RATIONALE-307: Safety analysis of patients receiving tislelizumab plus chemotherapy versus chemotherapy alone in advanced squamous NSCLC

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Background

- Tislelizumab is a humanized IgG4 monoclonal antibody with high affinity and binding specificity for programmed cell death protein 1 (PD-1). Tislelizumab was designed to minimize binding to Fcγ receptors on macrophages in order to abrogate antibody-dependent phagocytosis, a potential mechanism of resistance to anti-PD-1 therapy[1,2]
- RATIONALE-307 (NCT03594747) was an open-label, randomized, multicenter Phase 3 trial that compared the efficacy and safety of tislelizumab plus paclitaxel and carboplatin (Arm A) vs tislelizumab plus *nab*-paclitaxel and carboplatin (Arm B) vs paclitaxel and carboplatin alone (Arm C) as a first-line treatment for advanced squamous non-small cell lung cancer (sq NSCLC)[3]
- Independent review committee-assessed median progression-free survival 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 were 0.524 (95% confidence interval [CI]: 0.370, 0.742; p < 0.001 [Arm A vs Arm C]) and 0.478 (95% CI: 0.336, 0.679; p < 0.001 [Arm B vs Arm C]).[3] A manageable safety/tolerability profile was also observed[3]
- Here, we report results from a *post-hoc* safety analysis of RATIONALE-307

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Methods

Statistical analyses

- All safety analyses were performed in the safety analysis set. The safety analysis set included all randomized patients who received at least 1 dose of study treatment
- The incidence of treatment-emergent adverse events (TEAEs) by system organ class (SOC), and selected Standardized MedDRA Queries (SMQs), are presented between patients treated with tislelizumab plus chemotherapy vs chemotherapy alone for the first 4–6 cycles of treatment, when chemotherapy was administered in combination with tislelizumab or alone. Selected SMQs included, but were not limited to, hematological toxicities, gastrointestinal toxicities, endocrine disorders, hepatic toxicities, pneumonia, interstitial lung disease, and hypersensitivity
- The difference in incidence rates, and the 95% CI, between treatment arms was calculated using the Mantel-Haenszel Chi-square test
- All analyses were exploratory, and p values are provided for descriptive purposes only
- The analysis did not support statistically significant conclusions

Results

- In total, 355 patients were included in the safety analysis set (Arm A: n=120; Arm B: n=118; Arm C: n=117)
- TEAEs were reported in most patients across all arms during the chemotherapy combination phase (**Table 1**)
  - ≥ Grade 3 TEAEs were reported in 87.5%, 84.7%, and 83.8% of patients in Arms A, B and C, respectively, while serious TEAEs were reported in 30.8%, 31.4%, and 24.8% of patients in Arms A, B and C, respectively
  - TEAEs led to the discontinuation of any trial drug in 10.0%, 26.3%, and 15.4% of patients in Arms A, B and C, respectively. In total, 2.5% of TEAEs in Arm A, 3.4% in Arm B, and 4.3% in Arm C led to death, respectively
  - The 95% CIs of the rate differences all crossed 0, except for the incidence of TEAEs leading to discontinuation in Arm B vs C. This difference observed between Arms B and C may likely be due to the differences in weekly and once every 3 weeks administration in treatment for patients receiving *nab*-paclitaxel (Arm B) vs paclitaxel (Arm C)

Table 1. Summary of TEAEs during the chemotherapy combination phase

	TIS plus chemo		Chemo
	Arm A (n=120)	Arm B (n=118)	Arm C (n=117)
All TEAEs, n (%)	120 (100.0)	117 (99.2)	117 (100.0)
Rate diff (95% CI)	NA*	-0.8 (-4.7, 2.4)	–
≥ Grade 3 TEAEs, n (%)	105 (87.5)	100 (84.7)	98 (83.8)
Rate diff (95% CI)	3.7 (-5.3, 13.0)	1.0 (-8.5, 10.5)	–
Serious TEAEs, n (%)	37 (30.8)	37 (31.4)	29 (24.8)
Rate diff (95% CI)	6.0 (-5.4, 17.4)	6.6 (-5.0, 18.0)	–
TEAEs leading to discontinuation, n (%)	12 (10.0)	31 (26.3)	18 (15.4)
Rate diff (95% CI)	-5.4 (-14.2, 3.2)	10.9 (0.5, 21.3)	–
TEAEs leading to death, n (%)	3 (2.5)	4 (3.4)	5 (4.3)
Rate diff (95% CI)	-1.8 (-7.5, 3.4)	-0.9 (-6.7, 4.7)	–

*NA due to 100% TEAE incidence in both arms. TEAE rate differences between arms were calculated using the Mantel-Haenszel Chi-square test
Chemo, chemotherapy; CI, confidence interval; diff, difference; NA, not available; TEAE, treatment-emergent adverse event; TIS, tislelizumab

