RATIONALE 307: Tislelizumab plus chemotherapy versus chemotherapy alone as first-line treatment for advanced squamous non-small cell lung cancer in patients who were smokers versus 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, a monoclonal antibody with high binding affinity to the programmed cell death protein 1 (PD-1) receptor, was specifically engineered to minimize Fcγ receptor binding on macrophages, thereby abrogating antibody-dependent phagocytosis, a mechanism of T cell clearance and potential resistance to anti-PD-1 therapy[3,4]
- Primary results from the RATIONALE 307 study (NCT03594747) showed that the addition of tislelizumab to chemotherapy resulted in a significant PFS benefit and manageable safety/tolerability profile compared with chemotherapy alone in patients with locally advanced or metastatic squamous non-small cell lung cancer (NSCLC)[5]
- Here, we report the results of a sub-analysis of patients who were smokers or non-smokers from the Phase 3 RATIONALE 307 study
- Methods have been described previously[5,6]
- **Scan QR code to view the primary publication of RATIONALE 307:**

Results

Patients

- Between July 2018 and December 2019, 360 patients aged 34–74 years were randomized into Arm A (n=120), Arm B (n=119), or Arm C (n=121)[5]
- The median age was 62.0 years and 330 (91.7%) patients were male. The majority of patients were former smokers (63.6%), 20.0% were current smokers, and 16.4% never smoked. 66.1% had stage IV disease and 33.9% had stage IIIB disease (**Table 1**)

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

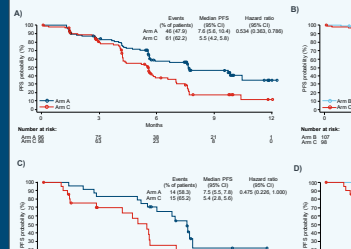
	Smokers			Non-smokers		
	Arm A TIS + PC (n=96)	Arm B TIS + nab-PC (n=107)	Arm C PC (n=98)	Arm A TIS + PC (n=24)	Arm B TIS +nab-PC (n=12)	Arm C PC (n=23)
Age (years)						
Median (min, max)	60.0 (41, 74)	63.0 (48, 74)	62.0 (47, 74)	57.0 (43, 73)	62.0 (38, 69)	57.0 (34, 70)
Sex, n (%)						
Male	95 (99.0)	106 (99.1)	98 (100.0)	12 (50.0)	6 (50.0)	13 (56.5)
ECOG PS, n (%)						
0	26 (27.1)	21 (19.6)	28 (28.6)	5 (20.8)	1 (8.3)	4 (17.4)
1	70 (72.9)	86 (80.4)	70 (71.4)	19 (79.2)	11 (91.7)	19 (82.6)
Smoking status, n (%)						
Never	0 (0.0)	0 (0.0)	0 (0.0)	24 (100.0)	12 (100.0)	23 (100.0)
Current	24 (25.0)	21 (19.6)	27 (27.6)	0 (0.0)	0 (0.0)	0 (0.0)
Former	72 (75.0)	86 (80.4)	71 (72.4)	0 (0.0)	0 (0.0)	0 (0.0)
Solid tumor stage, n (%)						
IIIB	31 (32.3)	40 (37.4)	36 (36.7)	7 (29.2)	0 (0.0)	8 (34.8)
IV	65 (67.7)	67 (62.6)	62 (63.3)	17 (70.8)	12 (100.0)	15 (65.2)
TC PD-L1 expression, n (%)						
< 1%	38 (39.6)	43 (40.2)	42 (42.9)	10 (41.7)	4 (33.3)	7 (30.4)
1–49%	27 (28.1)	27 (25.2)	27 (27.6)	3 (12.5)	3 (25.0)	4 (17.4)
≥ 50%	31 (32.3)	37 (34.6)	29 (29.6)	11 (45.8)	5 (41.7)	12 (52.2)

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; TIS, tislelizumab

Conclusions

- In this sub-analysis, improvements in PFS and ORR suggests that the observed treatment benefits of tislelizumab plus paclitaxel/*nab*-paclitaxel and carboplatin in patients with advanced squamous NSCLC are consistent with the ITT population, irrespective of smoking status
- The safety profile of tislelizumab plus paclitaxel/*nab*-paclitaxel and carboplatin in patients who were smokers or non-smokers was consistent with the safety results for the overall patient population[5,6]

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



Data cut-off: December 6, 2019
CI, confidence interval; IRC, independent review committee; ITT, intention-to-treat; NE, not estimable; PFS, progression-free survival

- At data cut-off on December 6, 2019, a total of 129 patients remained on treatment, of whom 108 (83.7%) patients were smokers and 21 (16.3%) patients were non-smokers
  - The most common reasons for treatment discontinuation for patients who were smokers were complete chemotherapy (22.3%) and progressive disease (18.9%)
  - The most common reasons for treatment discontinuation for patients who were non-smokers were complete chemotherapy (25.4%) and progressive disease (20.3%)

