RATIONALE 307: A subgroup analysis of tislelizumab plus chemotherapy versus chemotherapy alone as first-line treatment for Stage IIIB advanced squamous NSCLC

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Presenter DISCLOSURES

Ineligible Company (formerly: Commercial Interest)	**Relationship(s)**
AstraZeneca, BeiGene, BMS, Hansoh, Hengrui Therapeutics, Hutchison, Roche	Research Funding
AstraZeneca, Hansoh, Hengrui Therapeutics, Roche	Speaker's Bureau
AstraZeneca, BoehringerIngelheim, GenomiCare, Hutchison MediPharma, Menarini, Pfizer, PrIME Oncology, Roche, Simcere, Yuan Corporation, ZaiLab	Consultant

Introduction

- Lung cancer survival rates are lower when diagnosed at advanced disease stages.[1,2] Therefore, it is important to compare the efficacy and safety of immunotherapy amongst patients with advanced disease

- Tislelizumab is a humanized IgG4 monoclonal antibody with high affinity and binding specificity for PD-1.[1,2] Tislelizumab in combination with chemotherapy has been approved for first-line advanced squamous NSCLC in China, based on the RATIONALE 307 (NCT03594747) study[3]

- RATIONALE 307 was an open-label, randomized, multicenter Phase 3 study that compared the efficacy and safety of tislelizumab plus chemotherapy versus chemotherapy alone as first-line treatment for advanced squamous NSCLC[4]

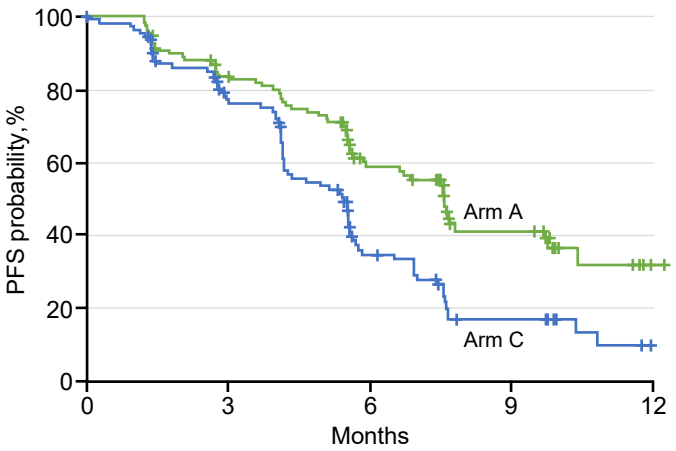
Ig, immunoglobulin; PD-1, programmed cell death protein 1; NSCLC, non-small cell lung cancer;
1. Qin S, et al. Future Oncol 2019;15:1811–22; 2. Zhang T, et al. Cancer Immunol Immunother 2018;67:1079–90; 3. BeiGene. Press Releases: China National Medical Products Administration Approves Tislelizumab in Combination with Chemotherapy in First-Line Advanced Squamous Non-Small Cell Lung Cancer. Available at: https://ir.beigene.com/news-releases/news-release-details/china-national-medical-products-administration-approves. Accessed May 2021 4. Wang J, et al. JAMA Oncol 2021. DOI: 10.1001/jamaoncol.2021.0366. Online ahead of print

Introduction

- IRC-assessed PFS was significantly improved with tislelizumab plus chemotherapy[1]
- Here, we report the results of a subgroup analysis of patients with Stage IIIB and Stage IV disease from the RATIONALE 307 study
- **Scan QR code to view the primary publication of RATIONALE 307:**

Tislelizumab plus PC versus PC

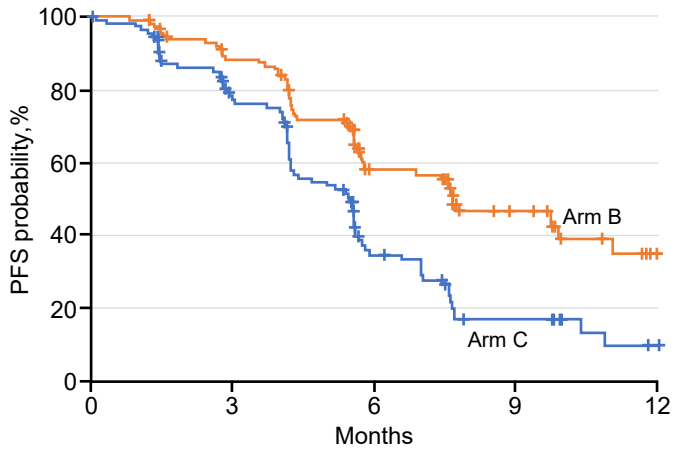
Source	Events, No. (%)	Median (95% C)	Hazard ratio (95% CI)	P value
Arm A	60 (50.0)	7.6 (6.0–9.8)	0.52 (0.37–0.74)	<.001
Arm C	76 (62.8)	5.5 (4.2–5.7)		



