2nd ESMO Consensus Conference on Lung Cancer: non-small-cell lung cancer first-line/second and further lines of treatment in advanced disease

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To complement the existing treatment guidelines for all tumour types, ESMO organises consensus conferences to focus on specific issues in each type of tumour. The 2nd ESMO Consensus Conference on Lung Cancer was held on 11–12 May 2013 in Lugano. A total of 35 experts met to address several questions on non-small-cell lung cancer (NSCLC) in each of four areas: pathology and molecular biomarkers, first-line/second and further lines of treatment in advanced disease, early-stage disease and locally advanced disease. For each question, recommendations were made including reference to the grade of recommendation and level of evidence. This consensus paper focuses on first line/second and further lines of treatment in advanced disease.

Key words: ESMO, consensus, non-small-cell lung cancer, first line, second line, further lines

background

In 2009, ESMO decided to complement the ESMO Clinical Practice Guidelines (CPGs) with further recommendations from 'Consensus Conferences'. For lung cancer, the first meeting of this kind was held in Lugano in 2010, which resulted in the publication of two consensus manuscripts [1, 2].

The 2nd meeting, held in Lugano in May 2013, followed the same format as the first edition. Four working groups were appointed, each with 8–10 participants from several disciplines and led by a chair. A total of 35 experts were involved in this consensus process (see Panel Members listed in the Appendix). The four specific areas were:

- NSCLC pathology and molecular biomarkers,
- First line, second line and further lines of treatment in advanced NSCLC,
- Early-stage NSCLC (stages I–II),
- Locally advanced NSCLC (stage III).

Before the conference, each working group identified a number of clinically relevant questions suitable for consensus discussion and provided the available literature. At the conference, in 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 the full panel of experts and discussed, and a general consensus was reached. The Infectious Diseases Society of America grading system was used to assign levels of evidence and grades of recommendation [3].

The consensus findings of the group on first line/second and further lines of treatment in advanced disease—approved by the Consensus Conference panel of experts—is reported here.

introduction

Around 70% of NSCLC patients are diagnosed with advanced disease at diagnosis. The majority of patients diagnosed with NSCLC are unsuitable for curative treatment. Molecular characterisation has led to the definition of new subgroups, e.g. epidermal

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growth factor receptor (*EGFR*)-mutated NSCLC, anaplastic lymphoma kinase (ALK)-rearranged NSCLC that need specific treatments and strategies and are thus discussed here in specific sections. The 'all comers' section concerns all advanced NSCLC patients, whatever the tumour mutational profile, while tumours of patients without any known driver mutation are specifically addressed by the panel.

NSCLC all comers

should we start first-line chemotherapy in asymptomatic patients with advanced NSCLC at diagnosis or at occurrence of symptoms?

The survival benefit achieved by palliative chemotherapy in asymptomatic patients with metastatic NSCLC is of the same relative magnitude as in symptomatic ones [4]. Furthermore, quality of life (QoL) was either no worse or improved for those patients receiving chemotherapy in eight clinical trials, four with platinum-based and four with single-agent third-generation drugs [5]. 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 [6].

> Recommendation 1: the administration of first-line chemotherapy should be offered at diagnosis to asymptomatic patients with metastatic NSCLC.
> Strength of recommendation: B
> Level of evidence: III

should we use cisplatin or carboplatin-based chemotherapy?

Concerns about the toxic effects associated with cisplatin-based chemotherapy and the availability of platinum analogues with fewer side-effects have led to a number of randomised trials in metastatic NSCLC patients. Two meta-analyses have been published that address this issue [7, 8]. Hotta et al. [7] analysed eight trials and reported a higher response rate (RR) 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 [hazard ratio (HR) 1.106, 95% confidence interval (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. [8] observed a significant increase in response for the cisplatin-treated patients, with no significant survival difference. In a pre-specified analysis, the authors found an interaction between histology and the use of third-generation agents; patients with non-squamous tumours 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 when compared with those treated with carboplatin plus the same agent. The results were similar to the Hotta et al. [7] analysis with regard to toxic effects. Cisplatin has been evaluated at a dose of at least 75 mg/

m² in most of the pivotal studies with third-generation compounds [9, 10].

