UPDATED ANALYSIS OF TISLELIZUMAB PLUS CHEMOTHERAPY VS CHEMOTHERAPY ALONE AS FIRST-LINE TREATMENT OF ADVANCED SQUAMOUS NON-SMALL CELL LUNG CANCER

RATIONALE TRIAL PROGRAM

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Poster: 1264P
European Society of Medical Oncology
September 19-21, 2020, Virtual Congress

BACKGROUND

- Both globally and in China, lung cancer is the most commonly diagnosed cancer and is the leading cause of cancer-related death[1]
  - The prognosis has been particularly poor for patients with squamous non-small cell lung cancer (NSCLC), with chemotherapy studies reporting a median overall survival (OS) of 9-11 months[2]
- First-line treatment for squamous NSCLC has historically included platinum-doublet chemotherapy (eg, vinorelbine, gemcitabine, docetaxel, or paclitaxel plus platinum)[2-5]
- Combining standard first-line regimens with antibodies against programmed cell death protein-1 (PD-1) and its ligand, programmed death-ligand 1 (PD-L1), has led to advancements in the treatment of NSCLC[6-8]
- In addition to commonly assessed PD-L1 expression, tumor mutational burden (TMB) is a biomarker of interest in NSCLC due to its association with response to immunotherapy treatment[9-11]
- Tislelizumab is a humanized monoclonal antibody with high affinity and specificity for PD-1 that was engineered to minimize binding to FcγR on macrophages in order to abrogate antibody dependent phagocytosis, a potential mechanism of T-cell clearance and resistance to anti-PD-1 therapy[12]
- Tislelizumab, as a single agent and in combination with chemotherapy, was generally well tolerated and demonstrated evidence of antitumor activity in Asian and non-Asian populations with solid tumors, including advanced lung cancers (BGB-A317-001, BGB-A317-102, BGB-A317-206)[13-15]
- Here we present the efficacy, safety/tolerability, and TMB data from a pivotal open-label phase 3 clinical trial (RATIONALE 307; BGB-A317-307) conducted in China of tislelizumab in combination with platinum-doublet chemotherapy as first-line treatment for patients with advanced squamous NSCLC

METHODS

Overall Design and Study Objectives

- In this open-label phase 3 study, patients with squamous NSCLC were randomized 1:1:1 into three arms (**Supplemental Fig. 1**)
  - *Arm A:* Tislelizumab 200 mg (Day 1) + paclitaxel 175 mg/m² (Day 1) and carboplatin AUC 5 (Day 1) intravenously (IV) every 3 weeks (Q3W)
  - *Arm B:* Tislelizumab + nanoparticle albumin-bound (nab)-paclitaxel 100 mg/m² (Days 1, 8, and 15) and carboplatin IV Q3W
  - *Arm C:* Paclitaxel and carboplatin IV Q3W
- Paclitaxel, nab-paclitaxel, and carboplatin were administered for 4-6 cycles; tislelizumab was administered in combination with chemotherapy for 4-6 cycles, then as tislelizumab monotherapy until loss of clinical benefit (per investigator assessment), start of a new anticancer therapy, or death, whichever occurs first
  - Patients randomized to *Arm C* were allowed to cross over to tislelizumab maintenance upon disease progression
- The primary objective compared progression-free survival assessed by Independent Review Committee (PFS_{IRC}) per RECIST v1.1, between tislelizumab combined with either paclitaxel and carboplatin (*Arm A*) or nab-paclitaxel and carboplatin (*Arm B*), and paclitaxel and carboplatin alone (*Arm C*)
- Additional objectives compared OS, as well as duration of response (DOR) and objective response rate (ORR) by IRC, PFS assessed by investigators (PFS_{INV}), safety/tolerability profile and association of blood TMB (bTMB) with efficacy between *Arms A* or *B* and *Arm C*

Study Population

- Adults (aged 18-75 years) with histologically confirmed squamous NSCLC, with at least one measurable lesion, were eligible for inclusion if they provided fresh or archival tumor tissues for PD-L1 expression analysis
  - Patients must have had no prior systemic therapy for advanced or metastatic disease
  - Patients with known *EGFR*-sensitizing mutation or *ALK* gene translocation, or prior treatment with EGFR, ALK, or PD-1/L1 inhibitors were ineligible

