RATIONALE-307: Tislelizumab plus chemotherapy versus chemotherapy alone as first-line treatment for advanced squamous NSCLC in patients aged ≥ 65 years

Jie Wang,[1] Shun Lu,[2] Xinmin Yu,[3] Yanping Hu,[4] Yuping Sun,[5] Zhijie Wang,[1] Jun Zhao,[6] Yan Yu,[7] Chunhong Hu,[8] Kunyu Yang,[9] Guosheng Feng,[10] Kejing Ying,[11] Wu Zhuang,[12] Jianying Zhou,[13] Jingxun Wu,[14] Shiang Jiin Leaw,[15] Jing Zhang,[15] Xiao Lin,[15] Nong Yang[16]

[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]Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China; [3]Zhejiang Cancer Hospital, Hangzhou, China; [4]Hubei Cancer Hospital, Wuhan, China; [5]Jinan Central Hospital, Shandong, China; [6]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education, Beijing), Department of Thoracic Medical Oncology, Peking University Cancer Hospital & Institute, Beijing, China; [7]Harbin Medical University Cancer Hospital, Harbin, China; [8]The Second Hospital of Central South University, Changsha, China; [9]Union Hospital Tongji Medical College Huazhong University of Science and Technology, Hubei, China; [10]The People's Hospital of Guangxi Zhuang Autonomous Region, Nanning, China; [11]Sir Run Run Shaw Hospital, Zhejiang University, School of Medicine, Zhejiang, China; [12]Fujian Tumor Hospital, Fuzhou, China; [13]The First Affiliated Hospital, Zhejiang University, Zhejiang, China; [14]The First Affiliated Hospital of Xiamen University, Fujian, China; [15]BeiGene (Beijing) Co., Ltd., Beijing, China; [16]Department of Medical Oncology, Lung Cancer and Gastrointestinal Unit, Hunan Cancer Hospital/The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, China.

Disclosures

- **Consulting or Advisory Role**
  - Roche, AstraZeneca, Boehringer Ingelheim, Hutchison MediPharma, Simcere Pharmaceutical Group, Pfizer, Zai Lab, GenomiCare, Yuhan, PrIME Oncology, Menarini
- **Speakers' Bureau**
  - Roche, AstraZeneca, Hansoh, Hengrui Therapeutics
- **Research Funding**
  - Roche, AstraZeneca, Hansoh, Hengrui Therapeutics, Bristol-Myers Squibb

Background

Tislelizumab is an anti-PD-1 antibody engineered to minimize binding to FcγR on macrophages, thereby abrogating antibody-dependent phagocytosis, a potential mechanism of resistance to anti-PD-1 therapies[1,2]

RATIONALE-307 (NCT03594747) was an open-label, randomized, multicenter Phase 3 study that aimed to compare the efficacy and safety of tislelizumab plus chemotherapy versus chemotherapy alone as a first-line treatment for advanced squamous NSCLC[3]

Patients were randomized (1:1:1) to receive one of the following regimens intravenously on a 21-day cycle: **Arm A,** tislelizumab plus paclitaxel and carboplatin; **Arm B**, tislelizumab plus nab-paclitaxel and carboplatin; **Arm C**, paclitaxel and carboplatin[3]

IRC-assessed PFS was significantly improved with tislelizumab plus chemotherapy (Arm A, 7.6 months; Arm B, 7.6 months) versus chemotherapy alone (Arm C, 5.5 months; HR 0.52 (95% CI, 0.37–0.74; P < 0.001 [A versus C]) and 0.48 (95% CI, 0.34–0.68; P < 0.001 [B versus C])[3]

Tislelizumab in combination with chemotherapy has been approved for first-line advanced squamous NSCLC in China, based on the RATIONALE-307 study[4]

Here, we report the results of a sub-analysis of patients ≥ 65 years of age from the RATIONALE 307 study. Methods have been described previously[3,5]

1. Qin S, et al. Future Oncol 2019;15:1811–22; 2. Zhang T, et al. Cancer Immunol Immunother 2018;67:1079–90; 3. Wang J, et al. JAMA Oncol 2021:7:709–17; 4. BeiGene. Press Releases: China National Medical Products Administration Approves Tislelizumab in Combination with Chemotherapy in First-Line Advanced Squamous Non-Small Cell Lung Cancer. Available at: https://ir.beigene.com/news-releases/news-release-details/china-national-medical-products-administration-approves Accessed April 2021; 5. Wang J, et al. JAMA Oncol 2021:7:709–17, S1.

