incidence and epidemiology

Primary lung cancer is the most common malignancy after non-melanocytic skin cancer with deaths from lung cancer exceeding those from any other type of malignancy worldwide [1]. While it has been the most important cause of cancer mortality in men since the 1960s, it has equalled breast cancer as a cause of mortality in women since the 1990s. To date, prevention and smoking cessation are still the main methods to reduce the death toll [2]. Lung cancer is still increasing both in incidence and mortality worldwide. In countries with effective tobacco control measures, the incidence of new lung cancer has begun to decline in men and is reaching a plateau for women [3, 4]. In the European Union in 2013, lung cancer mortality fell in men (−6%) compared with 2009 while cancer death rates in women are increasing (+7%) and approaching those of men [5].

Non-small-cell lung cancers (NSCLC) account for 85%–90% of lung cancers, while small-cell lung cancer (SCLC) has been decreasing in frequency in many countries over the last two decades [1].

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

Prevalence of lung cancer in females without a history of tobacco smoking is estimated to represent 19% compared with 9% of male lung carcinoma in the United States [6]. Women are over-represented among younger patients, raising the question of gender-specific differences in the susceptibility to lung carcinogens [7]. In recent times, an increase in the proportion of NSCLC patients who are never smokers has been observed, especially in Asian countries [8]. 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 are being recognised.

diagnosis

Therapeutic decisions for NSCLC patients rely on tumour subtype definition. Immunohistochemistry (IHC) should be used to reduce the NSCLC-NOS (not otherwise specified) rate to under 10% of cases diagnosed [9]. Obtaining adequate tissue material for histological diagnosis and molecular testing is important in order to allow individual treatment decisions. Biopsy at disease progression may be considered [10, 11].

Pathological diagnosis should generally be made according to the World Health Organisation (WHO) classification. The International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) classification document on adenocarcinoma, however, provides new recommendations and also addresses important issues not covered by the current WHO classification concerning small biopsy samples and cytology. Adoption of these recommendations is strongly advised [9], and will be integrated into the revised 2015 WHO classification.

Genetic alterations which are key oncogenic events have been identified in numerous small subsets of NSCLC. Two of these alterations have been validated as reliable targets for selective pathway directed systemic therapy. The opportunity of applying
Activating (sensitising) epidermal growth factor receptor (EGFR) mutations are predictive for response to the EGFR tyrosine kinase inhibitors (TKIs) gefitinib, erlotinib, and afatinib, resulting, in this context, in an improved response rate (RR), progression-free survival (PFS), and quality of life (QoL) as well as a better tolerability when compared with first-line chemotherapy, as demonstrated in several phase III randomised trials. The incidence of EGFR mutations in the Caucasian population is about 10% and is higher in never smokers, adenocarcinoma subtype, and women. Prevalence has also been shown to be higher in East-Asian patients. EGFR mutation testing is recommended in all patients with advanced NSCLC of a non-squamous subtype [I, A]. Testing is not recommended in patients with a confident diagnosis of squamous cell carcinoma, except in never/former light smokers (<15 packs per year) [IV, A] [13]. It should be systematically analysed—with a validated mutation detection platform in a laboratory participating in an external quality assurance scheme—in all such patient subgroups [V, A]. Choice of methodology will vary but should provide the test sensitivity required for the tumour content of the sample, and provide an adequate coverage of all clinically relevant mutations [11]. Laboratories should validate their practice internally and through external quality assurance programmes.

The anaplastic lymphoma kinase (ALK) fusion genes have been identified as important oncogenic drivers [14]. ALK fusion is encountered more frequently in never smokers, the adenocarcinoma subtype, and in younger patients, representing an incidence of around 5% in adenocarcinomas [15]. ALK activity can be effectively targeted by the ALK TKIs, and routine testing for ALK rearrangements is now a standard of care. Testing should focus on the same group of patients selected as for EGFR mutation [II, A]. Testing should be carried out, if at all possible, in parallel with EGFR mutation analysis. Currently, the standard test for detecting ALK fusion remains the break-apart fluorescence in situ hybridisation (FISH) test. A multiplex polymerase chain reaction (PCR) approach may be successful but requires an adequate coverage of the many possible fusion genes now recognised and is challenged by the availability of adequate quality nucleic acid from typical samples, and by the methodology itself. High sensitivity IHC has been shown to have a high positive and negative predictive value for the presence and absence, respectively, of ALK fusion and, while not a recognised primary biomarker for ALK TKI therapy, it is widely used to screen patients for possible ALK FISH testing. Next-generation sequencing approaches for detecting fusion genes are in development.

staging and risk assessment

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

laboratory

Standard tests include routine haematology, renal and hepatic function, and bone biochemistry tests. Routine use of serum markers—such as carcinoembryonic antigen (CEA)—is not recommended.

radiology

Contrast-enhanced computed tomography (CT) scan of the chest and upper abdomen should be carried out.

- Imaging of the central nervous system (CNS) is reserved for patients with neurological symptoms or signs. Magnetic resonance imaging (MRI) is more sensitive than CT scan.
- If metastatic disease has been shown on the CT scan of the chest and upper abdomen or on brain imaging, other imaging is only necessary when it might impact treatment.
- If bone metastases are clinically suspected, bone imaging is required. Positron emission tomography (PET), CT, and bone scan are helpful for the systemic screening for bone metastasis with a slightly higher sensitivity for PET [16]. MRI might be useful to document and describe a localised bone metastasis.
- Fluorodeoxyglucose (FDG)–PET-CT scan offers the highest sensitivity for mediastinal lymph nodes and distant metastasis assessment.

