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

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Poster No. 9102

Introduction and methods

- Tislelizumab is an anti-PD-1 antibody engineered to minimize binding to Fcγ receptors (FcγR) on macrophages, thereby abrogating antibody-dependent phagocytosis, a potential mechanism of resistance to anti-PD-1 therapies[1,2]
- RATIONALE 307 was an open-label, randomized, multicenter Phase 3 study that aimed to compare the efficacy and safety of tislelizumab plus chemotherapy vs chemotherapy alone as a first-line treatment for advanced squamous non-small cell lung cancer (NSCLC)[3]
- Independent review committee (IRC)-assessed progression-free survival (PFS) was significantly improved with tislelizumab plus chemotherapy (arm A, 7.6 months; arm B, 7.6 months) vs chemotherapy alone (arm C, 5.5 months; hazard ratios (HRs) were 0.524 (95% CI, 0.370–0.742; $P < 0.001$ [A vs C]) and 0.478 (95% CI, 0.336–0.679; $P < 0.001$ [B vs C])[3]
- Tislelizumab in combination with chemotherapy has been approved for first-line advanced squamous NSCLC in China, based on the RATIONALE 307 (NCT03594747) 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]
- **Scan QR code to view the primary publication of RATIONALE 307:**

Results

Patients

- 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 68.0 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 (**Table 1**)

Table 1. Demographics and baseline characteristics in patients ≥ 65 years old (ITT analysis set)

	Arm A Tislelizumab + PC (n=39)	Arm B Tislelizumab + nab-PC (n=52)	Arm C PC (n=36)	Total (n=127)
Age (years)				
Median (min, max)	67.0 (65, 74)	68.0 (65, 74)	68.0 (65, 74)	68.0 (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)
Current 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)

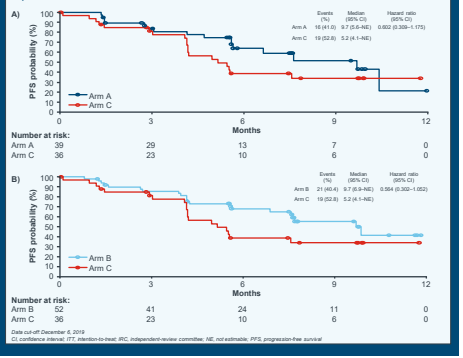
Data cut-off: December 6, 2019
ECOG PS, Eastern Cooperative Oncology Group Performance Status; ITT, intention-to-treat; PC, paclitaxel and carboplatin; PD-L1, programmed death-ligand 1; TC, tumor cell

Conclusions

- Lung cancer is most frequently diagnosed among people aged 65–74 years.[6,7] Older patients often have a higher rate of immunosenescence[8]* and comorbidities compared with younger patients. Therefore, it is important to assess efficacy and safety of immunotherapy in this subgroup of patients[8–10]
- In this sub-analysis, improvements in PFS and ORR 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[3,5]

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

Figure 1. PFS by IRC in patients ≥ 65 years old (ITT analysis set) in:
A) Arm A vs Arm C
B) Arm B vs Arm C



CI, confidence interval; ITT, intention-to-treat; IRC, independent-review committee; NE, not estimable; PFS, progression-free survival

- As of 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

Tumor response and efficacy

- The PFS by IRC was longer in patients treated with tislelizumab plus chemotherapy (Arm A and Arm B) compared with chemotherapy alone (Arm C) (**Figure 1**)
  - The median PFS by IRC was 9.7 months in Arm A and 5.2 months in Arm C (HR: 0.602; 95% CI, 0.309–1.175)
  - The median PFS by IRC was 9.7 months in Arm B and 5.2 months in Arm C (HR: 0.564; 95% CI, 0.302–1.052)
- The objective response rate (ORR) by IRC was higher in Arms A (69.2%) and B (75.0%) vs Arm C (50.0%) (**Table 2**)
- The median duration of response (DoR) was 6.9 months in Arm A and 6.2 months in Arm C (HR: 0.694; 95% CI, 0.258–1.864). The median DoR was not reached in Arm B (**Table 2**)

Table 2. Disease response and DoR by IRC in patients ≥ 65 years old (ITT analysis set)

	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)	0.694 (0.258–1.864)	0.512 (0.201–1.307)	

Data cut-off: December 6, 2019
CI, confidence interval; DoR, duration of response; HR, hazard ratio; IRC, independent-review committee; NE, not estimable; ORR, objective response rate; PC, paclitaxel and carboplatin

Safety

- Tislelizumab's safety profile in patients ≥ 65 years of age is outlined in **Table 3**
- The safety profile in patients ≥ 65 years of age was consistent with the overall patient population (≥ 18 years of age)[3]
  - In the full patient population, most patients experienced ≥ 1 treatment-emergent adverse event (TEAE) and 88.3%, 86.4%, and 83.8% experienced Grade ≥ 3 TEAEs in treatments Arms A, B and C, respectively[5]
- In patients ≥ 65 years of age, TEAEs leading to permanent discontinuation of tislelizumab were similar between Arm A (6 patients [15.4%]) and B (8 patients [15.4%])
- Treatment-related adverse events (TRAEs) occurring in ≥ 20% of patients in any treatment group are listed in **Table 4**
  - 2 (5.1%) patients in Arm A, 4 (7.7%) in Arm B and 2 (5.9%) in Arm C reported a TEAE leading to death. 1 in Arm A and 1 in Arm B were reported as related to tislelizumab
- 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 was hypothyroidism (10 patients [11%]), and the most common Grade ≥ 3 immune-mediated TEAE was immune-mediated pneumonitis (2 patients [2%])

Table 3. Overall summary of TEAEs and TRAEs in patients ≥ 65 years old (safety analysis set)

n (%)	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)

Data cut-off: December 6, 2019
PC, paclitaxel and carboplatin; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event

Table 4. TRAEs (≥ 20%) in patients ≥ 65 years old (safety analysis set)

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
TRAE, treatment-related adverse event; PC, paclitaxel and carboplatin

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Acknowledgements

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.

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