Ministry of Health
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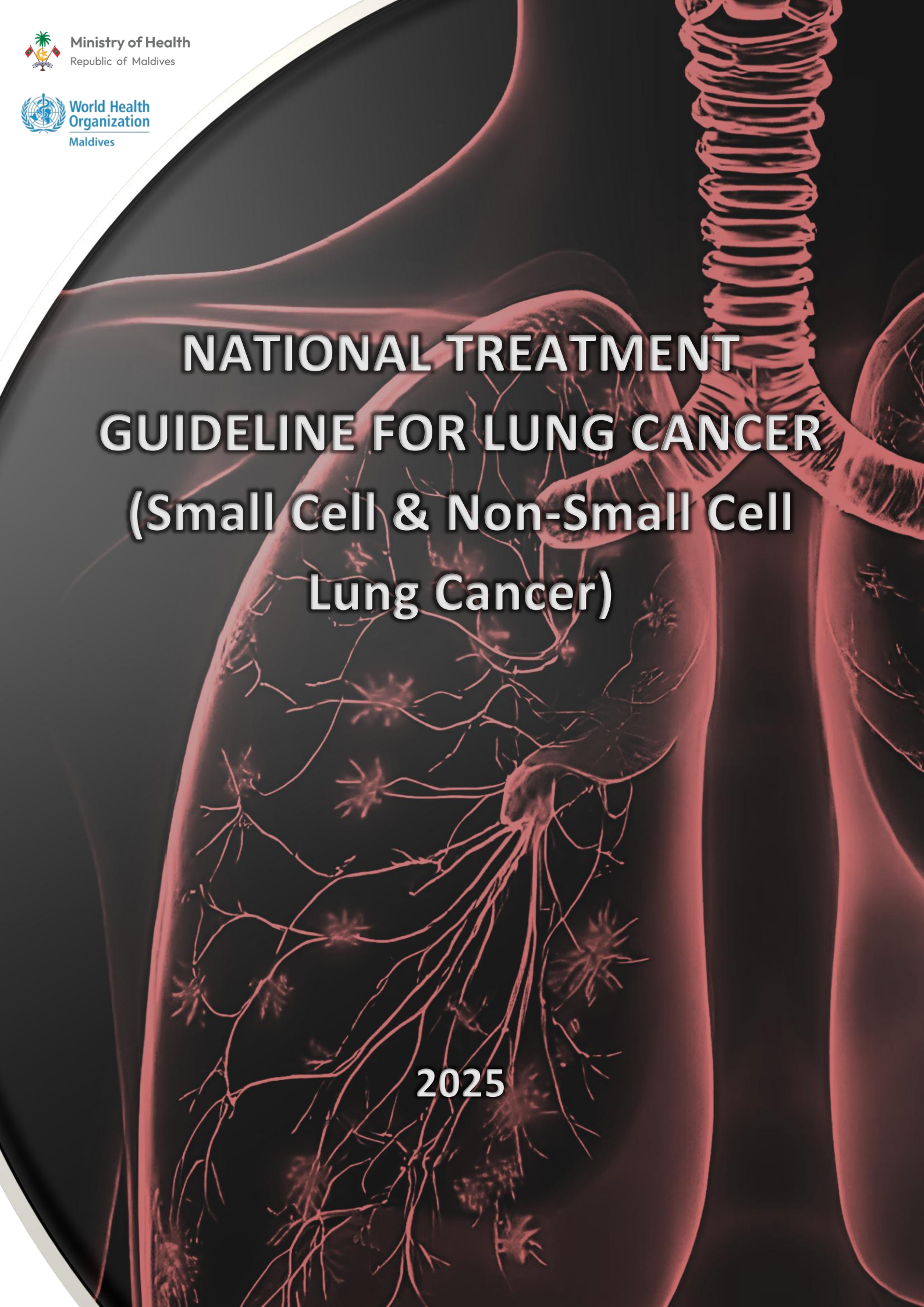
Maldives



NATIONAL TREATMENT GUIDELINE FOR LUNG CANCER (Small Cell & Non-Small Cell Lung Cancer)

2025

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National Treatment Guideline for Small Cell Lung Cancer (SCLC) in the Maldives

(Adapted from ESMO Guidelines)

INTRODUCTION

Small Cell Lung Cancer (SCLC) represents a highly aggressive form of lung cancer, making up approximately 10-15% of all lung cancer cases worldwide. The Maldives, a nation of islands in the Indian Ocean, faces unique challenges in managing healthcare, particularly with diseases like cancer that require specialized treatment and continuous care. The limited health infrastructure, shortage of specialized medical professionals, and geographic dispersion of the population add a layer of complexity to the fight against SCLC. The primary risk factor for SCLC in the Maldives is tobacco use, a prevalent issue that significantly affects public health. The aim of this guideline is to provide a comprehensive, standardized approach to the diagnosis, management, and referral of SCLC, ensuring that patients receive optimal care based on the best available evidence and practices.

The Ministry of Health, in collaboration with regional healthcare providers and international agencies, has undertaken this initiative to improve cancer care infrastructure, increase awareness about early symptoms, and streamline referral processes to enhance patient outcomes. Given the aggressive nature of SCLC and its tendency to metastasize early, the importance of early detection and prompt, effective treatment cannot be overstated. This guideline is an effort towards establishing a cohesive healthcare protocol that aligns with international standards, yet remains adaptable to the local context of the Maldives.

LITERATURE REVIEW

Extensive research has established SCLC as a distinct clinical entity characterized by rapid growth and early metastatic spread. Historically, it has been associated with smoking, with over 95% of patients having a significant smoking history. The literature review emphasizes the importance of early diagnosis and the multimodal treatment approach, combining chemotherapy, radiotherapy, and, in selected cases, surgery.

Global guidelines, particularly those from the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO), provide robust frameworks for the diagnosis, staging, and treatment of SCLC. These guidelines advocate for a combination of chemotherapy and radiotherapy, given the high rate of initial response despite frequent relapses.

Recent advancements have highlighted the role of immunotherapy in the treatment landscape of SCLC. Immune checkpoint inhibitors, such as atezolizumab and durvalumab, have been integrated into treatment regimens, particularly for extensive-stage SCLC, showing improved survival outcomes when combined with traditional chemotherapy.

In the Maldivian context, challenges such as limited access to advanced diagnostic tools and treatment facilities necessitate tailored strategies to manage SCLC effectively. This involves integrating telemedicine for specialist consultations, strengthening local capacities for basic diagnostic and therapeutic measures, and establishing clear referral pathways to regional centers equipped to provide comprehensive cancer care.

SCOPE OF THE GUIDELINE

This guideline takes into reference international best practice and incorporates it into local standards. This includes cost, availability of treatments and access to medical facilities.

The Maldives is an archipelago of 1190 islands scattered into numerous atolls off the southwest coast of India and Sri Lanka. The unique geography poses unique challenges for the delivery of cancer treatments in this country of roughly 400,000 population. As small island communities are scattered around an area of approximately 90,000 square kilometers providing local health centers become very challenging. There is a financial burden on health care providers in establishing multiple centers to treat cancer. Centralizing care also poses challenges in matters of transport and prompt care. This guideline hopes to tackle these challenges in providing a streamlined guidance from the primary level to the tertiary health care center in line with international and regional standards.

The guideline will cover the following areas:

1. Diagnosis
    - Standardized diagnostic protocols for SCLC, including clinical evaluation, imaging (CT scans, PET scans), bronchoscopy, and biopsy techniques.
    - Use of histopathological and immunohistochemistry for accurate diagnosis
    - Referral pathways for accurate and timely diagnosis, including multidisciplinary team involvement.

2. Staging
    - Guidelines for the staging of SCLC using the TNM classification system, including imaging modalities like CT, MRI, PET scan, and the role of biopsy for staging.
    - Considerations for the management of early-stage versus advanced-stage disease.
3. Treatment
    - Recommendations for the treatment of localized NSCLC, including surgery (lobectomy, pneumonectomy), radiation therapy, and adjuvant chemotherapy.
    - Protocols for the treatment of advanced-stage NSCLC, including targeted therapies, immunotherapies, chemotherapy regimens, and radiotherapy options.
    - Multidisciplinary treatment strategies for resectable and non-resectable NSCLC.
    - Treatment of special populations, such as elderly patients and those with comorbidities.
4. Follow-up and Surveillance
    - Post-treatment surveillance strategies, including frequency of imaging and laboratory tests.
    - Guidelines for monitoring for recurrence, secondary malignancies, and managing long-term effects of treatment.
5. Multidisciplinary Team (MDT) Management
    - Structure and roles of the multidisciplinary team in the management of NSCLC, ensuring coordinated care across oncologists, pulmonologists, surgeons, radiologists, and other relevant healthcare professionals.
    - Collaborative decision-making for personalized treatment plans.
6. Prevention and Early Detection
    - Recommendations on smoking cessation programs and public health initiatives to reduce the burden of SCLC.
    - Guidance on screening programs for high-risk individuals, considering the local healthcare infrastructure.
    - Recommendations for early detection strategies, including imaging and biomarker testing.
7. Health System Considerations

    - Assessment of the available resources for managing NSCLC, including access to medications, diagnostic tools, and treatment facilities.
    - Strategies for enhancing the capacity of the Maldives' healthcare system to manage the growing burden of lung cancer, including workforce development and resource allocation.

8. Research and Data Collection

    - Recommendations for research priorities, including local epidemiological studies, clinical trials, and biomarker research specific to the Maldivian population.
    - Strategies to improve data collection on NSCLC incidence, treatment outcomes, and survival rates.

TARGET AUDIENCE

The guideline is intended for:

- Healthcare providers involved in the care of patients with NSCLC, including oncologists, pulmonologists, radiologists, pathologists, and primary care providers.
- Healthcare administrators and policy-makers for the implementation of these guidelines at a national level.
- Medical and nursing educators to ensure the continual development of knowledge and skills related to NSCLC.
- Patient advocacy groups and support organizations to help with community education and engagement.

METHODOLOGY

The guideline will be developed using:

- A review of the latest international evidence from authoritative sources such as the, National Comprehensive Cancer Network (NCCN), and European Society for Medical Oncology (ESMO).
- Expert consensus from local healthcare professionals within the Maldives.
- Consideration of available resources, infrastructure, and the unique health challenges of the Maldives.

IMPLEMENTATION AND EVALUATION

The guideline will be implemented through:

- Distribution to healthcare facilities across the Maldives.
- Integration into continuing medical education (CME) programs for relevant healthcare workers.
- Regular review and updates to ensure the guideline remains current with advances in SCLC management.

Regular monitoring and evaluation will be conducted to assess the impact of the guideline on patient outcomes, including survival rates, quality of life, and healthcare system capacity.

CASE DEFINITIONS

Histological Confirmation: Small Cell Lung Cancer is typically confirmed via histological examination. The defining characteristics include:

- Small cells with scant cytoplasm.
- Ill-defined cell borders.
- Finely granular chromatin.
- Absent or inconspicuous nucleoli.
- High mitotic count.

Staging: Proper staging using the TNM system (Tumor, Nodes, Metastasis) is crucial for determining the appropriate management plan. SCLC is further classified into according to the Veterans' Administration Lung Study Group (VALSG):

- **Limited-Stage Disease (LD-SCLC)**: Confined to one hemithorax, which can be encompassed within a tolerable radiation field.
- **Extensive-Stage Disease (ED-SCLC)**: Disease that has spread beyond the ipsilateral hemithorax, which may include malignant pleural effusion or distant metastases.

Staging evaluations often include imaging such as CT scans, MRI, or PET scans, and bone scans to assess the extent of disease spread.

CLINICAL RISK ASSESSMENT TOOLS

- **Risk Scoring Models**: Implement clinical risk assessment tools that integrate various risk factors, including age, smoking history, occupational exposure, and family history, to stratify patients based on their risk for developing SCLC.
- **Standardization of Assessment**: Use standardized questionnaires and risk assessment tools to ensure consistency in evaluating patients at risk for lung cancer.

Regular Monitoring and Follow-Up

- **Surveillance for High-Risk Individuals**: Establish protocols for regular follow-up and monitoring of high-risk patients. This may include annual LDCT screenings and clinical evaluations to detect any early signs of lung cancer.
- **Symptom Awareness Education**: Educate patients about the early symptoms of SCLC, such as persistent cough, chest pain, and unexplained weight loss, encouraging prompt medical consultation.

Multidisciplinary Approach

- **Collaboration with Specialists**: Engage a multidisciplinary team including primary care physicians, pulmonologists, oncologists, and smoking cessation specialists to address and manage risk factors effectively.
- **Personalized Risk Management Plans**: Develop individualized risk management plans for high-risk patients that encompass smoking cessation support, regular screenings, and lifestyle modifications.

Health System and Policy Implications

- **Integrating Risk Assessment in Healthcare Policy**: Advocate for the integration of comprehensive risk assessment protocols into national healthcare policies to prioritize prevention and early detection of SCLC.
- **Training for Healthcare Providers**: Ensure that healthcare providers are trained in risk assessment techniques and can effectively communicate the importance of early detection strategies to their patients.

SIGNS AND SYMPTOMS

Early detection of SCLC hinges on awareness of its common presenting symptoms. However, due to its aggressive nature, symptoms often indicate advanced disease. Common signs and symptoms include:

- **Persistent Cough**: Often the most common initial symptom.
- **Chest Pain**: May be dull, aching, or sharp.
- **Dyspnea (Shortness of Breath)**: Can result from obstruction or pleural effusion.
- **Hemoptysis (Coughing Up Blood)**: Occurs due to tumor erosion into blood vessels.
- **Unexplained Weight Loss**: Common in many cancers.
- **Fatigue**: General malaise, often severe.
- **Hoarseness**: Resulting from recurrent laryngeal nerve involvement.
- **Superior Vena Cava Syndrome**: Facial edema, swelling of veins in the neck and upper chest, indicative of obstruction.

These symptoms necessitate prompt evaluation, especially in high-risk individuals such as smokers or those with a significant exposure history to other risk factors.

DIFFERENTIAL DIAGNOSIS

SCLC can mimic other pulmonary and systemic conditions, making differential diagnosis critical. Similar conditions may include:

- Non-Small Cell Lung Cancer (NSCLC): Requires histological differentiation.
- Metastatic Cancers to the Lung: Other primaries like colorectal, breast or kidney cancers.
- Benign Lung Tumors: Including hamartomas.
- Infectious Diseases: Such as tuberculosis and fungal infections.
- Inflammatory Conditions: Including sarcoidosis and chronic obstructive pulmonary disease (COPD).

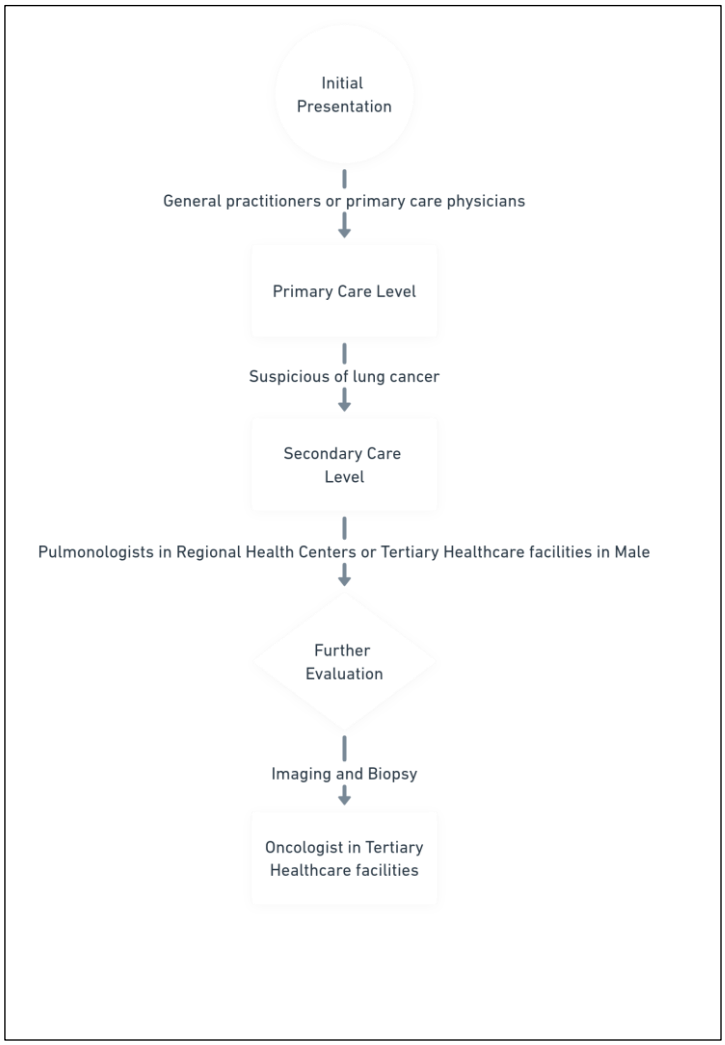
A comprehensive diagnostic workup involving imaging, biopsy, and possibly molecular profiling is necessary to differentiate these conditions.

