

ESMO VIRTUAL PLENARY

WITH AACR EXPERT COMMENTARY

RATIONALE-315: Event-Free Survival (EFS) and Overall Survival (OS) of Neoadjuvant Tislelizumab (TIS) plus Chemotherapy (CT) with Adjuvant TIS in Resectable Non-Small Cell Lung Cancer (NSCLC)

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Declaration of Interests

- Dongsheng Yue reports no conflicts of interest

Background



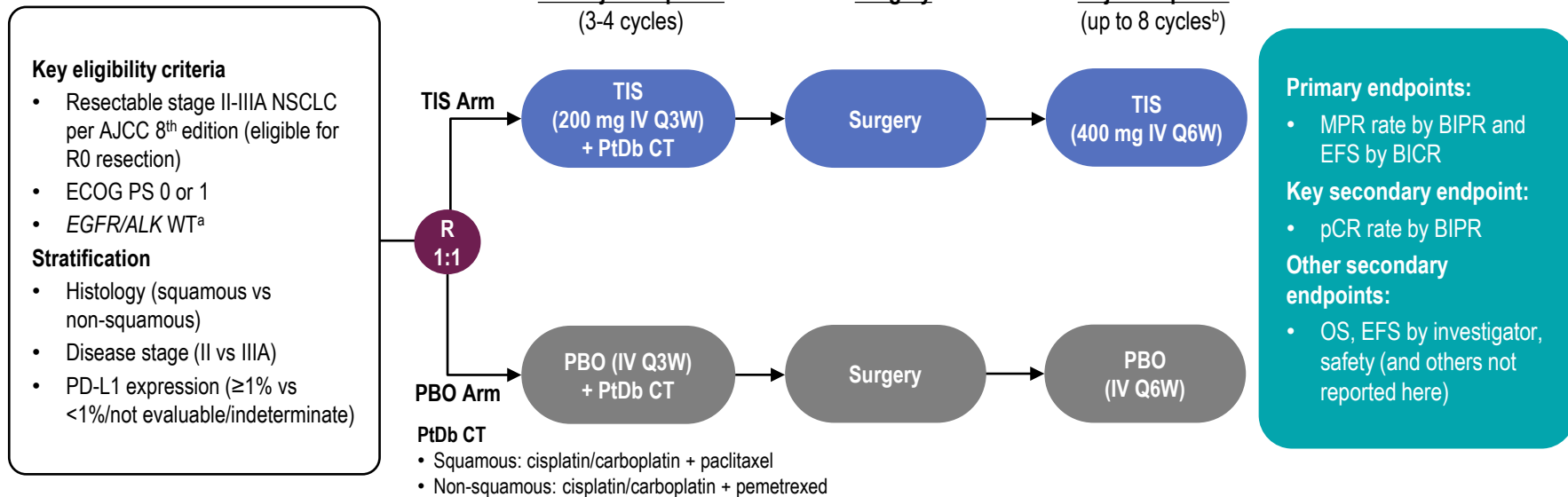
- Surgery offers the highest likelihood of cure for patients with resectable, early-stage NSCLC; however, the 5-year tumour recurrence rate can be as high as 67% (depending on disease stage)¹⁻⁵
- In recent years, management of resectable NSCLC has evolved rapidly with emerging evidence of clinical benefit for perioperative anti-PD-(L)1 mAb treatment in combination with neoadjuvant CT⁶⁻¹⁰

RATIONALE-315 (NCT04379635) is investigating the efficacy and safety of perioperative TIS (anti-PD-1 mAb) or PBO plus neoadjuvant PtDb CT in patients with resectable stage II-IIIa NSCLC in China

Here, we present the interim results for EFS and OS

Abbreviations: CT, chemotherapy; EFS, event-free survival; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; OS, overall survival; PBO, placebo; PD-1, programmed-death 1; PD-L1, programmed death-ligand 1; PtDb, platinum-based doublet; TIS, tislelizumab.
1. Uramoto H and Tanaka F. *Transl Lung Cancer Res.* 2014;3:242-249. 2. Kelsey CR, et al. *Cancer.* 2009;115:5218-5227. 3. Gourcerol D, et al. *Eur Respir J.* 2013;42:1357-1364. 4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Non-Small Cell Lung Cancer: Version 5.2023. [nsccl.pdf \(nccn.org\)](https://www.nccn.org). 5. West H, et al. *Clin Lung Cancer.* 2023;24:260-268. 6. Forde PM, et al. *N Engl J Med.* 2022;386:1973-1985. 7. Felip E, et al. *Lancet.* 2021;398:1344-1357. 8. O'Brien M, et al. *Lancet Oncol.* 2022;23:1274-1286. 9. Wakelee H, et al. *N Engl J Med.* 2023;389:491-503. 10. Heymach JV, et al. *N Engl J Med.* 2023;389:1672-1684.

