

NAUTIKA1: pathological response and safety of neoadjuvant entrectinib or atezolizumab plus radiation in biomarker-selected NSCLC

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BACKGROUND

- Many of the checkpoint inhibitors currently approved as treatment for resectable early non-small cell lung cancer (eNSCLC) in the neoadjuvant setting are in combination with chemotherapy,¹ while adjuvant treatment with the programmed death ligand 1 (PD-L1) inhibitor atezolizumab is approved for resected stage II-IIIa, PD-L1+ non-small cell lung cancer (NSCLC)²
 - Opportunities for chemotherapy-free regimens in the neoadjuvant space include combinations involving targeted therapies,³ and checkpoint inhibitors with radiation⁴
- NAUTIKA1 (NCT04302025) is a Phase II umbrella study of multiple pre- and post-operative treatments in biomarker-selected cohorts of patients with resectable eNSCLC⁵
- Although neoadjuvant treatment with tyrosine kinase inhibitors (TKIs) has been evaluated in numerous Phase II studies in patients with *EGFR*-mutated NSCLC, the preoperative use of TKIs in patients with NSCLC harboring *ROS1* or *NTRK* alterations is less well studied
- The combination of checkpoint inhibitors and low-dose stereotactic body radiotherapy (SBRT) in the neoadjuvant setting has been previously described;⁶ one of the signal-seeking cohorts in NAUTIKA1 further explored the chemotherapy-free option of atezolizumab in combination with low-dose SBRT as neoadjuvant therapy
- We report pathological, surgical, clinical and safety outcomes with neoadjuvant TKI (entrectinib) or PD-L1 inhibitor (atezolizumab) therapy in the following cohorts:
 - Entrectinib in the *ROS1*+ and *NTRK*+ cohorts
 - Atezolizumab combined with low-dose SBRT in the PD-L1+ cohort

METHODS

- NAUTIKA1 enrolled eligible patients with resectable, stage IB-III eNSCLC into cohorts based on biomarker results from blood-/tumor-based assays, and they received neoadjuvant treatment (Figure 1)
- In all cohorts, the primary tumor and mediastinal lymph nodes were surgically resected within 10 days of completing neoadjuvant therapy
- Patients without progressive disease (PD) who completed surgery received adjuvant therapy as shown (Figure 1)

