TISLELIZUMAB PLUS CHEMOTHERAPY AS FIRST-LINE TREATMENT FOR LUNG CANCER

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66P
European Society of Medical Oncology Immuno-Oncology
December 9-12, 2020, Virtual Congress

BACKGROUND

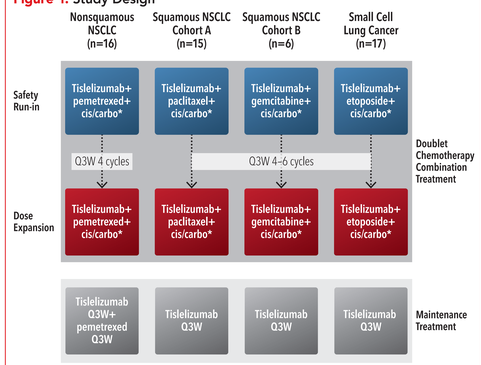
- Tislelizumab is a humanized monoclonal antibody with high affinity and specificity for programmed cell death protein-1 (PD-1) that was engineered to minimize binding to FcγR on macrophages in order to abrogate antibody-dependent phagocytosis, a potential mechanism of T-cell clearance and resistance 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

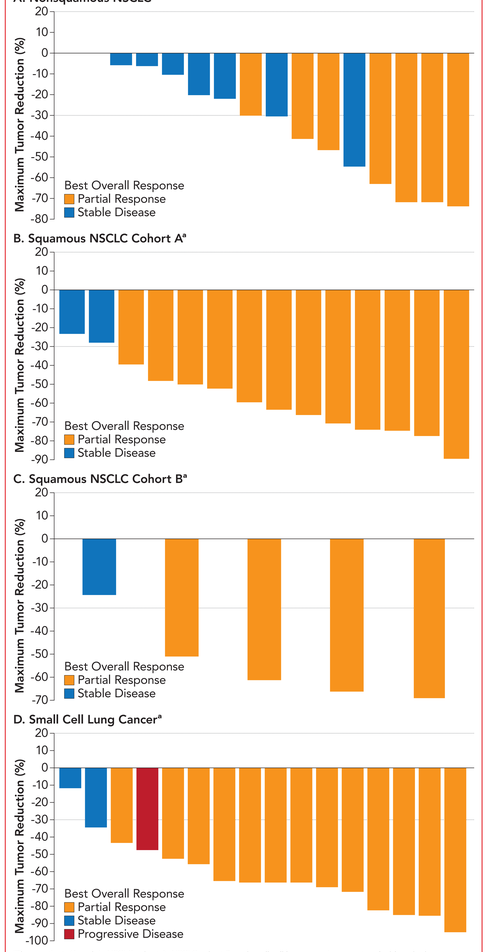
Table 2: Confirmed Best Overall Responses

		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.

ACKNOWLEDGMENTS

The authors wish to acknowledge the investigative centers' study staff and study patients, and to recognize those from BeiGene, Ltd. who have substantially contributed to the development of this presentation. This study was sponsored by BeiGene, Ltd. Writing and editorial assistance was provided by Stephan Lindsey, PhD, and Elizabeth Hermans, PhD (OPEN Health Medical Communications, Chicago, IL), and funded by the study sponsor.

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