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Surgical results of the Lung Cancer Mutation Consortium 3 trial: A phase II multicenter single-arm study to investigate the efficacy and safety of atezolizumab as neoadjuvant therapy in patients with stages IB-select IIIB resectable non-small cell lung cancer



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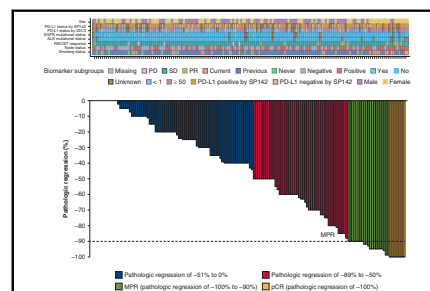
ABSTRACT

Objective: Multimodality treatment for resectable non-small cell lung cancer has long remained at a therapeutic plateau. Immune checkpoint inhibitors are highly effective in advanced non-small cell lung cancer and promising preoperatively in small clinical trials for resectable non-small cell lung cancer. This large multicenter trial tested the safety and efficacy of neoadjuvant atezolizumab and surgery.

Methods: Patients with stage IB to select IIIB resectable non-small cell lung cancer and Eastern Cooperative Oncology Group performance status 0/1 were eligible. Patients received atezolizumab 1200 mg intravenously every 3 weeks for 2 cycles or less followed by resection. The primary end point was major pathological response in patients without *EGFR/ALK*+ alterations. Pre- and post-treatment computed tomography, positron emission tomography, pulmonary function tests, and biopspecimens were obtained. Adverse events were recorded by Common Terminology Criteria for Adverse Events v.4.0.

Results: From April 2017 to February 2020, 181 patients were entered in the study. Baseline characteristics were mean age, 65.1 years; female, 93 of 181 (51%); nonsquamous histology, 112 of 181 (62%); and clinical stages IIB to IIIB, 147 of 181 (81%). In patients without *EGFR/ALK* alterations who underwent surgery, the major pathological response rate was 20% (29/143; 95% confidence interval, 14-28) and the pathological complete response rate was 6% (8/143; 95% confidence interval, 2-11). There were no grade 4/5 treatment-related adverse events preoperatively. Of 159 patients (87.8%) undergoing surgery, 145 (91%) had pathologic complete resection. There were 5 (3%) intraoperative complications, no intraoperative deaths, and 2 postoperative deaths within 90 days, 1 treatment related. Median disease-free and overall survival have not been reached.

Conclusions: Neoadjuvant atezolizumab in resectable stage IB to IIIB non-small cell lung cancer was well tolerated, yielded a 20% major pathological response rate, and allowed safe, complete surgical resection. These results strongly support the further development of immune checkpoint inhibitors as preoperative therapy in locally advanced non-small cell lung cancer. (J Thorac Cardiovasc Surg 2023;165:828-39)



After neoadjuvant atezolizumab immunotherapy in patients with stage IB to IIIB NSCLC, the MPR rate was 20%.

CENTRAL MESSAGE

In this large multicenter trial, neoadjuvant atezolizumab immunotherapy plus surgical resection for stage IB to IIIB NSCLC was well tolerated, associated with a 20% MPR rate and encouraging OS.

PERSPECTIVE

In metastatic NSCLC, immunotherapy has improved OS. This phase II multicenter trial, the largest reported to date, showed that neoadjuvant atezolizumab immunotherapy plus surgical resection in stage IB to IIIB NSCLC was well tolerated, associated with a 20% MPR rate and encouraging OS, thus providing a strong rationale for this treatment approach in locally advanced, resectable NSCLC.

See Commentary on page 840.

Abbreviations and Acronyms

AE	= adverse event
ALK	= anaplastic lymphoma kinase
CT	= computed tomography
DFS	= disease-free survival
DLCO	= diffusion capacity for carbon monoxide
EGFR	= epidermal growth factor receptor
FEV1	= forced expiratory volume in 1 second
IO	= immune checkpoint inhibitor
LCMC	= Lung Cancer Mutation Consortium
MIS	= minimally invasive surgery
MPR	= major pathologic response
NSCLC	= non-small cell lung cancer
OS	= overall survival
PD-L1	= programmed death ligand 1
PFT	= pulmonary function test
RECIST	= Response Evaluation Criteria In Solid Tumors
R0	= pathologic complete resection
VATS	= video-assisted thoracic surgery



Scanning this QR code will take you to the table of contents to access supplementary information.



Surgery is considered the primary curative therapy for patients with early-stage non-small cell lung cancer (NSCLC) who are medically fit for pulmonary resection. However, 5-year overall survival (OS) for patients with resectable, locally advanced NSCLC (stage IB to IIIB disease) is only 26% to 68%. Patients who progress after resection

typically develop distant metastatic disease.¹ During the past 35 years, multiple clinical trials have shown that the addition of either adjuvant or neoadjuvant platinum-based chemotherapy to surgical resection in patients with locally advanced NSCLC is feasible and increases the 5-year OS.²⁻¹³ Unfortunately, the absolute OS benefit with this approach is only approximately 5%, and patients experience significant toxicity. Although neoadjuvant therapy plus resection of locally advanced NSCLC has never been proven superior to postoperative adjuvant chemotherapy, it is widely used for locally advanced NSCLC. It has the potential advantages of early control of micrometastatic disease and is associated with better overall drug delivery because patients who start adjuvant therapy receive approximately 55% of the planned total dose. The neoadjuvant approach facilitates assessment of treatment safety and efficacy through serial scans before resection and pathologic evaluation of the degree of treatment response. It also enables pre- and post-treatment biomarker studies.¹⁴⁻¹⁶

Multimodality treatment using platinum-based chemotherapy and either surgery or radiation for locally advanced NSCLC has remained at a therapeutic plateau for over 2 decades. The discovery of immune regulatory pathways in cancer, including the important role of the programmed death-1/programmed death ligand 1 (PD-L1) pathways, and the development of drugs targeting those pathways, have revolutionized the treatment of many solid tumors, including NSCLC.¹⁷ These immune checkpoint inhibitors (IOs), particularly those targeting the programmed death-1/PD-L1 pathway, have been tested in large randomized clinical trials in metastatic NSCLC. In that setting, they were associated with significantly better OS when compared with cytotoxic chemotherapy as second- and then as first-line monotherapy, and when combined with platinum-based chemotherapy compared with chemotherapy alone.¹⁸⁻²⁶ Consequently, combined chemotherapy

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This study was approved by the Institutional Review Board at each of the participating institutions, and all patients provided informed consent before entry on study.

Number and Dates of Institutional Review Board approval: 295131 4/19/2022; 294898 1/24/2018; 294886 4/15/2022; 294889 4/1/2021; 295677 6/2/2021; 301840 5/19/2022; 294903 3/21/2022; 294899 4/15/2022; 294887 3/9/2022; 295326 4/27/2022; 295678 5/11/2021; 301242 6/1/2021; 294888 8/5/2021; 294904 8/21/2022; 294895 4/14/2022.

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and IO therapy (commonly termed “chemoIO”) has become standard of care for metastatic NSCLC without targetable oncogene driver gene mutations (eg, epidermal growth factor receptor [EGFR]).

