# Defining resectability: When do you try to take it out?



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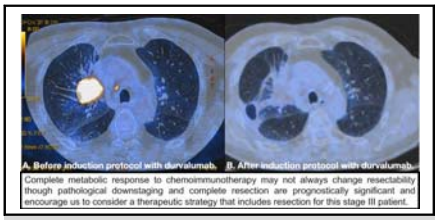
The 5-year survival rates decrease from 92% in patients with resected stage IA1 disease to 36% in patients with stage IIIA disease.[1] Improvements in outcome for locally advanced non–small cell lung cancer (NSCLC) have been achieved via improvements in systemic therapy and proper allocation to local therapy such as surgical resection or radiotherapy. New, attractive modalities such as immune checkpoint inhibitors (ICI) in patients with resectable stage IB to IIIB disease provide promising 2-year overall survival (OS) rates of 83% or 85%.[2-5] In contrast, overall 2-year survival has been reported to be 66.3% if stage III tumors were judged unresectable and treated with concurrent chemoradiotherapy and consolidation ICIs. However, poorer performance status scores and the inclusion of patients with stage IIIC disease in the cohort make a head-to-head comparison inappropriate.[6] Given the wish to offer patients the opportunity for the highest probability of disease control, a critical decision point after completion of the diagnostic and staging evaluations centers on the concept of resectability, which is best determined in a multidisciplinary tumor board setting. Unfortunately, there is no standardized definition of resectability, neither for clinical decision making, nor for inclusion into clinical trials; and definitions vary between available guidelines (Table 1). Additionally, the complexity of defining resectability at baseline presentation is further challenged by the fact that clinical and pathological downstaging occurs in a significant number of patients undergoing induction regimens with ICI alone or in combination with chemotherapy. This downstaging effect results in prolongation of disease-free survival and OS. The objective of this article is to discuss how to define resectability in the midst of these important and evolving paradigm shifts. Medical operability influencing surgical risk, an important though perhaps less plastic or modifiable factor in decision making, will not be discussed.




**Complete pathological response and node downstaging might redefine resectability.**

**CENTRAL MESSAGE**

A standardized definition of resectability for lung cancer is desirable for treatment allocation with the advent of new induction therapy regimens. Complete resection remains the central objective.

## DEFINITION OF RESECTABILITY

The aim of any curative intent surgery for primary lung cancer is to achieve a complete resection, otherwise known as an R0 resection.[13] According to the International Association for the Study of Lung Cancer (IASLC), complete resection is defined as[13]:

- En bloc resection of the tumor with microscopically free margins;
- Systematic lymph node dissection or lobe-specific systematic nodal dissection;
- No extracapsular nodal extension of the tumor;
- The highest mediastinal lymph node negative for tumor; and
- Pleural and pericardial cytology negative.

If any of these conditions are not fulfilled, the resection is not considered complete by these rigorous standards. Uncertain resections have all margins free of tumors but have not fulfilled all the complete resection criteria.[14]

Complete resection and proper documentation of the R status in usual practice is recommended. A large data analysis from the IASLC Lung Cancer Staging Project demonstrated that R1 and R2 resections are associated with a significantly poorer survival than R0 (R1 hazard ratio [HR], 1.85 and R2 HR, 2.14; $P < .0001$), but this remains

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**TABLE 1. Summary of UK, European, and American guidelines on the management of potentially resectable N2 non–small cell lung cancer (NSCLC)***

| Guideline | Definition of resectable | Recommendations | Notes |
|---|---|---|---|
| BTS and SCTS[7] (2010) | Nonfixed lymph nodes Nonbulky lymph nodes Single-zone N2 disease Reasonable chance of: Complete resection, clear pathological margins | Consider surgery as part of multimodality treatment in nonfixed, nonbulky, single-zone N2 NSCLC Further research into the role of surgery in nonfixed, nonbulky, multizone N2 NSCLC | Significant weight placed on IASLC staging database outcomes despite lack of comparator group and lack of clinical N2 Guidelines consider evidence for adjuvant chemotherapy more robust than preoperative chemotherapy |
| ACCP[8] (2013) | Discrete lymph nodes Easily measurable and defined lymph nodes Free from major structures, such as the great vessels and trachea | Definitive CRT or induction therapy (chemotherapy or CRT) followed by surgery Surgery followed by adjuvant chemotherapy not recommended | Does not support the concept that surgery can only be justified in patients with minimal N2 disease Preoperative chemotherapy better than surgery alone in all NSCLC (small studies) and therefore surgery plus adjuvant chemotherapy is not recommended |
| ESMO[9] (2017) | Minimal, nonbulky N2 disease Single-station N2 disease | Definitive CRT, induction chemotherapy followed by surgery or induction CRT followed by surgery | Paramount importance of an experienced and high-volume multidisciplinary team and treatment centers able to minimize risk and complications from multimodality treatment highlighted |
| NICE[10] (2019) | None provided | Consider CRT followed by surgery | CRT followed by surgery improves PFS and might improve survival compared with CRT alone |
| NCCN[11] (2023) | Single lymph node smaller than 3 cm | Definitive CRT or induction chemotherapy followed by surgery or induction CRT followed by surgery Maintenance durvalumab following cCRT | Benefit from preoperative chemotherapy is similar to that of postoperative chemotherapy and either approach is justified |

