



# Multidisciplinary approach for patients with early and locally advanced non-small cell lung cancer (NSCLC): 2nd Spanish Lung Cancer Group (GECP) expert consensus statement

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**Background:** In light of the ongoing advancements in the treatment of patients with early- and locally advanced-stage non-small cell lung cancer (NSCLC), the members of the Spanish Lung Cancer Group (GECP) deemed it necessary to update its 2023 consensus suggestions for the management of these patients.

**Methods:** From July to November 2024, a panel of experts, including thoracic surgeons, radiation oncologists, and medical oncologists, was convened. The consensus process was developed using a mixed approach that incorporated Delphi and nominal group techniques. The consensus coordination group reviewed the relevant scientific literature for the update and developed a questionnaire for the panel of experts to vote on. Two rounds of voting were conducted, followed by a final nominal group meeting to discuss clinical situations where consensus had not been reached and draw final conclusions. In instances where high-quality scientific data were not available or were the subject of controversy, final suggestions were based on the expertise of the participants.

**Results:** Thirty experts from the multidisciplinary team participated in the voting and discussions. The document was updated to incorporate recent advancements in molecular diagnosis and biomarkers, the role of the multidisciplinary thoracic committee, criteria for neoadjuvant/perioperative treatment, approaches to inoperable/unresectable disease, and adjuvant treatment. Proposals that did not require updating were not voted on again and remain part of the document, maintaining their first version.

**Conclusions:** Updated suggestions were developed for the most relevant situations in the treatment of patients with early-stage and locally advanced NSCLC. These suggestions will support clinical decision-making in daily practice. This paper presents the statements developed by the expert panel and summarizes the scientific evidence supporting them.

**Keywords:** Early; locally advanced; non-small cell lung cancer (NSCLC); treatment; expert consensus

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## Introduction

Locally advanced or stage III non-small cell lung cancer (NSCLC) is a highly heterogeneous disease, which has made it difficult to classify, and there is a lack of consistency in treatment approaches (1,2). Although complete surgical resection is the cornerstone of curative treatment, about 70% of patients have metastatic or locally advanced unresectable disease at diagnosis (1,2). For patients with high-risk early-stage or resectable stage III NSCLC, the historical approach of using adjuvant or neoadjuvant platinum-based doublet chemotherapy provided a modest 5% survival benefit at five years, and there were no significant improvements in this result for a long time (3,4).

Recent data on chemoimmunotherapy in the neoadjuvant and perioperative settings for treating patients with NSCLC have changed the standard of care. This approach has been shown to significantly improve tumor response rates and survival, as demonstrated by several phase 2 and 3 trials (5-13). Based on these new findings, the Food and Drug Administration (FDA) approved the

use of nivolumab in combination with platinum-based chemotherapy in the neoadjuvant setting in March 2023. Similarly, pembrolizumab (October 2023), durvalumab and nivolumab (August and October 2024, respectively) were approved also in combination with platinum-based chemotherapy in the perioperative setting. Additionally, the neoadjuvant chemoimmunotherapy approach for patients with locally advanced NSCLC was included in guidelines such as those from the National Comprehensive Cancer Network (NCCN), the National Institute for Health and Care Excellence (NICE), and the American Society of Clinical Oncology (ASCO) (14-17).

In an effort to standardize diagnostic and therapeutic approaches for patients and encourage multidisciplinary oncology team evaluations, the Spanish Lung Cancer Group (GECP) drafted a consensus document in 2023. The aim was to provide clinical suggestions that would be useful for selecting patients most likely to benefit from neoadjuvant treatment. These suggestions addressed issues that were controversial and/or lacked sufficient data and/or had uncertain clinical applications (18).

Given the continuing advances in the management of patients with early and locally advanced NSCLC and the availability of new data, an update of the first consensus document was undertaken. This manuscript presents the updated suggestions developed by the expert panel.

## Methods

From July to November of 2024, the GECP invited a group of 30 experts, including 17 medical oncologists, 11 thoracic surgeons, and two radiation oncologists who belong to major institutions in Spain. All participants had experience with the neoadjuvant and/or adjuvant treatment of patients

with early-stage and locally advanced NSCLC through their participation in clinical research, including studies led by the GECP such as NADIM and NADIM II (7,19,20).

Under the guidance of the Coordinating Group, consensus was reached through a four-step process. The mixed technique (Delphi/nominal group) was used to allow experts to anonymously rate the clinical issues in several rounds, followed by a nominal group meeting as a last activity to discuss the vote results and reach conclusions (21,22) (*Figure 1*).

For the first consensus document, the literature search was performed in PubMed, selecting publications from 1997 to March 2023. For this update, publications from March 2023 to July 2024 on the diagnosis and treatment of early and locally advanced NSCLC, abstracts and full texts of randomized clinical trials, meta-analyses, systematic reviews, and oncologic management guidelines performed by scientific associations or academic institutions were additionally included. Oral and written abstracts presented at international oncology meetings were also included.

Based on the previous document, it was determined that the subjects that required update included molecular diagnosis and biomarkers, the role of the multidisciplinary thoracic committee (MTC), indications for neoadjuvant/perioperative treatment, and follow-up/adjuvant treatment.

Previous proposals that did not require updating were not subject to re-vote and remain part of the document. A 19-question questionnaire was developed for the first round of voting. For the second round, the anonymized consolidated responses were shared with the expert panel, along with the adapted questionnaire that included non-consensual situations.

After each round of voting, responses were summarized in an analysis matrix using medians and interquartile ranges (IQRs). Consensus was reached when the median response was within an IQR of 1–3 and 7–9. The threshold for agreement in the expert vote was 85%. In the final nominal meeting, attended by 85% of the expert panel members, the situations that were not consensual after the last round of voting were discussed and a common agreement was obtained (*Figure 2*).

For the consensus statements, the Infectious Diseases Society of America-US Public Health Service Grading System for ranking recommendations in Clinical Guidelines was used to assign levels of evidence and grades of recommendation, as follows (23):

- (I) Levels of evidence:
  - (i) Evidence from at least one large randomized,

### Highlight box

#### Key recommendations

- The crucial contribution of the multidisciplinary thoracic committee to the decision-making process regarding the diagnostic and therapeutic approaches for patients with early-stage and locally advanced non-small cell lung cancer (NSCLC) must be recognized.

#### What was recommended and what is new?

- The Spanish Lung Cancer Group (GECP) developed a consensus document with suggestions for the management of patients with locally advanced NSCLC in 2023. Topics discussed in this document included criteria for pathological, radiological, and surgical diagnoses, as well as mediastinal staging; the role of the thoracic multidisciplinary committee; indications and controversial situations related to the neoadjuvant chemoimmunotherapy approach; postsurgical evaluation after neoadjuvant chemoimmunotherapy; and suggestions for oncological follow-up of patients.
- Considering the continuous advances in the treatment of patients with early- and locally advanced NSCLC, an update to the previous suggestions was deemed necessary to address the following topics: criteria for the initial surgical treatment of patients with early-stage disease; management of patients with tumors harboring therapeutic targets in the neoadjuvant, adjuvant, and unresectable stages; the role of chemoradiotherapy; criteria for selecting neoadjuvant vs. perioperative approaches; and new adjuvant treatment options for patients with resected tumors without therapeutic targets.

#### What is the implication, and what should change now?

- Given the recent changes in therapeutic standards of patients with early and locally advanced NSCLC and the difficulties and barriers that may arise in their implementation, an expert consensus document is a valuable tool for standardizing and supporting clinical practice. The purpose of our suggestions is to provide a framework for clinical practice in real-world scenarios, especially when scientific evidence is lacking and situations involving uncertainty arise.

