RATIONALE 304: Tislelizumab plus chemotherapy vs chemotherapy alone as first-line treatment for non-squamous non-small cell lung cancer in patients who are smokers vs non-smokers

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Introduction and methods

- Smoking is the leading risk factor for developing lung cancer in adults, with the risk of lung cancer increasing by up to 30-fold in smokers compared to non-smokers[1,2]
- Tislelizumab is a humanized immunoglobulin G4 monoclonal antibody with high affinity and binding specificity for programmed death protein 1 (PD-1)[3,4]
- Primary results from the RATIONALE 304 study showed that the addition of tislelizumab to chemotherapy resulted in significantly improved progression-free survival (PFS) and a consistent safety and tolerability profile compared with chemotherapy alone in the first-line treatment of advanced non-squamous non-small cell lung cancer (non-sq NSCLC)[5]
- Here, we report the results of a sub-analysis of patients who were smokers or non-smokers from the Phase 3 RATIONALE 304 study
- Methods have been described previously[5]
- **Scan QR code to view the primary publication of RATIONALE 304:**

Results

Patients

- Between July 2018 and July 2019, 334 patients aged 25–75 years were randomized 2:1 to either Arm A (n=223) or Arm B (n=111)[5]
- The median age was 61.0 years and 247 (74.0%) patients were male[5]
- In total, 213 (63.8%) patients were smokers and 121 (36.2%) were non-smokers (**Table 1**)

Table 1. Demographics and baseline characteristics in patients who were smokers or non-smokers (ITT analysis set)

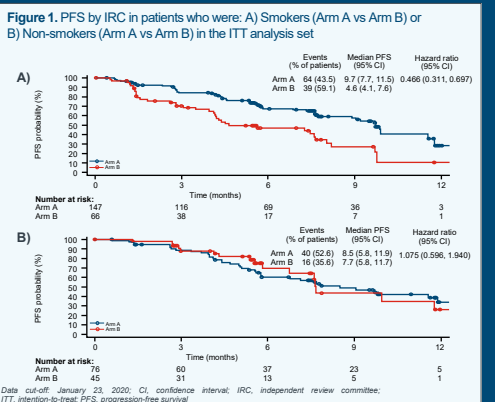
	Smokers		Non-smokers	
	Arm A TIS + PP (n=147)	Arm B PP (n=66)	Arm A TIS + PP (n=76)	Arm B PP (n=45)
Age (years)				
Median (min–max)	61.0 (27–75)	63.0 (25–74)	58.0 (32–75)	59.0 (40–74)
Sex, n (%)				
Male	147 (100.0)	64 (97.0)	21 (27.6)	15 (33.3)
ECOG PS, n (%)				
0	38 (25.9)	15 (22.7)	16 (21.1)	9 (20.0)
1	109 (74.1)	51 (77.3)	60 (78.9)	36 (80.0)
Smoking status, n (%)				
Never	0 (0.0)	0 (0.0)	76 (100.0)	45 (100.0)
Current	32 (21.8)	13 (19.7)	0 (0.0)	0 (0.0)
Former	115 (78.2)	53 (80.3)	0 (0.0)	0 (0.0)
Solid tumor stage, n (%)				
IIIB	26 (17.7)	13 (19.7)	14 (18.4)	8 (17.8)
IV	121 (82.3)	53 (80.3)	62 (81.6)	37 (82.2)
TC PD-L1 expression, n (%)				
< 1%	72 (49.0)	24 (36.4)	24 (31.6)	24 (53.3)
1–49%	32 (21.8)	15 (22.7)	21 (27.6)	12 (26.7)
≥ 50%	43 (29.3)	27 (40.9)	31 (40.8)	9 (20.0)

Data cut-off: January 23, 2020; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention-to-treat; PD-L1, programmed death-ligand 1; PP, pemetrexed + platinum; TC, tumor cell; TIS, tislelizumab

Conclusions

- In this sub-analysis, observed improvements in PFS and ORR suggest treatment benefits of tislelizumab plus chemotherapy in patients with advanced non-sq NSCLC
- The efficacy and safety results of tislelizumab plus chemotherapy in patients who were smokers with advanced non-sq NSCLC were consistent with the overall population of this Phase 3 RATIONALE 304 study[5]

