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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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Dr Wang Has Nothing to Disclose

- 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; [8]Shen, et al. *J Immunother Cancer*. 2020;8(1):e000437; [9]Wang, et al. *Lung Cancer*. 2020; 147:259-268.

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 translocation
- ECOG ≤1
- At least 1 measurable lesion as per RECIST v1.1
- Fresh or archival tissue for PD-L1 assessment (Ventana SP263 assay)

Stratification factors

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

R 1:1:1

Initial Treatment
Q3W 4-6 cycles

***Arm A* (n=120)**
Tislelizumab 200 mg+ paclitaxel 175 mg/m^2+ carboplatin AUC 5

***Arm B* (n=118)**
Tislelizumab 200 mg+ nab-paclitaxel 100 mg/m^2+ carboplatin AUC 5

***Arm C* (n=117)**
Paclitaxel 175 mg/m^2+ carboplatin AUC 5

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

Maintenance Treatment
Q3W
Tislelizumab 200 mg

Crossover allowed upon disease progression

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

*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; nsq, nonsquamous; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; Q3W, every 3 weeks; R, randomized; RECIST; Response Evaluation Criteria in Solid Tumors; sq, squamous; TC, tumor cell.

360 patients enrolled

Arm A:
Tislelizumab + PC
120 patients

57 discontinued treatment
- 32 progressive disease
- 11 adverse event
- 9 consent withdrawal
- 2 investigator decision
- 1 lost to follow-up
- 1 complete chemotherapy
- 1 other

63 treatment ongoing

Arm B:
Tislelizumab + nab-PC
119 patients
1 patient not treated
Investigator decision

52 discontinued treatment
- 28 progressive disease
- 12 adverse event
- 8 consent withdrawal
- 2 investigator decision
- 1 start of new anticancer therapy
- 1 other

66 treatment ongoing

***Arm C:* PC**
121 patients
4 patients not treated
- 2 serious adverse event
- 1 withdrawal of consent
- 1 inclusion criteria not met

117 discontinued treatment*
- 81 complete chemotherapy
- 16 adverse event
- 9 progressive disease†
- 8 consent withdrawal
- 2 investigator decision
- 1 non-compliance

0 treatment ongoing

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

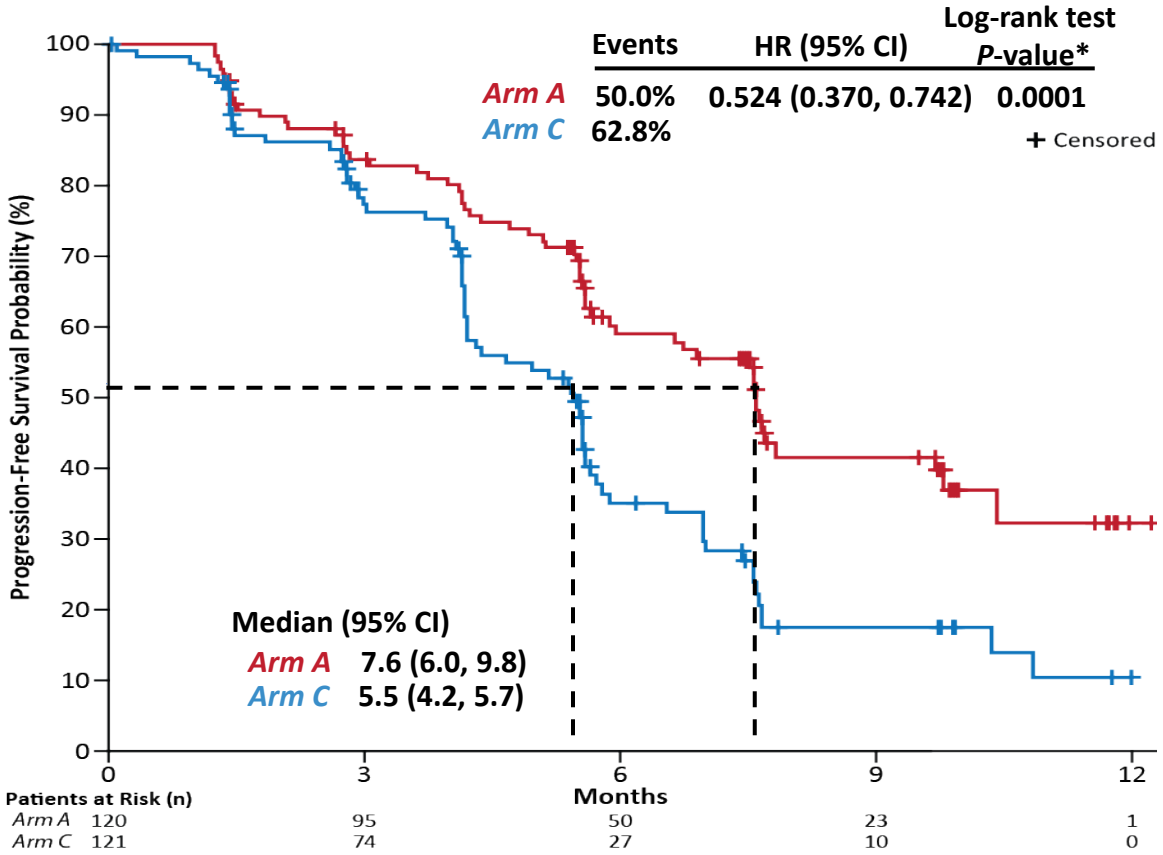
*A total of 54 patients crossed over to receive tislelizumab maintenance upon disease progression.
† Disease progression occurring during the limited cycles of prescribed chemotherapy. **Abbreviations:** CI, confidence interval; nab, nanoparticle albumin-bound; PC, paclitaxel and carboplatin.