RATIONALE-315 Study Design



Data cut-off: August 21, 2023 (median study follow-up: 22.0 months [range: 0.1, 38.4]).

ClinicalTrials.gov Identifier: NCT04379635.

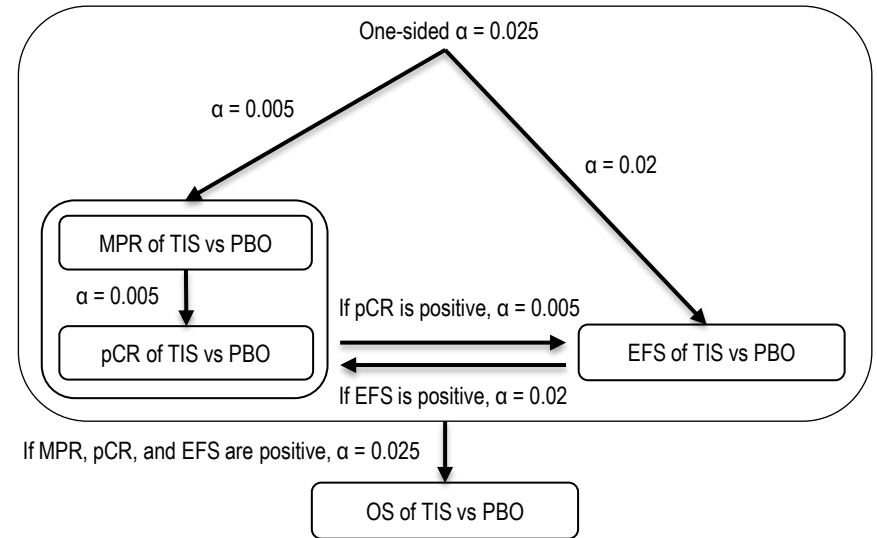
^a EGFR testing was mandatory for non-squamous NSCLC. ^b Adjuvant treatment was only received by patients with an ECOG PS of 0 or 1 and adequate organ function for ≤ 8 cycles or until disease recurrence/progression, unacceptable adverse events, or death occurs, or if the patient and/or investigator decided to discontinue study treatment.

Abbreviations: 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.

Statistical Considerations

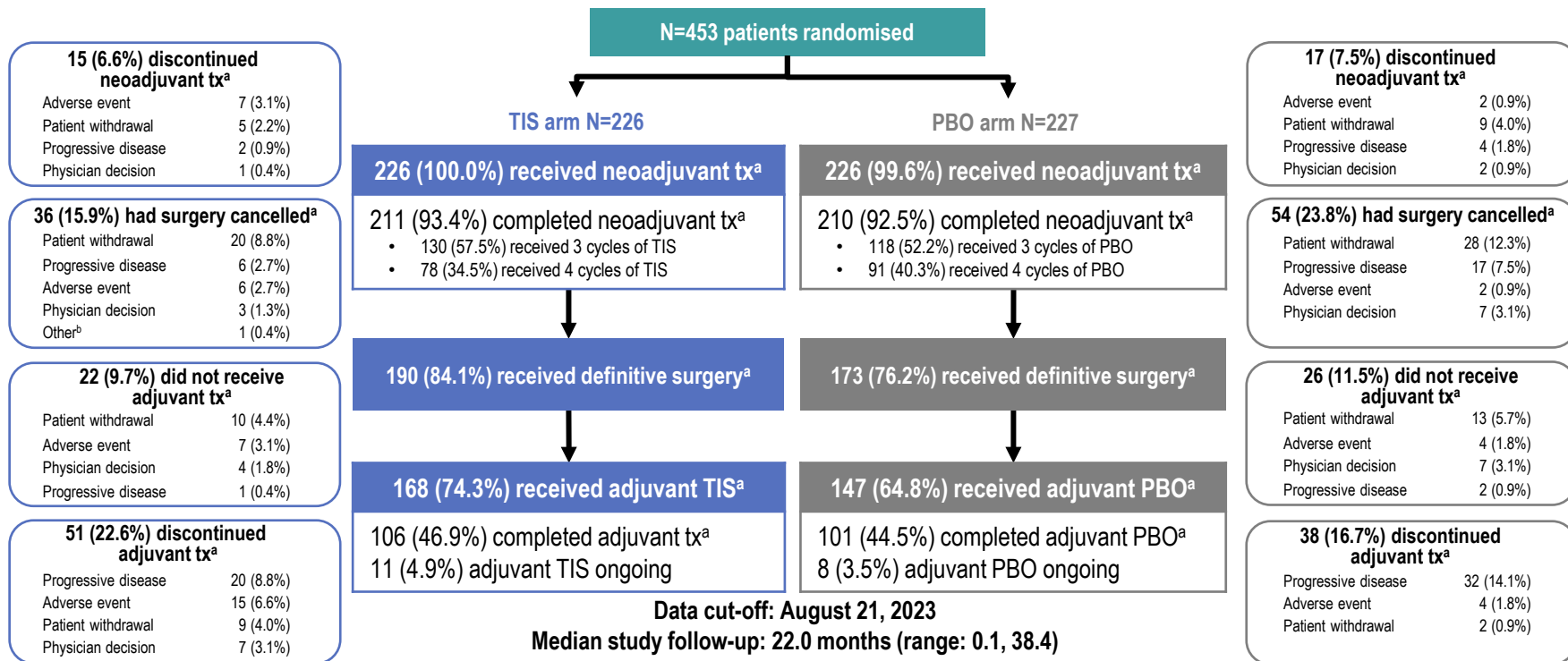
- Overall type I error was strongly controlled at a one-sided alpha of 0.025
- The interim analysis for EFS was planned for when ~75% of the targeted EFS events (184 EFS events) had occurred, with Lan-DeMets α spending function approximation to the O'Brien–Fleming boundary
- The OS interim analysis was to be tested with Haybittle–Peto P -value boundary at 0.0001 at this interim analysis