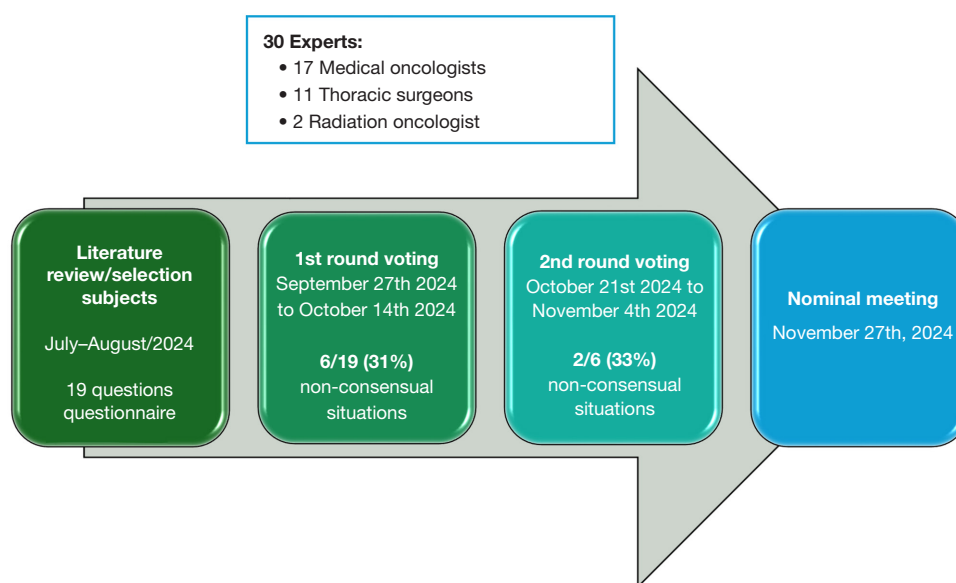


**Figure 1** Consensus process methodology (mixed technique Delphi/nominal group).

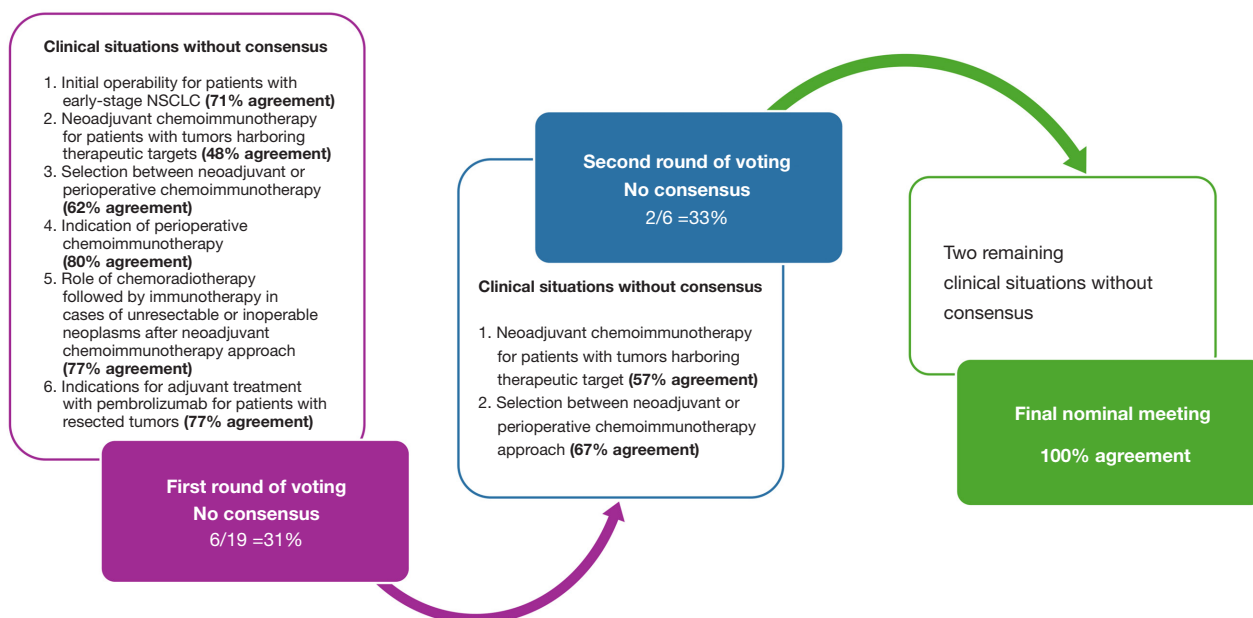


**Figure 2** Results of voting phases. NSCLC, non-small cell lung cancer.

- controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity;
- (ii) Small randomized trials or large randomized

- trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity;
- (iii) Prospective cohort studies;

- (iv) Retrospective cohort studies or case-control studies;
- (v) Studies without control group, case reports, expert opinions.
- (II) Grades of recommendation:
  - (i) Strong evidence for efficacy with a substantial clinical benefit, strongly recommended;
  - (ii) Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended;
  - (iii) Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional;
  - (iv) Moderate evidence against efficacy or for adverse outcome, generally not recommended;
  - (v) Strong evidence against efficacy or for adverse outcome, never recommended.

According to the American Association for Thoracic Surgery/Society of Thoracic Surgeons Position Statement on the Development of Clinical Practice Documents recommendations, the consensus results are presented as clinical suggestions (24).

## Results

The suggestions were developed considering the best scientific evidence. In cases where there was inadequate support or controversial data, the suggestions were based on the participating experts' experience.

### *Molecular diagnosis and biomarkers (updated\*)*

Multiple studies on neoadjuvant and adjuvant chemoimmunotherapy support the use of programmed death-1 ligand 1 (PD-L1) expression as a predictive biomarker of response to treatment. Therefore, it has been determined that this biomarker should always be assessed in the diagnostic biopsy (5,7,8,10,12,13,25).

Due to the benefits in overall survival (OS) and the regulatory approvals of osimertinib and, more recently, alectinib as adjuvant treatments for patients with resected NSCLC harboring epidermal growth factor receptor (*EGFR*) mutations or anaplastic lymphoma kinase (*ALK*) rearrangements, respectively, it was deemed necessary to evaluate the presence of these oncogenic drivers at diagnosis to inform treatment decisions (26,27).

It was also concluded that genomic profiling at the initial diagnosis is not currently a priority due to the limited access

and inconsistent reimbursement within the healthcare system (*Table 1*).

### *Radiological diagnosis*

Patients should always undergo contrast-enhanced thoracoabdominal computed tomography (CT) with supraclavicular and upper abdominal extension, as the sensitivity and specificity for detecting mediastinal lymph node metastases are 55% and 81%, respectively. Similarly, given the sensitivity and specificity of positron emission tomography-computed tomography (PET-CT) to detect mediastinal tumoral involvement of 77% and 86%, respectively, this study should also be performed to detect possible distant or occult metastases that cannot be identified through conventional methods (17,28-30). Since the false positive rate of PET-CT scans ranges from 10% to 30%, it was agreed that all suspicious findings should be confirmed histologically. To achieve optimal staging, contrast-enhanced magnetic resonance imaging (MRI) of the brain is preferred over brain CT because it is more sensitive in detecting brain metastases, including those smaller than 1 cm (72.8% *vs.* 50% and 36.3% *vs.* 16.7%, respectively). If an MRI cannot be performed or is unavailable, it is reasonable to perform a contrast-enhanced CT scan of the brain instead (31,32). In cases of Pancoast tumors with suspected infiltration of mediastinal structures, additional cervicothoracic MRIs may be considered to help define surgical management (33,34) (*Table 1*).

### *Surgical diagnosis and mediastinal staging*

It was discussed that staging of the mediastinum is essential to define the extent of disease and to define surgical and neoadjuvant treatment (30,35-37).

Agreement was reached that mediastinal staging should be indicated by a central airway tumor, a tumor greater than 3 cm, and/or enlarged hilar or mediastinal lymph nodes on a chest CT scan, as well as an elevated or pathological standardized uptake value (SUV) on a PET-CT scan (28,36-39).

For diagnosis and mediastinal staging, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) or endobronchial ultrasound-guided fine needle aspiration (EUS-FNA) were considered the preferred techniques, given their sensitivity of 80% when used separately, which increases to 90-99% when used together. The effectiveness of these techniques is dependent on the

