ORIGINAL ARTICLE

Neoadjuvant and Adjuvant Treatments for Early Stage Resectable NSCLC: Consensus Recommendations From the International Association for the Study of Lung Cancer

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ABSTRACT

Advances in the multidisciplinary care of early stage resectable NSCLC (rNSCLC) are emerging at an unprecedented pace. Numerous phase 3 trials produced results that have transformed patient outcomes for the better, yet these findings also require important modifications to the patient treatment journey trajectory and reorganization of care pathways. Perhaps, most notably, the need for multispecialty collaboration for this patient population has never been greater. These rapid advances have inevitably left us with important gaps in knowledge for which definitive answers will only become available in several years. To this end, the International Association for the Study of Lung Cancer commissioned a diverse multidisciplinary international expert panel to evaluate the current landscape and provide diagnostic, staging, and therapeutic recommendations for patients with rNSCLC, with particular emphasis on patients with American Joint Committee on Cancer-Union for International Cancer Control TNM eighth edition stages II and III disease. Using a team-based approach, we generated 19 recommendations, of which all but one achieved greater than 85% consensus among panel members. A public voting process was initiated, which successfully validated and provided qualitative nuance to our recommendations. Highlights include the following: (1) the critical importance of a multidisciplinary approach to the evaluation of patients with rNSCLC driven by shared clinical decision-making of a multispecialty team of expert providers; (2) biomarker testing for rNSCLC; (3) a preference for neoadjuvant chemoimmunotherapy for stage III rNSCLC; (4) equipoise regarding the optimal management of patients with stage II between upfront surgery followed by adjuvant therapy and neoadjuvant or perioperative strategies; and (5) the robust preference for adjuvant targeted therapy for patients with rNSCLC and sensitizing *EGFR* and *ALK* tumor alterations. Our primary goals were to provide practical recommendations sensitive to the global differences in biology and resources for patients with rNSCLC and to provide expert consensus guidance tailored to the individualized patient needs, goals, and preferences in their cancer care journey as these are areas where physicians must make daily clinical decisions in the absence of definitive data. These recommendations will continue to evolve as the treatment landscape for rNSCLC expands and more knowledge is acquired on the best therapeutic approach in specific patient and disease subgroups.

Keywords: Lung cancer; Surgery; Neoadjuvant; Adjuvant; Immunotherapy; Targeted therapy; Chemotherapy; Radiation

Introduction

The most frequently used treatment paradigm for medically fit patients with early stage NSCLC has been curative-intent surgery, followed by adjuvant (postoperative) platinum-based chemotherapy and radiation therapy, either together or separately. Unfortunately, most patients experience recurrence and only approximately 60% of patients with stage II disease will survive five years; this decreases to 41% for stage IIIA and 24% for stage IIIB despite the curative-intent therapies.[1] In the past few years, the treatment paradigm for localized resectable NSCLC (rNSCLC) has shifted as targeted therapies and immune checkpoint inhibitors (ICIs) have moved into the earlier disease stage arena, revealed having efficacy in the advanced or metastatic NSCLC setting. Notably, multiple monoclonal antibodies that target the programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) immune checkpoint axis—including, atezolizumab, durvalumab, nivolumab, and pembrolizumab—and the EGFR-targeted therapy, osimertinib, have been approved by regulatory bodies in several countries for use in early stage NSCLC.

Results from several trials evaluating neoadjuvant (preoperative) and perioperative (neoadjuvant and adjuvant) ICI-based therapies revealed significant benefit of these approaches compared with neoadjuvant chemotherapy alone. Nevertheless, lack of direct comparisons to upfront surgery followed by adjuvant therapy has created considerable dilemmas in terms of the logistical reorganization of care pathways for patients with rNSCLC and with respect to the choice of optimal approach. Owing to the fast pace at which data from neoadjuvant and adjuvant trials of additional ICIs and targeted therapy agents are being generated and the increasing number of approvals in early stage NSCLC, health care providers and patients are suddenly faced with a wide array of choices and the challenge of deciding which therapeutic options or approach are best suited for each individual patient. Furthermore, we will not have data from any phase 3 trials that directly compare neoadjuvant or perioperative strategies versus upfront surgery followed by adjuvant options for years to come. Thus, clinicians and patients will have to contend with this gap in knowledge in their treatment approach for the foreseeable future.

As an international multidisciplinary society, the International Association for the Study of Lung Cancer (IASLC) is uniquely positioned to provide guidance to clinicians on the use of neoadjuvant and adjuvant treatments in early stage NSCLC based on existing evidence as IASLC has focused on neoadjuvant therapies since 2018 after convening a multidisciplinary conference to review progress in the field, identify

opportunities, and prioritize research to fill knowledge gaps.[2] The IASLC is the only global organization dedicated solely to the study of lung cancer and other thoracic malignancies. The authors of this manuscript are members of IASLC and comprise a comprehensive and diverse multidisciplinary group of international expert physicians that manage patients with early stage lung cancers being considered for curative-intent local therapy and neoadjuvant or adjuvant treatments. The consensus recommendations from this expert panel are listed in Table 1 and the rationale for each recommendation is provided in the body of the manuscript. The goal of these recommendations is to provide pragmatic direction to help physicians select and recommend the optimal therapeutic strategy for their patients, and to this end, workflow diagrams for clinical stages II and III are found in Figures 1 and 2, respectively. Physicians should also consider a patient's needs and personal goals in their cancer journey when planning therapeutic interventions. In addition, physicians should consider the realities of their respective countries in terms of access to molecular testing and novel therapies. We endeavored to take a position in areas where data may be lacking or incomplete, but choices still need to be made. Although some recommendations achieved unanimity, others did not, and the outcome of these discussions is presented here for guidance where the decision-making process is currently based on evolving evidence lacking many important direct comparisons.

Methods

The multidisciplinary voting panel consisted of 20 international members, including four thoracic surgeons, 12 medical oncologists, two pathologists, and two radiation oncologists. The group held a predominantly in-person meeting on February 25 to 26, 2023, in Santa Monica, CA, with a few members attending virtually because of country-imposed travel restrictions. Two subsequent virtual meetings were held on July 14, 2023, and August 8, 2023, to review new data and finalize the recommendations.

Before the meeting, a literature search identified recently completed and ongoing randomized phase 3 trials, including randomized and nonrandomized phase 2 trials of neoadjuvant, perioperative, and adjuvant therapies in operable patients with previously untreated, early stage rNSCLC, with an original data release cutoff date of June 5, 2023, and an update on October 31, 2023, allowing incorporation of newly released data.

To establish a threshold for recommendation consensus on voting, the expert panel members evaluated the consensus and guideline thresholds used by other major oncology organizations, including the National Comprehensive Cancer Network, the American Society for Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), and the American Association for Thoracic Surgery. The expert group defined a threshold of 85% as achievement of consensus, which enabled achievement of consensus in scenarios in which up to three voting members dissented. The group reasoned that a relatively high threshold was needed considering the importance of the recommendations in the context of a still emerging domain of data. If consensus was not reached in the first round of voting, a second and a final voting session were conducted. If no consensus was reached on the third vote, a recommendation of no consensus was noted. The recommendations were also sent out through e-blasts and social media platforms for open comment with the responder being asked to vote, agree or not, on the recommendations and to add any free text comments. The authors reviewed the results and comments of the open voting and made considerations in the manuscript, where appropriate. The results of the open votes and comments were overall deemed similar to the expert panel votes (Table 1). The open text comments were considered confidential.

The expert panel reviewed and discussed the results of multiple completed or ongoing phase 2 and 3 clinical trials evaluating therapeutic strategies in the neoadjuvant, perioperative, and adjuvant settings (Table 2). When considering the data from the trials listed in Table 2, it is important to note several key differences in trial design that can influence interpretation. Factors that should be considered include, but are not limited to, the TNM stage classification edition, tumor PD-L1 expression percentage thresholds (and the companion diagnostic[s] used), inclusion of patients with *EGFR*-mutated or *ALK*-rearranged lung cancer (and the companion diagnostic[s] used), and efficacy outcome definitions (e.g., event-free survival [EFS] or disease-free survival [DFS], pathologic complete response [pCR], major pathologic response [MPR], and overall survival [OS]), with nuances in end points used for each trial. The following general definitions used in the trials and discussed in this manuscript are as follows: EFS, time from randomization to any progression or recurrence of disease or death from any cause; DFS, time from completion of primary treatment to disease recurrence or death from any cause; pCR, 0% residual viable tumor cells in the primary tumor and sampled lymph nodes; MPR, less than or equal to 10% residual viable tumor cells in the primary tumor and sampled lymph nodes; and OS, time from randomization to death from any cause. Readers should refer to each trial publication and appended protocol for specific nuances to these definitions.

Some of the trials staged patients according to the seventh edition of the American Joint Committee on Cancer (AJCC)-Union for International Cancer Control (UICC) Staging Manual (published in 2010), whereas others used the eighth edition (published in 2017 and

Table 1. General and Specific Recommendations for Neoadjuvant and Adjuvant Treatment in Early Stage rNSCLC

Recommendation		Expert Panel Agreement, %	Open Comment Agreement, %
General recommendations			
Recommendation 1	Patients should be evaluated by a multidisciplinary team to devise an individualized treatment plan, ideally in a tumor board setting consisting of surgeons, medical oncologists, radiation oncologists, pathologists, pulmonologists, radiologists, and supportive care staff.	100	97
Recommendation 2	Contrast-enhanced computed tomography (CT) of the chest and upper abdomen, positron emission tomography (PET), and invasive mediastinal staging, to rule out contralateral mediastinal nodal involvement (if suspicion exists), along with recent contrast-enhanced CT or magnetic resonance (MR) brain imaging, are strongly recommended for all patients at diagnosis.	100	90
Recommendation 3	Surgical evaluation is required, preferably by a thoracic surgeon, to determine operability (medical fitness) and resectability (likelihood of R0 resection).	95	90
Recommendation 4	Thoracic surgeons planning to operate on patients treated with neoadjuvant chemoimmunotherapy must be skilled in performing advanced pulmonary surgical maneuvers.	100	95
Recommendation 5	Evaluation of the patient by a physician skilled in administering systemic therapy to patients with early stage disease is required.	100	89
Recommendation 6	For patients being considered for neoadjuvant or adjuvant systemic therapy, at a minimum, determination of *EGFR* and *ALK* alteration status is required. Tumor proportion score measurement for determination of PD-L1 status should also be considered.	100	93
Neoadjuvant treatment—consensus recommendations			
Recommendation 7	Neoadjuvant chemoimmunotherapy is strongly preferred to upfront surgery for medically operable patients with resectable clinical stage IIIA or IIIB NSCLC at first presentation, irrespective of PD-L1 expression level.	94	79
Recommendation 8	Following surgery in patients who receive neoadjuvant chemoimmunotherapy, adjuvant immunotherapy can be considered.	94	93
Recommendation 9	For patients with TKI-sensitizing *EGFR* or *ALK* alterations, neoadjuvant chemoimmunotherapy or adjuvant immunotherapy is not recommended.	95	89
Recommendation 10	Contrast-enhanced CT of the chest is required before surgery. In the absence of radiographic progression after neoadjuvant chemoimmunotherapy, invasive mediastinal restaging is not routinely required.	100	96
Recommendation 11	In the absence of disease spread, patients who remain operable and resectable should proceed to surgery. For patients with evidence of cancer progression or for whom feasibility of surgery is in question, a multidisciplinary tumor board should be convened.	100	95
Recommendation 12	Use of intraoperative frozen sectioning is recommended to assure complete resection and limit excessive parenchymal resection.	88	78
Recommendation 13	Surgical pathology reporting for neoadjuvant therapy-treated patients including, at minimum, a determination of pathologic complete response, percent residual viable tumor, and ypTNM status, is recommended.	100	98
Recommendation 14	A multidisciplinary group, ideally in a tumor board setting, consisting of medical or pulmonary oncology, pathology, surgery, radiation oncology, and radiology should reconvene after surgery to recommend additional treatment and surveillance plans.	95	94

(continued)

Table 1. Continued

Recommendation		Expert Panel Agreement, %	Open Comment Agreement, %
Neoadjuvant treatment—nonconsensus recommendations			
Recommendation 15	Neoadjuvant chemoimmunotherapy followed by surgery is preferred to upfront surgery for medically operable patients with technically resectable clinical stage II NSCLC at first presentation, regardless of PD-L1 expression level.	65	55
Adjuvant treatment-consensus recommendations			
Recommendation 16	Adjuvant chemotherapy is required before adjuvant immunotherapy	88	80
Recommendation 17	Patients with stage II or IIIA *EGFR*- and *ALK*-wild-type disease who have undergone complete resection followed by chemotherapy should be considered for adjuvant immunotherapy based on PD-L1 results as follows: • PD-L1 $<$ 1%: Discourage • PD-L1 1%–49%: Consider • PD-L1 $\geq$ 50%: Recommend	100	91
Recommendation 18	In the light of ongoing trials in populations with specific driver alterations and with extrapolation of the limited efficacy of PD-1 and PD-L1 inhibitors in patients with driver alterations, in addition to assessing *EGFR* and *ALK* alteration status, biomarker testing for other oncogenic drivers is highly encouraged in patients with early stage disease.	94	91
Recommendation 19	For patients with stage II or IIIA disease with *EGFR*-sensitizing mutations, adjuvant osimertinib is recommended. Adjuvant platinum-based chemotherapy before osimertinib is encouraged. For patients with stage IB (T3-4cmN0) disease, adjuvant osimertinib alone is recommended.	94	92
Recommendation 20	For patients with stages IB (tumors $\geq$ 4 cm) to IIIA disease with ALK alterations, adjuvant alectinib is recommended. Adjuvant chemotherapy before alectinib can be considered at the discretion of the treating providers.	95	ND

Note: The recommendation was added after the open comment period for the other recommendations after the approval of adjuvant alectinib by the U.S. FDA.
CT, computed tomography; FDA, Food and Drug Administration; MR, magnetic resonance; ND, not done; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PET, positron emission tomography; R0, no residual tumor, complete resection; TKI, tyrosine kinase inhibitor.

2016, respectively; effective for all cancer cases recorded on or after January 1, 2018).[3–5] The classification of NSCLC tumors differs in several ways between the two editions. Most relevant to the discussion of patients with early stage disease is the redefinition of tumors more than 4 to 5 cm from T2a to T2b. In the absence of nodal involvement (i.e., N0), this reclassifies patients with tumors more than 4 to 5 cm from having stage IB disease (AJCC-UICC seventh edition) to having stage IIA disease (AJCC-UICC eighth edition). Thus, it is important to consider which edition of the staging manual was used to classify patients enrolled in NSCLC clinical trials. For this reason, most clinical study outcomes describe stage with respect to not only the T and N parameters but also include the tumor size (in cm) and nodal involvement. Recommendations in this manuscript use the AJCC-UICC eighth edition. It is also important to note that neoadjuvant and perioperative trials use clinical stage for study eligibility, whereas adjuvant trials use pathologic stage; therefore, direct comparison of the patient populations enrolled is challenging.