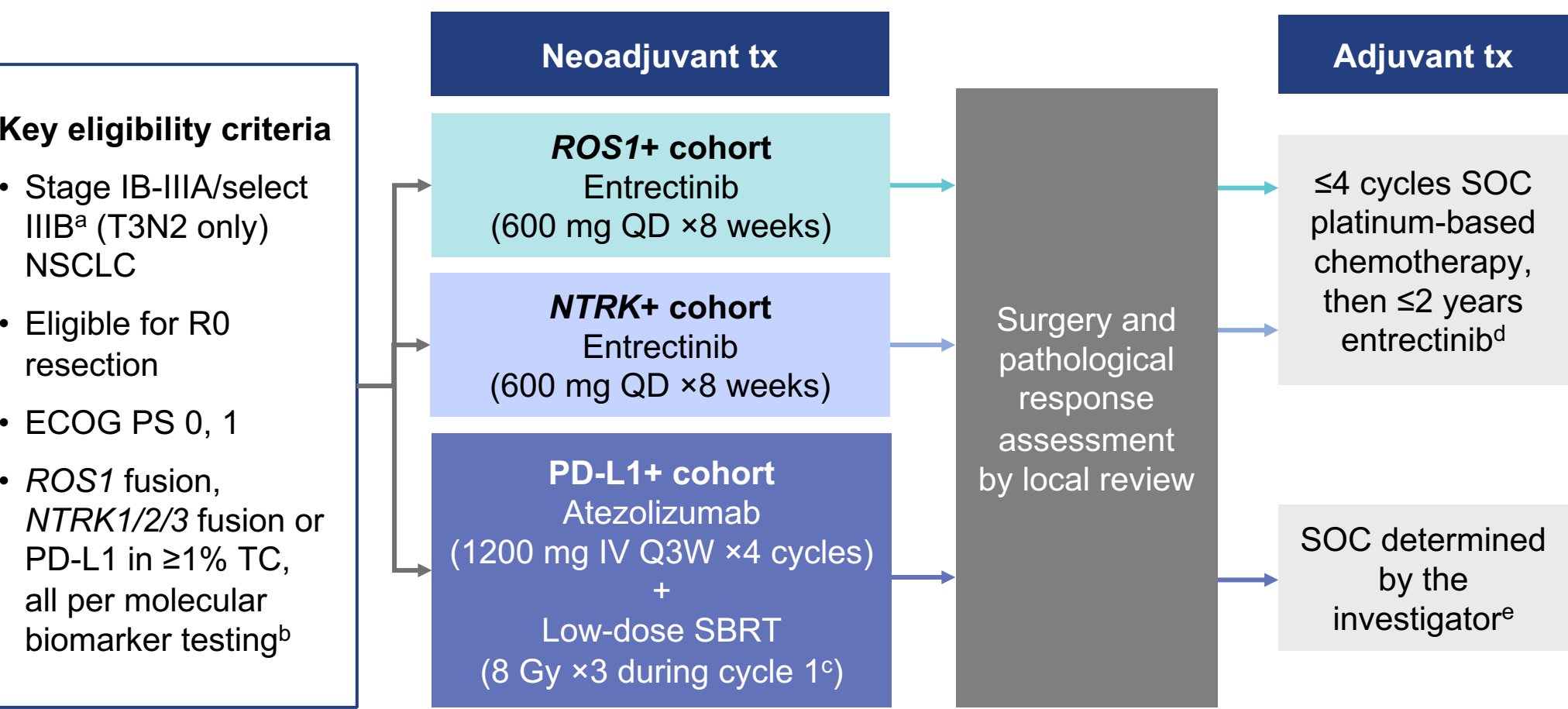
ROS1+ and *NTRK*+ cohorts

- ROS1*+ cohort: patients with *ROS1* fusion
- NTRK*+ cohort: patients with *NTRK1/2/3* fusion
- Neoadjuvant treatment was 600 mg entrectinib once daily for 8 weeks
- The primary endpoint was major pathologic response (MPR, defined as ≤10% residual viable tumor cells) scored by a local pathologist

PD-L1 cohort

- PD-L1+ cohort: patients with PD-L1 expression in ≥1% of tumor cells
- Neoadjuvant treatment was 1200 mg atezolizumab intravenously every 3 weeks for 4 cycles combined with low-dose SBRT targeted to the primary tumor (8 Gy delivered on days 1–3 of atezolizumab cycle 1)
- The primary endpoint was pathologic complete response (pCR) determined by a local pathologist

Figure 1: NAUTIKA1 study design, treatment, and endpoints



Endpoints	TKI-treated cohorts (<i>ROS1</i> +, <i>NTRK</i> +)	PD-L1 cohort
Primary	MPR ^{f,g}	pCR ^g
Secondary	MPR, ^{f,h} pCR ^{a,h}	MPR, ^{f,g,h} pCR ^h
	Pathological regression ⁱ , ORR, DFS, EFS, OS, nodal downstaging, ctDNA clearance rate ⁱ	

