TISLELIZUMAB COMBINED WITH CHEMOTHERAPY AS FIRST-LINE TREATMENT IN CHINESE PATIENTS WITH ADVANCED LUNG CANCER

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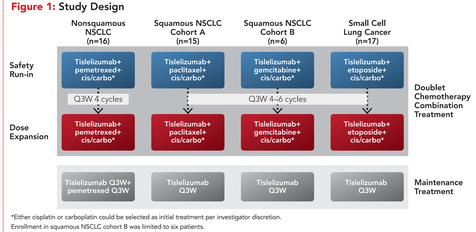
BACKGROUND

- Non-small cell lung cancer (NSCLC) accounts for 80–85%[1] and small cell lung cancer (SCLC) for approximately 15% of all lung cancers.[2] In China, lung cancer is the second most prevalent cancer among men and fourth among women[1]
- For patients with NSCLC and SCLC, first-line therapy includes platinum-doublet chemotherapy (eg, vinorelbine, gemcitabine, docetaxel, or paclitaxel plus platinum)[3]
- Chemotherapy has been shown to induce PD-L1 expression on tumor cells[4]
- Recent studies of immune checkpoint inhibitors have shown efficacy in patients with advanced NSCLC[5–7] as well as in patients with SCLC[8] as monotherapy and in combination with chemotherapy[9–12]
- Tislelizumab is a humanized IgG4 monoclonal antibody (mAb) with high affinity and specificity for PD-1 that was specifically engineered to minimize $Fc\gamma R$ binding on macrophages, thereby abrogating antibody-dependent phagocytosis, a potential mechanism of T-cell clearance and resistance to anti-PD-1 therapy[13]
- In a first-in-human, phase 1A/1B study (NCT02407990), single-agent tislelizumab was generally well tolerated and demonstrated evidence of antitumor activity in patients with solid tumors, including NSCLC[14]
  - A recommended dose of 200 mg administered intravenously (IV) every 3 weeks (Q3W) was identified for tislelizumab
- This phase 2 study (NCT03432598) with safety run-in and dose-expansion phases was designed to assess the preliminary efficacy and safety/tolerability of tislelizumab in combination with platinum-based chemotherapy as first-line treatment for Chinese patients with lung cancer

METHODS

- The overall design of the study is detailed in Figure 1
  - In the safety run-in stage, 3–6 evaluable patients were enrolled in each cohort and followed up for ≥21 days
  - Safety data were reviewed by a Safety Monitoring Committee (SMC) after the first 3–6 patients in each cohort completed at least one cycle (21 days) of treatment; no unexpected safety signals were observed and enrollment was expanded up to approximately 15 patients per cohort
- Patients were enrolled into one of four cohorts according to the histology of their primary disease and received tislelizumab 200 mg Q3W in combination with either of the following chemotherapies whereby the choice of platinum therapy was at the investigator's discretion:
  - Nonsquamous NSCLC (NSQ): pemetrexed (500 mg/m²)+cisplatin (75 mg/m²) or carboplatin (AUC 5) Q3W
  - Squamous NSCLC cohort A (SQ-A): paclitaxel (175 mg/m²)+cisplatin (75 mg/m²) or carboplatin (AUC 5) Q3W
  - Squamous NSCLC cohort B (SQ-B): gemcitabine (1250 mg/m²)+cisplatin (75 mg/m²) or carboplatin (AUC 5) Q3W
  - SCLC: etoposide (100 mg/m²)+cisplatin (75 mg/m²) or carboplatin (AUC 5) Q3W
- For all cohorts, tislelizumab was continually administered Q3W until the patient no longer benefitted from therapy, experienced intolerable toxicity, or withdrew consent; doublet chemotherapy was given until either completion of 4–6 cycles (4 cycles for the NSQ cohort) or occurrence of disease progression, assessed by RECIST 1.1, intolerable toxicity, or withdrawal of consent
- Tumor assessment by radiographic imaging was performed approximately every 6 weeks during the first 12 months and every 12 weeks thereafter; tumor response was assessed by the investigator based on RECIST v1.1 criteria
- Safety and tolerability were assessed throughout the study by monitoring adverse events (AEs), which were graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE v4.03), as well as by assessing changes in clinical laboratory values, vital signs, and physical examinations
- Pretreatment tumor samples were evaluated for PD-L1 membrane expression on tumor cells (TCs) by immunohistochemistry performed on an automated platform

