0003-4975
 https://doi.org/10.1016/j.athoracsur.2024.09.041

EXPERT CONSENSUS DOCUMENT

The Society of Thoracic Surgeons Expert Consensus on the Multidisciplinary Management and Resectability of Locally Advanced Non-small Cell Lung Cancer

Samuel S. Kim, MD,[1] David T. Cooke, MD,[2] Biniam Kidane, MD, MSC,[3] Luis F. Tapias, MD,[4] John F. Lazar, MD,[5] Jeremiah W. Awori Hayanga, MD,[6] Jyoti D. Patel, MD,[7] Joel W. Neal, MD, PhD,[8] Mohamed E. Abazeed, MD, PhD,[9] Henning Willers, MD,[10] and Joseph B. Shrager, MD[11,12]

ABSTRACT

BACKGROUND The contemporary management and resectability of locally advanced lung cancer are undergoing significant changes as new data emerge regarding immunotherapy and targeted treatments. The objective of this document is to review the literature and present consensus among a group of multidisciplinary experts to guide the determination of resectability and management of locally advanced non-small cell lung cancer (NSCLC) in the context of contemporary evidence.

METHODS The Society of Thoracic Surgeon Workforce on Thoracic Surgery assembled a multidisciplinary expert panel composed of thoracic surgeons and medical and radiation oncologists with established expertise in the management of lung cancer. A focused literature review was performed, and expert consensus statements were developed using a modified Delphi process to address 3 major themes: (1) assessing resectability and multidisciplinary management of locally advanced lung cancer, (2) neoadjuvant (including perioperative) therapy, and (3) adjuvant therapy.

RESULTS A consensus was reached on 19 recommendations. These consensus statements reflect updated insights on resectability and multidisciplinary management of locally advanced lung cancer based on the latest literature and current clinical experience, mainly focusing on the appropriateness of surgical therapy and emerging data regarding neoadjuvant and adjuvant therapies.

CONCLUSIONS Despite the complex decision-making process in managing locally advanced lung cancer, this expert panel agreed on several key recommendations. This document provides guidance for thoracic surgeons and other medical professionals in the optimal management of locally advanced lung cancer based on the most updated evidence and literature.

(Ann Thorac Surg 2025;119:16-33)

Accepted for publication Sep 26, 2024.

The Society of Thoracic Surgeons Executive Committee approved this document.

[1]Canning Thoracic Institute, Northwestern Memorial Hospital, Northwestern University Feinberg School of Medicine, Chicago, Illinois; [2]Division of General Thoracic Surgery, University of California Davis Health, Sacramento, California; [3]Section of Thoracic Surgery, CancerCare Manitoba and University of Manitoba, Winnipeg, Manitoba, Canada; [4]Division of Thoracic Surgery, Mayo Clinic, Rochester, Minnesota; [5]Division of Thoracic Surgery, Ascension Saint Thomas Hospital, University of Tennessee Health Science Center, Nashville, Tennessee; [6]Department of Cardiothoracic and Vascular Surgery, West Virginia University Medicine, Morgantown, West Virginia; [7]Division of Hematology/Oncology, Department of Medicine, Northwestern University, Chicago, Illinois; [8]Division of Oncology, Department of Medicine, Stanford Cancer Institute, Stanford, California; [9]Department of Radiation Oncology, Northwestern University, Feinberg School of Medicine, Chicago, Illinois; [10]Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; [11]Division of Thoracic Surgery, Department of Cardiothoracic Surgery, Stanford University School of Medicine, Stanford, California; and [12]Department of Surgery, Veterans Affairs Palo Altos Health Care System, Stanford, California

Address correspondence to Dr Kim, Northwestern Medicine Canning Thoracic Institute, 675 N St Clair St, Suite 2140, Arkes Pavilion, Chicago, IL 60611; email: samuel.kim2@nm.org.

Abbreviations and Acronyms

ALK = anaplastic lymphoma kinase
CT = computed tomography
DFS = disease-free survival
EFS = event-free survival
EGFR = epidermal growth factor receptor
ERBB2 = erythroblastic oncogene B
INT = Intergroup Trial
HER2 = human epidermal growth factor receptor 2
MDT board = multidisciplinary tumor board
MPR = major pathologic response
NSCLC = non-small cell lung cancer
NTRK = neurotrophic tyrosine receptor kinase
OS = overall survival
pCR = pathologic complete response
PD-L1 = program death-ligand 1
PFS = progression-free survival
PICO = P, population, patients, or problem; I, intervention; C, comparison; O, outcome
PORT = postoperative radiotherapy
ROS1 = ROS proto-oncogene 1, receptor tyrosine kinase
RET = rearranged during transfection
STS = The Society of Thoracic Surgeons
TKI = tyrosine kinase inhibitor

EXECUTIVE SUMMARY

The Society of Thoracic Surgeons Workforce on Thoracic Surgery assembled a multidisciplinary expert panel to provide this professional society's perspective on determining resectability and managing locally advanced non-small cell lung cancer (NSCLC) in the context of contemporary evidence. This document was created by generating appropriate questions according to the PICO format (P, population, patients, or problem; I, intervention; C, comparison; O, outcome) to address 3 major themes: (1) assessing resectability and multidisciplinary management of locally advanced lung cancer, (2) neoadjuvant (including perioperative) therapy, and (3) adjuvant therapy. Literature evidence was gathered from search engines, and once appropriate statements were generated, a consensus on statements was reached using a modified Delphi method.

Despite the complex decision-making process in managing locally advanced lung cancer, this expert panel agreed on several key recommendations. A multidisciplinary tumor (MDT) board should discuss the patients with locally advanced NSCLC to determine optimal treatment options, and until more data emerge in the future, the surgical resectability should be decided up-front at the time of presentation. In medically operable patients with locally advanced lung cancer without driver mutation (clinical stage II to III), our panel recommends neoadjuvant platinum-based chemotherapy with immunotherapy (neoadjuvant or perioperative) before surgical resection over adjuvant therapy, and the surgical resection should proceed as long as there is no progression of disease after induction treatment. In NSCLC patients with driver mutations, the addition of neoadjuvant immunotherapy to chemotherapy has minimal to no additional efficacy; therefore, patients can be treated with neoadjuvant chemotherapy or chemotherapy with radiotherapy, followed by surgical resection and, when approved, adjuvant-targeted therapy. Alternatively, when appropriate, surgery followed by adjuvant targeted therapy (with or without chemotherapy) is an alternative treatment paradigm. The investigation of neoadjuvant-targeted therapies is in its early stages, and patients with stage II or III NSCLC (majority adenocarcinoma histology) with driver mutations should be considered for induction treatment only in the context of clinical trials until more data emerge.

Patients with multistation N2 disease are generally not considered candidates for surgical resection, especially in bulky nodal disease, because they experience poor long-term outcomes. However, surgical resection can be considered in select cases with nonbulky, 2 to 3 involved N2 stations, particularly if lobectomy is considered likely. Patients with clinical T4 NSCLC (including Pancoast tumor) represent a heterogeneous group. The surgeon must consider the institution's experience and expertise in determining resectability, because achieving complete resection and postoperative management can be challenging. The surgical resection can be considered after induction therapy after MDT board discussion at highly experienced centers.

Offering adjuvant immunotherapy after surgical resection for locally advanced lung cancer may be reasonable based on reported perioperative immunotherapy trials, especially in patients with persistent nodal disease after neoadjuvant treatment, although data are unclear on those with pathologic complete response. For epidermal growth factor receptor mutant NSCLC, adjuvant osimertinib should be offered for 3 years (ideally without prior immunotherapy exposure in the neoadjuvant setting). Postoperative radiotherapy is not routinely indicated unless the surgical pathology indicates an R1/R2 resection.

INTRODUCTION

Lung cancer remains the leading cause of cancer mortality worldwide, with a 5-year survival of

only 18% across all stages.[1] For patients with early-stage (stage IA/B) non-small cell lung cancer (NSCLC) and select patients with locally advanced (stage II-IIIA/B) NSCLC, surgery remains a mainstay of treatment.[2] With advancements in systemic medical therapy, radiotherapy, and operative techniques, the role of surgical intervention is rapidly evolving. Increasingly, the optimal management of the patient with locally advanced lung cancer, which includes both surgical and nonsurgical therapies, is predicated on an appropriate assessment of "resectability." Therefore, carefully defining resectability takes on the utmost importance.

Obtaining a consensus on what is both possible and appropriate to resect has been challenging due to inconsistent terminology and the lack of standardization of surgical assessment. For example, the terms *resectability* and *operability* are often used interchangeably and imprecisely in describing surgical candidacy. Operability is traditionally used to reflect the patient's state of health to tolerate a surgical procedure. On the other hand, resectability typically refers to the anatomic feasibility of achieving microscopically negative margins or an R0 resection.[3] Conventional resectability criteria focus solely on the anatomical tumor extent, but biological factors relevant to prognosis and effectiveness of alternative treatments are increasingly important as personalized treatments using various tumor markers are rapidly integrated into routine clinical practice.[4] As a result, we propose to redefine the term *resectability* to include not only the technical ability to achieve R0 resection but also many biological factors relevant to prognosis, the short-term and long-term risks of the operation, and the effectiveness of alternative treatments that do not include surgery—in other words, the *appropriateness* of surgical therapy as part of the patient's overall treatment.

This document aims to present a consensus among expert members of The Society of Thoracic Surgeons (STS), with input from experts in allied disciplines, to guide the determination of the resectability of locally advanced NSCLC in the context of contemporary evidence.

METHODS

ASSEMBLY OF A WRITING GROUP OF EXPERTS. The STS Workforce on General Thoracic Surgery assembled a national multidisciplinary writing group consisting of 6 thoracic surgeons, 2 medical oncologists, and 2 radiation oncologists with expertise in lung cancer treatment and evidence-based medicine. A task force chair was appointed (S.K.). All members completed the conflict of interest disclosures before embarking on committee work. The STS Quality and Research Council Operating Board reviewed and provided feedback on the expert consensus document and recommendations.

