

Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]

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incidence and epidemiology

Primary lung cancer is the most common malignancy after non-melanocytic skin cancer, and the leading cause of human cancer deaths worldwide [1]. While it has been the most important cause of cancer mortality in men since the 1960s, it has equaled breast cancer as a cause of mortality in women since the 1990s. Lung cancer is still increasing both in prevalence and mortality worldwide. In developed countries, the latter has begun to decline in men, reflecting a decrease in smoking, and is reaching a plateau for women in most European countries and in the United States—where lung cancer death rates in women are approaching those of men. Lung cancer deaths in women are expected to increase (+7%) in the EU in 2012 [2].

Non-small-cell lung cancer (NSCLC) accounts for 80–85% of lung cancers, while small-cell lung cancer has been decreasing in frequency over the last two decades.

Smoking is the main cause of lung cancer, responsible for 80% of cases. The observed variations in lung cancer rates across countries largely reflect differences in the stage and degree of the tobacco epidemic, with reported crude incidence rates between 2/100 000–80/100 000 and 1/100 000–39/100 000 for men and women, respectively. There are several other known risk factors including exposure to asbestos, arsenic, radon, and non-tobacco-related polycyclic aromatic hydrocarbons, and interesting hypotheses about indoor air pollution (e.g. coal-fueled stoves and cooking fumes) suspected to contribute to the relatively high burden of non-smoking-related lung cancer in women.

Prevalence of lung cancer in females without a history of tobacco smoking is estimated to represent 19% compared with 9% of male lung carcinoma in the United States [3]. Women

are overrepresented among younger patients, raising the question of gender-specific differences in the susceptibility to lung carcinogens [4]. In recent times, an increase in the proportion of NSCLC patients who are never smokers has been observed, particularly in Asian countries [5]. These new epidemiological data have resulted in 'non-smoking-associated lung cancer' being considered a distinct disease entity, where specific molecular and genetic tumor characteristics are being recognized.

diagnosis

Pathological diagnosis should generally be made according to the World Health Organization (WHO) classification. The International Association for the Study of Lung Cancer (IASLC) classification of adenocarcinoma, however, provides new recommendations and also addresses important issues not covered by the WHO classification concerning small biopsy samples and cytology. Adoption of these recommendations is strongly advised [6]. Specific subtyping of all NSCLC is now necessary for therapeutic decision-making and should be carried out wherever possible. Predictive immunohistochemistry should be used to reduce the NSCLC not otherwise specified (NSCLC-NOS) rate to fewer than 10% of cases diagnosed [6]. Obtaining adequate tissue material for histological diagnosis and molecular testing is important to allow individual treatment decisions. Re-biopsy at disease progression should be considered [7].

Genetic alterations that are key oncogenic events have been identified in NSCLC, with two of these to date offering the chance of selective pathway-directed systemic therapy.

Activating (sensitizing) epidermal growth factor receptor (EGFR) mutations are predictive for response to the EGFR tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib and result, in this context, in an improved response rate (RR) and progression-free survival (PFS) in combination with better tolerability of treatment and a better quality of life (QoL) when compared with chemotherapy as first-line therapy, as demonstrated in several randomized trials. The incidence of

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EGFR mutations in the Caucasian population is ~10% and is higher in never-smokers, the adenocarcinoma subtype, and in women and is also higher in East-Asian patients. An EGFR mutation status should be systematically analyzed—with sequencing as a standard—in advanced NSCLC with a non-squamous histology [II, A]. Testing is not recommended in patients with a confident diagnosis of squamous cell carcinoma, except in never/former light smokers (<15 packs per year) [II, A] [8].

The EML4-ALK fusion gene, resulting from an inversion in chromosome 2, has been identified as an oncogenic driver [9]. It is encountered more frequently in never-smokers, the adenocarcinoma subtype and in younger patients, representing probably ~5% of adenocarcinoma [10]. ALK activity can be efficiently targeted by the TKI crizotinib, and routine testing for ALK rearrangements should be discussed where this drug is available. Testing may focus upon a non-squamous histology and never/former light smokers particularly in the absence of an activating (sensitizing) EGFR mutation or a KRAS mutation [II, A]. However, testing protocols may include smokers and be carried out in parallel with EGFR/KRAS mutation analysis.

