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A Phase 2 Study of Tislelizumab in Combination With Platinum-Based Chemotherapy as First-line Treatment for Advanced Lung Cancer in Chinese Patients

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ABSTRACT

Objectives: This phase 2 study explored tislelizumab, an anti-PD-1 antibody, in combination with platinum-based chemotherapy as first-line treatment of advanced lung cancer.

Material and Methods: Eligible patients had histologically/cytologically confirmed advanced/metastatic non-squamous non-small cell lung cancer (NSQ), squamous NSCLC (SQ), or extensive-stage small cell lung cancer (SCLC). All patients received tislelizumab 200 mg in combination with 4–6 cycles of platinum-doublet. The NSQ cohort received pemetrexed + platinum Q3W for 4 cycles followed by pemetrexed maintenance, the SQ cohort received paclitaxel + platinum (A) or gemcitabine + platinum (B) Q3W, and the SCLC cohort received etoposide + platinum Q3W. The primary endpoint was investigator-assessed objective response rate (ORR) per RECIST v1.1. Progression-free survival (PFS) and tolerability profile were secondary endpoints; exploratory endpoints included overall survival (OS) and predictive biomarkers.

Results: Fifty-four patients (NSQ, n = 16; SQ = 21 [SQ-A, n = 15; SQ-B, n = 6]; SCLC, n = 17) were enrolled; as of February 25, 2019, 14 remained on treatment. Confirmed ORRs were 44% (NSQ), 80% (SQ-A), 67% (SQ-B), and 77% (SCLC). Median PFS were 9.0 months (NSQ), 7.0 months (SQ-A), and 6.9 months (SCLC); PFS in SQ-B are not mature. Median OS was not reached in all cohorts except for SCLC (15.6 months). Common treatment-emergent AEs included anemia (79.6%, n = 43) and decreased white blood cell count (74.1%, n = 40). Gene expression analyses revealed distinct patterns by histology type; lower tumor inflammation signature levels were observed among nonresponding patients with NSQ and SCLC.

Conclusions: Tislelizumab plus chemotherapy demonstrated encouraging antitumor activity, was generally well tolerated, and distinct immune- and cell cycle–related gene signatures were associated with efficacy across cohorts.

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1. Introduction

Lung cancer is the leading cause of cancer-related death worldwide [1]. Non-small cell lung cancer (NSCLC) accounts for the majority of lung cancers and is categorized into two histology types: nonsquamous (NSQ) and squamous (SQ) [2]. Small cell lung cancer (SCLC) is less prevalent than NSCLC and accounts for approximately 15–20% of all lung cancers [2,3]. Strategies for first-line treatment for advanced-stage lung cancer continue to evolve to address the high mortality rate. The FDA has approved combination therapy consisting of chemotherapy plus antibodies targeting either programmed cell death protein-1 (PD-1) or programmed death-ligand 1 (PD-L1) as first-line treatment for SQ NSCLC, NSQ NSCLC without *EGFR* or *ALK* mutations, as well as extensive-stage SCLC [4,5]. All approved therapies were generally well tolerated and demonstrated improved survivability over standard of care chemotherapy [6–10]. A clearer understanding of the roles that immune checkpoint inhibitors (ICIs) and chemotherapy play during combination therapy will allow for the identification of better treatment guidelines, leading to improved survival in patients with lung cancer.

Chemotherapy reduces immunosuppressive factor release and promotes the release of antigens for presentation by tumors and infiltrating antigen presenting cells, thereby improving T-cell responses and increasing antitumor activity [11–13]. Chemotherapy can also induce high-level expression of PD-L1 on tumor cells [14,15], which has been associated with chemotherapy-resistance in patients with NSCLC receiving neo-adjuvant chemotherapy [15]. Increased T-cell activity in the tumor microenvironment and elevated PD-L1 expression from chemotherapy creates potential synergistic activity between chemotherapy and ICIs, facilitating a therapeutic advantage for combination treatment [11,16,17].

Although ICIs combined with chemotherapy enhance antitumor activity versus chemotherapy alone, roughly one-third of patients fail to respond to combination therapy or have a survival benefit at 1 year, indicating that an exploration of predictive biomarkers could be beneficial [7,8,12,18]. While PD-L1 expression is a commonly used predictive biomarker of response to ICIs, an optimal cut-off has not been determined [7,8,12,18]. Considering the complexity of the tumor immune microenvironment, additional functional biomarkers involved in tumor immunity, such as neo-antigen specific T-cell receptor repertoires, regulating immune cells, and gene expression signatures, should be explored.

Tislelizumab is a monoclonal antibody with high affinity and specificity for PD-1 that was specifically engineered to minimize FcγR binding on macrophages, thereby abrogating antibody-dependent phagocytosis, a potential mechanism of T-cell clearance and resistance to anti-PD-1 therapy [19]. Tislelizumab has shown higher affinity to PD-1 than pembrolizumab and nivolumab with an approximately 100- and 50-fold slower off-rate, respectively [20]. Moreover, tislelizumab has a different binding orientation to PD-1 compared with pembrolizumab and nivolumab. While the binding surface on PD-1 for tislelizumab partially overlaps with that for pembrolizumab, it significantly differs from that for nivolumab [20]. In two early phase studies, single-agent tislelizumab (200 mg) administered intravenously (IV) every 3 weeks (Q3W) was generally well tolerated and showed antitumor activity in both Caucasian and Asian patients [21,22]. This multicenter, open-label, phase 2 study (NCT03432598) conducted in China is the first trial to evaluate the efficacy, safety, tolerability, and potential predictive biomarkers of tislelizumab plus platinum-based chemotherapy as first-line treatment for patients with advanced lung cancer.

2. Material and methods

2.1. Study design and treatment

This phase 2 study included a safety run-in and a dose-expansion stage (Supplemental Fig. A.1). In the safety run-in, 3–6 patients were enrolled in each cohort (minimum follow-up: 21 days) for an initial safety evaluation. Safety/tolerability data for evaluable patients were reviewed by a Safety Monitoring Committee when ≥1 cycle (21 days) was completed. Patients who discontinued before completing one treatment cycle due to reasons unrelated to study treatment were considered not evaluable for the safety assessment. If no unexpected safety events were observed, enrollment was expanded to approximately 15 patients per cohort for dose expansion.

