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Metastatic non-small-cell lung cancer: consensus on pathology and molecular tests, first-line, second-line, and third-line therapy
1st ESMO Consensus Conference in Lung Cancer; Lugano 2010

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The 1st ESMO Consensus Conference on lung cancer was held in Lugano, Switzerland on 21 and 22 May 2010 with the participation of a multidisciplinary panel of leading professionals in pathology and molecular diagnostics, medical oncology, surgical oncology and radiation oncology. Before the conference, the expert panel prepared clinically relevant questions concerning five areas: early and locally advanced non-small-cell lung cancer (NSCLC), first-line metastatic NSCLC, second-/third-line NSCLC, NSCLC pathology and molecular testing, and small-cell lung cancer to be addressed through discussion at the Consensus Conference. All relevant scientific literature for each question was reviewed in advance. During the Consensus Conference, the panel developed recommendations for each specific question. The consensus agreement on three of these areas: NSCLC pathology and molecular testing, the treatment of first-line, and second-line/third-line therapy in metastatic NSCLC are reported in this article. The recommendations detailed here are based on an expert consensus after careful review of published data. All participants have approved this final update.

Lugano 2010: Background to the ESMO Consensus Conference

In 2009, European Society for Medical Oncology (ESMO) decided to update the ESMO clinical recommendations in lung cancer through a consensus process addressing five specific areas:

Early and locally advanced non-small-cell lung cancer (NSCLC)
NSCLC pathology and molecular testing
First-line metastatic NSCLC
Second-/third-line NSCLC
Small-cell-lung cancer (SCLC)

Five working groups were appointed, each comprised five to nine participants with multidisciplinary involvement and led by a chair, and with the assistance of one expert in methodological aspects. A total of 39 experts were involved in this consensus process (see Panel members listed in the Appendix).

The 1st ESMO Consensus Conference on Lung Cancer was held in May 2010 in Lugano. Before the conference, each group identified a number of clinically relevant questions suitable for consensus discussion and provided the available literature. At the Conference, in five parallel sessions, each group discussed and reached agreement on the questions previously chosen. Decisions were made using studies published in peer review journals. The consideration of abstracts was at the discretion of the groups. All relevant scientific literature, as identified by the experts, was considered. A systematic literature search was not carried out. The recommendations from each group were then presented to all the experts and discussed, and a general consensus was reached. The 'Infectious Diseases Society of American-United States Public Health Service Grading System' was used (shown in Tables 1 and 2) for level of evidence and strength of recommendation for each question raised [1].

The consensus on three of the five areas discussed—NSCLC pathology and molecular testing, first-line metastatic NSCLC, and second- and third-line NSCLC—are detailed here.Table 3 provides a summary of the recommendations. The consensus

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† See Appendix for members of the Panel.

Table 1. Level of evidence [1]

I	Evidence from at least one large randomized control trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, experts opinions

Table 2. Strength of recommendation [1]

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

on early and locally advanced NSCLC, and SCLC will be reported separately. The final recommendations listed here have been approved by all participants.

Non-small-cell lung cancer pathology and molecular testing (Chair: R. Rosell, participants in this working group: F. Blackhall, F. Ciardiello, P. A. Jänne, K. Kerr, T. Mok, K. O'Byrne, M. Taron)

Lung cancer is the leading cause of cancer-related deaths, with current chemotherapies lacking adequate specificity and efficacy. It is possible to subdivide NSCLC patients into genetically discrete subsets on the basis of the activating mutations that they harbor [2]. Certain subsets of patients can benefit from treatment with specific inhibitors; e.g. in Caucasian patients harboring activating mutations in the epidermal growth factor receptor (EGFR) kinase domain, landmark outcomes of a 70% response rate, 14-month progression-free survival (PFS) and 27-month median overall survival (OS) have been attained with erlotinib [3]. In three phase III trials of Asian patients with EGFR mutations, median PFS was significantly longer in patients receiving gefitinib (9.2–10.8 months) than in those receiving chemotherapy (5.4–6.3 months), with a significant improvement in the hazard ratios (HRs) for progression [estimates ranging from 0.30 to 0.48; $P < 0.001$ [4–6] (95% confidence intervals (CI) 0.22–0.41 [6], 0.36–0.64 [4], 0.34–0.71 [5]] (reviewed in Pao and Chmielecki [7]). Currently, however, EGFR mutation analysis and other molecular assessments are yet to be implemented as routine practice [8].

To optimize and unify genetic testing in NSCLC patients, the panel members agreed on the need to maximize tumor tissue acquisition. Today, the majority of NSCLCs are diagnosed at an advanced stage, and the most common diagnostic procedure is bronchoscopy, which might not provide enough tumor tissue for molecular assessment. Frequently, the diagnosis is based on cytology. The role of a multidisciplinary team, including thoracic surgeons, radiologists and pulmonologists, is essential to obtain more tumor tissue, through the use of novel techniques, such as transthoracic biopsy under CT guidance and endobronchial ultrasound-guided transbronchial needle aspiration [9, 10]. Imaging-guided needle biopsy is satisfactory for EGFR mutation analysis. An average of 1.8 needle passes with small (18–20 gauge) core needles yielded sufficient and reliable samples for mutation analysis [11].

Specific subtyping of NSCLC is essential for accurate treatment decisions; however, the World Health Organisation lung cancer classification is applicable in full only to surgically resected tumors [12]. A new classification of lung adenocarcinoma has recently been published which addresses both resected tumors and small biopsies and cytology [13]. Adenocarcinoma is the most frequent histological subtype of lung carcinoma worldwide and is also the most histologically variable heterogeneous form of lung cancer. Small biopsy samples may not be representative of the whole tumor or allow appreciation of tumor architecture. The vast majority of pulmonary adenocarcinomas are heterogeneous tumors showing a mixture of patterns that may well have different biological behavior and thus potential therapeutic implications for the patient [14]. When pathologists use the term 'non-small-cell carcinoma,' a case could be made for adding 'NOS' (not otherwise specified). Immunohistochemistry may be used to predict a likely specific subtype in NSCLC 'NOS' cases. Immunohistochemistry markers used for subtyping should be validated with clear definitions of a positive test. Thyroid transcription factor (TTF)-1 is positive in ~80%–85% of pulmonary adenocarcinomas. It is also found in 20%–30% of resected large cell undifferentiated carcinomas, in 50% of large cell neuroendocrine carcinomas, and in some adenocarcinomas that may metastasize to the lung [14]. p63 is expressed in all squamous cell carcinomas, but also in around one-third of adenocarcinomas (reviewed by Kerr [14]). Between 80% and 90% of surgically resected adenocarcinomas show more than one of the common patterns (acinar, papillary, bronchioloalveolar or solid). Consequently, there are a number of issues to consider when reporting tumor type [13].