Currently, the detection of the translocation by fluorescence in situ hybridization (FISH) is standard, but immunohistochemistry may have a role in screening out negative cases [11].

staging and risk assessment

A complete history including smoking history and comorbidities, weight loss, performance status (PS), and physical examination must be recorded.

Laboratory: Standard tests including routine hematology, renal and hepatic function, and bone biochemistry tests are required. The routine use of serum markers—such as carcinoembryonic antigen (CEA)—is not recommended.

Table 1. Tumor–node–metastasis classification

TX	Positive cytology only
T1	≤3 cm
T1a	≤2 cm
T1b	>2–3 cm
T2	Main bronchus ≥2 cm from carina invades visceral pleura, partial atelectasis
T2a	>3–5 cm
T2b	>5–7 cm
T3	>7 cm; chest wall, diaphragm, pericardium, mediastinal pleura, main bronchus <2 cm from carina, total atelectasis, separate nodule(s) in the same lobe
T4	Mediastinum, heart, great vessels, carina, trachea, esophagus, vertebra; separate tumor nodule(s) in a different ipsilateral lobe
N1	Ipsilateral peribronchial, ipsilateral hilar
N2	Subcarinal, ipsilateral mediastinal
N3	Contralateral mediastinal or hilar, scalene, or supraclavicular
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; pleural nodules or malignant pleural, or pericardial effusion
M1b	Distant metastasis

Table 2. Stage grouping

Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a,b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T1a,b	N1	M0
	T2a	N1	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a,b, T2a,b	N2	M0
	T3	N1, N2	M0
	T4	N0, N1	M0
Stage IIIB	T4	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

radiology

- Contrast-enhanced computed tomography (CT) scan of the chest and upper abdomen.
- Imaging of the central nervous system (CNS) is reserved for patients with neurological symptoms or signs.
- Brain imaging should be performed in patients eligible for a loco-regional treatment. Magnetic resonance imaging (MRI) is more sensitive than CT scan.
- Bone scan or local bone imaging (including MRI) is required in the presence of clinical suspicion of bony lesions not evaluable on CT scan.
- Positron emission tomography (PET) CT scan offers the highest sensitivity for mediastinal lymph nodes and distant metastasis assessment.

NSCLC is staged according to the Union for International Cancer Control (UICC) system (7th edition) and is grouped into the stage categories shown in Tables 1 and 2. Measurement of lesions should follow RECIST criteria v1.1 [12].

In the presence of a solitary metastatic site on imaging studies, including pleural and pericardial effusion, efforts should be made to obtain a cytological or histological confirmation of stage IV disease. An evaluation of resectability or the suitability of radiotherapy with curative intent should be made in the context of a solitary brain or adrenal lesion or oligometastatic disease confined to the lungs. This would include functional cardio-respiratory evaluation, brain imaging, PET and, if needed for decision-making, invasive mediastinal node evaluation.

treatment of stage IV NSCLC

The treatment strategy should take into account the histology, molecular pathology, age, PS, comorbidities, and patient's preferences. Treatment decisions should ideally be discussed within a multidisciplinary tumor board. Systemic therapy should be offered to all stage IV NSCLC patients with a PS 0–2 [I, A].

In any stage of NSCLC, smoking cessation should be highly encouraged because it improves the outcome.

first-line treatment

Platinum-based combination chemotherapy prolongs survival, improves QoL, and controls symptoms in patients with a PS 0–1.

Several regimens have shown comparable efficacy [13]. The expected toxicity profile should contribute to the selection of the chemotherapy regimen, taking into account the following conditions:

