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CLINICAL PRACTICE GUIDELINES

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

D. Planchard[1], S. Popat[2], K. Kerr[3], S. Novello[4], E. F. Smit[5], C. Faivre-Finn[6], T. S. Mok[7], M. Reck[8], P. E. Van Schil[9], M. D. Hellmann[10] & S. Peters[11], on behalf of the ESMO Guidelines Committee*

[1]Department of Medical Oncology, Thoracic Group, Gustave-Roussy Villejuif, France; [2]Royal Marsden Hospital, London; [3]Aberdeen Royal Infirmary, Aberdeen University Medical School, Aberdeen, UK; [4]Department of Oncology, University of Turin, San Luigi Hospital, Orbassano, Italy; [5]Thoracic Oncology Service, Netherlands Cancer Institute, Amsterdam, The Netherlands; [6]Division of Cancer Sciences, University of Manchester, Manchester, UK; [7]Department of Clinical Oncology, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China; [8]LungenClinic Airway Research Center North (ARCN), German Center for Lung Research, Grosshansdorf, Germany; [9]Department of Thoracic and Vascular Surgery, Antwerp University Hospital and Antwerp University, Antwerp, Belgium; [10]Weill Cornell Medical College, New York, USA; [11]Medical Oncology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

**Correspondence to*: ESMO Guidelines Committee, ESMO Head Office, Via Ginevra 4, CH-6900 Lugano, Switzerland. E-mail: clinicalguidelines@esmo.org

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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 in males with an estimated 1.2 million incident cases worldwide. 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 [1]. The highest incidence is found in Central/Eastern Europe and Asia with age-standardised incidence rates of 53.5 and 50.4 per 100 000, respectively. European projections for 2017 indicate a 10.7% drop in 5 years with an incidence of 33.3/100 000 in males and a rise of 5.1% and an incidence of 14.6/100 000 in females [2]. Contrary to the United States, the death rate in females is increasing in Europe [3]. The number of lung cancer-related deaths in Europe for 2017 is estimated to represent the leading cause of cancer deaths in both genders, accounting for 24% in males and 15% in females, respectively [2].

Non-small cell lung cancer (NSCLC) accounts for 80%–90% of lung cancers, while small cell lung cancer (SCLC) has been decreasing in frequency in many countries over the past two decades [4]. During the last 25 years, the distribution of histological types of NSCLC has changed: in the United States, squamous cell carcinoma (SCC), formerly 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 [5].

The World Health Organization (WHO) estimates that lung cancer is the cause of 1.59 million deaths globally per year, with 71% of them caused by smoking. Tobacco smoking remains the main cause of lung cancer and the geographical 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 lung cancers [6]. In countries with active tobacco control measures, the incidence of lung cancer has begun to decline in men and is reaching a plateau for women [1, 7–9]. Several other factors have been described as lung cancer risk factors, including exposure to asbestos, arsenic, radon and non-tobacco-related polycyclic aromatic hydrocarbons. Hypotheses about indoor air pollution (e.g. coal-fuelled stoves and cooking fumes) are made for the relatively high burden of non-smoking-related lung cancer in women in some countries [10]. 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.

About 500 000 deaths annually are attributed to lung cancer in lifetime never-smokers [1]. Absence of any history of tobacco smoking characterises 19% of female compared with 9% of male lung carcinoma in the United States [11, 12]. An increase in the proportion of NSCLC in never-smokers has been observed, especially in Asian countries [13]. 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 [14].

Use of non-cigarette tobacco products such as cigars and pipes has been increasing. A pooled analysis highlighted the increased risk, particularly for lung and head and neck cancers, in smokers (former and current) of cigars and pipes [15].

Familial risk of lung cancer has been reported in several registry-based studies after careful adjustment for smoking [16]. A recent study estimated the heritability of lung cancer at 18% but many of the genetic components remain unidentified. Genome-wide association studies (GWAS) have identified lung cancer susceptibility loci including *CHRNA3, CHRNA5, TERT, BRCA2, CHECK2* and the human leukocyte antigen (*HLA*) region [17–19]. Another trial, including data from 29 266 cases and 56 450 controls from European descent, found 18 susceptibility loci reaching genome-wide significance, among which 10 were previously unknown. Interestingly, while four of the latter were associated with overall lung cancer risk, six were associated with lung adenocarcinoma only [20].

Diagnosis and pathology/molecular biology

Diagnosis

Changes in the therapeutic scenario in the last 15 years have emphasised the need for a multidisciplinary approach in lung cancer. Data show that high-volume centres and multidisciplinary teams are more efficient at managing patients with lung cancer than low-volume or non-multidisciplinary centres, by providing more complete staging, better adherence to guidelines and increased survival [21, 22]. Multidisciplinary tumour boards influence providers' initial plans in 26%–40% of cases [23]. The absolute need to reach a proper and precise morphological and biological definition often requires challenging tissue sampling, with most treatment decisions depending on the information obtained from the specimen collected at diagnosis.

Bronchoscopy is a technique ideally suited to large, central lesions and offers the advantage of minimal morbidity. Bronchoscopy can be used for bronchial washing, brushing, bronchial and transbronchial biopsy, with a diagnostic yield of 65%–88% [24–26]. By combining direct bronchoscopic airway visualisation with ultrasound-guided biopsy of the lesion, endobronchial ultrasound (EBUS) provides a diagnostic yield of 75%–85% in large, centrally located lesions [27, 28]. Fibre optic bronchoscopy allows for the evaluation of regional lymph nodes by EBUS and/or endoscopic ultrasound (EUS). EBUS-guided transbronchial needle aspiration (TBNA) is less invasive and at least as accurate as mediastinoscopy [29]. Several studies have shown that cytological specimens obtained by EBUS-TBNA are suitable for molecular testing for epidermal growth factor receptor (EGFR), Kirsten rat sarcoma viral oncogene homologue (KRAS) and anaplastic lymphoma kinase (ALK) status [30–33]; however, collection of samples suitable for broader molecular diagnostic testing should be encouraged.

In case of peripheral lesions, transthoracic percutaneous fine needle aspiration and/or core biopsy, under imaging guidance [typically computed tomography (CT)] is proposed [34]. Needle biopsy is associated with a diagnostic accuracy of > 88% yield, a sensitivity of 90% and a false-negative rate of 22% [25, 35–38]. The most significant disadvantage of transthoracic needle biopsy is a procedural risk of pneumothorax, ranging from 17% to 50% [37, 38].

In the presence of a pleural effusion, thoracentesis could represent both a diagnostic tool and a palliative treatment. If fluid cytology examination is negative, image-guided pleural biopsy or surgical thoracoscopy should be carried out. More invasive, surgical approaches [mediastinoscopy, mediastinotomy, thoracoscopy, video-assisted thoracoscopic surgery (VATS), secondary lesion resection etc.] in the diagnostic workup are considered when the previously described techniques cannot allow for an accurate diagnosis.

Pathology/molecular biology

Histological diagnosis. Histological diagnosis of NSCLC is crucial to many treatment decisions and should be as exact and detailed as the samples and available technology allow. Diagnosis should be based upon the criteria laid out in the WHO classification [39]. This classification details the complete diagnostic approach for surgically resected tumours but, importantly, also provides guidance for assessing and reporting small biopsy and cytology samples where complete morphological criteria for specific diagnosis may not be met [39–41].

Most patients with NSCLC present with advanced stage unresectable disease, therefore all treatment-determining diagnoses must be made on small biopsy and/or cytology-type samples. Sampling may be carried out of the primary tumour or any accessible metastases, taken under direct vision or more usually with image-guided assistance, which greatly increases the diagnostic yield (hit rate). Sampling metastatic disease may facilitate staging, as well as diagnosis. These diagnostic samples frequently have limited tumour material and must therefore be handled accordingly; ensuring processing is suitable for all likely diagnostic procedures and that material is used sparingly at each step, since many diagnostic tests may be required [42].

Immunohistochemistry (IHC) has become a key technique in primary diagnosis as well as in predictive biomarker assessment. In those cases of NSCLC where specific subtyping is not possible by morphology alone, a limited panel of IHC is recommended to determine the subtype [39, 40]. Thyroid transcription factor 1 (TTF1) positivity is associated with probable diagnosis of adenocarcinoma, p40 positivity with probable diagnosis of SCC; if neither are positive the diagnosis remains NSCLC-not otherwise specified (NOS). IHC staining should be used to reduce the NSCLC-NOS rate to < 10% of cases diagnosed [IV, A]. Pathologists are urged to conserve tissue at every stage of diagnosis, to use only two tissue sections for IHC NSCLC subtyping and to avoid excessive IHC investigation, which may not be clinically relevant.

Molecular diagnostics. After morphological diagnosis, the next consideration is therapy-predictive biomarker testing. This practice will be driven by the availability of treatments and will vary widely between different geopolitical health systems [43–45]. Contemporary practice has now evolved into two testing streams, one for the detection of targetable, usually addictive, oncogenic alterations and the other for immuno-oncology therapy biomarker testing. A personalised medicine synopsis table is shown in Table 1.

Several molecular drivers for oncogene addiction represent strong predictive biomarkers and excellent therapeutic targets. They are generally mutually exclusive of each other [43–45]. These tumours are much more common in never- (never smoked or who smoked < 100 cigarettes in lifetime), long-time ex- (> 10 years) or light-smokers (< 15 pack-years) but they can also be found in patients who smoke. The vast majority of oncogene-addicted lung cancers are adenocarcinomas. Patients, in general, tend to be younger, while female gender and East Asian ethnicity particularly enriches for *EGFR*-mutant tumours. Nonetheless, guidelines suggest that all patients with advanced, possible, probable or definite, adenocarcinoma should be tested for oncogenic drivers [43–46]. Molecular testing is not recommended in SCC, except in those rare circumstances when SCC is found in a never-, long-time ex- or light-smoker (< 15 pack-years) [IV, A]. Testing for *EGFR* mutations and rearrangements involving the *ALK* and *ROS1* genes are now considered mandatory in most European countries. *BRAF V600E* mutations are rapidly approaching this status as first-line BRAF/MEK inhibitors are more widely approved, while HER2 (human epidermal growth factor receptor 2) and MET exon 14 mutations and fusion genes involving RET and NTRK1 (neurotropic tropomyosin receptor kinase 1) are evolving targets/biomarkers [43–46].

EGFR tyrosine kinase inhibitors (TKIs) are established effective therapies in patients who have activating and sensitising mutations in exons 18–21 of *EGFR* [47]. Prevalence is around 10%–20% of a Caucasian population with adenocarcinoma but much higher in Asian population. Around 90% of the most common mutations comprise deletions in exon 19 and the *L858R* substitution mutation in exon 21. Any testing approach must cover these mutations [I, A]; however, complete coverage to include exons 18–21 is recommended [III, B]. The *T790M* exon 20 substitution mutation is only rarely found in EGFR TKI-naive disease using standard techniques but is the most frequent cause of resistance to first- and second-generation EGFR TKIs (50%–60% of cases). Cases of patients carrying germline *T790M* mutation have also been reported [48]. Further studies to better understand the prevalence, familial penetrance and lifetime lung cancer risk in germline *T790M*-mutant patients are warranted. Implications of this mutation in TKI-naive disease are unclear, but the availability of TKIs effective against *T790M*-mutant recurrent disease makes *T790M* testing on disease relapse mandatory [I, A]. Cell-free DNA (cfDNA) blood testing is an acceptable approach to detect *T790M* at relapse but lacks sensitivity, so all patients with a negative blood test still require tissue biopsy [II, A] [49]. Tissue biopsy may also be more effective in identifying other resistance mechanisms which may require alternative treatment (SCLC transformation, *MET* amplification, *HER2* alterations etc.).

Table 1. A personalised medicine synopsis table for metastatic NSCLC

Biomarker	Method	Use	LoE, GoR
EGFR mutation	Any appropriate, validated method, subject to external quality assurance	To select those patients with *EGFR*-sensitising mutations most likely to respond to EGFR TKI therapy	I, A
ALK rearrangement	Any appropriate, validated method, subject to external quality assurance. FISH is the historical standard but IHC is now becoming the primary therapy-determining test, provided the method is validated against FISH or some other orthogonal test approach. NGS is an emerging technology	To select those patients with *ALK* gene rearrangements most likely to respond to ALK TKI therapy	I, A
ROS1 rearrangement	FISH is the trial-validated standard. IHC may be used to select patients for confirmatory FISH testing but currently lacks specificity. NGS is an emerging technology. External quality assurance is essential	To select those patients with *ROS1* gene rearrangements most likely to respond to ROS1 TKI therapy	II, A
BRAF mutation	Any appropriate, validated method, subject to external quality assurance	To select those patients with *BRAF V600*-sensitising mutations most likely to respond to BRAF inhibitor, with or without MEK inhibitor therapy	II, A
PD-L1 expression	IHC to identify PD-L1 expression at the appropriate level and on the appropriate cell population(s) as determined by the intended drug and line of therapy. Only specific trial assays are validated. Internal and external quality assurance are essential	To enrich for those patients more likely to benefit from anti-PD-1 or anti-PD-L1 therapy. For pembrolizumab, testing is a companion diagnostic for nivolumab and atezolizumab, testing is complementary	I, A

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; FISH, fluorescent *in situ* hybridisation; GoR, grade of recommendation; IHC, immunohistochemistry; LoE, level of evidence; MEK, mitogen-activated protein kinase kinase; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TKI, tyrosine kinase inhibitor.

Fusion genes involving *ALK* and a number of partners (most commonly *EML4)* account for around 2%–5% of the same population that is routinely tested for *EGFR* mutations [50]. *ALK*-driven adenocarcinoma is very sensitive to several ALK TKIs. Early trials validated break-apart fluorescent *in situ* hybridisation (FISH) as the test to identify *ALK* gene rearrangement but the close association between a positive FISH test and modestly elevated ALK protein in tumour cells allows ALK IHC to be used, either to select cases for confirmatory FISH testing or as the primary therapy-determining test [50, 51]. ALK IHC must reliably detect low levels of ALK protein and be validated against alternative tests to detect *ALK* fusion genes, especially if ALK IHC is used as the therapy-determining assay, without confirmation by FISH [II, A]. Emerging data demonstrate that the presence of the ALK protein (positive IHC staining) is associated with treatment response [I, A] [52, 53]. Recently, IHC has been accepted as an equivalent alternative to FISH for ALK testing [54]. Testing for *ALK* rearrangement should be systematically carried out in advanced non-squamous NSCLC [I, A]. *ALK* mutations are emerging as important resistance mechanisms to ALK TKIs and *ALK* mutation testing may soon become a routine test at relapse as newer-generation ALK TKIs show differential efficacy against different *ALK* mutations [55].

ROS1 fusion genes are yet another addictive oncogenic driver that occurs in ∼1%–4% of the same testing population. Like *ALK*, *ROS1* has several potential fusion gene partners. Crizotinib, a TKI effective against ALK and MET, is also approved by the European Medicines Agency (EMA) for use in *ROS1*-rearranged adenocarcinomas. FISH has been the standard approach to detecting *ROS1* rearrangements. IHC may be used in a manner similar to ALK testing, to identify candidate tumours for confirmatory FISH testing. The sensitivity of this approach is high, using currently available IHC, but specificity of IHC is low [IV, C]. FISH or other testing is required to confirm the diagnosis; IHC is currently not recommended as the primary treatment determining test [IV, A] [45, 46, 50]. Testing for *ROS1* rearrangement should be systematically carried out in advanced non-squamous NSCLC [III, A].

BRAF mutation testing is now required in many countries after the approval of BRAF and MEK inhibitors for *BRAF V600*-mutant NSCLC. Any method is valid provided that it is adequately sensitive for the samples used and has been appropriately quality-assured, both within the laboratory and through external quality assurance. The *V600E* mutation is the most common of the *BRAF V600* family and, overall, these *BRAF* mutations are found in ∼2% of cases. *BRAF V600* mutations appear mutually exclusive to *EGFR* and *KRAS* mutations, *ALK* and *ROS1* rearrangements and are similarly much more common in adenocarcinoma. *BRAF V600* mutation status should be systematically analysed in advanced non-squamous NSCLC for the prescription of BRAF/MEK inhibitors [II, A].

For many laboratories, testing for *EGFR* and *BRAF* mutations and *ALK* and *ROS1* rearrangements involves individual standalone tests. Multiplex, massively parallel, so-called next-generation sequencing (NGS) of various sorts is rapidly being adopted as the standard approach to screening adenocarcinomas for oncogenic targets [III, A] [45, 49, 50, 56]. Platform-specific, commercially available panels can cover genes of interest and provide a comprehensive, multiplex test for mutations and, in some cases, fusion genes. NGS will not address biomarkers that require testing at the protein level (requires IHC) and the question of whether NGS-detected fusion genes require an orthogonal test (IHC, FISH) for confirmation remains open. Whatever testing modality is used, it is mandatory that adequate internal validation and quality control measures are in place and that laboratories participate in, and perform adequately, external quality assurance schemes for each biomarker test [III, A].

The approval of the anti-programmed cell death protein 1 (PD-1) agent pembrolizumab as a standard-of-care first-line treatment in selected patients has made programmed death-ligand 1 (PD-L1) IHC a mandatory test in all patients with advanced NSCLC. Although the PD-L1 IHC 22C3 assay was the only test validated in clinical trials of pembrolizumab, extensive technical comparison studies suggest that trial-validated commercial kit assays based on the 28-8 and SP263 PD-L1 IHC clones may be alternative tests [III, A] [57–61]. If laboratories use, by choice or force of circumstances, a non-trial-validated PD-L1 IHC test, i.e. a laboratory developed test (LDT), there is a high risk that the assay may fail quality assurance and a very careful, extensive validation is essential before clinical use [IV, A] [35, 36]. There is a relationship between the extent of PD-L1 expression on tumour cells, or in some trials in tumour infiltrating immune cells, and the probability of clinical benefit from numerous anti-PD-1 or PD-L1 agents, in first- and second-line therapy [57]. For pembrolizumab, the mandatory treatment threshold is a tumour proportion score (TPS, presence of PD-L1 signal on tumour cell membranes) $\geq$ 50% in first line and $\geq$ 1% in second line [62, 63]. PD-L1 expression testing is recommended for all patients with newly diagnosed advanced NSCLC [I, A]. For nivolumab and atezolizumab in second line, PD-L1 testing is not required for drug prescription. PD-L1 IHC is an approved biomarker test for immunotherapeutics in NSCLC but it is not a perfect biomarker; less than half of biomarker-selected patients benefit from treatment and some responses may be encountered in 'biomarker-negative' cohorts. Much work is underway to identify alternative, or more likely, additional biomarkers to enrich patient populations for response. Various measures of tumour mutational burden (TMB) are being explored and TMB has been validated prospectively in a unique prospective clinical trial to date [64]. An international effort is ongoing to define a consensus on how TMB should be measured [65–67]. Assessment of tumour inflammation is also of interest, but again, various approaches are being pursued, including histological assessment of immune cell infiltrates and mRNA-based expression signatures of immune-related genes. More data are required before any of these new approaches can be routinely incorporated into NSCLC biomarker testing.

Blood monitoring. The ability to detect oncogenic driver genomic alterations, or factors associated with disease resistance to treatment in peripheral blood, opens the way to disease monitoring in a way that would not be practically feasible were repeat testing solely based upon tumour biopsy testing. In practice, and with current knowledge, this is more likely to involve the use of cfDNA rather than circulating tumour cells (CTCs); the vast majority of existing data concern *EGFR* mutation testing in blood [68]. Currently, much *EGFR* plasma testing is based upon highly sensitive allele-specific polymerase chain reaction (ASPCR).

Plasma genotyping may be considered before undergoing a tumour biopsy to detect the *T790M* mutation. However, if the plasma testing is negative for *T790M*, the tissue biopsy is strongly recommended to determine *T790M* status because of the risks of false-negative plasma results [III, A]. NGS techniques can be used; as more biomarkers are identified and validated, more NGS-based gene panels would be available.

Notwithstanding the issues regarding sensitivity of blood testing, potentially clinically valuable information may be derived from serial blood testing during treatment. For example, the disappearance from the blood of the primary sensitising *EGFR* mutation is associated with clinical and radiological evidence of response to EGFR TKIs and is a good prognostic indicator [IV, C].

After maximum response to EGFR TKI therapy and disappearance of the mutation from the plasma, the reappearance of the primary sensitising mutation, with or without detection of the *T790M* resistance mutation, may be an indicator of 'biochemical' disease relapse. This occurrence may predate radiological relapse, which, in turn, may predate clinical/symptomatic disease relapse. Currently, such findings are essentially exploratory since there is no consensus as to when and how any clinical intervention should be managed. There is no doubt, however, that this kind of molecular monitoring could, in the future, offer benefit to patients in a number of different personalised treatment scenarios.

TMB was evaluated in patient tissue as well as blood samples in different trials. Unique assays and cut-offs are not yet defined but preliminary data from the POPLAR and OAK trials found TMB in blood is associated with improved atezolizumab clinical benefit in patients with NSCLC [69]. Preliminary data suggesting blood TMB as a predictive biomarker for atezolizumab activity have recently been presented [70]. A prospective trial in the first-line setting is exploring the same biomarker [NCT03178552].

Staging and risk assessment

A complete medical history with comorbidities, weight loss, performance status (PS) and physical examination must be recorded. An exhaustive smoking habit assessment has to be included, indicating type, quantity and timing.

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 [IV, B] [71].

The neutrophil to lymphocyte ratio (NLR) is a widely available blood-based data point, validated in numerous oncological settings as a potential prognostic marker. NLR has been considered as a potential dynamic marker but further prospective validations are needed [IV, C] [72, 73].

Radiology

Baseline imaging. A contrast-enhanced 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 [IV, A]; however, if available, imaging of the CNS with magnetic resonance imaging (MRI, preferably with gadolinium enhancement) or CT of the brain with iodinated contrast should be carried out at diagnosis [IV, B]. MRI is more sensitive than CT scan [III, B] [74].