Type I Error Control Scheme



Abbreviations: EFS, event-free survival; MPR, major pathological response; OS, overall survival; PBO, placebo; pCR, pathological complete response; TIS, tislelizumab.

Patient Disposition (ITT Analysis Set)



The ITT analysis set included all randomised patients. ^a Denominator based on randomised patients. ^b Patient was reported to cancel surgery due to lost to follow-up.

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

Demographics and Baseline Characteristics

ITT Analysis Set

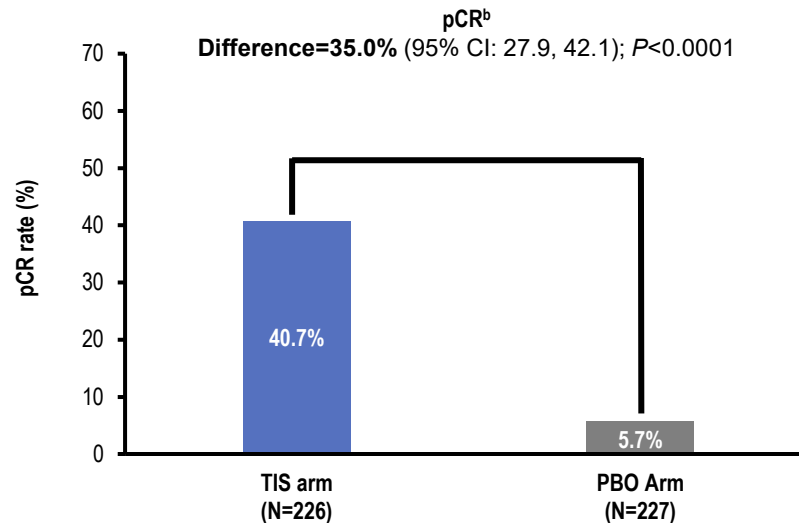
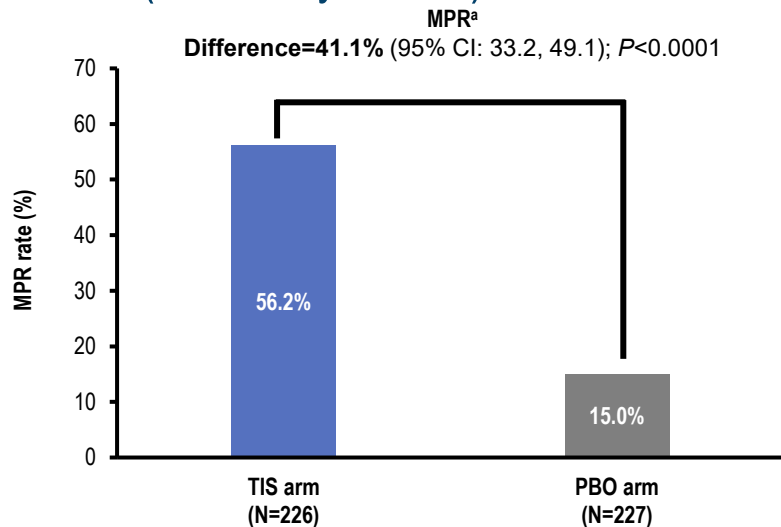
	TIS arm (N=226)	PBO arm (N=227)
Age, median (IQR), years	62.0 (57.0, 67.0)	63.0 (56.0, 68.0)
Male sex, n (%)	205 (90.7)	205 (90.3)
Asian race, n (%)	226 (100.0)	227 (100.0)
ECOG PS, n (%)^a		
0	142 (62.8)	154 (67.8)
1	83 (36.7)	73 (32.2)
Smoking status, n (%)		
Current/former	193 (85.4)	190 (83.7)
Never	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 (%)		
II	92 (40.7)	91 (40.1)
IIIA	132 (58.4)	133 (58.6)
cN status, n (%)^c		
N0	60 (26.5)	54 (23.8)
N1	84 (37.2)	93 (41)
N2	82 (36.3)	79 (34.8)
PD-L1 expression, n (%)^d		
<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; patients with mixed histology were categorised as 'Other' (n=2 [0.9%] in each arm). ^c One patient was enrolled (PBO arm) with N3. ^d PD-L1 expression from Central Lab.

