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SPECIAL ARTICLE

Pan-Asian adapted Clinical Practice Guidelines for the management of patients with metastatic non-small-cell lung cancer: a CSCO–ESMO initiative endorsed by JSMO, KSMO, MOS, SSO and TOS

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The most recent version of the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for the diagnosis, treatment and follow-up of metastatic non-small-cell lung cancer (NSCLC) was published in 2016. At the ESMO Asia Meeting in November 2017 it was decided by both ESMO and the Chinese Society of Clinical Oncology (CSCO) to convene a special guidelines meeting immediately after the Chinese Thoracic Oncology Group Annual Meeting 2018, in Guangzhou, China. The aim was to adapt the ESMO 2016 guidelines to take into account the ethnic differences associated with the treatment of metastatic NSCLC cancer in Asian patients. These guidelines represent the consensus opinions reached by experts in the treatment of patients with metastatic NSCLC representing the oncological societies of China (CSCO), Japan (JSMO), Korea (KSMO), Malaysia (MOS), Singapore (SSO) and Taiwan (TOS). The voting was based on scientific evidence, and was independent of both the current treatment practices and the drug availability and reimbursement situations in the six participating Asian countries. During the review process, the updated ESMO 2018 Clinical Practice Guidelines for metastatic NSCLC were released and were also considered, during the final stages of the development of the Pan-Asian adapted Clinical Practice Guidelines.

Key words: metastatic NSCLC, Pan-Asian, consensus, guidelines

Introduction

Worldwide lung cancer is the leading cause of cancer death with ~1.6 million deaths annually, exceeding those from any other malignancy [1]. Lung cancer is the most common cause of cancer death in men and the second leading cause of cancer death in women, worldwide. It is the commonest cancer in Asia and is the leading cause of death in Southern, Eastern and South Eastern Asia [2]. Fifty-one percent of the world's lung cancer cases occur in Asia [3], and 21% of cancer deaths in Asia are due to lung cancer [4]. The number of cases and the crude and standardised incidence rates (both sexes) for lung cancer in 5 Asian countries per 100 000 people in the population were as follows: for China 774 323, 47.8 and 22.8 [5]; for South Korea 22 873, 47.1 and 28.7; for Singapore 1974, 37.6 and 24.9; for Japan 94 855, 75.0 and 24.6 and for Malaysia 4403, 15.0 and 17.9 [2]. Globally cigarette smoking alone is responsible for over 80% of cases of lung cancer [6]. China is currently the largest consumer of tobacco in the world

with ~301 million smokers [7]. Approximately two-thirds of young Chinese men smoke, and estimates indicate that half of them will die as a result of smoking if they do not quit [8]. It is estimated that deaths from smoking in China will have reached around 2 million annually by 2030 and 3 million annually by 2050 [4, 9]. Lung cancer is responsible for the highest number of cancer deaths in Korea [10], and is the leading cause of cancer death in men in Japan [11]. In both countries, the rate of smoking has declined although in Korea the prevalence of lung cancer is expected to continue to rise for the next 20–30 years. In Japan, there is also the 'the Japanese Lung Cancer Smoking Paradox', where although the prevalence of cigarette smoking amongst Japanese men has been consistently higher than amongst their Western counterparts, the incidence of and mortality rates for lung cancer in Japan have been consistently lower than those for Western countries [12–14].

Interest is also increasing in understanding the aetiology of lung cancer in non-smokers [15, 16]. Worldwide, ~500 000 deaths annually are attributed to lung cancer in individuals who have never smoked [4], with the increase in the proportion of non-small-cell lung cancer (NSCLC) in individuals who have never smoked being especially marked in Asian countries [17]. A recent Korean study of 5456 cases of lung cancer in a community cancer centre showed the proportion of cases in never smokers to have increased from 19.4% between 2004 and 2008 to 25.4% between 2009 and 2012 [18].

Epidemiological data have resulted in 'non-smoking-associated lung cancer' being considered a distinct disease entity, where specific molecular and genetic differences have been identified between the lung cancers of smokers compared with those of never smokers [19]. Data from the analysis of six, large, Western population-based cohorts, showed the differences between the lung cancers in those individuals who had never smoked and those who were long-term smokers to be apparent in their differential responses to epidermal growth factor receptor (EGFR) inhibitors and in the increased prevalence of adenocarcinomas in never smokers [16]. These data also supported the observation that women are more likely than men to have non-smoking-associated lung cancer, and were consistent with the data for Asian women with lung cancer who never smoked [20].

There are no comprehensive guidelines for the treatment of metastatic NSCLC (mNSCLC) in Asia, although Japan [21] has its own lung cancer treatment guidelines and China has the Chinese Society of Clinical Oncology (CSCO) Lung Cancer Practice guidelines stratified by resource availability and treatment values [22]. A decision was taken by CSCO, the Chinese Thoracic Oncology Group (CTONG) and European Society of Medical oncology (ESMO) to develop guidelines adapted from the most recent 2016 and 2018 versions of the ESMO Clinical Practice Guidelines for the treatment and management of Asian patients with mNSCLC [23, 24]. A 1-day working meeting was held on the 5 August 2018 in Guangzhou, China, for this purpose.

Methodology

This Pan-Asian adaptation of the ESMO guidelines was prepared in accordance with the processes and format developed for the preparation of the first Pan-Asian adapted ESMO guidelines for the management of patients with metastatic colorectal cancer [25].

Composition of expert panel

The international panel of experts was selected according to their demonstrable knowledge of the field of NSCLC patient treatment and management in terms of publications and/or their participation in the development of national or international treatment guidelines. More specifically this included two expert members of the CSCO, two expert members from the ESMO and two experts each from the oncological societies of Japan (JSMO), Korea, (KMSO), Malaysia (MOS), Singapore (SSO) and Taiwan (TOS). Only Asian expert members were allowed to vote on the recommendations.

Provisional statements

A set of preformulated topics and 24 recommendations for the treatment of mNSCLC, from those in the latest ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of mNSCLC [23], were circulated, before the meeting, to each of the 12 Asian experts representing the six Asian oncological societies to gather their comments and input on each of the recommendations with specific emphasis being placed on the current practice in their countries and the data available from studies in Asian patients. The Asian experts were specifically asked 'Is this recommendation adaptable for use in your country?' The 12 experts were also asked to provide details of the reasoning behind their responses and the relevant references to support their decisions. In the case of the present guidelines, a second survey was circulated shortly before the face-to-face meeting to ask the opinion of the experts on the updates to the recent ESMO Clinical Practice Guidelines for diagnosis treatment and follow-up submitted to Annals of Oncology July 2018 [24].

Voting process

A modified Delphi process was used to develop each individual statement before the final discussion and final voting process at the face-to-face working meeting in Guangzhou. The 12 Asian experts were asked to vote based on the evidence available, on a scale of A to E, where A = accept completely; B = accept with some reservation; C = accept with major reservation; D = reject with some reservation and E = reject completely (Table 1). An adapted version of the 'Infectious Diseases Society of America-United States Public Health Service Grading System' [26] was used to define the level of evidence and strength (grade) of each recommendation proposed by the group, as for all of the ESMO Consensus and ESMO Clinical Practice Guidelines (Table 1) and are given in the text in square brackets after each recommendation together with details of the levels of agreement. Most statements on the level of agreement were based on peer-reviewed manuscript data or peer-reviewed abstract data, although statements made based on expert opinion were also considered to be justified standard clinical practice by the experts and the CSCO and ESMO faculty. Whenever possible, the score of the ESMO Magnitude of Clinical Benefit Scale (MCBS) was provided for the most recently approved drugs (all MCBS scores are available in

Table 1. Voting on levels of agreement and definition of levels of evidence and grades of recommendation used by the panel of Asian experts in evaluating the ESMO consensus guidelines for the management of patients with metastatic non-small-cell lung cancer of Asian ethnicity

Voting on level of agreement	
A	Accept completely
B	Accept with some reservation
C	Accept with major reservation
D	Reject with some reservation
E	Reject completely
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 (low methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies of 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 of the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

Open Access at https://www.esmo.org/score/cards). The Asian experts were asked to make their decisions based on the available 'scientific evidence' rather than on some of the current practices in their respective countries, and also, independently of the approval and reimbursement status of certain drugs in their individual countries. The two experts, from ESMO (JYD and DP) were present at the face-to-face meeting in Guangzhou, China to offer their expert opinion if and as required.

Final consensus statements

A consensus was considered to have been achieved when ≥80% of experts voted to accept completely or accept with reservation a specific recommendation. A recommendation was considered to have been rejected when >80% of the voting members indicated 'reject completely' or 'reject with reservation'. For recommendations where a consensus was not reached initially the panel of Asian experts was invited to discuss and modify the recommendation(s) at the face-to-face meeting and a second round of voting was conducted. If still no consensus could be reached, the recommendation could be modified one more time, and a third and last vote was conducted to determine the definitive acceptance or rejection of a recommendation.

Results

Before the face-to-face meeting, the 12 experts representing the oncological societies of the 6 Asian countries and associated regions (China, Japan, Korea, Malaysia, Singapore and Taiwan) reported on the applicability of 137 recommendations from the 2016 ESMO NSCLC Clinical Practice Guidelines [23] and subsequently the updated ESMO 2018 Clinical Practice Guidelines for the diagnosis treatment and follow-up of mNSCLC [24]. These were in the 24 categories:

1. Diagnosis (1a–f)
2. Pathology/molecular biology (2a–k)
3. Staging and risk assessment (3a–m)
4. Management of advanced metastatic disease (4a–c)
5. First-line treatment of NSCLC without a druggable oncogene driver (5a–n)
6. Maintenance (6a–d)
7. Patients with a performance status (PS) of 2 and beyond (7a–d)
8. Elderly patients (8a–c)
9. Second-line treatment in patients with mNSCLC without a druggable oncogene driver (9a–k)
10. First-line treatment of EGFR-mutated NSCLC (10a–g)
11. Second-line treatment of EGFR-mutated NSCLC (11a–g)
12. First-line treatment of patients with ALK-rearranged NSCLC (12a–d)
13. Second-line treatment of patients with ALK-rearranged NSCLC (13a–f)
14. Patients with *ROS1*-rearranged mNSCLC (14a–d)
15. Patients with *BRA*F-mutated NSCLC (15a and b)
16. Patients with NSCLC and other druggable oncogene drivers (16a–g)
17. Role of radiotherapy in stage IV NSCLC (17a–e)
18. Brain metastases (18a–k)
19. LM carcinomatosis (19a, b and c)
20. Treatment of oligometastatic disease (OMD) (20a–e)
21. Bone metastases (21a, b and c)
22. The role of minimally invasive procedures in patients with stage IV NSCLC (22a, b and c)
23. Palliative care in patients with stage IV NSCLC
24. Follow-up in patients with stage IV NSCLC,

and for the purposes of the evaluation and voting process were numbered recommendations 1–24 with the subcategories assigned a letter code (a, b, c etc.). An unqualified response of YES in the pre-meeting surveys equated with 'accept completely' in the final voting, i.e. A = 100%. Following the pre-meeting surveys agreement was not reached between the six Asian countries on recommendations 2f and g, 3c, e, f, g and l, 5c and n, 6d, 7d, 9d, e, j and k, 10d, 11e and g, 13d and f, 18a and i, 19c and 20e (supplementary Table S1–S12, available at *Annals of Oncology* online). At the face-to-face meeting in Guangzhou, the nine Asian experts in the treatment of NSCLC present (two Japanese experts and one Malaysian expert were unable to attend) were asked to

vote again on these recommendations. Voting on the other recommendations and subcategories was not necessary as there was complete consensus, with all countries voting 'yes' in response to the question 'Is this recommendation adaptable for use in your country?' i.e. accepting completely [A = 100%]. The final levels of agreement and levels of evidence and strength of support recorded for each ESMO recommendation by the Asian panel members are provided in the text below, for each of the 24 recommendations and their sub-categories, as appropriate and in supplementary Table S13, available at *Annals of Oncology* online. Where changes to the original text have been made, including the addition of new subcategories and in some cases the revision of an existing recommendation, these are emphasised in bold both in the main text of the manuscript and in Table 2, and reference made to the change in the text as appropriate. In parallel, the final voting patterns of the representatives of each of the participating regions for the ESMO recommendations at the face-to-face meeting in Guangzhou are presented in supplementary Table S13, available at *Annals of Oncology* online.