Leptomeningeal disease (LMD) is a deadly complication of solid tumours and has a poor prognosis. Adenocarcinomas are the most common tumours to metastasise to the leptomeninges. In case of clinical suspicion, LMD diagnostic imaging should include the brain and the spinal cord, as LMD can impact the entire neuraxis. 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 [IV, B]. Bone scan or positron emission tomography (PET), ideally coupled with CT, can be used for detection of bone metastasis [IV, B]. PET-CT is the most sensitive modality in detecting bone metastasis [II, B] [75]. Fluorodeoxyglucose (FDG)-PET or PET-CT has higher sensitivity and specificity than bone scintigraphy [76]. FDG-PET-CT scan also has high sensitivity for the evaluation of solitary pulmonary nodules, intra-thoracic pathological lymph nodes and distant metastatic disease [77]. However, the low sensitivity of this exam in small lesions, in lesions close to FDG-avid structures (overprojection) or in lesions that move extensively, such as those just above the diaphragm, should be considered. MRI may complement or improve the diagnostic staging accuracy of FDG-PET-CT imaging, particularly in assessing local chest wall, vascular or vertebra invasion and is also effective for identification of nodal and distant metastatic disease. NSCLC is staged according to the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) system (8th edition) and is grouped into the stage categories shown in Tables 2 and 3 [78, 79].

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 [IV, A].

Response evaluation. Response evaluation is recommended after two to three cycles of chemotherapy (ChT) or immunotherapy, using the same initial radiographic investigation that demonstrated tumour lesions [IV, B]. 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 [IV, B]. Follow-up with PET is not routinely recommended, due to its high sensitivity and relatively low specificity [IV, C].

Measurement of lesions should follow Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 [IV, A] [80]. 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 [IV, B]. In these two subgroups of patients (and in other actionable oncogene alterations), treatment beyond RECIST progression is a common approach, pursuing clinical benefit more than morphological response. This approach differs from what was carried out historically with cytotoxic agents. The conventional radiological response criteria are unable to describe pseudoprogression (PsPD) and can result in underestimation of the therapeutic

Table 2. Clinical classification UICC TNM 8 [79]

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 *in situ*[a]
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)[b]
T1mi	Minimally invasive adenocarcinoma[c]
T1a	Tumour 1 cm or less in greatest dimension[b]
T1b	Tumour more than 1 cm but not more than 2 cm in greatest dimension[b]
T1c	Tumour more than 2 cm but not more than 3 cm in greatest dimension[b]
T2	Tumour more than 3 cm but not more than 5 cm; or tumour with any of the following features[d]
	-Involves main bronchus regardless of distance to the carina, but without involvement of the carina
	-Invades visceral pleura
	-Associated with atelectasis or obstructive pneumonitis that extends to the hilar region either involving part of or the entire lung
T2a	Tumour more than 3 cm but not more than 4 cm in greatest dimension
T2b	Tumour more than 4 cm but not more than 5 cm in greatest dimension
T3	Tumour more than 5 cm but not more than 7 cm in greatest dimension or one that directly invades any of the following: parietal pleura, chest wall (including superior sulcus tumours) phrenic nerve, parietal pericardium; or separate tumour nodule(s) in the same lobe as the primary
T4	Tumour more than 7 cm or of any size that invades any of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina; separate tumour nodule(s) in a different ipsilateral lobe to that of the primary
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 lobe; tumour with pleural or pericardial nodules or malignant pleural or pericardial effusion[e]
M1b	Single extrathoracic metastasis in a single organ[f]
M1c	Multiple extrathoracic metastasis in a single or multiple organs

[a]Tis includes adenocarcinoma *in situ* and squamous carcinoma *in situ*.
[b]The uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a.
[c]Solitary adenocarcinoma (not more than 3 cm in greatest dimension), with a predominantly lepidic pattern and not more than 5 mm invasion in greatest dimension in any one focus.
[d]T2 tumours with these features are classified T2a if 4 cm or less, or if size cannot be determined and T2b if greater than 4 cm but not larger than 5 cm.
[e]Most pleural (pericardial) effusions with lung cancer are due to tumour. In a few patients, however, multiple microscopic 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 descriptor.
[f]This includes involvement of a single non-regional node.
TNM, tumour, node and metastasis; UICC, Union for International Cancer Control.
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benefit of immune checkpoint blockade. Several radiological criteria have been developed specifically for immunotherapy, to better define the tumour response in this context. Two-dimensional immune-related response criteria (irRC) were proposed in 2009 and modified in 2013 with the immune-related RECIST (irRECIST) [81, 82]. More recently, the RECIST working group published a proposition of new criteria called immune-RECIST (iRECIST), to standardise response assessment among immunotherapy clinical trials [83]. A subsequent adaption of RECIST designed to better capture cancer immunotherapy responses has been published: immune-modified RECIST (imRECIST) [84]. More data are needed to compare the RECIST, iRECIST,

Table 3. Staging and stage grouping UICC TNM 8 [79]

Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IA1	T1mi	N0	M0
	T1a	N0	M0
Stage IA2	T1b	N0	M0
Stage IA3	T1c	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
Stage IIB	T1a-c T2a,b	N1	M0
	T3	N0	M0
Stage IIIA	T1a-c T2a,b	N2	M0
	T3	N1	M0
	T4	N0, N1	M0
Stage IIIB	T1a-c T2a,b	N3	M0
	T3, T4	N2	M0
Stage IIIC	T3, T4	N3	M0
Stage IV	Any T	Any N	M1
Stage IVA	Any T	Any N	M1a, M1b
Stage IVB	Any T	Any N	M1c

TNM, tumour, node and metastasis; UICC, Union for International Cancer Control.

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imRECIST and irRECIST to quantify the differences in outcome estimation before using of them in clinical practice. Non-conventional responses and PsPD are very rarely observed in NSCLC, ranging generally under 5% of all cases, and RECIST v1.1 should still be used in routine practice [IV, B] [85–88].

Management of advanced/metastatic NSCLC

The treatment strategy (Figures 1–7) should take into account factors such as 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 [89]. 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: it can improve outcome and smoking may interact with systemic therapy [II, A]. For example, smoking reduces erlotinib bioavailability [90, 91]. 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 quality of life (QoL) [92].

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.

First-line treatment of *EGFR*- and *ALK*-negative NSCLC, PD-L1 $\geq$ 50%

Lung cancers were previously considered poorly immunogenic, with minimal benefit seen in historical studies of cytokine modulation or vaccines. However, the recent development of immune checkpoint inhibitors has upended this belief and provided proof of principle that immunotherapy can play an important role in the treatment of patients with lung cancers.

The phase III KEYNOTE-024 study has established the role for pembrolizumab as first-line treatment in patients with untreated, advanced NSCLC and tumour characterised by PD-L1 expression $\geq$ 50% [62], in absence of *EGFR* mutation or *ALK* translocations. In KEYNOTE-024, 1934 patients were screened to identify 500 patients (30%) with tumour PD-L1 expression $\geq$ 50%. Of these patients, 305 patients were randomised to receive 200 mg pembrolizumab every 3 weeks (up to 2 years) or four to six cycles of standard platinum-doublet ChT. All efficacy measures favoured pembrolizumab, including objective response rate (ORR 45% versus 28%), progression-free survival [PFS, hazard ratio (HR) 0.5, 95% confidence interval (CI) 0.37–0.68, $P < 0.001$] and overall survival (OS, HR 0.6, 95% CI 0.41–0.89, $P = 0.005$). Safety and QoL also favoured pembrolizumab [93]. Continued follow-up has further emphasised the effectiveness of pembrolizumab, with median OS (mOS) doubled in those who received pembrolizumab compared with ChT (30 versus 14 months) [94].

Pembrolizumab is considered a standard first-line option for patients with advanced NSCLC and PD-L1 expression $\geq$ 50% who do not otherwise have contraindications to use of immunotherapy (such as severe autoimmune disease or organ transplantation) [I, A; European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: 5].

Other studies, KEYNOTE-042 and CheckMate 026, examined a lower threshold for PD-L1 [66, 95]. Recent results from KEYNOTE-042, a phase III study of patients with PD-L1 $\geq$ 1% who were randomised to either pembrolizumab or ChT, demonstrated improved OS in patients treated with pembrolizumab at three thresholds of PD-L1: $\geq$ 50%, $\geq$ 20% and $\geq$ 1%. The HR for OS was 0.69, 0.77 and 0.81, respectively. Overall, the preponderance of the OS benefit was driven by patients with $\geq$ 50%, while no significant increase was seen in those patients with 1%–49% PD-L1 expression (HR 0.92, 95% CI 0.77–1.11).

In CheckMate 026, patients with untreated, advanced NSCLC and PD-L1 $\geq$ 1% (analysis based on 5% threshold) were randomised to nivolumab or platinum-doublet ChT [66]. There were no improvements in any efficacy metrics. However, an exploratory retrospective and unplanned analysis examined the impact of TMB on benefit of nivolumab. A total of 312 patients (58% of randomised patients) had sufficient tissue for whole exome sequencing. In those patients with the highest tertile of TMB (> 243 missense non-synonymous somatic mutations per sample), ORR (47% versus 28% with ChT) and PFS (HR 0.62, 95% CI 0.38–1.0) favoured those who received nivolumab. Meanwhile, among patients with low or medium TMB, ORR was numerically better in those who received ChT (33% versus 23% with nivolumab).

Overall, these results confirm the benefit of pembrolizumab in the first-line setting seen in KEYNOTE-024, restricted to patients with high PD-L1 expression ($\geq$ 50%).

First-line treatment of *EGFR*- and *ALK*-negative NSCLC disease, regardless of PD-L1 status

Recently, results of the phase III trials KEYNOTE-189, IMpower150 and IMpower132 have brought new options for the therapeutic choices in first line of non-squamous NSCLC and trials KEYNOTE-407 and IMpower131 for patients with squamous NSCLC.

In KEYNOTE-189, patients with metastatic non-squamous NSCLC, PS 0–1, without sensitising *EGFR* or *ALK* mutations, were randomised to receive pemetrexed and cisplatin or carboplatin plus either 200 mg of pembrolizumab or placebo every 3 weeks for 4 cycles, followed by pembrolizumab or placebo for up to a total of 35 cycles plus pemetrexed maintenance therapy [96]. The mOS was not reached in the pembrolizumab/ChT arm versus 11.3 months (95% CI 8.7–15.1) in the ChT arm (HR 0.49; 95% CI 0.38–0.64; $P < 0.001$). The PFS also favoured the pembrolizumab/ChT combination (HR 0.52; 95% CI 0.43–0.64; $P < 0.001$). The OS benefit of pembrolizumab/ChT was observed in all PD-L1 tumour subgroups. Notably, among the PD-L1 TPS < 1%, there was not a clear PFS benefit with pembrolizumab/ChT (HR 0.75, 95% CI 0.53–1.05), such that the degree of durable benefit in this group remains limited. Still, based on the results from KEYNOTE-189, pembrolizumab in combination with pemetrexed and a platinum-based ChT should be considered a standard option in metastatic non-squamous NSCLC [I, A; ESMO-MCBS v1.1 score: 4].

In IMpower150, the addition of atezolizumab to bevacizumab plus ChT significantly improved PFS and OS among patients with metastatic non-squamous NSCLC, regardless of PD-L1 expression [97]. The PFS was longer in the atezolizumab/bevacizumab/ChT arm compared with bevacizumab/ChT [median PFS (mPFS) 8.3 versus 6.8 months; HR 0.59; 95% CI 0.50–0.70; $P < 0.001$]. Survival was longer in the atezolizumab/bevacizumab/ChT arm compared with bevacizumab/ChT (mOS 19.2 versus 14.7 months; HR 0.78; 95% CI 0.64–0.96; $P = 0.02$; 12-month OS 67% versus 61%). Results from IMpower150 place the combination of atezolizumab and bevacizumab with carboplatin and paclitaxel as a therapeutic option in patients with PS 0–1 with metastatic non-squamous NSCLC, in absence of contraindications to use of immunotherapy [I, A]. Of note, this is the only trial to date also including patients with *EGFR* or *ALK* genetic alterations and demonstrating a stringent OS benefit (PFS HR 0.59, 95% CI 0.37–0.94; OS HR 0.54, 95% CI 0.29–1.03). This association in *EGFR*- or *ALK*-positive NSCLC patients defines a treatment opportunity for this subgroup after targeted therapies have been exploited [I, A in unselected non-squamous NSCLC including *EGFR*- and *ALK*-driven NSCLC, specifically [III, A] for *EGFR* and [III, B] for *ALK* subgroups; not EMA-approved].

Recently, the combination of carboplatin or cisplatin with pemetrexed and atezolizumab followed by maintenance pemetrexed and atezolizumab has been shown, in the context of the IMpower132 trial, to be superior to the ChT doublet followed by maintenance pemetrexed. An improvement in mPFS from 5.2 to 7.6 months was observed (HR 0.6; 95% CI 0.49−0.72; $P < 0.0001$) while OS was not statistically significantly increased at the time of analysis with mOS of 18.1 versus 13.6 months (HR 0.81; 95% CI 0.64−1.03; $P = 0.0797$), suggesting another potential treatment opportunity [I, B, not EMA approved] [98].

KEYNOTE-407 is a randomised, placebo-controlled study of patients with metastatic squamous NSCLC [99]. Patients were randomised 1:1 to receive carboplatin and paclitaxel every 3 weeks, or albumin-bound paclitaxel (nab-P) weekly plus pembrolizumab or placebo for 4 cycles, followed by pembrolizumab or placebo for a total of 35 treatments. The combination of ChT plus pembrolizumab was associated with improved ORR (58.4% versus 35.0%, $P = 0.0004$) and improved OS (HR 0.64, mOS 15.9 versus 11.3 months, $P = 0.0008$). The benefit in OS was seen across PD-L1 expression strata (TPS < 1% HR 0.61, TPS 1%–49% HR 0.57, TPS ≥ 50% HR 0.64). No new safety concerns were observed. Results from KEYNOTE-407 place the combination of pembrolizumab plus carboplatin and paclitaxel or nab-P as a standard choice in patients with metastatic squamous NSCLC [I, A; not EMA-approved].

Atezolizumab was studied in patients with metastatic squamous NSCLC in the IMpower131 study. Patients were randomised to atezolizumab/carboplatin/paclitaxel, atezolizumab/carboplatin/nab-P or carboplatin/nab-P [100]. Atezolizumab/carboplatin/nab-P had improved PFS compared with carboplatin/nab-P (HR 0.715, $P = 0.0001$), but no improvement in OS was seen at the first interim analysis (mOS 14 versus 13.9 months). More mature data are needed to evalute the long-term benefit of the strategy; with the use of atezolizumab with carboplatin and nab-P today representing an option in patients with metastatic squamous NSCLC [I, B; not EMA-approved].

One key area of uncertainty is among PD-L1 TPS ≥ 50%, as none of these trials provide a direct comparison between ChT plus checkpoint inhibitors versus pembrolizumab monotherapy. However, cross-trial comparison between trials suggest similar OS outcomes among PD-L1 ≥ 50%, with very different toxicity profiles, suggesting that pembrolizumab monotherapy may remain a reasonable choice for patients with PD-L1 ≥ 50% [101].

TMB has shown encouraging results as a predictive biomarker in retrospective studies in NSCLC and SCLC. The first prespecified analysis of TMB as a biomarker was reported in the phase III trial CheckMate 227, evaluating nivolumab plus ipilimumab versus ChT in first-line NSCLC [64]. The TMB cut-off of 10 mutations per megabase (Mb) was determined based on data from CheckMate 568 based on receiver operating characteristic (ROC) curves and clinical impact analysis [102]. Patients with newly diagnosed advanced NSCLC were randomised based on PD-L1 expression. Those who had PD-L1 TPS ≥ 1% received nivolumab/ipilimumab, nivolumab monotherapy or ChT; and those with a PD-L1 TPS < 1% received nivolumab/ipilimumab, nivolumab/ChT or ChT. In patients with high TMB (≥ 10 mutations/Mb, 44% of assessable patients), nivolumab/ipilimumab was associated with longer PFS than ChT (HR 0.58; 97.5% CI: 0.41–0.81; $P < 0.001$), and more than tripling of 1-year PFS (42.6% versus 13.2%). The PFS benefit with nivolumab/ipilimumab was seen irrespective of PD-L1, wherein the HR similarly favoured nivolumab plus ipilimumab in patients with a PD-L1 TPS ≥ 1% and those < 1% (HR 0.62 and HR 0.48, respectively). A similar benefit was seen in both squamous and non-squamous histologies (squamous HR 0.63, non-squamous HR 0.55). Of importance, there was no difference in PFS among patients with < 10 mutations/Mb (HR 1.07; 95% CI 0.84–1.35).

Grade 3–4 treatment-related adverse events (AEs) leading to discontinuation were more common with ChT than nivolumab plus ipilimumab (36% versus 31%), with more subsequent discontinuations with immunotherapy (12% versus 5%).

CheckMate 227 continues for the coprimary endpoint of OS in PD-L1 selected patients. For now, nivolumab plus ipilimumab represents an optional treatment regimen for patients with NSCLC with a high TMB [I, A; not EMA-approved]. Important questions remain regarding the role of immunotherapy combinations versus PD-1 monotherapy in PD-L1 TPS $\geq$ 50% and how TMB may inform the optimal use of PD-(L)1 plus ChT versus immunotherapy alone combinations in NSCLC. Additional clinical data and evaluation of long-term benefit of these new strategies are needed. Physicians and patients will need to conduct individualised discussions regarding benefit and risks of available therapies over time.

Overall, the results from the KEYNOTE-024, IMpower150, KEYNOTE-189, IMpower132, CheckMate 227, KEYNOTE-407 and IMpower131 trials suggest that introducing immunotherapy will be a standard new approach for most patients with newly diagnosed NSCLC.

First-line treatment of NSCLC without actionable oncogenic driver, with contraindications to use of immunotherapy

ChT with platinum doublets should be considered in all stage IV NSCLC patients without an actionable oncogenic driver, without major comorbidities and PS 0–2 [I, A]. Benefits of ChT versus best supportive care (BSC), namely a 23% reduction of risk of death, a 1-year survival gain of 9% and a 1.5-month absolute increase in median survival and improved QoL, were observed irrespective of age, sex, histology and PS in two meta-analyses [103–105]. The survival benefit of two-agent over one-agent ChT regimens was reported in a meta-analysis in 2004; no survival benefit was observed for three-agent over two-agent regimens [106]. 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] [107]. Neither a large individual trial nor a meta-analysis found an 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 [108, 109]. Therefore, four cycles of platinum-based doublets followed by less toxic maintenance monotherapy [I, A], or four cycles in patients not suitable for maintenance monotherapy [I, A], up to a maximum of six [IV, B], are currently recommended.

Several platinum-based regimens with third-generation cytotoxics (paclitaxel, gemcitabine, docetaxel, vinorelbine) have shown comparable efficacy [110, 111]. The expected toxicity profile should contribute to the selection of the ChT regimen, taking into account that:

- A recent Cochrane review including 10 trials with 3973 patients available for meta-analysis could not demonstrate any difference between carboplatin-based and cisplatin-based ChT in OS. Cisplatin had higher ORRs in an overall analysis but trials using paclitaxel or gemcitabine plus a platinum agent in both arms had equivalent response. Cisplatin caused more nausea or vomiting and carboplatin caused more thrombocytopaenia and neurotoxicity, while no difference in the incidence of grade 3-4 anaemia, neutropaenia, alopaecia or renal toxicity was observed [112].
- The carboplatin/nab-P regimen has been shown in a large phase III trial to have a significantly higher ORR compared with solvent-based paclitaxel/carboplatin (sb-PC), and less neurotoxicity [I, B] [113]. The benefits were observed in both SCC and non-SCC (NSCC), with a larger impact on response in SCC. For this reason, the carboplatin/nab-P 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 ChT options in the first-line treatment of advanced NSCLC did not report any differential efficacy in patients with SCC [104]. 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] (Figure 1).

