

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

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Incidence and epidemiology

Primary lung cancer remains the most common malignancy after non-melanocytic skin cancer, and deaths from lung cancer exceed those from any other malignancy worldwide [1].

In 2012, lung cancer was the most frequently diagnosed cancer and the leading cause of cancer death in male populations. Among females, lung cancer was the leading cause of cancer death in more developed countries, and the second leading cause of cancer death in less developed countries [2]. In 2013 in the European Union, lung cancer mortality fell in men by 6% compared with 2009, while cancer death rates increased in women by 7%, thereby approaching male counterparts [3].

A significantly higher proportion of lung cancer is diagnosed in patients aged 65 and over [4], and the median age at diagnosis is around 70 years [5]. Data from 2012 revealed that in the USA, lung cancer did represent the leading cause of cancer death in males from the age of 40 years and in females from the age of 60 years [6]. A subset of patients with non-small-cell lung cancers (NSCLCs) presents at a younger age (<40 years), but the incidence in this population has decreased in the USA from 1978 to 2010 [7].

The number of cancer deaths expected to occur in 2016 in the USA has been estimated, still reporting lung cancer as the leading cause of death in both genders, despite declines in lung

cancer incidence from the mid-1980s in men and in the mid-2000s in women [6].

NSCLCs account for 85%–90% of lung cancers, while small-cell lung cancer (SCLC) has been decreasing in frequency in many countries over the past two decades [1]. During the last 25 years, the distribution of histological types of NSCLC has changed: in the USA, squamous cell carcinoma (SCC, which was formally the predominant histotype) decreased, while adenocarcinoma has increased in both genders. In Europe, similar trends have occurred in men, while in women, both SCC and adenocarcinoma are still increasing [8].

Tobacco smoking is still the main cause of lung cancer in most of the patients, and the geographic and temporal patterns of the disease largely reflect tobacco consumption during the previous decades. Both smoking prevention and smoking cessation can lead to a reduction in a large fraction of human cancers. In countries with effective tobacco control measures, the incidence of new lung cancer has begun to decline in men and is reaching a plateau for women [3, 9, 10]. Several other factors have been described, including exposure to asbestos, arsenic, radon and non-tobacco-related polycyclic aromatic hydrocarbons. There is evidence that lung cancer rates are higher in cities than in rural settings, but many confounding factors other than outdoor air pollution may be responsible for this pattern. Interesting hypotheses about indoor air pollution (e.g. coal-fuelled stoves and cooking fumes) are available, showing a correlation with the relatively high burden of non-smoking-related lung cancer in women in some countries [11]. Evidence for a genetic predisposition to lung cancer has been difficult to establish as it is confounded by environmental exposures, but there are emerging data suggesting that single-

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nucleotide polymorphisms in genes in certain loci—15q24-25 (*CHRNA3*, *CHRNA5*, *CHRNAB4*), 6p21.33, 5p15.23—have some association with lung cancer risk [12, 13].

The World Health Organization (WHO) estimates that lung cancer is the cause of 1.37 million deaths globally per year. An estimated 71% of these deaths are caused by smoking, indicating that ~400 000 deaths annually are attributed to lung cancer in lifetime never smokers [1]. 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 USA [14, 15]. Especially in Asian countries, an increase in the proportion of NSCLC in never smokers has been observed [16]. These new epidemiological data have resulted in ‘non-smoking-associated lung cancer’ being considered a distinct disease entity, where specific molecular and genetic tumour characteristics have been identified [17]. However, other clinical series do not report differences by sex after adjusting for age and for the higher number of women >60 years who do not smoke compared with men. This could justify the different incidence, which may not be due to a real difference among genders specifically.

diagnosis and personalised medicine

Pathological diagnosis of all sample types should be made according to the 2015 WHO classification. The classification discusses the approach to surgically resected tumours, but also has recommendations for small biopsy and cytology diagnosis, which are the only samples available for most patients. Therapeutic decisions for NSCLC patients are dependent upon specific tumour histological subtype, and this should be given whenever possible. Immunohistochemistry (IHC) should be used to increase the specificity of diagnosis in the small sample setting and reduce the NSCLC-NOS (not otherwise specified) rate to fewer than 10% of cases diagnosed [IV, A] [18]. Minimal IHC should be used. Two markers only, p40 or p63 to predict squamous cell carcinoma and TTF1 to predict adenocarcinoma, are generally all that is required [18]. Excessive, unnecessary IHC will consume tumour tissue and may prevent subsequent molecular analysis. Obtaining adequate tissue material for histological diagnosis and molecular testing is important, to allow for individual treatment decisions. Tumour rebiopsy at disease

progression should be considered and is recommended in the subgroups where it might guide subsequent treatment [IV, A]. An example is the use of third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) against T790M-mutated resistant tumours, the most common finding in EGFR-mutated tumours relapsing after first-/second-generation EGFR TKI therapy [19]. Pathologists should take steps to ensure that tissue handling and processing prioritises all testing required for treatment selection.

Genetic alterations, which are key oncogenic events (driver mutations), have been identified in NSCLC, with two of these—EGFR mutations and the anaplastic lymphoma kinase (ALK) rearrangements—determining approved, selective pathway-directed systemic therapy. A personalised medicine synopsis table is shown in Table 1.

Activating (sensitising) EGFR mutations are predictive for response to the EGFR TKIs gefitinib, erlotinib and afatinib. Such treatments result in improved response rate (RR) and progression-free survival (PFS), better tolerability and superior quality of life (QoL) compared with platinum-based chemotherapy in the first-line setting, as demonstrated in several randomised trials [21]. EGFR mutations are found in ~10%–12% of Caucasians with adenocarcinoma and are more frequent in never smokers, females and in patients of East Asian ethnicity. EGFR mutation testing is recommended in all patients with advanced non-squamous cell carcinoma (NSCC) [I, A] [20]. Molecular EGFR testing is not recommended in patients with an unequivocal diagnosis of SCC, except in never/former light smokers (<15 pack years) [IV, A] [22]. EGFR mutation testing should use validated methodology in a laboratory participating in an external quality assurance scheme in all such patient subgroups. The methodology used should provide the test sensitivity required for the tumour content of the sample and provide an adequate coverage of all clinically relevant mutations. Test methodology should have adequate coverage of mutations in exons 18–21, including those associated with specific drug resistance. At a minimum, when resources or material are limited, the most common activating mutations (exon 19 deletion and exon 21 L858R point mutation, including exon 20 T790M) should be determined [I, A].

ALK fusion is encountered more frequently, but not exclusively, in never smokers, adenocarcinoma subtype and in

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Table 1. A personalised medicine synopsis table for metastatic NSCLC [20]

Biomarker	Method	Use	LOE, GOR
EGFR mutation	Any appropriate validated method, subject to external quality assurance	Used to select patients for EGFR TKI therapy, identifying those, with sensitising mutations, most likely to respond	V, A
ALK gene rearrangement	Any appropriate validated method, subject to external quality assurance. Standard approach has been FISH, or less often, multiplex PCR or RT-PCR. Certain IHC approaches may be used as a substitute primary test. IHC may also be used to screen patients, positive cases confirmed by an orthogonal method (FISH, PCR)	Used to select patients for ALK tyrosine kinase inhibitor therapy, identifying those, with a positive test, most likely to respond	V, A

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NSCLC, non-small-cell lung cancer; LOE, level of evidence; GOR, grade of recommendation; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; ALK, anaplastic lymphoma kinase; FISH, fluorescence *in situ* hybridisation; PCR, polymerase chain reaction; RT-PCR, reverse transcription polymerase chain reaction; IHC, immunohistochemistry.

younger patients, with a prevalence of around 5% in adenocarcinomas [23, 24]. ALK TKIs are effective therapies, and routine testing for ALK rearrangements is recommended in the same patient groups tested for EGFR mutations, principally those with NSCC [II, A]. As ALK TKIs are now approved for first-line therapy, ALK and EGFR testing should be carried out simultaneously [25]. The break-apart fluorescence *in situ* hybridisation (FISH) test remains a core approach to detect ALK rearrangements. Multiplex polymerase chain reaction (PCR) may be successful but requires an adequate coverage of the many possible fusion genes now recognised and is challenged by the availability of adequate quality of nucleic acid from the tumour, and by validation of the methodology itself. IHC has a high positive and negative predictive value for ALK fusion. It is widely used to screen patients for possible confirmatory ALK FISH testing but is rapidly being adopted in Europe as the primary test for prescribing ALK TKIs. Similar approaches may be taken for ROS1 fusion gene testing in those centres with access to drugs active in this setting.

Next-generation sequencing (NGS) is also used by many centres to facilitate testing for multiple gene mutations, as well as (less frequently) for gene fusions involving ALK, RET and ROS1 [III, A]. NGS testing panels will also provide data on HER2, BRAF and MET mutations, for example, which may allow access to targeted treatment in late lines of therapy, often in the context of a clinical trial, and, in addition, with a significant survival outcome [26–28].

FISH quantitative analysis might allow for the documentation of MET gene amplification, another strong tumour driver, allowing for MET-directed therapy, mainly in the context of clinical trials.

Apart from a pivotal role in the subtyping of poorly differentiated NSCLC in small samples, in ALK testing and probably also in ROS1 testing [29, 30], IHC is emerging as a useful tool in lung cancer diagnostics in other settings, including rapid screening for EGFR and BRAF mutations. The use of programmed death ligand 1 (PD-L1) IHC for selecting patients for anti-programmed death 1 (PD1) or anti-PD-L1 immunotherapy is controversial, and is not yet considered as harbouring a sufficient negative predictive value for checkpoint inhibitor-related treatment decisions. It is, however, likely to emerge as a requirement for selected patients, at least in some treatment contexts to be defined in ongoing clinical trials.

staging and risk assessment

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

laboratory

Standard tests including routine haematology, renal and hepatic function, and bone biochemistry tests are required. The routine use of serum markers, such as carcinoembryonic antigen (CEA), is not recommended [31].

radiology

A contrast-enhanced computed tomography (CT) scan of the chest and upper abdomen including complete assessment of

liver, kidneys and adrenal glands should be carried out. Imaging of the central nervous system (CNS) is most relevant in those patients with neurological symptoms or signs, however, if available, imaging of the CNS with magnetic resonance imaging (MRI, preferably with gadolinium enhancement) or CT brain with iodine contrast should be carried out at diagnosis. MRI is more sensitive than CT scan [32].

If metastatic disease has been determined by CT scan of the chest and upper abdomen or by brain imaging, other imaging is only necessary if it has an impact on treatment strategy.

If bone metastases are clinically suspected, bone imaging is required. Positron emission tomography (PET), ideally coupled with CT, and bone scans are helpful for the systemic screening for bone metastasis. PET/CT is the most sensitive modality in detecting bone metastasis [33]. Fluorodeoxyglucose (FDG)-PET or PET/CT has higher sensitivity and specificity than bone scintigraphy [34]. MRI can be useful to document and characterise a localised bone metastasis.

FDG-PET/CT scan offers the highest sensitivity for mediastinal lymph nodes [35] and distant metastasis assessment.

NSCLC is staged according to the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) system (7th edition) and is grouped into the stage categories shown in Tables 2 and 3. Measurement of lesions should follow Response Evaluation Criteria in Solid Tumours (RECIST) criteria v1.1 [36].

In the presence of a solitary metastatic lesion on imaging studies, including pleural and pericardial effusion, efforts should be made to obtain a cytological or histological confirmation of stage IV disease.

A proposal for an eighth staging edition has been made by the International Association for the Study of Lung Cancer (IASLC) and will be submitted to the UICC and the AJCC for inclusion in the new TNM classification for lung cancer, which is due to be published in late 2016 and enacted in January 2017 [37].

management of advanced/metastatic disease

The treatment strategy (Figures 1–4) should take into account factors like histology, molecular pathology, age, PS, comorbidities and the patient's preferences. Treatment decisions should ideally be discussed within a multidisciplinary tumour board, who can evaluate and change management plans including recommending additional investigations and changes in treatment modality [38]. 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 outcome and because smoking may interact with systemic therapy [II, A] [39]; for example, smoking reduces erlotinib bioavailability [40]. Given the established relationship between smoking and lung cancer, patients who have smoked may feel stigmatised or guilty after diagnosis and more pessimistic about their illness and likely outcomes, all of which may have adverse implications for health-related QoL [41]. For these reasons, healthcare professionals should give clear advice about the adverse implications of continued smoking and include smoking cessation programmes in the therapeutic algorithm.