Logically, the use of IO was next tested in locally advanced NSCLC. A large randomized clinical trial comparing the addition of IO (durvalumab) versus placebo as consolidation treatment after chemoradiotherapy for locally advanced, unresectable NSCLC yielded improved OS, thus altering the standard of care for this patient population.²⁷⁻³⁰ As a next step, studies examined the benefit of IO for resectable disease. Small neoadjuvant mono or dual immunotherapy trials demonstrated favorable rates of pathologic regression (major pathologic response [MPR] 14%-45% and pathological complete response 5%-16%) with acceptable treatment-related toxicity (grade ≥ 3 treatment-related adverse event [AE] 0%-14%) and low attrition of patients to surgery (0%-14%).^{29,31} Therefore, more detailed studies in larger clinical trials were needed to further confirm the safety and efficacy of IO followed by potentially curative surgery. We report the results of a large, multicenter trial of neoadjuvant atezolizumab with a focus on surgically related outcomes and view those results within the context of a recently published trial showing the superiority of neoadjuvant chemoIO to chemotherapy alone.^{32,33}

MATERIALS AND METHODS

Study Design, Eligibility Criteria, and Required Interventions

This was a phase II multicenter single arm study investigating the efficacy and safety of atezolizumab (a PD-L1 checkpoint inhibitor) as neoadjuvant therapy in patients with previously untreated clinical stages IB to select IIIB (T3N2, but not T4 or N3 by 8th edition American Joint Commission on Cancer/Union for International Cancer Control staging) NSCLC. Pretreatment pathological documentation of NSCLC was required. Tumors were staged at screening by chest computed tomography (CT) scan, positron emission tomography imaging, and brain magnetic resonance imaging. Documentation of lymph node involvement by endobronchial ultrasound or mediastinoscopy for patients with clinical stages II and IIIA disease was encouraged. The primary tumor had to be measurable by Response Evaluation Criteria In Solid Tumors (RECIST) criteria. Tumors of pure ground-glass opacity appearance on CT were excluded. All patients were evaluated jointly by a thoracic surgeon and a medical oncologist to verify study eligibility and to ensure that the primary tumor and involved lymph nodes were technically resectable. Patients needed to have adequate cardiopulmonary function for surgical resection. Postoperative forced expiratory volume in 1 second (FEV1) and diffusion capacity for carbon monoxide (DLCO) had to be at least 40% of predicted and/or maximal oxygen consumption greater than 10 mL/kg/min. Patients with a history of bone marrow or solid organ transplantation, autoimmune disease, idiopathic pulmonary fibrosis/pneumonitis, active hepatitis, active malignancy within 3 years of entry on study, or prior IO therapy were excluded. An Eastern Cooperative Oncology Group performance status score of 0 to 1 was required. PD-L1 testing on the primary tumor or lymph nodes was not required for study inclusion.

The study design is shown in Figure 1, A. A primary tumor core biopsy and blood samples for correlative biomarker studies were required before treatment initiation. Patients then received 2 cycles of atezolizumab at a dose of 1200 mg on days 1 and 22 followed by repeat imaging with CT

and positron emission tomography, and repeat pulmonary function tests (PFTs). Surgical resection was allowed after an 8-day washout period from cycle 2 of atezolizumab within a 20-day window (ie, 30-50 days after cycle 1, Figure 1, B). Resection could be accomplished via thoracotomy, video-assisted thoracic surgery (VATS), or robotic VATS to allow pathologic complete (R0) resection. Anatomic resection via segmentectomy, lobectomy, bilobectomy, or pneumonectomy was strongly preferred, although wedge resection of peripheral tumors less than 2 cm in size was allowed provided at least a 1-cm circumferential margin could be obtained. Hilar and mediastinal lymph node dissection was required. For right-sided resections, this involved at least lymph nodes from levels 4R, 7, 10R, and 11R based on the International Association for the Study of Lung Cancer lymph node map.³⁴ For left-sided resections, this involved at least lymph nodes from levels 5/6, 7, 10L, and 11L. Patients in whom a complete resection was not achieved were discontinued from the study. A sample of the primary tumor, draining lymph nodes, and blood samples were submitted at the time of surgery for additional post-treatment correlative biomarker studies.

Part 1 of this study ended when the last data point required for primary efficacy analysis was obtained, which was expected to occur approximately 30 days after surgery. Patients were permitted to receive standard of care adjuvant chemotherapy and/or radiation therapy. Patients whose tumors showed evidence of pathologic response or lack of radiographic progression were eligible to participate in Part 2 of the study in which adjuvant atezolizumab was administered for up to a maximum of 12 additional months. Analysis of Part 2 will be reported in another publication. After completing all treatment, patients were followed for disease-free survival (DFS) and OS.

Study Objectives and End Points

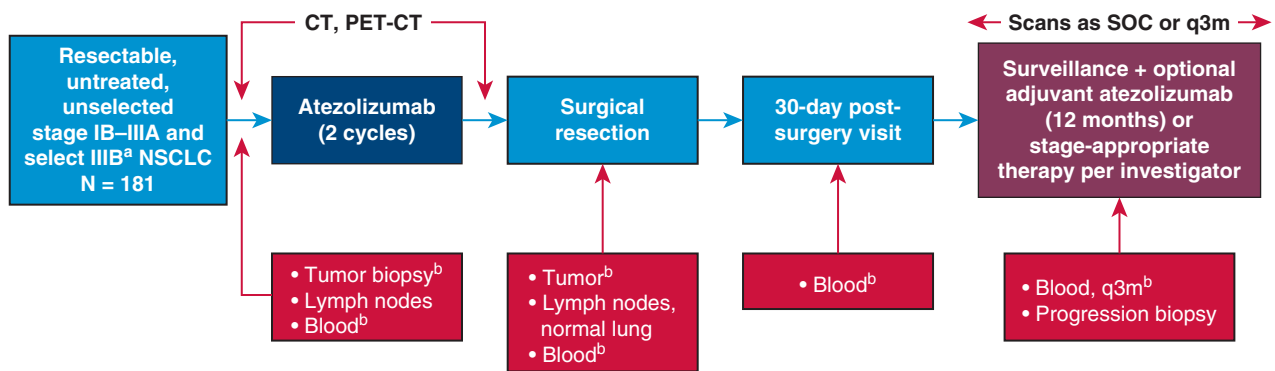
The primary objective was to evaluate the efficacy of atezolizumab as neoadjuvant treatment based on MPR, defined as 10% or less viable tumor tissue scored by the designated institutional pathologist using standardized criteria, an end point previously reported to associate with OS.³⁵ Secondary efficacy objectives included safety per National Cancer Institute Common Terminology Criteria for Adverse Events v.4.0,³⁶ radiologic response (RECIST v1.1), pathologic complete response in the primary tumor, pathologic response according to tumor PD-L1 expression, and tumor mutation burden. Exploratory efficacy objectives included DFS and OS, as well as multiple exploratory biomarker objectives designed to identify predictors of response to atezolizumab. These will be the subject of future reports.

