PHASE 3 STUDY OF TISLELIZUMAB PLUS CHEMOTHERAPY VERSUS CHEMOTHERAPY ALONE AS FIRST-LINE TREATMENT FOR ADVANCED SQUAMOUS NON-SMALL CELL LUNG CANCER

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BACKGROUND

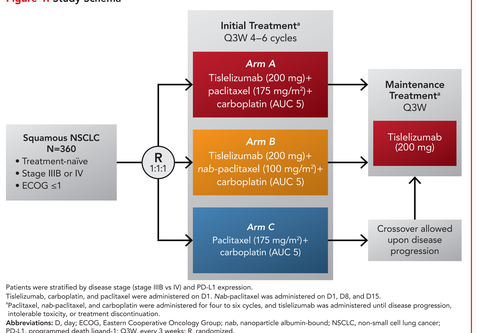
- In China, lung cancer is the most commonly diagnosed cancer and is the leading cause of cancer-related death[1]
- First-line treatment for advanced squamous non-small cell lung cancer (NSCLC) in China has historically included platinum-doublet chemotherapy (eg, vinorelbine, gemcitabine, docetaxel, or paclitaxel plus platinum)[2]
  - Nanoparticle albumin-bound (*nab*)-paclitaxel is not currently approved for NSCLC in China
  - Prognosis for patients diagnosed with advanced squamous NSCLC remains poor[2]
- Tislelizumab is a humanized monoclonal antibody with high affinity and specificity for programmed cell death protein 1 (PD-1) that was engineered to minimize binding to FcγR on macrophages in order to abrogate antibody dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy[3,4]
- Tislelizumab, as a single agent, was generally well tolerated and demonstrated evidence of antitumor activity in Asian and non-Asian populations with solid tumors, including advanced lung cancers[5,6]
- Data from a phase 2 study (NCT03432598) suggested that tislelizumab in combination with platinum-based doublet chemotherapy was generally well tolerated and demonstrated antitumor activity in Chinese patients with squamous NSCLC[7]
- We present efficacy and safety/tolerability data from a pivotal open-label phase 3 clinical trial (NCT03594747) conducted in China of tislelizumab in combination with doublet chemotherapy as first-line treatment for patients with advanced squamous NSCLC

METHODS

Overall Design and Study Objectives

- The study design is detailed in **Figure 1**
  - The primary objective compared progression-free survival (PFS) by Independent Review Committee (IRC) between tislelizumab combined with either paclitaxel and carboplatin (*Arm A*) or *nab*-paclitaxel and carboplatin (*Arm B*), and paclitaxel and carboplatin alone (*Arm C*)
  - Secondary objectives compared overall survival (OS), as well as duration of response (DoR) and objective response rate (ORR) by IRC, and safety/tolerability profile, between *Arms A* or *B* and *Arm C*
- Radiological assessment of tumor-response status was performed per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Safety was assessed through physical examinations, monitoring of treatment-emergent adverse events (TEAEs), vital signs, clinical laboratory assessments, and 12-lead electrocardiogram

Figure 1: Study Schema



Patients were stratified by disease stage (stage IIIB vs IV) and PD-L1 expression.
Tislelizumab, carboplatin, and paclitaxel were administered on D1. Nab-paclitaxel was administered on D1, D8, and D15.
[a]Paclitaxel, nab-paclitaxel, and carboplatin were administered for four to six cycles, and tislelizumab was administered until disease progression, intolerable toxicity, or treatment discontinuation.
Abbreviations: D, day; ECOG, Eastern Cooperative Oncology Group; nab, nanoparticle albumin-bound; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand-1; Q3W, every 3 weeks; R, randomized.

Study Population

- Adult patients (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 programmed death ligand-1 (PD-L1) expression analysis
  - Patients must have had no prior systemic therapy for advanced or metastatic disease
    - Prior neoadjuvant/adjuvant therapy or chemoradiation therapy was allowed if completed ≥6 months prior to randomization
  - Patients with a known *EGFR*-sensitizing mutation or *ALK* gene translocation, or prior treatment with EGFR inhibitors, ALK inhibitors, and/or therapies targeting PD-1/L1 were ineligible

Study Endpoints and Statistical Analyses

- The primary endpoint was PFS following RECIST v1.1 guidelines in the intent-to-treat (ITT) analysis set (all randomized patients) and median PFS was estimated using Kaplan-Meier analysis
  - The Brookmeyer and Crowley method was used to construct 95% confidence intervals (CIs) for the median PFS of each treatment arm
  - Hazard ratios for comparisons between *Arm A* or *Arm B* with *Arm C* were estimated using the stratified Cox proportional model
  - Stratified log-rank test was used to test significance between treatment arms
- Secondary endpoints included OS in the ITT analysis set, ORR (complete response [CR] + partial response [PR]), DoR, and the safety of tislelizumab in combination with chemotherapy or chemotherapy alone
- PD-L1 membrane staining on tumor cells was assessed by the VENTANA PD-L1 (SP263) assay at a central laboratory
  - PD-L1 results were blinded to investigators, patients, and sponsors