**Table 1** Suggestions for the diagnosis of patients with early and locally advanced NSCLC (updated\*)

| Statement                                                                                                                                                                                                                                                                                                                | GoR/LoE        |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| <b>(I) Molecular diagnosis and biomarkers</b>                                                                                                                                                                                                                                                                            |                |
| PD-L1 levels, <i>EGFR</i> mutation and <i>ALK</i> rearrangement* should always be evaluated at diagnosis biopsy tissue                                                                                                                                                                                                   | IA             |
| It is reasonable to determine <i>KRAS</i> mutation and ROS1 translocation if there is availability to administer targeted therapy in a clinical trial setting                                                                                                                                                            | Expert opinion |
| A comprehensive genomic profiling could be performed only if there is availability to obtain it shortly                                                                                                                                                                                                                  | Expert opinion |
| <b>(II) Radiological diagnosis</b>                                                                                                                                                                                                                                                                                       |                |
| Thoracoabdominal CT with contrast including supraclavicular region, thorax, and upper abdomen should always be performed                                                                                                                                                                                                 | IIIC           |
| PET-CT should always be performed                                                                                                                                                                                                                                                                                        | IIIC           |
| Brain MRI with contrast should be indicated to complete the staging. If brain MRI it is no available, it is reasonable perform brain CT with contrast                                                                                                                                                                    | IIIC           |
| Cervicothoracic MRI may be considered in some cases of Pancoast tumors with suspected infiltration of mediastinal structures                                                                                                                                                                                             | IIIC           |
| <b>(III) Surgical diagnosis and mediastinal staging</b>                                                                                                                                                                                                                                                                  |                |
| The indications that should be considered for mediastinal staging are:                                                                                                                                                                                                                                                   | IIIC           |
| <ul style="list-style-type: none"> <li>• Presence of central airway tumor</li> <li>• Tumor &gt;3 cm</li> <li>• Enlarged hilar or mediastinal lymph nodes on CT scan or with elevated/pathologic SUV on PET-CT</li> </ul>                                                                                                 |                |
| Mediastinal diagnosis/staging should be performed by EBUS-TBNA or EUS-FNA in a center with extensive experience                                                                                                                                                                                                          | IIA            |
| It is reasonable to perform surgical exploration of the mediastinum with the most efficient technique defined by the MTC (mediastinoscopy, video thoracoscopy, etc.), if EBUS or EUS did not obtain satisfactory results, or it was not possible to perform them and there is strong suspicion of lymph node involvement | Expert opinion |

\*, NEW/MODIFIED suggestions with consensus voting. This table was adapted from an Open Access article (18) under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>). *ALK*, anaplastic lymphoma kinase; CT, computed tomography; *EGFR*, epidermal growth factor receptor; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; EUS-FNA, endobronchial ultrasound-guided fine needle aspiration; GoR, grades of recommendation; *KRAS*, Kirsten rat sarcoma; LoE, levels of evidence; MRI, magnetic resonance image; MTC, multidisciplinary thoracic committee; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; PET-CT, positron emission tomography-computed tomography; ROS1, C-ROS oncogene 1 receptor tyrosine kinase; SUV, standardized uptake value.

expertise of the operator, so their undertaking should be in centers with extensive experience (40-45). When EBUS or EUS cannot be performed or do not yield satisfactory results, it is reasonable to perform a surgical examination of the mediastinum using the most optimal technique (mediastinoscopy, thoracoscopy, etc.), as defined by MTC (17,40,46) (Table 1, Figure 3).

### Role of the MTC (updated\*)

In view of the new treatment options, it was discussed that patients with stage IB and II NSCLC with borderline

resectability criteria, in addition to all patients with locally advanced disease, could benefit from evaluation by an MTC. A growing body of research has demonstrated that patients diagnosed with lung cancer who receive treatment in a multidisciplinary setting have a higher probability of receiving active management and optimal utilization of all available treatment modalities, including surgery, radiation therapy, and chemotherapy. This collaborative approach has been shown to result in enhanced survival outcomes (47-49). According to this evidence, a multidisciplinary approach is recommended in the management guidelines for oncology, including those of the American Association of Clinical

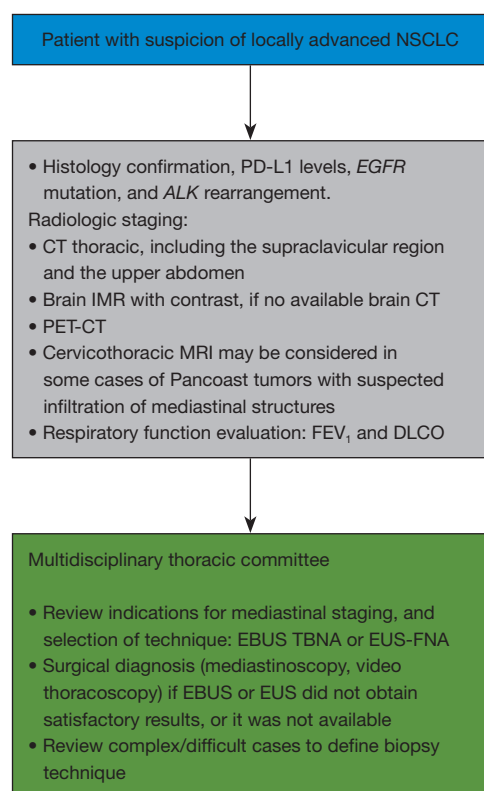


**Figure 3** Expert consensus GECP updated suggestions: multidisciplinary approach algorithm for diagnosis and staging on patients with locally advanced NSCLC. This figure was adapted from an Open Access article (18) under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>). ALK, anaplastic lymphoma kinase; CT, computed tomography; DLCO, lung diffusion capacity for carbon monoxide; EGFR, epidermal growth factor receptor; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; EUS-FNA, endobronchial ultrasound-guided fine needle aspiration; FEV<sub>1</sub>, forced expiratory volume in 1 second; GECP, Spanish Lung Cancer Group; MRI, magnetic resonance image; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; PET-CT, positron emission tomography-computed tomography.

Oncology (ASCO), the European Society of Medical Oncology (ESMO), and the NCCN (17,47-49).

There was a consensus on the composition of the thoracic committee, with the inclusion of specialists in the following fields: pathology, radiology, nuclear medicine, pulmonary medicine, palliative care/oncology support, thoracic surgery, radiation oncology, and medical oncology. It was also suggested that a case manager be appointed

to provide logistical support to patients and ensure timely diagnostic procedures and complementary clinical evaluations.

According to the resources of each healthcare institution, it was deemed appropriate to include additional professionals participating in the healthcare of patients with lung cancer in the committee.

In recognition of the importance of incorporating the perspectives of all specialists involved in the thoracic tumor committee when making treatment decisions, the main clinical situations in which patients' cases should be discussed by the MTC were defined (Table 2).

### *Neoadjuvant and perioperative treatment (updated\*)*

Recent data have supported the efficacy of neoadjuvant and more recently, perioperative\* chemo-immunotherapy, achieving pathologic complete response (pCR) rates of 17–40% *vs.* 9% with chemotherapy, and median event-free survival (EFS) at 24 months of 63–70% *vs.* 40–50% with chemotherapy. Based on this, it has been suggested that all patients with resectable locally NSCLC should be offered neoadjuvant or perioperative\* treatment with chemo-immunotherapy if there are no absolute reasons to contraindicate immunotherapy (6-8,10,11,20,25,50-59) (Table 3).

Among the most controversial aspects of the selection of patients for neoadjuvant or perioperative treatment, the following issues were identified (Figure 4):

### **Timing of tumor resectability assessment\***

In the CheckMate-816 Phase I3 study, the chemotherapy-immunotherapy combination increased the proportion of patients undergoing definitive surgery from 75% to 83% and improved the pCR rate from 2.2% to 24.0% [odds ratio (OR), 13.94; 95% confidence interval (CI): 3.49–55.75;  $P < 0.001$ ]. This finding was observed regardless of clinical staging, PD-L1 expression, or tumor mutational burden (TMB) (5). Likewise, the NADIM II trial demonstrated pCR in 37% of patients in the experimental group *vs.* 7% in the control group [relative risk (RR), 5.34; 95% CI: 1.34–21.23;  $P = 0.02$ ]. There was a 93% rate of surgery in the experimental group and a 69% rate in the control group (RR 1.35; 95% CI: 1.05–1.74) (19). This increase in pCR was also reported in perioperative studies. In AEGEAN trial, the pCR rate was 17.2% in the durvalumab plus platinum-based chemotherapy arm *vs.* 4.3% in the control arm (95% CI: 8.7–17.6),  $P < 0.001$ , while in the KEYNOTE

