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Pathological Response to Neoadjuvant Tislelizumab Plus Platinum-Doublet Chemotherapy in Resectable Stage II-IIIA NSCLC Patients in the Phase 3 RATIONALE-315 Trial

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DECLARATION OF INTERESTS

Dongsheng Yue

No conflicts of interest are reported.

Background

- Lung cancer is the 2nd 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-PD-(L)1 mAbs ± CT[5]
  - However, post-op 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 20th, 2023

CT, chemotherapy; mAb, monoclonal antibody; MPR, major pathological response; NSCLC, non-small cell lung cancer; OS, overall survival; pCR, pathological complete response; PD-1, programmed-death 1; PD-L1, programmed-death ligand 1; TIS, tislelizumab.

1. Sung H, et al. *CA Cancer J Clin*. 2021;71(3):209-249. 2. Ganti AK, et al. *Jama Oncol*. 2021;7(12):1824-1832. 3. Ettinger DS, et al. Non-Small Cell Lung Cancer, Version 3.2023. NCCN Clinical Practice Guidelines in Oncology. 2023. nscl.pdf (nccn.org). 4. Forde PM, et al. *N Engl J Med*. 2022;386(21):1973-1985. 5. Heymach JV, et al. *Clin Lung Cancer*. 2022;23(3):e247-e251.

Study Design

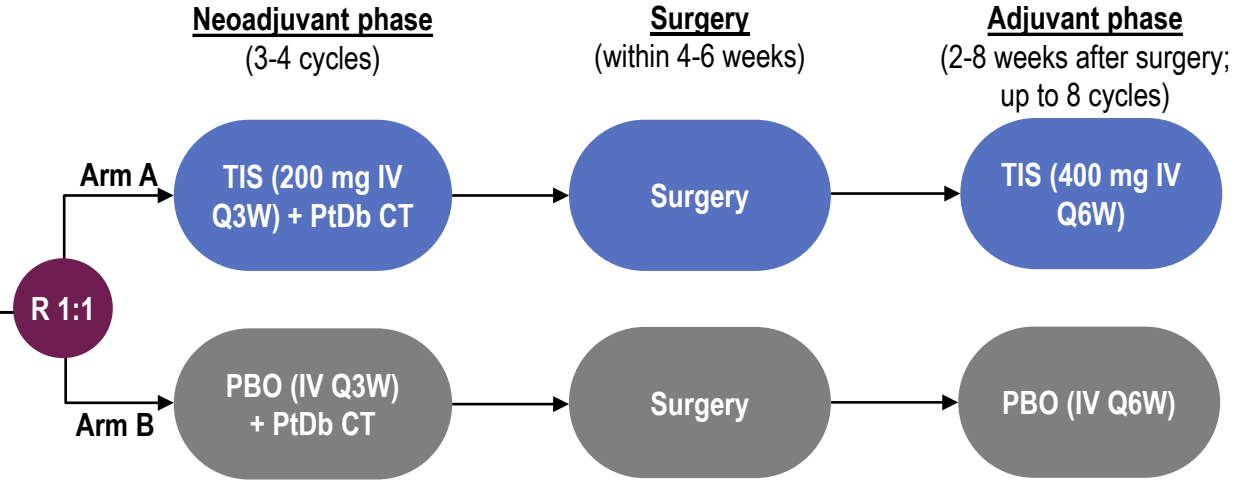
RATIONALE-315: randomized, double-blind, placebo-controlled, phase 3 study

Key eligibility criteria

- Resectable stage II-IIIA NSCLC (eligible for R0 resection)
- ECOG PS 0 or 1
- *EGFR/ALK* WT

Stratification

- Histology (sq vs nsq)
- Disease stage (II vs IIIA)
- PD-L1 expression (≥1% vs <1%/not evaluable/indeterminate)



Platinum-based doublet CT
- Squamous: cisplatin/carboplatin + paclitaxel
- Non-squamous: cisplatin/carboplatin + pemetrexed

Primary endpoints:

- MPR rate by BIPR & EFS by BICR

Key secondary endpoint:

- pCR

Other secondary endpoints:

- OS, ORR, EFS by investigator, safety, HRQoL

Planned interim analysis:

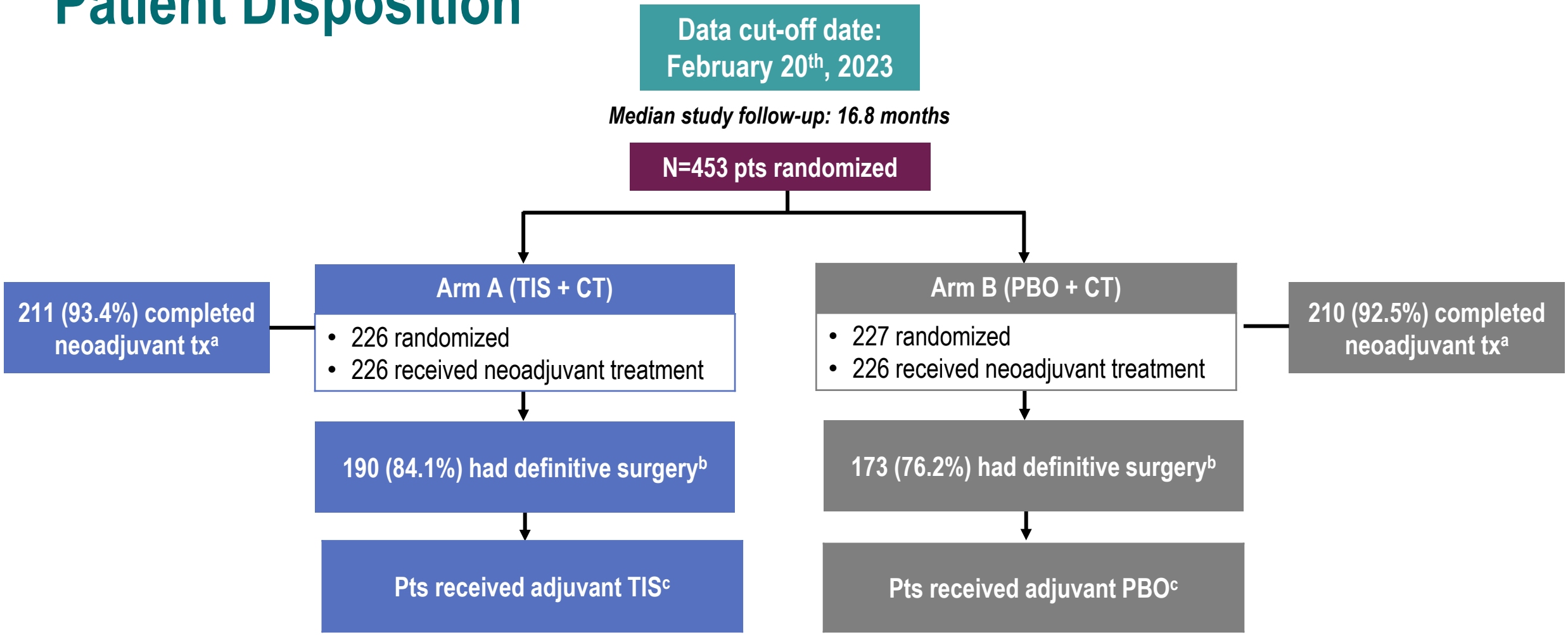
- Final analysis of MPR and pCR per blinded IRC
- EFS at 75% of the target number of events

Statistical Considerations

- The ITT analysis set (TIS + CT, n=226; PBO + CT, n=227) included all randomized patients
- The safety analysis set (TIS + CT, n=226; PBO + CT, n=226) included all randomized patients who received ≥1 dose of any study drug
- 1-sided α at 0.005 is allocated for the MPR test; if MPR is statistically significant, 0.005 will pass to the pCR test

BICR, blinded independent central review; BIPR, blinded independent pathology review; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EFS, event-free survival; HRQoL, health-related quality of life; IRC, independent review committee; ITT, intention-to-treat; IV, intravenously; MPR, major pathological response; NSCLC, non-small cell lung cancer; nsq, nonsquamous; 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; sq, squamous; R0, pathological complete resection of the primary tumor; TIS, tislelizumab; WT, wild type.