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

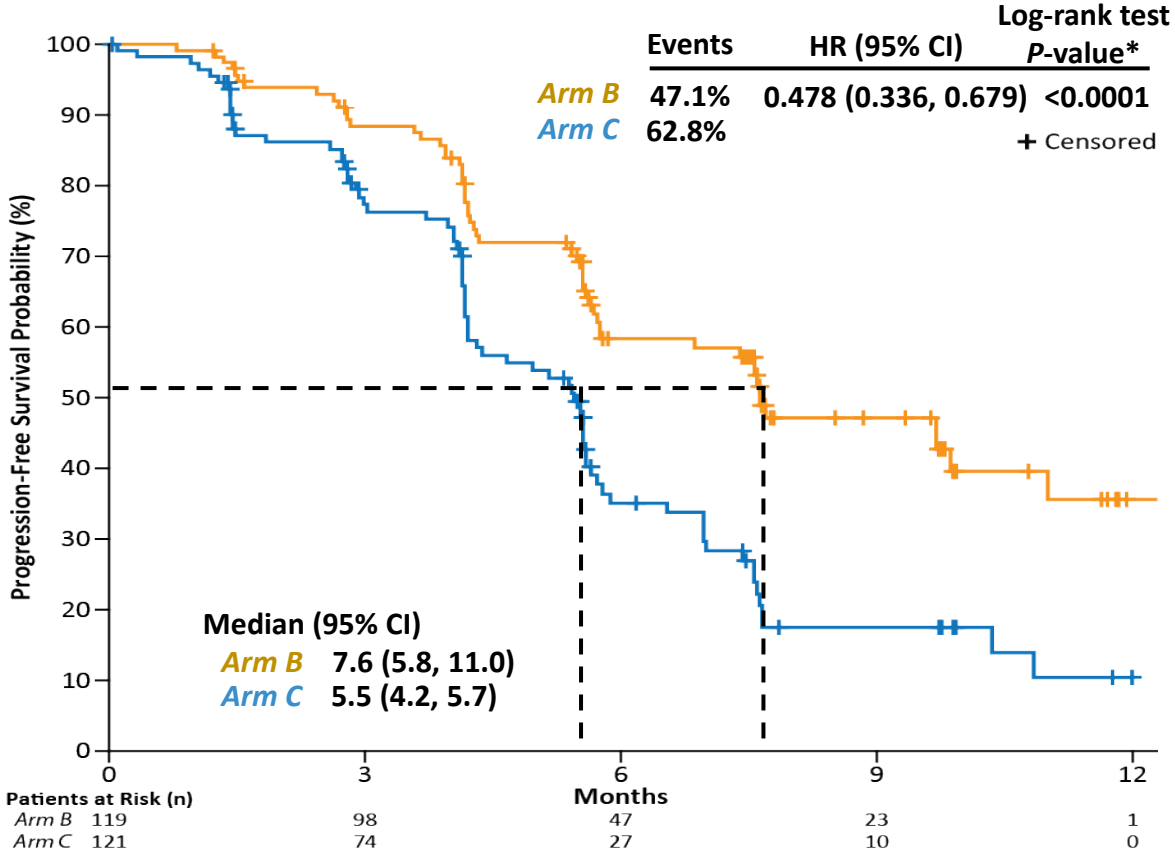
		Arm A Tislelizumab + PC (n=120)	*Arm B* Tislelizumab + nab-PC (n=119)	*Arm C* PC (n=121)
Median age, years (range)		60 (41-74)	63 (38-74)	62 (34-74)
Sex, n (%)	Male	107 (89.2)	112 (94.1)	111 (91.7)
Tobacco use, n (%)	Current/former	96 (80.0)	107 (89.9)	98 (81.0)
	Never	24 (20.0)	12 (10.1)	23 (19.0)
ECOG 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.

