Tislelizumab Plus Chemotherapy vs Chemotherapy Alone as First-line Treatment for Advanced Squamous Non-Small Cell Lung Cancer

Jie Wang[1], Shun Lu[2], Chunhong Hu[3], Yuping Sun[4], Kunyu Yang[5], Mingwei Chen[6], Jun Zhao[7], Guohua Yu[8], Xiangdong Zhou[9], Guosheng Feng[10], Yueyin Pan[11], Yan Yu[12], Jing Zhang[13], Liang Liang[13], Xiao Lin[13] Jiuwei Cui[14]

[1]National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China; [2]Shanghai Chest Hospital, Shanghai, China; [3]The Second Hospital of Central South University, Changsha, China; [4]Jinan Central Hospital, Shandong, China; [5]Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Hubei, China; [6]The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; [7]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education, Beijing), Department of Thoracic Medical Oncology, Peking University Cancer Hospital & Institute, Beijing, China; [8]Weifang People's Hospital, Weifang, China; [9]The First Hospital Affiliated to AMU (Southwest Hospital), Luzhou, China; [10]The People's Hospital of Guangxi Zhuang Autonomous Region, Nanning, China; [11]Anhui Provincial Hospital, Hefei, China; [12]The Harbin Medical Cancer Hospital, The 3rd Department of Thoracic Oncology, Harbin, China; [13]BeiGene (Beijing) Co., Ltd., Beijing, China; [14]The First Hospital of Jilin University, Changchun, China

Background PD-1/L1 inhibitors have provided new treatment approaches for patients with advanced NSCLC; however, resistance or low PD-L1 expression may limit clinical benefit. Tislelizumab, an anti-PD-1 monoclonal antibody, was engineered to minimize binding to FcγR on macrophages to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy. Tislelizumab, alone and with chemotherapy, demonstrated antitumor activity and was generally well tolerated in patients with advanced NSCLC, irrespective of PD-L1 expression.

Method This open-label phase 3 study (NCT03594747) evaluated the efficacy and safety/tolerability of tislelizumab plus chemotherapy as first-line treatment in Chinese patients with histologically confirmed stage IIIB/IV squamous NSCLC. Patients (randomized 1:1:1) received IV Q3W: tislelizumab (200 mg, D1) plus paclitaxel (175 mg/m^2, D1) and carboplatin (AUC 5, D1) (*Arm A*); tislelizumab plus *nab*-paclitaxel (100 mg/m^2; D1, 8, and 15) and carboplatin (AUC 5, D1) (*Arm B*); or paclitaxel (175 mg/m^2, D1) and carboplatin (AUC 5, D1) (*Arm C*). Patients were stratified by disease stage (IIIB vs IV) and tumor cell PD-L1 expression (<1% vs 1-49% vs ≥50%) as assessed using VENTANA PD-L1 (SP263) Assay. Chemotherapy was administered for 4-6 cycles at investigator's discretion; cross over to tislelizumab monotherapy was allowed for patients in *Arm C*. The primary endpoint was PFS by Independent Review Committee per RECIST v1.1; secondary endpoints included ORR, DoR per RECIST v1.1, OS, and safety/tolerability.

Results Across the 360 patients, PFS was significantly improved and higher ORR/DoR was observed with combination treatment (*A* and *B*) versus chemotherapy (*C*); there was no apparent relationship between PD-L1 expression and PFS or ORR (**Table**). Across all arms, median OS was not reached. Median number of treatment cycles was comparable across all arms and discontinuation of any treatment due to AEs was reported in 12.5%, 29.7%, and 15.4% of patients in *Arms A*, *B*, and *C*, respectively. The most common grade ≥3 AE was decreased neutrophil count, in line with known hematological toxicity of chemotherapy. Treatment-related AEs leading to death occurred in six patients (n=1 [*A*]; n=2 [*B*]; n=3 [*C*]); none were solely attributed to tislelizumab.

Conclusion First-line tislelizumab plus paclitaxel/carboplatin or *nab*-paclitaxel/carboplatin significantly improved PFS for patients with squamous NSCLC and demonstrated higher ORR than

chemotherapy alone, irrespective of PD-L1 expression. The safety profile was comparable with those of tislelizumab, chemotherapy, and underlying NSCLC; no new safety signals were identified with the addition of tislelizumab to chemotherapy.

ITT Population (N=360)	***Arm A* (n=120)**	***Arm B* (n=119)**	***Arm C* (n=121)**
Median PFS, mo (95% CI)	**7.6 (6.0-9.8)**	**7.6 (5.8-11.0)**	**5.5 (4.2-5.7)**
HR[a] (95% CI)	0.52 (0.4-0.7)	0.48 (0.3-0.7)	NA
P-value[b]	0.0001	<0.0001	
ORR, % (95% CI)	**72.5 (63.6, 80.3)**	**74.8 (66.0, 82.3)**	**49.6 (40.4, 58.8)**
Median DoR, (95% CI)	**8.2 (5.0, NE)**	**8.6 (6.3, NE)**	**4.2 (2.8, 4.9)**
PD-L1 ≥50% TC (N=125)	***Arm A* (n=42)**	***Arm B* (n=42)**	***Arm C* (n=41)**
Median PFS, mo (95% CI)	**7.6 (5.6, 9.8)**	**7.6 (5.6, NE)**	**5.5 (4.1, 7.0)**
HR[c] (95% CI)	0.501 (0.282, 0.891)	0.425 (0.232, 0.776)	NA
ORR, % (95% CI)	**78.6 (63.2, 89.7)**	**88.1 (74.4, 96.0)**	**53.7 (37.4, 69.3)**
PD-L1 1-49% TC (N=91)	***Arm A* (n=30)**	***Arm B* (n=30)**	***Arm C* (n=31)**
Median PFS, mo (95% CI)	**7.6 (5.5, NE)**	**NE (5.6, NE)**	**4.2 (2.8, 6.5)**
HR[c] (95% CI)	0.439 (0.221, 0.870)	0.311 (0.145, 0.664)	NA
ORR, % (95% CI)	**70.0 (50.6, 85.3)**	**66.7 (47.2, 82.7)**	**41.9 (24.5, 60.9)**
PD-L1 <1% TC (N=144)	***Arm A* (n=48)**	***Arm B* (n=47)**	***Arm C* (n=49)**
Median PFS, mo (95% CI)	**7.6 (5.5, NE)**	**7.4 (5.6, 9.7)**	**5.5 (4.2, 7.0)**
HR[c] (95% CI)	0.636 (0.368, 1.101)	0.692 (0.406, 1.178)	NA
ORR, % (95% CI)	**68.8 (53.7, 81.3)**	**68.1 (52.9, 80.9)**	**51.0 (36.3, 65.6)**

Abbreviations: CI, confidence interval; DoR, duration of response; HR, hazard ratio; ITT, intention-to-treat; mo, months; NA, not available; NE, not evaluable; ORR, objective response rate; PFS, progression-free survival; TC, tumor cell.
[a]Stratified; [b]One-sided log-rank test; [c]Non-stratified.