Study Assessments and Statistical Analyses

- Efficacy endpoints were assessed in the intent-to-treat (ITT) analysis set (all randomized patients); median PFS was estimated using Kaplan-Meier analysis
- PD-L1 membrane staining on tumor cells (TCs) was prospectively assessed by the VENTANA PD-L1 (SP263) assay at a central laboratory
  - PD-L1 results were blinded to investigators, patients, and sponsors
- bTMB was retrospectively evaluated by OncoScreen Plus (Burning Rock Biotech, Guangzhou, China) in circulating cell-free DNA collected at baseline
- Safety was assessed in the safety analysis set through physical examinations, monitoring of treatment-emergent adverse events (TEAEs), vital signs, clinical laboratory assessments, and 12-lead electrocardiogram
  - Potential immune-mediated adverse events (AEs) were selected from a group of preferred terms regardless of whether the investigator attributed the event to a treatment or considered the event to be immune related

RESULTS

Patients

- As of December 6, 2019, 360 patients with advanced squamous NSCLC were randomized
- At the time of data cut-off, 63 patients (52.5%) in *Arm A* and 66 patients (55.5%) in *Arm B* remained on treatment; 81 patients (66.9%) completed chemotherapy in *Arm C*
  - The most common reason for discontinuation of tislelizumab treatment was progressive disease (n=60; 16.7%), followed by AE (n=24; 6.7%) and consent withdrawal (n=17; 4.7%)
- Patient demographics and baseline disease characteristics were well balanced across all arms (**Table 1**)

Table 1: Demographics and Baseline Characteristics (ITT Analysis Set, N=360)

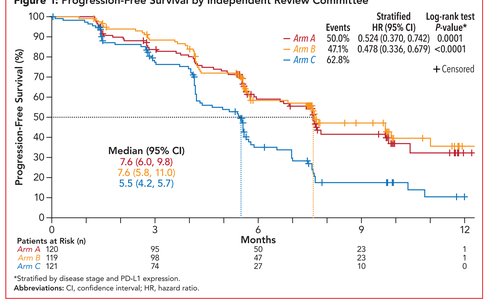
ITT Population		*Arm A* Tislelizumab + PC (n=120)	*Arm B* Tislelizumab + nab-PC (n=119)	*Arm C* PC (n=121)	Total (N=360)
Median age, years (range)		60 (41-74)	63 (38-74)	62 (34-74)	62 (34-74)
Sex, male n (%)		107 (89.2)	112 (94.1)	111 (91.7)	330 (91.7)
Tobacco use, n (%)	Current/former	96 (80.0)	107 (89.9)	98 (81.0)	301 (83.6)
	Never	24 (20.0)	12 (10.1)	23 (19.0)	59 (16.4)
ECOG status, n (%)	0	31 (25.8)	22 (18.5)	32 (26.4)	85 (23.6)
	1	89 (74.2)	97 (81.5)	89 (73.6)	275 (76.4)
Solid tumor stage, n (%)	Stage IIIB	38 (31.7)	40 (33.6)	44 (36.4)	122 (33.9)
	Stage IV	82 (68.3)	79 (66.4)	77 (63.6)	238 (66.1)
PD-L1 % expression on TC, n (%)	<1%[a]	48 (40.0)	47 (39.5)	49 (40.5)	144 (40.0)
	1-49%	30 (25.0)	30 (25.2)	31 (25.6)	91 (25.3)
	≥50%	42 (35.0)	42 (35.3)	41 (33.9)	125 (34.7)
Confirmed distant metastatic site(s)[b], n (%)	Bone	24 (20.0)	16 (13.4)	21 (17.4)	61 (16.9)
	Liver	15 (12.5)	15 (12.6)	14 (11.6)	44 (12.2)
	Brain	2 (1.7)	3 (2.5)	1 (0.8)	6 (1.7)

