PRELIMINARY RESULTS WITH TISLELIZUMAB IN CHINESE PATIENTS WITH NON-SMALL CELL LUNG CANCER

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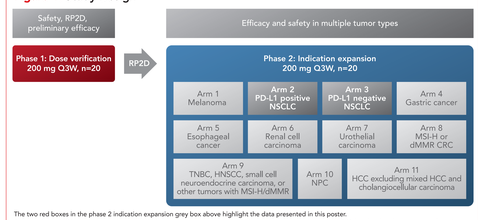
INTRODUCTION

- Non-small cell lung cancer (NSCLC) accounts for 80–85% of all lung cancers[1]
- The prognosis for patients with NSCLC is relatively poor, particularly when it is diagnosed in later stages where 5-year survival rates are approximately 36% for Stage IIIA, 26% for Stage IIIB, and 1% for Stage IV[2]
- Recent studies of immune checkpoint inhibitors have shown efficacy in patients with PD-L1-positive (PD-L1+) advanced NSCLC[3-5] as well as patients with PD-L1-negative (PD-L1–) NSCLC[5]
- Tislelizumab is a humanized IgG4 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
- 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[6]
  - A recommended dose of 200 mg administered intravenously (IV) every 3 weeks (Q3W) was identified for tislelizumab
- The safety and efficacy of tislelizumab as a single agent or in combination with chemotherapy are currently being evaluated in phase 3 studies in patients with NSCLC (NCT03358875 and NCT03594747)
- A dose-verification and indication-expansion study of tislelizumab was conducted in Chinese patients with advanced malignant solid tumors, with the purpose of determining the safety, tolerability, pharmacokinetic characteristics, and preliminary efficacy of tislelizumab in Chinese patients with advanced solid tumors (CTR20160872)
  - Data presented here are the efficacy and safety results from patients with PD-L1+ (Arm 2) and PD-L1– (Arm 3) NSCLC in the indication-expansion phase of the study

METHODS

- The overall design of the study is detailed in Figure 1
- In the dose-verification phase 1 study, patients were administered tislelizumab at 200 mg Q3W IV until they demonstrated no evidence of continued clinical benefit, unacceptable toxicity in the opinion of the investigator, or until they chose to withdraw informed consent
- Once the recommended phase 2 dose (RP2D) of tislelizumab was confirmed to be 200 mg Q3W IV, patients were enrolled into 11 groups of tumor types in the indication-expansion phase 2 study and were administered tislelizumab at this dose level
- Disease assessment by radiographic imaging (enhanced CT or MRI) was performed approximately every 9 weeks during first 12 months and approximately every 12 weeks thereafter; response was assessed by the investigator according to RECIST v1.1 criteria
- Vital signs, weight, physical examinations, Eastern Cooperative Oncology Group (ECOG) performance status, electrocardiograms and laboratory safety tests (eg, hematology, serum chemistry, urinalysis, coagulation, anti-tislelizumab antibodies, thyroid function, viral antigen reactions) were assessed locally throughout the study
- Adverse events (AEs) were graded and recorded throughout the study according to NCI-CTCAE, version 4.03

Figure 1: Study Design



The two red boxes in the phase 2 indication expansion grey box above highlight the data presented in this poster.

Abbreviations: CRC, colorectal carcinoma; dMMR, mismatch repair deficient; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; MSI-H, microsatellite instability-high; NPC, nasopharyngeal carcinoma; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand-1; Q3W, every three weeks; RP2D, recommended phase 2 dose; TNBC, triple-negative breast cancer.

