

Research Paper

CHIO3: CHemotherapy combined with immune checkpoint inhibitor for operable stage IIIA/B (N2) Non-Small cell lung cancer (AFT-46)

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ABSTRACT

BACKGROUND: Despite a deluge of perioperative non-small cell lung cancer (NSCLC) checkpoint inhibitor trials, none have looked exclusively at an N2+ population. This trial focused on operable N2+ NSCLC and uniquely sought to evaluate N2 nodal clearance (N2NC) rates after treatment with chemotherapy and durvalumab.

METHODS: We conducted a single arm multi-institutional phase 2 trial. Eligible subjects had surgically resectable stage III NSCLC with pathologically proven N2 disease, performance status 0–1. N3 disease and EGFR mutation were exclusionary. Participants received 4 cycles of platinum doublet + durvalumab followed by lobectomy or greater, and adjuvant durvalumab Q4 weeks for one year. The primary endpoint (PEP) was N2NC (ypN0-1); the objective was an increase of N2NC to $\geq 50\%$ from a historical rate of 30% with platinum doublet chemotherapy. Secondary endpoints were resection rates, safety, feasibility, overall survival (OS) and event-free survival (EFS) at 18 months. Planned accrual was 55 patients, anticipating 42 patients undergoing resection.

RESULTS: Between 2021 and 2023, 37 patients were enrolled and 30 patients (81%) underwent resection. The study was closed early because the PEP was exceeded on interim analysis. N2NC was 73.3% (22/30); pathologic complete response (pCR) 30% (9/30); R0 resection 93.3% (28/30). At median follow up of 16.3 months, EFS at 18 months was 60.6% (95% CI 44–83%) overall, and 73.4% (95% CI 56–97%) for the resected cohort (n = 30). 16% (6/37) had grade 3 and higher treatment-related adverse events, most commonly lymphopenia.

CONCLUSIONS: In this surgically challenging, documented N2 + NSCLC population, neoadjuvant durvalumab plus chemotherapy was feasible with low toxicity, high rates of mediastinal nodal clearance, and complete resection.

Glossary of Abbreviations.

1. Introduction

Stage IIIA/B non-small cell lung cancer (NSCLC) remains a clinical challenge with historical 5-year survival rates of 24–41% [1]. Both local and distant recurrence plagues this population. Optimal management

remains uncertain, in part because of the heterogeneity of the disease burden and performance status of this group of patients. People with stage IIIA/B NSCLC who have discrete ipsilateral mediastinal nodal involvement [N2] and sufficient cardiopulmonary reserve may be candidates for surgical resection. Such individuals stand to benefit from

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some combination of systemic therapy, radiation, and surgery. However, the use of surgery has diminished over the last two decades, especially since the publication of the PACIFIC trial [2], with only approximately 10–15% of all patients with stage III NSCLC undergoing resection [3].

An induction strategy with enhanced response rate is appealing for many reasons, including the goal of allowing more people with NSCLC to undergo surgery, as well as the potential for better early systemic disease control. The NADIM trial recently reported 5-year survival of 69% in a mixed stage III population [4], far surpassing the PACIFIC trial's 5-year overall survival of 43%. [5] Certainly this could be attributed to operable vs. inoperable status, though the PACIFIC trial did not specify how inoperable status was determined. Nonetheless, the appeal of curative intent resection in stage III lung cancer is experiencing a resurgence in the lung cancer community.

The population targeted in this trial is operable stage IIIA/B NSCLC specifically with histologically proven N2 disease – to our knowledge, the only trial to date focusing on this group with a chemioimmunotherapy (ChIO) induction approach. We sought to determine the feasibility and clinical impact of using combined neoadjuvant platinum doublet chemotherapy with durvalumab for operable stage III (N2) NSCLC, followed by anatomic resection, and durvalumab for 1 year. We hypothesized that this strategy would increase N2 nodal clearance (N2NC).

2. Methods

2.1. Participants

Adults with potentially resectable pathologically proven N2 disease in clinical stage IIIA/B NSCLC (per American Joint Commission on Cancer [AJCC] 8th edition), with an Eastern Cooperative Oncology Group performance status (ECOG) of 0 or 1, and no previous anticancer therapy were eligible for enrollment. Additionally, surgery with an R0 resection had to be deemed possible by an American Board of Thoracic Surgery certified, or equivalent, study-approved thoracic surgeon based on tumor characteristics and patient fitness. Involved N2 (ipsilateral mediastinal) nodes on imaging had to be discrete (i.e., not invading surrounding structures) and less than 3 cm in maximum diameter. N2 node involvement was required to be histologically proven within 4 weeks of registration, with the exception of the following: tumor is left sided; only mediastinal involvement is in the level 5 or 6 region on CT scan; there is a distinct primary tumor separate from the nodes; and biopsy of the primary tumor showed NSCLC. Presence of an epidermal growth factor receptor (EGFR) mutation or N3 nodal involvement were exclusionary. Any mediastinal nodes > 1.5 cm by CT, or FDG-avid on PET in N3 locations had to be biopsied, and if positive, patients were excluded. See the full protocol in the Appendix for a complete list of inclusion and exclusion criteria.

2.2. Trial design and treatment

This was a single-arm multicenter North American phase 2 trial (see Fig. S1 for trial schema, and protocol in Appendix) wherein four cycles of histology-specific combined platinum doublet chemotherapy and durvalumab were delivered, followed by anatomic surgical resection (lobectomy or greater), and then up to one year of adjuvant durvalumab.

The primary endpoint was N2NC, with the primary objective being to increase N2 nodal clearance 50% or more for combined platinum doublet chemotherapy with durvalumab induction therapy from the historical rate of 20%–40% (30% on average) for platinum doublet chemotherapy alone in people with potentially resectable stage IIIA/B (T1–4, N2) NSCLC. This endpoint was considered evaluable for those who completed neoadjuvant therapy and underwent resection. The investigators chose 50% N2NC as the benchmark typically achieved with neoadjuvant chemoradiation, hypothesizing that this degree of nodal

clearance could be realized with more effective systemic therapy, without use of radiation.

