5)	0	38 (32.2)	1 (0.8)	13 (11.1)	0
Nausea	34 (28.3)	0	48 (40.7)	0	29 (24.8)	1 (0.9)
Thrombocytopenia	33 (27.5)	7 (5.8)	47 (39.8)	15 (12.7)	32 (27.4)	7 (6.0)
Pain in extremity	33 (27.5)	3 (2.5)	8 (6.8)	0	23 (19.7)	0
Increased blood bilirubin	27 (22.5)	0	14 (11.9)	0	15 (12.8)	0
Asthenia	26 (21.7)	0	19 (16.1)	0	23 (19.7)	1 (0.9)
Hypoesthesia	25 (20.8)	0	11 (9.3)	0	19 (16.2)	0
Vomiting	24 (20.0)	0	22 (18.6)	0	15 (12.8)	2 (1.7)
Rash	23 (19.2)	4 (3.3)	25 (21.2)	2 (1.7)	4 (3.4)	0
Constipation	23 (19.2)	0	13 (11.0)	0	18 (15.4)	0
Arthralgia	22 (18.3)	0	16 (13.6)	0	16 (13.7)	0
Increased blood lactate dehydrogenase	18 (15.0)	0	15 (12.7)	0	9 (7.7)	0
Malaise	17 (14.2)	1 (0.8)	19 (16.1)	0	17 (14.5)	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; nab, nanoparticle albumin-bound; TRAE, treatment-related adverse event.