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Surgical Outcomes from RATIONALE-315: Randomised, Double-Blind, Phase 3 Study of Perioperative Tislelizumab with Neoadjuvant Chemotherapy in Resectable NSCLC

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on behalf of the RATIONALE-315 Investigators

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Declaration of Interests

- Dongsheng Yue reports no conflicts of interest

Background

- Surgery offers the highest likelihood of cure for patients with resectable, early-stage NSCLC; however, the 5-year tumour recurrence rate can be as high as 67% (depending on disease stage)[1-5]
- At the interim analysis of RATIONALE-315 (NCT04379635), perioperative TIS (anti-PD-1 mAb) plus neoadjuvant PtDb CT showed statistically significant and clinically meaningful improvements in MPR, pCR rates, and EFS vs PBO + PtDb CT as neoadjuvant treatment in patients in China with resectable stage II-IIIA NSCLC, as well as a tolerable and manageable safety profile[6-7]

Here we present and report on key surgery outcomes from this study

Abbreviations: EFS, event-free survival; mAb, monoclonal antibody; MPR, major pathological response; NSCLC, non-small cell lung cancer; PBO, placebo; pCR, pathological complete response; PD-1, programmed-death 1; PtDb CT, platinum-based doublet chemotherapy; TIS, tislelizumab.

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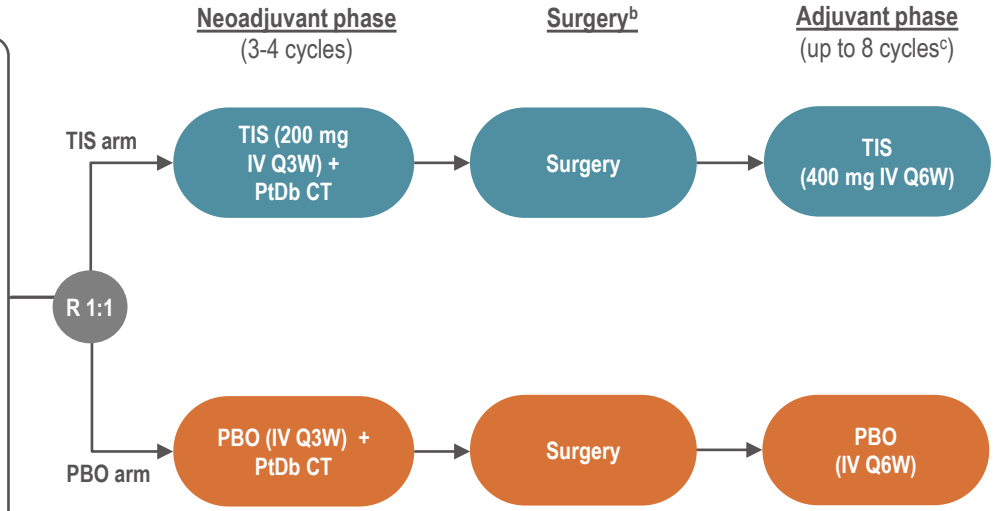
RATIONALE-315 Study Design

Key eligibility criteria

- Resectable stage II-IIIA NSCLC per AJCC 8th Cancer Staging Manual (eligible for R0 resection)
- ECOG PS 0 or 1
- *EGFR/ALK* WT[a]

Stratification

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



PtDb CT

- Squamous: cisplatin/carboplatin + paclitaxel
- Non-squamous: cisplatin/carboplatin + pemetrexed

Primary endpoints:

- MPR rate by BIPR and EFS by BICR

Secondary endpoints:

- pCR rate by BIPR
- OS, EFS by investigator, safety (and others not reported here)

Exploratory endpoint:

- Surgery outcomes

ClinicalTrials.gov Identifier: NCT04379635.
Median study follow-up: 22.0 months (range: 0.1-38.4); data cut-off: August 21, 2023.
[a] *EGFR* testing was not mandatory for squamous NSCLC. [b] Surgery should be scheduled between 4 and 6 weeks from the last dose of neoadjuvant therapy. [c] Patients who continued to have ECOG PS 0 or 1 and adequate organ function were eligible to receive adjuvant treatment for up to 8 cycles or until disease recurrence/progression, unacceptable adverse events, or death occurs, or if the patient and/or investigator decided to discontinue study treatment. The first dose of adjuvant therapy should be administered within 2 to 8 weeks after surgery.
Abbreviations: AJCC, American Joint Committee on Cancer; ALK, anaplastic large-cell lymphoma kinase; BICR, blinded independent central review; BIPR, blinded independent pathology review; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; EGFR, epidermal growth factor receptor; IV, intravenously; MPR, major pathological response; NSCLC, non-small cell lung cancer; OS, overall survival; PBO, placebo; pCR, pathological complete response; PD-L1, programmed death-ligand 1; PtDb CT, platinum-based doublet chemotherapy; Q3W, once every 3 weeks; Q6W, once every 6 weeks; R, randomised; R0, pathological complete resection of the primary tumour; TIS, tislelizumab; WT, wild-type.