> Recommendation 2: cisplatin should be used in fit patients with performance status (PS) 0–1 who have adequate organ function.
> Strength of recommendation: B
> Level of evidence: I

> Recommendation 3: cisplatin at ≥75 mg/m² q3wks should be used with third-generation drugs.
> Strength of recommendation: B
> Level of evidence: V

is there a single platinum-based doublet standard chemotherapy in squamous and non-squamous NSCLC?

Randomised studies that have compared platinum-based doublets including third-generation drugs (vinorelbine, gemcitabine, taxanes) among themselves [10–12] 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 randomised study [12] has not been confirmed elsewhere. A phase III randomised trial comparing cisplatin/pemetrexed versus cisplatin/gemcitabine showed no difference in outcome between the two combinations with a lower haematological toxicity profile for the pemetrexed-based regimen [10]. A pre-planned subgroup analysis showed a survival advantage for cisplatin/pemetrexed when compared with cisplatin/gemcitabine in non-squamous 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 confirmatory trials have been carried out. To date, no comparative data of cisplatin/pemetrexed versus other platinum-based doublets are available.

> Recommendation 4: there is no single platinum-based doublet standard chemotherapy.
> Pemetrexed-based doublets are restricted to non-squamous NSCLC.
> Strength of recommendation: A
> Level of evidence: I

how many cycles of platinum-based chemotherapy?

Two randomised phase III trials compared three versus six cycles of chemotherapy with cisplatin/vinblastine/mitomycin C, and carboplatin/vinorelbine, respectively [13, 14]. 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. Only one randomised phase III trial formally compared four with six cycles of a third-generation regimen in Asian patients who were non-progressing after two cycles [15]. There was a benefit in time to progression (TTP) with six cycles compared with four cycles (HR 0.63, 95% CI 0.50–0.80, $P = 0.001$), but this did not translate into survival benefit (HR 1.11, 95% CI 0.83–1.51, $P = 461$). Lima's systematic review and meta-analysis indicated that more than four cycles was

associated with a longer progression-free survival (PFS) (HR 0.75, 95% CI 0.60–0.85; $P < 0.0001$) and a non-statistically significant decrease in mortality (HR 0.97, 95% CI 0.84–1.11; $P = 0.65$) but with increased haematological toxicity [16]. Soon et al. found in analysis of 13 randomised, controlled trials (3027 patients) that PFS was increased (HR 0.75, 95% CI 0.69–0.81; $P < 0.00001$) with a small increase in survival (HR 0.92, 95% CI 0.86–0.99; $P = 0.03$) [17].

Recommendation 5: four cycles of chemotherapy is standard.
Strength of recommendation: A
Level of evidence: I

Recommendation 6: continuation of a doublet regimen beyond 4 cycles may be considered in selected, non-progressing patients
Strength of recommendation: C
Level of evidence: I

is there any indication for an anti-angiogenic treatment in NSCLC?

A meta-analysis showed superiority of platinum-based chemotherapy plus bevacizumab (an anti-VEGF antibody), when compared with chemotherapy alone [18]. Studies were conducted in chemotherapy-naive patients with stage IIIB/IV non-squamous NSCLC and PS of 0–1; due to safety concerns, patients with brain metastases, gross haemoptysis and those receiving therapeutic anticoagulation were excluded. In the ECOG 4599 study, bevacizumab/carboplatin/paclitaxel versus carboplatin/paclitaxel was evaluated [19]. Overall survival (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 RRs of 35% and 15% ($P < 0.001$). A second phase III trial, enrolling outside the United States, has evaluated the combination of bevacizumab (15 or 7.5 mg/kg every 3 weeks until disease progression) with gemcitabine/cisplatin versus gemcitabine/cisplatin plus placebo [20]. 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 [21]. Two doses of bevacizumab may be delivered (7.5 or 15 mg/kg). After failure of a platinum-based chemotherapy, the benefit of bevacizumab has not been demonstrated so far [22]. Tyrosine kinase inhibitors (TKIs) of vascular endothelial growth factor receptor do not increase the efficacy of platinum-based chemotherapy. Some efficacy has been demonstrated when combined to a second-line therapy but none of these agents is currently approved in this setting [23].

