RATIONALE 307: Phase 3 Study of Tislelizumab Plus Chemotherapy vs Chemotherapy Alone as First-line Treatment for Advanced Squamous Non-Small Cell Lung Cancer

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COI and Financial Disclosure Information

Introduction

- Lung cancer is the leading cause of cancer incidence both globally and in China[1]
- Platinum-based regimens are the standard first-line therapy for Chinese patients with locally advanced or metastatic squamous non-small cell lung cancer (NSCLC)[2]
- Recent global studies have examined whether better patient outcomes could be achieved using an anti-PD-1/L1 antibody in combination with chemotherapy[3-5]
- Tislelizumab is a humanized IgG4 monoclonal antibody against 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[6-8]

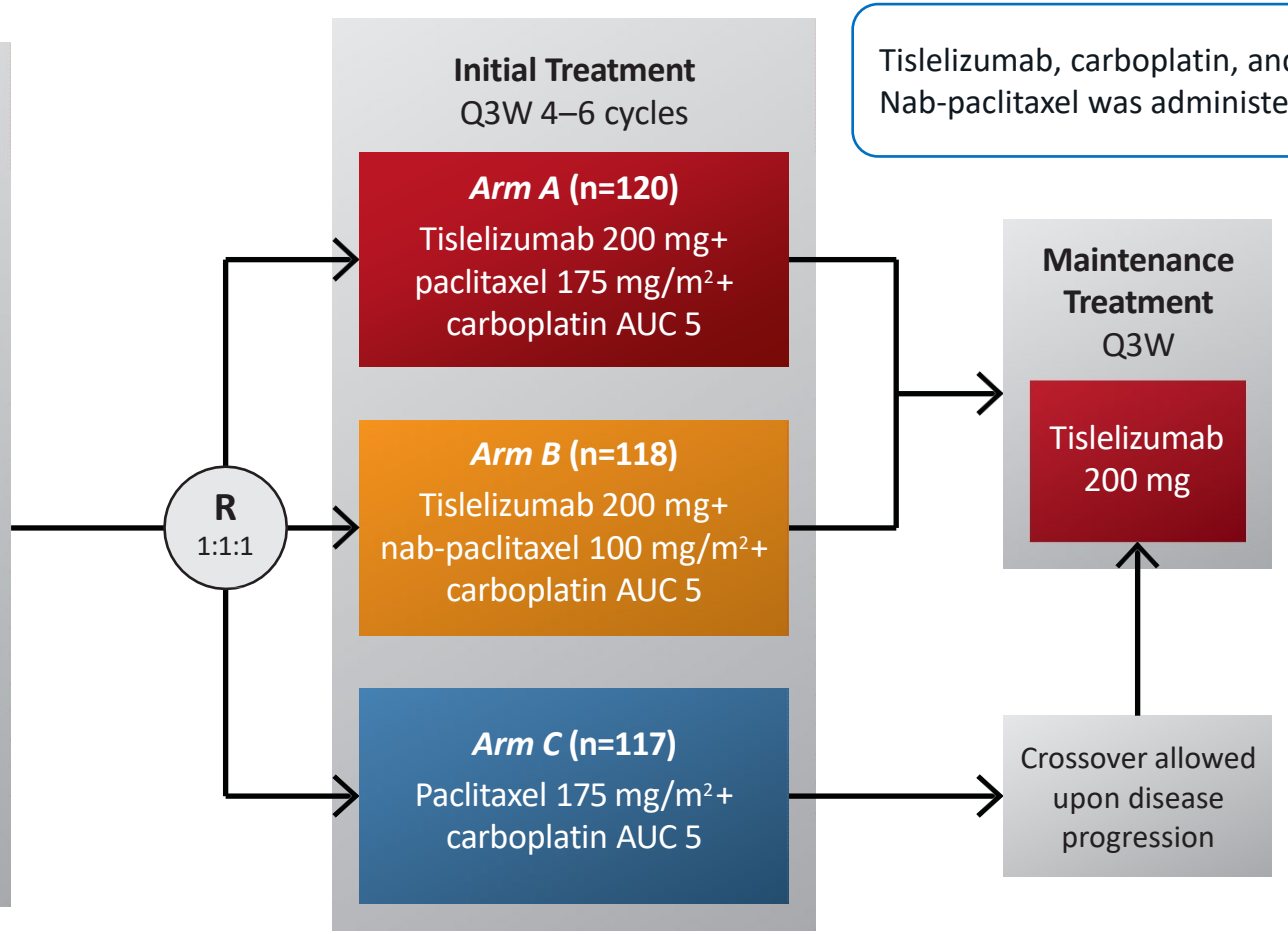
[1]Bray, et al. *CA Cancer J Clin.* 2018;68(66):394-424; [2]Wu, et al. *Lung Cancer*. 2014;85(3):401-407; [3]Paz-Ares, et al, Abstract presented at: ESMO Immuno-Oncology Congress 2019; December 12, 2019; Geneva, Switzerland; [4]Jotte, et al. *J Thorac Oncol*. 2020; 15(8):1351-1360; [5]Paz-Ares, et al. *N Engl J Med*. 2018;379(21):2040-2051; [6]Desai, et al. *J Immunother Cancer*. 2020;8(1):e000453; [7]Shen, et al. *J Immunother Cancer*. 2020;8(1):e000437; [8]Wang, et al. *Lung Cancer*. 2020; 147:259-268.