Demographics and Baseline Characteristics

ITT Analysis Set

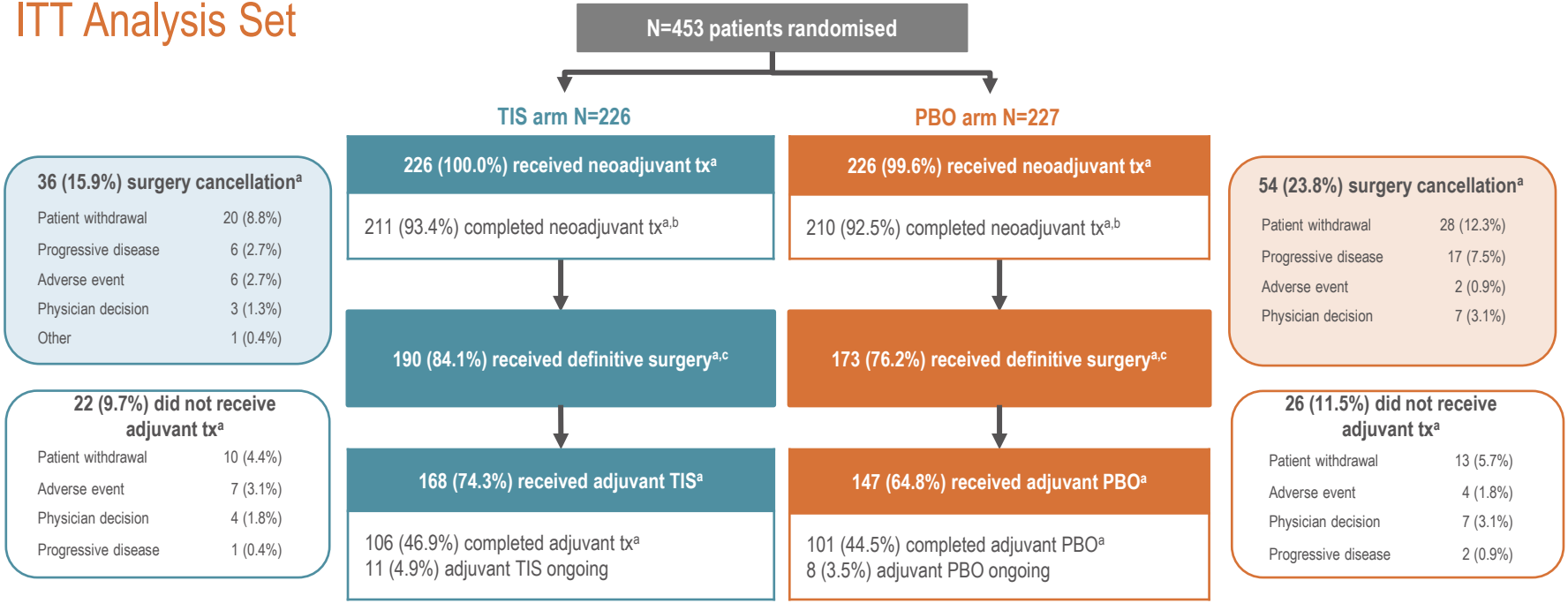
	TIS arm (N=226)	PBO arm (N=227)
Age, median (IQR), years	62.0 (57.0-67.0)	63.0 (56.0-68.0)
Male sex, n (%)	205 (90.7)	205 (90.3)
Asian race, n (%)	226 (100.0)	227 (100.0)
ECOG PS 1, n (%)[a]	83 (36.7)	73 (32.2)
Smoking status, n (%)		
Current/former	193 (85.4)	190 (83.7)
Never	33 (14.6)	37 (16.3)
Histology, n (%)[b]		
Squamous	179 (79.2)	175 (77.1)
Non-squamous	45 (19.9)	50 (22.0)
Disease stage, n (%)[c]		
II	92 (40.7)	91 (40.1)
IIIA	132 (58.4)	133 (58.6)