Figure 1: Study Design



*Either cisplatin or carboplatin could be selected as initial treatment per investigator discretion.
Enrollment in squamous NSCLC cohort B was limited to six patients.
Abbreviations: Cis, cisplatin; Carbo, carboplatin; NSCLC, non-small cell lung cancer; Q3W, every 3 weeks.

Lung Cancer Study Population

- Adult Chinese patients (aged ≥18 years) with histologically or cytologically confirmed locally advanced or metastatic nonsquamous NSCLC, squamous NSCLC, or extensive-stage SCLC were eligible to enroll
  - Patients with nonsquamous NSCLC of unknown *EGFR* and/or *ALK* mutation status were required to provide tumor tissue for testing
- Patients must have had no prior systemic therapy for advanced or metastatic disease
  - Prior neoadjuvant/adjuvant therapy or chemo-radiation therapy with curative intent was allowed but needed to have been completed at least 6 months prior to documentation of recurrence of disease
- Patients were excluded if they had a sensitizing mutation in the *EGFR* gene or an *ALK* fusion oncogene; prior active malignancies within 2 years of study entry or locally recurring cancers that have undergone curative treatment; ≥30Gy of radiation for the lungs within 6 months of the first administration of study treatment; or a history of interstitial lung disease or non-infectious pneumonitis, except for those induced by radiation therapies

Phase 2 Study Assessments

- Objective response rate (ORR), assessed by investigator per RECIST v1.1, was the primary endpoint
  - Disease control rate (DCR), clinical benefit rate (CBR), progression-free survival (PFS), overall survival (OS), and duration of response (DoR) were secondary endpoints
  - PFS, DoR, and OS results were not mature at data cut-off to be included in this presentation
- Evaluation of the safety/tolerability profile of tislelizumab in combination with platinum-doublet chemotherapy was a secondary objective

RESULTS

Patient Disposition

- As of 5 June, 2018, 54 patients with lung cancer (NSQ, n=16; SQ-A, n=15; SQ-B, n=6; SCLC, n=17) had been enrolled in the study (Table 1)
  - A total of 35 remained on treatment; 19 discontinued treatment (AE [n=3], disease progression [n=9], and other [n=7])
- The majority of patients were male (n=40; 74.1%) and former/current smokers (n=39; 72.2%)
- As of data cut-off, the majority of patients had received ≥4 cycles of study treatment; on average, patients from the two squamous NSCLC cohorts were exposed to more cycles of study treatment

Table 1: Patient Demographics and Disease Characteristics in Advanced Lung Cancer