Nodal clearance has been used as a surrogate for outcome in stage III NSCLC. It was the primary endpoint in two major cooperative group trials (RTOG 0229 [6] and RTOG 0839 [7]). Pathologic N2NC, as determined at the time of resection, historically occurs 20% to 40% of the time in chemotherapy induction strategies [8–11] and approximately 40% to 65% of the time when chemoradiation is the induction strategy. [6,7,12,13] In a phase 2 trial of neoadjuvant chemotherapy, [14] participants with downstaging to N0–1 compared with persistent N2 disease had a superior overall survival ($p < 0.001$), and the improvement was significant on multivariable analyses ($HR = 0.22$, $p = 0.0003$.) We chose this endpoint as a means of gaining an early signal on a novel treatment strategy for operable, N2 + NSCLC.

Secondary endpoints included safety and tolerability of the treatment protocol; the major pathological response rate (mPR; defined as < 10% residual viable tumor) and pathologic complete response (pCR) rates in the resected primary tumor and lymph nodes. Additional endpoints were event-free survival (EFS) from the time of registration to one of the following events, whichever came first: a) radiographic disease progression, b) local progression as defined by lymph node progression precluding surgery, c) inability to resect the tumor d) local or distant recurrence e) death due to any cause; overall survival (OS) rate from the time of registration to death from any cause; rate of complete resection; and postoperative complications (within 30 days of surgery). Adverse events were collected and reviewed.

Subjects received durvalumab plus histology-dependent platinum doublet chemotherapy every 3-week treatment cycle up to a maximum of 4 cycles:

- Non-squamous NSCLC: durvalumab 1500 mg, followed by pemetrexed 500 mg/m² IV with cisplatin 75 mg/m² IV.
- Squamous NSCLC: durvalumab 1500 mg, followed by docetaxel 75 mg/m² IV with cisplatin 75 mg/m² IV. Carboplatin was allowed for either histologic type with approval of the medical oncology principal investigator.

Prior to surgery and 4–8 weeks after the last cycle of neoadjuvant therapy, trial subjects were restaged with chest and upper abdominal CT scan, or whole body FDG-PET scan, and reassessment by the surgeon for fitness and resectability. All participants who met the criteria of no progression in the chest or elsewhere, including stable disease on re-evaluation, were eligible to proceed to surgery, which was to be performed 4–8 weeks after completion of induction therapy. A lobectomy, bilobectomy, sleeve resection, or pneumonectomy was allowed at the discretion of the thoracic surgeon. A formal systematic mediastinal lymph node dissection was required. Adjuvant radiation was initially part of the study protocol, but was made optional after study initiation, based on results of the Lung ART trial. [15] Adjuvant systemic therapy consisted of durvalumab 1500 mg IV every 4 weeks administered for up to 13 cycles, and was due to begin between 1 and 6 weeks after surgery.

2.3. Trial oversight

The trial was approved by a central Institutional Review Board (IRB) and site IRBs. Data collection and monitoring were controlled by the study sponsor under regular oversight of the Data and Safety Monitoring Board (DSMB). All participants provided written informed consent.

2.4. Statistical analysis

Planned sample size was 55, anticipating 20% attrition rate from neoadjuvant therapy to surgery, with 42 evaluable subjects undergoing resection for whom N2NC could be assessed. This was to achieve 90% power to detect an improvement in N2NC from 30% to 50%.

All consented participants who initiated neoadjuvant therapy were

included in the safety and time-to-event analyses. Subjects were eligible for the primary endpoint analysis if they completed neoadjuvant therapy and had their mediastinal nodal status reassessed at surgery (N2NC). Secondary analyses (EFS, OS) included all patients who received ≥ 1 cycle of neoadjuvant therapy.

Baseline characteristics were summarized using counts (percentages) for categorical variables and means (SD) and medians (IQR) for continuous variables. Given the small sample and sparseness of several categories, between-group summaries are presented descriptively; where hypothesis tests were computed, Fisher's exact tests (categorical) and Kruskal–Wallis tests (continuous) were preferred over large-sample χ^2 tests.

The N2NC rate is reported with an exact (Clopper–Pearson) 95% confidence interval (CI). If a design-specified null rate (θ_0) was pre-specified, a one-sample exact binomial test was used to compare the observed N2NC to θ_0 ; otherwise we present the estimate with its exact CI without formal hypothesis testing. EFS and OS were estimated by the Kaplan–Meier method. We report median survival with 95% CIs and landmark survival probabilities with Greenwood standard errors. Given the small sample and the single-arm design, subgroup contrasts are exploratory and primarily descriptive. A swimmer's plot was constructed to visualize patient-level trajectories, annotated by histology, smoking, pathological response, PD-L1 status, and sex.

All adverse events (AE) were coded using Common Terminology Criteria for Adverse Events v5.0 and tabulated by maximum grade. We present counts of patients with at least one AE by grade and category. We explicitly report the denominator used for each analysis. Analyses were conducted in SAS using procedures for exact logistic regression and Kaplan–Meier estimation. Data were locked on August 25, 2025.

3. Results

3.1. Cohort characteristics

Between May 2021 and December 2023, 38 patients were enrolled at 9 institutions in the United States. One participant was withdrawn during cycle 1 of therapy as an activating *EGFR* mutation was detected upon further ctDNA testing after the initial tumor testing did not reveal an *EGFR* mutation. Thus, 37 patients were included in the intention to treat cohort (Fig. 1). Patient demographics are listed in Table 1. The most common histology was adenocarcinoma. Invasive mediastinal staging proved N2 involvement in 34/37 patients; the other 3 patients had biopsy proven left sided NSCLC with single station level 5 or 6 nodal involvement based on PET scan, and invasive staging did not identify N3 involvement. PD-L1 testing was not yet standard at several participating sites, thus data are unavailable for 27% of enrolled patients. Multistation N2 involvement was allowed per protocol, however all patients had single station N2 involvement except for one with 2 stations involved (4R, 7 with a right lower lobe T1c tumor).