No. at risk					
Arm A	120	95	50	23	1
Arm C	121	74	27	10	0

Tislelizumab plus *nab*-PC versus PC

Source	Events, No. (%)	Median (95% C)	Hazard ratio (95% CI)	P value
Arm B	56 (47.1)	7.6 (5.8–11.0)	0.48 (0.34–0.68)	<.001
Arm C	76 (62.8)	5.5 (4.2–5.7)		

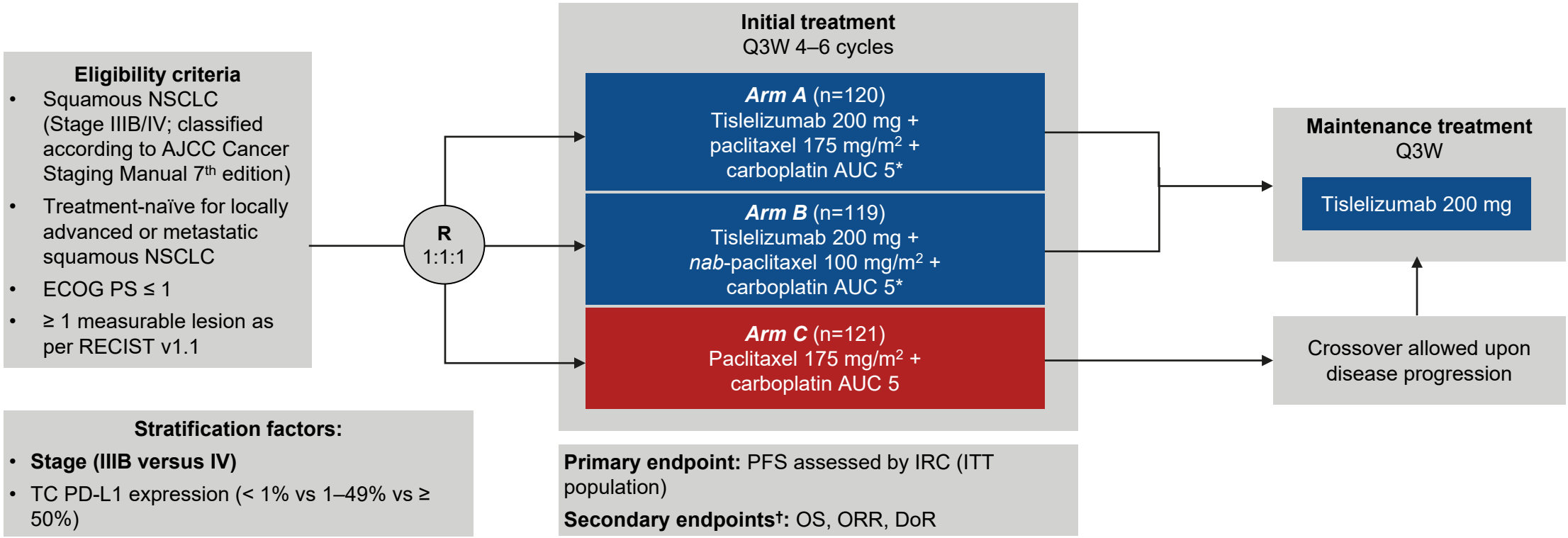


No. at risk					
Arm B	119	98	47	23	1
Arm C	121	74	27	10	0

Arm A: tislelizumab 200 mg + paclitaxel 175 mg/m^2 + carboplatin AUC 5, Arm B: tislelizumab 200 mg + *nab*-paclitaxel 100 mg/m^2 + carboplatin AUC 5, Arm C: Paclitaxel 175 mg/m^2 + carboplatin AUC 5
C, carboplatin; CI, confidence interval; IRC, independent review committee; *nab,* nanoparticle albumin-bound; P, paclitaxel; PFS, progression-free surviva;