Recommendations

In addition to providing recommendations for neoadjuvant and adjuvant therapies of early stage rNSCLC, the expert panel recognized the importance of providing consensus recommendations on the initial evaluation, staging, and a multidisciplinary discussion to assist the clinical team in selecting a treatment and an approach. These are referred to as the general recommendations.

General Recommendations

Recommendation 1: Patients should be evaluated by a multidisciplinary team to devise an individualized treatment plan, ideally in a tumor board setting consisting of surgeons, medical oncologists, radiation oncologists, pathologists, pulmonologists, radiologists, and supportive care staff.

Agreement: 100%

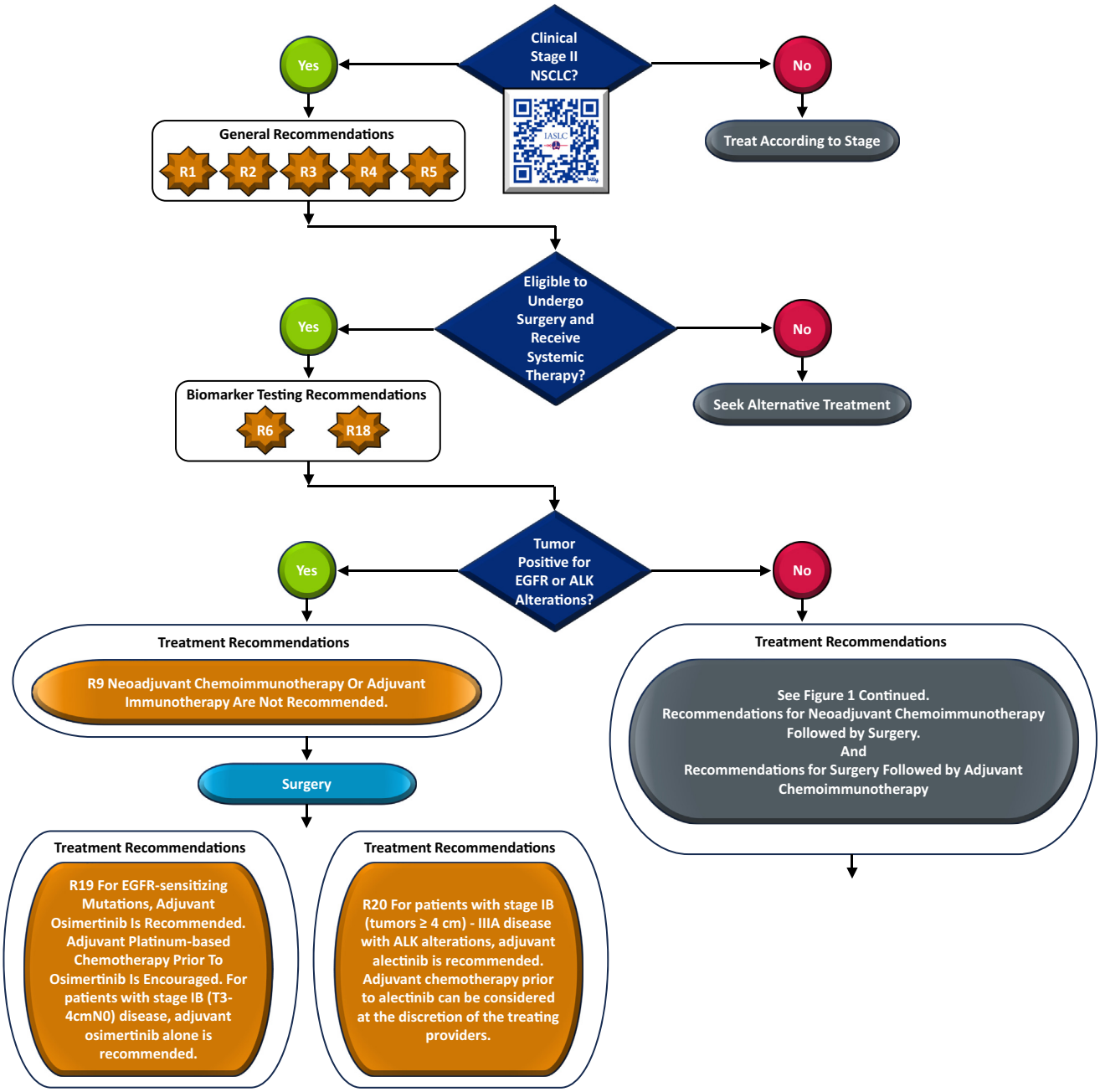

Figure 1. Workflow for neoadjuvant or adjuvant therapy for clinical stage II NSCLC.

The increasing number of treatment options for patients with resectable disease makes evaluation by a multidisciplinary team essential. Management guidelines from ASCO, ESMO, National Comprehensive Cancer Network, and other agencies across the world recommend a multidisciplinary care team approach. By working together, specialists can develop a personalized treatment plan that considers the patient's unique medical history, histology, stage, biomarker profile, and individual preferences. Two approaches to the delivery of multidisciplinary care include multidisciplinary tumor boards or multidisciplinary clinics. A literature review on the impact of multidisciplinary care revealed that this approach led to better outcomes across all stages of lung cancer, improved use of all treatment modalities, reduced health care costs, and resulted in high patient satisfaction.[6] A recent meta-analysis performed a systematic review of trials evaluating the intervention of a multidisciplinary case conference for the shared

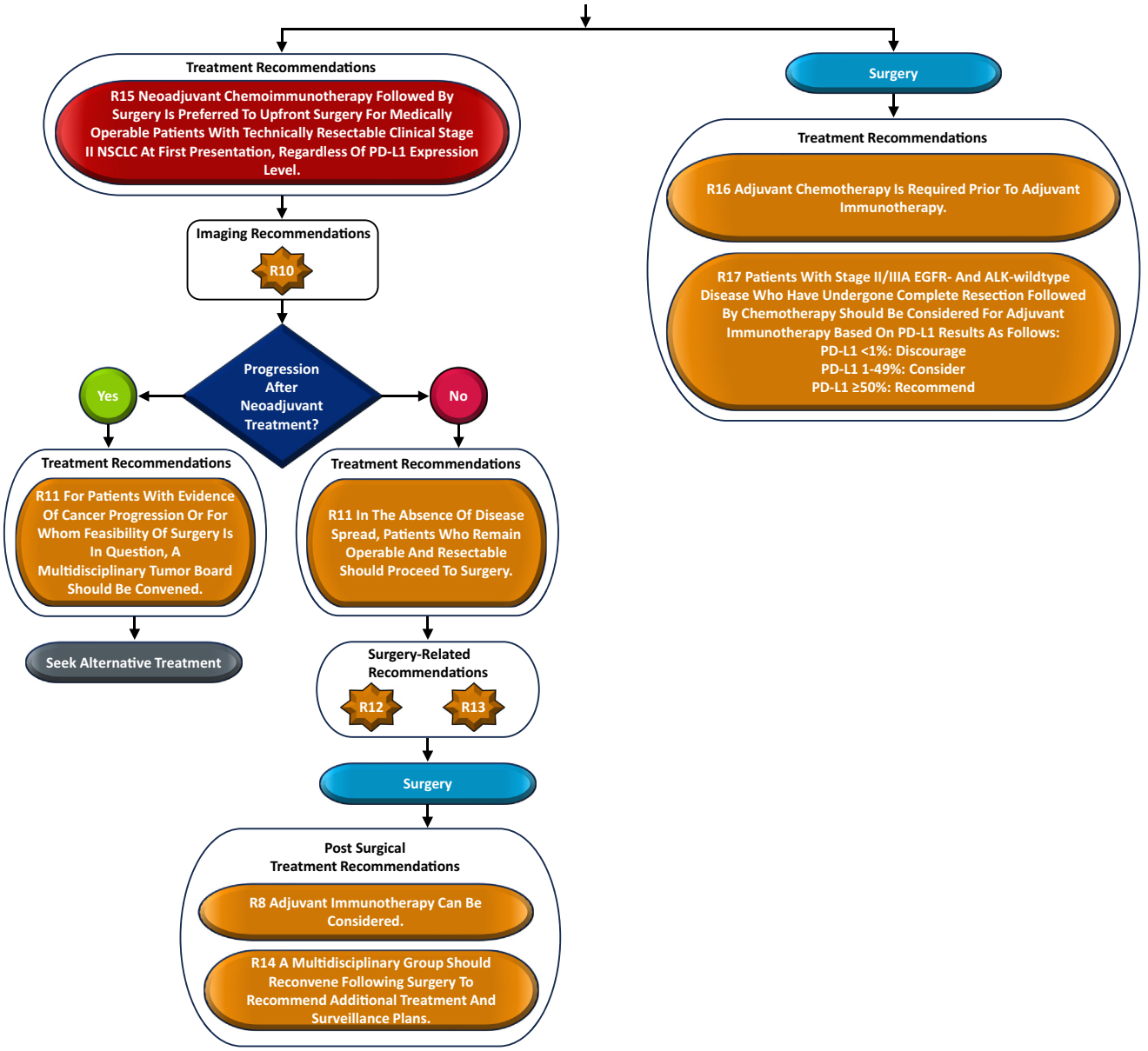

Figure 1. Continued.

clinical decision-making in cancer care. They identified 59 studies comprising 134,287 patients assigned to multidisciplinary care versus control across all cancer types. The hazard ratio (HR) was 0.67 and statistically significant in favor of multidisciplinary care for the outcome of OS with a median survival time of 30.2 months in the multidisciplinary care intervention group versus 19 months in the control group.[7] Given the growing complexity of care in early stage NSCLC requiring multispecialty expertise and the high level of evidence supporting multidisciplinary care in cancer, this recommendation was adopted unanimously.

Recommendation 2: Contrast-enhanced computed tomography (CT) of the chest and upper abdomen, positron emission tomography (PET), and invasive mediastinal staging, to rule out contralateral mediastinal nodal involvement (if suspicion exists), along with recent contrast-enhanced CT or magnetic resonance (MR) brain imaging, are strongly recommended for all patients at diagnosis.

Agreement: 100%

Accurate lung cancer staging is required to devise an optimal treatment plan. Contrast-enhanced CT of the chest

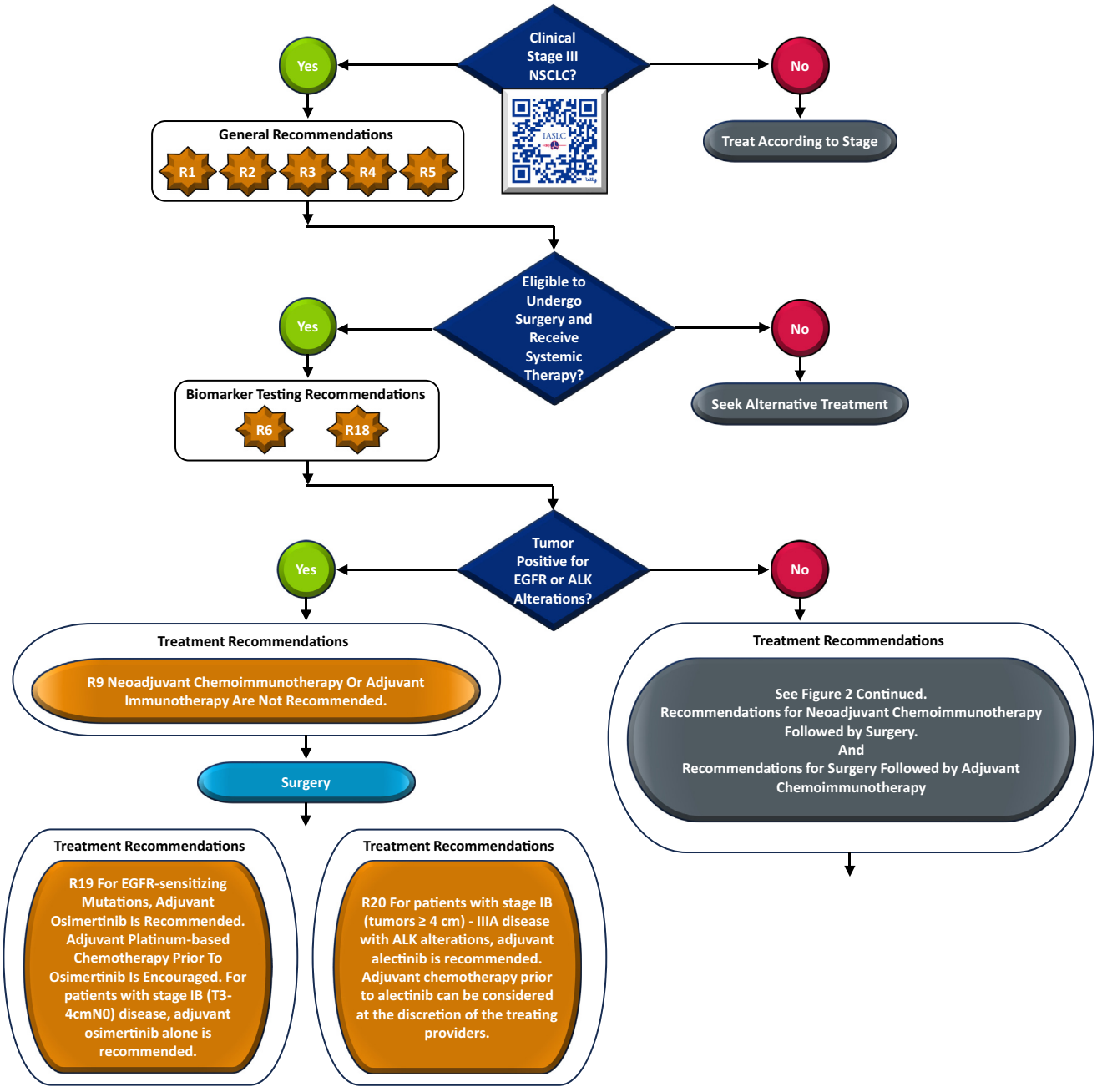

Figure 2. Workflow for neoadjuvant or adjuvant therapy for clinical stage III NSCLC. PD-L1, programmed death-ligand 1.

and upper abdomen is the minimal imaging tool for detection of mediastinal and extrathoracic disease.[8] A standalone PET scan provides additional information about occult metastases, but integrated PET-CT is preferred, if available, due to its increased diagnostic accuracy compared with either CT or PET alone.[8–12] A notable limitation of PET and PET-CT is the rate of false positives (ranging between 10% and 30%); therefore, equivocal results should be histologically confirmed. This is particularly critical in low- and middle-income countries (LMICs), where the high prevalence of infectious granulomatous diseases can otherwise lead to misleading staging. Invasive staging may be done to rule out contralateral disease. We acknowledge that endoscopic invasive mediastinal staging techniques, such as endobronchial ultrasound and endoscopic ultrasound, are not widely available in resource-limited countries and practices; however, surgical evaluation through mediastinoscopy or video-assisted thoracoscopic surgery serves as a viable alternative.[13] Furthermore, the committee understands global discrepancies in care and that some teams may work in a setting where access to PET is limited or unavailable. Our position is that use of PET is an optimal approach; however, use of contrast-enhanced CT with invasive mediastinal staging is an acceptable, although not optimal,