Necitumumab, an immunoglobulin G1 (IgG1) monoclonal antibody against EGFR, did not demonstrate a significant impact in first-line treatment of metastatic NSCC when added to cisplatin/pemetrexed [114]. However, outcomes were different when necitumumab was combined with different ChT 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, 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 [115]. In a retrospective analysis, the group of patients expressing EGFR (assessed by IHC) showed an improvement in OS and PFS [mOS 11.7 months versus 10.0 months; HR 0.79, 95% CI 0.69–0.92; $P = 0.002$; mPFS 5.7 versus 5.5 months, HR 0.84, 95% CI 0.72–0.92; $P = 0.018$] [116]. Based on these results, due to the limited clinical improvement, the addition of necitumumab to cisplatin and gemcitabine has not been adopted as a standard in Europe for advanced SCC and its use should be carefully evaluated [I, C; ESMO-MCBS v1.1 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 (Figure 2). The incorporation of pemetrexed and bevacizumab into individual treatment schedules should be considered, based on the following:

- Pemetrexed-based combination ChT 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] [117, 118]. Pemetrexed use should be

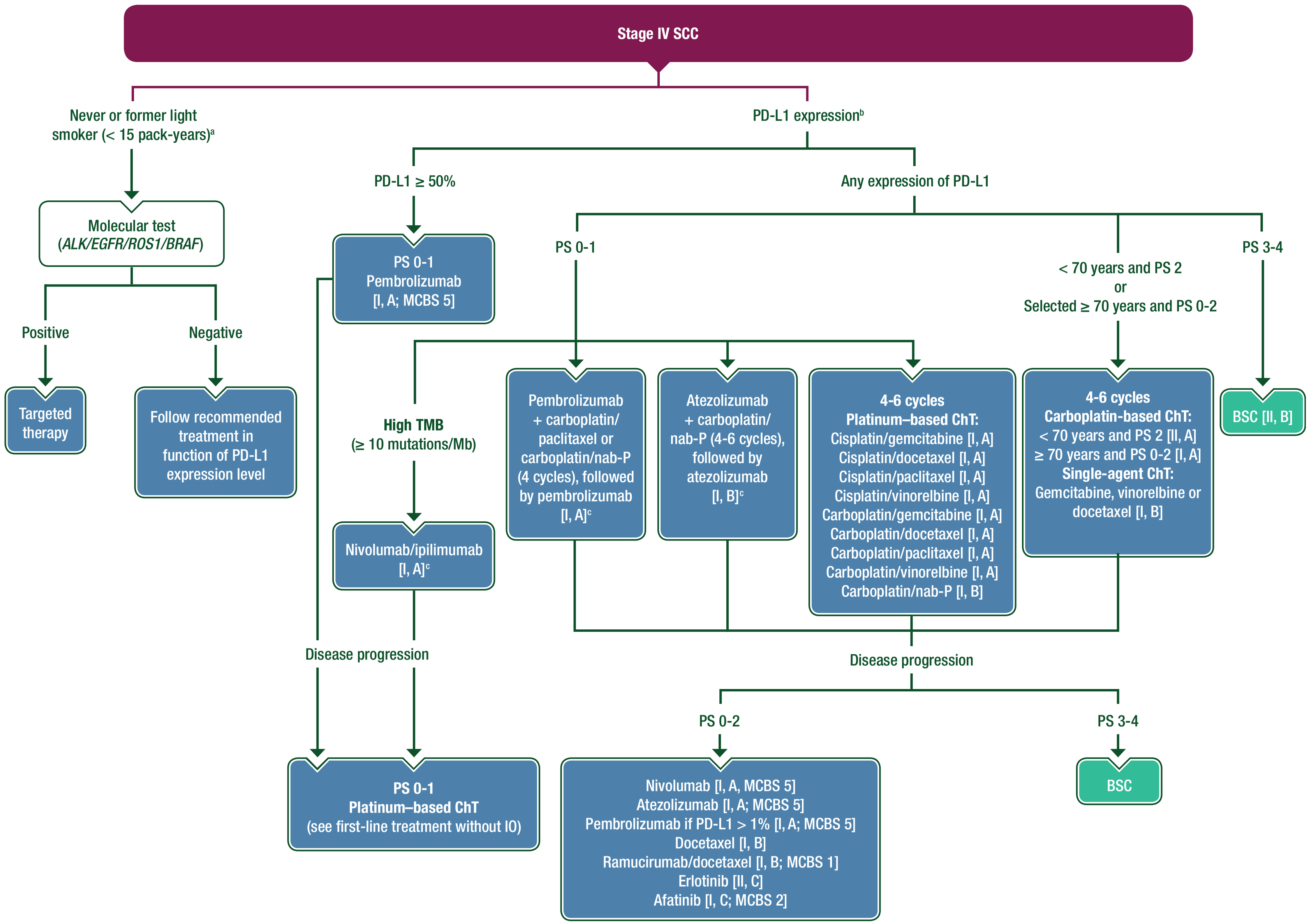

Figure 1. Treatment algorithm for stage IV SCC.

[a]Molecular testing is not recommended in SCC, except in those rare circumstances when SCC is found in a never-, long-time ex- or light-smoker (< 15 pack-years).

[b]In absence of contraindications and conditioned by the registration and accessibility of anti-PD-(L)1 combinations with platinum-based ChT, this strategy will be preferred to platinum-based ChT in patients with PS 0-1 and PD-L1 < 50%. Alternatively, if TMB can accurately be evaluated, and conditioned by the registration and accessibility, nivolumab plus ipilimumab should be preferred to platinum-based standard ChT in patients with NSCLC with a high TMB.

[c]Not EMA-approved.

ALK, anaplastic lymphoma kinase; BSC, best supportive care; ChT, chemotherapy; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; IO, immuno-oncology; Mb, megabase; MCBS, ESMO-Magnitude of Clinical Benefit Scale; nab-P, albumin-bound paclitaxel; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PS, performance status; SCC, squamous cell carcinoma; TMB, tumour mutation burden.

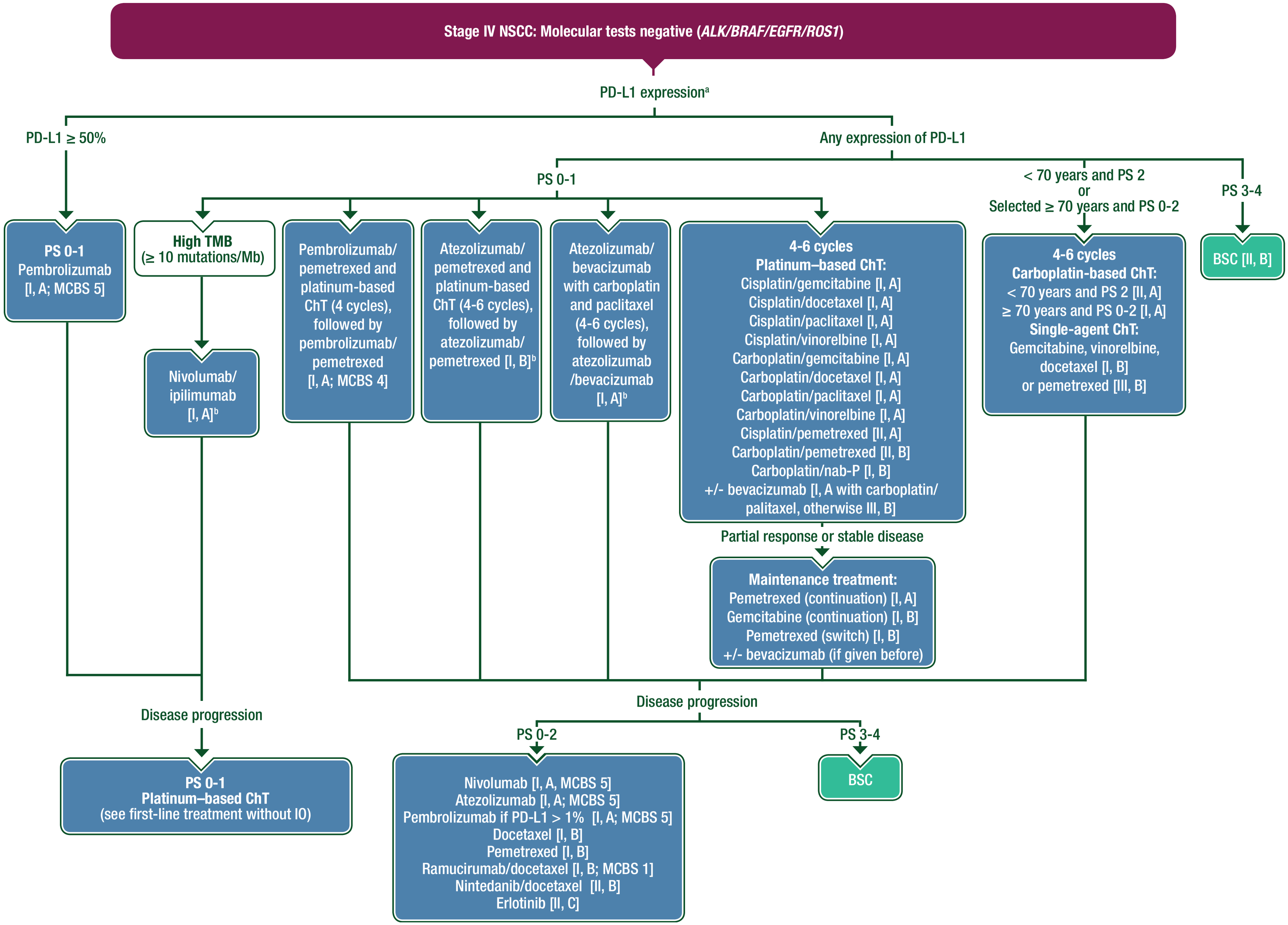

Figure 2. Treatment algorithm for stage IV NSCC, molecular tests negative (*ALK/BRAF/EGFR/ROS1*).

[a]In absence of contraindications and conditioned by the registration and accessibility of anti-PD-(L)1 combinations with platinum-based ChT, this strategy will be preferred to platinum-based ChT in patients with PS 0-1 and PD-L1 < 50%. Alternatively, if TMB can accurately be evaluated, and conditioned by the registration and accessibility, nivolumab plus ipilimumab should be preferred to platinum-based standard ChT in patients with NSCLC with a high TMB.

[b]Not EMA-approved.

ALK, anaplastic lymphoma kinase; BSC, best supportive care; ChT, chemotherapy; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; IO, immuno-oncology; Mb, megabase; MCBS, ESMO-Magnitude of Clinical Benefit Scale; nab-P, albumin-bound paclitaxel; NSCC, non-squamous cell carcinoma; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PS, performance status; TMB, tumour mutation burden.

restricted to NSCC in any line of treatment in advanced disease [II, A] [119, 120].

- 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; however, results from prospective randomised studies investigating this question are not yet available [117]. The combination of carboplatin with pemetrexed can be an option in patients with a contraindication to cisplatin [II, B].
- 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 (bevacizumab should be given until progression) [I, A] [121, 122]. A randomised phase III trial evaluating gemcitabine/cisplatin combination with or without bevacizumab demonstrated an ORR and modest PFS advantage, but no OS benefit [123].

Two meta-analyses showed a consistent significant improvement in ORR, PFS and OS for the combination of bevacizumab and platinum-based ChT, compared with platinum-based ChT alone in eligible patients with NSCC [124, 125]. Bevacizumab might therefore be considered with platinum-based regimens beyond paclitaxel/carboplatin in the absence of contraindications [II, B]. Treatment with bevacizumab has also shown encouraging efficacy and acceptable safety in patients with NSCC and asymptomatic, untreated brain metastases [126].

Maintenance

Decision-making about maintenance therapy must take into account histology, residual toxicity after first-line ChT, 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 to the maintained use of an agent included in first-line treatment or the introduction of a new agent after four cycles of platinum-based ChT, respectively. One randomised phase III switch maintenance trial has reported improvements in PFS and OS with pemetrexed [120] and erlotinib [127] versus placebo, following four cycles of platinum-based ChT. In the case of pemetrexed, this benefit was seen only in patients with NSCC [I, B]. Furthermore, the phase III IUNO study (maintenance erlotinib) failed to meet its primary endpoint of OS (HR 1.02; 95% CI 0.85–1.22; $P = 0.85$) [128]. Maintenance treatment with erlotinib is only recommended for NSCC patients with an *EGFR*-sensitising mutation [III, B]. Randomised trials investigating continuation maintenance have shown an improvement in PFS and OS. A large phase III randomised trial of continuation maintenance with pemetrexed versus placebo after four induction cycles of cisplatin plus pemetrexed ChT demonstrated a PFS and OS improvement in patients with a PS 0–1, confirmed at long-term follow-up [129, 130]. mOS was 13.9 months (95% CI 12.8–16.0) with pemetrexed and 11.0 months (95% CI 10.0–12.5) with 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 [131], although a trend towards improved OS was seen when analysing 58% of events of 253 patients randomised for this study [132]. In the PointBreak trial, which compared carboplatin/paclitaxel/bevacizumab followed by bevacizumab with carboplatin/pemetrexed/bevacizumab followed by pemetrexed/bevacizumab, OS was comparable in both arms (12.6 versus 13.4 months; HR 1.00; 95% CI 0.86–1.16; $P = 0.949$) [133]. In a phase III trial, it was also shown that continuation maintenance with gemcitabine significantly reduces disease progression (mPFS, 3.8 versus 1.9 months; HR 0.56; 95% CI 0.44–0.72) with a non-significant OS improvement in patients with advanced NSCLC treated with four cycles of cisplatin/gemcitabine as first-line ChT [I, C] [134]. Continuing pemetrexed following completion of four cycles of first-line cisplatin/pemetrexed ChT is, therefore, recommended in patients with NSCC, in the absence of progression after first-line ChT 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 ChT and further continued as monotherapy until disease progression, have demonstrated survival benefits; however, the specific role of the maintenance phase cannot be appreciated in this context [115, 121, 135].

PS 2 and beyond

ChT prolongs survival and improves QoL in NSCLC patients with PS 2 when compared with BSC [I, A] [136, 137].

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 ORR and survival despite an increase in toxicities (mainly haematological) [138]. The superiority of carboplatin-based combinations over monotherapy in PS 2 patients has been identified within two large phase III trials [137, 139], with an acceptable toxicity profile. Therefore, platinum-based (preferably carboplatin) doublets should be considered in eligible PS 2 patients [I, A]. Single-agent ChT with gemcitabine, vinorelbine, docetaxel [I, B] or pemetrexed (restricted to NSCC) [II, B] is an alternative treatment option [139, 140].

All phase III studies with immunotherapies reported until today excluded patients with PS $\geq$ 2. Reported in abstract form only, CheckMate 153 included 108 patients with advanced NSCLC and PS 2 treated with single-agent nivolumab [141]. mOS was 3.9 months and 1-year survival 23%, being lower than observed in patients with PS 0–1. Toxicities associated with treatment were comparable between PS 0–1 and PS 2 patients. Interestingly, an improvement in patient-reported outcomes was observed for non-squamous NSCLC patients in the context of this trial. In a European-based safety phase II trial (CheckMate 171), among 809 patients enrolled, 98 PS 2 patients were treated with nivolumab; the safety was comparable to the overall population with an mOS of 5.4 months [142]. In conclusion, insufficient data are available to date on the use of checkpoint inhibitors for these patients, but this treatment option can be considered [III, B].

Poor PS (3–4) patients should be offered BSC in the absence of documented sensitising alterations such as *EGFR* mutations, *ALK* or *ROS1* rearrangements or *BRAF V600* mutation [III, B].

Elderly patients

In the early 2000s, based on several phase III trials, single-agent ChT over BSC was established as the standard of care for first-line therapy of advanced NSCLC patients aged > 70 years [140, 143]. A recent systematic review identified platinum-based combination ChT as the preferred option for patients > 70 years of age with PS 0–2 and adequate organ function [144]. Here, data from 13 randomised controlled trials (RCTs) with 1705 patients > 70 years of age showed that the addition of platinum agents resulted in improvement in OS (HR 0.76; 95% CI 0.69–0.85), PFS (HR 0.76; 95% CI 0.61–0.93) and ORR (RR 1.57; 95% CI 1.32–1.85) compared with non-platinum containing therapy. Carboplatin was associated with an OS benefit (HR 0.67; 95% CI 0.59–0.78) whereas cisplatin was not (HR 0.91; 95% CI 0.77–1.08). Treatment with platinum-based combinations comes at the expense of more treatment-related morbidity, mainly anaemia, thrombocytopaenia, emesis, diarrhoea and peripheral neuropathy; this should be weighed against the expected survival benefit. It is noteworthy that those RCTs that included formal QoL analysis found no difference in QoL between treatment with platinum-based combinations or single agents in this population [137, 145]. Nevertheless, concerns about treatment-related toxicity in the elderly population has led to the study of comprehensive geriatric assessment (CGA) as a selection tool for treatment with either platinum-based regimens, single-agent therapy or BSC based on patient's fitness or frailty. The sole prospective randomised trial reported failed to demonstrate an improvement in time to treatment failure and OS for advanced NSCLC patients > 70 years when treatment (carboplatin doublet, single-agent ChT or BSC) was allocated based on CGA alone or a combination of PS and age. Also, the incidence of grade 3–4 toxicities was not different between the two arms in this study [146]. Carboplatin-based doublet ChT is recommended in eligible elderly patients with PS 0–2 and with adequate organ function [I, A]. For those patients not eligible for doublet ChT, single-agent ChT remains the standard of care [I, B].

Evidence is accumulating for immune checkpoint inhibitors in elderly patients with advanced NSCLC. Although no studies dedicated to elderly patients were reported yet, it can be inferred that ORRs and survival are not different between patients ≤ 65 years and those > 65, based on subgroup analysis of the randomised second-line trials [63, 147–150]. Of note, no differences in toxicities were observed [149]. In KEYNOTE-024, comparing first-line pembrolizumab with combination ChT in advanced NSCLC patients whose tumours expressed PD-L1 > 50%, half the randomised patients were > 65 years of age. In the subgroup analysis, the beneficial effect of pembrolizumab was not different between patients aged ≤ 65 years and > 65 years of age (HR 0.61 versus 0.45) [62]. Likewise, in CheckMate 026, comparing nivolumab with combination ChT in unselected first-line advanced NSCLC patients, there was no difference in survival outcomes between patients treated with nivolumab aged ≤ 65 years and those > 65 years [66]. Immunotherapy should therefore be considered according to standard recommendations in elderly patients [III, A].

Second-line treatment of NSCLC without actionable oncogenic driver

In the few years since benefit was shown with PD-1 blockade in lung cancers, three PD-1 or PD-L1 therapies have been approved by the United States Food and Drug Administration (FDA) and the EMA in the second-line setting.

The three approved therapies in the immunotherapy-naive, second-line setting include nivolumab, pembrolizumab and atezolizumab. Each has been approved on the basis of phase III studies demonstrating improved OS in comparison with docetaxel. Results are summarised below. Overall, there are no major differences in terms of efficacy or safety among these three therapies to inform a single optimal choice, and no comparative studies have been conducted. There are two key distinctions between the three approved therapies, which can affect choice and use:

1. PD-L1 expression: nivolumab and atezolizumab are approved in patients with previously treated, advanced NSCLC irrespective of PD-L1 expression, while pembrolizumab is approved only in patients with PD-L1 ≥ 1%.
2. Schedule of administration: atezolizumab and pembrolizumab are approved to be given once every three weeks, while nivolumab is given once every two weeks based on current EMA approval. Of note, the FDA has recently approved a 4-weekly schedule for nivolumab.

Overall, any of these three therapies represents reasonable standard therapy for most patients with advanced, previously treated, PD-L1-naive NSCLC. Treatment of patients with a history of autoimmune disease should be considered only with caution and after discussion of risks/benefits. Because of the risk of graft rejection, anti-PD-1/PD-L1 agents should be avoided in patients with solid organ transplantation. For reference, we summarise the key data from the relevant phase III studies here:

- Nivolumab: two phase III studies, CheckMate 017 and CheckMate 057, have established the effectiveness of nivolumab in the second-line setting [147, 148]. In CheckMate 017, 272 patients with squamous NSCLC were randomised to nivolumab or docetaxel. OS was significantly improved in those who received nivolumab (HR 0.59, 95% CI 0.44–0.79, $P < 0.001$). In CheckMate 057, 582 patients with non-squamous NSCLC were randomised to nivolumab or docetaxel. OS was significantly improved with nivolumab (HR 0.73, 95% CI 0.59–0.89, $P = 0.002$). In a recent update of these studies, 2-year OS favoured nivolumab in both squamous (29% versus 16% with docetaxel) [I, A; ESMO-MCBS v1.1 score: 5] and non-squamous NSCLC (23% versus 8%) [I, A; ESMO-MCBS v1.1 score: 5]. Tolerability also favoured nivolumab, with 10% of patients experiencing grade 3–4 treatment-related AEs compared with 55% with docetaxel.
- Pembrolizumab: The KEYNOTE-010 trial randomised 1034 patients with previously treated NSCLC with PD-L1 expression on at least 1% of tumour cells to receive pembrolizumab (tested at two doses, 2 mg/kg or 10 mg/kg, each given every three weeks) or docetaxel 75 mg/m^2 every 3 weeks [63, 151]. OS was significantly longer for pembrolizumab versus docetaxel (2 mg/kg, HR 0.71, 95% CI 0.58−0.88; $P < 0.001$; 10 mg/kg, HR 0.61, 95% CI 0.49−0.75; $P < 0.001$), with a recently reported 2-year OS rate of 14.5% versus 30.1% (2 mg/kg group)

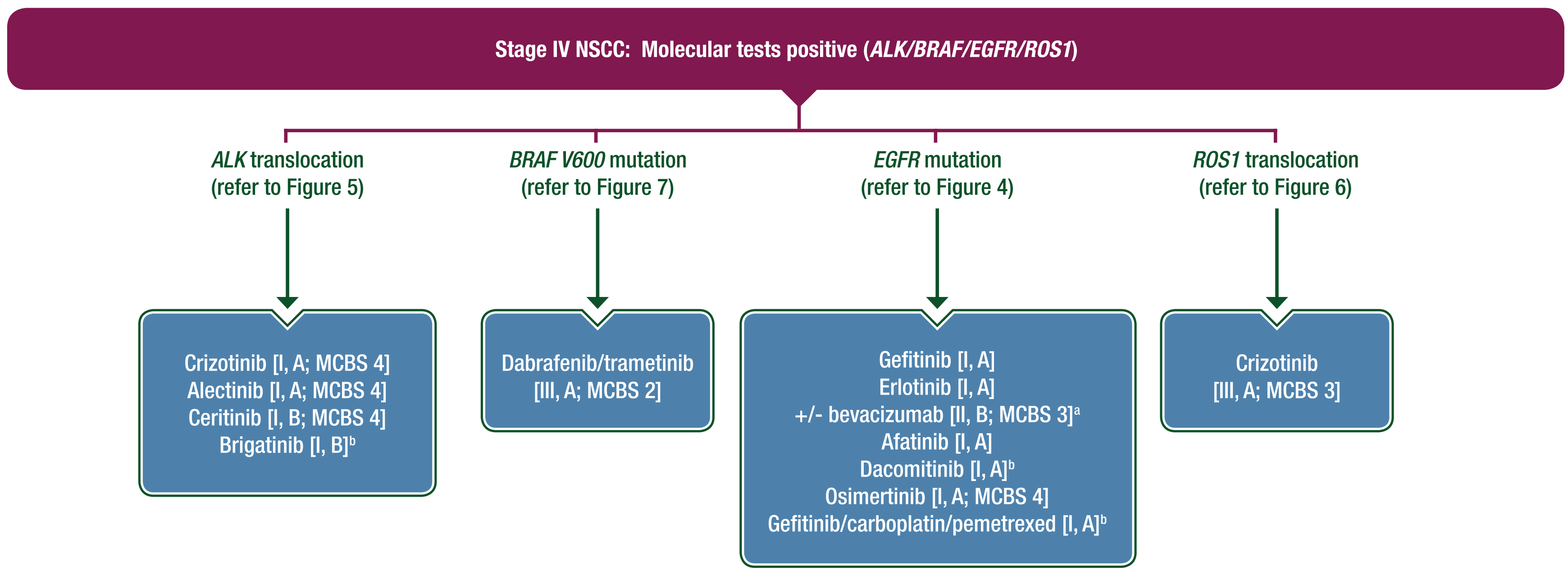

Figure 3. Treatment algorithm for stage IV NSCC, molecular tests positive (*ALK/BRAF/EGFR/ROS1*).
[a]MCBS score for the combination of bevacizumab with gefitinib or erlotinib.
[b]Not EMA-approved.
ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; MCBS, ESMO-Magnitude of Clinical Benefit Scale; NSCC, non-squamous cell carcinoma.