3.2. Treatment

Outcomes are listed in Table 2 and are depicted in a swimmer's plot in Fig. 2. The majority of participants received 4 cycles of neoadjuvant combined therapy. Resection rate was 30/37 (81.1%). Seven patients did not undergo resection. Reasons were related to disease progression in 5 participants: 3 with progression noted at the time of restaging evaluation; 1 with pleural dissemination at the time of thoracoscopic evaluation resulting in aborted surgical resection; and 1 with massive hemoptysis and death 3 weeks into treatment, attributed to progression of a large central tumor. One patient had bowel obstruction, aspirated and died during chemotherapy, categorized as treatment related adverse event. One patient had a decrease in DLCO at restaging from 50% to 37%

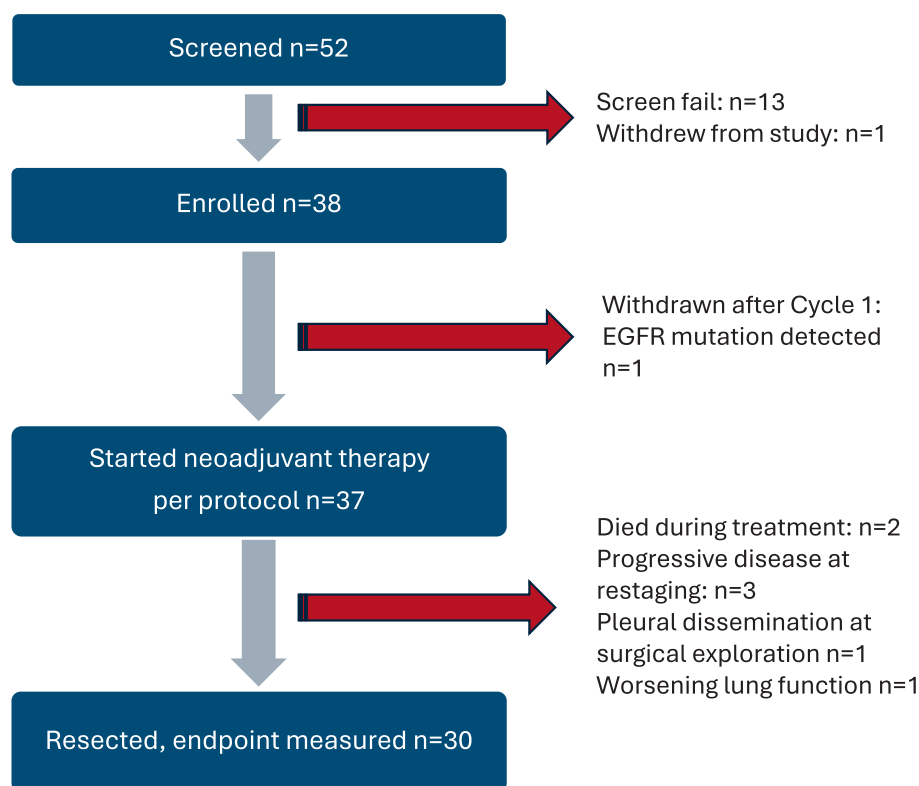


Fig. 1. CONSORT Diagram. Screen failure reasons: 3 patients declined participation; 2 ineligible cancer stage (IV, N3); 2 ineligible comorbidities (peripheral neuropathy, second malignancy); 1 insufficient archival tumor tissue; 1 difficulty adhering to assessments; 1 out of window due to COVID; 3 did not meet inclusion criteria, no other details available.

Table 1
Demographics.

Characteristic		N = 37	Percent
Sex		17 female	45.9%
Age in years (mean, median, (range))		66, 67 (39–82)	—
ECOG performance status	0	29	78.4%
	1	8	21.6%
Smoking Status	Never	3	8.1%
	Former	30	81.1%
	Current	4	10.8%
Race	Asian	2	5%
	Black	3	8.1%
	White	28	75.7%
	Not reported	4	10.8%
Histology	Squamous	12	32.4%
	Adenocarcinoma	24	64.9%
	Large Cell/NE	1	2.7%
cTNM AJCC 8th edition	cT1N2	14	37.8%
	cT2N2	11	29.7%
	cT3N2	9	24.3%
	cT4N2	2	5.4%
	cTxN2	1	2.7%
N2 histologically proven pre-treatment		34/37	91.8%
PD-L1 status	<1%	9	24.3%
	1–49%	11	29.7%
	≥50%	7	18.9%
	unknown	10	27%

ECOG: Eastern Cooperative Oncology Group Performance Status.

NE = neuroendocrine.

PD-L1: programmed for death ligand 1.

Table 2
Results.

Characteristic	No. of patients	Percent
Total number of neoadjuvant cycles (4 prescribed)	1 2 3 4	0/37 2/37 2/37 33/37
Surgical Resection	30/37	81.1%
Margin Status	R0 R1 R2	28/30 2/30 0/30
Pathologic Response	>10% RVT 1–10% RVT Complete (0% RVT)	15/30 6/30 9/30
N2 Nodal Clearance	22/30	73.3%

N2 Nodal clearance: N2 disease converts to ypN0 or ypN1 at resection

RVT: residual viable tumor.

and the site study team deemed that resection should not be done; this was attributed to treatment-related immune-mediated pneumonitis. Although it was optional, no patients received adjuvant radiation therapy.

3.3. N2 nodal clearance rate (primary endpoint)

After 37 patients were enrolled and 30 had undergone surgery, the N2NC had far exceeded the goal of 50% N2NC, at 73.3%, and thus the Data and Safety Monitoring Board urged study closure as the objective had been substantially exceeded (unplanned interim analysis).

3.4. Secondary endpoints

pCR rate was 30% and mPR was 50%, all based on local assessment. OS and EFS were evaluated at 18-month landmark from enrollment and were 80.7% (95% CI: 65.6–99.2%) and 60.6% (95% CI: 44.1–83.1%), respectively (Fig. 3A and 3B). All resected patients (n = 30) were alive at 18 months and all unresected patients (n = 7) had died at a median of 8.7 months (95% CI: 1.9 months –not evaluable). EFS at 18 months for

all resected patients was 73.4% (95% CI: 55.7–96.6%). When evaluating resected patients for N2NC, the 8 with ypN2 disease had 18-month EFS of 50% (95%CI: 25–100%), and for the 22 who experienced N2NC, it was 81.8% (95% CI: 59.7–100%) (p = 0.64) (Fig. 3C).