NSCLC is staged according to the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) system (7th edition) and is grouped into the stage categories shown in Tables 1 and 2. Measurement of lesions should follow Response Evaluation Criteria in Solid Tumors (RECIST) criteria v1.1 [17].

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. An evaluation of resectability or the suitability of high-dose radiotherapy with curative intent should be made at least in the context of a solitary brain or adrenal lesion or oligometastatic disease confined to the lungs.

treatment of stage IV NSCLC

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

In any stage of NSCLC, smoking cessation should be highly encouraged because it improves outcome, and as smoking may interact with systemic therapy [II, A] [18]. For example, smoking reduces erlotinib bioavailability [19].

first-line treatment

Platinum-based doublet chemotherapy prolongs survival and improves QoL in patients with PS 0–2 [I, A]. Chemotherapy should be initiated while the patient maintains a good PS. For most patients, four cycles of chemotherapy are recommended, notably when maintenance treatment is considered, with a maximum of six cycles [20] [II, B].

Several regimens have shown comparable efficacy [21]. The expected toxicity profile should contribute to the selection of the chemotherapy regimen, taking into account that:

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

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

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

Meta-analyses have shown higher RRs for cisplatin combinations when compared with carboplatin combinations. The overall survival (OS) was significantly superior for cisplatin in the subgroup of non-squamous tumours and in patients treated with third-generation regimens, including gemcitabine and taxanes in one meta-analysis [I, B] [22]. Cisplatin-based chemotherapy is associated with more digestive, neuro-, and nephrotoxicity, while hematotoxicity is more often observed with carboplatin.

Pemetrexed-based combination chemotherapy represents a therapeutic option in patients with advanced non-squamous NSCLC 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 preplanned subgroup analysis of a large randomised phase III trial [II, A] [23, 24]. Pemetrexed use should be restricted to non-squamous NSCLC in any line of treatment [I, A] [25, 26].

The survival benefit of carboplatin in combination with pemetrexed has been investigated in an exploratory subgroup analysis of a recent meta-analysis, where the survival benefit for pemetrexed plus platinum held true for cisplatin-containing regimens but not carboplatin-based regimens [23]. However, there is no prospective randomised study available investigating this question.

According to a randomised clinical trial, bevacizumab improves OS when combined with paclitaxel–carboplatin regimens in patients with non-squamous histology and PS 0–1, and may be offered after exclusion of contraindications [I, A] [27]. Recently, adding bevacizumab to carboplatin and paclitaxel chemotherapy significantly improved PFS in 276 Chinese patients with non-squamous NSCLC, while OS data are pending [28]. While one trial of cisplatin–gemcitabine with/without bevacizumab demonstrated an objective RR (ORR), and modest PFS advantage, but no OS benefit [AVAII], two meta-analyses showed a consistent significant improvement of RR, PFS, and OS for the combination of bevacizumab and platinum-based chemotherapy compared with platinum-based chemotherapy in eligible patients with non-squamous NSCLC [29, 30]. Therefore, the combination of bevacizumab and other platinum-based chemotherapies may be considered in eligible patients [I, A] [1].

- Non-platinum-based combination chemotherapy with third-generation agents should be considered only if platinum therapy is contraindicated. Several meta-analyses show lower RRs for non-platinum combinations with one of them showing inferior survival [31] [I, A].

### PS ≥ 2 patients
Chemotherapy prolongs survival and possibly improves QoL [32] in NSCLC patients with PS 2, when compared with best supportive care (BSC) [I, B]. Single-agent chemotherapy with gemcitabine, vinorelbine, and taxanes represents an option [I, B] [33]. Superiority of carboplatin-based combinations over supportive care (BSC) [I, B] [33]. Superiority of carboplatin-based combinations over monotherapy has been identified in a subgroup analysis within large phase III trials, with an acceptable toxicity profile [34, 35]. Moreover, combination chemotherapy with carboplatin significantly improved survival compared with monotherapy alone in 205 NSCLC patients with Eastern Cooperative Oncology Group (ECOG) PS 2.

Carboplatin-based combination chemotherapy should be considered in eligible PS 2 patients [II, A] [36].

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

### elderly patients
Two randomised phase III trials established single-agent chemotherapy as the standard of care for first-line therapy for clinically unselected elderly advanced NSCLC patients [33, 37]. A recent prospective randomised trial comparing monthly carboplatin plus weekly paclitaxel versus single-agent vinorelbine or gemcitabine in patients aged 70–89 years with PS 0–2 has reported a survival advantage for combination therapy [35].

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

### use of tyrosine kinase inhibitors
Multiple phase III studies have tested the use of EGFR TKIs in patients of different ethnicity with NSCLC harbouring activating

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**Table 2.** Anatomic stage/prognostic groups according to the AJCC/UICC TNM staging system, 7th edition (from Edge SB, Byrd DR, Compton CC, eds. AJCC Cancer Staging Handbook. 7th ed. New York, NY: Springer, 2010).