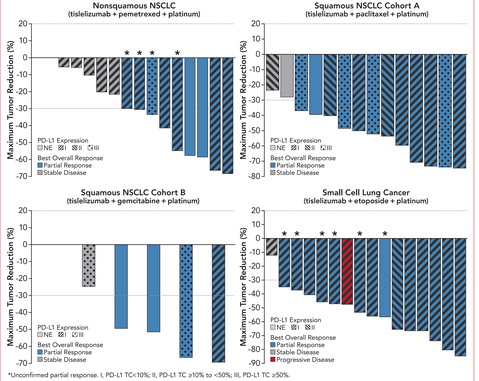
		NSQ Tislelizumab + pemetrexed + P (n=16)	SQ-A Tislelizumab + paclitaxel + P (n=15)	SQ-B Tislelizumab + gemcitabine + P (n=6)	SCLC Tislelizumab + etoposide + P (n=17)	Total (N=54)
Median age, years		63.5	59.0	63.0	60.0	61.0
Sex, n (%)	Female	7 (43.8)	3 (20.0)	0	4 (23.5)	14 (25.9)
	Male	9 (56.3)	12 (80.0)	6 (100.0)	13 (76.5)	40 (74.1)
Tobacco use, n (%)	Never	10 (62.5)	2 (13.3)	0	3 (17.6)	15 (27.8)
	Current	0	13 (76.5)	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)
PD-L1 in TC, n (%)	<10%	9 (56.3)	5 (33.3)	1 (16.7)	15 (88.2)	30 (55.6)
	≥10% to <25%	1 (6.3)	2 (13.3)	0	1 (5.9)	4 (7.4)
	≥25% to <50%	3 (18.8)	1 (6.7)	0	0	4 (7.4)
	≥50%	1 (6.3)	5 (33.3)	3 (50.0)	0	9 (16.7)
	Not evaluable	2 (12.5)	2 (13.3)	2 (33.3)	1 (5.9)	7 (13.0)
Platinum treatment, n (%)	Carboplatin	13 (81.3)	14 (93.3)	3 (50.0)	15 (88.2)	45 (83.3)
	Cisplatin	3 (18.8)	1 (6.7)	3 (50.0)	2 (11.8)	9 (16.7)

Abbreviations: NSCLC, non-small cell lung cancer; NSQ, non-squamous NSCLC; P, platinum therapy; PD-L1, programmed cell death ligand-1; PD-L1 TC, PD-L1 % expression on tumor cells; SCLC, small cell lung cancer; SQ-A, squamous NSCLC cohort A; SQ-B, squamous NSCLC cohort B.

Preliminary Antitumor Activity

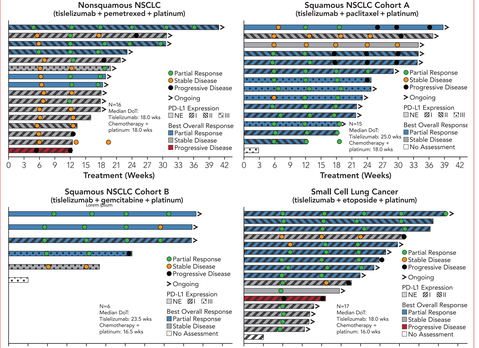
- All 54 patients were evaluable for response; 51 patients were evaluated for response post-treatment
- As detailed in Table 2, clinical response to treatment was observed across all cohorts
  - The confirmed ORRs (CR+PR) ranged from 31% (NSQ) to 80% (SQ-A) and overall clinical benefit rates (CR+PR+SD ≥24 weeks) ranged from 38% (NSQ) to 93% (SQ-A)
  - Disease control rates (CR+PR+SD) were high (87.5%, NSQ; 93%, SQ-A; 83%, SQ-B; 76.5%, SCLC)
  - The antitumor activity of tislelizumab is presented in Figure 2 and Figure 3

Figure 2: Maximum Tumor Shrinkage in All Treated Patients



*Unconfirmed partial response. I, PD-L1 TC<10%; II, PD-L1 TC ≥10% to <50%; III, PD-L1 TC ≥50%.
Abbreviations: NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand-1; PD-L1 TC, PD-L1 % expression on tumor cells.

Figure 3: Duration of Treatment and Response in All Treated Patients



I, PD-L1 TC <10%; II, PD-L1 TC ≥10% to <50%; III, PD-L1 TC ≥50%.
Abbreviations: DoT, duration of treatment; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand-1; PD-L1 TC, PD-L1 % expression on tumor cells.

Table 2: Best Tumor Response following Tislelizumab in Combination With Chemotherapy