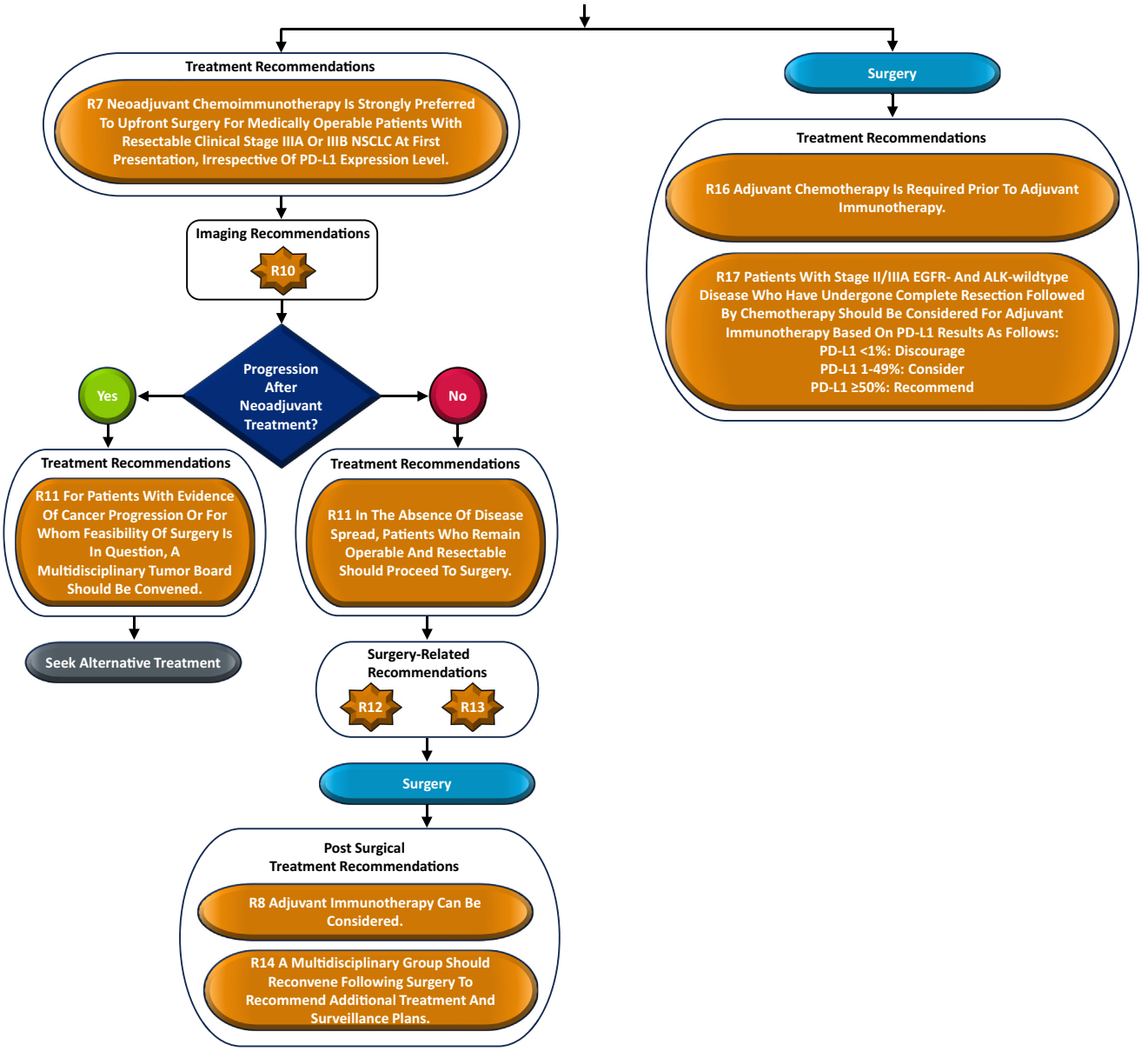

Figure 2. Continued.

alternative. To complete the imaging workup, a contrast-enhanced brain MR imaging (MRI) or CT scan is mandatory. It has been well established that MRI is more sensitive in detecting small brain metastases. Furthermore, the prevalence of brain metastases increases with higher disease stages. In a review of the National Cancer Database for patients with isolated brain metastases, the authors reported a prevalence of 1.7% and 3.7% in patients with stage IA and IB disease, respectively, and approximately 6% for patients with stages II and III disease (AJCC-UICC seventh edition).[14] There is a debate about the necessity for brain imaging in otherwise appropriately evaluated patients with clinical stage I disease where its omission in this setting, if asymptomatic, can be acceptable based on the very low rates of detection.

Recommendation 3: Surgical evaluation is required, preferably by a thoracic surgeon, to determine operability (medical fitness) and resectability (likelihood of R0 resection).

Agreement: 95%

Recommendation 4: Thoracic surgeons planning to operate on patients treated with neoadjuvant chemoimmunotherapy must be skilled in performing advanced pulmonary surgical maneuvers.

Agreement: 100%

Table 2. Recently Completed and Ongoing Phase 2 and 3 Clinical Trials Evaluating Neoadjuvant and Adjuvant Therapies in Early Stage Resectable NSCLC

Study	Study Design	Treatment Arms	Stage	Primary End Point(s)	PD-L1 Testing Requirement and Stratification	Allowance of EGFR-Mutated/ ALK-Rearranged Tumors	Primary Outcome Data	Regulatory Approval
Trials of Neoadjuvant Regimens								
CheckMate 816 (NCT02998528)	Randomized, phase 3, open label	• Neoadjuvant nivolumab ×3, q2w + ipilimumab ×1[a] • Neoadjuvant nivolumab + platinum doublet ×3, q3w n = 179) • Neoadjuvant platinum doublet ×3, q3w (n = 179) • Up to four cycles of adjuvant chemotherapy, radiotherapy, or both at investigator discretion	Resectable stage IB (≥4 cm) to IIIA (AJCC-UICC 7th edition)	• EFS • pCR	Required Stratification: <1 % vs. ≥ 1% 1%–49% vs. ≥50%	Excluded if known (in Asian countries, EGFR testing was mandatory but not in other regions)	Median follow-up 41.4 mo Median EFS: • Nivolumab + platinum doublet: NR (95% CI: 31.6–NR) • Platinum doublet: 21.1 mo (95% CI: 14.8–42.1) • HR 0.68; (95% CI: 0.49–0.93) pCR rate: • Nivolumab + platinum doublet: 24.0% (95% CI: 18.0–31.0) • Platinum doublet: 2.2% (95% CI: 0.6–5.6)[22,66]	• US FDA - neoadjuvant nivolumab with platinum-doublet chemotherapy for adult patients with resectable NSCLC.[60] • EMA - nivolumab with platinum-based chemotherapy for the neoadjuvant treatment of resectable NSCLC at high risk of recurrence in adult patients with tumor cell PD-L1 expression ≥1%.[50] • NICE - nivolumab with chemotherapy as an option for the neoadjuvant treatment of resectable (tumors at least 4 cm or node positive) NSCLC in adults.[56] • Health Canada – Neoadjuvant treatment of adult patients with resectable NSCLC (tumors ≥4 cm or node positive) when used in combination with platinum-doublet chemotherapy.[52]

(continued)

Table 2. Continued

Study	Study Design	Treatment Arms	Stage	Primary End Point(s)	PD-L1 Testing Requirement and Stratification	Allowance of EGFR-Mutated/ ALK-Rearranged Tumors	Primary Outcome Data	Regulatory Approval
								• Japan - neoadjuvant nivolumab in combination with chemotherapy for the treatment of NSCLC. • Australia - nivolumab, in combination with platinum-doublet chemotherapy, is indicated for the neoadjuvant treatment of patients with resectable NSCLC.[58]
NeoCOAST (NCT03794544)	Randomized phase 2, platform, open label	• Neoadjuvant durvalumab ×1 q4w (n = 26) • Neoadjuvant durvalumab ×1 q4w + oleclumab ×2 q2w (n = 21) • Neoadjuvant durvalumab ×1 q4w + monalizumab ×2 q2w (n = 20) • Neoadjuvant durvalumab ×1 q4w + danvatirsen ×4 q1w (n = 16)	Resectable stage I (>2 cm) to IIIA (for participants with N2 disease, only those with 1 single nodal station ≤3 cm are eligible) (AJCC-UICC 8th edition)	• MPR	Required Stratification: <1% vs. ≥1%	NR	MPR • Durvalumab: 11.1% (95% CI: 2.4-29.2) • Durvalumab + oleclumab: 19.0% (95% CI: 5.4-41.9) • Durvalumab + monalizumab: 30.0% (95% CI: 11.9-54.3) • Durvalumab + danvatirsen: 31.3% (95% CI: 11.0-58.7)[20]	

(continued)

Table 2. Continued

Study	Study Design	Treatment Arms	Stage	Primary End Point(s)	PD-L1 Testing Requirement and Stratification	Allowance of EGFR-Mutated/ ALK-Rearranged Tumors	Primary Outcome Data	Regulatory Approval
Trials of combined neoadjuvant followed by adjuvant regimens								
KEYNOTE-671 (NCT03425643)	Randomized, phase 3, double blind	• Neoadjuvant pembrolizumab + platinum doublet ×4, q3w followed by adjuvant pembrolizumab ×13, q3w (n = 397) • Neoadjuvant placebo + platinum doublet ×4, q3w followed by adjuvant placebo ×13, q3w (n = 400)	Resectable stage II, IIIA, and IIIB (T3-4N2) (AJCC-UICC 8th edition)	• EFS, per investigator • OS	Required Stratification: <50% vs. ≥50%	Allowed	Median follow-up 36.6 mo Median EFS • Pembrolizumab + platinum doublet then pembrolizumab: 47.2 (95% CI: 32.9-NR) • Placebo + platinum doublet then placebo: 18.3 mo (95% CI: 14.8-22.1) • HR = 0.59; (95% CI: 0.48-0.72); $p < 0.0001$ Median OS • Pembrolizumab + platinum doublet then pembrolizumab: NR (95% CI: NR-NR) • Placebo + platinum doublet then placebo: 52.4 mo (95% CI: 45.7-NR) • HR 0.72; (95% CI: 0.56-0.93); $p = 0.00517$[28,29]	• US FDA pembrolizumab with platinum-containing chemotherapy as neoadjuvant treatment, with continuation of single-agent pembrolizumab as adjuvant treatment.[61] • EMA - pembrolizumab in combination with platinum-containing chemotherapy as neoadjuvant treatment, then continued as monotherapy as adjuvant treatment, for resectable NSCLC at high risk of recurrence in adults.[63]

(continued)

Table 2. Continued

Study	Study Design	Treatment Arms	Stage	Primary End Point(s)	PD-L1 Testing Requirement and Stratification	Allowance of EGFR-Mutated/ ALK-Rearranged Tumors	Primary Outcome Data	Regulatory Approval
AEGEAN (NCT03800134)	Randomized, phase 3, double blind	• Neoadjuvant durvalumab + platinum doublet ×4, q3w followed by adjuvant durvalumab ×12, q4w (n = 366) • Neoadjuvant placebo + platinum doublet ×4, q3w followed by adjuvant placebo ×12, q4w (n = 374)	Resectable stage IIA to select (i.e., N2) Stage IIIB (AJCC-UICC 8th edition)	• pCR • EFS	Required Stratification: <1% vs. ≥1%	Originally included but later excluded per protocol revision	pCR • Durvalumab + platinum doublet then durvalumab: 17.2% • Placebo + platinum doublet then placebo: 4.3% Different, 13.0% (95% CI: 8.7–17.6); $p < 0.001$ Median Follow-up 11.7 mo Median EFS • Durvalumab + platinum doublet then durvalumab: NR (95% CI: 31.9-NR) • Placebo + platinum doublet then placebo: 25.9 mo (95% CI: 18.9-NR) HR 0.68; (95% CI: 0.53–0.88); $p = 0.004$[23]	

(continued)

Table 2. Continued

Study	Study Design	Treatment Arms	Stage	Primary End Point(s)	PD-L1 Testing Requirement and Stratification	Allowance of EGFR-Mutated/ ALK-Rearranged Tumors	Primary Outcome Data	Regulatory Approval
Neotorch (NCT04158440)	Randomized, phase 3, double blind	• Neoadjuvant toripalimab + platinum doublet ×3 q3w followed by adjuvant toripalimab + platinum doublet ×1 followed by adjuvant toripalimab ×13, q3w (stage III n = 202) • Neoadjuvant placebo + platinum doublet ×3, q3w followed by placebo + platinum ×1 followed by adjuvant placebo ×13, q3w (stage III n = 202)	Resectable stage II, IIIA, IIIB (N2) (AJCC-UICC 8th edition)[b,c]	• MPR stage III by BIPR • EFS stage III by investigator • MPR stage II-III by BIPR • EFS stage II-III by investigator	Required Stratification: <1% vs. ≥1%	Excluded	Median follow-up 18.3 mo Median EFS stage III • Toripalimab + platinum doublet then toripalimab: NR (95% CI: 24.4-NR) • Placebo + platinum doublet then placebo: 15.1 mo (95% CI: 10.6-21.9) • HR 0.40; (95% CI: 0.277-0.565); $p < 0.0001$ MPR Stage III • Toripalimab + platinum doublet then toripalimab: 48.5% (95% CI: 41.4-55.6) • Placebo + platinum doublet then placebo: 8.4% (95% CI: 5.0-13.1) • Difference between arms (stratified analysis), 40.2; (95% CI: 32.2-48.1); $p < 0.0001$[24]	

(continued)

Table 2. Continued

Study	Study Design	Treatment Arms	Stage	Primary End Point(s)	PD-L1 Testing Requirement and Stratification	Allowance of EGFR-Mutated/ ALK-Rearranged Tumors	Primary Outcome Data	Regulatory Approval
CheckMate 77T (NCT04025879)	Randomized, phase 3, double blind	• Neoadjuvant nivolumab + platinum doublet ×4, q3w followed by adjuvant nivolumab ×12, q4w (n = 229) • Neoadjuvant placebo + platinum doublet ×4, q3w followed by adjuvant placebo ×12, q4w (n = 232)	Resectable stage IIA (> 4 cm) to IIIB (T3N2) (AJCC-UICC 8th edition)	• EFS	NR	Excluded	Median follow-up 25.4 mo Median EFS • Nivolumab + platinum doublet followed by nivolumab: NR (95% CI: 28.9-NR) • Placebo + platinum doublet followed by placebo: 18.4 mo (95% CI: 13.6-28.1) • HR 0.58; (97.36% CI: 0.42-0.81); $p < 0.001$[78]	
IMpower 030 (NCT03456063)	Randomized, phase 3, double blind	• Neoadjuvant atezolizumab + platinum doublet ×4 q3w followed adjuvant atezolizumab ×16 q3w • Neoadjuvant placebo + platinum doublet ×4 q3w followed by best supportive care	Resectable Stage II, IIIA, or Select IIIB (T3N2 only) (AJCC-UICC 8th edition)	• EFS	Required but not stratified	Excluded	NR	
RATIONALE 315 (NCT04379635)	Randomized phase 3, double blind	• Neoadjuvant tislelizumab + platinum doublet 3-4×, q3w followed by adjuvant tislelizumab 8×, q6w (n = 226) • Neoadjuvant placebo + platinum doublet 3-4×, q3w followed by adjuvant placebo 8×, q6w (n = 227)	Resectable stage II or IIIA (AJCC-UICC edition not stated)	• MPR • EFS	Required Stratification: <1% vs. ≥1%	Excluded	Median follow-up 16.8 mo MPR • Tislelizumab + platinum doublet followed by tislelizumab 56.2% (95% CI: 49.5-62.8) • Placebo + platinum double followed by placebo 15.0% (95% CI: 10.6-20.3) • Difference 41.1% (95% CI: 33.2-49.1); $p < 0.0001$ EFS • NR[68]	