1. Is there sufficient evidence to support the routine application of EGFR somatic mutation assessment?

EGFR-mutant NSCLC was first recognized in 2004 as a distinct clinically relevant molecular subset of lung cancer

Table 3. Summary of recommendations

NSCLC pathology and molecular testing	
Recommendation 1	–EGFR somatic mutation testing should be carried out to identify patients eligible for first-line treatment with EGFR TKIs –Never/former light smokers (<15 packs per year) or patients withnonsquamous histology should be tested for EGFR mutation status regardless of PS –Patients harboring sensitizing EGFR mutations should be treated with EGFR TKIs regardless of the genotype of the sensitizing mutation (del 19 versus L858R in exon 21) –IHC and FISH for EGFR are not recommended for routine clinical use –The concomitant presence of T790M resistance mutation shouldnot preclude the use of EGFR TKIs in the first-line setting –DNA derived from tumor biopsy is the optimal source for EGFR somatic mutation testing; repeat biopsy may be indicated to gain sufficient material to test. There is no evidence to mandate testing for an EGFR somatic mutation outside the first-line setting
Recommendation 2	–A pathologist should be involved in sample preparation and result interpretation of EGFR mutation status. Micro- or macrodissection of samples can maximize tumor cell content before DNA extraction. The report should include comment on source, quantity and quality of tested sample and should follow guidance on genetic test reporting such as that provided by the Swiss Society of Medical Genetics (http://www.sgmg.chand) and the Human Genome Variation Society for nomenclature guidelines (http://www.hgvs.org)
Recommendation 3	–Somatic mutation tests that are required for clinical decision making should be carried out in laboratories that are compliant with country-specific standards for clinical diagnostic testing (UK, Clinical Pathology Accredited Laboratories; USA, CLIA Laboratories). The laboratory should have accreditation to conduct the test and should participate in internal and external quality assurance to maintain accreditation (EMQN, UKNEQAS)
Recommendation 4	–Routine testing for EML4-ALK is not currently recommended outside of clinical trials. However, emerging data for ALK inhibition are promising and may lead to a clinical indication for routine testing
Recommendation 5	–Routine testing for KRAS, BRAF, ERBB2, PIK3CA somatic gene mutations is not currently recommended outside of clinical trials
Recommendation 6	–Routine testing for mRNA levels of ERCC1, RRM1, TS and BRCA1 is not currently recommended outside of clinical trials
First-line metastatic NSCLC	
Recommendation 1	–First-line chemotherapy should be offered to patients with metastatic NSCLC and PS 0–2
Recommendation 2	–The administration of first-line chemotherapy should be offered at diagnosis to asymptomatic patients with metastatic NSCLC
Recommendation 3	–Platinum-based chemotherapy is preferred to non-platinum-based chemotherapy in eligible patients with metastatic NSCLC
Recommendation 4	–Cisplatin should be used in fit patients with PS 0–1 who have adequate organ function
Recommendation 5	–In PS 2 patients either single-agent chemotherapy or platinum-based combinations are valid options
Recommendation 6	–Platinum-based chemotherapy is preferred in fit elderly patients with PS 0–1 and adequate organ function. Single-agent third-generation drugs are preferred in unfit elderly patients
Recommendation 7	– There is no standard platinum-based doublet for metastatic NSCLC. In a preplanned subgroup analysis cisplatin/pemetrexed was shown to be superior in nonsquamous histology and inferior in squamous histology as compared with cisplatin/gemcitabine, but without comparison with other doublets
Recommendation 8	– Four to six chemotherapy cycles should be given
Recommendation 9	– 'Switch maintenance' treatment with erlotinib or pemetrexed following completion of first-line chemotherapy is an option. Decision factors for the use of 'switch maintenance' include histology, type and response to first-line chemotherapy, residual toxicity, patient's symptoms and preference. Any patient whose tumor harbors an EGFR activating mutation should receive an EGFR TKI as maintenance, if not yet received as first line
Recommendation 10	– Bevacizumab combined with platinum-based chemotherapy is a treatment option in eligible patients with nonsquamous NSCLC, in particular when carboplatin/paclitaxel combination is the chemotherapy backbone
Recommendation 11	– Cetuximab added to platinum-based chemotherapy can be considered as a treatment option for patients with EGFR IHC-positive metastatic NSCLC, in particular when cisplatin/vinorelbine is the chemotherapy backbone

Table 3. (*Continued*)

Recommendation 12	– An EGFR TKI is the preferred first-line treatment in patients whose tumor harbors an activating EGFR mutation
Recommendation 13	– Local treatment to brain followed by systemic therapy is the standard approach for patients with brain metastases at diagnosis. Local treatment may be delayed in asymptomatic patients
Second-/third-line NSCLC	
Recommendation 1	– Second- or third-line therapy should be offered to patients with good PS who present with signs of disease progression (radiological and/or clinical) after first or second-line therapy
Recommendation 2	– In second-line, chemotherapy or an EGFR TKI can be offered to patients. In third-line, an EGFR TKI may be considered when patients have not received EGFR TKIs previously. Patients in good general condition in third or subsequent lines should be entered in clinical studies
Recommendation 3	– Patients with symptomatic brain metastases may be considered for treatment with an EGFR TKI
Recommendation 4	– Age alone is not considered to be an exclusion criterion for second or third-line therapy
Recommendation 5	– Different drugs have been registered for treating patients who progress during first-line therapy
Recommendation 6	– For non-squamous tumors, data support the use of second-line pemetrexed or EGFR TKIs – For squamous tumors, data support the use of second-line docetaxel or EGFR TKIs
Recommendation 7	– In the presence of EGFR sensitizing mutations, the use of an EGFR TKI is recommended if not received previously – Second or third-line therapy with an EGFR TKI might be considered even in patients with PS 3-4 harboring an activating EGFR mutation

EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; NSCLC, non-small-cell lung cancer; PS, performance status; TKIs, tyrosine kinase inhibitors.