3.5. Adverse events

Overall, treatment was well tolerated (Table 3). There were 2 grade 5 events, as described above. Aside from these, 4 of 37 patients experienced grade 3 or 4 events during neoadjuvant therapy, mostly due to lymphopenia (Supplementary Table 1). No patients experienced grade 3–5 toxicity during adjuvant durvalumab (Supplementary Table 2). Thirty-one participants (31/37, 84%) had an adverse event attributed to systemic treatment during neoadjuvant therapy, and 1/20 (5%) during adjuvant therapy, which led to discontinuation of at least one agent in 7 (19%; 6 during neoadjuvant, 1 during adjuvant). Most toxicity was attributable to chemotherapy.

4. Discussion

To our knowledge, this is the first trial specifically focused on a histologically proven N2 + NSCLC population testing the benefit of neoadjuvant chemotherapy and immune checkpoint inhibitor. 81% of this oncologically and surgically challenging category of patients were able to undergo resection, including 93.3% with negative margins, and microscopic margin involvement (R1) in 6.7%. Only 2 people (6.7%) required pneumonectomy, whereas historically pneumonectomy has been needed in this clinical setting in as many as 11–35% of cases. [12,13,16] N2NC far exceeded our estimates at the time of trial design, occurring in 73.3% of cases – substantially higher than historical rates of 30% with chemotherapy alone. This is also higher than most previous trials with radiation included in the induction strategy (40–68%) arguably with much less toxicity. [7,12,13].

It is noteworthy that nodal clearance rates are tracked only in patients who undergo surgery, which is typically about 80% of patients who start neoadjuvant therapy; [6,8,12,13] Reports are therefore often based on a selected population enriched with responders. Data on N2NC following neoadjuvant ChIO are found only on subset analysis of several trials reporting on stage IB–III cases. Importantly, histologic confirmation of N2 involvement pre-treatment was not rigorously documented in these large trials, thus N2NC was often based on PET positivity pre-treatment, and then nodal status at resection. With this caveat in mind, the N2NC rates, when reported, have ranged from 57% to 72%. [17,18].

The use of N2NC as surrogate for OS and EFS dates back to neoadjuvant trials using platinum doublet alone or chemoradiation with doses ranging from 45–60 Gy. In the Intergroup 0139 trial, [12] in patients undergoing thoracotomy with ypN0 status, the 5-year OS was 41%, which was significantly longer than patients with ypN1–3 status or not undergoing surgery (p < 0.0001). A phase II trial that investigated induction chemotherapy in pathological N2 disease revealed a N2NC rate of 21%. [19] Patients with N2NC compared to patients with residual N2 disease had a superior survival (median EFS of 47.8 versus 8.2 months, p = 0.01). We do not yet know if N2NC will prove to be the best surrogate in the modern era of neoadjuvant ChIO trials. At 18 months of follow-up thus far, in this trial we observed a 31.8% absolute difference in EFS for those that achieved N2NC or not (Fig. 3c) (numbers too small for statistical evaluation). We will continue to assess the merit of this endpoint as our data mature. It is remarkable that N2NC is so high in our trial as well as other neoadjuvant ChIO trials, without the use of a local modality – supporting the hypothesis that a more effective systemic regimen can overcome the need for enhanced local control that comes with radiation in the neoadjuvant setting.

In comparing our outcomes for the more traditional early outcome measures, pCR and mPR, our results are congruent with several recent neoadjuvant ChIO trials (Table 4). In many instances, specific results for