PATHWAY OF PATIENT REFERRALS

Initial Presentation:

Patients, particularly those with a history of smoking or other risk factors, presenting with symptoms suggestive of SCLC should be promptly evaluated:

- **Primary Care Level**: Initial assessment and referral by general practitioners or primary care physicians at Island Health centers and Atoll Hospitals and then to secondary care level if found to suspicious of lung cancer.
- **Secondary Care Level**: Referral to pulmonologists in Regional Health Centers or Tertiary Healthcare facilities in Male for further evaluation including imaging and biopsy.
- **Tertiary Care level**: Referral To Oncologist in Tertiary Healthcare facilities for Chemotherapy and radiotherapy.



INVESTIGATIONS:

Accurate diagnosis often requires the expertise of specialized centers:

- **Biopsy**: To obtain tissue samples for histological examination. In cases where biopsy is challenging, liquid biopsies or cytological examination of sputum or pleural fluid might be considered.
- **Imaging**: Comprehensive imaging to stage the disease, which might include CT scans, MRIs, PET scans, and bone scans.

TREATMENT:

The management plan should involve multidisciplinary care:

- **Limited-Stage Disease**: Coordination between oncologists, radiologists, and thoracic surgeons.
- **Extensive-Stage Disease**: Oncologist-led treatment with chemotherapy and immunotherapy, supported by palliative care services.
- **Supportive Care**: Referral to nutritionists, physiotherapists, and psychological support to manage side effects and improve quality of life.

Management Based on ESMO and NCCN Guidelines

Limited-Stage Disease (LD-SCLC):

The treatment of limited-stage SCLC involves a multimodal approach. Key components include:

- **Chemotherapy**: Standard regimens typically include combinations like cisplatin or carboplatin with etoposide. These regimens have shown high response rates.
- **Radiotherapy**: Concurrent thoracic radiotherapy with chemotherapy is recommended due to its synergistic effect.
- **Prophylactic Cranial Irradiation (PCI)**: For patients who achieve a complete or partial response to initial therapy, PCI is recommended to reduce the risk of brain metastases.

STAGE I DISEASE (T1 TO T2, N0)

- For patients with stage I (T1 to 2, N0) LS-SCLC who have no evidence of distant metastases, histologic confirmation that the hilar and mediastinal lymph nodes are **not** involved, and no contraindications to surgery, we suggest resection of the primary tumor with lobectomy, plus mediastinal lymph node sampling or dissection. If performed, this should then be followed by adjuvant chemotherapy with four cycles of

cisplatin-based therapy, extrapolating from benefits observed largely in patients with node-positive disease (although not typically administered with radiation.

- **Postoperative chemotherapy** — We suggest adjuvant chemotherapy for patients who have undergone a complete resection for SCLC. Regimen selection is the same as for patients who do not undergo surgery.

STAGE II TO III DISEASE

Components of treatment

Chemotherapy

Preferred regimen: Etoposide plus cisplatin — Etoposide plus cisplatin (EP) is the standard regimen for chemotherapy in patients with LS-SCLC along with early, concurrent thoracic radiation therapy (RT)

Consolidative durvalumab — For patients with LS-SCLC who have not experienced progression after concurrent chemoradiation, we recommend consolidation with durvalumab. We treat up to two years or until progression (whichever comes first).

Extensive-Stage Disease (ED-SCLC):

Management of extensive-stage disease relies primarily on systemic therapy due to widespread disease:

- **Chemotherapy**: The combination of platinum-based chemotherapy (cisplatin or carboplatin) with etoposide remains the cornerstone.
- **Immunotherapy**: Recent guidelines advocate the inclusion of immune checkpoint inhibitors like atezolizumab or durvalumab with frontline chemotherapy, which has shown to improve overall survival.
- **Radiotherapy**: Palliative radiotherapy for symptomatic relief or to manage specific metastases.

FOLLOW-UP CARE

Regular follow-up is essential to monitor for recurrence and manage long-term side effects.

Response assessment following primary treatment:

Limited-Stage SCLC (Post-chemoradiation ± PCI)

Years 1–2:

- Every 3–6 months:
  - History and physical exam (H&P)
  - Contrast-enhanced CT chest and upper abdomen (liver, adrenals)
- Brain MRI:
  - Every 3–6 months if PCI not done or patient is symptomatic.

After 2 years:

- Every 6–12 months for up to 5 years, then annually or as clinically indicated.
- Imaging may be spaced out or discontinued depending on risk and patient status.

Extensive-Stage SCLC (Post systemic therapy ± RT)

Years 1–2:

- Every 2–3 months:
  - H&P
  - CT chest and abdomen with contrast
- Brain MRI:
  - Every 3–6 months if no PCI; or earlier if neurologic symptoms arise

After 2 years (if patient remains in remission):

- Every 6 months or individualized based on status.

Special Note on Brain Imaging:

- Prophylactic cranial irradiation (PCI) reduces the need for frequent brain MRI, but it is not always used in ES-SCLC.
- If PCI is omitted, MRI brain every 3–6 months for 2 years is recommended.

Subsequent Therapy/ Palliative Therapy

In case of relapse:

Performance Status	Treatment Approach	Systemic Therapy Options	Comments
ECOG 0–2	Subsequent systemic therapy	- **Topotecan** (IV or oral) - **Irinotecan** - **Paclitaxel** - **Docetaxel** - **Gemcitabine** - **Oral etoposide** - **CAV**(Cyclophosphamide + Doxorubicin + Vincristine) - **Pembrolizumab** or **Nivolumab** *(if PCI-naïve)*	Choice depends on prior therapy, time to relapse, and comorbidities. PCI only if not previously given.
ECOG 3–4	**Best supportive care / symptom control**	- Palliative care - Symptom-directed management - Psychosocial and spiritual support	Focus on quality of life. Systemic therapy generally **not recommended** in poor PS patients.

SCREENING RECOMMENDATIONS

- **High-Risk Population Identification**: Targeted screening should focus on high-risk groups, primarily current and former smokers aged 55-80 years, as well as individuals with a significant smoking history or exposure to occupational carcinogens.
- **Low-Dose Computed Tomography (LDCT)**: Annual LDCT screening is recommended for high-risk individuals to facilitate early detection of lung cancer. The use of LDCT has shown effectiveness in reducing mortality in high-risk populations.

PREVENTION

Smoking Cessation Programs

- **Public Health Initiatives**: Implement comprehensive smoking cessation programs to educate the public about the dangers of tobacco use and provide resources for quitting.
- **Access to Nicotine Replacement Therapies**: Ensure that individuals trying to quit smoking have access to nicotine replacement therapies, counseling, and support services.

Community Education

- **Awareness Campaigns**: Launch community-based awareness initiatives to educate the public about the symptoms of SCLC and the importance of early detection.
- **Risk Factor Education**: Inform individuals about the risk factors associated with SCLC, including smoking and environmental exposures, to promote preventive measures.

PALLIATIVE CARE AND END OF LIFE CARE

1. EARLY INTEGRATION OF PALLIATIVE CARE

- Palliative care should be **initiated at the time of diagnosis** of **extensive-stage SCLC** or **symptomatic limited-stage disease**.
- It is **not reserved for end-of-life only**; it's a **parallel track** with active anticancer therapy.
- Core goals:
    - Symptom management (dyspnea, cough, pain, fatigue, anxiety)
    - Advance care planning (ACP)
    - Psychosocial and spiritual support
    - Coordination of care

2. SYMPTOM MANAGEMENT

Symptom	Recommended Management
Dyspnea	Opioids (morphine), oxygen (if hypoxic), fan therapy, benzodiazepines (if anxious)
Pain	WHO analgesic ladder, adjuvants (gabapentin, amitriptyline), palliative RT if localized
Fatigue	Energy conservation, low-dose corticosteroids, psychosocial support
Cough	Opioids, antitussives
Anxiety/Depression	SSRIs, counseling, benzodiazepines short-term
Brain mets	Corticosteroids (e.g., dexamethasone), palliative whole brain RT if appropriate

3. ADVANCE CARE PLANNING (ACP)

- Begin **early in the disease course**.
- Includes:
    - Prognostic disclosure
    - Code status (DNR/DNI)
    - Preferences for hospitalization and ICU admission
    - Living wills, health care proxies

4. TRANSITION TO END-OF-LIFE (EOL) CARE

Aspect	
Criteria for EOL focus	Refractory symptoms, lack of benefit from therapy
Hospice referral	Recommended once active therapy is no longer beneficial
Hospitalization	Focus on **home or hospice-based care** when possible
Communication	Honest, empathetic, culturally sensitive communication
Spiritual & Cultural	Holistic care including psychosocial and spiritual domains

5. CHEMOTHERAPY NEAR END OF LIFE

- Strongly discourages systemic therapy in patients with:
    - ECOG PS ≥3
    - Rapidly progressive disease despite two prior regimens
    - Life expectancy <2–3 months

6. FAMILY AND CAREGIVER SUPPORT

- **Caregiver assessments**
- **Bereavement support**
- Access to **psychological counseling and education**

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National Treatment Guideline for Non-Small Cell Lung Cancer (NSCLC) in the Maldives

(Adapted from ESMO Guidelines)

INTRODUCTION

Non-small cell lung cancer (NSCLC) is a significant global health concern, with a high burden on healthcare systems worldwide. According to the latest data from Globocan 2022, NSCLC remains one of the most prevalent forms of cancer, accounting for a substantial number of new cases and deaths each year. The complex nature of NSCLC, its diverse subtypes, and the challenges associated with its diagnosis and treatment make it a critical area of focus for healthcare providers and policymakers alike.

In the Maldives, epidemiological data based on Globocan 2022 highlights the increasing incidence and mortality rates of NSCLC, underscoring the urgent need for comprehensive management guidelines tailored to the local context. According to Globocan, the year 2022 saw 479 newly diagnosed cancer cases in the country. There were 241 deaths due to cancer and the 5-year prevalence remained at 1321. Out of this lung cancer accounted for 37 cases which accounted for 13% of all newly diagnosed cancer cases in the country. The Maldives, like many other countries, is facing a rising burden of cancer, including lung cancer, which poses unique challenges due to limited resources, geographical constraints, and the dispersed nature of the population across islands.

The criticality of addressing NSCLC in the Maldives is further emphasized by the high fatality rates associated with the disease. NSCLC is known for its aggressive nature and often presents at advanced stages, leading to poorer outcomes and limited treatment options. The impact of NSCLC extends beyond individual patients, placing significant strain on the healthcare system and resources. The cost of managing NSCLC, including diagnostics, treatments, and supportive care, can be substantial, further underscoring the need for effective guidelines to optimize resource allocation and improve patient outcomes.

As such, there is a pressing need for national management guidelines that can effectively guide healthcare providers in the diagnosis, treatment, and follow-up care of NSCLC patients in the Maldives. These guidelines should be evidence-based, taking into account the latest advancements in NSCLC research and treatment modalities. They should also consider the unique challenges faced by healthcare providers in the Maldives, such as limited access to specialized care, variability in diagnostic capabilities across islands, and cultural factors that may influence patient care decisions.

In addition to the epidemiological data and fatality rates, other peculiar information, such as the prevalence of specific NSCLC subtypes or unique challenges faced in the Maldivian healthcare landscape, should be considered in the development of these guidelines. For example, the impact of environmental factors, such as air quality and smoking prevalence, on

NSCLC incidence in the Maldives may differ from global trends and require tailored interventions.

By addressing these factors comprehensively, the guidelines can better meet the specific needs of NSCLC patients in the Maldives and improve outcomes for this vulnerable population. The development of national management guidelines for NSCLC in the Maldives is crucial to ensure standardized, evidence-based care, optimize resource allocation, and ultimately reduce the burden of this disease on individuals, families, and the healthcare system.

NSCLC represents a significant public health challenge in the Maldives, requiring a coordinated and multidisciplinary approach to diagnosis, treatment, and care. The development of national management guidelines for NSCLC is a critical step towards improving outcomes for patients, enhancing healthcare system efficiency, and reducing the burden of this disease on society as a whole. By leveraging the latest data, evidence-based practices, and local insights, these guidelines have the potential to transform the landscape of NSCLC care in the Maldives and pave the way for better outcomes for patients affected by this devastating disease.

LITRATURE REVIEW

Non-small cell lung cancer (NSCLC) accounts for 80-90% of lung cancer cases and includes several distinct types. Most notable subtypes of NSCLC include adenocarcinoma, squamous cell carcinoma and large cell carcinoma. While tobacco smoking remains the leading cause of lung cancer, responsible for about 85% of lung cancer diagnoses, NSCLC can also affect non-smokers with approximately 500,00 deaths attributed annually to these cases. In addition to smoking, other occupational factors such as asbestos, arsenic, radon and air pollution have also been linked to the development of lung cancer.
The World-Health Organisation (WHO) estimates that lung cancer is the leading cause of cancer-related deaths worldwide, with approximately 1.8 million deaths annually. Advocating for primary prevention and screening of high-risk individuals aid in reducing the incidences of lung cancer. Early detection and timely management are key to improving the survival rates and outcomes for patients.

National comprehensive cancer network (NCCN) and European Society for medical oncology (ESMO) provides framework for screening, diagnosis, staging and management of NSCLC. Treatments are individualised based on factors such as age, comorbidities, histology and molecular profiling.

The three main modalities of treatment in NSCLC include surgery, radiation therapy and systemic therapy. Advances in recent years shed light on the use of testing for biomarkers and targetable mutation and its critical nature on treatment of advanced NSCLC. Evaluation for targetable mutations include epidermal growth factor (EGFR), anaplastic lymphoma kinase (ALK), ROS1, BRAF, RET, TRK, MET, KRAS and integration of their specific inhibitors into treatment plan has significantly improved the quality of life and prognosis of patients with NSCLC. Patients with advanced NSCLC should also be screened for expression of PDL-1

Similarly, in the Maldives, incidence of lung cancer has significantly increased over the last 5 years. Limitations in diagnosis and molecular profiling present challenges to early detection and management as well as overall survival rate. Efforts are underway to enhance basic diagnostic and therapeutic measures, including improving referral pathway from regional to tertiary centres with available oncologists, with the aim of providing a more comprehensive cancer care.

CASE DEFINITIONS

1. Histologically Confirmed NSCLC:

- A patient must have a definitive diagnosis of NSCLC confirmed by histopathological examination. This can be done through:
- Tissue Biopsy: Obtained via bronchoscopy, surgical resection, or needle aspiration.
- Cytological Evaluation: Examination of cells from body fluids (e.g., pleural effusion) or bronchial washings.

2. Classification of NSCLC Subtypes:

- NSCLC is divided into several distinct subtypes, each with unique characteristics:
- Adenocarcinoma: Often found in the outer regions of the lungs; associated with non-smokers and smokers.
- Squamous Cell Carcinoma: Typically located in the central areas of the lungs and often associated with smoking.
- Large Cell Carcinoma: A heterogeneous group of NSCLC subtypes that can be found in any part of the lung and tends to grow and spread more quickly.

3. Clinical Staging:

- Patients should be staged using the AJCC TNM classification:
- T (Tumor): Defines the size and extent of the primary tumor.
- N (Nodes): Determines the extent of regional lymph node involvement.
- M (Metastasis): Indicates whether there is distant metastasis (stage IV).
- Staging is essential for guiding treatment decisions and predicting prognosis.

4. Advanced NSCLC:

- Stage III NSCLC: Locally advanced cancer that may be unresectable due to involvement of nearby structures.
- Stage IV NSCLC: Cancer that has metastasized to distant parts of the body, including the liver, bones, or brain.

5. Symptomatic Presentation:

- Patients may present with one or more of the following symptoms:
- Persistent cough
- Hemoptysis (coughing up blood)
- Chest pain (sharp, dull, or aching)
- Dyspnea (shortness of breath)
- Unexplained weight loss and fatigue
- Hoarseness due to recurrent laryngeal nerve involvement

6. Radiological Findings:

- Abnormalities on imaging studies (such as chest X-rays and CT scans) that suggest the presence of a lung tumor or metastatic disease:
- Masses, nodules, or consolidation in the lung parenchyma.
- Enlarged mediastinal and hilar lymph nodes.
- Pleural effusions or other signs of advanced disease.

7. Biomarker Testing:

- Patients, particularly those with advanced NSCLC, should undergo molecular testing for specific driver mutations, including:
- EGFR (Epidermal Growth Factor Receptor)
- ALK (Anaplastic Lymphoma Kinase)
- ROS1, BRAF, RET, and others
- Testing for PD-L1 expression is relevant to determine eligibility for immune checkpoint inhibitors.

8. Histological and Molecular Subtyping:

- If histological typing is uncertain, immunohistochemistry (IHC) and molecular profiling should be utilized to classify the tumor accurately and reduce the incidence of NSCLC-NOS (not otherwise specified).