RATIONALE 307 Study (BGB-A317-307)

Stage IIIB/IV Squamous NSCLC

Key eligibility criteria

- Histologically confirmed, locally advanced (Stage IIIB) not amenable to curative surgery or radiotherapy, or metastatic (Stage IV) sq-NSCLC
- No prior systemic chemotherapy for advanced or metastatic disease*
- No *EGFR*-sensitizing mutations or known *ALK* gene translocations
- ECOG ≤1
- At least 1 measurable lesion as per RECIST v1.1
- Fresh or archival tissue for PD-L1 assessment (Ventana SP263 assay)



Tislelizumab, carboplatin, and paclitaxel were administered on D1
Nab-paclitaxel was administered on D1, D8, and D15

Stratification factors

- **Stage (IIIB vs IV)**
- **PD-L1 TC (<1% vs 1%-49% vs ≥50%)**

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

*Patients receiving 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.

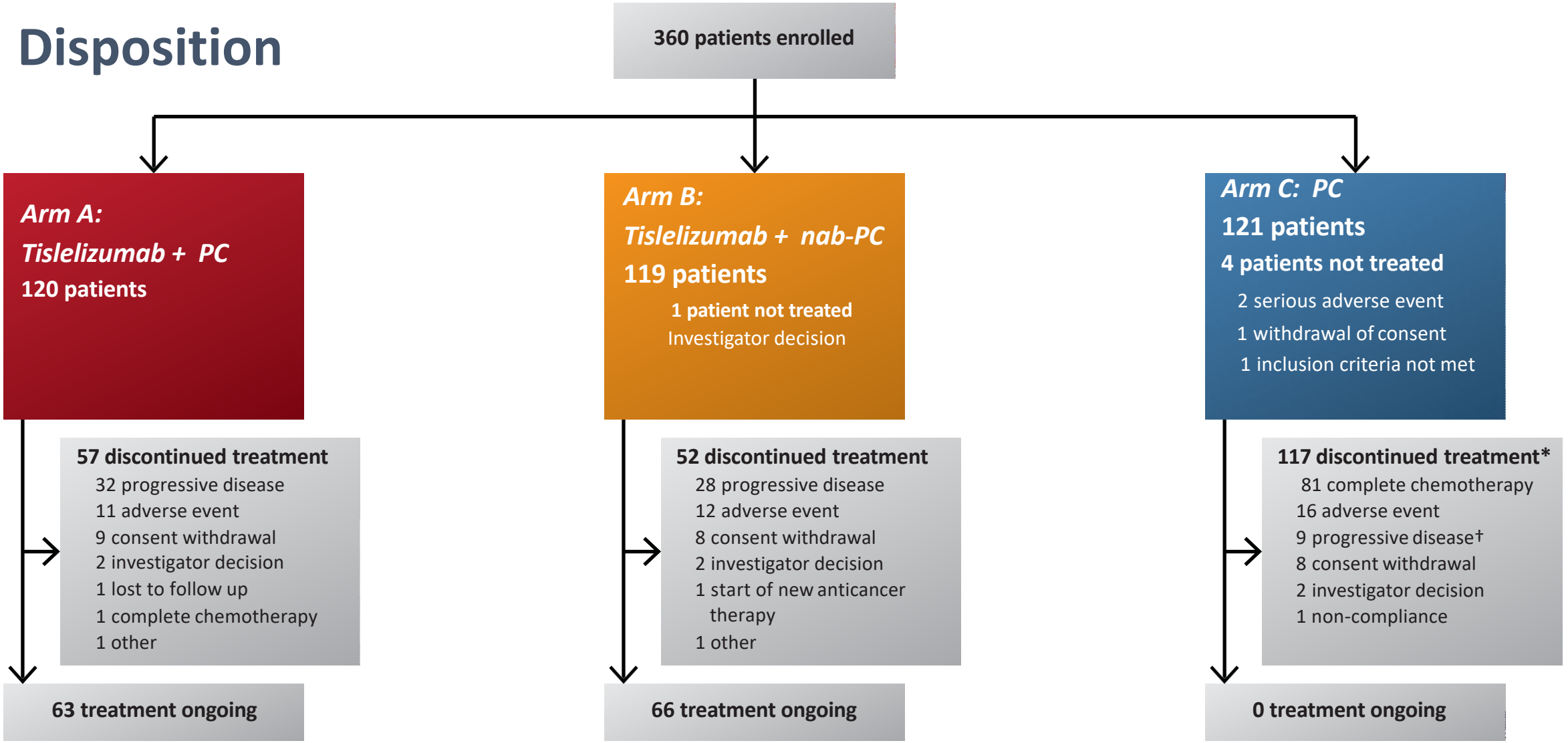
Abbreviations: D, day; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; IRC, independent review committee; nab, nanoparticle albumin-bound; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; R, randomized; RECIST, response evaluation criteria in solid tumors; sq, squamous; TC, tumor cell.

Statistical Considerations

- **Planned enrollment:** 342 patients
- **Overall alpha for study: strictly controlled at one-sided 0.025**
  - Sample size was determined by the number of PFS events required to demonstrate superiority of tislelizumab-containing arms (*Arm A* or *B*) to chemotherapy (*Arm C*)
  - Sample size was estimated to allow an 80% power to detect a HR of 0.65 comparing *Arm A* or *Arm B* to *Arm C* at a one-sided alpha level of 0.025
  - Type I error was strongly controlled at 0.025 by using sequential testing of *Arm A* vs *Arm C* followed by *Arm B* vs *C*, until the first nonrejection
- **Interim analysis (reviewed by IRC)**
  - Protocol specified one interim analysis for PFS that was planned to occur after ~130 (75%) PFS events had been observed in each comparison
  - Observed number of PFS events: 136 (79%) in *Arms A* vs *C* and 132 (76%) in *Arms B* vs *C*
  - One-sided alpha level: 0.0115 in *Arms A* vs *C* and 0.0103 in *Arms B* vs *C*
    - One-sided alpha was adjusted based on the observed number of events using O'Brien-Fleming method

Abbreviations: HR, hazard ratio; IRC, independent review committee; PFS, progression-free survival.