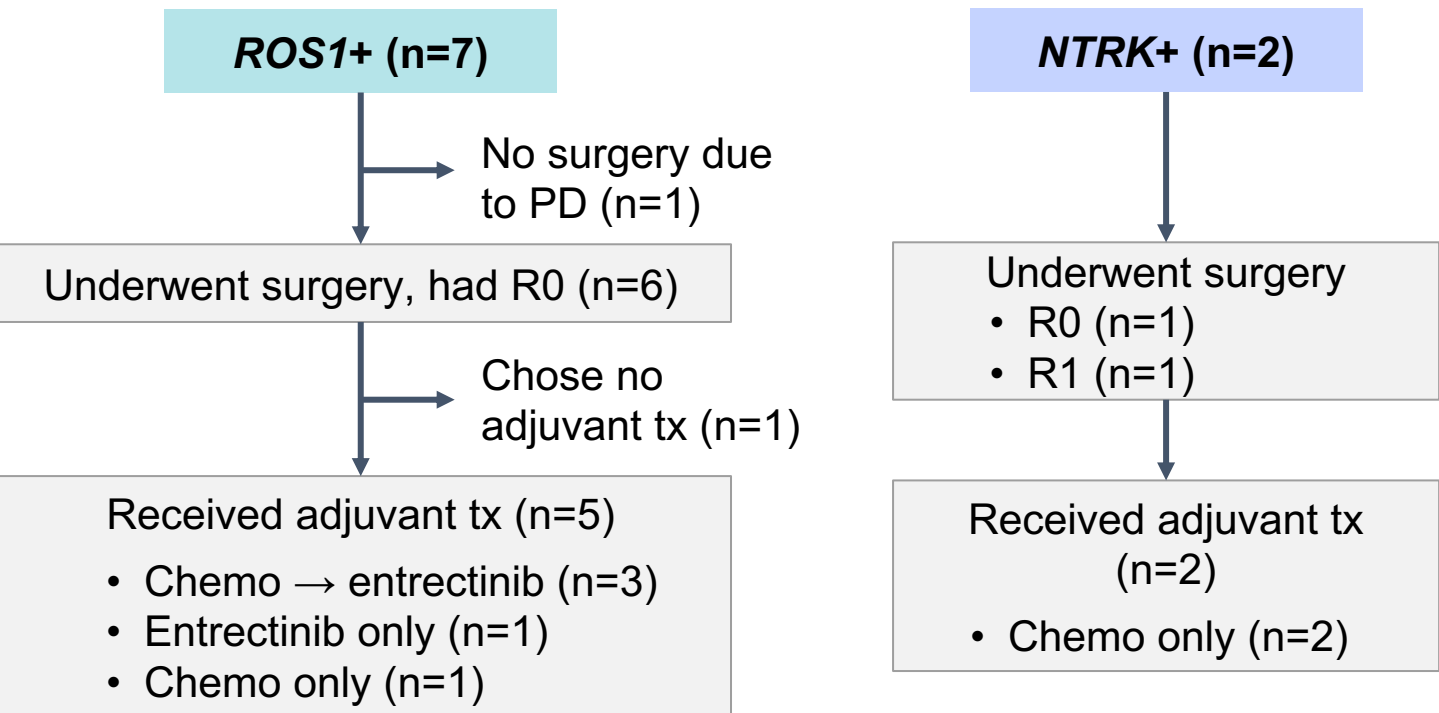
AJCC, American Joint Committee on Cancer; CLIA, Clinical Laboratory Improvement Amendments; ctDNA, circulating tumor DNA; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; IV, intravenous; ORR, objective response rate; OS, overall survival; QD, once daily; Q3W, every 3 weeks; R0, complete resection; SOC, standard of care; TC, tumor cells; tx, treatment. *AJCC 8th edition. ^aIn a local CLIA-certified laboratory. ^bTargeted to the primary tumor. The first 8-Gy fraction was initiated immediately before the first dose of atezolizumab on day 1 of cycle 1; the subsequent two doses were delivered in the next two consecutive days. ^cInitiated within 60 days of last chemotherapy treatment. ^dInitiated within 90 days of surgery. ^eDefined as ≤10% residual viable tumor cells. ^fLocally assessed. ^gCentrally assessed. ^hBased on weighted % of viable tumor cells. ⁱPrior to surgery.

RESULTS

ROS1+ and *NTRK*+ cohorts

- Patients in the *ROS1*+ (n=7) and *NTRK*+ (n=2) cohorts were enrolled and treated with neoadjuvant entrectinib, then surgery, then 4 cycles of adjuvant standard-of-care chemotherapy followed by entrectinib for up to 2 years (Figure 2)
- Patients in the *ROS1*+ cohort had a median age of 63 years, and 100% had stage IIIa non-squamous NSCLC (Table 1)
- Patients in the *NTRK*+ cohort had a median age of 59 years; 1 patient had stage IIB and 1 had stage IIIa NSCLC; 1 patient each had squamous and non-squamous NSCLC, respectively (Table 1)

Figure 2: Patient disposition in the TKI-treated cohorts



chemo, chemotherapy; PD, progressive disease; R1, microscopic residual tumor.