*BTS*, British Thoracic Society; *SCTS*, The Society for Cardiothoracic Surgery in Great Britain and Ireland; *IASLC*, International Association for the Study of Lung Cancer; *ACCP*, American College of Chest Physicians; *CRT*, chemoradiotherapy; *ESMO*, European Society of Medical Oncology; *NICE*, National Institute for Health and Care Excellence; *NCCN*, National Comprehensive Cancer Network; *PFS*, progression-free survival; *cCRT*, concurrent chemoradiotherapy. *This table, under the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), was duplicated and updated from a previous table.[12]

a prognosis based on historical IASLC data.[15] Similarly, higher rates of recurrence and mortality have been shown for uncertain resections in retrospective studies.[11,16]

This highlights the importance of rigorously determining the precise stage of the tumor locally (T factor) and in the lymph nodes (N factor) not only by imaging, but also by mediastinal staging to assess the probability to achieve a complete resection via upfront surgery. Whereas the T stage is important to assess the technicality of resecting a tumor completely, so is the assessment of N2 disease more a prognostic then a technical factor because it has been demonstrated that increased node involvement influences survival.[17] However, in patients with bulky or invasive mediastinal lymph node metastases, significant technical considerations can arise, much like in invasive T4 stages.

## T STAGING

T3 and T4 tumors are not only characterized by their size and the number of lesions present, but also by their invasion of local structures ranging from chest wall for T3 tumors to

the mediastinum (diaphragm, heart, great vessels, carina, trachea, esophagus, and spine) for T4 tumors.[1] Surgery in case of invasion of local structures requires an extended resection to the organs invaded to achieve R0 resection.[18] Initial workup for assessing resectability of these tumors includes:

- Contrast-enhanced chest computed tomography to better define anatomical relations with the surrounding structures;
- Positron emission computed tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose, with or without contrast to search for distant metastases and evaluate mediastinal lymph nodes;
- Invasive mediastinal/node staging (endobronchial ultrasound,[7] esophageal ultrasound,[7] combined endobronchial ultrasound-esophageal ultrasound (EBUS-EUS), and/mediastinoscopy);
- Chest magnetic resonance imaging to assess extension to the chest wall, the spine, the great vessels, the mediastinum, and in particular in case of Pancoast tumors;
- EUS and cardiac gated magnetic resonance imaging or computed tomography to assess extension to the esophagus or the left atrium; and
- Flexible bronchoscopy to evaluate the endoluminal extension to the bronchus tree, the carina, or the trachea.

T4 tumors require special attention due to the frequent need for special and multidisciplinary surgical expertise, including cardiac or vascular expertise (vena cava or aorta), orthopedic or neurosurgeons (vertebral body), and plastic surgeons (brachial plexus or flap reconstruction). Furthermore, special infrastructural care platforms are required, such as access to extracorporeal membrane oxygenation or cardiopulmonary bypass. Indeed, the experience of other disciplines such as anesthesiology and intensive care available in specialized centers is essential to an optimal surgical outcome. Some tumor locations such as the heart, aorta, trachea, and esophagus are generally considered unresectable. However, some rare cases can be R0 resected with the support of extracorporeal membrane oxygenation/cardiopulmonary bypass, complex soft tissue or digestive reconstructive techniques, or the preoperative application of endovascular aortic stents (Figure 1). Such advanced surgical expertise is not available in every institution and needs extended training of the lead surgeon and his or her team of specialized surgical collaborators.[8] Numerous case series have demonstrated that these extended resections can be

