TISLELIZUMAB PLUS CHEMOTHERAPY AS FIRST-LINE TREATMENT FOR LUNG CANCER

Zhijie Wang[1], Jun Zhao[2], Zhiyong Ma[3], Jiuwei Cui[4], Yongqian Shu[5], Zhe Liu[6], Ying Cheng[7], Shiang J. Leaw[8], Yanjie Wu[8], Yan Ma[8], Wei Tan[8], Jie Wang[1]

[1]State Key Laboratory of Molecular Oncology, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [2]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education, Beijing), Department of Thoracic Medical Oncology, Peking University Cancer Hospital & Institute, Beijing, China; [3]The Affiliated Cancer Hospital of Zhengzhou University/Henan Cancer Hospital, Zhengzhou, China; [4]The First Hospital of Jilin University, Changchun, China; [5]Jiangsu Province Hospital, Nanjing, China; [6]Beijing Chest Hospital, Capital Medical University, Beijing, China; [7]Jilin Cancer Hospital, Changchun, China; [8]BeiGene (Beijing) Co., Ltd., Beijing, China

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BACKGROUND

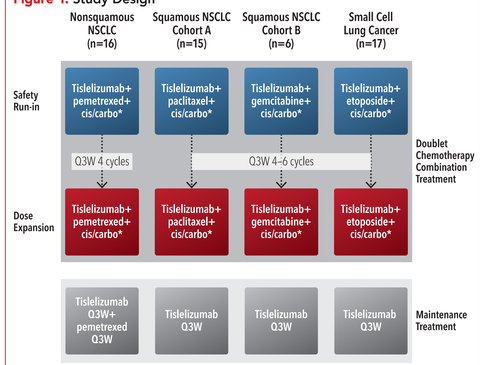
- Tislelizumab is a humanized monoclonal antibody with high affinity and specificity for programmed cell death protein-1 (PD-1) that was engineered to minimize binding to FcγR on macrophages in order to abrogate antibody-dependent phagocytosis, a potential mechanism of T-cell clearance and resistance to anti-PD-1 therapy[1,2]
- BGB-A317-206 (NCT03432598) is a phase 2 study that previously reported that the addition of tislelizumab to chemotherapy was well tolerated and showed durable antitumor activity in Chinese patients with advanced lung cancer[3]
  - Median progression-free survival (PFS) was estimated to be 6.9 months in patients with small cell lung cancer (SCLC) and 9.0 months for patients with nonsquamous (NSQ) NSCLC; median overall survival (OS) was not reached in any cohort except for SCLC (15.6 months)
  - Tislelizumab plus chemotherapy was well tolerated in patients with advanced lung cancers and reported adverse events were consistent with the known tolerability profile of PD-1 inhibitors in combination with chemotherapy
- Here, we present updated efficacy and safety data from the BGB-A317-206 study, using a data cut-off of 31 December 2019

METHODS

Overall Design and Study Objectives

- The overall design of this first-line study in Chinese patients with advanced lung cancer is detailed in Figure 1
  - A full description of the design, patient population, and treatment administration for this study is presented in the primary publication[3]

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: carbo, carboplatin; cis, cisplatin; NSCLC, non-small cell lung cancer; Q3W, every 3 weeks.

- The primary endpoint was investigator-assessed objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1; PFS, OS, duration of response (DoR), disease control rate (DCR; defined as complete response + partial response + stable disease), and safety/tolerability profile were additional endpoints
- Disease assessment by radiographic imaging (enhanced CT or MRI) was performed approximately every 6 weeks during the first 6 months, every 9 weeks for the next 6 months, and every 12 weeks thereafter according to RECIST v1.1 criteria
- Adverse events (AEs) were graded and recorded throughout the study according to NCI CTCAE v.4.03
- Pretreatment tumor samples were evaluated for PD-L1 membrane expression on tumor cells (TCs) by immunohistochemistry assessed by the central laboratory with the VENTANA PD-L1 (SP263) assay