Statistical Considerations

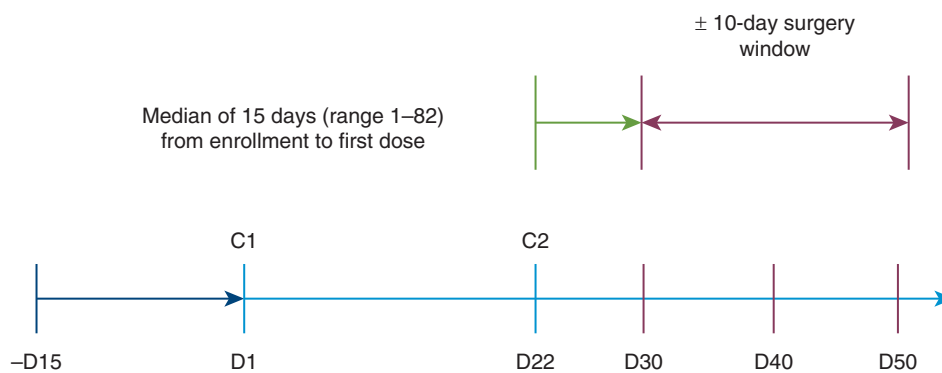
The sample size was based on the primary objective of determining the MPR rate of 15%. The primary end point was assessed by a statistical test of a single proportion of responders against the simple alternative of 5% response. The design provided a 95% statistical power to detect a difference of 10% at a significance level of 0.05 (1-sided test). To achieve this, approximately 180 patients were required for the study. If there were at least 17 patients with primary tumor demonstrating MPR, then the statistical test would reject the null hypothesis of a 5% response rate in favor of a higher response rate. Two interim analyses were performed: a safety analysis after 30 patients and a utility analysis after 90 patients were accrued. For exploratory efficacy end points, DFS and OS were calculated using the Kaplan–Meier method.

Ethical Considerations

The study was approved by the Institutional Review Board at each of the participating institutions, and all patients provided informed consent before entry on study. (Number and dates of Institutional Review Board approval: 295131 4/19/2022; 294898 1/24/2018; 294886 4/15/2022; 294889 4/1/2021; 295677 6/2/2021; 301840 5/19/2022; 294903 3/21/2022; 294899 4/15/2022; 294887 3/9/2022; 295326 4/27/2022; 295678 5/11/2021; 301242 6/1/2021; 294888 8/5/2021; 294904 8/21/2022; 294895 4/14/2022.)



A



B

FIGURE 1. Study overview. A, Design. B, Protocol mandated timing of surgery in relationship to neoadjuvant therapy. ^aT4 due to mediastinal organ invasion and N3 disease were excluded. ^bMandatory: Driver mutations were removed. *CT*, Computed tomography; *PET*, positron emission tomography; *SOC*, standard of care; *q3m*, every 3 months; *NSCLC*, non-small cell lung cancer; *C*, cycle.

RESULTS

Patient Demographics and Study Flow

From April 20, 2017, to February 3, 2020, a total of 181 eligible patients with NSCLC from 13 sites were enrolled. The final data cut for this study was October 15, 2021. Baseline patient and tumor characteristics are shown in Table 1. Approximately half of patients were female, and 81% were White. Only 18 tumors (10%) were clinical stage IB, and 147 tumors (81%) were stages IIB to select IIIB. Forty-nine of 181 patients had pretreatment staging via mediastinoscopy or endobronchial ultrasound. Most patients (n = 163, 90%) were former or current smokers. A minority of tumors showed squamous histology (n = 69, 38%). Fifty-two patients (29%) had greater than 50% of the tumor cells stain positive for PD-L1, and an additional 30 tumors (17%) showed immunostaining in the 1% to 49% range.

The patient populations at primary analysis are shown in Figure E1. All 181 patients with NSCLC received at least 1 cycle of atezolizumab with 171 completing the planned 2 cycles (safety population) and 159 (88%) proceeding to surgery. Reasons for no surgery (Figure E1) included radiographic disease progression (n = 10, 6%), physician

decision (n = 2, 3%), and other, not specified (n = 3, 2%). The sites of radiographic disease progression in 10 patients were local (lung) in 3, regional (mediastinal or supraclavicular lymph nodes) in 3, and distant (brain, pleura, bone, duodenum) in 4. Of the 159 patients who underwent surgery, 16 proved to have a tumor EGFR mutation or anaplastic lymphoma kinase (ALK) translocation and were excluded per protocol. At the time of the original study design, data on the effect of EGFR mutation/ALK alterations on IOs were only beginning to emerge, and only in the metastatic setting. The effect of PD-L1 therapy on early-stage disease in patients with EGFR mutations had not yet been studied. Subsequently, these molecular alterations were shown to associate with failure to respond to IO,³⁵ and the protocol was amended accordingly. Thus, the primary efficacy population (without EGFR or ALK alterations) for pathological response is considered to be 143 patients (79%).³⁷

Primary Outcomes

During the study, both the prespecified interim safety (at 30 patients) and futility analyses (at 90 patients) were

TABLE 1. Baseline patient and tumor characteristics

	Patients (N = 181)
Median age, y (range)	65.0 (37-83)
Female, n (%)	93 (51)
Race, n (%)	
White	145 (81)
Black/African American	13 (7)
Asian	9 (5)
Unknown	12 (7)
ECOG performance status score, n (%)	
0	104 (57)
1	77 (43)
Clinical stage, n (%)	
IB	18 (10)
IIA	16 (9)
IIB	55 (30)
IIIA	70 (39)
IIIB*	22 (12)
Histology, n (%)	
Nonsquamous	112 (62)
Squamous	69 (38)
History of tobacco use, n (%)	
Never	18 (10)
Current	35 (19)
Former	128 (71)
Median pack-y, n (range)	22.75 (0-162.0)
PD-L1 TPS at screening, n (%)†	
<1%	69 (38)
1%-49%	28 (15)
≥50%	49 (27)
Unknown‡	35 (19)
EGFR mutation, n (%)§	
Positive	11 (6)
Negative	154 (85)
Unknown	16 (9)
ALK rearrangement, n (%)	
Positive	6 (3)
Negative	162 (90)
Unknown¶	13 (7)

ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death ligand 1; TPS, tumor proportion score; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase. *Select IIIB includes T3N2 or T4 (by size criteria, not by mediastinal invasion) per the American Joint Committee on Cancer Staging System (8th edition). †PD-L1 status was centrally determined by immunohistochemistry using the DAKO PD-L1 (22C3) assay. ‡The large number of patients with “unknown” PD-L1 status was due to missing samples and failed testing. §Determined either locally or centrally from screening tissue (when adequate) or resected tumor tissue. ||EGFR status was unknown in 16 patients (nonsquamous, n = 5; squamous, n = 11). ¶ALK rearrangement status was unknown in 13 patients (nonsquamous, n = 5; squamous, n = 8).

successfully met. At completion, the study met the primary end point (Figure E2) with an MPR seen in 29 of 143 patients (20%) and pathologic complete response in 8 of 143 patients (6%) in the primary efficacy population (Figure E3). The pretreatment clinical stage (cStage) in

relationship to the post-treatment pathological stage (yp-Stage) is shown in Figure 2. The pretreatment (cN) and post-treatment (ypN) nodal status are shown in Figure E2. Recognizing the discrepancies that may occur between clinical and pathological staging, these results indicate that 66 of the 155 tumors (43%) for which both c and ypStage were available were downstaged after atezolizumab and 19% were upstaged. The lack of association between radiologic response and final pathological TNM and stage is shown in Table E1. Of the 29 patients who had an MPR, 25 had stable disease and 4 had a partial response by RECIST criteria. Additional results, including information about adjuvant therapies, subgroup analyses of factors associated with MPR, and key biomarker correlative data are presented in a previous manuscript.³⁸

Surgical Outcomes

Of the 159 patients who underwent surgery, 140 (88%) had the operation performed within the prespecified window at a median time of 22 days after cycle 2 of atezolizumab. In only 4 patients were the delays to surgery considered treatment related (Table E2).