Disposition



At time of data cutoff date, median follow-up: 8.6 months (95% CI: 8.1, 9.0)

*A total of 54 patients crossed over to receive tislelizumab maintenance upon disease progression.
† Disease progression occurring during the limited cycles of prescribed chemotherapy.
Abbreviations: CI, confidence interval; nab, nanoparticle albumin-bound; PC, paclitaxel and carboplatin.

Data cut-off: 6 Dec 2019

Demographics and Baseline Disease Characteristics

- Demographics and disease characteristics were balanced between arms including the stratification factors, disease stage, and PD-L1 expression

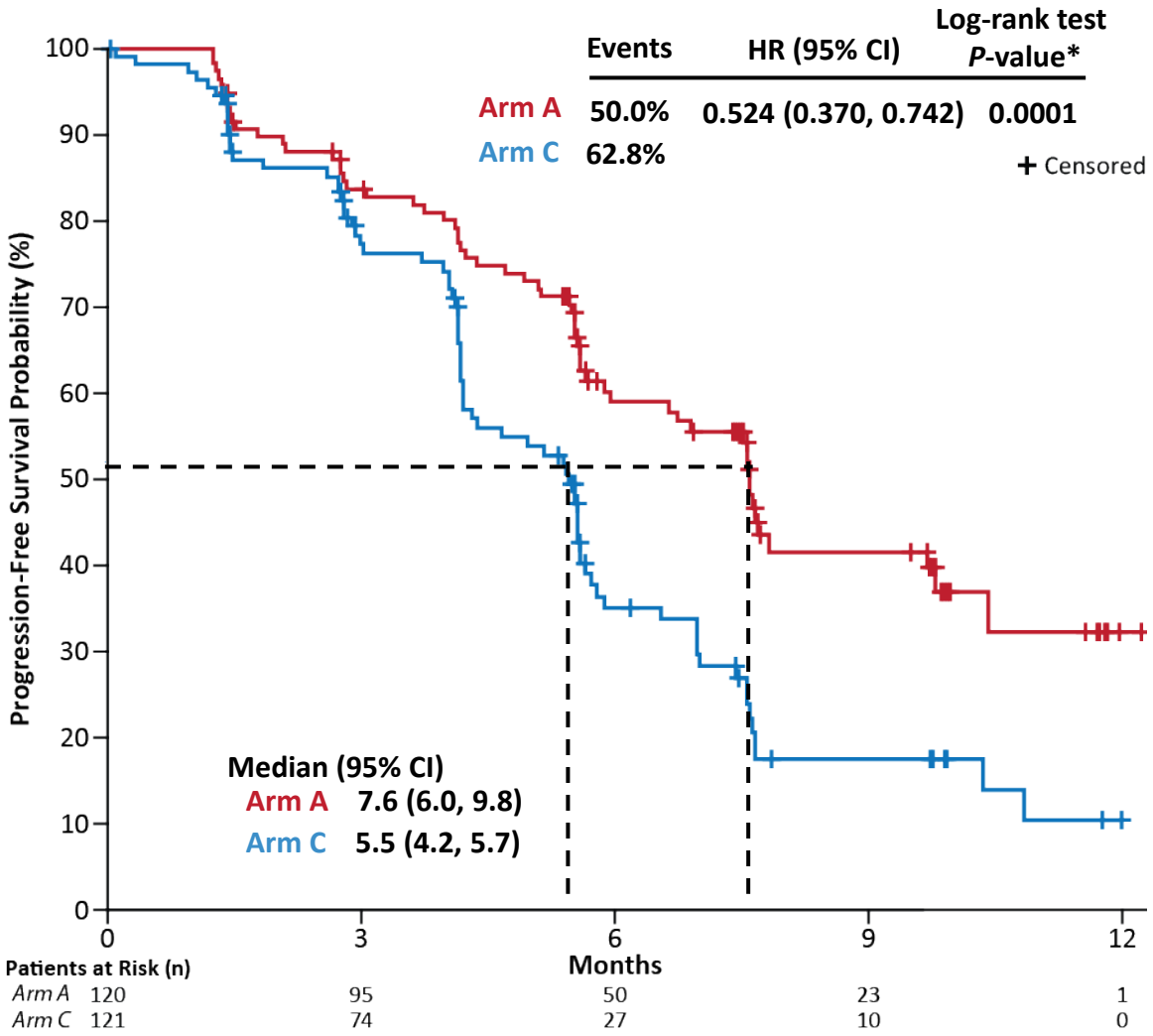
		Arm A Tislelizumab + PC (n=120)	*Arm B* Tislelizumab + nab-PC (n=119)	*Arm C* PC (n=121)
Median age, years (range)		60 (41-74)	63 (38-74)	62 (34-74)
Sex, n (%)	Male	107 (89.2)	112 (94.1)	111 (91.7)
Tobacco use, n (%)	Current/former	96 (80.0)	107 (89.9)	98 (81.0)
	Never	24 (20.0)	12 (10.1)	23 (19.0)
ECOG PS, n (%)	0	31 (25.8)	22 (18.5)	32 (26.4)
	1	89 (74.2)	97 (81.5)	89 (73.6)
Disease stage, n (%)	IIIB	38 (31.7)	40 (33.6)	44 (36.4)
	IV	82 (68.3)	79 (66.4)	77 (63.6)
Location of Distant Metastases, n (%)[a]	Bone	24 (20.0)	16 (13.4)	21 (17.4)
	Liver	15 (12.5)	15 (12.6)	14 (11.6)
	Brain	2 (1.7)	3 (2.5)	1 (0.8)
PD-L1 on TC, n (%)	<1%[b]	48 (40.0)	47 (39.5)	49 (40.5)
	≥1%	72 (60.0)	72 (60.5)	72 (59.5)
	1-49%	30 (25.0)	30 (25.2)	31 (25.6)
	≥50%	42 (35.0)	42 (35.3)	41 (33.9)

[a]Patient was counted only once within each category but may be counted in multiple categories.
[b]Patients with non-evaluable tumor samples were included in the <1% PD-L1 expression tumor cell subgroup.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; nab, nanoparticle albumin-bound; PC, paclitaxel and carboplatin; PD-L1, programmed death-ligand 1; TC, tumor cell.

