BARCELONA 2024 ESMO congress

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

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 CT[6-10]

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.

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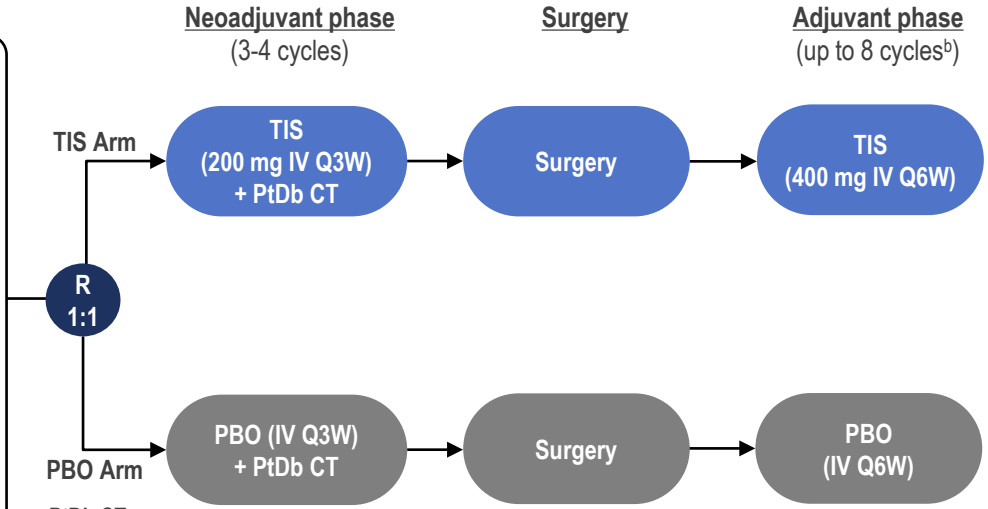
RATIONALE-315 Study Design

Key eligibility criteria

- Resectable stage II-IIIA NSCLC per AJCC 8th edition (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

Key secondary endpoint:

- pCR rate by BIPR

Other secondary endpoints:

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

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

ClinicalTrials.gov Identifier: NCT04379635.

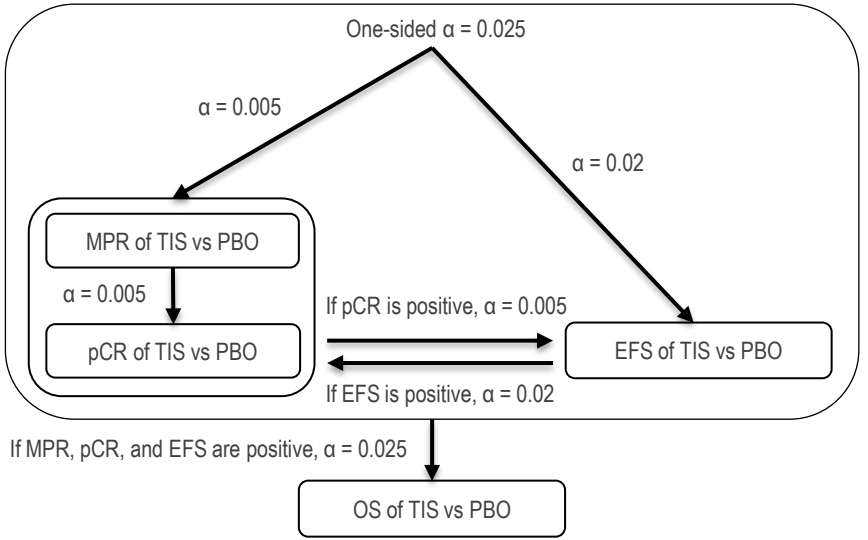
[a] EGFR testing was mandatory for non-squamous NSCLC. [b] Adjuvant treatment was only received by patients with an ECOG PS of 0 or 1 and adequate organ function for ≤8 cycles or until disease recurrence/progression, unacceptable adverse events, or death occurs, or if the patient and/or investigator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

Abbreviations: 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.