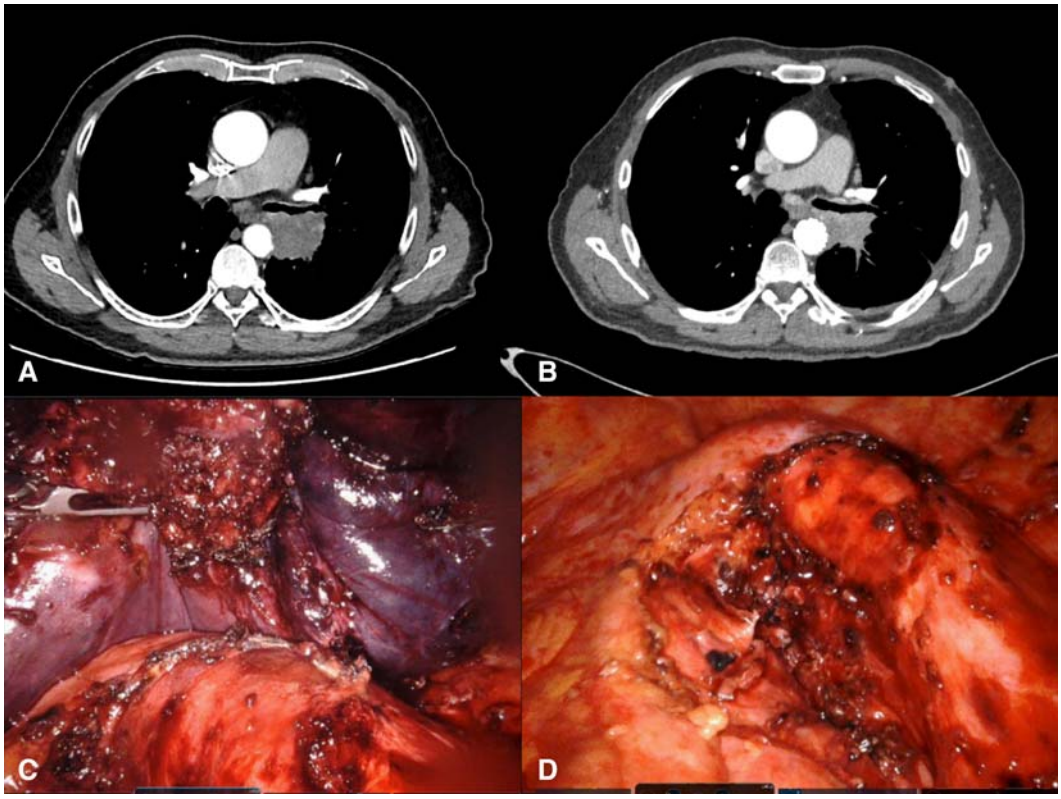


**FIGURE 1.** A 66-year-old patient was admitted to our department for a cT2 cN0 cM0 left central squamous cell carcinoma invading the descending thoracic aorta (A). After partial response from induction treatment using the Checkmate 816 protocol, an aortic stent graft was placed before surgery (B). Separation of the tumor from the aorta (C). End-result after extended left pneumonectomy and dissection along the aortic adventitia (D).

performed safely with good outcome and high R0 rates.[8,18] The current National Comprehensive Cancer Network guidelines thus recommend considering seeking an additional surgical opinion from a high-volume specialized center if a complete resection is considered uncertain.[9]

With a protocol of ipilimumab plus nivolumab (NIVO) and chemoradiotherapy followed by surgery, the Ipilimumab plus Nivolumab and Chemoradiotherapy Followed by Surgery in Patients With Resectable and Borderline Resectable T3-4 N0-1 NSCLC (INCREASE) trial assessed pathologic complete response (pCR) rates, event-free survival (EFS), and OS in a single-arm, prospective Phase 2 trial with either resectable or borderline resectable T3-4 N0-1 tumors.[10] In this study, patients considered upfront unresectable were included if expected to be resectable after a chemoradiotherapy and ICI induction protocol. Preliminary results from 25 patients were reported, amongst which were 7 Pancoast tumors and 4 chest wall tumors.[19] With a pCR rate of 60%, it appeared more than twice those reported in recent studies with induction chemotherapy (chemo) plus ICI protocols[2-4,19,20] (Table 2). Despite these outstanding results, more than 80% of patients experienced grade 3 and 4 adverse events, suggesting that such a regimen is only suitable for the fittest of patients. Furthermore, the addition of radiotherapy ensures a higher pCR rate in the locoregional basin, but this may not translate to equivalent distant control, which is where most of these patients usually progress. Indeed, high pCR or minimal residual tumor rates of 72% have been reported in the Southwest Oncology Group-Intergroup Trial S0220 in patients with superior sulcus tumors (N0-1 M0) treated in a trimodality concept using neoadjuvant chemoradiotherapy (cisplatin-etoposide and thoracic radiotherapy of 45 Gy) followed by surgical resection and adjuvant docetaxel.[21] Despite the excellent pathological response after induction radiotherapy, the 3-year OS was 61% (95% CI, 44-74%) and high rates of distant recurrences, particularly in the brain were a major problem.[21] It is possible that intensified systemic therapy will resolve these problems, but additional data are required to address this question.