Recommendation 1: diagnosis

1a. Bronchoscopy is a technique ideally suited to central lesions and can be used with bronchial washing, brushing, and transbronchial needle biopsy [A = 100% and I, A].
1b. Endobronchial ultrasound (EBUS) and/or endoscopic US allows evaluation of regional lymph nodes [A = 100% and I, A].
1c. Transthoracic fine needle aspiration and/or core biopsy, i.e. passing a needle through the parenchyma under imaging guidance (typically CT), is indicated in the case of mid to peripheral lesions [A = 100% and I, A].
1d. In the presence of a pleural effusion, thoracentesis could represent both a diagnostic tool and a palliative treatment [A = 100% and I, A].
1e. More invasive, surgical approaches (mediastinoscopy, mediastinotomy, thoracoscopy, etc.) in the diagnostic work-up can be considered when the previously described techniques cannot allow for an accurate diagnosis [A = 100% and I, A].
1f. With systematic collaboration and constant communication between pathologists and procedure performers, diagnostic yields will be significantly greater than with blind biopsies [A = 100% and I, A].

All 12 Asian experts agreed with and accepted completely [A = 100%] 'recommendations 1a–f' above taken from the ESMO 2018 guidelines for mNSCLC [24]. The evidence from Western studies shows that multidisciplinary teams improve the management and clinical outcomes of patients with NSCLC [27–30]. Most patients with suspected lung cancer require a tissue-based diagnosis often involving challenging tissue sampling. Tissue sampling provides for the confirmation of the initial diagnosis [e.g. non-squamous cell carcinoma (NSCC) versus squamous cell carcinoma (SCC)], facilitates molecular testing and informs the individual patient treatment decisions and care.

As described previously [24], bronchoscopy is ideally suited to large, central lesions and can be used for bronchial washing, brushing, and transbronchial needle biopsy with the advantage of minimal morbidity [31–33]. Bronchoscopic airway visualisation combined with ultrasound, EBUS, can also be used to biopsy large, centrally located lesions [34, 35], diagnose and stage lung cancer, and to determine if the disease has spread to e.g. the lymph nodes. EBUS-guided transbronchial needle aspiration (TBNA) is reported to be at least as accurate as mediastinoscopy but less invasive [36]. Cytological specimens obtained by EBUS–TBNA have been shown to be suitable for molecular testing [37–40]. For peripheral lesions, transthoracic percutaneous fine needle aspiration and/or core biopsy, under imaging guidance (typically computed tomography [CT]) is proposed/recommended [41], and is associated with high diagnostic accuracy [32, 42–45], although there is a risk of pneumothorax [44, 45]. In cases of pleural effusion, thoracentesis can be used for both diagnosis and palliative treatment. If the fluid cytology results are negative, an image-guided pleural biopsy or surgical thoracoscopy should be carried out. Where the techniques described above are unable to provide an accurate diagnosis more invasive, surgical approaches should be considered.

Recommendation 2: pathology/molecular biology

2a. Adequate tissue material for histological diagnosis and molecular testing should be obtained to allow for individual treatment decisions [A = 100%].
2b. Pathological diagnosis should be made according to the 2015 WHO classification of lung tumours [A=100%].
2c. Specific subtyping of all NSCLCs is necessary for therapeutic decision making and should be carried out wherever possible. IHC stains should be used to reduce the NSCLC-NOS rate to fewer than 10% of cases diagnosed [A=100% and IV, A].
2d. EGFR mutation status should be systematically analysed in advanced NSCC [A=100% and I, A]. Test methodology should have adequate coverage of mutations in exons 18–21, including those associated with resistance to some therapies [A=100% and III, B]. At a minimum, when resources or material are limited, the most common activating mutations (exon 19 deletion, exon 21 L858R point mutation) should be determined [A=100% and I, A].
2d-1 ***The availability of a tyrosine kinase inhibitor (TKI) effective against T790M-mutant recurrent disease makes T790M testing mandatory on the occurrence of first-/second-generation EGFR-TKI resistance.***
2e. Testing for ALK rearrangement should be systematically carried out in advanced NSCC [A=100% and I, A].
2f. Detection of the ALK translocation by fluorescent in situ hybridisation (FISH) remains a standard, but IHC with high-performance ALK antibodies and validated assays may be used for screening [A=100% and III, A] and have recently been accepted as an equivalent alternative to FISH for ALK testing. and 1, A]
2g. Testing for ROS1 rearrangement should be systematically carried out in advanced NSCC [A = 100% and II, A]. Detection of the ROS1 translocation by FISH remains a standard. ***A validated RT-PCR test may be used as an alternative****. IHC may be used as a screening approach [A=100% and IV, A].*

Table 2. Summary of final recommendations by Asian experts

Recommendation 1: diagnosis

1a. Bronchoscopy is a technique ideally suited to central lesions and can be used with bronchial washing, brushing, and transbronchial needle biopsy [A=100% and I, A].

1b. Endobronchial ultrasound (EBUS) and/or endoscopic US allows evaluation of regional lymph nodes [A=100% and I, A].

1c. Transthoracic fine needle aspiration and/or core biopsy, or passing a needle through the parenchyma under imaging guidance (typically CT), is indicated in the case of mid to peripheral lesions [A=100% and I, A].

1d. In presence of a pleural effusion, thoracentesis could represent both a diagnostic tool and a palliative treatment [A=100% and I, A].

1e. More invasive, surgical approaches (mediastinoscopy, mediastinotomy, thoracoscopy, etc.) in the diagnostic workup can be considered when the previously described techniques cannot allow for an accurate diagnosis [A=100% and I, A].

1f. With systematic collaboration and constant communication between pathologists and procedure performers, diagnostic yields will be significantly greater than with blind biopsies [A=100% and I, A].

Recommendation 2: pathology/molecular biology

2a. Adequate tissue material for histological diagnosis and molecular testing should be obtained to allow for individual treatment decisions [A=100%].

2b. Pathological diagnosis should be made according to the 2015 WHO classification of lung tumours [A=100%].

2c. Specific subtyping of all NSCLCs is necessary for therapeutic decision making and should be carried out wherever possible. IHC stains should be used to reduce the NSCLC-NOS rate to fewer than 10% of cases diagnosed [A=100% and 1V, A].

2d. *EGFR* mutation status should be systematically analysed in advanced NSCC [A=100% and I, A]. Test methodology should have adequate coverage of mutations in exons 18–21, including those associated with resistance to some therapies [A=100% and III, B]. At a minimum, when resources or material are limited, the most common activating mutations (exon 19 deletion, exon 21 *L858R* point mutation) should be determined [A=100% and I, A].

2d-**1 The availability of a TKI effective against *T790M*-mutant recurrent disease makes *T790M* testing mandatory on the occurrence of first-/second-generation EGFR-TKI resistance** (added retrospectively).

2e. Testing for *ALK* rearrangement should be systematically carried out in advanced NSCC [A=100% and I, A].

2f. Detection of the *ALK* translocation by FISH remains a standard, but IHC with high-performance ALK antibodies and validated assays may be used for screening [A=100% and III, A] and have recently been accepted as an equivalent alternative to FISH for ALK testing.

2g. Testing for *ROS1* rearrangement should be systematically carried out in advanced NSCC [A=100% and II, A]. Detection of the *ROS1* translocation by FISH remains a standard. **A validated RT-PCR test may be used as an alternative.** IHC may be used as a screening approach [A=100% and IV, A].

2h. *BRAF V600* mutation status should be systematically analysed in advanced NSCC for the prescription of BRAF/MEK inhibitors [A=100% and II, A].

2i. Molecular *EGFR* and *ALK* testing is not recommended in patients with a confident diagnosis of SCC, except in unusual cases, e.g. never/former light smokers or long-time ex-smoker [A=100% and IV, A].

2j. If available, multiplex platforms for molecular testing are preferable [A=100% and III, A].

2k. PD-L1 IHC should be systematically determined in advanced NSCLC. Testing is required for pembrolizumab therapy **in all lines of treatment** and may also be informative when nivolumab or atezolizumab are used **as monotherapy in the second-line setting** [A=100% and I, A].

Recommendation 3: staging and risk assessment

3a. A complete history including a precise smoking history and comorbidities, weight loss, PS and physical examination must be recorded [A=100%].

3b. Laboratory standard tests including routine haematology, renal and hepatic functions and bone biochemistry tests are required [A=100%].

3c. Routine use of serum tumour markers, such as CEA, is not recommended [A=100% and IV, B].

3d. A contrast-enhanced CT scan of the chest and upper abdomen including the liver and the adrenal glands should be carried out at diagnosis [A=100%].

3e. Imaging of CNS should be considered at diagnosis for all patients with metastatic disease [A=100% and IV, C] and is required for patients with neurological symptoms or signs [A=100% and IV, A]. MRI is more sensitive than a CT scan [A=100% and IV, B].

3f. If bone metastases are clinically suspected, bone imaging is required [A=100% and IV, B].

3g. Bone scan or PET, ideally coupled with CT, can be used for the detection of bone metastasis [A=100% and IV, B].

3h. NSCLC is staged according to the AJCC/UICC system (8th edition) and is grouped into the stage categories shown in Tables 3 and 4.

3i. 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 [A=100% and IV, A].