During dose expansion, patients were enrolled concurrently by lung cancer histology type and all treatments were administered IV on Day 1 of each 21-day cycle. All patients received platinum-based chemotherapy of either cisplatin (75 mg/m^2/day) or carboplatin (AUC 5) at the investigator's discretion. Patients with NSQ received pemetrexed (500 mg/m^2) plus cisplatin/carboplatin. Patients with SQ NSCLC enrolled in cohort A (SQ-A) received paclitaxel (175 mg/m^2) plus cisplatin/carboplatin. Patients with SQ NSCLC enrolled in cohort B (SQ-B) received gemcitabine (1250 mg/m^2, Days 1 and 8) plus cisplatin/carboplatin. Patients with SCLC received etoposide (100 mg/m^2, Days 1, 2, and 3) plus cisplatin/carboplatin.

Tislelizumab was administered Q3W until lack of clinical benefit, intolerable toxicity, or withdrawal of consent. Doublet chemotherapy was administered until completion of 4–6 cycles (NSQ: four cycles) or disease progression (assessed by Response Evaluation Criteria in Solid Tumors [RECIST] v1.1), intolerable toxicity, or withdrawal of consent. Maintenance therapy with pemetrexed (500 mg/m^2, Day 1 Q3W) was allowed in patients with NSQ who demonstrated partial response (PR) or stable disease (SD) after four cycles. Guidelines for study treatment dose modifications are outlined in the Supplemental Appendix.

2.2. Eligibility

Adult Chinese patients (aged ≥18 years) with histologically or cytologically confirmed locally advanced or metastatic NSQ NSCLC, SQ NSCLC, or extensive-stage SCLC with measurable disease (defined by RECIST v1.1), an Eastern Cooperative Oncology Group (ECOG) performance score of ≤1, life expectancy of ≥12 weeks, and adequate organ function were eligible for enrollment. Patients with mixed adenosquamous carcinoma were eligible on a case-by-case basis. While all patients were required to have fresh or archival tumor tissue for biomarker assessment, patients with NSQ of unknown *EGFR* and/or *ALK* mutation status were required to provide additional tumor tissue for testing. Prior systemic therapy for advanced or metastatic disease was not allowed. Prior neoadjuvant, adjuvant, or chemoradiation therapy was allowed if completed ≥6 months prior to documentation of disease recurrence. Additional inclusion/exclusion criteria are detailed in the Supplemental Appendix.

2.3. Endpoints and assessments

The primary endpoint was objective response rate (ORR; confirmed complete response [CR] + confirmed PR), as assessed by the investigator per RECIST v1.1. Radiographic imaging by MRI or CT were performed approximately every 6 weeks (± 5 days) during the first 6 months, every 9 weeks (± 5 days) for the remainder of Year 1, and every 12 weeks (± 5 days) thereafter. Secondary efficacy endpoints included disease control rate (DCR; CR + PR + SD), duration of response (DoR), and progression-free survival (PFS). An additional secondary endpoint of incidence and severity of adverse events (AEs) was assessed throughout the study by monitoring AEs—graded according to NCI Common Terminology Criteria for Adverse Events Version 4.03

(CTCAE v4.03)—as well as changes in clinical laboratory values, vital signs, and physical examinations. Overall survival and predictive biomarkers were exploratory endpoints.

2.4. Biomarker expression profiles of tumor tissue samples

For translational research, biomarker analyses were performed on formalin-fixed, paraffin-embedded (FFPE) tumor tissue prior to study treatment. PD-L1 expression was assessed by immunohistochemistry (IHC) with the VENTANA™ PD-L1 (SP263) assay (Ventana Medical Systems, Oro Valley, AZ, USA) at a central laboratory. Samples were categorized by the percentage of PD-L1 membranous staining on tumor cells.

Gene expression analyses used the Precision Immuno-Oncology Panel assay consisting of 1392 genes (HTG Molecular Diagnostics, Inc., Tucson, AZ, USA), per manufacturer's specifications. The library was sequenced on the Illumina Nextseq 500 platform (Illumina, Inc., San Diego, CA, USA), and data were processed by HTG EdgeSeq parser software. Adjustments for batch effects were made using the ComBat method, by R package "sva," and gene expression (log_2CPM, Counts Per Million reads) was further normalized by Quantile normalization. Enrichment scores of immune, cell cycle, and DNA repair–related gene signatures (Supplemental Table A.1) were calculated using the Gene Set Variation Analysis (GSVA) package [23]. Gene expression profile (GEP) results were organized by histology type, response to study treatment, and GSVA scores.

Immune-related gene expression was assessed on FFPE tumor tissue using a multiplex immunofluorescence (mIF) panel (Supplemental Table A.2). Immunofluorescence data were generated using the Opal 7-Color Automation IHC Kit (PerkinElmer, Inc., Waltham, MA, USA) on the BOND Rx platform (Leica Biosystems, Wetzlar, Germany) as described in the Supplemental Appendix.

2.5. Study populations and statistical analyses

Approximately 15 patients per cohort were enrolled for preliminary safety and efficacy assessments. The efficacy-evaluable set included patients receiving ≥1 dose of study treatment with measurable baseline disease. The biomarker analysis set included patients with evaluable tumor tissue samples. The safety analysis set included patients who received any dose of tislelizumab and/or chemotherapy.

Demographics/baseline characteristics, clinical laboratory data, efficacy, safety/tolerability, and AEs were summarized using descriptive statistics. Kaplan-Meier estimates were provided for specific time-to-event variables. The 95% confidence intervals (CIs) for DoR, PFS, and OS were calculated using the Brookmeyer and Crowley method following the censoring rule of the US Food and Drug Administration's Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007). Event-free rates at selected time points were estimated with 95% CIs using the Greenwood formula. For ORR and DCR, 95% CIs were constructed using exact method. Fisher's test analyzed differences between biomarker-evaluable and the overall population. The Mann-Whitney U test evaluated differences in biomarker variables derived from mIF and GEP analyses between two defined groups. Kaplan-Meier curves of PFS by PD-L1 expression subgroup were generated and tested descriptively using a log-rank test.

2.6. Study oversight

This study was performed according to the ethical principles of the International Council for Harmonisation and the Declaration of Helsinki Good Clinical Practice guidelines, or the laws and regulations of China, whichever afforded the greatest protection to the individual. The research protocol, informed consent forms, and relevant supporting information were approved by each site's Institutional Review Board/Independent Ethics Committee prior to study initiation. Informed consent was obtained from all study participants at the time of enrollment.

Table 1
Demographics and Baseline Disease Characteristics of Patients With Advanced Lung Cancer Treated in Combination With Tislelizumab Plus Chemotherapy.