Efficacy

- Progression-free survival (PFS) by independent review committee (IRC) was longer in Arms A and B compared with Arm C, regardless of smoking status (**Figure 1**)
  - In patients who were smokers, median PFS by IRC was:
    - 7.6 months in Arm A vs 5.5 months in Arm C (HR: 0.534; 95% CI, 0.363, 0.786)
    - 7.6 months in Arm B vs 5.5 months in Arm C (HR: 0.556; 95% CI, 0.384, 0.803)
  - In patients who were non-smokers, median PFS by IRC was:
    - 7.5 months in Arm A vs 5.4 months in Arm C (HR: 0.475; 95% CI, 0.226, 1.000)
    - Non-evaluable (NE) in Arm B vs 5.4 months in Arm C (HR: 0.119; 95% CI, 0.027, 0.533)
- The objective response rates (ORR) for patients who were smokers or non-smokers are shown in **Table 2**. Regardless of smoking status, ORR was higher with tislelizumab plus chemotherapy vs chemotherapy alone
- The median duration of response (DoR) for patients who were smokers or non-smokers are shown in **Table 2**

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 + PC (n=96)	Arm B TIS + *nab*-PC (n=107)	Arm C PC (n=98)	Arm A TIS + PC (n=24)	Arm B TIS + *nab*-PC (n=12)	Arm C PC (n=23)
ORR, n (%)	72.0 (75.0)	79.0 (73.8)	49.0 (50.0)	15 (62.5)	10 (83.3)	11 (47.8)
(95% CI)	(65.1, 83.3)	(64.4, 81.9)	(39.7, 60.3)	(40.6, 81.2)	(51.6, 97.9)	(26.8, 69.4)
Odds ratio (95% CI)	3.30 (1.748, 6.221)	2.75 (1.520, 4.968)	-	1.93 (0.578, 6.448)	8.19 (1.157, 57.953)	-
ORR difference, % (95% CI)	25.8 (12.95, 38.61)	23.0 (10.04, 35.90)	-	15.6 (-12.35, 43.51)	44.5 (12.50, 76.55)	-
Median DoR, months (95% CI)	NE (5.03, NE)	8.3 (4.80, NE)	4.3 (2.83, 5.55)	5.2 (2.99, NE)	NE (2.76, NE)	4.1 (1.91, 5.59)
HR (95% CI)	0.443 (0.262, 0.748)	0.505 (0.308, 0.828)	-	0.511 (0.184, 1.422)	0.099 (0.012, 0.821)	-

Data cut-off: December 6, 2019. 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; nab, nanoparticle albumin-bound; PC, paclitaxel and carboplatin; TIS, tislelizumab

Safety

- The safety profile of tislelizumab plus chemotherapy and chemotherapy alone in patients who were smokers or non-smokers was consistent with the overall patient population (**Table 3**)[5]
  - Regardless of smoking status, most patients experienced ≥ 1 treatment-emergent adverse event (TEAE)
  - Of the patients who were smokers, 90.6% and 85.8% experienced Grade ≥ 3 TEAEs in Arms A and B, respectively, vs 87.2% in Arm C
  - Of the patients who were non-smokers 79.2% and 91.7% experienced Grade ≥ 3 TEAEs in Arms A and B, respectively, vs 69.6% in Arm C
- Treatment-related adverse events (TRAEs) occurring in ≥ 20% of patients in any treatment group are listed in **Table 4**
- Confirmed immune-mediated TEAEs were reported in 30 (31.3%) patients in Arm A and 34 (32.1%) patients in Arm B for smokers, and 7 (29.2%) patients in Arm A and 1 (8.3%) patient in Arm B for non-smokers
  - 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 (11 patients [11.5%] in Arm A; 14 patients [13.2%] in Arm B) in the smoker population, and rash (3 patients [12.5%] in Arm A; 0 patients [0.0%] in Arm B) in the non-smoker population

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

	Smokers			Non-smokers		
n (%)	Arm A TIS + PC (n=96)	Arm B TIS + *nab*-PC (n=106)	Arm C PC (n=94)	Arm A TIS + PC (n=24)	Arm B TIS+ *nab*-PC (n=12)	Arm C PC (n=23)
Patients with ≥ 1 TEAE	96 (100.0)	105 (99.1)	94 (100.0)	24 (100.0)	12 (100.0)	23 (100.0)
≥ Grade 3	87 (90.6)	91 (85.8)	82 (87.2)	19 (79.2)	11 (91.7)	16 (69.6)
Serious	36 (37.5)	42 (39.6)	23 (24.5)	8 (33.3)	3 (25.0)	6 (26.1)
≥ Grade 3 serious	26 (27.1)	34 (32.1)	14 (14.9)	6 (25.0)	3 (25.0)	2 (8.7)
Leading to treatment discontinuation	12 (12.5)	32 (30.2)	14 (14.9)	3 (12.5)	3 (25.0)	4 (17.4)
Leading to death	3 (3.1)	5 (4.7)	5 (5.3)	1 (4.2)	0 (0.0)	0 (0.0)
Patients with ≥ 1 TRAE	95 (99.0)	105 (99.1)	94 (100.0)	24 (100.0)	12 (100.0)	23 (100.0)
≥ Grade 3	85 (88.5)	88 (83.0)	79 (84.0)	18 (75.0)	11 (91.7)	15 (65.2)
Serious	22 (22.9)	26 (24.5)	14 (14.9)	5 (20.8)	2 (16.7)	3 (13.0)
Leading to death	1 (1.0)	2 (1.9)	3 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)