Recommendation 7: when platinum-based chemotherapy is indicated, a combination with bevacizumab is a treatment option in eligible patients with non-squamous NSCLC.

In this case, carboplatin/paclitaxel is the preferred combination.
Strength of recommendation: I
Level of evidence: A

should we offer switch maintenance treatment and, if yes, to which patients?

Two phase III randomised trials addressed the issue of 'switch maintenance' therapy with pemetrexed or erlotinib after four cycles of platinum-based chemotherapy [24, 25]. Both trials reported PFS and OS advantages for maintenance therapy (pemetrexed or erlotinib) versus placebo. In the pemetrexed study, OS for non-squamous 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; $P = 0.002$). In the erlotinib versus placebo study, a survival advantage was observed (median survival of 12 versus 11 months, HR 0.81, 95% CI 0.70–0.95; $P = 0.0088$) [25].

Subgroup analyses showed a greater benefit for erlotinib in patients with stable disease after induction chemotherapy. Unfortunately, neither trial addressed the question of 'early second-line' (or 'switch maintenance') versus common second-line treatment started at disease progression.

Recommendation 8: switch maintenance with pemetrexed may be offered to patients with advanced non-squamous carcinoma (EGFR wild type [WT]) who are not treated with pemetrexed first-line treatment.
Strength of recommendation: B
Level of evidence: II

Recommendation 9: switch maintenance with erlotinib is a treatment option for patients with advanced NSCLC who have stable disease after first-line platin-based chemotherapy.
Strength of recommendation: B
Level of evidence: IV

should we offer 'continuation' maintenance treatment and, if yes, to which patients?

The PARAMOUNT phase III trial randomised 539 patients with advanced non-squamous NSCLC who did not progress on induction cisplatin–pemetrexed to either maintenance pemetrexed or best supportive care (BSC). Both PFS (HR 0.64, 95% CI 0.51–0.81) and OS (HR 0.78, 95% CI 0.64–0.96) improved significantly ($P = 0.0002$ and $P = 0.0195$, respectively) in the pemetrexed maintenance treated patients [26]. There are no other trials available with adequate power to detect PFS or OS differences that tested the continuation maintenance concept.

Recommendation 10: continuation maintenance treatment with pemetrexed may be offered to patients with advanced non-squamous NSCLC not progressing after first-line pemetrexed-cisplatin therapy.
Strength of recommendation: A
Level of evidence: I

which chemotherapy for elderly patients?

More than 50% of NSCLCs are diagnosed in patients aged >65 years with 30% being in patients >70 years. Elderly patients

are under-represented in clinical trials [27], but two main randomised 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 [5, 28]. However, retrospective analyses from large phase III randomised trials showed similar efficacy and tolerability when elderly and adult patients were compared. This issue has recently been addressed in a prospective randomised trial comparing monthly carboplatin plus weekly paclitaxel versus single-agent vinorelbine or gemcitabine, reporting an increased RR and a survival advantage for combination therapy but with increased toxicity (neutropenia and febrile neutropenia) [29]. 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 11: 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

should we re-challenge with platinum compounds and, if yes, when and in which patients?

Two identical design phase II trials randomised advanced NSCLC patients who progressed on first-line cisplatin-based chemotherapy to either pemetrexed monotherapy or the combination of carboplatin and pemetrexed [30, 31]. While neither of the trials was adequately powered to detect a survival difference, in the pooled analysis comprising 479 patients, there was no difference in OS (HR 0.90, 95% CI 0.74–1.10, $P = 0.316$). No other randomised trials are available that investigate the role of re-challenge with platinum compounds.

Recommendation 12: in advanced NSCLC patients treated with first-line cisplatin-doublet chemotherapy, there is no proven role for re-challenge with platinum compounds.
Strength of recommendation: D
Level of evidence: II

is there any indication for systemic treatment beyond second line?