## MEDIASTINAL STAGING

Indications for invasive mediastinal staging are[7]:

- Tumors larger than 3 cm;
- Positive lymph nodes on positron emission tomography/computed tomography scan;
- Lymph nodes with small axis superior to 1 cm; or
- Central tumors.

Mediastinal staging is performed by EBUS and/or EUS in first intention, to determine N2 disease or by EBUS or ultrasound-guided biopsy to eliminate N3 disease.[7] N3 patients are usually not considered candidates for surgery, whereas N2 patients are potential surgical candidates after

**TABLE 2. Main results from Phase 3 randomized trials on induction immune checkpoint inhibitors for resectable non–small cell lung cancer (NSCLC)**

| Study | Neoadjuvant | N | Adjuvant | Stage | Primary end point | Preoperative patient attrition | DFS or EFS HR | OS HR | DFS or EFS | OS | R0 | pCR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Neoadjuvant or perioperative (neoadjuvant + adjuvant) | | | | | | | | | | | | |
| AEGEAN[4] | Durvalumab + CT vs CT (4 cycles; 12 wk) | 802 | Durvalumab vs supportive care | IIA-IIIB | pCR<br>EFS | 19% vs 19% | 0.68 ($P < .004$) | NR | 73.2% vs 63% at 2 y | NR | 94.7% vs 91.3% | 17.2% vs 4.3% |
| Checkmate 816[2] | Nivolumab + CT vs CT (3 cycles) | 358 | None | IB-IIIA | pCR<br>EFS | 16% vs 21% | 0.63; 97.38% CI, 0.43-0.91; $P = .005$ | 0.57 (99.67% CI, 0.30-1.07) | Median EFS 31.6 mo vs 20.8 mo | 83% at 2 y<br>78% at 3 y | 83.2% vs 77.8% | 24% vs 2.2% |
| Keynote 671[5] | Pembrolizumab + CT vs CT (4 cycles; 12 wk) | 797 | Pembrolizumab vs supportive care | II-IIIB | EFS<br>OS | 18% vs 21% | HR, 0.58 (95% CI, 0.46-0.72); $P < .00001$ | HR, 0.73 (95% CI, 0.54-0.99); $P = .02124$ | (2-y EFS rate, 62.4% vs 40.6% | NR | 92% vs 84.2% | 18.1% vs 4% |
| Neotorch[20] | Toripalimab + CT vs CT (3 cycles) | 404 | Toripalimab vs supportive care after 1 cycle CT | II-III | EFS<br>MPR | 18% vs 27% | HR, 0.40 (95% CI (0.277-0.565); $P < .0001$ | NR | Median NR vs 15.1 mo | NR | 95.8% vs 92.6% | 24.8% vs 1% |

*DFS*, Disease-free survival; *EFS*, event-free survival; *HR*, hazard ratio; *OS*, overall survival; *pCR*, pathological complete response; *CT*, chemotherapy; *NR*, not reported.