The surgical approach and the extent and completeness of resection are shown in Figure 3. Of 159 patients, 73 (46%) underwent thoracotomy, and the remaining 86 (54%) had the operation performed via minimally invasive surgery (MIS), either VATS or robotic VATS. Fifteen of 101 patients (15%) underwent MIS that was then converted to thoracotomy. Most patients received a lobectomy (125 patients, 79%). Of these, 5 patients underwent sleeve lobectomies (4 bronchial, 1 bronchial and vascular). Only 3 patients had a wedge resection, and 5 patients had no resection due to the extent of disease. A complete resection (R0) was achieved in 145 patients (91%). Among the patients who had resection and lymph node dissection (n = 140), the median (range) number of sampled lymph node stations per patients was 6 (2-9), including a median of 3 (1-5) N1 stations and a median of 3 (1-6) N2 stations.

Pre- and postneoadjuvant treatment PFTs are shown in Table 2. The mean change in percent predicted FEV1, forced vital capacity, and DLCO were 3.0% or less. Five intraoperative complications (4 vascular injuries, 1 bronchial injury) occurred and were successfully repaired. Four of 159 patients (2.5%) had chest tube air leak reported as an AE (1 grade 1, 3 grade 3). Ten patients (6.2%) experienced postoperative atrial fibrillation (7 had grade 2, 2 had grade 3, 1 had grade 4, 0 had grade 5). Among the 14 patients receiving pneumonectomy, 14 had AEs: 3 grade 4 AEs (21.4%) and 1 grade 5 AE (7.1%). Among the overall surgery population, excluding the patients who underwent pneumonectomy (n = 145), 10 patients had grade 4 AEs (6.9%) and 4 patients had grade 5 AEs (2.8%). Because of the small number of pneumonectomies, we did not perform statistical comparisons with the rest of the patients

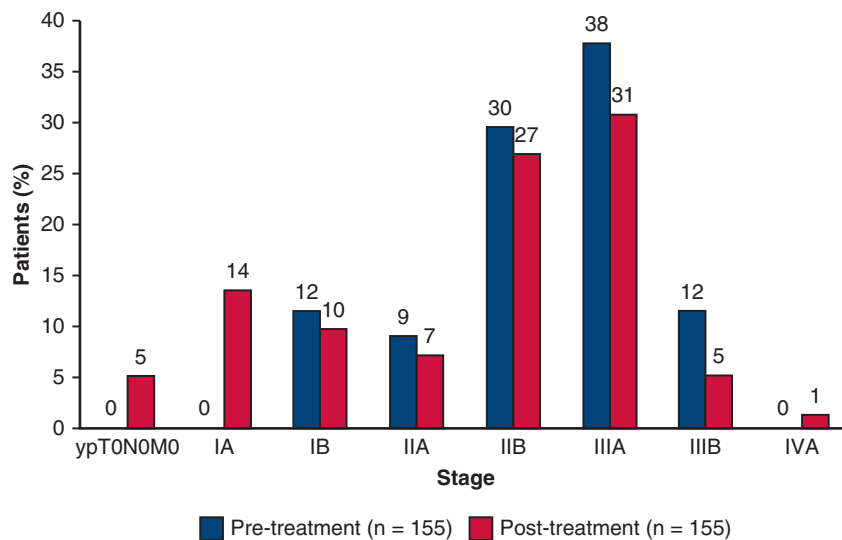


FIGURE 2. Association between pretreatment clinical stage and final pathologic stage at resection. Figure reflects patients with both clinical stage and pathologic stage per American Joint Commission on Cancer 8th edition staging system. Four patients did not have a pathologic stage evaluation.

who underwent surgery. The median length of hospitalization was 7.5 days. Within 30 days of surgery, 1 patient died of an unexplained cardiac arrest after discharge from the hospital. One patient died 2.5 months postoperatively with pneumonitis, considered treatment related.

Pre- and postoperative treatment-related and immune-related AEs are shown in Figure 4. There were no grade 4/5 treatment-related AEs preoperatively and only 4 grade 4 AEs and, as noted, 2 grade 5 AEs postoperatively. By contrast with the toxicities usually seen with neoadjuvant chemotherapy, the types of AEs reported, although generally mild, are consistent with those known to occur with IO, specifically pneumonitis, hypothyroidism, colitis, and hepatitis.

Exploratory End Points: Efficacy Outcomes

For the 145 patients who had R0 resections, DFS and OS in relationship to initial clinical disease stage and nodal status are shown in Figure E4. Median DFS and OS were not reached. Three-year DFS and OS for patients with stage I/II disease were 73% and 79%, and 68% and 78% for those with stage III disease, respectively.

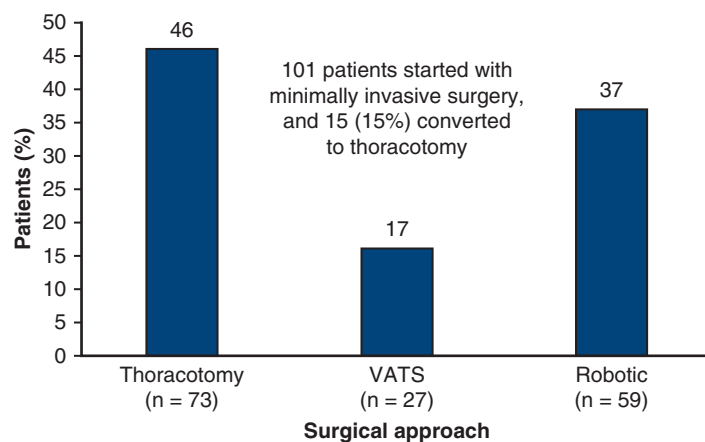
DISCUSSION

To date, Lung Cancer Mutation Consortium (LCMC) 3 is the largest multicenter Phase II trial showing the safety and efficacy of neoadjuvant monotherapy IO and surgery in patients with locally advanced NSCLC. Notably, in this group of predominantly clinical stage II to IIIB NSCLC, short-course, single-agent, low-toxicity neoadjuvant therapy was associated with an MPR rate of 20% and a complete pathologic response rate of 6% in the primary efficacy patient population. Surgery was performed within a short interval after