- Several meta-analyses have showed higher RRs for cisplatin combinations when compared with carboplatin combinations. The overall survival (OS) was significantly superior for cisplatin in the subgroup of non-squamous tumors and in patients treated with third-generation regimens, including gemcitabine and taxanes in one meta-analysis [I, B] [14]. Cisplatin-based chemotherapy is associated with more digestive, and neuro- and nephrotoxicity; while hematotoxicity is more often observed with carboplatin.
- Pemetrexed is preferred to gemcitabine in patients with non-squamous tumors, based upon a survival benefit demonstrated in a pre-planned subgroup analysis of one large randomized clinical trial [II, B] [15]. Pemetrexed use should be restricted to non-squamous NSCLC in any line of treatment [16, 17].
- According to a randomized clinical trial, bevacizumab improves OS when combined with a paclitaxel–carboplatin regimen in patients with non-squamous histology NSCLC and PS 0–1 and may be offered after the exclusion of contraindications [I, A] [18]. While its addition to gemcitabine–cisplatin improved the RR and PFS, but not the OS in a subsequent phase III trial [19], two meta-analyses showed a consistent substantial improvement of the RR, PFS, and OS for the combination of bevacizumab- and platinum-based chemotherapy compared with platinum-based chemotherapy in eligible patients with non-squamous NSCLC [20, 21]. Therefore, the combination of bevacizumab and other platinum-based chemotherapies may be considered in eligible patients [I, A].
- A randomized phase III trial demonstrated an OS benefit of cetuximab when delivered with vinorelbine–cisplatin in EGFR-expressing NSCLC patients with PS 0–2, independently of histology; however, this did not lead to regulatory approval [I, B] [22]. A subset analysis reported that quantitative evaluation of EGFR expression by immunohistochemistry (H-score) identified a subgroup of patients with high EGFR expressing tumors who selectively benefited from the addition of cetuximab to chemotherapy [23]. Prospective H-score data are, however, lacking.
- Non-platinum-based combination chemotherapy with third-generation agents should be considered only if platinum therapy is contraindicated. Several meta-analyses show lower RRs for non-platinum combinations, with one of them showing inferior survival [24] [I, A].

Timing and duration of palliative first-line treatment: Chemotherapy should be initiated, while the patient has a good PS. For most patients, four cycles of chemotherapy are recommended, notably when maintenance treatment is considered, with a maximum of six cycles [25] [II, B].

PS \geq 2 patients

Chemotherapy prolongs survival and possibly improves QoL [26] in NSCLC patients with a PS of 2, when compared with

best supportive care (BSC) [I, B]. Single-agent chemotherapy with gemcitabine, vinorelbine, and taxanes represents an option [27]. Superiority of carboplatin and paclitaxel combination over monotherapy has been identified in a subgroup analysis within large phase III trials, with an acceptable toxicity profile [28, 29]. A prospective phase III trial randomizing 217 patients between single-agent pemetrexed versus carboplatin and pemetrexed was presented at ASCO 2012, showing a strong benefit in OS for the platinum doublet [30]. Therefore, platinum-based combinations may also be considered as an alternative [II, B].

Poor PS (PS 3–4) patients should be offered BSC [II, B] in the absence of tumors with activating (sensitizing) EGFR mutations.

elderly patients

Two randomized phase III trials established single-agent chemotherapy as the standard of care for first-line therapy for clinically unselected elderly advanced NSCLC patients [27, 31]. A recent prospective randomized trial comparing monthly carboplatin plus weekly paclitaxel versus single-agent vinorelbine or gemcitabine in patients aged 70–89 years with a PS of 0–2 has reported a survival advantage for combination therapy [29].

Benefit was observed across all subgroups, but increased toxicity (notably febrile neutropenia and sepsis-related deaths) was observed. Platinum-based chemotherapy is the preferred option for elderly patients with PS 0–1—as well as selected PS2—and adequate organ function, while a single-agent approach might remain the recommended treatment of elderly unfit or comorbid patients, who are more likely to present with more treatment-related adverse events [I, B].

use of TKIs

First-line treatment with a TKI (erlotinib or gefitinib) should be prescribed to patients with tumors bearing an activating (sensitizing) EGFR mutation because of significantly higher RR, longer PFS, and better QoL when compared with first-line chemotherapy [32, 33] [I, A]. Patients with PS 3–4 may also be offered an EGFR TKI [II, A]. Continuation treatment beyond progression is an issue remaining to be defined. In EGFR wild-type (WT) patients, EGFR TKIs are not recommended as first-line therapy, being inferior to chemotherapy [I, A].

Patients with NSCLC harboring an ALK rearrangement should be considered for crizotinib, a dual ALK and MET TKI, during the course of their disease. Upfront comparisons with chemotherapy are not available to date and the optimal strategy of treatment is still to be determined [34].

brain metastasis treatment

There are several approaches to the treatment of limited-number metastatic brain lesions, including surgery and radiosurgery, alone or in combination with whole-brain radiation therapy (WBRT). WBRT remains standard when local approaches are not possible. Brain responses to chemotherapy have been reported at a comparable level to extracranial disease. The OS was not modified by delaying WBRT after front-line cisplatin-based chemotherapy in a randomized phase III trial [35] [II, B]. In patients with EGFR-mutated NSCLC, the place of WBRT in addition to EGFR TKI, which was shown to result in a response also at the brain level in several reports, remains to be prospectively evaluated [36].

