Pathological Response to Neoadjuvant Tislelizumab (TIS) Plus Platinum-Doublet (PtDb) Chemotherapy (CT) in Resectable Stage II-IIIA NSCLC Patients (pts) in the Phase 3 (Ph3) RATIONALE-315 Trial

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Conclusions

- **Tislelizumab (TIS) + chemotherapy (CT) showed statistically significant and clinically meaningful improvements in major pathological response (MPR) and pathological complete response (pCR) rates versus placebo (PBO) + CT as neoadjuvant treatment**
- **The safety profile of TIS + CT is manageable and consistent with previous reports, further supporting this treatment combination for patients with resectable stage II or IIIA non-small cell cancer (NSCLC)**
- **The RATIONALE-315 study is ongoing; a subsequent interim analysis showed significant improvement in event-free survival (EFS) in the TIS arm (these data will be shared at a future meeting)**

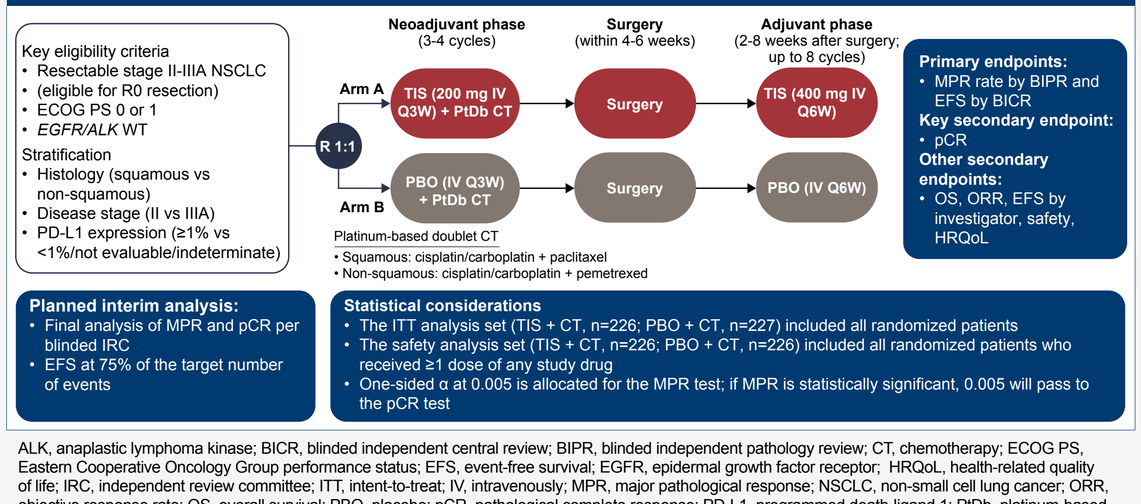
Background

- Lung cancer is the second most diagnosed cancer globally and the leading cause of cancer-related mortality worldwide[1]
  - NSCLC is the predominant subtype of lung cancer, accounting for nearly 85% of lung cancer cases[2]
- Surgery offers the highest likelihood of curing patients with early stage NSCLC,[3] but approximately 30% to 55% of patients experience disease recurrence after curative surgery[4]
- (Neo)adjuvant CT has been recommended for patients with resectable stage II-IIIA NSCLC[5]
  - Studies have shown promising pathological response rates (ie, MPR, pCR) with neoadjuvant anti-programmed cell death protein-1 or programmed death-ligand 1 (PD-[L]1) monoclonal antibodies (mAbs) ± CT[5]
  - However, post-operative recurrence remains a concern[5]
- RATIONALE-315 (NCT04379635) is investigating the efficacy and safety of neoadjuvant TIS (anti-PD-1 mAb) + CT or PBO + CT, then adjuvant TIS or PBO, in patients with resectable stage II-IIIA NSCLC in China
- Here we present the MPR and pCR results at the data cutoff of February 20, 2023

Methods

- RATIONALE-315 is a randomized, double-blind, placebo-controlled, phase 3 study (**Figure 1**)
- Patients were required to have resectable stage II or IIIA NSCLC, be eligible for R0 resection, and have an ECOG PS of 0 or 1
- Eligible patients stratified by histology, disease stage, and PD-L1 expression were randomized 1:1 to either Arm A (TIS + CT) or Arm B (PBO + CT)
- The surgical procedure was performed within 4 to 6 weeks after the last dose of neoadjuvant treatment
- Eligible patients entered the adjuvant phase 2 to 8 weeks after surgery