FORMULATION OF OBJECTIVES AND CLINICAL QUESTIONS. Several meetings were held to discuss and develop themes, concepts, and organizational frameworks. This resulted in the creation of subgroups to address 3 major themes: (1) assessing resectability and multidisciplinary management of locally advanced lung cancer, (2) neoadjuvant (including perioperative) therapy, and (3) adjuvant therapy. The subgroups met several times to formulate questions according to the PICO format (P, population, patients, or problem; I, intervention; C, comparison; O, outcome). These questions were reviewed by the entire group and were refined to produce a finalized list of focused clinical questions. These questions were returned to the subgroups for literature review and evidence synthesis.

LITERATURE REVIEW AND EVIDENCE SYNTHESIS. Literature searches were performed using PubMed and Google search engines for each PICO question from 2002 to the present, limiting studies to the English language. Searches were conducted on a continuous updating basis between July 1, 2023, and February 1, 2024. The task force chair screened the titles and abstracts of the search results for relevance, and 154 papers relevant to the PICO questions were identified. Additional papers were added to the body of literature by the group members. The members of each subgroup reviewed these articles in full text and extracted and synthesized data to formulate a series of evidence-based recommendations. Table 1 summarizes some of the major trials referenced in the recommendations.[5-20] Each statement was critically examined and revised by the entire group.

DEVELOPMENT OF EXPERT CONSENSUS. The entire expert consensus panel was then asked to evaluate each statement on a 5-point Likert scale. Using the modified Delphi method,[21] 100% participation was required to achieve an 80% consensus rate ("agree" or "strongly agree"). A second or third round of voting after proper revision was used if the threshold was not achieved. Once the consensus statements were accepted, each expert member from the subgroups contributed substantially to writing sections. The document was then reviewed

TABLE 1 A Summary of Major Trials Referenced in the Consensus Statements

Trial Name	Author/Year	Intervention Timing	Treatment Type	Study Design	Result
CheckMate-816	Forde et al,[5] 2022	Neoadjuvant	Immunotherapy/ immune CPI	Phase III trial: Induction nivolumab + chemotherapy vs chemotherapy alone followed by surgical resection	The neoadjuvant group had longer EFS and MPR.
KEYNOTE-671	Wakelee et al,[6] 2023	Perioperative	Immunotherapy/ immune CPI	Phase III trial: Induction pembrolizumab + chemotherapy followed by adjuvant pembrolizumab vs induction chemotherapy followed placebo after surgical resection	The perioperative pembrolizumab improved EFS, MPR compared with neoadjuvant chemotherapy group.
IMpower010	Felip et al,[7] 2021	Adjuvant	Immunotherapy/ immune CPI	Phase III trial: Adjuvant chemotherapy followed by atezolizumab vs adjuvant chemotherapy after surgical resection	The adjuvant atezolizumab group had improved DFS compared with adjuvant chemotherapy-only group.
PEARLS/ KEYNOTE-091	O'Brien et al,[8] 2022	Adjuvant	Immunotherapy/ immune CPI	Phase III trial: Adjuvant chemotherapy followed by pembrolizumab vs adjuvant chemotherapy after surgical resection	The adjuvant pembrolizumab group had improved DFS compared with adjuvant chemotherapy-only group, regardless of PD-1 expression.
ADAURA	Wu et al,[9] 2020	Adjuvant	Targeted therapy/ *EGFR* TKI	Phase III trial: *EGFR*+ NSCLC received adjuvant osimertinib vs placebo after surgical resection	The adjuvant osimertinib group had improved DFS compared with placebo group.
ALINA	Solomon et al,[10] 2023	Adjuvant	Targeted therapy/ *ALK* TKI	Phase III trial: *ALK*+ NSCLC received adjuvant alectinib vs chemotherapy after surgical resection	The adjuvant alectinib group had improved DFS compared with placebo group.
NADIM II	Provencio et al,[11] 2023	Perioperative	Immunotherapy/ immune CPI	Phase II trial: Induction nivolumab + chemotherapy followed by adjuvant nivolumab	The perioperative nivolumab + chemotherapy had improved OS and pCR than chemotherapy alone in patients with resectable stage IIIA NSCLC.
CheckMate-77T	Cascone et al,[12] 2023	Perioperative	Immunotherapy/ immune CPI	Phase III trial: Induction nivolumab + chemotherapy followed by adjuvant nivolumab vs induction chemotherapy followed placebo after surgical resection	The perioperative nivolumab group had improved EFS compared with neoadjuvant chemotherapy group.
AEGEAN	Heymach et al,[13] 2023	Perioperative	Immunotherapy/ immune CPI	Phase III trial: Induction durvalumab + chemotherapy followed by adjuvant durvalumab vs induction chemotherapy followed placebo after surgical resection	The perioperative durvalumab group had improved EFS and pCR compared with neoadjuvant chemotherapy group.
NeoADURA	Tsuboi et al,[14] 2021	Neoadjuvant	Targeted therapy/ *EGFR* TKI	Phase III trial: *EGFR*+ NSCLC received induction osimertinib +/− chemotherapy vs chemotherapy alone followed by surgical resection	On-going study
NEOS	Lv et al,[15] 2023	Neoadjuvant	Targeted therapy/ *EGFR* TKI	Phase II trial: *EGFR*+ NSCLC received induction osimertinib followed by surgical resection	Neoadjuvant osimertinib is safe and effective in patients with *EGFR*+ NSCLC.
ALNEO	Leonetti et al,[16] 2021	Neoadjuvant	Targeted therapy/ *ALK* TKI	Phase II trial: Feasibility neoadjuvant alectinib for *ALK*+ NSCLC	On-going study

(*Continued*)

TABLE 1 Continued

Trial Name	Author/Year	Intervention Timing	Treatment Type	Study Design	Result
INT 0139	Albain et al,[17] 2009	Neoadjuvant	Chemoradiotherapy	Phase III trial: Chemoradiotherapy with or without surgical resection for stage IIIA NSCLC	No difference in OS between 2 groups; in subgroup analysis, the patients who underwent lobectomy had improved OS compared with matched cohort with chemoradiotherapy.
INT 0160	Rusch et al,[18] 2007	Neoadjuvant	Chemoradiotherapy	Phase II trial: Induction concurrent chemoradiotherapy treatment followed by surgical resection for superior sulcus tumor	The induction chemoradiotherapy is feasible and is associated with high complete resection and pCR.
LUNGART	Pechoux et al,[19] 2022	Adjuvant	Radiotherapy	Phase III trial: 3D conformal PORT vs no PORT in stage IIIA–N2 NSCLC	PORT was not associated with an improved DFS compared with no PORT.
PORT-C	Hui et al,[20] 2021	Adjuvant	Radiotherapy	Phase III trial: PORT vs no PORT in resected stage III A–N2 NSCLC + adjuvant chemotherapy	The PORT did not improve OS or DFS.

ADAURA, AZD9291 Versus Placebo in Patients With Stage IB–IIIA Non-small Cell Lung Carcinoma, Following Complete Tumour Resection With or Without Adjuvant Chemotherapy; AEGEAN, A Study of Neoadjuvant/Adjuvant Durvalumab for the Treatment of Patients With Resectable Non-small Cell Lung Cancer; ALINA, A Study Comparing Adjuvant Alectinib Versus Adjuvant Platinum-Based Chemotherapy in Patients With ALK Positive Non-Small Cell Lung Cancer; *ALK*, anaplastic lymphoma kinase; ALNEO, Phase II, open-label, single-arm, multicenter study to assess the activity and safety of ALectinib as NEO-adjuvant therapy in patients with anaplastic lymphoma kinase-positive (ALK+) locally advanced stage III ALK-positive NSCLC patients; CheckMate-77T, A Study of Neoadjuvant Chemotherapy Plus Nivolumab Versus Neoadjuvant Chemotherapy Plus Placebo, Followed by Surgical Removal and Adjuvant Treatment With Nivolumab or Placebo for Participants With Surgically Removable Early Stage Non-small Cell Lung Cancer; CheckMate-816, A Neoadjuvant Study of Nivolumab Plus Ipilimumab or Nivolumab Plus Chemotherapy Versus Chemotherapy Alone in Early Stage Non-Small Cell Lung Cancer (NSCLC); CPI, check point inhibitor; DFS, disease-free survival; EFS, event-free survival; EGFR, epidermal growth factor receptor; IMpower010, Study to Assess Safety and Efficacy of Atezolizumab (MPDL3280A) Compared to Best Supportive Care Following Chemotherapy in Patients With Lung Cancer; INT 0139, Chemotherapy Plus Radiation Therapy With or Without Surgery in Treating Patients With Stage IIIA Non-small Cell Lung Cancer; INT 0160, Southwest Oncology Group Trial 9416; KEYNOTE-671, Efficacy and Safety of Pembrolizumab (MK-3475) With Platinum Doublet Chemotherapy as Neoadjuvant/Adjuvant Therapy for Participants With Resectable Stage II, IIIA, and Resectable IIIB (T3-4N2) Non-small Cell Lung Cancer; LUNGART, Radiation Therapy in Treating Patients With Non Small Cell Lung Cancer That Has Been Completely Removed by Surgery; MPR, and major pathologic response; NADIM II, NADIM II: Neo-Adjuvant Immunotherapy; NeoADAURA, A Study of Osimertinib With or Without Chemotherapy Versus Chemotherapy Alone as Neoadjuvant Therapy for Patients With EGFRm Positive Resectable Non-Small Cell Lung Cancer; NEOS, Trial of Neoadjuvant Therapy With Paclitaxel and Carboplatin in Operable Locally Advanced Head and Neck Cancer Patients; NSCLC, non-small cell lung cancer; OS, overall survival; pCR, pathologic complete response; PD-1, programmed cell death protein 1; PEARLS/KEYNOTE-091, Study of Pembrolizumab (MK-3475) vs Placebo for Participants With Non-small Cell Lung Cancer After Resection With or Without Standard Adjuvant Therapy; PORT, postoperative radiotherapy; PORT-C, Postoperative Radiotherapy for Patients With IIIA (N2) Non-small Cell Lung Cancer; TKI, tyrosine kinase inhibitor; 3D, 3-dimensional.

again by the group, finalized, and sent to the STS Workforce on Evidence-Based Surgery for final approval.