3j. Response evaluation is recommended after 6–9 weeks of systemic therapy using the same radiographic investigation that initially demonstrated tumour lesions [A=100% and IV, B].

3k. Follow-up with PET is not routinely recommended, due to its high sensitivity and relatively low specificity [A=100% and IV, C].

3l. Measurements and response assessment should follow RECIST criteria v1.1 [B=100% and IV, A]. However, the adequacy of RECIST in evaluating the response to targeted therapy like EGFR or ALK TKI in respective genetically-driven NSCLC is debatable [B=100% and IV, B].

3m. In the case of immune checkpoint inhibitor therapy, RECIST criteria should be used, although irRECIST, iRECIST, imRECIST may have a role in the overall assessment of therapy [A=100% and IV, B].

Continued

Table 2. *Continued*

Recommendation 4: management of advanced metastatic disease

4a. The treatment strategy should consider the histology, molecular pathology, age, PS, comorbidities and the patient's preferences [A=100%].

4b. Systemic therapy should be offered to all stage IV patients with PS 0–2 [A=100% and I, A].

4c. In any stage of NSCLC, smoking cessation should be highly encouraged, because it improves the outcome [A=100% and II, A].

Recommendation 5: first-line treatment of NSCLC without a druggable oncogene driver

5a. Chemotherapy should be considered for all stage IV NSCLC patients with *EGFR*- and *ALK*-negative disease, in the case of a contraindication to immunotherapy, and who are without major comorbidities and PS 0–2 [A=100% and I, A].

5b. Single agent pembrolizumab should be considered in eligible patients with PS 0–1, *EGFR*- and *ALK*-negative NSCLC and a tumour with a TPS of PD-L1 ≥50% [A=100% and I, A]. Chemotherapy should be provided in the case of contraindication to pembrolizumab.

5c. Pembrolizumab plus chemotherapy (with pemetrexed plus platinum) should be considered in patients with PS 0–1, non-squamous NSCLC without *EGFR* or *ALK* mutations, in absence of contraindications to the use of immunotherapy, if approved and available [A=17%, B=83% and I, A] (Figure 2). The survival benefit for pembrolizumab-combination therapy is observed across all categories of PD-L1 expression, but diminished among PD-L1-negative patients and it is unclear if chemotherapy adds a benefit in patients with PD-L1 ≥50%.

5d. Combination of atezolizumab and bevacizumab with carboplatin and paclitaxel should be considered as a therapeutic option in patients with PS 0–1 and metastatic non-squamous NSCLC, in absence of contraindications to use of immunotherapy, if approved and available [A=100% and I, A]. Combination of pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel should be considered as a standard choice in patients with PS 0–1 and metastatic squamous NSCLC in absence of contraindications to the use of immunotherapy, if approved and available [A=100% and I, A] (Figure 1).

5e. Association of atezolizumab with carboplatin and nab-paclitaxel represent an option in patients with PS 0–1 and metastatic squamous NSCLC in the absence of contraindications to use of immunotherapy, if approved and available [A=83%, B=17% and I, B] (Figure 1).

5f. Nivolumab plus ipilimumab represents a treatment option regimen for patients with PS 0–1, EGFR and ALK negative NSCLC with a high TMB, regardless of tumour PD-L1 expression level, if approved and available [A=83%, B=17% and I, A].

5g. Platinum-based doublets are the recommended chemotherapy option in all stage IV NSCLC patients with no contraindications to platinum compounds [A=100% and I, A].

5h. Four cycles of platinum-based doublets followed by less toxic maintenance monotherapy [I, A], or four, up to a maximum of six cycles [A=100% and IV, B], in patients not suitable for maintenance monotherapy, are currently recommended.

5i. The nab-paclitaxel regimen could be considered a chemotherapeutic option in advanced NSCLC patients, particularly in patients with greater risk of neurotoxicity, pre-existing hypersensitivity to paclitaxel or contraindications for standard paclitaxel premedication [A=100% and I, B].

5j. Platinum-based doublets with a third-generation cytotoxic agent (gemcitabine, vinorelbine, taxanes) are recommended in advanced SCC patients [A=100% and I, A].

5k. Pemetrexed is preferred to gemcitabine or docetaxel in patients with non-squamous tumours [II, A]. Pemetrexed use is restricted to NSCC in any line of treatment [A=100% and I, A].

5l. Necitumumab/gemcitabine/cisplatin represents a treatment option for advanced SCC expressing EGFR by IHC [A=83%, B=17% and II, C].

5m. Bevacizumab improves overall survival when combined with paclitaxel/carboplatin regimens in patients with NSCC and PS 0–1, and, therefore, may be offered in the absence of contraindications (bevacizumab should be given until progression or unacceptable toxicity) [A=100% and I, A].

5n. Bevacizumab might be considered with platinum-based regimens beyond paclitaxel/carboplatin in the absence of contraindications [A=17%, C=83% and III, B].

Recommendation 6: maintenance

6a. Maintenance chemotherapy should be offered only to patients with PS 0–1 after first-line chemotherapy. Decisions about maintenance should consider histology, response to platinum-doublet chemotherapy and remaining toxicity after first-line chemotherapy, PS and patient's preference [A=83%; C=17%].

6b. In patients with NSCC and PS 0–1, pemetrexed switch maintenance should be considered in patients having disease control following four cycles of non-pemetrexed containing platinum-based chemotherapy [A=100% and I, B]. Pemetrexed continuation maintenance should be considered in patients having disease control following four cycles of cisplatin-pemetrexed [A=100% and I, A], **or pemetrexed switch maintenance plus or minus bevacizumab**.

6c. Continuation maintenance with gemcitabine is an option in NSCLC patients treated with four cycles of cisplatin-gemcitabine [A=100% and I, C].

6d. Maintenance treatment with erlotinib is only recommended for NSCC patients with an *EGFR* sensitising mutation [A=100% and II, B].

Recommendation 7: patients with a PS of 2 and beyond

7a. In patients with PS 2, chemotherapy compared with BSC prolongs survival and improves QoL [A=100% and I, A].

7b. Carboplatin-based combination therapy should be considered in eligible PS 2 patients [A=100% and II, A].

7c. Single-agent chemotherapy with gemcitabine, vinorelbine, docetaxel [A=100% and I, B] or pemetrexed (restricted to NSCC) [A=100% and III, B] is an alternative treatment option.

7d. Poor PS (3–4) patients should be treated with BSC only [A=100% and II, B], unless a molecularly targetable alteration is identified where treatment has minimal toxicity.

Continued

Table 2. *Continued*

Recommendation 8: elderly patients

8a. Immunotherapy should be considered according to standard recommendations in elderly patients [A=100% and IV, A].

8b. Carboplatin-based doublet chemotherapy should be provided to eligible patients aged ≥70 years with PS 0–2 and with adequate organ function [A=100% and I, A].

8c. For those patients not eligible for doublet chemotherapy, single-agent chemotherapy remains the standard of care [A=100% and I, B].

Recommendation 9: second-line treatment of patients with mNSCLC without a druggable oncogene driver

9a. Patients clinically or radiologically progressing after first-line therapy with a PS of 0–2 should be offered second-line therapy [A=100% and I, A].

9b. PD-L1 testing is routinely recommended at diagnosis [A=100% and I, A] to inform the use of pembrolizumab in the first-line setting or second-line setting.

9c. For patients with progression after first-line immunotherapy with pembrolizumab, platinum-based chemotherapy is recommended as the second-line treatment option [A=100% and V, B].

9d. There is a general trend across each of the phase III studies in second-line (nivolumab, pembrolizumab and atezolizumab versus docetaxel) for enriched efficacy of anti-PD1/PDL1 agents in patients with higher PD-L1 expression compared with those with no/less PD-L1 expression. However, unselected patients may still have improved survival and tolerability with anti-PD1/PDL1 agents compared with docetaxel [A=100% and I, A].

9e. PD-L1 and PD-1 inhibitors (nivolumab, pembrolizumab, and atezolizumab) are the treatment of choice for most patients with advanced, previously treated, PD-L1 **inhibitor**-naive NSCLC, irrespective of PD-L1 expression [A=100% and I, A].

9f. In patients not suitable for immunotherapy, second-line chemotherapy is recommended. Comparable options as second-line therapy consist of pemetrexed, for NSCC only, or docetaxel, with a more favourable tolerability profile for pemetrexed [A=100% and I, B].

9g. Treatment may be prolonged if disease is controlled and toxicity acceptable [A=100% and II, B].

9h. Nintedanib/docetaxel is a treatment option in patients with adenocarcinoma, especially in those progressing within 9 months from the start of first-line chemotherapy, *with PS 0–2* [A=83%, B=17% and II, B].

9i. Ramucirumab/docetaxel is a treatment option in patients with NSCLC progressing after first-line chemotherapy with PS 0–2 [A=100% and I, B].

9j. Erlotinib represents a potential second/third-line treatment option in particular for patients not suitable for immunotherapy or second-line chemotherapy in unknown *EGFR* status or *EGFR* WT tumours [D=66%, E=34% and II, C].

9k. In **platinum-pretreated** patients with SCC unfit for chemotherapy or immunotherapy, afatinib is a potential option in patients with unknown *EGFR* status or *EGFR* WT patients with PS 0–2 [C=100% and I, C].

Recommendation 10: first-line treatment of EGFR-mutated NSCLC

10a. Patients with a tumour with a sensitising *EGFR* mutation should receive first-line EGFR TKIs including erlotinib, gefitinib or afatinib [I, A]. None of the three EGFR TKIs is consensually considered as a preferred option [III, C]. Dacomitinib will be added to the list when the drug is approved by regulatory agencies, the United States FDA and the EMA [A=100% and I, A].

10b. First-line osimertinib is now considered one of the options for patients with a tumour with sensitising *EGFR* mutations [A=100% and I, A].

10c. All patients should be considered for EGFR TKIs irrespective of clinical parameters, including PS, gender, tobacco exposure, histology and line of therapy [A=100% and I, A].

10d. Erlotinib and bevacizumab represent a front-line treatment option in patients with *EGFR*-mutated tumour [A=100% and II, A].

10e. Addition of carboplatin and pemetrexed to gefitinib represents a first-line option in patients with *EGFR*-mutated tumour [A=100% and I, B].

10f. Patients who have radiological progression with ongoing clinical benefit may continue with EGFR TKI [A=100% and II, A].

10g. In *EGFR*-mutated NSCLC patients with localised distant progression and ongoing systemic control, continuation of treatment with EGFR TKI in combination with local treatment of progressing metastatic sites may be considered [A=100% and III, B].

Recommendation 11: second-line treatment of EGFR-mutated NSCLC

11a. EGFR TKI should be stopped at the time when a patient starts chemotherapy for treatment of TKI resistance [A=100% and I, A].

11b. All tumours with clinical evidence of EGFR TKI resistance, not previously treated with osimertinib, should be tested for the presence of the *EGFR* exon 20 *T790M* mutation [A=100% and I, A].