Statistical Considerations

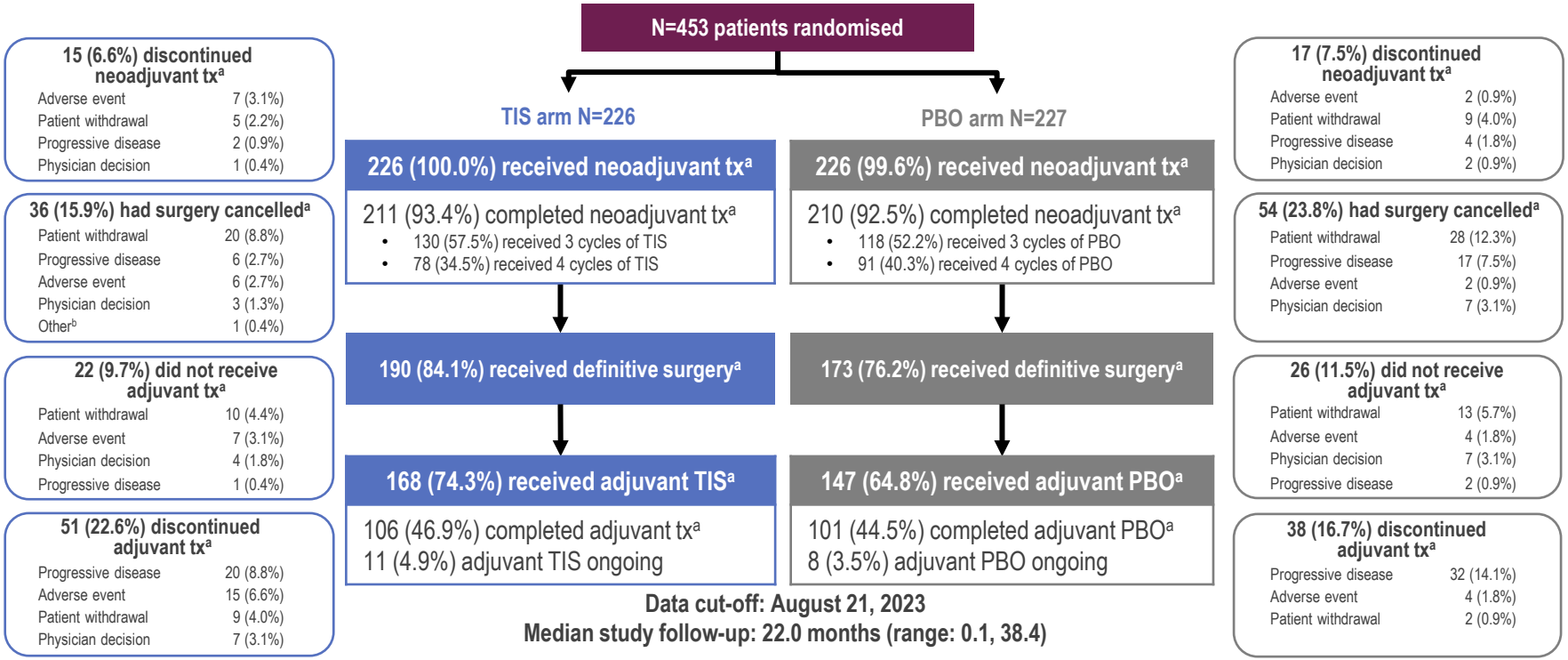
- Overall type I error was strongly controlled at a one-sided alpha of 0.025
- The interim analysis for EFS was planned for when ~75% of the targeted EFS events (184 EFS events) had occurred, with Lan-DeMets alpha spending function approximation to the O'Brien–Fleming boundary
- The OS interim analysis 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, tislelizumab; tx, treatment.