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

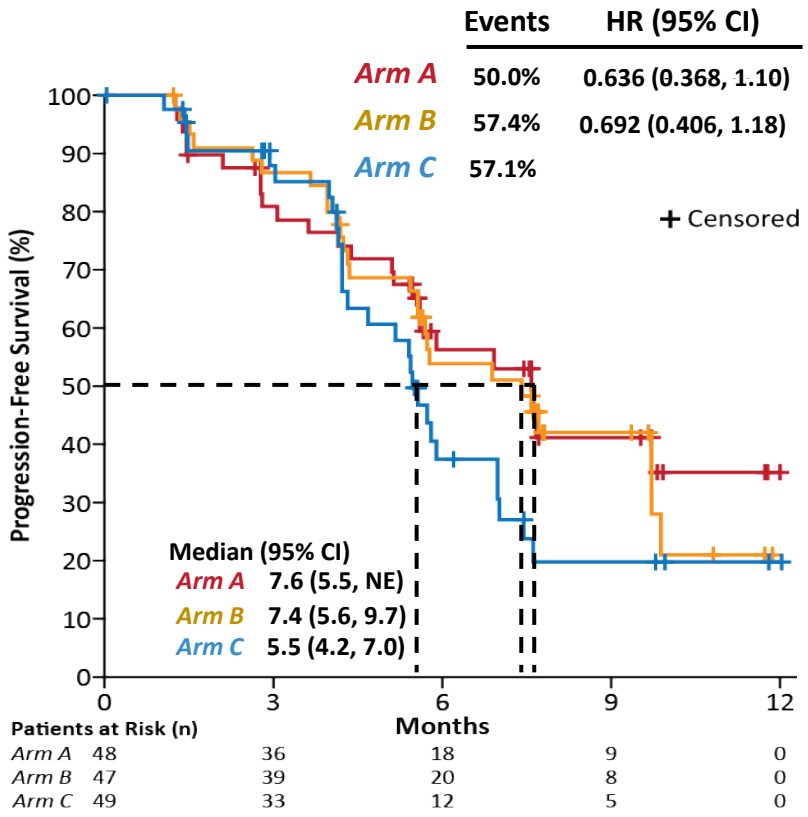


Tislelizumab + nab-PC (*Arm B*) vs PC (*Arm C*)