[15–17]. The disease has been the subject of intensive research at the basic and clinical levels, becoming a paradigm for how to understand and treat oncogene-driven carcinomas [7]. In 2009, trials in EGFR-mutant lung cancer with EGFR tyrosine kinase inhibitors (TKIs) reported the longest survival rates currently seen for metastatic NSCLC [3, 4]. Although patients with EGFR-mutant tumors have increased sensitivity to an EGFR TKI, primary and acquired resistance to these agents remains a major clinical problem. The T790M 'acquired resistance mutation' was observed in 45 of 129 patients (35%) [18]. Three different studies showed that patients with EGFR mutations had shorter PFS when the tumor had a very small amount of T790M before EGFR TKI therapy [18–20].

Recommendation 1.1: EGFR somatic mutation testing should be carried out to identify patients eligible for first-line treatment with EGFR TKIs.

Strength of recommendation: A

Level of evidence: I

Recommendation 1.2: never/former light smokers (< 15 packs per year) or patients with nonsquamous histology should be tested regardless of performance status (PS).

Strength of recommendation: B

Level of evidence: II

Recommendation 1.3: patients harboring sensitizing EGFR mutations should be treated with EGFR TKIs regardless of the genotype of the sensitizing mutation (deletion in exon 19 [del 19] versus L858R in exon 21) [3–6, 21].

Strength of recommendation: A

Level of evidence: II

Recommendation 1.4: immunohistochemistry and FISH for EGFR are not recommended for routine clinical use [4, 21].

Strength of recommendation: A

Level of evidence: II

Other recommendations: the concomitant presence of T790M resistance mutation should not preclude the use of EGFR TKIs in the first-line setting. DNA derived from tumor biopsy is the optimal source for EGFR somatic mutation testing; repeat biopsy may be indicated to gain sufficient material to test. There is no evidence to mandate testing for an EGFR somatic mutation outside the first-line setting.

2. Guidance on tissue handling and reporting for EGFR somatic mutation testing

Handling of tumor specimens has yet to be standardized. In a previous workshop on EGFR mutation testing [8], the participants reached an agreement that 10% neutral-buffered formalin is the optimum fixative, whereas Bouin's fluid should not be used and other fixatives have yet to be validated against formalin. The fixation time should be optimal for tissue specimen and not prolonged, yet sufficient to permit diagnosis. Sections cut from the formalin-fixed paraffin-embedded tissue block are the standard resource used for DNA extraction. Between one and six sections of 5- to 10-μm thickness should be used. Laboratories that use laser capture microdissection will require thinner sections. Tissue fixation and processing have the potential to denature DNA, especially when using automated processes [8].

Recommendation 2: a pathologist should be involved in sample preparation and result interpretation. Micro- or macrodissection of samples can maximize tumor cell content before DNA extraction. The report should include comment on source, quantity and quality of tested sample and should follow guidance on genetic test reporting such as that provided by the Swiss Society of Medical Genetics (http://www.sgmg.chand) and the

Human Genome Variation Society for nomenclature guidelines (http://www.hgvs.org).

Strength of recommendation: A

Level of evidence: I

3. The relevance of participation in quality assurance programs for genetic testing

Molecular genetic techniques have been included in many areas of clinical practice. To maintain confidence in this technology, it is essential that the steps taken to ensure quality are clear and transparent to participants and public. External quality assessment schemes provide a mean of monitoring compliance with best practice procedures [22].

Recommendation 3: somatic mutation tests that are required for clinical decision making should be carried out in laboratories that are compliant with country-specific standards for clinical diagnostic testing (UK, Clinical Pathology Accredited Laboratories; USA, CLIA Laboratories). The laboratory should have accreditation to conduct the test and should participate in internal and external quality assurance to maintain accreditation (The European Molecular Genetics Quality Network, United Kingdom National External Quality Assessment Service).

Strength of recommendation: A

Level of evidence: V

4. Guidelines for testing EML4-ALK for treatment selection

Oncogenic fusion genes consisting of EML4 and anaplastic lymphoma kinase (ALK) are present in a subgroup of NSCLC, representing 2%–7% of tumors. Echinoderm microtubule-associated protein-like 4 (EML4)-ALK is more prevalent in patients who have never smoked or who have a history of light smoking and in patients with adenocarcinomas, particularly those with the rare signet-ring appearance. Among never-smokers and light smokers without EGFR mutations, the frequency of EML4-ALK rearrangement was 33% [23]. In a more recent study, the frequency reached 44.8% [24]. ALK-rearranged tumors (82%) showed, at least focally, tumor cells with abundant intracellular mucin and small marginalized nuclei. This distinct cytological characteristic, unusual for lung carcinoma, is reminiscent of the signet-ring cells more commonly seen in gastric, colon and breast adenocarcinomas [25]. However, ALK rearrangements are also found in other subtypes of lung adenocarcinomas. Crizotinib is an oral ATP-competitive selective inhibitor of the ALK and MET tyrosine kinases. In a recent phase II trial, the response rate to crizotinib was 57% in patients with FISH-positive EML4-ALK rearrangements, and 77% of patients were continuing to receive crizotinib at the time of data cut-off. The estimated probability of 6 months PFS was 72%, with no median for the study reached [26].

Recommendation 4: routine testing for EML4-ALK is not currently recommended outside of clinical trials. However, emerging data for ALK inhibition are promising and may lead to a clinical indication for routine testing.