induction treatment.[9] Nodal status is linked to survival and defines which extent of surgery is reasonable. Indeed, analysis from large historical databases showed that patients with N2 disease have significantly worse outcomes compared with patients with N1 and N0 disease[1,22]: 5-year survival of patients with pN0, pN1, pN2, and pN3 are, respectively, 75%, 49%, 36%, and 20%.[17] However, many of these recommendations are based on historical, real-world data with conventional chemo as induction treatment. In this context, it needs to be mentioned that several retrospective analyses and case series have reported encouraging long-term results, including 5-year OS of 39% after surgery within a multimodality treatment concept for stage III (N3) NSCLC.[23-26] Overall, mediastinal staging is important for determining and guiding treatment decisions. Intrinsic to these shared decisions between the patient and the multidisciplinary team is a personalized adjustment of risk versus potential benefit of all available treatment modalities. Careful and transparent weighing of short-term risks of the available therapeutic strategies against the potential survival from their stage and biology of disease is critical to a treatment course that will fit with the patient's overall therapeutic goals. Nevertheless, it is important to remember that these prognostic data do not uniformly represent patients being treated with modern treatment concepts. An update of the N-staging was presented at the 2023 World Conference on Lung Cancer and further stratifies the anatomic classification of NSCLC in the ninth edition of the TNM classification. Yet, it provides no insight into the relevant aspects of lung cancer biology that are becoming part of usual diagnostics in the resectable stages of lung cancer. In the upcoming version, the N-staging will be further subclassified into single- (N2a) and multistation (N2b) N2 disease: based on the T descriptor, single-station N2 tumors are newly classified as Union for International Cancer Control-stage II, whereas N2b tumors remain in Union for International Cancer Control-stage III. This new classification is set to be applied in January 2024.[27] This might equally change our inclusion criteria and assessment of resectability because, historically, multistation N2 disease has been judged unresectable by many colleagues around the world.

A major problem that surgeons must address is that invasive mediastinal staging is not broadly applied. Many patients' treatment is managed based on clinical staging purely following imaging and this is not a reliable strategy. The risk of both under- and overstaging has been well described in a meta-analysis by Navani and colleagues[14,28] and should be minimized in clinical practice. An understaging of nodal disease occurs in up to 34% of cases and is associated with poorer survival due to a potential delay in or lack of receipt of indicated systemic treatment. In contrast, clinical overstaging was seen in 14% of the patients included in the meta-analysis and may result in an exclusion of patients from potentially curative surgery.[14]

When it comes to the decision making about resectability based on the extent of mediastinal disease, looking at available guidelines, there is no consensus about the degree of mediastinal lymph node invasion that should be considered resectable (Table 1).[12] The current UK, European, and American guidelines use varying definitions for resectable N2 NSCLC ranging from "nonfixed, nonbulky nodes, single zone N2-disease with a reasonable chance of complete resection, and clear pathological margins," to "pathologically proven, low-volume (<3 cm), noninvasive lymph nodes."[12] These criteria are not applicable given the new IASLC mediastinal subclassification of single and multiple N2, and is based on historical data.[27]

The European Organization for Research and Treatment of Cancer Lung Cancer Group launched a multistep initiative together with other scientific societies involved in lung cancer treatment (European Thoracic Oncology Platform, European Society of Thoracic Radiation Oncology, European Society of Thoracic Surgery, European Respiratory Society, IASLC, and European Society of Pathology) to find a definition for resectability to be used in future clinical trials. In their conclusion, areas of future research interest were largely defined by the challenge of multiple-station N2 tumors.

## Defining Resectability in the Era of Immunotherapy Trials

Results from several Phase 2 and 3 trials with ICIs in patients with stage IIA to IIIB disease showed unprecedented rates of pCR. High rates of tumor and node downstaging, including the context of multistation N2 disease, and the major reduction in subsequent distant metastases have changed the concept of resectability by rendering a single static definition very challenging to outline (Table 1).[2,3]

A single-arm multicenter Phase 2 trial, the Swiss Group for Clinical Cancer Research, evaluated the additional benefit of durvalumab with induction chemo (cisplatin and docetaxel) in patients with stage IIIA (N2) NSCLC.[29] Compared with a historical cohort of stage III (N2) patients treated by induction chemo (cisplatin and docetaxel) followed by surgery where 1-year EFS rate was 48%, the addition of perioperative durvalumab helped achieve a 1-year EFS rate of 73%. Major pathologic response was 62% and pCR was 18%. Node downstaging was confirmed in 67% of patients: node downstaging to ypN1 occurred in 11 (20%) of 55 patients, whereas ypN0 was found in 26 (47%) of 55 patients. There was no information on multistation N2 or bulky N2 tumors.