RESULTS

Patients

- As of 6 December 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%)
- Demographics and baseline characteristics were well balanced across all arms (**Table 1**)

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

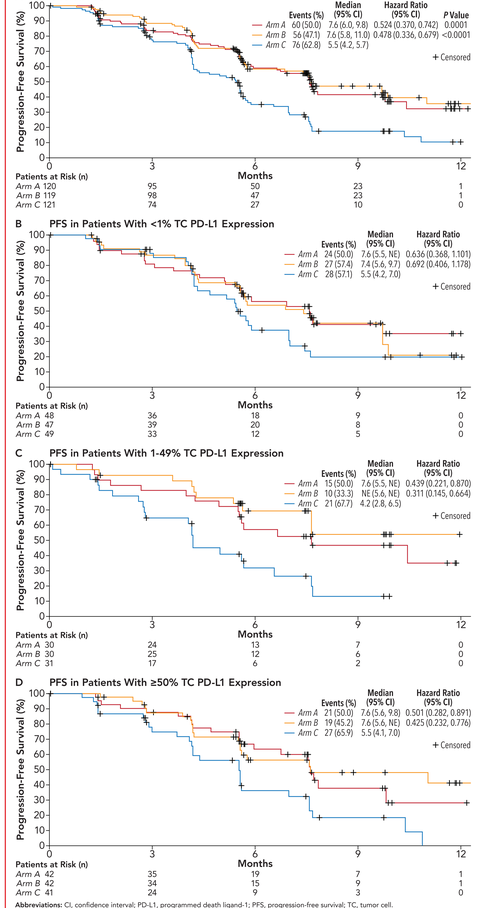
		Arm A Tislelizumab + PC (n=120)	*Arm B* Tislelizumab + *nab*-PC (n=119)	*Arm C* PC (n=121)	Total (N=360)
Median age, years (range)		60 (41-74)	63 (38-74)	62 (34-74)	62 (34-74)
Age group, n (%)	<65	81 (67.5)	67 (56.3)	85 (70.2)	233 (64.7)
	≥65	39 (32.5)	52 (43.7)	36 (29.8)	127 (35.3)
Sex, n (%)	Male	107 (89.2)	112 (94.1)	111 (91.7)	330 (91.7)
	Female	13 (10.8)	7 (5.9)	10 (8.3)	30 (8.3)
Tobacco use, n (%)	Former	72 (60.0)	86 (72.3)	71 (58.7)	229 (63.6)
	Current	24 (20.0)	21 (17.6)	27 (22.3)	72 (20.0)
	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 tumor cells, n (%)	<1%	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)[a], 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)

[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.

Antitumor Activity of Combination Therapy Versus Chemotherapy Alone

- Median PFS was 7.6 months (95% CI: 6.0, 9.8) and 7.6 months (95% CI: 5.8, 11.0) in *Arms A* and *B*, respectively, both of which were significantly longer than the median PFS in *Arm C* (5.5 months [95% CI: 4.2, 5.7]) (**Figure 2A**)
- PFS was improved regardless of tumor cell PD-L1 expression (**Figure 2B-D**)
- With a median study follow-up time of 8.6 months, median OS had not been reached
- ORR was 73% (95% CI: 63.6, 80.3) and 75% (95% CI: 66.0, 82.3) in *Arms A* and *B*, respectively, and higher compared with *Arm C* (50% [95% CI: 40.4, 58.8]) (**Table 2**)
  - Similarly, DoR was longer in both tislelizumab-containing arms compared with chemotherapy alone

Figure 2: Progression-Free Survival by Independent Review Committee



Abbreviations: CI, confidence interval; PD-L1, programmed death ligand-1; PFS, progression-free survival; TC, tumor cell.

Table 2: Disease Response per RECIST by IRC (ITT Analysis Set, N=360)

		Arm A Tislelizumab + PC (n=120)	*Arm B* Tislelizumab + *nab*-PC (n=119)	*Arm C* PC (n=121)
BOR, n (%)	CR	5 (4)	3 (3)	1 (<1)
	PR	82 (68)	86 (72)	59 (49)
	SD	18 (15)	19 (16)	36 (30)
	Non-CR/non-PD	0	0	1 (<1)
	PD	12 (10)	5 (4)	11 (9)
	NE/missing	3 (3)	6 (5)	13 (11)
ORR, % (95% CI)		73 (63.6, 80.3)	75 (66.0, 82.3)	50 (40.4, 58.8)
DCR, % (95% CI)		88 (80.2, 92.8)	91 (84.1, 95.3)	80 (71.9, 86.9)
CBR, %* (95% CI)		81 (72.6, 87.4)	80 (71.5, 86.6)	56 (46.9, 65.2)
Median DoR, months (95% CI)		8.2 (5.0, NE)	8.6 (6.3, NE)	4.2 (2.8, 4.9)