Table 1: Baseline characteristics in the TKI-treated cohorts

Baseline characteristics	<i>ROS1</i> + (n=7)	<i>NTRK</i> + (n=2)
Age, median (range), years	63 (40–66)	59 (55–62)
Sex, n		
Female Male	6 1	0 2
Tobacco use, n		
Current Former Never	1 3 3	1 0 1
ECOG PS, n		
0 1	4 3	2 0
Lung cancer histology, n		
Non-squamous Squamous	7 0	1 1
Clinical staging (AJCC 8th edition), n		
Stage IB IIA IIB IIIA IIIB	0 0 0 7 0	0 0 1 1 0
Lymph node stage, n		
N0 N1 N2	0 0 7	0 2 0
Tumor stage, n		
T0 T1a T1b T1c T2a T2b T3 T4	0 0 0 2 4 1 0 0	0 0 1 1 0 0 1 0

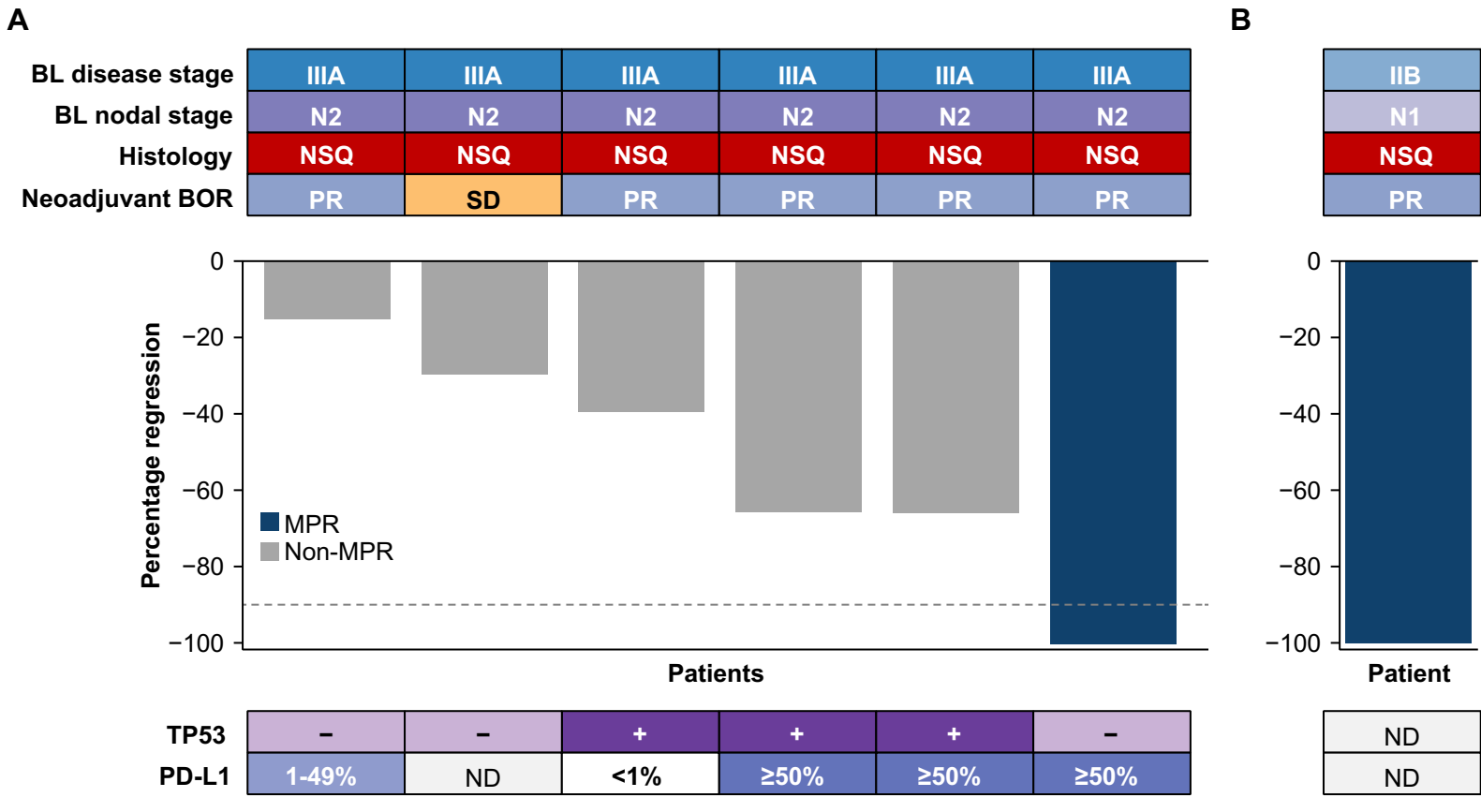
Table 2: Pathological and radiographic response and downstaging by cohort