Figure 1. PFS by IRC in patients who were: A) Smokers (Arm A vs Arm B) or B) Non-smokers (Arm A vs Arm B) in the ITT analysis set



Data cut-off: January 23, 2020; CI, confidence interval; IRC, independent review committee; ITT, intention-to-treat; PFS, progression-free survival

- As of data cut-off on January 23, 2020, 117 patients (35.0%) remained on treatment, of whom 75 (35.2%) patients were smokers and 42 (34.7%) patients were non-smokers
  - The most common reasons for discontinuation for patients who were smokers were radiographic progression (43.7%) and adverse events (9.4%). The most common reasons for discontinuation for patients who were non-smokers were radiographic progression (40.5%) and patient withdrawal of consent (14.0%)

Efficacy

- In patients who were smokers, PFS by independent review committee (IRC) was longer in Arm A compared with Arm B (**Figure 1A**)
  - Median PFS was 9.7 months in Arm A and 4.6 months in Arm B (HR: 0.466 [95% CI: 0.311, 0.697])
- In patients who were non-smokers, PFS by the IRC was similar between the two arms (**Figure 1B**)
  - Median PFS was 8.5 months in Arm A and 7.7 months in Arm B (HR: 1.075 [95% CI: 0.596, 1.940])
- The objective response rate (ORR) and median duration of response (DoR) for patients who were smokers or non-smokers are shown in **Table 2**
  - Regardless of smoking status, the ORR was higher with tislelizumab plus chemotherapy (Arm A) vs chemotherapy alone (Arm B)

Table 2. Disease response and DoR by IRC in patients who were smokers or non-smokers (ITT analysis set)

	Smokers		Non-smokers	
	Arm A TIS + PP (n=147)	Arm B PP (n=66)	Arm A TIS + PP (n=76)	Arm B PP (n=45)
ORR, % (95% CI)	61.2 (52.8, 69.1)	31.8 (20.9, 44.4)	50.0 (38.3, 61.7)	44.4 (29.6, 60.0)
Complete response, n (%)	5 (3.4)	0 (0.0)	2 (2.6)	1 (2.2)
Partial response, n (%)	85 (57.8)	21 (31.8)	36 (47.4)	19 (42.2)
Median DoR, months (95% CI)	8.5 (6.34, NE)	8.5 (5.98, NE)	7.4 (4.96, NE)	5.4 (4.44, NE)
HR, (95% CI)	0.938 (0.389, 2.262)		0.788 (0.354, 1.752)	

Data cut-off: January 23, 2020; CI, confidence interval; DoR, duration of response; HR, hazard ratio; IRC, independent review committee; ITT, intention-to-treat; NE, not estimable; ORR, objective response rate; PP, pemetrexed + platinum; TIS, tislelizumab

Safety

- The safety profile of tislelizumab plus chemotherapy and chemotherapy alone in patients who were smokers or non-smokers is outlined in **Table 3**
- The safety profile in patients who were smokers or non-smokers was consistent with the overall patient population[5]
  - Regardless of smoking status, most patients (97.7%–100.0%) experienced ≥ 1 treatment-emergent adverse event (TEAE)
  - Of the patients who were smokers, 67.8% and 54.5% of patients experienced ≥ 3 Grade TEAEs in Arms A and B, respectively
  - Of the patients who were non-smokers, 67.1% and 52.3% experienced ≥ 3 Grade TEAEs in Arms A and B, respectively
- In patients who were smokers, five (3.4%) patients in Arm A and two (3.0%) patients in Arm B reported a TEAE leading to death. Two TEAEs leading to death in Arm A were reported to be related to tislelizumab treatment (**Table 3**)
- In patients who were non-smokers, two (2.6%) patients in Arm A and no (0.0%) patients in Arm B reported a TEAE leading to death. One TEAE leading to death in Arm A was reported to be related to tislelizumab treatment (**Table 3**)
- Treatment-related adverse events (TRAEs) occurring in ≥ 20% of patients in any treatment group are listed in **Table 4**
- The most common immune-mediated TEAE occurring in patients who were smokers or non-smokers was pneumonitis (11.0%) and hypothyroidism (10.5%), respectively

Table 3. Overall summary of TEAEs and TRAEs in patients who were smokers or non-smokers (safety analysis set)