DCR=CR+PR+SD.
*Includes patients with BOR in CR or PR or ≥24 weeks SD.
Abbreviations: BOR, best overall response; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DCR, disease control rate; IRC, Independent Review Committee; ITT, intent-to-treat; nab, nanoparticle albumin-bound; NE, not evaluable; ORR, objective response rate; PC, paclitaxel and carboplatin; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Safety and Tolerability of Combination Therapy Versus Chemotherapy Alone

- Investigator-assessed TEAEs were reported in 100%, 99.2%, and 100% of patients in *Arms A*, *B*, and *C*, respectively (**Table 3**)
  - A total of 68 (19.2%) patients experienced a TEAE that led to treatment discontinuation
- The most commonly reported treatment-related AEs (TRAEs) associated with any study component were mainly hematologic in nature (**Table 4**)

Table 3: 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)
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 4: TRAEs Associated With Any Study Component and Occurring in ≥20% in Any Arm of Patients Treated With Tislelizumab Plus Doublet Chemotherapy or Chemotherapy Alone

Preferred Term, n (%)	*Arm A* Tislelizumab + PC (n=120)		*Arm B* Tislelizumab + *nab*-PC (n=118)		*Arm C* PC (n=117)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥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
Neutrophil count decreased	75 (62.5)	62 (51.7)	72 (61.0)	54 (45.8)	68 (58.1)	53 (45.3)
White blood cell count decreased	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)
ALT increased	48 (40.0)	2 (1.7)	40 (33.9)	2 (1.7)	27 (23.1)	0
Platelet count decreased	40 (33.3)	5 (4.2)	52 (44.1)	16 (13.6)	28 (23.9)	2 (1.7)
AST increased	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
Blood bilirubin increased	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)

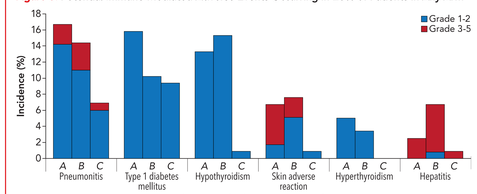
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; nab, nanoparticle albumin-bound; PC, paclitaxel and carboplatin; TRAE, treatment-related adverse event.

CONCLUSIONS

- Tislelizumab plus chemotherapy provided durable responses and improved antitumor activity compared with chemotherapy alone in patients with advanced squamous NSCLC, addressing a high unmet need
  - The addition of tislelizumab resulted in significantly improved PFS as well as higher ORR and longer DoR than chemotherapy alone
- 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 observed AEs (including grade ≥3) were similar between the three arms
  - Most AEs were mild or moderate in severity and manageable
- Reported TRAEs were consistent with known tolerability profiles of doublet chemotherapy; no new safety signals were identified with the addition of tislelizumab to both chemotherapy backbones
- 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, irrespective of PD-L1 expression

- Adverse events reported as related to tislelizumab occurred in 86.7% and 88.1% of patients in *Arm A* and *Arm B*, respectively; tislelizumab-related grade ≥3 AEs occurred in 36.7% and 40.7% of patients in *Arm A* and *Arm B*, respectively
- Serious TRAEs were reported in 27 patients in *Arm A*, 28 patients in *Arm B*, and 17 patients in *Arm C*
  - Serious TRAEs reported in ≥2 patients in *Arm A* and *B* were decreased neutrophil count (n=4 [*A*]; n=4 [*B*]), febrile neutropenia (n=2 [*A*]; n=3 [*B*]), pneumonitis (n=3 [*A*]; n=2 [*B*]), leukopenia (n=2 [*A*]; n=1 [*B*]), increased blood creatine phosphokinase (n=2 [*B*]), decreased platelet count (n=1 [*A*]; n=2 [*B*]), bone marrow failure (n=2 [*A*]; n=1 [*B*]), and rash and pyrexia (n=2 each [*A*])
  - The most commonly reported serious TRAEs in *Arm C* were thrombocytopenia (n=3) and decreased neutrophil count, decreased white blood cell count, and septic shock (n=2 each)
  - Tislelizumab-related serious AEs (SAEs) occurred in 39 patients (n=21 [*A*]; n=18 [*B*])
  - Chemotherapy-related SAEs occurred in 59 patients (n=18 [*A*]; n=24 [*B*]; n=17 [*C*])
- Treatment-related AEs leading to death were reported in six patients (n=1 [*A*]; n=2 [*B*]; n=3 [*C*]); none were solely attributed to tislelizumab
- Potential immune-mediated AEs occurred in 51.7% (*A*), 47.5% (*B*), and 18.8% (*C*) of patients
  - The 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
  - Most were low grade, did not require corticosteroid treatments, and did not lead to discontinuation of any treatment component
  - The most commonly reported immune-mediated AE was pneumonitis; grade ≥3 pneumonitis occurred in 2.5%, 3.4%, and 0.9% of patients in *Arms A*, *B*, and *C*, respectively (**Figure 3**)

Figure 3: Potential Immune-Mediated Adverse Events Occurring in ≥5% of Patients in Any Arm



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