Conclusions

- In this Phase 3 RATIONALE-307 trial, **tislelizumab** plus chemotherapy had a **tolerable safety profile in patients with locally advanced or metastatic sq NSCLC**
- The most commonly reported TEAEs by SOC were comparable for tislelizumab plus chemotherapy vs chemotherapy alone, indicating that **tislelizumab did not compound chemotherapy-specific toxicity**
- The safety profile of tislelizumab was consistent with that of other checkpoint inhibitors, including PD-1 inhibitors.[5,6] such as the higher incidence of endocrine disorder TEAEs, which are one of the most common TEAES for this drug class[7,8]

- The most frequently reported TEAEs by SOC during the chemotherapy combination phase, and with ≥ 10% occurrence in any arm, were blood and lymphatic system disorders, and investigations (**Table 2**). Incidence of endocrine disorder TEAEs was greater in Arms A and B than Arm C, with both rate difference p values < 0.01. These endocrine disorder TEAEs included hypothyroidism, hyperthyroidism, and autoimmune thyroiditis. Rate difference p values for all other TEAEs were > 0.01

Table 2. TEAEs by SOC occurring during the chemotherapy combination phase (≥ 10% occurrence in any arm)

	TIS plus chemo		Chemo
	Arm A (n=120)	Arm B (n=118)	Arm C (n=117)
Blood and lymphatic system disorders, n (%)	112 (93.3)	114 (96.6)	106 (90.6)
Rate diff (95% CI); p value	2.7 (-4.5, 10.3); 0.4392	6.0 (-0.3, 13.1); 0.0600	–
Investigations, n (%)	106 (88.3)	108 (91.5)	100 (85.5)
Rate diff (95% CI); p value	2.9 (-5.9, 11.8); 0.5143	6.1 (-2.2, 14.6); 0.1464	–
Metabolism and nutrition disorders, n (%)	90 (75.0)	84 (71.2)	73 (62.4)
Rate diff (95% CI); p value	12.6 (0.8, 24.2); 0.0367	8.8 (-3.3, 20.7); 0.1532	–
Skin and subcutaneous tissue disorders, n (%)	83 (69.2)	92 (78.0)	74 (63.2)
Rate diff (95% CI); p value	5.9 (-6.1, 17.9); 0.3364	14.7 (3.1, 26.1); 0.0134	–
Gastrointestinal disorders, n (%)	71 (59.2)	79 (66.9)	60 (51.3)
Rate diff (95% CI); p value	7.9 (-4.8, 20.3); 0.2232	15.7 (3.1, 27.8); 0.0148	–
General disorders and administration site conditions, n (%)	68 (56.7)	61 (51.7)	62 (53.0)
Rate diff (95% CI); p value	3.7 (-9.0, 16.2); 0.5706	-1.3 (-14.0, 11.4); 0.8426	–
Musculoskeletal and connective tissue disorders, n (%)	63 (52.5)	45 (38.1)	51 (43.6)
Rate diff (95% CI); p value	8.9 (-3.8, 21.4); 0.1708	-5.5 (-17.9, 7.1); 0.3961	–
Nervous system disorders, n (%)	58 (48.3)	28 (23.7)	44 (37.6)
Rate diff (95% CI); p value	10.7 (-1.9, 23.0); 0.0961	-13.9 (-25.4, -2.1); 0.0213	–
Infections and infestations, n (%)	36 (30.0)	36 (30.5)	26 (22.2)
Rate diff (95% CI); p value	7.8 (-3.5, 18.9); 0.1741	8.3 (-3.0, 19.5); 0.1504	–
Respiratory, thoracic and mediastinal disorders, n (%)	36 (30.0)	44 (37.3)	36 (30.8)
Rate diff (95% CI); p value	-0.8 (-12.5, 10.9); 0.8978	6.5 (-5.6, 18.5); 0.2927	–
Endocrine disorders, n (%)	**15 (12.5)**	**8 (6.8)**	0 (0)
Rate diff (95% CI); p value	**12.5 (7.7, 19.6); < 0.0001**	**6.8 (3.5, 12.8); 0.0042**	–
Hepatobiliary disorders, n (%)	11 (9.2)	8 (6.8)	13 (11.1)
Rate diff (95% CI); p value	-1.9 (-10.1, 6.0); 0.6206	-4.3 (-12.2, 3.2); 0.2455	–
Psychiatric disorders, n (%)	7 (5.8)	8 (6.8)	15 (12.8)
Rate diff (95% CI); p value	-7.0 (-15.0, 0.4); 0.0644	-6.0 (-14.2, 1.7); 0.1200	–