Strength of recommendation: A

Level of evidence: V

5. Guidelines for testing other somatic gene mutations for treatment selection: KRAS, BRAF, ERBB2, PIK3CA

PIK3CA mutations were identified in 4.7% of NSCLC cell lines and in 1.6% of tumors of all major histological types among 691 resected NSCLC patients. Mutational status of PIK3CA was not mutually exclusive to EGFR or KRAS mutations [27]. In addition, ERBB2 mutations were present in 1.6% of NSCLC patients. All ERBB2 mutations were in-frame insertions in exon 20 that target the identical corresponding region as EGFR insertions. ERBB2 mutations were significantly more frequent in never-smokers and those with adenocarcinomas. EGFR, ERBB2 and KRAS mutations were mutually exclusive [28, 29]. Mutations in BRAF are observed at low frequency (2% of NSCLCs) [30].

Recommendation 5: routine testing for KRAS, BRAF, ERBB2, PIK3CA somatic gene mutations is not currently recommended outside of clinical trials.

Strength of recommendation: A

Level of evidence: V

6. What is the role of customizing chemotherapy based on mRNA levels of ERCC1, RRM1, TS and BRCA1?

A trial of customized treatment based on ERCC1 mRNA levels did not demonstrate a benefit for this approach [31]. Retrospective assessment of RRM1 and TS in stage IV NSCLC patients treated with cisplatin/gemcitabine indicated a potential role for these biomarkers [32, 33]. Based on the differential modulating effect of BRCA1 observed in the breast cancer cell line with mutant BRCA1 HCC1937 [34], BRCA1 mRNA levels have been examined retrospectively in NSCLC patients to predict outcome to cisplatin-based chemotherapy [35, 36]. A prospective phase II study of customized chemotherapy based on BRCA1 levels showed no conclusive evidence for improved outcome in stage IV NSCLC patients. However, an exploratory analysis of RAP80 mRNA levels showed substantial benefit in patients with low levels of both RAP80 and BRCA1 treated with cisplatin/gemcitabine [37]. Based on these findings, two phase III randomized trials of customized chemotherapy based on RAP80 and BRCA1 levels are being carried out.

Recommendation 6: routine testing for mRNA levels of ERCC1, RRM1, TS and BRCA1 is not currently recommended outside of clinical trials.

Strength of recommendation: A

Level of evidence: V

First-line metastatic non-small-cell lung cancer (Chair: C. Gridelli, participants in this working group: B. Besse, D. Gandara, F. de Marinis, J.P. van Meerbeeck, L. Paz-Ares, R. Pirker, M. Reck, E.F. Smit)

Lung cancer is the most common cancer in the world and the leading cause of cancer-related deaths worldwide with ~1.35

million new diagnoses and 1.18 million deaths worldwide in 2002 [38]. Every year, in Europe, >200 000 new cancer cases are diagnosed, accounting for ∼20% of all cancer deaths [39]. NSCLC, including adenocarcinoma, squamous carcinoma and large-cell carcinoma, make up >80%–85% of all lung cancer types with ∼70% of patients presenting with advanced disease at diagnosis. The majority of patients diagnosed with NSCLC are unsuitable for curative treatment due to advanced disease, thus systemic therapy is the standard approach with palliation, patients' quality of life (QOL) and prolongation of life being the goal of therapy.

1. Should first-line chemotherapy be offered to all patients with metastatic NSCLC?

First-line chemotherapy is shown to be effective in metastatic NSCLC patients with PS 0-2 in trials comparing platinum-based chemotherapy or even single-agent chemotherapy with best supportive care (BSC) [40].

Recommendation 1: first-line chemotherapy should be offered to patients with metastatic NSCLC and PS 0–2.

Strength of recommendation: A

Level of evidence: I

2. Should we start first-line chemotherapy in asymptomatic stable patients with metastatic NSCLC immediately or at onset/progression of symptoms?

The survival benefit achieved by palliative chemotherapy in asymptomatic patients with metastatic NSCLC is of the same magnitude as in symptomatic ones [40]. Furthermore, QOL either was not worse or improved for those patients receiving chemotherapy in eight clinical trials, four with platinum-based and four with single-agent third-generation drugs [41].

Although not less effective, delaying palliative chemotherapy until symptomatic progression may result in shorter time to progression, worsening of QOL and less drug exposure, all of which are potentially detrimental to outcome [42].

Recommendation 2: the administration of first-line chemotherapy should be offered at diagnosis to asymptomatic patients with metastatic NSCLC.

Strength of recommendation: C

Level of evidence: III

3. Should we use platinum or non-platinum-based chemotherapy?

Non-platinum-based chemotherapy regimens have been proposed as alternatives to platinum-based doublets for the treatment of metastatic NSCLC. Two meta-analyses have addressed this issue [43, 44]. D'Addario et al. [43] analyzed the outcomes of 37 randomized phase II and III studies including 7633 patients and 42 pairwise comparisons (platinum versus nonplatinum). When analyzed for response rate, platinum-containing regimens yielded a 62% increase in the odds for response (95% CI for odds ratio [OR], 1.46–1.8, $P < 0.0001$). There was a 5% increase in 1-year survival rate (OR 1.21; 95% CI 1.09–1.35, $P = 0.0003$) with platinum-based regimens but nonstatistically significant differences were found when only regimens including third-generation drugs were included. Platinum-based regimens are associated with higher frequencies of nausea and vomiting, and renal and hematological toxic effects, although none led to increases in febrile neutropenia or toxic death rate. Pujol et al. analyzed the outcomes of 11 randomized phase III studies including 4602 patients that had 1-year survival as one of the endpoints [44]. The absolute survival benefit for patients treated with platinum-based chemotherapy was 3% at 1 year, corresponding to a reduction in the risk of death within the first year with an OR of 0.88 (95% CI 0.78–0.99, $P = 0.044$). Again, there was a slight increase in the incidence of gastrointestinal toxicity but no increase in the rate of toxic deaths. Both meta-analyses concluded platinum-based chemotherapy to be superior to non-platinum-based chemotherapy in metastatic NSCLC.