<table>
<thead>
<tr>
<th>Anatomic stage/prognostic groups</th>
<th>Occult carcinoma</th>
<th>Stage 0</th>
<th>Stage IA</th>
<th>Stage IB</th>
<th>Stage IIA</th>
<th>Stage IIB</th>
<th>Stage IIIA</th>
<th>Stage IIIB</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX N0 M0</td>
<td>Tis N0 M0</td>
<td>T1a,b N0 M0</td>
<td>T2a N0 M0</td>
<td>T2b N0 M0</td>
<td>T1a,b N1 M0</td>
<td>T2a N1 M0</td>
<td>T3 N0 M0</td>
<td>T1a,b N2, T2a,b</td>
<td>T3 N1, N2 M0</td>
</tr>
</tbody>
</table>

(sensitising) EGFR mutations and have shown similar results. In patients with activating EGFR mutations, EGFR-TKIs therapy statistically significantly delays disease progression and should be considered as front-line therapy [38]. Hence, NSCLC patients should be tested for EGFR mutations before initiation of first-line treatment. Besides longer PFS, first-line treatment with a TKI (afatinib, erlotinib, or gefitinib) has also been associated with significantly higher RRs and better QoL when compared with first-line chemotherapy in EGFR mutation (L858R, exon 19 deletion)-positive NSCLC patients [38–41] [I, A]. Patients with PS 3–4 may also be offered an EGFR TKI [II, A]. Evidence of clinical benefit related to continuation of EGFR TKI due to progression in selected patients is accumulating, but formally remains an issue to be prospectively studied before firm conclusions can be drawn.

No large clinical trial comparing the efficacy of different EGFR TKIs in patients carrying tumours with EGFR mutations has been reported as yet.

In EGFR wild-type (WT) patients, EGFR TKIs are not recommended in first line, being inferior to chemotherapy and no better than placebo [42, 43] [I, A].

Patients with NSCLC harbouring an ALK rearrangement should be considered for crizotinib, a dual ALK and mesenchymal epithelial transition factor (MET) TKI, during the course of their disease [I, A]. Upfront comparisons with chemotherapy are not available to date [44]. Despite the improved patient outcome with tumours harbouring EGFR mutations or ALK fusions while treated with specific TKIs, all patients will eventually experience disease progression through primary or acquired resistance. Various resistance mechanisms have been identified, resulting in the development of new therapeutic approaches and novel TKIs that are being tested in clinical studies. Most of these new TKIs are characterised by either a higher potency of binding to their respective target or affecting a specific but broader spectrum of genetic alterations including mutations that may mediate resistance against the conventional TKIs.

**maintenance treatment**

In order to prolong the effect of first-line chemotherapy on tumour control, various trials investigated the efficacy of maintenance treatment in patients with good PS (0, 1) either as ‘continuation maintenance’ or as ‘switch maintenance’. ‘Continuation maintenance’ and ‘switch maintenance’ therapies refer, respectively, to either the maintained use of an agent included in first-line treatment or the introduction of a new agent after four cycles of platinum-based chemotherapy.

Two recent randomised phase III switch maintenance trials have reported improvements in PFS and OS with pemetrexed [26] and erlotinib [45] versus placebo following four cycles of platinum-based chemotherapy. In the case of pemetrexed this benefit was seen only in patients with non-squamous histology. In the erlotinib trial, subgroup analyses revealed the highest benefit in efficacy in patients with stable disease (SD) after induction treatment compared with patients with confirmed response. These results led to the label for switch maintenance with erlotinib in patients with SD after induction treatment [26, 45]. Decision-making about maintenance therapy must additionally take into account histology, remaining toxicity after first-line chemotherapy, PS, and patient preference [I, B].

Randomised trials investigating continuation maintenance have shown an improvement of PFS and OS [46, 47]. A large phase III randomised trial of continuation maintenance with pemetrexed versus placebo after four induction cycles of cisplatin plus pemetrexed chemotherapy demonstrated a PFS and OS improvement in patients with an ECOG PS 0–1 [47]. Another phase III study comparing maintenance bevazucimab, with or without pemetrexed, after first-line induction with bevacizumab, cisplatin, and pemetrexed showed a benefit of PFS for the pemetrexed-bevacizumab combination, but no OS benefit [48], although a trend towards improved OS was seen when analysing 58% of events of 253 patients randomised for this study [49]. Continuing pemetrexed following completion of first-line cisplatin plus pemetrexed chemotherapy is therefore recommended in patients with non-squamous chemotherapy, tumour stabilisation, or response after first-line chemotherapy and recovery from toxicity of the previous treatment [I, B].

**second-line treatment**

Patients clinically or radiologically progressing after first-line chemotherapy, irrespective of administration of maintenance chemotherapy, with a PS 0–2 should be offered second-line chemotherapy. Combination regimens failed to show any OS benefit over single-agent treatments [50]. Single agents improve disease-related symptoms and OS. Comparable options in the second line consist of pemetrexed—for non-squamous histology only [51]—or docetaxel [52] [I, B]. Erlotinib was shown to improve OS in second line or in third line—in all NSCLC histological subtype patients, not eligible for further chemotherapy, including patients with PS 3 [53]. Erlotinib was shown to be equivalent to pemetrexed or docetaxel in refractory (progression during the four cycles of a standard platinum-based chemotherapy doublet) patients unselected for EGFR status in a randomised trial [54]. Similarly, in molecularly unselected patients, gefitinib was proven non-inferior to docetaxel in a large randomised trial [55] with a better toxicity profile and QoL. Finally, a randomised phase II trial showed comparable outcome with pemetrexed or erlotinib [56].