Abbreviations: CRF, case report form; 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; cN, clinical N.

Major Pathological and Pathological Complete Responses

Per BIPR (ITT Analysis Set)



- Neoadjuvant TIS + PtDb CT showed a statistically significant and clinically meaningful improvement in MPR and pCR rates vs neoadjuvant PBO + PtDb CT

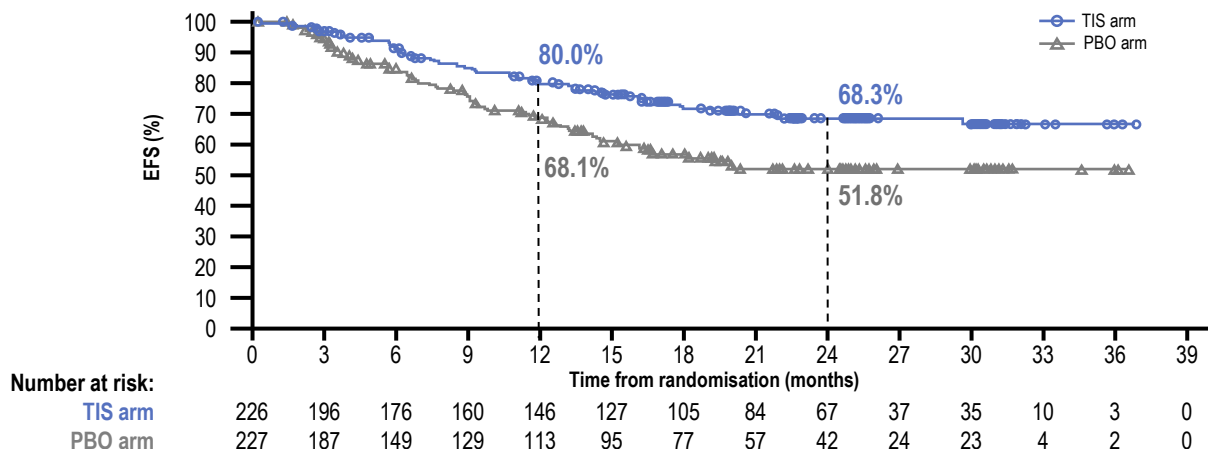
Final MPR and pCR analysis at the February 20, 2023, cut-off. Patients who did not receive surgical resection were considered non-responders. ^aMPR was defined as the proportion of patients with $\leq 10\%$ residual viable tumour in the resected primary tumour and resected lymph nodes after completion. ^bpCR was defined as the proportion of patients absent of residual viable tumour in the resected primary tumour and resected lymph nodes after treatment.

Abbreviations: BIPR, blinded independent pathology review; CI, confidence interval; CT, chemotherapy; 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; pCR, pathological complete response; PtDb, platinum-based doublet; TIS, tislelizumab. Yue D, et al. Presented at ESMO, Madrid, Spain; October 23, 2023.

Event-Free Survival

Per BICR (ITT Analysis Set)

	Events (%)	Median (95% CI), months	HR (95% CI)	P-value
TIS arm	58 (25.7)	NR (NE, NE)	0.56 (0.40, 0.79)	0.0003
PBO arm	83 (36.6)	NR (16.6, NE)		