	NSQ (n = 16)	SQ-A (n = 15)	SQ-B (n = 6)	SCLC (n = 17)	Total (N = 54)
Median age, years (range)	64 (36 – 75)	59 (40 – 74)	63 (42 – 72)	60 (36 – 72)	61 (36 – 75)
Age group, n (%)					
< 65	9 (56.3)	12 (80.0)	4 (66.7)	14 (82.4)	39 (72.2)
≥65	7 (43.8)	3 (20.0)	2 (33.3)	3 (17.6)	15 (27.8)
Sex, n (%)					
Male	9 (56.3)	12 (80.0)	6 (100.0)	13 (76.5)	40 (74.1)
Female	7 (43.8)	3 (20.0)	0 (0.0)	4 (23.5)	14 (25.9)
Tobacco use, n (%)					
Never	10 (62.5)	2 (13.3)	0 (0.0)	3 (17.6)	15 (27.8)
Current	0 (0.0)	3 (20.0)	2 (33.3)	3 (17.6)	8 (14.8)
Former	6 (37.5)	10 (66.7)	4 (66.7)	11 (64.7)	31 (57.4)
ECOG status, n (%)					
0	2 (12.5)	4 (26.7)	1 (16.7)	2 (11.8)	9 (16.7)
1	14 (87.5)	11 (73.3)	5 (83.3)	15 (88.2)	45 (83.3)
Solid tumor stage, n (%)					
Stage III	0	6 (40)	0	4 (23.5)	10 (18.5)
Stage IV	16 (100)	9 (60)	6 (100)	13 (76.5)	44 (81.5)
Confirmed metastatic site(s), n (%)					
Lymph node	12 (75.0)	7 (46.7)	4 (66.7)	13 (76.5)	36 (66.7)
Lung	13 (81.3)	5 (33.3)	4 (66.7)	2 (11.8)	24 (44.4)
Bone	6 (37.5)	4 (26.7)	1 (16.7)	5 (29.4)	16 (29.6)
Liver	3 (18.8)	3 (20.0)	0	5 (29.4)	11 (20.4)
Brain	4 (25.0)	0	1 (16.7)	2 (11.8)	7 (13.0)
Abdominal cavity	0	0	0	1 (5.9)	1 (1.9)
Pelvic cavity	0	0	0	1 (5.9)	1 (1.9)
Other	9 (56.3)	3 (20.0)	4 (66.7)	9 (52.9)	25 (46.3)
Any prior systemic therapy, n (%)	15 (93.8)	11 (73.3)	3 (50.0)	12 (70.6)	41 (75.9)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; NSQ, nonsquamous NSCLC; SCLC, small cell lung cancer; SQ-A, squamous NSCLC cohort A (tislelizumab + paclitaxel + cisplatin/carboplatin); SQ-B, squamous NSCLC cohort B (tislelizumab + gemcitabine + cisplatin/carboplatin).

3. Results

3.1. Patient demographics, baseline disease characteristics, and disposition

A total of 54 Chinese patients with locally advanced or metastatic lung cancer (NSQ, n = 16; SQ = 21 [SQ-A, n = 15; SQ-B, n = 6]; SCLC, n = 17) were enrolled. Overall, the median age was 61 years (range: 36 – 75), and more patients were ≥65 years in the NSQ cohort compared with the other cohorts (Table 1). All 16 patients with NSQ were negative for *EGFR* and *ALK* mutations. Most patients had stage IV disease (81.5%, n = 44/54), and 75.9% (n = 41/54) had received prior systemic therapy; confirmed metastatic sites were mainly located in the lymph node (66.7%, n = 36/54), lung (44.4%, n = 24/54), bone (29.6%, n = 16/54), and liver (20.4%, n = 11/54).

As of February 25, 2019, 14 patients remained on treatment. The primary reason for discontinuation (n = 40) was progressive disease (NSQ, n = 7; SQ = 6 [SQ-A, n = 4; SQ-B, n = 2]; SCLC, n = 12), followed by AE (13.0%, n = 7), withdrawal of consent (5.6%, n = 3), investigator decision (1.9%, n = 1), and lost to follow-up (1.9%, n = 1) (Supplemental Fig. A.2). Adverse events leading to tislelizumab discontinuation were pneumonitis (3.7%, n = 2), and dyspnea, increased conjugated bilirubin, decreased platelet count, myocarditis, immune-mediated hepatitis, post-procedural discomfort, and rhabdomyolysis

Table 2
Best Confirmed Overall Response in Patients With Advanced Lung Cancer Treated With Tislelizumab and Doublet Chemotherapy.

Confirmed Responses	NSQ (n = 16)	SQ-A (n = 15)	SQ-B (n = 6)	SCLC (n = 17)
BOR, n (%[a])				
CR	0	0	0	0
PR	7 (44)	12 (80)	4 (67)	13 (77)
SD	8 (50)	2 (13)	1 (17)	2 (12)
PD	1 (6)	0	0	1 (6)
Missing	0	1 (7)	1 (17)	1 (6)
ORR, % (95% CI)	**44 (19.8, 70.1)**	**80 (51.9, 95.7)**	**67 (22.3, 95.7)**	**77 (50.1, 93.2)**
DCR, % (95% CI)	**94 (69.8, 99.8)**	**93 (68.1, 99.8)**	**83 (35.9, 99.6)**	**88 (63.6, 98.5)**
CBR, % (95% CI)	**56 (29.9, 80.2)**	**93 (68.1, 99.8)**	**67 (22.3, 95.7)**	**82 (56.6, 96.2)**
Time to initial response (month), median (range)	**2.76 (1.15, 4.37)**	**1.36 (1.38, 2.76)**	**1.31 (1.38, 1.61)**	**1.38 (1.38, 2.99)**

Abbreviations: BOR, best overall response; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DCR, disease control rate; NSCLC, non-small cell lung cancer; NSQ, nonsquamous NSCLC; ORR, objective response rate; PD, progressive disease; PR, partial response; SCLC, small cell lung cancer; SD, stable disease; SQ-A, squamous NSCLC cohort A (tislelizumab + paclitaxel + cisplatin/carboplatin); SQ-B, squamous NSCLC cohort B (tislelizumab + gemcitabine + cisplatin/carboplatin).

[a] Based on a total of 54 patients.

(1.9%, n = 1 each). Exposure to treatment data are presented in the Supplemental Appendix.