Figure 1. RATIONALE-315 Study Design

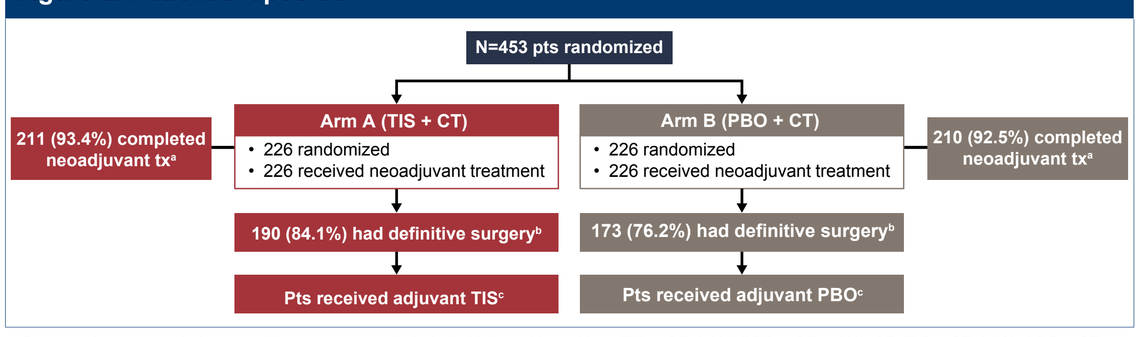


ALK, anaplastic lymphoma kinase; BICR, blinded independent central review; BIPR, blinded independent pathology review; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; EGFR, epidermal growth factor receptor; HRQoL, health-related quality of life; IRC, independent review committee; ITT, intent-to-treat; IV, intravenously; MPR, major pathological response; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PBO, placebo; pCR, pathological complete response; PD-L1, programmed death-ligand 1; PtDb, platinum-based doublet; Q3W, once every 3 weeks; Q6W, once every 6 weeks; R0, pathological complete resection of the primary tumor; TIS, tislelizumab; WT, wild type.

Results

- A total of 453 patients were randomized to receive TIS + CT or PBO + CT (**Figure 2**)
- At data cutoff (February 20, 2023), median study follow up time was 16.8 months
- In Arm A, all 226 randomized patients received TIS + CT in the neoadjuvant phase, of whom 93.4% completed treatment; 190 patients had definitive surgery and eligible patients received adjuvant TIS
- In Arm B, 226 of the 227 randomized patients received PBO + CT in the neoadjuvant phase, of whom 92.5% completed treatment; 173 patients had definitive surgery and eligible patients received PBO as adjuvant treatment
- Demographics and baseline characteristics were similar between the two arms (**Table 1**)

Figure 2. Patient Disposition



[a]Reasons for not completing neoadjuvant treatment included withdrawal by subject (TIS + CT, 2.2%; PBO + CT, 4.0%), AE (TIS + CT, 3.1%; PBO + CT, 0.9%), PD (TIS + CT, 0.9%; PBO + CT, 1.8%), and physician decision (TIS + CT, 0.4%; PBO + CT, 0.9%). [b]Denominator based on randomized patients. Reasons for cancelled surgeries included withdrawal by subject (TIS + CT, 8.8%; PBO + CT, 12.3%), PD (TIS + CT, 2.2%; PBO + CT, 5.3%), physician decision (TIS + CT, 1.8%; PBO + CT, 5.3%), AE (TIS + CT, 2.7%; PBO + CT, 0.9%), and other reasons (TIS + CT, 0.4%). [c]Not all patients who completed surgery entered the adjuvant phase.
AE, adverse event; CT, chemotherapy; PBO, placebo; PD, progressive disease; pts, patients; TIS, tislelizumab; tx, treatment.

Table 1. Demographics and Baseline Characteristics[a]