RESULTS

SECTION 1: ASSESSING SURGICAL RESECTABILITY AND MANAGEMENT OF LOCALLY ADVANCED LUNG CANCER.

A. The role of the multidisciplinary tumor board.

- Patients with locally advanced NSCLC (clinical stage IIA-III) should be discussed by a multidisciplinary tumor (MDT) board, including but not limited to board-certified thoracic surgeons experienced in lung cancer surgery and thoracic-focused medical and radiation oncologists to discuss optimal treatment options, including a determination of feasibility and appropriateness of resection, potential induction therapies, and alternative treatment options.
- Surgical resectability should be decided upfront. Until more data emerge, patients who are deemed unresectable at the outset should not be given neoadjuvant therapy in an attempt to convert unresectable to resectable disease.

In the current landscape of lung cancer treatment, the integration of MDT board discussions, particularly for patients with locally advanced NSCLC (clinical stage IIA-III), is pivotal. The complexity of treatment options, bolstered by the United States Food and Drug Administration's approval of neoadjuvant (CheckMate-816: A Neoadjuvant Study of Nivolumab Plus Ipilimumab or Nivolumab Plus Chemotherapy Versus Chemotherapy Alone in Early Stage Non-Small Cell Lung Cancer),[5] perioperative (KEYNOTE-671: Efficacy and Safety of Pembrolizumab With Platinum Doublet Chemotherapy as Neoadjuvant/Adjuvant Therapy for Participants With Resectable Stage II, IIIA, and Resectable IIIB [T3-4N2] Non-small Cell Lung Cancer),[6] adjuvant immunotherapy (IMpower010: Study to Assess Safety and Efficacy of Atezolizumab Compared to Best Supportive Care Following Chemotherapy in Patients With Lung Cancer, and KEYNOTE-091: Study of Pembrolizumab vs Placebo for Participants With Non-small Cell Lung Cancer After Resection With or Without Standard Adjuvant Therapy),[7,8] and targeted adjuvant therapy (ADAURA: AZD9291 Versus Placebo in Patient with Stage IB-IIIA Non-small Cell Lung Carcinoma, Following Complete Tumour Resection With or Without Adjuvant Chemotherapy, and ALINA: A Study Comparing Adjuvant Alectinib Versus Adjuvant Platinum-Based Chemotherapy in Patients With ALK Positive Non-Small Cell Lung Cancer)[9,10] regimens, necessitates collaborative decision-making.

Lung cancer treatment guideline adherence is high for patients presented in an MDT board, with >90% adherence to the standard of care and guideline-concordant algorithms,[22] whereas nonconcordant care is very common outside of this setting.[23] The decision regarding resectability is discussed in the MDT board, but the final decision on resectability is the responsibility of the thoracic surgeon(s). The treatment algorithm should be an intention-to-treat approach.

Patients who are deemed initially with unresectable disease should not be treated with neoadjuvant therapy in an attempt to render it resectable. This will only serve to delay or compromise definitive nonsurgical therapy. Early investigations are underway to provide more insight into the question of whether conversion to resectability is feasible for those with borderline status based on the tumor's pretreatment status.[24] However, this approach remains exploratory and should only be attempted in the context of a clinical trial.

The advent of telehealth and virtual and hybrid (combined in-person and virtual) MDT boards offers opportunities for improving access to multidisciplinary care, particularly in the postpandemic era. These platforms facilitate broader participation and ensure continuity in the evaluation and management of complex patients, democratizing access to expert, evidenced-based opinions and therapeutic clinical trials. This shift toward hybrid or completely virtual MDT board meetings not only addresses logistical barriers but also supports equitable patient care by extending specialized consultation to remote and underserved regions.[25,26]

B. Multidisciplinary management of clinical T2b/T3 N0 NSCLC.

- In medically operable patients with 4- to 7-cm NSCLC without clinical nodal metastasis and without a driver mutation, neoadjuvant platinum-based chemotherapy with immunotherapy before surgical resection is preferred over adjuvant therapy, particularly in tumors with elevated program death-ligand 1 (PD-L1) expression; the data are less clear in

4- to 5-cm tumors whether neoadjuvant chemoimmunotherapy is superior to adjuvant therapy.

The 5-year survival rate for patients with resected NSCLC >4 cm and pathologic N0 is only 59%.[27] Systemic therapy is traditionally recommended because it has been shown to improve overall survival (OS).[23] The recommendation for systemic treatment is even more compelling based on the impressive survival benefits of adding immunotherapy to traditional chemotherapy regimens in recent studies. However, consensus is still lacking about whether systemic treatment should be given before or after surgical intervention, because no studies to date have directly compared neoadjuvant and adjuvant chemoimmunotherapy. The decisions regarding which approach to take must therefore be informed by the interpretation of the available evidence and the potential advantages/disadvantages of each approach at the point of care.

Updated data from CheckMate-816 and a recently published meta-analysis demonstrate that event-free survival (EFS) and OS are improved, respectively,[28,29] with neoadjuvant chemoimmunotherapy compared with neoadjuvant platinum-based chemotherapy alone in stage II to IIIA patients with PDL-1 >1%; however, the major driver of this effect is likely the stage IIIA patients. Thus, this provides a rationale for offering neoadjuvant chemoimmunotherapy. In addition, published data have shown patients with clinically node-negative 5-cm to 7-cm NSCLC treated with neoadjuvant chemoimmunotherapy compared with neoadjuvant platinum-based chemotherapy have higher tumor pathologic complete response (pCR) and major pathologic response (MPR) rates,[5] which may translate into long-term OS benefits. The nature of the smaller T2B N0/T3 N0 patient subgroups and the appearance of the survival curves suggest that a longer time horizon is required to determine whether the neoadjuvant approach is advantageous in these patients.

When considering the evidence in support of adjuvant chemoimmunotherapy, it is important to consider that the 2 existing major trials do not represent chemoimmunotherapy but rather sequential therapy with 1 to 4 cycles of platinum-based chemotherapy, followed by 1 year of immunotherapy as monotherapy. The IMPOWER-010 and PEARLS/KEYNOTE-091 trials both required completion of at least 1 cycle of platinum-based chemotherapy before patients were randomized to immunotherapy or placebo.[7,8] It is unclear whether outcomes from these studies can be compared with neoadjuvant trials where all eligible patients were randomized and then underwent concurrent chemoimmunotherapy. The adjuvant trials have a potential selection bias that automatically favors the appearance of superior outcomes of adjuvant immunotherapy. Thus, it seems more likely than not that the neoadjuvant approaches are optimal based on observing similar outcomes between the 2 approaches while being exposed to less selection bias.

From a logistical perspective, a neoadjuvant approach allows for a higher receipt of therapy. In IMPOWER-010 and PEARLS/KEYNOTE-091, the adjuvant therapy trials, only 65% and 52% of patients completed therapy, respectively, compared with 94% and 100% of patients in the CheckMate-816 and NADIM (Neo-Adjuvant Immunotherapy With Nivolumab for Non Small Cell Lung Cancer Patients) trials.[5,7,8,30] This finding has been replicated in comparisons of neoadjuvant vs adjuvant therapy both in lung cancer and other cancer sites (eg, esophageal cancer).[31] Some of this effect is likely related to the fitness of patients to tolerate systemic therapies after surgery or patients' preference or higher tolerance for a shorter course of neoadjuvant therapy (3-4 months) compared with a 1-year-long immunotherapy regimen after several months of cytotoxic chemotherapy.

On the other hand, a major criticism against the neoadjuvant approach for these patients with early-stage disease is that it may prevent them from getting the most important component of their curative therapy, which is surgery. In the published neoadjuvant/perioperative chemoimmunotherapy trials, up to 20% of patients do not reach planned surgery due to adverse events; however, most of these patients are not those in the T2b/T3 N0 group.[5,6]

Finally, neoadjuvant therapy has theoretical benefits related to the antigen-priming effects of receiving immunotherapy while the tumor is in situ.[32] Although preclinical and mechanistic studies speculate potential benefits, no randomized or controlled trials demonstrate that this translates to clinically meaningful improvements in survival.

C. Multidisciplinary management of clinical T1–3 N1 NSCLC.

- In medically operable patients with clinically involved single or multiple N1 nodes without driver mutations, neoadjuvant platinum-

based chemotherapy with immunotherapy before surgery is preferred over adjuvant therapy, particularly in tumors with elevated PD-L1 expression.

In selected patients with NSCLC with N1 involvement and lacking a driver mutation, neoadjuvant chemoimmunotherapy is likely to provide greater oncologic benefit than adjuvant sequential chemoimmunotherapy. However, no randomized study to date has directly compared the 2 approaches. The subgroup analyses of KEYNOTE-671 show similarly impressive EFS and ultimately OS for patients with stage II and stage III disease compared with historical controls.[6] It must be noted, however, that the confidence intervals for the hazard ratio for EFS for patients with stage II barely reach across 1.

The case for induction chemoimmunotherapy is even more compelling for patients with tumors with elevated PD-L1 expression, because higher PD-L1 expression correlates with greater response rates. For example, in NADIM, the PD-L1 percentage was predictive of pathologic response, with an area under the curve of 0.785 for PD-L1 percentage to distinguish MPR from incomplete pathologic response. A PD-L1 percentage ≥25 predicted MPR with 65% sensitivity and 100% specificity.[30]

Finally, a substantial number of patients with clinical N1 disease will, in fact, prove to have pathologic N2 disease, and the recommendation for induction chemoimmunotherapy is stronger in N2 disease.[33] Furthermore, the involvement of a single N1 lymph node is likely different than that of multiple N1 lymph nodes, with multiple involvement behaving more like N2 disease and thus with a stronger likely benefit from induction over adjuvant therapy.