Pathological response ^a	<i>ROS1</i> + (n=7)	<i>NTRK</i> + (n=2)
MPR, n (%)	1 (14)	1 (50)
[95% CI]	[0, 58]	[1, 99]
pCR, n (%)	0	0
Radiographic response ^b	(n=7)	(n=2)
ORR by investigator, n (%)	5 (71)	1 (50)
[95% CI]	[29, 96]	[1, 99]
PR	5 (71)	1 (50)
SD	1 (14)	1 (50)
PD	1 (14)	0
NE	0	0
Clinical downstaging, ^c n (%)	0	1 (50)
Pathological downstaging, n (%)	1 (14)	0 (2 upstaged from N1 to N2)
Downstaged to ypN0, n (%)	1 (14)	0

AE, adverse event; CI, confidence interval; NE, not evaluable; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; PR, partial response; SD, stable disease. Data snapshot: 30 June 2026. 95% CIs were constructed using the Clopper Pearson method. ^aAssessed locally. The pathological response analysis population was defined as all eligible and treated patients who either underwent post-neoadjuvant surgery (with or without resection) or discontinued due to an AE or PD with pathological response for patients without R0 resection set to non-MPR. ^bAssessed per RECIST v1.1 in efficacy-evaluable patients; unconfirmed. ^cPer AJCC v8 criteria after neoadjuvant treatment.

- Efficacy outcomes with neoadjuvant entrectinib varied by cohort (Table 2, Figure 3)
- ROS1*+:
 - 1/7 patients (14%) had an MPR; 0% achieved a pCR
 - The ORR was 71% (5/7 patients had PR)
 - 1/7 patients (14%) had pathological nodal downstaging to pathologically negative nodes (ypN0)
- NTRK*+:
 - 1 patient had PR, MPR, and clinical downstaging

Figure 3: Weighted percentage tumor regression^a in the TKI-treated cohorts (A) *ROS1*+ cohort; (B) *NTRK*+ cohort



BL, baseline; BOR, best overall response; ND, not done; TP53, tumor protein p53. ^aFor patients who did not undergo primary tumor R0 resection, weighted % viable tumor values are set to missing and excluded. BOR is the best overall response by investigator (confirmation not required) per RECIST v1.1 during the neoadjuvant phase.

- 6/7 patients in the *ROS1*+ cohort underwent surgery, among whom R0 resection was achieved in 100% (6/6); 2/2 patients in the *NTRK*+ cohort underwent surgery, among whom R0 resection was achieved in 50% (1/2) (Table 3)
- Median time from the last neoadjuvant treatment to surgery was 2 days in the *ROS1*+ cohort and 4 days in the *NTRK*+ cohort
- No intraoperative complications occurred in either cohort

Table 3: Surgical outcomes in patients who underwent surgery^a

Surgery	<i>ROS1</i> + (n=6)	<i>NTRK</i> + (n=2)
Last neoadjuvant treatment to surgery, median (range), days	2 (1–14)	4 (2–5)
Surgical delays, n	0	0
R0 resection, n (%)	6 (100)	1 (50)

^aData are from eligible, treated patients who underwent post-neoadjuvant surgery (with/without resection); 1 patient in the *ROS1*+ cohort had PD, precluding surgery.