Table 2. AJCC/UICC TNM staging system

Primary tumour (T)	
TX	Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualised by imaging or bronchoscopy
T0	No evidence of primary tumour
Tis	Carcinoma <i>in situ</i>
T1	Tumour 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e. not in the main bronchus) ^a
T1a	Tumour 2 cm or less in greatest dimension
T1b	Tumour >2 cm but 3 cm or less in greatest dimension
T2	Tumour >3 cm but 7 cm or less or tumour with any of the following features (T2 tumours with these features are classified T2a if 5 cm or less); involves main bronchus, 2 cm or more distal to the carina; invades visceral pleura (PL1 or PL2); associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumour >3 cm but 5 cm or less in greatest dimension
T2b	Tumour >5 cm but 7 cm or less in greatest dimension
T3	Tumour >7 cm or one that directly invades any of the following: parietal pleural (PL3) chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium or tumour in the main bronchus (<2 cm distal to the carina ^a but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumour nodule(s) in the same lobe)
T4	Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina, separate tumour nodule(s) in a different ipsilateral lobe
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumour nodule(s) in a contralateral tumour with pleural nodules or malignant pleural (or pericardial) effusion ^b
M1b	Distant metastasis

AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control; TNM, tumour-node-metastasis. Used with the permission of the AJCC, Chicago, IL, USA. The original source for this material is the AJCC Cancer Staging Handbook, 7th edition (2010) published by Springer Science and Business Media LLC, www.springerlink.com [183].

^aThe uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.

^bMost pleural (and pericardial) effusions with lung cancer are due to tumour. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumour, and the fluid is non-bloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging element and the patient should be classified as M0.

first-line treatment of EGFR and ALK-negative disease

Chemotherapy with platinum doublets should be considered in all stage IV NSCLC patients with EGFR- and ALK-negative disease, without major comorbidities and PS 0-2 [I, A]. Benefits of chemotherapy versus best supportive care (BSC, namely a 23% reduction of risk of death, a 1-year survival gain of 9% and 1.5-month absolute increase in median survival and improved QoL) are observed irrespective of age, sex, histology and PS in two meta-analyses [42, 43]. The survival benefit of two-agent over one-agent chemotherapy regimens was reported in a meta-analysis in 2004, with no survival benefit seen for three-agent over two-agent regimens [44]. Based on a 2006 meta-analysis, revealing a statistically significant reduction (equal to 22%) in

the risk of death at 1 year for platinum over non-platinum combinations, without induction of unacceptable increase in toxicity, platinum-based doublets are recommended in all patients with no contraindications to platinum compounds [I, A] [45]. Neither a large individual trial nor a meta-analysis found an overall survival (OS) benefit of six versus fewer cycles of first-line platinum-based doublets, although a longer PFS coupled with significantly higher toxicity was reported in patients receiving six cycles [46, 47]. Therefore, four cycles of platinum-based doublets followed by less toxic maintenance monotherapy, or four up to a maximum of six cycles in patients not suitable for maintenance monotherapy, are currently recommended [I, A].

Several platinum-based regimens with third-generation cytotoxics (cisplatin/paclitaxel, cisplatin/gemcitabine, cisplatin/

Table 3. Anatomic stage/prognostic groups according to the AJCC/UICC TNM staging system

Anatomic stage/prognostic groups			
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

AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control; TNM, tumour-node-metastasis. Used with the permission of the AJCC, Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Handbook, 7th edition (2010) published by Springer Science and Business Media LLC, www.springerlink.com [183].

docetaxel, carboplatin/paclitaxel) have shown comparable efficacy [48].

The expected toxicity profile should contribute to the selection of the chemotherapy regimen, taking into account that:

- Meta-analyses have shown higher RRs for cisplatin combinations compared with carboplatin combinations.
- One meta-analysis from individual patient data has shown slightly longer OS for cisplatin-based versus carboplatin-based doublet in patients with NSCC and treated with third-generation regimens [I, B] [49].
- Cisplatin-based chemotherapy is associated with more gastrointestinal, neuro- and nephrotoxicity, while bone marrow toxicity is more common with carboplatin.
- The albumin-bound paclitaxel (nab-paclitaxel)/carboplatin (nab-PC) regimen has been shown in a large phase 3 trial to have a significantly higher RR compared with the solvent-based paclitaxel/carboplatin (sb-PC) and less neurotoxicity [I, B] [50]. The benefits were observed in both SCC and NSCC, with a larger impact on response in SCC. Median OS was 12.1 months [95% confidence interval (CI): 10.8–12.9 months] in the nab-PC arm compared with 11.2 months (95% CI: 10.3–12.6 months) in the sb-PC arm. For this reason, the nab-PC regimen could be considered a chemotherapeutic option in advanced NSCLC patients, particularly in patients with greater risk of neurotoxicity, pre-existing hypersensitivity to paclitaxel or contraindications for standard paclitaxel premedication [I, B].

first-line treatment of SCC. Most individual trials and meta-analyses evaluating chemotherapy options in the first-line treatment of advanced NSCLC did not report any differential efficacy in patients with SCC [43]. Therefore, 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 [I, A].

Necitumumab, an immunoglobulin G1 (IgG1) monoclonal antibody against EGFR, did not show any evidence that its addition to cisplatin/pemetrexed is able to increase survival in first-line treatment of metastatic NSCC [51]. However, outcomes were different when necitumumab was combined with different chemotherapy regimens in SCC. In the SQUIRE trial, the addition of necitumumab to cisplatin/gemcitabine produced a significant OS improvement [11.5 versus 9.9 months, hazard ratio (HR) 0.84, 95% CI: 0.74–0.96; $P=0.01$] and PFS improvement, with a 1-year survival equal to 48% in the experimental arm versus 43% in the control arm [52]. In a retrospective analysis, tumours without EGFR expression as assessed by IHC, did not show any benefit from the addition of necitumumab. This improvement in OS and PFS was more pronounced in the group of patients with EGFR-expressing tumours (median OS 11.7 months versus 10.0 months; HR 0.79, 95% CI: 0.69–0.92; $P=0.002$; median PFS 5.7 months versus 5.5 months, HR 0.84, 95% CI: 0.72–0.92; $P=0.018$) [53]. On the basis of these results, necitumumab plus gemcitabine and cisplatin represents a new first-line treatment option for advanced SCC expressing EGFR by IHC [I, B; ESMO-MCBS (Magnitude of Clinical Benefit Scale) v1.0 score: 1].

first-line treatment of NSCC. Any platinum-based doublets with a third-generation agent including gemcitabine, vinorelbine or taxanes can be used in NSCC. The incorporation of pemetrexed and bevacizumab into individual treatment schedules should be considered based on the following:

- Pemetrexed-based combination chemotherapy represents a therapeutic option, based on the results of a recent meta-analysis that showed a slight but significant survival benefit compared with gemcitabine- or docetaxel-based combinations and of a pre-planned subgroup analysis of a large randomised phase III trial [II, A] [54, 55]. Pemetrexed use should be restricted to NSCC in any line of treatment in advanced disease [I, A] [56, 57].
- The survival benefit of carboplatin in combination with pemetrexed has been investigated in a meta-analysis (exploratory subgroup analysis); survival benefit for pemetrexed plus platinum held true for cisplatin-containing regimens but not for carboplatin-based regimens [54]; however, results from prospective randomised studies investigating this question are not yet available.
- Findings of two randomised clinical trials revealed that bevacizumab improves OS when combined with paclitaxel/carboplatin regimens in patients with NSCC and PS 0-1, and, therefore, may be offered in the absence of contraindications in eligible patients with advanced NSCC [I, A] [58, 59]. While one trial of non-taxane, gemcitabine/cisplatin combination with or without bevacizumab demonstrated an objective RR (ORR) and modest PFS advantage, but no OS benefit [60], two meta-analyses showed a consistent significant improvement of RR, PFS and OS for the combination of bevacizumab and platinum-based chemotherapy, compared with platinum-based chemotherapy alone in eligible patients with NSCC [61, 62]. Treatment with bevacizumab also delayed the incidence of brain metastases in a retrospective analysis [63].

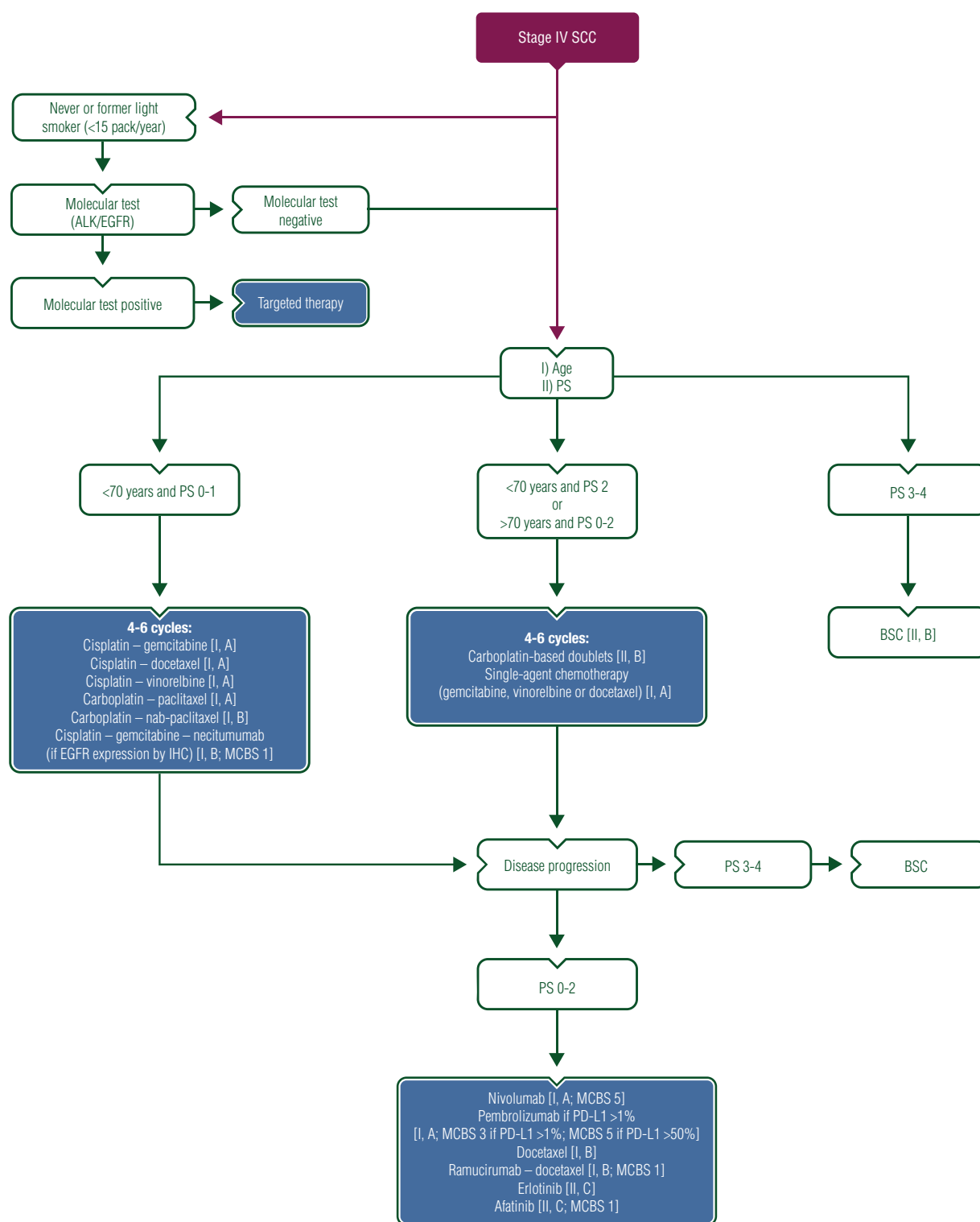


Figure 1. Treatment algorithm for stage IV SCC. SCC, squamous cell carcinoma; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; PS, performance status; IHC, immunohistochemistry; BSC, best supportive care; MCBS, Magnitude of Clinical Benefit Scale.

performance status 2 and beyond

Chemotherapy prolongs survival and improves QoL in NSCLC patients with PS 2 compared with BSC [I, B] [64].