In second and third line, erlotinib increases the OS by 2 months compared with placebo [32]. Systemic treatment can be safely administrated beyond second line. Sorafenib has been safely tested in third or fourth line compared with placebo in a randomised trial [33]. In a retrospective analysis of 613 consecutive patients receiving first-line therapy [34], 173 received a third line with chemotherapy (131) or a TKI (42). PS was improved in 52% and symptom relief was achieved in 92% (121 of 131 with symptoms). Predictors of the likelihood of benefiting from third-line therapy were: disease control to first- and second-line therapy (HR 0.47, 95% CI 0.33–0.67, $P = 0.001$), age <70 (HR 0.73, 95% CI 0.53–0.99, $P = 0.047$), smoking <10 pack-years (HR 0.82, 95% CI 0.57–0.93, $P = 0.036$), lack of symptoms (HR 0.75, 95% CI 0.61–0.92, $P = 0.007$), <5 kg weight loss since start of second-line therapy (HR 0.63, 95% CI 0.52–0.75, $P = 0.013$)

and no extra-thoracic spread at the initiation of the third-line treatment (HR 0.67, 95% CI 0.47–0.94, $P = 0.042$).

Recommendation 13: selected patients may benefit from third-line or fourth-line systemic treatment.
Strength of recommendation: C
Level of evidence: II

is there an optimal time and systemic treatment for bone metastasis?

Given the incidence of bone metastases in NSCLC (30%–40% of patients with NSCLC develop bone metastases), it may be reasonable to evaluate for bone disease upon disease diagnosis. Zoledronic acid (ZA) (4 mg Q4W) reduces skeletal-related events (pathologic fracture, radiation to or surgery of bone or spinal cord compression) [35]. In a subset analysis of a phase III trial, comparing denosumab (120 mg Q4W) with ZA in the treatment of bone metastases from solid tumours, denosumab was associated with improved median OS versus ZA in 702 patients with NSCLC (9.5 versus 8.0 months; HR 0.78; $P = 0.01$) [36]. Treatment with either agent should be continued for as long as it is practically feasible in the absence of any significant adverse effects.

Recommendation 14: systemic treatment may be offered upon diagnosis of bone metastases and may be continued for as long as it is practically feasible, in the absence of any significant adverse effects. Denosumab and zoledronic acid are valid options.
Strength of recommendation: B
Level of evidence: II

NSCLC without driver mutations (i.e. mutation of *EGFR* or *ALK* rearrangement)

should platinum-based chemotherapy be offered to PS 2 patients?

On the basis of current evidence, chemotherapy appears justified in patients with advanced NSCLC and a PS of 2 [37]. Subgroup analyses from several randomised trials suggest that several new-generation cytotoxic drugs are superior to BSC alone in this category of patients. Single-agent chemotherapy with these drugs (e.g. gemcitabine, vinorelbine and taxanes) represents a significant option for palliative treatment of these patients. Taking into account the superiority shown by the carboplatin/paclitaxel combination compared with paclitaxel alone in a subgroup analysis of PS 2 patients, and the efficacy and the tolerability shown by carboplatin-based doublets in three randomised phase III trials, platinum-based combinations are the preferred option for these patients [29, 38–40].

Recommendation 15: platin-based combinations are preferred over single-agent chemotherapy.
Strength of recommendation: B
Level of evidence: I

which patients should receive second- or third-line therapy?

In patients without *EGFR* mutations who have received prior chemotherapy, second- and third-line treatment might be

beneficial, when there are signs of both clinical and/or radiological progression. Various studies have reported RRs of 10% and some improvement in disease-related symptoms. Combination therapies did not show any advantage over single-agent treatment. In general, only an improvement in PFS is reported. Three phase III studies showed that in patients with a good performance status (PS 0–1): (i) docetaxel increases the OS by 9 weeks compared with BSC at the cost of some toxicity [41]; (ii) pemetrexed is as effective as docetaxel with fewer side-effects [42]; (iii) erlotinib increases the OS by 2 months compared with placebo [32].

The comparison of erlotinib with chemotherapy has only been addressed in patients who progressed during first-line therapy with no differences in PFS or OS [43]. Gefitinib was considered to be slightly superior to docetaxel in an Asian population with a high percentage of non-smokers and adenocarcinoma, but did not show an improvement in OS or QoL [44].

> Recommendation 16: second- or third-line therapy should be offered to patients with PS 0–1 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

what kind of treatment should be offered in second line?