RESULTS

Demographics and Baseline Disease Characteristics

- A total of 54 patients with lung cancer (NSQ, n=16; SQ-A, n=15; SQ-B, n=6; SCLC, n=17) were enrolled in the study (Table 1)
- As of 31 December 2019, the median study follow-up ranged from 15.5 months (SCLC) to 25.3 months (SQ-B) and 11 patients remained on treatment

Table 1: Demographics and Baseline Characteristics

		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)
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)
PD-L1 expression on tumor cells, n (%)	<1%	8 (50.0)	3 (20.0)	2 (33.3)	14 (82.4)	27 (50.0)
	1% to 49%	7 (43.8)	7 (46.7)	1 (16.7)	3 (17.6)	18 (33.3)
	≥50%	1 (6.3)	5 (33.3)	3 (50.0)	0 (0.0)	9 (16.7)
Median study follow-up time, months (range)		23.0 (8.0, 28.3)	24.2 (0.7, 27.6)	25.3 (0.7, 25.5)	15.5 (10.1, 26.0)	21.9 (0.7, 28.3)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; NSQ, nonsquamous NSCLC; PD-L1, programmed death-ligand 1; 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).

Antitumor Activity

- Clinical response, including ORR and DoR, for each cohort is shown in Table 2

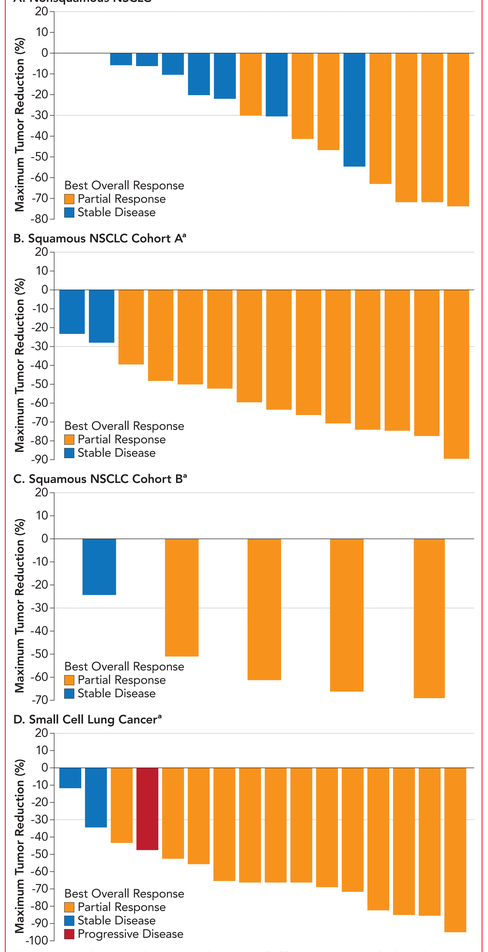
Table 2: Confirmed Best Overall Responses

		NSQ (n=16)	SQ-A (n=15)	SQ-B (n=6)	SCLC (n=17)
ORR, % (95% CI)		43.8 (19.8, 70.1)	80.0 (51.9, 95.7)	66.7 (22.3, 95.7)	76.5 (50.1, 93.2)
DoR, months (95% CI)		17.1 (6.28, NE)	5.6 (3.25, 17.31)	NE (2.96, NE)	6.5 (2.69, NE)
DCR (CR+PR+SD), % (95% CI)		93.8 (69.8, 99.8)	93.3 (68.1, 99.8)	83.3 (35.9, 99.6)	88.2 (63.6, 98.5)
Best overall response, n (%)	CR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	PR	7 (43.8)	12 (80.0)	4 (66.7)	13 (76.5)
	SD	8 (50.0)	2 (13.3)	1 (16.7)	2 (11.8)
	PD	1 (6.3)	0 (0.0)	0 (0.0)	1 (5.9)
	NA[a]	0 (0.0)	1 (6.7)	1 (16.7)	1 (5.9)

[a]Includes patients who were not evaluable or had no post-baseline assessment.
Abbreviations: CR, complete response; DCR, disease control rate; DoR, duration of response; NA, not applicable; NE, not estimable; 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).