Non-Small Cell Lung Cancer Study Population

- Adult patients (aged ≥18 years) with histologically or cytologically confirmed advanced/metastatic (unresectable) NSCLC, who had progressed on or were unable to tolerate standard antitumor treatment, and had no access to standard treatment or had refused standard therapy, were enrolled to receive tislelizumab 200 mg Q3W administered by IV infusion
  - PD-L1 expression status was tested prospectively at the central laboratory and determined by PD-L1 membranous staining using Ventana PD-L1 protocol (SP263 antibody)
  - PD-L1+ (Arm 2) was defined as expression of PD-L1 in ≥10% tumor cells; otherwise tumors were considered PD-L1– (Arm 3)
- Patients were excluded if they had known NSCLC with *EGFR* mutation or ALK rearrangement, a history of severe hypersensitivity reactions to other monoclonal antibodies, if they had received prior therapies targeting PD-1 or PD-L1, or if they had a prior malignancy active within the previous two years (except for NSCLC and locally curable cancers that have apparently been cured (eg, basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix or breast)
- Patients were also excluded if they had a history of interstitial lung disease, non-infectious pneumonitis or uncontrolled systemic diseases, including diabetes, hypertension, pulmonary fibrosis, acute lung diseases, or significant cardiovascular disease
- Patients with severe chronic or active infections requiring systemic antibacterial, antifungal, or antiviral therapy, including tuberculosis infections, were also excluded

Phase 2 Study Assessments

- Objective response rate (ORR) was the primary endpoint for these indication-expansion cohorts
- Disease control rate (DCR), clinical benefit rate (CBR), progression-free survival (PFS), overall survival (OS), and duration of response (DoR) were secondary endpoints (PFS and OS results were not mature enough at data cut-off to be included)
- Evaluation of the safety/tolerability profile of tislelizumab was a secondary objective

RESULTS

Patient Disposition

- As of May 11, 2018, 46 patients with NSCLC (n=21, PD-L1+; n=25, PD-L1–) were enrolled in the study (Table 1); 15 remained on treatment and 31 discontinued tislelizumab (reasons for discontinuation included AE [n=1], disease progression [n=23], death [n=2], withdrawal of consent [n=4], and other [n=1])
- The median duration of tislelizumab treatment was 4.14 months (0.2–11.27)
  - In Arm 2 (PD-L1+, n=21), the median duration of tislelizumab treatment was 3.45 months (0.2–11.2) and median follow-up duration was 6.28 months (0.2–11.83)
  - In Arm 3 (PD-L1–, n=25), the median duration of tislelizumab treatment was 4.37 months (0.69–11.27) and median follow-up duration was 8.61 months (2.0–10.84)
- The majority of patients were male (n=32; 69.6%), former smokers (n=26; 56.5%), and had received ≥1 prior anticancer therapy (n=44; 95.6%)
  - In Arm 2 (PD-L1+, n=21), 81% of patients were male, 71.4% were former smokers, and all had received ≥1 prior anticancer therapy
  - In Arm 3 (PD-L1–, n=25), 60% of patients were male, 44% were former smokers, and 92% had received ≥1 prior anticancer therapy

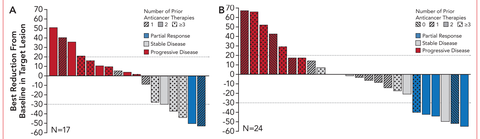
Table 1: Patient Demographics and Disease Characteristics in Non-small Cell Lung Cancer

		Arm 2: PD-L1+ (n=21)	Arm 3: PD-L1– (n=25)	Overall (N=46)
Median age, years (min, max)		58.0 (26, 72)	54.0 (37, 72)	55.5 (26, 72)
Sex, n (%)	Male	17 (81.0)	15 (60.0)	32 (69.6)
	Female	4 (19.0)	10 (40.0)	14 (30.4)
Smoking status, n (%)	Former	15 (71.4)	11 (44.0)	26 (56.5)
	Current	0	1 (4.0)	1 (2.2)
	Non-smoker	6 (28.6)	13 (52.0)	19 (41.3)
Prior lines of anticancer therapy regimens, n (%)	0	0	2 (8.0)	2 (4.3)
	1	5 (23.8)	9 (36.0)	14 (30.4)
	2	8 (38.1)	7 (28.0)	15 (32.6)
	≥3	8 (38.1)	7 (28.0)	15 (32.6)
Prior anticancer radiotherapy, n (%)		9 (42.9)	7 (28.0)	16 (34.8)