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

Efficacy of Tislelizumab Plus Chemotherapy Versus Chemotherapy Alone

- Median PFS_{IRC} was 7.6 months (95% CI: 6.0, 9.8) in *Arm A* and 7.6 months (95% CI: 5.8, 11.0) in *Arm B*, both of which were significantly longer than median PFS in *Arm C* (5.5 months [95% CI: 4.2, 5.7]) (**Fig. 1**)
  - Similar median PFS_{INV} results were observed for *Arm A* vs *Arm C* (*P*<0.0001; HR: 0.335 [0.231, 0.487]) and *Arm B* vs *Arm C* (*P*<0.0001; HR: 0.354 [0.243, 0.516])

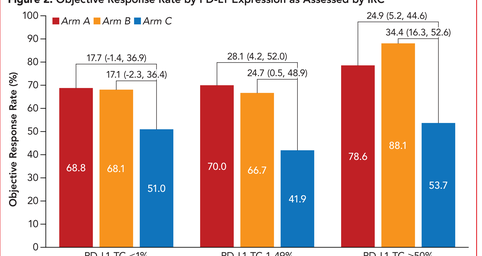
Figure 1: Progression-Free Survival by Independent Review Committee



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

- Objective response rate was 73% (95% CI: 63.6, 80.3) and 75% (95% CI: 66.0, 82.3) in *Arms A* and *B*, respectively, which was higher than the ORR in *Arm C* (50% [95% CI: 40.4, 58.8]) (**Supplemental Fig. 2**)
- Duration of response was also longer in both tislelizumab-containing arms compared with chemotherapy alone (**Supplemental Fig. 2**)
- Compared with chemotherapy alone, tislelizumab plus chemotherapy demonstrated increased ORR regardless of PD-L1 expression level (**Fig. 2**)

Figure 2: Objective Response Rate by PD-L1 Expression as Assessed by IRC



Data presented above the bars are the treatment differences (95% CI).
Abbreviations: CI, confidence interval; IRC, Independent Review Committee; PD-L1, programmed death-ligand 1; TC, tumor cell.

- Subgroup analysis of PFS_{IRC} showed consistent PFS benefit for *Arm A* vs *Arm C* (**Fig. 3A**) and *Arm B* vs *Arm C* (**Fig. 3B**) across all prespecified subgroups, including PD-L1 expression
- With a median study follow-up time of 8.6 months, median OS has not been reached

Figure 3: Subgroup Analysis of Tislelizumab + PC vs PC (*A*) and Tislelizumab + nab-PC vs PC (*B*)

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PD, progressive disease; PD-L1, programmed death-ligand 1; TC, tumor cell.

Safety and Tolerability of Combination Therapy Versus Chemotherapy Alone

- Treatment-emergent AEs occurred in 100.0%, 99.2%, and 100.0% in patients in *Arms A*, *B*, and *C*, respectively (**Table 2**)
  - A total of 68 (n=15, 12.5% [*A*], n=35, 29.7% [*B*], n=18, 15.4% [*C*]) patients experienced a TEAE that led to treatment discontinuation
- The most commonly reported TEAEs were anemia (88.3% [*A*], 93.2% [*B*], 80.3% [*C*]), alopecia (64.2% [*A*], 69.5% [*B*], 61.5% [*C*]), and decreased neutrophil count (63.3% [*A*], 61.0% [*B*], 58.1% [*C*]) (**Table 3**)
- Treatment-related AEs (TRAEs) occurred in 353 patients (99.4%); the most commonly reported TRAEs were hematological in nature (eg, anemia, alopecia, and decreased neutrophil count)
- Serious TRAEs were reported in 27 patients in *Arm A*, 28 patients in *Arm B*, and 17 patients in *Arm C*
  - The most common serious TRAEs in *Arms A* and *B* were decreased neutrophil count (3.3%, n=4 [*A*]; 3.4%, n=4 [*B*]), febrile neutropenia (1.7%, n=2 [*A*]; 2.5%, n=3 [*B*]), and pneumonitis (2.5%, n=3 [*A*]; 1.7%, n=2 [*B*])
  - The most commonly reported serious TRAE in *Arm C* was thrombocytopenia (2.6%, n=3)
- Treatment-related AEs leading to death were reported in six patients (0.8%, n=1 [*A*]; 1.7%, n=2 [*B*]; 2.6%, n=3 [*C*]); none were solely attributed to tislelizumab
- Potential immune-mediated AEs occurred in 51.7% (n= 62 [*A*]), 47.5% (n=56 [*B*]), and 18.8% (n=22 [*C*]) of patients
- The most commonly reported potential immune-mediated AEs in *Arms A* and *B* were hyperglycemia (15.8% [*A*], 9.3% [*B*]), hypothyroidism (11.7% [*A*], 12.7% [*B*]), and pneumonia (10.8% [*A*], 6.8% [*B*]) (**Supplemental Fig. 3**)
  - Most immune-mediated AEs were mild or moderate in severity, did not require corticosteroid treatments, and did not lead to discontinuation of any treatment component