In a randomised trial including 222 EGFR WT NSCLC patients, initially designed to assess selected biomarkers, second-line therapy with docetaxel was shown to be superior to erlotinib with respect to OS and PFS [57]. Subgroup analyses of a recent phase III trial of erlotinib versus docetaxel as second- or third-line therapy demonstrated superior PFS but not OS for docetaxel treatment in EGFR WT [58]. In conclusion, erlotinib represents a potential second-line treatment option in pre-treated patients with undetermined or WT EGFR status [II, B].

Any patient with a tumour bearing an activating (sensitising) EGFR mutation should receive an EGFR TKI as second-line, if not received previously [I, A].

In the presence of an ALK rearrangement, second-line treatment with crizotinib should be considered, as a large phase III trial comparing crizotinib with docetaxel or pemetrexed (based on investigator’s preference) has demonstrated significant ORR and PFS advantages for crizotinib [I, A] [59].
Second-line treatment duration should be individualised, as the registration trials of pemetrexed, docetaxel, and erlotinib did not limit therapy to a set number of treatment cycles. Notably, treatment may be prolonged if disease is controlled and toxicity acceptable [II, B].

**subsequent lines of treatment**

Upon progression after second-line chemotherapy, patients may be candidates for further treatment. Randomised phase III trial evidence is available only for erlotinib, which is indicated for EGFR WT patients who have not yet received EGFR TKIs, with PS 0–3 [II, B], not eligible for further chemotherapy [53]. Any patient with a tumour bearing an activating (sensitising) EGFR mutation should receive an EGFR TKI in third or subsequent lines, if not received previously [I, A].

**personalised medicine**

Any treatment strategy should take into account histology, molecular pathology, age, PS, comorbidities, and patient’s preferences. Genetic alterations, which are key oncogenic events, have been identified in numerous small subsets of NSCLC. Two of these alterations have been validated as reliable targets for selective pathway-directed systemic therapy.

The incidence of EGFR mutations in the Caucasian population is about 10% and is higher in never smokers, adenocarcinoma subtype and women. Prevalence has also been shown to be higher in East-Asian patients. EGFR mutation testing is recommended in all patients with advanced NSCLC of a non-squamous subtype before initiation of first-line treatment [I, A]. Testing is not recommended in patients with a confident diagnosis of squamous cell carcinoma, except in never/former light smokers (<15 packs per year) [IV, A] [13]. It should be systematically analysed—with a validated mutation detection platform in a laboratory participating in an external quality assurance scheme—in all such patient subgroups [V, A]. Choice of methodology will vary but should provide the test sensitivity required for the tumour content of the sample, and provide an adequate coverage of all clinically relevant mutations [11]. Laboratories should validate their practice internally and through external quality assurance programmes. Activating (sensitising) EGFR mutations are predictive for response to the EGFR TKIs resulting, in this context, in an improved RR, PFS, and QoL as well as a better tolerability when compared with first-line chemotherapy, as demonstrated in several phase III randomised trials. Hence, in patients with activating EGFR mutations, EGFR TKI therapy statistically significantly delays disease progression and should be considered as front-line therapy [38].

ALK fusion genes have been identified as important oncogenic drivers [14]. ALK fusion is encountered more frequently in never smokers, the adenocarcinoma subtype, and in younger patients, representing an incidence of around 5% in adenocarcinomas [15]. The ALK TKIs can effectively target ALK activity, and routine testing for ALK rearrangements is now a standard of care. Testing should focus on the same group of patients selected as for EGFR mutation [II, A]. Testing should be carried out, if at all possible, in parallel with EGFR mutation analysis. Currently, the standard test for detecting ALK fusion remains the break-apart FISH test. A multiplex PCR approach may be successful but requires an adequate coverage of the many possible fusion genes now recognised and is challenged by the availability of adequate quality nucleic acid from typical samples, and by the methodology itself. High sensitivity IHC has been shown to have a high positive and negative predictive value for the presence and absence, respectively, of ALK fusion, and while not a recognised primary biomarker for ALK TKI therapy, it is widely used to screen patients for possible ALK FISH testing. Next-generation sequencing approaches for detecting fusion genes are in development. Patients with NSCLC harbouring an ALK rearrangement should be considered for crizotinib, a dual ALK and MET TKI, during the course of their disease [I, A]. Upfront comparisons with chemotherapy are not available to date [44].

Despite the improved patient outcome with tumours harbouring EGFR mutations or ALK fusions while treated with specific TKIs, all patients will eventually experience disease progression through primary or acquired resistance. Various resistance mechanisms have been identified resulting in the development of new therapeutic approaches and novel TKIs that are being tested in clinical studies. Moreover, the opportunity of applying systemic molecular-based targeted approaches for other driver alterations (such as ROS1, BRAF, HER2, and RET) is currently under evaluation [11, 12]. In this disease setting, more research is needed to identify molecular markers which could lead to advances in personalised medicine.

**treatment of oligometastatic NSCLC**

Oligometastases are mostly defined as at maximum five metastatic lesions in the body. Oligometastases can be either synchronous, when diagnosed within 1 month before or after the primary tumour was identified, or metachronous when they appear after treatment of the primary. The biology and prognosis related to synchronous and metachronous oligometastases may differ.