(continued)

Table 2. Continued

Study	Study Design	Treatment Arms	Stage	Primary End Point(s)	PD-L1 Testing Requirement and Stratification	Allowance of EGFR-Mutated/ ALK-Rearranged Tumors	Primary Outcome Data	Regulatory Approval
NEOSTAR (NCT03158129)	Randomized, phase 2 platform, open label	• Neoadjuvant ipilimumab ×1 + nivolumab + platinum doublet ×3, q3w followed by adjuvant SOC (n = 22) • Neoadjuvant nivolumab + platinum doublet ×3, q3w followed by adjuvant SOC (n = 22)	Resectable stage IB (≥4 cm) to IIIA (N2 single station); (AJCC-UICC 7th edition)	• MPR	Required	Included	MPR • Nivolumab + platinum doublet: 32.1% (80% CI: 18.7-43.1); p = 0.036 • Ipilimumab + nivolumab + platinum doublet: 50% (80% CI: 34.6-61.1); p = 0.00012[21]	
LCMC3 (NCT02927301)	Single-arm phase 2	• Neoadjuvant atezolizumab ×2, q3w followed by adjuvant atezolizumab up to 12 mo (n = 181, primary analysis n = 143)	Resectable stage IB-IIIB, T4 due to mediastinal organ invasion excluded (AJCC-UICC 8th edition)	• MPR	Required	Initially allowed but later excluded	MPR • 20% (95% CI: 14%-28%)[76]	
NADIM II (NCT03838159)	Randomized phase 2, Open label	• Neoadjuvant nivolumab + platinum doublet ×3, q3w followed by adjuvant nivolumab ×6, q4w (n = 57) • Neoadjuvant platinum doublet ×3, q3w (n = 29)	Resectable stage IIIA-IIIB, T3N2 (AJCC-UICC 8th edition)	• pCR	Required	Excluded	pCR • Neoadjuvant nivolumab + platinum doublet: 37% • Neoadjuvant + platinum doublet: 7% RR = 5.34; (95% CI: 1.34-21.23); p = 0.02[25]	

(continued)

Table 2. Continued

Study	Study Design	Treatment Arms	Stage	Primary End Point(s)	PD-L1 Testing Requirement and Stratification	Allowance of EGFR-Mutated/ ALK-Rearranged Tumors	Primary Outcome Data	Regulatory Approval
Adjuvant regimens								
IMpower 010 (NCT02486718)	Randomized phase 3, open label	• Adjuvant platinum-doublet followed by adjuvant atezolizumab ×16, q3w (n = 507) • Adjuvant platinum-doublet, ×4, q3w followed by BSC (n = 498)	Resected stage IB (≥4 cm) to IIIA (T2-3 N0, T1-3 N1, T1-3 N2, T4 N0-1) (AJCC-UICC 7th edition)	• DFS, PD-L1 ≥1%, stage II-IIIA, stage IB-IIIA (ITT)	Required Stratification: <1% vs. ≥1% 1%-49% vs. ≥50%	Allowed	Median follow-up 32.2 mo DFS (Stage II-IIIA0 (PD-L1 ≥1%) • Adjuvant atezolizumab: NE mo (95% CI: 36.1-NE) • BSC: 35.3 mo (95% CI: 29.0-NE) • HR = 0.66; (95% CI:0.50-0.88), p = 0.0039 DFS (stage II-IIIA) • Adjuvant atezolizumab: 42.3 mo (95% CI: 36.0-NE) • BSC: 35.3 mo (95% CI: 30.4-46.4) • HR = 0.79; (95% CI:0.64-0.96); p = 0.02 DFS (stage IB-IIIA) • Adjuvant atezolizumab: NE mo (95% CI: 36.1-NE) • BSC: 37.2 mo (95% CI: 31.6-NE) • HR = 0.81; (95% CI: 0.67-0.99); p = 0.04[80,83]	• US FDA - atezolizumab following resection and platinum-based chemotherapy in patients with stage II to IIIA NSCLC whose tumors have PD-L1 expression on ≥1% of tumor cells, as determined by an FDA-approved test.[59] • EMA - atezolizumab following complete resection and platinum-based chemotherapy in adult patients with NSCLC and a high risk of recurrence whose tumors do not have EGFR mutations or ALK alterations but have a PD-L1 expression of 50% or higher.[49] • NICE -atezolizumab after complete tumor resection in adults with stage II to IIIA NSCLC whose tumors have PD-L1 expression ≥ 50% and not progressed after platinum-based chemotherapy.[55] • Health Canada - adjuvant atezolizumab following complete resection and no progression after platinum-based adjuvant chemotherapy for adult patients with Stage II to IIIA (7th ed) NSCLC whose tumours have PD-L1 expression on ≥50% of tumor cells.[53]

(continued)

Table 2. Continued

Study	Study Design	Treatment Arms	Stage	Primary End Point(s)	PD-L1 Testing Requirement and Stratification	Allowance of EGFR-Mutated/ ALK-Rearranged Tumors	Primary Outcome Data	Regulatory Approval
								• Japan – adjuvant atezolizumab for PD-L1 positive NSCLC. • Australia - atezolizumab adjuvant monotherapy treatment following complete resection and no progression after platinum-based adjuvant chemotherapy for adult patients with stage II to IIIA (as per 7th edition of the UICC-AJCC staging system) NSCLC whose tumors have PD-L1 expression on ≥50% of tumor cells.[57]
PEARLS/ KEYNOTE-091 (NCT02504372)	Randomized phase 3, Double blind	• Adjuvant pembrolizumab q3w for 1 year following with or without prior adjuvant platinum-doublet (n = 590) • Adjuvant placebo q3w for 1 year with or without prior adjuvant platinum-doublet (n = 587)	Resected stage IB (≥4 cm) to IIIA (AJCC-UICC 7th edition)	• DFS (overall population) • DFS (PD-L1 ≥50%)	Required Stratification: <1% vs. 1%-49% vs. ≥50%	Allowed	Median follow-up 35.6 mo DFS (overall population) • Adjuvant pembrolizumab: 53.6 mo (95% CI: 39.2-NR) • Adjuvant placebo: 42.0 mo (95% CI: 31.3-NR) • HR = 0.76; (95% CI: 0.63-0.91); p = 0.0014 DFS (PD-L1 ≥50%) • Adjuvant pembrolizumab: NR (95% CI: 44.3-NR) • Adjuvant placebo: NR (95% CI: 35.8-NR) HR = 0.82; (95% CI: 0.51-1.18); p = 0.014[117]	• US FDA - pembrolizumab for adjuvant treatment following resection and platinum-based chemotherapy for stage IB (T2a ≥4 cm), II, or IIIA NSCLC.[62] • EMA – pembrolizumab monotherapy for the adjuvant treatment of adults with NSCLC who are at high risk of recurrence following complete resection and platinum-based chemotherapy.[51] • Health Canada - Adjuvant treatment of adult patients with Stage IB (T2a ≥4 cm), II, or IIIA NSCLC who have undergone complete resection and platinum-based chemotherapy.[54]

(continued)

Table 2. Continued

Study	Study Design	Treatment Arms	Stage	Primary End Point(s)	PD-L1 Testing Requirement and Stratification	Allowance of EGFR-Mutated/ ALK-Rearranged Tumors	Primary Outcome Data	Regulatory Approval
ADAURA (NCT02511106)	Randomized phase 3, double blind	• Adjuvant osimertinib qd for up to 3 y with or without prior adjuvant chemotherapy • Adjuvant placebo qd for up to 3 y with or without prior adjuvant chemotherapy	Resected stage IB (T2a tumors >3 cm and ≤5 cm), II, or IIIA (AJCC-UICC 7th edition)	• DFS (stage II-IIIA) • DFS (stage IB-IIIA)	Not evaluated	Required to have exon 19 deletion or exon 21 L858R mutation, either alone or in combination with a T790M mutation ALK not evaluated	Median follow-up 44.2 mo DFS (stage II-IIIA) • Osimertinib: 65.8 mo (95% CI: 54.4-NC) • Placebo: 21.9 mo (95% CI: 16.6-27.5) HR = 0.23; (95% CI: 0.18-0.30) DFS (stage IB-IIIA) • Osimertinib: 68.8 mo (95% CI:61.7-NC) • Placebo: 28.1 mo (95% CI:22.1-35.0) • HR = 0.27; (95% CI: 0.21-0.34)[44,118]	• US FDA - osimertinib for adjuvant therapy after tumor resection in patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.[124] • EMA - osimertinib for the adjuvant treatment of adult patients with stage IB-IIIA NSCLC (EGFR exon 19 deletion or exon 21 L858R) after complete tumor resection with curative intent whose tumors have.[120] • NICE - Osimertinib as adjuvant treatment after complete tumor resection in adults with stage IB-IIIA NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. It is recommended only if osimertinib is stopped at 3 y, or earlier if there is disease recurrence or unacceptable toxicity and is provided by the company according to the managed access agreement.[122]

(continued)

Table 2. Continued

Study	Study Design	Treatment Arms	Stage	Primary End Point(s)	PD-L1 Testing Requirement and Stratification	Allowance of EGFR-Mutated/ ALK-Rearranged Tumors	Primary Outcome Data	Regulatory Approval
								• Health Canada - (osimertinib) is indicated as adjuvant therapy after tumor resection in patients with stageIB–IIIA1 non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.[121] • People's Republic of China - osimertinib for the adjuvant treatment of patients with IB, II and IIIA EGFR exon 19 deletion or exon 21 L858R mutation positive NSCLC after tumor resection with curative intent, with or without adjuvant chemotherapy as recommended by the patient's physician. • Japan - osimertinib) for the adjuvant treatment of patients with EGFR mutated NSCLC after surgery. • Australia - osimertinib as adjuvant therapy after tumor resection in patients with NSCLC whose tumors have activating EGFR mutations, as detected by a validated test.[123]

(continued)

Table 2. Continued

Study	Study Design	Treatment Arms	Stage	Primary End Point(s)	PD-L1 Testing Requirement and Stratification	Allowance of EGFR-Mutated/ ALK-Rearranged Tumors	Primary Outcome Data	Regulatory Approval
ALINA (NCT03456076)	Randomized phase III, open label	• Adjuvant alectinib bid for up to 2 y (n = 130) • Adjuvant platinum doublet, ×4, q3w (n = 127)	• Stage IB (≥4 cm) - IIIA (T2-3 N0, T1-3 N1, T1-3 N2, T4 N0-1) (AJCC-UICC 7th edition)	• DFS (stage II-IIIA) • DFS (stage IB-IIIA)	• Not evaluated	Required to have ALK mutations EGFR not evaluated	Median follow-up 27.8 mo chemotherapy and 27.9 mo alectinib • DFS (stage II-IIIA) • Alectinib: NR (95% CI: NE-NE) • Chemotherapy: 44.4 mo (95% CI: 27.8-NE) • HR = 0.24; (95% CI: 0.13-0.45), $p < 0.0001$ • DFS (stage IB-IIIA) • Alectinib: NR (95% CI: NE-NE) • Chemotherapy: 41.3 mo (95% CI: 28.5-NE) • HR = 0.24; (95% CI: 0.13-0.43), $p < 0.0001$[45,46]	• US FDA – adjuvant alectinib following tumor resection in patients with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test.[129]

[a]Nivolumab plus ipilimumab closed enrollment early on the basis of external trial data reported during the trial.
[b]Defined as eligible for radical resection evaluated by a qualified thoracic surgeon.
[c]Defined as "resectable" and "potential resectable" according to the Chinese expert consensus on the multidisciplinary diagnosis and treatment for stage III NSCLC (2019): resectable includes IIIA (N0-1), partial N2 with single-station mediastinal lymph node metastasis and the short diameter of lymph node <2 cm, partial T4 (satellite nodules in the adjacent lobe) N1; potential resectable includes partial stage IIIA and IIIB with the short diameter of single-station N2 mediastinal lymph node<3 cm, other potentially resectable T3 or T4 central tumor.[67]
AJCC, American Joint Committee on Cancer; BIPR, blind independent pathologic review; BSC, best supportive care; CI, confidence interval; DFS, disease-free survival; EFS, event-free survival; EMA, European Medicines Agency; HR, hazard ratio; ITT, intent to treat; MPR, major pathologic response; NICE, National Institute for Health and Care Excellence; NC, not calculated; NCT, ClinicalTrials.gov identifier; NE, not evaluable; NR, not reached; pCR, pathologic complete response; PD-L1, programmed death-ligand 1; rNSCLC, resectable NSCLC; RR, relative risk; q1w, every week; q3w, every 3 weeks; q4w, every 4 weeks; SOC, standard of care; TPS, tumor proportion score; UICC, Union for International Cancer Control; U.S. FDA, United States Food and Drug Administration.

These recommendations are based primarily on expert opinion and consensus agreement. The expert panel recognizes that globally there could be nuances in defining surgical skills[15] and this could apply to highly specialized centers performing such procedures, as there is a positive correlation between high volume centers and patient survival,[16] rather than a specific surgeon. Data from observational studies support evaluation by a thoracic surgeon, especially compared with a nonthoracic surgeon. For example, the rate of pulmonary resection in patients with NSCLC increased from 12% to 23% with the addition of dedicated thoracic surgeons to a multidisciplinary treatment group.[17] Furthermore, other data suggest that pulmonary resection after neoadjuvant immunotherapy is safe and feasible, albeit potentially challenging, including a conversion rate from a thoracoscopic approach to an open approach as high as 22% in one series of 25 patients.[18] In an era in which a minimally invasive approach is considered the standard of care,[19] the inclusion of a thoracic surgeon in the decision-making process about operability, including the conduct of safe, oncologically effective, and standard-of-care resection, should be considered mandatory. Recent trials evaluating neoadjuvant therapy have, in alignment with our recommendation, included a thoracic surgeon when determining resectability.[20–29] The definition of surgical resectability is a longstanding question in the field and is clearly guided by surgical expertise and multidisciplinary team experience with varying complementary and competing treatment modalities and has evolved with the increasing efficacy of systemic treatment to mitigate the impact of micrometastatic disease on long-term survival outcomes. An International European Organisation for Research and Treatment of Cancer (EORTC) Survey on Resectability of stage III NSCLC may be a future guide to help answer this question, in particular in the context of clinical trial protocol elaboration.[30] The primary objective of recommendation 3 is to ensure that a neoadjuvant strategy is not initiated for a patient before obtaining a thoracic surgical assessment. With respect to recommendation 4, advanced pulmonary surgical maneuvers, including extended pulmonary resection, bronchial and- vascular pulmonary reconstructions, are not common procedures in all surgical practices. Pulmonary resections for stage I disease require a different skill set than what is required for locally advanced disease. Although it is crucial to acknowledge that access to specialists who can perform high-quality lung cancer surgery, particularly those experienced with surgeries occurring post-neoadjuvant treatments, is limited in many LMICs, it is advisable to make every reasonable effort to refer patients to centers that offer safe surgical options for these scenarios when possible.[31,32] Furthermore, although there are limited data to support this statement, there is a pragmatic expectation that the complexity of surgery for locally advanced NSCLC is heightened, and neoadjuvant chemoimmunotherapy may create scenarios that require such advanced maneuvers more frequently.[33]

Recommendation 5: Evaluation of the patient by a physician skilled in administering systemic therapy to patients with early stage disease is required.