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.

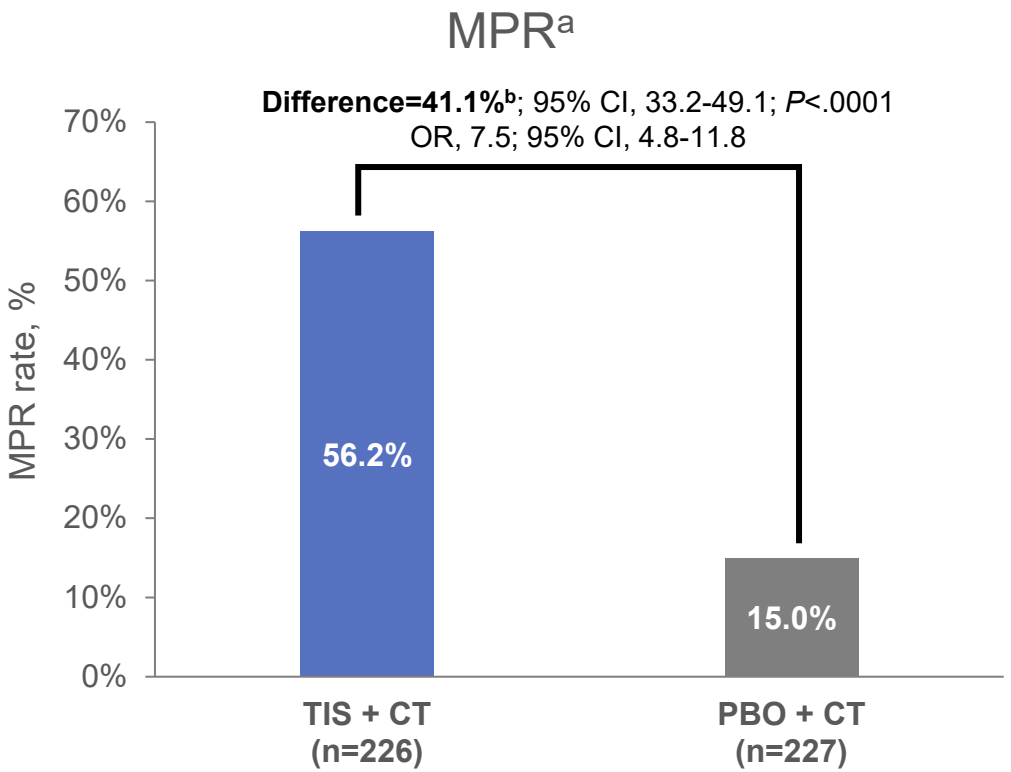
Demographics and Baseline Characteristics