9. Oligometastatic NSCLC:

- Defined as patients with a limited number of metastatic sites (usually 1-3) who may benefit from local therapies such as radiation or surgery after systemic treatment.

10. Recurrence and Follow-up:

- Cases of NSCLC should also include definitions of recurrence based on imaging and symptomatology after initial treatment, including local recurrence or distant metastasis.

11. Patient Selection for Clinical Trials:

- Definitions pertaining to eligibility for clinical trials, focusing on parameters including:
- Histological subtype
- Staging
- Prior treatment history
- Performance status as assessed by the Eastern Cooperative Oncology Group (ECOG) score.

SIGNS AND SYMPTOMS

Early detection of SCLC hinges on awareness of its common presenting symptoms. However, due to its aggressive nature, symptoms often indicate advanced disease. Common signs and symptoms include:

- Persistent Cough: Often the most common initial symptom.
- Chest Pain: May be dull, aching, or sharp.
- Dyspnea (Shortness of Breath): Can result from obstruction or pleural effusion.
- Hemoptysis (Coughing Up Blood): Occurs due to tumor erosion into blood vessels.
- Unexplained Weight Loss: Common in many cancers.
- Fatigue: General malaise, often severe.
- Hoarseness: Resulting from recurrent laryngeal nerve involvement.
- Superior Vena Cava Syndrome: Facial edema, swelling of veins in the neck and upper chest, indicative of obstruction.

These symptoms necessitate prompt evaluation, especially in high-risk individuals such as smokers or those with a significant exposure history to other risk factors.

DIFFERENTIAL DIAGNOSIS

SCLC can mimic other pulmonary and systemic conditions, making differential diagnosis critical. Similar conditions may include:

- Small Cell Lung Cancer (SCLC): Requires histological differentiation.
- Metastatic Cancers to the Lung: Other primaries like colorectal, breast or kidney cancers.
- Benign Lung Tumors: Including hamartomas.
- Infectious Diseases: Such as tuberculosis and fungal infections.
- Inflammatory Conditions: Including sarcoidosis and chronic obstructive pulmonary disease (COPD).

A comprehensive diagnostic workup involving imaging, biopsy, and possibly molecular profiling is necessary to differentiate these conditions.

INVESTIGATIONS

• The most common diagnostic test for lung cancer is fibre-optic bronchoscopy, often extended with evaluation of regional lymph nodes (LNs) by endobronchial ultrasound (EBUS) and/or endoscopic ultrasound (EUS)

°In most cases, bronchoscopy is sufficient to diagnose NSCLC, although detailed sub-classification may not be possible

• Commonly used tests for diagnosis and staging are shown in the table on the next page
• In patients with clinical stage I-III lesions, a pre-treatment pathological diagnosis is recommended prior to any curative treatment

°An exception to the requirement for a pre-treatment diagnosis can be made if a multidisciplinary team (MDT) decides that the risks of obtaining pathology are unacceptable in a patient in whom the likelihood of malignancy is high based on clinical and imaging findings

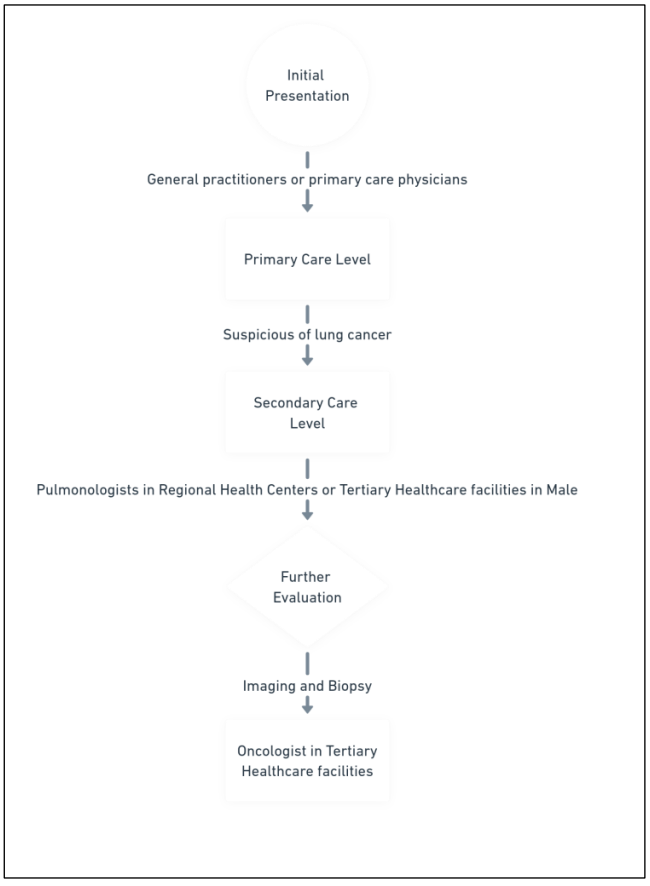
°Bronchoscopy is the recommended test to obtain a pathological diagnosis of centrally located stage I-III tumours with biopsy of any visible lesion

PATHWAY OF PATIENT REFERRALS

Initial Presentation:

Patients, particularly those with a history of smoking or other risk factors, presenting with symptoms suggestive of SCLC should be promptly evaluated:

- Primary Care Level: Initial assessment and referral by general practitioners or primary care physicians at Island Health centers and Atoll Hospitals and then to secondary care level if found to suspicious of lung cancer.
- Secondary Care Level: Referral to pulmonologists in Regional Health Centers or Tertiary Healthcare facilities in Male for further evaluation including imaging and biopsy.
- Tertiary Care level: Referral to Oncologist in Tertiary Healthcare facilities for Chemotherapy and radiotherapy.



Work-Up For Diagnosis and Staging

General:

1. Medical History
2. Physical examination
3. Assessing comorbidity
4. Performance Stats

Imaging

1. CT of thorax and upper abdomen
2. PET-CT
3. MRI of brain

Laboratory

1. Blood cell counts
2. Renal Function
3. Liver function

Cardiopulmonary Function

1. Echocardiogram
2. ECG
3. CPET (If indicated)

Tissue procurement

1. Bronchoscopy
2. EBUS, EUS mediastinal nodes
3. CT-Guided biopsy

Genomic profiling

1. EGFR mutation
2. ALK fusion status
3. PD-L1 expression

In patients with clinical stage I-III lesions, a pre-treatment pathological diagnosis is recommend prior to any curative treatment

- An exception to the requirement for a pre-treatment diagnosis can be made if a multidisciplinary team (MDT) decides that the risks of obtaining pathology are unacceptable in a patient in whom the likelihood of malignancy is high based on clinical and imaging findings

- Bronchoscopy is the recommended test to obtain a pathological diagnosis of centrally located tumours in stages I-III with biopsy of any visible lesion

- The pathological classification "not otherwise specified" (NOS) should be used only in cases where it is impossible to obtain enough tissue for further classification, or when steps to further classify the tumour are inconclusive

- A pre-treatment pathological diagnosis is strongly recommended for all patients before stereotactic ablative radiotherapy (SABR), unless an MDT decides that the risk-benefit ratio of the procedure is unacceptable

- In such a situation, the predicted likelihood of malignancy should preferably be ≥ 85% based upon accepted criteria, for example using [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET)-CT standardised uptake values

- The descriptive element of the recent World Health Organization (WHO) classification of (surgically resected) adenocarcinoma subtypes should be used to describe bronchoscopic and CT-guided biopsies whenever possible

- This classification shows differences in metastatic pattern, recurrence and survival between histological subtypes and may highlight differences in response to post-resection adjuvant chemotherapy (ChT)

- The revised adenocarcinoma classification may identify patient subtypes for whom an anatomical sublobar resection, rather than lobectomy, would be sufficient

- FDG-PET may contribute to the selection of patients for anatomical sublobar resections as low maximum standardised uptake values (SUV_{max}) of peripheral tumours indicate lack of mediastinal metastases

- This diagnosis may be made intraoperatively by video-assisted thoracoscopic biopsy and frozen section analysis

- In isolated cases, a diagnostic anatomical sublobar resection may be acceptable

The solitary pulmonary nodule

- The diagnostic approach to non-calcified pulmonary nodules should be based on existing standard guidelines (such as those published by the British Thoracic Society, the Fleischner Society or the clinical practice consensus guidelines for Asia), although new evidence on nodule management is emerging

- Likelihood of malignancy based upon risk calculation methods used in CT screening studies should be used only to guide the clinical assessment of pulmonary nodules detected in the wider population

STAGING AND RISK ASSESSMENT

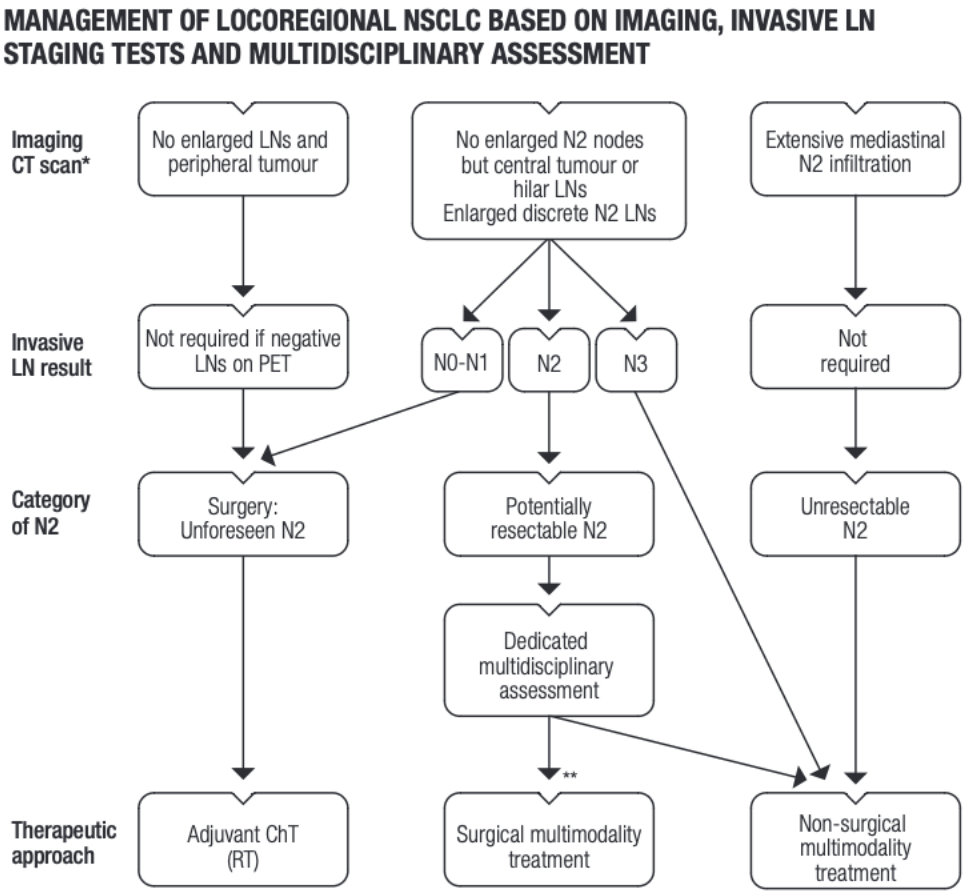
- In non-metastatic NSCLC, the revised Union for International Cancer Control (UICC) tumour–node–metastasis (TNM) staging classification of malignant tumours eighth edition (TNM 8) should be employed for detailed locoregional staging. TNM 8 staging, alongside the patient's cardiopulmonary fitness, should be used to determine the choice of treatment
- In the UICC TNM 8, the T stage has been further subdivided according to tumour size:

- T1 into T1a ≤ 1 cm, T1b > 1 cm to ≤ 2 cm, T1c > 2 cm to ≤ 3 cm
- T2 into T2a > 3 cm to ≤ 4 cm, T2b > 4 cm to ≤ 5 cm
- T3 > 5 cm to ≤ 7 cm
- T4 > 7 cm

- For part-solid tumours, the size of the invasive component should be used to assign the T category for clinical staging; however the whole size of the tumour should also be recorded
- Sub-solid lesions require dedicated radiological expertise to evaluate the lung lesion composition
- The International Association for the Study of Lung Cancer (IASLC) has proposed: determining the T of multifocal ground glass/lepidic tumours by the highest T lesion, with either the number of tumours or *m* in parentheses to denote the multifocal nature; and that a single N and M category be used for all these lesions collectively
- In daily practice, simply using *m* is preferred over trying to estimate the number of ground glass opacity (GGO) areas
- For pneumonic tumours, the IASLC suggests using size (or T3) if in one lobe, T4 if involving a different ipsilateral lobe, and M1a if contralateral; in this situation, the T stage will be based on the highest category in the most involved lung
- CT follow-up studies have shown that incidental non-calcified non-solid lung lesions do not need repeat CT examinations more frequently than every 1-2 years; these lesions are definitely less aggressive than solid or part-solid lesions and often even indolent
- If two lung lesions fulfil the criteria for two primaries, then these should be evaluated, staged and treated accordingly
- Concluding that two foci are indeed two different primaries is difficult; often it will be impossible to come to a definitive conclusion and the role of an MDT is important
- The TNM 8 staging suggests leaving the N categories unchanged from TNM 7, but suggests recording for future testing the sub-classification of single (N1a, N2a) or multiple (N1b, N2b) affected nodes
- For patients with abnormal mediastinal and/or hilar LNs using CT and/or PET, endosonography is recommended over surgical staging
- The preferred first technique for pathological confirmation of suspect nodes is needle aspiration under EBUS and/or EUS guidance
- If EBUS and/or EUS does not reveal nodal involvement in a situation of high clinical suspicion, mediastinoscopy is indicated

- Mediastinoscopy is the test with the highest negative predictive value (NPV) to rule out mediastinal LN disease
- Screening for brain metastases by magnetic resonance imaging (MRI) might be useful in patients considered for curative therapy

MANAGEMENT OF LOCOREGIONAL NSCLC BASED ON IMAGING, INVASIVE LN STAGING TESTS AND MULTIDISCIPLINARY ASSESSMENT



For part-solid tumours, the size of the invasive component should be used to assign the T category for clinical staging; however, the whole size of the tumour should also be recorded

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STAGING AND STAGE GROUPING OF OCCULT CARCINOMA ACCORDING TO THE UICC TNM EIGHTH EDITION

STAGE	PRIMARY TUMOUR (T)	REGIONAL LYMPH NODES (N)	DISTANT METASTISIS (M)
Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA1	T1a(mi) T1a	N0	M0
Stage IA2	T1b	N0	M0
Stage IA3	T1c	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
Stage IIB	T1a-c T2a-b T3	N1 N1 N0	M0
Stage IIIA	T1a-c T2a-b T3 T4 T4	N2 N2 N1 N0 N1	M0
Stage IIIB	T1a-c T2a-b T3 T4	N3 N3 N2 N2	M0
Stage IIIC	T3 T4	N3 N3	M0

CT follow-up studies have shown that incidental non-calcified non-solid lung lesions do not need repeat CT examinations more frequently than every 1-2 years; these lesions are definitely less aggressive than solid or part-solid lesions and often even indolent

• If two lung lesions fulfil the criteria for two primaries, then these should be evaluated, staged and treated accordingly°Concluding that two foci are indeed two different primaries is difficult; often it will be impossible to come to a definitive conclusion and the role of an MDT is important

• The TNM 8 suggests leaving the N categories unchanged from TNM 7, but suggests recording for future testing the sub-classification of single (N1a, N2a) or multiple (N1b, N2b) affected nodes

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°If EBUS and/or EUS does not reveal nodal involvement in a situation of high clinical suspicion, mediastinoscopy is indicated°Mediastinoscopy is the test with the highest negative predictive value (NPV) to rule out mediastinal LN disease

°A suggested algorithm for the locoregional staging of LNs is shown on page 7
• Screening for brain metastases by magnetic resonance imaging (MRI) might be useful in patients considered for curative therapyStaging for locally advanced (stage III) NSCLC

• All patients planned for definitive stage III NSCLC treatment should undergo a diagnostic contrast-enhanced CT scan of the chest and upper abdomen followed by a PET or a combined PET-CT with a CT technique with adequately high resolution for initial staging purposes, ideally within 4 weeks of the start of treatment. These techniques assist in:°Ruling out detectable extrathoracic, extracranial metastasis

°Assessing potential mediastinal LN involvement• Single PET-positive distant lesions need pathological confirmation• For patients with operable N2 disease, pathological staging of the mediastinum is advised