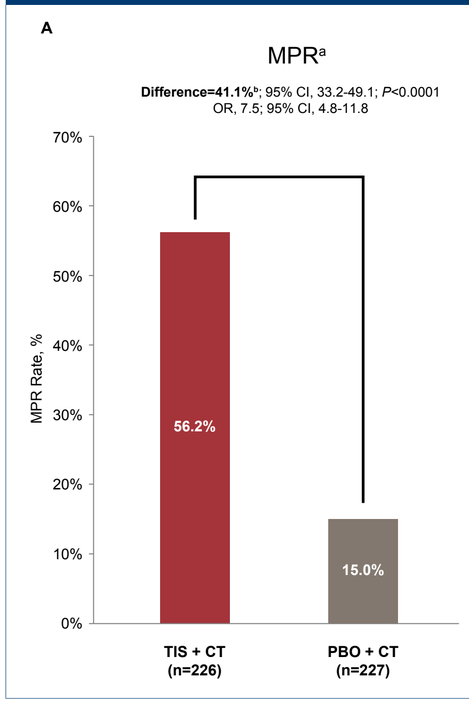
	TIS + CT (n=226)	PBO + CT (n=227)
Median age, years (range)	62.0 (30-80)	63.0 (36-78)
Sex, male	205 (90.7)	205 (90.3)
Race, Asian	226 (100.0)	227 (100.0)
ECOG performance status[b]		
0	142 (62.8)	154 (67.8)
1	83 (36.7)	73 (32.2)
Smoking status		
Current/former	192 (85.0)	188 (82.8)
Never	34 (15.0)	39 (17.2)
Histology[c]		
Squamous	179 (79.2)	175 (77.1)
Non-squamous	45 (19.9)	50 (22.0)
Disease stage[d]		
II	93 (41.2)	93 (41.0)
IIIA	132 (58.4)	132 (58.1)
PD-L1 expression[e]		
<1%	89 (39.4)	84 (37.0)
≥1%	130 (57.5)	131 (57.7)

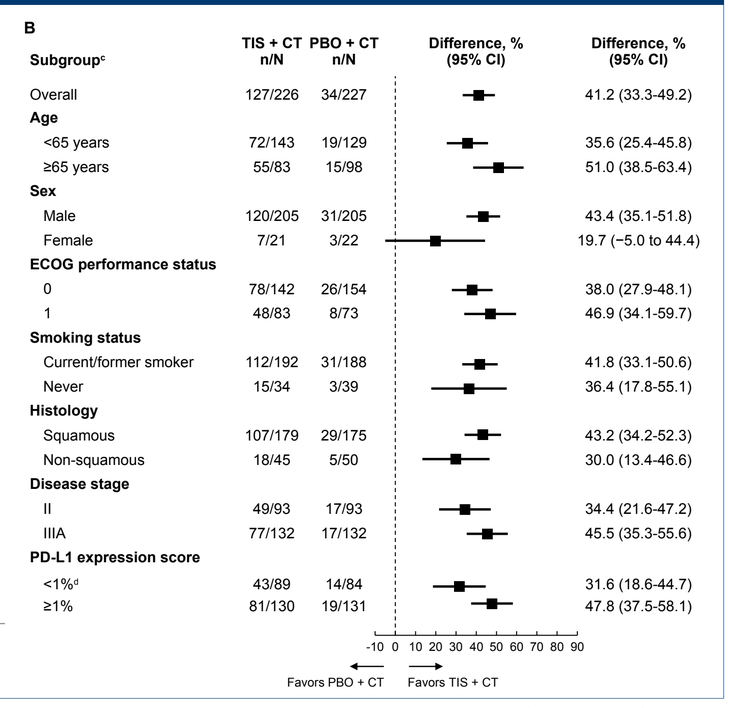
All data are n (%) unless otherwise stated. [a]ITT analysis set. [b]One pt in the TIS + CT arm had a missing ECOG PS. [c]Histology by CRF; not shown in table: pts with mixed histology (n=2 in each arm) were categorized as "other". [d]Disease stage by CRF, per AJCC 8th edition; not shown in table: 1 pt (TIS + CT arm) and 2 pts (PBO + CT arm) had stage IIIB disease. [e]PD-L1 expression from Central Lab; excluded pts with PD-L1 results that were not evaluable/indeterminate and/or missing.
AJCC, American Joint Committee on Cancer; CRF, case report form; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; PBO, placebo; PD-L1, programmed death-ligand 1; pts, patients; TIS, tislelizumab.

Major Pathological Response

- The MPR rate was significantly improved with TIS + CT versus PBO + CT (P<0.0001) in patients with resectable stage II-IIIA NSCLC; there was a 41.1% difference in MPR between the two arms (**Figure 3**)
- Improvement in MPR rate with TIS + CT compared with PBO + CT was consistent across subgroups