Chemo, chemotherapy; CI, confidence interval; diff, difference; SOC, system organ class; TEAE, treatment-emergent adverse event; TIS, tislelizumab

- Among TEAEs by selected SMQs (those with ≥ 10% occurrence in any arm and rate difference p values of < 0.01 for both Arm A vs Arm C, and Arm B vs Arm C), higher incidences of hypersensitivity (narrow search), and hypothyroidism (narrow and broad search) were observed in Arms A and B compared with Arm C (**Table 3**)
- TEAEs by SMQs that occurred at similar incidences across arms (those with ≥ 10% occurrence in any arm and rate difference p values of > 0.01 for both Arm A vs Arm C, and Arm B vs Arm C) are presented in **Table 4**

Table 3. TEAEs by selected SMQs occurring at different incidences across arms during the chemotherapy combination phase (≥ 10% occurrence in any arm; rate difference p values of < 0.01 for both Arm A vs Arm C, and Arm B vs Arm C)

	TIS plus chemo		Chemo
	Arm A (n=120)	Arm B (n=118)	Arm C (n=117)
Hypersensitivity (narrow), n (%)	31 (25.8)	36 (30.5)	14 (12.0)
Rate diff (95% CI); p value	13.9 (4.0, 23.8); 0.0066	18.5 (8.3, 28.8); 0.0005	–
Hypothyroidism (narrow + broad), n (%)	16 (13.3)	17 (14.4)	3 (2.6)
Rate diff (95% CI); p value	10.8 (4.3, 18.4); 0.0023	11.8 (5.2, 19.7); 0.0012	–

*TEAE rate differences between arms were calculated using the Mantel-Haenszel Chi-square test. TEAEs of interest were identified using a "narrow" search of SMQs. Any possible occurrences of TEAEs were identified using a "broad" search of SMQs.[4]
Chemo, chemotherapy; CI, confidence interval; diff, difference; SMQs, Standardized MedDRA Queries; TEAE, treatment-emergent adverse event; TIS, tislelizumab*

Table 4. TEAEs by SMQs occurring at similar incidences across arms during the chemotherapy combination phase (≥ 10% occurrence in any arm; rate difference p values of > 0.01 for both Arm A vs Arm C, and Arm B vs Arm C)

	TIS plus chemo		Chemo
	Arm A (n=120)	Arm B (n=118)	Arm C (n=117)
Gastrointestinal nonspecific symptoms and therapeutic procedures (narrow), n (%)	70 (58.3)	77 (65.3)	57 (48.7)
Rate diff (95% CI); p value	9.6 (-3.1, 22.0); 0.1386	16.5 (3.9, 28.7); 0.0106	–
Hematopoietic leukopenia (narrow + broad), n (%)	110 (91.7)	115 (97.5)	107 (91.5)
Rate diff (95% CI); p value	0.2 (-7.3, 7.8); 0.9529	6.0 (0.2, 12.8); 0.0445	–
Infective pneumonia (narrow), n (%)	13 (10.8)	16 (13.6)	13 (11.1)
Rate diff (95% CI); p value	-0.3 (-8.6, 8.0); 0.9456	2.4 (-6.2, 11.2); 0.5691	–
Liver-related investigations, signs and symptoms (narrow), n (%)	73 (60.8)	54 (45.8)	53 (45.3)
Rate diff (95% CI); p value	15.5 (2.8, 27.8); 0.0168	0.5 (-12.2, 13.1); 0.9432	–
Noninfectious diarrhea, n (%)	15 (12.5)	18 (15.3)	8 (6.8)
Rate diff (95% CI); p value	5.7 (-2.0, 13.7); 0.1418	8.4 (0.4, 16.9); 0.0401	–
Hyperglycemia/new onset diabetes mellitus (narrow), n (%)	21 (17.5)	11 (9.3)	12 (10.3)
Rate diff (95% CI); p value	7.2 (-1.7, 16.3); 0.1080	-0.9 (-8.9, 7.0); 0.8099	–
Hemorrhage terms (excluding laboratory terms) (narrow), n (%)	17 (14.2)	22 (18.6)	17 (14.5)
Rate diff (95% CI); p value	-0.4 (-9.6, 8.8); 0.9366	4.1 (-5.5, 13.8); 0.3977	–

*TEAE rate differences between arms were calculated using the Mantel-Haenszel Chi-square test. TEAEs of interest were identified using a "narrow" search of SMQs. Any possible occurrences of TEAEs were identified using a "broad" search of SMQs[4]
Chemo, chemotherapy; CI, confidence interval; diff, difference; SMQ, Standardized MedDRA Queries; TEAE, treatment-emergent adverse event; TIS, tislelizumab*

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X.Y. has no conflict of interest to declare.

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