RATIONALE-304: Tislelizumab plus chemotherapy versus chemotherapy alone as first-line treatment for non-squamous NSCLC in patients aged 65–75 years

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Background and Methods

- Lung cancer is the most common cause of cancer death in patients aged 60–74 years in China.[1] Older patients often have a higher rate of immunosenescence and comorbidities compared with younger patients.[2] Therefore, it is important to assess the impact of aging on the effectiveness and safety of immunotherapy[2,3]
- Tislelizumab is a humanized IgG4 anti-programmed cell death protein 1 (PD-1) monoclonal antibody that was designed to minimize Fcγ receptor binding on macrophages in order to abrogate antibody-dependent cellular phagocytosis, a potential mechanism of resistance to anti-PD-1 therapy[4,5]
- RATIONALE-304 (NCT03663205) was an open-label, randomized, multicenter Phase 3 study that compared the efficacy and safety of tislelizumab plus chemotherapy vs chemotherapy alone as first-line treatment for patients with advanced non-squamous non-small cell lung cancer (nsq-NSCLC)[6]
- Independent review committee (IRC)-assessed median progression-free survival (PFS) was significantly improved with first-line tislelizumab plus chemotherapy vs chemotherapy alone in patients with locally advanced or metastatic nsq-NSCLC (hazard ratio [HR]=0.65, p=0.0044, median PFS: 9.7 vs 7.6 months, respectively).[6] Tislelizumab plus chemotherapy was also generally well tolerated[6]
- Here we report the efficacy and safety results in patients aged 65–75 years from the RATIONALE-304 study. Methods have been described previously[6]

- **Scan QR code to view the primary publication of RATIONALE-304:**

Results

Patients

- The intent-to-treat (ITT) population consisted of 334 patients, among which 97 patients were aged 65–75 years
- Demographics and baseline characteristics of patients aged 65–75 years in each treatment arm are presented in **Table 1**; apart from sex and disease stage, these were generally well balanced between arms

Table 1. Demographics and baseline characteristics of patients aged 65–75 years (ITT analysis set)

	Arm A TIS + chemo (n=60)	Arm B Chemo (n=37)
Age, years		
Median	68.0	69.0
Min, max	65, 75	65, 74
Sex, n (%)		
Male	50 (83.3)	26 (70.3)
Female	10 (16.7)	11 (29.7)
ECOG PS, n (%)		
0	11 (18.3)	9 (24.3)
1	49 (81.7)	28 (75.7)
Smoking status, n (%)		
Never	15 (25.0)	11 (29.7)
Current	8 (13.3)	4 (10.8)
Former	37 (61.7)	22 (59.5)
Disease stage, n (%)		
IIIB	13 (21.7)	3 (8.1)
IV	47 (78.3)	34 (91.9)
TC PD-L1 expression, n (%)		
<1%*	23 (38.3)	11 (29.7)
1–49%	11 (18.3)	8 (21.6)
≥ 50%	26 (43.3)	18 (48.6)
Histology, n (%)		
Adenocarcinoma	58 (96.7)	36 (97.3)
Mixed adeno-squamous	0 (0)	0 (0)
Other	2 (3.3)	1 (2.7)

*One patient in Arm A with unevaluable PD-L1 expression was included in the TC PD-L1 < 1% category
Chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intent-to-treat; PD-L1, programmed death-ligand 1; TC, tumor cell; TIS, tislelizumab

Conclusions

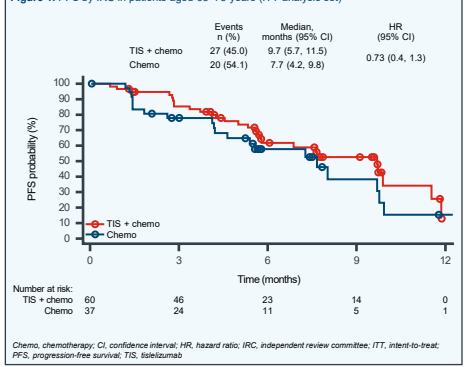
- In this subgroup analysis, observed **improvements in PFS and ORR** suggest **treatment benefits with tislelizumab combined with chemotherapy** in patients **aged 65–75 years** with locally advanced or metastatic **nsq-NSCLC**
- The **efficacy and safety results** observed in patients aged 65–75 years receiving tislelizumab in combination with chemotherapy were **consistent with those in the overall study patient population**[6]