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

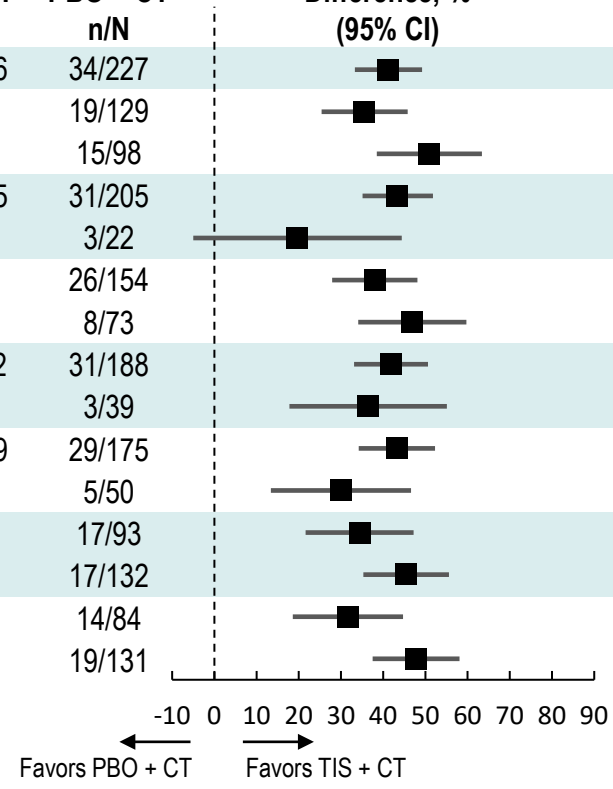
[a] ITT analysis set. [b] One pt in the TIS + CT arm had a missing ECOG PS. [c] Histology by CRF; not shown in table: pts with mixed histology (n=2 in each arm) were categorized as "other". [d] Disease stage by CRF, per AJCC 8th edition; not shown in table: 1 pt (TIS + CT arm) and 2 pts (PBO + CT arm) 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 PS, Eastern Cooperative Oncology Group Performance Status; ITT, intention-to-treat; PBO, placebo; PD-L1, programmed-death ligand 1; pts, patients; TIS, tislelizumab.

Results: Major Pathological Response

- The MPR rate was significantly improved with TIS + CT versus PBO + CT (*P*<.0001) in patients with resectable stage II-IIIA NSCLC



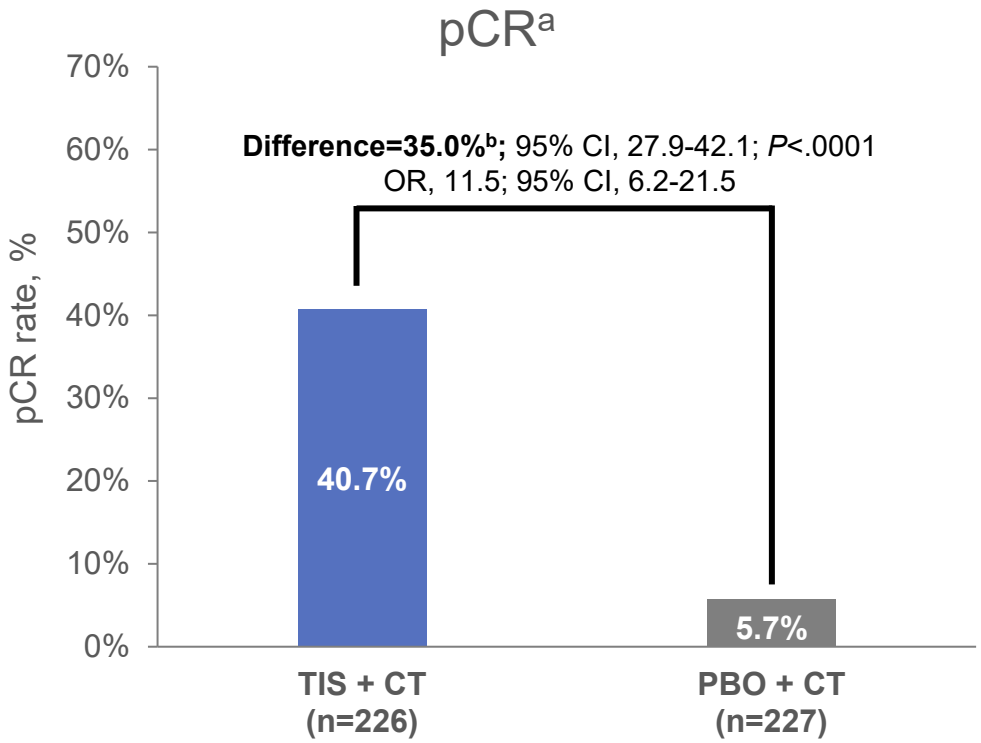
Subgroup[c]	TIS + CT n/N	PBO + CT n/N	Difference, % (95% CI)
Overall	127/226	34/227	41.2 (33.3-49.2)
Age <65 years	72/143	19/129	35.6 (25.4-45.8)
Age ≥65 years	55/83	15/98	51.0 (38.5-63.4)
Male	120/205	31/205	43.4 (35.1-51.8)
Female	7/21	3/22	19.7 (−5.0-44.4)
ECOG PS 0	78/142	26/154	38.0 (27.9-48.1)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