A recently published meta-analysis of randomised trials comparing the efficacy and safety of platinum-based doublets versus single-agent regimens in the first-line therapy of PS 2 patients

revealed platinum-based regimens to be superior in terms of RR and survival (74% higher probability of being alive after 1 year) despite an increase in toxicities (mainly haematological) [65]. In addition, the superiority of carboplatin-based combinations over monotherapy in PS 2 patients has been identified in a subgroup analysis within large phase III trials, with an acceptable toxicity profile [66]. Moreover, combination chemotherapy with

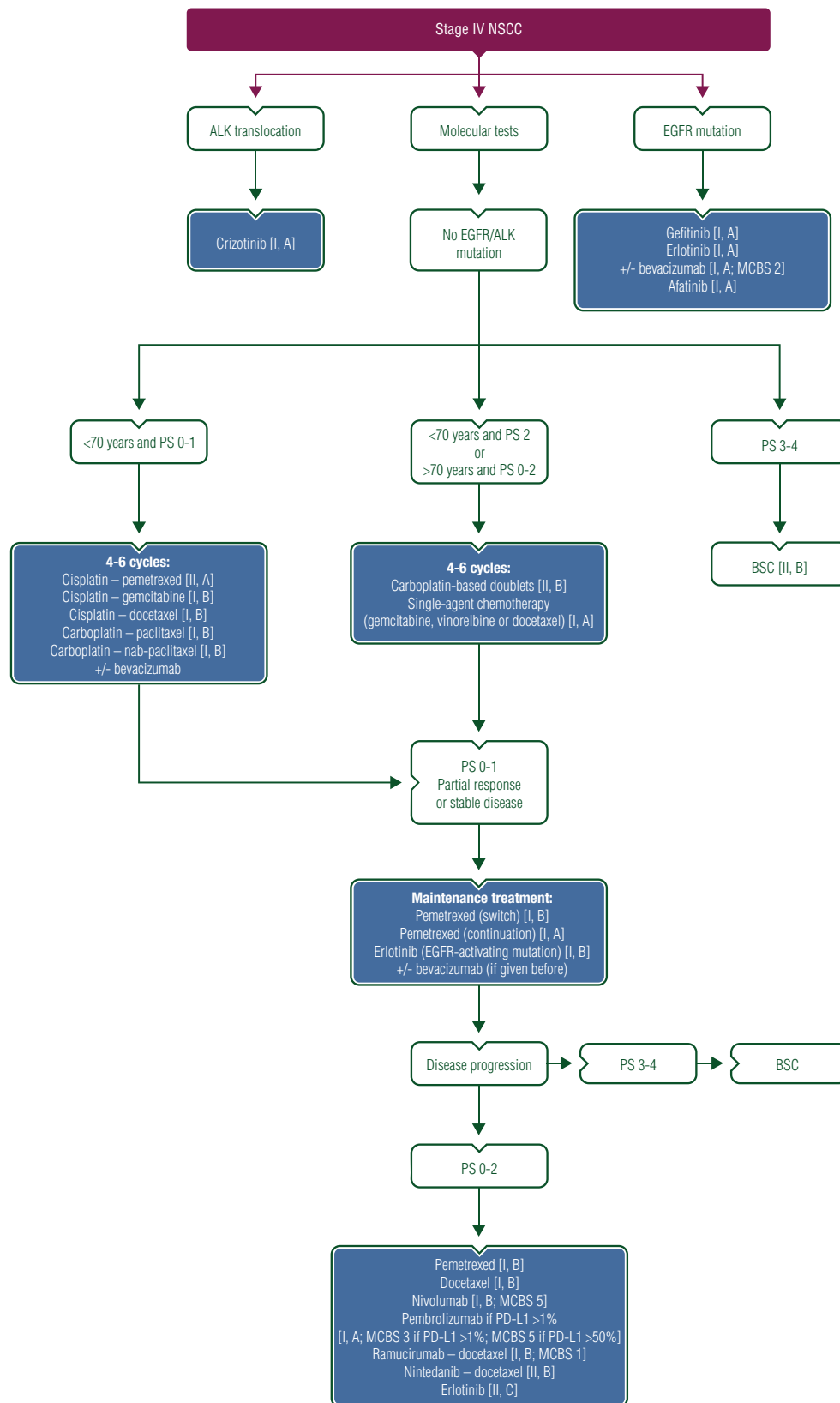


Figure 2. Treatment algorithm for stage IV NSCC. NSCC, non-squamous cell carcinoma; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; PS, performance status; BSC, best supportive care; MCBS, Magnitude of Clinical Benefit Scale.

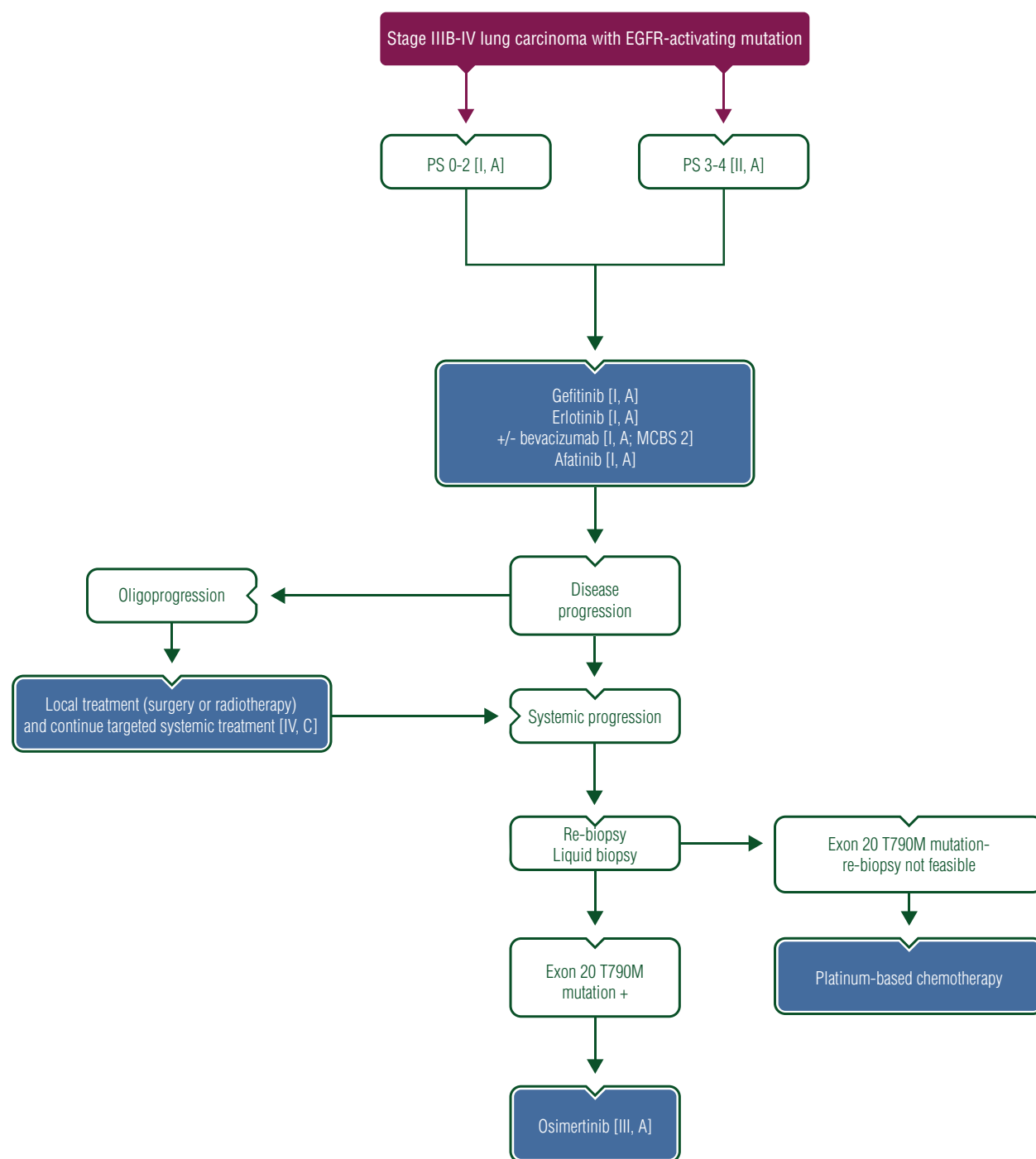


Figure 3. Treatment algorithm for stage IIIB–IV lung carcinoma with EGFR-activating mutation. EGFR, epidermal growth factor receptor; PS, performance status.

carboplatin significantly improved survival compared with monotherapy alone in patients with PS 2 [67]. Therefore, platinum-based (preferably carboplatin) doublets should be considered in eligible PS 2 patients [II, A] [68]. Single-agent chemotherapy with gemcitabine, vinorelbine and docetaxel represents an alternative treatment option [I, B] [69].

In this subgroup of patients, there are instances where poor PS is attributable to a high tumour burden, and improved PS may be expected in response to treatment. In other cases, poor PS may be related to co-morbidity, and a worsening PS may be

expected during treatment. Therefore, clinicians and patients should always discuss the risks and benefits of chemotherapy and should make a joint decision.

Poor PS (3–4) patients should be offered BSC in the absence of documented activating (sensitising) EGFR mutations or ALK rearrangements [II, B].

A phase II randomised trial compared three treatment strategies (gemcitabine, gefitinib or docetaxel) in chemotherapy-naïve patients with advanced NSCLC and PS 2-3, achieving similar results in terms of PFS and median survival time.

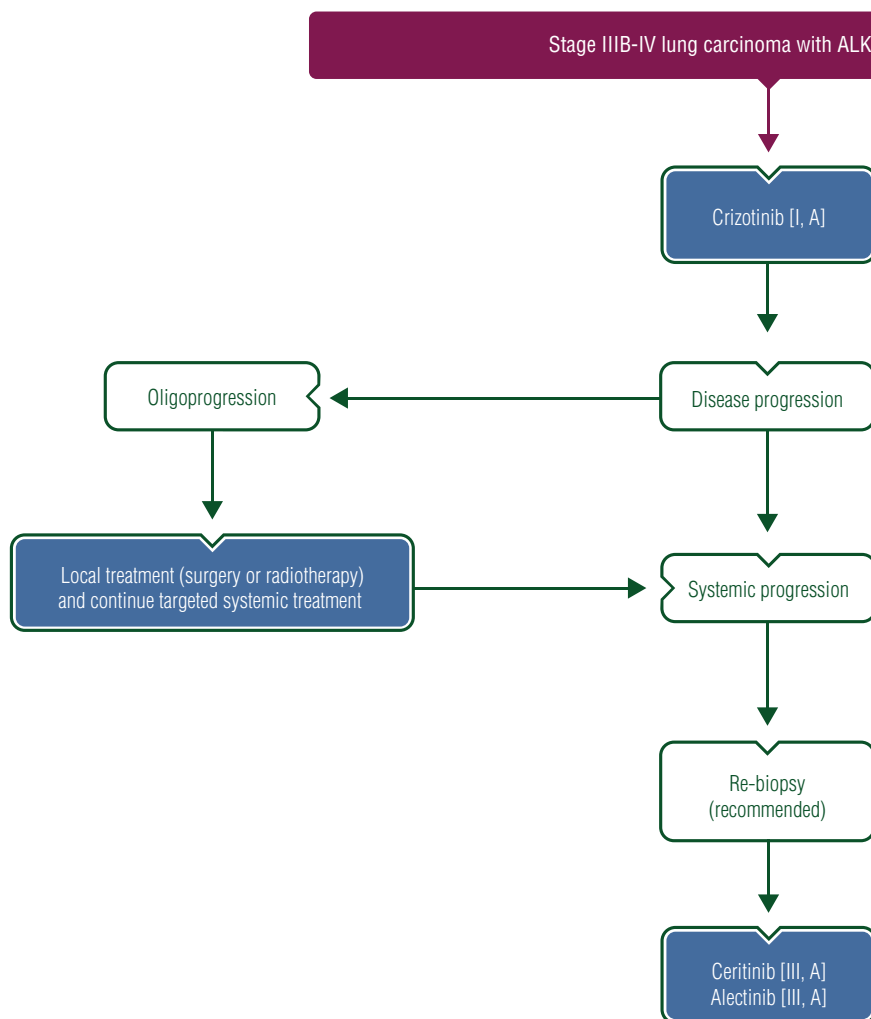


Figure 4. Treatment algorithm for stage IIIB–IV lung carcinoma with ALK translocation. ALK, anaplastic lymphoma kinase.

Median survival times were 2.2 months, 95% CI: 1.9–3.4, 2.4 months, 95% CI: 1.6–4.4 and 3.5 months, 95% CI: 1.8–6.6, for gemcitabine, gefitinib and docetaxel, respectively, with docetaxel being associated with higher rates of adverse events (AEs) [70].