The treatment approach to oligometastases in the brain has been discussed previously.

’Synchronous’ oligometastases occur in about 15% of all patients with NSCLC. Apart from a stereotactic body radiotherapy (SBRT) dose-escalation study, data from only one prospective single-arm phase II trial is available [60]. Nearly all patients had a single metastatic lesion and 75% had ‘locally advanced stage III’ disease. With systemic treatment and radical local radiotherapy (SBRT or high-dose fractionated irradiation) or surgery of all tumour lesions, 13% of patients remained disease-free at three years. All other studies are retrospective but suggest that a yet to be defined subgroup of stage IV patients with a few metastases at diagnosis may be cured with a radical approach [61–63]. Because of the lack of prospective data, it is unclear if some anatomical locations of the metastases have a worse prognosis [62, 63].

In general, patients with oligometastases outside of the brain should preferentially be included in trials.

Patients with ‘metachronous’ metastases may biologically have more indolent tumours than those with widespread disseminated disease leading to a more favourable prognosis [62, 63]. Only retrospective studies are available [61]. It is unclear whether the biology of the disease or the local therapy influences
the survival. Radical local therapy with high-dose radiotherapy or surgery is appealing, but these patients should also be preferentially included in prospective trials.

A special situation is a solitary lesion in the contralateral lung. In most cases, this should be considered as a synchronous secondary primary tumour, and treated, if possible, with surgery and adjuvant chemotherapy if indicated, definitive radiotherapy, or chemoradiotherapy [IV, B].

**brain metastasis treatment**

The treatment of patients with brain metastases depends heavily on the prognosis: recursive partitioning analysis (RPA) class I patients are <65 years old, have a good PS [Karnofsky Index (KI) ≥70%], have no other extra-cranial metastases and have a controlled primary tumour; class III are all patients with a KI <70%; and class II are all other patients [64]. In class III patients, only BSC is recommended, with a median survival of <2 months. To date, the standard treatment of class I/II patients with more than three brain metastases is whole-brain radiotherapy (WBRT). The most frequent schedules are 20 Gy in 5 fractions or 30 Gy in 10 fractions, with no difference in outcome [65] [I, A]. Simultaneous integrated boost techniques are frequently used, but thorough comparisons with WBRT have not been reported. Single brain metastases can be treated either by surgery or stereotactic radiosurgery (SRS), with equal results for appropriately selected patients [II, B]. SRS is the preferred treatment of two to three brain metastases. Adjuvant WBRT decreases brain relapses, but has no effect on survival. In case therapeutic options like SRS or surgery would still be envisaged in case of brain relapse [I, A], a follow-up MRI scan of the brain every three months after resection or SRS is recommended.

In patients with asymptomatic brain metastases who have not received prior systemic therapy (e.g. chemotherapy, TKIs), treatment with systemic chemotherapy and deferred WBRT should be considered [II, B] [66]. However, this recommendation does not apply to patients with isolated and oligometastatic CNS disease, for whom a radical, and potentially curative, approach (e.g. surgery, stereotactic radiotherapy) is contemplated.

For most patients with symptomatic brain metastases and/or significant oedema, a dose of dexamethasone of 4 mg/day or an equivalent dose of another corticosteroid is recommended [II, A] [67]. Tapering of the dose and, if possible, cessation after radiotherapy is recommended. Corticosteroids are not recommended in case of asymptomatic brain metastases.

**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 [II, B].

**role of palliative surgery in stage IV NSCLC.** Recurrent pleural effusions can be managed by pleurodesis. The preferred sclerosing agent is talc, which is more effective than bleomycin or tetracycline [68] [II, B]; thoracoscopic insufflation with talc (poudrage) is more effective than talc slurry sclerosis [69] [II, B]. If pleurodesis is not possible, recurrent pleural effusions may be managed using appropriate drainage catheter systems.

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

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

**role of bone modifying agents.** Zoledronic acid reduces skeletal-related events (pathological fracture, radiation or surgery to bone, or spinal cord compression, SRE) and is recommended in stage IV bone metastatic disease [II, B] [70].

Denosumab is not inferior [I, A] and shows a trend toward superiority [II, B] to zoledronic acid in lung cancer in terms of SRE prevention [II, B] [71]. In an exploratory analysis of a large phase III trial, denosumab was associated with improved median OS in the subgroup of 702 metastatic NSCLC patients [72].

**role of palliative care early intervention.** Early palliative care intervention is recommended, in parallel with standard oncological care [II, A]. Evidence demonstrating that palliative care interventions significantly improve QoL remains scarce. A randomised trial evaluating the impact of introducing specialised palliative care early after diagnosis of stage IV disease on patient QoL in ambulatory patients was able to show an improvement in QoL and mood, a reduction in aggressive treatment and an improvement in median survival [73].

**response evaluation**

Response evaluation is recommended after two to three cycles of chemotherapy using the same initial radiographic investigation which demonstrated tumour lesions. Follow-up with PET is not routinely recommended, due to its high sensitivity and relatively low specificity. Measurements and response reporting should follow RECIST criteria v1.1 [17]. However, the adequacy of RECIST in evaluating response to EGFR or ALK TKI in respectively genetically driven NSCLC is debatable.