D. Multidisciplinary management of clinical T1–3 single–station N2 NSCLC.

- In medically operable patients with biopsy specimen-proven NSCLC with single-station, nonbulky N2 disease without driver mutations, surgical resection is generally appropriate as part of a multimodality approach, and neoadjuvant platinum-based chemotherapy with immunotherapy before surgery is preferred over adjuvant therapy.
- In patients with NSCLC with pathologically proven single-station, bulky N2 disease, not enough data are currently available to guide whether surgical resection is superior to other treatment options. However, in select cases, particularly if lobectomy is considered likely, surgery may be considered as a part of multimodality therapy after MDT board discussion. Inclusion of these patients in clinical trials is strongly encouraged.

The optimal management of patients with clinical N2 disease remains unclear, with the role of surgical resection debated against other treatment options in the past due to poor long-term survival and high risk of distant metastasis. In several phase III randomized trials in which induction chemotherapy/chemoradiotherapy treatment, followed by surgery, was compared with definitive chemoradiotherapy treatment, there was no difference in overall survival.[34,35] However, in the Intergroup Trial (INT) 0139 (Chemotherapy Plus Radiation Therapy With or Without Surgery in Treating Patients With Stage IIIA Non-small Cell Lung Cancer) study, the progression-free survival was significantly better in the surgical arm.[36] Moreover, in a subgroup analysis, patients undergoing lobectomy had a better outcome than did a matched population treated by radiotherapy.

In multiple retrospective and meta-analysis studies, particularly in the setting of single-station nodal disease, the outcomes of surgical intervention in nonbulky single-station N2 disease appear to be favorable.[37,38] With encouraging recent findings from systemic chemotherapy with immunotherapy demonstrating significant improvement in OS and progression-free survival (PFS),[5,6] it is reasonable to offer surgical resection, particularly lobectomy, as a primary local therapy as long as there is no tumor progression on induction treatment. Induction therapy is generally recommended, as opposed to adjuvant therapy, because several studies have shown tumor regression, improved R0 resection, and low surgical attrition rates with neoadjuvant compared with adjuvant therapy, although this remains unexplored in a head-to-head trial.[6]

We define bulky mediastinal lymphadenopathy as lymph nodes ≥2.5 cm in short-axis diameter on computed tomographic (CT) imaging or those showing extranodal involvement or groupings of multiple smaller lymph nodes.[39] The radiographic findings of mediastinal infiltration with encasement of hilar vessels and airways preventing differentiation or measurement of discrete lymph nodes also fall into this category, according to the American College of Chest Physicians.[40] Retrospective series have shown that patients with NSCLC and bulky N2 disease

experience worse long-term cancer-specific outcomes compared with patients with nonbulky lymph nodes.[39-41] However, there are no data directly comparing outcomes between surgery and other treatment modalities in this group of patients.

Pathologic downstaging after neoadjuvant therapy has been associated with improved long-term cancer-specific outcomes in patients with N2 disease.[42] In light of higher response rates (ie, MPR and pCR) with the use of newer neoadjuvant therapy regimens combining a platinum doublet with an immune checkpoint inhibitor,[24,25] it is reasonable to offer multimodality therapy to a highly select group of patients with single-station bulky N2 disease after MDT board discussion. This is particularly true if surgery, as part of multimodality therapy, would involve a lobectomy, because this is associated with better perioperative outcomes and long-term survival compared with pneumonectomy.[36] Owing to the lack of data on the long-term outcomes of these patients with surgery vs other treatment modalities, inclusion in clinical trials is strongly recommended and should be discussed with the patient if a trial is available.

E. Multidisciplinary management of multistation (≥2) N2 NSCLC.

- Patients with NSCLC with pathologically proven multistation N2 disease are generally not considered candidates for surgical resection because they experience poor long-term outcomes after surgery, especially in bulky nodal disease. However, in select cases with nonbulky, 2 to 3 involved N2 stations, particularly if lobectomy is considered likely, surgery might be considered as a part of multimodality therapy after MDT board discussion. Inclusion of these patients in clinical trials is strongly encouraged.

Multistation N2 involvement has been consistently demonstrated to be associated with worse long-term cancer-specific outcomes after surgery as part of a multimodality therapy strategy.[38,39] As such, the International Association of Lung Cancer proposes a new N descriptor as part of the ninth edition of the TNM classification system, separating N2 disease into single (N2a) and multiple stations (N2b) to better reflect the differences in long-term survival.[43] In combination with the presence of bulky N2 disease, outcomes are expected to be worse.

In a survey of 21 National Comprehensive Cancer Network member institutions in 2010, only 16.7% would consider surgery in patients with multistation N2 disease with bulky lymph nodes.[44] Therefore, these patients are widely considered to have unresectable disease and should be referred for consideration of alternative nonsurgical treatment. In patients with nonbulky multistation N2 disease, 47.6% of the National Comprehensive Cancer Network institutions would consider surgery. In highly selected patients (eg, patients with high PDL-1 scores and only 2 or 3 involved N2 stations), surgery might be considered as a part of multimodality therapy after the MDT board discussion. Inclusion of these patients in clinical trials is strongly encouraged and should be discussed with the patient if a trial is available.

F. Multidisciplinary management of persistent N2 nodes after induction therapy and surgical resection.

- For patients with resectable NSCLC and persistent N2 disease after induction therapy, but without progression, proceeding with surgical resection is generally appropriate.

Patients with NSCLC and N2 disease deemed resectable by the MDT board who undergo multimodality therapy must undergo repeat staging after receiving neoadjuvant therapy. Restaging must include at least a chest CT scan and/or positron emission tomography/CT scan. These imaging studies intend to rule out disease progression. If there is no radiographic progression (ie, any response or stable disease), then proceeding with surgical resection is indicated. Certainly, response to neoadjuvant therapy has been associated with favorable long-term cancer-specific outcomes in patients with NSCLC and N2 disease who undergo multimodality therapy. In particular, pathologic downstaging or mediastinal clearance (ie, ypN0-1) has been associated with improved OS and PFS.[36,42] Invasive mediastinal restaging is not routinely indicated without suspected disease progression on imaging. Phase III randomized clinical trials studying multimodality therapy, including surgery, in patients with NSCLC and N2 disease have not mandated invasive mediastinal restaging in their protocols and only excluded patients in the event of disease progression after neoadjuvant therapy.[5,6,35,36]

G. Multidisciplinary management of T4 disease.

- Patients with clinical T4 NSCLC represent a heterogeneous group of patients, and in selected patients with T4 N0-1 disease, surgical resection can be considered after induction therapy after MDT board discussion at

highly experienced centers. Clinical examples include:
  - Patients with NSCLC >7 cm or satellite nodules in different lobes with N0 or N1 involvement
  - Patients with T4 N0-1 tumors invading the diaphragm, mediastinal structures, recurrent laryngeal nerve, vertebral body, or carina
- Patients with T4 N2 tumors are generally considered poor candidates for surgery for curative intent and are ideally treated with nonsurgical therapies.

Clinical T4 lung cancer represents a heterogeneous group of diseases defined by tumor size, tumor invasion into mediastinal structures, as well as the diaphragm and vertebral bodies, and metastasis to separate ipsilateral lobes.[45] Over the years, the role of surgical resection has been debated and studied, with the surgical and oncologic outcomes being highly variable on the institutional expertise to achieve R0 resection and clinical factors such as N2-3 involvement, which portend poor prognosis.[46,47] Therefore, surgical intervention is not generally recommended in patients with T4 N2-3 disease outside of a clinical trial. However, recent data suggest that surgery as part of multimodality therapy may confer a survival benefit compared with chemoradiotherapy alone in a subset of patients with T4 N2 NSCLC presenting as a small primary tumor (≤3 cm) with additional ipsilateral nodules.[48]

Surgery for T4 NSCLC appears effective in highly selected patients without N2 involvement and where an R0 resection can be achieved, with reported 5-year OS ranging from 30% to 60%.[49,50] No randomized study to date has compared surgical intervention with that of definitive chemoradiotherapy for operable T4 N0-1 NSCLC. Considering the 5-year survival of only 15% for patients with pathologic T4 N0-1 M0 NSCLC who received chemoradiotherapy in a subgroup analysis of the Southwest Oncology Group phase II 9019 study,[17] surgical interventions for curative intent should be considered if possible. However, surgical approaches must be balanced against the possibility of R1 resection and treatment-associated morbidity. Therefore, thorough mediastinal staging and robust discussion in the MDT board are a must before undertaking surgery on these patients.

Whether the prognosis is affected by the subtype of T4 tumor is unclear. Although some literature demonstrated no difference in patient survival among T4 subtypes,[49] more recent studies have indicated that patients with T4 involvement by satellite nodules and involvement of pulmonary great vessels had a lower risk of death compared with patients with tumor extension into other mediastinal structures or tumor >7 cm.[50,51] The surgical resection of other sites, including the vena cava, vertebral body, diaphragm, mediastinum, limited atrium, and carina, is technically feasible and with reasonable patient survival outcomes[52,53]; therefore, surgical resection can be pursued if R0 resection is anticipated. The surgical resection of T4 tumors involving the aorta or esophagus has also been described in the literature but is associated with high morbidity and poor prognosis[54]; therefore, surgical consideration should be made with extreme caution, if not altogether avoided.