Several agents have been registered for use in second-line (see above). The choice of therapy depends on the first-line treatment, co-morbidities and disease-free period [32, 41, 42, 45]. In third line, only erlotinib is registered for those who are EGFR TKI-naïve [32]. With every increase in line of therapy the RR and OS decrease. In fit patients, supportive care and inclusion in clinical studies should be offered.

> Recommendation 17: chemotherapy can be offered to patients who have a PS 0–1. Regardless of the WT status of the tumour a choice between docetaxel, pemetrexed or erlotinib can be made. For fit patients, chemotherapy may be more effective than erlotinib.
> Strength of recommendation: B
> Level of evidence: I

EGFR-mutated NSCLC

what is the preferred first-line treatment?

Gain-of-function mutations in the tyrosine kinase domain of the EGFR gene markedly increase sensitivity to EGFR TKIs. The most common oncogenic mutations are deletion in exon 19 (45%–50% of all somatic EGFR mutations) and a point mutation (L858R) in exon 21 (35%–45% of mutations) [46]. These mutations are predictive of clinical activity of the EGFR TKIs, which yield a superior RR and PFS as well as better QoL scores when compared with combination chemotherapy in the first-line setting, as demonstrated in several randomised trials [47–51].

> Recommendation 18: an EGFR TKI is the preferred first-line treatment in patients with EGFR-mutated NSCLC
> Strength of recommendation: A
> Level of evidence: I

what is the optimal management of brain metastases at diagnosis?

During the course of the disease, 20%–30% of patients with metastatic NSCLC will develop brain metastases [46–48]. A prospective phase II non-randomised trial demonstrated the safety of combining an EGFR TKI with whole-brain radiation therapy (WBRT). In that study, erlotinib was well-tolerated in combination with WBRT. Median survival time was 9.3 months for those with wild-type EGFR and 19.1 months for those with EGFR mutations, with a favourable objective RR (ORR) [52].

> Recommendation 19: patients with EGFR-mutated NSCLC and with brain metastases may be considered for treatment with an EGFR TKI. Radiotherapy can safely be given concomitantly to EGFR TKI.
> Strength of recommendation: C
> Level of evidence: V

what kind of treatment should be offered in second line?

In patients with EGFR mutations who had not previously received an EGFR TKI, second-line treatment with EGFR TKI has shown comparable efficacy compared with first-line treatment with an EGFR TKI [49] and a significant improvement of RR as well as PFS compared with chemotherapy [53, 54].

> Recommendation 20: the use of an EGFR TKI in second line is recommended if not received previously in patients with EGFR-mutated NSCLC.
> Strength of recommendation: A
> Level of evidence: I

In patients with EGFR mutations who had received prior treatment with an EGFR TKI, second-line treatment with platinum-based chemotherapy improved OS [47–51]. However, the decision about the appropriate time to change treatment should be made carefully because relevant impact on OS has been observed with treatment beyond progression with EGFR TKI in slowly progressing tumours [55]. Furthermore, an overlap of EGFR TKI and chemotherapy could be considered due to the risk of flare following abrupt discontinuation of EGFR TKI [56].

> Recommendation 21: the use of platinum-based chemotherapy is recommended if the patient with EGFR-mutated NSCLC has received first-line treatment with an EGFR TKI.
> Strength of recommendation: A
> Level of evidence: I

what kind of treatment should be offered in third line?

Retrospective case series with limited numbers of patients have shown that re-exposure to an EGFR TKI after prior treatment with EGFR TKI and chemotherapy may have an impact on tumour response and PFS [57]. In a randomised phase III trial, which investigated afatinib versus placebo, pre-treatment with an EGFR TKI and chemotherapy failed to demonstrate a significant improvement of OS but revealed a significant improvement of RR and PFS in favour of afatinib [58].

Recommendation 22: in patients with EGFR-mutated NSCLC who had already been treated with an EGFR TKI and chemotherapy, consider further EGFR TKIs as an option.
Strength of recommendation: C
Level of evidence: V

ALK-rearranged NSCLC

what is the preferred first-line treatment?