	TIS arm (N=226)	PBO arm (N=227)
cT status, n (%)		
T1	19 (8.4)	18 (8.2)
T2	126 (55.8)	120 (52.9)
T3	57 (25.2)	64 (28.2)
T4	24 (10.6)	25 (11.0)
cN status, n (%)[d]		
N0	60 (26.5)	54 (23.8)
N1	84 (37.2)	93 (41.0)
N2	82 (36.3)	79 (34.8)
PD-L1 expression, n (%)[e]		
<1%	89 (39.4)	84 (37.0)
≥1%	130 (57.5)	132 (58.1)
Not evaluable/indeterminate	7 (3.1)	11 (4.8)

[a] One patient in the TIS arm had a missing ECOG PS. [b] Histology by CRF; mixed histology was categorised as "Other" (n=2 [0.9%] in each arm). [c] One patient (TIS arm) with disease stage IB and four patients with disease stage IIIB were incorrectly enrolled.
[d] One patient was enrolled (PBO arm) with N3. [e] PD-L1 expression from Central Lab.
Abbreviations: cN, clinical node; CRF, case report form; cT, clinical T stage at baseline; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; ITT, intention-to-treat; PBO, placebo; PD-L1, programmed death-ligand 1; TIS, tislelizumab .

Patient Disposition

ITT Analysis Set



Median study follow-up: 22.0 months (range: 0.1-38.4). The ITT analysis set included all randomised patients.

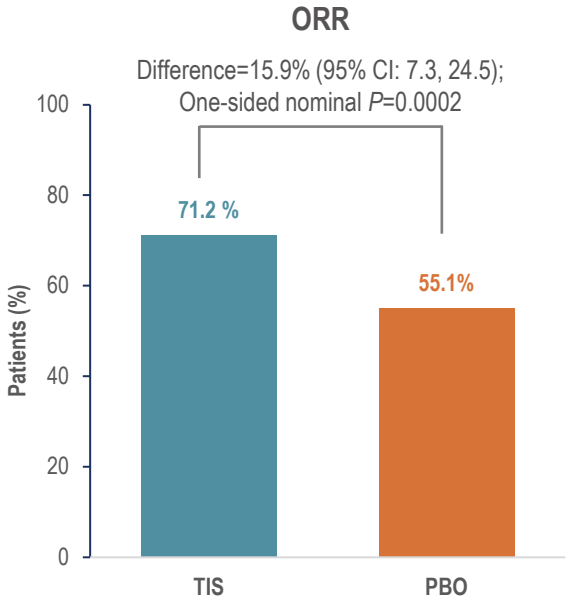
[a] Denominator based on randomised patients. [b] Completion of neoadjuvant treatment is based on whether patients received 3 to 4 cycles of neoadjuvant treatments. [c] Patients received postoperative radiotherapy (3 in TIS arm, 5 in PBO arm).

Abbreviations: ITT, intention-to-treat; PBO, placebo; TIS, tislelizumab; tx, treatment.

Objective Response Rate Before Surgery by BICR

ITT Analysis Set

Response Category	TIS arm (N=226)	PBO arm (N=227)
Best overall response[a], n (%)		
Complete response	1 (0.4)	3 (1.3)
Partial response	160 (70.8)	122 (53.7)
Stable disease	54 (23.9)	94 (41.4)
Progressive disease[b]	4 (1.8)	2 (0.9)
Could not be determined[c]	7 (3.1)	6 (2.6)



- ORR, including patients who had a best overall response of CR or PR before surgery, was higher in the TIS arm than in the PBO arm (risk difference of 15.9% [95% CI: 7.3%-24.5%])

[a] Tumour assessment on or prior to surgery (on or prior to progressive disease for patients without surgery), the start of new anti-cancer therapy, whichever comes first, are included. [b] 3 patients in TIS arm and 1 patient in PBO arm proceeded to complete surgery. [c] Patients with no postbaseline response assessment (Not Assessable) or assessment as Not Evaluable per RECIST v1.1.

Abbreviations: BICR, blinded independent central review; CI, confidence interval; CR, complete response; ITT, intention-to-treat; ORR, objective response rate; PBO, placebo; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; TIS, tislelizumab.