Demographics and Baseline Characteristics

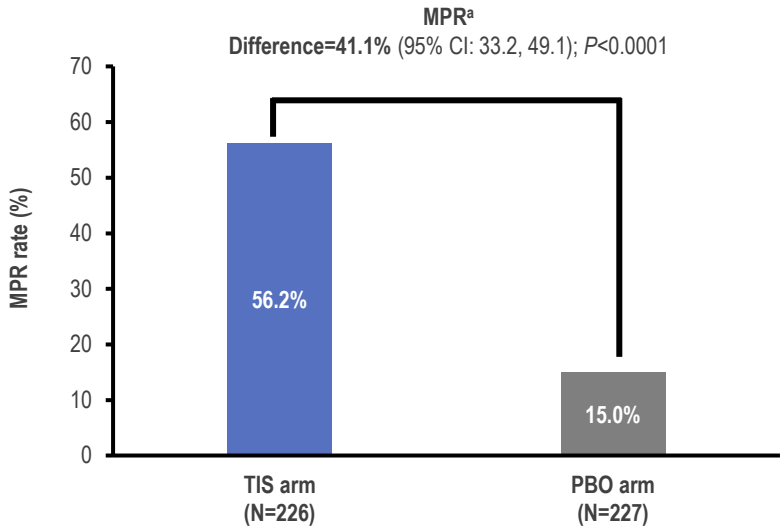
ITT Analysis Set

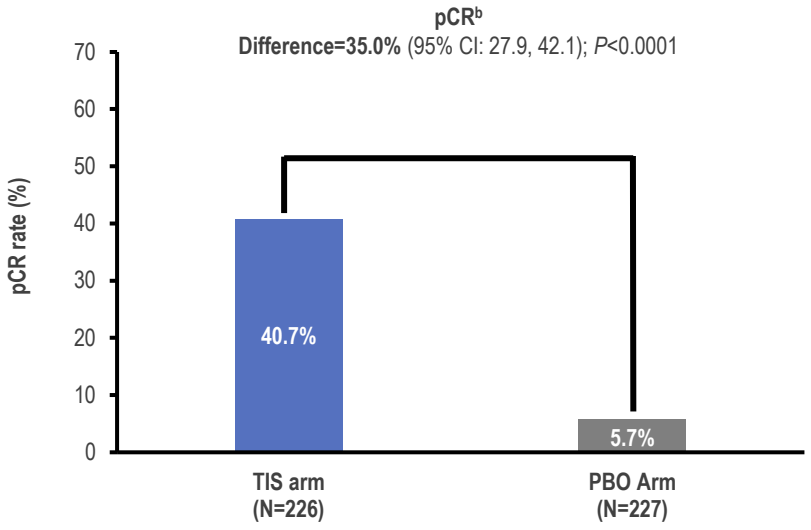
	TIS arm (N=226)	PBO arm (N=227)
Age, median (IQR), years	62.0 (57.0, 67.0)	63.0 (56.0, 68.0)
Male sex, n (%)	205 (90.7)	205 (90.3)
Asian race, n (%)	226 (100.0)	227 (100.0)
ECOG PS, n (%)[a]		
0	142 (62.8)	154 (67.8)
1	83 (36.7)	73 (32.2)
Smoking status, n (%)		
Current/former	193 (85.4)	190 (83.7)
Never	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: cN, clinical N; 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.

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. [a] MPR was defined as the proportion of patients with ≤10% residual viable tumour in the resected primary tumour and resected lymph nodes after completion. [b] pCR was defined as the proportion of patients absent of residual viable tumour in the resected primary tumour and resected lymph nodes after treatment.

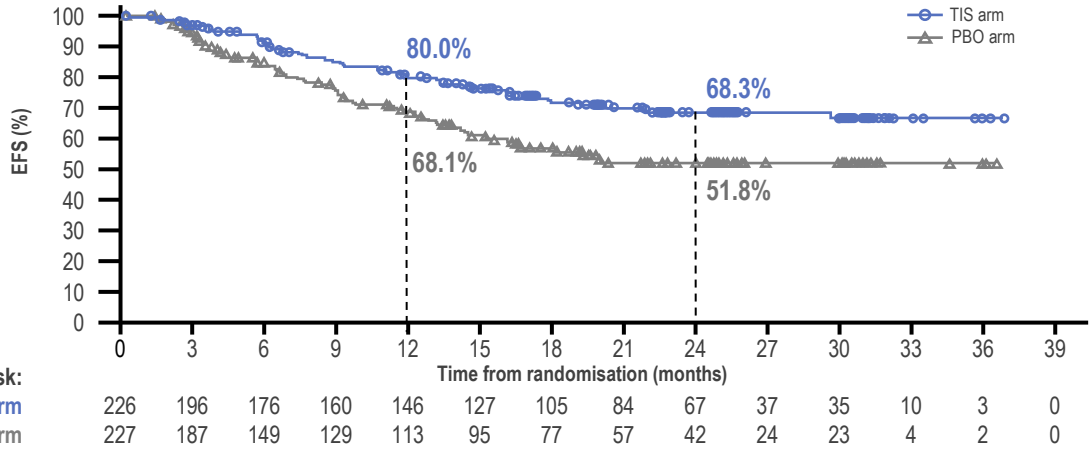
Abbreviations: BIPR, blinded independent pathology review; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention-to-treat; MPR, major pathological response; NSCLC, non-small cell lung cancer; OR, odds ratio; PBO, placebo; pCR, pathological complete response; PD-L1, programmed death-ligand 1; PtDb CT, platinum-based doublet chemotherapy; 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)		