Systemic therapy is therefore a reasonable option for patients with no or relatively minor symptoms from brain metastases with early radiotherapy intervention in the case of the development or progression of symptoms while on treatment [II, B].

maintenance treatment

So-called ‘continuation maintenance’ and ‘switch maintenance’ therapy are terms that have been used to refer respectively to either the use of an agent included in first-line treatment or the introduction of a new agent after completion of platinum-based chemotherapy.

Two recent randomized phase III switch maintenance trials have reported improvements in the PFS and OS with pemetrexed or erlotinib [16, 37] versus placebo following four cycles of platinum-based chemotherapy. In the case of pemetrexed, this benefit was seen only in patients with a non-squamous histology. Subgroup analyses revealed the greatest benefit in efficacy in patients with stable disease (SD) after induction treatment compared with patients with a confirmed response. These results led to a label restriction for switch maintenance with erlotinib in patients with SD after induction treatment [16, 37]. Neither trial addressed the question of the strategy of ‘early second-line’ versus similar second-line treatment at progression. Decisions about maintenance must take into account the histology, response to platinum-doublet chemotherapy, remaining toxicity after first-line chemotherapy, PS, and patient preference [I, B]. Any patient with a tumor bearing an activating (sensitizing) EGFR mutation should receive an EGFR TKI as maintenance, if not received as a first-line therapy [II, A].

Randomized trials investigating continuation maintenance have consistently shown an improvement of the PFS but not the OS [38]. Recently, a large phase III randomized trial of continuation maintenance with pemetrexed versus placebo after four induction cycles of cisplatin plus pemetrexed chemotherapy demonstrated a PFS and OS improvement [39]. Continuing pemetrexed following the completion of first-line cisplatin plus pemetrexed chemotherapy is therefore recommended in patients with a non-squamous histology [40] [I, B].

Of note, two studies employing cetuximab and bevacizumab, administered concomitantly to chemotherapy and further continued as monotherapy until disease progression, have demonstrated survival benefits, but the specific role of the maintenance phase cannot be appreciated in this context [18, 22].

second-line treatment

Patients clinically or radiologically progressing after first-line chemotherapy, irrespective of the administration of maintenance or adjuvant chemotherapy, with a PS 0–2, should be offered second-line chemotherapy. Combination regimens failed to show any benefit over single-agent treatments [41]. Single agents improve disease-related symptoms and survival. Comparable options as the second-line therapy consist of pemetrexed—for a non-squamous histology only [42]—or docetaxel [43] [I, B]. Erlotinib was shown to improve the OS in second-line or in third-line NSCLC patients of all histologies not eligible for further chemotherapy, including patients with PS 3 [44]. Erlotinib was shown to be equivalent to pemetrexed or docetaxel in refractory (progression during the four cycles of

a standard platinum-based chemotherapy doublet) patients in a randomized trial [45] [I, B]. Gefitinib was proved non-inferior to docetaxel in a large randomized trial [46] with a better toxicity profile and QoL. Finally, still unpublished data show a comparable outcome with pemetrexed or erlotinib [47]. Any patient with a tumor bearing an activating (sensitizing) EGFR mutation should receive an EGFR TKI as second-line therapy, if not received previously [I, A].

In the presence of an ALK rearrangement, second–third line treatment with crizotinib should be considered if not received as part of first-line therapy [10, 33], although at present approval of this compound by the European Medicines Agency is still pending.

There is no evidence about the second-line treatment duration, which should be individualized. Notably, treatment may be prolonged if the disease is controlled and the toxicity acceptable [II, B].

subsequent lines of treatment

Patients who progress after second-line chemotherapy may be candidates for further treatment. Evidence is available only for erlotinib, which is indicated for EGFR WT patients who have not yet received EGFR TKIs, with PS 0–3 [II, B].

Any patient with a tumor bearing an activating (sensitizing) EGFR mutation should receive an EGFR TKI in any line of therapy, if not received previously [I, A].

role of minimally invasive procedures in stage IV NSCLC

Endoscopy has a role to play in palliative care, notably in case of symptomatic major airway obstruction or post-obstructive infection, where endoscopic debulking by laser, cryotherapy or stent placement may be helpful [III; C]. Endoscopy is useful in the diagnosis and treatment (endobronchial or by guiding endovascular embolization) of hemoptysis [III; C].