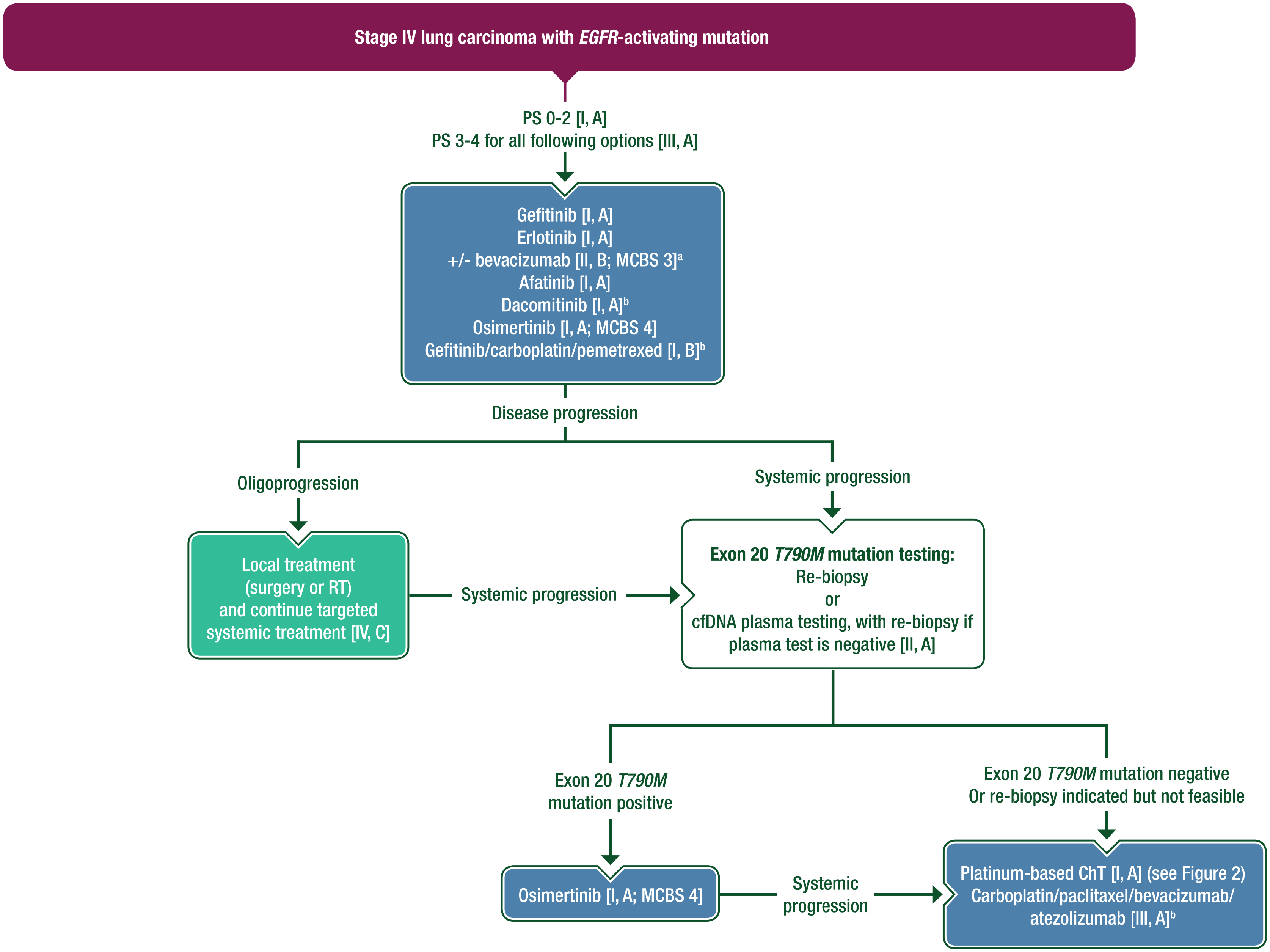

Figure 4. Treatment algorithm for stage IV lung carcinoma with *EGFR*-activating mutation.
[a]MCBS score for the combination of bevacizumab with gefitinib or erlotinib.
[b]Not EMA-approved.
cfDNA, cell-free DNA; ChT, chemotherapy; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; MCBS, ESMO-Magnitude of Clinical Benefit Scale; PS, performance status; RT, radiotherapy.

[I, A; ESMO-MCBS v1.1 score: 5]. Grade 3–5 treatment-related AEs were less common with pembrolizumab than with docetaxel (13%–16% versus 35%). There was no significant difference in the efficacy or safety of pembrolizumab at 2 or 10 mg/kg.

- Atezolizumab: The OAK trial [149] evaluated 850 patients with advanced NSCLC previously treated with one or two prior lines of ChT, who were randomised to atezolizumab or docetaxel. OS was significantly improved with atezolizumab (HR 0.73, 95% CI 0.62–0.87, $P<0.001$). Tolerability was also better with atezolizumab, with 15% of patients experiencing a grade 3–4 treatment-related toxicity compared with 43% of those treated with docetaxel [I, A; ESMO-MCBS v1.1 score: 5].

There is a general trend across each of the phase III studies in second-line (nivolumab, pembrolizumab and atezolizumab versus docetaxel) for enriched efficacy of anti-PD-1/PD-L1 agents in patients with higher PD-L1 expression compared with those with no/less PD-L1 expression. However, unselected patients may still have improved survival and tolerability with anti-PD-1/PD-L1 agents compared with docetaxel [I, A].

Therefore, anti-PD-1/PD-L1 agents are the treatment of choice for most patients with advanced, previously treated, PD-L1-naive NSCLC, irrespective of PD-L1 expression [I, A].

Combination ChT regimens failed to show any OS benefit over single-agent treatments in second line. Single agents improve disease-related symptoms and OS. Docetaxel has shown improved efficacy compared with BSC in randomised trials with a significant improvement in OS in the TAX 320 trial for those patients who received docetaxel at a dose of 75 mg/m^2 every 3 weeks [152, 153]. Similar efficacy, but more favourable tolerability for the weekly schedule, could be confirmed in randomised trials comparing 3-weekly to weekly schedules of docetaxel [I, B] [154, 155].

Pemetrexed demonstrated comparable OS to docetaxel in a randomised phase III trial but had a more favourable toxicity profile, with lower rates of neutropaenia, alopaecia and gastrointestinal events [156]. A retrospective analysis confirmed a predictive impact of histology with an improved efficacy of pemetrexed compared with docetaxel in patients with non-squamous NSCLC (mOS 9.0 versus 8.3 months; HR 0.78; 95% CI 0.61–1.0, $P = 0.004$) [119].

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

Docetaxel and pemetrexed (for NSCC only) are confirmed treatment options in second-line ChT, with comparable efficacy [I, B], taking into account that immunotherapy is now the current standard second-line systemic therapy and that these agents have not been formally assessed after checkpoint inhibitors.

In several trials, the combination of antiangiogenic agents with ChT has been investigated in patients with pretreated advanced NSCLC. In the REVEL trial, ramucirumab, a vascular endothelial growth factor receptor 2 (VEGFR2) antibody, in combination with docetaxel, showed a superior OS (mOS 10.5 versus 9.1 months, HR 0.86; 95% CI 0.75–0.98, $P = 0.032$) and PFS (mPFS 4.5 versus 3 months, $P < 0.0001$) compared with docetaxel and placebo regardless of histology [ESMO-MCBS v1.1 score: 1] [157]. The main AEs associated with ramucirumab consisted of myelotoxicity, oedema and mucositis. The efficacy of this combination was also preserved in the poor prognosis group of patients who did not show any response to first-line ChT [157, 158]. Nintedanib, an oral angiokinase inhibitor, improved PFS in combination with docetaxel compared with ChT alone in the LUME-1 trial (mPFS 3.4 versus 2.7 months, HR 0.79; 95% CI 0.68–0.92; $P = 0.0019$) [159]. A significant prolongation of OS was observed in the group of patients with adenocarcinoma histology (mOS 12.6 versus 10.3 months; HR 0.82, 95% CI 0.7–0.99, $P = 0.0359$). Gastrointestinal events and transient elevation of liver enzymes were the most frequent AEs associated with nintedanib. However, the QoL analyses did not show any impact on QoL measurements for this combination. Again, improved efficacy was seen in the poor prognostic group of patients with non-responding or fast progressing tumours [159, 160]. The efficacy of the combination of antiangiogenic agents and ChT was confirmed in the ULTIMATE trial, which showed prolongation of PFS for the combination of weekly paclitaxel and bi-weekly bevacizumab compared with docetaxel (mPFS 5.4 versus 3.9 months, HR 0.62; 95% CI 0.44–0.86; $P = 0.005$) with no difference in OS [161]. The combination of ramucirumab and docetaxel represents a treatment option for patients with NSCLC progressing after previous ChT or immunotherapy, with PS 0–2 [I, B]. The combination of nintedanib and docetaxel represents a treatment option for patients with adenocarcinoma progressing after previous ChT or immunotherapy [II, B]. Combination of paclitaxel and bevacizumab is another treatment option [I, C; not EMA-approved].

Erlotinib represents a potential second-/third-line treatment option, in particular for patients not suitable for immunotherapy or second-line ChT in unknown *EGFR* status or *EGFR* wild-type (WT) tumours [II, C]. Erlotinib has shown superiority in OS compared with BSC in pretreated patients not eligible for further ChT (mOS 6.7 versus 4.7 months, HR 0.7; 95% CI 0.58–0.85, $P < 0.001$) [162]. In two additional trials, comparable efficacy of erlotinib and ChT has been reported for patients with refractory NSCLC (progression during first-line platinum-based ChT) or in second-/third-line therapy [163, 164].

In the recent years, a growing number of reports revealed an inferior efficacy of EGFR TKIs in pretreated patients with *EGFR* WT tumours compared with ChT [165]. In a meta-analysis summarising the results of 6 randomised trials with 900 patients, PFS for EGFR TKI was significantly inferior to ChT in the group of patients with *EGFR* WT tumours (HR 1.37, 95% CI 1.20–1.56, $P < 0.00001$). However, these results did not translate into an OS difference (HR 1.02, 95% CI 0.87–12, $P = 0.81$) [166]. An additional analysis of the Biomarkers France study reported a significant improvement in PFS or OS for second-line ChT compared with second-line EGFR TKI in 1278 patients with pretreated NSCLC (PFS 4.3 versus 2.83 months, HR 0.66, 95% CI 0.57–0.77, OS 8.39 versus 4.99 months, HR 0.7, 95% CI 0.59–0.83, $P < 0.0001$) [167].

In patients with advanced SCC, afatinib was investigated versus erlotinib in the LUX-Lung 8 trial. PFS and OS were improved in favour of afatinib (PFS 2.4 versus 1.9 months, HR 0.82, 95% CI 0.68–1.00, $P = 0.041$; OS 7.9 versus 6.8 months, HR 0.81, 95% CI 0.69–0.95, $P = 0.0077$) [168]. Afatinib was associated with improved pre-specified disease-related symptoms and health-related QoL [169].

Afatinib could be a therapeutic option in patients with advanced SCC with PS 0–2 unfit for ChT or immunotherapy,

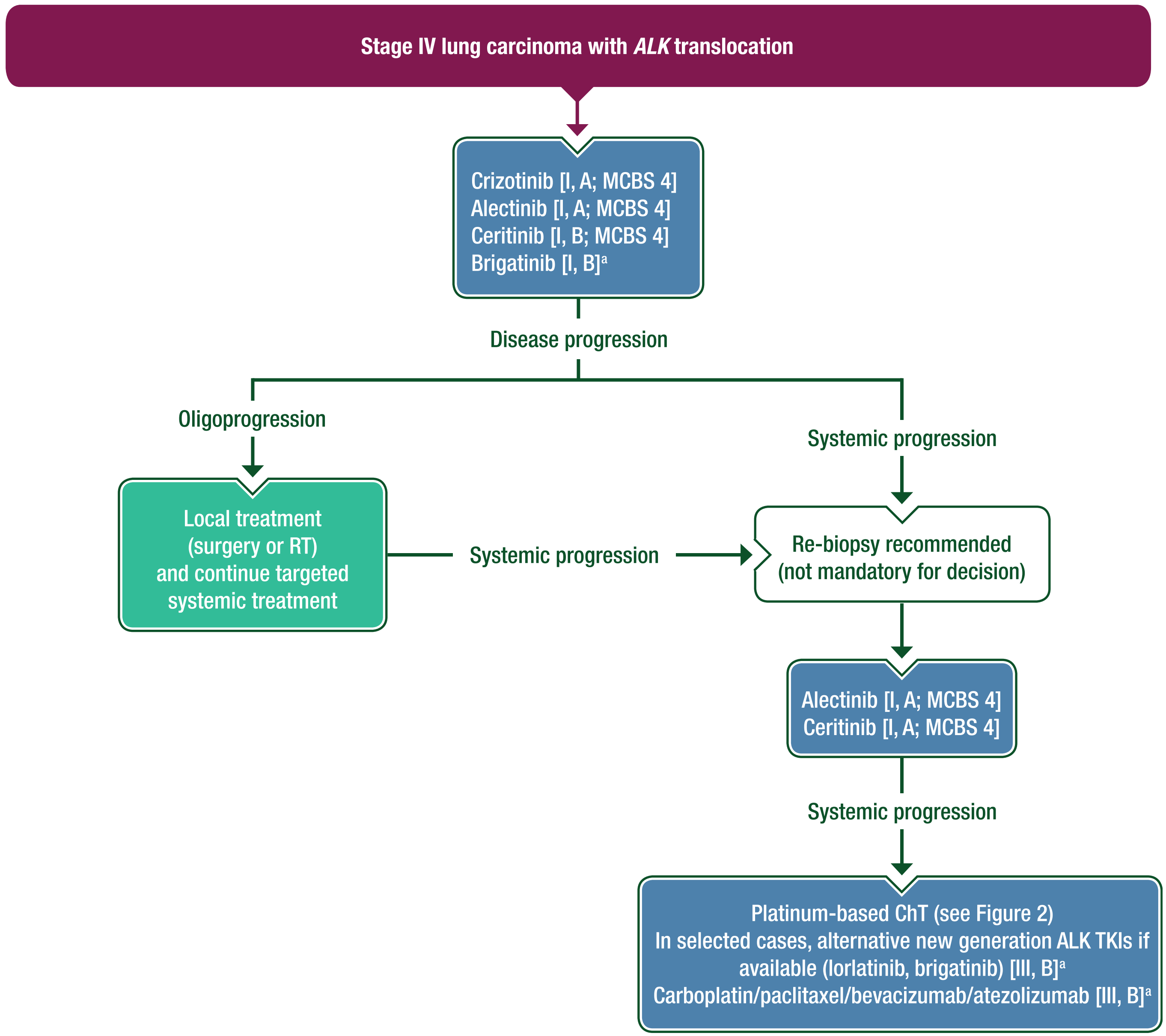

Figure 5. Treatment algorithm for stage IV lung carcinoma with *ALK* translocation.
[a]Not EMA-approved.
ALK, anaplastic lymphoma kinase; ChT, chemotherapy; EMA, European Medicines Agency; MCBS, ESMO-Magnitude of Clinical Benefit Scale; RT, radiotherapy; TKI, tyrosine kinase inhibitor.

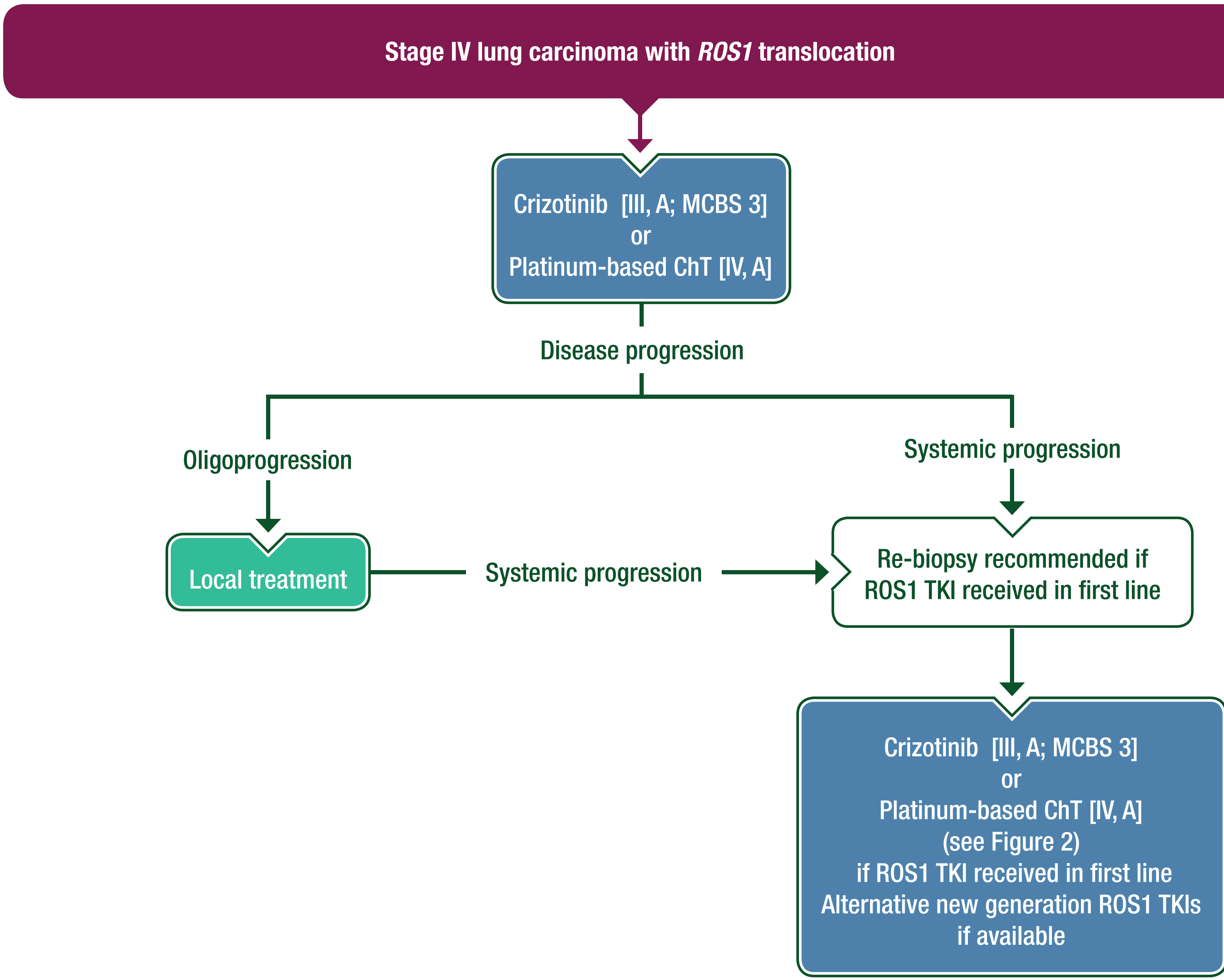

Figure 6. Treatment algorithm for stage IV lung carcinoma with *ROS1* translocation.
ChT, chemotherapy; MCBS, ESMO-Magnitude of Clinical Benefit Scale; TKI, tyrosine kinase inhibitor.

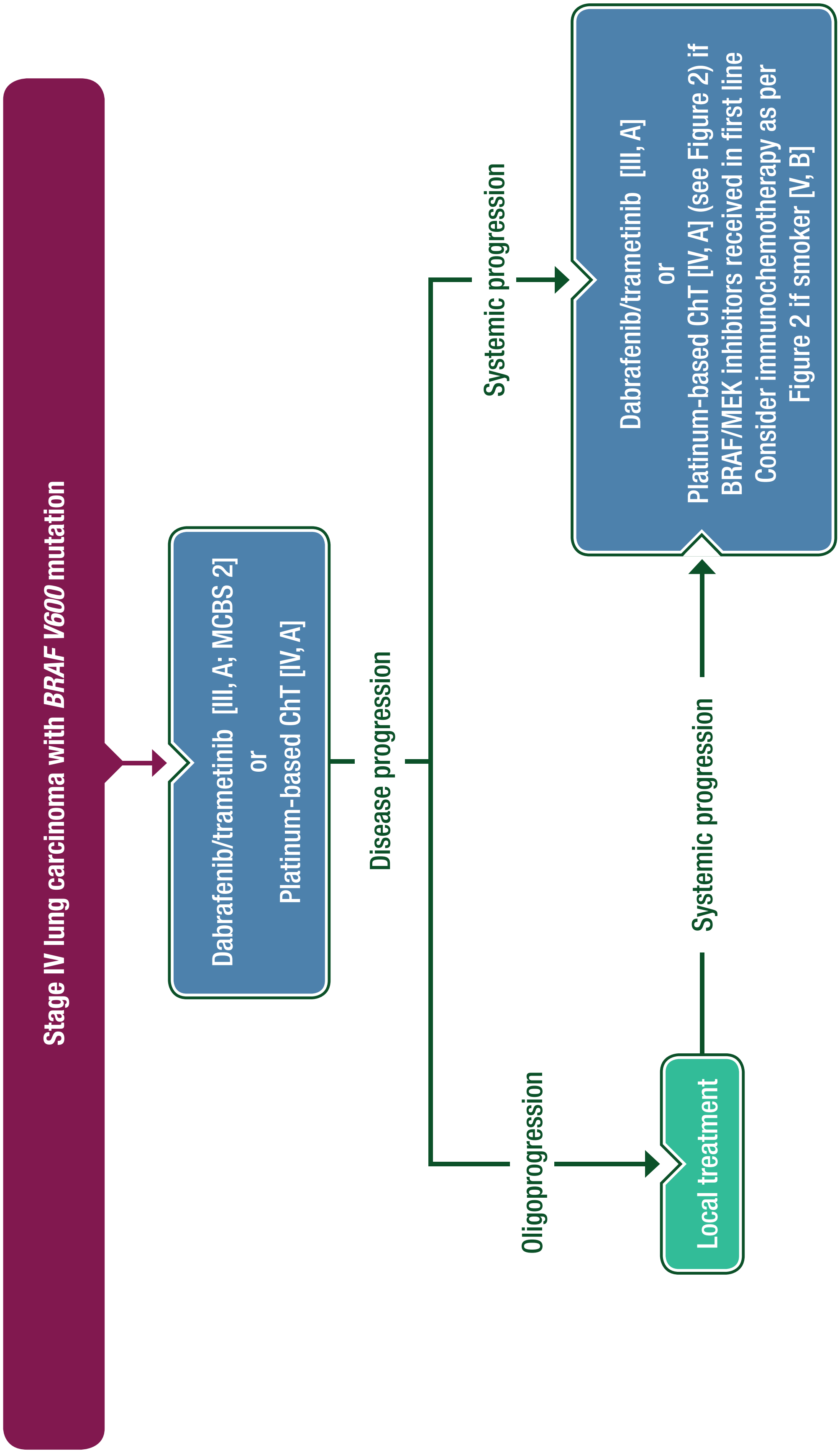

Figure 7. Treatment algorithm for stage IV lung carcinoma with *BRAF V600* mutation.
ChT, chemotherapy; MCBS, ESMO-Magnitude of Clinical Benefit Scale; MEK, mitogen-activated protein kinase.

progressing on or after ChT with unknown *EGFR* status or *EGFR* WT [I, C; ESMO-MCBS v1.1 score: 2].