Recommendation 3: platinum-based chemotherapy is preferred to non-platinum-based chemotherapy in eligible patients with metastatic NSCLC.

Strength of recommendation: A

Level of evidence: I

4. Should we use cisplatin or carboplatin-based chemotherapy?

Concerns about the toxic effects associated with cisplatin-based chemotherapy and the availability of platinum analogs with fewer side effects have led to a number of randomized trials in metastatic NSCLC patients. Two meta-analyses have been published that address this issue [45, 46]. Hotta et al. [45] analyzed eight trials and reported a higher response rate for cisplatin compared with carboplatin treatment with no survival difference. Subgroup analyses revealed that patients treated with a third-generation compound in conjunction with carboplatin had a shorter survival than those receiving cisplatin plus the same agents (HR 1.106, 95% CI 1.005–1.218; $P = 0.039$). This survival advantage was obtained at the cost of a higher but not statistically significant difference in terms of lethal toxic effects. In a more recent meta-analysis using individual patient data, Ardizzoni et al. [46] observed a significant increase in response for the cisplatin-treated patients, with no significant survival difference. In a prespecified analysis, the authors found an interaction between histology and the use of third-generation agents; patients with nonsquamous tumor fared better when treated with cisplatin-based chemotherapy. Furthermore, once again, patients treated with third-generation compounds in conjunction with cisplatin had a longer survival as compared with those treated with carboplatin plus the same agent. The results were similar to the Hotta et al. [45] analysis with regard to toxic effects.

Recommendation 4: cisplatin should be used in fit patients with PS 0-1 who have adequate organ function.

Strength of recommendation: B

Level of evidence: I

5. Which chemotherapy should we use for PS 2 patients?

On the basis of current evidence, chemotherapy appears justified in patients with advanced NSCLC and a PS of 2. Subgroup analyses from several randomized trials suggest that several new-generation cytotoxic drugs are superior to

BSC alone in this category of patients [47]. Therefore, single-agent chemotherapy with these drugs (e.g. gemcitabine, vinorelbine, and taxanes) represents an historical option for palliative treatment of these patients. No data justify the use of platinum-free or high-dose (>100 mg/m^2) cisplatin-based combination chemotherapy instead of single-agent treatment in this group of patients [47]. Taking into account the superiority shown by the carboplatin/paclitaxel combination compared with paclitaxel alone in a subgroup analysis of PS 2 patients [48], and the efficacy and the tolerability showed by carboplatin-based doublets [49] in one randomized trial, platinum-based combinations may also be considered as an option for these patients.

Recommendation 5: in PS 2 patients either single-agent chemotherapy or platinum-based combinations are valid options.

Strength of recommendation: B
Level of evidence: I

6. Which chemotherapy for elderly patients?

More than 50% of NSCLCs are diagnosed in patients aged >65 years with 30% being in patients >70 years. Two main randomized phase III trials showed single-agent chemotherapy with third-generation agents as the standard of care for first-line therapy for clinically unselected elderly advanced NSCLC patients [41, 50]. However, retrospective analyses from large phase III randomized trials showed similar efficacy and tolerability when elderly and adult patients were compared [51]. This issue has recently been addressed in a prospective randomized trial comparing monthly carboplatin plus weekly paclitaxel versus single-agent vinorelbine or gemcitabine, reporting a survival advantage for combination therapy but with increased toxicity (neutropenia and febrile neutropenia) [52]. Platinum-based chemotherapy may therefore be the preferred option for elderly patients with PS 0–1 and adequate organ function, while single-agent is recommended for unfit patients.

Recommendation 6: platinum-based chemotherapy is preferred in fit elderly patients with PS 0–1 and adequate organ function. Single-agent third-generation drugs are preferred in unfit elderly patients.

Strength of recommendation: B
Level of evidence: I

7. Is there a single standard platinum-based doublet chemotherapy option for metastatic NSCLC?

Randomized studies that have compared platinum-based doublets including third-generation drugs (vinorelbine, gemcitabine, taxanes) among themselves [53–55] did not show any differences in survival and gave no evidence for a single 'standard' doublet for the treatment of metastatic NSCLC. The observation that docetaxel/cisplatin was superior to vinorelbine/cisplatin in a randomized study [54] has not had other confirmations. A phase III randomized trial comparing cisplatin/pemetrexed versus cisplatin/gemcitabine showed no difference in outcome between the two combinations with a lower hematological toxicity profile for the pemetrexed-based regimen [56]. A preplanned subgroup analysis showed a survival advantage for cisplatin/pemetrexed as compared with cisplatin/gemcitabine in nonsquamous histology (11.8 versus 10.4 months, respectively; HR 0.81, 95% CI 0.70–0.94; $P = 0.005$), while a survival advantage for the gemcitabine-based combination was observed in squamous histology. No prospective confirmative trials have been carried out. To date no comparative data of cisplatin/pemetrexed versus other platinum-based doublets are available.

Recommendation 7: no, there is no standard platinum-based doublet for metastatic NSCLC. In a preplanned subgroup analysis cisplatin/pemetrexed was shown to be superior in nonsquamous histology and inferior in squamous histology as compared with cisplatin/gemcitabine, but without comparison with other doublets.

Strength of recommendation: A
Level of evidence: I

8. How many cycles of chemotherapy?

Two randomized phase III trials compared three versus six cycles of chemotherapy with cisplatin/vinblastine/mitomycin, and carboplatin/ vinorelbine, respectively [57, 58]. Both trials reported no significant differences in any of the outcomes, except increased toxicity for the more prolonged treatment. However these two trials were underpowered and considered inconclusive.

Recommendation 8: four cycles of chemotherapy appear sufficient in most NSCLC patients but six cycles may be considered depending on response and toxicity.