**Table 2** Suggestions on the role of the MTC in the evaluation of patients with locally advanced NSCLC (updated\*)

| Statement                                                                                                                                                                                                                                                                   | GoR/LoE        |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| <b>(IV) Role of the MTC</b>                                                                                                                                                                                                                                                 |                |
| The MTC should be constituted by pathologists, radiologists, nuclear medicine specialists, pulmonologists, palliative care and oncology support specialists, thoracic surgeons, radiation oncologists and medical oncologists                                               | Expert opinion |
| A case manager should be available to assist patients with the logistical requirements for performing diagnostic procedures and treatment defined by the MTC                                                                                                                | Expert opinion |
| According to the resources of each health institution, it is reasonable that other professionals involved in the care of patients with lung cancer also participate in the thoracic committee                                                                               | Expert opinion |
| <b>Clinical situations in which patients should be discussed in the MTC*</b>                                                                                                                                                                                                |                |
| Patients with stage IB and II disease with borderline resectability criteria* and all patients with stage III disease                                                                                                                                                       | Expert opinion |
| Patients after initial diagnosis with results of staging imaging and <i>EGFR</i> mutation and <i>ALK</i> rearrangement* results to evaluate the possibility of oncologic surgery, as well as the benefit of administering neoadjuvant, perioperative* or adjuvant treatment | Expert opinion |
| Highly complex cases or when it is difficult to define the technique to perform a biopsy                                                                                                                                                                                    | Expert opinion |
| To decide the best invasive mediastinal staging technique (EBUS-TBNA, EUS-FNA, mediastinoscopy or other surgical technique)                                                                                                                                                 | Expert opinion |
| After neoadjuvant treatment, with control imaging results are used to evaluate tumor response and define surgical treatment                                                                                                                                                 | Expert opinion |
| After surgical treatment, to review the anatomic pathology report and determine the requirement for additional/adjuvant interventions                                                                                                                                       | Expert opinion |

\*, NEW/MODIFIED suggestions with consensus voting. This table was adapted from an Open Access article (18) under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>). EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; EUS-FNA, endobronchial ultrasound-guided fine needle aspiration; GoR, grades of recommendation; LoE, levels of evidence; MTC, multidisciplinary thoracic committee; NSCLC, non-small cell lung cancer.

671 trial, a pCR occurred in 18.1% of participants (95% CI, 14.5–22.3) in the pembrolizumab group *vs.* 4.0% (95% CI: 2.3–6.4) in the placebo group,  $P<0.001$  (8,11). Additionally, in the Neotorch study, higher MPR and pCR rates in the toripalimab plus platinum-based chemotherapy arm *vs.* control arm (48.5% *vs.* 8.4% and 24.8% *vs.* 1.0%, respectively); 95% CI: 32.2–48.1,  $P<0.001$  (12). Recently, interim results from the phase 3 RATIONALE-315 trial of perioperative tislelizumab for the treatment of resectable NSCLC showed improved EFS *vs.* placebo [stratified hazard ratio 0.56 (95% CI: 0.40–0.79);  $P<0.001$ ] and better MPR rate [56% (95% CI: 50–63%) *vs.* 15% (95% CI: 11–20%) in the placebo group];  $P<0.001$  (59).

It was considered that these results provide support for all patients with locally advanced NSCLC to be subjected to evaluation by the MTC at the time of initial diagnosis to assess the feasibility of surgical resection and the potential benefit of neoadjuvant or perioperative\* treatment. Additionally, due to the high likelihood of tumor

shrinkage, patients should undergo a new tumor assessment after completing neoadjuvant treatment to reevaluate resectability based on tumor response.

### Resectability criteria

It was discussed that these criteria may vary according to the experience of different surgical teams, due to the complexity of the disease. For this reason, it was suggested that all patients should always be evaluated by MTC to determine the optimal approach to increase the possibility of surgical resection (48,60,61).

### Pulmonary function evaluation

Multiple studies support the concept that the diffusion lung diffusion for carbon monoxide (DLCO) is the best predictor of complications after lung resection and that it is not associated with the forced expiratory volume in 1 second ( $FEV_1$ ). Therefore, it is recommended that both DLCO and  $FEV_1$  be used in conjunction to assess respiratory function

**Table 3** Suggestions for neoadjuvant/perioperative approach of patients with locally advanced NSCLC (updated\*)

| Statement                                                                                                                                                                                                                                                                                                    | GoR/LoE        |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| (V) Neoadjuvant and perioperative treatment indication*                                                                                                                                                                                                                                                      |                |
| Neoadjuvant and perioperative approach with platinum-based chemotherapy plus immunotherapy should always be offered to all patients with potentially resectable NSCLC who are at least 4 cm or node-positive, regardless of PD-L1 levels, unless the patient has absolute contraindications to immunotherapy | IA             |
| General considerations for neoadjuvant and perioperative* treatment                                                                                                                                                                                                                                          |                |
| Resectability                                                                                                                                                                                                                                                                                                |                |
| • The possibility of resectability and benefit of neoadjuvant/perioperative treatment should be considered at diagnosis and confirmed according to the tumoral response after neoadjuvant treatment, in an MTC                                                                                               | Expert opinion |
| • Patients with early-stage/resectable and operable NSCLC with negative lymph nodes should be offered surgical treatment initially*                                                                                                                                                                          | IIA            |
| • The requirement of a pneumonectomy (either left or right) should not constitute an absolute contraindication to offer neoadjuvant or perioperative* treatment                                                                                                                                              | IIIC           |
| Evaluation of respiratory function                                                                                                                                                                                                                                                                           |                |
| • To evaluate respiratory function as part of the preoperative workup, FEV <sub>1</sub> and DLCO should always be performed at diagnosis and reevaluated after neoadjuvant treatment, according to the characteristics of the patient                                                                        | IIIC           |
| Type of oncological approach                                                                                                                                                                                                                                                                                 |                |
| • The intrinsic characteristics of the patient and the experience of the surgical team are the most important aspects to decide the type of oncologic approach                                                                                                                                               | Expert opinion |
| Duration of treatment                                                                                                                                                                                                                                                                                        |                |
| • The administration of 3 cycles of chemotherapy plus immunotherapy with neoadjuvant intent should be sufficient                                                                                                                                                                                             | IA             |
| Approach for patients with NSCLC harboring <i>EGFR</i> mutation or <i>ALK</i> rearrangement*                                                                                                                                                                                                                 |                |
| • In the absence of an option to participate in a clinical trial, there is no evidence of benefit from administering neoadjuvant treatment with chemotherapy and immunotherapy. These cases should be discussed in the MTC to define the best approach                                                       | Expert opinion |
| • Patients with unresectable locally advanced NSCLC harboring an <i>EGFR</i> exon 19 deletion or exon 21 L858R mutation who have received chemo-radiotherapy without disease progression must then receive osimertinib                                                                                       | IA             |
| Indications for chemoradiotherapy*                                                                                                                                                                                                                                                                           |                |
| • Neoadjuvant approach in cases of upper sulcus tumors                                                                                                                                                                                                                                                       | IVC            |
| • Definitive treatment for patients with unresectable locally advanced NSCLC, followed by durvalumab in patients who do not progress during radiation                                                                                                                                                        | IA             |
| Choice between neoadjuvant or perioperative treatment*                                                                                                                                                                                                                                                       |                |
| • Currently, there is no scientific evidence directly comparing neoadjuvant treatment with perioperative chemoimmunotherapy. Therefore, either approach would be acceptable*                                                                                                                                 | Expert opinion |
| • There is insufficient scientific evidence to define the profile of patients who benefit from adjuvant immunotherapy after receiving neoadjuvant chemoimmunotherapy*                                                                                                                                        | Expert opinion |
| • Nivolumab should be given with a platinum-based chemotherapy doublet in patients with indications for neoadjuvant treatment*                                                                                                                                                                               | IA             |
| • Patients eligible for perioperative treatment can receive either nivolumab, pembrolizumab or durvalumab combined with a platinum-based chemotherapy doublet and then continue adjuvant treatment with the same immunotherapy used in the neoadjuvant setting*                                              | IA             |