Table 2: Overall Summary of Treatment-Emergent Adverse Events

	Tislelizumab + PC (n=120)	Tislelizumab + nab-PC (n=118)	PC (n=117)
Patients with ≥1 TEAE	120 (100.0)	117 (99.2)	117 (100.0)
Grade ≥3	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.

Table 3: Incidence of Treatment-Emergent Adverse Events Occurring in ≥20% of Patients Treated With Tislelizumab Plus Chemotherapy or Chemotherapy Alone

Preferred Term	Tislelizumab + PC (n=120)		Tislelizumab + nab-PC (n=118)		PC (n=117)	
	All Grades, n (%)	Grade ≥3, n (%)	All Grades, n (%)	Grade ≥3, n (%)	All Grades, n (%)	Grade ≥3, n (%)
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
Hypoalbuminemia	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

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

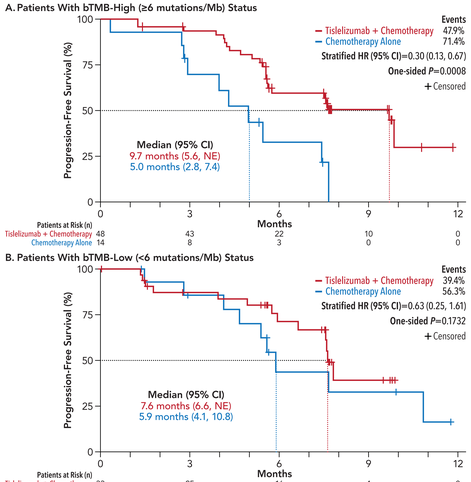
Exploratory Analysis of Blood Tumor Mutational Burden

- Across all three cohorts, 111 patients had evaluable bTMB (*Arm A* and *B*, n=81; *Arm C*, n=30)
  - Due to limited sample size, *Arm A* and *Arm B* were combined and analyzed as tislelizumab plus chemotherapy vs chemotherapy alone to balance baseline characteristics and efficacy
- bTMB optimal cut-off was selected by receiver operating characteristics
- Using a cut-off of six mutations/Mb, tislelizumab plus chemotherapy demonstrated ORR and PFS benefit vs chemotherapy in both bTMB-high and bTMB-low subgroups (**Fig. 4A and 4B**)
- The predictive value of bTMB in PFS for tislelizumab plus chemotherapy was not confirmed by interactive analysis (*P*=0.234), suggesting the clinical utility may be limited in the tislelizumab plus chemotherapy setting (**Table 4**)

CONCLUSIONS

- Tislelizumab plus chemotherapy resulted in significantly improved PFS, higher ORR, and longer DOR compared with chemotherapy alone in patients with advanced squamous NSCLC, addressing a high unmet need in this patient population
- The addition of tislelizumab to standard chemotherapy demonstrated clinical benefit across all subgroups, regardless of PD-L1 expression and bTMB status
- First-line treatment with tislelizumab in combination with paclitaxel and carboplatin or nab-paclitaxel and carboplatin was generally well tolerated
  - The incidence and frequency of TEAEs (including grade ≥3) were similar across the three arms
  - Most AEs were mild or moderate in severity and manageable
- The results from this pivotal phase 3 study support tislelizumab in combination with paclitaxel and carboplatin or nab-paclitaxel and carboplatin as a potential new standard for first-line treatment of advanced squamous NSCLC

Figure 4: Progression-Free Survival (IRC) by bTMB Status



Abbreviations: bTMB, blood tumor mutational burden; CI, confidence interval; HR, hazard ratio; IRC, Independent Review Committee; NE, not evaluable; PFS, progression-free survival.