Strength of recommendation: B
Level of evidence: II

9. Should we recommend maintenance treatment and if yes to which patients?

Maintenance therapy is the continued administration of therapy after a defined number of induction therapy cycles once disease stabilization or maximum tumor response has been achieved, and may be continued until either disease progression or unacceptable toxicity. It consists both of drugs included in the induction regimen or other non-cross-resistant agents defining the 'early second line' or 'switch maintenance' [59]. Two main phase III randomized trials addressed the issue of 'switch maintenance' therapy with pemetrexed or erlotinib after four cycles of platinum-based chemotherapy [21, 60]. Both trials reported PFS and OS advantages for maintenance therapy (pemetrexed or erlotinib) versus placebo. In the pemetrexed study, OS for nonsquamous histology was 15.5 versus 10.3 months in the pemetrexed and the placebo arms, respectively (HR 0.70, 95% CI 0.56–0.88; $P = 0.002$) [60]. PFS was also significantly improved with maintenance pemetrexed in this histological subgroup (4.4 versus 1.8 months, respectively; HR 0.47, 95% CI 0.37–0.60; $P < 0.0001$). In the erlotinib versus placebo study, PFS was significantly longer with erlotinib (HR 0.71, 95% CI 0.62–0.82; $P < 0.0001$) and also a survival advantage was observed (median survival of 12 versus 11 months, HR 0.81, 95% CI 0.70–0.95; $P = 0.0088$) [21]. Subgroup analyses showed a greater benefit for erlotinib in patients with stable disease

after induction chemotherapy and in patients with tumor harboring EGFR mutation. Unfortunately, neither trial addressed the question of 'early second line' (or 'switch maintenance') versus common second-line treatment started at disease progression. However, factors to consider for treatment in clinical practice include histology, type and response to first-line chemotherapy, residual toxicity, patient's symptoms and preference. Any patient with mutated EGFR tumor should receive an EGFR TKI as maintenance, if not received as first line.

Although randomized trials investigating the prolonged use of one of the components of the induction regimen have consistently shown an improvement of PFS, this does not translate in improved OS.

Recommendation 9: 'switch maintenance' treatment with erlotinib or pemetrexed following completion of first-line chemotherapy is an option. Decision factors for the use of 'switch maintenance' include histology, type and response to first-line chemotherapy, residual toxicity, patient's symptoms and preference. Any patient whose tumor harbors an activating EGFR mutation should receive an EGFR TKI as maintenance, if not yet received as first line.

Strength of recommendation: B

Level of evidence: I

10. The use of bevacizumab is restricted to selected patients with nonsquamous histology. With which chemotherapy should it be combined?

Two phase III randomized trials showed superiority of platinum-based chemotherapy plus bevacizumab as compared with chemotherapy alone [61, 62]. Both studies were conducted in chemotherapy-naive patients with stage IIIB/IV nonsquamous NSCLC and PS of 0-1; due to safety concerns, patients with brain metastases, gross hemoptysis and those receiving therapeutic anticoagulation were excluded. In the ECOG 4599 study, bevacizumab/carboplatin/paclitaxel versus carboplatin/paclitaxel was evaluated [61]. The OS was significantly longer in patients receiving combined treatment than in those receiving chemotherapy alone (median survival: 12.3 versus 10.3 months; HR 0.79, 95% CI 0.67–0.92; $P = 0.003$). Median PFS times in the two groups were 6.2 and 4.5 months, respectively (HR 0.66, 95% CI 0.57–0.77; $P < 0.001$), with corresponding response rates of 35% and 15% ($P < 0.001$) [61]. The second phase III trial, enrolling outside the United States, has evaluated the combination of bevacizumab (15 mg/kg or 7.5 mg/kg every 3 weeks until disease progression) with gemcitabine /cisplatin versus gemcitabine/cisplatin plus placebo [62]. The primary end point was PFS. This trial was not powered to compare the two doses of bevacizumab directly. The PFS was significantly longer in patients receiving chemotherapy plus bevacizumab than in those receiving chemotherapy plus placebo [placebo arm: median PFS 6.1 months; 7.5 mg/kg bevacizumab arm: median PFS 6.7 months (HR 0.75, 95% CI 0.64–0.87; $P = 0.0003$); 15 mg/kg bevacizumab arm: median PFS 6.5 months (HR 0.85, 95% CI 0.73–1.00; $P = 0.045$)]. In this trial, there was no survival benefit for patients receiving bevacizumab versus placebo.

Recommendation 10: bevacizumab combined with platinum-based chemotherapy is a treatment option in eligible patients with nonsquamous NSCLC, in particular when carboplatin/paclitaxel combination is the chemotherapy backbone.

Strength of recommendation: B

Level of evidence: I

11. Is there a role for cetuximab?

Cetuximab has been studied in combination with different chemotherapy regimens in patients with advanced NSCLC. In the phase III FLEX trial, cetuximab added to cisplatin/vinorelbine increased survival compared with the same chemotherapy alone in patients with advanced NSCLC expressing EGFR by immunohistochemistry (median survival 11.3 versus 10.1 months, HR 0.87, 95% CI 0.76–0.99; $P = 0.04$) [63]. In the second phase III trial in patients not selected according to EGFR expression, cetuximab added to carboplatin/paclitaxel or docetaxel failed to improve PFS, the primary end point [64]. A meta-analysis of 2018 patients from two randomized phase II trials and the two phase III trials confirmed the efficacy of cetuximab when added to chemotherapy [65]. The benefit of cetuximab was seen irrespective of either histological subtype or type of platinum-based chemotherapy. The main cetuximab-related adverse event is an acne-like rash that has been shown to be associated with prolonged survival [66].

At present cetuximab is not approved by regulatory agencies for the treatment of NSCLC.

Recommendation 11: cetuximab added to platinum-based chemotherapy can be considered as a treatment option for patients with EGFR immunohistochemistry positive metastatic NSCLC, in particular when cisplatin/vinorelbine is the chemotherapy backbone.