- At the data snapshot date of June 30, 2026:
 - Median follow-up in the *ROS1*+ cohort was 32.7 months and the 2-year EFS rate was 42%
 - Median follow-up in the *NTRK*+ cohort was 48.6 months; the 2-year EFS rate was 100%
- No AEs led to neoadjuvant treatment discontinuation in either cohort (Table 4)
- No new safety signals were observed in either cohort

Table 4: Safety of neoadjuvant therapy in safety-evaluable patients

AEs	<i>ROS1</i> + (n=7)	<i>NTRK</i> + (n=2)
Any-grade AE, n (%)	7 (100)	2 (100)
Grade 3–4	0	2 (100)
Serious	0	1 (50)
TRAE, n (%)	7 (100)	1 (50)
Grade 3–4	0	0
Serious	0	0
AE leading to dose reduction or interruption, n (%)	5 (71) ^a	1 (50) ^b
AE leading to treatment discontinuation, n (%)	0	0

TRAE, treatment-related adverse event. ^aIncluded blood creatinine increase, fatigue, nervous system disorders, and myalgia. ^bIncluded sepsis.

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PD-L1 cohort

- Patients in the PD-L1+ cohort (n=7) were enrolled and treated with neoadjuvant atezolizumab combined with SBRT, then surgery, and then investigator's choice of standard-of-care adjuvant chemotherapy only, or atezolizumab only, or chemotherapy followed by atezolizumab (Figure 4)
- Patients in this cohort had a median age of 61 years; 6/7 (86%) had non-squamous NSCLC, and 5/7 (71%) had stage IIIa NSCLC (Table 5)