**Table 3** (continued)

Table 3 (continued)

| Statement                                                                                                                                                                                                                                                                                                | GoR/LoE        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| TNM criteria for treatment in the neoadjuvant or perioperative* setting                                                                                                                                                                                                                                  |                |
| The AJCC 8th edition TNM staging criteria for identifying potentially resectable disease that could benefit from neoadjuvant or perioperative treatment should be as follows:                                                                                                                            |                |
| (a) Primary tumor 1–5 cm, T1, T2a and T2b, with N2 single or multiple station involvement (stage IIIA)                                                                                                                                                                                                   | IA             |
| (b) Primary tumor >5–7 cm, T3, with N1 lymph node involvement (stage IIIA)                                                                                                                                                                                                                               | IA             |
| (c) Primary tumor >7 cm, T4, with N0 or N1 lymph node involvement (stage IIIA)                                                                                                                                                                                                                           | IIIC           |
| (d) Primary tumor >5–7 cm, T3, with N2 single or multistation lymph node involvement (stage IIIB)                                                                                                                                                                                                        | IA             |
| (e) Cases of primary tumor T4, with N2 lymph node involvement (stage IIIB) are underrepresented in clinical trials, so it is considered reasonable to evaluate them individually and define management according to the clinical characteristics of the patient and the experience of the surgical group | Expert opinion |
| (f) Patients with any T and N3 lymph node involvement (stage IIIB and IIIC), are not considered to benefit from treatment with neoadjuvant intent and should receive treatment with concomitant chemo radiotherapy                                                                                       | IA             |
| Evaluation of response to neoadjuvant therapy                                                                                                                                                                                                                                                            |                |
| Radiological evaluation                                                                                                                                                                                                                                                                                  |                |
| • Chest CT with extension to contrasted upper abdomen should be performed after completion of neoadjuvant treatment                                                                                                                                                                                      | IVC            |
| • PET-CT should also be performed to evaluate distant metastatic disease                                                                                                                                                                                                                                 | IVC            |
| • MRI should be considered in case of suspicion in CT or PET-CT of infiltration of structures contiguous to the tumor                                                                                                                                                                                    | IVC            |
| • Additional imaging should be performed depending on symptoms and/or clinical evidence of tumoral progression. In this case, histological confirmation should be performed whenever technically possible                                                                                                | Expert opinion |
| Mediastinal restaging                                                                                                                                                                                                                                                                                    |                |
| • Mediastinal restaging should be performed after neoadjuvant treatment to guide surgical treatment if there is doubt about tumoral response on imaging                                                                                                                                                  | IIIC           |
| N2 nodal involvement response                                                                                                                                                                                                                                                                            |                |
| • Resectability criteria that should be considered after the end of neoadjuvant treatment include:                                                                                                                                                                                                       |                |
| (a) Initial N2 disease, either single or multiple nodal, with a complete or partial response on restaging imaging, and technically resectable                                                                                                                                                            | Expert opinion |
| (b) Initial N2 single or multiple nodal disease with stable disease on restaging imaging should be discussed in an MTC, considering the feasibility of resection and the intrinsic clinical characteristics of each patient                                                                              | Expert opinion |
| (c) In case of suspicious images of progression of tumor nodal involvement, a confirmatory biopsy should be performed if technically feasible                                                                                                                                                            | Expert opinion |
| • If the patient experiences tumoral progression during neoadjuvant treatment, it is recommended that surgery be withheld, and systemic treatment should be offered, taking into account the clinical and pathological/biomarker characteristics                                                         | Expert opinion |
| • In the case of patients without adequate tumor response after treatment with neoadjuvant chemoimmunotherapy (unresectable), or inoperable neoplasia, treatment with chemoradiotherapy followed by immunotherapy could be considered for patients who do not progress during chemoradiotherapy          | Expert opinion |

\*, NEW/MODIFIED suggestions with consensus voting. This table was adapted from an Open Access article (18) under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>). AJCC, American Joint Committee on Cancer; ALK, anaplastic lymphoma kinase; CT, computed tomography; DLCO, lung diffusion capacity for carbon monoxide; EGFR, epidermal growth factor receptor; FEV<sub>1</sub>, forced expiratory volume in 1 second; GoR, grades of recommendation; LoE, levels of evidence; MRI, magnetic resonance image; MTC, multidisciplinary thoracic committee; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; PET-CT, positron emission tomography-computed tomography; TNM, tumor-nodes-metastasis.

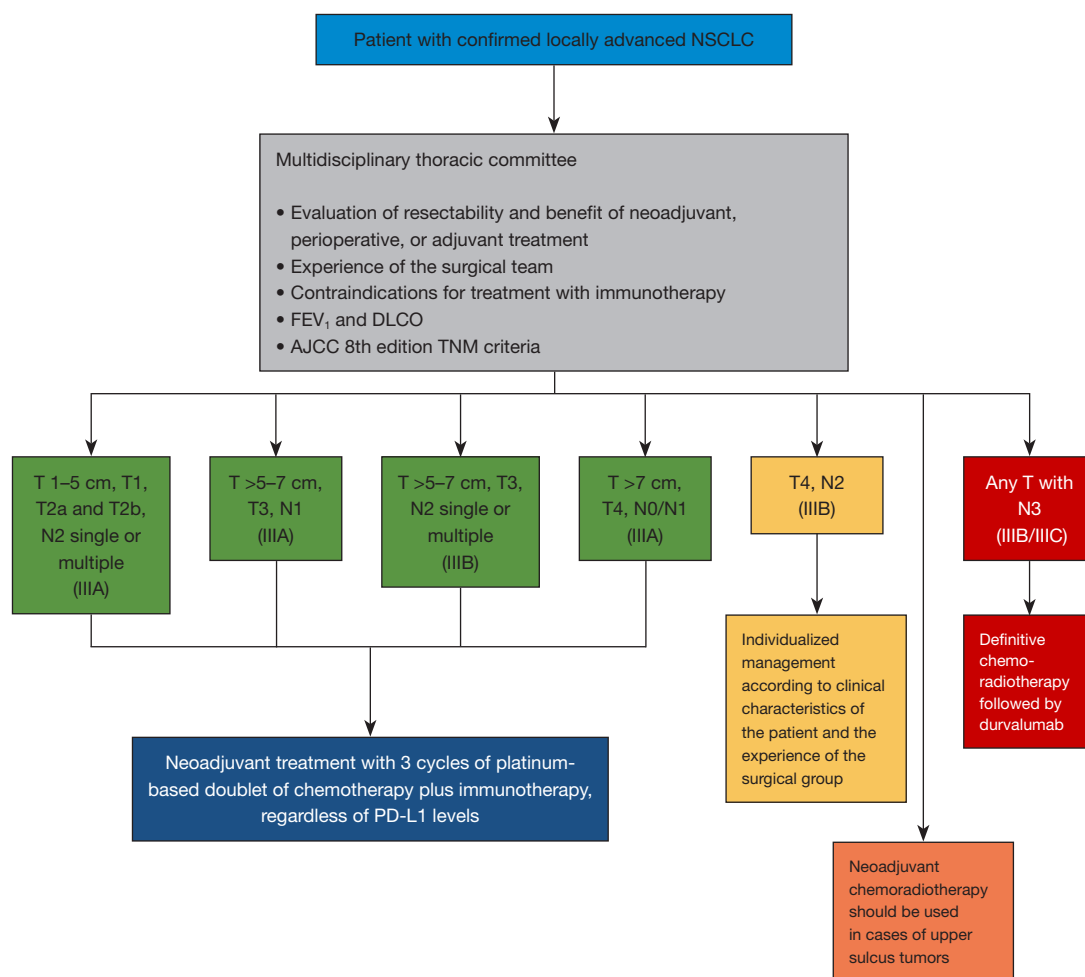


**Figure 4** Expert consensus GECP updated suggestions: multidisciplinary approach algorithm for selection of treatment on patients with locally advanced NSCLC. This figure was adapted from an Open Access article (18) under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>). AJCC, American Joint Committee on Cancer; DLCO, lung diffusion capacity for carbon monoxide; FEV<sub>1</sub>, forced expiratory volume in 1 second; GECP, Spanish Lung Cancer Group; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1.

(62-66). In this instance, it has been concluded that if the FEV<sub>1</sub> and DLCO values are both greater than 80%, the risk of complications from anatomical lung resection is low, and further testing is unnecessary (66,67). In addition, it was suggested that DCLO and FEV<sub>1</sub> should be performed at the time of initial diagnosis. Depending on the patient's characteristics and the test results, reassessment may be considered at the completion of neoadjuvant treatment to confirm the previous results.

### Type of oncological surgery

Given the potential for complications, there has been a high degree of conservatism in the performance of

pneumonectomies when the procedure is necessary, particularly on the right side, due to the heightened risk of bronchopleural fistula (68,69).

Considering the new data. It was discussed that the requirement of a pneumonectomy should not be considered an absolute exclusion from surgical treatment and that a neoadjuvant or perioperative approach should always be offered. This was based on the high tumor response achieved in the CheckMate-816 trial, which was associated with improvements in 3-year EFS irrespective of the extent of resection (64% in the experimental arm *vs.* 49% in the control arm for lobectomy, and 67% in the experimental arm *vs.* 48% in the control arm for pneumonectomy) (5).

Moreover, the available literature has documented that approximately 10% of pneumonectomies were performed in all available studies without complications or detrimental effects on survival rates. This suggestion is further supported by the current widespread use of video-assisted thoracic surgery (VATS), advancements in postoperative techniques, such as bronchial and vascular reconstructions to avoid pneumonectomy determined at the time of surgery, and recent improvements in immediate postoperative care (70).