11c. Liquid biopsy can be used as the initial test for detection of a *T790M* mutation, and if tests are negative, re-biopsy should be attempted if feasible [A=100% and II, A].

11d. Osimertinib is the standard therapy for patients whose tumours have tested positive for *T790M* either in liquid biopsy or re-biopsy, if not received previously and may be considered a therapeutic option [A=100% and I, A].

11e. In *EGFR*-mutated NSCLC with CNS disease, osimertinib is highly active and may be considered as a therapeutic option [A=100%].

11f. Platinum-based doublet is the standard therapy for patients whose tumour is tested *T790M* negative in either re-biopsy or in liquid biopsy (only when re-biopsy is not feasible) [A=100% and I, A].

11g. Combination of atezolizumab and bevacizumab with carboplatin and paclitaxel **might** be considered as a therapeutic option in patients with *EGFR*-mutated tumours, PS 0–1, in absence of contraindications to use of immunotherapy after targeted therapies has been exploited [A=100% and **IV, C**, after discussion].

Continued

Table 2. *Continued*

Recommendation 12: first-line treatment of ALK-rearranged NSCLC

12a. Patients with *ALK*-rearranged NSCLC should receive first-line treatment with an ALK TKI, including crizotinib [A=100% and I, A], ceritinib [A=100% and I, B] and alectinib [A=100% and I, A].

12b. Alectinib is associated with a longer PFS and lower toxicity than crizotinib and showed activity against CNS disease in previously untreated patients with *ALK*-positive NSCLC [A=100% and I, A].

12c. In patients with CNS involvement front-line use of ALK TKIs is effective, and alectinib [III, A] or ceritinib [IV, B] are recommended [A=100%]. **Ceritinib represents a better treatment strategy than chemotherapy [I, B] and presumably crizotinib [IV, B]; alectinib represents a better treatment option than crizotinib [I, A]; brigatinib represents a better treatment option than crizotinib [I, B].**

12d. In *ALK*-rearranged NSCLC patients with localised distant progression and ongoing systemic control, continuation of treatment with ALK TKI in combination with local treatment of the progressing metastatic sites may be considered [A=100% and III, B].

Recommendation 13: second-line treatment of ALK-rearranged NSCLC

13a. Ceritinib and alectinib are recommended in patients with *ALK*-positive advanced NSCLC who progress on treatment with or are intolerant to crizotinib [A=100% and I, A].

13b. In patients with *ALK*-positive NSCLC progressing on crizotinib with CNS progression, treatment should be a next-generation ALK TKI such as alectinib or ceritinib [A=100% and I, A].

13c. In patients who progress after a second-generation ALK TKI, the next-generation ALK inhibitors such as brigatinib or lorlatinib are an option if available [A=100% and III, C]. If not, pemetrexed and cisplatin should be considered.

13d. Assessment of the molecular mechanisms of resistance could also have an impact in the decision-making process [A=100% after discussion].

13e. The optimal sequencing of ALK-targeted agents remains to be established.

13f. Combination of atezolizumab and bevacizumab with carboplatin and paclitaxel **might** be considered as a therapeutic option in patients with *ALK*-mutated tumour, PS 0–1, in the absence of contraindications to use of immunotherapy after targeted therapies has been exploited [A=100% and **V, C** after discussion].

Recommendation 14: patients with ROS1-rearranged NSCLC

14a. Crizotinib is recommended in the first-line setting in patients with stage IV NSCLC with *ROS1* rearrangement, because it has shown results indicating improved response rate and duration of response [A=100% and III, A].

14b. In patients with *ROS1*-positive NSCLC, who have not received crizotinib in the first-line setting, single-agent crizotinib may be offered as second-line therapy [A=100% and III, A].

14c. Ceritinib might be considered in crizotinib-naive patients but is currently not approved by the EMA [A=100% and III, C].

14d. If patients have received crizotinib in the first-line setting, then they may be offered platinum-based chemotherapy therapy in the second-line setting [A=100% and IV, A].

Recommendation 15: patients with BRAF-mutated NSCLC

15a. Patients with stage IV NSCLC with a *BRAF V600* mutation should be exposed in first or second line to BRAF/MEK inhibition using dabrafenib/trametinib [A=100% and III, A].

15b. If patients have received BRAF/MEK inhibition in the first-line setting, then they may be offered platinum-based chemotherapy in the second-line setting [A=100% and IV, A].

Recommendation 16: patients with NSCLC with other druggable oncogene drivers

16a. Phase II trials suggest a clinically meaningful benefit using multitargeted agents with anti-RET activity in patients with *RET* rearranged NSCLC. However, these studies are small and subject to selection bias and results on benefit heterogeneous [A=100% and III, C].

16b. Targeting RET is not currently routinely recommended and recruitment into open trials is encouraged [A=100% and III, C].

16c. Targeting *MET* amplification is not currently routinely recommended and recruitment into open trials is encouraged [A=100% and III, C].

16d. Targeting *MET* exon14 variants (while evidence of benefit is stronger) is not currently routinely recommended and recruitment into open trials is encouraged [A=100% and III, C].

16e. Crizotinib has demonstrated potential clinical efficacy for *MET* exon14 variant NSCLC that needs to be confirmed [A=100% and III, C].

16f. Given the paucity of robust data, targeting *HER2* dysregulation is not currently recommended and recruitment into open trials is encouraged [A=100% and III, C].

16g. Targeting *NRTK* fusions is not currently recommended and recruitment into open trials is encouraged [A=100% and III, C].

Recommendation 17: role of radiation therapy (RT) in stage IV NSCLC

17a. RT can achieve symptom control for a variety of clinical scenarios including haemoptysis, symptomatic airway obstruction, painful chest wall disease and bone metastasis, superior vena cava syndrome, soft tissue or neural invasion [A=100% and II, B].

17b. Administration of high dose RT does not result in greater levels of palliation [A=100% and II, B].

17c. EBRT alone is more effective for palliation than EBB alone [A=100% and II, B].

Continued

Table 2. *Continued*

17d. For patients previously treated by EBRT who are symptomatic from recurrent endobronchial central obstruction, EBB may be considered in selected cases [A=100% and III, C].
17e. Neurological symptoms from spinal compression can be relieved by early RT [A=100% and II, B].

Recommendation 18: brain metastases
18a. Whole brain radiation therapy (WBRT) should not be offered in RPA class III patients in view of the dismal prognosis [I, E]; only BSC is recommended [A=100%].
18b. WBRT can be considered in selected patients, contingent on prognostic factors of better survival [A=100% and II, C].
18c. Hippocampus avoidance WBRT is not currently recommended as a standard treatment [A=100% and III, C].
18d. In the case of a single metastasis, stereotactic radiation surgery (SRS) alone, or resection, is the recommended treatment in patients with RPA class I–II [A=100% and III, B].
18e. Postoperative WBRT or SRS is recommended after surgical resection [I, A].
18f. SRS alone, without WBRT but with close MRI brain imaging follow-up, is an alternative strategy [A=100% and III, B].
18g. For two to four metastases, SRS alone is recommended in RPA class I–II patients [III, B].
18h. For symptomatic brain metastases and/or oedema, dexamethasone or an equivalent dose of another corticosteroid is recommended [A=100% and III, A].
18i. In patients with detected asymptomatic CNS metastases at presentation, systemic therapy with deferred RT **can** be considered due to similar intracranial and extracranial response [B=83%, C=17% and II, **C**].
18j. In patients with a druggable oncogene driver (e.g. EGFR, ALK) and clinically asymptomatic brain metastases, TKIs may restore control of brain disease and delay cranial RT [A=100% and II, B].
18k. In patients undergoing immune-checkpoint inhibitor therapy, limited data support safety in patients with small volume untreated CNS metastases [A=100% and III, B].

Recommendation 19: LM carcinomatosis
19a. A high index of suspicion should be borne for leptomeningeal involvement especially in patients with druggable oncogenic drivers having TKI treatment [V]. CSF sampling is diagnostic of LMD but limited by low sensitivity, albeit with high specificity [IV] [A=100%].
19b. Patients with druggable oncogenic drivers and LMD can be treated with CNS-penetrant next-generation TKIs [A=100% and III, B].
19c. Intra-CSF pharmacotherapy can be considered contingent on clinical factors [A=100% and V, C].

Recommendation 20: treatment of oligometastatic disease
20a. Stage IV patients with one to three synchronous metastases at diagnosis may experience long-term DFS following systemic therapy and local consolidative therapy (high-dose RT or surgery) [A=100% and II, B]. Because of the limited evidence, these patients should be discussed within a multidisciplinary tumour board [A=100% and II, B], and inclusion in clinical trials is preferred.
20b. Although operative risk is low and long-term survival may be obtained, current evidence for surgery in oligometastatic disease is limited, and the relative contribution of surgery versus RT as local treatment modality has not been established yet.
20c. Stage IV patients with limited metachronous metastases may be treated with a radical local therapy (high-dose RT or surgery) and may experience long-term DFS [A=100% and IV, C]. However, this is based mainly on retrospective data and inclusion in clinical trials is preferred.
20d. Stage IV patients with driver mutations, with oligoprogression while on molecular-targeted therapy, may be treated with a radical local treatment (high-dose RT or surgery) and may experience long-term DFS [A=100% and IV, C]. However, this is based mainly on retrospective data and inclusion in clinical trials is preferred.
20e. Solitary lesions in the contralateral lung should, in most cases, be treated with curative-intent therapy, **unless contraindicated** [A=100% and IV, B].

Recommendation 21: bone metastases
21a. Zoledronic acid reduces SREs (pathological fracture, radiation/surgery to bone or spinal cord compression) and is recommended in stage IV bone metastatic disease [A=100% and II, B].
21b. Denosumab shows a trend towards superiority to zoledronic acid in lung cancer in terms of SRE prevention [A=100% and II, B].
21c. In the case of uncomplicated painful bone metastases, single fraction EBRT is the recommended treatment on the basis of non-inferiority to multiple fraction RT [A=100% and I, A].

Recommendation 22: the role of minimally invasive procedures in patients with stage IV NSCLC
22a. In the case of symptomatic major airway obstruction or post-obstructive infection, endoscopy debulking by laser, cryotherapy or stent placement may be helpful [A=100% and III, C].
22b. Endoscopy is useful in the diagnosis and treatment (endobronchial or by guiding endovascular embolisation) of haemoptysis [A=100% and III, C].
22c. Vascular stenting might be useful in NSCLC-related superior vena cava compression [A=100% and II, B].

Continued

Table 2. *Continued*

Recommendation 23: palliative care in patients with stage IV NSCLC

23. Early palliative care intervention is recommended, in parallel with standard oncological care [A=100% and I, A].

Recommendation 24: follow-up in patients with stage IV NSCLC

24. Close follow-up, at least every 6–12 weeks to allow for early initiation of second-line therapy, is advised, but should depend on individual retreatment options [A=100% and III, B].