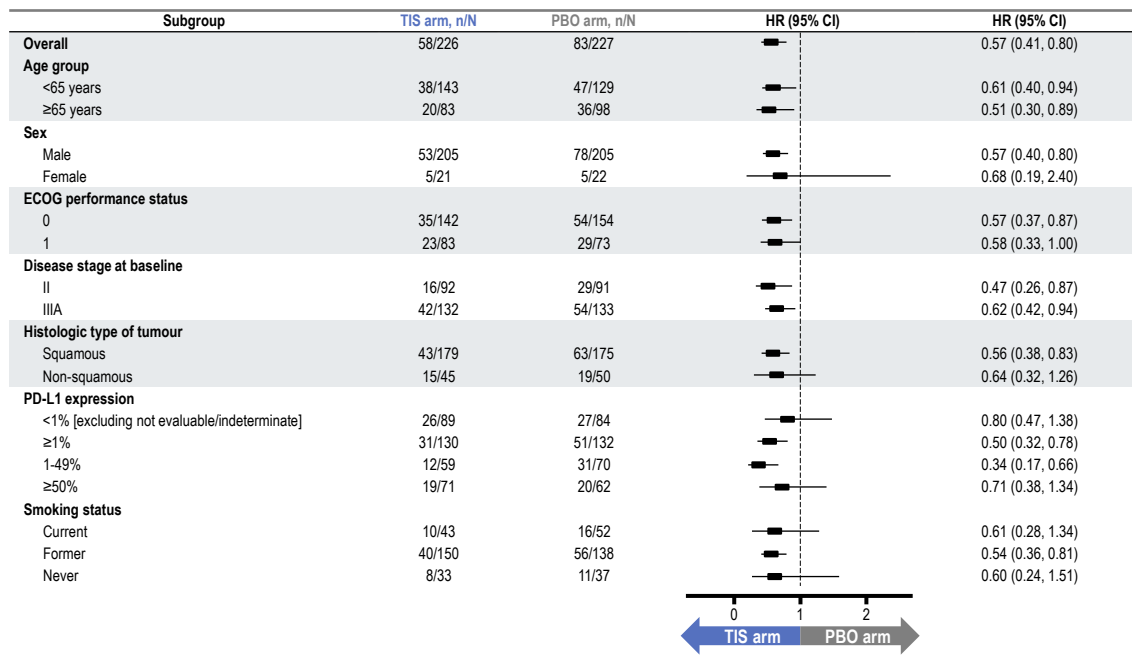
- A statistically significant and clinically meaningful improvement in EFS (HR=0.56 [95% CI: 0.40, 0.79]; one-sided P=0.0003) was observed favouring perioperative TIS
- A clinically meaningful improvement in EFS per investigator (HR=0.55 [95% CI: 0.39, 0.77]) was also observed

Analysis occurred at the August 21, 2023, cut-off. EFS was defined as the time from randomisation until any of the following, whichever occurred first: disease progression precluding surgery, local or distant recurrence, or death due to any cause. The significance boundary of the EFS interim analysis was 0.0105 (calculated based on 141 actual EFS events).

Abbreviations: CI, confidence interval; BICR, blinded independent central review; EFS, event-free survival; HR, hazard ratio; ITT, intention-to-treat; NE, not evaluable; NR, not reached; PBO, placebo; TIS, tislelizumab.

Event-Free Survival By Subgroups

ITT Analysis Set



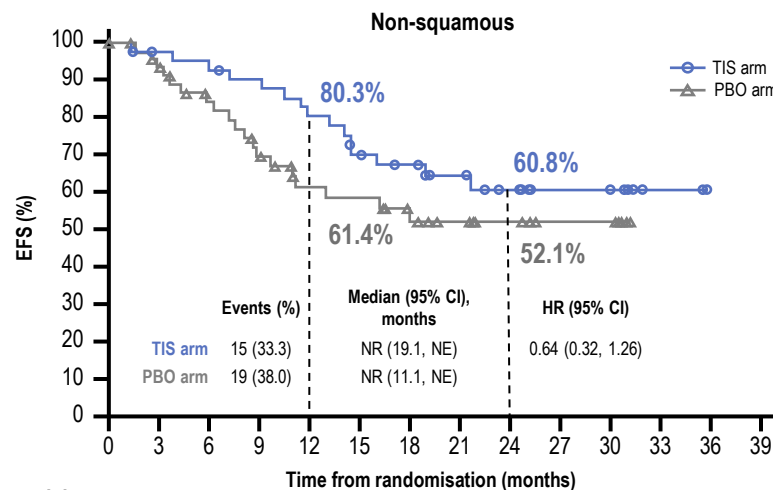
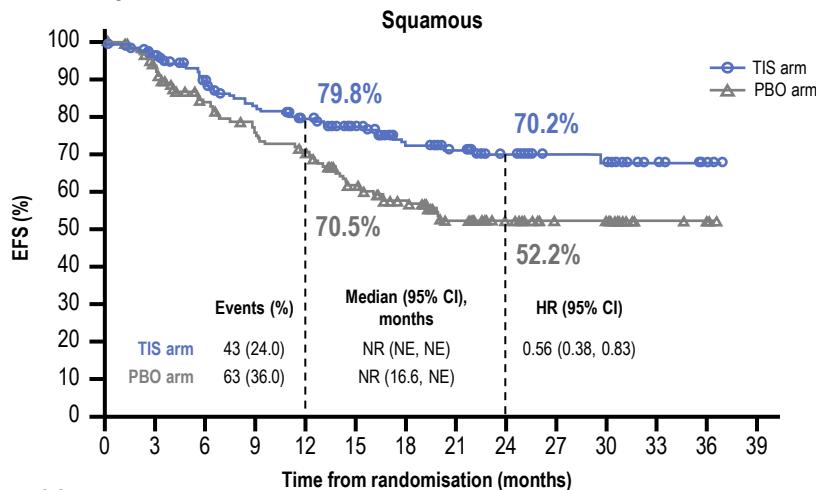
The EFS benefit with perioperative TIS over PBO was generally consistent across prespecified subgroups