Table 4: Interaction Analysis for bTMB as a Predictive Biomarker

Tislelizumab + Chemotherapy vs Chemotherapy Alone	bTMB-High (≥6 mutations/Mb)	bTMB-Low (<6 mutations/Mb)	Ratio of bTMB-High vs bTMB-Low	*P*-value of interaction: odds ratio
ORR OR	4.04 (1.13, 14.41)	0.63 (0.19, 2.18)	6.38 (1.07, 37.88)	0.042
PFS HR	0.30 (0.13, 0.67)	0.63 (0.25, 1.61)	0.47 (0.14, 1.63)	0.234

Abbreviations: bTMB, blood tumor mutational burden; HR, hazard ratio; Mb; megabase; *OR*, odds ratio; ORR, objective response rate; PFS, progression-free survival.

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CONFLICTS OF INTEREST

SL reports a consulting or advisory role for AstraZeneca, Boehringer Ingelheim, Hutchison MediPharma, Roche,and Simcere; Speakers' Bureau for AstraZeneca, Hanseng, and Roche; and Research Funding from AstraZeneca, BMS, Heng Ru, Hutchison MediPharma, and Roche. **LL**, **XL**, **XW**, **JZ** are employees with stock option at BeiGene, Ltd. **JC**, **MC**, **GF**, **CH**, **YP**, **YS**, **JW**, **OY**, **KY**, **YY**, **JZ**, and **XZ** have nothing to disclose.

ACKNOWLEDGMENTS

The authors wish to acknowledge the investigative centers' study staff and study patients, and to recognize those from BeiGene, Ltd. who have substantially contributed to the development of this presentation. This study was sponsored by BeiGene, Ltd. Writing and editorial assistance was provided by Agnieszka Laskowski, PhD, and Elizabeth Hermans, PhD (OPEN Health Medical Communications, Chicago, IL), and funded by the study sponsor.

Please address any questions or comments regarding this poster to Clinicaltrials@beigene.com

Poster: 1246P
European Society of Medical Oncology
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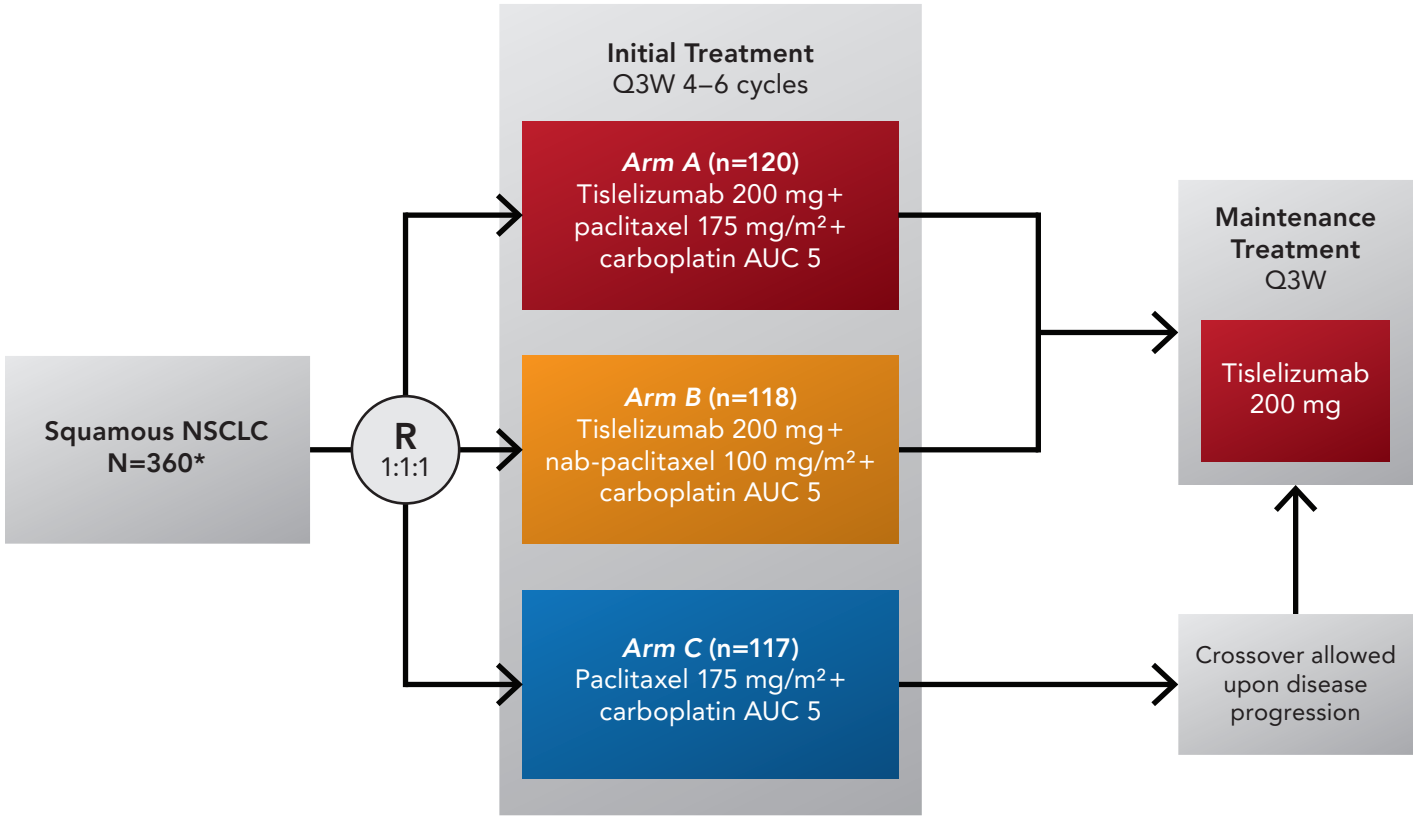
Supplemental Figure 1: Study Schema