Vascular stenting might be useful in NSCLC-related superior vena cava compression [II; B].

role of palliative surgery in stage IV NSCLC

Recurrent pleural effusions can be managed by pleurodesis. The preferred sclerosing agent is talc, which is more effective than bleomycin or tetracycline [48] [II, B]; thoracoscopic insufflation with talc (poudrage) is more effective than talc slurry sclerosis [49] [II, B].

Surgery might be necessary in case of significant local complications related to the primary tumor or metastasis, like abscess, uncontrolled massive hemoptysis, spinal cord compression, or pathologic bone fracture.

role of radiotherapy

Radiotherapy plays a major role in symptom control in case of bone and brain metastases. It is also effective in treating pain related to chest wall, soft tissue, or neural invasion. Neurological symptoms from spinal compression can be relieved by early radiotherapy. Radiotherapy is indicated in cases of hemoptysis, symptomatic airway compression or obstruction, and following CNS and, sometimes, bone surgery [II; B].

role of bisphosphonate administration

Zoledronic acid reduces skeletal-related events (SREs; pathologic fracture, radiation to or surgery of bone, or spinal cord compression) and is recommended in stage IV bone metastatic disease [50] [II; B].

Denosumab is not inferior [I; A] and shows a trend toward superiority, to zoledronic acid in lung cancer in terms of SRE prevention [51] [II; B].

role of early palliative-care intervention

Early palliative-care intervention is recommended, in parallel with standard oncologic care [I; A]. Evidence demonstrating that palliative-care interventions significantly improve the QoL remains scarce. A randomized trial evaluating the impact of introducing specialized palliative care early after the diagnosis of stage IV disease on the patient's QoL in ambulatory patients was able to show an improvement in the QoL and mood, a reduction in aggressive treatment, and an improvement in median survival [52].

response evaluation

Response evaluation is recommended after two to three cycles of chemotherapy using the same initial radiographic investigation that demonstrated tumor lesions. Follow-up with PET is not routinely recommended, due to its high sensitivity and relatively low specificity. Measurements and response reporting should follow RECIST 1.1 criteria [12]. However, the adequacy of RECIST in evaluating the response to EGFR or ALK TKI in respective genetically driven NSCLCs is debatable.

treatment of oligometastatic NSCLC

Stage IV NSCLC patients presenting with solitary metastases, if localized to brain, adrenals, or lung, can be treated with curative intent. This requires individual assessment, taking into account the timing of appearance of metastasis relative to the primary tumor (metachronous being of better prognosis than

synchronous disease [53]), patient PS and comorbidities, as well as local extension of the primary tumor.

- In the case of solitary brain metastasis, surgical resection followed by WBRT or alternatively radiosurgery with or without WBRT might be beneficial. WBRT after surgery prolongs the OS [II; A] [54], while this benefit was not reproduced after radiosurgery [55] [II; B]. Radiosurgery combined with WBRT is superior to WBRT alone in patients presenting with up to three brain metastases [56]. Further treatment options include surgical resection of lung primary tumor combined with systemic chemotherapy [II; B], or definitive chemoradiotherapy, preferred in the case of locally advanced primary, such as solitary station N2 disease [57] [III; B].
- In cases of solitary—histological proven—adrenal metastasis, prolonged survival after resection of adrenal and the primary tumor has been suggested in selected patients [II; B] [58].
- Solitary lesions in the contralateral lung should, in most cases, be considered as synchronous secondary primary tumors, and treated, if possible, with surgery and adjuvant chemotherapy if indicated, definitive radiotherapy or chemoradiotherapy [II;A].

follow-up

The optimal approach to post-treatment management of patients with NSCLC, including the role of radiological evaluation, is controversial, with very limited literature available.

Owing to the aggressive nature of this disease, generally close follow-up, at least every 6 weeks after the first-line therapy, is advised but should also depend on individual re-treatment options [III; B]. Given the clear benefits of second-line therapy in patients who presented an initial response to first-line chemotherapy and maintain a good PS, radiological follow-up should be considered every 6–12 weeks to allow for an early initiation of second-line therapy.

note

Summary of recommendations is provided in Table 3.