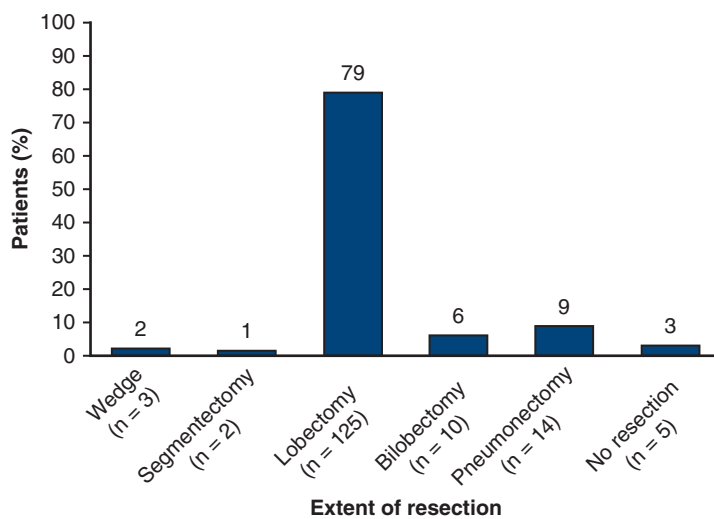
neoadjuvant therapy and was associated with low morbidity and mortality. By contrast, the established approach of longer-duration (3-4 cycles) neoadjuvant platinum-based chemotherapy is associated with at least moderate toxicity, the need for longer recovery time to surgery, and a pathologic complete response rate in the range of 5%.²⁻¹³

As reported in this article, patients who receive neoadjuvant IO may have toxicities that are different from what surgeons are familiar with from preoperative chemotherapy. The risk of pneumonitis appears to be low with the approach used in this trial. A unique feature of this study was the requirement for pre- and postneoadjuvant therapy PFTs, specifically to assess the potential impact of IO on lung function. We did not identify clinically significant differences in the key parameters percent predicted FEV1, forced vital capacity, and DLCO. Endocrinopathies including hyper- or hypothyroidism and pituitary or adrenal insufficiency, although uncommon, can occur, as can immune-related hepatitis, pancreatitis, myocarditis, or colitis. Although the frequency of these AEs is generally in the single digits, it is important for surgeons to be alert to them because they can affect perioperative care.

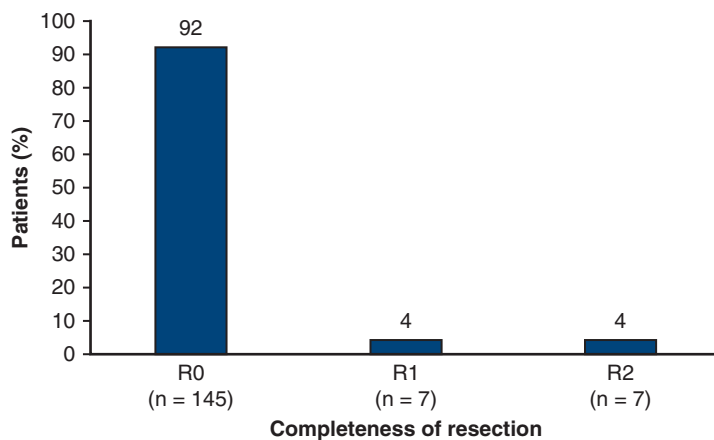
Based on the unequivocal improvement in OS observed in advanced NSCLC with combined chemoIO, 6 Phase III global clinical trials are now testing this approach in resectable NSCLC.³⁹ With several of these trials, using various IO agents in combination with chemotherapy, expected to be reported during the next few years, the results of the CheckMate 816 trial comparing induction nivolumab plus platinum-doublet chemotherapy with chemotherapy alone for resectable NSCLC were presented at the 2021 American Association for Cancer Research and American Society of Clinical Oncology meetings and were recently published,



A



B



C

FIGURE 3. Surgical overview in patients who underwent surgery (n = 159). A, Surgical approach used. B, Extent of resection. C, Completeness of resection. Five of the patients who underwent lobectomy had sleeve lobectomies (4 bronchial, 1 bronchial and vascular). VATS, Video-assisted thoracoscopic surgery.

TABLE 2. Pre- and post-atezolizumab pulmonary function tests*

PFT factor	Pre-atezolizumab (mean values)	Post-atezolizumab (mean values)	Mean change (95% CI)
FEV1 (n = 150)	85.6%	84.3%	-1.3% (-3.1% to 0.5%)
FVC (n = 152)	93.0%	92.9%	-0.1% (-1.8% to 1.7%)
DLCO (n = 126)	79.2%	76.2%	-3.0% (-4.9% to -1.2%)

Results are shown as percent predicted. *PFT*, Pulmonary function test; *CI*, confidence interval; *FEV1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *DLCO*, diffusion capacity for carbon monoxide. *Patients with paired values at screening and surgery visits.

establishing neoadjuvant chemoIO as a standard of care.^{32,33} However, the toxicities of the single-agent IO in large phase II trials are needed to assess the toxicities contributed by the IO in the chemotherapy plus IO regimens. In a patient population relatively similar to what we report, CheckMate 816 found a pathologic complete response of 2.2% and an MPR rate of 8.9% with chemotherapy alone. For patients receiving chemoIO, these were 24% and 37%, respectively. There did not appear to be significantly greater toxicity or delays to surgery with chemoIO. Indeed, the greater depth of pathological response seen with chemoIO appeared to be associated with a higher frequency of MIS to resection, fewer pneumonectomies, and similar postoperative complications and length of hospital stay. However, relative to this study, patients received longer (3 cycles over 9 weeks) duration neoadjuvant therapy with a longer delay (median of 5.3 weeks) to surgery. Surgery was performed outside of the defined protocol window in 12% of the LCMC3 study versus 21% in the CheckMate 816 trial. Although preoperative attrition was similar, serious treatment-related toxicity was expectantly higher (grade ≥3; 33.5%) in the CheckMate 816 chemoIO arm. In the context of multimodality therapy, more intense treatment is not always superior if toxicity or intolerance outweighs the benefits of higher response rates. This is particularly true in the usually older patient population with NSCLC being considered for surgical resection. Ultimately, as trial data mature and all of the correlative

analyses from the LCMC 3 trial become available, the most salient result may be improved patient selection. Just as we now recognize that NSCLC with driver mutations (eg, EGFR mutations) is most effectively treated with tyrosine kinase inhibitors rather than chemotherapy, it will be pivotal to identify the approximately 20% of patients who, based on this study, need only single-agent IO rather than more intensive preoperative regimens. Another important finding from this study is the discrepancy between radiological response and final pathological stage after neoadjuvant therapy. This has been noted in previous trials using neoadjuvant chemoradiotherapy⁴⁰ and in the early experience with resection after IO.⁴¹ Thus, radiological response cannot be used to predict final pathologic stage.