3.2. Antitumor activity of tislelizumab in combination with chemotherapy

3.2.1. Objective response rate

As of June 30, 2019, all 54 patients were included in the efficacy-evaluable set. Of these patients, clinical response to treatment was observed across all cohorts (Table 2). In the NSQ cohort, confirmed ORR was 44% (95% CI: 19.8, 70.1) with a DCR (CR + PR + SD ≥12 weeks) of 94% (95% CI: 69.8, 99.8). In the SQ-A and SQ-B cohorts, confirmed ORRs were 80% (95% CI: 51.9, 95.7) and 67% (95% CI: 22.3, 95.7), respectively, and DCRs were 93% (95% CI: 68.1, 99.8) and 83% (95% CI: 35.9, 99.6), respectively. In the SCLC cohort, the confirmed ORR was 77% (95% CI: 50.1, 93.2) with a DCR of 88% (95% CI: 63.6, 98.5). In the NSQ cohort, the clinical benefit rate (CBR; CR + PR + SD ≥24 weeks) was 56% (95% CI: 29.9, 80.2). In the SQ-A and SQ-B cohorts, the CBRs were 93% (95% CI: 68.1, 99.8) and 67% (95% CI: 22.3, 95.7), respectively, and in the SCLC cohort the CBR was 82% (95% CI: 56.6, 96.2). The median time to initial response was 2.76 months for the NSQ cohort, 1.36 months for the SQ-A cohort, 1.31 months for the SQ-B cohort, and 1.38 months for the SCLC cohort.

3.2.2. Progression-free and overall survival

As of June 30, 2019, the median survival follow-up ranged from 15.3 months (95% CI: 12.52, 16.92) for patients with SCLC to 18.3 months (95% CI: 16.23, 19.48) for those with SQ-A (Table 3). Median PFS for the NSQ cohort was 9.0 months (95% CI: 4.27, not evaluable [NE]) and the proportion of patients with PFS at 18 months was 32% (95% CI: 10, 57). Median PFS for the SQ-A cohort was 7.0 months (95% CI: 5.52, NE), but PFS was not mature for SQ-B, with two non-censored events (95% CI: 4.27, NE). The proportion of patients with PFS at 18 months was 30% (95% CI: 8, 55) and 50% (95% CI: 6, 84) for the SQ-A and SQ-B cohorts, respectively. Median PFS for SCLC was 6.9 months (95% CI: 4.9, 10.09), and the proportion of patients with PFS at 18 months was not reached. Despite a long follow-up, OS rates remain immature for all cohorts except SCLC (Table 3).

3.3. PD-L1 expression on tumor cells and association with response to tislelizumab plus doublet chemotherapy

Across the study, 47 of 54 patients had evaluable levels of PD-L1 expression on tumor cells; more than half of evaluable patients (55.3%, n = 26/47), including 24 patients with NSCLC and two patients with SCLC, had ≥1% of PD-L1 membranous staining on tumor cells (Supplemental Table A.4). When evaluating the relationship between PD-L1 expression and tumor response, increasing levels of PD-L1 expression correlated with increased ORR in the NSQ cohort (Supplemental Fig. A.3); however, this trend was not observed in either the SQ (A + B) or SCLC cohort, suggesting PD-L1 expression on tumor cells may correlate with the efficacy of tislelizumab plus chemotherapy in patients with NSQ, but not SQ or SCLC. The trend in the NSQ cohort was further confirmed by survival data showing longer median PFS in patients with higher PD-L1 expression. Although not statistically significant, this trend was not seen in the SQ or SCLC cohorts (Supplemental Fig. A.4).

Table 3
Progression-Free and Overall Survival.

	NSQ (n = 16)	SQ-A (n = 15)	SQ-B (n = 6)	SCLC (n = 17)
Survival follow-up time (months), median (95% CI)	17.4 (16.07, 18.10)	18.3 (16.23, 19.48)	18.1 (0.33, 19.45)	15.3 (12.52, 16.92)
Progression-free survival (months), median (95% CI)	9.0 (4.27, NE)	7.0 (5.52, NE)	NE (4.27, NE)	6.9 (4.90, 10.09)
Event-free rate at				
6 months, % (95% CI)	57 (27, 78)	71 (40, 88)	75 (13, 96)	63 (36, 82)
12 months, % (95% CI)	41 (15, 65)	39 (15, 64)	50 (6, 84)	25 (8, 48)
18 months, % (95% CI)	32 (10, 57)	30 (8, 55)	50 (6, 84)	NE (NE, NE)
Overall survival (months), median (95% CI)	NE (13.31, NE)	NE (15.44, NE)	NE (8.25, NE)	15.6 (11.79, NE)
Survival rate at				
6 months, % (95% CI)	100 (NE, NE)	93 (61, 99)	100 (NE, NE)	100 (NE, NE)
12 months, % (95% CI)	88 (59, 97)	93 (61, 99)	80 (20, 97)	76 (47, 90)
18 months, % (95% CI)	74 (45, 89)	72 (41, 88)	80 (20, 97)	NE (NE, NE)

Abbreviations: CI, confidence interval; NE, not evaluable; NSCLC, non-small cell lung cancer; NSQ, nonsquamous NSCLC; PFS, progression-free survival; SCLC, small cell lung cancer; SQ-A, squamous NSCLC cohort A (tislelizumab + paclitaxel + cisplatin/carboplatin); SQ-B, squamous NSCLC cohort B (tislelizumab + gemcitabine + cisplatin/carboplatin).