Nevertheless, there are no data to support the use of front-line cytotoxic treatment over BSC alone in PS >2 patients.

elderly patients

Several phase III trials established single-agent therapy (docetaxel, vinorelbine or gemcitabine) as the standard of care for first-line therapy for advanced NSCLC patients aged ≥ 70 [69, 71]. However, several platinum-based and non-platinum-based doublets have been tested in elderly patients in recent decades. Two meta-analyses reported a favourable RR but showed increased toxicity (notably haematological toxicity) with doublet- compared with single-agent therapy [72, 73], while a statistically superior OS was observed in one of them, in which a subgroup analysis favoured platinum-based doublets. Among the largest prospective phase III trials in elderly patients, one study comparing monthly carboplatin plus weekly paclitaxel versus single-agent vinorelbine or gemcitabine in patients aged 70–89 with PS 0–2 found a survival advantage for combination

therapy [66]. Median OS was 10.3 months for doublet chemotherapy and 6.2 months for monotherapy (HR 0.64, 95% CI: 0.52–0.78; $P < 0.0001$); 1-year survival was 44.5% (95% CI: 37.9–50.9) and 25.4% (95% CI: 19.9–31.3), respectively. Benefit was observed across all subgroups, but increased toxicity (notably febrile neutropaenia and sepsis-related deaths) was observed. With regard to particular platinum-based combinations, data show a good tolerability of nab-PC in patients aged ≥ 70 , a tolerability comparable to that in younger counterparts [74].

Platinum-based chemotherapy is the preferred option for elderly patients with PS 0–1, as well as selected PS 2 and adequate organ function, while a single-agent approach (vinorelbine, gemcitabine, docetaxel) might remain the recommended treatment of unfit or co-morbid patients, who are more likely to develop a higher incidence of treatment-related AEs [I, B].

Comprehensive geriatric assessment (CGA) is based on a multidisciplinary and global approach to elderly patients, covering functional status, cognitive capacities, emotional status, comorbidities, nutritional status, polypharmacy, social and environmental situations and a possible geriatric syndrome. CGA can predict morbidity and mortality in elderly patients with cancer [75] and can help to adapt cancer management to each

patient's fitness or frailty [III, C], even if a recently published phase III trial did not demonstrate an improvement in survival outcomes of elderly patients with advanced NSCLC deriving from CGA-based allocation of chemotherapy [76].

maintenance

Decision-making about maintenance therapy must take into account histology, residual toxicity after first-line chemotherapy, response to platinum doublet, PS and patient preference.

Several trials have investigated the role of maintenance treatment in patients with good PS (0, 1) either as 'continuation maintenance' or as 'switch maintenance'. 'Continuation maintenance' and 'switch maintenance' therapies refer, respectively, to either the maintained use of an agent included in first-line treatment or the introduction of a new agent after four cycles of platinum-based chemotherapy.

Two randomised phase III switch maintenance trials have reported improvements in PFS and OS with pemetrexed [57] and erlotinib [77] versus placebo following four cycles of platinum-based chemotherapy. In the case of pemetrexed, this benefit was seen only in patients with NSCC [I, B].

In the erlotinib trial, subgroup analyses revealed a benefit restricted to patients with stable disease (SD) after induction treatment, as opposed to patients with tumour response. These results initially led to the label for switch maintenance with erlotinib in patients with SD after induction treatment [57, 77]. However, this indication is no longer justified based on the findings in the IUNO study, which failed to meet its primary end point of OS. This phase III trial showed that in patients with EGFR wild-type (WT) tumours who had not progressed following four cycles of platinum-based chemotherapy, and who had received 'early erlotinib' in the first-line maintenance setting, OS was not superior to erlotinib treatment upon disease progression (HR 1.02; 95% CI: 0.85–1.22; $P = 0.8183$) and 1-year event-free rates were the same in both treatment groups [78]. Maintenance treatment with erlotinib is, therefore, not recommended for NSCLC patients without an EGFR-activating mutation [I, B].

Randomised trials investigating continuation maintenance have shown an improvement of PFS and OS [79, 80]. A large phase III randomised trial of continuation maintenance with pemetrexed versus placebo after four induction cycles of cisplatin plus pemetrexed chemotherapy demonstrated a PFS and OS improvement in patients with a PS 0–1, confirmed at long-term follow-up [80, 81]. Median OS was 13.9 months (95% CI: 12.8–16.0 months) pemetrexed and 11.0 months (95% CI: 10.0–12.5 months) placebo, with 1- and 2-year survival rates significantly longer for patients given pemetrexed (58% and 32%, respectively) than for those given placebo (45% and 21%). Another phase III study comparing maintenance bevacizumab, with or without pemetrexed, after first-line induction with bevacizumab, cisplatin and pemetrexed showed a benefit in PFS for the pemetrexed–bevacizumab combination but no improvement in OS [82], although a trend towards improved OS was seen when analysing 58% of events of 253 patients randomised for this study [83]. Continuing pemetrexed following completion of four cycles of first-line cisplatin/pemetrexed chemotherapy is, therefore, recommended in patients with NSCC, in the absence

of progression after first-line chemotherapy and upon recovery from toxicities from the previous treatment [I, A].

Of note, three studies, one employing bevacizumab and the other two using monoclonal antibodies against EGFR (cetuximab or necitumumab) 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 [52, 58, 84].

second-line treatment of EGFR- and ALK-negative disease

Patients clinically or radiologically progressing after first-line chemotherapy, irrespective of administration of maintenance chemotherapy, and with PS 0–2, should be offered second-line therapy [I, A]. Combination chemotherapy regimens failed to show any OS benefit over single-agent treatments [85]. Single agents improve disease-related symptoms and OS. Comparable options in the second line consist of pemetrexed (for NSCC only) [86] or docetaxel [I, B] [87]. Erlotinib improved OS in second line or in third line in all NSCLC histological subtype patients not eligible for further chemotherapy, including patients with PS 3 [88]. Erlotinib was shown to be equivalent to pemetrexed or docetaxel in refractory (progression during the four cycles of a standard platinum-based chemotherapy doublet), unselected patients in a randomised trial [89]. Finally, a large randomised phase III trial showed comparable outcome with pemetrexed or erlotinib [90].

In a randomised trial including 222 EGFR WT NSCLC patients, initially designed to assess selected biomarkers, second-line therapy with docetaxel was shown to be superior to erlotinib with respect to PFS, as well as to OS, but only using an unplanned adjusted HR for primary end-point analysis [91]. Subgroup analyses of a phase III trial of erlotinib versus docetaxel as second- or third-line therapy demonstrated superior PFS but not OS for docetaxel treatment in WT EGFR [92].

Similar results have been reported in a meta-analysis carried out on six randomised, controlled trials with a total of 990 patients with WT EGFR. Results indicated that, in the second-line treatment of EGFR WT-advanced NSCLC, PFS was significantly inferior in the EGFR TKI group versus the chemotherapy group (HR 1.37, 95% CI: 1.20–1.56, $P < 0.00001$). However, this did not translate into an OS difference (HR 1.02, 95% CI: 0.87–1.20, $P = 0.81$) [93].

In conclusion, erlotinib still represents a potential second-line treatment option in pretreated patients with unknown or WT EGFR status and preferably in patients not suitable for chemotherapy, with, however, limited efficacy in WT EGFR patients compared with chemotherapy [II, C].

Ramucirumab, a vascular endothelial growth factor receptor-2 (VEGFR2) inhibitor, was recently investigated as second-line therapy for stage IV NSCLC [94]. The study compared docetaxel with ramucirumab or placebo in patients who had progressed after platinum-based chemotherapy. Median OS was longer (10.5 versus 9.1 months, HR 0.86, 95% CI: 0.75–0.98, $P = 0.023$) in the ramucirumab arm compared with the placebo arm. Median PFS was also superior in the ramucirumab arm (4.5 versus 3 months, $P < 0.0001$). Ramucirumab combined

with docetaxel is, therefore, a treatment option in second-line treatment of advanced NSCLC with PS 0-2, regardless of histology [I, B; ESMO-MCBS v1.0 score: 1].

Bevacizumab administered every two weeks in association with weekly paclitaxel was recently investigated in patients with NSCC. The study compared the association of paclitaxel-bevacizumab versus docetaxel in second-third line of treatment; median PFS was longer (5.4 versus 3.9 months, HR 0.62, 95% CI: 0.44–0.86, $P=0.005$) in the paclitaxel-bevacizumab arm compared with docetaxel. No difference in median OS was observed (9.9 versus 10.8 months, HR 1.15, $P=0.49$) [95].

While registration trials of pemetrexed, docetaxel and erlotinib did not limit therapy to a set number of treatment cycles, second-line treatment duration should be individualised, and treatment may be prolonged if disease is controlled and toxicity acceptable [II, B].

Lung cancer has been historically considered poorly immunogenic, with no established benefit from cytokine modulation or vaccines. Nevertheless, the recent development of checkpoint inhibitors provided a promising new approach for immunotherapy in patients with NSCLC. Immune checkpoints are inhibitory pathways that maintain self-tolerance and protect peripheral tissues by restricting the immune responses. The two checkpoint targets that have been studied more extensively in lung cancer are the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and the PD-1 receptor. Among the antibodies against PD-1, nivolumab, a fully IgG4 PD-1 immune checkpoint inhibitor, was the first to be investigated in phase III trials, as reported below.

Pembrolizumab is another anti-PD-1 monoclonal antibody that has recently received European Medicines Agency (EMA) approval for the treatment of any histological type of NSCLC after failure of first-line therapy in patients with tumours expressing PD-L1 [I, A; ESMO-MCBS v1.0 score: 3 if PD-L1 >1%; 5 if PD-L1 >50%] (PD-L1 IHC 22C3 pharmDx is indicated as an aid in identifying NSCLC patients for treatment with pembrolizumab).

The phase III KEYNOTE-010 trial randomised 1034 patients with previously treated NSCLC with PD-L1 expression on at least 1% of tumour cells to receive pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg or docetaxel 75 mg/m² every 3 weeks. The primary end points were OS and PFS both in the total population and in the patients with PD-L1 expression on at least 50% of tumour cells [96]. In the entire population, OS was significantly longer for pembrolizumab 2 mg/kg versus docetaxel (HR 0.71, 95% CI: 0.58–0.88; $P=0.0008$) and for pembrolizumab 10 mg/kg versus docetaxel (HR 0.61, 95% CI: 0.49–0.75; $P<0.0001$), with median OS of 10.4, 12.7 and 8.5 months in the three arms, respectively. Pembrolizumab achieved a higher outcome for those patients with high PD-L1 expression (>50%). Grade 3–5 treatment-related AEs were less common with pembrolizumab than with docetaxel [43 (13%) of 339 patients given 2 mg/kg, 55 (16%) of 343 given 10 mg/kg and 109 (35%) of 309 given docetaxel]. The recommended dose and schedule of pembrolizumab is 2 mg/kg administered as an intravenous infusion over 30 min every 3 weeks.

second-line treatment in SCC. A phase III trial (CheckMate 017) in patients previously treated for SCC compared 3 mg/kg of nivolumab given every 2 weeks with docetaxel, showing an

improvement of 3.2 months [97, 98] leading to its approval by the FDA in March 2015 and by the EMA in July 2015. At the data cut-off, median OS was 9.2 months (95% CI: 7.3–13.3 months) on nivolumab compared with 6.0 months (95% CI: 5.1–7.3 months) on docetaxel, with a 41% reduction in the risk of death in the nivolumab arm (HR 0.59, 95% CI: 0.44–0.49; $P<0.001$). An updated follow-up reported an 18-month OS of 28% and 13% in the nivolumab and docetaxel arms, respectively, and an 18-month PFS equal to 17% for nivolumab and to 2.7% for docetaxel [99].

In the phase III trial, nivolumab was better tolerated than docetaxel, with 85% of nivolumab patients receiving at least 90% of their planned dose intensity, compared with 69% of docetaxel patients, together with a treatment discontinuation rate of 10% versus 3% of the patients treated with nivolumab and docetaxel, respectively. The experimental arm also showed a positive impact on QoL and a longer time to symptom deterioration compared with the standard arm [100]. The expression of PD-L1 was neither prognostic nor predictive of clinical benefit in a retrospective analysis using various cut points in this study.

Nivolumab at 3 mg/kg every 2 weeks is therefore recommended in unselected pretreated patients with platinum pretreated advanced SCC [I, A; ESMO-MCBS v1.0 score: 5].