Similar results were found in the Neoadjuvant Chemotherapy and Nivolumab in Resectable Non-Small-Cell Lung Cancer (NADIM) trial with an OS of 85% at 2 years in stage IIIA and IIIB patients who had received NIVO plus induction chemo followed by adjuvant NIVO. The NADIM II trial highlighted the potential long-term benefits of ICI in this highly heterogenous patient group.[3] The OS benefit for

the addition of perioperative NIVO was highly significant (HR for death, 0.43; 95% CI, 0.19-0.98). R0 resection was achieved in 94% and 85% of patients in the treatment arm and the control arm, respectively. This study was marked by a high rate of N2 disease in the NIVO + chemo group (n = 41 [72%]) compared with the chemo-alone group (n = 16 [55%]): more than half of the patients had multistation N2 disease but there was no mention of bulky N2.[3] The downstaging rate was 69.8% in the NIVO arm versus 40% in the chemo arm (odds ratio, 3.47; 95% CI, 1.19-10.1; $P = .04$). Six pneumonectomies (10.3%) were performed in the treatment arm and 2 pneumonectomies (10%) were performed in the control arm. In the treatment arm, 15 patients with T3 tumors (26.3%) and 14 patients with T4 tumors (24.6%) were included and compared with 6 (20%) T3 tumors and 12 (41%) T4 tumors in the control arm. These imbalances in the T-stage could explain the above-mentioned difference in the R0 resection rate and highlight the importance of Phase 3 blinded and stage-stratified trials.

Benefits of ICI in combination with conventional chemo for patients with resectable tumors has lately also been confirmed in Phase 3 trials. Checkmate 816, a randomized controlled open-label trial, has helped establish NIVO as a standard protocol treatment for induction therapy in patients with stage II to IIIA disease.[2] Indeed, by evaluating efficacy and safety of induction NIVO + chemo (3 cycles) compared with chemo alone (3 cycles) in patients with resectable NSCLC, median EFS was significantly improved with NIVO (31.6 months vs 20.8 months; $P = .005$). The HR for disease progression, disease recurrence, or death was 0.63 (97.38% CI, 0.43-0.91; $P = .005$) and the percentage of patients with pCR was 24% with NIVO compared with 2.2% without ($P < .001$).[2] R0 resection was achieved in 83.2% and 77.8% of the patients in the treatment arm and the placebo arm, respectively. Resectability and the operative approach were determined by the surgeon: lobectomy, bilobectomy, and pneumonectomy, as well as sleeve-resections were allowed. Twenty-five pneumonectomies (16.8%) were performed in the treatment group and 34 (25.2%) in the control arm. There was no information on T3 or T4 tumors. Patients deemed resectable by the investigator team with cT1-4 N0-2 were eligible for inclusion in this study. However, details of T4 extent, multiplicity of N2, or bulkiness at baseline were not captured in the original data collection forms.

Recently, the interim results of the Checkmate 77t trial assessing perioperative NIVO + chemo in resectable stage IIA through IIIB NSCLC were presented.[30] In this Phase 3, randomized, double-blind trial, patients were randomized to receive neoadjuvant NIVO + chemo followed by adjuvant NIVO (NIVO + chemo/NIVO group) or neoadjuvant chemo plus placebo followed by adjuvant placebo (chemo/placebo group).[30] At a minimum follow-up of 15.7 months, the interim results show a significantly improved median EFS in the NIVO + chemo/NIVO group when compared with the chemo/placebo group (median, not reached; 95% CI, 28.9 months-not reached vs median, 18.4 months; 95% CI, 13.6-28.1; HR, 0.58; 97.36% CI, 0.42-0.81; $P = .00025$).[30] Similar to the Checkmate 816 trial, pCR rates were significantly higher in the NIVO + chemo/NIVO group compared with the chemo/placebo group (25.3% vs 4.7%; odds ratio, 6.64; 95% CI, 3.40-12.97).[30]

The Keynote 671 trial is a randomized, double-blind Phase 3 trial where patients with resectable stage II, IIIA, or IIIB (N2) NSCLC were assigned to receive either induction pembrolizumab plus cisplatin-based chemo or induction placebo plus cisplatin, followed by surgical resection and adjuvant pembrolizumab or placebo.[5] A recently published first interim analysis showed a significantly improved EFS and an increased pCR (18.1% in the treatment arm vs 4.0% in the placebo arm). In addition, a numerically higher percentage of node downstaging was seen in the treatment arm (downstaging to N0: 34.3% vs 23.4%). A post hoc analysis of EFS showed that the EFS benefit of the treatment arm was only seen in the subgroup that received surgical resection (HR, 0.53; 95% CI, 0.42-0.67) and in the subgroup where R0 resection was achieved (HR, 0.53; 95% CI, 0.41-0.68).[31] Resectability was determined by surgical consultation and an investigator assessment. Lobectomy was the most common surgical procedure in both groups (treatment arm 78.8%, placebo arm 75.1%), followed by pneumonectomy (treatment arm 11.4%, placebo arm 12.3%). Ninety-two percent of patients in the treatment arm had an R0 resection, whereas 84.2% of patients in the control arm had an R0 resection. One hundred twenty-one T3 tumors (30.5%) and 115 T4 tumors (29%) were included in the treatment group compared with 109 T3 tumors (27.2%) and 104 T4 tumors (26.0%) included in the control group. One hundred sixty-eight patients (42.3%) had N2 disease in the treatment arm compared with 187 patients (46.8%) in the control group. There was no information about inclusion of N2 multistation and/or bulky N2 disease among these patients.