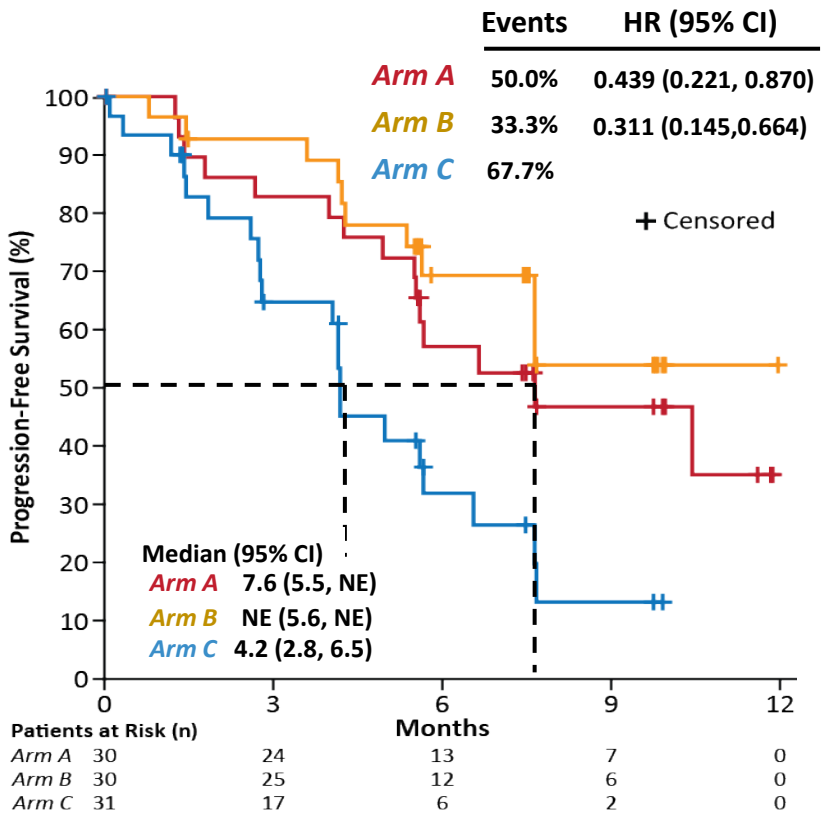


* Stratified by disease stage and PD-L1 expression.
Abbreviations: CI, confidence interval; HR, hazard ratio; PD-L1, programmed death-ligand 1.