Table 3. Summary of recommendations

Topic	Recommendations
Diagnosis	<ul style="list-style-type: none"> • Pathological diagnosis should be made according to the WHO classification and the IASLC classification of adenocarcinoma. • Specific subtyping of all NSCLCs is necessary for therapeutic decision-making and should be carried out wherever possible. • Predictive immunohistochemistry should be used to reduce the NSCLC-NOS rate to fewer than 10% of cases diagnosed. • Adequate tissue material for histological diagnosis and molecular testing should be obtained to allow individual treatment decisions. • Re-biopsy at disease progression should be considered. • EGFR mutation status should be systematically analyzed—with sequencing as a standard—in advanced NSCLC with a non-squamous histology [II, A]. • Testing is not recommended in patients with a confident diagnosis of squamous cell carcinoma, except in never/former light smokers (<15 packs per year) [II, A]. • ALK activity can be efficiently targeted by the TKI crizotinib, and routine testing for ALK rearrangements should be discussed where this drug is available. • Testing may focus upon a non-squamous histology and never/former light smokers especially in the absence of an activating (sensitizing) EGFR mutation or a KRAS mutation [II, A]. • Detection of the translocation by FISH is standard, but immunohistochemistry may have a role in screening out negative cases.

Continued

Table 3. Continued

Topic	Recommendations
Staging and risk assessment	<ul style="list-style-type: none"> • A complete history including smoking history and comorbidities, weight loss, PS and physical examination must be recorded. • Laboratory: standard tests including routine hematology, renal and hepatic function, and bone biochemistry tests are required. Routine use of serum markers—such as CEA—is not recommended. • Contrast-enhanced CT scan of the chest and upper abdomen should be performed. • Imaging of CNS is reserved for patients with neurological symptoms or signs. • Brain imaging should be performed in patients eligible for a loco-regional treatment. Magnetic resonance imaging (MRI) is more sensitive than CT scan. • Bone scan or local bone imaging is required in the presence of clinical suspicion of bony lesions not evaluable on a CT scan. • PET CT scan offers the highest sensitivity and is advised for mediastinal lymph nodes and distant metastasis assessment. • NSCLC is staged according to the UICC system (7th edition) and is grouped into the stage categories shown in Tables 1 and 2. Measurement of lesions should follow RECIST criteria v1.1. • In the presence of a solitary metastatic site on imaging studies, efforts should be made to obtain a cytological or histological confirmation of stage IV disease. • An evaluation of resectability or the suitability of radiotherapy with curative intent should be made in the context of a solitary brain or adrenal lesion or oligometastatic disease confined to the lungs: cardio-respiratory evaluation, brain imaging, PET and, if needed for decision-making, invasive mediastinal node evaluation.
Treatment strategy	<ul style="list-style-type: none"> • The treatment strategy should take into account the histology, molecular pathology, age, PS, comorbidities, and patient's preferences. • Treatment decisions should be discussed within a multidisciplinary tumor board. • Systemic therapy should be offered to all stage IV patients with PS 0–2 [I, A]. • In any stage of NSCLC, smoking cessation should be highly encouraged because it improves the outcome.
First-line treatment	<ul style="list-style-type: none"> • In the subgroup of non-squamous tumors and in patients treated with third-generation regimens, including gemcitabine and taxanes, cisplatin should be the treatment of choice [I, B]. • Pemetrexed is preferred to gemcitabine in patients with non-squamous tumors [II, B]. Pemetrexed use should be restricted to non-squamous NSCLC in any line of treatment. • Bevacizumab combined with a paclitaxel–carboplatin regimen may be offered to patients with non-squamous histology NSCLC and PS0–1 after exclusion of contraindications [I, A]. • The combination of bevacizumab and other platinum based chemotherapies may be considered in eligible patients with non-squamous NSCLC [I, A]. • Non-platinum-based combination chemotherapy with third-generation agents should be considered only if platinum therapy is contraindicated [I, A]. • The timing and duration of palliative first-line treatment: chemotherapy should be initiated while the patient has a good PS. For most patients, four cycles of chemotherapy are recommended, with a maximum of six cycles [II, B]. <p>PS ≥ 2 patients:</p> <ul style="list-style-type: none"> • Chemotherapy prolongs survival and possibly improves the QoL in NSCLC patients with a PS of 2, when compared with BSC [I, B]. Single-agent chemotherapy with gemcitabine, vinorelbine, and taxanes represents an option. Platinum-based combinations may also be considered as an alternative [II, B]. • Poor PS (3–4) patients should be offered best supportive care [II, B] in the absence of tumors with activating (sensitizing) EGFR mutations. <p>Elderly patients:</p> <ul style="list-style-type: none"> • Single-agent chemotherapy is the standard of care for first-line therapy for clinically unselected elderly advanced NSCLC patients. • A survival advantage has been seen for combination therapy in patients aged 70–89 with PS0–2. • Platinum-based chemotherapy is the preferred option for elderly patients with PS 0–1—as well as selected PS2—and adequate organ function. A single-agent approach might remain the recommended treatment of elderly unfit or comorbid patients who are more likely to present with more treatment-related adverse events [I, B]. <p>Use of TKIs:</p> <ul style="list-style-type: none"> • First-line treatment with a TKI (erlotinib or gefitinib) should be prescribed to patients with tumors bearing an activating (sensitizing) EGFR mutation [I, A]. • Patients with EGFR mutation and PS 3–4 may also be offered an EGFR TKI [II, A]. • In EGFR WT patients, EGFR TKIs are not recommended as first-line therapy, being inferior to chemotherapy [I, A]. • Patients with NSCLC harboring an ALK rearrangement should be considered for crizotinib, a dual ALK and MET TKI, during the course of their disease.