1. Wang J, et al. JAMA Oncol 2021. DOI: 10.1001/jamaoncol.2021.0366. Online ahead of print

Study design and patient population



Patients with Stage IIIB disease were not amendable to radiotherapy or surgery. *Tislelizumab, carboplatin, and paclitaxel were administered on D1. *Nab*-paclitaxel was administered on D1, D8, and D15. Paclitaxel, *nab*-paclitaxel, and carboplatin were administered for 4–6 cycles, followed by tislelizumab monotherapy until disease progression, intolerable toxicity, or treatment discontinuation; †Include but are not limited to.

AJCC, American Joint Committee on Cancer; AUC, area under the curve; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance score; IRC, independent review committee; ITT, intent-to-treat; *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; TC, tumor cell; v, version

1. Wang J, et al. JAMA Oncol 2021. DOI: 10.1001/jamaoncol.2021.0366. Online ahead of print

Demographics and baseline characteristics (1/2)

	Stage IIIB (N=122)			Stage IV (N=238)		
	Arm A Tislelizumab + PC (n=38)	**Arm B** Tislelizumab + *nab*-PC (n=40)	**Arm C** PC (n=44)	**Arm A** Tislelizumab + PC (n=82)	**Arm B** Tislelizumab + *nab*-PC (n=79)	**Arm C** PC (n=77)
Age (years)						
Median (range)	59.0 (43–74)	62.5 (48–74)	61.0 (34–74)	60.0 (41–74)	63.0 (38–73)	63.0 (37–72)
Sex, n (%)						
Male	33 (86.8)	40 (100.0)	41 (93.2)	74 (90.2)	72 (91.1)	70 (90.9)
ECOG PS, n (%)						
0	7 (18.4)	4 (10.0)	13 (29.5)	24 (29.3)	18 (22.8)	19 (24.7)
1	31 (81.6)	36 (90.0)	31 (70.5)	58 (70.7)	61 (77.2)	58 (75.3)

As of the data cut-off on December 6, 2019, median study follow-up duration was 9.1 months and 8.2 months in patients with Stage IIIB and IV disease, respectively

Data cut-off: December 6, 2019

C, carboplatin; ECOG PS, Eastern Cooperative Oncology Group performance score; *nab*, nanoparticle albumin-bound; P, paclitaxel

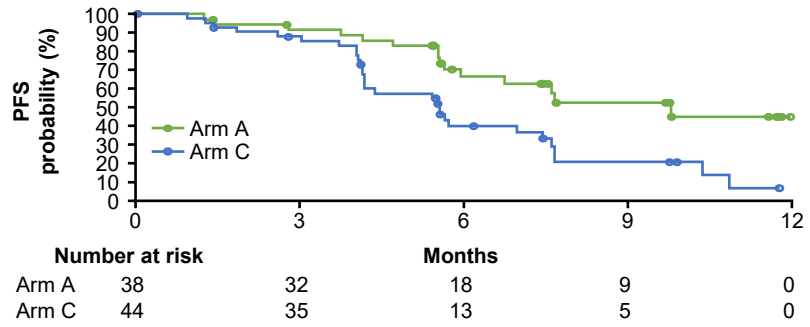
Demographics and baseline characteristics (2/2)

	Stage IIIB (N=122)			Stage IV (N=238)		
	Arm A Tislelizumab + PC (n=38)	**Arm B** Tislelizumab + *nab*-PC (n=40)	**Arm C** PC (n=44)	**Arm A** Tislelizumab + PC (n=82)	**Arm B** Tislelizumab + *nab*-PC (n=79)	**Arm C** PC (n=77)
Smoking status, n (%)						
Never	7 (18.4)	0 (0.0)	8 (18.2)	17 (20.7)	12 (15.2)	15 (19.5)
Current	7 (18.4)	7 (17.5)	11 (25.0)	17 (20.7)	14 (17.7)	16 (20.8)
Former	24 (63.2)	33 (82.5)	25 (56.8)	48 (58.5)	53 (67.1)	46 (59.7)
TC PD-L1 expression, n (%)						
< 1%	15 (39.5)	15 (37.5)	17 (38.6)	33 (40.2)	32 (40.5)	32 (41.6)
1–49%	8 (21.1)	10 (25.0)	11 (25.0)	22 (26.8)	20 (25.3)	20 (26.0)
≥ 50%	15 (39.5)	15 (37.5)	16 (36.4)	27 (32.9)	27 (34.2)	25 (32.5)
Median follow-up duration (months)	9.3	8.8	9.1	8.3	8.6	7.7