Preliminary Antitumor Activity

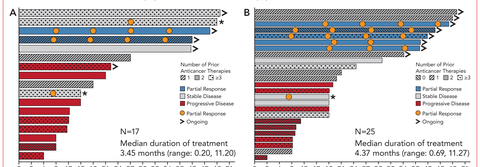
- At total of 42 patients were evaluable, defined as any patient who had measurable disease at baseline and at least one postbaseline tumor assessment
- A total of seven patients (n=2, PD-L1+; n=5, PD-L1–) achieved a confirmed partial response (PR); 17 patients achieved stable disease (SD) (Table 2)
- The objective response rates (ORR=CR+PR) for Arm 2 [PD-L1+, n=17] and Arm 3 (PD-L1–, n=25) were 11.8% (95% CI: 1.46–36.44) and 20% (95% CI: 6.83–40.7), respectively
- Across the two arms, clinical benefit and disease control rates were 28.6% and 57.1%, respectively
  - The clinical benefit rate (CR+PR+SD ≥24 weeks) was similar between PD-L1+ (29.4% [95% CI: 10.31–55.96]) and PD-L1– (28% [95% CI: 12.07–49.39]) NSCLC patients
  - The disease control rate (CR+PR+SD) was high (>45%) in both PD-L1+ (47.1% [95% CI: 22.98–72.19]) and PD-L1– (64.0% [95% CI: 42.52–82.03]) NSCLC patients
- The antitumor activity of tislelizumab is presented in Figures 2–4

Figure 2: Maximum Tumor Reduction in Evaluable Patients With PD-L1+ NSCLC (A) or PD-L1– NSCLC (B)



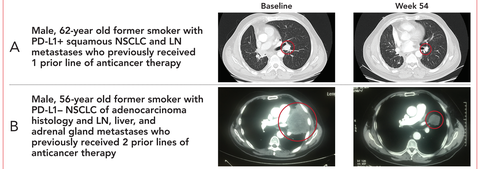
In Figure 2B, one patient did not have a postbaseline target lesion result and was excluded. The patients experienced progressive disease due to the development of a new lesion.

Figure 3: Duration of Treatment and Response in Evaluable Patients With PD-L1+ NSCLC (A) or PD-L1– NSCLC (B)



*Unconfirmed response.

Figure 4: Radiographic Images of a Patients with PD-L1+ (A) and PD-L1– (B) NSCLC



Abbreviations: LN, lymph node; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand-1.

Table 2: Best Overall Response Observed with Tislelizumab Evaluable Patients with PD-L1+ NSCLC or PD-L1– NSCLC

		Arm 2: PD-L1+ (n=17)	Arm 3: PD-L1– (n=25)	Overall (N=42)
BOR per RECIST 1.1 (confirmed), n (%)	CR	0	0	0
	PR	2 (11.8)	5 (20.0)	7 (16.7)
	SD	6 (35.3)	11 (44.0)	17 (40.5)
	PD	9 (52.9)	9 (36.0)	18 (42.9)
ORR (CR+PR), % (95% CI)		11.8 (1.46, 36.44)	20.0 (6.83, 40.70)	16.7 (6.97, 31.36)
CBR (CR+PR+ durable SD*), % (95% CI)		29.4 (10.31, 55.96)	28.0 (12.07, 49.39)	28.6 (15.72, 44.58)
DCR (CR+PR+SD), % (95% CI)		47.1 (22.98, 72.19)	64.0 (42.52, 82.03)	57.1 (40.96, 72.28)

*Durable SD: stable disease for ≥24 weeks.

Abbreviations: BOR, best overall response; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DCR, disease control rate; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PD-L1, programmed cell death ligand-1; PR, partial response; RECIST, response evaluation criteria in solid tumors; SD, stable disease.