EFS was defined as the time from randomisation until any of the following, whichever occurred first: disease progression precluding surgery, local or distant recurrence, or death due to any cause.

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; HR, hazard ratio; ITT, intention-to-treat; PD-L1, programmed death-ligand 1;

Event-Free Survival By Histology

ITT Analysis Set



Number at risk:

TIS arm	179	154	135	122	112	99	80	65	53	29	27	8	3	0
PBO arm	175	143	114	101	92	75	61	45	33	18	17	4	2	0

Number at risk:

TIS arm	45	40	39	36	32	27	24	18	13	8	8	2	0	0
PBO arm	50	43	35	28	21	20	16	12	9	6	6	0	0	0

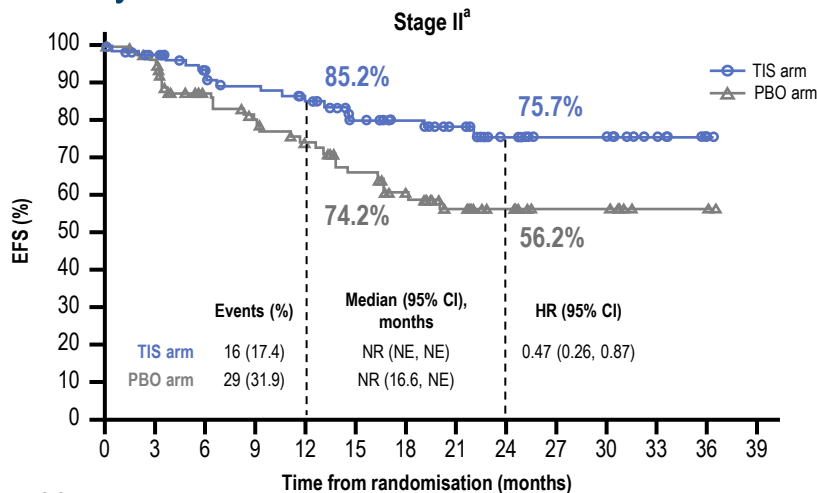
The EFS improvement with perioperative TIS over PBO was consistently observed in patients with squamous and non-squamous NSCLC

EFS was defined as the time from randomisation until any of the following, whichever occurred first: disease progression precluding surgery, local or distant recurrence, or death due to any cause.

Abbreviations: CI, confidence interval; EFS, event-free survival; HR, hazard ratio; ITT, intention-to-treat; NE, not evaluable; NR, not reached; NSCLC, non-small cell lung cancer; PBO, placebo; TIS, tislelizumab.

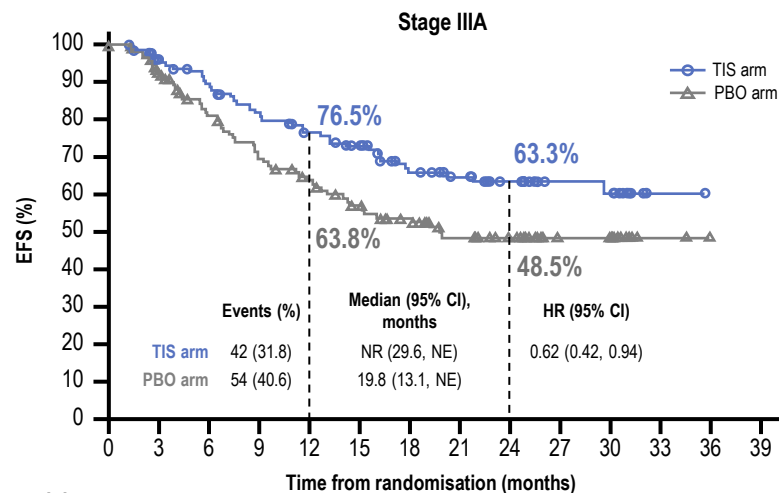
Event-Free Survival By Disease Stage

ITT Analysis Set



Number at risk:

	0	3	6	9	12	15	18	21	24	27	30	33	36	39
TIS arm	92	77	68	63	58	48	41	30	22	14	13	8	2	0
PBO arm	91	78	61	54	47	39	30	21	13	7	7	2	2	0



Number at risk:

	0	3	6	9	12	15	18	21	24	27	30	33	36	39
TIS arm	132	117	106	95	86	77	62	52	43	21	20	1	0	0
PBO arm	133	107	87	74	65	55	47	36	29	17	16	2	0	0

The EFS benefit with perioperative TIS over PBO was confirmed in patients with stage II and IIIA NSCLC

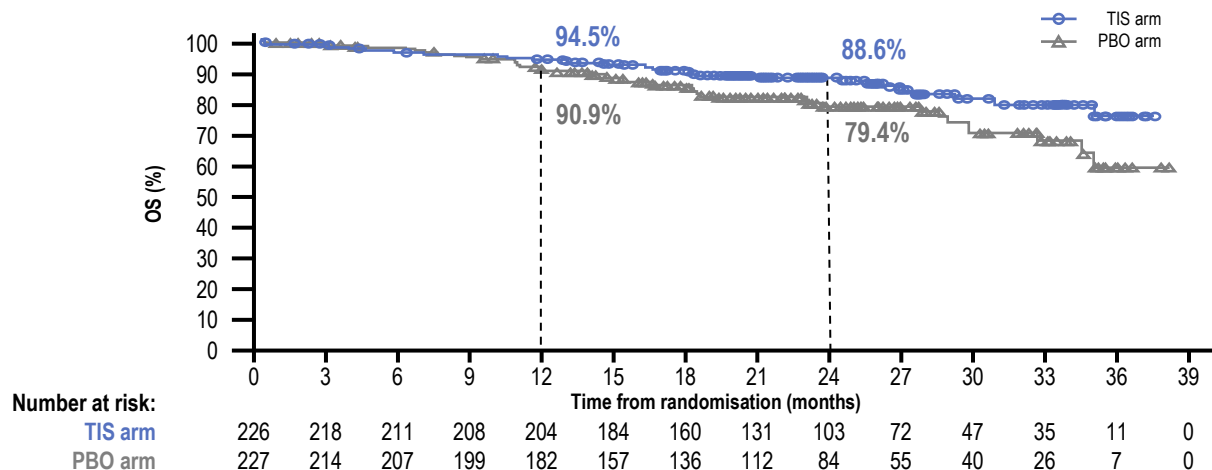
^aStage IIA, IIB: 6.2% and 34.5% in TIS arm, 4.8% and 35.2% in PBO arm. EFS was defined as the time from randomisation until any of the following, whichever occurred first: disease progression precluding surgery, local or distant recurrence, or death due to any cause.

Abbreviations: CI, confidence interval; EFS, event-free survival; HR, hazard ratio; ITT, intention-to-treat; NE, not evaluable; NR, not reached; NSCLC, non-small cell lung cancer; PBO, placebo; TIS, tislelizumab.

Overall Survival

ITT Analysis Set

	Events (%)	Median (95% CI), months	HR (95% CI)	P-value
TIS arm	31 (13.7)	NR (NE, NE)	0.62 (0.39, 0.98)	0.0193
PBO arm	45 (19.8)	NR (35.0, NE)		



An OS benefit trend (HR=0.62 [95% CI: 0.39, 0.98]; one-sided P=0.0193) was observed favouring perioperative TIS

OS was defined as the time from the date of randomisation to the date of death due to any cause.

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; NE, not evaluable; NR, not reached; OS, overall survival; PBO, placebo; TIS, tislelizumab.

Safety Summary

Safety Analysis Set

n (%)	TIS arm (N=226)	PBO arm (N=226)
Patients with ≥1 TRAE	224 (99.1)	225 (99.6)
Grade ≥3	163 (72.1)	150 (66.4)
Serious	35 (15.5)	18 (8.0)
Leading to death ^a	4 (1.8)	2 (0.9)
Leading to discontinuation	29 (12.8)	21 (9.3)
Leading to dose modification ^b	88 (38.9)	73 (32.3)
Leading to surgery delay ^c	12 (5.3)	4 (1.8)
Leading to surgery cancellation	1 (0.4)	1 (0.4)
Patients with ≥1 immune-mediated AE	90 (39.8)	40 (17.7)
Grade ≥3	21 (9.3)	6 (2.7)
Serious	23 (10.2)	5 (2.2)
Leading to death	2 (0.9) ^d	0
Leading to discontinuation	15 (6.6)	0
Leading to dose modification	30 (13.3)	6 (2.7)

^a TIS arm (n=1 each): infection, pneumonia, pneumonitis, immune-mediated lung disease. PBO arm: respiratory haemorrhage, cardiac failure. ^b Including temporary discontinuation of TIS/PBO in neoadjuvant phase, chemotherapy dose reduction, dose interruption, dose delay, and infusion rate decrease. ^c Defined as when date of surgery is beyond 6 weeks after last neoadjuvant treatment dose. ^d (n=1 each): pneumonitis, immune-mediated lung disease.

