TISLELIZUMAB PLUS CHEMOTHERAPY VERSUS CHEMOTHERAPY ALONE AS FIRST-LINE TREATMENT FOR LOCALLY ADVANCED/METASTATIC NONSQUAMOUS NSCLC

RATIONALE TRIAL PROGRAM

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BACKGROUND

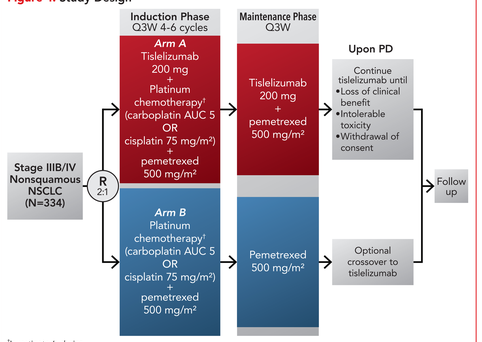
- Globally, there are approximately 2.1 million new lung cancer cases and 1.8 million deaths each year[1]
  - Lung cancer is the leading cause of cancer incidence and death, globally and in China
  - In China in 2015, it was estimated that there were 733,300 new cases and 610,200 deaths[2,3]
- While a PD-1 inhibitor in combination with chemotherapy has recently been approved in China as first-line treatment for advanced NSCLC, platinum-based regimens remain standard first-line therapy for Chinese patients who have no access to checkpoint inhibitors[4,5]
  - Overall survival (OS) remains low for patients with advanced NSCLC treated with platinum-based therapies which leaves considerable room for improvement for patient outcomes[6]
- Recent global studies have examined whether better patient outcomes could be achieved using immune checkpoint inhibitors targeting programmed cell death protein-1 (PD-1) or programmed death-ligand 1 (PD-L1) in combination with chemotherapy[7-9]
- Tislelizumab is a humanized monoclonal antibody with high affinity and specificity for 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[10,11]
- Reports from three early phase studies (BGB-A317-001, BGB-A317-102, BGB-A317-206) showed that tislelizumab, as a single agent and in combination with chemotherapy, was generally well tolerated and demonstrated antitumor activity in Asian and non-Asian populations with solid tumors, including advanced lung cancers[12-14]
- RATIONALE 304 is a phase 3, open-label, multicenter, randomized study to evaluate the efficacy and safety of tislelizumab in combination with platinum (cisplatin or carboplatin) and pemetrexed compared with platinum and pemetrexed alone as first-line treatment in patients with stage IIIB or IV nonsquamous (nsq)-NSCLC

METHODS

Overall Design and Study Objectives

- In this phase 3 study conducted at 47 study sites in China, patients with nsq-NSCLC were randomized 2:1 to receive either tislelizumab in combination with chemotherapy (*Arm A*) or chemotherapy alone (*Arm B*) (Figure 1)
  - Randomization was stratified by disease stage (IIIB vs IV) and tumor cell (TC) PD-L1 membrane expression (<1% vs 1-49% vs ≥50%)
- The primary objective was to compare progression-free survival assessed by the Independent Review Committee (PFS_{IRC}), between tislelizumab plus platinum-pemetrexed (*Arm A*) and platinum-pemetrexed alone (*Arm B*)
  - Additional objectives included PFS as assessed by investigator (PFS_{INV}), IRC-assessed objective response rate (ORR_{IRC}), disease control rate (DCR_{IRC}), and duration of response (DoR_{IRC}), as well as OS and the safety/tolerability of study treatment
- Radiological assessment of tumor-response status was performed per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Safety was assessed through physical examinations, monitoring of treatment-emergent adverse events (TEAEs), vital signs, clinical laboratory assessment, and 12-lead electrocardiogram
- PD-L1 membrane staining on TCs was assessed by the VENTANA PD-L1 (SP263) assay at a central laboratory
  - PD-L1 results were blinded to investigators, patients, and sponsors

Figure 1: Study Design



[a]Investigator's choice.
Abbreviations: NSCLC, non-small cell lung cancer; PD, progressive disease; Q3W, every 3 weeks; R, randomized.