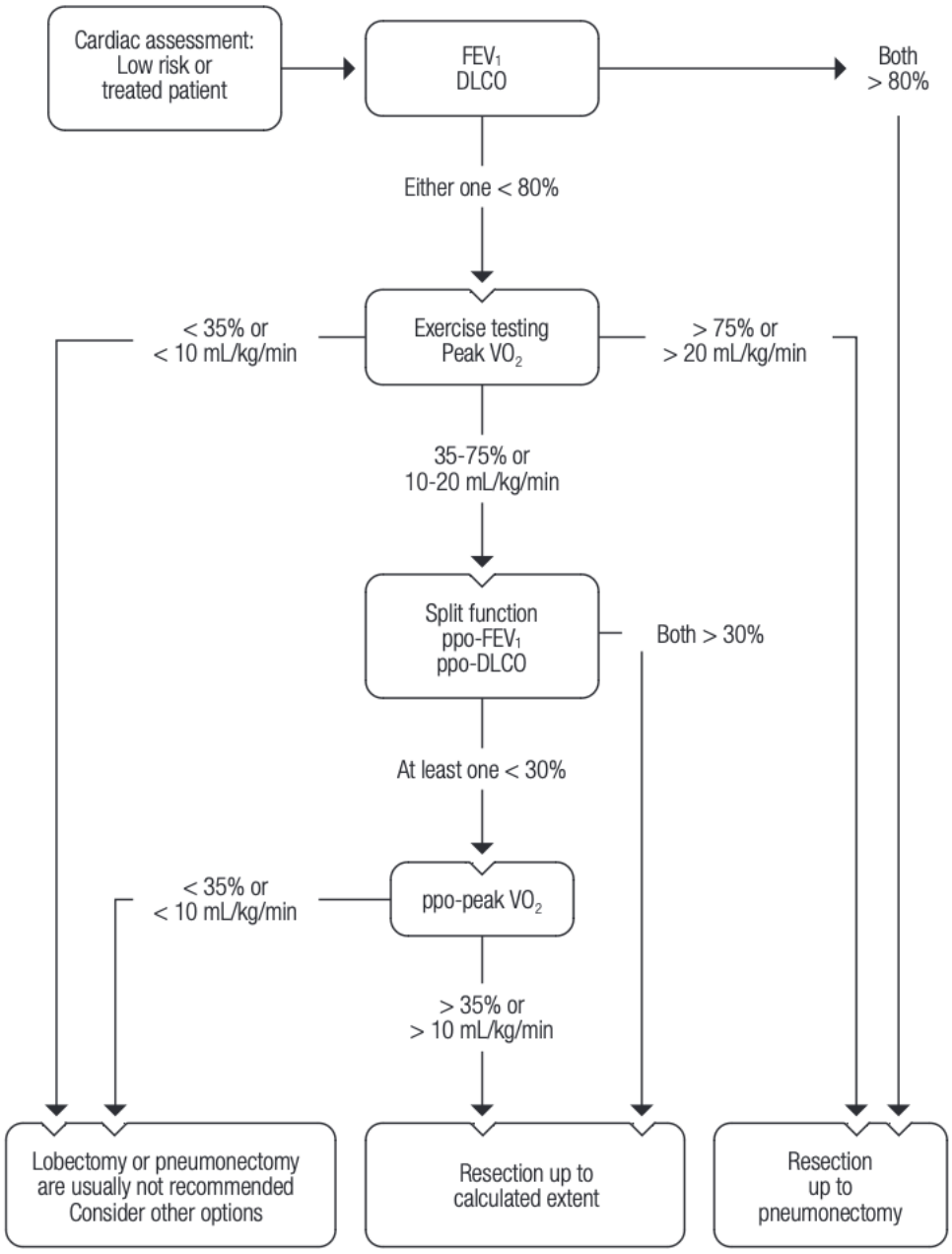
• All patients planned for curative stage III NSCLC treatment should receive brain imaging for initial staging°Contrast-enhanced brain MRI is the preferred method for staging of the brain in stage III disease; if this is not possible, dedicated contrast-enhanced brain CT scan is advisedPre-treatment risk assessment

• A therapeutic intervention for lung cancer reduces the pulmonary and vascular reserve capacity, either acutely following resection, or more gradually following radiotherapy (RT)

°Functional loss needs to be estimated pre-therapy to determine whether the patient will be able to cope and maintain an acceptable quality of life• The risk of postoperative morbidity and mortality can be estimated using risk-specific models, although none have been validated in a cancer population

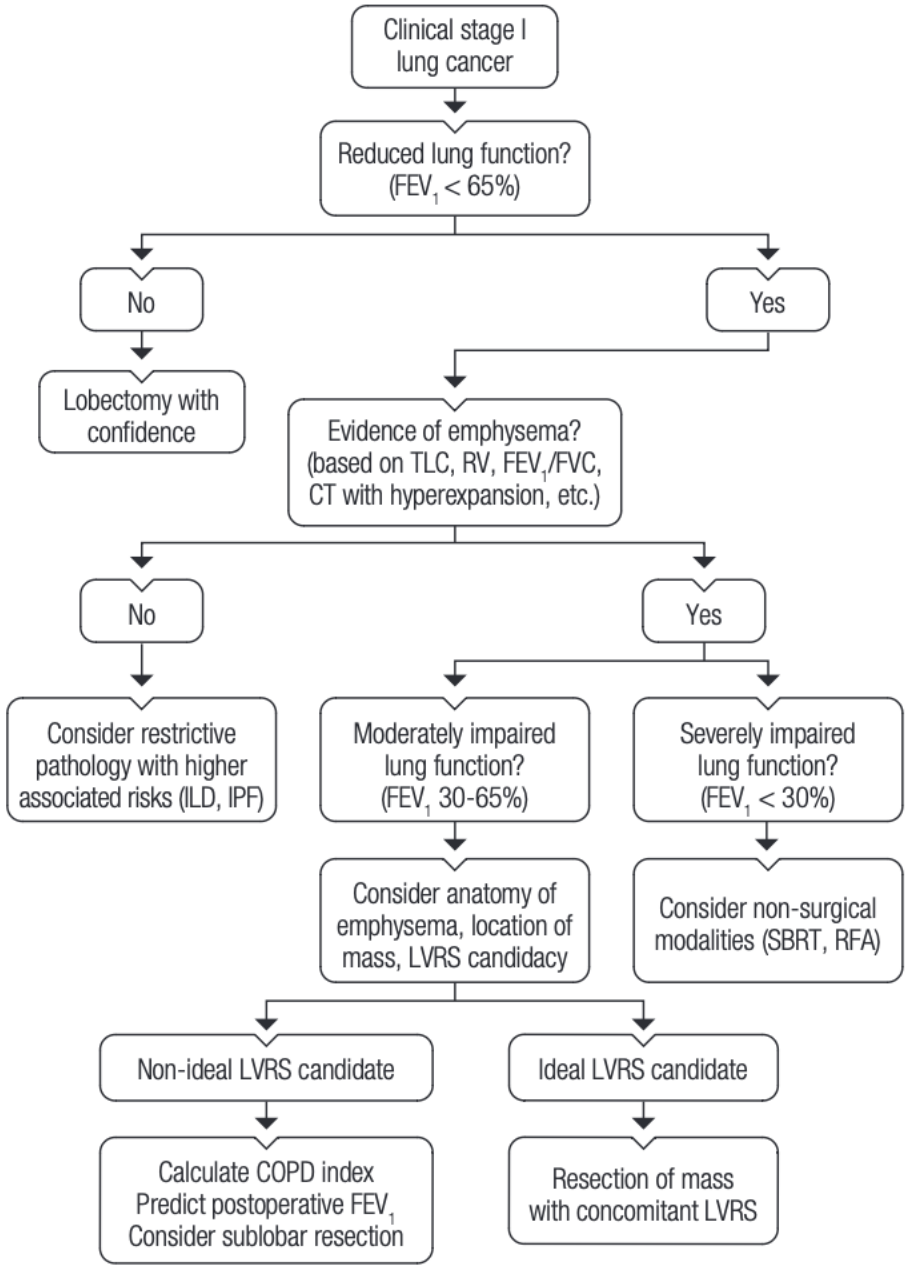
• In non-metastatic NSCLC, the cardiopulmonary fitness of the patient will determine the choice of treatment; before considering surgical resection, precise assessment of cardiac and pulmonary function is necessary to estimate risk of operative morbidity

PREOPERATIVE RESPIRATORY EVALUATION



DLCO, diffusing capacity of the lungs for carbon monoxide; FEV_1, forced expiratory volume in 1 second; ppo, predicted postoperative; VO_2, oxygen consumption

MANAGEMENT OF PATIENTS WITH CLINICAL STAGE I LUNG CANCER AND LIMITED PULMONARY FUNCTION DUE TO EMPHYSEMA



COPD, chronic obstructive pulmonary disease; CT, computed tomography; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; LVRS, lung volume reduction surgery; RFA, radiofrequency ablation; RV, reserve volume; SBRT, stereotactic body radiotherapy; TLC, total lung capacity

Formal lung function testing should be used to estimate postoperative lung function.

°Surgical resection is usually acceptable if the predicted postoperative forced expiratory volume in 1 second (FEV1) and diffusing capacity of the lungs for carbon monoxide (DLCO) values are > 40%°For patients with FEV1 and DLCO values > 80% of their predicted pulmonary function tests and no other major comorbidities, no further investigations are advised before surgical resection°For others, exercise testing and split lung function are recommended; maximum oxygen consumption (VO2max) can be used to measure exercise capacity and predict postoperative complications

• Standard risk assessments are not always directly applicable, as resection of poorly functioning parts of the lung might improve the situation instead of making it worse

°For example, in patients with limited pulmonary function due to emphysema, a lung volume reduction effect may be observed by resection of the lung cancer within emphysematous lung tissue.

For cardiac assessment, use of the recalibrated thoracic revised cardiac risk index (RCRI) shown in the table below is recommended. The steps required to undertake preoperative cardiac evaluation are shown in the figure on the next page (the figure is based on the original RCRI rather than the recalibrated RCRI)

• Comorbidities should be evaluated and optimised before surgery

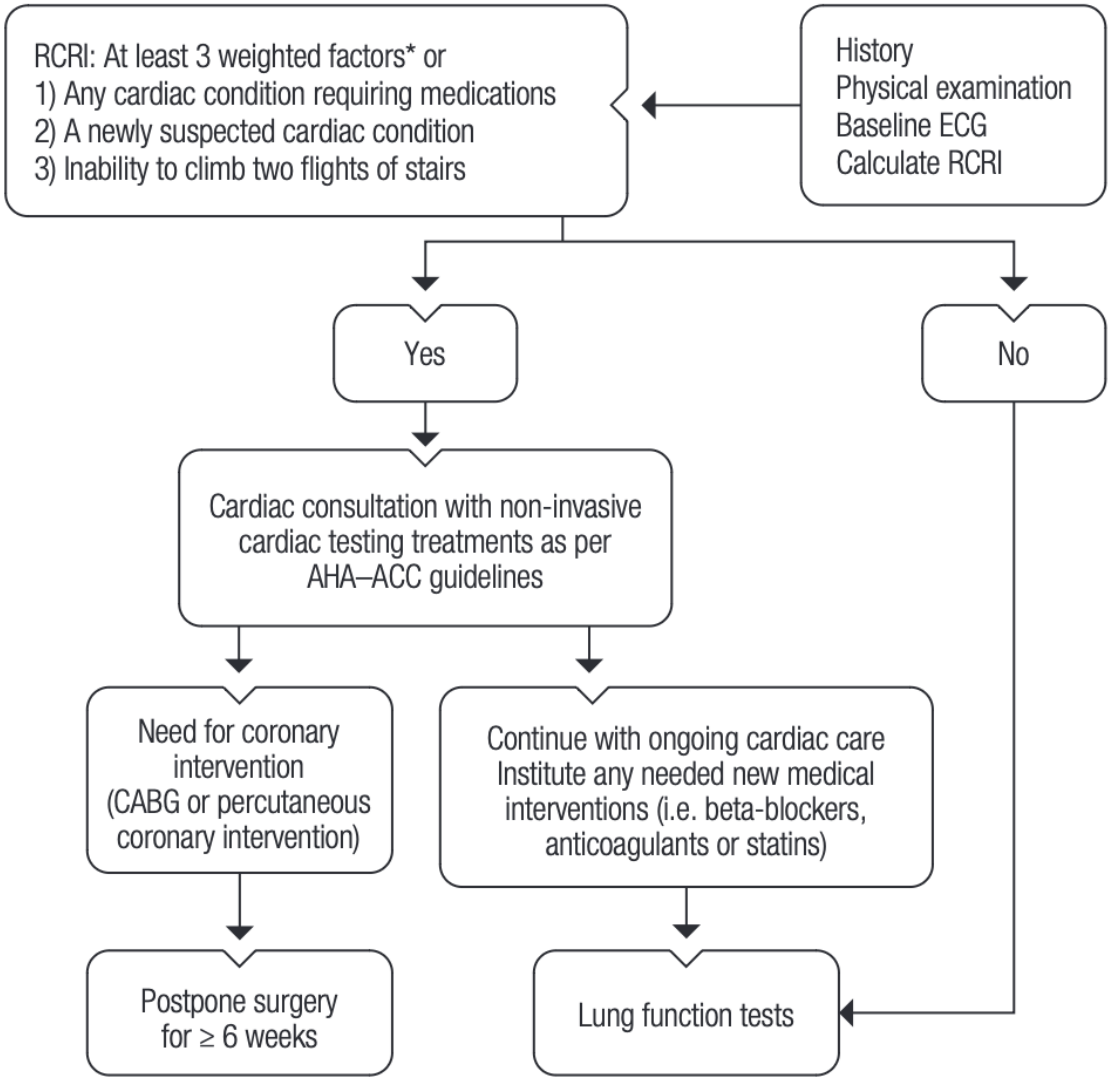
RECALIBRATED THORACIC REVISED CARDIAC RISK INDEX

	POINTS
Weighted factors	
Ischaemic heart disease*	1.5
History of cerebrovascular disease†	1.5
Serum creatinine > 2 mg/dL	1
Pneumonectomy planned	1.5
Class groupings	
A	0
B	1-1.5
C	2-2.5
D	> 2.5

*Ischaemic heart disease: History of myocardial infarction, history of positive exercise test, current complaint of chest pain (myocardial ischaemia), nitrate therapy, ECG with pathological Q waves

†Cerebrovascular disease: Transient ischaemic attack, stroke

PREOPERATIVE CARDIAC EVALUATION



*Original RCRI weighted factors: High-risk surgery (including lobectomy or pneumonectomy); ischaemic heart disease (prior myocardial infarction, angina pectoris); heart failure; insulin-dependent diabetes; previous stroke or TIA; creatinine > 2 mg/dL

ACC, American College of Cardiology; AHA, American Heart Association; CABG, coronary artery bypass grafting; ECG, electrocardiogram; RCRI, revised cardiac risk index; TIA, transient ischaemic attack

STAGE I NSCLC (T1–T2a N0)

Surgical Candidates

- Treatment: Lobectomy with systematic mediastinal lymph node dissection
- Alternative: Segmentectomy may be considered for small peripheral tumors (≤2 cm, favorable histology)
- Postoperative Treatment:
    - No adjuvant chemotherapy if completely resected Stage IA

- Consider **adjuvant chemotherapy** in **Stage IB (T2a)** if high-risk features present:
  - Poorly differentiated histology
  - Vascular invasion
  - Tumor >4 cm
  - Incomplete lymph node sampling

Non-Surgical Candidates

- **Preferred**: **Stereotactic Body Radiotherapy (SBRT)** with curative intent
- Tumors near central structures: Consider **hypofractionated or conventional RT**
-

STAGE II NSCLC (T2b–T3 N0 or T1–T2 N1)

Surgical Candidates

- **Treatment**: Surgical resection (lobectomy/pneumonectomy) + **systematic lymph node dissection**
- **Adjuvant therapy**:
  - **Adjuvant cisplatin-based chemotherapy** recommended for **completely resected Stage II**
  - **EGFR-mutant tumors (exon 19/21):** Add **adjuvant osimertinib for 3 years** after chemotherapy (ADAURA trial)
  - **PD-L1 ≥1% and no EGFR/ALK alteration**: Add **adjuvant atezolizumab x 1 year** (IMpower010 trial)

Non-Surgical Candidates

- **Concurrent chemoradiotherapy (CRT)** or **SBRT** depending on node status and tumor size/location

STAGE IIIA NSCLC (T1–T3 N2 / T3 N1)

Stage IIIA is heterogeneous; treatment is **individualized** based on **resectability** and **multidisciplinary tumor board** decision.