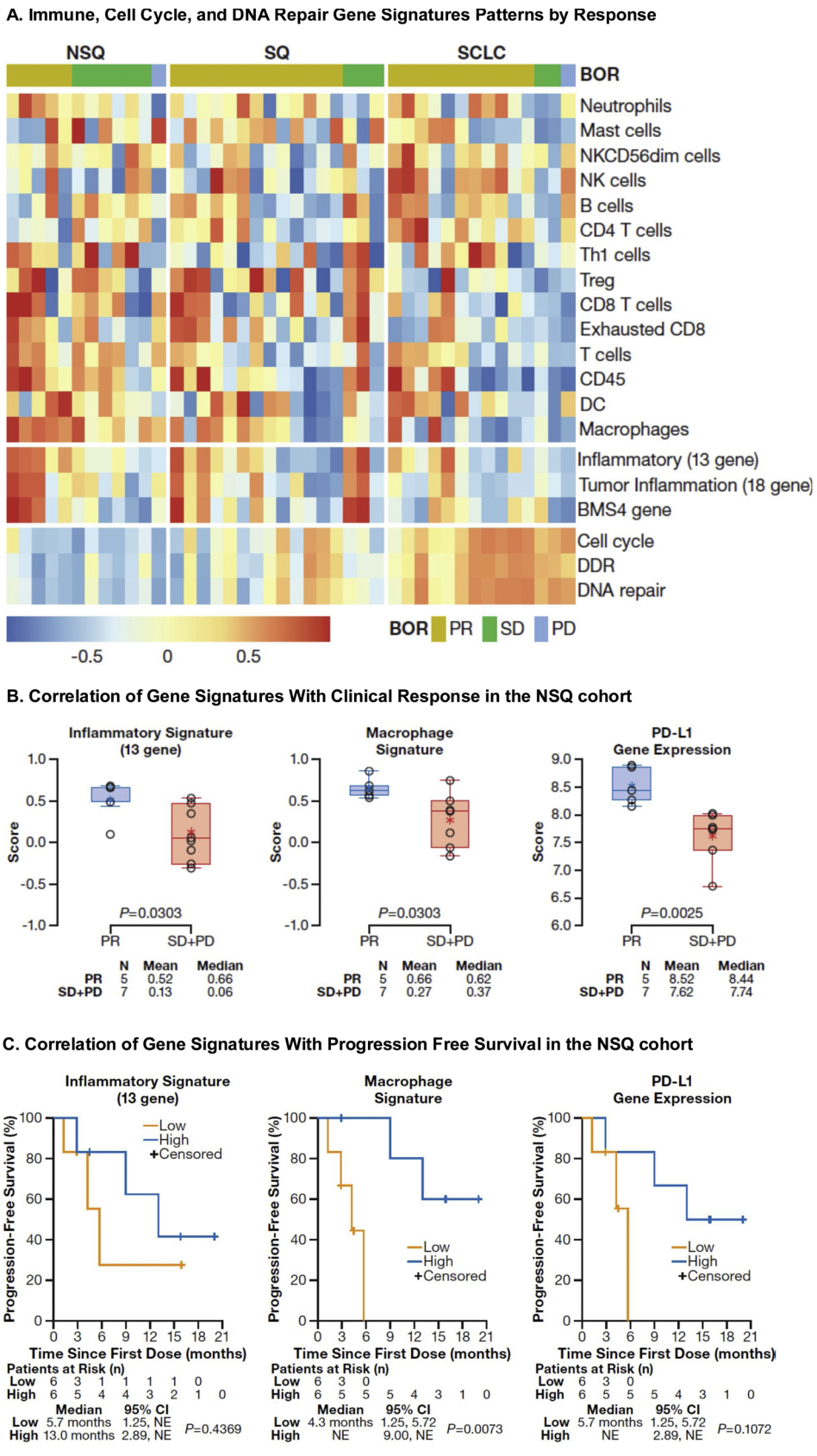

Fig. 1. Immune, Cell Cycle, and DNA Repair Signatures of Patient Tumor Tissue Samples Organized by Response to Tislelizumab and Chemotherapy.
A. Immune, Cell Cycle, and DNA Repair Gene Signatures Patterns by Response
B. Correlation of Gene Signatures With Clinical Response in the NSQ cohort
C. Correlation of Gene Signatures With Progression-Free Survival in the NSQ cohort
Abbreviations: BOR, best overall response; CI, confidence interval; KM, Kaplan-Meier; NE, not evaluable; NK, natural killer; NSCLC, non-small cell lung cancer; NSQ, nonsquamous NSCLC; PD, progressive disease; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; PR, partial response; SCLC, small cell lung cancer; SD, stable disease; SQ, squamous. The median within the box plots is indicated by a horizontal line.

3.4. Distinct gene expression profiles by histology type and clinical efficacy

To better identify the effect of immune-related gene expression on the antitumor activity of tislelizumab in combination with chemotherapy, gene expression analysis was performed on patient tumor tissue samples. Gene expression levels were analyzed in 42 of the 54 total patients (NSQ, n = 12; SQ, n = 16; SCLC, n = 14). No significant differences in primary disease histology, demographic

variables, or clinical benefit were detected in the gene expression–evaluable population versus the overall population (Supplemental Table A.5). Based on the GSVA enrichment scores of immune, cell cycle, and DNA repair–related gene signatures (Supplemental Table A.1), distinct gene expression patterns were observed among the NSQ, SQ, and SCLC cohorts (Fig. 1**A** and Supplemental Fig. A.5). The NSQ cohort expressed relatively low levels of cell cycle and DNA repair gene expression signatures, regardless of response to treatment; however, immune signature scores varied by patient and response. Responders in the NSQ cohort had relatively high inflammatory and tumor inflammation gene signature scores compared with non-responders. This was especially true in the 13-gene inflammatory (Fig. 1B, left panel), macrophage (Fig. 1B, center panel), 18-gene tumor inflammation, and BMS 4-gene signature scores (Supplemental Fig. A.6). The trend was further confirmed by survival data showing numerically longer median PFS in the signature-high versus -low groups (Fig. 1C, left and center panel). Consistent with PD-L1 IHC results, higher PD-L1 mRNA levels were observed in patients with NSQ who had objective responses and numerically longer PFS (Fig. 1B and 1C, right panel).

Patients with SQ NSCLC had heterogeneous expression patterns of cell cycle, DNA repair, and immune-related gene signatures. All three non-responders from the SQ cohort had relatively low cell cycle signatures. Two of these non-responders also had high inflammatory/tumor inflammation gene signature scores and high PD-L1 expression levels (40% and 90%). Unlike the NSQ and SQ cohorts, the SCLC cohort was characterized with high cell cycle and DNA repair signatures and relatively lower immune-related signatures, such as CD45 cell, CD8 T cell, T cell, macrophage, mast cell, and inflammatory signature (13 gene) (Fig. 1A and Supplemental Fig. A.5). All three non-responders in the SCLC cohort had a relatively low immune cell expression signature for both the innate and adaptive immune system (indicating an immune-cold phenotype [24]) compared with the responders.

3.5. PD-L1 + macrophage density as a potential biomarker predictive of study treatment

The immune context and the quantity and phenotype of key immune cells were assessed in the mIF-evaluable population (n = 28/54; NSQ, n = 10; SQ, n = 14; SCLC, n = 4) to further elucidate tumor immune microenvironment and its correlation with clinical efficacy. No significant differences in histology, demographic variables, or clinical benefit were observed between the mIF-evaluable population and the overall population (Supplemental Table A.5). The CD68+ macrophage density was numerically greater in patients with PR versus SD, though the statistical difference was not reached. However, no significant differences in CD8 + T-cell density or CD8+/CD68+ ratio were observed in patients who achieved PR versus patients who had SD (Supplemental Fig. A.7). Furthermore, a trend toward higher PD-L1+ macrophage (PD-L1+CD68+) density was observed in the PR group versus the SD group (Fig. 2A-B). For example, a patient in the PR group had immune infiltration in the tumor microenvironment, with CD8 + T cells and CD68+ macrophages present and PD-L1 highly expressed on macrophages and tumor cells (Fig. 2B, upper panels). In contrast, a patient from the SD group also had tumor infiltration of CD8 + T cells and CD68+ macrophages, but low PD-L1 expression on macrophages (Fig. 2B, lower panels).