CI, confidence interval; FcγR, Fcγ receptors; HR, hazard ratio; IRC, independent review committee; nab, nanoparticle albumin-bound; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein-1; PFS, progression-free survival

Results

- Between July 2018 and December 2019*, 127 patients **aged ≥ 65 years** were randomized to Arm A (n=39), Arm B (n=52), and Arm C (n=36)
- The median age was 68 years, and 120 (94.5%) patients were male
  - The majority of patients were former smokers (63.0%), 22.8% were current smokers, and 14.2% never smoked
  - 69.3% had stage IV disease and 30.7% had stage IIIB disease
- At the data cut-off on December 6, 2019, 53 patients (41.7%) remained on treatment
  - The most common reasons for discontinuation of tislelizumab plus chemotherapy treatment (Arms A and B) were adverse events (15.4%) and progressive disease (15.4%)
  - The most common reasons for discontinuation of chemotherapy only (Arm C) were adverse events (19.4%) and progressive disease (11.1%)
- 16 patients from Arm C crossed over to maintenance tislelizumab monotherapy upon disease progression

*Data cut-off: December 6, 2019

Demographics and baseline characteristics in patients ≥ 65 years old (ITT population)

	Arm A Tislelizumab + PC (n=39)	Arm B Tislelizumab + *nab*-PC (n=52)	Arm C PC (n=36)	Total (N=127)
Median age (range), years	67 (65–74)	68 (65–74)	68 (65–74)	68 (65–74)
Sex, n (%)				
Male	35 (89.7)	50 (96.2)	35 (97.2)	120 (94.5)
ECOG PS, n (%)				
0	12 (30.8)	12 (23.1)	10 (27.8)	34 (26.8)
1	27 (69.2)	40 (76.9)	26 (72.2)	93 (73.2)
Smoking status, n (%)				
Never	6 (15.4)	5 (9.6)	7 (19.4)	18 (14.2)
Current	10 (25.6)	11 (21.2)	8 (22.2)	29 (22.8)
Former	23 (59.0)	36 (69.2)	21 (58.3)	80 (63.0)
Disease stage, n (%)				
IIIB	10 (25.6)	15 (28.8)	14 (38.9)	39 (30.7)
IV	29 (74.4)	37 (71.2)	22 (61.1)	88 (69.3)
TC PD-L1 expression, n (%)				
< 1%	19 (48.7)	27 (51.9)	14 (38.9)	60 (47.2)
1–49%	9 (23.1)	15 (28.8)	8 (22.2)	32 (25.2)
≥ 50%	11 (28.2)	10 (19.2)	14 (38.9)	35 (27.6)

Data cut-off: December 6, 2019

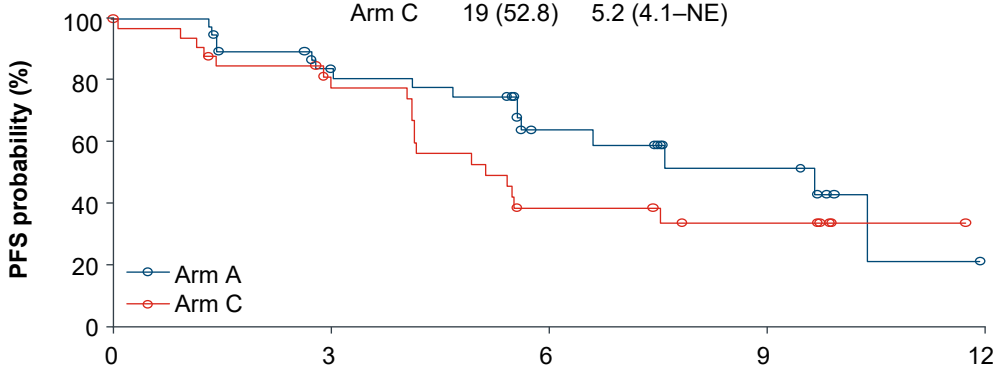
ECOG PS, Eastern Cooperative Oncology Group Performance Status; ITT, intention-to-treat; nab, nanoparticle albumin-bound; PC, paclitaxel and carboplatin; PD-L1, programmed death-ligand 1; TC, tumor cell

Results: Tumor response and efficacy in patients aged ≥ 65 years

The **PFS by IRC** was **longer** in patients treated with **tislelizumab plus chemotherapy** (Arm A and Arm B) compared with chemotherapy alone (Arm C)

Arm A vs Arm C

	Events (%)	Median (95% CI)	Hazard ratio (95% CI)
Arm A	16 (41.0)	9.7 (5.6–NE)	0.602 (0.309–1.175)
Arm C	19 (52.8)	5.2 (4.1–NE)	