Surgical Delay by Disease Stage

Safety Analysis Set (Surgery)

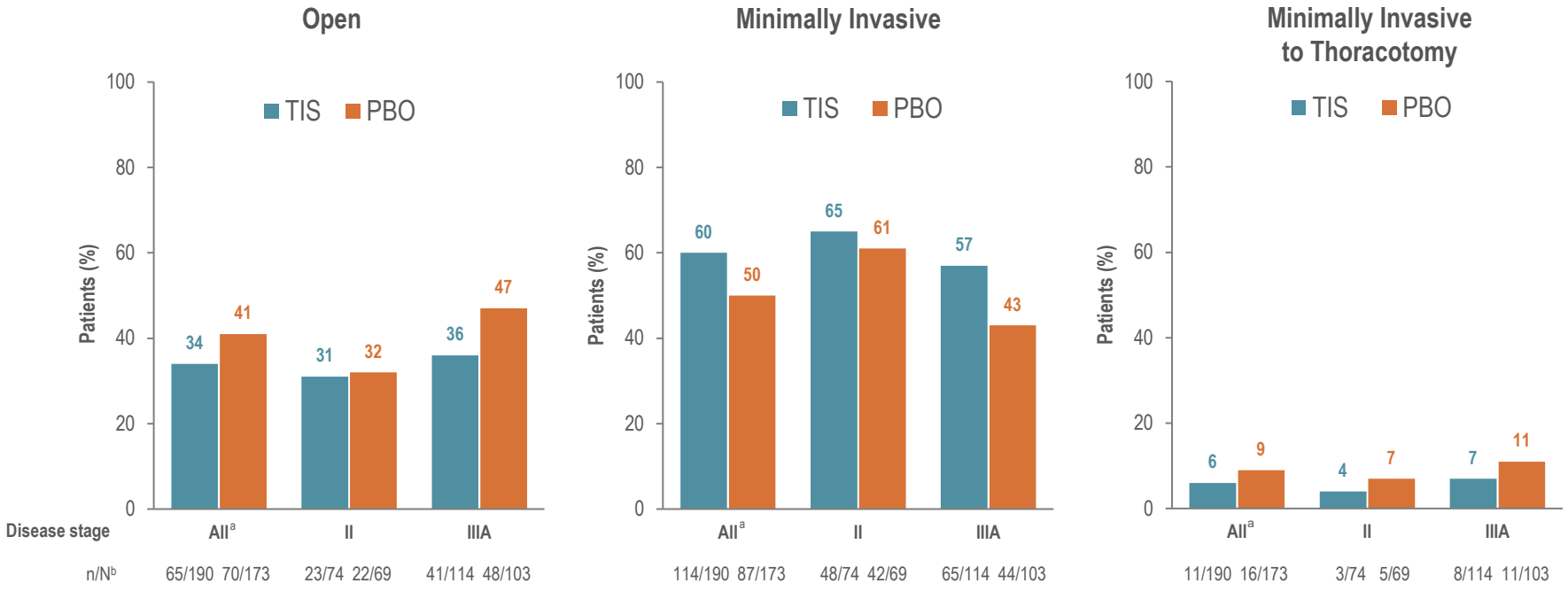
	All Stages		Stage II		Stage IIIA	
	TIS arm (N=190)	PBO arm (N=173)	TIS arm (N=74)	PBO arm (N=69)	TIS arm (N=114)	PBO arm (N=103)
Patients with delayed surgery[a], n (%)	31 (16.3)	22 (12.7)	19 (25.7)	6 (8.7)	12 (10.5)	16 (15.5)
Adverse events	12 (6.3)	6 (3.5)	9 (12.2)	3 (4.3)	3 (2.6)	3 (2.9)
Other	19 (10.0)	16 (9.2)	10 (13.5)	3 (4.3)	9 (7.9)	13 (12.6)
Related to COVID-19	8 (4.2)	7 (4.0)	6 (8.1)	2 (2.9)	2 (1.8)	5 (4.9)
Length of surgery delay[b], n (%)						
≤2 weeks	22 (11.6)	18 (10.4)	14 (18.9)	6 (8.7)	8 (7.0)	12 (11.7)
>2 and ≤4 weeks	5 (2.6)	3 (1.7)	2 (2.7)	0 (0.0)	3 (2.6)	3 (2.9)
>4 and ≤6 weeks	1 (0.5)	1 (0.6)	1 (1.4)	0 (0.0)	0 (0.0)	1 (1.0)
>6 weeks	2 (1.1)	0 (0.0)	2 (2.7)	0 (0.0)	–	–