To correlate the PD-L1+ macrophage with immune microenvironment index, differences in immune mRNA expression signature scores between PD-L1+CD68+ macrophage high- and low-density groups were assessed. As shown in Fig. 2C, higher exhausted CD8 T-cell scores but not regular CD8 + T-cell scores were observed in the PD-L1+CD68+ high-density group than in the low-density group, suggesting that CD8 + T cells tend to be exhausted in tumor microenvironments in the patients with more PD-L1 expressing macrophages. Moreover, higher inflammatory gene signature scores [25] were observed in the PD-L1+CD68+ high-density group versus the low-density group, indicating a relatively hot tumor immune microenvironment [24].

3.6. Safety and tolerability profile

As of February 25, 2019, all 54 patients (100%) experienced at least one treatment-emergent AE (TEAE) related to any study drug (Supplemental Table A.6); the most common TEAEs related to any study drug were anemia (79.6%, n = 43), decreased white blood cell count (74.1%, n = 40), and decreased neutrophil count (72.2%, n = 39) (Table 4). A total of 46 patients (85.2%) had AEs that were considered by the investigators to be related to tislelizumab (Supplemental Table A.6). The most commonly reported tislelizumab-related AEs were asthenia (18.5%, n = 10) and hypothyroidism (13.0%, n = 7) (Supplemental Table A.7). Forty-three (79.6%) patients had grade ≥3 TEAEs related to any study drug (Supplemental Table A.6). The most commonly reported grade ≥3 TEAEs related to any study drug were decreased neutrophil count (48.1%, n = 26) and anemia (18.5%, n = 10) (Table 4). The most common TEAEs leading to dose modifications were anemia (chemotherapy, 29.6%, n = 16; tislelizumab, 35.2%, n = 19) and decreased neutrophil count (chemotherapy, 22.2%, n = 12; tislelizumab, 16.7%, n = 9) (Supplemental Table A.8).

A total of 14 patients (25.9%) experienced at least one serious AE; anemia, thrombocytopenia, pneumonitis, and decreased platelet counts (3.7%, n = 2 each) were the most commonly reported. Serious AEs reported to be related to tislelizumab occurred in six patients (11.1%) (Supplemental Table A.6) and included pneumonitis (3.7%; n = 2), and dyspnea, immune-mediated pneumonitis, abnormal hepatic function, myocarditis, stomatitis, and rhabdomyolysis (1.9%, n = 1 each). A total of 14 patients (25.9%) experienced at least one immune-related AE (irAE), including thyroid disorders (16.7%; n = 9) and immune-mediated pneumonitis (7.4%; n = 4). Two patients experienced grade ≥3 irAEs (immune-mediated hepatitis [3.7%; n = 2] and immune-mediated myositis/rhabdomyolysis/cardiomyopathy [1.9%; n = 1]) (Supplemental Table A.9). One patient (1.9%) with SQ NSCLC experienced dyspnea, myocarditis, and rhabdomyolysis with a fatal outcome after one cycle of tislelizumab in combination with paclitaxel + cisplatin.

4. Discussion

Tislelizumab plus platinum-based chemotherapy was generally well tolerated in patients with advanced lung cancers. Adverse events experienced with combination therapy were manageable; treatment discontinuations to AEs were low. Moreover, the AEs reported were consistent with the known tolerability profile of PD-1 inhibitors in combination with chemotherapy [8,26,27].

Tislelizumab plus chemotherapy demonstrated encouraging antitumor activity in patients with advanced lung cancer, with notable response rates ranging from 44% (NSQ) to 80% (SQ-A). Further examination may be needed to provide a more definitive explanation of the differences in median time to initial response between patients with NSQ NSCLC (2.76 months) and SQ NSCLC (1.31 months [SQ-A] and 1.36 months [SQ-B]) observed in the current study. While the median time to initial response of the two SQ NSCLC cohorts was similar to a study of first-line pembrolizumab plus chemotherapy (1.4 months) [7], further investigation may be needed to determine if the role of clinical characteristics such as smoking history, comorbidities, age, or tumor microenvironment impact differences between patients with SQ NSCLC, NSQ NSCLC, and SCLC. Despite median follow-up ranging from 15.3–18.3 months, median OS was not reached in all cohorts except SCLC. Across most cohorts, the PFS and OS rates at 18 months were more than 30% and 70%, respectively. In terms of SCLC, the DCR and median OS of tislelizumab plus doublet chemotherapy were numerically superior compared with previous studies [6,28], although direct