During the past 2 decades, the thoracic surgical community has gradually transitioned from thoracotomy to minimally invasive approaches, VATS, and robotic VATS for the resection of early-stage NSCLC. This paradigm shift has taken time as surgeons gradually acquired the technical skill sets that are radically different from performing a thoracotomy and gained the confidence that they could offer patients comparable oncologic outcomes. The recently published Video-Assisted Thoracoscopic Versus Open Lobectomy in Patients With Early-Stage Lung Cancer (VIOLET) study was a large randomized trial in the United Kingdom comparing VATS with thoracotomy and lobectomy for resection of early-stage NSCLC. It established the superiority of VATS in terms of postoperative pain, functional recovery, complications,

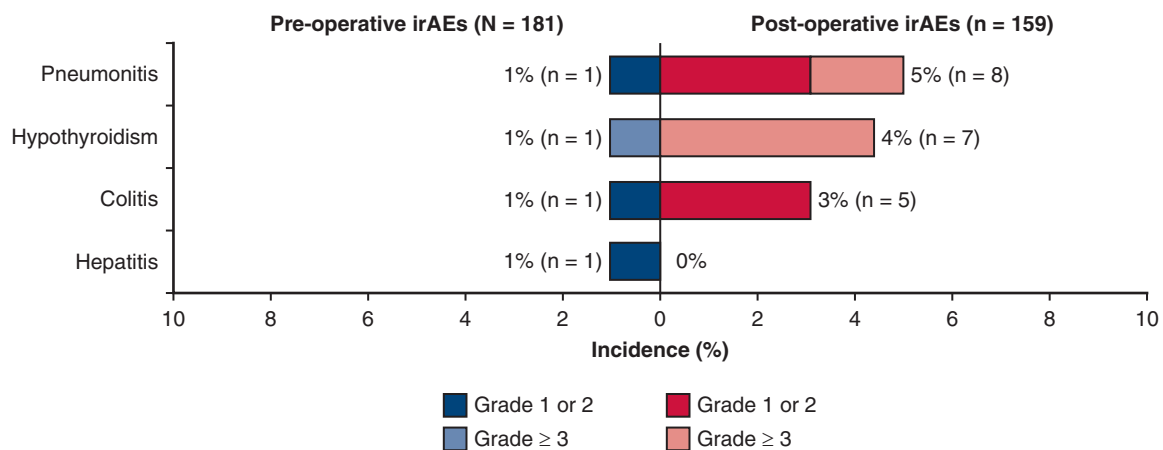
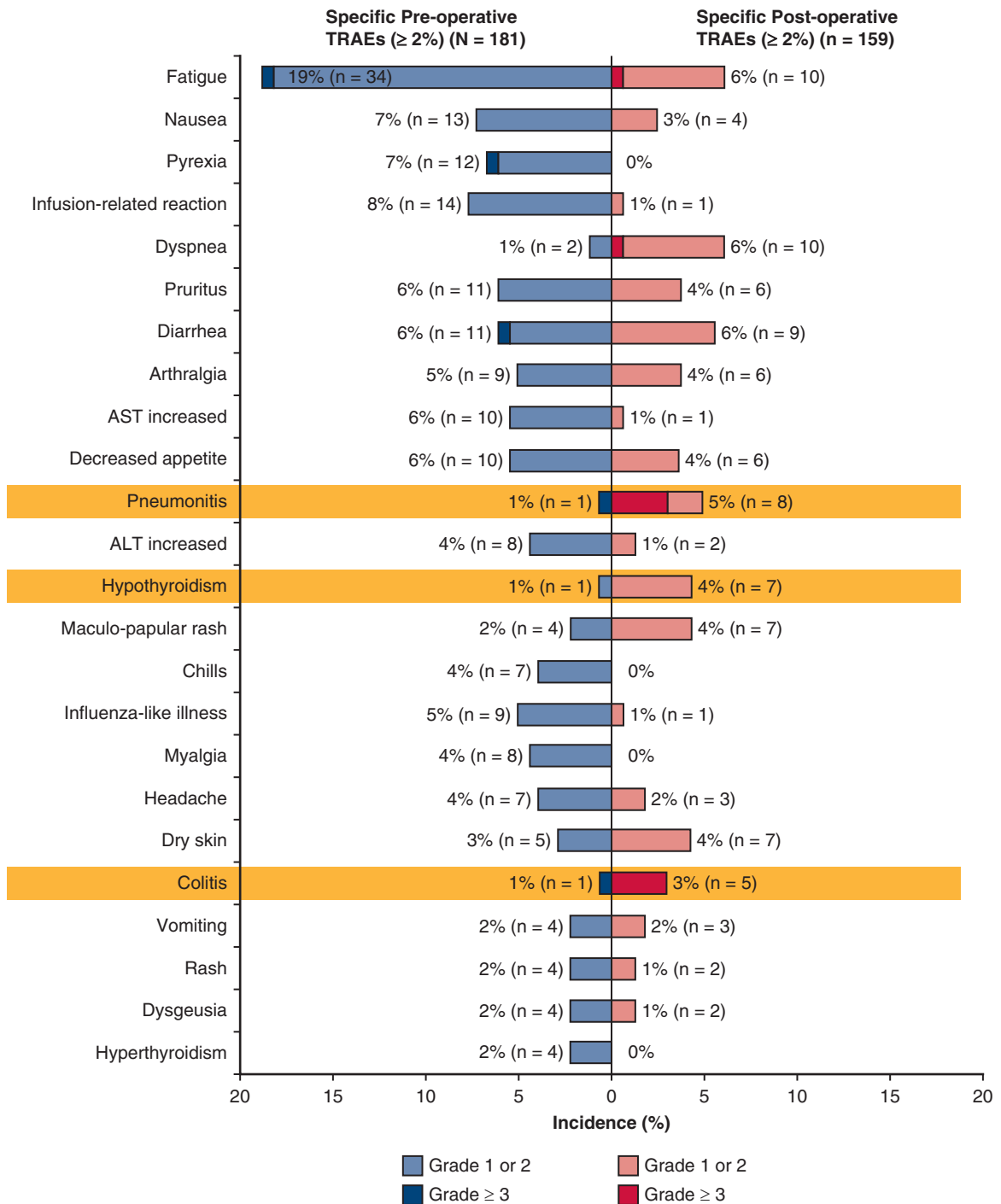


FIGURE 4. Pre- and postoperative treatment-related AEs. A, AEs considered to be immune-related are summarized. B, One patient had hypothyroidism preoperatively and postoperatively. *irAE*, Immune-related adverse event; *TRAE*, treatment-related adverse event; *AST*, aspartate aminotransferase; *ALT*, alanine aminotransferase.



B

FIGURE 4. (continued).

length of hospital stay, and economic outcomes. There were no differences in short- or long-term oncologic outcomes.⁴² A significant proportion of patients in both the LCMC3 and CheckMate 816 trials were able to have resections performed by VATS or robotic VATS. Whether the increasing use of

robotic VATS will influence the use of MIS after neoadjuvant therapy remains to be seen. As surgeons gain more experience with MIS in this context, it will be important to assess whether these techniques are associated with improved outcomes in patients with locally advanced NSCLC.

One of the sometimes technically challenging aspects of surgical resection in patients who have received neoadjuvant therapy for locally advanced NSCLC is perihilar fibrosis, particularly when this involves hilar vessels and can lead to intraoperative hemorrhage. Although a phenomenon well known to thoracic surgeons, perihilar fibrosis is not predictable and has never been quantified with respect to frequency or severity. The LCMC3 trial was not designed to assess this issue. The low frequency of intraoperative AEs suggests a lack of severity of this problem. However, future neoadjuvant trials should systematically analyze the frequency and severity of perihilar fibrosis, the presence of which can affect surgical approach, extent of lung resection, and operative morbidity and mortality. We propose that for future studies, the severity of perihilar fibrosis be systematically recorded according to a 0 to 3 grading scale, in which 0 would indicate normal hilar anatomy with no fibrosis; 3 would describe dense fibrosis with obliteration of anatomical planes; and 1 and 2 would describe intermediate findings (Table E3).