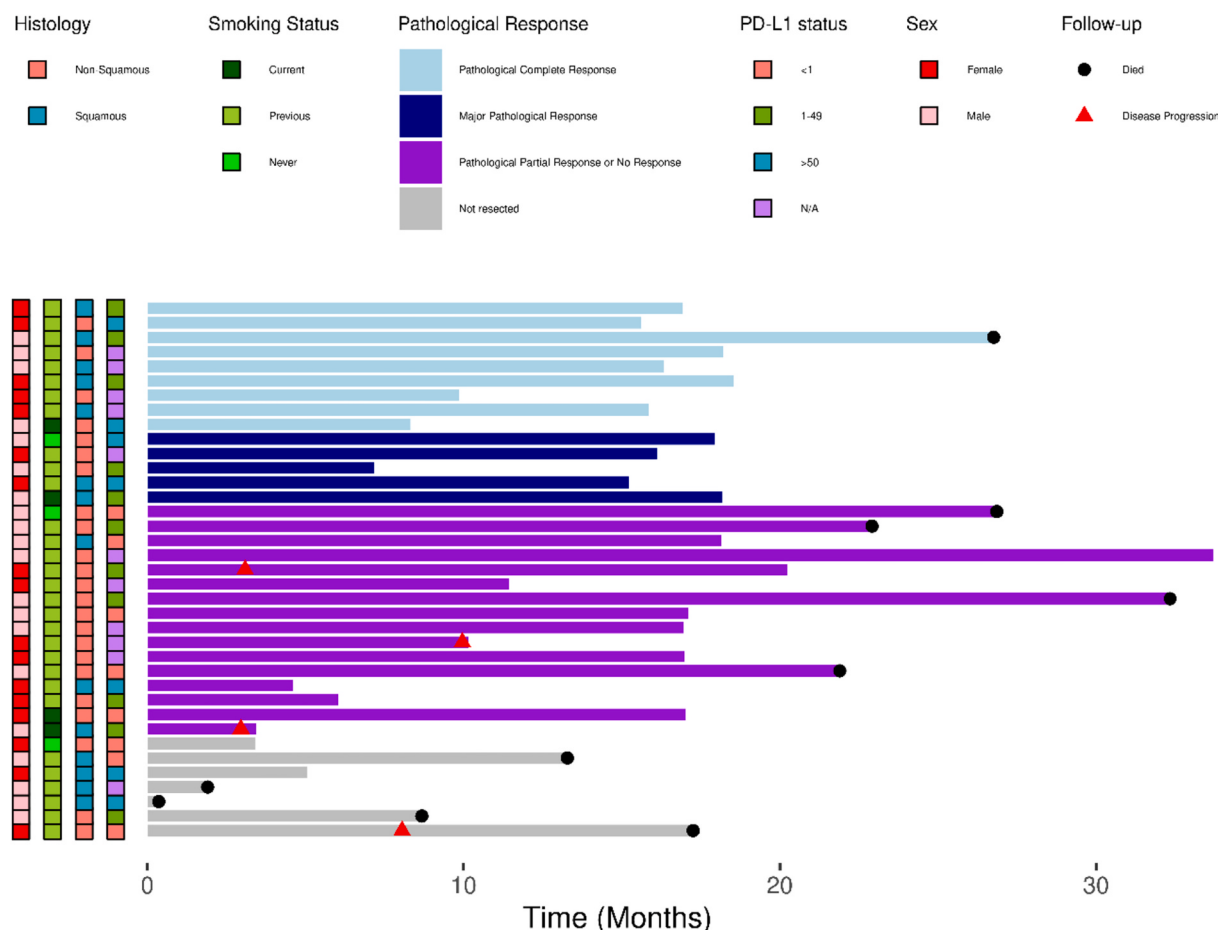


Fig. 2. Swimmers plot – intent-to-treat population, as of data cutoff August 25, 2025.

N2 + are not available, nor was pre-treatment histologic confirmation of N2 involvement required in larger, more inclusive trials. [17,18,20–23] N2NC was recently reported in an exploratory, post-hoc analysis from Checkmate 77 T, with nodal downstaging to ypN0-1 in 43/70 (61%). The hazard ratio for EFS in the N2 subgroup in the experimental arm was a remarkable 0.46, though specific results for those with nodal downstaging has not yet been reported. It is an open question whether N2NC, mPR, pCR, or clearance of circulating tumor DNA is the best surrogate for EFS and OS in this clinical setting. As this trial matures, we hope to shed light on the predictive value of each of these endpoints in locally advanced NSCLC.

With a median follow-up of 16 months, our 18-month landmark analysis is limited, but OS of 80.7% (95%CI: 65.6–99.2) and EFS of 60.6% (95% CI: 44.1–83.1) are comparable to what was reported in NADIM2 in a mixed stage 3 population. [18] There was a stark difference in OS and EFS for resected vs. nonresected patients in this and other recent trials, not surprisingly. Patients who were able to undergo surgery are all alive at 18 months, with only 3 recurrences reported thus far (Fig. 2), 1 with pCR, and 2 with partial response. Certainly, longer follow up will be needed before drawing meaningful conclusions regarding EFS and OS.

CHIO3 was designed for a resectable or possibly resectable stage III NSCLC population, as determined by the treating thoracic surgeon and medical oncologist. Stage III trials decades ago [24,25] began with surgery as the primary treatment and added perioperative chemotherapy as the intervention. The treatment landscape has evolved to such an extent that very few patients are offered resection – 10% in Canada, [26] 10.8% in California cancer registry 2004–2012, [27] 10–18% per National Cancer Database (NCDB), [3] 23% in KINDLE-

Asia, [28] likely due to the findings of Intergroup 0139, [12] and then PACIFIC. [2] The PACIFIC trial has led to a major paradigm shift with its 5-year survival of 44%, [5] nearly double what was observed in earlier eras for stage III NSCLC (25–41%), so much so that many lung cancer clinicians have abandoned surgery as a consideration. Unfortunately, the entry criteria for PACIFIC lacked a reproducible definition of “unresectable”, and did not involve surgeon assessment before assigning patients with stage III NSCLC to a nonsurgical approach. [29] Subsequently the phase 2 NADIM 5-year results have been reported, albeit for a broader, more heterogeneous group than included in this study, with 69.3% 5-year survival. [4] With our current trial findings in a histologically proven N2 + population, along with the results of NADIM, and subset analysis of pre- and peri-op ChIO trials, it is imperative to include all disciplines in the guiding the care of an individual with stage III NSCLC. Ideally, ChIO + resection vs. chemoradiation + immune checkpoint inhibitor would be compared head-to-head in a randomized trial. In a National Cancer Database propensity matched comparison of ChIO + resection vs. chemoradiation + immune checkpoint inhibitor, 3-year OS was 77% vs 63% ($p = 0.029$). [30] If surgery following ChIO can be accomplished safely, with an R0 resection, the outlook for that patient is substantially better than with a chemoradiation + immune checkpoint inhibitor strategy, a sentiment also echoed in recently published subset analysis of N2 + subjects in Checkmate 77 T.. [31].

5. Limitations

Rigorous clinical trials in stage III NSCLC have historically been difficult to execute, and ours was no different in this respect. CHIO3 is limited by relatively small numbers (30 patients with an evaluable