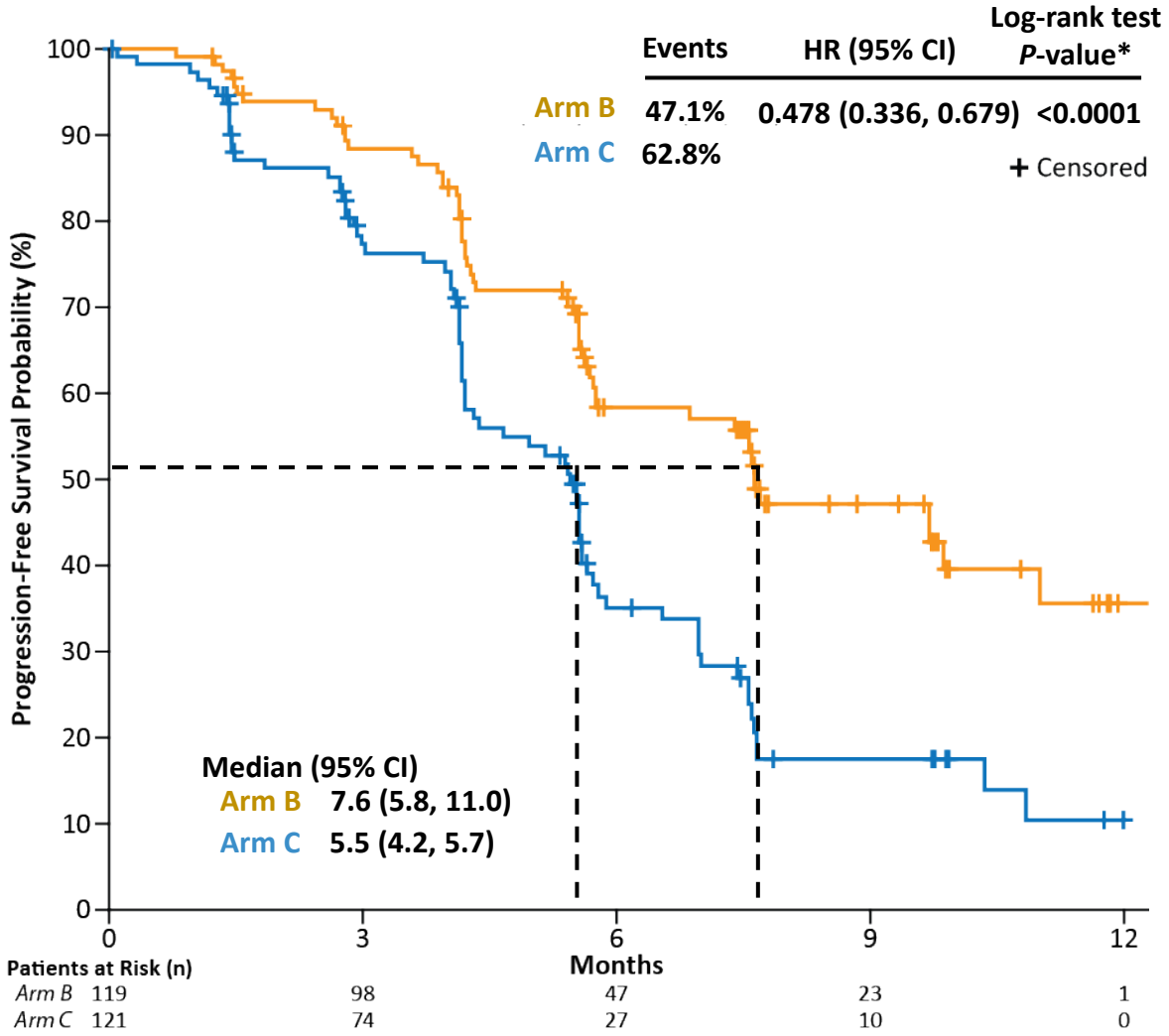
Data cut-off: 6 Dec 2019

Primary Endpoint: Progression-Free Survival as Assessed by IRC

Tislelizumab + PC (Arm A) vs PC (Arm C)



Tislelizumab + nab-PC (Arm B) vs PC (Arm C)