- Median (IQR) time from randomisation to definitive surgery was 13.4 (11.6-15.0) weeks with TIS and 12.7 (11.4-14.9) weeks with PBO for all patients with definitive surgery
- Median (IQR) time from last neoadjuvant dose to definitive surgery was 5.5 (5.0-6.0) weeks with TIS and 5.3 (5.0-5.9) weeks with PBO for all patients with definitive surgery

[a] Defined as when date of surgery is beyond 6 weeks after last neoadjuvant treatment dose. [b] Length of surgery delay is defined as (surgery start date - last neoadjuvant treatment date - 6 weeks*7)/7 for patients having surgery delayed.
Abbreviations: IQR, interquartile range; PBO, placebo; TIS, tislelizumab.

Surgical Approach

Safety Analysis Set (Surgery)



[a] Patients with all stages of disease and definitive surgery. [b] Denominator based on patients with definitive surgery.
Abbreviations: PBO, placebo; TIS, tislelizumab.

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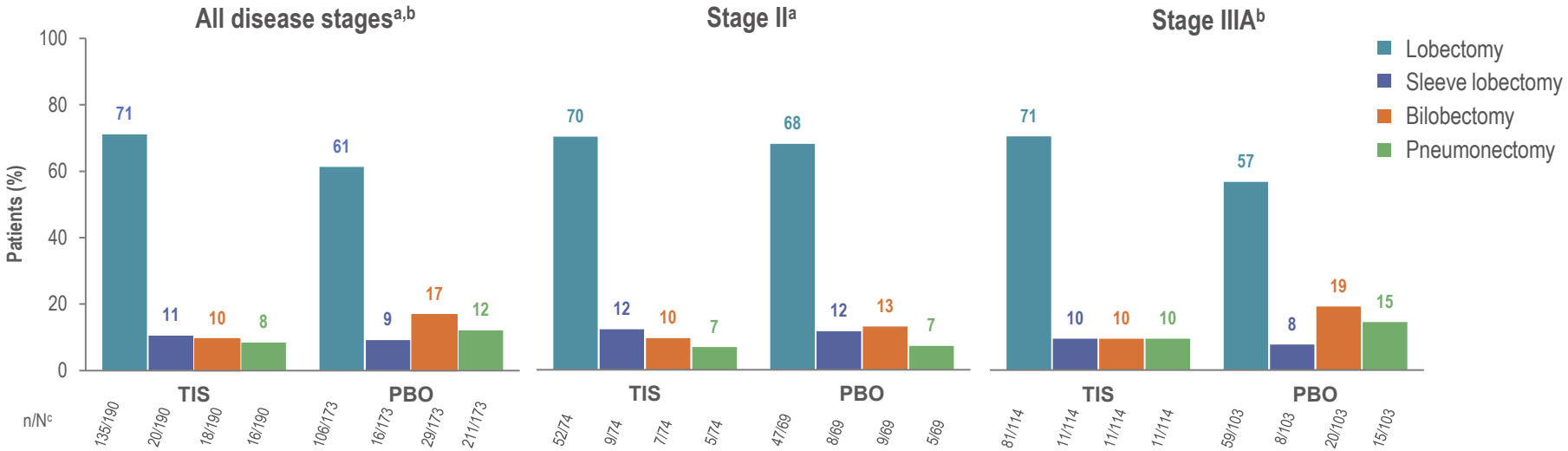
Type of Surgery

Safety Analysis Set (Surgery)