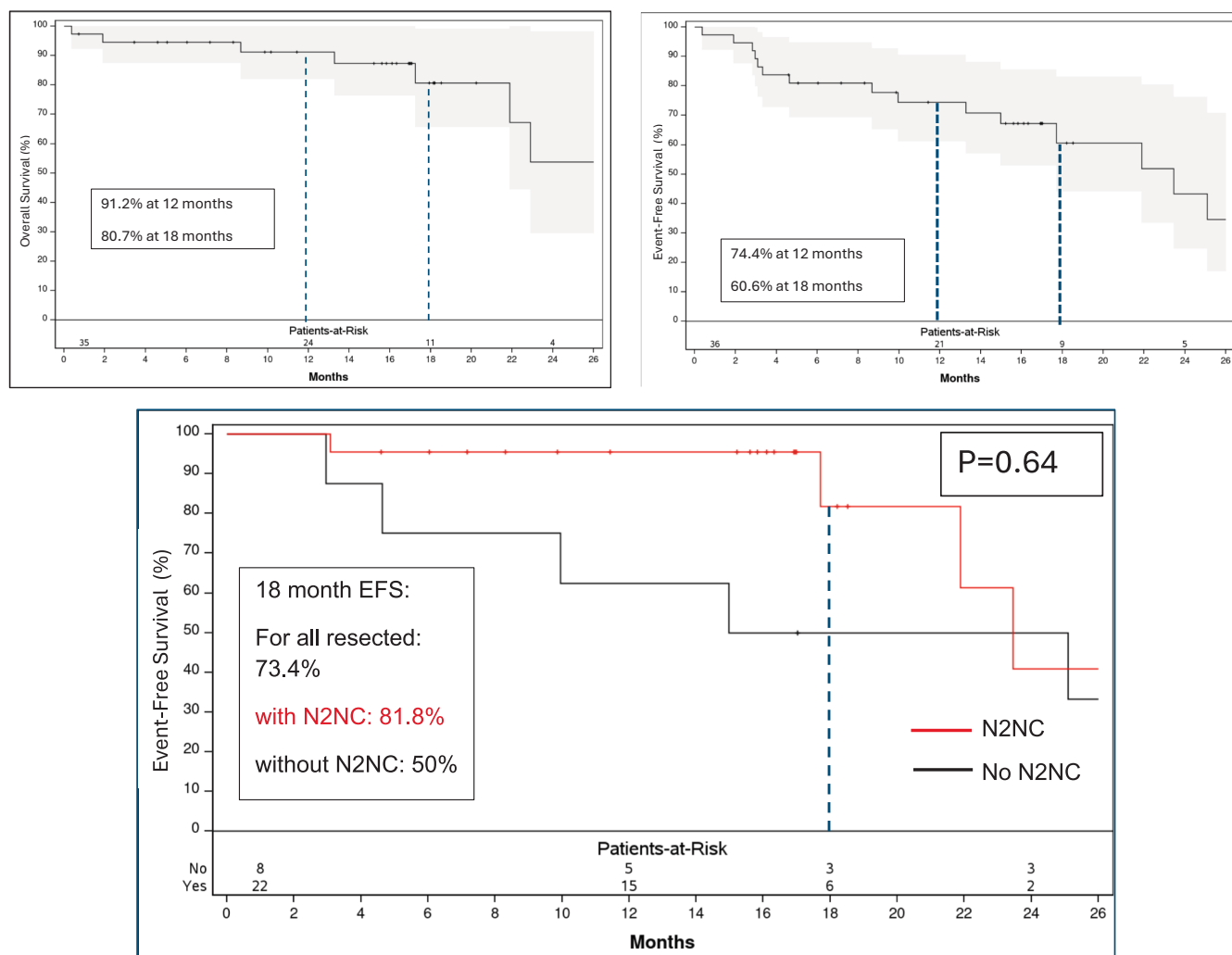


Fig. 3a. Overall Survival for entire cohort $n = 37$. At 12 month, 91.2% (95% CI: 82.1–100.0). At 18 months, 80.7% (95% CI: 65.6–99.2). **Fig. 3b.** EFS for entire cohort $n = 37$. At 12 months, 74.4% (95% CI: 61.1–90.5). At 18 months, 60.6% (95% CI: 44.1–83.1). **Fig. 3c.** EFS by N2 Nodal Clearance ($n = 30$, resected patients). EFS at 18 months overall: 73.4% (95% CI 55.7–96.6); for those with N2NC, 81.8% (95% CI 59.7–100%); without N2NC, 50% (95% CI 25–100%).

endpoint, beneath the target of 42), because our results exceeded the criteria for a positive PEP at an interim analysis, and the DSMB recommended trial closure. Secondary endpoint and subgroup inferences are exploratory, given early closure and limited follow-up (median of 16.3 months at data lock). The study also suffered from delays in launch, enrollment, and execution related to the COVID pandemic challenges in research staffing and patient access. The requirement for histologic proof of N2 involvement pre-treatment rendered several potential enrollees ineligible, though we were adamant that this proof was essential to reliably assess the endpoint of N2NC. We were unable to obtain PD-L1 status for every case, as it was not yet standard of care in many centers, thus reducing ability to evaluate the influence of this biomarker on outcome. Enrollment restricted to higher volume United States centers may impact generalizability.

6. Conclusions

Neoadjuvant durvalumab plus chemotherapy followed by resection is an effective strategy for stage III (N2 +) NSCLC, with N2NC rate more than twice the historical rate with chemotherapy alone (73.3% vs. 30%). In this surgically challenging cohort of a locally advanced population with proven N2 + NSCLC, resection after ChIO was feasible with low rates of perioperative toxicity and 93.3% rate of R0 resection. An effective neoadjuvant regimen that pairs a checkpoint inhibitor with

platinum chemotherapy facilitated surgical resection with acceptable toxicity and a high rate of pathologic response. From these results, as well as other trials, the treatment paradigm of induction chemotherapy with immunotherapy and resection is a treatment option for patients with N2 disease that warrants multidisciplinary evaluation whenever possible.

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DISCLOSURES

Please see attached ICJME disclosure statements.

Table 3

Neoadjuvant and adjuvant, on-treatment, treatment-related adverse events, graded by common terminology criteria for adverse events v5.0, as of data cutoff August 25, 2025. Neoadjuvant (N = 37) shaded blue, adjuvant (N = 20) shaded purple.