Figure 3. Major Pathological Response





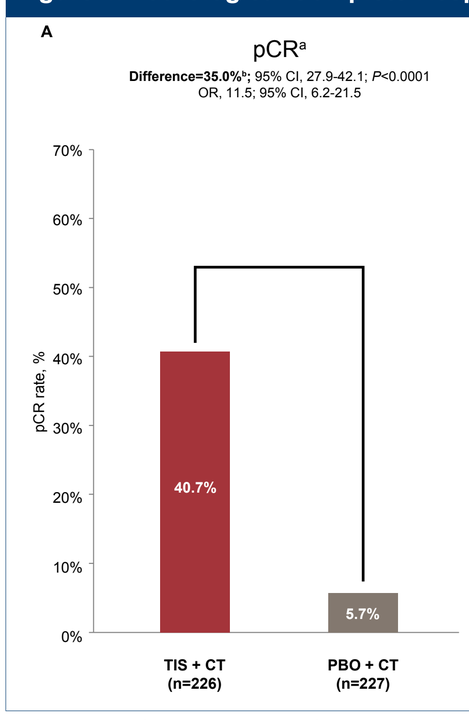
Subgroup[c]	TIS + CT n/N	PBO + CT n/N	Difference, % (95% CI)
Overall	127/226	34/227	41.2 (33.3-49.2)
Age			
<65 years	72/143	19/129	35.6 (25.4-45.8)
≥65 years	55/83	15/98	51.0 (38.5-63.4)
Sex			
Male	120/205	31/205	43.4 (35.1-51.8)
Female	7/21	3/22	19.7 (−5.0 to 44.4)
ECOG performance status			
0	78/142	26/154	38.0 (27.9-48.1)
1	48/83	8/73	46.9 (34.1-59.7)
Smoking status			
Current/former smoker	112/192	31/188	41.8 (33.1-50.6)
Never	15/34	3/39	36.4 (17.8-55.1)
Histology			
Squamous	107/179	29/175	43.2 (34.2-52.3)
Non-squamous	18/45	5/50	30.0 (13.4-46.6)
Disease stage			
II	49/93	17/93	34.4 (21.6-47.2)
IIIA	77/132	17/132	45.5 (35.3-55.6)
PD-L1 expression score			
<1%[d]	43/89	14/84	31.6 (18.6-44.7)
≥1%	81/130	19/131	47.8 (37.5-58.1)

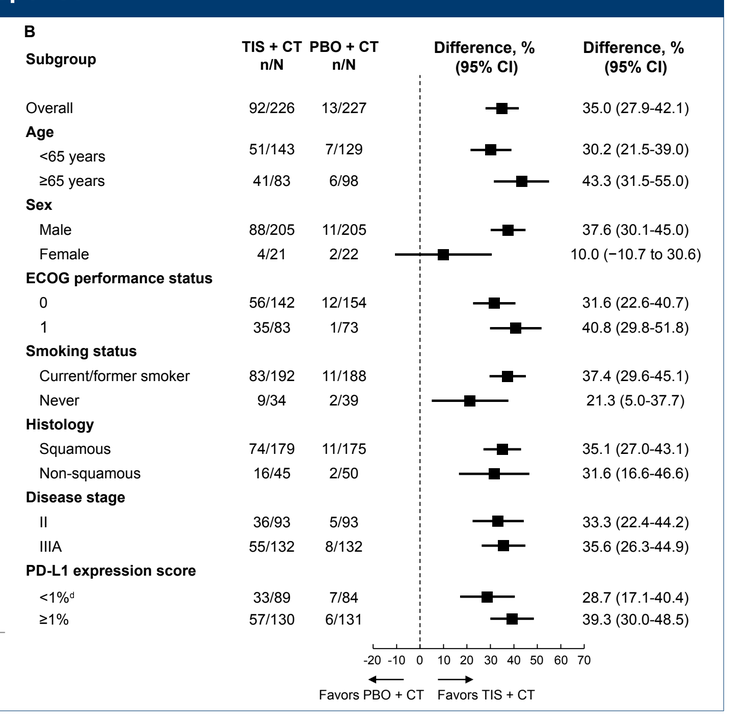
[a]MPR rate was defined as the proportion of pts with ≤10% residual viable tumor in the resected primary tumor and all resected lymph nodes after completion of neoadjuvant tx as assessed by BIPR in an ITT analysis set. Pts who did not receive surgical resection were considered as nonresponders in the analysis. MPR was compared between TIS + CT and PBO + CT using Cochran-Mantel-Haenszel chi-square test methodology. [b]Mantel-Haenszel common risk difference was estimated, along with its 95% CIs constructed by a normal approximation and Sato's variance estimator stratified by stratification factors. [c]In the subgroup analyses, risk difference and its 95% CI were estimated using the same method without stratification factors. [d]Excludes pts who were not evaluable/indeterminate.
BIPR, blinded independent pathology review; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ITT, intent-to-treat; MPR, major pathological response; NSCLC, non-small cell lung cancer; OR, odds ratio; PBO, placebo; PD-L1, programmed death-ligand 1; pts, patients; TIS, tislelizumab; tx, treatment.