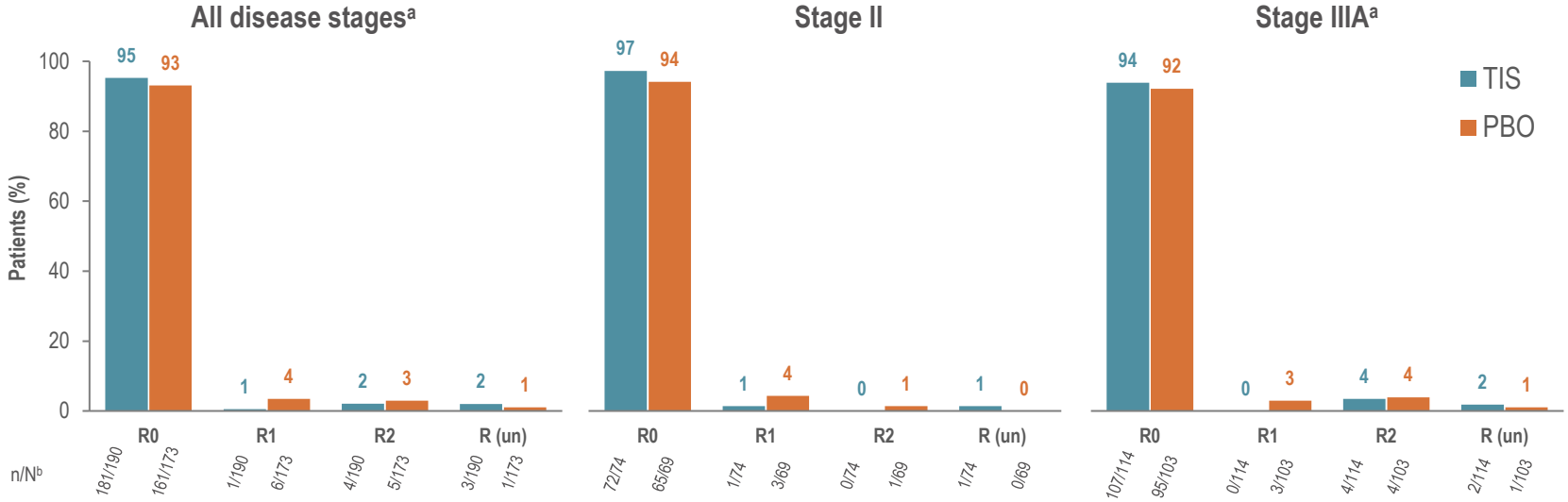


- The most common type of surgical procedure was lobectomy regardless of disease stage in both treatment arms
- Fewer pneumonectomies were reported in the TIS arm vs the PBO arm (16 [8.4%] vs 21 [12.1%])

[a] One patient received segmentectomy in the TIS arm. [b] One patient received segmentectomy in the PBO arm. [c] Denominator based on patients with definitive surgery.
Abbreviations: PBO, placebo; TIS, tislelizumab.

Completeness of Resection

Safety Analysis Set (Surgery)



- R0, R1, and R2 resection rates were similar regardless of disease stage in both treatment arms
- Median (IQR) number of lymph nodes dissected was similar between treatment arms: 18.0 (11.0-24.0) for the TIS arm and 16.0 (10.0-23.0) for the PBO arm

[a] One patient in the TIS arm had missing information on completeness of resection. [b] Denominator based on patients with definitive surgery.
Abbreviations: IQR, interquartile range; PBO, placebo; R0, pathological complete resection of the primary tumour; TIS, tislelizumab; un, uncertain.

Hospital Stay by Surgery Type and Disease Stage

Safety Analysis Set (Surgery)