The ALK inhibitor crizotinib has been evaluated in second line and beyond [59]. No randomised trial has presented data of its activity in first line compared with a platinum-based therapy; therefore, the use of platinum-based chemotherapy should be preferred in this setting in fit patients. Crizotinib may, however, be an option for patients who are not suitable candidates for chemotherapy. A subgroup analysis of a prospective study has shown a superior activity of pemetrexed compared with docetaxel [59]. The roles of bevacizumab and of maintenance therapy have not been studied in this specific subgroup.

Recommendation 23: platinum-based chemotherapy should be used in fit patients with ALK-rearranged NSCLC. In combination with platinum agents, pemetrexed is to be preferred over docetaxel.
Strength of recommendation: C
Level of evidence: II

what kind of treatment should be offered in second line?

A large open-label phase III trial compared oral treatment with crizotinib (250 mg, twice daily) with intravenous chemotherapy (either pemetrexed 500 mg/m^2 or docetaxel 75 mg/m^2) in 347 patients with locally advanced or metastatic *ALK*-positive NSCLC who had received one prior platinum-based regimen [59]. Patients in the chemotherapy group who had disease progression were permitted to cross-over to crizotinib. Median PFS was 7.7 months in the crizotinib group versus 3.0 months in the chemotherapy group (HR for progression or death with crizotinib, 0.49; 95% CI 0.37–0.64; $P < 0.001$). However, an interim analysis of OS showed no significant improvement with crizotinib (HR for death in the crizotinib group, 1.02; 95% CI 0.68–1.54; $P = 0.54$). Finally, greater reductions in symptoms of lung cancer and greater improvement in global QoL were recorded with crizotinib than with chemotherapy.

Recommendation 24: crizotinib is the standard of treatment in crizotinib-naïve ALK-rearranged NSCLC patients who have received one prior platinum-based regimen.
Strength of recommendation: A
Level of evidence: I

what kind of treatment should be offered in third line?

No prospective clinical trial data exist. Having received a platinum-based regimen in the first line and crizotinib in the second, these patients are expected to receive monotherapy pemetrexed, docetaxel or erlotinib. Retrospective analysis from the PROFILE 1005 trial suggests that pemetrexed (single-agent

or combination) may be effective in ALK-positive NSCLC. Although pemetrexed ORR and TTP in the first-line setting from PROFILE 1005 concur with those in landmark trials evaluating unselected NSCLC populations; there is, however, a tendency for a higher ORR and improved PFS or TTP with second-line pemetrexed-based regimens than in the unselected populations [59]. Since the majority of *ALK*-positive patients are of adenocarcinoma histological classification, pemetrexed may be offered for patients that were not exposed to pemetrexed previously. Active second-generation ALK inhibitors are under investigation and may lead to modification of this statement in the near future.

Recommendation 25: in third line, pemetrexed may be offered for ALK-rearranged NSCLC patients who were not previously exposed to pemetrexed.
Strength of recommendation: C
Level of evidence: V

emerging biomarkers and secondary resistance

do we need to re-biopsy a patient on disease progression after a targeted treatment for a tumour with a targetable genomic driving alteration (i.e. EGFR mutation)?

Several groups have reported on the molecular findings in biopsies taken at the time of disease progression in patients treated with inhibitors of activating mutations or translocations, particularly erlotinib or gefitinib and crizotinib. Consequently, relevant information is available on the most frequent mechanisms of resistance for EGFR inhibitors (T790M mutation, and less frequently *Met* amplification or HGF over-expression, small-cell transformation and others) or crizotinib (*ALK* mutation, *ALK* amplification and others such as *EGFR* mutation) [60–64]. However, only in very few circumstances (e.g. small-cell lung cancer [SCLC] transformation), does the information obtained after re-biopsy guide treatment decisions in clinical practice at this time.

Recommendation 26: on disease progression after a targeted treatment for a tumour with a targetable genomic driving alteration (i.e. EGFR mutation), re-biopsy is not mandatory. As some patients may derive benefit in terms of therapeutic guidance from genotyping and/or phenotyping at the time of disease progression (e.g. transformation to SCLC, inclusion in a specific clinical trial, etc.), benefits and risks of this approach are to be discussed with the patient.
Strength of recommendation: C
Level of evidence: III

how should oligometastatic progression during TKI be managed?