AJCC, American Joint Committee on Cancer; *ALK*, anaplastic lymphoma kinase; BSC, best supportive care; CEA, carcinoembryonic antigen; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; DFS, disease-free survival; EBB, endobronchial brachytherapy; EBRT, external beam radiotherapy; EBUS, endobronchial ultrasound; *EGFR*, epidermal growth factor receptor; EMA, European Medicines Agency; EUS, endoscopic ultrasound; FISH, fluorescent *in situ* hybridisation; *HER2*, human epidermal growth factor receptor 2; IHC, immunohistochemistry; imRECIST, immune-modified-RECIST; iRECIST, immune RECIST; irRECIST, immune-related RECIST; LM, leptomeningeal; LMD, leptomeningeal disease; *MEK*, mitogen-activated protein kinase; MRI, magnetic resonance imaging; nab-paclitaxel, albumin-bound paclitaxel; *NTRK*, neurotropic tropomyosin receptor kinase; NSCC, non-squamous cell carcinoma; NSCLC, non-small-cell lung cancer; NSCLC-NOS, non-small-cell lung cancer; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PET, positron emission tomography; PFS, progression-free survival; PS, performance status; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumours; RPA, recursive partitioning analysis; RT, radiotherapy; SCC, squamous cell carcinoma; SRE, skeletal-related event; SRS, stereotactic radiosurgery; TKI, tyrosine kinase inhibitor; TPS, tumour proportion score; UICC, Union for International Cancer Control; WBRT, whole-brain radiotherapy; WHO, World Health Organization; WT, wild-type.

2h. BRAF V600 mutation status should be systematically analysed in advanced NSCC for the prescription of BRAF/MEK inhibitors [A=100% and II, A].
2i. Molecular EGFR and ALK testing is not recommended in patients with a confident diagnosis of SCC, except in unusual cases, e.g. never/former light smokers or long-time ex-smoker [A=100% and IV, A].
2j. If available, multiplex platforms for molecular testing are preferable [A=100% and III, A].
2k. PD-L1 IHC should be systematically determined in advanced NSCLC. Testing is required for pembrolizumab therapy ***in all lines of treatment and*** *may also be informative when nivolumab or atezolizumab are used* ***as monotherapy in the second-line therapy setting*** *[A=100% and I, A].*

All 12 Asian experts agreed with and accepted completely [A = 100%] 'recommendations 2a–d, and 2h–k' above in the pre-meeting surveys. Two countries (see supplementary Table S1, available at *Annals of Oncology* online) were not in agreement, one country because FISH was not used for screening in their country (recommendation 2f) and the other because testing is not reimbursed in their country (it is only done if the drug company pays for the test) 'recommendation 2g'. After discussion at the face-to-face meeting, all countries accepted completely [A = 100%] 'recommendations 2a–k' based on the available scientific evidence rather than the situation in their countries. A minor revision was made to the wording of 'recommendation 2g' to include the addition of the words '**a validated** reverse transcription polymerase chain reaction (**RT-PCR**) **test may be used as an alternative**' (see also in bold text above), because in Asia the technique is standard. Minor revisions were also made to 'recommendation 2k' for clarity (see bold text above). The histological diagnosis of NSCLC from both surgically resected tumours and small biopsies should be based on the WHO classification published in 2015 [46, 47].

Therapeutic decisions are based on the specific histological subtype of the tumour. Sampling may be carried out on the primary tumour or any accessible metastases either surgically or using image-guided techniques. Immunohistochemistry (IHC) should be used, particularly in the small sample setting, where specific subtyping is not possible by morphology alone, and to reduce the number of patients classified as having NSCLC-NOS (not otherwise specified) to <10% of diagnosed cases [1V, A] [46]. IHC should be restricted to the use of thyroid transcription factor 1 (TTF1) to predict a probable diagnosis of adenocarcinoma, and p40 to predict a probable diagnosis of SCC. If neither are positive the diagnosis is NSCLC-NOS [46, 48].

IHC is also used for predictive biomarker assessment. Typically testing involves the detection of either targetable, usually addictive oncogenic changes, or biomarker testing for immuno-oncology therapy [49, 50]. The majority of oncogene-addicted lung cancers are adenocarcinomas and Western and international guidelines suggest that all patients with advanced probable or definitive adenocarcinoma should be tested for oncogenic drivers [49–52]. Molecular testing is not recommended for patients with SCC except in the case of never-, long-term ex- or light-(<15 packs/year) smokers. Although PD-L1 expression should be determined ahead of any treatment decision for patients with SCC ('recommendation 2k' and Figure 1).

In most European countries, genetic testing for *EGFR* mutations and rearrangements of *ALK* and *ROS1* are considered mandatory, and testing for *BRAF V600E* mutations is becoming essentially routine [24]. Evolving targets/biomarkers are human EGFR-2 (HER2), *MET* exon 14 mutations, and fusion genes involving *RET* and *NRK1*.

EGFR TKIs are established as effective therapies in patients who have activating and sensitising mutations in exons 18–21 of

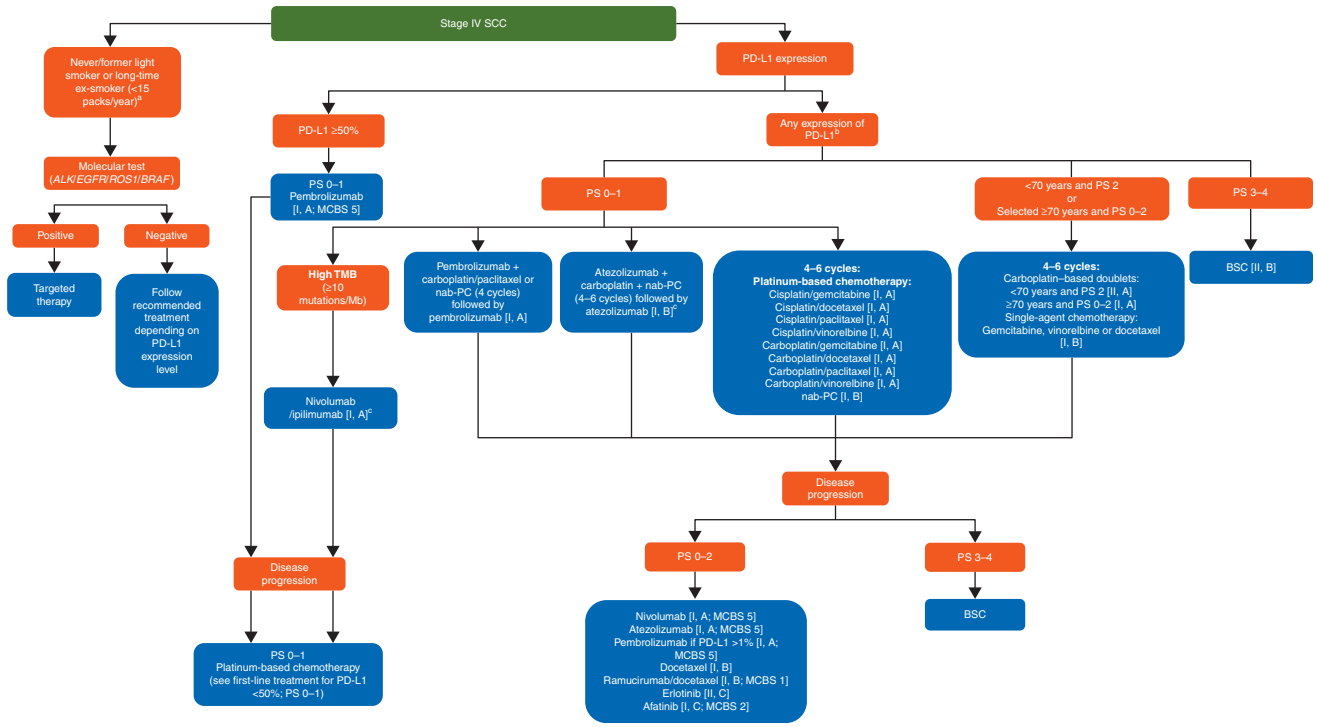

Figure 1. Treatment algorithm for stage IV lung SCC. [a]Molecular testing is not recommended in SCC, except in those rare cases of never/former light smokers or long-time ex-smokers (<15 packs/year). [b]In absence of contraindications and conditioned by the registration and accessibility of anti-PD-L1 combinations with platinum-based chemotherapy, this strategy will be favoured to platinum-based chemotherapy in patients with PS 0–1 and PD-L1 >50%. [c]Depending on approval status and reimbursement. *ALK*, anaplastic lymphoma kinase; BSC, best supportive care; *EGFR*, epidermal growth factor receptor; IHC, immunohistochemistry; Mb, megabase; MCBS, Magnitude of Clinical Benefit Scale; nab-PC, albumin-bound paclitaxel and carboplatin; PD-L1, programmed death-ligand 1; PS, performance status; SCC, squamous cell carcinoma; TMB, tumour mutation burden.

EGFR [53]. A meta-analysis has shown the overall pooled prevalence of *EGFR* mutations to be 32.3% (95% CI: 30.9% to 33.7%), and to range from 38.4% (95% CI: 36.5% to 40.3%) in China, 36.6% (95% CI: 33.2% to 40.0%) in Japan and 32.4% (95% CI: 28.0% to 36.8%) in Korea to 14.1% (95% CI: 12.7% to 15.5%) in Europe [54]. A study in multi-ethnic Malaysian patients with NSCLC showed the prevalence of *EGFR* mutations (36.4%) to be similar [55]. Generally, female sex, adenocarcinoma histology, never-smoking status, and Asian ethnicity are considered the most important factors associated with *EGFR* mutation positive disease and response to EGFR-TKIs [54, 56]. As stated previously [24], the most commonly occurring mutations comprise deletions in exon 19 and a substitution mutation (*L858R*) in exon 21, and testing should cover these mutations [1, A]. The *T790M* exon 20 mutation is the most frequent cause of resistance to first- and second-generation EGFR TKIs but is rarely found in TKI-untreated patients although patients with *T790M* germline mutations have been reported [57]. In the case of accessibility to a third-generation EGFR-TKI (e.g. osimertinib) that can overcome *T790M*-mediated resistance [58], testing for *T790M* mutations should be mandatory [1, A] (see the retrospective addition of 'recommendation 2d-1' and Table 2). The use of cell-free DNA (cfDNA) to 'rule in' targetable mutations should be used when sufficient tissue cannot be obtained. However, due to the lack of sensitivity of cfDNA blood testing, all patients who test negative for *a T790M* mutation at relapse will still require a tissue biopsy [59]. Emerging data also show the presence of the ALK protein (positive IHC staining) to be associated with treatment response [I, A] [60]. IHC has been accepted as an alternative to FISH for *ALK* testing [50]. *ALK* mutations represent an important mechanism of resistance to ALK TKIs and *ALK* mutation testing may therefore become routine at relapse as the newer generation ALK TKIs show differential efficacy against the different *ALK* mutations [61]. The updated molecular testing guidelines for the selection of lung cancer patients for treatment with targeted TKIs also recommend *ROS1* testing of all NSCL adenocarcinomas. *ROS1* gene fusions are found in 2.4% of Asian patients with lung adenocarcinomas and are associated with young age at diagnosis [62]. In fact, recommendations from the updated molecular testing guidelines [50] include the inclusion of the testing of additional genes (*ERBB2*, *MET*, *BRAF*, *KRAS* and *RET*) for laboratories that perform next-generation sequencing panels, with the use of 5% sensitivity assays for *EGFR T790M* mutations in patients with secondary resistance to EGFR inhibitors; as well as IHC as an alternative to FISH for both *ALK* diagnosis and *ROS1* screening.