Because CheckMate-816 demonstrated significant tumor regression, major pathologic response, and improved R0 resection with induction chemotherapy and immunotherapy,[5] induction chemotherapy and immunotherapy for patients with T4 disease, especially in tumors with N1 involvement and elevated PD-1 levels, can be considered. For patients with tumors with driver mutations or involving the vertebral body or some cases of chest wall (T3) where adequate resection margins are of a concern, neoadjuvant chemoradiotherapy may be used to optimize the probability of an R0 resection as retrospective single-institutional data and prospective single-arm phase II studies (eg, CJLSG0801 [Induction Chemoradiotherapy Followed by Surgical Resection for Non-Small Cell Lung Cancer Involving the Chest Wall: A Phase II Trial]) offer the best available data for optimal management of patients with chest wall and/or vertebral body invasion.[55,56]

H. Multidisciplinary management of superior sulcus (Pancoast) tumor.

- For patients with resectable Pancoast tumors without N2 node involvement, preoperative concurrent chemoradiotherapy, followed by surgery, remains the standard treatment over induction chemotherapy with immunotherapy, outside of clinical trials.

Superior sulcus tumors represent a challenging group of NSCLC. Currently, induction chemoradiotherapy, followed by surgery, is the standard treatment in patients without N2 involvement, given that the Pancoast Intergroup study of induction doublet chemotherapy with concurrent 45 Gy radiotherapy, followed by surgery, reported

significantly improved 5-year survival, high rates of complete resection, and pCR in both T3 and T4 tumors, 76% and 56%, respectively.[18] These excellent results have led some to speculate about the potentially distinct biology of these malignancies,[57] reinforcing the need for additional biological and biomarker stratification for these tumors.

It is important to note that only patients with N0-N1 disease were included in INT-0160. Outcomes data indicate that patients with N2/N3 disease have a substantially worse prognosis and, therefore, have not been considered candidates for surgical resection.[58] Other contraindications for surgery include extensive local involvement of the brachial plexus due to poor survival, morbidity, and a high rate of incomplete resection.[59] The resection of the lower parts of the plexus, especially of the C8-T1 roots, has been performed in the surgical treatment of the Pancoast tumor.[60] Loss of the T1 root is well tolerated, but the removal of the C8 or lower trunk of the brachial plexus leads to loss of hand function; therefore, consideration for surgical resection must be tempered with morbidity associated with the procedure. Vertebral body and vascular involvement can be resected with a good prognosis as long as R0 resection can be achieved.[61,62]

The preferred approach for patients with N0/1 disease is the use of neoadjuvant systemic chemotherapy with the addition of concurrent radiotherapy to optimize local control in a site where additional local invasion can lead to significant morbidity. The role of chemotherapy with immunotherapy, although intriguing, remains speculative for these tumors, and further investigations in the future will need to clarify this area.

SECTION 2: NEOADJUVANT THERAPY.

A. Neoadjuvant vs perioperative therapy in resectable NSCLC.

- Patients may receive neoadjuvant or perioperative (periadjuvant) chemoimmunotherapy with stage IIA and higher NSCLC. Which approach is superior remains unclear, but the attainment of a pCR after neoadjuvant therapy predicts event-free survival.

No studies to date have directly compared neoadjuvant vs perioperative chemoimmunotherapy; thus, the decisions regarding which approach to take must be informed by the interpretation of available evidence as well as the potential advantages and disadvantages of each approach. Whether the addition of the postoperative immunotherapy adds any additional survival benefit is still unclear, although the early reports of the perioperative KEYNOTE-671 and CheckMate-77T (A Study of Neoadjuvant Chemotherapy Plus Nivolumab Versus Neoadjuvant Chemotherapy Plus Placebo, Followed by Surgical Removal and Adjuvant Treatment With Nivolumab or Placebo for Participants With Surgically Removable Early Stage Non-small Cell Lung Cancer) trials show better EFS hazard ratios (both 0.58) compared with neoadjuvant CheckMate-816 (0.68).[5,6,12] Whether this translates to a persistent EFS or OS advantage remains to be seen as trial data mature. Other major unanswered questions are whether any potential incremental benefits are worth the potential increase in toxicity, cost, prolonged duration of therapy from a patient's quality of life, and how to select those patients who might benefit from postoperative immunotherapy.

B. The level of PD-L1 and guidance of preoperative therapy.

- In patients with surgically resectable stage II-III NSCLC eligible for neoadjuvant chemoimmunotherapy, tumor PD-L1 expression predicts response to neoadjuvant therapy, but lack of PD-L1 expression should not be used to exclude patients from consideration of neoadjuvant immunotherapy.

Tumor PD-L1 expression is an important predictor of response to anti-PD-1/PD-L1 immunotherapy in NSCLC.[63] PD-L1 expression is determined using a variety of validated antibody tests, including 22C3, 28-8, SP263, and SP142, and is categorized based on the percentage of tumor cells that stain positive, with the major division categories of $<$1% (0%), 1% to 49%, and $\geq$50%.[64] Approximately one-third of lung cancers fall into each of these categories, and expression appears relatively independent of histology and the presence of molecular driver mutations.

The correlation between increasing PD-L1 expression and immunotherapy response appears to apply in the neoadjuvant setting. In early phase II trials using neoadjuvant immunotherapy alone, responses were observed regardless of PD-L1 expression, but the numbers of patients were small, and many patients had tumors with unknown PD-L1 expression status.[65,66] Of the reported phase III trials that incorporate chemotherapy plus immunotherapy, most demonstrate a correlation between increasing

PD-L1 expression and pCR. With neoadjuvant nivolumab plus chemotherapy,[5] higher PD-L1 expression correlated with patients' improved disease-free survival (DFS) and tumor pCR rate. Similar trends were noticed with DFS after treating patients with perioperative nivolumab plus chemotherapy.[12] In phase III studies of perioperative pembrolizumab with chemotherapy, higher PD-L1 expression also correlated with improved patient DFS and OS.[6,67] When perioperative durvalumab was used with chemotherapy, a correlation with higher PD-L1 expression and patient DFS was also noted, but this was not statistically significant.[13] However, in all of these trials, there still appears to be a modest benefit from adding immunotherapy to chemotherapy treatment regimens, even in patients with PD-L1-negative tumors. Thus, although it is reasonable to consider PD-L1 expression as one of many factors guiding the decision to use immunotherapy, the absence of PD-L1 expression should not be used to exclude patients from its consideration.

C. Contraindications to induction chemoimmunotherapy.

- In patients with stage II-III NSCLC that is surgically resectable, the addition of neoadjuvant immunotherapy to chemotherapy has minimal to no additional efficacy in tumors with mutations in epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), ROS proto-oncogene 1, receptor tyrosine kinase (*ROS1*), rearranged during transfection (*RET*), erythroblastic oncogene B (*ERBB2*; human epidermal growth factor receptor 2 [*HER2*]), and neurotrophic tyrosine receptor kinase (*NTRK*), leading to a recommendation against use in these molecular subtypes. These patients can be treated with neoadjuvant chemotherapy or chemotherapy with radiotherapy, followed by surgical resection, and when approved, adjuvant-targeted therapy. Alternatively, surgery, when appropriate, followed by adjuvant targeted therapy (with or without chemotherapy), is an alternative treatment paradigm.

In stage IV metastatic NSCLC, immunotherapy is rarely effective for patients with tumors with driver mutations in *EGFR*, *ALK*, *ROS1*, *RET*, and *ERBB2* (*HER2*).[68] Additionally, targeted oral therapies, for example, osimertinib for patients with EGFR mutant NSCLC, have increased toxicity risks, including pneumonitis and liver function abnormalities after checkpoint immune therapy administration.[69] Although the KEYNOTE-671 and AEGEAN (A Study of Neoadjuvant/Adjuvant Durvalumab for the Treatment of Patients With Resectable Non-small Cell Lung Cancer) perioperative immunotherapy trials allowed enrollment of patients with *EGFR*-positive and *ALK*-positive NSCLC, very few patients were enrolled. But in these and the CheckMate-816 trial, never-smoking patients—who represent the majority with tumors bearing these mutations—did not have a significant survival benefit with the addition of immunotherapy to chemotherapy.[5,6] Therefore, we do not recommend neoadjuvant or adjuvant immunotherapy for these NSCLC subtypes.

The use of cytotoxic chemotherapy is still strongly encouraged in the neoadjuvant and/or adjuvant settings for patients with stage II-III NSCLC with driver mutations. For patients with *EGFR* mutant or *ALK*-positive NSCLC, there are data supporting treatment with adjuvant-targeted tyrosine kinase inhibitor (TKI) therapy. Patients with tumors harboring an *EGFR* driver mutation treated with osimertinib, given for 3 years after surgery, demonstrated an improved OS, and treating patients with *ALK*-positive NSCLC with adjuvant alectinib has demonstrated a prolonged DFS.[70,71]

D. The role of induction-targeted therapy.

- The investigation of neoadjuvant-targeted therapies is in its early stages, and patients with stage II-III NSCLC (majority adenocarcinoma histology) with driver mutations should be considered for, and if available, undergo active discussion about clinical trials that incorporate appropriate targeted therapies, including neoadjuvant therapy.

Despite the theoretical advantages of neoadjuvant therapy, the evidence for induction therapy using targeted agents remains sparse and inconclusive. Among several small nonrandomized neoadjuvant studies with TKI, the largest show impressive response rates of 55% to 71%, an MPR rate of 24%, and adverse events all grade 3 or less.[15,72] The only randomized neoadjuvant study tested erlotinib vs gemcitabine/cisplatin administered to patients both preoperatively and postoperatively ($n = 72$).[73] The response rate was 54% vs 34%, and the MPR rate was 10% vs 0%, both favoring the patient group treated with erlotinib. The PFS was significantly longer in patients treated with erlotinib (22 vs 11 months), but the median OS was ultimately no different (42 vs 37 months, $P = .51$).