Resectable Disease (Selected N2 or T3 tumors)

- **Preferred approach**:
  1. **Neoadjuvant chemotherapy** (platinum-doublet) ± immunotherapy (e.g., nivolumab per CheckMate 816)
  2. **Surgical resection**
  3. **± Adjuvant radiotherapy** in high-risk residual disease (not routine)

4. **EGFR-mutated**: Consider **adjuvant osimertinib**
5. **PD-L1 ≥1%, EGFR/ALK-negative**: Consider **adjuvant atezolizumab**

Unresectable or Inoperable

- **Concurrent chemoradiotherapy (CRT)** is standard of care:
  - Platinum doublet (e.g., cisplatin + etoposide or vinorelbine) + 60–66 Gy RT
  - Followed by **consolidation durvalumab** for up to 12 months (PACIFIC trial) if:
    - No progression
    - PD-L1 ≥1%
    - EGFR/ALK wild-type

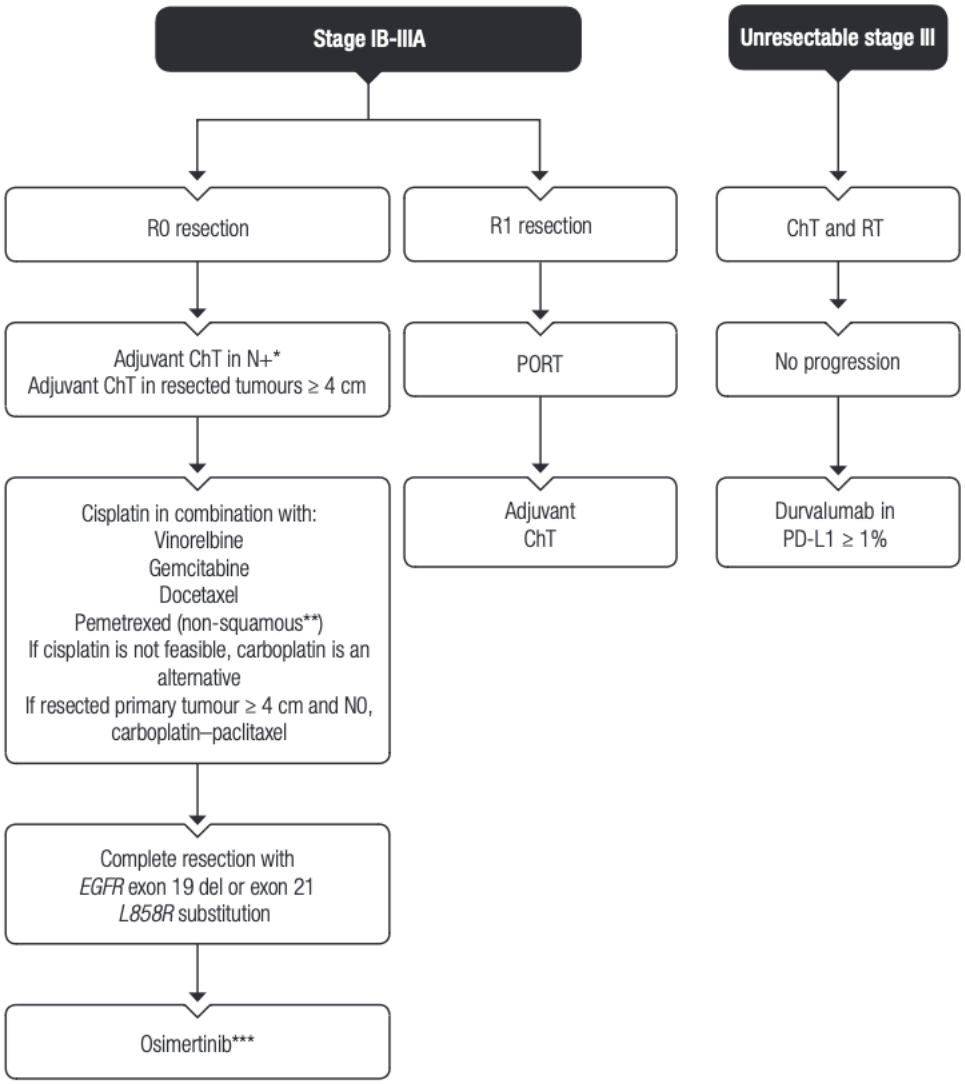
MOLECULAR & IMMUNOTHERAPY INTEGRATION

Mutation/Status	Adjuvant Option (after surgery ± chemo)
EGFR-mutant	**Osimertinib** x 3 years (ADAURA trial)
ALK-positive	No current approved adjuvant ALK inhibitor
PD-L1 ≥1%, EGFR/ALK WT	**Atezolizumab** x 1 year (IMpower010 trial)

SUMMARY TABLE

Stage	Primary Treatment	Adjuvant / Additional
IA	Surgery (lobectomy)	None
IB	Surgery	Chemo if high-risk features
II	Surgery	Cisplatin-based chemo + targeted/immunotherapy based on biomarkers
IIIA Resectable	Neoadjuvant chemo ± ICI → Surgery	± RT, targeted (EGFR) or immunotherapy (PD-L1+)
IIIA Unresectable	Concurrent chemoradiotherapy	Durvalumab if PD-L1 ≥1% and EGFR/ALK WT

SYSTEMIC TREATMENT OF EARLY STAGE (STAGE IB-IIIA) AND UNRESECTABLE LOCALLY ADVANCED (STAGE III) NSCLC



*For stage IB, adjuvant ChT in primary tumours ≥ 4 cm

**Only in adenocarcinoma tumours

***Primary endpoint of ADAURA trial was DFS in stage II-IIIA according to the 7th TNM (T > 5 cm or N+). Adjuvant osimertinib in stage IB (3 cm < T ≤ 5 cm) was a secondary endpoint. Stage was a stratification factor. Therefore, indication for osimertinib in T ≤ 5 cm N0 will follow local recommendations/physician's discretion

ChT, chemotherapy; DFS, disease-free survival; *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; PORT, postoperative radiotherapy; R0, no residual tumour at the margin; R1, microscopic residual tumour at the margin; RT, radiotherapy; TNM, tumour–node–metastasis

Adjuvant treatment with targeted therapies

• Osimertinib is indicated as adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA NSCLC whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations

Primary RT

• The non-surgical treatment of choice for stage I NSCLC is SABR [or stereotactic body RT (SBRT)]°This is most commonly used in patients with comorbidities or other reasons for inoperability with a peripherally-located stage I NSCLC or in patients who refuse surgery

°The dose should be to a biologically equivalent tumour dose of ≥ 100 Gy, prescribed at the encompassing isodose

• SABR for early-stage peripheral lung tumours is associated with low toxicity in patients with chronic obstructive pulmonary disease (COPD) and the elderly

°However, the risk of high-grade and fatal toxicity is high in patients with pre-existing interstitial lung fibrosis and careful evaluation of the risks and benefits of SABR should be considered by an expert tumour board

°If SABR is unavailable for elderly patients, radical RT using hypofractionated schedules is preferred over conventionally fractionated RT

• Salvage surgery, if feasible, may be offered to patients having complications post-SABR°Salvage surgery should use the same indications as for primary surgery in progressive disease after SABR, but surgery may be more difficult with higher operative risk

• For medically inoperable patients with tumours > 5 cm and/or a moderately centrallocation, radical RT using more conventional or accelerated schedules is recommended

°The IASLC has defined central tumours as those located within 2 cm in all directions of any mediastinal structure, including the bronchial tree, oesophagus, heart, brachial plexus, major vessels, spinal cord, phrenic nerve and recurrent laryngeal nerve

°Due to increased toxicity, SABR is not appropriate for “ultracentral” tumours (tumours with a planning target volume that overlaps the trachea or main bronchi)

°For tumours located in the hilar region, SABR using risk-adapted fractionation schemes can achieve high local control rates with limited toxicityRadiofrequency ablation

• Patients with stage I NSCLC with strong contraindications for surgery and/or SABR may be treated with radiofrequency ablation (RFA), although currently this recommendation is only supported by observational studies60

Postoperative RT

• Postoperative RT (PORT) is not recommended in completely resected early-stage NSCLC due to evidence of detrimental effects

• In the case of resection with microscopic residual tumour at the margin (R1; positive resection margin, chest wall), PORT should be considered

• Even if such patients were not included in randomised clinical trials, adjuvant ChT should be considered in patients with R1 resection of stage IIA-IIB-III disease

• If both ChT and RT are administered post-R1 resection, RT may be administered before ChTLocally advanced (stage III) NSCLCSystemic therapy

• For curative-intent management, patients should undergo platinum-based ChT (preferably cisplatin, although the optimal ChT has not been studied extensively in this setting)

• There is no beneficial role for induction ChT before chemoradiotherapy (CRT), although in many centres (for reasons relating to planning of RT), 1 cycle will be given prior to concurrent CRT• When delivered perioperatively, cisplatin-based combinations are considered the treatment of choice in the absence of contraindications• In the perioperative setting, 3-4 cycles of cisplatin-based ChT are recommended, with a target total cumulative dose of ≥ 300 mg/m2 cisplatin

• (Neo)adjuvant anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) checkpoint inhibitors are currently being evaluated in addition to current standard of careResectable locally advanced NSCLC

• “Resectable” in locally advanced NSCLC refers to the following situations:

°Single station N2 disease where other nodal stations have been biopsied and proven to be benign; postoperative ChT should then be advised°T4 N0 tumours where nodal disease was excluded by invasive methods when a resection with no residual tumour at the margin (R0) was considered feasible

°After induction therapy, when there has been nodal downstaging and a pneumonectomy can be avoided• If, despite adequate mediastinal staging procedures, N2 disease is only documented intraoperatively, surgery should be followed by adjuvant ChT

°PORT is not beneficial for patients with completely resected stage III pN2 NSCLC and should only be considered in the setting of residual microscopic or macroscopic disease

• If single station N2 disease can be demonstrated by preoperative pathological nodal analysis, resection followed by adjuvant ChT, induction ChT followed by surgery or induction CRT followed by surgery are options

°If induction ChT alone is given preoperatively, PORT is not standard treatment but may be an option based on critical evaluation of locoregional relapse risks

• In multistation N2 or N3 disease, concurrent definitive CRT is preferred°Any complex multimodality treatment strategy decision, including the role of surgery, should be evaluated by an experienced MDT

• In potentially resectable superior sulcus tumours, concurrent CRT induction followed by definitive surgery is the treatment of choice

°The same strategy may be applied for potentially resectable T3 or T4 central tumours in highly selected cases at experienced centres°In both situations, surgery should be carried out within 4 weeks after the end of RT

• There is no role for prophylactic cranial RT in stage III NSCLCUnresectable locally advanced NSCLC

• “Unresectable” in locally advance NSCLC refers to patients in whom – even after induction therapy – a complete resection (R0) would not be possible based on MDT evaluation

• Concurrent CRT is the treatment of choice in patients evaluated as unresectable in stage IIIA and IIIB°Concurrent CRT leads to higher 5-year survival rates than sequential CRT (induction ChT followed by RT) in patients who are fit, albeit at the cost of higher rates of reversible oesophagitis

°Early mortality rates are ~10% with concurrent CRT, with tumour volume and pulmonary function as associated risk factors

°If concurrent CRT is not possible, e.g. if the patient is elderly or less fit with clinically relevant comorbidities, sequential ChT followed by definitive RT represents a valid and effective alternative

• There is no role for prophylactic cranial RT in stage III NSCLC

• In the absence of contraindications, the optimal ChT to be combined with RT in stage III NSCLC should be based on cisplatin

°There are no firm conclusions supporting single-agent carboplatin as an RT sensitiser

• Most comparative studies of concurrent CRT versus sequential administration used cisplatin–etoposide or cisplatin + a vinca alkaloid (typically cisplatin–vinorelbine), or cisplatin–pemetrexed in the presence of non-squamous histology

MANAGEMENT OF METASTATIC NON-SMALL CELL LUNG CANCER

DIAGNOSIS

• Multidisciplinary teams are recommended

• In case of distant accessible lesions, core biopsy under imaging guidance [typically computed tomography (CT)] can be proposed

• Bronchoscopy is ideally suited to central lesions and can be used for bronchial washing, brushing, and bronchial and transbronchial biopsy

• Fibre optic bronchoscopy allows evaluation of regional lymph nodes by endobronchial ultrasound (EBUS) and/or endoscopic ultrasound (EUS)

• EBUS-guided transbronchial needle aspiration is less invasive and at least as accurate as mediastinoscopy

• For peripheral lesions, transthoracic percutaneous fine needle aspiration and/or core biopsy under imaging guidance (typically CT) is recommended

• In the presence of a pleural effusion, thoracentesis may be both diagnostic and palliative

• Image-guided pleural biopsy or surgical thoracoscopy is required if fluid cytology examination is negative

• More invasive surgical approaches, such as mediastinoscopy, mediastinotomy, thoracoscopy and video-assisted thorascopic surgery (VATS), should be considered in the diagnostic work-up when the previously described techniques are insufficientPathology/molecular biologyHistological diagnosis

• Pathological diagnosis should be made according to the 2015 World Health Organization (WHO) classification

• Most patients with non-small cell lung cancer (NSCLC) present with advanced stageunresectable disease and treatment-determining diagnoses must be made based on small biopsy and/or cytology samples from the primary tumour or accessible metastases

• Where specific subtyping is not possible by morphology alone, immunohistochemistry (IHC) is recommended for subtype determination and to reduce the NSCLC-not otherwise specified (NSCLC-NOS) rate to < 10% of cases diagnosedMolecular diagnostics

• A personalised medicine synopsis is shown in the next table

PERSONALISED MEDICINE SYNOPSIS FOR METASTATIC NSCLC

BIOMARKER	METHOD	USE
EGFR mutation	Any appropriate, validated method, subject to external quality assurance	To select those patients with *EGFR*-sensitising mutations most likely to respond to EGFR TKI therapy
ALK rearrangement	Any appropriate, validated method, subject to external quality assurance. FISH is the historical standard but IHC is now becoming the primary therapy-determining test, provided the method is validated against FISH or some other orthogonal test approach. NGS is an emerging technology	To select those patients with *ALK* gene rearrangements most likely to respond to ALK TKI therapy
ROS1 rearrangement	FISH is the trial-validated standard. IHC may be used to select patients for confirmatory FISH testing but it currently lacks specificity. NGS is an emerging technology. External quality assurance is essential	To select those patients with *ROS1* gene rearrangements most likely to respond to ROS1 TKI therapy
BRAF mutation	Any appropriate, validated method, subject to external quality assurance	To select those patients with *BRAF V600*-sensitising mutations most likely to respond to BRAF inhibitor ± MEK inhibitor therapy
NTRK rearrangement	Screening by IHC or RNA NGS. A positive with the former requires confirmation by a molecular method (FISH, NGS). The latter should probably be validated by IHC	To select those patients with *NTRK* gene fusions most likely to respond to NTRK TKI therapy
PD-L1 expression	IHC to identify PD-L1 expression at the appropriate level and on the appropriate cell population(s) as determined by the intended drug and line of therapy. Only specific trial assays are validated. Internal and external quality assurance are essential	To enrich for those patients more likely to benefit from anti-PD-1 or anti-PD-L1 therapy. For pembrolizumab, testing is a companion diagnostic; for nivolumab and atezolizumab, testing is complementary

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; FISH, fluorescence *in situ* hybridisation; IHC, immunohistochemistry; MEK, mitogen-activated protein kinase kinase; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; ROS1, ROS proto-oncogene 1; TKI, tyrosine kinase inhibitor

All patients with advanced and possible, probable or definite adenocarcinoma should be tested for oncogenic drivers

• Molecular testing is not recommended in squamous cell carcinoma (SCC), except in never-, long-time ex- or light-smokers (< 15 pack years)

• Epidermal growth factor receptor (EGFR) mutation status should be systematically analysed in advanced non-squamous cell carcinoma (NSCC)

GFR mutation status testing must cover exon 19 deletions, the exon 21 L858R substitution mutation and complete coverage of exons 18-21

• T790M testing is mandatory for relapsed disease; if cell-free DNA blood tests are negative, a tissue biopsy is required

• Testing for anaplastic lymphoma kinase (ALK) rearrangement should be systematically carried out in advanced non-squamous NSCLC

°IHC is an alternative to fluorescence in situ hybridisation (FISH) for ALK testing, provided the method is validated against FISH or some other orthogonal test approach

• Testing for ROS proto-oncogene 1 (ROS1) rearrangement should be systematically carried out in advanced NSCLC

°FISH is the standard approach for ROS testing; IHC can be used as a screening approach but is not recommended as the primary treatment-determining test

• Systematic analysis of BRAF V600 mutation status for the prescription of BRAF/ mitogen-activated protein kinase kinase (MEK) inhibitors is required in advanced NSCLC

• Screening for neurotrophic tyrosine receptor kinase (NTRK) rearrangement should be systematically carried out and may use IHC or next-generation sequencing (NGS), with appropriate testing follow-up to validate a positive result

• Multiplex NGS is becoming the standard approach to molecular testing but does not address biomarkers requiring testing at the protein level (requiring IHC); the question of whether NGS-detected fusion genes require an orthogonal test (IHC, FISH) for confirmation remains open

• Adequate internal validation and quality control measures are mandatory and laboratories must participate and perform adequately in external quality assurance schemes for each test

• Programmed death-ligand 1 (PD-L1) expression testing is recommended for all patients with newly diagnosed, advanced NSCLC

°The PD-L1 IHC 22C3 assay and trial-validated assays based on the 28-8 and SP263 PD-L1 IHC clones are recommended