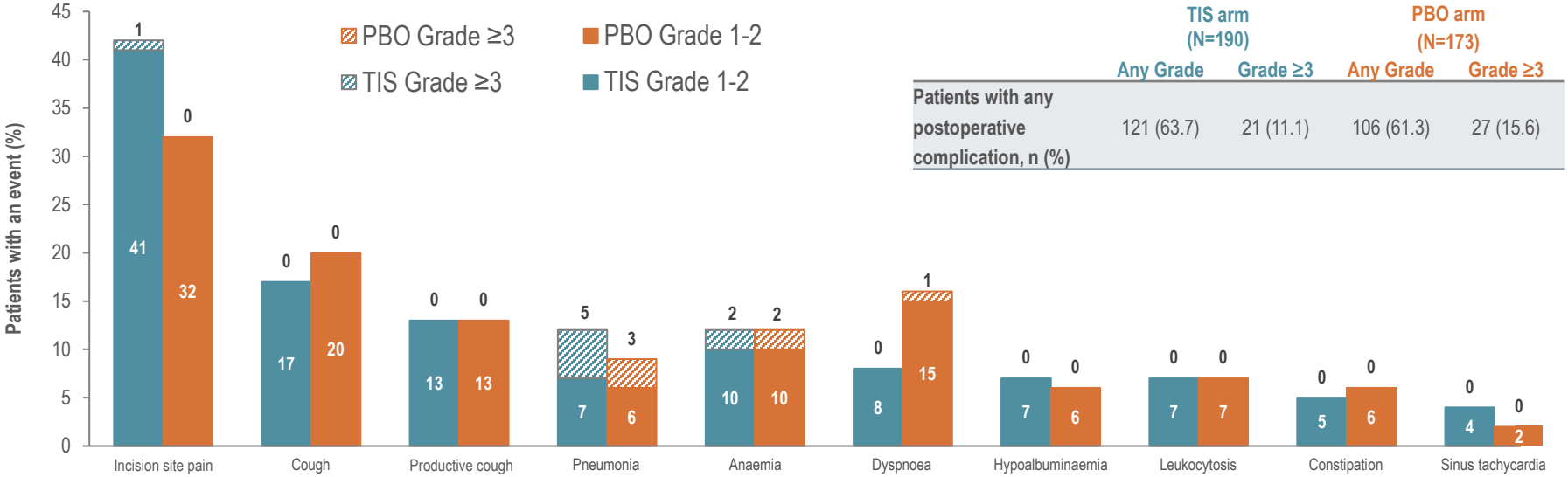
	TIS arm (N=190)	PBO arm (N=173)
Length of hospital stay, median (IQR), days	7.0 (5.0-9.0)	7.0 (6.0-9.0)
Length of hospital stay by surgery type, median (IQR), days		
Lobectomy	6.0 (5.0-8.0)	7.0 (5.0-9.0)
Pneumonectomy	8.0 (7.0-11.0)	7.0 (5.0-8.0)
Sleeve lobectomy	8.0 (6.0-13.5)	7.0 (6.0-7.5)
Bilobectomy	6.0 (5.0-9.0)	8.0 (6.0-10.0)
Length of hospital stay by disease stage, median (IQR), days		
II	7.0 (6.0-9.0)	7.0 (5.0-9.0)
IIIA	7.0 (5.0-9.0)	7.0 (6.0-9.0)

- Hospital stay rates were similar regardless of surgery type and disease stage in both treatment arms
- Median duration of surgery (2.7 vs 2.8 hours) was similar between arms

Abbreviations: IQR, interquartile range; PBO, placebo; TIS, tislelizumab.

90-Day Postoperative Complications Summary[a]

Safety Analysis Set (Surgery)



	TIS arm (N=190)		PBO arm (N=173)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with any postoperative complication, n (%)	121 (63.7)	21 (11.1)	106 (61.3)	27 (15.6)

- The 30-day and 90-day postsurgery mortality[b] rates were 2 (0.9%) and 3 (1.3%) patients in the TIS arm, and 2 (0.9%) and 4 (1.8%) patients in the PBO arm, respectively

[a] Adverse events assessed as postoperative complications from the date of surgery up to 90 days after surgery were included. [b] Denominator based on safety analysis set (overall).
Abbreviations: PBO, placebo; TIS, tislelizumab.

Conclusions

- In the RATIONALE-315 study, perioperative TIS plus neoadjuvant PtDb CT did not impact the feasibility and completeness of surgery
  - R0 resections were achieved in a similar percentage of patients in both arms (TIS: 95%, PBO: 93%)
  - 6.3% (TIS arm) and 3.5% (PBO arm) of surgical delays were due to adverse events, with the majority of the delays not exceeding 2 weeks
  - The median duration of surgery, length of hospital stays, and number of lymph nodes dissected were similar between the TIS and PBO arms
  - In the TIS arm, a higher proportion of patients received minimally invasive surgery compared with the PBO arm (TIS: 60%, PBO: 50%)
- The safety profile of perioperative TIS plus neoadjuvant PtDb CT was manageable, and treatment with TIS was not associated with increased rates of postoperative complications
- Taken together with previously reported statistically significant improvement in MPR, pCR, and EFS,[1-2] these data support the use of perioperative TIS plus neoadjuvant PtDb CT for patients with resectable stage II-IIIA NSCLC

Abbreviations: EFS, event-free survival; MPR, major pathological response; NSCLC, non-small cell lung cancer; PBO, placebo; pCR, pathological complete response; PtDb CT, platinum-based doublet chemotherapy; R0, pathological complete resection of the primary tumour; TIS, tislelizumab.

1. Yue D, et al. *Annal Oncol.* 2023;34(Suppl 2):S1299. 2. Yue D, et al. *Ann Oncol*. Published online February 15, 2024. doi:10.1016/j.annonc.2024.01.005.

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