- Tumor reductions were reported in all cohorts (Figure 2)
- The majority of responses were observed within the first two tumor assessments
  - 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

Figure 2: Best Percent Change in Sum of Target Lesion Diameters From Baseline



*Three patients (1 each in NSCLC cohort A, NSCLC cohort B, and small cell lung cancer) were not evaluable or had no post-baseline assessment.
Abbreviation: NSCLC, non-small cell lung cancer.

- Median PFS was 9.0 months, 7.0 months, and 6.9 months for the NSQ, SQ-A, and SCLC cohorts, respectively, but was not estimable for SQ-B (Table 3)
- After an additional 6 months of follow-up, median OS was only reached in the SCLC cohort (15.5 months; 95% CI: 11.8, not estimable) (Table 3)

Table 3: Progression-Free and Overall Survival

		NSQ (n=16)	SQ-A (n=15)	SQ-B (n=6)	SCLC (n=17)
Median PFS, mo (95% CI)		9.0 (4.27, 21.36)	7.0 (5.52, 18.63)	NE (4.27, NE)	6.9 (4.90, 10.09)
Median OS, mo (95% CI)		NE (13.3, NE)	NE (15.4, NE)	NE (8.3, NE)	15.5 (11.8, NE)
OS rate	12 months, % (95% CI)	88 (59, 97)	93 (61, 99)	80 (20, 97)	75 (46, 90)
	18 months, % (95% CI)	75 (46, 90)	72 (41, 88)	80 (20, 97)	38 (14, 62)
	24 months, % (95% CI)	51 (23, 74)	65 (35, 84)	80 (20, 97)	31 (10, 55)

Abbreviations: CI, confidence interval; NE, not estimable; NSQ, nonsquamous NSCLC; OS, overall survival; 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).

Safety and Tolerability

- The most common AEs were hematologic in nature (ie, anemia [n=44, 81.5%], decreased white blood cell count [n=41, 76%], and decreased neutrophil count [n=40, 74%]) (Table 4)
  - The only grade ≥3 AE experienced in more than 20% of patients was decreased neutrophil count (48%)
- Fifty-two of 54 patients (96%) experienced a chemotherapy-related AE; 36 (66.7%) were grade ≥3 in severity
- Forty-seven patients (87%) reported ≥1 AE related to tislelizumab; eight patients (15%) reported a tislelizumab-related AE of grade ≥3 in severity
  - The most common AEs related to tislelizumab were increased alanine aminotransferase, increased aspartate aminotransferase, and hypothyroidism (n=7 each)
  - No grade ≥3 AE reported to be related to tislelizumab occurred in more than one patient

Table 4: Treatment-Emergent Adverse Events in ≥15% of Patients (N=54)