°For pembrolizumab, the mandatory treatment threshold is a tumour proportion score (TPS) ≥ 50% in first line and ≥ 1% in second line

°PD-L1 testing is not required for nivolumab and atezolizumab in second line

°PD-L1 testing is not required for pembrolizumab when combined with platinum and pemetrexed

• Detection in peripheral blood of genomic alterations or factors associated with treatment resistance will facilitate disease monitoring and will become more commonplace as techniques improve

• The adequacy of RECIST in evaluating response to EGFR or ALK tyrosine kinase inhibitors (TKIs) in respective genetically-driven NSCLCs is debatable but it should still be used in clinical practice

°Immune-related RECIST (irRECIST), immune-RECIST (iRECIST) and immune- modified RECIST (imRECIST) have been developed but require further evaluation before being used in clinical practice

MANAGEMENT OF ADVANCED/METASTATIC NSCLC

• The treatment strategy should consider histology, molecular pathology, age, PS,comorbidities and the patient's preferences and should be discussed in a multidisciplinary tumour board

• Systemic therapy should be offered to all stage IV patients with PS 0-2

• Smoking cessation can improve outcome at any stage of NSCLC and should be strongly encouraged First-line treatment of EGFR- andALK-negative NSCLC, PD-L1 ≥ 50%

• Pembrolizumab is a standard first-line option for advanced NSCLC in patients with PD-L1 expression ≥ 50% and without contraindications to immunotherapy (such as severe autoimmune disease or organ transplantation)69

• Atezolizumab is approved for the first-line treatment of patients with PD-L1-high(≥ 50% of tumour cells) NSCLCFirst-line treatment of EGFR- and ALK-negative NSCLC regardless of PD-L1 status

• Pembrolizumab in combination with pemetrexed and platinum-based ChT should be considered a standard first-line option for metastatic non-squamous NSCLC

°Overall survival (OS) benefit was apparent across PD-L1 expression levels°The degree of durable benefit was limited in tumours with PD-L1 TPS < 1%

• The combination of atezolizumab, bevacizumab, carboplatin and paclitaxel is an option in PS 0-1 patients with metastatic non-squamous NSCLC in the absence of immunotherapy contraindications

°Improved OS with atezolizumab, bevacizumab, carboplatin and paclitaxel was observed in patients with sensitising EGFR mutations, defined as exon 19 deletions or L858R mutations. This association provides a treatment opportunity for this subgroup after targeted therapies have been exploited

• The combination of carboplatin or cisplatin with pemetrexed and atezolizumab is another potential treatment opportunity, based on data from the IMpower132 trial; it is not currently EMA approved

• The combination of pembrolizumab plus carboplatin and paclitaxel or albumin-bound paclitaxel (nab-P) is a standard choice in patients with metastatic squamous NSCLC

°OS benefit was apparent across PD-L1 expression levels

• Atezolizumab–carboplatin–nab-P is an option for patients with metastatic squamous NSCLC, although it is not EMA approved and was shown to improve PFS but not OS

• Nivolumab plus ipilimumab is an optional treatment for patients with NSCLC with a high tumour mutation burden [TMB, ≥ 10 mutations per megabase (mut/Mb)], although it is not EMA approved

°Nivolumab plus ipilimumab improved progression-free survival (PFS) versus ChT in patients with high TMB, irrespective of PD-L1, in both squamous and non-squamous histologies; there was no difference between treatments in PFS among patients with lower TMBsFirst-line treatment of NSCLC without an actionable oncogenic driver and with contraindications to immunotherapy

• ChT with platinum doublets should be considered in all stage IV NSCLC patients without an actionable oncogenic driver or major comorbidities and PS 0-2

• Benefits of ChT versus best supportive care (BSC) are observed irrespective of age, sex, histology and PS

• Doublets are superior to singe-agent ChT regimens and platinum-based doublets are recommended in all patients with no platinum contraindications

• Current recommendations are for 4 cycles of platinum-based doublets followed by less toxic maintenance monotherapy, or 4 cycles in patients not suitable for maintenance monotherapy, up to a maximum of 6 cycles

• Treatment selection should consider the expected toxicity profile

• The carboplatin–nab-P regimen has a significantly higher objective response rate (ORR) compared with solvent-based paclitaxel–carboplatin and less neurotoxicity, and is an option for advanced NSCLC, particularly in patients with greater risk of neurotoxicity, pre-existing hypersensitivity to paclitaxel or contraindications to standard paclitaxel premedicationFirst-line treatment of SCC

• Platinum-based doublets with the addition of a third-generation cytotoxic agent (gemcitabine, vinorelbine, taxanes) are recommended in advanced SCC patients without major comorbidities and PS 0-2.

• Addition of the anti-EGFR monoclonal antibody necitumumab to cisplatin and gemcitabine was associated with a modest clinical improvement. It has not been adopted as a standard in Europe for advanced SCC and its use should be carefully evaluated First-line treatment of NSCC

• Any platinum-based doublets with a third-generation agent including gemcitabine, vinorelbine or a taxane, can be used in NSCC
• The combination of atezolizumab and carboplatin–nab-P followed by maintenance atezolizumab represents a standard treatment opportunity based on data from the IMpower130 trial

• The incorporation of pemetrexed and bevacizumab into individual treatment schedules should be considered based on the following:

°Pemetrexed-based combination ChT should be restricted to NSCC in any line of treatment for advanced disease

°The combination of carboplatin with pemetrexed can be an option in patients with a contraindication to cisplatin

°The combination of bevacizumab (continued until progression) with paclitaxel–carboplatin is an option for advanced NSCC in patients with PS 0-1 in the absence of contraindications

°Bevacizumab can also be considered with platinum-based regimens beyond paclitaxel–carboplatin in the absence of contraindications

MAINTENANCE THERAPY

• Decisions on maintenance therapy must take into account histology, residual toxicity after first-line ChT, response to platinum doublet, PS and patient preference

• In patients with NSCC and a good PS (0-1), pemetrexed switch maintenance can be considered in patients having disease control following 4 cycles of platinum-based ChT

• Pemetrexed continuation maintenance following completion of 4 cycles of cisplatin–pemetrexed is recommended for NSCC in the absence of progression after first-line ChT and recovery from treatment-related toxicities

• Continuation maintenance with gemcitabine is an option in NSCLC patients treated with 4 cycles of cisplatin–gemcitabine

• Maintenance treatment with erlotinib is only recommended for NSCC patients with an EGFR-sensitising mutation Performance status 2 and beyond

• Compared with BSC, ChT prolongs survival and improves quality of life (QoL) in NSCLC patients with PS 2

• Platinum-based doublets (preferably carboplatin) should be considered for eligible PS 2 patients, with single-agent gemcitabine, vinorelbine, docetaxel or pemetrexed (restricted to NSCC) being alternative options

• Immune checkpoint inhibitor treatment can be considered for these patients, although data are scarce

°Safety appears to be comparable to that seen in patients with PS 0-1

• BSC is recommended for poor PS (3-4) patients in the absence of documented sensitising alterations, such as EGFR mutations, ALK or ROS1 rearrangements or BRAF V600 mutation Elderly patients

• Carboplatin-based doublet ChT is recommended for eligible elderly patients with PS 0-2 and adequate organ function

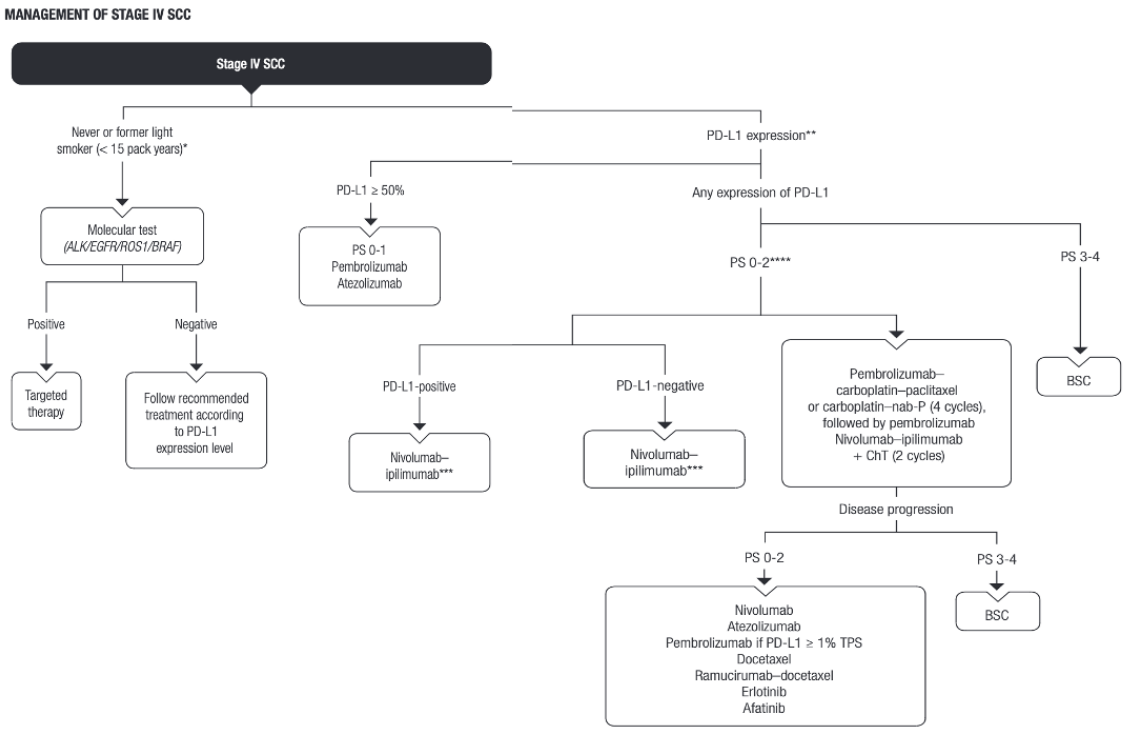
• Single-agent ChT remains the standard of care for patients not eligible for doublet ChT

• A comprehensive geriatric assessment can be used to guide the choice of platinum-based regimen, single-agent therapy or BSC

• There is no difference in response and survival with immunotherapy between patients ≤ 65 years and those > 65 years, and immunotherapy should be considered according to standard recommendations in elderly patients Second-line treatment of NSCLC without an actionable oncogenic driver

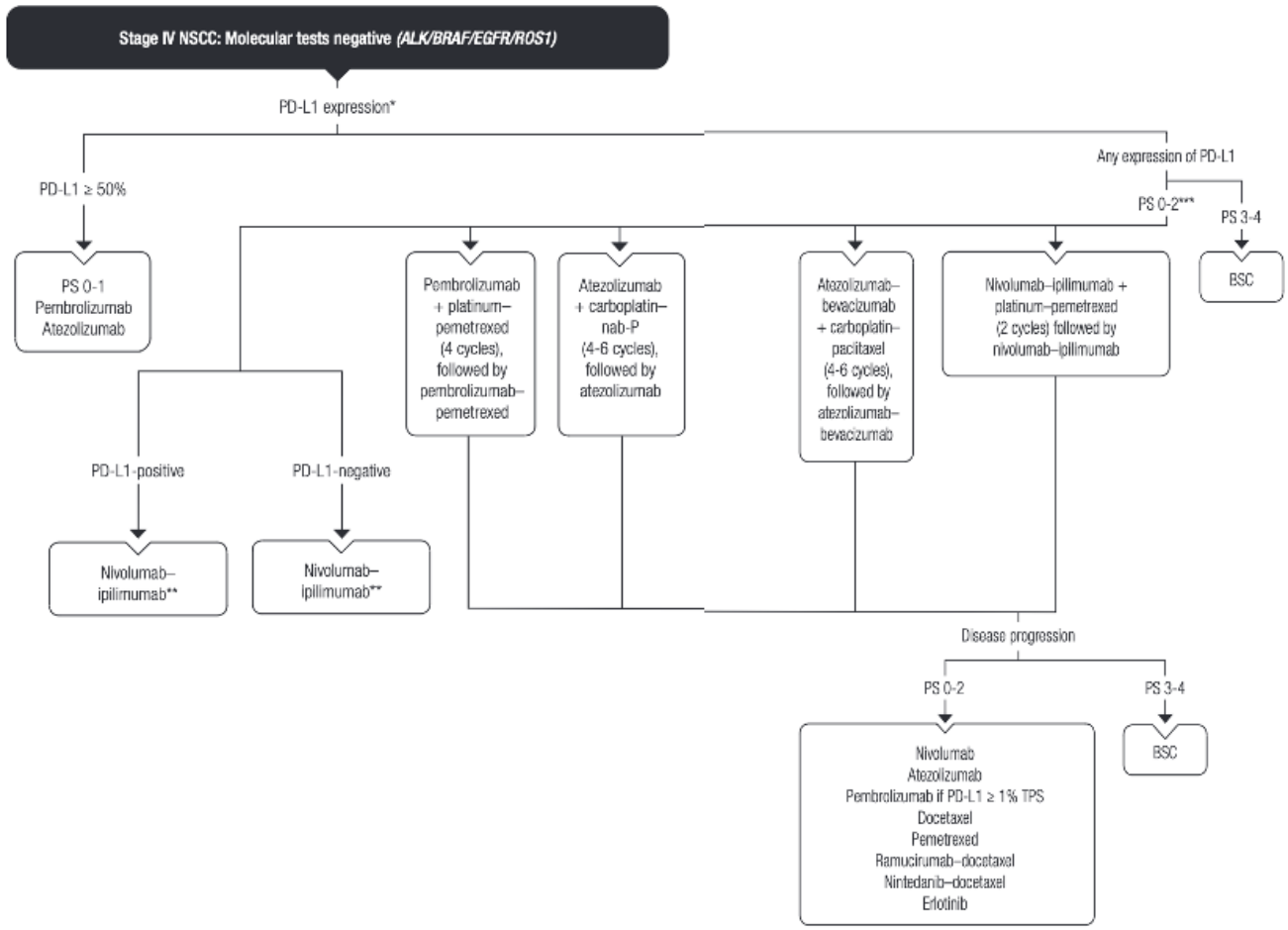
• Patients with PS 2 and clinically or radiologically progressing after first-line therapy should be offered second-line therapy, irrespective of administration of maintenance treatment

• Following failure of first-line treatment with pembrolizumab, platinum-based ChT is recommended



Molecular testing is not recommended in SCC, except in those rare circumstances when SCC is found in a never-, long-time ex- or light-smoker (< 15 pack years).**In the absence of contraindications and conditional on the registration and accessibility of anti-PD-(L)1 combinations with platinum-based ChT, this strategy will be preferred to platinum-based ChT in patients with PS 0-1 and PD-L1 < 50%. Alternatively, if TMB can be accurately evaluated, and conditional on the registration and accessibility, nivolumab–ipilimumab should be preferred to platinum-based standard ChT in patients with NSCLC***Not EMA approved. ****PS > 2 patients were not enrolled in available clinical trials. In the absence of contraindications and conditional on the registration and accessibility of anti-PD-(L)1 combinations with platinum-based ChT, this strategy might be chosen by analogy to PS 0-1 patients based on investigator opinion. Elderly patients are under-represented in available clinical trials, and frail or comorbid patients ≥ 70 years old should be evaluated for this treatment strategy with cautionALK, anaplastic lymphoma kinase; BSC, best supportive care; ChT, chemotherapy; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; nab-P, albumin-bound paclitaxel; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PS, performance status; ROS1, ROS proto-oncogene 1; SCC, squamous-cell carcinoma; TMB, tumour mutation burden; TPS, tumour proportion score74

MANAGEMENT OF STAGE IV NSCC, MOLECULAR TESTS NEGATIVE
(ALK/BRAF/EGFR/ROS1)



Anti-programmed cell death protein 1 (PD-1)/PD-L1 agents are the treatment of choice for most patients with advanced, previously treated, PD-L1-naive NSCLC, irrespective of PD-L1 expression

• There are no major safety or efficacy differences between the standard second-line treatments, nivolumab, pembrolizumab and atezolizumab, but choice can be influenced by:

°PD-L1 expression: Pembrolizumab is approved only in patients with PD-L1 ≥ 1% TPS°Approved schedules of administration: Once every 3 weeks for atezolizumab and pembrolizumab and once every 2 weeks for nivolumab [according to the EMA; the United States Food and Drug Administration (FDA) has approved a 4-weekly schedule for nivolumab]

• Nivolumab improved OS compared with docetaxel in squamous NSCLC and non-squamous NSCLC and also had better tolerability

• Pembrolizumab prolonged OS compared with docetaxel in previously treated NSCLC with PD-L1 expression > 1% of tumour cells and was associated with fewer side-effects

• Atezolizumab improved OS compared with docetaxel in advanced NSCLC previously treated with one or two prior lines of ChT and was better tolerated

• Single-agent ChT improves symptoms and survival compared with BSC

°Docetaxel and pemetrexed (NSCC only) are second-line ChT options with comparable efficacy, although pemetrexed has a more favourable tolerability profile