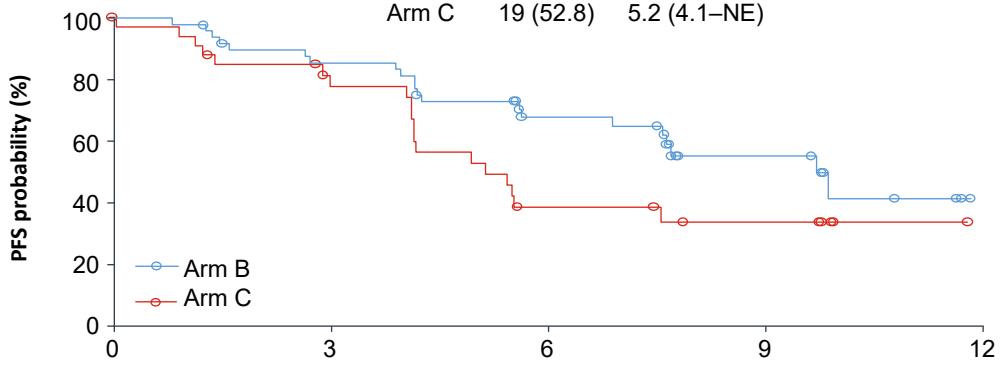


Number at risk:

Arm A	39	29	13	7	0
Arm C	36	23	10	6	0

Arm B vs Arm C

	Events (%)	Median (95% CI)	Hazard ratio (95% CI)
Arm B	21 (40.4)	9.7 (6.9–NE)	0.564 (0.302–1.052)
Arm C	19 (52.8)	5.2 (4.1–NE)	



Number at risk:

Arm B	52	41	24	11	0
Arm C	36	23	10	6	0

*Data cut-off: December 6, 2019

CI, confidence interval; DoR, duration of response; HR, hazard ratio; IRC, independent review committee; ORR, overall response rate; PFS, progression-free survival

Results: Tumor response and efficacy in patients aged ≥ 65 years

	Arm A Tislelizumab + PC (n=39)	Arm B Tislelizumab + *nab*-PC (n=52)	Arm C PC (n=36)
ORR, % (95% CI)	69.2 (52.4–83.0)	75.0 (61.1–86.0)	50.0 (32.9–67.1)
ORR difference, % (95% CI)	16.6 (-6.03–39.32)	27.8 (8.33–47.17)	
Complete response, n (%)	3 (7.7)	2 (3.8)	0 (0.0)
Partial response, n (%)	24 (61.5)	37 (71.2)	18 (50.0)
DoR, months, median (95% CI)	6.9 (2.79–NE)	NE (8.34–NE)	6.2 (2.76–NE)
HR (95% CI)	0.69 (0.26–1.87)	0.51 (0.20–1.31)	

ORR by IRC was higher in Arms A (69.2%) and B (75.0%) versus Arm C (50.0%)

The median DoR was 6.9 months in Arm A and 6.2 months in Arm C (HR: 0.69; 95% CI, 0.26–1.87). Median DoR was not reached in Arm B

*Data cut-off: December 6, 2019

CI, confidence interval; DoR, duration of response; HR, hazard ratio; IRC, independent-review committee; nab, nanoparticle albumin-bound; NE, not estimable; ORR, objective response rate; PC, paclitaxel and carboplatin

Results: Safety in patients aged ≥ 65 years

	Arm A Tislelizumab + PC (n=39)	Arm B Tislelizumab + *nab*-PC (n=52)	Arm C PC (n=34)
Patients with ≥1 TEAE	39 (100.0)	52 (100.0)	34 (100.0)
≥ Grade 3	34 (87.2)	45 (86.5)	30 (88.2)
Serious	17 (43.6)	22 (42.3)	9 (26.5)
≥ Grade 3 serious	13 (33.3)	19 (36.5)	5 (14.7)
Leading to treatment discontinuation	7 (17.9)	17 (32.7)	8 (23.5)
Leading to death	2 (5.1)	4 (7.7)	2 (5.9)
Patients with ≥1 TRAE	38 (97.4)	52 (100.0)	34 (100.0)
≥ Grade 3	33 (84.6)	44 (84.6)	28 (82.4)
Serious	12 (30.8)	17 (32.7)	6 (17.6)
Leading to death	1 (2.6)	1 (1.9)	1 (2.9)

The safety profile in patients ≥ 65 years of age was consistent with the overall patient population (≥ 18 years of age)[1]

In patients ≥ 65 years of age, TEAEs leading to permanent discontinuation of tislelizumab were similar between Arms A (6 patients [15.4%]) and B (8 patients [15.4%])

One TEAE-related death in Arm A and 1 in Arm B were reported as related to tislelizumab

*Data cut-off: December 6, 2019

nab, nanoparticle albumin-bound; PC, paclitaxel and carboplatin; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event

1. Wang J, et al. JAMA Oncol 2021:7:709–17

Results: Safety in patients aged ≥ 65 years

Confirmed immune-mediated TEAEs were reported in 14 (35.9%) patients in Arm A and 18 (34.6%) patients in Arm B

Most were mild or moderate, and did not lead to discontinuation of any treatment component