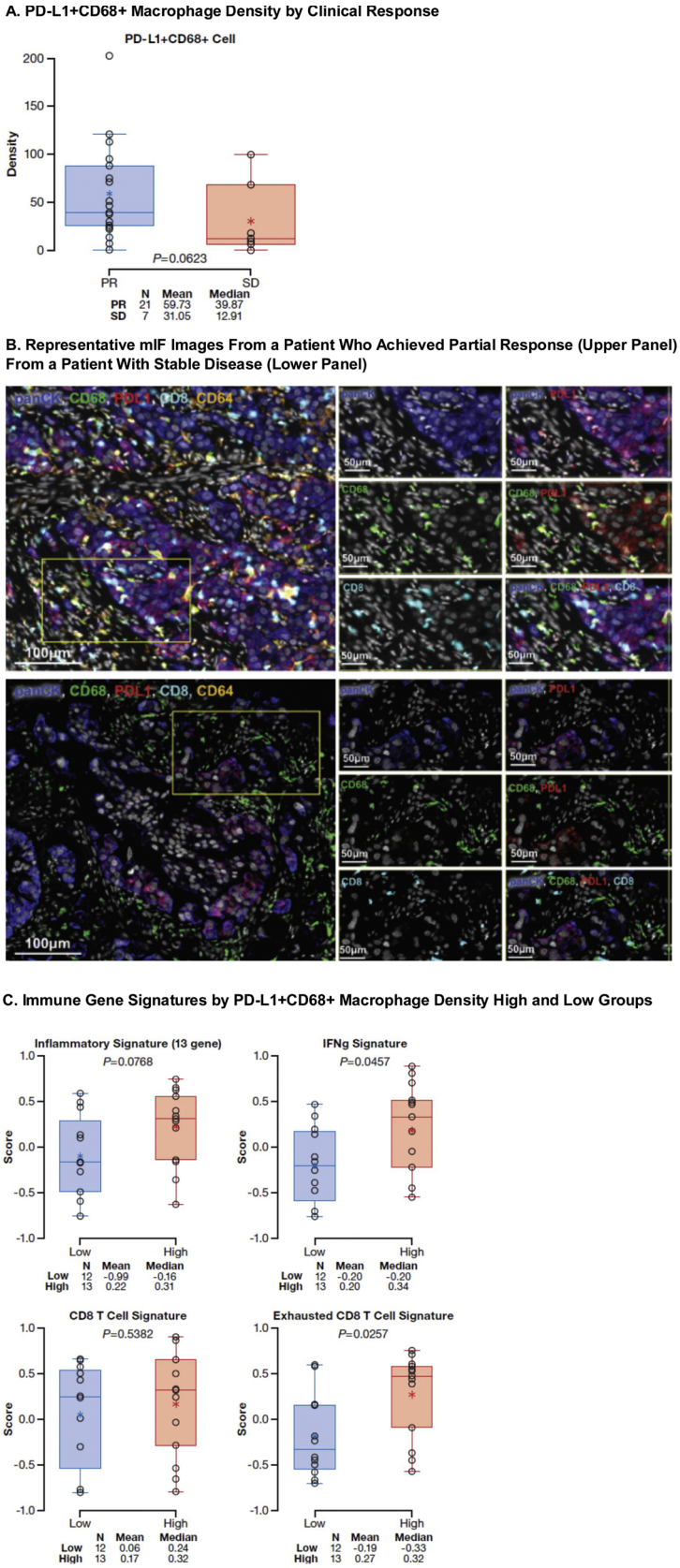

Fig. 2. Immune-related Gene Expression in Tumor Microenvironments.
A. PD-L1 + CD68 + Macrophage Density by Clinical Response
B. Representative mIF Images From a Patient Who Achieved Partial Response (Upper Panel) and From a Patient With Stable Disease (Lower Panel)
C. Immune Gene Signatures by PD-L1 + CD68 + Macrophage Density High and Low Groups
Abbreviations: mIF, multiplex immunofluorescence; PD-L1, programmed cell death ligand-1; PR, partial response; SD, stable disease. The median within the box plots is indicated by a horizontal line.

Table 4
Incidence of Treatment-Emergent Adverse Events Related to Any Study Drug Occurring in > 10% of Patients With Advanced Lung Cancer (N = 54).

	NSQ (n = 16)		SQ-A (n = 15)		SQ-B (n = 6)		SCLC (n = 17)		Total (N = 54)	
Patients with ≥1 AE	**Any Grade 16 (100.0)**	**Grade ≥3 11 (68.8)**	**Any Grade 15 (100.0)**	**Grade ≥3 13 (86.7)**	**Any Grade 6 (100.0)**	**Grade ≥3 2 (33.3)**	**Any Grade 17 (100.0)**	**Grade ≥3 13 (76.5)**	**Any Grade 54 (100.0)**	**Grade ≥3 39 (72.2)**
Anemia	13 (81.3)	2 (12.5)	10 (66.7)	2 (13.3)	5 (83.3)	1 (16.7)	15 (88.2)	5 (29.4)	43 (79.6)	10 (18.5)
Decreased WBC count	11 (68.8)	4 (25.0)	13 (86.7)	2 (13.3)	3 (50.0)	0	13 (76.5)	1 (5.9)	40 (74.1)	7 (13.0)
Decreased neutrophil count	11 (68.8)	6 (37.5)	12 (80.0)	11 (73.3)	3 (50.0)	1 (16.7)	13 (76.5)	8 (47.1)	39 (72.2)	26 (48.1)
Decreased platelet count	7 (43.8)	2 (12.5)	5 (33.3)	0	3 (50.0)	1 (16.7)	8 (47.1)	4 (23.5)	23 (42.6)	7 (13.0)
Increased ALT	7 (43.8)	1 (6.3)	4 (26.7)	2 (13.3)	2 (33.3)	0	7 (41.2)	0	20 (37.0)	3 (5.6)
Increased AST	7 (43.8)	0	6 (40.0)	1 (6.7)	2 (33.3)	0	5 (29.4)	0	20 (37.0)	1 (1.9)
Asthenia	8 (50.0)	1 (6.3)	7 (46.7)	0	2 (33.3)	0	2 (11.8)	0	19 (35.2)	1 (1.9)
Decreased appetite	6 (37.5)	0	4 (26.7)	0	2 (33.3)	0	7 (41.2)	0	19 (35.2)	0
Nausea	3 (18.8)	0	6 (40.0)	0	2 (33.3)	0	7 (41.2)	1 (5.9)	18 (33.3)	1 (1.9)
Rash	1 (6.3)	0	3 (20.0)	0	1 (16.7)	0	2 (11.8)	0	17 (13.3)	0
Vomiting	2 (12.5)	0	2 (13.3)	0	1 (16.7)	0	9 (52.9)	1 (5.9)	14 (25.9)	1 (1.9)
Thrombocytopenia	3 (18.8)	0	3 (20.0)	1 (6.7)	0	0	7 (41.2)	5 (29.4)	13 (24.1)	6 (11.1)
Alopecia	1 (6.3)	0	7 (46.7)	0	0	0	5 (29.4)	0	13 (24.1)	0
Leukopenia	2 (12.5)	0	0	0	0	0	6 (35.3)	0	8 (14.8)	0
Neutropenia	3 (18.8)	1 (6.3)	0	0	0	0	5 (29.4)	3 (17.6)	8 (14.8)	4 (7.4)

Data presented as n (%). Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NSCLC, non-small cell lung cancer; NSQ, nonsquamous NSCLC; SCLC, small cell lung cancer; SQ-A, squamous NSCLC cohort A (tislelizumab + paclitaxel + cisplatin/carboplatin); SQ-B, squamous NSCLC cohort B (tislelizumab + gemcitabine + cisplatin/carboplatin); WBC, white blood cell.

comparisons and a larger sample size cohort are needed for confirmation of these results. These promising results strongly support further development of tislelizumab plus platinum-based chemotherapy in phase 3 studies for patients with advanced lung cancer.

The combination of anti-PD-1/L1 and chemotherapy has remarkably improved the efficacy of first-line treatment for patients with advanced lung cancer [8,26,27,29]. However, factors associated with the efficacy of these treatments have not been fully addressed. In our study, improved ORR was observed in patients with high PD-L1 expressing NSQ NSCLC compared to low PD-L1 expressing NSQ NSCLC. Expression results were confirmed by both protein localization via IHC analysis and increased gene expression levels by RNA sequencing. These results, in combination with results from previous studies [8], suggest a potential predictive value of PD-L1 expression for clinical response to ICIs plus chemotherapy in patients with NSQ NSCLC.