Data cut-off: December 6, 2019. PD-L1 expression assessed using the SP263 assay
C, carboplatin; *nab*, nanoparticle albumin-bound; P, paclitaxel; PD-L1, programmed death ligand-1; TC, tumor cell

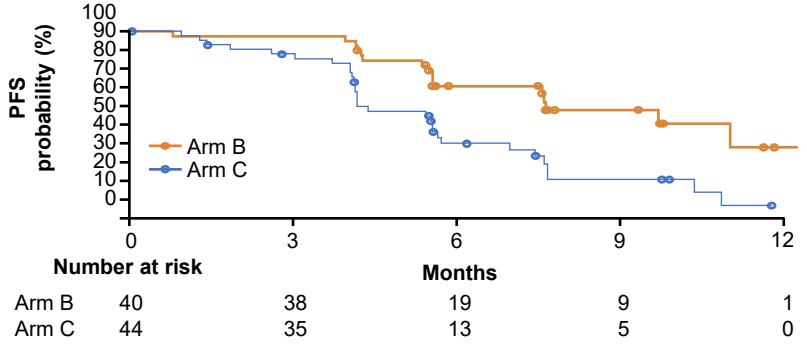
Progression-free survival by IRC in patients with Stage IIIB disease

Arm A versus Arm C



	Events n (%)	Median PFS, months (95% CI)	Hazard ratio (95% CI)
Arm A	15 (39.5)	9.8 (6.0, NE)	0.402 (0.215, 0.750)
Arm C	30 (68.2)	5.6 (4.2, 7.4)	-

Arm B versus Arm C



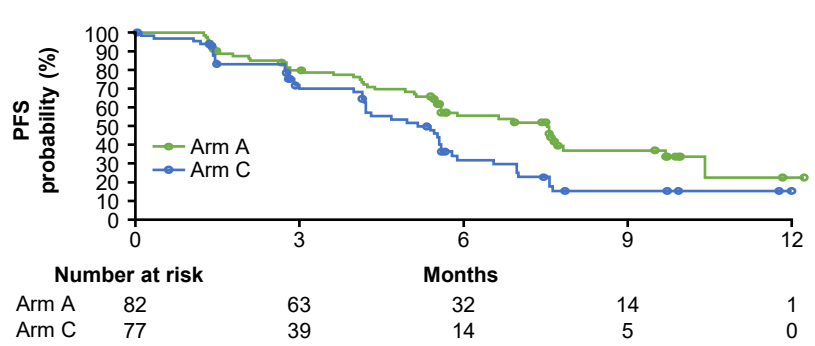
	Events n (%)	Median PFS, months (95% CI)	Hazard ratio (95% CI)
Arm B	16 (40.0)	11.0 (7.6, NE)	0.372 (0.202, 0.686)
Arm C	30 (68.2)	5.6 (4.2, 7.4)	-

For Stage IIIB disease, PFS by IRC was longer in patients treated with tislelizumab plus chemotherapy (Arm A and Arm B) compared with chemotherapy alone (Arm C)

Data cut-off: December 6, 2019. Median follow-up time was estimated by the reverse Kaplan-Meier method. Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula. Arm C was the reference group for hazard ratio. CI, confidence interval; IRC, independent review committee; NE, not estimable; PFS, progression-free survival