It is possible that because targeted treatments tend to reduce tumor burden rather than completely eliminate tumor cells, their use in the neoadjuvant setting will not prove as effective as chemoimmunotherapy. There is not the same benefit to administering targeted therapies to patients while their tumor/tumor antigens remain in place as there likely is with immunotherapy. Lastly, there is some concern that wound healing in patients treated with *EGFR* TKIs before surgery may be impaired, although this has not been borne out in the small studies published to date.[74]

Therefore, patients with resectable, locally advanced N0/N1 NSCLC-bearing targetable driver mutations should, outside of clinical trials, undergo either induction chemotherapy, followed by resection, or primary resection, followed by adjuvant targeted therapy with or without chemotherapy. However, the putative advantages of neoadjuvant treatment are sufficiently large that additional clinical trials of induction-targeted therapies should be performed. Current ongoing neoadjuvant targeted therapy trials include the randomized NeoADAURA (A Study of Osimertinib With or Without Chemotherapy Versus Chemotherapy Alone as Neoadjuvant Therapy for Patients With EGFRm Positive Resectable Non-Small Cell Lung Cancer) trial testing osimertinib and the phase II ALNEO (Phase II, open-label, single-arm, multicenter study to assess the activity and safety of ALectinib as NEO-adjuvant therapy in patients with anaplastic lymphoma kinase-positive [ALK+] locally advanced stage III ALK-positive NSCLC patients) trial testing alectinib.[14,16]

SECTION 3: ADJUVANT THERAPY.

A. The role of adjuvant systemic therapy for patients with persistent nodal disease who received preoperative induction therapy (ie, chemoimmunotherapy).

- Although patients with persistent N2 disease after neoadjuvant chemoimmunotherapy have inferior oncologic outcomes, the role of additional adjuvant chemotherapy is unknown. Offering adjuvant immunotherapy to patients may be reasonable based on reported perioperative immunotherapy trials.
- Adjuvant immunotherapy may be continued if after a perioperative regimen with phase III data, and for *EGFR* mutant NSCLC, adjuvant osimertinib should be offered for 3 years (ideally without prior immunotherapy exposure in the neoadjuvant setting).

Complete surgical resection, tumor downstaging, and pCR have been validated predictors of long-term patient survival after neoadjuvant therapy in the preimmunotherapy era. Patients with persistent N2 disease after neoadjuvant chemotherapy generally experience suboptimal survival outcomes, but aggressive local therapy is warranted in appropriate patients.[75] In the phase III perioperative chemoimmunotherapy trial, KEYNOTE-671, pathologic complete response was noted in 18.1% of patients receiving pembrolizumab and 4.0% of patients receiving placebo, and pembrolizumab significantly improved EFS.[6] An exploratory analysis showed an EFS benefit in the pembrolizumab group regardless of whether participants had an MPR or a pCR. Given these findings and those of other immunotherapy trials, it is appropriate to offer adjuvant immunotherapy in patients with persistent nodal disease.

For patients who are not appropriate for neoadjuvant immunotherapy, such as those patients whose tumors have activating *EGFR* mutations (del 19/exon 21 L858R) or *ALK* translocations, neoadjuvant chemotherapy alone is appropriate. A meta-analysis has suggested that cisplatin-based induction chemotherapy before surgery conferred an absolute benefit of 6%, increasing overall survival across all stages of the disease from 14% to 20% at 5 years.[76] With sensitive *EGFR* mutations, adjuvant osimertinib, given for 3 years, improves OS (hazard ratio, 0.49; 95% CI, 0.33-0.73) as the previously noted ADAURA trial.[9] For *ALK*-positive mutation, the ALINA trial (NCT03456076) demonstrated improved DFS in the alectinib group (median DFS not estimable vs 41.3 months; 24-month DFS rate 63.7% vs 93.6%; hazard ratio, 0.24; 95% CI, 0.13-0.43), and is now Food and Drug Administration approved, although in practice it is reasonable to consider adjuvant chemotherapy preceding it.[10]

B. The role of postoperative radiation therapy after induction therapy (ie, chemoimmunotherapy).

- In patients with NSCLC with N2 involvement who received neoadjuvant chemotherapy with immunotherapy, followed by surgery, postoperative radiotherapy (PORT) is not routinely indicated. If significant persistent mediastinal nodal disease exists (eg, ypN2 >1 nodal station), a small-volume, highly conformal PORT may be considered as an option (vs additional systemic therapy) after MDT board discussion. Enrollment in clinical

TABLE 2 Consensus Summary of Surgical Resectability for Non-small Cell Lung Cancer[a]

			Nonbulky		Bulky	
Variable	N0	N1	N2 Single	N2 Multstation	N2 Single	N2 Multistation
T1/T2	Resectable	Resectable	Resectable	Potentially resectable	Potentially resectable	Unresectable
T3	Resectable	Resectable	Resectable	Potentially resectable	Potentially resectable	Unresectable
T3 (Pancoast)	Potentially resectable	Potentially resectable	Unresectable	Unresectable	Unresectable	Unresectable
T4 size	Potentially resectable	Potentially resectable	Unresectable	Unresectable	Unresectable	Unresectable
T4 satellite	Potentially resectable	Potentially resectable	Potentially resectable	Unresectable	Unresectable	Unresectable
T4 invasion	Potentially resectable	Potentially resectable	Unresectable	Unresectable	Unresectable	Unresectable

[a]This table represents a general recommendation for the surgical management of locally advanced lung cancer. Every case is unique, and in selected "unresectable" patients, surgical resection may be considered after a multidisciplinary discussion in the institutions with expertise.

trials is strongly encouraged, and if available, clinical trials should be discussed with the patient.
- PORT should be considered if the surgical pathology indicates an R1/R2 resection.

Currently, there is insufficient evidence to support the routine use of PORT in the treatment of patients with resected pN2 NSCLC who have undergone neoadjuvant chemoimmunotherapy. PORT was not part of the perioperative/adjuvant strategy in the randomized trials of neoadjuvant chemoimmunotherapy vs chemotherapy alone that have been published to date. As such, it was administered only in a minority of patients; for instance, ~8% of patients received PORT, with or without chemotherapy, in CheckMate-816.[5] The historical rationale for PORT was the high rates of locoregional recurrence associated in patients with resected N2 disease (~20%-30%) that can be reduced by radiotherapy.[77] Similarly, in the contemporary PORT-C (Postoperative Radiotherapy for Patients With IIIA (N2) Non-small Cell Lung Cancer) trial randomizing patients with incidental or gross N2 disease to adjuvant chemotherapy vs adjuvant chemotherapy, followed by PORT, the 3-year rate of locoregional recurrence rate after adjuvant chemotherapy was 18.3%, which was decreased to 9.5% after PORT.[20]

Locoregional recurrence rates after neoadjuvant chemoimmunotherapy, with or without adjuvant immunotherapy, have yet to be firmly established. In the NADIM II trial of neoadjuvant chemoimmunotherapy vs chemotherapy alone for stage IIIA/B NSCLC, 16 of 53 resected tumors in the experimental arm recurred, with only 6 of 53 (11.3%) being local recurrences at a relatively short median follow-up time of 26.1 months.[11] No high-level evidence exists that a reduction in locoregional recurrence rates from PORT translates into an OS benefit. However, it is recognized that in individual patients, local tumor regrowth can be life-threatening, compromise quality of life, or lead to distant metastases.[20,78]

In general, PORT should be considered in uncommon cases of residual postoperative macroscopic or microscopic disease (R2 or R1). The least contentious microscopic residual disease states justifying the use of PORT include positive parenchymal, bronchovascular, and soft-tissue margins. The impact of other factors potentially increasing nodal recurrence risk, such as incomplete lymphadenectomy, significant residual nodal burden with >1 involved mediastinal lymph node (ie, persistent ypN2), or extracapsular nodal extension, is unclear.[78]

Consideration of PORT in individual patients must consider the well-established associations of PORT with mortality and cardiopulmonary morbidity, as reported in the LUNGART (Radiation Therapy in Treating Patients With Non Small Cell Lung Cancer That Has Been Completely Removed by Surgery) trial.[19] The use of highly conformal radiation techniques or protons may be associated with lower toxicity rates compared with the more traditional 3-dimensional fields prevalent in the LUNGART trial. Careful attention must also be given to the size and location of radiation target volumes and the sparing of the heart, its substructures, and lungs, especially in the setting of

additional adjuvant systemic therapy. Enrollment of patients into clinical trials examining adjuvant therapy strategies is strongly encouraged.

COMMENT

The contemporary management of patients with locally advanced lung cancer is undergoing significant changes as new data are emerging in the context of neoadjuvant and adjuvant immunotherapy and targeted treatments. As such, patients with locally advanced NSCLC should be presented at an MDT board to discuss optimal, evidence-based treatments. Complete surgical resection remains the most significant predictor of survival in patients with locally advanced lung cancer, and the term *resectability* should be understood by all to encompass not only the anticipated ability to achieve R0 resection but also the risks of the anticipated surgery, biological factors relevant to prognosis, and the effectiveness of possible alternative treatments.

Resectability should not mean that we "can" take it out, but rather we "should." Thus, a thoracic surgeon must be knowledgeable in the latest data to be the patient advocate for optimal surgical intervention. Table 2 highlights the consensus summary of the resectability of locally advanced NSCLC based on clinical stages. Accurate preoperative diagnosis, staging, and molecular classification are critical to guide patients and the multidisciplinary team in achieving the best possible care. Based on current data, the combination of neoadjuvant chemotherapy and immunotherapy (with or without additional adjuvant systemic therapy) is preferable for most patients with locally advanced NSCLC, without driver mutations, with N1 or N2 nodal metastasis or large tumors.

The role of adjuvant immunotherapy is unclear in patients with resected, persistent nodal disease (ie, present preoperatively), although there seem to be potential benefits. Adjuvant radiotherapy must take into account patient-specific factors, including the potential for significant toxicity. A clear indication for PORT exists only in patients with an R1 or greater resection. As it relates to resectability, induction treatments should not be given with the intention of "converting" a nonsurgical candidate to a surgical candidate.

Finally, surgeons should take responsibility in determining the feasibility of resection, considering the institutional surgical expertise and ability to achieve an R0 resection. Alternative treatments, including systemic treatments and radiotherapy, are likely better than suboptimal surgical resection.