Figure 4: Patient disposition in the PD-L1 cohort

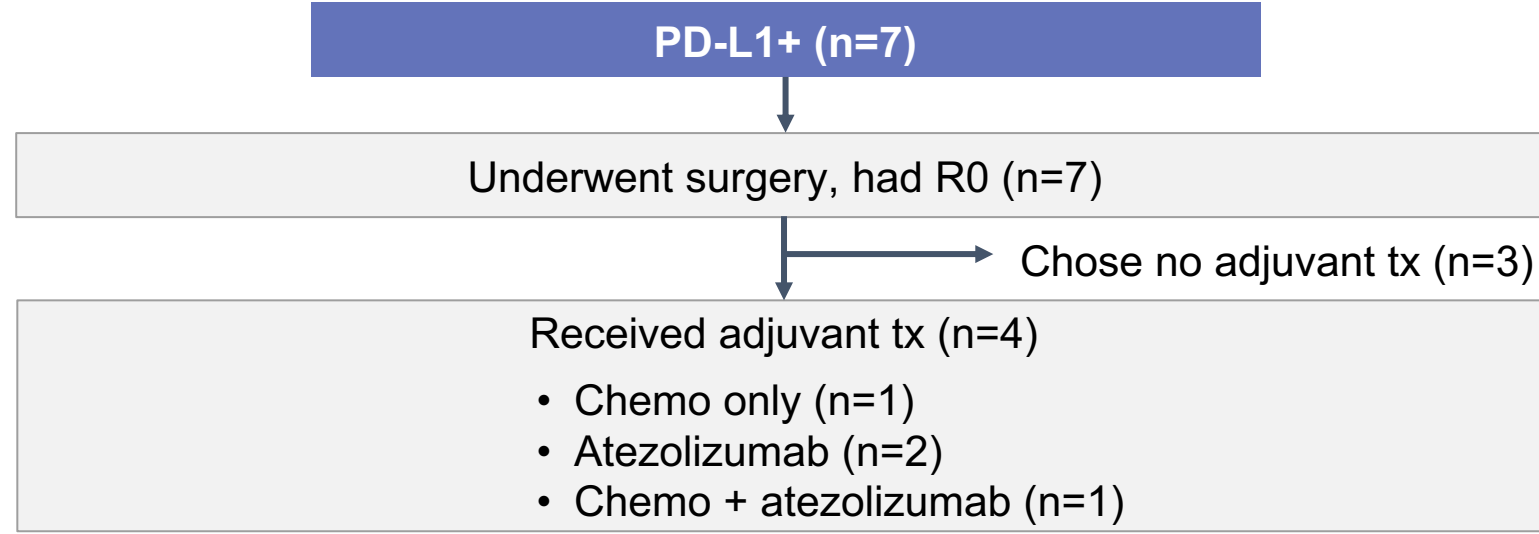
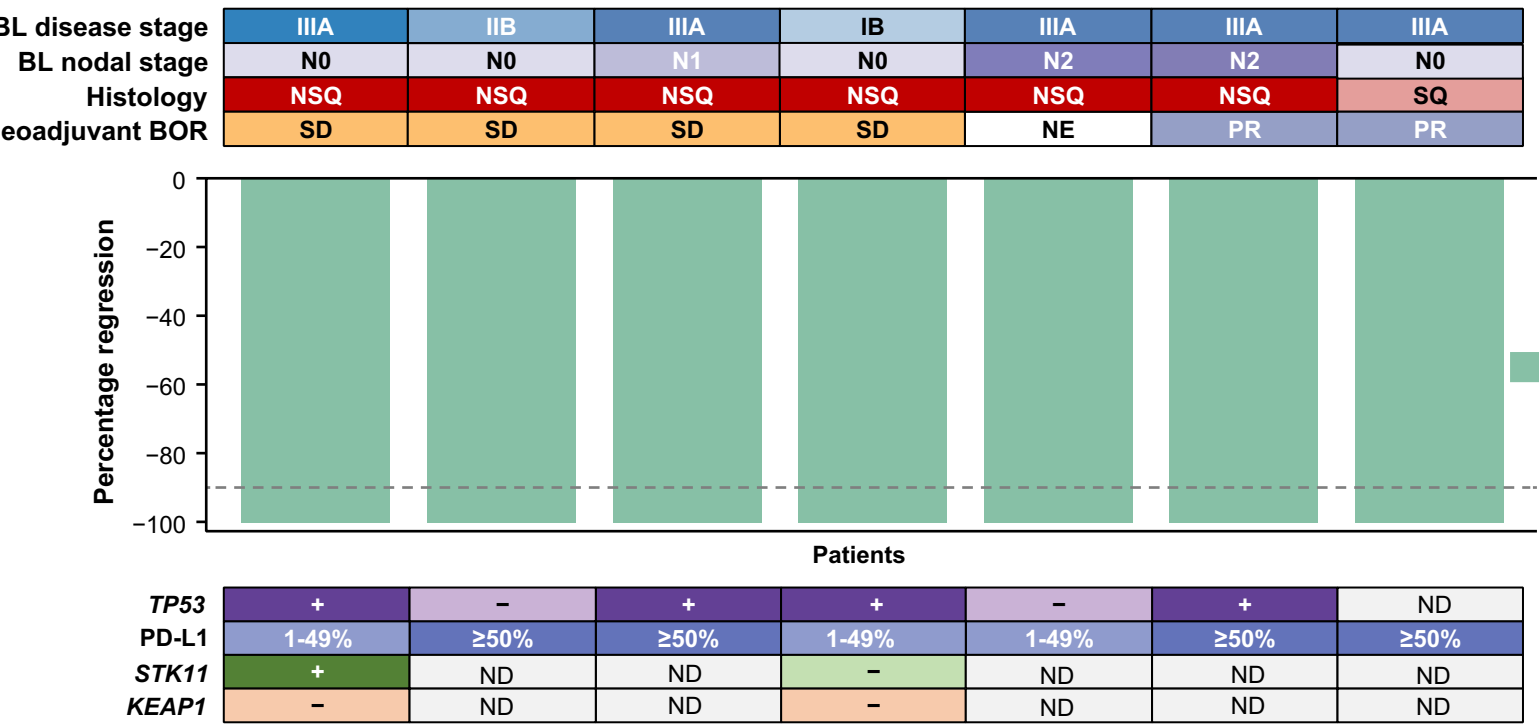


Table 5: Baseline characteristics in the PD-L1+ cohort

Baseline characteristics	PD-L1+ (n=7)
Age, median (range), years	61 (54–80)
Sex, n	
Female Male	2 5
Tobacco use, n	
Current Former Never	3 4 0
ECOG PS, n	
0 1	4 3
Lung cancer histology, n	
Non-squamous Squamous	6 1
Clinical staging (AJCC 8th edition), n	
Stage IB IIA IIB IIIA IIIB	1 0 1 5 0
Lymph node stage, n	
N0 N1 N2	4 1 2
Tumor stage, n	
T0 T1a T1b T1c T2a T2b T3 T4	0 0 1 1 1 0 2 2
PD-L1 status	
<1 ≥1–49% ≥50%	0 3 4