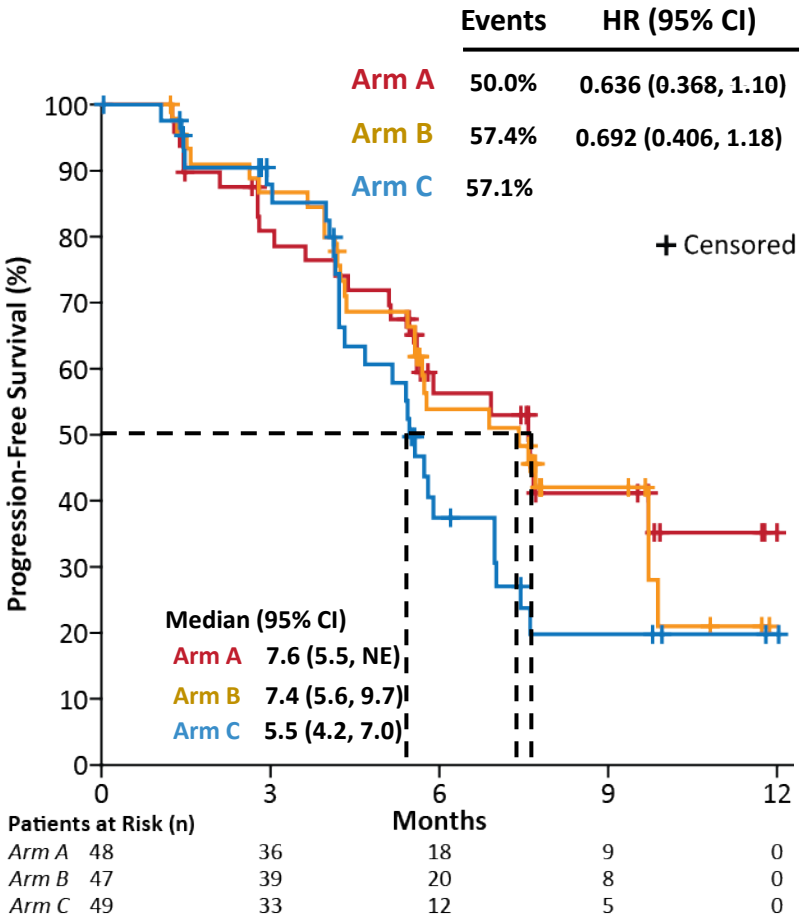
* Stratified by disease stage and PD-L1 expression.

Abbreviations: CI, confidence interval; HR, hazard ratio; IRC, independent review committee; nab, nanoparticle albumin-bound; PC, paclitaxel and carboplatin; PD-L1, programmed death-ligand 1.