Number at risk:

TIS arm	226	196	176	160	146	127	105	84	67	37	35	10	3	0
PBO arm	227	187	149	129	113	95	77	57	42	24	23	4	2	0

- **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

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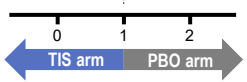
ITT Analysis Set

Subgroup	TIS arm, n/N	PBO arm, n/N	HR (95% CI)
Overall	58/226	83/227	0.57 (0.41, 0.80)
Age group			
<65 years	38/143	47/129	0.61 (0.40, 0.94)
≥65 years	20/83	36/98	0.51 (0.30, 0.89)
Sex			
Male	53/205	78/205	0.57 (0.40, 0.80)
Female	5/21	5/22	0.68 (0.19, 2.40)
ECOG performance status			
0	35/142	54/154	0.57 (0.37, 0.87)
1	23/83	29/73	0.58 (0.33, 1.00)
Disease stage at baseline			
II	16/92	29/91	0.47 (0.26, 0.87)
IIIA	42/132	54/133	0.62 (0.42, 0.94)
Histologic type of tumour			
Squamous	43/179	63/175	0.56 (0.38, 0.83)
Non-squamous	15/45	19/50	0.64 (0.32, 1.26)
PD-L1 expression			
<1% [excluding not evaluable/indeterminate]	26/89	27/84	0.80 (0.47, 1.38)
≥1%	31/130	51/132	0.50 (0.32, 0.78)
1-49%	12/59	31/70	0.34 (0.17, 0.66)
≥50%	19/71	20/62	0.71 (0.38, 1.34)
Smoking status			
Current	10/43	16/52	0.61 (0.28, 1.34)
Former	40/150	56/138	0.54 (0.36, 0.81)
Never	8/33	11/37	0.60 (0.24, 1.51)



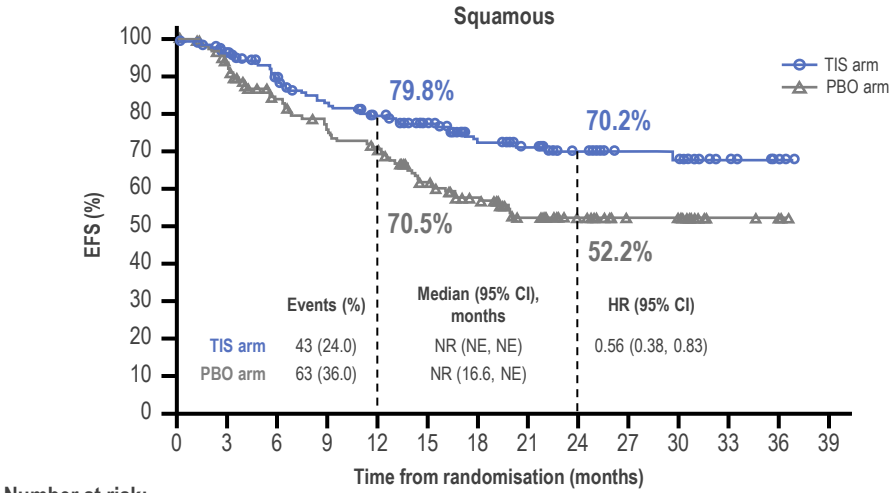
The EFS benefit with perioperative TIS over PBO was generally consistent across prespecified subgroups