Responses		NSQ Tislelizumab + pemetrexed + P (n=16)	SQ-A Tislelizumab + paclitaxel + P (n=15)	SQ-B Tislelizumab + gemcitabine + P (n=6)	SCLC Tislelizumab + etoposide + P (n=17)	Total (N=54)
BOR, n (%)	CR	0	0	0	0	0
	PR	5 (31.3)	12 (80.0)	4 (66.7)	8 (47.1)	29 (53.7)
	UPR	4 (25.0)	0	0	6 (35.3)	10 (18.5)
	SD	9 (56.3)	2 (13.3)	1 (16.7)	5 (29.4)	17 (31.5)
	PD	2 (12.5)	0	0	1 (5.9)	3 (5.6)
	NE	0	0	0	2 (11.8)	2 (3.7)
	Missing	0	1 (6.7)	1 (16.7)	1 (5.9)	3 (5.6)
Confirmed ORR, % (95% CI)		31.3 (11.0, 58.7)	80.0 (51.9, 95.7)	66.7 (22.3, 95.7)	47.1 (23.0, 72.2)	53.7 (39.6, 67.4)
Confirmed DCR, % (95% CI)		87.5 (61.7, 98.4)	93.3 (68.1, 99.8)	83.3 (35.9, 99.6)	76.5 (50.1, 93.2)	85.2 (72.9, 93.4)
Confirmed CBR, % (95% CI)		37.5 (15.2, 64.6)	93.3 (68.1, 99.8)	66.7 (22.3, 95.7)	52.9 (27.8, 77.0)	61.1 (46.9, 74.1)

*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; NE, not evaluable; NSCLC, non-small cell lung cancer; NSQ, nonsquamous NSCLC; ORR, objective response rate; P, platinum therapy; PD, progressive disease; PD-L1, programmed cell death ligand-1; PR, partial response; SCLC, small cell lung cancer; SD, stable disease; SQ-A, squamous NSCLC cohort A; SQ-B, squamous NSCLC cohort B; UPR, unconfirmed partial response.

Safety and Tolerability

- Tislelizumab in combination with chemotherapy was generally well tolerated (Table 3)

Table 3: Overview of Treatment-Emergent Adverse Events

	NSQ Tislelizumab + pemetrexed + P (n=16)	SQ-A Tislelizumab + paclitaxel + P (n=15)	SQ-B Tislelizumab + gemcitabine + P (n=6)	SCLC Tislelizumab + etoposide + P (n=17)	Total (N=54)
Any AE	16 (100.0)	15 (100.0)	6 (100.0)	17 (100.0)	54 (100.0)
≥Grade 3 AE	10 (62.5)	13 (86.7)	4 (66.7)	13 (76.5)	40 (74.1)
Serious AE	3 (18.8)	3 (20.0)	1 (16.7)	5 (29.4)	12 (22.2)
Fatal AE	0	1 (6.7)	0	0	1 (1.9)
Immune-related AE	3 (18.8)	4 (26.7)	2 (33.3)	4 (23.5)	13 (24.1)
AEs reported as related to tislelizumab or chemotherapy	16 (100.0)	15 (100.0)	6 (100.0)	17 (100.0)	54 (100.0)
Treatment-related ≥Grade 3	9 (56.3)	12 (80.0)	2 (33.3)	13 (76.5)	36 (66.7)
Treatment-related serious AE	2 (12.5)	3 (20.0)	1 (16.7)	5 (29.4)	11 (20.4)
AEs reported as related to tislelizumab	9 (56.3)	10 (66.7)	5 (83.3)	13 (76.5)	37 (68.5)
Tislelizumab-related ≥Grade 3 AE	1 (6.3)	2 (13.3)	0	2 (11.8)	5 (9.3)
Tislelizumab-related serious AE	1 (6.3)	2 (13.3)	0	0	3 (5.6)
AE leading to tislelizumab discontinuation	0	3 (20.0)	1 (16.7)	0	4 (7.4)

Data presented as *n* (%).
Abbreviations: AE, adverse event; NSCLC, non-small cell lung cancer; NSQ, nonsquamous NSCLC; SCLC, small cell lung cancer; SQ-A, squamous NSCLC cohort A; SQ-B, squamous NSCLC cohort B; TEAE,treatment-emergent adverse event.