**follow-up**

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

Due to the aggressive nature of this disease, generally close follow-up, at least every 6 weeks after first-line therapy, is advised but should also depend on individual re-treatment options [III, B]. Given the clear benefits of second-line therapy
### Table 3. Summary of recommendations

<table>
<thead>
<tr>
<th>Topic</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
<td>• Adequate tissue material for histological diagnosis and molecular testing should be obtained to allow individual treatment decisions.</td>
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<tr>
<td></td>
<td>• Pathological diagnosis should be made according to the WHO classification and the IASLC/ATS/ERS classification of adenocarcinoma.</td>
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<td></td>
<td>• Specific subtyping of all NSCLCs is necessary for therapeutic decision-making and should be carried out wherever possible.</td>
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<td></td>
<td>• IHC should be used to reduce the NSCLC-NOS rate to fewer than 10% of cases diagnosed.</td>
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<td></td>
<td>• EGFR mutation status should be systematically analysed in advanced NSCLC with a non-squamous histology [I, A]. Test methodology should have adequate coverage of relevant mutations.</td>
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<tr>
<td></td>
<td>• Testing is not recommended in patients with a confident diagnosis of squamous cell carcinoma, except in never/former light smokers (&lt;15 packs per year) [IV, A].</td>
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<td></td>
<td>• Testing for ALK rearrangement should be systematically carried out in advanced NSCLC with a non-squamous histology [II, A].</td>
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<td></td>
<td>• Detection of the ALK translocation by FISH remains the standard, but IHC may have a role in screening out negative cases.</td>
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<td></td>
<td>• If possible, parallel testing for molecular aberrations is preferable. Sequential testing may delay treatment.</td>
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<td></td>
<td>• Re-biopsy at disease progression should be considered.</td>
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<tr>
<td><strong>Staging and risk assessment</strong></td>
<td>• A complete history including smoking history and comorbidities, weight loss, PS, and physical examination must be recorded.</td>
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<td></td>
<td>• Laboratory: standard tests including routine haematology, renal and hepatic function, and bone biochemistry tests are required. Routine use of serum markers—such as CEA—is not recommended.</td>
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<td></td>
<td>• Contrast-enhanced CT scan of the chest and upper abdomen should be carried out.</td>
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<td></td>
<td>• Imaging of CNS is reserved for patients with neurological symptoms or signs.</td>
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<td></td>
<td>• Magnetic resonance imaging is more sensitive than CT scan.</td>
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<td></td>
<td>• Local bone imaging is required in the presence of clinical suspicion of bony lesions not evaluable on a CT scan. Bone scan may be helpful to detect systemic bone metastasis.</td>
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<tr>
<td></td>
<td>• PET-CT scan offers the highest sensitivity and is advised for mediastinal lymph nodes and distant metastasis assessment.</td>
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<td></td>
<td>• NSCLC is staged according to the AJCC/UICC system (7th edition) and is grouped into the stage categories shown in Tables 1 and 2. Measurement of lesions should follow RECIST criteria v1.1.</td>
</tr>
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<td></td>
<td>• 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.</td>
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<td></td>
<td>• An evaluation of resectability or the suitability of radiotherapy with curative intent should be made in the context of a solitary brain or adrenal lesion or oligometastatic disease confined to the lungs: cardiorespiratory evaluation, brain imaging, PET, and, if needed for decision-making, invasive mediastinal node evaluation.</td>
</tr>
<tr>
<td><strong>Treatment strategy</strong></td>
<td>• The treatment strategy should take into account the histology, molecular pathology, age, PS, comorbidities, and patient’s preferences.</td>
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<td></td>
<td>• Treatment decisions should be discussed within a multidisciplinary tumour board.</td>
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<td></td>
<td>• Systemic therapy should be offered to all stage IV patients with PS 0–2 [I, A].</td>
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<td>• In any stage of NSCLC, smoking cessation should be highly encouraged because it improves the outcome [II, A].</td>
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<tr>
<td><strong>First-line treatment</strong></td>
<td>• The standard first-line chemotherapy is a platinum-based doublet chemotherapy [I, A].</td>
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<td>• In the subgroup of non-squamous tumours and in patients treated with third-generation regimens, including gemcitabine and taxanes, cisplatin should be the treatment of choice [I, B].</td>
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<td></td>
<td>• Pemetrexed is preferred to gemcitabine or docetaxel in patients with non-squamous tumours [II, A]. Pemetrexed use should be restricted to non-squamous NSCLC in any line of treatment [I, A].</td>
</tr>
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<td>• Bevacizumab combined with a paclitaxel–carboplatin regimen may be offered to patients with non-squamous histology NSCLC and PS 0–1 after exclusion of contraindications [I, A].</td>
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<td></td>
<td>• The combination of bevacizumab and other platinum-based chemotherapies may be considered in eligible patients with non-squamous NSCLC [I, A].</td>
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<tr>
<td></td>
<td>• Non–platinum-based combination chemotherapy with third-generation agents should be considered only if platinum therapy is contraindicated [I, A].</td>
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<td></td>
<td>• Chemotherapy should be initiated while the patient has a good PS. For most patients, four cycles of chemotherapy are recommended, with a maximum of six cycles [II, B].</td>
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### Table 3. Continued