In the Neoadjuvant/Adjuvant Durvalumab for the Treatment of Patients With Resectable Non-Small Cell Lung Cancer (AEGEAN) trial—a randomized, double-blind, Phase 3-trial—802 treatment-naive patients with resectable stage II or IIIB (N2) NSCLC were assigned to either induction durvalumab plus platinum-based chemo or induction placebo plus platinum, followed by surgical resection and adjuvant durvalumab or placebo.[4] Surgery was performed in 77.6% and 76.7% of patients in the treatment arm and the placebo arm, respectively. The recent presentation of the results showed that pCR was achieved in 17.2% in the treatment arm versus 4.3% in the placebo arm. Median EFS was not reached in the treatment arm and thereby significantly prolonged when compared with the EFS of 25.9 months in the placebo arm. A total of

**TABLE 3. Subgroup analysis from Phase 3 randomized trials on induction immune checkpoint inhibitors for resectable non–small cell lung cancer (NSCLC)**

| | Neoadjuvant perioperative setting Primary end point: EFS | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | AEGEAN subgroup[4] | | | Keynote 671 subgroup[5] | | | Checkmate 816 subgroup[2] | | |
| Characteristic | Subgroup | N | Hazard ratio (95% CI) | Subgroup | N | Hazard ratio (95% CI) | Subgroup | N | Hazard ratio 95% CI) |
| Disease stage | II | 214 | 0.76 (0.43-1.34) | II | 239 | 0.65 (0.42-1.01) | IB-II | 126 | 0.94 |
| | IIIA | 338 | 0.67 (0.39-0.83) | IIIA | 442 | 0.64 (0.41-0.72) | IIIA | 229 | 0.57 |
| | IIIB | 189 | 0.83 (0.52-1.32) | IIIB | 116 | 0.52 (0.31-0.89) | | | |
| Nodal status | N2 single | 273 | 0.61 (0.30-0.94) | N0 | 290 | 0.67 (0.40-0.82) | N2 single | NR | NR |
| | N2 multi | 74 | 0.69 (0.33-1.38) | N1 | 152 | 0.60 (0.36-1.01) | N2 multi | | |
| | | | | N2 | 355 | 0.57 (0.42-078) | | | |

*NR*, Not reported.

94.7% of patients in the treatment arm had an R0 resection, whereas 91.3% of patients in the control arm had an R0 resection. In the AEGEAN trial, resectability was based on both the IASLC Staging Manual in Thoracic Oncology (version 8) and the opinion of a multidisciplinary evaluation. However, the planned surgical procedure needed to comprise either a lobectomy, a sleeve lobectomy, or a bilobectomy. No information has been yet published on T3 and T4 tumors, but all candidates with locally advanced tumors requiring pneumonectomy were therefore excluded. Similar results from the Perioperative Toripalimab Plus Chemotherapy for Patients With Resectable Non–Small Cell Lung Cancer (Neotorch) trial—a randomized, double-blind, placebo-controlled, Phase 3 trial, evaluating toripalimab plus chemo followed by toripalimab maintenance versus chemo in stage III resectable nonsquamous NSCLC, without *EGFR/ALK* alterations—are reported.[20] Two hundred two patients were recruited in each group. EFS was significantly improved in the toripalimab arm (HR, 0.4; 95% CI, 0.277-0.565; $P < .0001$). The major pathologic response and the pCR rates were also higher in the toripalimab arm, 48.5% versus 8.4% and 24.8% versus 1.0%, respectively. OS results are not yet available. A total of 95.8% of patients in the treatment arm had an R0 resection, whereas 92.6% of patients in the control arm had an R0 resection. No information was yet available on N2 tumors as well as T3 or T4 tumors.