#### **Duration of treatment in the neoadjuvant setting**

Given the variation in neoadjuvant regimens proposed in the current clinical trials and the high response rates reported with 3 cycles of treatment, it has been agreed upon that three cycles of treatment are sufficient to achieve maximum tumor response, and no further treatment is required (5,20,25,51).

#### **Role of neoadjuvant chemo-radiation therapy\***

The trials evaluating neoadjuvant chemoradiotherapy (INT0139, SAKK16/00, and WJTOG9903), and a combined analysis of 4 trials. These studies were conducted before the efficacy of the neoadjuvant approach was known, so they are not being compared to it. Although some uncontrolled phase II trials suggested improved survival after neoadjuvant chemoradiotherapy, this finding has not been confirmed by several randomized phase III trials. In the INT0139 trial, 396 patients with stage IIIA NSCLC with ipsilateral and/or subcarinal mediastinal lymphatic spread (N2 disease) who received induction chemoradiotherapy did not show an improvement in OS (71-75). On the other hand, recent data on chemoradiotherapy combined with immunotherapy from phase 2 trials, including INCREASE and SAKK16/18, showed an increased tumor response rate, but also higher grade 3 toxicities, and neither study demonstrated an improvement in OS (76,77).

According to these data, chemoradiotherapy was considered the appropriate treatment for patients with upper sulcus tumors, which are generally not surgical candidates due to the involvement of nearby anatomical locations (78-80).

#### **Approach for patients with NSCLC harboring EGFR mutation or ALK rearrangement\***

This population has not been consistently identified in the studies of neoadjuvant chemo-immunotherapy and has only been formally included in two phase 3 perioperative trials, KEYNOTE 671 and AEGEAN. In the former, malignancies

with *EGFR* mutations and *ALK* translocations represented 3.5% and 3%, respectively, of the population (n=576). In contrast, the AEGEAN study initially included 51 patients with NSCLC with *EGFR* mutation (6% of the total), who were subsequently excluded due to a protocol amendment. Given the small population size, it was discussed that the data derived from these studies are insufficient to support the role of perioperative immunotherapy in patients with *EGFR* mutations and *ALK* rearrangement (7-14). On the other hand, preliminary evidence suggests that targeted therapies may be effective in patients with resectable NSCLC with *EGFR* mutation or *ALK* rearrangement. Results from ongoing trials are necessary to provide further information on the safety and efficacy of perioperative tyrosine kinase inhibitor (TKi) therapy (81-86).

Whereas, in the case of patients with unresectable locally advanced NSCLC harboring an *EGFR* exon 19 deletion or exon 21 L858R mutation who have received chemoradiation therapy without disease progression, it has been suggested that they should then receive osimertinib according to the recent positive results of the LAURA trial (87).

#### **Choice between neoadjuvant or perioperative treatment\***

An examination of patient-level data from the CheckMate 816 and CheckMate 77T phase III trials showed that patients who received at least one dose of adjuvant nivolumab following neoadjuvant nivolumab plus chemotherapy and surgery had a 39% reduction in the risk of disease recurrence or death compared to patients who received nivolumab plus chemotherapy in the neoadjuvant setting (88). However, given the nature of this type of analysis, the expert panel believes that it is necessary to conduct additional studies to determine the profile of patients who may benefit from the perioperative approach. On this basis, it was concluded that since there is currently no scientific evidence that directly compares neoadjuvant treatment with perioperative chemoimmunotherapy and supports the superiority of either strategy, either approach would be acceptable. As per the currently available approvals, chemo-immunotherapy regimens should be administered according to those used in the pivotal trials. This includes nivolumab in the neoadjuvant setting and nivolumab, pembrolizumab, or durvalumab in the perioperative setting (8,9,11).

#### **Clinical staging criteria**

Available neoadjuvant and perioperative studies included

patients classified according to both the seventh and 8th versions of the American Joint Committee on Cancer (AJCC) staging system based on primary tumor size (T), lymph node involvement (N), and the presence of metastatic disease (M). In the seventh edition of staging, T3N1 tumors were classified as stage III, with a lower size threshold of 7 cm, and tumors measuring more than 7 cm without lymph node involvement were designated as stage IIB disease. In contrast, the eighth edition reclassified stage III to include tumors larger than 5 cm with hilar, intrapulmonary, or peribronchial lymph node involvement (T3N1), as well as tumors larger than 7 cm (T4), irrespective of lymph node involvement (89-91) (Table S1).

Although the description of lymph node involvement did not change between the seventh and eighth editions of the TNM staging system, a new category, stage IIIC, was created for patients with T3/T4 and N3 disease. Tumors with ipsilateral mediastinal N2 involvement are now staged as IIIB instead of IIIA (89-91).

After analyzing these data from the two staging systems and the trial results it was concluded that patients who should be considered to have potentially resectable tumor and who could benefit from neoadjuvant approach according to the AJCC 8th edition classification are: patients with primary tumor 1–5 cm (T1, T2a and T2b) and N2 single or multiple nodal involvement (stage IIIA), as well as those with primary tumor >5–7 cm (T3) with N1 nodal involvement (stage IIIA), primary tumor >7 cm (T4) with N0 or N1 nodal involvement (stage IIIA), and primary tumor >5–7 cm (T3) with N2 nodal involvement (stage IIIB).

Multi-stage N2 lymph node disease has traditionally been considered a limiting factor when offering curative surgical treatment. However, new data is currently available from the CheckMate-816, NADIM, and CheckMate-77T trials. In the former, almost two-thirds of the patients had stage IIA disease with N2 lymph node involvement and experienced the greatest survival benefit. In the NADIM study, 54% of the patients had N2 multiple lymph node station spread. After receiving neoadjuvant treatment, 89% of the patients were able to undergo R0 surgical resection. Pathological findings showed 83% MPR and 63% pCR. During the 3-year follow-up, the OS rate was 81.9% (5,7,20,51,89).

More recently, among results from the CheckMate-77T trial, improvement in median EFS in patients with N2 single and multiple lymph node station involvement was reported, 30.2 months and not reached, HR 95% CI: 0.49 (0.29–0.84) and 0.43 (0.21–0.88), respectively (9). This benefit has been sustained, as reported in a study update

in which patients with N2 lymph node involvement had improved EFS (70% *vs.* 45%) and higher pCR (22.0% *vs.* 5.6%) after a median follow-up of 25.4 months compared to the placebo group (92).

Based on these data, it was suggested that curative surgical treatment should be offered to all patients with initially resectable N2 single or multiple lymph node involvement, and that surgical treatment should be offered after completion of neoadjuvant treatment, based on tumor response and the feasibility of resection.

In the context of patients with T4 primary tumors and N2 lymph node involvement (stage IIIB), it was discussed that this group is underrepresented in clinical trials. Thus, evaluating each case individually and defining management according to the patient's clinical characteristics and the surgical team's experience is reasonable.

On the other hand, patients with a primary tumor of any size and N3 lymph node involvement (stage IIIB or IIIC) are considered unresectable. Therefore, it was considered that they would not benefit from neoadjuvant treatment. These patients should receive definitive chemoradiotherapy followed by durvalumab if they do not progress after radiation treatment, according to the results of the PACIFIC trial (93) (Table 3, Figure 4).

The 9th edition of the AJCC staging system has been available since the end of 2024 and is currently being implemented in clinical practice (94). However, it is not expected to impact the current suggestions generated by this consensus.

### *Evaluation of response to neoadjuvant treatment*

#### **Radiological evaluation**

After completing neoadjuvant treatment, a chest CT scan with contrast-enhanced imaging of the upper abdomen should be performed for comparison with the baseline study. Response measurements should be evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) (95). In addition, if distant disease is suspected, evaluation with a PET-CT should be performed (96,97). It was suggested that additional imaging should only be performed in cases of symptoms indicating tumor progression. Additionally, histologic confirmation should be obtained in all suspected cases of tumor progression, whenever technically possible (Table 4).