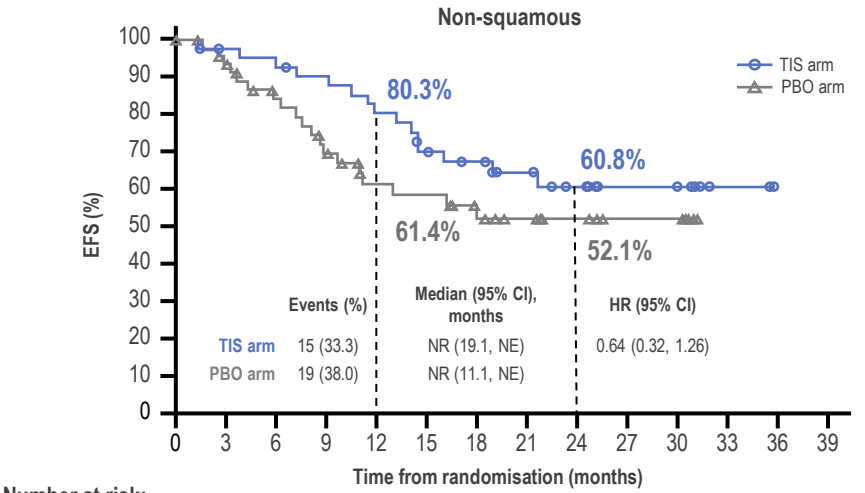
EFS was defined as the time from randomisation until any of the following, whichever occurred first: disease progression precluding surgery, local or distant recurrence, or death due to any cause.

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; TIS, tislelizumab.

Event-Free Survival By Histology

ITT Analysis Set





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.

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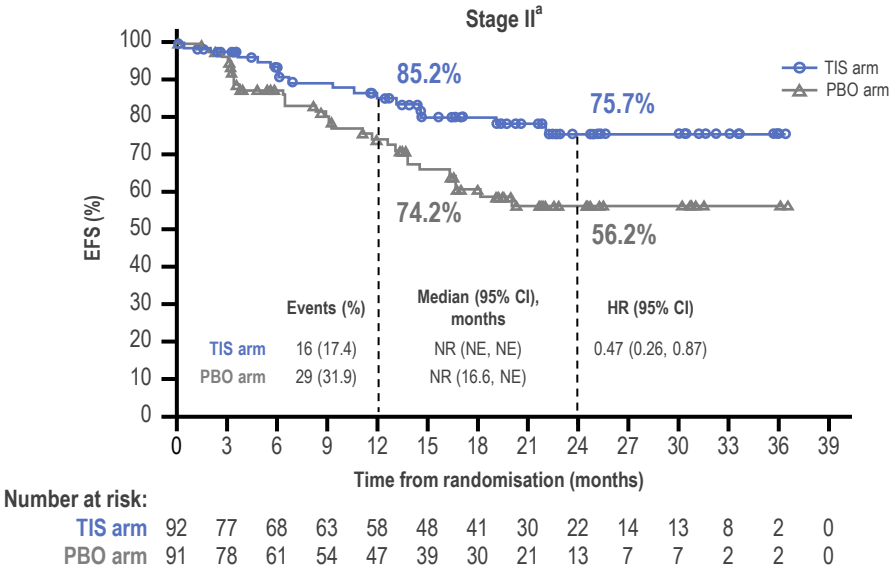
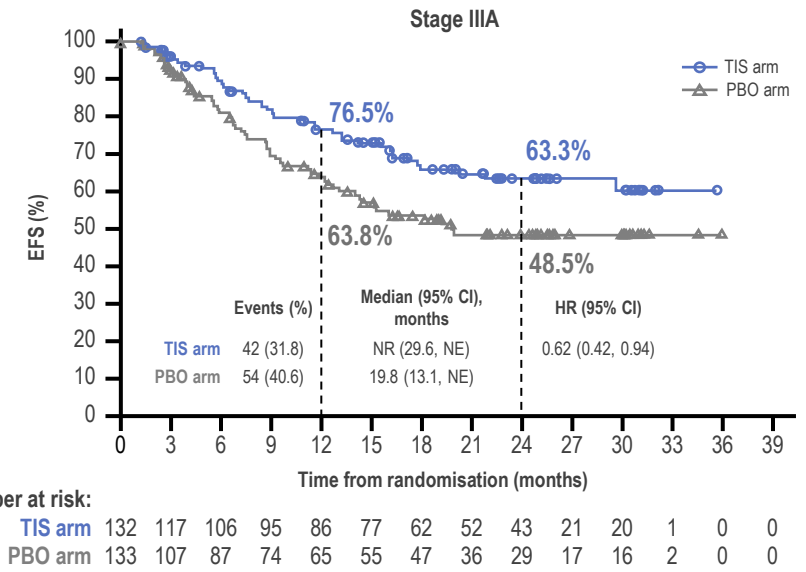
Event-Free Survival By Disease Stage