Agreement: 100%

In addition to achieving consensus on this recommendation, the panel unanimously agreed that no additional support from the literature was needed as this is standard medical practice. Owing to global variations in training requirements for such medical acts, the precise specialty or certification is not detailed in our recommendation. Recommendation 5 also aims to make clear that surgical suitability for neoadjuvant chemoimmunotherapy is only one part of the multidisciplinary assessment required for adoption of such an approach for a given patient. Expert assessment and skilled management of a patient's overall and changing medical fitness including, but not limited to, comorbidities and potential toxicities, throughout the therapeutic journey are required.

Recommendation 6: For patients being considered for neoadjuvant or adjuvant systemic therapy, at a minimum, determination of *EGFR* and *ALK* alteration status is required. Tumor proportion score measurement for determination of PD-L1 status should also be considered.

Agreement: 100%

Patients with NSCLC can generally be divided into two distinct treatment categories: those with actionable oncogenic drivers who are predominantly treated with targeted therapies and all other patients for whom ICI-based therapy is recommended if medically appropriate. Patients with driver genomic alteration-positive tumors are typically without a smoking history with a low mutational burden and do not experience meaningful responses to ICIs. Data in advanced NSCLC have consistently revealed limited or no benefit associated with administration of ICIs alone for patients with tumors harboring *EGFR* or *ALK* alterations.[34,35] Subset analyses of patients primarily with *EGFR*-mutated or *ALK*-rearranged tumors treated in randomized trials of ICI monotherapy versus docetaxel did not find a

meaningful survival improvement with ICIs.[36] Retrospective and single-arm phase 2 trials also support this observation.[35,37,38] As a result, most trials that evaluated ICIs as first-line treatment for advanced disease excluded patients whose tumors harbored an *EGFR* or *ALK* alteration. Recently, two prospective randomized trials specifically evaluating the role of chemotherapy plus an ICI versus chemotherapy alone after TKI failure in patients with advanced or metastatic *EGFR*-mutated tumors—CheckMate 722 and KEYNOTE-789—failed to meet their primary PFS and OS end points.[36,39] Nevertheless, a recent analysis of ORIENT-31 trial revealed a statistically significant PFS benefit for chemotherapy plus sintilimab versus chemotherapy alone in patients with *EGFR*-mutant and targeted therapy-refractory NSCLC, although OS did not differ between treatment arms. It is worth noting that, compared with the other phase 3 randomized studies mentioned previously, the ORIENT-31 exclusively enrolled subjects from People's Republic of China.[40] At this time, we cannot explain the discordance in these results; however, it is possible that differences in geographic distribution, patients, and tumor characteristics may have played a role. In patients with locally advanced and unresectable disease, a small subset of patients with EGFR or ALK-altered tumors receiving consolidation durvalumab did not derive benefit.[41] In patients with early stage resectable disease, the AEGEAN study testing perioperative durvalumab added to neoadjuvant chemotherapy in patients with early stage rNSCLC included 51 patients with *EGFR*-mutant NSCLC in both treatment arms and revealed that the perioperative ICI-based approach did not seem to provide improved benefit in the limited cohort of patients with *EGFR*-mutant disease compared with neoadjuvant chemotherapy alone, also supporting this observation.[23,42] Nevertheless, there are also conflicting data suggesting potential benefit of immunotherapy in limited subsets of patients with early stage rNSCLC in the literature, which are discussed under recommendation 9. Overall, the body of evidence does not support the role of ICIs in patients with *EGFR*- and *ALK*-aberrant tumors.

In addition to the lack of clear efficacy for ICIs in patients with NSCLC harboring *EFGR* or *ALK* alterations, another important observation is the relatively high rate of treatment-related toxicity for patients undergoing subsequent targeted therapy treatment after ICI therapy.[43] Given the recent demonstration of improved OS in the ADAURA trial in *EGFR*-mutant patients with resected stages II and III NSCLC[44] and the very significant improvement in DFS for patients with *ALK*-altered tumors who were treated in the ALINA trial,[45,46] one cannot recommend the use of any neoadjuvant -or adjuvant ICIs for such patients.

Regarding the type and extent of molecular testing in patients with early stage disease, testing by next-generation sequencing (NGS) is preferred due to the opportunity to effectively detect all actionable genomic alterations. We recognize that in some scenarios, such as LMICs, where access to NGS is restricted and molecular testing relies on drug companies, the use of single-alteration *EGFR* testing through polymerase chain reaction-based assays and immunohistochemistry (IHC), fluorescence in situ hybridization, or polymerase chain reaction assays for *ALK* would be acceptable.[47] Inevitably, as a more comprehensive and standardized panel of genomic alterations becomes increasingly available with molecular testing for patients with early stage rNSCLC, clinicians will have to contend with a growing body of biological information and detail for which there is a paucity of data to provide treatment guidance. Inferences from the metastatic setting are reasonable but susceptible to error without clear confirmatory data. For these reasons, the panel felt uneasy about recommending testing in patients with early stage NSCLC for additional molecular alterations, beyond *EGFR* and *ALK*, that were found to be associated with poor responses to ICIs and- for which neoadjuvant- or adjuvant-targeted therapy trials are ongoing in the resectable disease setting. Recommendations on the extent of molecular testing in the early stage rNSCLC are not broadly applicable and should be handled in a case-by-case manner. This certainly represents an important gap in knowledge as we move forward in this space.

PD-L1 expression on tumor cells as assessed by IHC, which ranges from 0% to 100%,[48] is mostly correlated with the ICI efficacy in the advanced disease setting, and the PD-L1 tumor proportion score (TPS) is routinely used to determine whether ICI monotherapy versus in combination with chemotherapy should be administered. Note that the PD-L1 antibody clones are different across trials. Reflex testing and physician ordering are two distinct approaches to request PD-L1 IHC analysis. Reflex testing can streamline the testing process by reducing back and forth communications between pathologists and treating physicians and ultimately accelerate time to treatment. Nevertheless, the ability of tumor PD-L1 status to predict outcomes for ICI-based regimens in the early stage setting is not yet fully understood, as several small- and large-scale studies have reported association, or lack thereof, between tumor PD-L1 expression and response to therapy in neoadjuvant and perioperative ICI trials. PD-L1 TPS has become an important metric for regulatory approvals (Table 2) in some jurisdictions but not others[49–63]; therefore, the expert panel felt that PD-L1 was not an essential factor in determining whether a patient should or should not be considered for neoadjuvant or

perioperative chemoimmunotherapy. Specifically, potential benefits can be found across PD-L1 strata,[64,65] albeit at a relatively lower magnitude of effect in PD-L1–negative patients.[21–24,28,29,66–68] Similarly, data from the adjuvant setting are conflicting on this subject and the value of PD-L1 testing should be considered in the context of the specific clone used to perform the test and the anticipated ICI agent to be used.

Neoadjuvant Treatment Recommendations

Background. The goal of neoadjuvant therapy is early eradication of micrometastatic disease, thus preparing patients for surgery that is more likely to be curative. Most patients whose disease recurs after surgical resection have distant metastasis and ultimately succumb to their disease. Neoadjuvant chemotherapy followed by surgery has yielded a modest improvement of 5% to 6% in 5-year recurrence-free survival and OS compared with surgery alone.[69] The efficacy of ICIs and targeted therapies in the advanced disease setting has led to enthusiasm for evaluating them in the earlier-stage, potentially curative, setting. ICIs are particularly attractive for evaluation in the neoadjuvant setting, when localized tumors are intact, as they can increase immunogenic cell death by releasing more neoantigens and further boosting an immunologic response and are thought to possess low clonal resistance.[70,71] In addition, intact lymph nodes are expected to facilitate priming of immune cells. This has been found in laboratory models and in patients with NSCLC.[72–74] The era of neoadjuvant ICI for rNSCLC was introduced when Forde et al.[75] reported results from a single-arm pilot study of two cycles of neoadjuvant nivolumab followed by resection in 21 patients with stages I to IIIA lung cancer. The regimen was found to be feasible and safe with a highly encouraging MPR rate of 45%, when considering a conservative 15% MPR rate observed with historical controls of neoadjuvant chemotherapy.[75] Other phase 2 studies corroborated and built on these findings in the context of ICI therapy as monotherapy, as dual ICI blockade or as ICI therapy combined with novel immuno-oncology agents. Even more impressive results in terms of pathologic response were observed when ICI single agents were combined with chemotherapy.[26,27] CheckMate 816 was the first phase 3 trial to evaluate three neoadjuvant cycles of nivolumab in combination with platinum doublet chemotherapy versus chemotherapy alone in patients with resectable stages IB to IIIA NSCLC (AJCC-UICC seventh edition) using EFS and pCR as primary end points of efficacy.[22] Compared with neoadjuvant chemotherapy alone, nivolumab plus chemotherapy significantly improved median EFS compared with chemotherapy alone (not reached [NR] [95% confidence interval [CI]: 31.6–NR] versus 21.1 [95% CI: 14.8–42.1] mo, respectively; HR for EFS, 0.68; 95% CI: 0.49–0.93, at a median follow-up of 41.4 mo).[66] These improvements in EFS were tightly linked to a dramatically higher rate of pCR compared with chemotherapy alone (24.0% versus 2.2%, respectively; OR = 13.94; 99% CI: 3.49–55.75; $p < 0.001$).[22] Indeed, patients in the nivolumab plus chemotherapy arm who achieved a pCR experienced a 3-year OS rate of 95% in a cohort composed of two-thirds stage III disease. In this study, higher pCR rates were numerically higher in the nivolumab plus chemotherapy group compared with chemotherapy alone arm irrespective of tumor PD-L1 expression levels (pCR rates for PD-L1 $< 1\%$ and PD-L1 $\geq 1\%$: nivolumab plus chemotherapy arm, 16.7% and 32.6%, respectively; chemotherapy arm: 2.6% and 2.2%, respectively). Although the Food and Drug Administration, National Institute for Health and Care Excellence, Health Canada, and other regulatory agencies approved the regimen in patients with tumors more than or equal to 4 cm or node-positive disease irrespective of PD-L1 expression level, the European Medicines Agency chose to restrict eligible patients for this approach to those with PD-L1 more than or equal to 1%.[49–62]

The perioperative ICI-based approach takes advantage of the administration of immunotherapy in both the neoadjuvant and adjuvant phases of the treatment to facilitate continuous micrometastatic killing and sustained antitumor immunity throughout the surgical setting. Encouraging results have been found with this strategy in small-scale phase 2 studies.[25,76] This approach has now been tested in several large-scale phase 3 trials for which results are now maturing (Table 2). Five phase 3 studies have reported on the use of ICIs as both neoadjuvant and adjuvant therapies (i.e., perioperative): AEGEAN, Neotorch, KEYNOTE-671, CheckMate 77T, and RATIONALE 315.

AEGEAN is a randomized phase 3 trial in patients with stage II or III (AJCC-UICC eighth edition) rNSCLC. Patients were randomized to neoadjuvant durvalumab plus platinum doublet followed by adjuvant durvalumab versus neoadjuvant placebo plus platinum doublet followed by adjuvant placebo. An interim analysis revealed a 13% (95% CI: 8.7–17.6) difference in pCR rate between the two treatment arms: 17.2% versus 4.2% for durvalumab versus placebo, respectively; this was statistically significant ($p = 0.000035$). The EFS, with a median follow-up of 11.7 months, was significantly longer in the durvalumab, not reached (95% CI: 31.9–NR), arm versus the placebo arm, 25.9 months (95% CI: 18.9–NR) with a HR of 0.68; (95% CI: 0.53–0.88; $p = 0.004$).[23]

Neotorch is an ongoing, randomized, phase 3 study comparing toripalimab (an anti–PD-1 antibody) plus

platinum doublet chemotherapy followed by adjuvant toripalimab with placebo plus platinum doublet chemotherapy followed by adjuvant placebo in patients with newly diagnosed stages II to III rNSCLC. The following definitions for "resectable" and "potential resectable," per the 2019 Chinese expert consensus criteria, were used in this trial: resectable includes stage IIIA (N0–1), partial N2 tumors with single-station mediastinal lymph node metastasis, and a short lymph node with a diameter of less than 2 cm and partial T4, N1 tumors (satellite nodules in the adjacent lobe), whereas potential resectable includes partial stage IIIA and IIIB tumors with a short diameter of single-station N2 mediastinal lymph nodes less than 3 cm and other potentially resectable T3 or T4 central tumors.[77] Co-primary end points were EFS by investigator among patients with stage III disease, EFS by investigator among patients with stages II and III disease, MPR by blind independent pathologic review among patients with stage III disease, and MPR by blind independent pathologic review among patients with stages II and III disease. In this trial, it is noteworthy that results are currently only available for patients with stage III, most of whom are male patients with squamous cell carcinoma. Among the patients with stage III disease, those who received toripalimab experienced significantly longer median EFS (not estimable [NE]; 95% CI: 24.4–NE) compared with placebo patients (15.1 mo [95% CI: 10.6–21.9]); HR equal to 0.40; 95% CI: 0.277–0.565; $p < 0.0001$. Toripalimab plus chemotherapy resulted in a significantly higher MPR rate compared with chemotherapy plus placebo (48.5% [95% CI: 41.4–55.6] versus 8.4% [95% CI: 5.0–13.1], respectively); difference between arms: 40.2; 95% CI: 32.2–48.1; $p < 0.0001$.[24]

The randomized phase 3 KEYNOTE-671 trial evaluated neoadjuvant pembrolizumab plus platinum doublet chemotherapy followed by adjuvant pembrolizumab compared with neoadjuvant placebo plus platinum doublet chemotherapy followed by adjuvant placebo in patients with stages II, IIIA, and IIIB rNSCLC (AJCC-UICC eighth edition). Both independent primary end points of EFS and OS have been met. Results at a median follow-up of 36.6 months revealed that patients who received neoadjuvant and adjuvant pembrolizumab experienced statistically significant improvement in median EFS by investigator compared with patients in the placebo arm. The median EFS was 47.2 months (95% CI: 39.2–NR) in the pembrolizumab arm compared with 18.3 months (95% CI: 14.8–22.1) in the placebo arm; HR equal to 0.59 (95% CI: 0.48–0.72); $p < 0.0001$. Median OS was not reached (95% CI: NR–NR) among patients who received pembrolizumab, compared with 52.4 months (95% CI: 45.7–NR) in placebo patients, $p = 0.00517$.[28]