Adverse Event by Treatment Period	Number of patients (percent) with Adverse Event by Grade			
	Grade 1 or 2	Grade 3	Grade 4	Grade 5
Maximum grade adverse event during neoadjuvant therapy (N = 37)	25 (68)	2(5)	2 (5)	2(5)
Hematologic Adverse Events				
Anemia	14 (38)	0	1 (3)	0
Blood and lymph system disorders – Other Specific	1 (3)	0	0	0
Lymphocyte count decreased	6 (16)	0	1 (3)	0
Neutrophil count decreased	4 (11)	1 (3)	2 (5)	0
Platelet count decreased	5 (14)	1 (3)	0	0
White blood cell decreased	7 (19)	2 (5)	0	0
*Non-Hematologic Adverse Events – most common				
Fatigue	20 (54)	1(3)	0	0
Diarrhea	6(16)	1(3)	0	0
Constipation	5(14)	0	0	0
Mucositis	6 (16)	1(3)	0	0
Hemoptysis	0	0	0	1(3)
Bowel obstruction and aspiration	0	0	0	1(3)
Maximum grade adverse event during adjuvant therapy (N = 20)	15 (75)	0	0	0
Hematologic Adverse Events				
Anemia	3 (15)	0	0	0
Lymphocyte count decreased	4 (20)	0	0	0
Neutrophil count decreased	2 (10)	0	0	0
Platelet count decreased	2 (10)	0	0	0
*Non-Hematologic Adverse Events – most common				
Rash maculo-papular	6 (30)	0	0	0
Thyroid stimulating hormone increased	5 (25)	0	0	0
Fatigue	3 (15)	0	0	0
Hypocalcemia	3 (15)	0	0	0

* See Supplementary Tables 1, 2 for complete details.

Table 4

Comparison of oncologic outcomes with other trials using neoadjuvant chemotherapy and checkpoint inhibitors.

Trial	Neoadjuvant Treatment	pathCR	mPR
NADIM II [18]	3 cycles platinum doublet + nivolumab	37% for all stage III	53% for all stage III
Checkmate 816 [21]	3 cycles platinum doublet + nivolumab	24% for stage IB-III	37% for stage IB-III
Checkmate 77T [31]	4 cycles platinum doublet + nivolumab	28.6% for N2 + resected	38.6% for N2 + resected
AEGEAN [23]	4 cycles platinum doublet + durvalumab	16.6% for N2+	32.6% for N2+
Keynote 671 [22]	4 cycles platinum doublet + pembrolizumab	16% for N1, N2+	28.2% for N1, N2+
CHIO3	4 cycles platinum doublet + durvalumab	30%	50%

CRediT authorship contribution statement

LW. Martin: Writing – review & editing, Writing – original draft, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **X. Wang:** Methodology, Formal analysis, Data curation. **D. Kozono:** Writing – review & editing, Supervision, Project administration, Funding acquisition. **J. Urbanic:** Writing – review & editing, Supervision, Investigation, Conceptualization. **S. Graziano:** Writing – review & editing, Investigation. **R. Osarogiabgon:** Writing – review & editing, Investigation. **R. Mehran:**

Writing – review & editing, Investigation. **J. Wain:** Writing – review & editing, Investigation. **C. Bestvina:** Writing – review & editing, Investigation. **S. Wolf:** Methodology, Formal analysis, Data curation. **JD. Patel:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **T. Stinchcombe:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Linda Martin reports a relationship with AstraZeneca Pharmaceuticals LP that includes: consulting or advisory. Linda Martin reports a relationship with Genentech Inc that includes:. Linda Martin reports a relationship with Johnson and Johnson that includes: speaking and lecture fees. Linda Martin reports a relationship with Natera, Inc. that includes: consulting or advisory. Linda Martin reports a relationship with On Target Laboratories LLC that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Dr. Linda W. Martin takes responsibility for the content of the manuscript, including data and analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.lungcan.2026.109374>.

REFERENCES

[1] P. Goldstraw, K. Chansky, J. Crowley, et al., The IASLC lung cancer Staging project: proposals for revision of the TNM Stage groupings in the forthcoming (eighth) edition of the TNM Classification for lung cancer, *J. Thorac. Oncol.* 11 (1) (2016) 39–51.

[2] S.J. Antonia, A. Villegas, D. Daniel, et al., Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC, *N. Engl. J. Med.* 379 (24) (2018) 2342–2350.

[3] E.A. David, S.W. Andersen, L.A. Beckett, et al., Survival benefits associated with surgery for advanced non-small cell lung cancer, *J. Thorac. Cardiovasc. Surg.* 157 (4) (2019) 1620–1628.

[4] M. Provencio, E. Nadal, A. Insa, et al., Perioperative chemotherapy and nivolumab in non-small-cell lung cancer (NADIM): 5-year clinical outcomes from a multicentre, single-arm, phase 2 trial, *Lancet Oncol.* 25 (11) (2024) 1453–1464.

[5] D.R. Spigel, C. Faivre-Finn, J.E. Gray, et al., Five-year survival outcomes from the PACIFIC trial: Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer, *J. Clin. Oncol.* 40 (12) (2022) 1301–1311.

[6] M. Suntharalingam, R. Paulus, M.J. Edelman, et al., Radiation therapy oncology group protocol 02-29: a phase II trial of neoadjuvant therapy with concurrent chemotherapy and full-dose radiation therapy followed by surgical resection and consolidative therapy for locally advanced non-small cell carcinoma of the lung, *Int. J. Radiat. Oncol. Biol. Phys.* 84 (2) (2012) 456–463.

[7] M.J. Edelman, C. Hu, Q.T. Le, et al., Randomized phase II study of preoperative chemoradiotherapy ± panitumumab followed by consolidation chemotherapy in potentially operable locally advanced (stage IIIa, N2+) non-small cell lung cancer: NRG Oncology RTOG 0839, *J. Thorac. Oncol.* 12 (9) (2017) 1413–1420.

[8] K. Higgins, J.P. Chino, L.B. Marks, et al., Preoperative chemotherapy versus preoperative chemoradiotherapy for stage III (N2) non-small-cell lung cancer, *Int. J. Radiat. Oncol. Biol. Phys.* 75 (5) (2009) 1462–1467.