Crizotinib, an inhibitor of ALK, ROS1 and MET, is approved in Europe and the United States for use in patients with *ROS1*-rearranged adenocarcinomas, has recently demonstrated antitumour activity, with no new safety signals, in East-Asian patients with ROS1-positive advanced NSCLC [63]. Approval of the

antiprogrammed cell death protein 1 (PD-1) agent pembrolizumab as a standard-of-care first-line treatment in selected patients with high programmed death-ligand 1 (PD-L1) expression (score of at least 50%), based on the findings from the KEYNOTE-024 trial [64], and subsequent confirmation in the KEYNOTE-042 trial [65], has resulted in PD-L1 IHC being mandatory for all patients with advanced NSCLC in the first-line setting [1, A]. Also, although the PD-L1 IHC 22C3 assay is the only test validated in clinical trials of pembrolizumab, extensive technical comparison studies suggest that trial-validated commercial kit assays based on the 28-8 and SP263 PD-L1 IHC clones may provide an alternative [III, A] [66–70]. If, by choice or force of circumstances, a laboratory-developed test is used, very careful and extensive validation is essential before clinical use [IV, A]. PD-L1 testing is not required for treatment with the antibody therapies nivolumab or atezolizumab in second line, but may be informative.

Furthermore, *EGFR* mutation status has been reported to be inversely associated with PD-L1 [71], with data in Asian studies suggesting that EGFR-TKIs might indirectly enhance antitumour immunity [72], and that changes in PD-L1 expression are seen in patients with *EGFR*-mutant NSCLC who acquire resistance to the TKI gefitinib [73]. Patients with *EGFR* mutations or *ALK* rearrangements have been shown to exhibit lower PD-L1 and CD8 co-expression levels in the tumour microenvironment, which could be responsible for a poor response to checkpoint inhibitors. PD-L1 and CD8 co-expression in *EGFR*-mutated or *ALK*-rearranged lung cancer has been shown to be a biomarker for poor prognosis with shorter overall survival [74]. A recent analysis also suggests that *TP53* and *KRAS* mutation status may be predictive of response to PD-1 blockade in patients with non-squamous NSCLC [75].

Measuring tumour mutational burden (TMB) is also being explored, and high TMB (≥10 mutations per megabase) has been validated prospectively in a unique prospective clinical trial which showed the PFS seen with nivolumab plus ipilimumab to be significantly longer than for chemotherapy irrespective of PD-L1 expression [76]. Studies are ongoing to define a consensus on how TMB should be measured [77–79]. Recently, data from the POPLAR and OAK trials showed TMB in blood is associated with atezolizumab clinical benefit in patients with NSCLC [80]. Also, preliminary data suggest that blood TMB may be a predictive biomarker for atezolizumab activity in an analysis of 58 biomarker assessable patients in the B-F1RST trial [81]. A prospective trial in the first-line setting, examining the same biomarker, is ongoing [NCT03178552].

Recommendation 3: staging and risk assessment

3a. A complete history including a precise smoking history and comorbidities, weight loss, PS and physical examination must be recorded [A=100%].

3b. Laboratory standard tests including routine haematology, renal and hepatic functions and bone biochemistry tests are required [A=100%].

3c. Routine use of serum tumour markers, such as carcinoembryonic antigen (CEA), is not recommended [A = 100% and IV, B].

3d. A contrast-enhanced CT scan of the chest and upper abdomen including the liver and the adrenal glands should be carried out at diagnosis [A = 100%].

3e. Imaging of the central nervous system (CNS) should be considered at diagnosis for all patients with metastatic disease [A = 100% and IV, C] and is required for patients with neurological symptoms or signs [A = 100% and IV, A]. Magnetic resonance imaging (MRI) is more sensitive than a CT scan [A = 100% and IV, B].

3f. If bone metastases are clinically suspected, bone imaging is required [A = 100% and IV, B].

3g. Bone scan or positron emission tomograpy (PET), ideally coupled with CT, can be used for detection of bone metastasis [A = 100% and IV, B].

3h. NSCLC is staged according to the AJCC/UICC system (8th edition) and is grouped into the stage categories shown in Tables 3 and 4.

3i. 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 [A = 100% and IV, A].

3j. Response evaluation is recommended after 6–9 weeks of systemic therapy using the same radiographic investigation that initially demonstrated tumour lesions [A = 100% and IV, B].

3k. Follow-up with PET is not routinely recommended, due to its high sensitivity and relatively low specificity [A = 100% and IV, C].

3l. Measurements and response assessment should follow RECIST criteria v1.1 [B = 100% and IV, A]. However, the adequacy of RECIST in evaluating the response to targeted therapy like EGFR or ALK TKI in respective genetically-driven NSCLC is debatable [B = 100% and IV, B].

3m. In the case of immune checkpoint inhibitor therapy, RECIST criteria should be used, although irRECIST, iRECIST, imRECIST may have a role in the overall assessment of therapy [A = 100% and IV, B].

All 12 Asian experts agreed with and accepted completely [A = 100%] 'recommendations 3a, b, d, h, i, j, k and m' above in the pre-meeting surveys (see supplementary Table S2, available at *Annals of Oncology* online). 'Recommendations 3c, e, f, g and l' were discussed at the face-to-face meeting. The issues over 'recommendations 3c, e and f' were resolved immediately with all the experts accepting them completely [A = 100%]. There was concern about the use of the word *should* in 'recommendations 3e and 3l', as in some Asian countries *should* is interpreted as *must*. Thus, *should* in the case of 'recommendations 3e and 3l' should *be* interpreted as *may*, and the same applies for other recommendations in this document where the word *should* has been used in a recommendation. All experts accepted 'recommendation 3g' completely [A = 100%], following discussion, with the understanding that in some Asian countries MRI is used to confirm metastases. 'Recommendation 3l' was accepted with some reservation [B = 100%] as Response Evaluation Criteria In Solid Tumors (RECIST) are only used in clinical trials.

As part of the diagnostic process, standard tests including routine haematology, renal and hepatic function, and bone biochemistry tests are required, but the routine use of serum markers,

Table 3. Clinical classification UICC TNM 8 [85, 86]

Primary tumour (T)	
TX	Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualised by imaging or bronchoscopy
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*[a]
T1	Tumour 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e. not in the main bronchus)[b]
T1mi	Minimally invasive adenocarcinoma[c]
T1a	Tumour 1 cm or less in greatest dimension[b]
T1b	Tumour more than 1 cm but not more than 2 cm in greatest dimension[b]
T1c	Tumour more than 2 cm but not more than 3 cm in greatest dimension[b]
T2	Tumour more than 3 cm but not more than 5 cm; or tumour with any of the following features[d] • Involves main bronchus regardless of distance to the carina, but without involvement of the carina • Invades visceral pleura • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region either involving part of or the entire lung
T2a	Tumour more than 3 cm but not more than 4 cm in greatest dimension
T2b	Tumour more than 4 cm but not more than 5 cm in greatest dimension
T3	Tumour more than 5 cm but not more than 7 cm in greatest dimension or one that directly invades any of the following: parietal pleura, chest wall (including superior sulcus tumours) phrenic nerve, parietal pericardium; or separate tumour nodule(s) in the same lobe as the primary
T4	Tumour more than 7 cm or of any size that invades any of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina; separate tumour nodule(s) in a different ipsilateral lobe to that of the primary
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumour nodule(s) in a contralateral lobe; tumour with pleural or pericardial nodules or malignant pleural or pericardial effusion[e]
M1b	Single extra thoracic metastasis in a single organ[f]
M1c	Multiple extra thoracic metastasis in a single or multiple organs

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[a]Tis includes adenocarcinoma *in situ* and squamous carcinoma *in situ*.

[b]The uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a.

[c]Solitary adenocarcinoma (not more than 3 cm in greatest dimension), with a predominantly lepidic pattern and not more than 5 mm invasion in greatest dimension in any one focus.

[d]T2 tumours with these features are classified T2a if 4 cm or less, or if size cannot be determined and T2b if >4 cm but not larger than 5 cm.

[e]Most pleural (pericardial) effusions with lung cancer are due to tumour. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumour, and the fluid is non-bloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging descriptor.

[f]This includes involvement of a single non-regional node.

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

such as CEA, is not recommended [IV, B] [82]. Contrast-enhanced CT scans of the chest and upper abdomen including complete assessment of liver, kidneys and adrenal glands should be carried out on all patients. Imaging of the CNS may be relevant in those patients with neurological symptoms [IV, A]; and if possible, imaging of the CNS with MRI, preferably with gadolinium enhancement, or a CT scan of the brain with iodine contrast should be carried out at diagnosis [IV, B]. MRI is more sensitive than a CT scan [III, B] [83]. If metastatic disease is identified, other imaging is only necessary if it will impact on treatment strategy. An Asian meta-analysis has shown 2-deoxy-2-[fluorine-18] fluoro-D-glucose (^{18}F-FDG) PET-CT to confer significantly higher sensitivity and specificity than contrast-enhanced CT and higher sensitivity than ^{18}F-FDG PET alone in staging NSCLC

Table 4. Lung cancer stage grouping TNM 8 eighth edition [85]

NNSCLC stages	T-classification	N-staging	M-staging
Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IA1	T1a (mi)	N0	M0
	T1a	N0	M0
Stage IA2	T1b	N0	M0
Stage IA3	T1c	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
Stage IIB	T1a–c	N1	M0
	T2a	N1	M0
	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a–c	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	T1a–c	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N2	M0
	T4	N2	M0
Stage IIIC	T3	N2	M0
	T4	N2	M0
Stage IV	Any T	Any N	M1
Stage IVA	Any T	Any N	M1a
	Any T	Any N	M1b
Stage IVB	Any T	Any N	M1c

TNM, tumour, node and metastasis; Tis, tumour in situ; T1a (mi), minimally invasive carcinoma; UICC, Union for International Cancer Control.