Distinct immune and cell cycle–related gene signatures were observed in the NSQ, SQ, and SCLC cohorts, as previously described [30–34]. In the NSQ cohort, responders had high immune-related signature scores but consistently low cell cycle scores, suggesting that ICIs might play a more important role in clinical response than previously realized, and that immune-related biomarkers should be tested for patient selection in clinical practice. Contrary to what was observed in patients with NSQ NSCLC, most patients with SCLC had “cold” immune-related signature scores, which suggests patients with SCLC may benefit from ICI in combination with chemotherapy compared with ICIs alone. In the future, a stricter criterion may be helpful for using ICI-based treatment for patients with SCLC. Unlike NSQ NSCLC and SCLC, patients with SQ NSCLC seemed to have more heterogeneous gene expression, with multiple patterns when stratified by different gene signature scores and clinical responses. This observation suggests that subset classification could be performed to identify patients with SQ NSCLC who are more likely to respond to ICI alone or ICI plus chemotherapy. To our knowledge, our study is the first to assess the predictive value of various gene signatures in lung tumors relative to response to ICIs and chemotherapy.

Density of PD-L1 + macrophages could represent a potential biomarker associated with response to ICIs, as PD-L1 + tumor–associated macrophages can promote tumor growth through multiple direct pathways [35]. One proposed direct mechanism involves expression of immune checkpoint proteins on the cell surface of macrophages to inhibit PD-1 + CD8 + T-cell function [35]. In our study, PD-L1-expressing macrophage density was correlated with response to tislelizumab plus chemotherapy, consistent with previous ICI monotherapy reports in NSCLC, melanoma, and ovarian cancer, where PDL1 expression levels on macrophages were correlated with clinical efficacy of anti-PD-1/L1 therapies [36–38]. Furthermore, in our study, CD8 + T cells tended to be exhausted in patients with more PD-L1-expressing macrophages in tumor microenvironments. Also, higher IFNγ and inflammatory gene signature scores were observed in the PD-L1 + CD68 + high-density group versus the low-density group. These results indicate that patients with PD-L1 + CD68 + high cell density represented a relatively “hot” tumor immune microenvironment, and PD-L1 + CD68 + cell density might be a novel, potentially functional biomarker for ICI plus chemotherapy treatment.

Limited by the small size and mixed histology, as well as the single-arm design, data from this study will need to be confirmed with further investigations with an enlarged and specific patient cohort. While the homogenous population of Chinese patients could be seen as a potential limitation to the generalizability of these data, subgroup analyses of tislelizumab monotherapy from 49 patients with advanced NSCLC enrolled in the indication-expansion arm of the first-in-human study demonstrated consistent clinical activity across Asian (n = 21) and non-Asian (n = 28) patients [39].

In summary, the safety/tolerability profile and antitumor activity from the current study support continued development of tislelizumab in combination with chemotherapy in patients with advanced lung cancer. Three phase 3 studies have been initiated to evaluate tislelizumab in combination with chemotherapy as first-line treatment in advanced lung cancers of diverse histology types (NCT03594747, NCT03663205, NCT04005716). Moreover, biomarker analyses of these three trials will be performed to further validate the potential predictive biomarkers for tislelizumab and chemotherapy treatment.

4.1. Conclusions

Addition of tislelizumab to chemotherapy was generally well tolerated and demonstrated durable antitumor activity in Chinese patients with advanced lung cancer. Furthermore, distinct gene expression signatures were observed in various patient response subgroups. These differential expression patterns are critically important in the era of personalized medicine, as they suggest that potential predictive biomarkers may differ between various subtypes of advanced lung cancer.

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The study protocol was developed by BeiGene, Ltd. in collaboration with the study investigators. BeiGene, Ltd. was also involved in data collection, analysis, and interpretation of results. Statistical analyses were performed by statisticians at BeiGene, Ltd.

All authors were in agreement regarding the submission of this manuscript and vouch for the completeness and accuracy of the data. Professional medical writers, funded by BeiGene, Ltd., assisted with the development and submission of this manuscript under the authors' guidance. The corresponding author had full access to all of the study data and was responsible for the decision to submit the manuscript for publication.

Data sharing statement

Upon request, and subject to certain criteria, conditions, and exceptions, BeiGene will provide access to individual de-identified participant data from BeiGene-sponsored global interventional clinical studies conducted for medicines (1) for indications that have been approved or (2) in programs that have been terminated. BeiGene will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data requests may be submitted to medicalinformation@beigene.com.

CRediT authorship contribution statement

Zhijie Wang: Conceptualization, Formal analysis, Supervision, Investigation, Writing - original draft, Project administration, Writing - review & editing. **Jun Zhao:** Conceptualization, Supervision, Investigation, Writing - review & editing. **Zhiyong Ma:** Conceptualization, Supervision, Investigation, Writing - review & editing. **Jiuwei Cui:** Conceptualization, Supervision, Investigation, Writing - review & editing. **Yongqian Shu:** Conceptualization, Supervision, Investigation, Writing - review & editing. **Zhe Liu:** Conceptualization, Supervision, Investigation, Writing - review & editing. **Ying Cheng:** Conceptualization, Supervision, Investigation, Writing - review & editing. **Shiang J. Leaw:** Conceptualization, Supervision, Funding acquisition, Validation, Investigation, Methodology, Writing - original draft, Project administration, Writing - review & editing. **Yanjie Wu:** Data curation, Validation, Investigation, Visualization, Writing - original draft, Project administration, Writing - review & editing. **Yan Ma:** Data curation, Software, Formal analysis, Validation, Visualization, Methodology, Writing - review & editing. **Wei Tan:** Data curation, Formal analysis, Validation, Investigation, Visualization, Methodology, Writing - original draft, Writing - review & editing. **Xiaopeng Ma:** Data curation, Software, Formal analysis, Validation, Visualization, Methodology, Writing - review & editing. **Yun Zhang:** Conceptualization, Formal analysis, Supervision, Funding acquisition, Validation, Investigation, Writing - original draft, Project administration, Writing - review & editing. **Jie Wang:** Conceptualization, Supervision, Funding acquisition, Investigation, Methodology, Writing - original draft, Project administration, Writing - review & editing.

Declaration of Competing Interest

Shiang J. Leaw, Yanjie Wu, Yan Ma, Wei Tan, Xiaopeng Ma, and Yun Zhang are employees of BeiGene (Beijing) Co., Ltd. Zhijie Wang, Jun Zhao, Zhiyong Ma, Jiuwei Cui, Yongqian Shu, Zhe Liu, Ying Cheng, and Jie Wang have no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2020.06.007.

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