In conclusion, patients clinically or radiologically progressing after first-line therapy with PS 0–2 should be offered second-line therapy, irrespective of administration of maintenance treatment [I, A]. So far, no prospective trials have determined the best second-line therapy following failure of first-line treatment with pembrolizumab; however, according to the first-line trial results, the preferred recommendation would be a platinum-based ChT, as discussed above [V, B] [62].

Treatment of *EGFR*-mutated NSCLC

First-line treatment. *EGFR* mutation is the best established oncogenic target for management of advanced stage NSCLC [170, 171]. The predictive power of *EGFR* mutation is confirmed in multiple randomised phase III studies comparing first- (erlotinib or gefitinib) or second-generation (afatinib) EGFR TKIs with standard platinum-based ChT [I, A] [172–177]. The benefit of improvement in ORR and PFS is consistent across all age groups, genders, smoking status and PS. Notably, none of the above studies have shown any benefit in OS for an EGFR TKI over platinum-based ChT, likely due to the high level of crossover. EGFR TKIs represent the standard of care as first-line treatment for advanced *EGFR*-mutated NSCLC [I, A] (Figures 3 and 4). Patients with PS 3–4 may also be offered an EGFR TKI as they are likely to receive a similar clinical benefit as patients with good PS [III, A] [178]. Patients who have benefited from EGFR TKI treatment may continue to receive the same therapy beyond initial radiological progression as long as they are clinically stable [II, A] [179]. Patients with localised distant progression and ongoing systemic control, continuation of treatment with EGFR TKI in combination with local treatment of progressing metastatic sites may be considered [III, B]. Continuous use of EGFR TKI in combination with ChT is not recommended as it was not associated with PFS improvement [I, A] and showed a detrimental effect on OS [II, B] [180].

The choice between first- and second-generation EGFR TKIs was investigated in two randomised studies. LUX-Lung 7 is a randomised phase IIB study that compares afatinib with gefitinib [181]. The study reported similar tumour ORR and a modest difference in PFS (mPFS 11.0 versus 10.9 months; HR 0.73, 95% CI 0.57–0.95, $P = 0.0165$). The other co-primary endpoint for this study was OS and was not statistically different (mOS 27.9 versus 24.5 months; HR 0.86, 95% CI 0.66–1.12, $P = 0.258$) [182]. More specifically, there was no difference in OS in patients with *EGFR* exon 19 mutation, which is contrary to the earlier claim of benefit in this subgroup from the pooled analysis of LUX-Lung 3 and LUX-Lung 6 studies [183].

ARCHER 1050 is a randomised phase III study that compares dacomitinib with gefitinib in stage IV *EGFR*-mutated lung cancer patients without CNS metastasis [184, 185]. The study reported significant improvement in PFS (mPFS 14.7 versus 9.2 months; HR 0.59, 95% CI 0.47–0.74, $P < 0.0001$). The mOS was 34.1 months with dacomitinib versus 26.8 months with gefitinib (HR 0.76, 95% CI 0.58–0.993, $P = 0.04$). The OS probabilities at 30 months were 56.2% and 46.3% with dacomitinib and gefitinib, respectively. Both afatinib and dacomitinib are associated with higher incidence of grade 3 skin and gastrointestinal toxicity and a significant proportion of patients require dose reduction. Erlotinib, gefitinib and afatinib are recommended as first-line therapy in patients with advanced NSCLC who have active sensitising *EGFR* mutations, regardless of their PS [I, A]. Dacomitinib will be added to the list when the drug is approved by regulatory agencies, the United States FDA and the EMA [I, A; not EMA-approved]. There is no consensus preferring any of the three currently available first-line EGFR TKIs over others [IV, C].

Osimertinib is a third-generation EGFR TKI that targets both sensitising *EGFR* mutation and the resistant exon 20 *T790M* mutation [186]. The drug was compared with a standard first-generation EGFR TKI (gefitinib or erlotinib) in the FLAURA phase III study [187]. Significant improvement in PFS was observed (mPFS 18.9 versus 10.2 months; HR 0.46, 95% CI 0.37–0.57, $P < 0.0001$). More importantly, a similar degree of improvement was observed in the subgroup of patients with CNS metastasis (mPFS 15.2 versus 9.6 months; HR 0.47, 95% CI 0.30–0.74, $P = 0.0009$). OS data were immature, while authors reported an HR of 0.63, which was not statistically significant. First-line osimertinib is now considered one of the options for NSCLC patients with sensitising *EGFR* mutations [I, A; MBCS score v1.1 score: 4].

The combination of ChT with gefitinib, at progression with gefitinib, has not shown any clinical benefit (IMPRESS Trial) [188]. The NEJ009 trial is the first phase III study that evaluated the efficacy of a combination of EGFR TKI (gefitinib) and platinum doublet ChT (carboplatin/pemetrexed) in untreated advanced NSCLC patients with *EGFR* mutations [189]. Carboplatin/pemetrexed/gefitinib demonstrated significantly better PFS (mPFS: 20.9 versus 11.2 months, HR 0.49, 95% CI 0.39–0.62) and OS (mOS: 52.2 versus 38.8 months, HR 0.69, 95% CI 0.52–0.92) compared with gefitinib, in advanced *EGFR*-mutated NSCLC, representing a first-line therapy option [I, B; not EMA-approved].

The combination of EGFR TKI and antiangiogenesis was first investigated in Japan. A randomised phase II study compared the combination of erlotinib and bevacizumab with erlotinib alone as first-line therapy for patients with *EGFR*-mutant NSCLC. Seto et al. reported mPFS of 16.4 and 9.8 months (HR 0.52, 95% CI 0.35–0.76), respectively [II, A] [190, 191]. However, the significant difference of PFS did not translate into a difference of OS between these treatments (mOS: 47 versus 47.4 months). A similar PFS was described in a European phase II trial that also evaluated the combination of erlotinib and bevacizumab, which was determined to be suitable as a front-line treatment option in *EGFR*-mutated NSCLC [III, B] [192]. A phase III trial (NEJ026) comparing bevacizumab/erlotinib to erlotinib in this patient population reported encouraging interim analysis results with significant benefit on PFS (mPFS 16.9 versus 13.3 months, HR 0.60, 95% CI 0.41–0.87); survival results are pending [II, A] [193]. While active research is ongoing, the EMA has approved the use of the combination of erlotinib and bevacizumab [ESMO-MCBS v1.1 score: 3]. Erlotinib/bevacizumab represents a front-line treatment option in *EGFR*-mutated tumours [II, B].

Beyond first-line treatment. Almost all patients who benefit from EGFR TKIs will eventually develop clinical resistance. About half of the resistance is explained by the acquired *EGFR* exon 20 *T790M* mutations [194]. Osimertinib and several other third-generation EGFR TKIs were developed targeting the *T790M* mutation. To date, the only approved medication for patients with *T790M* mutation is osimertinib. AURA3 is a randomised phase III study that compared osimertinib with pemetrexed/platinum in patients with proven *T790M* mutation at time of progression on first-/second-generation EGFR TKI [195]. Tumour ORR was 71% and 31%, respectively (HR 5.39, 95% CI 3.46–8.48, $P < 0.001$). The primary endpoint of PFS was also significantly different (mPFS 10.2 versus 4.4 months; HR 0.30, 95% CI 0.23–0.41, $P < 0.0001$). Osimertinib also showed a significantly longer CNS PFS (11.7 months) and higher CNS ORR (70%, 95% CI 51–85) compared with ChT (CNS PFS 5.6 months, CNS ORR 31%, 95% CI 11–59) in patients with CNS metastases at baseline [196]. The probability of experiencing a CNS progression event was lower for osimertinib than for ChT at both 3 months (2.7% versus 8.2%, respectively) and 6 months (11.5% versus 28.2%, respectively). This study has established a new paradigm: all patients with clinical resistance to first-/second-generation EGFR TKIs should be tested for the presence of *T790M* mutation and osimertinib should be offered as standard treatment for patients who test positive [I, A; ESMO-MCBS v1.1 score: 4].

Molecular mechanisms of resistance to EGFR TKIs were complex and heterogenous in patients without *T790M* mutation. These include *MET* amplification, *HER2* amplification, *PIK3CA* alternations, *BRAF* mutation, *KRAS* mutation and small cell transformation. The current standard in this scenario is platinum-based doublet ChT [I, A] and the expected ORR and PFS are 31% and 5.4 months, respectively [188], and should be considered as a therapeutic option in patients with *EGFR*-mutated tumour, PS 0–1, in absence of contraindications to use of immunotherapy after targeted therapies have been exploited [III, A; not EMA-approved] [97].

Treatment of *ALK*-rearranged NSCLC

First-line treatment. The anti-tumour activity of crizotinib was initially demonstrated in two multicentre single-arm studies, with significant ORR and PFS advantages, as well as a survival advantage, compared with other treatment options [197, 198]. The phase III study, PROFILE 1014, compared crizotinib with platinum–pemetrexed (without maintenance pemetrexed) as first-line treatment in *ALK*-rearranged advanced NSCLC. It demonstrated a significantly longer PFS (mPFS 10.9 versus 7.0 months; HR 0.45; 95% CI 0.35–0.60; $P < 0.001$) and higher ORR with crizotinib compared with ChT [199]. First-line treatment with crizotinib is a treatment option for patients with *ALK*-rearranged NSCLC [I, A; ESMO-MBCS v1.1 score: 4] (Figures 3 and 5).

Ceritinib and alectinib are second-generation ALK inhibitors that have shown robust antitumour efficacy, along with intracranial activity, in patients with *ALK*-rearranged NSCLC. The ASCEND-4 trial compared ceritinib (750 mg/day) with platinum-based ChT (cisplatin or carboplatin plus pemetrexed followed by maintenance pemetrexed) in untreated advanced *ALK*-rearranged non-squamous NSCLC [200]. Overall, ceritinib improved ORR over ChT: 72.5% (95% CI 65.5–78.7) compared with 26.7% (95% CI 20.5–33.7). mPFS was 16.6 months (95% CI 12.6–27.2) with ceritinib versus 8.1 months (95% CI 5.8–11.1) with ChT (HR 0.55, 95% CI 0.42–0.73, $P < 0.01$). At baseline, 59 patients in the ceritinib arm and 62 patients in the ChT arm had CNS metastasis. Among them, the intracranial ORR by RECIST was 72.7% (95% CI 49.8–89.3) with ceritinib versus 27.3% (95% CI 10.7–50.2) with ChT. In patients without baseline brain CNS metastasis, the mPFS with ceritinib was 26.3 months (95% CI 15.4–27.7), versus 8.3 months (95% CI 6.0–13.7) in the ChT arm. The most common AEs (all grades) in the ceritinib group were diarrhoea (85%), nausea (69%), vomiting (66%) and an increase in alanine aminotransferase (ALT, 60%) [ESMO-MCBS v1.1 score: 4]. Considering the safety profile of ceritinib, the influence of food on its oral bioavailability and the fact that food may improve gastrointestinal tolerability, a trial was conducted with a lower dose of ceritinib taken with a low-fat meal (ASCEND-8) [201]. A 450 mg dose of ceritinib taken once daily with food provides similar systemic exposure as the currently approved daily dose of 750 mg in a fasted state, and preliminary safety results demonstrated a reduction of the gastrointestinal toxicities when compared with the 750 mg fasted dose. These results suggest this dosing regimen as an alternative to the ceritinib 750 mg fasted dose [III, B].

The efficacy of alectinib was tested in a phase III head-to-head trial comparing this molecule [300 mg twice daily (b.i.d.)] with crizotinib (250 mg b.i.d.) in ALK TKI-naive *ALK*-rearranged advanced NSCLC Japanese patients (J-ALEX trial), demonstrating the superiority of alectinib as an initial targeted treatment [202]. The PFS HR of the alectinib arm compared with the crizotinib arm was 0.34 (95% CI 0.17–0.70, $P < 0.0001$). mPFS was not reached [95% CI 20.3–not evaluable (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*-rearranged treatment-naive patients was conducted (ALEX trial). Patients were randomised to receive either alectinib (600 mg b.i.d.) or crizotinib (250 mg b.i.d.) [53]. The investigator-assessed mPFS with alectinib was 34.8 (95% CI 17.7–not reached), compared with 10.9 months (95% CI 9.1–12.9) with crizotinib [203]. PFS assessed by the independent review committee was also significantly longer with alectinib than with crizotinib (mPFS 25.7 months; 95% CI 19.9–NE versus 10.4 months; 95% CI 7.7–14.6, respectively). In patients with baseline CNS metastases, mPFS was 27.7 months for alectinib versus 7.4 months for crizotinib. The time to CNS progression was significantly longer with alectinib than with crizotinib (cause-specific HR 0.16, 95% CI 0.10–0.28, $P < 0.001$). The mOS was not estimable in either group. Grade 3–5 AEs were less frequent with alectinib (41% versus 50% with crizotinib) [ESMO-MCBS v1.1 score: 4]. In patients with CNS involvement, front-line use of ALK TKIs is effective, and alectinib [III, A] or ceritinib [IV, B] are recommended. While ceritinib represents a better treatment strategy than ChT [I, B] and presumably crizotinib [IV, B], alectinib represents a better treatment option than ChT [III, A] and crizotinib [I, A].

Beyond first-line treatment. The benefit of crizotinib over second-line ChT in TKI-naive patients with previously treated *ALK*-rearranged NSCLC was confirmed in the phase III PROFILE 1007, with better ORR and PFS [204]. The mPFS 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 ChT group. Any patient with NSCLC harbouring an *ALK* fusion should receive crizotinib as next-line therapy, if not received previously [I, A]. Despite improved outcome in patients with tumours harbouring *ALK* rearrangements and treated with crizotinib (mainly in first line), 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 [205]. Ceritinib (ASCEND-5) and alectinib (ALUR) were compared with ChT in patients with *ALK*-positive NSCLC previously treated with crizotinib and ChT [206, 207]. Both trials showed a significant improvement in mPFS compared with ChT (5.4 months, 95% CI 4.1–6.9 for ceritinib versus 1.6 months, 95% CI 1.4–2.8 for ChT; HR 0.49, 95% CI 0.36–0.6, $P < 0.0001$ and 9.6 months, 95% CI 6.9–12.2 for alectinib versus 1.4 months, 95% CI 1.3–1.6 for ChT; HR 0.15, 95% CI 0.08–0.29; $P < 0.001$). CNS ORR was 54.2% and 35% with alectinib or ceritinib, respectively, versus 0% or 5% with ChT in the ALUR and ASCEND-5 trials, respectively [206–208]. Based on this data, ceritinib and alectinib are recommended in patients with *ALK*-positive advanced NSCLC who progress on treatment with or are intolerant to crizotinib [I, A; ESMO-MBCS v1.1 score: 4].

In *ALK*-rearranged patients progressing on crizotinib with CNS progression, treatment with next-generation ALK TKIs, such as alectinib or ceritinib, is recommended [I, A]. The next-generation ALK inhibitors, such as brigatinib or lorlatinib, have a wider coverage of *ALK* resistance mutations, and sequential therapy with these ALK inhibitors is the preferred treatment approach in crizotinib-resistant and/or the second generation-resistant populations. The ALTA trial evaluated the brigatinib in crizotinib-resistant *ALK*-rearranged NSCLC patients. Patients were randomised (1:1) to receive oral brigatinib 90 mg once daily (arm A) or 180 mg once daily with a 7-day run-in at 90 mg (arm B) [209]. The ORR was 46% (arm A) and 55% (arm B) and mPFS was 9.2 months in arm A and 15.6 months in arm B. mOS was not reached in arm A and was 27.6 months in arm B. CNS ORRs were 50% and 67% in arms A and B, respectively. In results from a phase I study, lorlatinib demonstrated significant activity reporting ORRs of 46% and 42% among *ALK*-rearranged patients pretreated with one or with two or more ALK TKIs, respectively, including patients with CNS metastases at baseline (intracranial ORR 42%) [210]. A phase II study at the recommended dose (100 mg once a day) is demonstrating 69% RR in crizotinib pretreated patients and 39% after two or more previous ALK TKIs [211]. Of interest, in patients previously treated with one or more second-generation ALK TKIs, a higher proportion of patients harbouring an *ALK* secondary mutation responded to treatment with lorlatinib compared to those without detectable *ALK* mutations (ORR: 61% versus 26%) [212]. Lorlatinib and brigatinib are in phase III testing to investigate whether upfront treatment with the next generation can further improve clinical outcomes for patients with advanced *ALK*-rearranged NSCLC compared with crizotinib treatment [213, 214]. At the first interim analysis, brigatinib was shown to improve PFS compared with crizotinib (HR 0.49; 95% CI 0.33−0.74; $P < 0.001$) [I, B, not EMA approved] [215]. In patients with baseline CNS metastases, intracranial objective response rate was 78% for brigatinib versus 29% for crizotinib. In patients who progress after a second-generation ALK TKI, the next-generation ALK inhibitors such as brigatinib or lorlatinib are recommended if available [III, B]. They are currently not approved by the EMA.

Treatment of *ROS1*-rearranged NSCLC

On the basis of the available preclinical data, the phase I PROFILE 1001 study of crizotinib was amended to include patients with *ROS1*-rearranged NSCLC in the expansion cohort [216]. Among 50 patients with *ROS1*-rearranged NSCLC in this trial cohort, the ORR to crizotinib was 72%, with a disease control rate equal to 90% and an mPFS of 19.2 months. In a prospective French phase II study and in the retrospective EUROS1 study of crizotinib for *ROS1*-rearranged NSCLC, mPFS was 10 and 9.1 months and ORR was 72% and 80%, respectively, although both of these studies enrolled only approximately 30 patients [217, 218]. In a larger East Asian phase II study of crizotinib, the mPFS among 127 patients with *ROS1*-rearranged lung cancer was 13.4 months [219]. Each study included patients who had received varying numbers of prior lines of systemic therapy, although for all of these patients, crizotinib remained the first ROS1-directed TKI. Single-agent crizotinib is recommended in the first-line setting or as second line in patients with stage IV NSCLC with *ROS1* rearrangement [III, A; ESMO-MBCS v1.1 score: 3] (Figures 3 and 6). If patients have received crizotinib in the first-line setting, then they may be offered platinum-based ChT therapy in the second-line setting [IV, A].

Ceritinib is a potent and selective ALK inhibitor that also inhibits ROS1. In a Korean phase II study, 32 patients with *ROS1*-rearranged advanced NSCLC were treated with ceritinib, 750 mg daily [220]. Among crizotinib-naive patients, the ORR was 67%, with a disease control rate of 87%. The mPFS was 9.3 months for the entire cohort and reached 19.3 months for crizotinib-naive patients. Of note, in those two patients who had received prior crizotinib, no clinical response was observed. Ceritinib might be considered in crizotinib-naive patients but is currently not approved by the EMA [III, C].

Brigatinib, lorlatinib and entrectinib also have a potential anti-ROS1 activity on the basis of preclinical studies and limited phase I/II encouraging clinical data [221].

Treatment of *BRAF*-mutated NSCLC

The most common *BRAF* mutation, *V600E* (Val600Glu), is observed in 1%–2% of lung adenocarcinomas [222–224], more frequently in patients with smoking history. In a retrospective multicentre cohort study in Europe, patients with advanced *BRAF*-mutant lung cancer received treatment with either vemurafenib ($n = 29$), dabrafenib ($n = 9$) or sorafenib ($n = 1$) [225]. Of the *BRAF* mutations, 83% were *BRAF V600E.* The ORR was 53% and the PFS and OS were 5 and 10.8 months, respectively.

In a vemurafenib basket trial (VE-BASKET), patients with various *BRAF V600* mutation-positive non-melanoma tumours were enrolled in six prespecified cancer cohorts, including an NSCLC cohort with 20 patients [226]. A total of 19 NSCLC patients were evaluable for response. Overall, one patient was treatment-naive and 50% and 45% of patients received one or two or more lines of therapy before study inclusion, respectively. The ORR, mPFS and mOS were 42%, 7.3 months and not yet reached, respectively.