- As of data cut-off (January 23, 2020), 40.0% of patients aged 65–75 years in Arm A and 16.2% in Arm B remained on treatment:
  - The most common reasons for discontinuation in Arm A vs Arm B included radiographic progression (30.0% vs 43.2%, respectively) and adverse events (13.3% vs 13.5%, respectively)
  - Nine patients from Arm B crossed over to receive tislelizumab monotherapy upon disease progression

Efficacy

- PFS by IRC in patients aged 65–75 years was longer in Arm A (tislelizumab plus chemotherapy) vs Arm B (chemotherapy alone). The HR was 0.73 (95% confidence interval [CI]: 0.4, 1.3), and median PFS was 9.7 vs 7.7 months, respectively (**Figure 1**; **Table 2**)
- Objective response rate (ORR) by IRC was 53.3% in Arm A versus 40.5% in Arm B. Out of 32 responders by IRC in Arm A and 15 responders by IRC in Arm B, median duration of response (DoR) by IRC was 8.5 months in both arms (**Table 2**)
- Investigator-assessed PFS, ORR and DoR were similar to the results by IRC (**Table 2**)

Figure 1. PFS by IRC in patients aged 65–75 years (ITT analysis set)



Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; IRC, independent review committee; ITT, intent-to-treat; PFS, progression-free survival; TIS, tislelizumab

Table 2. PFS and disease response in patients aged 65–75 years (ITT analysis set)

	IRC assessment		Investigator assessment	
	Arm A TIS + chemo (n=60)	Arm B Chemo (n=37)	Arm A TIS + chemo (n=60)	Arm B Chemo (n=37)
PFS				
Events, n (%)	27 (45.0)	20 (54.1)	26 (43.3)	21 (56.8)
HR (95% CI)	0.73 (0.4, 1.3)		0.63 (0.4, 1.1)	
Median, months	9.7	7.7	8.5	7.7
ORR, % (95% CI)	53.3 (40.0, 66.3)	40.5 (24.8, 57.9)	56.7 (43.2, 69.4)	37.8 (22.5, 55.2)
CR, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
PR, n (%)	32 (53.3)	15 (40.5)	34 (56.7)	14 (37.8)
DoR				
HR (95% CI)	0.99 (0.3, 3.1)		0.51 (0.2, 1.5)	
Median, months	8.5	8.5	8.5	7.1

HR for PFS was estimated using the Cox model. Median PFS was estimated using the Kaplan-Meier method. 95% CIs for ORR were calculated using the Clopper-Pearson method. DoR analysis included patients with objective response
Chemo, chemotherapy; CI, confidence interval; CR, complete response; DoR, duration of response; HR, hazard ratio; IRC, independent review committee; ITT, intent-to-treat; ORR, objective response rate; PFS, progression-free survival; PR, partial response; TIS, tislelizumab