#### **Mediastinal restaging**

In terms of mediastinal restaging following neoadjuvant

**Table 4** Suggestions for postoperative evaluation of patients with resected NSCLC (updated\*)

| Statement                                                                                                                                                                                                                                                                                                                                                                                         | GoR/LoE        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| (VI) Post-operative evaluation of patients with NSCLC treated with neoadjuvant chemotherapy and immunotherapy                                                                                                                                                                                                                                                                                     |                |
| The cases should always be reviewed after surgery, in the MTC, with an anatomical and pathological report to define the requirement to offer adjuvant treatment (systemic or radiotherapy) or to initiate follow-up                                                                                                                                                                               | Expert opinion |
| The anatomy pathologic report should follow the recommendations of the IASCL guidelines for evaluation of response to neoadjuvant treatment and include information about the percentage of residual tumor and determination of response in primary tumor, number of resected nodes, lymph node involvement, the characteristics of the resection margins and the staging pTNM                    | Expert opinion |
| (VII) Adjuvant treatment*                                                                                                                                                                                                                                                                                                                                                                         |                |
| Patients with resected stage IB (>4 cm), II and IIIA NSCLC harboring <i>EGFR</i> exon 19 deletion or exon 21 L858R mutation should be offered osimertinib for 3 years after platinum-based chemotherapy as adjuvant treatment                                                                                                                                                                     | IA             |
| Patients with resected NSCLC harboring <i>ALK</i> rearrangement and tumors $\geq 4$ cm or with positive lymph nodes should be offered alectinib for 24 months as adjuvant treatment*                                                                                                                                                                                                              | IA             |
| Adjuvant radiation therapy for patients with resected NSCLC indication should be individualized and discussed within an MTC. It is reasonable to administer this local treatment in case of R1 resection. In case of confirmed N2 nodal involvement, it is also reasonable in specific cases, including extracapsular nodal disease in the affected N2 station and R1 and R2 lymph node resection | IIIC           |
| Patients with resected NSCLC, tumors $\geq 5$ cm or with positive nodes and PD-L1 $\geq 50\%$ , non-mutated <i>EGFR</i> and without <i>ALK</i> rearrangement should receive platinum-based chemotherapy followed by atezolizumab as adjuvant treatment*                                                                                                                                           | IA             |
| Patients with resected NSCLC, tumors $\geq 4$ cm, or positive nodes, regardless of PD-L1 level, should receive platinum-based chemotherapy followed by pembrolizumab as adjuvant treatment*                                                                                                                                                                                                       | IA             |

\*, NEW/MODIFIED suggestions with consensus voting. This table was adapted from an Open Access article (18) under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>). *EGFR*, epidermal growth factor receptor; GoR, grades of recommendation; IASCL, International Association for the Study of Lung Cancer; LoE, levels of evidence; MTC, multidisciplinary thoracic committee; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; TNM, tumor-nodes-metastasis.

therapy, it has been proposed that this procedure should only be carried out if the tumor response is unclear based on imaging findings. Some studies have shown that the negative predictive value (NPV) ranges from 20% to 78% when endoscopic techniques such as EBUS-TBNA are performed after induction therapy, indicating significant variability in diagnosis (98,99). In addition, data regarding mediastinoscopy after induction therapy has shown reduced sensitivity compared to the primary procedure due to adhesions and fibrotic changes following neoadjuvant treatment (100-102).

### N2 nodal involvement response

Based on reports from available clinical trials, the following criteria were suggested for resectability of N2 disease after neoadjuvant chemoimmunotherapy (5,7,9,20,51,92):

- (I) Initial N2 disease, either single or multiple nodal, with a complete or partial response on restaging imaging, and technically resectable;
- (II) In case of initial N2 single or multiple nodal

disease with stable disease on restaging imaging, the patients should be discussed in an MTC, considering the feasibility of tumoral resection and the intrinsic clinical characteristics of each patient.

- (III) In case of suspicious images of progression of tumor nodal involvement, a confirmatory biopsy should be performed if technically feasible.

It was agreed that if the patient presents with confirmed tumor progression during induction treatment, surgical treatment should be discarded. On the other hand, if the patient has unresectable neoplasia after receiving neoadjuvant treatment, definitive chemoradiotherapy followed by immunotherapy could be offered to patients if there is no tumor progression after loco-regional radiotherapy (93,103) (Table 4, Figure 5).

### Post-operative evaluation of patients with resected NSCLC

It was considered that, after surgery, patients should be reevaluated by the MTC along with the anatomic pathology

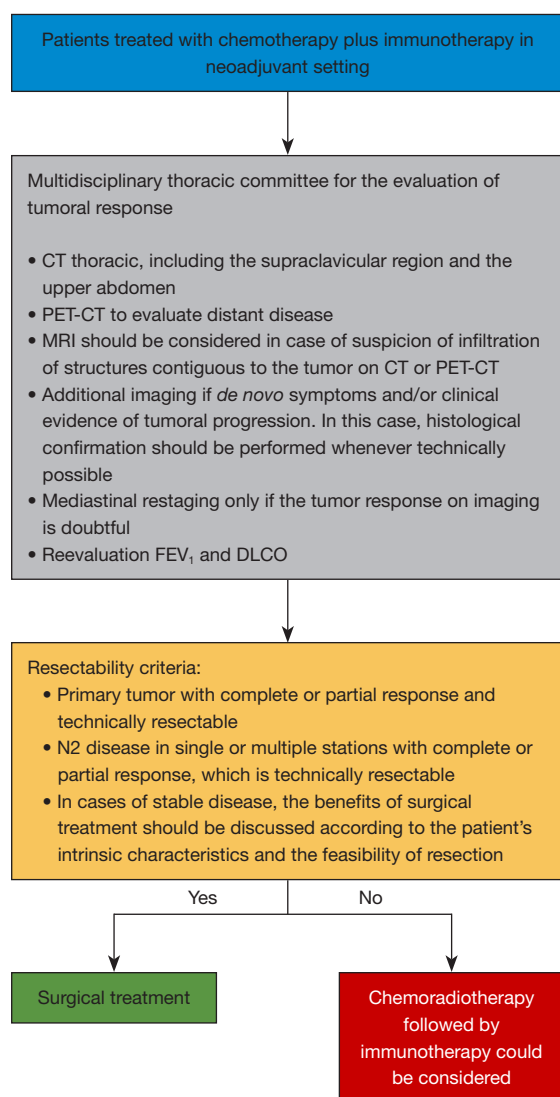


**Figure 5** Expert consensus GECP updated suggestions: multidisciplinary approach algorithm for treatment on patients with locally advanced NSCLC that received chemotherapy plus immunotherapy in neoadjuvant setting. This figure was adapted from an Open Access article (18) under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>). CT, computed tomography; DLCO, lung diffusion capacity for carbon monoxide; FEV<sub>1</sub>, forced expiratory volume in 1 second; GECP, Spanish Lung Cancer Group; MRI, magnetic resonance image; PET-CT, positron emission tomography-computed tomography.

report, in order to discuss the need for adjuvant treatment or to begin follow-up.

The pathology report should adhere to the International Association for the Study of Lung Cancer's (IASLC) multidisciplinary recommendations for the pathological evaluation of lung cancer resection specimens after neoadjuvant therapy. These recommendations include (104):

- (I) The surgeon must provide information on the type of treatment the patient received, the presence of multiple tumors in the specimen, the correct labeling of the specimen with the resected lobe(s), and the involvement of other structures, such as the pericardium, diaphragm, or chest wall.
- (II) Report the effect of the treatment on the primary tumor, specifying the percentage of viable tumor, tumor necrosis, stroma, and degree of inflammation.
- (III) Describe the effect of the treatment on the primary tumor. Specify the percentage of viable tumor, tumor necrosis, stroma, and degree of inflammation (Table 4, Figure 5).

#### *Adjuvant treatment\**

It was discussed that current data are insufficient to clearly define the profile of patients who benefit from adjuvant immunotherapy after receiving neoadjuvant chemoimmunotherapy. For this reason, a perioperative approach could be offered to patients who meet the inclusion criteria of pivotal trials supporting this approach.

In regard to the use of adjuvant radiotherapy for patients with resected NSCLC, it was generally agreed that the indication should be individualized and discussed within an MTC. Considering the potential of local recurrence, it was deemed appropriate to offer this treatment in cases of patients after resection with a microscopically positive margin (R1 resection). Likewise, according to the most recent scientific evidence regarding N2 lymph node involvement, it was suggested that adjuvant radiation therapy should be offered in specific cases with an elevated risk of recurrence. These cases include extracapsular extension in the involved N2 station, as well as R1 and gross unresected tumor remaining (R2 resection), lymph node

resection (105-110).