	NSQ (n=16)		SQ-A (n=15)		SQ-B (n=6)		SCLC (n=17)		Total (N=54)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with ≥1 AE	16 (100.0)	12 (75.0)	15 (100.0)	14 (93.3)	6 (100.0)	4 (66.7)	17 (100.0)	13 (76.5)	54 (100.0)	43 (79.6)
Anemia	14 (87.5)	2 (12.5)	10 (66.7)	2 (13.3)	5 (83.3)	1 (16.7)	15 (88.2)	5 (29.4)	44 (81.5)	10 (18.5)
Decreased WBC count	11 (68.8)	4 (25.0)	13 (86.7)	2 (13.3)	3 (50.0)	0	14 (82.4)	2 (11.8)	41 (75.9)	8 (14.8)
Decreased neutrophil count	12 (75.0)	6 (37.5)	12 (80.0)	11 (73.3)	3 (50.0)	1 (16.7)	13 (76.5)	8 (47.1)	40 (74.1)	26 (48.1)
Decreased platelet count	7 (43.8)	3 (18.8)	6 (40.0)	0	3 (50.0)	1 (16.7)	8 (47.1)	4 (23.5)	24 (44.4)	8 (14.8)
Increased AST	8 (50.0)	0	7 (46.7)	1 (6.7)	2 (33.3)	0	6 (35.3)	0	23 (42.6)	1 (1.9)
Increased ALT	7 (43.8)	1 (6.3)	6 (40.0)	2 (13.3)	2 (33.3)	0	7 (41.2)	0	22 (40.7)	3 (5.6)
Asthenia	10 (62.5)	1 (6.3)	8 (53.3)	0	2 (33.3)	0	2 (11.8)	0	22 (40.7)	1 (1.9)
Decreased appetite	7 (43.8)	0	5 (33.3)	0	2 (33.3)	0	8 (47.1)	0	22 (40.7)	0
Nausea	6 (37.5)	0	6 (40.0)	0	2 (33.3)	0	7 (41.2)	1 (5.9)	21 (38.9)	1 (1.9)
Vomiting	2 (12.5)	0	2 (13.3)	0	1 (16.7)	0	10 (58.8)	1 (5.9)	15 (27.8)	1 (1.9)
Thrombocytopenia	3 (18.8)	0	4 (26.7)	1 (6.7)	0	0	7 (41.2)	5 (29.4)	14 (25.9)	6 (11.1)
Alopecia	1 (6.3)	0	7 (46.7)	0	0	0	5 (29.4)	0	13 (24.1)	0
Constipation	4 (25.0)	0	1 (6.7)	0	1 (16.7)	0	6 (35.3)	0	12 (22.2)	0
Cough	1 (6.3)	0	4 (26.7)	0	1 (16.7)	0	5 (29.4)	0	11 (20.4)	0
Pyrexia	1 (6.3)	0	3 (20.0)	0	2 (33.3)	0	5 (29.4)	0	11 (20.4)	0
Productive cough	3 (18.8)	0	2 (13.3)	0	1 (16.7)	0	3 (17.6)	0	9 (16.7)	0

Data presented as n (%).
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, alanine 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.

CONCLUSIONS/DISCUSSION

- With a median study follow-up of up to 25.3 months, treatment with tislelizumab in combination with chemotherapy continued to be well tolerated
  - After an additional 6 months of potential exposure, AEs were consistent with the known tislelizumab tolerability profile as no new safety signals were identified
- Tislelizumab plus chemotherapy demonstrated encouraging antitumor activity in patients with advanced lung cancer, with ORRs ranging from 44% (NSQ) to 80% (SQ-A)
  - The majority of responses were observed within the first two tumor assessments
  - Responses were durable with median DoRs ranging from 5.6 (SQ-A) to 17.1 months (NSQ); DoR was not estimable for the SQ-B cohort
- After an additional 6 months of follow-up, median OS in SCLC was 15.5 months but median OS was not reached in any NSCLC cohort
  - The two-year OS rate was 31% for the SCLC cohort and 51%, 65%, and 80% for the NSQ, SQ-A, and SQ-B cohorts, respectively
- The results from this phase 2 Chinese study are consistent with data from two global, first-line phase 3 studies of tislelizumab plus chemotherapy as treatment for NSQ NSCLC (RATIONALE 304)[4] and in SQ NSCLC (RATIONALE 307)[5-7]
- Sixteen patients (29.6%) experienced a serious AE; eight (14.8%) experienced serious AEs assessed by investigators to be related to tislelizumab
  - Pneumonitis (n=2) was the only serious AE related to tislelizumab occurring in more than one patient
- A patient in the SQ-A cohort experienced dyspnea, myocarditis, rhabdomyolysis; this patient had received only one dose of tislelizumab
- Immune-related AEs were reported in 18 patients (33.3%); four patients experienced at least one grade ≥3 immune-mediated AE
  - Immune-mediated hepatitis (n=2; 3.7%) was the only grade ≥3 immune-mediated AE occurring in more than one patient (both events occurred in the SQ-A cohort)

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CONFLICTS OF INTEREST

SL, **YW**, **YM**, and **WT** are employees with stock optiond at BeiGene, Ltd. **ZW**, **JZ**, **ZM**, **JC**, **YS**, **ZL**, **YC**, and **JW** have nothing to disclose.

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