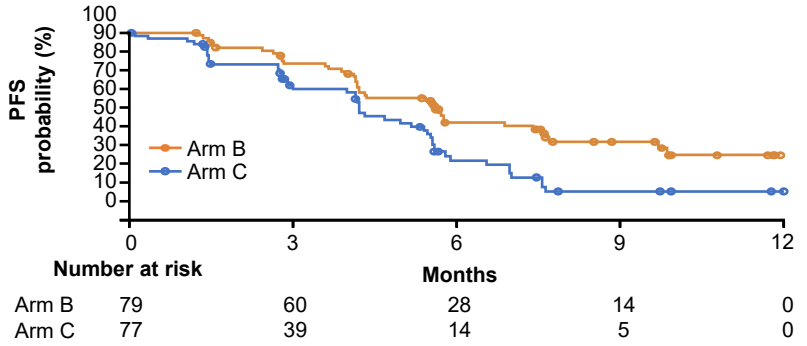
Progression-free survival by IRC in patients with Stage IV disease

Arm A versus Arm C



	Events n (%)	Median PFS, months (95% CI)	Hazard ratio (95% CI)
Arm A	45 (54.9)	7.6 (5.6, 7.8)	0.570 (0.376, 0.862)
Arm C	46 (59.7)	5.2 (4.2, 5.6)	-

Arm B versus Arm C



	Events (%)	Median PFS, months (95% CI)	Hazard ratio (95% CI)
Arm B	40 (50.6)	7.4 (5.6, 9.9)	0.537 (0.350, 0.824)
Arm C	46 (59.7)	5.2 (4.2, 5.6)	-

For Stage IV disease, PFS by IRC was longer in patients treated with tislelizumab plus chemotherapy (Arm A and Arm B) compared with chemotherapy alone (Arm C)

Data cut-off: December 6, 2019. Median follow-up time was estimated by the reverse Kaplan-Meier method. Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula. Paclitaxel+Carboplatin arm was the reference group for hazard ratio. CI, confidence interval; IRC, independent review committee; PFS, progression-free survival

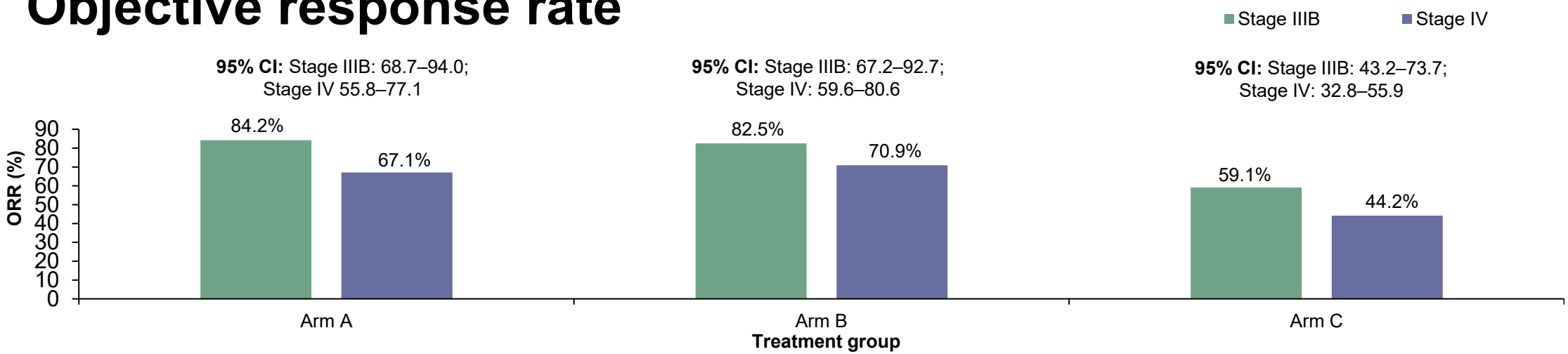
Duration of response

	Stage IIIB (N=122)			Stage IV (N=238)		
	Arm A Tislelizumab + PC (n=38)	**Arm B** Tislelizumab + *nab*-PC (n=40)	**Arm C** PC (n=44)	**Arm A** Tislelizumab + PC (n=82)	**Arm B** Tislelizumab + *nab*-PC (n=79)	**Arm C** PC (n=77)
DoR, months, median (95% CI)	NE (5.03, NE)	9.7 (4.67, NE)	4.0 (2.66, 5.59)	6.9 (3.65, NE)	8.6 (4.80, NE)	4.2 (2.83, 5.72)
HR (95% CI)	0.274 (0.127–0.590)	0.344 (0.162–0.729)	-	0.622 (0.343–1.126)	0.530 (0.290–0.969)	-