($P < 0.05$) [84]. MRI may complement or improve the diagnostic staging accuracy of ^{18}F-FDG-PET-CT imaging, particularly in assessing the extent of local chest wall, vascular or skeletal invasion and in the identification of nodal and distant metastatic disease. NSCLC is staged according to the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) system (8th edition) and is grouped into the stage categories shown in Tables 3 and 4 [85, 86].

As described previously, response evaluation is recommended after two to three cycles of chemotherapy or immunotherapy, using the same initial radiographic investigation techniques used for the original diagnosis [IV, B], and every 6–9 weeks in patients treated with targeted therapies and/or immunotherapy [IV, B] [24]. Lesions should be assessed according RECIST v1.1 [IV, A] [87]. However, it should be noted that evaluating responses to EGFR or ALK TKIs in genetically driven NSCLCs is challenging as treatment beyond RECIST progression is common in these patients in the pursuit of clinical benefit rather than a measurable response. Several radiological criteria have been developed specifically for immunotherapy, namely two-dimensional immune-related response criteria (irRC) immune-related RECIST (irRECIST) [88, 89] and more recently iRECIST [90], and immune-modified RECIST (imRECIST) [91] in a bid to standardise the assessment of response for immunotherapy clinical trials. However, non-conventional responses and pseudo progression are very rarely observed in patients being treated for NSCLC, <5% of all cases, and ideally RECIST 1.1 should still be used in routine clinical practice [IV, B] [92–95].

Recommendation 4: management of advanced metastatic disease

4a The treatment strategy should consider the histology, molecular pathology, age, PS, comorbidities and the patient's preferences [A = 100%].
4b Systemic therapy should be offered to all stage IV patients with PS 0–2 [A = 100% and I, A].
4c In any stage of NSCLC, smoking cessation should be highly encouraged, because it improves the outcome [A = 100% and II, A].

All 12 Asian experts agreed with and accepted completely [A = 100%] 'recommendations 4a, b and c' in the pre-meeting surveys. As discussed previously 'recommendation 1', treatment decisions should ideally be discussed within a multidisciplinary team, that is able to evaluate and change patient management, including the recommendation of additional investigations and changes in treatment approach [96]. Smoking cessation should be strongly encouraged as it can improve outcome by improving PS [97]. Also, continued smoking may impact on the efficacy of systemic therapy. For example, smoking is known to reduce the bioavailability of erlotinib [98].

Recommendation 5: first-line treatment of NSCLC without a druggable oncogene driver

5a. Chemotherapy should be considered for all stage IV NSCLC patients with EGFR- and ALK-negative disease, in the case of a contraindication to immunotherapy, and who are without major comorbidities and PS 0–2 [A = 100% and I, A].
5b. Single-agent pembrolizumab should be considered in eligible patients with PS 0–1, EGFR- and ALK-negative NSCLC and a tumour with a tumour proportion score (TPS) of PD-L1 ≥50% [A = 100% and I, A]. Chemotherapy should be provided in the case of contraindication to pembrolizumab.
5c. Pembrolizumab plus chemotherapy (with pemetrexed plus platinum) should be considered in patients with PS 0–1, non-squamous NSCLC without EGFR or ALK mutations, in absence of contraindications to the use of immunotherapy, if approved and available [A = 17%, B = 83% and I, A] (Figure 2). The survival benefit for pembrolizumab-combination therapy is observed across all categories of PD-L1 expression, but diminished among PD-L1-negative patients and it is unclear if chemotherapy adds a benefit in patients with PD-L1 ≥50%.
5d. Combination of atezolizumab and bevacizumab with carboplatin and paclitaxel should be considered as a therapeutic option in patients with PS 0–1 and metastatic non-squamous NSCLC, in the absence of contraindications to

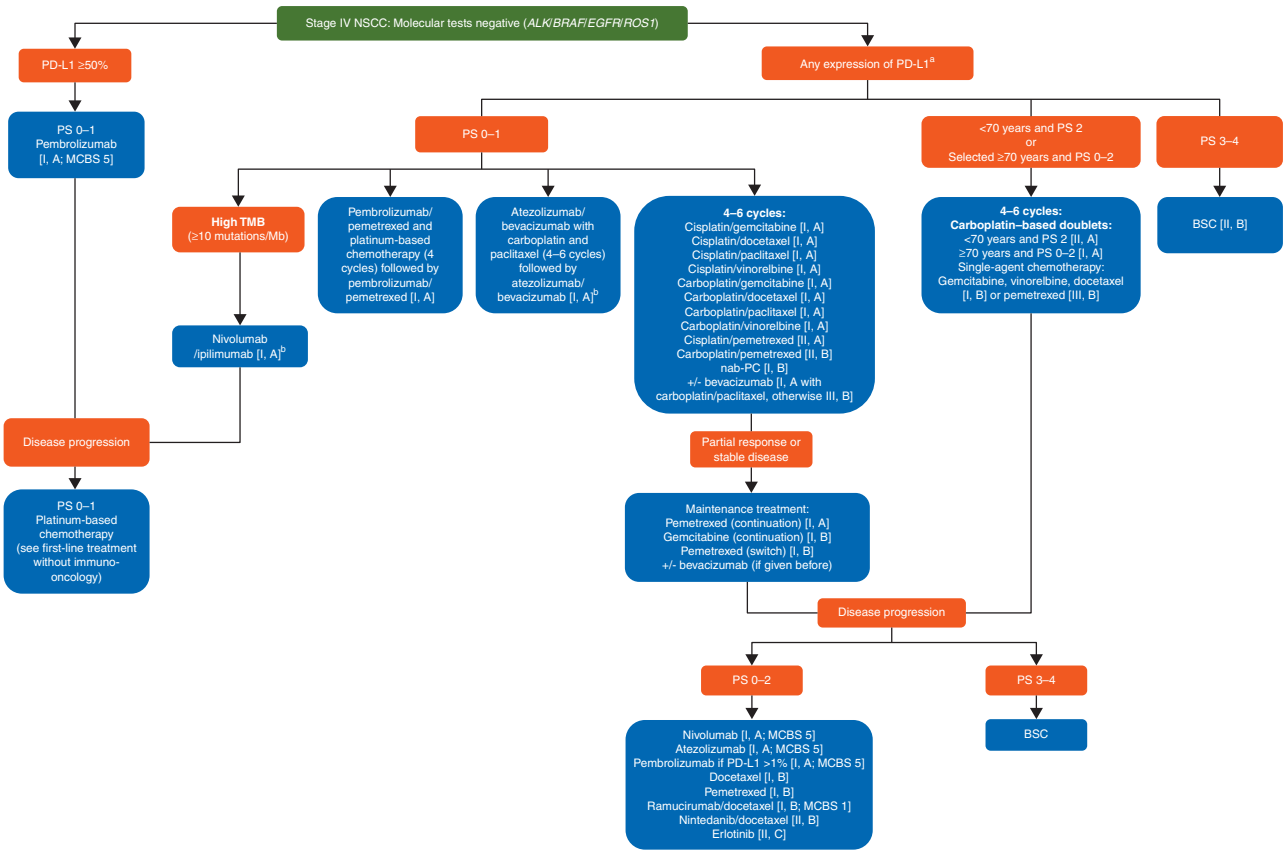

Figure 2. Treatment algorithm for stage IV lung NSCC negative for *ALK/BRAF/EGFR/ROS1* alterations. [a]In absence of contraindications and conditioned by the registration and accessibility of anti-PD-L1 combinations with platinum-based chemotherapy, this strategy will be favoured to platinum-based chemotherapy in patients with PS 0–1 and PD-L1 <50%. [b]Depending on approval status and reimbursement. *ALK*, anaplastic lymphoma kinase; BSC, best supportive care; *EGFR*, epidermal growth factor receptor; Mb, megabase; MCBS, Magnitude of Clinical Benefit Scale; nab-PC, albumin-bound paclitaxel and carboplatin; NSCC, non-squamous cell carcinoma; PD-L1, programmed death-ligand 1; PS, performance status; TMB, tumour mutation burden.

the use of immunotherapy if approved and available. [A = 100% and I, A]. Combination of pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel should be considered a standard choice in patients with PS 0–1 and metastatic squamous NSCLC in absence of contraindications to use of immunotherapy, if approved and available. [A = 100% and I, A] (Figure 1).

5e. Association of atezolizumab with carboplatin and nab-paclitaxel represents an option in patients with PS 0–1 and metastatic squamous NSCLC in the absence of contraindications to use of immunotherapy), if approved and available [A = 83%, B = 17% and I; B] (Figure 1).

5f. Nivolumab plus ipilimumab represents a treatment option for patients with PS 0–1, EGFR and ALK negative mNSCLC with a high TMB, regardless of tumour PD-L1 expression level if approved and available [A = 83%, B = 17% and I, A].

5g. Platinum-based doublets are the recommended chemotherapy option in all stage IV NSCLC patients with no contraindications to platinum compounds [A = 100% and I, A].

5h. Four cycles of platinum-based doublets followed by less toxic maintenance monotherapy [I, A], or four, up to a maximum of six cycles [A = 100% and IV, B], in patients not suitable for maintenance monotherapy, are currently recommended.

5i. The nab-paclitaxel regimen could be considered a chemotherapeutic option in advanced NSCLC patients, particularly in patients with a greater risk of neurotoxicity, pre-existing hypersensitivity to paclitaxel or contraindications for standard paclitaxel premedication [A = 100% and I, B].

5j. Platinum-based doublets with a third-generation cytotoxic agent (gemcitabine, vinorelbine, taxanes) are recommended in advanced SCC patients [A = 100% and I, A] (Figure 1).

5k. Pemetrexed is preferred to gemcitabine or docetaxel in patients with non-squamous tumours [II, A]. Pemetrexed use is restricted to NSCC in any line of treatment [A = 100% and I, A].

5l. Necitumumab/gemcitabine/cisplatin represents a treatment option for advanced SCC expressing EGFR by IHC [A = 83%, B = 17% and II, C].

5m. Bevacizumab improves overall survival when combined with paclitaxel/carboplatin regimens in patients with NSCC and PS 0–1, and, therefore, may be offered in the absence of contraindications (bevacizumab should be given until progression or unacceptable toxicity) [A = 1001% and I, A].

5n. Bevacizumab might be considered with platinum-based regimens beyond paclitaxel/carboplatin in the absence of contraindications [A = 17%, C = 83%% and III, B].

All 12 Asian experts agreed with and accepted completely [A = 100%] 'recommendations 5a, b, g, h, i, j and k' [A = 100%] in the pre-meeting surveys, and after resolving the issues surrounding the lack of approval and reimbursement of the newer agents in certain countries 'recommendations 5d, and m' were accepted completely [A = 100%] and 'recommendations 5e, f, l' were accepted completely or with some reservation [A = 83% and B = 17%) (supplementary Table S13, available at *Annals of Oncology* online). Thus, only 'recommendations 5c and n 'were discussed at the face-to-face meeting (see supplementary Table S3, available at *Annals of Oncology* online).