Based on the KEYNOTE-010 trial [96], pembrolizumab is another immunotherapy option in second-line but also in third-line therapy in patients with SCC expressing PD-L1 [I, A; ESMO-MCBS v1.0 score: 3 if PD-L1 >1%; 5 if PD-L1 >50%].

Afatinib versus erlotinib was tested in a phase III trial on 795 advanced SCC patients. PFS at the primary analysis was significantly longer with afatinib than with erlotinib, with a median of 2.4 months (95% CI: 1.9–2.9) versus 1.9 months (95% CI: 1.9–2.2); HR 0.82, 95% CI: 0.68–1.00, $P=0.0427$. OS was a median of 7.9 months (95% CI: 7.2–8.7) versus 6.8 months (95% CI: 5.9–7.8); HR 0.81, 95% CI: 0.69–0.95, $P=0.0077$.

Afatinib could be an additional option for the treatment of Eastern Cooperative Oncology Group PS 0-2 patients locally advanced or metastatic SCC progressing on or after platinum-based chemotherapy [II, C; ESMO-MCBS v1.0 score: 1] [101].

second-line treatment in NSCC

pemetrexed: A phase III second-line study demonstrated non-inferiority for OS between pemetrexed and docetaxel (8.3 versus 7.9 months, HR 0.99, 95% CI: 0.8–1.2). However, pemetrexed showed a better toxicity profile with a significantly lower rate of neutropaenia and alopecia as well as lower rates of gastrointestinal AEs [86]. In a retrospective analysis, a predictive impact of histology on outcome by pemetrexed was reported favouring those patients with NSCC (median OS: 8.0 versus 9.3 months, docetaxel versus pemetrexed, HR 0.78, 95% CI: 0.61–1.0, $P=0.004$) [56]. Pemetrexed is a treatment option for those patients with NSCC who did not receive this drug as first-line therapy [I, B].

docetaxel and nintedanib: The combination of docetaxel and the angiokinase inhibitor nintedanib has been investigated in 1314 patients with pretreated advanced NSCLC in the LUME Lung 1 trial. Compared with docetaxel, a significant prolongation of PFS, the primary end point, was observed in the intent-to-treat (ITT) population (median PFS 3.4 versus 2.7 months, HR 0.79,

95% CI: 0.68–0.92; $P = 0.0019$), while a significant prolongation of OS was reported for patients with adenocarcinoma histology (median OS 12.6 versus 10.3 months, HR 0.82, 95% CI: 0.7–0.99; $P = 0.0359$). Additional unplanned analyses revealed a pronounced impact on OS in patients with fast-progressing disease and patients who were refractory to first-line chemotherapy. Compared with docetaxel, the combination of nintedanib and docetaxel was associated with a higher incidence of gastrointestinal AEs and transient elevation of liver enzymes [102]. However, no impact on QoL has been reported by the analysis of patient-reported outcomes [103]. The combination of docetaxel and nintedanib should be considered as a second-line option in patients with adenocarcinoma, especially in those progressing within 9 months from the start of first-line chemotherapy [II, B].

nivolumab: Nivolumab led to a significant prolongation of OS compared with docetaxel in 582 pretreated patients with NSCC, who were recruited to the Checkmate-057 trial (median OS 12.2 versus 9.4 months, HR 0.73, 95% CI: 0.59–0.89; $P = 0.002$), although a small excess of early progression and/or death events were observed for nivolumab, compared with docetaxel. In addition, RR (19% versus 12%, $P = 0.021$) and duration of response (17.2 versus 5.6 months) were in favour of nivolumab, while no significant difference has been reported for PFS (median PFS 2.3 versus 4.2 months, HR 0.92, 95% CI: 0.77–1.1). An exploratory retrospective analysis revealed an association of efficacy by nivolumab and the level of tumour membrane expression of PD-L1. However, this analysis is limited by the retrospective and unplanned nature of this biomarker assessment. In the nivolumab arm, compared with docetaxel, a lower frequency of both serious adverse events (SAEs; CTC grade 3/4 events: 10% versus 54%) and AEs leading to treatment discontinuation (5% versus 15%) were observed. The most frequent selected AEs were rash, pruritus, diarrhoea, hypothyroidism, elevation of liver enzymes and pneumonitis [104].

Nivolumab at 3 mg/kg every 2 weeks represents a treatment option in pretreated patients with advanced NSCC [I, B; ESMO-MCBS v1.0 score: 5] and should be administered in second-line NSCC patients. Patients with PD-L1-positive tumours extract an OS benefit compared with docetaxel [I, B], while in PD-L1-negative tumours, both the use of nivolumab and docetaxel resulted in similar OS outcomes, with a more favourable profile regarding nivolumab [II, A].

pembrolizumab: Based on the KEYNOTE-010 trial [96], pembrolizumab is another immunotherapy option in second-line but also in third-line therapy in patients with NSCC expressing PD-L1 [I, A; ESMO-MCBS v1.0 score: 3 if PD-L1 <1%; 5 if PD-L1 >50%].

EGFR-mutated NSCLC patients

Several studies have consistently demonstrated that the EGFR TKIs (gefitinib, erlotinib and afatinib) produce higher RRs, longer PFS and improve QoL compared with standard platinum-based doublet chemotherapy in patients with good PS (PS 0-2), whose tumour harbours an activating (sensitising) EGFR mutation [105–112]. Patients with PS 3-4 may also be offered an EGFR TKI, as they are likely to receive a similar clinical benefit to patients with good PS [II, A] [113].

The recently presented phase IIb study LUX-LUNG 7 showed that afatinib achieves a modestly higher RR and a longer PFS [11 versus 10.9 months, HR (95% CI): 0.73 (0.57–0.95); $P = 0.0165$] than gefitinib as first-line treatment of patients with advanced NSCLC with common activating mutations (del19 or L858R) [II, B]. Data on OS (co-primary end point) are still immature and data on QoL have not been presented [114].

EGFR TKIs represent the standard of care as first-line treatment of advanced EGFR-mutated NSCLC [I, A].

Notably, none of the above studies have shown any benefit in OS for an EGFR TKI over platinum-based chemotherapy, likely due to the high level of crossover.

However, an unplanned pooled OS analysis of patients who have been recruited to either the LUX-Lung 3 or the LUX-Lung 6 trial revealed an OS benefit for afatinib compared with chemotherapy in patients with EGFR del-19 mutations (median OS: 27.3 versus 24.3 months; HR 0.81, 95% CI: 0.66–0.99; $P = 0.0374$), whereas this improvement was not observed in patients with EGFR L858R mutations [II, A] [115].

Should the information on the presence of an EGFR-sensitising mutation become available during first-line platinum-based chemotherapy, it is recommended to continue chemotherapy for up to four cycles, and then to offer the EGFR TKI as maintenance treatment in those patients achieving disease control [77], or as second-line treatment at the time of progression [I, A].

In a Japanese randomised trial, 154 EGFR-mutated patients were randomised to receive erlotinib and bevacizumab or erlotinib alone (75 patients in the combination arm and 77 in the erlotinib alone arm were included in the efficacy analyses) [116]. Median PFS was 16.0 months (95% CI: 13.9–18.1) with erlotinib plus bevacizumab and 9.7 months (95% CI: 5.7–11.1) with erlotinib alone (HR 0.54, 95% CI: 0.36–0.79; log-rank test $P = 0.0015$). No new safety signals were identified with the combination treatment, and the incidence of AEs (any grade) and SAEs were similar between the treatment arms. There was a higher frequency of grade 3 or worse AEs with the combination and a relatively high incidence of bevacizumab discontinuation due to AEs (41%); however, most of these AEs were non-serious and reversible. A similar PFS was described in a European phase II trial that also evaluated the combination of erlotinib and bevacizumab, which represents a front-line treatment option in EGFR-mutated patients [I, A; ESMO-MCBS v1.0 score: 2] [117].

The majority of patients will progress after 9–12 months of treatment with an EGFR TKI, and various mechanisms of acquired resistance to first-generation EGFR TKIs have been described [118]. The most common (49%–60%) mechanism of acquired resistance is the acquisition of a single recurrent missense mutation within exon 20, the T790M mutation [119, 120]. This mutation leads to the substitution of threonine by methionine at position 790, which encodes part of the kinase domain of the receptor and results in increased affinity for ATP, causing resistance to competitive inhibition by reversible EGFR TKIs such as gefitinib and erlotinib [121, 122].

A number of third-generation EGFR TKIs that are specifically designed to target EGFR T790M mutation have undergone clinical development. Among these, osimertinib, an oral, selective, third-generation, irreversible EGFR TKI inhibitor with activity against T790M mutation, is licensed for use in patients who

have developed the EGFR T790M resistance mutation and should be the treatment of choice in this setting [123, 124]. Patients who progress after an EGFR TKI should undergo a rebiopsy to perform molecular analysis specifically looking for EGFR T790M mutation. This approach could influence the next therapeutic step or reveal alternative EGFR TKI resistance mechanisms such as transformation to SCLC or bypass tracks that could potentially be addressed in clinical trials.

In patients with clinically relevant progression after previous treatment with an EGFR TKI and confirmed T790M mutation, treatment with osimertinib at a dose of 80 mg/day p.o. should be considered [III, A].

At the present time, when rebiopsy is not feasible or when the EGFR T790M mutation is not detected as a resistance mechanism, the standard of care is represented by platinum-based chemotherapy alone. There is no data to support continuation of the EGFR TKI with platinum-based chemotherapy [I, A] [125].

A valid alternative to tissue rebiopsy is represented by liquid biopsy, which has been validated [126], represents a surrogate source of DNA and is a new strategy for tumour genotyping, mainly at the time of progression for EGFR-mutated patients [III, A] [127–129]. In the event that a T790M mutation in peripheral blood is observed, treatment with third-generation EGFR TKIs is justified [130]. If a T790M-negative liquid biopsy is observed, a tissue rebiopsy is recommended if feasible and if accepted by the patient.

A phase II study has demonstrated benefit in PFS in patients who continued first-line erlotinib beyond radiological progression [131]; therefore, this strategy could be considered in patients with asymptomatic progression. Evidence from retrospective series and case reports suggests that, in patients where there is evidence of radiological progression in a single site (i.e. CNS metastasis or adrenal gland), but with ongoing dependence on the driver oncogene addiction and without rapid systemic progression, the combination of continuing the EGFR TKI with local treatment (radiotherapy or surgery) may represent a reasonable option and could be considered on an individualised basis [III, B] [132].

ALK-rearranged NSCLC patients

The anti-tumour activity of crizotinib, a dual ALK and MET TKI, was initially demonstrated in two multicentre single-arm studies, with significant ORR and PFS advantages [133] as well as a survival advantage compared with other treatment options [134].

The phase III PROFILE 1007 study confirmed the benefit of crizotinib over chemotherapy, pemetrexed or docetaxel (investigator's choice), as second-line treatment with better ORR and PFS [135]. The median PFS, as determined by independent radiological review, was 7.7 months (95% CI: 6.0–8.8) in the crizotinib group, compared with 3.0 months (95% CI: 2.6–4.3) in the chemotherapy group (HR for disease progression or death with crizotinib 0.49, 95% CI: 0.37–0.64, $P < 0.001$). Crizotinib also showed an advantage over both pemetrexed and docetaxel with regards to the improvement in symptoms and QoL [136].

Based on these data, any patient with NSCLC harbouring an ALK fusion and previously treated should receive crizotinib in second line, if this was not previously administered [I, A].

Subsequently, the phase III study PROFILE 1014 compared crizotinib with cisplatin–pemetrexed without maintenance pemetrexed as first-line treatment in ALK-positive advanced NSCC [137], and demonstrated a significantly longer PFS (median of 10.9 versus 7.0 months; HR for progression or death with crizotinib 0.45; 95% CI: 0.35–0.60; $P < 0.001$) and higher ORR with crizotinib compared with chemotherapy (74% and 45%, respectively; $P < 0.001$). Median OS was not reached in either group.

First-line treatment with crizotinib is the preferred treatment of patients with ALK-rearranged NSCLC [I, A].

As for the EGFR-mutated, ALK-rearranged NSCLC patients, the combination of continuing the ALK TKI with local treatment (radiotherapy or surgery) may represent a reasonable option and could be considered on an individualised basis [III, B] [132].

Despite improved outcome in patients with tumours harbouring ALK rearrangements and treated with crizotinib, all patients will eventually experience disease progression through primary or acquired resistance. Furthermore, crizotinib penetration into the cerebrospinal fluid (CSF) is negligible, and this pharmacological limitation is extremely relevant in treatment decisions, taking into account the high propensity of ALK-rearranged NSCLC to metastasise to the brain [138]. Various resistance mechanisms to ALK inhibitors have been identified, resulting in the development of new therapeutic approaches and novel TKIs.