DoR was longer in Arm B versus Arm C in patients with Stage IIIB disease, and in Arms A and B versus Arm C in patients with Stage IV disease. The median DoR was not reached in Arm A for Stage IIIB disease

Data cut-off: December 6, 2019
DoR analysis included patients with objective response. Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the Brookmeyer and Crowley method. Arm C was the reference group.
C, carboplatin; CI, confidence interval; DoR, duration of response; HR, hazard ratio; *nab*, nanoparticle albumin-bound; NE, not estimable; P, paclitaxel

Objective response rate



	Stage IIIB (N=122)			Stage IV (N=238)		
	Arm A Tislelizumab + PC (n=38)	**Arm B** Tislelizumab + *nab*-PC (n=40)	**Arm C** PC (n=44)	**Arm A** Tislelizumab + PC (n=82)	**Arm B** Tislelizumab + *nab*-PC (n=79)	**Arm C** PC (n=77)
ORR difference, %	25.3	23.4	-	23.0	26.4	-
95% CI	6.43–44.18	4.23–42.55	-	7.99–37.92	11.62–41.26	-
Complete response, n (%)	2 (5.3)	3 (7.5)	1 (2.3)	3 (3.7)	0 (0.0)	0 (0.0)
Partial response, n (%)	30 (78.9)	30 (75.0)	25 (56.8)	52 (63.4)	56 (70.9)	34 (44.2)

ORR by IRC was higher in Arms A and B compared with Arm C regardless of disease stage

Data cut-off: December 6, 2019; ORR differences between arms were calculated using the Cochran-Mantel-Haenszel Chi-square test with actual stratification factors as strata
C, carboplatin; CI, confidence interval; IRC, independent review committee; *nab*, nanoparticle albumin-bound; ORR, objective response rate; P, paclitaxel

Treatment-emergent adverse events

	Stage IIIB (N=121)			Stage IV (N=234)		
n (%)	**Arm A** Tislelizumab + PC (n=38)	**Arm B** Tislelizumab + *nab*-PC (n=40)	**Arm C** PC (n=43)	**Arm A** Tislelizumab + PC (n=82)	**Arm B** Tislelizumab + *nab-PC* (n=78)	**Arm C** PC (n=74)
Patients with ≥ 1 TEAE	38 (100.0)	39 (97.5)	43 (100.0)	82 (100.0)	78 (100.0)	74 (100.0)
≥ Grade 3	34 (89.5)	35 (87.5)	34 (79.1)	72 (87.8)	67 (85.9)	64 (86.5)
Serious	12 (31.6)	18 (45.0)	7 (16.3)	32 (39.0)	27 (34.6)	22 (29.7)
≥ Grade 3 serious	11 (28.9)	15 (37.5)	4 (9.3)	21 (25.6)	22 (28.2)	12 (16.2)
Leading to treatment discontinuation	5 (13.2)	12 (30.0)	6 (14.0)	10 (12.2)	23 (29.5)	12 (16.2)
Leading to death	0 (0.0)	1 (2.5)	1 (2.3)	4 (4.9)	4 (5.1)	4 (5.4)

In the full patient population, most patients experienced ≥ 1 TEAE and 88.3%, 86.4%, and 83.8% of patients experienced Grade ≥ 3 TEAEs in Arms A, B, and C, respectively[1]

Data cut-off: December 6, 2019.
Adverse event grades were evaluated based on NCI-CTCAE (version 5.0)
C, carboplatin; *nab*, nanoparticle albumin-bound; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; P, paclitaxel; TEAE, treatment-emergent adverse event.
1. Wang J, et al. JAMA Oncol 2021. DOI: 10.1001/jamaoncol.2021.0366. Online ahead of print. Supplement 1