A prospective multicentre multicohort phase II study of dabrafenib monotherapy (cohort A), or combination therapy with a MEK inhibitor (trametinib) (cohort B, beyond first-line and cohort C in first-line treatment) in patients with *BRAF V600E*-mutant metastatic NSCLC (BRF113928) was reported. With dabrafenib monotherapy (cohort A, $n = 78$), the ORR was 33% and mPFS and median duration of response (mDoR) were 5.5 and 9.6 months, respectively [227]. With combination dabrafenib and trametinib in pretreated patients (cohort B, $n = 57$), the ORR was 66% and mPFS and mDoR were 10.2 and 9.8 months, respectively [228, 229]. With combination dabrafenib and trametinib therapy in unpretreated patients (cohort C, $n = 36$), the ORR was 64% and mPFS and DoR were 10.9 and 10.4 months, respectively [230]. The mOS was 24.6 months and half of the patients were still alive at two years from treatment beginning. The EMA and the United States FDA have approved dabrafenib in combination with trametinib for the treatment of patients with *BRAF V600* mutation-positive advanced or metastatic NSCLC. BRAF/MEK inhibition using dabrafenib with trametinib is recommended in patients with BRAF inhibitor naive, stage IV NSCLC with *BRAF V600E* mutation [III, A; ESMO-MBCS v1.1 score: 2] (Figures 3 and 7). If patients have received BRAF/MEK inhibition in the first-line setting, then they may be offered platinum-based ChT in the second-line setting [IV, A].

Treatment of NSCLC with other actionable oncogenic drivers

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

RET fusions are found in 1%–2% of NSCLC and tend to be mutually exclusive to other lung cancer drivers [231, 232]. Although RET-selective inhibitors have not yet been developed, several multitarget agents with anti-RET activity have been evaluated in preclinical models and clinical trials. The activity of multikinase inhibitors (cabozantinib, vandetanib, sunitinib, sorafenib, alectinib, lenvatinib, nintedanib, ponatinib, regorafenib) in patients with *RET*-rearranged NSCLC (ORR 16%–47% and mPFS 2.3–7.3 months) is clearly inferior to the responses and survival outcomes seen with selective TKIs in other oncogene-addicted NSCLC models [233–236]. These studies are small and subject to selection bias and results of heterogeneous benefit [III, C]. Further studies are needed to confirm the benefit of current treatments as well as the development of more specific inhibitors (i.e: BLU-667, LOXO-292) [237]. Targeting RET is not currently routinely recommended and recruitment into open trials is encouraged [III, C].

Somatic dysregulation at *MET* occurs through a number of different non-exclusive mechanisms in NSCLC including overexpression, amplification, mutation and gene-rearrangement. Previous trials aimed at targeting MET overexpression (e.g. onartuzumab or tivantinib) have failed, and as the relationship between expression and genomics is now better understood, focus has shifted to targeting genomic variants [238–240]. Two major *MET* variants may play a key role as NSCLC oncogenic drivers: *MET* exon 14 variants (*METex14*) and *MET* amplification. *MET* amplification can occur as either acquired (as a resistance mechanism to EGFR TKI therapy) or *de novo*. While a promising target, targeting MET dysregulation by *MET* amplification is not currently routinely recommended and recruitment into open trials is encouraged [III, C]. *METex14* mutations are similarly as common as *ALK* rearrangements, occurring in 3%–4% of NSCLC. They are more frequently but not exclusively identified in adenocarcinoma and sarcomatoid carcinoma histological subtypes (especially those with an adenocarcinoma component), observed in current, ex- and never-smokers, more frequently observed in older than in younger patients. *METex14* mutations are extremely diverse and result in aberrant splicing and exon 14 skipping, resulting in loss of the MET Y1003 c-Cbl binding site and reduced MET degradation, detectable as increased expression by IHC. Moreover, *METex14* mutations are mutually exclusive to other drivers (*EGFR*, *ALK*, *BRAF*), further reinforcing *MET* status as an oncogenic driver, more often encountered in smokers. Multiple case series and cohorts have now demonstrated durable ORRs with MET-targeting TKIs including crizotinib, capmatinib and cabozantinib in *METex14* patients, with the PROFILE 1001 trial *METex14* cohort reporting an ORR of 44% and a global retrospective series demonstrating a PFS of 7 months, both with crizotinib [241, 242]. A variety of MET-directed TKIs are undergoing development against this target. For *METex14* variants, while evidence of benefit is stronger, recruitment into open trials is encouraged [III, C]. Crizotinib has demonstrated potential clinical efficacy that needs to be confirmed [III, C].

HER2 dysregulation is another promising target for advanced NSCLC and is abrogated via different mechanisms including exon 20 mutations, transmembrane domain mutations, amplification and protein overexpression. Mutations in exon 20 were the first *HER2* mutations described and occur in 1%–5% of patients, over-represented in young patients, never-smokers, females, patients without ethnic clustering and typically in adenocarcinomas [243]. Such mutations are analogous to *EGFR* exon 20 insertions, being mutually exclusive to other oncogenic drivers, and are usually 3–12 bp in-frame insertions between codons 775–881, the most common being the YVMA insertion at codon 775. *HER2* insertions are typically resistant to HER-targeting TKIs afatinib, dacomitinib and neratinib [244, 245], although some specific genotypes, e.g. those resulting in Gly770 insertion, may retain sensitivity [246]. Afatinib and poziotinib have demonstrated some activity in *HER2*-mutated NSCLC in small series [247, 248]. More recently, targeting *HER2* mutation with ado-trastuzumab emtansine (TDM-1) has shown promise with two cohorts demonstrating responses including mutants with no copy-number change [249]. Abnormal gene copy-number is also identified at *HER2*, although is typically polysomy, with *HER2* exon 20 insertions and amplification usually mutually exclusive [243]. Targeting *HER2* amplification or protein expression with trastuzumab monotherapy has not consistently demonstrated benefit, but may have a role in *HER2*-mutant NSCLC, although data are usually based on cases confounded by concurrent ChT and variable HER2 expression. The antibody–drug conjugate TDM-1 has shown very modest activity in HER2-overexpressing NSCLC [250]. Rarer *HER2* variants include transmembrane domain mutations (e.g. *V659*, *G660*) that have reported sensitivity to afatinib and TDM-1 [251]. Nevertheless, given the paucity of robust data, targeting *HER2* dysregulation is not currently recommended and recruitment into open trials is encouraged [III, C].

Table 4. Summary of recommendations

Diagnosis

- Bronchoscopy is a technique ideally suited to central lesions and can be used with bronchial washing, brushing, bronchial and transbronchial biopsy
- EBUS and/or EUS allows evaluation of regional lymph nodes
- Transthoracic fine needle aspiration and/or core biopsy, passing a needle through the parenchyma under imaging guidance (typically CT), is indicated in case of mid to peripheral lesions
- In presence of a pleural effusion, thoracentesis could represent both a diagnostic tool and a palliative treatment
- More invasive, surgical approaches (mediastinoscopy, mediastinotomy, thoracoscopy etc.) in the diagnostic workup can be considered when the previously described techniques cannot allow for an accurate diagnosis
- With systematic collaboration and constant communication between pathologists and procedure performers, diagnostic yields will be significantly greater than with blind biopsies

Pathology/molecular biology

- 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 of lung tumours
- 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 resistance to some therapies [III, B]. At a minimum, when resources or material are limited, the most common activating mutations (exon 19 deletion, exon 21 *L858R* point mutation) should be determined [I, A]
- The availability of TKIs effective against *T790M*-mutant recurrent disease makes *T790M* testing on disease relapse mandatory [I, A]
- All patients with a negative cfDNA blood test still require tissue biopsy [II, A]
- Testing for *ALK* rearrangement should be systematically carried out in advanced non-squamous NSCLC [I, A]
- Detection of the *ALK* translocation by FISH remains a standard, but IHC with high-performance ALK antibodies and validated assays may be used for screening [III, A] and have recently been accepted as an equivalent alternative to FISH for ALK testing
- Testing for *ROS1* rearrangement should be systematically carried out in advanced NSCLC [III, A]. Detection of the *ROS1* translocation by FISH remains a standard; IHC may be used as a screening approach [IV, A]
- *BRAF V600* mutation status should be systematically analysed in advanced NSCLC for the prescription of BRAF/MEK inhibitors [II, A]
- Molecular *EGFR* and *ALK* testing are not recommended in patients with a confident diagnosis of SCC, except in unusual cases, e.g. never/former light smokers or long-time ex-smokers [IV, A]
- If available, multiplex platforms (NGS) for molecular testing are preferable [III, A]. Whatever testing modality is used, it is mandatory that adequate internal validation and quality control measures are in place and that laboratories participate in, and perform adequately in, external quality assurance schemes for each biomarker test [III, A]
- PD-L1 IHC should be systematically determined in advanced NSCLC [I, A]
- Testing is required for pembrolizumab therapy but may also be informative when nivolumab or atezolizumab are used [I, A]

Staging and risk assessment

- A complete history including a precise smoking history and comorbidities, weight loss, PS and physical examination must be recorded
- Laboratory: standard tests including routine haematology, renal and hepatic functions and bone biochemistry tests are required
- Routine use of serum tumour markers, such as CEA, is not recommended [IV, B]
- Contrast-enhanced CT scan of the chest and upper abdomen including the liver and the adrenal glands should be carried out at diagnosis
- Imaging of CNS should be considered at diagnosis for all patients with metastatic disease [IV, B] and is required for patients with neurological symptoms or signs [IV, A]. MRI is more sensitive than CT scan [III, B]
- If bone metastases are clinically suspected, bone imaging is required [IV, B]
- Bone scan or PET, ideally coupled with CT, can be used for detection of bone metastasis [IV, B]. PET-CT is the most sensitive modality in detecting bone metastasis [II, B]
- NSCLC is staged according to the UICC system (8th 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 [IV, A]
- Response evaluation is recommended after two to three cycles of ChT or immunotherapy, using the same initial radiographic investigation that demonstrated tumour lesions [IV, B]. 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 [IV, B]. Follow-up with PET is not routinely recommended, due to its high sensitivity and relatively low specificity [IV, C]
- Measurements and response assessment should follow RECIST v1.1 [IV, A]. The adequacy of RECIST in evaluating the response to EGFR or ALK TKI in respective genetically driven NSCLC is debatable [IV, B]
- In the case of immune checkpoint inhibitor therapy, RECIST should be used, although irRECIST, iRECIST, imRECIST may have a role in the overall assessment of therapy [IV, B]

Management of advanced/metastatic disease

- The treatment strategy should consider the histology, molecular pathology, age, PS, comorbidities and the patient's preferences
- 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]

Continued

First-line treatment of *EGFR*- and *ALK*-negative NSCLC, PD-L1 ≥ 50%

- Pembrolizumab is considered a standard first-line option for patients with advanced NSCLC and PD-L1 expression ≥ 50% who do not have contraindications to use of immunotherapy [I, A; ESMO-MCBS v1.1 score: 5]

First-line treatment of NSCLC without actionable oncogenic driver regardless of PD-L1 status

- ChT with platinum doublets should be considered in all stage IV NSCLC patients without an actionable oncogenic driver, without major comorbidities and PS 0–2 [I, A]
- Platinum-based doublets are the recommended ChT 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 [I, A], or four cycles in patients not suitable for maintenance monotherapy [I, A], up to a maximum of six [IV, B], are currently recommended
- The carboplatin/nab-P regimen could be considered a chemotherapeutic option in advanced NSCLC patients, particularly in patients with greater risk of neurotoxicity, preexisting hypersensitivity to paclitaxel or contraindications for standard paclitaxel premedication [I, B]
- Combinations of platinum-based ChT and anti-PD-(L1) inhibitors have reproducibly demonstrated superiority to standard platinum-based ChT. In the absence of contraindications and conditioned by the registration and accessibility of anti-PD-(L)1 combinations with platinum-based ChT, this strategy will be preferred to platinum-based ChT in patients with PS 0-1 and PD-L1 < 50%.
- Nivolumab plus ipilimumab represents an optional treatment regimen for patients with NSCLC with a high TMB [I, A; not EMA-approved]

First-line treatment of SCC

- Platinum-based doublets with a third-generation cytotoxic agent (gemcitabine, vinorelbine, taxanes) are recommended in advanced SCC patients without major comorbidities and PS 0–2 [I, A]
- The addition of necitumumab to cisplatin/gemcitabine has not been adopted as a standard in Europe for advanced SCC and its use should be carefully evaluated [I, C; ESMO-MCBS v1.1 score: 1]
- Combination of pembrolizumab and carboplatin with paclitaxel or nab-P is a standard choice in patients with metastatic squamous NSCLC [I, A; not EMA approved]
- The use of atezolizumab with carboplatin and nab-P today represents an option in patients with metastatic squamous NSCLC [I, B; not EMA-approved]
- Other combinations of platinum-based ChT and anti-PD-(L1) inhibitors will demonstrate superiority to standard platinum-based ChT. In the absence of contraindications and conditioned by the registration and accessibility of anti-PD-(L)1 combinations with platinum-based ChT, this strategy should be preferred to platinum-based ChT in patients with PS 0-1 and PD-L1 < 50%.
- Nivolumab plus ipilimumab represents an optional treatment regimen for patients with SCC with a high TMB [I, A; not EMA-approved]

First-line treatment of NSCC

- Pemetrexed-based combination ChT is preferred to gemcitabine- or docetaxel-based combinations in patients with non-squamous tumours [II, A]
- Pemetrexed use is restricted to NSCC in any line of treatment in advanced disease [II, A]
- The combination of carboplatin with pemetrexed can be an option in patients with a contraindication to cisplatin [II, B]
- Pembrolizumab in combination with pemetrexed and a platinum-based ChT should be considered a standard option in metastatic non-squamous NSCLC [I, A; ESMO-MCBS v1.1 score: 4]
- Atezolizumab in combination with pemetrexed and a platinum-based ChT is a therapeutic option in metastatic non-squamous NSCLC [I, B; not EMA-approved]
- Combination of atezolizumab and bevacizumab with carboplatin and paclitaxel is a therapeutic option in patients with PS 0-1 with metastatic non-squamous NSCLC, in the absence of contraindications to use of immunotherapy [I, A; not EMA-approved]
- Other combinations of platinum-based ChT and anti-PD-(L1) inhibitors will demonstrate superiority to standard platinum-based ChT. In the absence of contraindications and conditioned by the registration and accessibility of anti-PD-(L)1 combinations with platinum-based ChT, this strategy should be preferred to platinum-based ChT in patients with PS 0-1 and PD-L1 < 50%.
- Nivolumab plus ipilimumab represents an optional treatment regimen for patients with NSCC with a high TMB [I, A; not EMA-approved]
- If PD-(L)1 is not available for ChT combinations, bevacizumab combined with paclitaxel/carboplatin may be offered in the absence of contraindications in patients with advanced NSCC and PS 0-1 (bevacizumab should be given until progression) [I, A]
- Bevacizumab might be considered with platinum-based regimens beyond paclitaxel/carboplatin in absence of contraindications [II, B]

Maintenance

- Maintenance ChT should be offered only to patients with PS 0–1 after first-line ChT. Decisions about maintenance should consider histology, response to platinum-doublet ChT and remaining toxicity after first-line ChT, PS and patient's 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 ChT [I, B]
- Pemetrexed continuation maintenance should be considered in patients having disease control following four cycles of cisplatin/pemetrexed [I, A]
- Continuation maintenance with gemcitabine is an option in NSCLC patients treated with four cycles of cisplatin/gemcitabine [I, C]
- Maintenance treatment with erlotinib is only recommended for NSCC patients with an *EGFR*-sensitising mutation [III, B]

PS 2 and beyond

- ChT prolongs survival and improves QoL in NSCLC patients with PS 2 when compared with BSC [I, A]
- Platinum-based (preferably carboplatin) combination ChT should be considered in eligible PS 2 patients [I, A]. Single-agent ChT with gemcitabine, vinorelbine, docetaxel [I, B] or pemetrexed (restricted to NSCC) [II, B] is an alternative treatment option
- The use of checkpoint inhibitors for patients with advanced NSCLC and PS 2 can be considered [III, B]
- Poor PS (3–4) patients should be treated with BSC only in the absence of molecularly targetable alterations, such as *EGFR* mutations, *ALK* or *ROS1* rearrangements or *BRAF V600* mutation [III, B]

Continued

Elderly patients

- Immunotherapy should be considered according to standard recommendations in elderly patients [III, A]
- Carboplatin-based doublet ChT is recommended in eligible elderly patients with PS 0–2 and with adequate organ function [I, A]
- For those patients not eligible for doublet ChT, single-agent ChT remains the standard of care [I, B]

Second-line treatment of NSCLC without actionable oncogenic driver

- Patients clinically or radiologically progressing after first-line therapy with PS 0–2 should be offered second-line therapy irrespective of administration of maintenance treatment [I, A]
- In patients with progression after first-line immunotherapy with pembrolizumab, platinum-based ChT is recommended as second-line treatment option [V, B]
- There is a general trend across each of the phase III studies in second-line (nivolumab, pembrolizumab and atezolizumab versus docetaxel) for enriched efficacy of anti-PD-1/PD-L1 agents in patients with higher PD-L1 expression compared with those with no/less PD-L1 expression. However, unselected patients may still have improved survival and tolerability with anti-PD-1/PD-L1 agents compared with docetaxel [I, A].
- PD-L1 and PD-1 inhibitors (nivolumab, pembrolizumab and atezolizumab) are the treatment of choice for most patients with advanced, previously treated, PD-L1-naive NSCLC, irrespective of PD-L1 expression [I, A]
- Nivolumab is recommended in both squamous [I, A; ESMO-MBCS v1.1 score: 5] and non-squamous NSCLC [I, A; ESMO-MBCS v1.1 score: 5]
- Pembrolizumab is recommended in patients with previously treated NSCLC with PD-L1 expression > 1% [I, A; ESMO-MCBS v1.1 score: 5]
- Atezolizumab is recommended in patients with advanced NSCLC previously treated with one or two prior lines of ChT [I, A; ESMO-MCBS v1.1 score: 5]
- In patients not suitable for immunotherapy, second-line ChT is recommended. Comparable options as second-line therapy consist of pemetrexed, for NSCC only, or docetaxel, with a more favourable tolerability profile for pemetrexed [I, B]
- Treatment may be prolonged if disease is controlled and toxicity acceptable [II, B]
- Nintedanib/docetaxel is a treatment option in patients with adenocarcinoma progressing after previous ChT or immunotherapy [II, B]
- Ramucirumab/docetaxel is a treatment option in patients with NSCLC progressing after first-line ChT or immunotherapy with PS 0–2 [I, B]
- Combination of paclitaxel and bevacizumab is another treatment option [I, C] but it is not EMA-approved
- Erlotinib represents a potential second/third-line treatment option in particular for patients not suitable for immunotherapy or second-line ChT in unknown *EGFR* status or *EGFR* WT tumours [II, C]
- In patients with advanced SCC with PS 0–2 unfit for ChT or immunotherapy, afatinib is a potential option with unknown *EGFR* status or *EGFR* WT patients [I, C; ESMO-MCBS v1.1 score: 2]

First-line treatment of *EGFR*-mutated NSCLC

- Patients with a tumour with a sensitising *EGFR* mutation should receive first-line EGFR TKIs including erlotinib, gefitinib or afatinib [I, A]. None of the three EGFR TKIs is consensually considered as a preferred option [IV, C]
- Dacomitinib will be added to the list when the drug will be approved by regulatory agencies, the United States FDA and the EMA [I, A]
- First-line osimertinib is now considered one of the options for patients with a tumour with sensitising *EGFR* mutations [I, A; MBCS score v1.1 score: 4]
- All patients should be considered for EGFR TKIs irrespective of clinical parameters, including PS, gender, tobacco exposure, histology and line of therapy [I, A]
- Erlotinib/bevacizumab represents a front-line treatment option in patients with *EGFR*-mutated tumours [II, B; ESMO-MCBS v1.1 score: 3]
- Addition of carboplatin and pemetrexed to gefitinib represents a first-line option in patients with *EGFR*-mutated tumours [I, B; not EMA-approved]
- Patients who have radiological progression with ongoing clinical benefit may continue with EGFR TKI [II, A]
- In *EGFR*-mutated NSCLC patients with localised distant progression and ongoing systemic control, continuation of treatment with EGFR TKI in combination with local treatment of progressing metastatic sites may be considered [III, B]

Second-line treatment of *EGFR*-mutated NSCLC

- EGFR TKI should be stopped at the time when patient starts ChT for treatment of TKI resistance [I, A]
- All tumours with clinical evidence of EGFR TKI resistance, not previously treated with osimertinib, should be tested for presence of *EGFR* exon 20 *T790M* mutation [I, A]
- Liquid biopsy can be used as the initial test for detection of *T790M* mutation, and if tested negative, re-biopsy should be attempted if feasible [II, A]
- Osimertinib is the standard therapy for patients whose tumours are tested positive for *T790M* either in liquid biopsy or re-biopsy, if not received previously [I, A; ESMO-MCBS v1.1 score: 4]
- In *EGFR*-mutated NSCLC with CNS disease, osimertinib is highly active
- Platinum-based doublet is the standard therapy for patients whose tumour is tested *T790M* negative in either re-biopsy or in liquid biopsy (only when re-biopsy is not feasible) [I, A]
- Combination of atezolizumab and bevacizumab with carboplatin and paclitaxel should be considered as a therapeutic option in patients with *EGFR*-mutated tumour, PS 0–1, in absence of contraindications to use of immunotherapy after targeted therapies have been exploited [III, A; not EMA-approved]

First-line treatment of *ALK*-rearranged NSCLC

- Patients with *ALK*-rearranged NSCLC should receive first-line ALK TKI including crizotinib [I, A; ESMO-MBCS v1.1 score: 4], ceritinib [I, B; ESMO-MCBS v1.1 score: 4], alectinib [I, A] or brigatinib [I, B; not EMA-approved]
- Alectinib is associated with longer PFS and lower toxicity than crizotinib and showed activity against CNS disease in patients previously untreated with *ALK*-positive NSCLC [I, A]
- Brigatinib is associated with longer PFS than crizotinib at the first interim analysis and showed activity against CNS disease in previously untreated patients with *ALK*-positive NSCLC [I, B, not EMA approved]
- In patients with CNS involvement, front-line use of ALK TKIs is effective, and alectinib [III, A], brigatinib [III, B] or ceritinib [IV, B] are recommended. Ceritinib represents a better treatment strategy than ChT [I, B] and presumably crizotinib [IV, B]; alectinib represents a better treatment option than crizotinib [I, A]; brigatinib represents a better treatment option than crizotinib [I, B; not EMA-approved]
- In *ALK*-rearranged NSCLC patients with localised distant progression and ongoing systemic control, continuation of treatment with ALK TKI in combination with local treatment of progressing metastatic sites may be considered [III, B]