Two phase I studies, including the multicentre open-label ASCEND-1 study, showed a significant activity of ceritinib, based on an ORR of 56% and 6.9 months of PFS in patients with ALK-rearranged NSCLC with crizotinib resistance [139]. The benefit also included intracranial responses in patients with brain metastasis.

Based on this data, ceritinib can be recommended in patients with ALK-positive advanced NSCLC who progress on treatment with or are intolerant to crizotinib [III, A].

Alectinib is another second-generation ALK inhibitor, which has been approved in Japan for all patients with advanced ALK-positive NSCLC. Two phase II studies have also demonstrated RR between 45% and 50% and PFS of 8.9 months [140, 141]. Alectinib was also effective for brain metastases. Furthermore, alectinib was tested in a phase III head-to-head trial comparing this molecule (300 mg b.i.d.) with crizotinib (250 mg b.i.d.) in untreated ALK-positive advanced NSCLC patients, demonstrating the superiority of alectinib as an initial targeted treatment [142]. Two hundred and seven patients were enrolled, when an independent data monitoring committee recommended the release of study data, because the superiority in the primary end-point PFS had been demonstrated at planned interim analysis. The PFS HR of the alectinib arm compared with the crizotinib arm was 0.34 (99.6826% CI: 0.17–0.70, $P < 0.0001$). Median PFS was not reached (95% CI: 20.3–NE) in the alectinib arm, while it was 10.2 months (95% CI: 8.2–12.0) in the crizotinib arm. A similar global trial in ALK+ treatment-naïve patients has completed accrual, and results are pending.

Several alternative ALK inhibitors are currently in clinical development, with broader activity against a number of mutated ALK genes and mainly characterised by higher brain activity [143].

role of radiotherapy in stage IV NSCLC

Radiotherapy plays a major role in the symptom control of metastases, such as painful chest wall disease, superior vena cava syndrome, soft tissue or neural invasion. Neurological symptoms from spinal cord compression can be relieved by early radiotherapy.

Radiotherapy is indicated in cases of haemoptysis, symptomatic airway obstruction and following surgery for CNS, and, sometimes, bone surgery [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 [II, B] [144]; thoracoscopic insufflation with talc (poudrage) is more effective than talc slurry sclerosis [II, B] [145]. If pleurodesis is not possible due to bronchial obstruction or trapped lung, or in the case of pleurodesis failure, recurrent pleural effusions may be managed by indwelling subcutaneous pleural catheters [146].

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

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 postobstructive 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 embolisation) of haemoptysis [III, C]. Vascular stenting might be useful in NSCLC-related superior vena cava compression [II, B].

role of palliative care in stage IV NSCLC

Early palliative care intervention is recommended, in parallel with standard oncological care [II, A]. Evidence demonstrating that palliative care interventions significantly improve QoL remains scarce. A randomised trial evaluating the impact of introducing specialised palliative care early after diagnosis of stage IV disease on patient QoL in ambulatory patients was able to show an improvement in QoL and mood, a reduction in aggressive treatment and an improvement in median OS [147].

focus on brain and bone metastases

brain metastases. The treatment of patients with brain metastases, and no driver mutations, is dependent on the prognosis. Prognosis can be estimated based on the Radiation Therapy Oncology Group recursive partitioning analysis (RPA) [148]: class I patients are those <65 years old, with a good PS [Karnofsky Index (KI) $\geq 70\%$], and no other extracranial metastases and a controlled primary tumour; class III patients have a KI <70%; and class II represents all other patients [148]. In RPA class III patients, radiotherapy is not recommended in view of the dismal prognosis [I, B]; only BSC is recommended, as their median survival is <2 months.

In the case of a single metastasis, stereotactic radiosurgery (SRS) or resection is the recommended treatment [II, B] [149, 150]. For two to three metastases, SRS is recommended in patients with RPA class I–II [II, B]. There is currently no evidence that adding upfront whole brain radiotherapy (WBRT) to surgery or to SRS has an impact on OS [I, A] [151].

Data from a prospective observational Japanese study suggested that the use of SRS may have a role in patients with more than three metastases [152]. The observational study enrolled 1194 eligible patients with 1–10 newly diagnosed brain metastases in a 3-year period, with the largest tumour <10 ml in volume and <3 cm in longest diameter; total cumulative volume ≤ 15 ml, and a KPS score of 70 or higher, with all patients undergoing standard SRS [152]. Median OS after SRS was 13.9 months (95% CI: 12.0–15.6) in the 455 patients with a single metastasis, 10.8 months (95% CI: 9.4–12.4) in the 531 patients with 2–4 tumours and 10.8 months (95% CI: 9.1–12.7) in the 208 patients with 5–10 tumours. OS was similar in patients with 2–4 tumours and in those with 5–10. In outpatients undergoing SRS, treatment-related side-effects occur in 8% of cases, findings that indicate SRS as a valid alternative to WBRT in fit patients [IV, C]. SRS, with or without WBRT, has recently been further investigated in an individual patient data meta-analysis of three phase III trials [153]. The age of the patient significantly influenced survival ($P = 0.04$), with SRS alone favoured in patients aged 50 or younger, and with no significant survival differences in patients aged >50. Patient age was also a significant factor for brain failure outside of the radiation field(s) ($P = 0.043$), with similar failure rates in both arms for patients ≤ 50 years of age, while the risk was reduced with WBRT for patients aged >50.

When more than three brain metastases are diagnosed, WBRT is recommended in patients with RPA class I–II [II, B], although the benefit of WBRT compared with supportive care alone has not been formally studied in randomised trials.

The role of WBRT has been questioned by data from a phase III non-inferiority study, in which patients were randomised to either BSC including dexamethasone plus WBRT 20 Gy in 4 Gy fractions or to the same BSC without WBRT. This trial (QUARTZ) demonstrated no difference between the treatment arms regarding the relief of symptoms, steroid use, OS, QoL or quality-adjusted life years, but full publication is awaited [154]. The WBRT most frequent schedules are 20 Gy in 5 fractions or 30 Gy in 10 fractions, with no difference in outcome [I, A] [155].

In patients with asymptomatic brain metastases who have not yet received prior systemic therapy (i.e. chemotherapy, TKIs) however, treatment with upfront systemic chemotherapy and deferred WBRT should be considered [II, B] [156, 157].

For most patients with symptomatic brain metastases and/or significant oedema, a dose of dexamethasone of 4 mg/day or an equivalent dose of another corticosteroid is recommended [II, A] [158]. Tapering of the dose and, if possible, cessation after radiotherapy are recommended. Corticosteroids are not recommended in the case of asymptomatic brain metastases.

Among those patients with a druggable oncogene driver (EGFR, ALK), between 44% and 60% develop brain metastases in the course of their disease [153]. In such patients with clinically asymptomatic brain metastases, the use of next-generation TKIs may restore control of brain disease, with the possibility to delay cranial radiotherapy [III, B]. In those oncogene-addicted

cases with symptomatic brain metastases, the indication and schedules are those indicated in the other NSCLC patients and already discussed above.

In patients with EGFR mutation and brain metastases, the PFS improvement with the irreversible inhibitor afatinib was similar to that observed in patients without brain metastases [159]. The PFS was significantly better with afatinib versus chemotherapy (8.2 versus 5.4 months; HR 0.50; $P = 0.0297$). Results with third-generation TKIs, such as osimertinib, are awaited.

In ALK-positive patients progressing on crizotinib, treatment with ceritinib or alectinib shows activity against CNS disease [III, B]. ALK-positive patients often have brain progression while on crizotinib, as the CSF concentration of the latter is very low [138]. Retrospective review of 94 ALK-rearranged NSCLC patients with brain metastases in a phase I expansion study of ceritinib, of which 75 were ALK inhibitor-pretreated, revealed an intracranial disease control rate (DCR) of 65.3% in crizotinib-pretreated patients and 78.9% in TKI-naïve patients [139].

In a phase II trial, alectinib at crizotinib resistance has demonstrated activity for brain metastases, with an ORR of 57% in patients with measurable lesions and complete response observed in 20% of patients [140]. A CNS DCR of 83% was reported in all 84 patients with baseline CNS metastases. In another small cohort of patients with measurable brain disease being enrolled in another phase 2 trial, 75% of patients achieved an intracranial objective response [141].

bone metastases. Given the incidence of bone metastases in NSCLC (30%–40% of patients with NSCLC develop bone metastases), it may be reasonable to evaluate for bone disease upon disease diagnosis.

Zoledronic acid reduces skeletal-related events (SREs) (pathological fracture, radiation or surgery to bone, or spinal cord compression) and is recommended in stage IV bone metastatic disease [II, B] [160].

Denosumab is not inferior to [I, B] and shows a trend towards superiority to zoledronic acid in lung cancer in terms of SRE prevention [II, B] [161]. In an exploratory analysis of a large phase III trial, denosumab was associated with improved median OS in the subgroup of 702 metastatic NSCLC patients [162].

In the study of denosumab versus zoledronic acid in patients with advanced cancers, the time extent to which pain interfered with daily life (used as surrogate for QoL) was longer in patients treated with denosumab and with no pain or mild pain interference at baseline [163].

A systematic review analysed the use of radionuclide treatment in lung cancer and in the eligible trials, pain relief was reported in 75% of the patients having the onset of pain relief within 1–5 weeks after treatment, lasting up to 6 months [164]. However, the methodology in the included trials was poor; only two randomised trials were eligible, and neither compared radionuclide treatments with placebo or best standard of care. Thus, further data are needed in this field.

treatment of oligometastatic NSCLC

The term 'oligometastases' refers to a limited number of haematogenous metastases, although there is no consensus on what 'limited' means. Some groups propose a definition of up to three, others up to five metastatic lesions, yet others limit the

number of organs in which these metastases are present [165]. The growing interest in oligometastases is based on the concept that long-term disease control, or even cure, may be achieved in some subgroups of these patients [166].

Oligometastases can be either synchronous, when diagnosed within 1 month before or after the primary tumour was identified, or metachronous when they appear after treatment of the primary tumour [165]. The biology and prognosis related to synchronous and metachronous oligometastases may differ.

In patients receiving systemic therapy (mainly those oncogene-addicted tumours treated with TKIs), the term oligoprogression can be also applied in the case of clonal progression of a limited number of metastatic lesions, when all the other lesions remain stable.

Stage IV patients with one to three synchronous metastases at diagnosis may experience long-term disease-free survival (DFS) following systemic therapy and radical local treatment (high-dose radiotherapy or surgery) [III, B]. However, because of the limited evidence available, inclusion in clinical trials is preferred. Stage IV patients with limited metachronous metastases may be treated with a radical local treatment as some may experience long-term DFS [III, B]. However, this is based only on retrospective data.

A systematic literature review identified 757 NSCLC patients treated with 1–5 synchronous or metachronous metastases [167]. These patients had a median age at diagnosis of 61 years, 98% had a good PS and two-thirds of patients had early-stage intrathoracic disease staged IA–IIB (after excluding metastatic disease). Surgery was the most common treatment modality for both primary ($n = 635$, 83.9%) and metastases ($n = 339$, 62.3%). Predictive factors for OS were synchronous versus metachronous metastases ($P < 0.001$), N-stage ($P = 0.002$) and adenocarcinoma histology ($P = 0.036$). RPA for risk groups identified a good prognosis (low-risk) group presenting with metachronous metastases (5-year OS of 48%), an intermediate-risk group presenting with synchronous metastases and N0 disease (5-year OS of 36%) and, finally, a high-risk group presenting with synchronous metastases and intrathoracic N1/N2 disease (5-year OS of 14%). Caution is warranted before concluding that positive outcomes in these patients are due solely to the treatment intervention, rather than population selection or other biases [165].

In this heterogeneous group of patients with oligometastases, the specific approach to oligometastases in the brain has been discussed above.

One further subgroup is that of patients with a solitary lesion in the contralateral lung. The IASLC Staging and Prognostic Factors Committee carried out a systematic literature review, aiming at distinguishing a second primary and a metastasis in patients who have more than one pulmonary site of cancer [168]. This review concluded that few features are definitive, with many commonly used factors being suggestive, but carry a substantial risk of misclassification as the majority of second primary lung tumours are of the same histology. For these cases, the IASLC recommended a careful review by a multidisciplinary tumour board, and pursuit of radical therapy, such as that for a synchronous secondary primary tumour, when possible. Both surgery [169, 170] and SRS [171, 172] have been shown to result in long-term survivors in this setting [IV, B].