CheckMate 77T is a phase 3 randomized control trial that compared neoadjuvant nivolumab plus platinum doublet chemotherapy followed by curative-intent surgery and adjuvant nivolumab to neoadjuvant placebo plus platinum doublet followed by surgery and adjuvant placebo in patients with stages IIA to IIIB rNSCLC (AJCC-UICC eighth edition)[78] The primary end point was EFS by blinded independent central review, and at a median follow-up of 25.4 months, the percentage of patients with 18-month EFS was 70.2% in the nivolumab arm and 50.0% in the chemotherapy group (HR for disease progression or recurrence, abandoned surgery, or death, 0.58; 97.36% CI: 0.42–0.81; $p < 0.001$).[78] Interestingly, in an exploratory post hoc landmark analysis of efficacy according to adjuvant treatment status, EFS from definitive surgery seemed to be improved among patients who had received adjuvant therapy in the nivolumab arm as compared with patients treated in the chemotherapy group, and among the patients who could not receive adjuvant therapy, EFS from definitive surgery also seemed to be improved with nivolumab treatment compared with chemotherapy. Patient and disease characteristics in these subgroups are heterogeneous, and, therefore, the results of these exploratory analyses should be taken with caution, and future trials testing adjuvant immunotherapy after neoadjuvant chemoimmunotherapy in rNSCLC will be of critical importance to depict the specific contribution of each treatment component in this setting.[78]

Another ongoing phase 3 trial (RATIONALE 315) randomized patients with stage II or IIIA rNSCLC to either neoadjuvant tislelizumab plus platinum doublet followed by adjuvant tislelizumab or neoadjuvant placebo plus platinum doublet followed by adjuvant placebo. The EFS at a median follow-up of 16.8 months was yet to be reported at the time of this writing; however, the MPR was found to be 56.2% (95% CI: 49.5–62.8) in the tislelizumab-treated patients versus 15.0% (95% CI: 10.6–20.3) in those patients who received placebo. This difference of 41.1% (95% CI: 33.2–49.1) was significant ($p < 0.0001$).[68]

Neoadjuvant Treatment—Consensus Recommendations

Recommendation 7: Neoadjuvant chemoimmunotherapy is strongly preferred to upfront surgery for medically operable patients with resectable clinical stage IIIA or IIIB NSCLC at first presentation, irrespective of PD-L1 expression level.

Agreement: 94%

Recommendation 8: Following surgery in patients who receive neoadjuvant chemoimmunotherapy, adjuvant immunotherapy can be considered.

Agreement: 94%

The panel expressed a clear preference for neoadjuvant chemoimmunotherapy for eligible patients with clinical stage III given the robust and consistent EFS benefit across the reported phase 3 trials, in addition to a significant OS benefit. Survival benefits measurable in the context of the adjuvant immunotherapy trials omit all patients who had grade 5 complications after surgery and those with positive margins, which all constitute events when using EFS as the outcome of interest as opposed to DFS. Furthermore, the benefits of adjuvant immunotherapy after upfront surgery seem to only be present in patients who receive platinum doublet chemotherapy. Results from the VIOLET trial indicate that no more than 50% of eligible patients after complete surgery who meet indications will proceed to adjuvant chemotherapy.[19,79] Notably, OS benefits of adjuvant ICI therapy seem limited to patients with PD-L1 levels equal to or greater than 50% based on the IMpower 010 trial.[80] Thus, survival benefits of adjuvant ICI in patients with stage III rNSCLC are limited to a reduced cohort of patients. Conversely, receipt of a complete therapeutic course consisting of meaningful systemic therapy and curative surgery or definitive locoregional control through radiotherapy is far more likely with a neoadjuvant approach. These data were corroborated in the KEYNOTE-671 trial where more than 90% of patients completed either surgery or in-protocol chemoradiotherapy after neoadjuvant chemotherapy and pembrolizumab.[28,29] KEYNOTE-671 is currently the only trial in the neoadjuvant, perioperative, or adjuvant ICI setting to find an OS benefit in the intention-to-treat population across all PD-L1 strata, with a favorable HR of 0.74 for stage IIIA and a HR of 0.69 for stage IIIB disease. Finally, a recent meta-analysis finds clear OS benefit in patients with stage III regardless of PD-L1 status when all randomized neoadjuvant and perioperative trials with available OS data are pooled, revealing a statistically significant HR of 0.67 (95% CI:0.53–0.85).[65] Nevertheless, it is important to note that no study compares neoadjuvant chemoimmunotherapy with adjuvant chemotherapy followed by immunotherapy, and although studies comparing these approaches may be launched in the near future, we will not have results for such trials for many years. In this regard, the expert panel felt that it was important to express the preferred approach based on the totality of data available on the subject.

Recommendation 9: For patients with TKI-sensitizing *EGFR* or *ALK* alterations, neoadjuvant chemoimmunotherapy or adjuvant immunotherapy is not recommended.

Agreement: 95%

Three key lines of evidence support this recommendation: (1) there is proven DFS and OS benefit for the addition of adjuvant osimertinib in resected stages II and III *EGFR*-mutated NSCLC and DFS benefit for the addition of adjuvant alectinib in resected stages II and III *ALK*-translocated NSCLC[44,45]; (2) evidence from the metastatic setting and from most phase 3 neoadjuvant trials that included *EGFR* or *ALK*-altered patients points to an absence of benefit when treated with ICIs[34,81]; (3) evidence from the AEGEAN study suggests no benefit from chemoimmunotherapy with perioperative durvalumab in a limited cohort of patients with *EGFR*-mutant rNSCLC[23]; and (4) evidence from the metastatic setting suggests strongly that increased adverse events are experienced by patients who receive ICI before receipt of TKI.[43] Nevertheless, in a subset analysis of KEYNOTE-671, the EFS HR was improved in favor of the pembrolizumab arm in patients with *EGFR* mutations (0.09 [95% CI: 0.01–0.74]) compared with patients with *EGFR* wild-type disease (0.48 [95% CI: 0.31–0.34]), albeit in a very small number of patients. In addition, a retrospective analysis from People's Republic of China revealed that MPR and pCR were obtained in 42% and 11%, respectively, of 19 patients with *EGFR*-mutated NSCLC who received chemoimmunotherapy.[82] Furthermore, it is important to mention that in the IMpower-010 trial, in patients with stages IIA to IIIA resected NSCLC with tumor cell PD-L1 expression equal to or greater than 1% and with an *EGFR* mutation (total 43 in 476 patients in both treatment arms), the HR for DFS was 0.57 in favor of adjuvant atezolizumab compared with best supportive care, suggesting a potential benefit from ICI in a specific subset of patients with resected NSCLC, although caution is needed in interpreting these results given the limited number of patients with EGFR-mutated NSCLC in this cohort.[83]

Thus, it is unclear from the available results whether a subset of patients with *EGFR* mutations may at all benefit from neoadjuvant chemoimmunotherapy, and this question could be tested in future clinical trials. Looking at the totality of available data on this subject and by extrapolation of relevant trials, there is very limited rationale to support the current use of neoadjuvant chemoimmunotherapy for patients with TKI-sensitizing alterations in the *EGFR* or *ALK* genes.

Recommendation 10: Contrast-enhanced CT of the chest is required before surgery. In the absence of radiographic progression after neoadjuvant chemoimmunotherapy, invasive mediastinal restaging is not routinely required.

Agreement: 100%.

Recommendation 11: In the absence of disease spread, patients who remain operable and resectable should proceed to surgery. For patients with evidence of cancer progression or for whom feasibility of surgery is in question, a multidisciplinary tumor board should be convened.

Agreement: 100%.

The panelists discussed that contrast-enhanced CT provides the information needed to determine whether patients treated with neoadjuvant therapy should proceed to surgery. The group agreed that invasive restaging should not be done in most cases. None of the phase 3 neoadjuvant protocols mandated invasive mediastinal restaging, and data regarding the value of this practice in terms of optimizing patient outcomes are lacking. Some centers have a practice that declines surgery to patients with persistent N2 disease; however, to our knowledge, there are no reported data to suggest that these patients are better served by nonsurgical treatments. Although some teams may decide to continue to routinely perform invasive mediastinal restaging, the expert panel felt that this may pose logistical challenges, be resource intensive, and create a risk for increasing delays to surgery. In addition, in contexts where resources are scarce or endoscopic methods for mediastinal restaging are not widely available—such as in many LMICs—performing a re-mediastinoscopy can be extremely challenging and is often associated with a high rate of complications. Nevertheless, certain scenarios such as nodal immune flare should trigger invasive restaging to avoid declining surgery to a patient who may be experiencing a form of apparent radiographic nodal disease progression, which in fact represents an immune-related phenomenon post-ICI therapy.[84] Overall, this is an area for which data in larger patient cohorts are needed, perhaps in the context of real-world studies with surgical engagement. In summary, although patients with no evidence of disease progression on contrast-enhanced CT should proceed directly to surgery, the presence of disease that compromises the feasibility of an R0 resection or is suggestive of frank metastatic disease warrants multidisciplinary tumor board discussion to reconvene to select the best course of action for each individual patient.

Few data exist regarding the safety and efficacy of locoregional consolidation using radiation with or without concurrent chemotherapy in patients who have received neoadjuvant chemoimmunotherapy. Nevertheless, local consolidative therapy in the context of oligometastatic disease is a common practice after much longer courses of ICI-based therapy, suggesting that this is likely the preferred approach when feasible. To date, the only data we have on this subject from the available neoadjuvant or perioperative studies are those originating from CheckMate 816 among patients with progressive disease during neoadjuvant therapy.[85] In this cohort, patients had predominantly stage III disease and many were offered consolidative radiotherapy. For patients with distant metastatic dissemination, the recommended approach would follow the algorithm for metastatic patients who are refractory to first-line chemoimmunotherapy.

Recommendation 12: Use of intraoperative frozen sectioning is recommended to assure complete resection and limit excessive parenchymal resection.

Agreement: 88%

Recent large databases, such as the IASLC Lung Cancer Staging Project[86] and the U.S. National Cancer Data Base,[87,88] have confirmed that the completeness of resection (R0) status has a favorable survival impact in patients with (stages I–IIIA) rNSCLC (however, it is important to note that the definition of R0 resection differs between trials). The incidence of an R1 lung cancer resection reported in 19 studies published between 1945 and 2003 was approximately 4% to 5% (range: 1.2%–17%).[89] The definition of complete resection (R0) status requires the fulfillment of all the following conditions: (1) all free resection margins have been proven microscopically; these include bronchial, venous, arterial stumps, peribronchial soft tissue, and any peripheral margin near the tumor or of additional resected tissue; (2) systematic nodal dissection in its wider form or lobe-specific systematic nodal dissection must have been performed and proven negative; (3) no extracapsular extension of tumor in lymph nodes removed separately or in those at the margin of the main lung specimen; and (4) the highest mediastinal node that has been removed must be negative.[86,90]

Intraoperative frozen section examination is frequently requested by surgeons for various reasons, one of which is to determine the completeness of resection.[91] Intraoperative frozen sectioning has also

been used by thoracic surgeons to determine mediastinal lymph node involvement.[92,93] In studies of lung cancer resection involving a high percentage of frozen section assessment of the resection margins, the incidence of positive margins has been reported to be 2.2% to 5.4%.[94–99] Owing to the low frequency of positivity, some groups[94,97] have advocated against the unselected use of intraoperative frozen section on margin determination. Nevertheless, microscopically positive bronchial resection margins have been associated with higher rates of stump recurrence and poorer OS, especially among patients with stage IB or II disease.[95,98,100,101]

In the new context of surgery after chemoimmunotherapy, it is likely that surgeons will be operating on a higher proportion of patients who had clinically node-positive disease or had larger tumors requiring extended pulmonary resections. To assure high rates of R0 resection, one needs to know whether the dissected lymph nodes still harbor disease to ensure that the highest dissected lymph node is in fact negative. Furthermore, interpretation of post-neoadjuvant therapy imaging can be misleading and may result in an unnecessarily wide resection, given the challenges of predicting the extent of pathologic response after neoadjuvant therapy based on radiographic imaging. In this regard, frozen section and intraoperative consultation with the pathologist can assist the surgeon to tailor the extent of resection to the residual disease. Although EFS outcomes for patients who were treated by pneumonectomy were remarkably encouraging in CheckMate 816,[22] a pneumonectomy for a patient with a pCR is something that should be avoided whenever feasible. The panel recognizes the constraints and difficulties associated with intraoperative consultation in some resource-limited settings, including challenges in this context, and recommends judicious use of this resource in a collaborative fashion between surgeon and pathologist.

Recommendation 13: Surgical pathology reporting for neoadjuvant therapy-treated patients including, at minimum, a determination of pathologic complete response, percent residual viable tumor, and ypTNM status, is recommended.

Agreement: 100%

Surgical pathology reporting for resected lung cancers after neoadjuvant chemotherapy has been inconsistent, mostly due to a lack of practice recommendations. Recently, the IASLC published multidisciplinary recommendations for standardized gross processing and microscopic assessment of NSCLC after neoadjuvant therapy.[102] Clinical reports must include statements about pathologic response in the primary tumor site (tumor bed) and lymph nodes. For clinical reporting, the histologic features after review of all hematoxylin-eosin slides of the tumor bed should include percentages of viable tumor, necrosis, and stroma, which include both fibrosis and inflammation. Each component should be assessed in 10% increments for a total of 100% unless the amount is less than 5%. Pathologic response should also be evaluated in metastatic lymph nodes. Studies have revealed that patients with MPR-positive lymph nodes experience longer survival than those with MPR-negative lymph nodes.[103,104] The same approach that is used for tumor bed reporting can be used for histologic evaluation of lymph nodes, including percent viable tumor, necrosis, and stroma, although this can be challenging as no consensus exists on MPR cutoffs for lymph nodes. pCR in a lymph node can be microscopically recognized as a scar or tumor necrosis in the absence of viable tumor cells and should be documented in the pathology report. No evidence of viable tumor in both the tumor bed and the sample lymph nodes represent pCR and must be documented in the report. A retrospective study in a single-institution cohort of rNSCLCs after neoadjuvant immunotherapy suggested that accuracy rates of at least 90% for percentage of residual viable tumor (%RVT), MPR, and pCR are achieved with either submission of all residual primary tumor or at least 20 tumor sections.[105] The IASLC has recently conducted a large initiative across immunotherapy trials which revealed a high rate of reproducibility of pathologic response assessment after neoadjuvant therapy, further supporting the implementation of this metric as standard practice.[106]

Recently, investigators from the CheckMate 816 trial reported EFS outcomes by degree of pathologic response using the immune-response pathologic response criteria.[107] This methodology incorporates the notion of the tumoral regression bed in the assessment of %RVT, which includes a comprehensive assessment of both the primary tumor and resected lymph nodes. EFS was strongly associated with each increment in %RVT found in the resection specimen, and this assessment outperformed other metrics such as Response Evaluation Criteria in Solid Tumors version 1.1 radiographic response and circulating tumor DNA clearance as a means of predicting EFS outcome.