Continued

Second and further lines of treatment of *ALK*-rearranged NSCLC

- Any patient with NSCLC harbouring an *ALK* fusion should receive crizotinib as next-line therapy, if not received previously [I, A]
- Ceritinib and alectinib are recommended in patients with *ALK*-positive advanced NSCLC who progress on treatment with or are intolerant to crizotinib [I, A; ESMO-MBCS v1.1 score: 4]
- In patients with *ALK*-positive NSCLC progressing on crizotinib with CNS progression, treatment should be a next-generation ALK TKIs such as alectinib or ceritinib [I, A]. In patients who progress after a second-generation ALK TKI, the next-generation ALK inhibitors such as brigatinib or lorlatinib are an option if available [III, B]. They are currently not approved by the EMA

Treatment of *ROS1*-rearranged NSCLC

- Crizotinib is recommended in the first-line setting in patients with stage IV NSCLC with *ROS1* rearrangement [III, A; ESMO-MBCS v1.1 score: 3]
- In patients with *ROS1*-positive NSCLC, who have not received crizotinib in the first-line setting, single-agent crizotinib may be offered as second-line therapy [III, A]
- Ceritinib might be considered in crizotinib-naive patients but is currently not approved by the EMA [III, C]
- If patients have received crizotinib in the first-line setting, then they may be offered platinum-based ChT therapy in the second-line setting [IV, A]

Treatment of *BRAF*-mutated NSCLC

- Patients with stage IV NSCLC with *BRAF V600* mutation should be exposed in first or second line to BRAF/MEK inhibition using dabrafenib/trametinib [III, A; ESMO-MBCS v1.1 score: 2]
- If patients have received BRAF/MEK inhibition in the first-line setting, then they may be offered platinum-based ChT in the second-line setting [IV, A]

Patients with NSCLC with other actionable oncogenic driver

- Targeting RET is not currently routinely recommended and recruitment into open trials is encouraged [III, C]
- Targeting *MET* amplification is not currently routinely recommended and recruitment into open trials is encouraged [III, C]
- Targeting *METex14* variants (while evidence of benefit is stronger) is not currently routinely recommended and recruitment into open trials is encouraged [III, C]
- Crizotinib has demonstrated potential clinical efficacy for *METex14* variant NSCLC that needs to be confirmed [III, C]
- Given the paucity of robust data, targeting *HER2* dysregulation is not currently recommended and recruitment into open trials is encouraged [III, C]
- Targeting *NRTK* fusions is not currently recommended and recruitment into open trials is encouraged [III, C]

Role of RT in stage IV

- EBRT is indicated in cases of haemoptysis and symptomatic airway obstruction [III, B]
- RT can achieve symptom control for a variety of clinical scenarios including haemoptysis, symptomatic airway obstruction, painful chest wall disease and bone metastasis, superior vena cava syndrome, soft tissue or neural invasion [II, B]
- Administration of high-dose RT does not result in greater levels of palliation [II, B]
- EBRT alone is more effective for palliation than EBB alone [II, B]
- For patients previously treated by EBRT who are symptomatic from recurrent endobronchial central obstruction, EBB may be considered in selected cases [III, C]
- Neurological symptoms from spinal cord compression can be relieved by early RT [II, B]

Brain metastases

- WBRT can be considered in selected patients, contingent on prognostic factors of better survival [III, C]. WBRT should not be offered in RPA class III patients in view of the dismal prognosis [I, A]; only BSC is recommended
- The most frequent WBRT schedules are 20 Gy in 5 fractions or 30 Gy in 10 fractions, with no difference in outcome [I, A]
- For most patients with symptomatic brain metastases and/or significant oedema, dexamethasone or equivalent corticosteroid is recommended [III, A]
- Neuroprotective agents are not recommended for routine use [II, C]
- Hippocampus avoidance WBRT is not currently recommended as a standard treatment [III, C]
- In case of single brain metastases surgical resection can be considered [III, B]
- Postoperative WBRT or SRS is recommended after surgical resection [I, A]
- In the case of a limited number of metastasis, SRS alone is the recommended treatment in patients with RPA class I–II [III, B]
- SRS alone, without WBRT but with close MRI brain imaging follow-up, is an alternative strategy [III, B]
- The indication for SRS is based on total tumour volume rather than numbers of metastases, as the risk of radionecrosis increases with tumour volume [III, C]
- In patients with asymptomatically detected CNS metastases at presentation, systemic therapy with deferred RT should be considered due to similar intracranial and extra cranial response [II, B]
- In patients with an actionable oncogenic driver (e.g. *EGFR, ALK*) and clinically asymptomatic brain metastases, next-generation TKIs may restore control of brain disease and delay cranial RT [II, A]
- There is currently limited trial data demonstrating safety and efficacy of immunotherapy in patients with small-volume untreated CNS metastases [III, B]

LM carcinomatosis

- A high index of suspicion should be borne for LM involvement especially in patients with actionable oncogenic drivers having TKI treatment [V]. CSF sampling is diagnostic of LMD but limited by low sensitivity, albeit with high specificity [IV, A]
- Patients with actionable oncogenic drivers and LMD can be treated with CNS-penetrant next-generation TKIs [III, B]
- ChT and bevacizumab may have activity both extra-cranially and intra-cranially, and also in the context of LMD [IV, C]
- Intra-CSF pharmacotherapy can be considered contingent on clinical factors [V, C]
- In exceptional cases, focal RT can be considered for circumscribed, notably symptomatic, lesions [V, C]

Continued

Surgery in stage IV

- Surgery may be indicated for diagnosis, evaluation of response to systemic therapy and palliation
- Highly selected patients may be considered for lung resection with therapeutic intent or even for a salvage procedure [IV, C]
- When metastatic disease is suspected on PET scanning, invasive surgical procedures such as incisional biopsies, mediastinoscopy, thoracoscopy (VATS) or laparoscopy may be required to obtain relevant biopsy samples. Adequate samples should be provided to the pathologist for detailed routine staining, IHC and molecular genetic testing [III, B]
- Persisting or recurrent pleural effusions are usually managed by pleurodesis to improve dyspnoea. Talc is the preferred agent and thoracoscopic poudrage may be better than injection of talc slurry in patients with primary lung cancer [II, B]
- In case of a trapped lung by a thickened visceral pleural peel, indwelling pleural catheters or pleuroperitoneal shunts provide symptomatic relief [IV, 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 local consolidative therapy (high-dose RT or surgery) [III, B]. Because of the limited evidence, these patients should be discussed within a multidisciplinary tumour board [II, B], and inclusion in clinical trials is preferred
- Although operative risk is low and long-term survival may be achieved, current evidence for surgery in oligometastatic disease is limited, and the relative contribution of surgery versus RT as local treatment modality has not been established yet
- Stage IV patients with limited metachronous metastases may be treated with a radical local therapy (high-dose RT or surgery) and may experience long-term DFS [IV, B]. However, this is based mainly on retrospective data and inclusion in clinical trials is preferred
- Stage IV patients with driver mutations, with oligoprogression while on molecular-targeted therapy, may be treated with a radical local treatment (high-dose RT or surgery) and may experience long-term DFS [IV, C]. However, this is based mainly on retrospective data and inclusion in clinical trials is preferred
- Solitary lesions in the contralateral lung should, in most cases, be considered as synchronous secondary primary tumours and, if possible, treated with curative-intent therapy [IV, B]

Bone metastases

- Zoledronic acid reduces SREs (pathological fracture, radiation/surgery to bone or spinal cord compression) [II, B] and is recommended in stage IV bone metastatic disease [I, B]
- Denosumab shows a trend towards superiority to zoledronic acid in lung cancer in terms of SRE prevention [II, B] and is recommended in selected patients with advanced lung cancer with bone metastases [I, B]
- In the case of uncomplicated painful bone metastases, single fraction EBRT is the recommended treatment on the basis of non-inferiority to multiple fraction RT [I, A]

Role of minimally invasive procedures in stage IV NSCLC

- In case of symptomatic major airways obstruction or post-obstructive infection, endoscopy 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 [III, B]

Palliative care in stage IV NSCLC

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

Follow-up

- Close follow-up, at least every 6–12 weeks after first-line therapy, is advised to allow for early initiation of second-line therapy but should depend on individual retreatment options [III, B]

ALK, anaplastic lymphoma kinase; BSC, best supportive care; CEA, carcinoembryonic antigen; cfDNA, cell-free DNA; ChT, chemotherapy; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; DFS, disease-free survival; EBB, endobronchial brachytherapy; EBRT, external beam radiotherapy; EBUS, endobronchial ultrasound; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; EUS, endoscopic ultrasound; FDA, Food and Drug Administration; FISH, fluorescent *in situ* hybridisation; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; imRECIST, immune-modified RECIST; iRECIST, immune RECIST; irRECIST, immune-related RECIST; LM, leptomeningeal; LMD, leptomeningeal disease; MEK, mitogen-activated protein kinase; MRI, magnetic resonance imaging; nab-P, albumin-bound paclitaxel; NGS, next-generation sequencing; NSCC, non-squamous cell carcinoma; NSCLC, non-small cell lung cancer; NSCLC-NOS, non-small cell lung cancer-not otherwise specified; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PET, positron emission tomography; PFS, progression-free survival; PS, performance status; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumours; RPA, recursive partitioning analysis; RT, radiotherapy; SCC, squamous cell carcinoma; SRE, skeletal-related event; SRS, stereotactic radiosurgery; TKI, tyrosine kinase inhibitor; TMB, tumour mutational burden; UICC, Union for International Cancer Control; VATS, video-assisted thoracoscopic surgery; WBRT, whole-brain radiotherapy; WHO, World Health Organization; WT, wild-type.

Somatic fusions involving the neurotropic tropomyosin receptor kinase genes (*NTRK1-3*) are rare oncogenic drivers occurring at low prevalence ($< 1\%$) in a variety of tumours including NSCLC [252], again typically in adenocarcinomas (although non-adenocarcinoma cases are reported) and never-smokers. The rarity of these fusions across different cancer types has resulted in basket trial design for drug development. *NRTK1-3* fusions encode oncogenic TRKA-C fusion proteins, respectively, that can be targeted by therapies in development, including larotrectinib (LOXO-101) and entrectinib (RXDX-101) [253–256]. Both have demonstrated marked durable responses in NTRK fusion-positive NSCLC in early reports from ongoing single

Table 5. ESMO-MCBS table for new therapies/indications in NSCLC[a]

Therapy	Disease setting	Trial	Control	Absolute survival gain	HR (95% CI)	QoL/toxicity	ESMO-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 III trial [168, 169] Phase III NCT01523587	Erlotinib, as second-line treatment of patients with advanced SCC of the lung Control median OS: 6.8 months	OS gain: 1.1 months	OS: HR for death 0.81 (0.69–0.95)	Similar toxicity profile Improved overall health-related QoL	2 (Form 2a)
Alectinib, potent ALK tyrosine kinase inhibitor	Advanced	Alectinib versus chemotherapy in crizotinib-pretreated *ALK*-positive non-small-cell lung cancer: results from the phase III ALUR study [207] Phase III NCT02604342	ChT (pemetrexed or docetaxel) in previously treated *ALK*-rearranged patients Control PFS (investigator assessment): 1.4 months	PFS gain: 8.2 months	PFS: HR 0.15 (0.08–0.29)	Improved toxicity profile	4 (Form 2b)
Alectinib, potent ALK tyrosine kinase inhibitor	Advanced	Alectinib versus crizotinib in untreated *ALK*-positive NSCLC [202] Phase III NCT02075840	Crizotinib in untreated, ALK-rearranged patients Control PFS, investigator-assessed: not reached Control PFS, independent review committee-assessed: 10.4 months	PFS gain (independent review committee-assessed): 15.3 months	PFS (independent review committee-assessed): HR 0.50 (0.36–0.70)	Improved toxicity profile	4 (Form 2b)
Atezolizumab, humanised engineered IgG1 monoclonal antibody targeting PD-L1	Advanced	Atezolizumab versus docetaxel in patients with previously treated NSCLC (OAK): a phase III, open-label, multicentre randomised controlled trial [149] Phase III NCT02008227	Docetaxel in squamous or non-squamous patients stage IIIB or IV who had received one to two previous cytotoxic ChT regimens Control OS: 9.6 months	OS gain: 4.2 months	OS: HR 0.73 (0.62–0.87)	Improved toxicity profile	5 (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 NSCLC harbouring *EGFR* mutations (JO25567): an open-label, randomised, multicentre, phase II study [190] Phase II Japan Pharmaceutical Information Center, number Japic CTI-111390	Erlotinib alone as a first-line therapy until disease progression or unacceptable toxicity Control median PFS: 9.7 months	PFS gain: 6.3 months	PFS: HR 0.54 (0.36–0.79)	Deteriorated toxicity profile not reaching the toxicity thresholds for penalty No improvement in QoL	3 (Form 2b)

Continued

Table 5. *Continued*

Therapy	Disease setting	Trial	Control	Absolute survival gain	HR (95% CI)	QoL/toxicity	ESMO-MCBS score[b]
Ceritinib, potent and selective oral tyrosine kinase inhibitor of ALK	Advanced	Ceritinib versus chemotherapy in patients with *ALK*-rearranged NSCLC previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase III trial [206] Phase III NCT01828112	ChT, pemetrexed or docetaxel (investigator choice), in patients with *ALK*-rearranged stage IIIB or IV Control PFS: 1.6 months	PFS gain: 3.8 months	PFS: HR 0.49 (0.36–0.67)	Similar treatment related serious adverse events Improved overall health-related QoL	4 (Form 2b)
Ceritinib, potent and selective oral tyrosine kinase inhibitor of ALK	Advanced	First-line ceritinib versus platinum-based chemotherapy in advanced *ALK*-rearranged NSCLC (ASCEND-4): a randomised, open-label, phase III study [200] Phase III NCT01828099	Platinum-based ChT in untreated patients stage IIIB/IV *ALK*-rearranged non-squamous NSCLC Control PFS: 8.1 months	PFS gain: 8.5 months	PFS: HR 0.55 (0.42–0.73)	Delayed deterioration in overall health-related QoL	4 (Form 2b)
Crizotinib, a small-molecule tyrosine kinase inhibitor of ALK, ROS1 and MET	Advanced	First-line crizotinib versus chemotherapy in *ALK*-positive lung cancer [199] Phase III NCT01154140	Pemetrexedplus platinum ChT Control PFS: 7.0 months	PFS gain: 3.9 months	PFS: HR 0.45 (0.35–0.60)	Improved QoL	4 (Form 2b)
Crizotinib, a small-molecule tyrosine kinase inhibitor of ALK, ROS1 and MET	Advanced	Crizotinib in *ROS1*-rearranged NSCLC [216] Phase I (expansion cohort) NCT000585195	Cohort study: 50 patients (86% had received at least one previous line) (no control)	72% achieved an overall response and mPFS was 19.2 months	ORR: 72% (58–84) mPFS: 19.2 months (14.4–not reached)		3 (Form 3)
Dabrafenib, a selective inhibitor of mutated forms of BRAF kinase and trametinib, a MEK1/MEK2 inhibitor	Advanced	Dabrafenib plus trametinib in patients with previously untreated *BRAF V600E*-mutant metastatic NSCLC: an open-label, phase II trial [230] Phase II NCT01336634	Cohort study: 36 patients (no control)	Independent review committee-assessed confirmed overall response: 64% mPFS: 10.9 months	ORR: 64%, (46–79) mPFS: 10.9 months (7.0–16.6)	Serious adverse events: 57%	2 (Form 3)
Dabrafenib, a selective inhibitor of mutated forms of BRAF kinase and trametinib, a MEK1/MEK2 inhibitor	Advanced	Dabrafenib plus trametinib in patients with previously treated *BRAF V600E*-mutant metastatic NSCLC: an open-label, multicentre phase II trial [228] Phase II NCT01336634	Cohort study: 57 patients (no control)	Independent review committee–assessed confirmed overall response: 63.2% mPFS: 9.7 months	ORR: 63.2% (49.3–75.6) mPFS: 9.7 months (6.9–19.6)	Serious adverse events: 56%	2 (Form 3)

Continued

Table 5. *Continued*

Therapy	Disease setting	Trial	Control	Absolute survival gain	HR (95% CI)	QoL/toxicity	ESMO-MCBS score[b]
Erlotinib, an EGFR TKI	Advanced	Erlotinib as maintenance treatment in advanced NSCLC: a multicentre, randomised, placebo-controlled phase III study [127] 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 III trial [115] Phase III NCT00981058	Gemcitabine and cisplatin as first-line therapy in patients with stage IV SCC Control OS: 9.9 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 non-squamous NSCLC [148, 323] Phase III NCT01673867	Docetaxel in patients with NSCC that had progressed during or after platinum-based doublet ChT Control OS: 9.4 months	OS gain: 2.8 months 2-year survival gain: 13% 2-year OS: 29% versus 16%	OS: HR for death 0.73 (0.59–0.89)	Improved toxicity profile	5 (Form 2a)
Nivolumab, a fully human IgG4 PD-1 immune checkpoint inhibitor antibody	Advanced	Nivolumab versus docetaxel in advanced squamous-cell NSCLC [147] Phase III NCT01642004	Docetaxel in patients with advanced SCC who have disease progression during or after first-line ChT Control OS: 6 months	OS gain: 3.2 months 2-year survival gain: 15%. 2-year OS: 23% versus 8%	OS: HR for death 0.59 (0.44–0.79)	Improved toxicity profile	5[c] (Form 2a)
Osimertinib, oral, irreversible EGFR TKI, selective for both *EGFR* and *T790M* resistance mutations	Advanced	Osimertinib in untreated *EGFR*-mutated advanced NSCLC [187] Phase III NCT02296125	Gefitinib or erlotinib in patients with previously untreated, *EGFR* mutation (exon 19 deletion or L858R) Control PFS: 10.2 months	PFS gain: 8.7 months	PFS: HR 0.46 (0.37–0.57)	Improved toxicity profile	4 (Form 2b)
Osimertinib, oral, irreversible EGFR TKI, selective for both *EGFR* and T790M resistance mutations	Advanced	Osimertinib or platinum-pemetrexed in *EGFR T790M*-positive lung cancer [195] Phase III NCT02151981	Pemetrexed plus either carboplatin or cisplatin in patients with *T790M*-positive, who had disease progression after first-line EGFR TKI therapy Control PFS: 4.4 months	PFS gain: 5.7 months	PFS: HR 0.30 (0.23–0.41)	Improved toxicity profile Improved patient-reported outcomes	4 (Form 2b)

Continued

Table 5. *Continued*

Therapy	Disease setting	Trial	Control	Absolute survival gain	HR (95% CI)	QoL/toxicity	ESMO-MCBS score[b]
Pembrolizumab, an anti-PD-1 monoclonal antibody	Advanced	Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced NSCLC (KEYNOTE-010): a randomised controlled trial [63] Phase III NCT01905657	Docetaxel in patients with previously treated, PD-L1-positive, advanced NSCLC Control OS: 8.5 months	2-year OS rates of 14.5% for docetaxel versus 30.1% for pembrolizumab (2 mg/kg)	HR 0.71 (0.58–0.88)	Improved toxicity profile	5 (Form 2a)
Pembrolizumab, humanised, IgG4 monoclonal antibody against PD-1	Advanced	Pembrolizumab versus ChT for PD-L1-positive NSCLC [62, 94] Phase III NCT02142738	Investigator's choice of platinum-based ChT in stage IV untreated patients with PD-L1 expression on at least 50% of tumour cells Control OS: 14.2 months	OS gain: 15.8 months	OS: HR 0.63 (0.47–0.86)	Improved toxicity profile	5[d] (Form 2a)
Pembrolizumab, an anti-PD-1 monoclonal antibody	Advanced	Pembrolizumab/pemetrexed with platinum ChT in metastatic non-squamous NSCLC without *EGFR* or *ALK* mutations [96] Phase III NCT02578680	Pemetrexed/platinum ChT alone in patients with advanced or mNSCLC who have not previously received systemic therapy for advanced disease Control OS: 11.3 months	OS gain above the cut-off of 3 months	OS: HR 0.49 (0.38-0.64)	Improved QoL with delayed deterioration	4 (Form 2a)[e]
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 III trial [157] Phase III NCT01168973	Placebo plus docetaxel in patients with SCC or NSCC who had progressed during or after a first-line platinum-based ChT regimen Control OS: 9.1 months	OS gain: 1.4 months	OS: HR for death 0.86 (0.75–0.98)	No change	1 (Form 2a)

[a]EMA approvals from January 2016 to 20 September 2018.
[b]ESMO-MCBS version 1.1 [322].
[c]EMA approval, October 2015.
[d]Updated OS is currently available in abstract form only.
[e]QoL data are currently available in abstract form only.
ALK, anaplastic lymphoma kinase; ChT, chemotherapy; CI, confidence interval; EGFR, endothelial growth factor receptor; EMA, European Medicines Agency; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; HR, hazard ratio; IgG, immunoglobulin G; mPFS, medical progression-free survival; NSCC, non-squamous cell carcinoma; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; QoL, quality of life; SCC, squamous cell carcinoma; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2.

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, expert 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

[a]By permission of the Infectious Diseases Society of America [324].

arm basket studies but are not currently recommended for routine care and recruitment into open trials is therefore encouraged [III, C].