Pathological Complete Response

- The pCR rate was significantly improved with TIS + CT versus PBO + CT (P<0.0001) in patients with resectable stage II-IIIA NSCLC; there was a 35% difference in pCR between the two arms (**Figure 4**)
- Improvements in pCR rate were consistent across subgroups

Figure 4. Pathological Complete Response





Subgroup	TIS + CT n/N	PBO + CT n/N	Difference, % (95% CI)
Overall	92/226	13/227	35.0 (27.9-42.1)
Age			
<65 years	51/143	7/129	30.2 (21.5-39.0)
≥65 years	41/83	6/98	43.3 (31.5-55.0)
Sex			
Male	88/205	11/205	37.6 (30.1-45.0)
Female	4/21	2/22	10.0 (−10.7 to 30.6)
ECOG performance status			
0	56/142	12/154	31.6 (22.6-40.7)
1	35/83	1/73	40.8 (29.8-51.8)
Smoking status			
Current/former smoker	83/192	11/188	37.4 (29.6-45.1)
Never	9/34	2/39	21.3 (5.0-37.7)
Histology			
Squamous	74/179	11/175	35.1 (27.0-43.1)
Non-squamous	16/45	2/50	31.6 (16.6-46.6)
Disease stage			
II	36/93	5/93	33.3 (22.4-44.2)
IIIA	55/132	8/132	35.6 (26.3-44.9)
PD-L1 expression score			
<1%[d]	33/89	7/84	28.7 (17.1-40.4)
≥1%	57/130	6/131	39.3 (30.0-48.5)

[a]pCR rate was defined as the proportion of pts absent of residual viable tumor in the resected primary tumor and all resected lymph nodes after completion of neoadjuvant tx as assessed by BIPR in an ITT analysis set. Pts who do not receive surgical resection were considered as non-responders in the analysis. pCR was compared between TIS + CT and PBO + CT using Cochran-Mantel-Haenszel chi-square test methodology. [b]Mantel-Haenszel common risk difference was estimated, along with its 95% CIs constructed by a normal approximation and Sato's variance estimator stratified by stratification factors. cIn the subgroup analyses, risk difference and its 95% CI were estimated using the same method without stratification factors. [d]Excludes pts who were not evaluable/indeterminate.
BIPR, blinded independent pathology review; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ITT, intent-to-treat; NSCLC, non-small cell lung cancer; nsq, nonsquamous; OR, odds ratio; PBO, placebo; pCR, pathological complete response; PD-L1, programmed death-ligand 1; pts, patients; sq, squamous; TIS, tislelizumab; tx, treatment.

Safety (Neoadjuvant Phase)

- The safety profile of TIS + CT was consistent with the known risks of each treatment and was well tolerated in patients with resectable stage II-IIIA NSCLC (**Table 2**)

Table 2. Safety (Neoadjuvant Phase)

	Study Drug Exposure	
	TIS + CT (n=226)	PBO + CT (n=226)
Median duration of treatment, weeks (range)	9.6 (1.6-18.0)	9.4 (3.0-18.1)
No. of cycles received, n (%)		
≤2	19 (8.4)	17 (7.5)
3	129 (57.1)	118 (52.2)
4	78 (34.5)	91 (40.3)
	Overall Safety Profiles[a]	
Pts with ≥1 TEAE, n (%)	224 (99.1)	225 (99.6)
Grade ≥3	157 (69.5)	148 (65.5)
Treatment-related	223 (98.7)	225 (99.6)
Serious	25 (11.1)	24 (10.6)
Related to TIS/PBO	11 (4.9)	7 (3.1)
Leading to death	3 (1.3)	0
Related to TIS/PBO	2 (0.9)	0
Leading to treatment discontinuation	20 (8.8)	19 (8.4)
TIS/PBO	7 (3.1)	2 (0.9)
Any component of CT	17 (7.5)	19 (8.4)
Leading to dose modification	70 (31.0)	69 (30.5)
TIS/PBO[b]	36 (15.9)	37 (16.4)
Any component of CT[c]	66 (29.2)	66 (29.2)

[a]The safety analysis set only included pts in the neoadjuvant phase. [b]Dose modifications for TIS/PBO included dose interruption, dose delay and infusion rate decrease. [c]Dose modifications for CT included dose reduction, dose interruption, dose delay and infusion rate decrease.
CT, chemotherapy; PBO, placebo; pts, patients; TEAE, treatment-emergent adverse event; TIS, tislelizumab.

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Presenter Disclosures

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