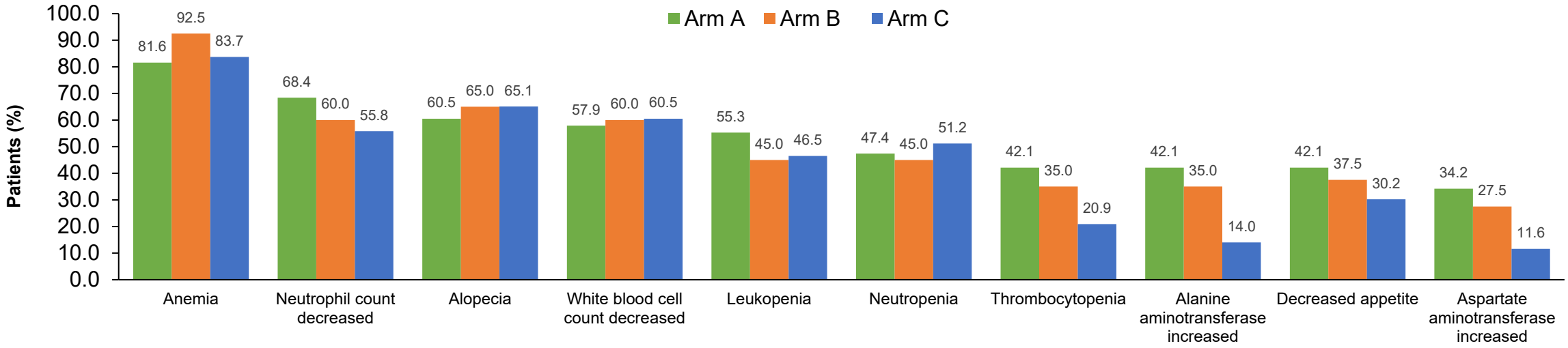
Treatment-related adverse events

	Stage IIIB (N=121)			Stage IV (N=234)		
n (%)	**Arm A** Tislelizumab + PC (n=38)	**Arm B** Tislelizumab + *nab-PC* (n=40)	**Arm C** PC (n=43)	**Arm A** Tislelizumab + PC (n=82)	**Arm B** Tislelizumab + *nab-PC* (n=78)	**Arm C** PC (n=74)
Patients with ≥ 1 TRAE	37 (97.4)	39 (97.5)	43 (100.0)	82 (100.0)	78 (100.0)	74 (100.0)
≥ Grade 3	33 (86.8)	34 (85.0)	34 (79.1)	70 (85.4)	65 (83.3)	60 (81.1)
Serious	8 (21.1)	10 (25.0)	6 (14.0)	19 (23.2)	18 (23.1)	11 (14.9)
Leading to death	0 (0.0)	0 (0.0)	1 (2.3)	1 (1.2)	2 (2.6)	2 (2.7)

In the full patient population, most patients experienced ≥ 1 TRAE; 85.8%, 83.9%, and 80.3% of patients in Arms A, B, and C, respectively, experienced Grade ≥ 3 TRAEs[1]

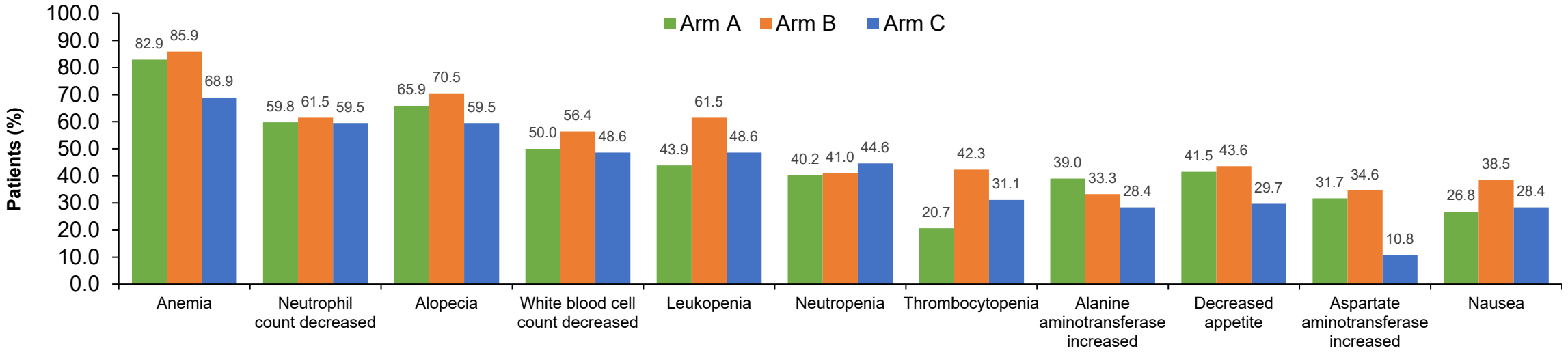
Data cut-off: December 6, 2019.
Adverse event grades were evaluated based on NCI-CTCAE (version 5.0)
C, carboplatin; *nab*, nanoparticle albumin-bound; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; P, paclitaxel; TRAE, treatment-related adverse event
1. Wang J, et al. JAMA Oncol 2021. DOI: 10.1001/jamaoncol.2021.0366. Online ahead of print. Supplement 1