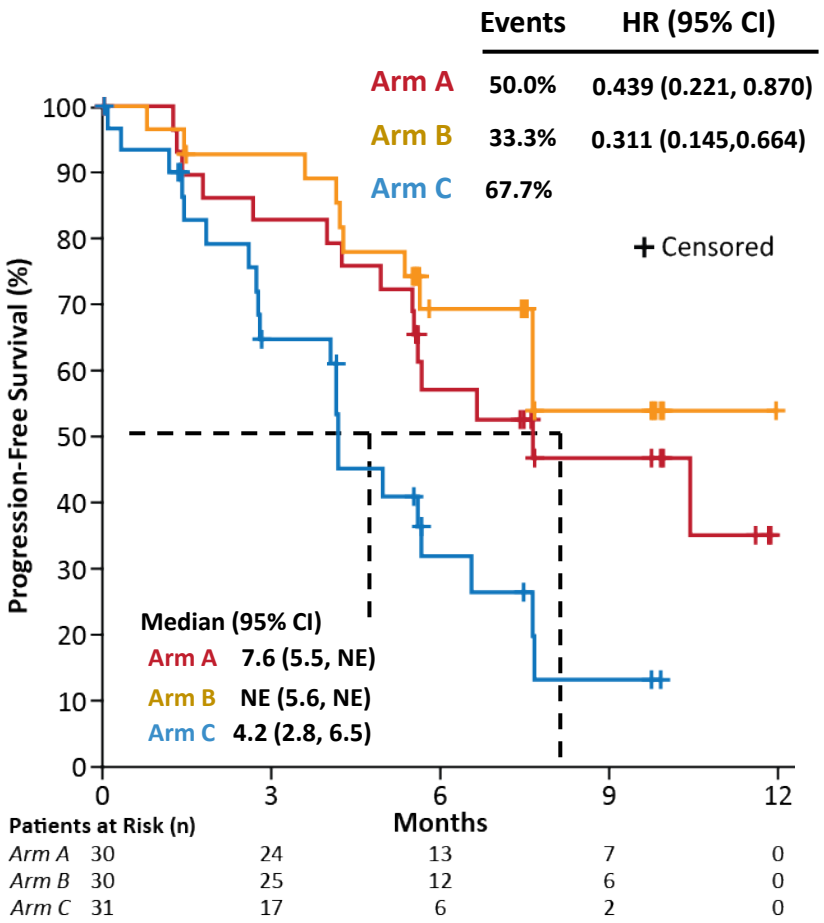
Data cut-off: 6 Dec 2019

Progression-Free Survival by Tumor Cell PD-L1 Expression

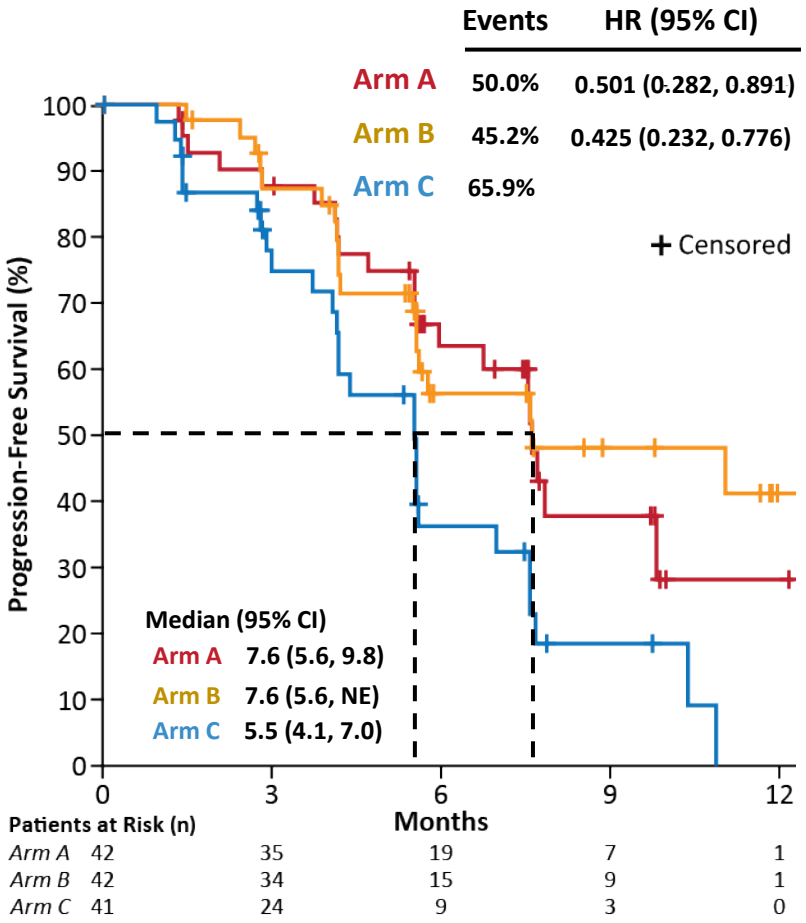
PD-L1 TC<1%



PD-L1 TC 1-49%



PD-L1 TC ≥50%



Arm A: Tislelizumab + PC; Arm B, Tislelizumab + nab-PC; Arm C: PC alone.

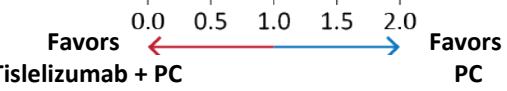
Abbreviations: CI, confidence interval; HR, hazard ratio; nab, nanoparticle albumin-bound; PC, paclitaxel and carboplatin; PD-L1, programmed death-ligand 1; TC, tumor cell.

Data cut-off: 6 Dec 2019

Subgroup Analysis of Progression-Free Survival Following Treatment of Tislelizumab Plus Chemotherapy Versus Chemotherapy Alone

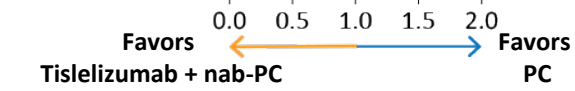
Tislelizumab + PC (*Arm A*) vs PC (*Arm C*)

		Events/Patients (n)	Hazard Ratio for PD or Death (95% CI)
Overall		136/241	0.522 (0.371, 0.734)
Age	<65 years	101/166	0.468 (0.313, 0.699)
	≥65 years	35/75	0.602 (0.309, 1.175)
Sex	Female	13/23	0.527 (0.173, 1.607)
	Male	123/218	0.528 (0.368, 0.756)
ECOG Performance Status	0	39/63	0.795 (0.423, 1.491)
	1	97/178	0.448 (0.297, 0.674)
Smoking Status	Never	29/47	0.475 (0.226, 1.000)
	Current or Former	107/194	0.534 (0.363, 0.786)
Disease Stage	IIIB	45/82	0.402 (0.215, 0.750)
	IV	91/159	0.570 (0.376, 0.862)
Liver Metastasis	Yes	18/29	0.477 (0.187, 1.219)
	No	118/212	0.508 (0.352, 0.734)
PD-L1 Expression in TC	<1%	52/97	0.636 (0.368, 1.101)
	≥1%	84/144	0.453 (0.293, 0.703)
	1-49%	36/61	0.439 (0.221, 0.870)
	≥50%	48/63	0.501 (0.282, 0.891)



Tislelizumab + nab-PC (*Arm B*) vs PC (*Arm C*)