Study Population

- Adult patients (aged 18-75 years) with histologically confirmed advanced (stage IIIB) or metastatic (stage IV) nsq-NSCLC, with at least one measurable lesion, were eligible for inclusion if they provided fresh or archival tumor tissues for PD-L1 expression analysis
  - Patients with mixed non-small cell histology tumors were eligible if the major histological component was nonsquamous
  - Patients must have had no prior systemic anticancer therapy for advanced or metastatic disease
- Patients with known *EGFR*-sensitizing mutations or known *ALK* gene translocation, prior treatment with EGFR, ALK, PD-(L)-1 inhibitors, or systemic immunosuppressive agents ≤14 days prior to randomization, a history of interstitial lung disease, or noninfectious pneumonitis were ineligible

Study Endpoints and Statistical Analyses

- The primary endpoint was PFS_{IRC}, in the intent-to-treat (ITT) analysis set (all randomized patients)
  - Median PFS was estimated using the Kaplan-Meier method
  - Hazard ratio for comparison between *Arm A* and *Arm B* was estimated using the stratified Cox proportional hazard model
  - *P*-value was generated from a stratified log-rank test
- Additional endpoints included PFS_{INV} and OS in the ITT analysis set, ORR_{IRC} (complete response [CR] + partial response [PR]), DCR_{IRC} (CR + PR + non-CR/non-progressive disease [PD] + stable disease ≥6 weeks), DoR_{IRC}, and the safety of tislelizumab in combination with chemotherapy or chemotherapy alone
- An interim analysis was planned when approximately 153 PFS_{IRC} (71% of the targeted number of events) were observed in the ITT population
  - The superiority boundary of the *P*-value used in the interim analysis was adjusted to 0.0092 according to the actual 159 PFS_{IRC} events using the prespecified Lan-DeMets O'Brien-Fleming approximation spending function

RESULTS

Patients

- A total of 334 eligible patients were randomized to receive treatment; as of 23 January 2020, 97 patients (43.5%) in *Arm A* and 20 patients (18.0%) in *Arm B* remained on treatment
  - The most common reason for discontinuation of study treatment was PD per RECIST v1.1 (n=142; 42.5%), followed by consent withdrawal (n=31; 9.3%) and AE (n=25; 7.5%)
  - Median study follow-up time of 9.8 months (95% CI: 9.23, 10.38)
- Demographics and baseline characteristics were well balanced between arms (Table 1)

Table 1: Demographics and Baseline Characteristics (ITT Analysis Set)

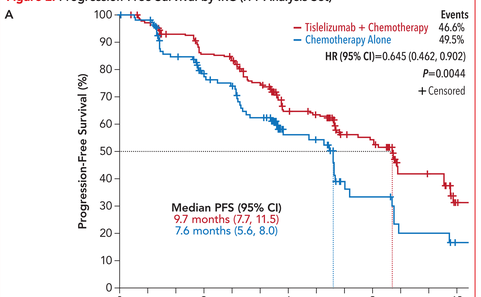
		Arm A Tislelizumab + PP (n=223)	*Arm B* PP (n=111)	Total (N=334)
Median age, years (range)		60 (27, 75)	61 (25, 74)	61 (25, 75)
Age group, n (%)	<65 years	163 (73.1)	74 (66.7)	237 (71.0)
	≥65 years	60 (26.9)	37 (33.3)	97 (29.0)
Sex, n (%)	Male	168 (75.3)	79 (71.2)	247 (74.0)
	Female	55 (24.7)	32 (28.8)	87 (26.0)
Smoking status, n (%)	Former	115 (51.6)	53 (47.7)	168 (50.3)
	Never	76 (34.1)	45 (40.5)	121 (36.2)
	Current	32 (14.3)	13 (11.7)	45 (13.5)
ECOG performance status, n (%)	0	54 (24.2)	24 (21.6)	78 (23.4)
	1	169 (75.8)	87 (78.4)	256 (76.6)
Disease stage, n (%)	Stage IIIB	40 (17.9)	21 (18.9)	61 (18.3)
	Stage IV	183 (82.1)	90 (81.1)	273 (81.7)
PD-L1 % expression in tumor cells, n (%)	<1%[a]	96 (43.0)	48 (43.2)	144 (43.1)
	1-49%	53 (23.8)	27 (24.3)	80 (24.0)
	≥50%	74 (33.2)	36 (32.4)	110 (32.9)
EGFR-sensitizing mutation status, n (%)	Negative	218 (97.8)	109 (98.2)	327 (97.9)
	Positive/unknown[b]	5 (2.2)	2 (1.8)	7 (2.1)
ALK rearrangement status, n (%)	Negative	166 (74.4)	79 (71.2)	245 (73.4)
	Unknown	57 (25.6)	32 (28.8)	89 (26.6)
Location of distant metastases[c], n (%)	Bone	75 (33.6)	41 (36.9)	116 (34.7)
	Liver	20 (9.0)	17 (15.3)	37 (11.1)
	Brain	11 (4.9)	7 (6.3)	18 (5.4)