Data cut-off: December 6, 2019; nab, nanoparticle albumin-bound; PC, paclitaxel and carboplatin; TEAE, treatment-emergent adverse event; TIS, tislelizumab; TRAE, treatment-related adverse events

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

	Smokers						Non-smokers					
	Arm A TIS + PC (n=96)		Arm B TIS + *nab*-PC (n=106)		Arm C PC (n=94)		Arm A TIS + PC (n=24)		Arm B TIS + *nab*-PC (n=12)		Arm C PC (n=23)	
Preferred term, n (%)	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Patients with at least one event	95 (99.0)	85 (88.5)	105 (99.1)	88 (83.0)	94 (100.0)	79 (84.0)	24 (100.0)	18 (75.0)	12 (100.0)	11 (91.7)	23 (100.0)	15 (65.2)
Anemia	78 (81.3)	5 (5.2)	93 (87.7)	19 (17.9)	70 (74.5)	9 (9.6)	21 (87.5)	1 (4.2)	11 (91.7)	1 (8.3)	17 (73.9)	2 (8.7)
Alopecia	60 (62.5)	0 (0.0)	72 (67.9)	0 (0.0)	58 (61.7)	0 (0.0)	17 (70.8)	0 (0.0)	9 (75.0)	0 (0.0)	14 (60.9)	0 (0.0)
Leukopenia	48 (50.0)	14 (14.6)	55 (51.9)	23 (21.7)	44 (46.8)	19 (20.2)	9 (37.5)	5 (20.8)	7 (58.3)	6 (50.0)	12 (52.2)	3 (13.0)
Neutropenia	43 (44.8)	35 (36.5)	47 (44.3)	30 (28.3)	44 (46.8)	38 (40.4)	8 (33.3)	5 (20.8)	3 (25.0)	2 (16.7)	11 (47.8)	9 (39.1)
Neutrophil count decreased	56 (58.3)	48 (50.0)	62 (58.5)	45 (42.5)	54 (57.4)	45 (47.9)	19 (79.2)	14 (58.3)	10 (83.3)	9 (75.0)	14 (60.9)	8 (34.8)
White blood cell count decreased	48 (50.0)	20 (20.8)	61 (57.5)	30 (28.3)	49 (52.1)	23 (24.5)	15 (62.5)	6 (25.0)	7 (58.3)	2 (16.7)	13 (56.5)	5 (21.7)
Alanine aminotransferase increased	37 (38.5)	1 (1.0)	34 (32.1)	2 (1.9)	23 (24.5)	0 (0.0)	11 (45.8)	1 (4.2)	6 (50.0)	0 (0.0)	4 (17.4)	0 (0.0)
Platelet count decreased	32 (33.3)	4 (4.2)	46 (43.4)	12 (11.3)	24 (25.5)	2 (2.1)	8 (33.3)	1 (4.2)	6 (50.0)	1 (8.3)	4 (17.4)	0 (0.0)
Aspartate aminotransferase increased	29 (29.2)	2 (2.0)	33 (31.1)	10 (9.4)	9 (9.6)	1 (1.1)	11 (45.8)	3 (12.5)	6 (50.0)	1 (8.3)	4 (17.4)	0 (0.0)
Blood bilirubin increased	26 (26.0)	0 (0.0)	14 (13.2)	5 (4.7)	13 (13.8)	1 (1.1)	2 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.7)	0 (0.0)
Rash	18 (18.8)	1 (1.0)	21 (19.8)	2 (1.9)	3 (3.2)	0 (0.0)	5 (20.8)	3 (12.5)	4 (33.3)	0 (0.0)	1 (4.3)	0 (0.0)
Decreased appetite	45 (46.9)	1 (1.0)	44 (41.5)	1 (0.9)	28 (29.8)	1 (1.1)	5 (20.8)	0 (0.0)	5 (41.7)	0 (0.0)	7 (30.4)	0 (0.0)
Hypokalemia	6 (6.3)	2 (2.1)	10 (9.4)	1 (0.9)	4 (4.3)	0 (0.0)	5 (20.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)

Data cut-off: December 6, 2019; nab, nanoparticle albumin-bound; PC, paclitaxel and carboplatin; TIS, tislelizumab; TRAE, treatment-related adverse event

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