Continued

Table 3. Continued

Topic	Recommendations
	Brain metastases treatment: <ul style="list-style-type: none"> • WBRT remains the standard treatment of limited-number metastatic brain lesions when local approaches are not possible. • Delaying WBRT after front-line cisplatin-based chemotherapy does not modify the OS according to a randomized phase III trial. • Systemic therapy is a reasonable option for patients with no or relatively minor symptoms from brain metastases with early radiotherapy intervention in the case of the development or progression of symptoms while on treatment [II, B].
Maintenance treatment	<ul style="list-style-type: none"> • In patients with a non-squamous histology, improvements in PFS and OS were observed with pemetrexed switch maintenance versus placebo following four cycles of platinum-based chemotherapy. • Switch maintenance with erlotinib versus placebo demonstrated PFS and OS benefit in all histologies, with a greatest benefit in efficacy in patients with stable disease (SD) after induction treatment leading to a label restriction for such patients. • Decisions about maintenance must take into account the histology, response to platinum-doublet chemotherapy, remaining toxicity after first-line chemotherapy, PS, and patient preference [I, B]. • Any patient with a tumor bearing an activating (sensitizing) EGFR mutation should receive an EGFR TKI as maintenance, if not received as the first-line therapy [II, A]. • Continuing pemetrexed following completion of first-line cisplatin plus pemetrexed chemotherapy is recommended in patients with a non-squamous histology [I, B].
Second-line treatment	<ul style="list-style-type: none"> • Patients clinically or radiologically progressing after first-line chemotherapy with PS 0–2 should be offered second-line chemotherapy. • Comparable options as the second-line therapy consist of pemetrexed—for a non-squamous histology only—or docetaxel [I, B]. Erlotinib is an additional option in EGFR WT patients with PS 0–3 [II, B]. • Any patient with a tumor bearing an activating (sensitizing) EGFR mutation should receive an EGFR TKI as the second-line therapy, if not received previously [I, A]. • Treatment may be prolonged if the disease is controlled and the toxicity acceptable [II, B].
Subsequent lines of treatment	<ul style="list-style-type: none"> • Erlotinib is indicated for EGFR WT patients who have not yet received EGFR TKIs, with PS 0–3 [II, B]. • Any patient with a tumor bearing an activating (sensitizing) EGFR mutation should receive an EGFR TKI in any line of therapy, if not received previously [I, A].
Role of minimally-invasive procedures in stage IV NSCLC	<ul style="list-style-type: none"> • In case of symptomatic major airway obstruction or post-obstructive infection, endoscopic debulking by laser, cryotherapy, or stent placement may be helpful [III; C]. • Endoscopy is useful in the diagnosis and treatment (endobronchial or by guiding endovascular embolization) of hemoptysis [III; C]. • Vascular stenting might be useful in NSCLC-related superior vena cava compression [II; B].
Role of palliative surgery in stage IV NSCLC	<ul style="list-style-type: none"> • Recurrent pleural effusions can be managed by pleurodesis. • The preferred sclerosing agent is talc, which is more effective than bleomycin or tetracycline [II, B]; thoroscopic insufflation with talc (poudrage) is more effective than talc slurry sclerosis [II, B].
Role of radiotherapy	<ul style="list-style-type: none"> • Radiotherapy plays a major role in symptom control in the case of bone and brain metastases and is also effective in treating pain related to chest wall, soft tissue, or neural invasion. • Neurological symptoms from spinal compression can be relieved by early radiotherapy. • Radiotherapy is indicated in cases of hemoptysis, symptomatic airway compression or obstruction, and following CNS and, sometimes, bone surgery [II; B].
Role of bisphosphonate administration	<ul style="list-style-type: none"> • Zoledronic acid reduces SRE (pathologic fracture, radiation/surgery to bone, or spinal cord compression) and is recommended in stage IV bone metastatic disease [II; B]. • Denosumab is not inferior [I; A], and shows a trend toward superiority, to zoledronic acid in lung cancer in terms of SRE prevention [II; B].
Role of palliative-care early intervention	Early palliative-care intervention is recommended, in parallel with standard oncologic care [I; A].
Response evaluation	<ul style="list-style-type: none"> • Response evaluation is recommended after two to three cycles of chemotherapy using the same initial radiographic investigation which demonstrated tumor lesions. • Follow-up with PET is not routinely recommended, due to its high sensitivity and relatively low specificity. • Measurements and response reporting should follow RECIST 1.1 criteria. However, the adequacy of RECIST in evaluating the response to EGFR or ALK TKI in respective genetically driven NSCLC is debatable.