Surgical therapy remains an invaluable part of the multidisciplinary management of locally advanced lung cancer. "Resectability" will continue to evolve as cancer treatments become more personalized based on factors such as predictive biomarkers, circulating DNA, radiographic imaging features, and other currently unknown technological advances. Thoracic surgeons will continue to adapt and play a critical role in patient management and care.

The authors would like to acknowledge Meredith Herzog of The Society of Thoracic Surgeons for expert coordination.

FUNDING SOURCES

The authors have no funding sources to disclose.

DISCLOSURES

Samuel S. Kim reports a relationship with Intuitive Surgical Inc that includes: funding grants and speaking and lecture fees. David T. Cooke reports a relationship with Bristol-Myers Squibb Co that includes: speaking and lecture fees. Biniam Kidane reports a relationship with AstraZeneca Pharmaceuticals LP that includes: consulting or advisory and speaking and lecture fees; with Merck & Co Inc that includes: consulting or advisory and speaking and lecture fees; with Roche that includes: consulting or advisory and speaking and lecture fees; with Medtronic that includes: consulting or advisory and speaking and lecture fees; and with Olympus Corporation that includes: consulting or advisory and speaking and lecture fees. Samuel S. Kim reports a relationship with AstraZeneca Pharmaceuticals LP that includes: consulting or advisory. Luis Tapia Vargas reports a relationship with AstraZeneca Pharmaceuticals LP that includes: consulting or advisory. Jyoti Patel reports a relationship with AbbVie Inc that includes: consulting or advisory; with AstraZeneca Pharmaceuticals LP that includes: consulting or advisory; with Bristol-Myers Squibb Co that includes: consulting or advisory; with Gilead Sciences Inc that includes: consulting or advisory; with Guardant Health Inc that includes: consulting or advisory; with Sanofi that includes: consulting or advisory; with Tempus that includes: consulting or advisory; with AnHeart Therapeutics that includes: consulting or advisory; with Blueprint Genetics that includes: consulting or advisory; and with Black Diamond Therapeutics that includes: consulting or advisory. Joel Neal reports a relationship with AstraZeneca Pharmaceuticals LP that includes: consulting or advisory; with Genetec Inc that includes: consulting or advisory; with Exelixis Inc that includes: consulting or advisory; with Takeda Pharmaceutical Company Ltd that includes: consulting or advisory; with Eli Lilly and Company that includes: consulting or advisory; with Amgen Inc that includes: consulting or advisory; with Sanofi that includes: consulting or advisory; and with Bristol-Myers Squibb Co that includes: consulting or advisory. Joseph Shrager reports a relationship with AstraZeneca Pharmaceuticals LP that includes: consulting or advisory and with Becton Dickinson and Company that includes: consulting or advisory. The other authors have no conflicts of interest to disclose.

REFERENCES

1. Torre LA, Siegel RL, Jemal A. Lung cancer statistics. *Adv Exp Med Biol*. 2016;893:1–19.

2. Ettinger DS, Wood DE, Aisner DL, et al. Non–Small Cell Lung Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2022;20:497–530.

3. Streit A, Lampridis S, Seitlinger J, et al. Resectability versus operability in early-stage non-small cell lung cancer. *Curr Oncol Rep*. 2024;26:55–64.

4. Montagne F, Guisier F, Venissac N, et al. The role of surgery in lung cancer treatment: present indications and future perspectives–state of art. *Cancers*. 2021;13:3711.

5. Forde PM, Spicer J, Lu S, et al; CheckMate 816 Investigators. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med*. 2022;386:1973–1985.

6. Wakelee H, Liberman M, Kato T, et al; KEYNOTE-671 Investigators. Perioperative pembrolizumab for early-stage non-small-cell lung cancer. *N Engl J Med*. 2023;389:491–503.

7. Felip E, Altorki N, Zhou C, et al; IMpower010 Investigators. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. *Lancet*. 2021;398:1344–1357.

8. O'Brien M, Paz-Ares L, Marreaud S, et al; EORTC-1416-LCG/ETOP 8-15—PEARLS/KEYNOTE-091 Investigators. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB–IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. *Lancet Oncol*. 2022;23:1274–1286.

9. Wu Y-L, Tsuboi M, He J, et al. Osimertinib in resected *EGFR*-mutated non-small-cell lung cancer. *N Engl J Med*. 2020;383:1711–1712.

10. Solomon BJ, Ahn JS, Dziadziuszko R, et al. LBA2 ALINA: Efficacy and safety of adjuvant alectinib versus chemotherapy in patients with early-stage ALK+ non-small cell lung cancer (NSCLC). ESMO Congress 2023 Abstract 34(suppl 2):S1295–S1296. https://www.annalsofoncology.org/article/S0923-7534(23)04195-9/fulltext

11. Provencio M, Nadal E, Gonzalez-Larriba JL, et al. Perioperative nivolumab and chemotherapy in stage III non-small-cell lung cancer. *N Engl J Med*. 2023;389:504–513.

12. Cascone T, Awad MM, Spicer JD, et al. LBA1 CheckMate 77T: Phase III study comparing neoadjuvant nivolumab (NIVO) plus chemotherapy (chemo) vs neoadjuvant placebo plus chemo followed by surgery and adjuvant NIVO or placebo for previously untreated, resectable stage II–IIIb NSCLC. ESMO 2023, Madrid, Spain. *Ann Oncol*. 2023;34:S1295 https://www.annalsofoncology.org/article/S0923-7534(23)04194-7/fulltext

13. Heymach JV, Harpole D, Mitsudomi T, et al; AEGEAN Investigators. Perioperative durvalumab for resectable non-small-cell lung cancer. *N Engl J Med*. 2023;389:1672–1684.

14. Tsuboi M, Weder W, Escriu, et al. Neoadjuvant osimertinib with/without chemotherapy versus chemotherapy alone for *EGFR*-mutated resectable non-small-cell lung cancer: NeoADAURA. *Future Oncol*. 2021;17:4045–4055.

15. Lv C, Fang W, Wu Nan, et al. Osimertinib as neoadjuvant therapy in patients with EGFR-mutant resectable stage II-IIIB lung cancer (NEOS): a multicenter, single-arm, open-label phase 2b trial. *Lung Cancer*. 2023;178:P151–P156.

16. Leonetti A, Minari R, Boni L, et al. Phase II, open-label, single-arm, multicenter study to assess the activity and safety of Alectinib as neoadjuvant treatment in surgically resectable stage II ALK-positive NSCLC: ALNEO trial. *Clin Lung Cancer*. 2021;22:473–477.

17. Albain KS, Crowley JJ, Turrisi AT 3rd, et al. Concurrent cisplatin, etoposide, and chest radiotherapy in pathologic stage IIIB non-small-cell lung cancer: a Southwest Oncology Group phase II study, SWOG 9019. *J Clin Oncol*. 2002;20:3454–3460.

18. Rusch VW, Giroux DJ, Kraut MJ, et al. Induction chemoradiation and surgical resection for superior sulcus non-small-cell lung carcinomas: long-term results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). *J Clin Oncol*. 2007;25:313–318.

19. Pechoux CL, Pourel N, Barlesi PF, 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, IFCT 0503): an open-label randomized, phase 3 trial. *Lancet Oncol*. 2022;1:104–114.

20. Hui Z, Hu Chen, Kang J, et al. Effect of postoperative radiotherapy for patients with pIIIA-N2 non-small cell lung cancer after complete resection and adjuvant chemotherapy: the phase 3 PORT-C randomized clinical trial. *JAMA Oncol*. 2021;7:1178–1185.

21. Humphrey-Murto S, Varpio L, Wood TJ, et al. The use of the Delphi and other consensus group methods in medical education research: a review. *Acad Med*. 2017;92:1491–1498.

22. Walter J, Moeller C, Resuli B, et al. Guideline adherence of tumor board recommendations in lung cancer and transfer into clinical practice. *J Cancer Res Clin Oncol*. 2023;149:11679–11688.

23. Chen YF, Chen YL, Liu CC, et al. Adjuvant chemotherapy in pathological node-negative non-small cell lung cancer. *Sci Rep*. 2023;13:19137.

24. ClinicalTrial.gov. Study to Assess Neoadjuvant Durvalumab (D) and Platinum-Based Chemotherapy (CT), Followed by Either Surgery and Adjuvant D or CRT and Consolidation D, in Resectable or Borderline Resectable Stage IIB–IIIB NSCLC (MDT-BRIDGE)—MDT-BRIDGE. NCT05925530. 2023.

25. Clark JM, Heifetz LJ, Palmer D, et al. Telehealth allows for clinical trial participation and multimodality therapy in a rural patient with stage 4 non-small cell lung cancer. *Cancer Treat Res Commun*. 2016;9:139–142.

26. Davis CH, Ho J, Stephenson R, et al. Virtual tumor board increases provider attendance and case presentations. *JCO Oncol Pract*. 2022;18:e1603–e1610.

27. Kay FU, Kandathil A, Batra K, Saboo SS, Abbara S, Rajiah P. Revisions to the Tumor, Node, Metastasis Staging of Lung Cancer (8th edition): rationale, radiologic findings and clinical implications. *World J Radiol*. 2017;9:269–279.

28. Provencio Pulla M, Forde JD, Spicer C, et al. LBA57—Neoadjuvant nivolumab (N) + chemotherapy (C) in the phase III CheckMate 816 study: 3-y results by tumor PD-L1 expression. ESMO 2023, Madrid, Spain. *Ann Oncol*. 2023;34(suppl 2):S1298–S1299. https://www.annalsofoncology.org/article/S0923-7534(23)04194-7/fulltext

29. Sorin M, Prosty C, Ghleb C, et al. Neoadjuvant chemoimmunotherapy for NSCLC: a systematic review and meta-analysis. *JAMA Oncol*. 2024;10:621–633.

30. Provencio M, Nadal E, Insa A, 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*. 2020;21:1413–1422.

31. van Hagen P, Hulshof MC, van Lanschot JJ, et al. CROSS Group. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med*. 2012;366:2074–2084.