Outcomes of radical approaches in patients with oligometastases in other organs (such as bone, liver, adrenal glands or other)

Table 4. Summary of recommendations

Diagnosis and personalised medicine

- Adequate tissue material for histological diagnosis and molecular testing should be obtained to allow for individual treatment decisions.
- Pathological diagnosis should be made according to the 2015 WHO classification and the IASLC/ATS/ERS classification of adenocarcinoma.
- Specific subtyping of all NSCLCs is necessary for therapeutic decision-making and should be carried out wherever possible. IHC stains should be used to reduce the NSCLC-NOS rate to fewer than 10% of cases diagnosed [IV, A].
- EGFR mutation status should be systematically analysed in advanced NSCC [I, A]. Test methodology should have adequate coverage of mutations in exons 18–21, including those associated with specific drug resistance. At a minimum, when resources or material are limited, the most common activating mutations (exon 19 deletion and exon 21 L858R point mutation, including exon 20 T790M) should be determined [I, A].
- Molecular EGFR testing is not recommended in patients with a confident diagnosis of SCC, except in never/former light smokers (<15 pack years) [IV, A].
- Testing for ALK rearrangement should be systematically carried out in advanced NSCC [II, A].
- Detection of the ALK translocation by FISH remains the standard, but IHC with high-performance ALK antibodies may be considered for screening.
- If possible, multiplex platforms for molecular testing are preferable [III, A]. Sequential testing may delay treatment.
- In NSCLC with EGFR-sensitising mutations or ALK translocations, a rebiopsy at the time of progression is encouraged [IV, A].

Staging and risk assessment

- A complete history including smoking history and co-morbidities, weight loss, PS and physical examination must be recorded.
- Laboratory: standard tests including routine haematology, 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 including the liver and the adrenal glands should be carried out.
- Imaging of CNS is reserved for patients with neurological symptoms or signs. MRI is more sensitive than CT scan.
- If bone metastases are clinically suspected, bone imaging is required.
- PET, ideally coupled with CT, and bone scans are helpful for the systemic screening for bone metastasis. Moreover, PET-CT scan may demonstrate unexpected metastases in 5%–10% of the patients with presumed non-metastatic stage based on conventional imaging.
- NSCLC is staged according to the AJCC/UICC system (7th edition) and is grouped into the stage categories shown in Tables 2 and 3.
- 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.

Management of advanced metastatic disease

- The treatment strategy should take into account the histology, molecular pathology, age, PS, co-morbidities and the patient's preferences.
- Treatment decisions should be discussed within a multidisciplinary tumour 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 [II, A].

First-line treatment of EGFR and ALK-negative disease (SCC and NSCC)

- Chemotherapy should be considered in all stage IV NSCLC patients with EGFR- and ALK-negative disease, without major co-morbidities and PS 0–2 [I, A].
- Platinum-based doublets are the recommended option in all stage IV NSCLC patients with no contraindications to platinum compounds [I, A].
- Four cycles of platinum-based doublets followed by less toxic maintenance monotherapy, or four up to a maximum of six cycles in patients not suitable for maintenance monotherapy, are currently recommended [I, A].
- In non-squamous tumours and in patients treated with third-generation regimens, cisplatin should be the treatment of choice [I, B].
- The nab-PC regimen could be considered a chemotherapeutic option in advanced NSCLC patients, particularly in patients with greater risk of neurotoxicity, pre-existing hypersensitivity to paclitaxel or contraindications for standard paclitaxel premedication [I, B].
- Platinum-based doublets with a third-generation cytotoxic agent (gemcitabine, vinorelbine, taxanes) are recommended in advanced SCC patients [I, A].
- Necitumumab plus gemcitabine and cisplatin represents a treatment option for advanced SCC expressing EGFR by IHC [I, B; ESMO-MCBS v1.0 score: 1].
- Pemetrexed is preferred to gemcitabine or docetaxel in patients with non-squamous tumours [II, A]. Pemetrexed use is restricted to NSCC in any line of treatment [I, A].
- The combination of bevacizumab and other platinum-based chemotherapies may be considered in eligible patients with NSCC and PS 0–1 [I, A].

PS 2 and beyond

- In patients with PS 2, chemotherapy compared with BSC prolongs survival and improves QoL [I, B].
- Carboplatin-based combination chemotherapy should be considered in eligible PS 2 patients [II, A].
- Single-agent chemotherapy with gemcitabine, vinorelbine and docetaxel is an alternative treatment option [I, B].
- Poor PS (3–4) patients should be treated with BSC only [II, B].

Elderly patients

- Carboplatin-based doublet chemotherapy is recommended in eligible patients aged 70–89 with PS 0–2 and with adequate organ function [I, B].
- For those patients not eligible for doublet chemotherapy, single-agent chemotherapy remains the standard of care [I, B].
- CGA can predict morbidity and mortality in elderly patients with cancer and can help to adapt cancer management to each patient's fitness or frailty [III, C].

Continued

Table 4. *Continued***Maintenance**

- Maintenance chemotherapy should be offered only to patients with PS of 0-1 after first-line chemotherapy. Decisions about maintenance should consider histology, response to platinum-doublet chemotherapy and remaining toxicity after first-line chemotherapy, PS and patient preference.
- In patients with NSCC and PS 0-1, pemetrexed switch maintenance should be considered in patients having disease control following four cycles of non-pemetrexed containing platinum-based chemotherapy [I, B]. Pemetrexed continuation maintenance should be considered in patients having disease control following four cycles of cisplatin-pemetrexed [I, A].
- Erlotinib is indicated for switch maintenance treatment, but limited to patients with locally advanced or metastatic NSCLC with EGFR-activating mutations [I, B].

Second-line treatment of EGFR- and ALK-negative disease (SCC and NSCC)

- Patients clinically or radiologically progressing after first-line chemotherapy with PS 0-2 should be offered second-line chemotherapy [I, A].
- Treatment may be prolonged if disease is controlled and toxicity acceptable [II, B].
- Comparable options as second-line therapy consist of pemetrexed—for NSCC only—or docetaxel [I, B].
- Nivolumab at 3 mg/kg every 2 weeks is recommended in pretreated patients with advanced SCC [I, A; ESMO-MCBS v1.0 score: 5]. It represents a treatment option in pretreated patients with advanced NSCC [I, B; ESMO-MCBS v1.0 score: 5]. PD-L1-positive tumour patients benefitted from the use of nivolumab, compared with docetaxel [I, B]. In PD-L1-negative tumours, nivolumab and docetaxel showed similar results, with a more favourable toxicity profile for nivolumab [II, A].
- Nintedanib combined with docetaxel is a treatment option in patients with adenocarcinoma, especially in those progressing within 9 months from the start of first-line chemotherapy [II, B].
- Ramucirumab combined with docetaxel is a treatment option in patients with NSCLC progressing after first-line chemotherapy with PS 0-2 [I, B; ESMO-MCBS v1.0 score: 1].
- Pembrolizumab at 2mg/kg every 3 weeks is recommended in pretreated patients with platinum-pretreated, advanced SCC or NSCC expressing PD-L1 [I, A; ESMO-MCBS v1.0 score: 3 if PD-L1 >1%; 5 if PD-L1 >50%].
- In patients unfit for chemotherapy, erlotinib is a potential option in patients with unknown EGFR status, WT EGFR and unfit for chemotherapy [II, C].
- In patients with SCC unfit for chemotherapy, afatinib is a potential option in patients with unknown EGFR status or EGFR WT patients with PS 0-2 [II, C; ESMO-MCBS v1.0 score: 1].

Tumours with an activating EGFR mutation

- First-line treatment with an EGFR TKI (erlotinib, gefitinib or afatinib) is the standard of care for tumours bearing an activating (sensitising) EGFR mutation [I, A].
- Patients with EGFR mutation and PS 3-4 may also be offered an EGFR TKI [II, A].
- If information on an EGFR-sensitising mutation becomes available during first-line platinum-based chemotherapy, continue chemotherapy for up to four cycles and offer the EGFR TKI as maintenance treatment in patients achieving disease control, or as second-line treatment at the time of progression [I, A].
- In patients who progress after an EGFR TKI, rebiopsy is strongly encouraged to look for EGFR T790M mutation, relevant for therapeutic strategy. An alternative to tissue rebiopsy is represented by liquid biopsy [III, A].
- Osimertinib is recommended in patients who have developed the EGFR T790M resistance mutation after EGFR TKI treatment [III, A].
- When a rebiopsy is not feasible, or when the EGFR T790M mutation is not detected in patients who progress after an EGFR TKI, the standard of care is platinum-based doublet chemotherapy. No data support the concurrent use of EGFR TKI and platinum-based doublet chemotherapy [I, A].

Tumours with ALK rearrangement

- First-line treatment with crizotinib is preferred for patients with ALK-rearranged NSCLC [I, A].
- Any patient with NSCLC harbouring an ALK fusion should receive crizotinib as next-line therapy, if not received previously [I, A].
- In patients who progress after an ALK TKI, second-generation ALK inhibitors such as ceritinib are recommended [III, A]. Several alternative ALK inhibitors, such as alectinib, are currently in clinical development.

Role of radiotherapy

- Radiotherapy can achieve symptom control for 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 haemoptysis, symptomatic airway obstruction and following surgery for CNS, and, sometimes, bone surgery [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 [II, B]; thoracoscopic insufflation with talc (poudrage) is more effective than talc slurry sclerosis [II, B].

Role of minimal invasive procedures in stage IV NSCLC

- In case of symptomatic major airways obstruction or postobstructive infection, endoscopy debulking by laser, cryotherapy or stent placement may be helpful [III, C].

Continued

Table 4. Continued

- Endoscopy is useful in the diagnosis and treatment (endobronchial or by guiding endovascular embolisation) of haemoptysis [III, C].
- Vascular stenting might be useful in NSCLC-related superior vena cava compression [II, B].

Role of palliative care in stage IV NSCLC

- Early palliative care intervention is recommended, in parallel with standard oncological care [II, A].

Brain metastases

- Treatment is recommended in RPA class I patients (<65 years old, KI \geq 70%, no other extracranial metastases and controlled primary tumour) or class II patients (KI \geq 70%, with other extracranial metastases and/or an uncontrolled primary tumour).
- In the case of a single metastasis, SRS or resection is the recommended treatment [II, B].
- For two to three metastases, SRS is recommended in patients with RPA class I–II [II, B]. When more than three brain metastases are diagnosed, WBRT is recommended in patients with RPA class I–II [II, B].
- RPA class III patients (KI <70%) should not receive radiotherapy in view of the dismal prognosis [I, B]; only BSC is recommended.
- WBRT schedules of 20 Gy in 5 fractions or 30 Gy in 10 fractions have no difference in outcome [I, A].
- Systemic therapy is a reasonable option for patients with no or relatively minor symptoms from brain metastases. Radiotherapy is recommended in the case of the development or progression of symptoms while on treatment [II, B].
- For symptomatic brain metastases and/or oedema, dexamethasone 4 mg/day or an equivalent dose of another corticosteroid is recommended [II, A].
- In fit patients, options other than WBRT for the treatment of brain metastases could be considered [IV, C].
- In patients with a druggable oncogene driver and clinically asymptomatic brain metastases, next-generation TKIs may restore control of brain disease and delay cranial radiotherapy [III, B].
- In ALK-positive patients progressing on crizotinib, treatment with ceritinib or alectinib shows activity against CNS disease [III, B].

Bone metastases

- Zoledronic acid reduces SREs (pathological fracture, radiation/surgery to bone or spinal cord compression) and is recommended in stage IV bone metastatic disease [II, B].
- Denosumab is not inferior to [I, B] and shows a trend towards superiority to zoledronic acid in lung cancer in terms of SRE prevention [II, B].

Treatment of oligometastatic disease

- Stage IV patients with one to three synchronous metastases at diagnosis may experience long-term DFS following systemic therapy and radical local treatment (high-dose radiotherapy or surgery) [III, B]. Because of limited evidence, inclusion in clinical trials is preferred.
- Stage IV patients with limited metachronous metastases may be treated with a radical local treatment and may experience long-term DFS [III, B]. However, this is based only on retrospective data.
- Solitary lesions in the contralateral lung should, in most cases, be considered as synchronous secondary primary tumours and, if possible, treated with radical intent [IV, B].
- In patients with driver mutations for whom active systemic therapies are available, the use of ablative therapies such as SABR or surgery is likely to increase. However, there is limited prospective data to support this policy [IV, C].