Strength of recommendation: B

Level of evidence: I

12. What is the preferred first-line treatment in patients with a tumor harboring an activating EGFR mutation?

In 2004, two research groups discovered the existence of certain tumor-associated activating mutations in the tyrosine-kinase domain of the *EGFR* gene of NSCLC [15, 16]. These gain-of-function mutations enhance EGFR activation, are transforming and markedly increase sensitivity to EGFR TKIs. The most common oncogenic mutations are deletions in exon 19 (45%–50% of all somatic EGFR mutations) and a point mutation (L858R) in exon 21 (35%–45% of mutations) [3, 4]. The presence of these mutations has been associated with specific clinical and epidemiological characteristics (females, Asians, nonsmokers, and adenocarcinoma histology). Furthermore, patients with tumors harboring these mutations had an extraordinary outcome with EGFR TKIs, including response rates >60% and median survival exceeding 24 months [3, 4].

In a phase III open-label study, previously untreated patients in East Asia who had advanced pulmonary adenocarcinoma and who were never-smokers or former

light smokers were randomized to receive gefitinib (609 patients) or carboplatin/paclitaxel (608 patients) [4]. In the subgroup of 261 patients who had EGFR-mutation-positive tumors, PFS was significantly longer among those who received gefitinib than among those who received carboplatin/paclitaxel (HR 0.48; 95% CI 0.36–0.64; $P < 0.001$), whereas in the subgroup of 176 patients whose tumors were negative for the mutation, PFS was significantly longer among those who received carboplatin/paclitaxel (HR 2.85; 95% CI 2.05–3.98; $P < 0.001$). Two phase III trials in East Asian patients selected because of having a tumor harboring EGFR mutation compared gefitinib with platinum-based chemotherapy and gave consistent results in terms of PFS [5, 6]. Other randomized phase III trials have been designed to test the efficacy of erlotinib as first-line treatment of patients with EGFR-mutation-positive tumors. The OPTIMAL phase III trial, conducted in China, showed erlotinib significantly superior to carboplatin/gemcitabine chemotherapy in terms of PFS, which was the primary end point: median PFS was 4.6 months with chemotherapy compared with 13.1 months with erlotinib (HR 0.16, 95% CI 0.10–0.26; $P < 0.0001$) [67]. Phase III randomized trials comparing erlotinib or afatinib with chemotherapy in untreated patients harboring EGFR mutations are ongoing.

Currently, gefitinib is registered for this indication within the EU. Erlotinib, another EGFR TKI, is not yet approved for this indication by regulatory agencies.

Recommendation 12: an EGFR TKI is the preferred first-line treatment in patients whose tumor harbors an activating EGFR mutation.

Strength of recommendation: A

Level of evidence: I

13. What is the optimal sequence of local and systemic treatment of patients with brain metastases at diagnosis?

Approximately 18% of all brain metastases are caused by lung cancer [68]. Treatment options are usually based on local approaches [surgery, radiosurgery or whole-brain radiation therapy (WBRT)] depending on the number and site of brain metastases. Systemic treatment has been thought to be inadequate due to the blood–brain barrier. However, previously untreated patients with brain metastases have been shown to have response rates with chemotherapy that are comparable with those found in extracranial disease [69]. In a randomized phase III trial, OS was not modified by delaying WBRT in patients with brain metastases at diagnosis who received front-line cisplatin-based chemotherapy [69]. However, the control of neurological symptoms influences QOL and should drive the therapeutic strategy.

Recommendation 13: local treatment to brain followed by systemic therapy is the standard approach for patients with brain metastases at diagnosis. Local treatment may be delayed in asymptomatic patients.

Strength of recommendation: B

Level of evidence: II

Second- and third-line therapy in non-small-cell lung cancer (Chair: P. Baas, participants in this working group: F. Cappuzzo, R. Dziadziuszko, G. Goss, S.M. Lee, C. Manegold, A. Vergnenegre)

Treatment decisions in second and third-line therapy should take into account a number of factors: histology, age, PS, comorbidities, previous therapy, molecular features, potential side effects, ultimate goal of the treatment and patients' preferences. The choice of therapy should be made preferably at a tumor board conference or during a multidisciplinary discussion.

Second-line therapy can be defined as any treatment following first-line therapy for metastatic NSCLC, irrespective of any maintenance or adjuvant therapy. The goal of second- or third-line treatment is prolongation of life and symptom control. Patients who are candidates for this indication should be selected on the basis of the time to progression, PS, and the kind of first-line treatment previously delivered. Age alone is not considered to be an exclusion criterion for treatment and those presenting with symptomatic brain metastases might be considered for EGFR TKI treatment. There is no convincing evidence that patients with PS > 2 will benefit from chemotherapy, but selected patients with PS 4 and sensitizing EGFR mutations might benefit from the administration of EGFR TKIs. The registered options for second-line treatment are presented in Table 4 [70–73].

Patients who progress after second-line chemotherapy may be candidates for further treatment. Currently, only erlotinib is registered for this indication. This treatment is only indicated for patients who have not yet received EGFR TKIs regardless of the PS. There are no randomized studies addressing how long second-line treatment should continue. In both the erlotinib versus placebo and the pemetrexed versus docetaxel studies in second-line therapy was given until disease progression. It is generally accepted that in the case of response and acceptable toxicity, a minimum of four cycles is advisable. Continuation of treatment can be considered in selected cases. Continuing treatment beyond disease progression is not recommended.

1. Which patients should receive second or third-line therapy?

Patients who show signs of radiological or clinical progression after first- or second-line therapy should be considered for second-/third-line therapy. Various studies have shown

Table 4. Second-line treatment

Drug registered for NSCLC	Line of treatment
Erlotinib [70]	Second or third line
Pemetrexed [71]	Second line
Docetaxel [72]	Second line

NSCLC, non-small-cell lung cancer.

response rates ~10%, improvement in disease related symptoms and increased time to progression associated with the use of second-/third-line therapy. However, there is a prerequisite that these patients are in a relatively good general condition (PS 0–2) [71,72]. Second-line combination regimens failed to show any benefit over single-agent treatment.

Recommendation 1: second or third-line therapy should be offered to patients with good PS who present with signs of disease progression (radiological and/or clinical) after first or second-line therapy.