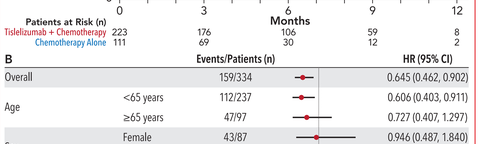
[a]Five patients with unevaluable PD-L1 status were included in PD-L1 <1% category.
[b]Includes patients with *EGFR* sensitizing mutant or indeterminate status that were identified via tissue-based test, reported as major protocol deviations.
[c]Patients were counted once within each category but may have been counted in multiple categories.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; PP, pemetrexed + platinum; PD-L1, programmed death-ligand 1.

Efficacy of Combination Therapy Versus Chemotherapy Alone

- PFS_{IRC} was significantly longer with tislelizumab in combination with chemotherapy than chemotherapy alone (stratified HR=0.645 [95% CI: 0.462, 0.902]; *P*=0.0044); median PFS_{IRC} was 9.7 months in *Arm A* and 7.6 months in *Arm B* (Figure 2A)
  - Similar median PFS results were observed for *Arm A* vs *Arm B* (HR=0.561 [95% CI: 0.411, 0.767]; *P*=0.0001) when assessed by the investigator
- Subgroup analyses of prespecified demographic and baseline disease characteristics indicated that a consistent PFS benefit was observed across most subgroups analyzed (Figure 2B)
- With more than 75% of the patients censored in both arms, median OS was not reached in either arm

Figure 2: Progression-Free Survival by IRC (ITT Analysis Set)

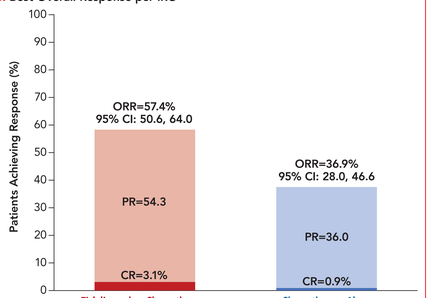




Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IRC, Independent Review Committee; ITT, intent-to-treat; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TC, tumor cell.

- Higher ORR_{IRC} and DCR_{IRC} were observed in the tislelizumab plus chemotherapy arm compared with chemotherapy alone (Figure 3)
  - Among 128 responders with tislelizumab combination therapy, median DoR_{IRC} was 8.5 months (95% CI: 6.80, 10.58)
  - In the 41 patients who achieved a response with chemotherapy alone, median DoR_{IRC} was 6.0 months (95% CI: 4.99, not evaluable)
  - At time of data cut-off, >62% of patients were censored in each arm, suggesting DoR_{IRC} was not fully mature in either arm

Figure 3: Best Overall Response per IRC



	Tislelizumab + Chemotherapy (N=223)	Chemotherapy Alone (N=111)
Disease Control Rate, (95% CI)	89.2% (84.4, 93.0)	81.1% (72.5, 87.9)
Duration of Response, median (95% CI)	8.5 months (6.80, 10.58)	6.0 months (4.99, NE)

Abbreviations: CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; IRC, Independent Review Committee; NE, not estimable; ORR, objective response rate; PR, partial response.

Safety and Tolerability of Combination Therapy Versus Chemotherapy Alone

- A total of 222 patients (100%) in *Arm A* and 109 patients (99.1%) in *Arm B* experienced ≥1 TEAE regardless of investigator-assessed causality
  - Grade ≥3 TEAEs occurred in 67.6% (n=150) and 53.6% (n=59) of the patients in *Arm A* and *Arm B*, respectively
  - Treatment-emergent AEs leading to permanent discontinuation of any component of study drug occurred in 25.7% (n=57) of the patients in *Arm A* and 9.1% (n=10) in *Arm B*
- The most commonly reported treatment-related AEs (TRAEs) were hematologic in nature (eg, anemia, leukopenia, thrombocytopenia) and primarily mild-to-moderate in severity (Table 2)

Table 2: Incidence of Treatment-Related Adverse Events Occurring in ≥20% of Patients Treated With Tislelizumab Plus Chemotherapy or Chemotherapy Alone