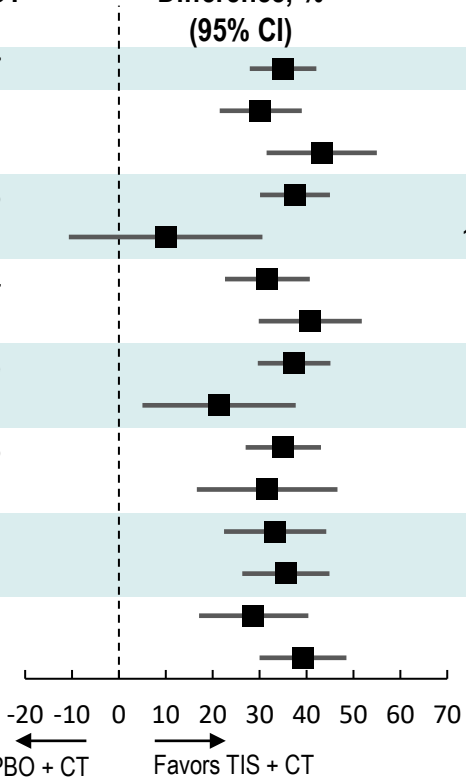
[a] MPR rate was defined as the proportion of pts with ≤10% residual viable tumor in the resected primary tumor and all resected lymph nodes after completion of neoadjuvant tx as assessed by BIPR in an ITT analysis set. Pts who did not receive surgical resection were considered as nonresponders in the 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, intention-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.

Results: Pathological Complete Response

- The pCR rate was significantly improved with TIS + CT versus PBO + CT (*P*<.0001) in patients with resectable stage II-IIIA NSCLC



Subgroup[c]	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)
Age ≥65 years	41/83	6/98	43.3 (31.5-55.0)
Male	88/205	11/205	37.6 (30.1-45.0)
Female	4/21	2/22	10.0 (−10.7-30.6)
ECOG PS 0	56/142	12/154	31.6 (22.6-40.7)
ECOG PS 1	35/83	1/73	40.8 (29.8-51.8)
Current/former smoker	83/192	11/188	37.4 (29.6-45.1)
Never a smoker	9/34	2/39	21.3 (5.0-37.7)
Squamous histology	74/179	11/175	35.1 (27.0-43.1)
Non-squamous histology	16/45	2/50	31.6 (16.6-46.6)
Disease stage II	36/93	5/93	33.3 (22.4-44.2)
Disease stage IIIA	55/132	8/132	35.6 (26.3-44.9)
PD-L1 expression <1%[d]	33/89	7/84	28.7 (17.1-40.4)
PD-L1 expression ≥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 nonresponders 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. [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, intention-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[a] of TIS + CT was consistent with the known risks of each treatment and was well tolerated in patients with resectable stage II-IIIA NSCLC

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	TIS + CT (n=226)	PBO + CT (n=226)
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.

Conclusions

- TIS + CT showed statistically significant and clinically meaningful improvements in MPR and pCR rates versus PBO + CT as neoadjuvant tx
- The safety profile of TIS + CT is manageable and consistent with previous reports, further supporting this treatment combination for pts with resectable stage II or IIIA NSCLC
- The RATIONALE-315 study is ongoing; a subsequent interim analysis showed significant improvement in EFS in the TIS arm (these data will be shared at a future meeting)

CT, chemotherapy; EFS, event-free survival; MPR, major pathological response; NSCLC, non-small cell lung cancer; PBO, placebo; pCR, pathological complete response; TIS, tislelizumab.

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