Continued

Table 3. Continued

Topic	Recommendations
Treatment of oligometastatic NSCLC	<ul style="list-style-type: none"> • Stage IV NSCLC patients presenting with solitary metastases, if localized to brain, adrenals, or lung, can be treated with curative intent. • In the case of solitary brain metastasis, surgical resection followed by WBRT or alternatively radiosurgery ± WBRT might be beneficial. Further options include surgical resection of the primary lung combined with systemic chemotherapy [II; B], or definitive chemoradiotherapy, preferred in the case of locally advanced primary, such as solitary station N2 disease [III; B]. • In cases of solitary—histological proven—adrenal metastasis, prolonged survival after resection of the adrenal and the primary tumor has been suggested in selected patients [II; B]. • Solitary lesions in the contralateral lung should, in most cases, be considered as synchronous secondary primary tumors and treated, if possible, with surgery and adjuvant chemotherapy (if indicated), definitive radiotherapy or chemoradiotherapy [II;A].
Follow-up	<ul style="list-style-type: none"> • Close follow-up, at least every 6 weeks after first-line therapy, is advised but should depend on individual retreatment options [III; B]. • Radiological follow-up should be considered every 6–12 weeks to allow for early initiation of second-line therapy.

IASLC, International Association for the Study of Lung Cancer; WHO, World Health Organization; NSCLC, non-small-cell lung cancer; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; PS, performance status; CT, computed tomography; CNS, central nervous system; MRI, magnetic resonance imaging; PET, positron emission tomography; QoL, quality of life; BSC, best supportive care; WT, wild-type; OS, overall survival; SRE, skeletal-related event; WBRT, whole-brain radiation therapy; NSCLC-NOS; NSCLC not otherwise specified.

conflict of interest

Dr. Felip has reported: consultancy/honoraria: Lilly, GlaxoSmithKline, Merck Serono, Roche, Boehringer Ingelheim. Dr. Gridelli has reported: honoraria for speakers' bureau and advisory board for Eli Lilly and Roche. Dr. Reck has reported: compensated advisory board for Hoffmann-La Roche, Lilly, AstraZeneca, Bristol-Myers Squibb, Daiichi-Sankyo; honoraria for lectures: Hoffmann-La Roche, Lilly, AstraZeneca, Daiichi-Sankyo. Prof. Kerr has reported: speakers' bureau and consultant for Eli Lilly, Roche, AstraZeneca, Daiichi Sankyo, Abbott, Pfizer, Boehringer Ingelheim, Bayer, Merck Serono and GlaxoSmithKline. Dr. Peters has reported: consultancy/honoraria, advisory boards and/or lectures for F. Hoffmann–La Roche, Ltd., Eli Lilly, AstraZeneca, Pfizer, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, and Merck Serono.

Dr. Adjei has reported no potential conflicts of interest.

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