Response evaluation

- Response evaluation is recommended after two to three cycles of chemotherapy using the same radiographic investigation that initially demonstrated tumour lesions.
- Measurements and response assessment should follow RECIST criteria v1.1. However, the adequacy of RECIST in evaluating the response to EGFR or ALK TKI in respective genetically driven NSCLC is debatable.
- In the case of immune checkpoint inhibitor therapy, RECIST criteria should be used, although irRC may have a role in the overall assessment of therapy.

Follow-up

- Close follow-up, at least every 6–12 weeks to allow for early initiation of second-line therapy, is advised, but should depend on individual retreatment options [III, B].
- Follow-up with PET is not routinely recommended, due to its high sensitivity and relatively low specificity.

WHO, World Health Organisation; IASLC, International Association for the Study of Lung Cancer; ATS, American Thoracic Society; ERS, European Respiratory Society; NSCLC, non-small-cell lung cancer; IHC, immunohistochemistry; NSCLC-NOS, non-small-cell lung cancer-not otherwise specified; EGFR, epidermal growth factor receptor; NSCC, non-squamous cell carcinoma; SCC, squamous cell carcinoma; ALK, anaplastic lymphoma kinase; FISH, fluorescence *in situ* hybridisation; PS, performance status; CEA, carcinoembryonic antigen; CT, computed tomography; CNS, central nervous system; MRI, magnetic resonance imaging; PET, positron emission tomography; AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control; BSC, best supportive care; QoL, quality of life; CGA, comprehensive geriatric assessment; PD-L1, programmed death ligand 1; WT, wild-type; TKI, tyrosine kinase inhibitor; RPA, recursive partitioning analysis; KI, Karnofsky Index; SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy; SRE, skeletal-related event; DFS, disease-free survival; SABR, stereotactic ablative radiotherapy; RECIST, Response Evaluation Criteria in Solid Tumours; irRC, immune-related response criteria.

Table 5. Magnitude of Clinical Benefit Scale (MCBS) table for new therapies/indications in non-small-cell lung cancer (NSCLC)^a

Therapy	Disease setting	Trial	Control	Absolute survival gain	HR (95% CI)	QoL/toxicity	MCBS score ^b
Afatinib, an irreversible ErbB family blocker	Advanced	Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial [101] Phase III NCT01523587	Erlotinib, as second-line treatment of patients with advanced SCC of the lung. Median OS 6.6 months	OS gain: 1.1 months	OS: HR for death 0.81 (0.69–0.95)	Similar toxicity profile Improved overall health-related QoL	1 (Form 2a)
Bevacizumab, a humanised anti-VEGF monoclonal antibody, in combination with erlotinib	Advanced	Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer (NSCLC) harbouring EGFR mutations (JO25567): an open-label, randomised, multicentre, phase 2 study [116] Phase II Japan Pharmaceutical Information Center, number JapicCTI-111390	Erlotinib alone as a first-line therapy until disease progression or unacceptable toxicity. Median PFS 9.7 months	PFS gain: 6.3 months	PFS HR: 0.54 (0.36–0.79)	Deteriorated toxicity profile. No improvement in QoL	2 (Form 2b)
Erlotinib, an EGFR TKI	Advanced	Erlotinib as maintenance treatment in advanced NSCLC: a multicentre, randomised, placebo-controlled phase 3 study [77] Phase III NCT00556712	Placebo, as maintenance treatment in advanced NSCLC. Control PFS 11.1 weeks	PFS gain: 1.2 weeks	PFS: HR 0.71 (0.62–0.82)	Deteriorated toxicity profile	1 (Form 2b)
Necitumumab, a second-generation, recombinant, human IgG1 EGFR antibody in combination with gemcitabine and cisplatin	Advanced	Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous NSCLC (SQUIRE): an open-label, randomised, controlled phase 3 trial. [52] Phase III NCT00981058	Gemcitabine and cisplatin as first-line therapy in patients with stage IV SCC. Control OS 9.6 months	OS gain: 1.6 months	OS: HR for death 0.84 (0.74–0.96)	Deteriorated toxicity profile	1 (Form 2a)
Nivolumab, a fully human IgG4 PD-1 immune-checkpoint-inhibitor antibody	Advanced	Nivolumab versus docetaxel in advanced squamous cell NSCLC [98] Phase III NCT01642004	Docetaxel in patients with advanced SCC who have disease progression during or after first-line chemotherapy. Control OS 6 months	OS gain: 3.2 months. 2-year survival gain 15%	OS: HR for death 0.59 (0.44–0.79)	Improved toxicity profile	5 (Form 2a) ^c

Continued

Table 5. *Continued*

Therapy	Disease setting	Trial	Control	Absolute survival gain	HR (95% CI)	QoL/toxicity	MCBS score ^b
Nivolumab, a fully human IgG4 PD-1 immune-checkpoint-inhibitor antibody	Advanced	Nivolumab versus docetaxel in advanced non-squamous NSCLC [104] Phase III NCT01673867	Docetaxel in patients with NSCC that had progressed during or after platinum-based doublet chemotherapy. Control OS 9.4 months	OS gain: 2.8 months. 2-year survival gain 16%	OS: HR for death 0.73 (0.59–0.89)	Improved toxicity profile	5 (Form 2a)
Ramucirumab, a human IgG1 monoclonal antibody that targets the extracellular domain of VEGFR2, in combination with docetaxel	Advanced	Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV NSCLC after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial [94] Phase III NCT01168973	Placebo plus docetaxel in patients with SCC or NSCC who had progressed during or after a first-line platinum-based chemotherapy regimen. Control OS 9.1 months	OS gain: 1.4 months	OS: HR for death 0.86 (0.75–0.98)	Deteriorated toxicity profile	1 (Form 2a)
Pembrolizumab, an anti-PD-1 monoclonal antibody	Advanced	Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial [96] Phase III NCT01905657	Docetaxel in patients with previously treated, PD-L1-positive, advanced NSCLC. Control OS 8.5 months	In PD-L1 >1%: ^d OS gain: 1.9 months In PD- L1 >50%: ^d OS gain: 6.7 months	In PD-L1 >1%:d OS: HR for death 0.71, (0.58–0.88) In PD-L1 >50%: d OS: HR for death 0.54, (0.38–0.77)	Improved toxicity profile	In PD-L1 >1%: 3 (Form 2a) In PD-L1 >50%: 5 (Form 2a)

HR, hazard ratio; CI, confidence interval; QoL, quality of life; OS, overall survival; VEGF, vascular endothelial growth factor; EGFR, endothelial growth factor receptor; TKI, tyrosine kinase inhibitor; PFS, progression-free survival; NSCC, non-squamous cell carcinoma; SCC, squamous cell carcinoma; IgG1, immunoglobulin G1; PD-1, programmed death 1; VEGFR2, VEGF receptor 2.

^aEMA approvals in 2016 to end of August 2016.

^bESMO-MCBS version 1.0 [181].

^cEMA approval, October 2015.

^dCo-primary end points (overall survival and progression-free survival both in the total population and in patients with PD-L1 expression on at least 50% of tumour cells)

are based on often small retrospective series. One prospective single-arm phase II trial was reported, in which the majority of patients had a single metastatic lesion [173]. With systemic treatment and radical local radiotherapy (brain SRS or high-dose fractionated radiotherapy) or surgery of all tumour lesions, the trial reported that 13% of patients remained disease free at 3 years.

In a retrospective study of 37 patients with synchronous NSCLC and brain metastasis, which were both surgically excised [174], the 1- and 2-year OS rates were 62% and 24%, respectively. It is to note that in this series nodal status did not affect survival on univariate analysis. Nevertheless, lymph node involvement by the primary tumour is usually considered a contraindication for further surgical therapy, and thorough invasive assessment of the mediastinum is recommended before any attempt of surgical treatment of synchronous oligometastatic disease [169].

Analysis of the IASLC Lung Cancer Staging Project database for the eighth TNM has proposed the category M1b for a single metastatic lesion in a single distant organ, and M1c for either multiple metastases to a single organ or for multiple lesions to multiple organs [175]. This proposal will allow for prospective collection and evaluation of staging and outcomes data for these subgroups of oligometastatic patients.

At present, it is recommended that patients with multiple synchronous metastases should be treated within prospective clinical trials.

With the advent of long-term survivors following treatment of patients with druggable mutations, who may develop oligoprogression, use of ablative therapies such as stereotactic ablative radiotherapy (SABR) or surgery is likely to increase. Nevertheless, there is a paucity of prospective data to support this policy [IV, C].

response evaluation

Response evaluation is recommended after 2–3 cycles of chemotherapy, using the same initial radiographic investigation that demonstrated tumour lesions. The same procedure and timing (every 6–9 weeks) should be applied for the response evaluation

in patients treated with targeted therapies and/or immunotherapy. Follow-up with PET is not routinely recommended, due to its high sensitivity and relatively low specificity. Measurements and response reporting should follow RECIST criteria v1.1 [36]. The adequacy of RECIST in evaluating response to EGFR or ALK TKI in respective genetically driven NSCLC is still debatable even if this remains the standard method of evaluation for these patients. In these two subgroups of patients, treatment beyond RECIST progression is a common approach, pursuing clinical benefit more than morphologic response. This approach differs from what was carried out historically in non-oncogene-addicted tumours treated with cytotoxic agents.

Criteria for response evaluation with immunostimulatory monoclonal antibodies (imAbs) are currently the matter of intense work and debate. The vast majority of trials in NSCLC evaluating anti-PD1/PD-L1 antibodies have traditionally used RECIST v1.0/v1.1 criteria, which remain standard criteria in NSCLC. More recently, immune-related response criteria (irRC) have been proposed and validated in malignant melanoma to better assess the variety of responses that can be generated upon imAbs [176, 177]. IrRC undoubtedly allows better taking into account the potential for an initial ‘flare-up’ or pseudo-progression at the tumour site, for the appearance of new non-target lesions as well as for the difference between kinetics of response observed between imAbs and cytotoxic therapy; however, it is still insufficient to describe all response profiles or clinical benefits observed, and further data are needed in this context. Also, alternative end points for clinical trials evaluating imAbs, such as DCR and tumour growth rate, could be probably implemented, especially considering the highly variable timing of response, ranging from 6 weeks to several months after treatment initiation, or even after treatment cessation [178, 180].

follow-up

The optimal approach to post-treatment management of patients with NSCLC, including the role of radiological

Table 6. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America–United States Public Health Service Grading System^a)

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

^aBy permission of the Infectious Diseases Society of America [182].

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

methodology

These clinical practice guidelines were developed in accordance with the ESMO standard operating procedures for clinical practice guidelines development, <http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology>. The relevant literature has been selected by the expert authors. A summary of recommendations is provided in Table 4. An MCBS table with ESMO-MCBS scores is included in Table 5. ESMO-MCBS v1.0 [181] was used to calculate scores for new therapies/indications approved by the EMA since 1 January 2016. Levels of evidence and grades of recommendation have been applied using the system shown in Table 6. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

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conflict of interest

S.N. has reported speaker honoraria from Hoffmann-La Roche, Eli Lilly, MSD, Boehringer Ingelheim, AstraZeneca and Bristol-Myers Squibb. F.B. has received honoraria from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Clovis Oncology, Eli Lilly Oncology, F. Hoffmann-La Roche Ltd, Novartis, Merck, MSD, Pierre Fabre and Pfizer. R.C. has received honoraria from Roche, Eli Lilly, MSD, Boehringer Ingelheim, AstraZeneca, Novartis, Clovis and Bristol-Myers Squibb. T.C. has received consultant honoraria from Boehringer Ingelheim, Pfizer and Bristol-Myers Squibb. S.E. is a consultant to Lilly, Novartis, Bristol-Myers Squibb, Roche and Boehringer Ingelheim. K.K. has reported advisory and/or lecture fees from AstraZeneca, Roche, Lilly, Boehringer Ingelheim, Pfizer, Novartis, Bristol-Myers Squibb and MSD. S.Po. is an uncompensated consultant to Ariad, AstraZeneca, Bristol-Myers Squibb, Clovis Oncology, MSD, Novartis and Pfizer and has received honoraria from Eli Lilly. M.R. has received honoraria for lectures and consultancy from Roche, Lilly, Bristol-Myers Squibb, MSD, AstraZeneca, Boehringer Ingelheim, Pfizer, Novartis and Celgene. S.S. has received honoraria from Eli Lilly, and honoraria and research support from Varian Medical Systems. G.V.S. has reported advisory role for Johnson & Johnson, speaker's honoraria from Bard, investigation grants from Baxter and team support from Medtronic. J.V. has

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