Pathology reports should include ypTNM stage, and for pathologists in the United States, this information is required to be included in the College of American Pathologists (CAP) synoptic report. ypT stage can be determined by measuring the viable tumor on a slide if the tumor is present on a single slide.[102] To determine tumor size in the neoadjuvant setting when residual viable tumor does not form a single discrete

measurable focus, the percentage of viable invasive tumor is multiplied by the tumor bed size. For lepidic tumors, in addition to this formula, the eighth edition AJCC-UICC recommendation for subtraction of lepidic component from the tumor size should be followed.[3] In rare cases with resected lung containing multiple tumor nodules, the pathologic response or percent viable tumor should be reported for each tumor unless the nodules are too numerous to count. If no viable tumor is identified on resection, ypT0 is the appropriate designation.

Recommendation 14: A multidisciplinary group, ideally in a tumor board setting, consisting of medical or pulmonary oncology, pathology, surgery, radiation oncology, and radiology should reconvene after surgery to recommend additional treatment and surveillance plans.

Agreement: 95%

This recommendation is based primarily on consensus agreement and the emerging option of additional adjuvant therapy for this population of patients. Primary objectives of such a meeting are to take stock of the patient's postoperative condition and ability to receive further indicated therapy. Inclusion of lung cancer specialist nurses to report on patient-related status has been associated with improved survival and should be considered an important part of a multidisciplinary group.[108,109] Available and possibly indicated therapies include additional adjuvant chemotherapy, radiation, or continued ICI. Exact indications for these subsequent treatments after surgery remain somewhat unclear and subject to individualization after a multidisciplinary team meeting. Observational studies support multidisciplinary decision-making in patients with various malignancies, including NSCLC. In one retrospective series of thoracic oncology patients at a single institution, multidisciplinary group meetings affected patient management by changing the outpatient clinical hypothesis in 11% of cases, with modification rates in defining solitary pulmonary nodules and proven or suspected recurrence of 15% and 13%, respectively.[110] In a retrospective Taiwanese national database study, the receipt of multidisciplinary care was associated with higher survival in patients with stages III to IV NSCLC.[111] A study of patients newly diagnosed with lung cancer in Southwest Sydney revealed that multidisciplinary team discussion was associated independently with increased receipt of radiation therapy, chemotherapy, and referral to palliative care, although no association with survival was found.[112] As stated previously, recent meta-analysis–level data indicate improved OS for patients with cancer treated in the context of multidisciplinary care.[7] Given the known impact of chemoimmunotherapy and surgery on the patient's performance status and the availability of new and important prognostic information, this juncture in the therapeutic trajectory is a major milestone, which may mark an important transition to surveillance or could indicate the need for additional diverse treatments. This is a point in time where numerous specialists may weigh in on the relative benefits of an array of treatments and where quality assurance regarding such metrics as pathologic response and resection status are warranted. As such, this panel feels that it is critical to reconvene the multidisciplinary team to reassess subsequent steps—particularly as the adjuvant landscape continues to evolve in the context of greater adoption of neoadjuvant therapy—which should take into consideration response to neoadjuvant therapy if given, features of surgical resection, potential toxicity, and a patient's needs and goals in the therapeutic journey.

Neoadjuvant Treatment—Nonconsensus Recommendations

Recommendation 15: Neoadjuvant chemoimmunotherapy followed by surgery is preferred to upfront surgery for medically operable patients with technically resectable clinical stage II NSCLC at first presentation, regardless of PD-L1 expression level.

Agreement: 65%

The panel was split with regard to the role of neoadjuvant chemoimmunotherapy in patients with stage II disease. The subgroup analyses in CheckMate 816 suggested that patients with stage IB or II NSCLC (AJCC-UICC seventh edition; these would all be classified as stage II AJCC-UICC eighth edition), which represented a little more than one-third of the patient population, derived a lower magnitude of benefit with respect to EFS from the addition of nivolumab to neoadjuvant platinum doublet chemotherapy compared with patients with stage III disease. Median EFS was not reached in either treatment arm among patients with stage IB or II disease (nivolumab, NR [95% CI: 27.8–NR]; chemotherapy alone, NR [95% CI: 16.8–NR]; HR = 0.87 [95% CI: 0.48–156]).[22] In KEYNOTE-671, the OS benefit from perioperative pembrolizumab was comparable in patients with stage II disease (HR = 0.67 [95% CI:0.41–1.10]) and those with node-negative disease (HR = 0.7 [95% CI: 0.46–1.06]) compared with patients with stage III disease. Patients with stage II disease in the AEGEAN trial

(214 of 738 patients) seemed to benefit from neoadjuvant chemoimmunotherapy: median EFS was not reached (95% CI: NR–NR) for stage II patients in the durvalumab arm compared with 31.1 months (95% CI: 25.4–NR) for those in the placebo arm (HR = 0.76 [95% CI: 0.43–1.34]).[23] In the CheckMate 77T study, the HR between perioperative nivolumab and placebo arms in stage II patients trended in favor of nivolumab (HR = 0.81 [95% CI: 046–1.43]), although median EFS was not reached in both arms, suggesting that longer follow-up is needed in this subgroup.[78]

Although not available to the panel at the time of voting, a recent meta-analysis revealed a statistically positive EFS benefit in favor of immunotherapy in patients with stage II disease when all neoadjuvant and perioperative trials were pooled with a statistically significant HR of 0.71 [95% CI: 0.55–0.92].[65] Nevertheless, no subanalyzes of efficacy by PD-L1 expression level in these trials in patients with stage II versus stage III NSCLC have been reported, largely due to the small sample sizes for patients with stage II in each trial.

Some consider the magnitude of benefit found in CheckMate 816 to be too low to justify the regimen. Nevertheless, it is important to recall the VIOLET trial data where only 50% of patients made it to indicated adjuvant chemotherapy,[19] whereas more than 95% of patients in the chemo-nivolumab cohort completed all three cycles of neoadjuvant therapy and only three patients with stage II disease in the chemo-nivolumab arm were unable to proceed to surgery due to disease progression.[85] Hence, in many respects, the neoadjuvant strategy for stage II patients assures the highest probability that patients will receive all potentially beneficial aspects of care. Nevertheless, the nonreceipt of surgery in a fair proportion of patients from available phase 3 neoadjuvant and perioperative trials raises concerns for some panelists that patients with stage II disease may not receive surgery after neoadjuvant therapy where surgery constitutes the essential therapy to provide an opportunity for durable disease control.[113]

Despite the magnitude of benefit from neoadjuvant chemoimmunotherapy being somewhat smaller in stage II patients than for that derived from patients with stage III disease, the evidence still suggests a potentially important clinical advantage associated with this treatment approach for the patients with stage II disease. The panelists who support this recommendation agree that this approach provides an important treatment option for patients, with no overall increased toxicity risks compared with previous standards of care. Finally, the proponents of this recommendation emphasize the validity of the recommendation, even though they acknowledge that some patient-specific considerations might affect the ultimate choice of therapeutic strategy. With respect to patients with clinical stage II disease who underwent neoadjuvant chemoimmunotherapy, continuation of adjuvant immunotherapy after surgery remains an option to be considered. The only neoadjuvant or perioperative study to have a HR that does not cross unity for the outcome of EFS in clinical stage II disease is the KEYNOTE-671 trial (HR = 0.59 [95% CI: 0.4–0.88]).[28] When taken together, the combined results in stage II for the outcome of EFS reveal a statistically significant improvement with the addition of neoadjuvant chemoimmunotherapy plus or minus adjuvant immunotherapy.[65,114] Similarly, to what we found for patients with stage III disease, no strong recommendation regarding the adjuvant component could be made at this point in time.

The panelists who do not support this recommendation express concern regarding the strength and sufficiency of available data. They note that the evidence is neither sufficiently convincing nor robust enough to support a preference for neoadjuvant treatment in this population. These panelists emphasize that HRs from relevant trials crossed unity, suggesting potential limited benefit. It is important to note that the HR for patients with stage II (AJCC-UICC eighth edition) for OS in IMpower 010 in the PD-L1 more than or equal to 1% cohort is 0.71 [95% CI: 0.40–1.26]. Similarly, in KEYNOTE-091, the HR for stage IB patients (AJCC-UICC seventh edition) was 0.76 (95% CI: 0.43–1.37) and for stage II 0.70 (95% CI: 0.55–0.91) for the outcome of DFS, irrespective of PD-L1 level. An important caveat to most analyses of stage II patients is the lack of differentiation between node-negative patients and those with N1-positive nodes. Thus, we have few data to support an approach that separates stage IIA patients from stage IIB patients. In addition, some of the dissenters argue that subgroup analyses and comparisons with other treatment strategies, including adjuvant immunotherapy, are required to make a definitive recommendation. Finally, these panelists highlight the need for more substantial data and caution against premature endorsement of neoadjuvant chemoimmunotherapy for all patients with stage II NSCLC.

Adjuvant Treatment—Consensus Recommendations

Background. Although adjuvant chemotherapy has been widely adopted after complete surgical resection in patients with NSCLC, its impact on survival has been modest.[115,116] In recent years, the incorporation of immunotherapy or targeted therapy in the adjuvant setting has improved patient outcomes and led to regulatory approval of three agents in this space: atezolizumab, pembrolizumab, and osimertinib (Table 2).

The phase 3, randomized IMpower 010 trial compared adjuvant platinum-based doublet followed by adjuvant atezolizumab with adjuvant platinum-based doublet followed by best supportive care (BSC). The enrolled 1005 patients had stage IB (≥4 cm) to IIIA rNSCLC (AJCC-UICC seventh edition). Although patients with PD-L1 levels less than 1% were enrolled, emerging biomarker data and the evolving PD-L1 diagnostic test landscape led to a protocol amendment in which only patients with PD-L1 levels more than or equal to 1% were included in the analysis for the primary efficacy end point of DFS. Among these patients who had stages II to IIIA disease at a median follow-up of 32.2 months, those in the atezolizumab arm experienced significantly longer DFS, NE months (95% CI: 36.1–NE), compared with those who received BSC, 35.3 months (95% CI: 29.0–NE), HR equal to 0.66 (95% CI: 0.50–0.88; $p = 0.0039$).[80,83]

The PEARLS/KEYNOTE-091 trial is a phase 3 randomized study that evaluated pembrolizumab in the adjuvant setting. A total of 1177 participants with resected stages IB (≥4 cm) to IIIA NSCLC (AJCC-UICC seventh edition) received adjuvant platinum-based doublet followed by adjuvant pembrolizumab or adjuvant platinum-based doublet followed by adjuvant placebo. An interim analysis with a median follow-up of 35.6 months revealed that in the overall patient population, median DFS was significantly higher in the pembrolizumab arm compared with that in the placebo arm (53.6 mo [95% CI: 39.2–NR] versus 42.0 mo [95% CI: 31.3–NR]; HR = 0.76 [95% CI: 0.63–0.91]; $p = 0.0014$).[117]

ADAURA is an ongoing, phase 3, randomized study comparing adjuvant osimertinib to adjuvant placebo in 682 patients with resected *EGFR*-mutated, stage IB (T2a tumors >3 cm and ≤5 cm), II, or IIIA NSCLC (AJCC-UICC seventh edition). The use of adjuvant chemotherapy before osimertinib or placebo was optional. Among patients with stages II to IIIA disease, median DFS at a median follow-up of 44.2 months was longer in those who received osimertinib than in those treated with placebo (65.8 mo [95% CI: 54.4–not calculated (NC)] versus 21.9 mo [95% CI: 16.6–27.5], respectively; HR = 0.23 [95% CI: 0.18–0.30]). In the overall population (stages IB–IIIA NSCLC), median DFS was also longer among patients in the osimertinib arm versus the placebo arm (68.8 [95% CI: 61.7–NC] mo versus 28.1 [95% CI: 22.1–35.0] mo, respectively; HR = 0.27 [95% CI: 0.21–0.34]).[118] In patients with stages II to IIIA disease, the 5-year OS rates were 85% in the osimertinib group and 73% in the placebo group (HR = 0.49 [95.03% CI: 0.33–0.73; $p < 0.001$]). In the overall population of patients with stages IB to IIIA disease, the 5-year OS rates were 88% in the osimertinib group and 78% in the placebo group (HR = 0.49 [95.03% CI: 0.34–0.70; $p < 0.001$]).[44] These results have prompted early closure of the clinical trial ALCHEMIST (EGFR), which was comparing adjuvant erlotinib with observation, as they suggest that a control arm lacking EGFR inhibitor treatment is no longer appropriate.

Recommendation 16: Adjuvant chemotherapy is required before adjuvant immunotherapy.

Agreement: 88%

Adjuvant platinum-based chemotherapy is currently the standard of care for completely resected stages IB (≥4 cm) to IIIA NSCLC (AJCC-UICC seventh edition). The panel felt that adjuvant chemotherapy continues to be recommended whenever feasible due to the proven OS benefits for resected stage II and III patients. It is clear in the setting of adjuvant immunotherapy that chemotherapy is a required part of the regimen to derive benefit. Although adjuvant chemotherapy was required before randomization in IMpower 010, it was optional in PEARLS/KEYNOTE-091, and the subgroup analysis for patients who did not receive adjuvant chemotherapy in PEARLS/KEYNOTE-091 revealed no benefit with the addition of pembrolizumab versus placebo.

Recommendation 17: Patients with stage II or IIIA *EGFR* and *ALK* wild-type disease who have undergone complete resection followed by chemotherapy should be considered for adjuvant immunotherapy based on PD-L1 results as follows:

- PD-L1 < 1%: Discourage
- PD-L1 1%–49%: Consider
- PD-L1 ≥ 50%: Recommended

Agreement: 100%

In addition to the unanimity of the recommendation, the panel clearly expressed consternation around the discrepant results regarding efficacy by PD-L1 strata of adjuvant anti–PD-(L)1 therapy in the two completed trials in this space, IMpower 010 and PEARLS/KEYNOTE-091.

As mentioned earlier in this manuscript and Table 2, in IMpower 010, the primary outcome was DFS in patients with stages II to IIIA disease (AJCC-UICC seventh edition) and PD-L1 levels more than or equal to 1%. The trial met this end point, with patients who received adjuvant atezolizumab experiencing significantly longer DFS compared with those who received BSC. In contrast, subgroup analysis revealed that this benefit did not extend to patients with PD-L1 levels less than 1%, median DFS of 36.1 months (95% CI: 30.2–NE) versus 37.0 months (95% CI: 28.6–NE), HR equal to 0.97 (95% CI: 0.72–1.31). Furthermore, the DFS benefit was most

pronounced among patients with PD-L1 levels more than or equal to 50% NE (95% CI: 42.3–NE) versus 35.7 mo (29.7–NE), HR 0.43 (95% CI: 0.27–0.68).[83] OS presented in 2022 had a nonsignificant favorable trend in OS among patients with stages II to IIIA disease and PD-L1 more than or equal to 1% (median OS: atezolizumab, not estimable versus best supportive care, not estimable; HR = 0.71 [95% CI: 0.49–1.03], $p = 0.067$). Nevertheless, patients with stages II to IIIA disease and PD-L1 more than or equal to 50% who received adjuvant atezolizumab experienced a significant OS benefit compared with those in the best supportive care arm (median OS, not estimable versus not reached; HR = 0.42 [95% CI: 0.23–0.78], $p = 0.005$).[80] Finally, the HR for patients with PD-L1 less than 1% tumors for OS in IMpower 010 suggested potential harm (HR 1.36 [95% CI: 0.93–1.99], $p = 0.109$), and these findings contribute to the recommendation being listed by PD-L1 strata.