Safety and Tolerability

- Adverse events considered at least possibly related to tislelizumab were reported in 30 out of a total 46 patients with NSCLC (Table 3)
- Across the two NSCLC populations, the most commonly reported treatment-related AEs (TRAEs) considered were increases in AST (n=11)/ALT (n=10), rash (n=5), and hypothyroidism (n=5)
  - The majority of the TRAEs were grade ≤2 in severity; five patients experienced grade ≥3 TRAEs (increased AST, n=3; increased ALT, n=2; increased gamma-glutamyltransferase (GGT), n=1; maculo-papular rash, n=1; hyperglycemia, n=1)
- A total of 26 patients experienced immune-related AEs (irAEs)
  - The most common irAEs were increased AST (n=11), increased ALT (n=10), hypothyroidism (n=5), and rash (n=5)
- One patient discontinued due to a Grade 3 AE (hypotension) considered not related to treatment
- Fourteen patients had serious AEs; three patients experienced serious TRAEs (nausea and vomiting, n=1; increased AST, n=1; hyperglycemia, n=1)
- Across these two study arms, three patients had a TEAE with a fatal outcome (multiple organ dysfunction syndrome, n=1; central nervous system metastases, n=1; hypotension, n=1); none were determined to be related to treatment

Table 3: Treatment-Related Adverse Events Occurring in ≥2 Patients in Either Treatment Arm

	Arm 2: PD-L1+		Arm 3: PD-L1–		Overall	
	All grades (n=21)	Grade ≥3 (n=21)	All grades (n=25)	Grade ≥3 (n=25)	All grades (N=46)	Grade ≥3 (N=46)
Patients who had ≥1 TRAE	15 (71.4)	0	15 (60.0)	5 (20.0)	30 (65.2)	5 (10.9)
Transaminases increased	5 (23.8)	0	7 (28.0)	3 (12.0)	12 (26.1)	3 (6.5)
Increased AST	5 (23.8)	0	6 (24.0)	3 (12.0)	11 (23.9)	3 (6.5)
Increased ALT	4 (19.0)	0	6 (24.0)	2 (8.0)	10 (21.7)	2 (4.3)
Rash	2 (9.5)	0	3 (12.0)	0	5 (10.9)	0
Hypothyroidism	3 (14.3)	0	2 (8.0)	0	5 (10.9)	0
Increased bilirubin	3 (14.3)	0	1 (4.0)	0	4 (8.7)	0
Increased GGT	3 (14.3)	0	1 (4.0)	1 (4.0)	4 (8.7)	1 (2.2)
Nausea	2 (9.5)	0	2 (8.0)	0	4 (8.7)	0
Pyrexia	2 (9.5)	0	2 (8.0)	0	4 (8.7)	0
Decreased blood TSH	0	0	3 (12.0)	0	3 (6.5)	0
Increased blood TSH	0	0	3 (12.0)	0	3 (6.5)	0
Vomiting	1 (4.8)	0	2 (8.0)	0	3 (6.5)	0
Increased free thyroxin	0	0	2 (8.0)	0	2 (4.3)	0
Decreased weight	0	0	2 (8.0)	0	2 (4.3)	0
Anemia	2 (9.5)	0	0	0	2 (4.3)	0

Data presented as n, (%).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; PD-L1, programmed cell death ligand-1; TRAE, treatment-related adverse event; TSH, thyroid stimulating hormone.

CONCLUSIONS

- Preliminary data suggest treatment with tislelizumab was generally well tolerated and has antitumor activity in patients with advanced NSCLC
  - With a median follow-up of 8.4 months, 15 (32.6%) patients remain on study
  - The rate of treatment discontinuation due to an AE was low (n=1/46)
- Partial responses were observed in seven patients (n=2/17 [PD-L1+]; n=5/25 [PD-L1–])
- Disease control rate was ≥45% in both NSCLC expansion cohorts
- There was no clear relationship between PD-L1 status and clinical efficacy measures based on the small sample size
- Adverse events reported in the two cohorts of PD-L1+ and PD-L1– were consistent with the overall safety profile of tislelizumab observed in previous studies with other tumor types and were generally of low severity
- The preliminary safety profile and antitumor activity support continued development of tislelizumab in patients with advanced NSCLC; phase 3 studies of tislelizumab as treatment for NSCLC have been initiated (NCT03358875 and NCT03594747)

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