Tables 2 and 3 highlight the results from the Phase 2 and 3 randomized trials on adjuvant ICIs for resectable NSCLC that are already published or currently ongoing; they show a range of pCR from 17.2% to 37% and EFS of 62.4% to 73.2% at 2 years.

In comparison to this stands the Durvalumab After Chemoradiotherapy in Unresectable Stage III Non–Small-Cell Lung Cancer (PACIFIC) trial, where 709 patients with unresectable stage III NSCLC were randomized to receive consolidation therapy (236 patients received placebo and 473 received durvalumab) after definitive chemoradiotherapy.[6] The median progression-free survival in patients treated with durvalumab compared with the placebo was significantly improved (16.8 vs 5.6 months; HR, 0.52; 95% CI, 0.42-0.65; $P < .001$). The 2-year OS was significantly higher in the durvalumab group compared with the placebo group (66.3% vs 55.6%; $P < .0025$), as well as the 5-year OS (42.9% vs 33.4%).[6,32] In the PACIFIC trial, resectability was defined according to the seventh edition of the IASLC Staging Manual in Thoracic Oncology.[32] However, no standardized protocol for the definition of resectability was used before trial inclusion, nor was a surgical opinion required. The application of the PACIFIC trial protocol is a valuable option for patients with primarily unresectable stage III disease and especially for patients who are deemed inoperable due to limited cardiorespiratory reserve and/or other comorbidities.

## CONCLUSIONS

Anatomical lung resection remains a key and ever-growing element in management of locally advanced NSCLC within multimodality treatment. To achieve an R0 resection, which guarantees the best OS rate, systemic treatment options have been reinforced by ICI. Concurrent chemotherapy with ICI promotes downstaging and increases pathological response, which translates to better EFS and OS. Accordingly, in multidisciplinary tumor boards, induction treatment protocols have evolved towards chemoimmunotherapy for patients with stage II to IIIA disease, especially with confirmed N2 disease or tumors larger than 4 cm. This approach is also considered in more borderline situations where patients with complex T4 disease and/or extensive node involvement such as multiple or bulky N2 should be assessed on a case-by-case basis. In light of the promising results of the available Phase 2 and 3 trials investigating induction chemoimmunotherapy, we expect a continued paradigm shift in the resectability assessment of locally advanced NSCLC in the future. Initial results from trials

assessing the value of triple induction by adding radiotherapy to turn unresectable tumors into resectable ones have shown even more promising response rates. Given the outstanding response rates, re-evaluation of resectability should eventually considered after completion of induction and restaging for borderline patients. At this time information on radiological and metabolic response can be integrated into the decision-making process. Of course, the counterpoint will emerge if we can accurately predict the occurrence of pCR before resection—will resection still be required? Without a doubt, future trials will need to track much more granular clinical staging information throughout the trajectory of treatment and consider resectability at baseline, after completion of induction and benchmarked to the operation performed and whether it yielded an R0 resection. This approach should provide better guidance for patient in special subsets who were traditionally are deemed unresectable such as T4 or multistation/bulky N2 tumors.

Until then, surgical indication depends on a multidisciplinary discussion involving surgeons, radiation oncologists, pathologists, medical oncologist, and radiologists who will integrate all available data on the backdrop of each patient's goals of care and risk tolerance. If a surgeon or center is uncertain about potential complete resection, obtaining an additional multidisciplinary team evaluation from a high-volume center with the required specialized surgical expertise should be considered.

## Conflict of Interest Statement

Dr Opitz reports the following disclosures: Roche (institutional grant for fellowship and speakers bureau), Roche Genentech (steering committee), AstraZeneca (advisory board and speakers bureau, steering committee), Medtronic (institutional grant and advisory board), MSD (advisory board), BMS (advisory board), and Intuitive (proctorship). Dr Spicer reports the following disclosures: AstraZeneca (advisory board, speakers bureau, grant to institution, clinical trial leadership), Merck (advisory board, speakers bureau, grant to institution, clinical trial leadership), BMS (advisory board, speakers bureau, grant to institution), Roche (advisory board, grant to institution), Regeneron (advisory board), Amgen (honoraria), Novartis (advisory board), Eisai (advisory board), Protalix Biotherapeutics (advisory board, grant to institution), and CLS Therapeutics (grant to institution). Dr Werner reports the following disclosure: BMS (advisory board). All other authors reported no conflicts of interest.

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

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