Local therapies including radiation, radiofrequency ablation and metastasectomy are established treatment strategies in certain cancers including renal cell carcinoma, sarcoma and colorectal cancer. Several experiences also support the use of local therapies (surgery, stereotactic radiation) with continued

EGFR or ALK inhibition in cases of oligometastatic progression, resulting in minimal toxicity and in months to years of disease control [65].

Before proceeding with local therapy, patients should have a full evaluation of the extent of disease, including CNS imaging.

Recommendation 27: in case of oligometastatic progression during TKI treatment, use a local treatment (such as surgery or radiotherapy) and continue/resume TKI.
Strength of recommendation: C
Level of evidence: V

what is the optimal treatment for patients with ROS1, RET, BRAF or HER2 genomic alterations after standard treatment?

Beyond the most common driver genomic alterations with amenable specific therapies (*EGFR* mutation and *ALK* translocation), there are a number of other low prevalence (<2%) potentially actionable mutations (e.g. *BRAF*, *HER2*, etc.) or translocations (*ROS1*, *RET* etc.) identifiable in lung cancers [66]. Pre-clinical data with specific inhibitors of these targets are encouraging but clinical data are limited so far. Small phase II trials have shown encouraging RRs with dabrafenib (60% RR in 20 patients with *BRAF* V600E mutated NSCLC) [67], and crizotinib (56% RR in 30 patients with *ROS1* translocated NSCLC). Trastuzumab and dacomitinib have shown signs of activity in *HER2*-mutated NSCLC [68]. RET inhibitors are effective growth inhibitors but clinical experiences are limited to isolated cases. At present, testing for these genomic alterations, if feasible, may identify appropriate candidates for clinical trials or off-label treatment with specific inhibitors, once standard therapies have been used and patients understand and accept the limited evidence available and potential risks.

Recommendation 28: specific targeted treatments (e.g. crizotinib, vandetanib, dabrafenib, trastuzumab) should be discussed with the patient and may be considered in individual patients based on expected risk-benefit, biological plausibility, pre-clinical data and limited clinical efficacy data for authorised therapies in different indications.
Strength of recommendation: C
Level of evidence: V except ROS1 (III)

note

Levels of evidence and grades of recommendation have been applied using the system shown in Table 1. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

funding

Table 1. Levels of evidence and grades of recommendation [adapted from the Infectious Diseases Society of America–United States Public Health Service Grading System [3] (by permission of the Infectious Diseases Society of America)]

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

Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, …), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

disclosure

Merck, Boehringer Ingelheim, Desi pharma, Celgene. PM has reported Speakers' bureau: Roche. MN has reported Speakers' bureau: Roche, Lilly, Boehringer Ingelheim, Pfizer, Otsuka; Research grants: Roche, Lilly, Boehringer Ingelheim, Pfizer, Novartis. SS has reported Research grants and honoraria: Varian Medical Systems; member of phase III trial management group conducted by Lilly Oncology. CF-F has reported Research grants AstraZeneca, Eli Lilly. GR has reported Speakers' bureau/grants: Covidien. EL has reported Research support: ScreenCell and PointHope; previously Speakers' bureau for Roche and Imedex and Advisory board for Strategen, Abbott Molecular and GlaxoSmithKline; patent pending with Clearbridge BioMedics; stock in Pfizer. VW has reported Consultancy/honoraria: Lilly, Roche, Boehringer Ingelheim and AstraZeneca (for lectures); Advisory role: Lilly, Roche and AstraZeneca; currently conducting research sponsored by Merck Serono. TM has reported: Speakers' bureau and Honoraria from: AstraZeneca, Roche, Eli Lilly, Merck Serono, Eisai, Bristol-Myers Squibb, BeiGene, AVEO, Pfizer, Taiho, Boehringer Ingelheim, GlaxoSmithKline Biologicals, Clovis Oncology; Research funding from AstraZeneca. LB has reported Speakers' honoraria: Pfizer, Roche, and Abbott Molecular, Inc.; research supported by and stock held in Roche. SN, AM, KS, EFS, AA, PVS, J-YD, WW, DDR, CLP, PDL, GV and CD have declared no potential conflicts of interest. LC and KO'B have not reported any potential conflicts of interest.

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appendix

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