<table>
<thead>
<tr>
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| **PS ≥2 patients:** | **Chemotherapy prolongs survival and possibly improves the QoL in NSCLC patients with PS 2, when compared with BSC [I, B]. Single-agent chemotherapy with gemcitabine, vinorelbine, and taxanes represents an option [I, B].**  
**Carboplatin-based combination chemotherapy should be considered in eligible PS 2 patients [II, A].**  
**Poor PS (3–4) patients should be offered BSC [II, B] in the absence of tumours with activating (sensitising) EGFR mutations.**  
**Elderly patients:**  
A survival advantage has been seen for carboplatin-based chemotherapy in eligible patients aged 70–89 years with PS 0–2 with adequate organ function [I, B].  
For the other clinically unselected patients with advanced NSCLC, single-agent chemotherapy remains the standard of care for first-line therapy patients [I, B].  
**Use of TKIs:**  
First-line treatment with a TKI (erlotinib, gefitinib, or afatinib) is the preferred treatment of patients with tumours bearing an activating (sensitising) EGFR mutation [I, A].  
Patients with EGFR mutation and PS 3–4 may also be offered an EGFR TKI [II, A].  
In EGFR WT patients, EGFR TKIs are not recommended as first-line therapy, being inferior to chemotherapy [I, A].  
Patients with NSCLC harbouring an ALK fusion should be offered treatment with crizotinib during the course of their disease [I, A].  
**Maintenance treatment**  
Maintenance chemotherapy should be offered only to patients with PS of 0–1 after first-line chemotherapy.  
In patients with a non-squamous histology and PS 0–1, improvements in PFS and OS were observed with pemetrexed switch maintenance versus placebo following four cycles of platinum-based chemotherapy [I, B].  
Switch maintenance with erlotinib versus placebo demonstrated PFS and OS benefit in all histologies, with the greatest benefit in patients with SD after first-line treatment [I, B].  
Decisions about maintenance must take into account the histology, response to platinum-doublet chemotherapy, remaining toxicity after first-line chemotherapy, PS, and patient preference [I, B].  
Continuing pemetrexed following four cycles of first-line cisplatin plus pemetrexed chemotherapy is recommended in patients with non-squamous histology [I, B].  
**Second-line treatment**  
Patients clinically or radiologically progressing after first-line chemotherapy with PS 0–2 should be offered second-line chemotherapy.  
Comparable options as the second-line therapy consist of pemetrexed—for a non-squamous histology only—or docetaxel [I, B]. Erlotinib is an additional potential option in patients with unknown EGFR status or EGFR WT patients with PS 0–2 [II, B].  
Any patient with a tumour bearing an activating (sensitising) EGFR mutation should receive an EGFR TKI as second-line therapy, if not received previously [I, A].  
Any patient with NSCLC harbouring an ALK fusion should receive crizotinib as second-line therapy, if not received previously [I, A].  
Treatment may be prolonged if the disease is controlled and the toxicity acceptable [II, B].  
**Subsequent lines of treatment**  
Erlotinib is indicated for patients with unknown EGFR status or EGFR WT patients who have not yet received EGFR TKIs, with PS 0–3 [II, B].  
Any patient with a tumour bearing an activating (sensitising) EGFR mutation should receive an EGFR TKI in any line of therapy, if not received previously [I, A]. Similarly, patients with NSCLC harbouring an ALK fusion should receive treatment with crizotinib, if not received previously [I, A].  
**Treatment of oligometastatic NSCLC**  
Stage IV NSCLC patients with oligometastases in the brain: See recommendations for brain metastases treatment.  
Stage IV patients with one to three synchronous metastases may experience long-term disease-free survival (DFS) after systemic therapy and a radical local treatment (high-dose radiotherapy or surgery) [II, B]. Because only one non-randomised phase II trial is available, inclusion in trials is preferred.  
Stage IV patients with a few metachronous metastases may be treated with a radical local treatment and experience long-term DFS [III, B]. However, this is based only on retrospective data.  
Solitary lesions in the contralateral lung should, in most cases, be considered as synchronous secondary primary tumours and, if possible, treated with radical intent [IV, B].

*Continued*
in patients who presented an initial response to first-line chemotherapy and maintain good PS, radiological follow-up should be considered every 6–9 weeks to allow for early initiation of second-line therapy.

**note**

A summary of recommendations is provided in Table 3. Levels of evidence and grades of recommendation have been applied using the system shown in Table 4. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