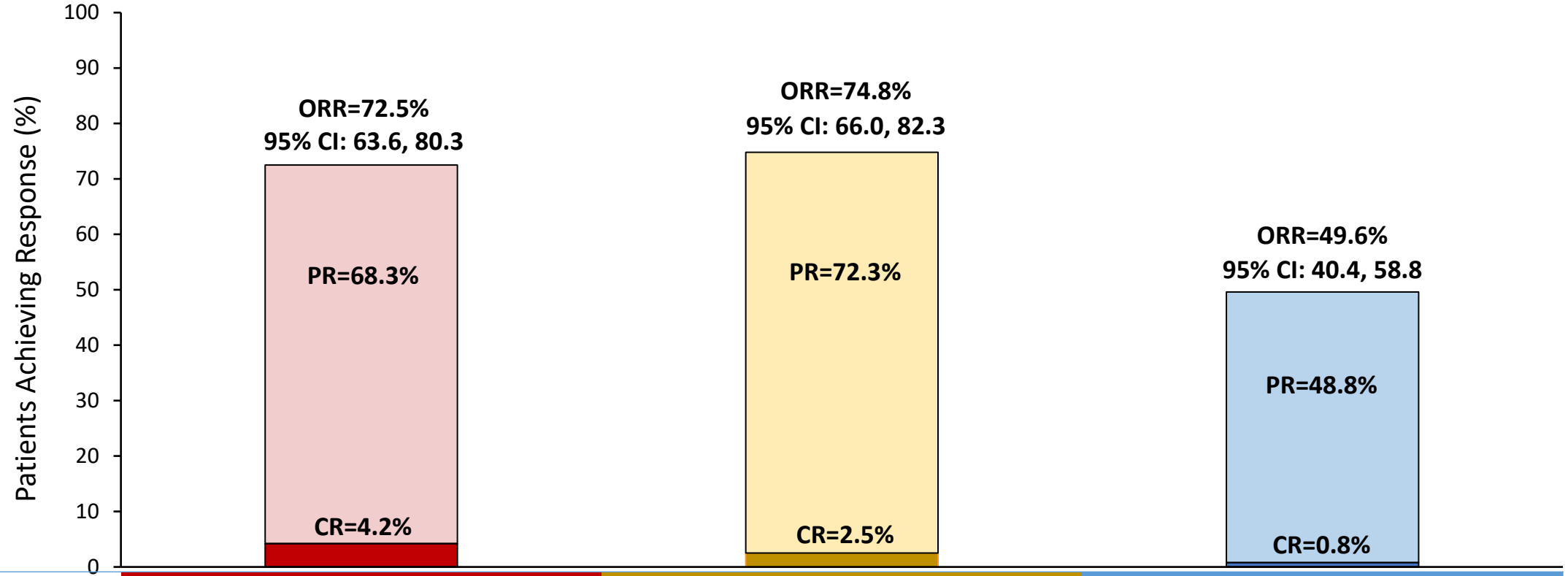
		Events/Patients (n)	Hazard Ratio for PD or Death (95% CI)
Overall		132/240	0.481 (0.339, 0.681)
Age	<65 years	92/152	0.472 (0.308, 0.721)
	≥65 years	40/88	0.564 (0.302, 1.052)
Sex	Female	9/17	0.357 (0.086, 1.473)
	Male	123/223	0.495 (0.346, 0.709)
ECOG Performance Status	0	32/54	0.883 (0.435, 1.792)
	1	100/186	0.398 (0.266, 0.595)
Smoking Status	Never	17/35	0.119 (0.027, 0.533)
	Current or Former	115/205	0.556 (0.384, 0.803)
Disease Stage	IIIB	46/84	0.372 (0.202, 0.686)
	IV	86/156	0.537 (0.350, 0.824)
Liver Metastasis	Yes	20/29	0.478 (0.193, 1.188)
	No	112/211	0.455 (0.311, 0.666)
PD-L1 Expression in TC	<1%	55/96	0.692 (0.406, 1.178)
	≥1%	77/144	0.367 (0.229, 0.588)
	1-49%	31/61	0.311 (0.145, 0.664)
	≥50%	46/83	0.425 (0.232, 0.776)



Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; nab, nanoparticle albumin-bound; PC, paclitaxel and carboplatin; PD-L1, programmed death-ligand 1; TC, tumor cell.

Data cut-off: 6 Dec 2019

Best Overall Response by IRC Following Tislelizumab Plus Chemotherapy Treatment or Chemotherapy Alone



	Tislelizumab + PC (n=120)	Tislelizumab + nab-PC (n=119)	Chemotherapy Alone (n=121)
Disease Control Rate, % (95% CI)	87.5 (80.2, 92.8)	90.8 (84.1, 95.3)	80.2 (71.9, 86.9)
Duration of Response, median, months (95% CI)	8.2 (5.0, NE)	8.6 (6.3, NE)	4.2 (2.8, 4.9)

Abbreviations: CI, confidence interval; CR, complete response; IRC, independent review committee; nab, nanoparticle albumin-bound; NE, not estimable; ORR, objective response rate; PC, paclitaxel and carboplatin; PR, partial response.

Data cut-off: 6 Dec 2019

Overall Summary of Treatment-Emergent Adverse Events

	Arm A Tislelizumab + PC (n=120)	*Arm B* Tislelizumab + nab-PC (n=118)	*Arm C* PC (n=117)
Patients with ≥1 TEAE	120 (100.0)	117 (99.2)	117 (100.0)
Patients with 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 permanent discontinuation of any study treatment component	15 (12.5)	35 (29.7)	18 (15.4)
TEAE leading to death	4 (3.3)	5 (4.2)	5 (4.3)

Data presented as n (%).
Abbreviations: nab, nanoparticle albumin-bound; PC, paclitaxel and carboplatin; TEAE, treatment-emergent adverse event.

Data cut-off: 6 Dec 2019

Treatment-Emergent Adverse Events (≥20% Patients, All Grades and Grade ≥3)

	Arm A Tislelizumab + PC (n=120)		*Arm B* Tislelizumab + nab-PC (n=118)		*Arm C* PC (n=117)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Anemia	106 (88.3)	9 (7.5)	110 (93.2)	27 (22.9)	94 (80.3)	14 (12.0)
Alopecia	77 (64.2)	0	82 (69.5)	0	72 (61.5)	0
Neutrophil count decreased	76 (63.3)	62 (51.7)	72 (61.0)	54 (45.8)	68 (58.1)	53 (45.3)
White blood cell count decreased	64 (53.3)	27 (22.5)	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)
Decreased appetite	52 (43.3)	1 (0.8)	52 (44.1)	1 (0.8)	36 (30.8)	1 (0.9)
Neutropenia	51 (42.5)	40 (33.3)	50 (42.4)	32 (27.1)	55 (47.0)	47 (40.2)
ALT increased	50 (41.7)	2 (1.7)	41 (34.7)	2 (1.7)	27 (23.1)	0
AST increased	43 (35.8)	0	40 (33.9)	1 (0.8)	14 (12.0)	0
Platelet count decreased	41 (34.2)	5 (4.2)	52 (44.1)	16 (13.6)	28 (23.9)	2 (1.7)
Pain in extremity	40 (33.3)	3 (2.5)	17 (14.4)	0	27 (23.1)	0
Nausea	36 (30.0)	0	51 (43.2)	0	35 (29.9)	1 (0.9)
Constipation	36 (30.0)	0	33 (28.0)	0	27 (23.1)	0
Thrombocytopenia	33 (27.5)	7 (5.8)	47 (39.8)	15 (12.7)	32 (27.4)	7 (6.0)
Asthenia	29 (24.2)	0	21 (17.8)	0	24 (20.5)	1 (0.9)
Vomiting	28 (23.3)	1 (0.8)	27 (22.9)	0	20 (17.1)	2 (1.7)
Blood bilirubin increased	27 (22.5)	0	15 (12.7)	0	15 (12.8)	0
Hypoesthesia	27 (22.5)	0	12 (10.2)	0	19 (16.2)	0
Hypoalbumenia	27 (22.5)	1 (0.8)	21 (17.8)	0	19 (16.2)	0
Rash	25 (20.8)	4 (3.3)	26 (22.0)	2 (1.7)	4 (3.4)	0
Arthralgia	25 (20.8)	0	21 (17.8)	0	19 (16.2)	0
Pyrexia	24 (20.0)	0	24 (20.3)	1 (0.8)	18 (15.4)	0