The safety analysis set included all randomised patients who received ≥1 dose of any study drug. AEs were classified based on MedDRA v26.0. AEs were graded for severity using Common Terminology Criteria for AEs v5.0.

Abbreviations: AE, adverse event; PBO, placebo; MedDRA, Medical Dictionary for Regulatory Activities; TIS, tislelizumab; TRAE, treatment-related adverse event.

Most Frequently Reported TRAEs

≥20% of Patients; Safety Analysis Set

n (%)	TIS arm (N=226)		PBO arm (N=226)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Neutrophil count decreased	177 (78.3)	138 (61.1)	176 (77.9)	134 (59.3)
White blood cell count decreased	143 (63.3)	38 (16.8)	152 (67.3)	32 (14.2)
Alopecia	106 (46.9)	1 (0.4)	118 (52.2)	1 (0.4)
Anaemia	91 (40.3)	11 (4.9)	96 (42.5)	15 (6.6)
ALT increased	65 (28.8)	2 (0.9)	48 (21.2)	1 (0.4)
Nausea	60 (26.5)	1 (0.4)	59 (26.1)	0 (0.0)
AST increased	53 (23.5)	2 (0.9)	38 (16.8)	0 (0.0)
Platelet count decreased	47 (20.8)	5 (2.2)	49 (21.7)	6 (2.7)
Hypoaesthesia	44 (19.5)	0 (0.0)	47 (20.8)	0 (0.0)
Decreased appetite	40 (17.7)	1 (0.4)	47 (20.8)	0 (0.0)

AEs were classified based on MedDRA v26.0 and were graded for severity using Common Terminology Criteria for Adverse Events v5.0.

Abbreviations: AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; PBO, placebo; MedDRA, Medical Dictionary for Regulatory Activities; TIS, tislelizumab; TRAE, treatment-related adverse event.

Most Frequently Reported Immune-Mediated AEs

≥1% of Patients; Safety Analysis Set

n (%)	TIS arm (N=226)		PBO arm (N=226)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Immune-mediated skin adverse reaction	39 (17.3)	5 (2.2)	24 (10.6)	0 (0.0)
Immune-mediated pneumonitis	18 (8.0)	7 (3.1)	4 (1.8)	0 (0.0)
Immune-mediated hepatitis	5 (2.2)	4 (1.8)	5 (2.2)	5 (2.2)
Immune-mediated endocrinopathies				
Hypothyroidism	33 (14.6)	2 (0.9)	6 (2.7)	0 (0.0)
Hyperthyroidism	16 (7.1)	1 (0.4)	7 (3.1)	0 (0.0)
Thyroiditis	5 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
Adrenal insufficiency	3 (1.3)	1 (0.4)	0 (0.0)	0 (0.0)

AEs were classified based on MedDRA v26.0 and were graded for severity using Common Terminology Criteria for Adverse Events v5.0.

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PBO, placebo; TIS, tislelizumab.

Conclusions

- RATIONALE-315 demonstrated a clinically meaningful and statistically significant benefit in EFS with perioperative TIS plus PtDb CT vs PBO plus neoadjuvant PtDb CT at this interim analysis
 - HR=0.56 [95% CI: 0.40, 0.79]; one-sided $P=0.0003$
 - EFS benefit was generally consistent across predefined subgroups
- MPR and pCR rate were significantly improved: 56.2% vs 15.0% ($P<.0001$) and 40.7% vs 5.7% ($P<.0001$), respectively
- An OS benefit trend favouring perioperative TIS (HR=0.62 [95% CI: 0.39, 0.98]; one-sided $P=0.0193$) was observed at this interim analysis. The trial will continue to assess OS with longer follow-up
- The safety profile of perioperative TIS plus PtDb CT was manageable and consistent with the known risks of the individual therapies
- Taken together, the statistically and clinically significant EFS, MPR, and pCR benefits, alongside manageable safety, support the use of perioperative TIS plus neoadjuvant PtDb CT for patients with resectable stage II-IIIa NSCLC

Abbreviations: CI, confidence interval; EFS, event-free survival; HR, hazard ratio; MPR, major pathological response; NSCLC, non-small cell lung cancer; OS, overall survival; PBO, placebo; PtDb CT, platinum-based doublet chemotherapy; TIS, tislelizumab.

1. Yue D, et al. *Annals Oncol.* 2023;34(Suppl 2):S1299.

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