• Second-line treatment duration should be individualised and treatment may be prolonged if disease is controlled and toxicity acceptable

• The combination of ramucirumab–docetaxel is an option for patients with NSCLC progressing after previous ChT or immunotherapy

• The combination of nintedanib–docetaxel is an option for patients with adenocarcinoma progressing after previous ChT or immunotherapy

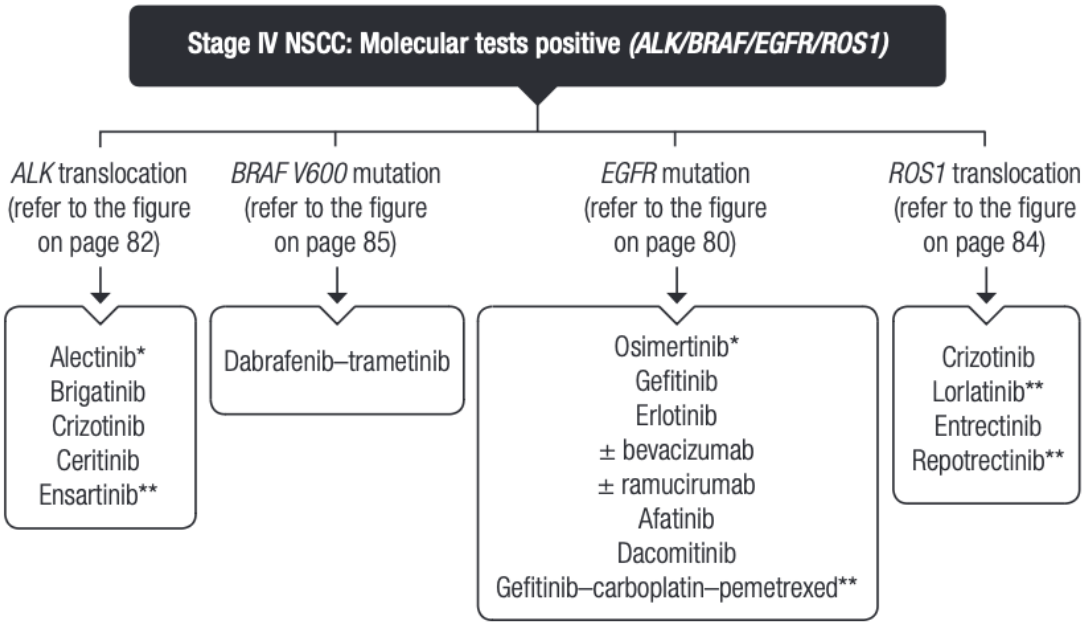
• The combination of paclitaxel–bevacizumab is another treatment option, although it is not EMA approved

• Erlotinib is a potential second- or third-line treatment option, particularly for patients not suitable for immunotherapy or second-line ChT in EGFR status unknown or EGFRwild-type (WT) tumours

• Afatinib is a therapeutic option in patients with advanced SCC (PS 0-2) with EGFRstatus or unknown or EGFR WT tumours who are unfit for ChT or immunotherapy and progressing on or after ChTManagement of stage IV NSCLC with an actionable oncogenic driver

• The management of patients with stage IV NSCC and an actionable oncogenic driver is shown in the next figure

MANAGEMENT OF STAGE IV NSCC, MOLECULAR TESTS POSITIVE *(ALK/BRAF/EGFR/ROS1)*



*Preferred option

**Not EMA approved

ALK, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; EMA, European Medicines Agency; NSCC, non-squamous cell carcinoma; *ROS1*, ROS proto-oncogene 1

Treatment of EGFR-mutated NSCLC

First-line treatment

• The EGFR TKIs erlotinib, gefitinib, afatinib and dacomitinib are standard first-line treatments for advanced EGFR-mutated NSCLC, as shown in the figure on the next page, with similar clinical benefits in PS 3-4 and good PS patients

°First-line osimertinib is the preferred option for patients with sensitising EGFRmutations

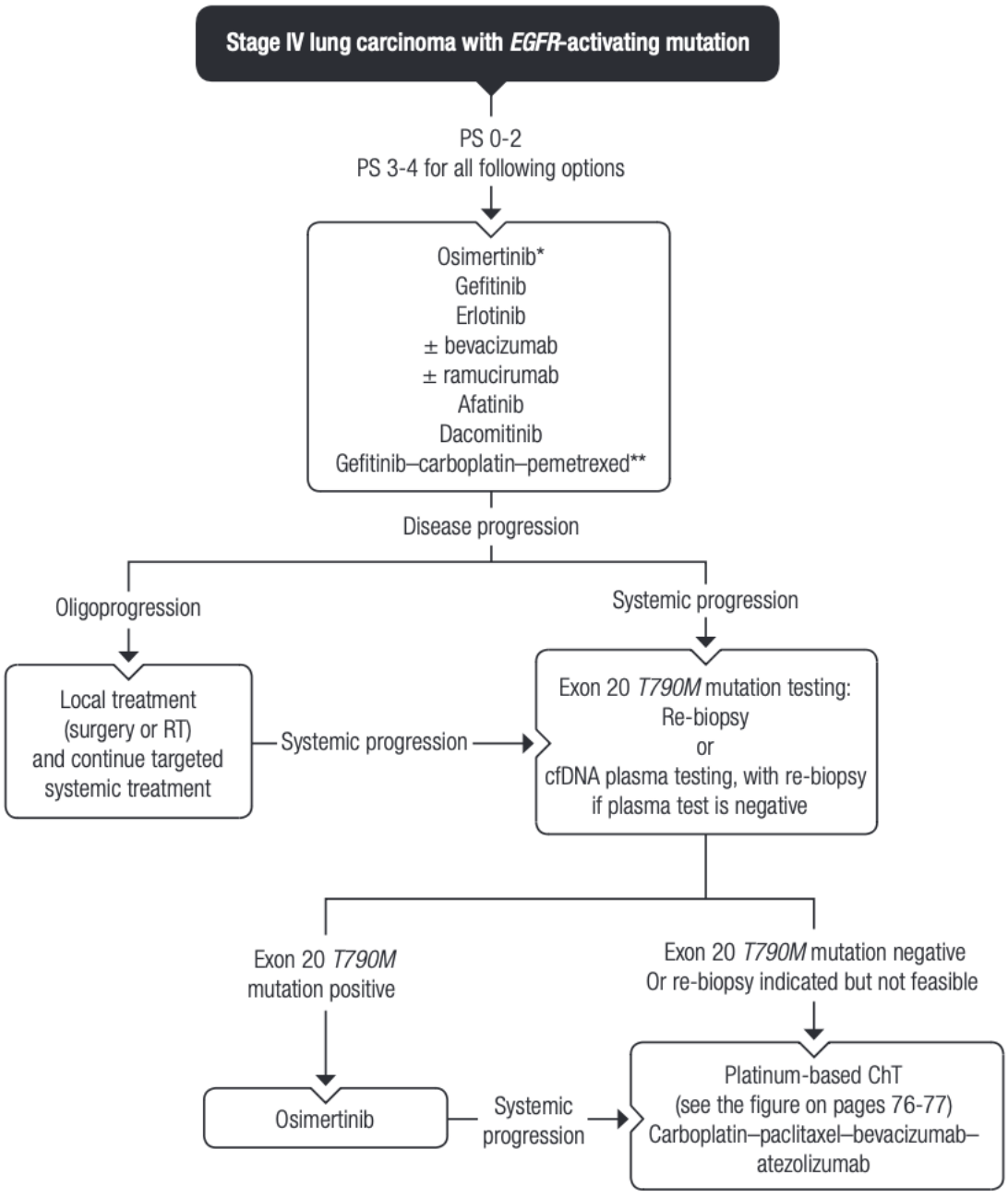
• There is no consensus regarding the preference of any of the four currently available first-line EGFR TKIs

• Clinically stable patients benefiting from EGFR TKIs may continue to receive the same therapy beyond initial radiological progression

• Continuous use of EGFR TKIs in combination with ChT is not recommended

• The addition of carboplatin–pemetrexed to gefitinib improved OS and PFS compared with gefitinib, and this combination is a first-line therapy option in advanced EGFR-mutated NSCLC, although it is not EMA approved

MANAGEMENT OF STAGE IV LUNG CARCINOMA WITH *EGFR*-ACTIVATING MUTATION



***Preferred option**

****Not EMA approved**

cfDNA, cell-free DNA; ChT, chemotherapy; *EGFR*, epidermal growth factor receptor; EMA, European Medicines Agency; PS, performance status; RT, radiotherapy

The addition of ramucirumab to erlotinib led to superior PFS in first-line EGFR-mutated NSCLC in a phase III trial and is EMA approved

• Erlotinib–bevacizumab is an EMA approved front-line treatment option for EGFR-mutated tumours Beyond first-line treatment

• Almost all patients who benefit from EGFR TKIs will develop clinical resistance, often due to acquired EGFR exon 20 T790M mutations

• All patients with clinical resistance to first-/second-generation EGFR TKIs should undergo T790M mutation testing and osimertinib is the standard treatment for patients testing positive

• Molecular mechanisms of resistance to EGFR TKIs in patients without T790Mmutations include MET proto-oncogene receptor tyrosine kinase (MET) amplification, human epidermal growth factor receptor 2 (HER2) amplification, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) alternations, Kirsten rat sarcoma virus (KRAS) mutation and small cell transformation

°The current standard approach in this scenario is platinum-based doublet ChT, particularly in combination with atezolizumab and bevacizumab, which is EMA approved Treatment of ALK-rearranged NSCLCFirst-line treatment

• First-line treatment for ALK-rearranged NSCLC is an ALK TKI, including alectinib, crizotinib, ceritinib and brigatinib (EMA approved) and ensartinib (not EMA approved), as shown in the figure on the next page

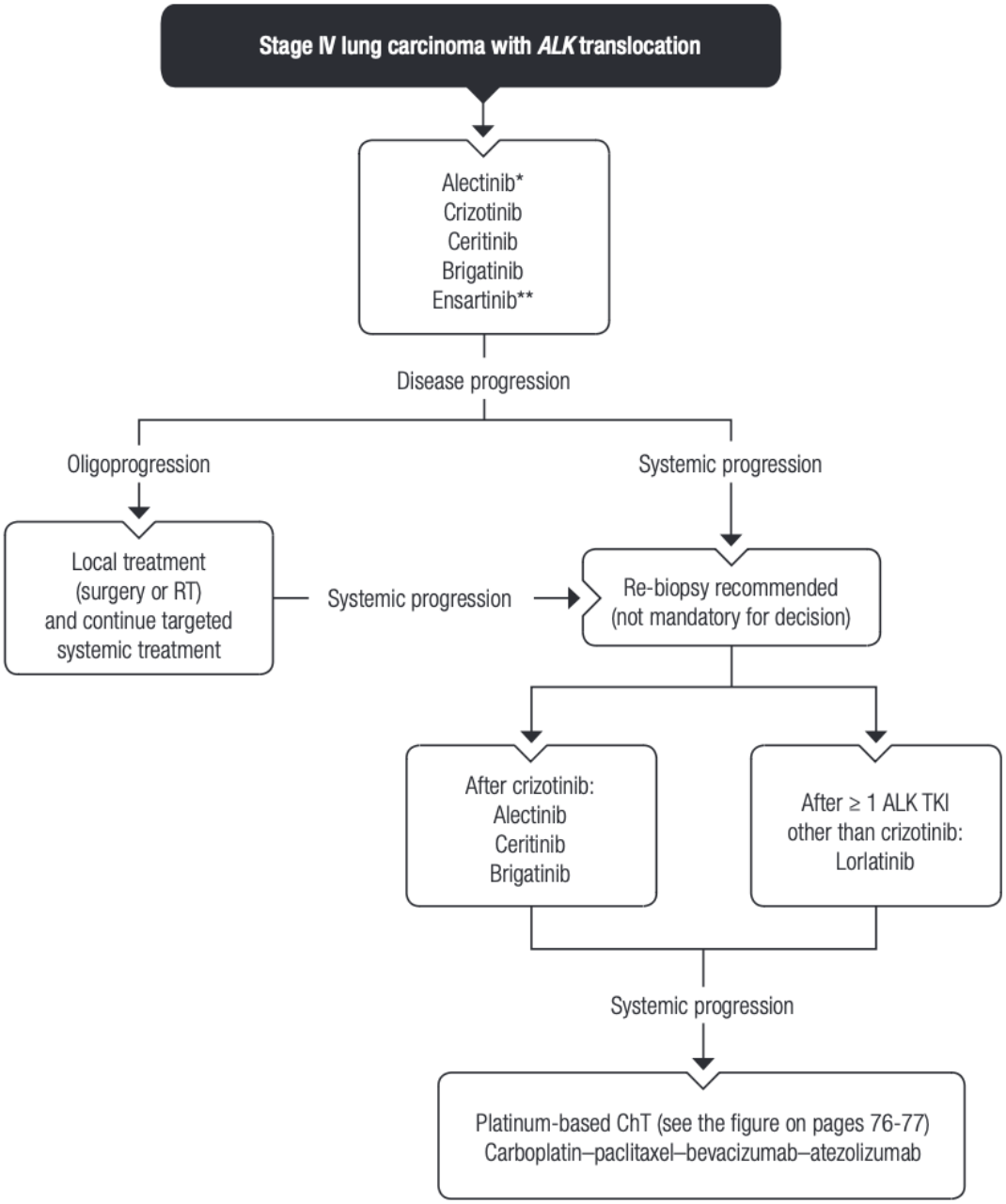
• The next-generation TKI, lorlatinib, improved clinical outcomes compared with crizotinib as upfront treatment in patients with advanced ALK-rearranged NSCLC in a phase III trial (EMA approved)

• An alternative daily dose of ceritinib (450 mg with food) to the currently approved dose (750 mg in a fasted state) may help to reduce gastrointestinal toxicities

• Front-line use of ALK TKIs is effective in patients with CNS involvement• While ceritinib represents a better treatment strategy than ChT and presumably crizotinib, alectinib represents a better treatment option than ChT and crizotinib Beyond first-line treatment

• Crizotinib improves ORR and PFS compared with second-line ChT in TKI-naive patients with previously treated ALK-rearranged NSCLC, and any patient with NSCLC harbouring an ALK fusion should receive crizotinib as next-line therapy, if not received previously

MANAGEMENT OF STAGE IV LUNG CARCINOMA WITH *ALK* TRANSLOCATION



***Preferred option**

****Not EMA approved**

ALK, anaplastic lymphoma kinase; ChT, chemotherapy; EMA, European Medicines Agency; RT, radiotherapy; TKI, tyrosine kinase inhibitor

- In *ALK*-rearranged patients progressing on crizotinib, treatment with next-generation ALK TKIs, such as alectinib, ceritinib, brigatinib or lorlatinib, is recommended

In ALK-rearranged patients progressing on crizotinib, treatment with next-generation ALK TKIs, such as alectinib, ceritinib, brigatinib or lorlatinib, is recommended

• Ensartinib shows high activity against a broad range of known crizotinib-resistant ALKmutations and CNS metastases, and also showed potential post-crizotinib efficacy
•In patients who progress after a second-generation ALK TKI, the next-generation ALK inhibitor lorlatinib is recommendedTreatment of ROS1-rearranged NSCLC

• Single-agent crizotinib is recommended as first- or second-line treatment in patients with stage IV NSCLC with ROS1 rearrangement, as shown in the figure on the next page

• Ceritinib may be considered in crizotinib-naive patients but is currently not EMA approved • Brigatinib, lorlatinib, repotrectinib and entrectinib also have potential anti-ROS1 activity on the basis of preclinical studies and encouraging but limited phase I/II clinical data

• Patients receiving first-line crizotinib can be offered second-line platinum-based ChT

• Entrectinib is EMA approved for the treatment of NSCLC patients positive for ROS1mutations (patients who have not previously received other ROS1 inhibitors)

Treatment of BRAF-mutated NSCLC

• The EMA approved combination of dabrafenib–trametinib is recommended for patients with BRAF inhibitor-naive, stage IV NSCLC with BRAF V600E mutation
• Vemurafenib is showing encouraging results in subsequent-line studies

• Patients receiving a first-line BRAF/MEK inhibitor combination may be offered second-line platinum-based ChTTreatment of NSCLC with other actionable oncogenic drivers

• Several other molecular targets harbouring somatic variants with therapeutic potential have been identified, including RET, MET, HER2 and NTRK