In case of patients with initially resected early malignancy, it was suggested:

- (I) For patients with resected stage IB (>4 cm), II and IIIA NSCLC harboring *EGFR* exon 19 deletion or exon 21 L858R mutation should be offered osimertinib for 3 years after platinum-based chemotherapy as adjuvant treatment, according to results of the ADAURA trial (17,26).
- (II) Patients with resected NSCLC harboring *ALK* rearrangement and tumors  $\geq 4$  cm or with positive lymph nodes should be offered alectinib for 24 months as adjuvant treatment according to the results of the ALINA trial\* (17,27).
- (III) Patients with resected NSCLC, tumors  $\geq 5$  cm (8th edition AJCC) or with positive nodes and PD-L1  $\geq 50\%$ , *EGFR* wild type and not harboring *ALK* rearrangement should receive platinum-based chemotherapy followed by atezolizumab as one year adjuvant treatment, according to results of IMpower110 trial\* (111).
- (IV) Patients with resected NSCLC, tumors  $\geq 4$  cm (8th edition AJCC), or positive nodes, regardless of PD-L1 level, *EGFR* wild type and not harboring *ALK* rearrangement, should receive platinum-based chemotherapy followed by pembrolizumab as one year adjuvant treatment, according to results of the KEYNOTE 091/Pearls trial\* (112) (Table 4).

#### **Follow-up of patients with resected NSCLC**

In case of high potential of recurrence due to the characteristics of the disease and for patients who received systemic neoadjuvant and/or adjuvant treatment, oncological follow-up should always be indicated (113,114).

Counseling and pharmacologic smoking cessation programs should be continued as these are highly effective strategies for reducing the risk of tumor recurrence and the development of secondary lung neoplasms and further pulmonary damage in patients with reduced respiratory function (114-119).

To perform the oncological follow-up, it was found that the publications and available guidelines contain multiple and heterogeneous recommendations. Consequently, there is no high-quality evidence in the literature supporting the performance of blood tests or the types and frequencies of imaging. During the discussion of this topic, it was determined that blood tests performed during follow-up

should include renal function testing. This is useful for detecting late nephrotoxicity, as patients with lung cancer often receive platinum-based chemotherapy. Additionally, radiology centers typically require this testing before performing CT scans or MRIs. The need for additional blood tests should be guided by the patient's symptoms and the physician's clinical judgment. Therefore, it was agreed that blood tests and a contrast-enhanced chest CT scan would be performed every six months during the first two years, followed by blood tests and a low-dose chest CT scan annually for three years. After that, low-dose CT scans would be performed annually according to each patient's risk characteristics (17,114,120).

If suspicious radiologic abnormalities are identified during routine follow-up, a confirmatory biopsy should be performed to confirm tumor recurrence. Regarding PET/CT, it was agreed that it should not be performed routinely for follow-up and should be limited to cases with inconclusive conventional imaging results. It was also suggested that brain MRIs or CT scans with contrast should not be performed annually in the absence of neurological symptoms (114) (Table 5).

#### **Discussion**

Following a discussion among specialists from various disciplines involved in the care of patients with lung cancer, updated consensus suggestions were established for managing key clinical scenarios in the treatment of patients with early-stage and locally advanced NSCLC.

We consider that, given the recent changes in treatment standards and the difficulties and barriers that may arise in their implementation, an expert consensus document is a valuable tool for standardizing and supporting clinical practice.

It is important to highlight that, although not all physicians involved in diagnosing and managing patients with early- and locally advanced NSCLC were part of the voting consensus process, including pneumologists, pathologists, radiologists, and nuclear medicine specialists, their participation is recognized as necessary and crucial in this document when describing the specialists that should comprise the MTC that evaluates patients.

The goal of this consensus was to address the most controversial aspects of the current general oncological approach. Based on our clinical experience, we identified the following areas: determining the minimum necessary diagnostic tests for an oncological approach (including

**Table 5** Suggestions for follow-up of patients with resected NSCLC

| Statement                                                                                                                                                                                                                                                                                                     | GoR/LoE        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| (VIII) Follow-up of patients with locally advanced NSCLC                                                                                                                                                                                                                                                      |                |
| Follow-up should always be indicated for patients with high potential of relapse and for patients who received systemic oncologic treatment for early and locally advanced disease                                                                                                                            | Expert opinion |
| Counseling and pharmacological programs for smoking cessation should be continued                                                                                                                                                                                                                             | IIIC           |
| It is reasonable to perform blood tests ( $\alpha$ ) and chest CT scan with contrast and medical visit every 6 months for 2 years, then blood tests ( $\alpha$ ) and a low-dose chest CT scan every year for 3 years, followed by an annual low-dose CT scan according to the characteristics of each patient | Expert opinion |
| In case of adiplastic abnormalities, imaging control should be performed more frequently, and biopsy should be taken in cases suggestive of tumoral recurrence                                                                                                                                                | Expert opinion |
| PET-CT should not be routinely performed for follow-up; it should be indicated in case of suspicious findings in conventional images                                                                                                                                                                          | Expert opinion |
| Brain MRI or brain CT with contrast should not be annually performed in the absence of neurological symptoms                                                                                                                                                                                                  | Expert opinion |

$\alpha$ , renal function to evaluate late nephrotoxicity and previously of CT, PET-CT or MRI, additional blood tests according to symptoms and clinical judgement. This table was adapted from an Open Access article (18) under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>). CT, computed tomography; GoR, grades of recommendation; LoE, levels of evidence; MRI, magnetic resonance image; NSCLC, non-small cell lung cancer; PET-CT, positron emission tomography-computed tomography.

standardized anatomical diagnosis, biomarker testing, and required imaging, endoscopic, or invasive procedures for tumor stratification), identifying the minimum necessary respiratory function tests, and defining and unifying criteria for an initial surgical approach *vs.* administering neoadjuvant or perioperative chemoimmunotherapy treatment. Consequently, other important topics related to patient management were not included.

In relation to the results of the consensus, based on how the vote was presented (*Figure 2*), we conclude that situations that did not initially reach a consensus but were close to the defined threshold of 85% were easily agreed upon in the second round of voting. This is consistent with the objectives of the Delphi methodology (21,22). Meanwhile, the most controversial situations, such as the role of chemoimmunotherapy in patients with tumors harboring therapeutic targets and the criteria for choosing between neoadjuvant and perioperative strategies, required further discussion due to a lack of evidence for direct comparison. These situations may represent potential real-life controversies. Ultimately, our recommendations were based on the inclusion criteria of the available clinical trials. We acknowledge that there is no evidence showing that administering neoadjuvant treatment with chemotherapy and immunotherapy benefits patients with tumors harboring therapeutic targets. Regarding the selection of

neoadjuvant *vs.* perioperative approaches, we agreed that there is currently no scientific evidence directly comparing the two strategies or supporting the superiority of either.

We consider that the suggestions generated in this consensus can be generalized in clinical practice worldwide, given that the recommendations for diagnostic, treatment, and follow-up standards set forth in cancer management guidelines generated by globally recognized academic entities such as the NCCN, ASCO, and ESMO were taken into account (16,17,47,120). Furthermore, the updated approvals of oncology drugs by global regulatory agencies were included. As a fundamental point, we wanted to reinforce the importance of a multidisciplinary approach to early-stage and locally advanced NSCLC to improve patient outcomes, as demonstrated in multiple observational studies (17,49,60,61). This issue is considered crucial, and this consensus also aims to encourage the oncology team to establish and perform periodic MTC. On this specific topic, the GECP also produced a document on the requirements and quality indicators necessary for the proper functioning of multidisciplinary teams at the national level. This document served as a reference for the present document, but we consider it equally applicable worldwide (48).

The results of the ongoing trials that evaluate the benefits of including targeted therapy into the neoadjuvant approach for patients with actionable molecular targets, as

well as the role of chemoradiotherapy plus immunotherapy in the neoadjuvant setting, will help clarify unresolved clinical scenarios in future debates. Additionally, it is crucial to obtain prospective data on the benefit of adjuvant immunotherapy after neoadjuvant chemoimmunotherapy on survival and to define the profile of patients who may benefit most from this intervention. Other areas, such as preoperative optimization of lung function and prehabilitation programs, could also be important topics for subsequent discussions to unify criteria and complement care for patients with early-stage or locally advanced NSCLC.

## Conclusions

New suggestions about criteria for initial surgical treatment, management of patients with tumors harboring therapeutic targets in the neoadjuvant, adjuvant, and unresectable stages, the role of chemoradiotherapy, criteria for selecting neoadjuvant *vs.* perioperative chemo immunotherapy approaches, and new options for adjuvant treatment of patients with resected tumors without therapeutic targets were considered.

Given the lack of scientific data on all clinical scenarios and the uncertainty of some situations, these suggestions are aimed at guiding decisions in real-world clinical practice.

In addition, it is paramount to recognize the pivotal role of the MTC in selecting the most appropriate approach for patients with early and locally advanced NSCLC, given the complexity of the cases.

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