	Arm A Tislelizumab + PP (N=222)		*Arm B* PP (N=110)	
	Grade 1-2	Grade ≥3	Grade 1-2	Grade ≥3
Anemia[1]	151 (68.0)	30 (13.5)	71 (64.5)	11 (10.0)
Leukopenia[2]	135 (60.8)	48 (21.6)	65 (59.1)	16 (14.5)
Thrombocytopenia[3]	112 (50.5)	43 (19.4)	55 (50.0)	15 (13.6)
Nausea	94 (42.3)	1 (0.5)	43 (39.1)	1 (0.9)
Alanine aminotransferase increased	92 (41.4)	8 (3.6)	45 (40.9)	3 (2.7)
Aspartate aminotransferase increased	86 (38.7)	4 (1.8)	49 (44.5)	0
Neutropenia[4]	83 (37.4)	99 (44.6)	42 (38.2)	39 (35.5)
Fatigue[5]	74 (33.3)	3 (1.4)	35 (31.8)	1 (0.9)
Decreased appetite	63 (28.4)	3 (1.4)	28 (25.5)	1 (0.9)
Vomiting	55 (24.8)	1 (0.5)	23 (20.9)	1 (0.9)

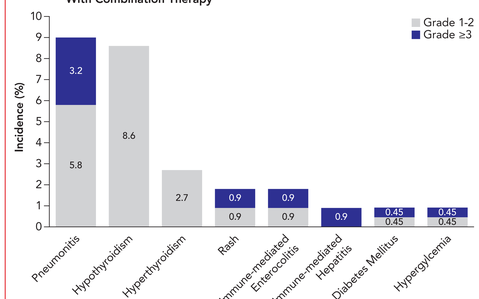
Data presented as n (%).
[1]Anemia included reports of anemia, hemoglobin decreased, and red blood cell count decreased.
[2]Leukopenia included reports of white blood cell count decreased and leukopenia.
[3]Thrombocytopenia included reports of platelet count decreased and thrombocytopenia.
[4]Neutropenia included reports of neutrophil count decreased and neutropenia.
[5]Fatigue included asthenia, fatigue, and malaise.
Abbreviations: PP, pemetrexed+platinum.

CONCLUSIONS

- The addition of tislelizumab resulted in significantly improved PFS_{IRC} (9.7 months vs 7.6 months; *P*=0.0044, HR=0.645 [95% CI: 0.462, 0.902]) as well as higher ORR_{IRC} and longer DoR_{IRC} than observed with chemotherapy alone in patients with advanced nsq-NSCLC
- First-line treatment with tislelizumab in combination with platinum and pemetrexed was generally well tolerated
  - Most AEs were mild or moderate in severity and were manageable
  - No new safety signals were identified with the addition of tislelizumab to standard chemotherapy
- The results from this pivotal phase 3 study support tislelizumab in combination with platinum and pemetrexed as a potential new standard for first-line treatment of advanced nsq-NSCLC

- Across the entire study, nine patients (n=7 [*A*]; n=2 [*B*]) experienced a TEAE that led to death
  - In *Arm A*, fatal TEAEs were pneumonitis (n=3), asphyxia, atrial fibrillation, cerebellar hemorrhage, and unspecified death (n=1 each)
  - In *Arm B*, fatal TEAEs were pneumonitis and embolism (n=1 each)
  - Four patients experienced AEs leading to death that were considered by the investigator to be related to any component of study treatment (1%; n=3 [*A*]; n=1 [*B*]; all were pneumonitis)
- Immune-mediated AEs were reported in 57 patients (25.7%) in the tislelizumab plus chemotherapy treatment arm, of which 30 were treated with systemic corticosteroids/immunosuppressive drugs
- The most commonly reported immune-mediated AEs were pneumonitis (n=20, 9.0%), hypothyroidism (n=19, 8.6%), and hyperthyroidism (n=6, 2.7%); most were mild-to-moderate in severity (Figure 4)

Figure 4: Immune-Mediated AEs by Preferred Term Occurring in ≥2 Patients Treated With Combination Therapy



Immune-mediated AEs were selected from a list of preferred terms specified by the sponsor regardless of whether the investigator attributed the event to a trial regimen or considered the event to be immune-mediated.
Abbreviation: AE, adverse event.

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CONFLICTS OF INTEREST

SL reports a consulting or advisory role with AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Hengrui Therapeutics, Hutchison Medipharma, and Roche; speaker fees from AstraZeneca, Hanaoh Pharma, and Roche; and is an advisor and consultant for AstraZeneca, Boehringer Ingelheim, GenomiCare Biotechnology, Hutchison Medipharma, Roche, Simcere, and Zai Lab. **YB, JQ, LL** are employees of Beigene with stock options. **JC, YH, XL, CX, DW, YL, WL, ZM, JW, YS, MW, ZW, YY, XY, JZ,** and **WZ** have nothing to disclose.

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