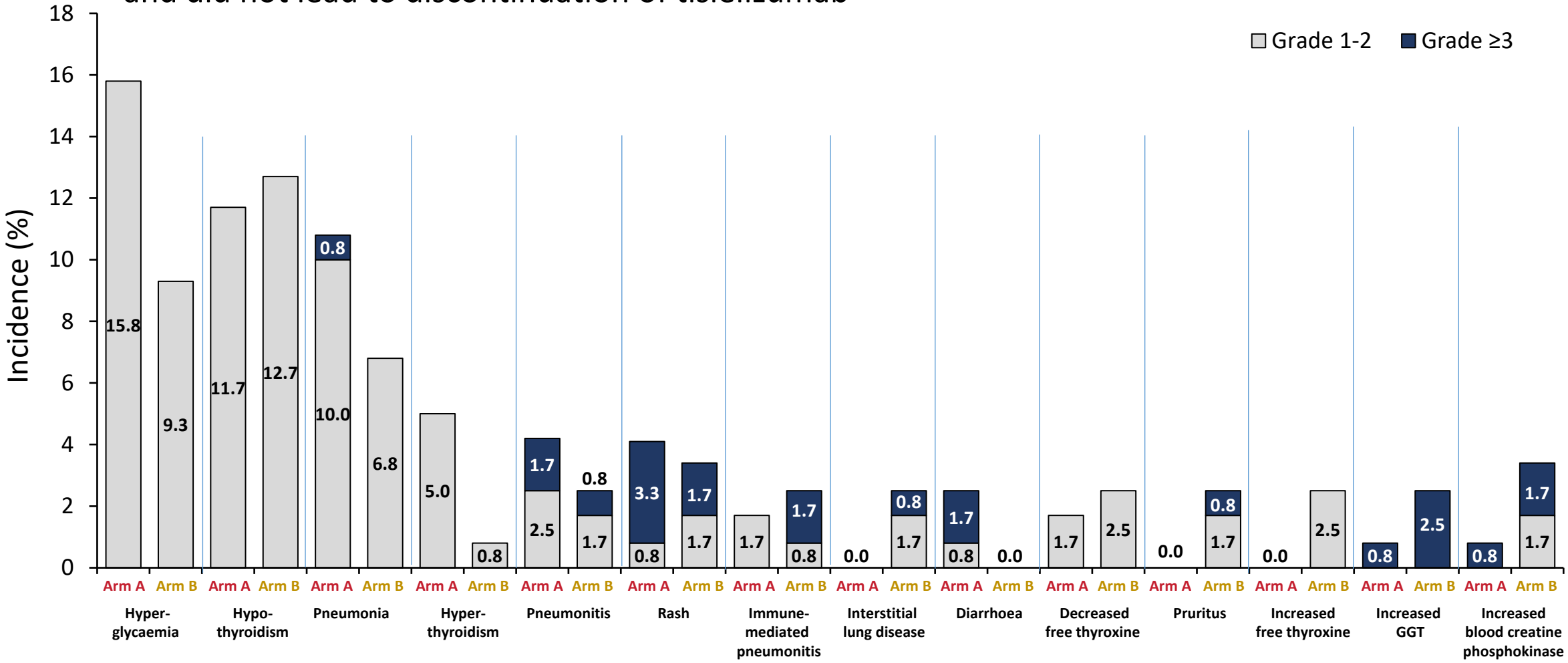
Data presented as n (%).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; nab, nanoparticle albumin-bound; PC, paclitaxel and carboplatin.

Data cut-off: 6 Dec 2019

Immune-Mediated AEs by Preferred Term Occurring in >2 Patients in Tislelizumab + Chemotherapy Groups

- Most potential immune-mediated AEs were of low grade, did not require corticosteroid treatment, and did not lead to discontinuation of tislelizumab



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

Data cut-off: 6 Dec 2019

Summary and Future Directions

- Progression-free survival was significantly improved with tislelizumab in combination with paclitaxel/carboplatin (HR=0.524 [95% CI: 0.370, 0.742]; *P*=0.0001) or nab-paclitaxel/carboplatin (HR=0.478 [95% CI: 0.336, 0.679]; *P*<0.0001) compared with paclitaxel/carboplatin alone
  - Progression-free survival was prolonged irrespective of PD-L1 expression
  - Combination treatment also resulted in higher objective response rate and longer duration of response versus chemotherapy alone
- Tislelizumab in combination with chemotherapy was generally well tolerated
  - Most adverse events were mild or moderate in severity and manageable
  - No new safety signals were identified with the addition of tislelizumab to standard chemotherapy
- Results from this pivotal phase 3 study support tislelizumab in combination with chemotherapy as a potential new standard first-line treatment for advanced squamous NSCLC

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