CONCLUSIONS

The outcomes in this large multicenter trial provide a strong rationale for neoadjuvant IO and surgery in the management of some patients with resectable NSCLC. Correlative biomarker studies from the LCMC3 study, still under analysis, will hopefully identify which patients may be treated with monotherapy alone and which may require more intensive preoperative regimens.

Data Availability Statement

Qualified researchers may request access to individual patient-level clinical data through Vivli (data request platform being used at the time of this writing): <https://vivli.org/ourmember/roche/>.

For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see https://go.roche.com/data_sharing.

Anonymized records for individual patients across more than 1 data source external to Roche cannot and should not be linked because of potential increase in risk of patient re-identification.

Data will be available within 2 years after last patient survival follow-up visit and indefinitely.

Conflict of Interest Statement

V.W.R. is a member of the Data Safety and Monitoring Committee for the MARS2 trial (UK), serves as Co-Chair of the National Cancer Institute Thoracic Staging Malignancy Committee, and reports institutional funding from Genentech. A.N. is an employee of Genentech and reports stock ownership with Roche. S.N.W. reports research support

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The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: immunotherapy, lung cancer, neoadjuvant therapy

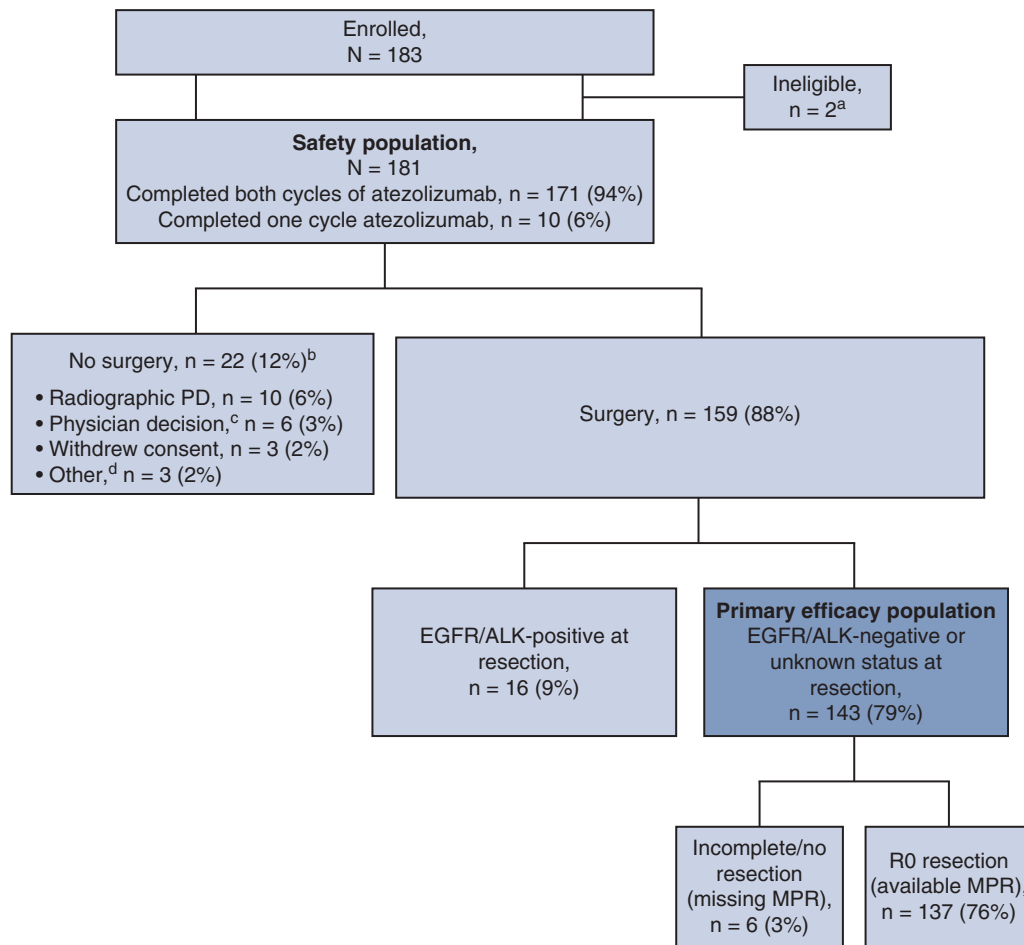


FIGURE E1. Consort diagram. Patient disposition: The primary efficacy population is in bold. ^aTwo patients were determined to have hemangioma and solitary fibrous tumor at resection despite initial pathology consistent with NSCLC. ^bIncludes 1 EGFR-positive patient. ^cThe reasons were as follows: clinical progression (n = 3); physician did not want to delay patient surgery (n = 1); physician did not consider the patient a good surgical candidate (n = 1); and physician discontinued patient from the study because of an AE (n = 1). ^dOne patient was determined to have preexisting congestive heart failure, 1 declined surgery, and 1 was lost to follow-up. *PD*, Progressive disease; *EGFR*, epidermal growth factor receptor; *ALK*, anaplastic lymphoma kinase; *MPR*, major pathological response.

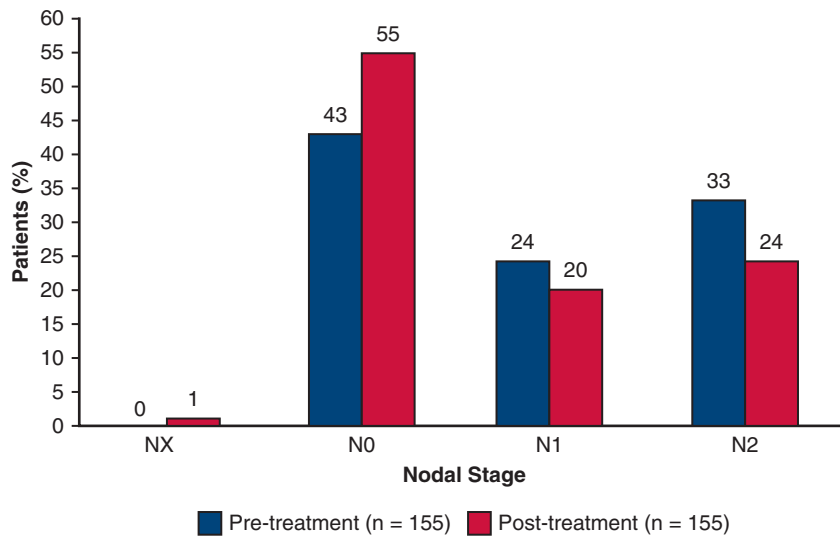
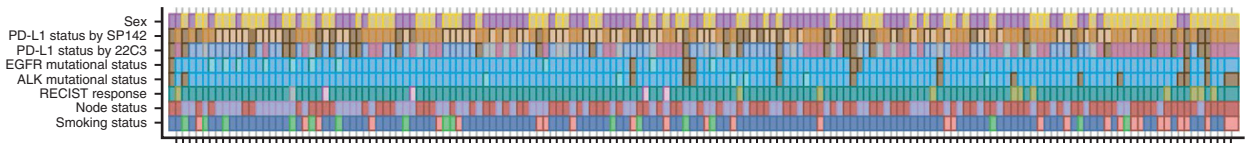


FIGURE E2. Association of pretreatment clinical nodal stage with final pathologic nodal stage after surgery.