Compared with IMpower 010, the PD-L1 subgroup analyses in PEARLS/KEYNOTE-091 yielded conflicting results. As noted previously and in Table 2, in the overall trial population (14% of which had PD-L1 levels < 1%), adjuvant pembrolizumab was associated with a significant benefit in DFS. Nevertheless, in contrast to the results of IMpower010, the difference in DFS between arms did not reach significance in patients with PD-L1 levels more than or equal to 50%. Nevertheless, the study authors noted that among patients with PD-L1 levels more than or equal to 50%, DFS was not reached in either group (HR 0.82 [95% CI: 0.57–1.18, $p = 0.14$]), so it could not be numerically compared and suggested that these results may reflect placebo overperformance. DFS in the population of patients with PD-L1 levels more than or equal to 50% will be calculated again in the next interim analysis of PEARLS/KEYNOTE-091. Regarding stage, patients with stage II disease (AJCC-UICC seventh edition) in PEARLS/KEYNOTE-091 derived the largest DFS benefit, followed by those with stage IB disease; the DFS benefit in patients with stage IIIA NSCLC was minimal.[117]

Recommendation 18: In the light of ongoing trials in populations with specific driver alterations and with extrapolation of the limited efficacy of PD-1 and PD-L1 inhibitors in patients with driver alterations, in addition to assessing *EGFR* and *ALK* alteration status, biomarker testing for other oncogenic drivers is highly encouraged in patients with early stage disease.

Agreement: 94%

A substantial proportion of patients with NSCLC have actionable driver mutations in one of nine established biomarkers. On the basis of the results of trials that have revealed that patients with specific oncogenic driver mutations derive less benefit from PD-1 and PD-L1 inhibitors compared with patients who lack any actionable mutations, the current standard of care is to perform mutation testing before treatment selection.[119] Although single-gene testing is frequently performed to assess *EGFR* and *ALK* mutation status, NGS is more efficient for evaluating actionable gene alterations in all nine established biomarkers simultaneously. Compared with sequential single-gene testing, NGS can yield results for all nine biomarkers in a shorter time, uses less tissue, and avoids administration of PD-1 and PD-L1 inhibitors (and associated adverse effects) that may not be as effective as targeted molecular therapies.[115]

Recommendation 19: For patients with stage II or IIIA disease with *EGFR*-sensitizing mutations, adjuvant osimertinib is recommended. Adjuvant platinum-based chemotherapy before osimertinib is encouraged. For patients with stage IB (T3-4cmN0) disease, adjuvant osimertinib alone is recommended.

Agreement: 94%

Results from the ADAURA trial for adjuvant osimertinib versus placebo in EGFR-mutated stages IB to IIIA NSCLC after complete tumor resection support this recommendation. Adjuvant osimertinib was associated with a significant OS benefit in patients with stage II or IIIA NSCLC: the 5-year OS rate was 85% (95% CI: 79–89) for osimertinib compared with 73% for placebo (95% CI: 66–78); HR equal to 0.49 (95.03% CI: 0.33–0.73, $p < 0.001$). The 4-year DFS rate in stages II to IIIA disease was 70% in the osimertinib arm versus 29% in the placebo, with a median follow-up of 44.2 months and 19.6 months, for osimertinib and placebo, respectively. The DFS HR was 0.23 (95% CI: 0.18–0.30). Furthermore, among patients with stage II or IIIA disease, central nervous system (CNS) recurrences occurred in 8% of osimertinib patients versus 15% of placebo patients. Median CNS DFS was not reached in either group; the HR for DFS among stage II or IIIA disease was 0.24 (95% CI: 0.14–0.42) for the comparison between groups.[118] The results of ADAURA resulted in the approval of osimertinib in the adjuvant setting by many international regulatory agencies.[120–124]

Clinicians had the option of preceding osimertinib with adjuvant chemotherapy. Of the 682 efficacy assessable patients, approximately 60% were given adjuvant chemotherapy, whereas 40% received osimertinib alone. Subgroup analysis of the overall patient population revealed that compared with placebo, patients who received adjuvant chemotherapy before

osimertinib derived a numerically larger EFS benefit (HR = 0.29 [95% CI: 0.21–0.39]) than did patients who did not get adjuvant chemotherapy (HR = 0.36 [95% CI: 0.24–0.55]).[118] The OS at 5 years was similar in those who received adjuvant chemotherapy before osimertinib compared with those who did not receive adjuvant chemotherapy before osimertinib (87%, HR 0.49 [95% CI: 0.30–0.79] versus 88%, 0.47 [95% CI: 0.25–0.83], respectively).[44] Although the OS and DFS benefits in the osimertinib group seemed to persist even in the patients who did not receive adjuvant chemotherapy, ADAURA was not designed to test the utility of chemotherapy in this setting. Therefore, the panel continues to encourage its use whenever feasible and after an informed discussion with the patients about potential risks and benefits.

Note that adjuvant therapy with a first-generation EGFR inhibitor (gefitinib, erlotinib, or icotinib) is not recommended, based on the results of clinical trials revealing that adjuvant first-generation EGFR inhibitor therapy provides little benefit with respect to DFS and even less, or no, OS benefit in patients with early stage *EGFR*-mutated NSCLC.[125–128]

Recommendation 20: For patients with stages IB (tumors $\geq$ 4 cm) to IIIA disease with ALK alterations, adjuvant alectinib is recommended. Adjuvant chemotherapy before alectinib can be considered at the discretion of the treating providers.

Agreement: 95%

In the setting of *ALK*-translocated patients, the ALINA trial randomized patients to either chemotherapy or alectinib alone and did not have an arm incorporating both chemotherapy and alectinib. In this trial, the DFS benefit in the absence of chemotherapy was very impressive. At a median follow-up of 27.9 months for alectinib and 27.8 months for chemotherapy, the median DFS in the patients with stages II to IIIA NSCLC receiving alectinib was NR (95% CI: NE, NE) versus 44.4 months (95% CI: 27.8–NE) for those receiving chemotherapy (HR 0.24 [95% CI: 0.13–0.45], $p < 0.0001$). For the co-primary end point of DFS in stages IB to IIIA, the median DFS for alectinib was NR (95% CI: NE, NE) whereas that for chemotherapy was 41.3 months (95% CI: 28.5–NE) (HR = 0.24 [95% CI: 0.13–0.43], $p < 0.0001$). Alectinib was associated with a clinically meaningful benefit with respect to CNS DFS as compared with chemotherapy (HR 0.22 [95% CI: 0.08–0.58]).[45,46] Nevertheless, OS data for this cohort are not yet mature and awaited. The results of ALINA led to the approval of alectinib in the adjuvant setting by the U.S. Food and Drug Administration.[129] Given the history on adjuvant trials in the patients with targeted therapy, it is reasonable to continue to recommend adjuvant chemotherapy in fit patients in addition to adjuvant alectinib after an informed decision with the patient.

Additional Issues, Unanswered Questions, and Future Directions

During development of the recommendations presented in this manuscript, the panel identified additional areas that warranted discussion. Although not addressed in the recommendations, these issues are briefly covered here.

What Is the Optimal Timing of Surgery After Neoadjuvant Therapy?

The panelists agreed that typical timing ranges from a minimum of 3 weeks (to allow for bone marrow recovery after platinum doublet chemotherapy) and up to 6 weeks. At this point in time, we have no data to support a specific optimal window during which surgery should be performed other than what was recommended in the various phase 3 trials. The maximum number of patients should proceed to surgery because there are overall reproducible data across large trials revealing that those patients who had operations were the ones who derived the most benefit from these approaches. How timing of surgery after neoadjuvant therapy affects surgical complexity and outcomes needs to be studied in a dedicated fashion. Moreover, timing of resection could have an important impact on the degree of pathologic response.

How Can Future Neoadjuvant and Adjuvant Trials in NSCLC Be Improved?

1. There is an intrinsic risk for all perioperative therapies to cause toxicity without benefit when applied to the wrong patient, and even when successful from a survival standpoint, such complications can dramatically limit potential quality of life benefits. Indeed, immunotherapy can induce long-lasting complications that may not be adequately captured by our current assessment of toxicity during the active therapeutic phases of our trials. Our current understanding of the potential toxicities induced by these new treatments in combination with surgical resection and on eventual relapse is evolving and requires greater study.
2. The importance of standardization of clinical trial end points was raised by the panelists several times during the meetings. The panel commended the IASLC's ongoing Pathologic Response Project. In addition, international standardization of nomenclature with respect to "resectable" versus "borderline

resectable" and "unresectable" disease and descriptions of lymph node involvement (e.g., "bulky," "extranodal," "invasive," "multi-station") would help trial design, and, ultimately, patient care.

3. Decentralization of select testing in neoadjuvant and perioperative trials to align with the rapidly evolving treatment landscape for rNSCLC and provision of investigational treatment regimens and strategies to a larger proportion of patients in a more expedited fashion are worth consideration. This approach could also foster increased diversity and equity in enrollment into these trials, which may lead to a better understanding of potential differences in response and outcomes across racial and socioeconomic subgroups and the causes underlying these differences.
4. Implementation of robust sample collection for the purpose of meaningful and rigorous translational analyses using pretherapy and surgical post-neoadjuvant therapy samples can inform biomarker selection, novel target discovery, and the design of next-generation clinical trials. At present, many combinatorial regimens are being tested in trials based on signals identified and scientific work performed in early generation trials.
5. It is important to note that some stage III patient subgroups were excluded from recent neoadjuvant and adjuvant studies. For example, it is unclear whether individuals presenting with locally advanced disease that invaded adjacent organs, such as superior sulcus tumors, were enrolled. Some surgeons consider such tumors to be resectable, and furthermore, the 2021 ASCO guidelines on the management of stage III NSCLC recommend administration of neoadjuvant concurrent chemoradiation to patients with resectable superior sulcus tumors (the 2017 ESMO early and locally advanced NSCLC guidelines are similarly worded).[116,130] Inclusion of such patients in future trials has the potential to improve their outcomes and clarify how their treatment paradigm fits with other patients within the clinical TNM classification. To achieve this important improvement, clinical trials need to capture and report granular TNM details that accurately portray the extent of disease.
6. There is a need to better understand how the receipt of neoadjuvant therapy affects the planning and conduct of surgery. Prospective collection of surgeon-level data documenting the proposed approach and extent of resection at baseline compared with after completion of neoadjuvant therapy and referenced to the actual operation performed—and its complexities—would provide us with a vital understanding of how these treatments affect the surgeon and the surgical experience of the patient.
7. There is the need for a thorough and standardized collection of patient-reported outcome measures in clinical trials at longitudinal time points throughout the perioperative setting. This effort will enable us to globally assess the impact of neoadjuvant across studies, adjuvant and perioperative chemo-immunotherapy on the health status and the quality of life of patients receiving these therapies, and how, as providers, we can better tailor these therapies on individual patient's needs and preferences.
8. More prospective data are needed to address the risks of using neoadjuvant chemoimmunotherapy in patients with interstitial lung disease (ILD) or interstitial lung abnormalities; the latter are being increasingly recognized as a common CT feature in older individuals.[131] For example, fibrotic ILD is a risk factor for 30-day operative mortality and morbidity after lung cancer resection, even in patients with normal pulmonary function.[132,133] In addition, toxicities associated with administration of ICIs are increased in patients with ILD and interstitial lung abnormalities.
9. Defining the role of circulating tumor DNA in measurement of minimal residual disease (MRD) in patients who undergo neoadjuvant chemoimmunotherapy should be addressed in clinical trials. MRD is a prognostic marker in patients with NSCLC, as MRD-positive patients may require more rational and effective therapeutic strategies. Novel trials are needed where such assays are incorporated as decisional tools for a therapeutic intervention or de-escalation of approved treatments. Indeed, these and other technologies based in machine learning from such patients may provide further insights on prediction of pathologic complete response, magnitude of pathologic regression after neoadjuvant treatment that could be helpful in the decision to administer adjuvant immunotherapy and survival metrics. Such predictive technologies could be of great utility to the future care of this patient population.
10. There remains a high degree of uncertainty regarding the optimal number of cycles of neoadjuvant therapy. At this point, a minimum of three are required, but that four cycles may be what are tied to the statistically significant OS benefit found in KEYNOTE-671. As none of the trials are designed to specifically address this question, the authorship group remains aligned with the notion that 3 to 4 cycles are recommended with no specific preference to say which of 3 or 4 cycles is best. This subject of dose optimization both for chemotherapy and ICI is an area of future investigations.

11. The role of radiation before or after surgery remains an area of active study, and the exact scenarios for its use as a neoadjuvant therapy need to be better defined. How it can be combined with novel therapies and its potential to augment response in the context of immunotherapy are exciting areas of investigation. Moreover, the potential for benefit in the adjuvant setting may still exist where patients have persistent mediastinal nodal disease or positive surgical margins.

Neoadjuvant Therapy, Adjuvant Therapy, or Both?

1. No studies have directly compared neoadjuvant chemoimmunotherapy with adjuvant immunotherapy. On the basis of the panel's position and the agreement found with the external voting process with regard to stage III disease, it seems that many clinicians will not have equipoise to randomize such patients to an upfront surgery arm. Nevertheless, for patients with stage II disease, equipoise exists and dedicated trials in this area along with high-risk patients with stage I may be warranted.
2. Several studies that evaluated neoadjuvant chemoimmunotherapy followed by surgery revealed that patients who achieved a pCR experienced long-term EFS benefit, suggesting these patients may not require further adjuvant immunotherapy. In contrast, patients treated with neoadjuvant chemoimmunotherapy followed by surgery who achieve MPR or disease stabilization are more likely to experience shorter EFS. These results suggest that achievement of a pCR potentially has both quality of life and treatment cost implications. This could be particularly relevant in LMICs, where efficient resource allocation is critical. Nevertheless, further long-term follow-up is needed to confirm this. The critical question which will likely require dedicated large-scale trials is whether the addition of adjuvant therapy in a perioperative approach offers distinct benefit of that found with a pure neoadjuvant approach like that tested in CheckMate-816. Answering this question will help us to individualize the safest and more effective treatment approach to specific subgroups of patients, including those who achieve a pCR, where potential clinical and financial toxicities may be spared if the continuation of adjuvant immunotherapy is deemed not necessary, whereas in patients without a pCR intensification of adjuvant therapy with the same immunotherapy agent administered in the neoadjuvant phase or with a switch-agent type of approach may be more effective. In the meantime, more effective neoadjuvant therapies that can improve pCR are needed, particularly in patients with low PD-L1 expression where there is a large unmet need. Evaluation of agents with novel mechanisms of action, such as antibody-drug conjugates and bispecific antibodies, is therefore warranted.
3. Finally, it is important to appreciate that most of the available trial data testing novel targeted or immune-based treatments remain relatively immature. Further long-term follow-up is needed to establish the durability of these interventions in terms of OS which remains the clear objective for these patients in the curative setting.

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