- Neoadjuvant atezolizumab combined with SBRT resulted in a pCR rate of 100% and an MPR rate of 100% (7/7 patients) (Table 6; Figure 5)
 - pCR was observed irrespective of whether the patients had PD-L1 expression in 1–49% or in ≥50% of tumor cells in the tumor sample (Figure 5)
- The ORR was 29% (2/7 PRs; Table 6)
- Clinical downstaging was achieved in 2/7 patients (29%) and pathological downstaging to ypN0 in 3/7 patients (Table 6)

Figure 5: Weighted percentage tumor regression^a in the PD-L1+ cohort



^aFor patients who did not undergo primary tumor R0 resection, weighted % viable tumor values are set to missing and excluded. BOR is the best overall response by investigator (confirmation not required) per RECIST v1.1 during the neoadjuvant phase

Table 6: Pathological and radiographic response and downstaging in the PD-L1+ cohort

Pathological response ^a	PD-L1+ (n=7)
pCR, n (%)	7 (100)
[95% CI]	[59, 100]
MPR, n (%)	7 (100)
[95% CI]	[59, 100]
Radiographic response ^b	(n=7)
ORR by investigator, n (%)	2 (29)
[95% CI]	[4, 71]
PR	2 (29)
SD	4 (57)
PD	0
NE	1 (14)
Clinical downstaging, ^c n (%)	2 (29)
Pathological downstaging, n	3 (out of 3 with N1/N2 at baseline)
Downstaged to ypN0, n	3

Data snapshot: 30 June 2026. 95% CIs were constructed using the Clopper Pearson method. ^aAssessed locally. The pathological response analysis population was defined as all eligible and treated patients who either underwent post-neoadjuvant surgery (with or without resection) or discontinued due to AE or PD with pathological response for patients without R0 resection set to non-MPR. ^bAssessed per RECIST v1.1 in efficacy-evaluable patients; unconfirmed. ^cPer AJCC v8 criteria after neoadjuvant treatment.

- R0 resection was achieved in 100% of the PD-L1+ cohort (7/7 patients) (Table 7)
- Median time from the last neoadjuvant treatment to surgery was 6 days
- No intraoperative complications occurred

Table 7: Surgical outcomes in patients who underwent surgery^a

Surgery	PD-L1+ (n=7)
Last neoadjuvant tx to surgery, median (range), days	6 (1–28)
Surgical delays, n	1 ^b
R0 resection, n (%)	7 (100)

^aData are from eligible and treated patients who underwent post-neoadjuvant surgery. ^bDue to non-related pneumonia.

- At the data snapshot of June 30, 2026, median follow-up in this cohort was 22.4 months, and the 2-year EFS rate was 100%
- All AEs and TRAEs with neoadjuvant atezolizumab + SBRT in the PD-L1+ cohort were Grade 1 or 2 (Table 8)
- Hypothyroidism in 1 patient (14%) led to neoadjuvant treatment discontinuation
- No new safety signals were observed

Table 8: Safety of neoadjuvant therapy in safety-evaluable patients

AEs	PD-L1+ (n=7)
Any-grade AE, n (%)	7 (100)
Grade 3–4	0
Serious	0
TRAE, n (%)	6 (86) ^a
Grade 3–4	0
Serious	0
AE leading to dose interruption, n (%)	1 (14) ^b
AE leading to treatment discontinuation, n (%)	1 (14) ^c

^a6 patients had atezolizumab-related AEs and 4 patients had SBRT-related AEs. ^bInfection-related reaction. ^cHypothyroidism.

CONCLUSIONS

- Entrectinib may be a feasible neoadjuvant therapy in patients with resectable *ROS1*+ or *NTRK*+ eNSCLC
- Neoadjuvant atezolizumab plus low-dose SBRT showed encouraging efficacy and tolerable safety in patients with resectable PD-L1+ eNSCLC
- These data should be interpreted with caution due to small cohort sizes