- All but one patient in the SQ-B cohort (98%) experienced a chemotherapy-related AE; 68.5% of patients across all cohorts (n=37/54) experienced an AE that was reported to be possibly related to tislelizumab
- Adverse events reported to be related to tislelizumab that occurred in ≥2 patients are detailed by grade in Table 4

Table 4: Adverse Events Reported as Related to Tislelizumab and Occurring in ≥2 Patients per Cohort

	NSQ Tislelizumab + pemtrexed + P (n=16)		SQ-A Tislelizumab + paclitaxel + P (n=15)		SQ-B Tislelizumab + gemcitabine + P (n=6)		SCLC Tislelizumab + etolposide + P (n=17)		Total (N=54)	
CTCAE Grade AE	≤2	≥3	≤2	≥3	≤2	≥3	≤2	≥3	≤2	≥3
Asthenia	3 (18.8)	0	4 (26.7)	0	1 (16.7)	0	2 (11.8)	0	10 (18.5)	0
Decreased appetite	2 (12.5)	0	1 (6.7)	0	0	0	3 (17.6)	0	6 (11.1)	0
Increased ALT	1 (6.3)	0	1 (6.7)	0	1 (16.7)	0	2 (11.8)	0	5 (9.3)	0
Increased AST	0	0	2 (13.3)	0	1 (16.7)	0	2 (11.8)	0	5 (9.3)	0
Pyrexia	0	0	0	0	1 (16.7)	0	2 (11.8)	0	3 (5.6)	0
Decreased T3	2 (12.5)	0	0	0	0	0	0	0	2 (3.7)	0
Pruritus	0	0	0	0	0	0	2 (11.8)	0	2 (3.7)	0

Data presented as *n* (%).
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NSCLC, non-small cell lung cancer; NSQ, nonsquamous NSCLC; P, platinum therapy; SCLC, small cell lung cancer; SQ-A, squamous NSCLC cohort A; SQ-B, squamous NSCLC cohort B; T3, tri-iodothyronine.

CONCLUSIONS

- Treatment with tislelizumab in combination with chemotherapy was generally well tolerated in patients with advanced lung cancer
- Adverse events reported across all cohorts were consistent with the known tolerability profile of PD-1 inhibitors in combination with chemotherapy
  - As of 5 June, 2018, 35 (64.8%) patients remain on treatment
  - Most AEs were reported to be mild or moderate in severity
  - The rate of treatment discontinuation due to an AE was low (n=3/54)
- Preliminary data suggest antitumor activity in patients with advanced lung cancer
  - Across all cohorts, objective response rates ranged from 31.3% (NSQ) to 80% (SQ-A), with data being more mature among squamous NSCLC cohorts
  - The majority of responses were observed within the first two tumor assessments
- The preliminary safety/tolerability profile and antitumor activity support continued development of tislelizumab in patients with advanced lung cancer
  - A phase 3 study has been initiated to evaluate tislelizumab as a single agent as second/third-line treatment (NCT03358875)
  - Three phase 3 studies have been initiated to evaluate tislelizumab in combination with chemotherapy as first-line treatment (NCT03594747, NCT03432598, NCT03663205)
- A total of 12 patients experienced serious AEs; anemia, thrombocytopenia, decreased platelet counts, and pneumonitis (n=2 each) were the most commonly reported (defined as occurring in ≥2 patients)
- Five serious AEs (pneumonitis, dyspnea, autoimmune hepatitis, rhabdomyolysis, and myocarditis) reported to be related to tislelizumab occurred in three patients
  - The myocarditis AE, which occurred in the SQ-B cohort, was fatal
- A total of 13 patients experienced ≥1 immune-related AE (irAE)
  - Across the study, hypothyroidism (n=3), hyperthyroidism, decreased tri-iodothyronine, pneumonitis, pyrexia, and rash (n=2 each) were irAEs occurring in ≥2 patients
- All AEs were manageable and reversible, with chemotherapy dose modifications or tislelizumab dose holds, except for one fatal event of myocarditis/myositis
  - Chemotherapy dose modifications: (76.5%)
  - Tislelizumab dose holds (35.2%)
  - Fatal myocarditis/myositis: patient, who experienced both myocarditis and rhabdomyolysis, had an onset of AEs on Day 10 and died on Day 19 of treatment administration

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