32. Bracci L, Schiavoni G, Sistigu A, et al. Immune-based mechanisms of cytotoxic chemotherapy: implications for the design of novel and rationale-based combined treatments against cancer. *Cell Death Differ*. 2014;21:15–25.

33. Glover J, Velez-Cubian FO, Toosi K, et al. Perioperative outcomes and lymph node assessment after induction therapy in patients with clinical N1 or N2 non-small cell lung cancer. *J Thorac Dis*. 2016;8:2165–2174.

34. Pless M, Stupp R, Ris HB, et al. Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial. *Lancet*. 2015;386:1049–1056.

35. van Meerbeeck JP, Kramer GW, Van Schil P, 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*. 2007;99:442–450.

36. Albain KS, Swann RS, Rusch VW, 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*. 2009;374:379–386.

37. Darling GE, Li F, Patsios D, et al. Neoadjuvant chemoradiation and surgery improves survival outcomes compared with definitive chemoradiation in the treatment of stage IIIA N2 non–small–cell lung cancer. *Eur J Cardiothorac Surg*. 2015;48:684–690.

38. McElnay PJ, Choong A, Jordan E, et al. Outcome of surgery versus radiotherapy after induction treatment in patients with N2 disease: systematic review and meta–analysis of randomized trials. *Thorax*. 2015;70:764–768.

39. De Leyn P, Dooms C, Kuzdzal J, et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non–small–cell lung cancer. *Eur J Cardiothoracic Surg*. 2014;45:787–798.

40. Silvestri GA, Gonzalez AV, Jantz MA, et al. Methods for staging non–small cell lung cancer: Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians evidence–based clinical practice guidelines. *Chest*. 2013;143:e211S–e250S.

41. Stefani A, Alifano M, Bobbio A, et al. Which patients should be operated on after induction chemotherapy for N2 non–small cell lung cancer? Analysis of a 7–year experience in 175 patients. *J Thorac Cardiovasc Surg*. 2010;140:356–363.

42. Betticher DC, Schmitz SFH, Tötsch M, 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*. 2003;21:1752–1759.

43. Huang J, Osarogiagbon RU, Giroux DJ, et al. The International Association for the Study of Lung Cancer Staging Project for Lung Cancer: proposals for the revision of the N descriptors in the forthcoming Ninth Edition of the TNM Classification for Lung Cancer. *Thorac Oncol*. 2024;19:766–785.

44. Martins RG, D'Amico TA, Loo BW, et al. The management of patients with stage IIIA non–small cell lung cancer with N2 mediastinal node involvement. *J Natl Compr Canc Netw*. 2012;10:599–613.

45. Detterbeck F, Boffa D, Kim A, Tanoue L. The Eighth Edition Lung Cancer Stage Classification. *Chest*. 2017;151:193–203.

46. Yang HY, Hou X, Lin P, et al. Survival and risk factors of surgically treated mediastinal invasion T4 non–small cell lung cancer. *Ann Thorac Surg*. 2009;88:372–379.

47. Lucchi M, Viti A, Melfi F, et al. IIIB–T4 non–small cell lung cancer: indications and results of surgical treatment. *J Cardiovasc Surg*. 2007;48:369–374.

48. Kumar A, Gandhi K, Shivee G, et al. Multimodal therapy for T4 N2 non–small cell lung cancer with additional ipsilateral pulmonary nodules. *Ann Thorac Surg Short Rep*. 2023;1:566–569.

49. Yamanashi K, Menju T, Hamaji M, et al. Prognostic factors related to postoperative survival in the newly classified clinical T4 lung cancer. *Eur J Cardiothorac Surg*. 2020;57:754–761.

50. Wang F, Su Hang, Haoran E, et al. Reconsidering T component of cancer staging for T3/T4 non–small–cell lung cancer with additional nodule. *Ther Adv Med Oncol*. 2022;14:17588359221130502.

51. Li Q, Zhang P, Wang Y, et al. T4 extension alone is more predictive of better survival than a tumor size >7cm for resected T4N0–1M0 non–small cell lung cancer. *Eur J Cardiothorac Surg*. 2019;55:682–690.

52. de Perrot M, Fadel E, Mercier O, et al. Long–term results after carinal resection for carcinoma: does the benefit warrant the risk? *J Thorac Cardiovasc Surg*. 2006;131:81–89.

53. DiPerna CA, Wood DE. Surgical management of T3 and T4 lung cancer. *Clin Cancer Res*. 2005;11:5038–5044.

54. Shen KR, Meyers BF, Larner JM, Jones DR, American College of Chest Physicians. Special treatment issues in lung cancer: ACCP evidence–based clinical practice guidelines (2nd ed). *Chest*. 2007;132:290–305.

55. Kawaguchi K, Yokoi K, Niwa H, et al. A prospective, multi–institutional phase II study of induction chemoradiotherapy followed by surgery in patients with non–small cell lung cancer involving the chest wall (CJLSG0801). *Lung Cancer*. 2017;104:79–84.

56. Anraku M, Waddell TK, de Perrot M, et al. Induction chemo–radiotherapy facilitates radical resection of T4 non–small cell lung cancer invading the spine. *J Thorac Cardiovasc Surg*. 2009;137:441–447.

57. Detterbeck FC. Changes in the treatment of Pancoast tumors. *Ann Thorac Surg*. 2003;75:1990–1997.

58. Panagopoulos N, Leivaditis V, Koletsis E, et al. Pancoast tumors: characteristics and preoperative assessment. *J Thorac Dis*. Mar 2014;6(suppl 1):S108–S115.

59. Pitz CC, de la Rivière AB, van Swieten HA, Duurkens VA, Lammers JW, van den Bosch JM. Surgical treatment of Pancoast tumours. *Eur J Cardiothorac Surg*. 2004;26:202–208.

60. Parissis H, Young V. Treatment of Pancoast tumors from surgeons prospective: re–appraisal of the anterior manubrial sternal approach. *J Cardiothorac Surg*. 2010;5:102.

61. Unal S, Winkelman JA, Heineman DJ, et al. Long–term outcome after chemoradiotherapy and surgery for superior sulcus tumors. *JTO Clin Res Rep*. 2023;4:100474.

62. Collaud S, Waddell TK, Yasufuk K, et al. Long–term outcome after en bloc resection of non–small–cell lung cancer invading the pulmonary sulcus and spine. *J Thorac Oncol*. 2013;8:1538–1544.

63. Doroshow DB, Bhalla S, Beasley MB, et al. PD–L1 as a biomarker of response to immune–checkpoint inhibitor. *Nat Rev Clin Oncol*. 2021;18:345–362.

64. Ming ST, Kerr KM, Mark K, et al. PD–L1 Immunohistochemistry comparability study in real–life clinical samples: results of Blueprint phase 2 project. *J Thorac Oncol*. 2018;13:1302–1311.

65. Forde PM, Chaft JE, Smith KN, et al. Neoadjuvant PD–1 blockade in resectable lung cancer. *N Engl J Med*. 2018;378:1976–1986.

66. Chaft JE, Oezkan F, Kris MG, et al. Neoadjuvant atezolizumab for resectable non–small cell lung cancer: an open–label, single–arm phase II trial. *Nat Med*. 2022;28:2155–2161.

67. Spicer JD, Gao S, Liberman M, et al. LBA56 Overall survival in the KEYNOTE–671 study of perioperative pembrolizumab for early–stage non–small–cell lung cancer (NSCLC). *Ann Oncol*. 2023;34:S1297–S1298. https://www.annalsofoncology.org/article/S0923–7534(23)04196–0/fulltext

68. Mazieres J, Drilon A, Lusque A, et al. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry. *Ann Oncol*. 2019;30:1321–1328.

69. Schoenfeld AJ, Arbour KC, Rizvi H, et al. Severe immune–related adverse events are common with sequential PD–(L)1 blockade and osimertinib. *Ann Oncol*. 2019;30:839–844.

70. Herbst RS, Wu Y, John T, et al. Adjuvant osimertinib for resected EGFR–mutated stage IB–IIIA non–small–cell lung cancer: updated results from the phase III randomized ADAURA Trial. *J Clin Oncol*. 2023;41:1830–1840.

71. Wu YL, Dziadziuszko R, Ahn JS, et al. ALINA Investigators. Alectinib in resected *ALK*–positive non–small–cell lung cancer. *N Engl J Med*. 2024;390:1265–1276.

72. Zhang Y, Fangqiu F, Haichuan H, et al. Gefitinb as neoadjuvant therapy for resectable stage II–III non–small cell lung cancer: a phase II study. *J Thorac Cardiovasc Surg*. 2021;161:434–442.

73. Zhong WZ, Chen KN, Chen C, et al. Erlotinib Versus Gemcitabine Plus Cisplatin as Neoadjuvant Treatment of Stage IIIA–N2 *EGFR*–Mutant Non–Small–Cell Lung Cancer (EMERGING–CTONG 1103): a randomized phase II study. *J Clin Oncol*. 2019;37:2235–2245.

74. Shah DR, Dholakia S, Sha RR. Effect of tyrosine kinase inhibitors on wound healing and tissue repair: implications for surgery in cancer patients. *Drug Saf*. 2014;37:135–149.

75. Higgins KA, Chino JP, Ready N, et al. Persistent N2 disease after neoadjuvant chemotherapy for non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2011;142:1175–1179.

76. Burdett S, Stewart LA, Rydzewska L. A systemic review and meta-analysis of the literature: chemotherapy and surgery versus surgery alone in non-small cell lung cancer. *J Thorac Oncol*. 2006;1:611–621.

77. Pechoux CL. Role of postoperative radiotherapy in resected non-small cell lung cancer: a reassessment based on new data. *Oncologist*. 2011;16:672–681.

78. Suveg K, Pechoux CL, Faivre-Finn C, et al. Role of postoperative radiotherapy in the management for resected NSCLC—decision criteria in clinical routine pre-and post-LungART. *Clin Lung Cancer*. 2021;22:579–586.