	Smokers		Non-smokers	
n (%)	Arm A TIS + PP (n=146)	Arm B PP (n=66)	Arm A TIS + PP (n=76)	Arm B PP (n=44)
Patients with ≥ 1 TEAE	146 (100.0)	66 (100.0)	76 (100.0)	43 (97.7)
≥ Grade 3	99 (67.8)	36 (54.5)	51 (67.1)	23 (52.3)
Serious	52 (35.6)	15 (22.7)	22 (28.9)	8 (18.2)
≥ Grade 3 serious	39 (26.7)	12 (18.2)	15 (19.7)	3 (6.8)
Leading to treatment discontinuation	39 (26.7)	6 (9.1)	18 (23.7)	4 (9.1)
Leading to death	5 (3.4)	2 (3.0)	2 (2.6)	0 (0.0)
Patients with ≥1 TRAE	145 (99.3)	64 (97.0)	76 (100.0)	43 (97.7)
≥ Grade 3	90 (61.6)	30 (45.5)	50 (65.8)	20 (45.5)
Serious	34 (23.3)	9 (13.6)	15 (19.7)	6 (13.6)
Leading to death	2 (1.4)	1 (1.5)	1 (1.3)	0 (0.0)

Data cut-off: January 23, 2020; PP, pemetrexed + platinum; TEAE, treatment-emergent adverse event; TIS, tislelizumab; TRAE, treatment-related adverse event

Table 4. TRAEs (≥ 20%) in patients who were smokers or non-smokers (safety analysis set)

	Smokers				Non-smokers			
Preferred term, n (%)	Arm A TIS + PP (n=146)		Arm B PP (n=66)		Arm A TIS + PP (n=76)		Arm B PP (n=44)	
	Grades 1–2	≥ Grade 3	Grades 1–2	≥ Grade 3	Grades 1–2	≥ Grade 3	Grades 1–2	≥ Grade 3
Patients with ≥ 1 event	145 (99.3)	90 (61.6)	64 (97.0)	30 (45.5)	76 (100.0)	50 (65.8)	43 (97.7)	20 (45.5)
Anemia[a]	97 (66.4)	24 (16.4)	44 (66.7)	7 (10.6)	54 (71.1)	6 (7.9)	27 (61.4)	4 (9.1)
Leukopenia[b]	86 (58.9)	34 (23.3)	38 (57.6)	9 (13.6)	49 (64.5)	14 (18.4)	27 (61.4)	7 (15.9)
Thrombocytopenia[c]	67 (45.9)	32 (21.9)	28 (42.4)	9 (13.6)	45 (59.2)	11 (14.5)	27 (61.4)	6 (13.6)
Alanine aminotransferase increased	63 (43.2)	3 (2.1)	20 (30.3)	2 (3.0)	29 (38.2)	5 (6.6)	25 (56.8)	1 (2.3)
Neutropenia[d]	61 (41.8)	60 (41.1)	25 (37.9)	24 (36.4)	22 (28.9)	39 (51.3)	17 (38.6)	15 (34.1)
Nausea	55 (37.7)	1 (0.7)	23 (34.8)	1 (1.5)	39 (51.3)	0 (0.0)	20 (45.5)	0 (0.0)
Aspartate aminotransferase increased	53 (36.3)	1 (0.7)	24 (36.4)	0 (0.0)	33 (43.4)	3 (3.9)	25 (56.8)	0 (0.0)
Decreased appetite	45 (30.8)	2 (1.4)	18 (27.3)	1 (1.5)	18 (23.7)	1 (1.3)	10 (22.7)	0 (0.0)
Fatigue[e]	45 (30.8)	3 (2.1)	18 (27.3)	1 (1.5)	29 (38.2)	0 (0.0)	17 (38.6)	0 (0.0)
Vomiting	30 (20.5)	1 (0.7)	11 (16.7)	1 (1.5)	25 (32.9)	0 (0.0)	12 (27.3)	0 (0.0)

Data cut-off: January 23, 2020; [a]Anemia included: reports of anemia, hemoglobin decreased, and red blood cell count decreased. [b]Leukopenia included reports of white blood cell count decreased and leukopenia.[c]Thrombocytopenia included: reports of platelet count decreased and thrombocytopenia. [d]Neutropenia included: reports of neutrophil count decreased and neutropenia. [e]Fatigue included asthenia, fatigue, and malaise; PP, pemetrexed + platinum; TIS, tislelizumab; TRAE, treatment-related adverse event

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