### Table 3. Continued

<table>
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<td>Brain metastases treatment</td>
<td>• RPA class I patients (&lt;65 years old, KI ≥70%, no other extra-cranial metastases and controlled primary tumour) or class II patients are treated with SRS in case of two to three metastases or with either SRS or resection when a single brain metastasis is diagnosed [II, B]. When more than three brain metastases are diagnosed, WBRT is recommended [I, A]. • RPA class III patients (KI &lt;70%) should not be treated in view of the dismal prognosis [I, B]. • Asymptomatic brain metastases should not be treated with radiotherapy: Deferred irradiation in case of progression is a valuable option [II, B]. • Systemic therapy is a reasonable option for patients with no or relatively minor symptoms from brain metastases with early radiotherapy intervention in the case of the development of progression of symptoms while on treatment [II, B]. • For most patients with symptomatic brain metastases and/or significant oedema, a dose of dexamethasone of 4 mg/day or an equivalent dose of another corticosteroid is recommended with early tapering off after radiotherapy [II, A].</td>
</tr>
<tr>
<td>Role of interventional procedures in stage IV NSCLC</td>
<td>• In case of symptomatic major airway obstruction or post-obstructive infection, endoscopic debulking by laser, cryotherapy, or stent placement may be helpful [III, C]. • Endoscopy is useful in the diagnosis and treatment (endobronchial or by guiding endovascular embolisation) of haemoptysis [III, C]. • Vascular stenting might be useful in NSCLC-related superior vena cava compression [II, B].</td>
</tr>
<tr>
<td>Role of palliative surgery in stage IV NSCLC</td>
<td>• The preferred sclerosing agent is tcalc, which is more effective than bleomycin or tetracycline [II, B]; thoracoscopic insufflation with tcalc (poudrage) is more effective than tcalc slurry sclerosis [II, B].</td>
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<td>Role of radiotherapy</td>
<td>• Radiotherapy plays a major role in symptom control in the case of bone and brain metastases and is also effective in treating pain related to chest wall, soft tissue, or neural invasion. • Neurological symptoms from spinal compression can be relieved by early radiotherapy. • Radiotherapy is indicated in cases of haemoptysis, symptomatic airway compression or obstruction, and following CNS and, sometimes, bone surgery [II, B].</td>
</tr>
<tr>
<td>Bone metastasis modifying agents</td>
<td>• Zoledronic acid reduces SRE (pathological fracture, radiation/surgery to bone, or spinal cord compression) and is recommended in stage IV bone metastatic disease [II, B]. • Denosumab is not inferior [I, A], and shows a trend toward superiority, to zoledronic acid in lung cancer in terms of SRE prevention [II, B].</td>
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<td>Role of palliative care early intervention</td>
<td>• Early palliative care intervention is recommended, in parallel with standard oncological care [II, A].</td>
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<tr>
<td>Response evaluation and follow-up</td>
<td>• Response evaluation is recommended after two to three cycles of chemothreatment using the same initial radiographic investigation which demonstrated tumour lesions. • Measurements and response reporting should follow RECIST criteria v1.1. However, the adequacy of RECIST in evaluating the response to EGFR or ALK TKI in respective genetically driven NSCLC is debatable. • Close follow-up, at least every 6 weeks after first-line therapy, is advised but should depend on individual retreatment options [III, B]. • Radiological follow-up should be considered every 6–12 weeks to allow for early initiation of second-line therapy. • Follow-up with PET is not routinely recommended, due to its high sensitivity and relatively low specificity.</td>
</tr>
</tbody>
</table>

**conflict of interest**

MR has reported: consultant to Hoffmann-La Roche, Lilly, Bristol-Myers Squibb, Novartis, Boehringer Ingelheim, Pfizer, AstraZeneca; Speaker Honoraria from Hoffmann-La Roche, Lilly, Bristol-Myers Squibb, Novartis, Boehringer Ingelheim, Pfizer, AstraZeneca. SPo has reported: consultant to AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novartis, Pfizer; Research funding from Pierre Fabre. NR has reported: consultant to Hoffmann-La Roche, Lilly, Amgen and Bristol-Myers Squibb; Speaker Honoraria from Hoffmann-La Roche, Lilly, Novartis, Boehringer Ingelheim, Otsuka and Bristol-Myers Squibb.
Table 4. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System*)

<table>
<thead>
<tr>
<th>Levels of evidence</th>
<th>Grades of recommendation</th>
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<tbody>
<tr>
<td>I</td>
<td>Strong evidence for efficacy with a substantial clinical benefit, strongly recommended</td>
</tr>
<tr>
<td>II</td>
<td>Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended</td>
</tr>
<tr>
<td>III</td>
<td>Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional</td>
</tr>
<tr>
<td>IV</td>
<td>Moderate evidence against efficacy or for adverse outcome, generally not recommended</td>
</tr>
<tr>
<td>V</td>
<td>Strong evidence against efficacy or for adverse outcome, never recommended</td>
</tr>
</tbody>
</table>

*By permission of the Infectious Diseases Society of America [74].

Squibb. KK has reported: speakers’ bureau: Abbott Diagnostics, Roche, AstraZeneca, Eli Lilly, Pfizer. SP has reported: consultancy/honoraria: Roche, Eli Lilly, AstraZeneca, Pfizer, Boehringer Ingelheim, Bristol-Myers Squibb, Merck Serono, Daiichi Sankyo, Tesaro. DDR has declared no potential conflicts of interest.

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42. Okano Y, Ando M, Asami K et al. Randomized phase III trial of erlotinib versus docetaxel as second or third line therapy in patients with advanced non-squamous non-small cell lung cancer (NSCLC) who have wild type or mutant epidermal growth factor receptor (EGFR): Docetaxel and Erlotinib Lung Cancer Trial (DELTA). J Clin Oncol 2012; 31(suppl); abstr 2103.


58. Okano Y, Ando M, Asami K et al. Randomized phase III trial of erlotinib versus docetaxel as second or third line therapy in patients with advanced non-small cell lung cancer (NSCLC) who have wild type or mutant epidermal growth factor receptor (EGFR): Docetaxel and Erlotinib Lung Cancer Trial (DELTA). J Clin Oncol 2013; 31(suppl); abstr 8006.