Biomarker subgroups: Missing, PD, SD, PR, Current, Previous, Never, Negative, Positive, Yes, No, Unknown, < 1, ≥ 50, PD-L1 positive by SP142, PD-L1 negative by SP142, Male, Female

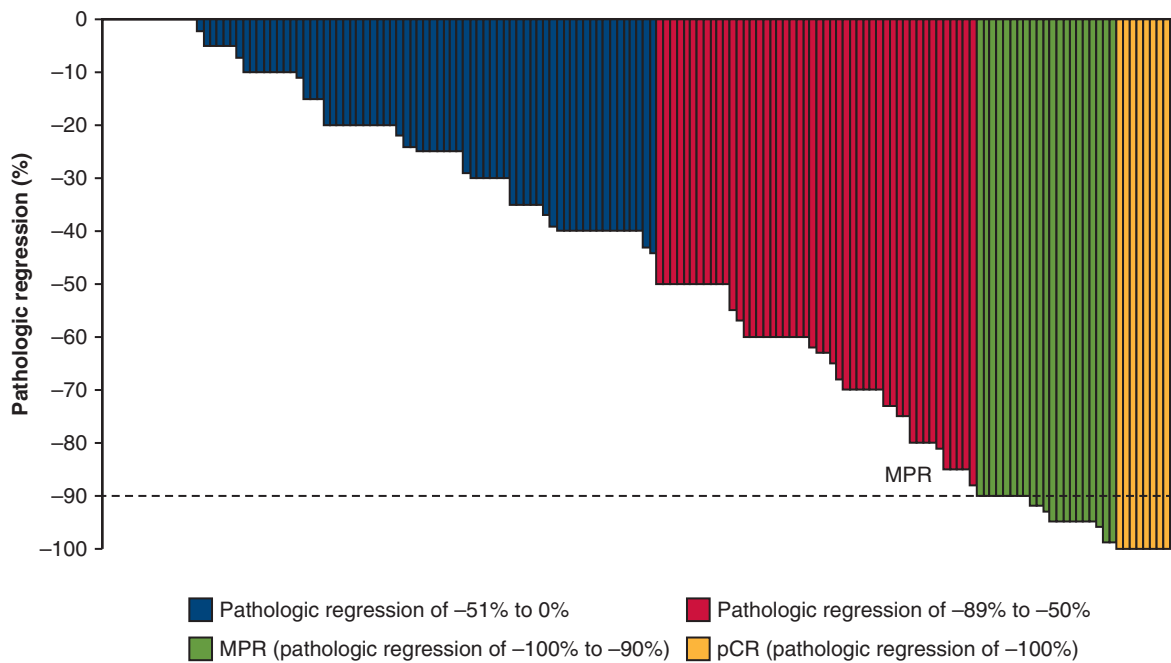


FIGURE E3. Waterfall plot of pathologic response to atezolizumab in the surgical population (n = 159). PD, Progressive disease; SD, stable disease; PR, partial response; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; RECIST, Response Evaluation Criteria In Solid Tumors; MPR, major pathologic response; pCR, pathological complete response.

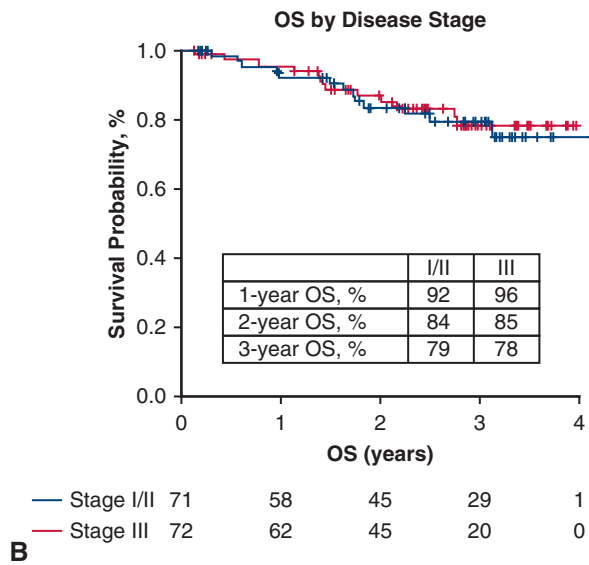
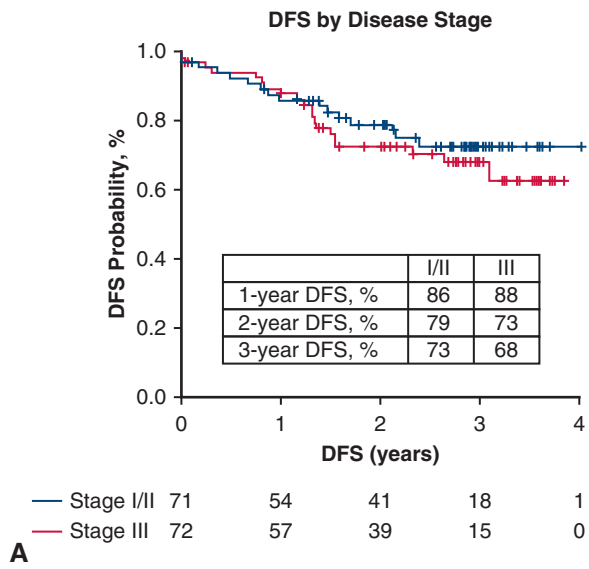


FIGURE E4. Survival by initial disease stage. A, DFS. B, OS. *DFS*, Disease-free survival; *OS*, overall survival.

TABLE E1. Presurgery radiological response by RECIST v1.1 was not associated with major pathologic response for patients undergoing surgery (N = 159)

RECIST	MPR yes (%)	MPR no	MPR missing
PR	4 (36% 4/11)	6	1
SD	25 (17% 25/143)	112	6
PD	0 (0% 0/4)	4	0
Missing	0 (0% 0/1)	1	0

RECIST, Response Evaluation Criteria In Solid Tumors; MPR, major pathologic response; PR, partial response; SD, stable disease; PD, progressive disease.

TABLE E2. Reasons for surgery being performed outside of protocol window

Surgery window	N = 159
Within \pm 10 d protocol window, n (%)	140 (88)
Outside \pm 10 d window, n (%)	19 (12)
Treatment related, n	4
Other medical reasons, n	6
Patient or surgeon logistical reason, n	9
Median time outside window, d (range)	8 (1-45)
Median time from end of cycle 2 (d 22) to surgery* (range)	22 (11-74)

*n = 152.

TABLE E3. Proposed scoring system to describe severity of fibrosis in the hilum or mediastinum after neoadjuvant therapy

Score	Descriptions
0	Normal hilar and mediastinal tissue planes; no fibrosis
1	Mild hilar (1a) or mediastinal (1b) fibrosis not complicating dissection
2	Moderate hilar (2a) or mediastinal (2b) fibrosis creating technically challenging dissection
3	Severe hilar (3a) or mediastinal (3b) fibrosis with obliteration of anatomical planes, precluding resection.