Role of radiotherapy in stage IV NSCLC

External beam radiotherapy (EBRT) plays a major role in the symptom control of metastases, such as painful chest wall disease, painful bone metastasis, superior vena cava syndrome, soft tissue or neural invasion. EBRT is indicated in cases of haemoptysis and symptomatic airway obstruction [III, B]. A Cochrane systematic review of palliative EBRT regimens for patients with thoracic symptoms from NSCLC included 14 RCTs (3576 patients) [257]. Doses of radiation ranged from 10 Gy in 1 fraction to 60 Gy in 30 fractions, with a total of 19 different dose/fractionation regimens. There was no strong evidence that any regimen achieved a greater level of palliation [II, B]. Furthermore, higher dose regimens were associated with higher rates of acute toxicity. However, it should be noted that the studies were heterogeneous and most were conducted in the 1980s and 1990s, therefore using dated radiotherapy (RT) techniques. There are few data on the optimal timing of thoracic RT and systemic therapy in the stage IV NSCLC setting. Furthermore, there is no evidence to date that the concurrent administration of ChT, targeted agents or immunotherapy to palliative RT is beneficial in this group of patients.

Another method of palliation of thoracic symptoms is endobronchial brachytherapy (EBB). The effectiveness of EBB compared with EBRT or other alternative endoluminal treatments was assessed in a Cochrane systematic review [258]. The authors concluded that EBRT alone is more effective for palliation than EBB alone [II, B]. However, evidence was limited with regard to the comparison of EBB plus EBRT over EBRT alone for symptom relief. For patients previously treated by EBRT who are symptomatic from recurrent endobronchial central obstruction, EBB may be considered in selected cases [III, C].

Neurological symptoms from spinal cord compression can be relieved by early RT [II, B] [259].

Focus on brain metastases

CNS metastases are commonly identified with NSCLC, predominantly with adenocarcinoma. LMD is a deadly complication of solid tumours and is associated with a poor prognosis. Adenocarcinomas are the most common tumours to metastasise to the CNS. Of the patients with NSCLC, 30%–64% have CNS metastases, of which 4%–7% present LMD [260]. Incidence and prevalence of LMD are both increasing due to brain metastases screening, better imaging modalities as well as prolongation of patients' survival.

Presence of malignant cells on CSF cytology provides the gold-standard for diagnosing leptomeningeal (LM) carcinomatosis. Abnormalities on imaging can be found in 70%–80% of patients with LMD and the imaging modality of choice is high quality, T1-weighted MRI with gadolinium contrast, which has been shown to be more sensitive compared with contrast-enhanced CT [261, 262].

The treatment of patients with brain metastases, with/without LM involvement and no driver mutations, is dependent on the prognosis. Prognosis can be estimated based on the Radiation Therapy Oncology Group recursive partitioning analysis (RPA): class I patients are those < 65 years old, with a good PS [Karnofsky Index (KI) $\geq 70\%$], no other extracranial metastases and a controlled primary tumour; class III patients have a KI $< 70\%$; and class II represents all other patients [263]. In RPA class III patients, RT is not recommended in view of the dismal prognosis [I, A]; only BSC is recommended, as their median survival is generally $<$ 2 months. The role of whole-brain RT (WBRT) in unselected patients has been questioned by the QUARTZ trial data, a phase III non-inferiority study, in which patients were randomised to either BSC including dexamethasone plus WBRT 20 Gy in 5 daily fractions or to the same BSC without WBRT [264]. This trial demonstrated no difference between the treatment arms regarding the relief of symptoms, steroid use, OS, QoL or quality-adjusted life years in the intention-to-treat (ITT) population, confirming no benefit for WBRT in the RPA class III subset [I, A]. However, the median survival in the trial was poor (8.5–9.2 weeks) and the trial recruited over 7 years, a time during which considerable advances in molecular selection, systemic therapy, stereotactic radiosurgery (SRS) patient selection and MRI brain surveillance have been implemented. A signal for WBRT benefit was seen for younger patients with better Karnofsky PS and either controlled primary or no extracranial disease. WBRT can therefore be considered for patients contingent on prognostic factors of better survival such as driver mutations [III, C].

The most frequent WBRT schedules are 20 Gy in 5 fractions or 30 Gy in 10 fractions, with no difference in outcome [I, A] [265]. For most patients with symptomatic brain metastases and/or significant oedema, dexamethasone or equivalent corticosteroid is recommended [III, A] [266]. Tapering of the dose and, if possible, cessation after RT, are recommended. Corticosteroids are not recommended in the case of asymptomatic brain metastases. WBRT may be associated with delayed progressive cognitive impairment in responders, as tumour progression affects this parameter more than radiation toxicity [267]. Neuroprotective agents have not shown a convincing role and are not recommended for routine use [II, C], with a small phase III trial of memantine on 149 assessable patients (RTOG 0614) suggesting benefit [268]. Hippocampus avoidance WBRT has been shown to be probably safe [269], but is still undergoing trial evaluation and is not currently recommended for routine care [III, C].

Recent data showed that SRS can be considered as another standard of care for this patient population as a less toxic alternative to WBRT. SRS of the surgical cavity in patients who have had complete resection of 1–3 brain metastases significantly lowers local recurrence compared with that noted for observation alone [270].

In case of single brain metastases surgical resection can be considered [III, B] [271–273]. Postoperative WBRT or SRS is generally recommended after surgical resection [I, A] [274].

Another treatment strategy, in the case of a limited number of metastases and RPA class I and II, is SRS alone [III, B] [275–278]. The randomised trials evaluating SRS have included patients with 1–4 brain metastases. SRS has increasingly become the favoured modality due to reduced morbidity compared with WBRT, but it should be noted that there is no randomised trial comparing SRS alone to WBRT. A survival advantage in favour of WBRT plus SRS has been demonstrated against WBRT but only for the subgroup of patients with a single brain metastasis [279]. The majority of studies evaluating WBRT in addition of SRS or neurosurgery have shown a decline in cognitive function in the combined arm [278, 279]. SRS alone with close follow-up, without WBRT consolidation, is therefore a recommended strategy [III, B].

Although it is generally accepted that SRS should generally be considered in patients with $\leq$ 4 brain metastases, a prospective observational study from Japan challenged this prevailing concept [280]. The study enrolled 1194 eligible patients (76% had lung cancer) with 1 to 10 newly diagnosed brain metastases, longest diameter $<$ 3 cm, largest tumour $<$ 10 mL in volume and a total cumulative volume of $\leq$ 15 mL. OS did not differ between patients treated with SRS with 2-4 metastases and those with 5-10 metastases. This study therefore suggested the use of tumour volume and absolute size, rather than the number of metastases, as treatment criteria. In some territories, the indication for SRS is now based on total tumour volume rather than number of metastases, as the risk of radionecrosis increases with tumour volume [III, C] [278]. In patients undergoing SRS, radionecrosis is a challenging complication to manage.

In patients with asymptomatic brain metastases who have not yet received prior systemic therapy (i.e. ChT, TKIs), treatment with upfront systemic therapy and deferred RT should be considered, with trial data suggesting similar intracranial and extracranial ORRs [II, B] [281, 282]. In patients suitable for first-line immune-checkpoint inhibitor therapy, CNS metastases were generally mandated to have been treated before therapy, with evidence of intracranial response. There is currently limited trial data demonstrating safety and efficacy of immunotherapy in patients with small-volume untreated CNS metastases [III, B] [283].

Among those patients with an actionable oncogenic driver (e.g. EGFR, ALK), between 44% and 60% develop brain metastases in the course of their disease [284, 285]. In such patients, the use of CNS-penetrant next-generation TKIs (e.g. osimertinib, alectinib, ceritinib) may restore control of brain disease, thereby potentially delaying cranial RT [II, A] [53, 187, 200]. Moreover, next-generation TKIs may also reduce the incidence of new CNS metastases, thereby significantly postponing the time to need CNS RT [53].

Focus on LM carcinomatosis

LMD may present with non-specific neurological symptoms (headaches, nausea, vomiting) as well as discrete signs due to the CNS area involved (gait difficulties, cranial nerve palsies), and a high index of suspicion is required, particularly in those with actionable oncogenic drivers due to higher prevalence [V]. Diagnostic modalities include cerebrospinal MRI with contrast enhancement, ideally before CSF intervention. CSF sampling with cytological assessment is diagnostic but limited by low sensitivity but high specificity [IV, A]. The prognosis from LMD due to NSCLC is poor, and treatment aim is to prolong survival with acceptable QoL. Patients with actionable oncogenic drivers may derive benefit from a CNS-penetrant next-generation TKI as per those with brain metastases [III, B]; otherwise, systemic therapy strategies vary widely across Europe. ChT and bevacizumab may have activity both extra-cranially and intra-cranially, and also in the context of LMD [IV, C] [126, 286]. Intra-CSF pharmacotherapy may be considered through either repeated lumbar punctures, a reservoir or ventricular device, although consideration should be given to patient factors, e.g. PS, extra-cranial control and likely benefit [V, C]. No randomised data exist to support the role of RT for LMD. In exceptional cases, focal RT can be considered for circumscribed, notably symptomatic, lesions [V, C].

Role of surgery in stage IV NSCLC

As prognosis in the majority of patients with stage IV NSCLC is poor, the role of surgery is traditionally limited in this patient group. However, with the widespread introduction of targeted therapies and immunotherapy improving prognosis in specific subcategories, the role of thoracic surgery is currently redefined. At the present time, surgery may be indicated for diagnosis, evaluation of response to systemic therapy and palliation, and highly selected patients may be considered for lung resection with therapeutic intent or even for a salvage procedure. In the last two categories, surgery can be carried out with a mortality < 2%, a low morbidity rate and 5-year survival rates in the range of 11%–30% in retrospective series [IV, C] [287, 288]. Whether there is a significant difference between synchronous and metachronous metastases and between different distant sites has not been clearly established and more prospective data are needed.

When metastatic disease is suspected on PET scanning, invasive surgical procedures such as incisional biopsies, mediastinoscopy, thoracoscopy (VATS) or laparoscopy may be required to obtain relevant biopsy samples. Examples include patients with contralateral lung nodules, distant metastases or suspicion of mediastinal nodal involvement who do not qualify for minimally invasive biopsies or in whom results of the latter are equivocal. Adequate samples should be provided to the pathologist for detailed routine staining, IHC and molecular genetic testing [III, B].

Palliative interventions may be useful in case of local complications related to the primary tumour or metastatic foci which cannot be managed by conservative measures, e.g. lung abscess, empyema, massive haemoptysis, spinal cord compression and pathological bone fractures.

In the 8th edition of the tumour, node, metastasis (TNM) classification a new subcategory was introduced comprising patients with one metastasis in a single distant organ, defined as M1b disease, in contrast to patients with multiple metastases in one or more distant organs, currently M1c disease [289]. There is no general consensus on the precise definition of oligometastatic disease and clear evidence for surgical treatment is limited, as only relatively small prospective series are available [III, B] [290–292]. Prospective series suggest that complete surgical resection is necessary to obtain long-term survival and that mediastinal nodal involvement carries a poor prognosis [293]. This is further discussed in the section 'Treatment of oligometastatic NSCLC'.

A specific subgroup consists of patients with malignant pleural nodules or malignant pleural effusion [293]. Extensive surgical procedures consisting of extrapleural pneumonectomy sometimes in combination with intraoperative ChT or hyperthermic ChT, have been described when extrathoracic metastases or mediastinal lymph node involvement have been excluded [294, 295]. However, these interventions carry a higher operative risk and prospective studies are currently not yet available [IV, D]. Persisting or recurrent pleural effusions are usually managed by pleurodesis to improve dyspnoea. Talc is the preferred agent and thoracoscopic poudrage may be better than injection of talc slurry in patients with primary lung cancer [II, B] [296, 297]. In case of a trapped lung by a thickened visceral pleural peel, indwelling pleural catheters or pleuroperitoneal shunts provide symptomatic relief [IV, B] [298, 299].

Lastly, salvage surgery may be considered in case of residual or progressive disease in the primary tumour or metastatic site when no other treatment options remain or specific complications occur, such as formation of a lung abscess in a necrotic cavity [300]. Long-term survival may be obtained in selected patients with limited distant involvement, but only case reports have been published so far [V, C] [301].

In a recent retrospective analysis of the National Cancer Database, a cohort of 300 572 patients with stage IIIA, IIIB or IV NSCLC were studied, of whom 4568 had a surgical intervention for stage IV disease [302]. A surgical selection score could be constructed comprising histology, tumour size, TNM status, Charlson comorbidity index, age, race, facility type, insurance and income. In a logistic regression model this score was found to be a good predictor of survival. However, it should be noted that further prospective validation is necessary, and that the relative contribution of surgery versus RT in a multimodality setting for stage IV disease was not studied in this analysis.

Treatment of oligometastatic disease

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 with aggressive local treatment of distant metastases (surgery or high-dose RT) [303]. The term 'oligometastases' refers to a limited number of distant metastases, although there is no consensus on the appropriate cut-off to define the oligometastatic state. Almost all published clinical trials investigating local treatment of oligometastatic disease have limited inclusion to patients with ≤ 5 metastases. In addition, the vast majority of the trials included patients with ≤ 3 metastases and in an individual patients meta-analysis published in 2014, almost 90% of the patients had a single metastasis [303]. Some studies also limited the number of organs in which these metastases are present [304]. It should be noted that many of these studies did not include PET-CT staging.

Oligometastases can be either synchronous, when a patient presents with a limited number of metastases at initial diagnosis, or metachronous when metastases are identified after treatment of the primary tumour [305]. The biology of synchronous and metachronous oligometastases may differ as illustrated by the fact that patients with metachronous presentation have a better prognosis [303]. In patients receiving systemic therapy (mainly in tumours with driver mutations treated with TKIs), the term oligoprogression can be also applied in the case of progression of a limited number of metastatic lesions, when all the other lesions remain stable. Clinical trials are ongoing in this setting.

In this heterogeneous group of patients with oligometastases, the specific approach to oligometastases in the brain has been discussed above. Another subgroup requiring further discussion is that of patients with a solitary lesion in the contralateral lung. The International Association for the Study of Lung Cancer (IASLC) Staging and Prognostic Factors Committee carried out a systematic literature review, aiming at distinguishing a second primary from a metastasis in patients who have more than one pulmonary nodule [306]. 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 [307, 308] and SRS [309, 310] have been shown to result in long-term survivors in this setting [IV, B].

A systematic literature review identified 757 NSCLC patients treated with 1–5 (88% single metastases) synchronous or metachronous metastases [303]. 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 patient selection or other biases [305].

Stage IV patients with limited synchronous metastases at diagnosis may experience long-term disease-free survival (DFS) following systemic therapy and local consolidative therapy [LCT: high-dose RT including stereotactic ablative body RT (SABR) or surgery] [III, B]. Five phase II trials evaluating LCT in patients with NSCLC and synchronous oligometastases have been published. Three of these studies are small, single arm studies which generally showed durable PFS in a subgroup of patients [290, 291, 311]. Two out of the five studies are randomised phase II studies that were stopped early after interim analysis. The first study randomised NSCLC patients between maintenance therapy (RT or surgery) in patients with ≤ 3 metastases, without progression after first-line systemic therapy ($n = 49$). There was a significant difference in PFS time between the two groups (mPFS 11.9 months in the LCT group versus 3.9 months in the maintenance group; HR = 0.35, $P = 0.005$) [292]. The second study randomised patients with ≤ 5 metastatic sites between maintenance ChT alone versus SABR followed by maintenance ChT ($n = 29$) [312]. So far, there are no published data on the impact of LCT on OS and long-term toxicity. Several clinical trials are ongoing to evaluate these important endpoints.

Stage IV patients with limited metachronous metastases may be treated with a local treatment as some may experience long-term DFS [IV, B]. However, this is based mainly on retrospective data. Although operative risk is low and long-term survival may be achieved, current evidence for surgery in oligometastatic disease is limited, and the relative contribution of surgery versus RT as local treatment modality has not yet been established. Solitary lesions in the contralateral lung should, in most cases, be considered as synchronous secondary primary tumours and, if possible, treated with curative-intent therapy [IV, B].

Similarly, there are few prospective data to support this treatment approach in patients with driver mutations who present with oligoprogression on molecular-targeted therapies [IV, C]. Furthermore, there is little data on the safety of combining SABR with molecularly targeted agents.

Some recommendations for the implementation of standard of care and advanced imaging modalities for identifying and following up patients with oligometastatic disease have been published by the European Organisation for Research and Treatment of Cancer (EORTC) imaging group [313]. In the synchronous, metachronous and oligoprogessive setting, because of the limited evidence available, inclusion in clinical trials is preferred.

Focus on 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. In general, the management aim is to palliate symptoms and prevent complications. Palliative RT is highly effective, usually with rapid pain relief. Both standard EBRT and SABR can be used to palliate painful, uncomplicated bone pain. However, the data on efficacy and safety of SABR are mainly from retrospective single institution studies. Systematic reviews of palliative RT trials for bone metastases showed that single and multiple fraction regimens provided equal pain relief; however, retreatment rates were significantly higher in patients receiving single fraction treatment [I, A] [314, 315].

Zoledronic acid reduces skeletal-related events (SREs) (pathological fracture, radiation/surgery to bone or spinal cord compression) [II, B] [316]. Denosumab shows a trend towards superiority to zoledronic acid in lung cancer in terms of SRE prevention [II, B] [317]. In an exploratory analysis of a large phase III trial, denosumab was associated with improved mOS in the subgroup of 702 metastatic NSCLC patients [318]. 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 [319]. Both agents are associated with increased risk of osteonecrosis of the jaw. Zoledronic acid or denosumab are thus recommended in selected patients with advanced lung cancer with bone metastases [I, B]. Patients should be selected if they have a life expectancy of > 3 months and are considered at high risk of SREs.

Role of minimally invasive procedures in stage IV NSCLC

Endoscopy has a role to play in palliative care, notably in case of symptomatic major airway obstruction or post-obstructive infection, where endoscopic debulking by laser, cryotherapy or stent placement may be helpful [III, C]. Endoscopy is useful in the diagnosis and treatment (endobronchial or by guiding endovascular embolisation) of haemoptysis [III, C]. Vascular stenting might be useful in NSCLC-related superior vena cava compression [III, B].

Role of palliative care in stage IV NSCLC

Early palliative care intervention is recommended, in parallel with standard oncological care [I, A], with evidence demonstrating that palliative care interventions significantly improve QoL. Two randomised trials evaluating the impact of introducing specialised palliative care early after diagnosis of stage IV disease on patient QoL in ambulatory patients were able to show improvements in QoL and mood, and, in one trial, a reduction in aggressive treatment and an improvement in mOS [320, 321].

Follow-up, long-term implications and survivorship

The optimal approach to post-treatment management of patients with NSCLC, including the role of radiological 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 to allow for early initiation of second-line therapy but should also depend on individual retreatment options [III, B].

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. A MCBS table with ESMO-MCBS scores is included in Table 5. ESMO-MCBS v1.1 was used to calculate scores for new therapies/indications approved by the EMA since 1 January 2016 [322]. Levels of evidence and grades of recommendation have been applied using the system shown in Table 6; some statements may be accompanied by a grade of recommendation alone. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

Disclosure

DP has reported honoraria from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, Merck, Merck Sharp and Dohme Oncology, Novartis, Pfizer, prIME Oncology, Roche; consulting, advisory role or lectures for AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, Merck Sharp and Dohme Oncology, Novartis, Pfizer, prIME Oncology, Roche and has received travel grants from AstraZeneca, Roche, Novartis, prIME Oncology and Pfizer; SPo has reported honoraria from Pfizer, Boehringer Ingelheim, AstraZeneca, Roche, Lilly, Novartis, Takeda, Guardant Health, Bristol-Myers Squibb and consulting/advisory role for Boehinger Ingleheim, Roche, Lilly, Novartis, Pfizer and research funding from Boehringer Ingelheim, Epizyme, Bristol-Myers Squibb, Clovis Oncology, Roche, Lilly, Takeda; KMK has reported lecture fees and consultancy for AstraZeneca, AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Lilly, Merck Sharpe & Dohme, Merck Serono, Novartis, Pfizer, Roche, Roche Diagnostics; SN has reported membership of the speaker bureau of Eli Lilly, Bristol-Myers Squibb, Merck Sharpe & Dohme, AstraZeneca, Boehringer Ingelheim, Roche, Incyte, Takeda; CFF has reported research/travel funding from AstraZeneca and Merck Sharpe & Dohme; TM has reported holding stock in Sanomics Ltd. and Hutchison Chi-Med, conducting research sponsored by AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Clovis oncology, Merck Sharp and Dohme, Novartis, Pfizer, Roche, SFJ Pharmaceuticals and XCovery; has received speaker's fee from AstraZeneca, Roche/Genentech, Pfizer, Eli Lilly, Boehringer Ingelheim, Merck Sharp and Dohme, Novartis, BMS, Taiho, Takeda Oncology, prIME Oncology and Amoy Diagnostics Co, LTD and honoraria from AstraZeneca, Boehringer Ingelheim, Roche/Genentech, Pfizer, Eli Lilly, Merck Sorono, Merck Sharp and Dohme, Novartis, SFJ Pharmaceuticals, ACEA Biosciences Inc, Vertex Pharmaceuticals, Bristol-Myers Squibb, OncoGenex Technologies Inc, Celgene, Ignyta Inc, Cirina, Fishawack Facilitate Ltd, Janssen, Takeda, Hutchison Chi-Med, OrigiMed, Henfrui Therapeutics Inc, Sanofi-Aventis R&D and Yuhan Corporation for attending advisory boards; MH has reported honoraria for consultancy for Roche/Genentech, AstraZeneca, Merck, Bristol–Myers Squibb, Janssen, Mirati, Syndax, Shattuck Labs and has received research funding from Bristol-Myers Squibb; MR has reported honoraria for lectures and consultancy from AstraZeneca, Bristol-Myers Squibb, Celgene, Boehringer Ingelheim, Novartis, Abbvie, Pfizer, Merck Sharpe & Dohme, Merck, Roche, Lilly; SPe has reported educational grants, consultation, advisory boards and/or lectures for Amgen, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Clovis, Eli Lilly, F. Hoffmann-La Roche, Janssen, Merck Sharp & Dohme, Novartis, Merck Serono, Pfizer, Regeneron and Takeda; PEVS has reported no conflicts of interest. ES has not reported any potential conflicts of interest.

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