The most common immune-mediated TEAE of any Grade was **hypothyroidism** (10 patients [11%])

The most common Grade ≥ 3 immune-mediated TEAE was immune-mediated **pneumonitis** (2 patients [2%])

*Data cut-off: December 6, 2019
TEAE, treatment-emergent adverse event

Results: Safety

TRAEs (≥ 20%) in patients ≥ 65 years old (safety population)

Preferred term, n (%)	Arm A Tislelizumab + PC (n=39)		Arm B Tislelizumab + *nab*-PC (n=52)		Arm C PC (n=34)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Patients with at least one event	38 (97.4)	33 (84.6)	52 (100.0)	44 (84.6)	34 (100.0)	28 (82.4)
Anemia	32 (82.1)	2 (5.1)	45 (86.5)	10 (19.2)	25 (73.5)	4 (11.8)
Alopecia	23 (59.0)	0 (0.0)	35 (67.3)	0 (0.0)	24 (70.6)	0 (0.0)
Leukopenia	16 (41.0)	7 (17.9)	27 (51.9)	15 (28.8)	20 (58.8)	9 (26.5)
Neutropenia	16 (41.0)	11 (28.2)	19 (36.5)	12 (23.1)	18 (52.9)	16 (47.1)
Decreased appetite	14 (35.9)	0 (0.0)	21 (40.4)	0 (0.0)	9 (26.5)	0 (0.0)
Alanine aminotransferase increased	13 (33.3)	1 (2.6)	16 (30.8)	1 (1.9)	4 (11.8)	0 (0.0)
Platelet count decreased	13 (33.3)	2 (5.1)	20 (38.5)	6 (11.5)	9 (26.5)	1 (2.9)
Aspartate aminotransferase increased	12 (30.8)	0 (0.0)	14 (26.9)	1 (1.9)	2 (5.9)	0 (0.0)
Pain in extremity	11 (28.2)	1 (2.6)	3 (5.8)	0 (0.0)	11 (32.4)	0 (0.0)
Thrombocytopenia	8 (20.5)	1 (2.6)	18 (34.6)	2 (3.8)	10 (29.4)	3 (8.8)
Nausea	8 (20.5)	0 (0.0)	16 (30.8)	0 (0.0)	10 (29.4)	0 (0.0)
Vomiting	8 (20.5)	0 (0.0)	10 (19.2)	0 (0.0)	4 (11.8)	0 (0.0)
Asthenia	8 (20.5)	0 (0.0)	7 (13.5)	0 (0.0)	5 (14.7)	0 (0.0)
Neurotoxicity	8 (20.5)	0 (0.0)	3 (5.8)	0 (0.0)	2 (5.9)	0 (0.0)
Malaise	5 (12.8)	1 (2.6)	10 (19.2)	0 (0.0)	9 (26.5)	0 (0.0)

*Data cut-off: December 6, 2019

TEAE, treatment-emergent adverse event; PC, paclitaxel and carboplatin

Summary and conclusions

- Lung cancer is most frequently diagnosed among people aged 65–74 years[1,2]
- Older patients often have a higher rate of immunosenescence[3]* and comorbidities compared with younger patients. Therefore, it is important to assess efficacy and safety of immunotherapy in this subgroup of patients[3–5]
- The majority of the total of 127 patients aged ≥ 65 years in all 3 Arms were former or current smokers
- In this sub-analysis, improvements in PFS, ORR and DoR demonstrated the treatment benefits of tislelizumab in combination with paclitaxel/nab-paclitaxel and carboplatin in patients aged ≥ 65 years with advanced squamous NSCLC
- The safety profile, including immune-mediated TEAEs, of tislelizumab in patients aged ≥ 65 years was consistent with the safety profile for the overall patient population[6,7]

*Immunosenescence refers to the gradual deterioration of our immune system as we get older[8]

ORR, overall response rate; PFS, progression-free survival; TRAE, treatment-related adverse event

1. de Groot PM, et al. Transl Lung Cancer Res 2018;7(3):220–233; 2. Zhou C. Transl Lung Cancer Res 2014;3(5):270–279; 3. Sun YM, et al. Front Oncol 2020;10:558454; 4. Takigawa N, et al. Cancers (Basel) 2020;12:1995; 5. Aiello A, et al. Front Immunol 2019;25;10:2247; 6. Wang J, et al. JAMA Oncol 2021:7:709–17; 7. Wang J, et al. JAMA Oncol 2021:7:709–17 doi: 10.1001/jamaoncol.2021.0366. Online ahead of print. Supplement 1

Acknowledgements

- The authors would like to thank the patients and their families for their participation in the study, and the site personnel for their support during the conduct of this important trial
- This study is sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Tamsin Grewal, MSc, and Jenny Feehan, BSc, of Ashfield MedComms, an Ashfield Health company, and was funded by BeiGene, Ltd