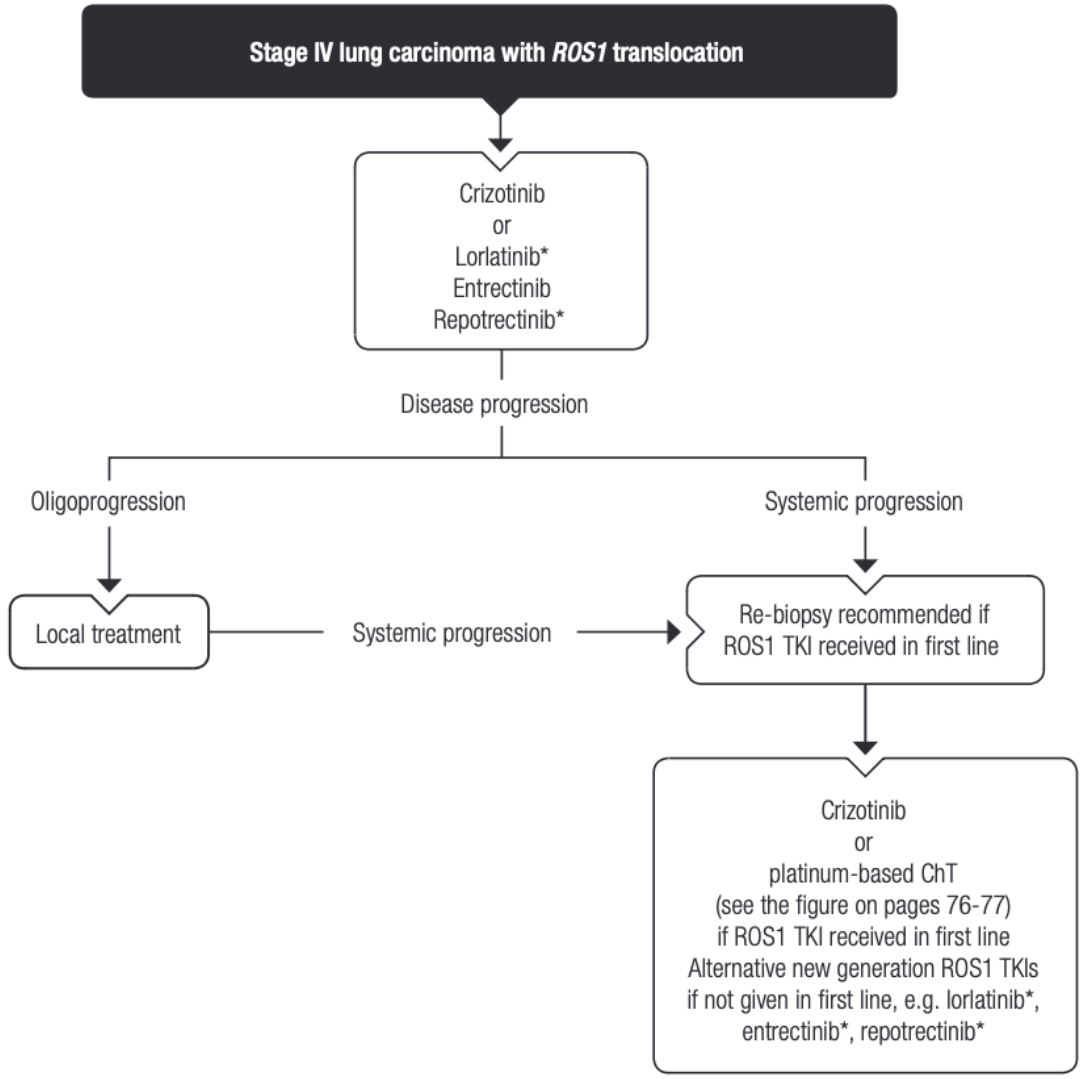
• Multitarget agents, including cabozantinib, vandetanib, sunitinib, sorafenib, alectinib, lenvatinib, nintedanib, ponatinib and regorafenib, with anti-RET activity, have shown disappointing activity in trials, although the studies are small and subject to selection bias and results of heterogeneous benefit

• In contrast, selpercatinib and pralsetinib selectively block RET, avoiding other targets and the associated treatment-limiting side-effects

°Selpercatinib is EMA approved for the treatment of advanced RET fusion-positive NSCLC in adults who have previously received immunotherapy or platinum-based cancer medicines or both

°Pralsetinib is EMA approved for the treatment of adults with RET fusion-positive advanced NSCLC not previously treated with a RET inhibitor

MANAGEMENT OF STAGE IV LUNG CARCINOMA WITH *ROS1* TRANSLOCATION



*Not EMA approved

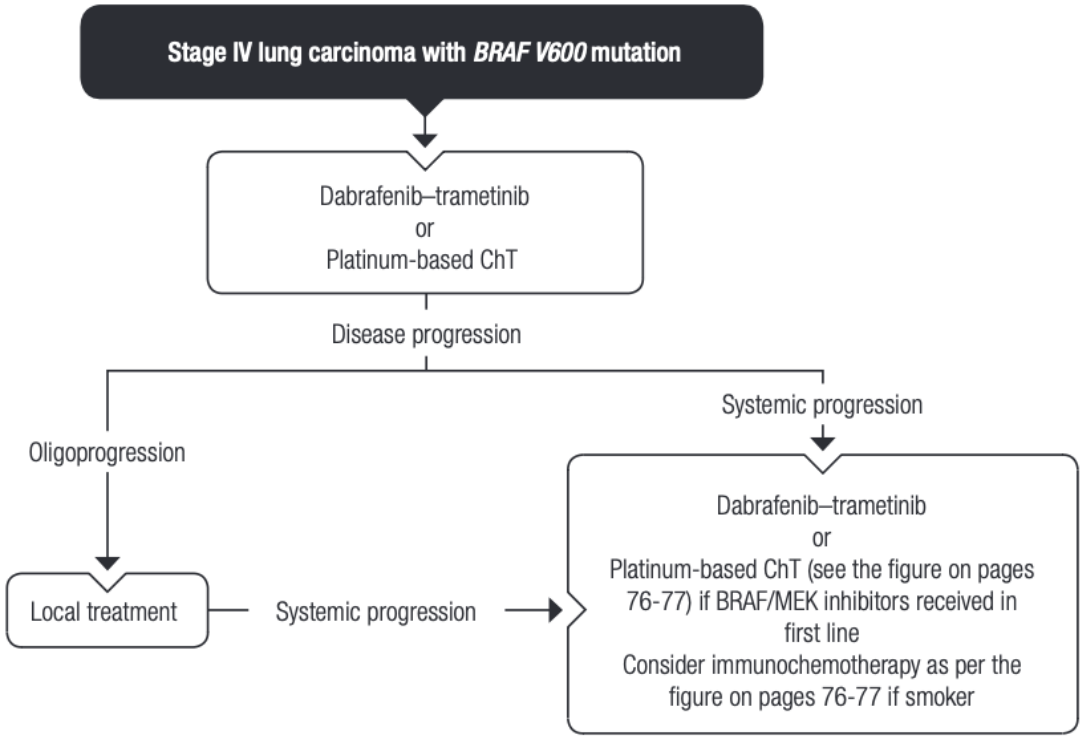
ChT, chemotherapy; EMA, European Medicines Agency; *ROS1*, ROS proto-oncogene 1; TKI, tyrosine kinase inhibitor

Crizotinib has demonstrated potential clinical efficacy against the METex14 variant that needs to be confirmed

• Capmatinib and tepotinib are both EMA approved for the treatment of patients with advanced NSCLC with alterations leading to METex14 skipping who require systemic treatment after immunotherapy and/or platinum-based ChT

• Other MET-directed TKIs are undergoing development against this target, including salvolitinib

MANAGEMENT OF STAGE IV LUNG CARCINOMA WITH *BRAF V600* MUTATION



ChT, chemotherapy; MEK, mitogen-activated protein kinase kinase

HER2 dysregulation is another promising target for advanced NSCLC but there is a lack of robust data; targeting HER2 dysregulation is not recommended and recruitment into clinical trials is encouraged

°Trastuzumab deruxtecan is a novel antibody–drug conjugate whose use is mainly restricted to clinical trials, while activity is promising

• For disease with somatic fusions involving the rare oncogenic drivers NTRK1-3,larotrectinib and entrectinib show promising clinical activity

°Larotrectinib is the first tumour-agnostic drug to be approved in the European Union for the treatment of adult and paediatric patients with solid tumours displaying a NTRK gene fusion and who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity and who have no satisfactory treatment options

°In August 2020, the EMA granted a conditional marketing authorisation to entrectinib as monotherapy for the treatment of adult and paediatric patients 12 years of age and older with solid tumours expressing an NTRK gene fusion and:-Who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and have not received a prior NTRK inhibitor-Who have no satisfactory treatment option

Role of radiotherapy in stage IV NSCLC

• External beam radiotherapy (EBRT) plays a major role in the symptom control of metastases and is indicated in cases of haemoptysis and symptomatic airway obstruction

• Higher doses of radiotherapy (RT) do not lead to greater palliation and are associated with higher rates of acute toxicity

• There are few data on the optimal timing of thoracic RT and systemic therapy in stage IV disease and no evidence that the concurrent administration of ChT, targeted agents or immunotherapy to palliative RT is beneficial

• EBRT alone is more effective than endobronchial brachytherapy (EBB) alone for palliation

• EBB may be considered in selected patients previously treated by EBRT who are symptomatic from recurrent endobronchial central obstruction

• Neurological symptoms from spinal cord compression can be relieved by early RT Management of brain metastases

• The treatment of patients with brain metastases with or without leptomeningeal (LM) involvement and no driver mutations is dependent on prognosis, based on the Radiation Therapy Oncology Group recursive partitioning analysis (RPA)

• RPA class I patients are those < 65 years old with a good Karnofsky Performance Score (KPS) (≥ 70%), no other extracranial metastases and a controlled primary tumour; class III patients have a KPS < 70%; class II represents all other patients

• BSC, and not whole-brain RT (WBRT), is recommended for RPA class III patients because of the dismal prognosis

• WBRT can be considered for patients contingent on prognostic factors of better survival, such as driver mutations

• The most frequent WBRT schedules are 20 Gy in 5 fractions or 30 Gy in 10 fractions, with no difference in outcome • For most patients with symptomatic brain metastases and/or significant oedema, dexamethasone or equivalent corticosteroid is recommended

°Tapering of the dose and cessation after RT are recommended°Corticosteroids are not recommended for asymptomatic brain metastases

• Neuroprotective agents have not shown convincing benefit and are not recommended for routine use • Hippocampus avoidance WBRT is still undergoing evaluation and is not currently recommended for routine care• Surgical resection can be considered for single brain metastases, with postoperative WBRT or stereotactic radiosurgery (SRS)

• SRS alone with close follow-up, without WBRT consolidation, is recommended where there are a limited number of metastases and RPA class I or II

°SRS is preferred due to reduced morbidity compared with WBRT, but there is no randomised trial comparing the two approaches

• SRS should generally be considered in patients with ≤ 4 brain metastases, but there is a move to base SRS decisions on total tumour volume because the risk of radionecrosis increases with tumour volume

• Systemic therapy and deferred RT should be considered for patients with asymptomatic brain metastases who have not received prior systemic therapy

• There are limited trial data on the safety and efficacy of immunotherapy in patients with small-volume untreated CNS metastases

• In patients with an actionable oncogenic driver (e.g. EGFR, ALK), the use of CNS-penetrant next-generation TKIs may restore control of brain disease, delay cranial RT and reduce the incidence of new CNS metastasesManagement of leptomeningeal carcinomatosis

• Diagnostic modalities include cerebrospinal MRI with contrast enhancement, ideally before cerebrospinal fluid (CSF) intervention

• CSF sampling with cytological assessment is diagnostic but limited by low sensitivity but high specificity • Prognosis is poor and the treatment aim is to prolong survival with acceptable QoL • Patients with actionable oncogenic drivers may derive benefit from a CNS-penetrant next-generation TKI, otherwise systemic therapy strategies vary widely across Europe

• ChT and bevacizumab may have activity both extracranially and intracranially and also in the context of LMD • Intra-CSF pharmacotherapy may be considered, although consideration should be given to patient factors, e.g. PS, extracranial control and likely benefit

• No randomised data exist to support the role of RT for LMD, but focal RT can be considered in exceptional cases of circumscribed, symptomatic lesions Role of surgery in stage IV NSCLC

• Surgery may be indicated for diagnosis, evaluation of response to systemic therapy and palliation, and highly selected patients may be considered for lung resection with therapeutic intent or even for a salvage procedure

• When metastatic disease is suspected on PET scanning, invasive surgical procedures, such as incisional biopsies, mediastinoscopy, thoracoscopy (VATS) or laparoscopy, may be required to obtain adequate samples, which require detailed routine staining, IHC and molecular genetic testing

• Palliative interventions may be useful for primary tumour- or metastasis-related local complications which cannot be managed by conservative measures, e.g. lung abscess, empyema, massive haemoptysis, spinal cord compression and pathological bone fractures

• There is no general consensus on the precise definition of oligometastatic disease and clear evidence for surgical treatment is limited

• Extensive extrapleural pneumonectomy, sometimes in combination with intraoperative ChT or hyperthermic ChT, in patients with malignant pleural nodules or malignant pleural effusion carries a higher operative risk and prospective studies are not available

• Pleurodesis for persisting or recurrent pleural effusions improves dyspnoea; talc is the preferred agent and thoracoscopic poudrage may be better than injection of talc slurry in patients with primary lung cancer • Indwelling pleural catheters or pleuroperitoneal shunts may provide symptomatic relief for trapped lung with a thickened visceral pleural peel

• Salvage surgery may be considered for residual or progressive disease in the primary tumour or metastatic site when no other treatment options remain or specific complications occur• A surgical selection score, comprising histology, tumour size, TNM status, Charlson comorbidity index, age, race, facility type, insurance and income, may be a good predictor of survival but requires further prospective validationManagement of oligometastatic disease

• Stage IV patients with limited synchronous metastases at diagnosis may experience long-term disease-free survival (DFS) following systemic therapy and local consolidative therapy (LCT) [high-dose RT including stereotactic ablative body RT (SABR) or surgery]

°There are no published data on the impact of LCT on OS and long-term toxicity°These patients should be discussed within a multidisciplinary tumour board and inclusion in clinical trials is preferred

• Although operative risk is low and long-term survival may be obtained, current evidence for surgery in oligometastatic disease is limited and the relative contribution of surgery versus RT as a local treatment modality has not yet been established

• In patients with a solitary lesion in the contralateral lung, radical therapy is recommended and both surgery and SRS are associated with long-term survival

FOLLOW-UP CARE FOR NON-SMALL CELL LUNG CANCER (NSCLC)

Post-Treatment Surveillance:

- Patients who have completed initial treatment (surgery, radiation, or systemic therapy) require a structured follow-up plan to monitor for recurrence, manage side effects, and address any late complications.
- Follow-up care should be individualized based on the stage of cancer, treatment modalities used, and patient's overall health.

Follow-Up Schedule:

- The follow-up schedule typically includes:
- Every 3 to 6 months for the first 2 years.
- Every 6 to 12 months for the next 3 years.
- Annually thereafter, depending on individual risk factors.
- These visits usually include clinical evaluations, imaging studies, and laboratory tests as indicated.

Clinical Evaluation:

- Routine assessments during follow-up visits to monitor any person-reported outcomes, including:
- Symptoms: Addressing any new or recurrent symptoms (such as cough, weight loss, or fatigue).
- Performance Status: Evaluating the patient's ability to perform daily activities and overall functional status.

Imaging and Diagnostic Tests:

- Imaging studies are critical in the follow-up of NSCLC patients and may include:
- Chest X-rays or CT scans at scheduled intervals to assess for signs of recurrence.
- Bone scans or PET scans if there is clinical suspicion of metastasis.
- Tests should be determined based on the initial stage of cancer and the treatment course.

Management of Late Effects:

- Addressing potential long-term side effects of treatment, which may include:
- Respiratory issues due to surgery or radiation.
- Cardiac complications related to certain chemotherapy regimens.
- Management of fatigue, nutritional support, and psychosocial support.

Survivorship Care Plan:

- Development of a personalized survivorship care plan that includes:
- A summary of the cancer diagnosis, treatments received, and recommendations for follow-up care.
- Education on lifestyle modifications such as smoking cessation, dietary changes, and physical activity to reduce recurrence risk.

Psychosocial Support:

- Ensuring ongoing psychosocial support for the patient and family:
- Referrals to counseling services or support groups for emotional and psychological support post-treatment.
- Regular assessments for anxiety, depression, or quality of life using validated screening tools.

PALLIATIVE CARE CONSIDERATIONS:

- Patients with advanced NSCLC may require ongoing palliative support:
- Pain management and symptom relief should be prioritized.
- Coordination with a palliative care team to focus on quality of life, addressing comprehensive needs including physical, emotional, and spiritual aspects.

Regular Assessment of Comorbidities:

- Monitoring and managing any comorbid conditions throughout the follow-up period is essential, particularly respiratory or cardiovascular diseases that may affect overall health and treatment options.

Referral for Specialized Care:

- Patients should have access to specialists such as oncologists, pulmonologists, and other relevant healthcare providers for comprehensive care and management.
- Multidisciplinary team meetings may be employed to strategize optimal patient management plans based on evolving needs.

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