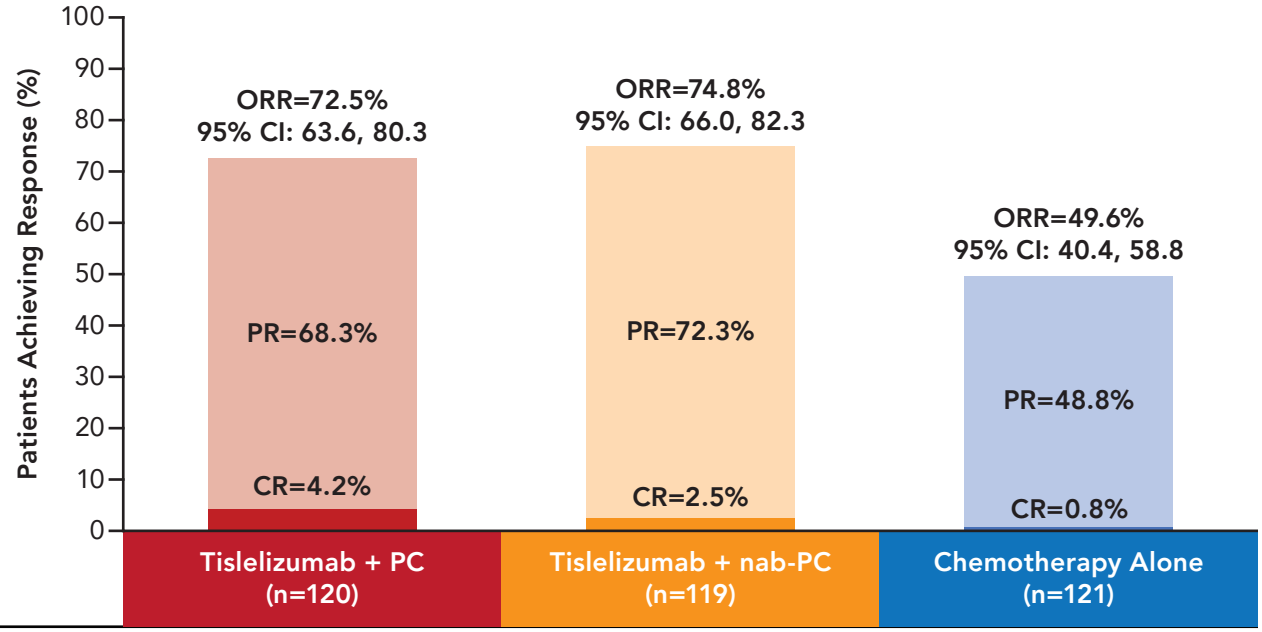


*Five patients (*Arm B*, n=1; *Arm C*, n =4) were randomized, but excluded from treatment due to serious adverse event (n=2), investigator's decision (n=1), withdrawal of consent (n=1), and ineligibility (n=1).

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

Abbreviations: D, day; nab, nanoparticle albumin-bound; NSCLC, non-small cell lung cancer; Q3W, every 3 weeks; R, randomized.

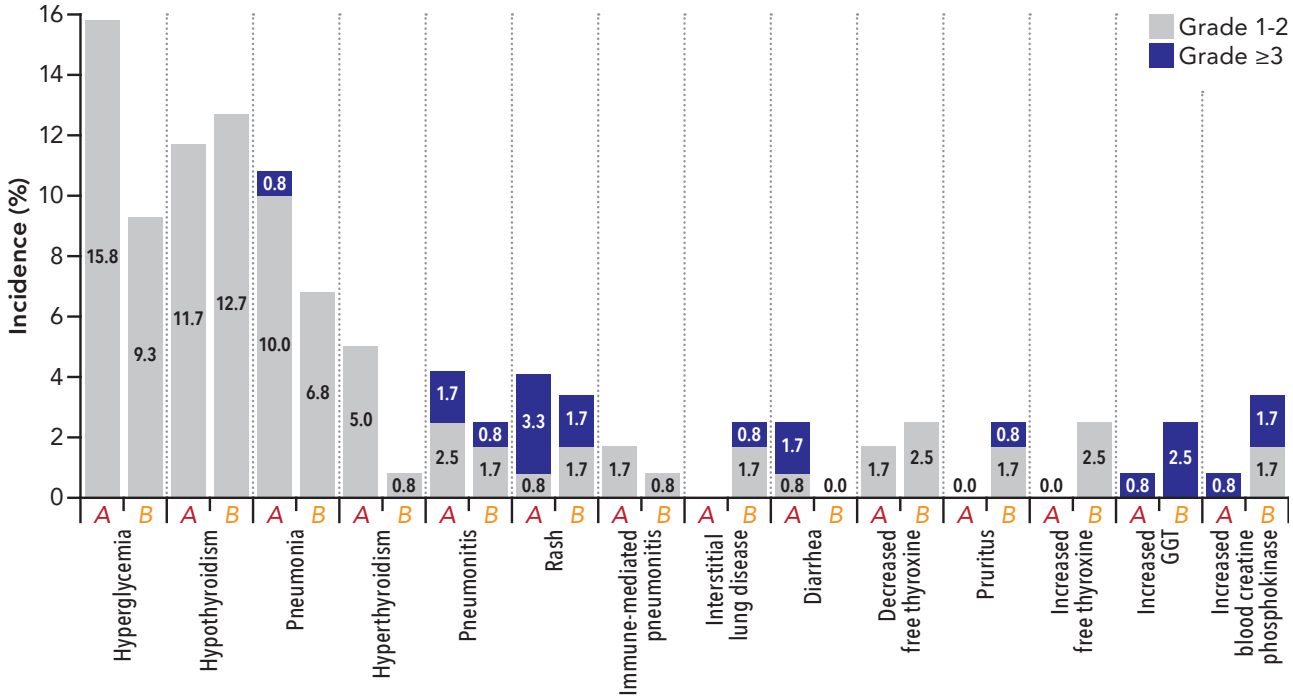
Supplemental Figure 2: Disease Response per IRC (ITT Population)



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

Abbreviations: CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of reasponse; IRC, Independent Review Committee; ITT, intent-to-treat; NE, not evaluable; ORR, objective response rate; PR, partial response.

Supplemental Figure 3: Potential Immune-Mediated Adverse Events Occurring in >2 Patients in Tislelizumab Plus Chemotherapy Groups



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