ITT Analysis Set





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

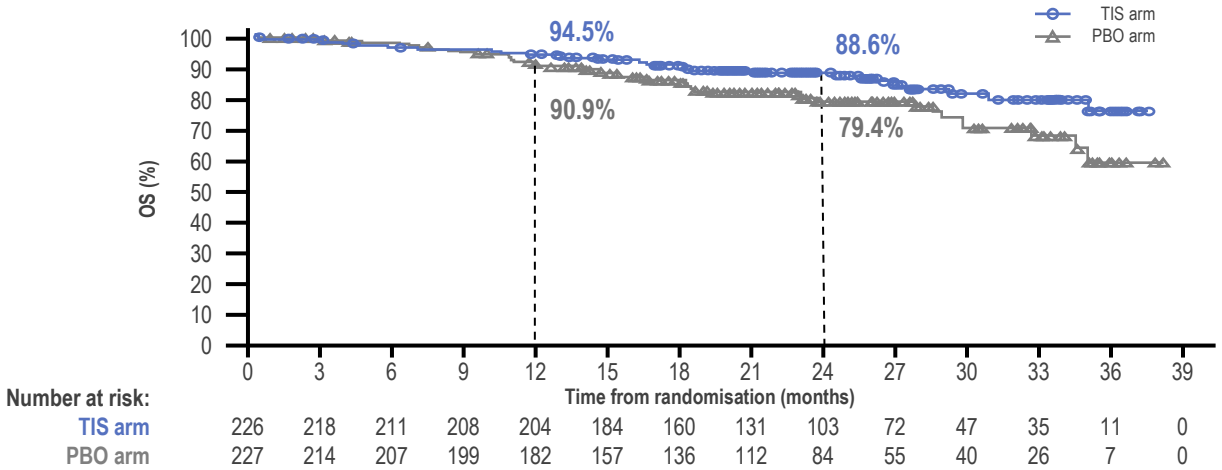
[a] Stage IIA, IIB: 6.2% and 34.5% in TIS arm, 4.8% and 35.2% in PBO arm. EFS was defined as the time from randomisation until any of the following, whichever occurred first: disease progression precluding surgery, local or distant recurrence, or death due to any cause.

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)

The safety profile in the TIS arm was manageable and consistent with the known risks of the individual therapies

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

Most Frequently Reported TRAEs

≥20% of Patients; Safety Analysis Set

	TIS arm (N=226)		PBO arm (N=226)	
n (%)	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)

The most frequently reported TRAEs were neutrophil count decreased, white blood cell count decreased, and alopecia; no new safety signals were identified

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

Most Frequently Reported Immune-Mediated AEs

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≥1% of Patients; Safety Analysis Set

	TIS arm (N=226)		PBO arm (N=226)	
n (%)	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)

The most common immune-mediated AE category was skin adverse reaction, with <10% of patients experiencing grade ≥3 immune-mediated AEs

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 neoadjuvant 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 rates were significantly improved with neoadjuvant TIS plus PtDb CT vs PBO plus PtDb CT: 56.2% vs 15.0% (*P*<0.0001) and 40.7% vs 5.7% (*P*<0.0001), 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 neoadjuvant 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; pCR, pathological complete response; PtDb CT, platinum-based doublet chemotherapy; TIS, tislelizumab.

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