- [9] M. Thomas, C. Rübe, P. Hoffknecht, et al., Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer, *Lancet Oncol.* 9 (7) (2008) 636–648.
- [10] Ripley RT, Suzuki K, Tan KS, et al. Postinduction positron emission tomography assessment of N2 nodes is not associated with ypN2 disease or overall survival in stage IIIA non-small cell lung cancer. *J Thorac Cardiovasc Surg.* 2016;151(4):969-977, 979.e1-3.
- [11] J.P. van Meerbeeck, G.W.P.M. Kramer, P.E.Y. Van Schil, et al., Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer, *J. Natl Cancer Inst.* 99 (6) (2007) 442–450.
- [12] K.S. Albain, R.S. Swann, V.W. Rusch, et al., Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial, *Lancet* 374 (9687) (2009) 379–386.
- [13] M. Pless, R. Stupp, H.B. Ris, et al., Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial, *Lancet* 386 (9998) (2015) 1049–1056.
- [14] D.C. Betticher, S.F. Hsu Schmitz, M. Tötsch, et al., Mediastinal lymph node clearance after docetaxel-cisplatin neoadjuvant chemotherapy is prognostic of survival in patients with stage IIIA pN2 non-small-cell lung cancer: a multicenter phase II trial, *J. Clin. Oncol.* 21 (9) (2003) 1752–1759.
- [15] C. Le Pechoux, N. Pirel, F. Barlesi, et al., Postoperative radiotherapy versus no postoperative radiotherapy in patients with completely resected non-small-cell lung cancer and proven mediastinal N2 involvement (lung ART): an open-label, randomised, phase 3 trial, *Lancet Oncol.* 23 (1) (2022) 104–114.
- [16] D. Boffa, F.G. Fernandez, S. Kim, et al., Surgically managed clinical stage IIIA–clinical N2 lung cancer in the society of thoracic surgeons database, *Ann. Thorac. Surg.* 104 (2) (2017) 395–403.
- [17] M. Provencio, M.M. Awad, J. Spicer, et al., Clinical outcomes with perioperative nivolumab (NIVO) by nodal status among patients (pts) with stage III resectable NSCLC: results from the phase 3 CheckMate 77T study, *J. Clin. Oncol.* 42(17_suppl):LBA8007-LBA8007 (2024).
- [18] M. Provencio, E. Nadal, J.L. González-Larriba, et al., Perioperative nivolumab and chemotherapy in stage III non-small-cell lung cancer, *N. Engl. J. Med.* 389 (6) (2023) 504–513.
- [19] M.T. Jaklitsch, J.E. Herndon 2nd, M.M. DeCamp Jr, et al., Nodal downstaging predicts survival following induction chemotherapy for stage IIIA (N2) non-small cell lung cancer in CALGB protocol #8935, *J. Surg. Oncol.* 94 (7) (2006) 599–606.
- [20] M. Provencio, E. Nadal, A. Insa, et al., Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial, *Lancet Oncol.* 21 (11) (2020) 1413–1422.
- [21] P.M. Forde, J. Spicer, S. Lu, et al., Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer, *N. Engl. J. Med.* 386 (21) (2022) 1973–1985.
- [22] H. Wakelee, I. Demedts, A. Langleben, et al., MA04.04 Perioperative Pembrolizumab in Non-Small Cell Cancer (NSCLC): 4-Year Outcomes by Nodal Status in the KEYNOTE-671 Study. In: *World Conference for Lung Cancer 2025*, 2025.
- [23] J. Heymach, M. Reck, T. Mitsudomi, et al., Outcomes with perioperative durvalumab (D) in pts with resectable NSCLC and baseline N2 lymph node involvement (N2 R-NSCLC): an exploratory subgroup analysis of AEGEAN, *J. Clin. Oncol.* 42(16_suppl):8011–8011 (2024).
- [24] J.A. Roth, F. Fossella, R. Komaki, et al., A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer, *J. Natl Cancer Inst.* 86 (9) (1994) 673–680.
- [25] R. Rosell, J. Gómez-Codina, C. Camps, et al., A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer, *N. Engl. J. Med.* 330 (3) (1994) 153–158.
- [26] S. Moore, B. Leung, J. Wu, C. Ho, Real-world treatment of stage III NSCLC: the role of trimodality treatment in the era of immunotherapy, *J. Thorac. Oncol.* 14 (8) (2019) 1430–1439.
- [27] E.A. David, R.J. Canter, Y. Chen, D.T. Cooke, R.D. Cress, Surgical management of advanced non-small cell lung cancer is decreasing but is associated with improved survival, *Ann. Thorac. Surg.* 102 (4) (2016) 1101–1109.
- [28] K. Prabhaskar, D.S.W. Tan, R.A. Soo, et al., Real-world clinical practice and outcomes in treating stage III non-small cell lung cancer: KINDLE-Asia subset, *Front. Oncol.* 13 (2023) 1117348.
- [29] H.I. Pass, PACIFIC: Time for a surgical IIIA uprising, *J. Thorac. Cardiovasc. Surg.* 156 (3) (2018) 1249–1254.
- [30] A. Kumar, D. Srinivasan, A.L. Potter, et al., Induction chemioimmunotherapy with surgery versus concurrent chemoradiation followed by immunotherapy for stage III-N2 non-small cell lung cancer, *J. Thorac. Cardiovasc. Surg.* 167 (6) (2024) 1895–1905.e2.
- [31] M. Provencio, M.M. Awad, J.D. Spicer, et al., Clinical outcomes with perioperative nivolumab by nodal status in patients with stage III resectable NSCLC: phase 3 CheckMate 77T exploratory analysis, *Nat Cancer.* 7 (1) (2026) 169–181.

Glossary

NSCLC: Non-small cell Lung Cancer
 PEP: primary endpoint
 EGFR: epidermal growth factor receptor
 EFS: Event Free Survival
 OS: Overall Survival
 N2NC: N2 ipsilateral mediastinal node clearance (cN2 converting to ypN0-1)
 pCR: pathologic complete response, ypT0N0
 mPR: major pathologic response, <10% residual viable tumor
 RVT: residual viable tumor
 DSMB: data and safety monitoring board
 CT: computed tomography
 FDG-PET: fluoro deoxyglucose positron emission tomography
 SD: Standard Deviation
 IQR: Interquartile Range
 DLCO: Diffusing capacity of the lung for carbon monoxide
 ChIO: Chemotherapy + Immunotherapy (immune checkpoint inhibitor)