Most commonly occurring (≥ 20%) treatment-related adverse events in Stage IIIB patients



Data cut-off: December 6, 2019
Patients with multiple events for a given preferred term and system organ class were counted only once at the maximum grade for the preferred term and system organ class, respectively. Adverse events coded according to MedDRA Version: 22.0
MedDRA, Medical Dictionary for Regulatory Activities

Most commonly occurring (≥ 20%) treatment-related adverse events in Stage IV patients



Data cut-off: December 6, 2019
Patients with multiple events for a given preferred term and system organ class were counted only once at the maximum grade for the preferred term and system organ class, respectively. Adverse events coded according to MedDRA Version: 22.0
MedDRA, Medical Dictionary for Regulatory Activities

Reasons for discontinuation

	Stage IIIB (N=121)			Stage IV (N=234)		
n (%)	**Arm A** Tislelizumab + PC (n=38)	**Arm B** Tislelizumab + *nab*-PC (n=40)	**Arm C** PC (n=43)	**Arm A** Tislelizumab + PC (n=82)	**Arm B** Tislelizumab + *nab*-PC (n=78)	**Arm C** PC (n=74)
Patients discontinued from all study drugs	18 (47.4)	17 (42.5)	43 (97.7)	39 (47.6)	35 (44.3)	74 (96.1)
Patients discontinued from the study	5 (13.2)	5 (12.5)	5 (11.4)	18 (22.0)	16 (20.3)	27 (35.1)
Primary reason for discontinuation from the study						
Death	4 (10.5)	3 (7.5)	4 (9.1)	16 (19.5)	13 (16.5)	14 (18.2)
Voluntary withdrawal	1 (2.6)	2 (5.0)	1 (2.3)	2 (2.4)	2 (2.5)	12 (15.6)
Other	-	-	-	0 (0.0)	1 (1.3)	1 (1.3)
Patients remaining in the study	33 (86.8)	35 (87.5)	39 (88.6)	64 (78.0)	63 (79.7)	50 (64.9)

Discontinuation from tislelizumab plus chemotherapy

Stage IIIB: **progressive disease** (23.7% in Arm A and 25.0% in Arm B) and **voluntary withdrawal** (13.2% in Arm A and 5.0% in Arm B)

Stage IV: **progressive disease** (28.0% in Arm A and 22.8% in Arm B) and **adverse events** (11.0% in Arm A and 10.1% in Arm B)

Discontinuation from chemotherapy only

Completion of chemotherapy (Stage IIIB: 75.0%, Stage IV: 62.3%), **progressive disease** (Stage IIIB: 4.5%, Stage IV: 9.1%), and **adverse events** (Stage IIIB: 11.4%, Stage IV: 14.3%)

Data cut-off: December 6, 2019; Primary reason for treatment discontinuation referred to the primary reason for the study drug discontinued last
C, carboplatin; *nab*, nanoparticle albumin-bound; P, paclitaxel

Conclusions

- In this subgroup analysis, clinically meaningful improvements in PFS and higher ORR were observed with tislelizumab in combination with paclitaxel/*nab*-paclitaxel and carboplatin versus standard of care in patients with Stage IIIB or Stage IV advanced squamous NSCLC
- Tislelizumab was generally well tolerated. There was no difference between the safety profiles of the Stage IIIB and IV subgroups, which were also consistent with the full population

nab, nanoparticle albumin-bound; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival

1. Walters S, et al. Thorax 2013;68:551–64; 2. Wang J, et al. JAMA Oncol 2021. DOI: 10.1001/jamaoncol.2021.0366. Online ahead of print. Supplement 1

Acknowledgements

- This study was sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Tamsin Grewal, MSc, of Ashfield MedComms, an Ashfield Health company, and funded by BeiGene, Ltd.