Strength of recommendation: A

Level of evidence: I

2. What kind of treatment should be offered in second line? What kind of treatment should be offered in third line?

There are a number of agents registered for use in second-line therapy (see Table 4) [70–72]. The choice of therapy should take into consideration what was given in first line, the time that has elapsed since first-line treatment, and co-morbidities.

For treatment in third line, only erlotinib has been registered for the treatment of patients with PS 0–3 who progress after second line and who are EGFR TKI naive. This approach is based on one randomized trial where erlotinib was compared with placebo in previously treated patients. This trial included patients who had received one or two prior regimens and who were not eligible for further cytotoxic treatment. Erlotinib seems to be as beneficial in third line as in second line [70].

A retrospective study in third-line NSCLC of 700 patients found that survival and response rates decreased with each subsequent regimen [74]. These patients should be offered supportive care in addition to inclusion in clinical trials.

Recommendation 2: in second-line, chemotherapy or an EGFR TKI can be offered to patients. In third line, an EGFR TKI may be considered when patients have not received EGFR TKIs previously. Patients in good general condition in third or subsequent lines should be entered in clinical studies.

Strength of recommendation: B

Level of evidence: II

3. Should patients with symptomatic brain metastases be considered for treatment with EGFR TKIs?

During the course of the disease 20%–30% of patients will have brain metastases. After initial treatment with steroids, anticonvulsive therapy and/or radiation, patients who are stable might benefit from treatment with EGFR TKIs, albeit controversial when the mutation status is unknown. Only one single-center, single-arm study has reported response in 6 of 14 Japanese patients with brain metastases [75].

Recommendation 3: patients with symptomatic brain metastases may be considered for treatment with an EGFR TKI.

Strength of recommendation: B

Level of evidence: V

4. Is age alone an exclusion criterion for withholding treatment in second or third-line?

One recent retrospective analysis of 461 patients aged <70 versus >70 years showed no differences in median PFS (P = 0.08) and less nonsignificant toxicity in the nonelderly group for all different treatments [76].

In the study comparing pemetrexed versus docetaxel in second line, a subset analysis in the elderly population was carried out. There was no statistically significant difference in survival for patients >70 years of age (7.7 versus 8.0 months) between the two treatment arms [77]. Elderly patients had longer OS in the pemetrexed arm, but this was not statistically significant.

Recommendation 4: age alone is not considered to be an exclusion criterion for second- or third-line therapy.

Strength of recommendation: A

Level of evidence: III

5. Is second-line therapy indicated in patients with progressive disease during first-line chemotherapy?

Docetaxel [72], erlotinib [70], gefitinib (harboring an EGFR mutation) [78], or pemetrexed [71] is considered acceptable as second-line therapy for patients with NSCLC and good PS who progressed during first-line therapy.

Recommendation 5: different drugs have been registered for the treatment of patients who progress during first-line therapy.

Strength of recommendation: B

Level of evidence: I

6. Are there any selection criteria for the choice of treatment in second or third-line NSCLC with regard to histology?

Recommendation 6.1: for nonsquamous tumors, data support the use of pemetrexed or EGFR TKIs.

Strength of recommendation: B

Level of evidence: II

Recommendation 6.2: for squamous tumors, data support the use of docetaxel or EGFR TKIs.

Strength of recommendation: B

Level of evidence: II

7. Are there any selection criteria for the choice of treatment in second- or third-line NSCLC with regard to EGFR mutation status?

Recommendation 7.1: in the presence of EGFR sensitizing mutations, the use of an EGFR TKI is recommended if not received previously.

Strength of recommendation: B

Level of evidence: II

There are no convincing data to support the use of chemotherapy or an EGFR TKI in patients with PS 3 or 4. However, patients with activating EGFR mutations might benefit from EGFR TKIs. In daily practice, there are many patients in whom only supportive treatment is recommended.

Recommendation 7.2: second- or third-line therapy with an EGFR TKI might be considered even in patients with PS 3-4 harboring an activating EGFR mutation.

Strength of recommendation: C

Level of evidence: V

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appendix

Members of the panel are listed below. Prof. L. Crino, D. Gandara, and M. Reck, were unable to attend the conference, but had a major impact on the preparatory work for the conference and on the final manuscript.

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disclosure

Rafal Dziadziuszko (speakers' bureau and advisory board role—Roche, GSK, AstraZeneca); Wilfried Eberhardt (speakers' bureau and advisory board role—AstraZeneca, GSK, Merck Serono, Roche, Novartis, sanofi-aventis, ImClone, Bristol-Myers Squibb, Eli Lilly, Merck USA, Bayer Schering, OSI, Pfizer); Enriqueta Felip (speakers' bureau and advisory board role—Eli Lilly, AstraZeneca, GSK, Merck Serono, Roche, Boehringer Ingelheim); David Gandara (consulting—Amgen, AstraZeneca, Biodesix, Boehringer-Ingelheim, Bristol-Myers Squibb, ImClone, GSK, Genentech, Lilly, Merck, Novartis, Pfizer, sanofi-aventis); Cesare Gridelli (speakers' bureau and advisory board role—Roche, AstraZeneca, Eli Lilly, Merck Serono); Glenwood D Goss (research funding—Roche Canada); Pasi Jänne (consulting—Pfizer, AstraZeneca, Roche, Genentech, Boehringer Ingelheim; stock ownership—Gatekeeper Pharmaceuticals; other—royalties from patent in EGFR mutation); Tony Mok (honoraria & consulting—AstraZeneca, Roche, Pfizer; honoraria—Eli Lilly, Merck; consulting—Bristol-Myers Squibb, Eisai); Kenneth O'Byrne (advisory board role and research funding—Merck Serono, Roche, AstraZeneca); Robert Pirker (speakers' bureau and advisory board role—AstraZeneca, Eli Lilly, Merck Serono, Roche, Pierre Fabre; advisory board role—Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer); Martin Reck (speakers' bureau and consulting—Hoffmann-La Roche, Lilly, Merck, AstraZeneca; consulting—Bristol-Myers Squibb);

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