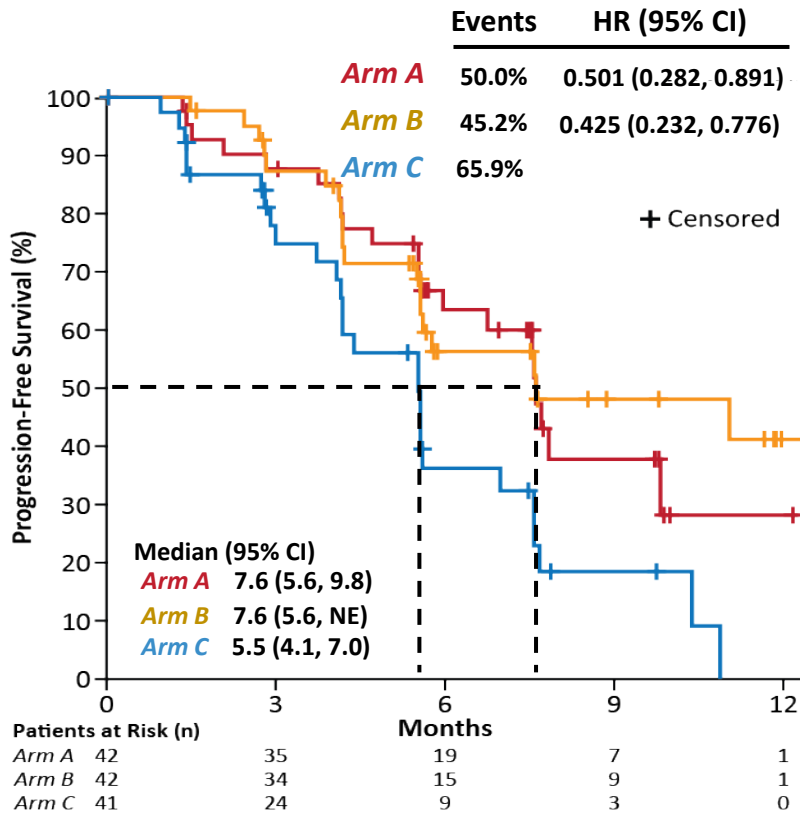
PD-L1 TC<1%



PD-L1 TC 1-49%



PD-L1 TC ≥50%



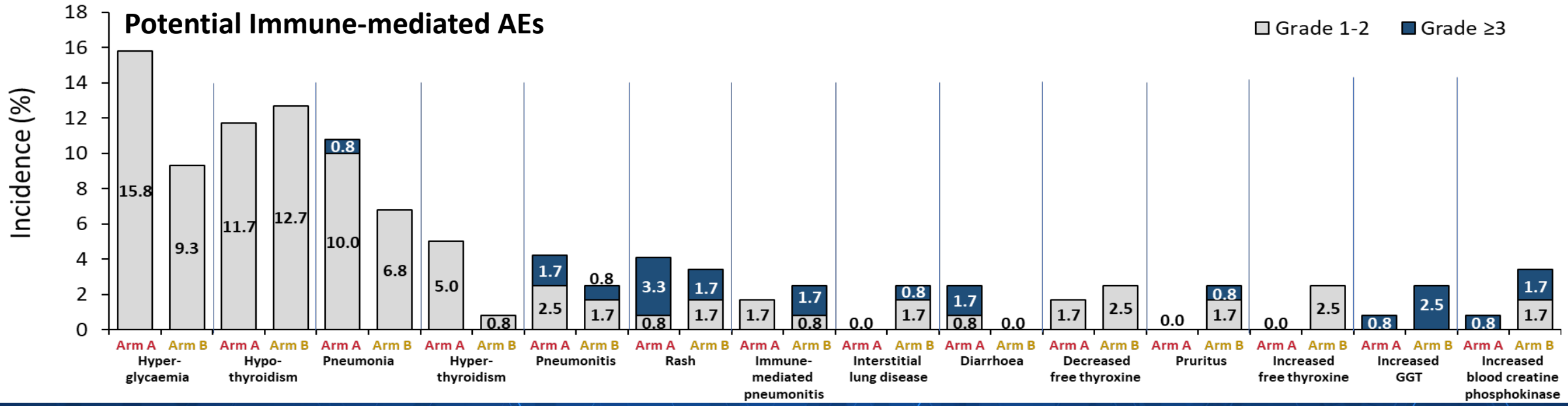
Arm A: Tislelizumab + PC; *Arm B*: Tislelizumab + nab-PC; *Arm C*: PC alone.

Abbreviations: CI, confidence interval; HR, hazard ratio; nab, nanoparticle albumin-bound; NE, not estimable; PC, paclitaxel and carboplatin; PD-L1, programmed death-ligand 1; TC, tumor cell.

	Tislelizumab + PC (n=120)	Tislelizumab + nab-PC (n=119)	PC (n=121)
Complete response	5 (4.2)	3 (2.5)	1 (0.8)
Partial response	82 (68.3)	86 (72.3)	59 (48.8)
Stable disease	18 (15.0)	19 (16.0)	36 (29.8)
Progressive disease	12 (10.0)	5 (4.2)	11 (9.1)
Not evaluable/missing	3 (2.5)	6 (5.0)	13 (10.7)
Objective response rate, % (95% CI)	**72.5 (63.6, 80.3)**	**74.8 (66.0, 82.3)**	**49.6 (40.4, 58.8)**
Disease control rate[a], % (95% CI)	**87.5 (80.2, 92.8)**	**90.8 (84.1, 95.3)**	**80.2 (71.9, 86.9)**
Median duration of response, month (95% CI)	**8.2 (5.0, NE)**	**8.6 (6.3, NE)**	**4.2 (2.8, 4.9)**

[a]Disease control rate = complete response (CR) + partial response (PR) + non-CR/non-PR + stable disease ≥6 weeks.
Abbreviations: CI, confidence interval; IRC, independent review committee; nab, nanoparticle albumin-bound; PC, paclitaxel and carboplatin.

	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)



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, g-glutamyltransferase; nab, nanoparticle albumin-bound; PC, paclitaxel and carboplatin.

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.

- 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