Safety

- The safety profile of tislelizumab plus chemotherapy and chemotherapy alone in patients aged 65–75 years is outlined in **Table 3**, and was consistent with that in the overall patient population (≥ 18 years old)[6]
  - In the overall population, most patients experienced ≥ 1 treatment-emergent adverse event (TEAE), and 67.6% and 53.6% of patients experienced ≥ 1 TEAE at ≥ Grade 3 in Arms A and B, respectively[6,7]
  - All patients aged 65–75 years experienced ≥ 1 TEAE (**Table 3**)
  - Forty-three patients (72.9%) in Arm A and 18 patients (48.6%) in Arm B experienced ≥ 1 TEAE at ≥ Grade 3, while 26 patients (44.1%) in Arm A and nine patients (24.3%) in Arm B experienced ≥ 1 serious TEAE (**Table 3**); the percentage difference between the treatment arms was slightly larger in this cohort vs the overall population[7]
  - TEAEs leading to permanent discontinuation of any component of study treatment occurred in 19 patients (32.2%) in Arm A and five patients (13.5%) in Arm B (**Table 3**)
  - Treatment-related adverse events (TRAEs) were reported in 100.0% of patients in Arm A compared with 97.3% of patients in Arm B (**Table 3**)
- There were no TEAEs leading to death in Arm A (**Table 3**). One patient (2.7%) in Arm B experienced a TEAE leading to death (pneumonitis); this was considered related to treatment
- TRAEs occurring in ≥ 20% of patients in either treatment arm are listed in **Table 4**
- In Arm A, immune-mediated TEAEs were reported in 21 patients (35.6%). Most immune-mediated TEAEs were mild to moderate in severity, and ≥ Grade 3 immune-mediated TEAEs were reported in 8 patients (13.6%)
- The most common immune-mediated TEAEs were pneumonitis (n=8, 13.6%), colitis (n=4, 6.8%), and hypothyroidism (n=4, 6.8%)

Table 3. Overall summary of TEAEs and TRAEs in patients aged 65–75 years (safety analysis set)

TEAEs, n (%)	Arm A; TIS + chemo (n=59)	Arm B; Chemo (n=37)
Patients with ≥ 1 TEAE	59 (100.0)	37 (100.0)
≥ Grade 3	43 (72.9)	18 (48.6)
Serious	26 (44.1)	9 (24.3)
≥ Grade 3 serious	17 (28.8)	8 (21.6)
Leading to treatment discontinuation	19 (32.2)	5 (13.5)
Leading to death	0 (0)	1 (2.7)
Patients with ≥ 1 TRAE	59 (100.0)	36 (97.3)
≥ Grade 3	41 (69.5)	16 (43.2)
Serious	20 (33.9)	6 (16.2)
Leading to death	0 (0)	1 (2.7)

Adverse event grades were evaluated based on NCI CTCAE (version 5.0)
Chemo, chemotherapy; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; TIS, tislelizumab

Table 4. TRAEs (≥ 20%) in patients aged 65–75 years (safety analysis set)

Preferred term, n (%)	Arm A; TIS + chemo (n=59)		Arm B; Chemo (n=37)	
	Grade 1/2	≥ Grade 3	Grade 1/2	≥ Grade 3
Patients with ≥ 1 TRAE	59 (100.0)	41 (69.5)	36 (97.3)	16 (43.2)
Anemia*	41 (69.5)	12 (20.3)	22 (59.5)	5 (13.5)
Leukopenia†	37 (62.7)	13 (22.0)	22 (59.5)	7 (18.9)
Thrombocytopenia‡	33 (55.9)	12 (20.3)	20 (54.1)	7 (18.9)
Nausea	28 (47.5)	1 (1.7)	19 (51.4)	0 (0)
Decreased appetite	25 (42.4)	1 (1.7)	9 (24.3)	1 (2.7)
Neutropenia§	25 (42.4)	25 (42.4)	16 (43.2)	12 (32.4)
Alanine aminotransferase increased	22 (37.3)	1 (1.7)	11 (29.7)	0 (0)
Fatigue¶	22 (37.3)	2 (3.4)	14 (37.8)	1 (2.7)
Aspartate aminotransferase increased	21 (35.6)	1 (1.7)	14 (37.8)	0 (0)
Vomiting	16 (27.1)	1 (1.7)	7 (18.9)	0 (0)
Rash	13 (22.0)	0 (0)	1 (2.7)	0 (0)

Anemia included: Reports of anemia, hemoglobin decrease, and red blood cell count decrease; †Leukopenia included: Reports of white blood cell count decrease, and leukopenia; ‡Thrombocytopenia included: Reports of platelet count decrease and thrombocytopenia; §Neutropenia included: Reports of neutrophil count decrease and neutropenia; ¶Fatigue included: Asthenia, fatigue, and malaise
Chemo, chemotherapy; TRAE, treatment-related adverse event; TIS, tislelizumab

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