First-line treatment with ICT mAbs in patients with no druggable oncogene driver and no contradictions for the use of immunotherapy. Historically, lung cancers have been considered to be poorly immunogenic, but the emergence of clinical data related to the use of immune checkpoint targeted monoclonal antibodies (ICT mAbs) directed against PD-1, PD-L1 and the cytotoxic T-lymphocyte-associated protein 4 (CTL-4), suggests that immunotherapy has a role to play in the treatment and management of patients with NSCLC. The KEYNOTE-024 trial emphasised the efficacy of single-agent pembrolizumab compared with a platinum chemotherapy doublet (median overall survival 30 versus 14 months) in previously untreated NSCLC patients with a TPS for PD-L1 expression of ≥50%, and no *EGFR or ALK* gene alterations [64, 99] (ESMO MCBS 4). As a consequence pembrolizumab is now considered a standard treatment option in patients with advanced/mNSCLC and TPS for PD-L1 expression of ≥50%, who do not have contraindications to immunotherapy [1, A]. The KEYNOTE-042 trial including Asian patients [65] investigated pembrolizumab in patients with a TPS for PD-L1 of ≥1% disease and showed the overall survival benefit observed for pembrolizumab to be driven by patients with a TPS for PD-L1 expression of ≥50%. This provides confirmation of the fact that the benefit of single-agent pembrolizumab in the first-line setting reported in the KEYNOTE-024 trial, is restricted to patients with high tumour PD-L1 expression (TPS ≥50%).

Also, the KEYNOTE-189 trial in PS 0–1 patients, without sensitising *EGFR* or *ALK* mutations, showed the addition of pembrolizumab to pemetrexed and platinum-based chemotherapy (four cycles followed by pembrolizumab + pemetrexed maintenance) to result in a superior response rate, median progression-free survival (PFS) and estimated overall survival compared with pemetrexed and chemotherapy plus placebo [median overall survival (mOS) not reached versus 11.3 months, hazard ratio (HR) 0.49, 95% CI 0.38–0.64] [100]. In the KEYNOTE-407 trial in patients with metastatic squamous NSCLC, patients were randomised 1 : 1 to receive carboplatin and paclitaxel (or nab-paclitaxel) plus either pembrolizumab or placebo for four cycles, followed by pembrolizumab or placebo. Chemotherapy in combination with pembrolizumab was associated with an improved ORR and an improved overall survival (5.9 versus 11.3 months, $P = 0.0008$) [101]. Based on these results, pembrolizumab in combination with platinum-based chemotherapy or pemetrexed and platinum-based chemotherapy should be considered as a standard first-line treatment option in patients with squamous and non-squamous mNSCLC, respectively [I, A] (Figures 1 and 2).

In IMpower 150, the only published trial at the time of the special guidelines meeting in Guangzhou to report data on patients with NSCLC with *EGFR* or *ALK* gene changes, the addition of atezolizumab to bevacizumab plus chemotherapy (four or six cycles followed by atezolizumab or atezolizumab + bevacizumab or bevacizumab maintenance) in patients with non-squamous mNSCLC with a wild-type genotype (i.e. excluding patients with *EGFR* or *ALK* mutations) significantly improved PFS and overall survival (mOS 19.2 versus 14.7 months, HR 0.78, 95% CI 0.64–0.96, $P = 0.02$) irrespective of tumour PD-L1 expression [102]. PFS was also longer for patients receiving atezolizumab, bevacizumab and chemotherapy than for those receiving bevacizumab and chemotherapy in the ITT patient population which included patients with NSCLC with *EGFR* or *ALK* mutations. These results support the use of a combination of atezolizumab (anti-PD-L1) and bevacizumab [antivascular endothelial growth factor (VEGF)] with carboplatin and paclitaxel as a therapeutic option in patients with non-squamous mNSCLC, and a PS of 0–1, in the absence of contraindications to the use of immunotherapy [I, A].

The addition of atezolizumab to platinum and taxane chemotherapy combinations (four or six cycles followed by atezolizumab) has also been studied in patients with squamous mNSCLC in the IMpower 131 study, but no improvement in overall survival was seen at first interim analysis (mOS 14.0 versus 13.9 months, HR 0.96, 95% CI 0.76–1.18) [103]. More mature data are needed to evaluate the long-term benefit but atezolizumab with carboplatin/nab-paclitaxel represents a potential option for patients with squamous mNSCLC [I; B].

The combination of carboplatin or cisplatin with pemetrexed and atezolizumab (four or six cycles followed by atezolizumab + pemetrexed) in the IMpower132 trial has been shown to be superior to the chemotherapy doublet although overall survival was not statistically different at the time of analysis (mOS 18.1 versus 13.6 months, HR: 0.81, 95% CI: 0.64–1.03) suggesting another possible treatment opportunity [I, B] [104]. The combination of carboplatin nab-paclitaxel and atezolizumab (four or six cycles followed by atezolizumab) in the IMpower130 trial has been shown to be superior to the chemotherapy doublet, with an improvement of PFS and overall survival (mOS 18.6 versus 13.9 months; HR: 0.79; 95% CI: 0.64–0.98) suggesting an additional treatment opportunity [I, A) [105]. No benefit for the addition of atezolizumab to chemotherapy was observed in patients with *EGFR/ALK* gene alterations [105]. Atezolizumab is not approved by the European Medicines Agency (EMA) for use in the first-line treatment of NSCLC, but has been approved in certain Asian countries. In the KEYNOTE-189/407 trials as well as the IMpower 130/131/132 trials, the magnitude of the benefit was related to tumour PD-L1 expression.

As mentioned previously 'recommendation 2', a pre-specified analysis of TMB as a biomarker was reported in the phase III CheckMate 227 trial, evaluating the ICT mAbs nivolumab (anti-PD-1) plus ipilimumab (anti-CTLA-4) versus chemotherapy first-line in patients with stage IV or recurrent NSCLC that had not been previously treated with chemotherapy [76]. Patients with tumour PD-L1 expression of ≥1% and those with PD-L1 expression <1% were randomly assigned, in a 1 : 1 : 1 ratio, to

receive nivolumab plus ipilimumab, nivolumab monotherapy or chemotherapy. The PFS benefit seen with nivolumab plus ipilimumab was irrespective of tumour PD-L1 expression with the HRs for nivolumab plus ipilimumab in patients with a tumour PD-L1 TPS ≥1% and those <1% of 0.62 and 0.48, respectively. A similar benefit was seen for patients with either squamous or non-squamous histologies (squamous HR 0.63, non-squamous HR 0.55). For now, nivolumab plus ipilimumab represents an option for the treatment of patients with NSCLC with a high TMB [I, A]. Ipilumumab and its combination with nivolumab are not currently approved by the EMA for use in the treatment of patients with NSCLC.

The impact of the TMB on the benefit of nivolumab was also examined in the CheckMate-026 trial in a retrospective unplanned analysis and showed patients with the highest TMB to benefit from nivolumab in terms of response and PFS [77]. Overall, the data from the trials cited above suggest that immunotherapy is emerging as a new treatment approach for most patients with newly diagnosed mNSCLC. However, the Asian experts were uncertain about the benefit conferred by the addition of pembrolizumab to chemotherapy in patients with high tumour cell PD-L1 (≥50%) given that there is no randomised trial that compares chemotherapy plus checkpoint inhibitors versus pembrolizumab monotherapy, and voted to accept 'recommendation 5c' above with some reservation [A = 17% and B = 83%].

First-line treatment in NSCLC patients with no druggable oncogene driver but with contradictions for the use of immunotherapy. Platinum doublet chemotherapy should be considered for all stage IV lung cancer patients PS 0–2 without a druggable oncogene driver and without major comorbidities, 'recommendation 5g' above' [1, A]. This recommendation is based on the benefits demonstrated for chemotherapy over best supportive care (BSC) [106–108] and by the survival benefit demonstrated for the use of chemotherapy doublets over single-agent therapy [109, 110]. No overall survival benefit was found for the use of six versus fewer cycles of first-line platinum-based doublets, although a longer PFS coupled with significantly higher toxicity was reported in patients receiving six cycles [111, 112]. Thus, four cycles of platinum-based doublets followed by less toxic maintenance monotherapy [I, A], or four cycles of platinum-based therapy in patients not suitable for maintenance monotherapy [I, A], up to a maximum of six [IV, B], are currently recommended. Several platinum-based combinations with paclitaxel, docetaxel, gemcitabine and vinorelbine have shown comparable efficacy [113, 114].

Selection of the appropriate regimen for the treatment of a particular patient should involve consideration of the balance between the efficacy and the toxicity profiles of the individual regimens. For example, cisplatin was shown to achieve higher response rates than carboplatin in a retrospective Cochrane review [115], but trials using paclitaxel or gemcitabine plus a platinum agent had equivalent response rates. However, cisplatin was associated with more nausea or vomiting and carboplatin caused more thrombocytopaenia and neurotoxicity, whilst no difference in the incidence of grade 3/4 anaemia, neutropenia, alopecia or renal toxicity was observed [115]. Also, the incorporation of pemetrexed (a novel multi-targeted antifolate that inhibits three enzymes involved in folate metabolism and purine and pyrimidine synthesis) represents a therapeutic option based on data from the comparison of pemetrexed cisplatin with gemcitabine or docetaxel platinum combinations [116, 117] that should be restricted to use in non-squamous NSCLC patients only [118, 119]. Whilst, the albumin-bound nab-paclitaxel/carboplatin regimen has been shown in a large phase III trial to have a significantly higher overall response rate (ORR) compared with the solvent-based paclitaxel/carboplatin and less neurotoxicity, but no significant difference in PFS or overall survival [I, B] [120]. The nab-paclitaxel/carboplatin regimen could therefore be considered a therapeutic option in patients with advanced NSCLC, particularly in those patients with a greater risk of neurotoxicity, pre-existing hypersensitivity to paclitaxel or contraindications for standard paclitaxel premedication [I, B]. The benefits were observed in both SCC and NSCC, with a larger impact on response in patients with SCC [120].

In fact, most individual trials and meta-analyses evaluating the chemotherapy options for the first-line treatment of patients with advanced/mNSCLC did not report any differential efficacy between patients with NSCC and SCC histologies [107]. Therefore, platinum-based doublets involving a third-generation cytotoxic agent (gemcitabine, vinorelbine, taxane) are recommended for both NSCC and SCC NSCLC patients without major comorbidities and PS 0–2 [I, A] (Figures 1 and 2). However, there are some treatment strategies that are specific for the treatment of either NSCC or SCC. For example, necitumumab, a monoclonal antibody against EGFR, which failed to demonstrate a significant impact in the first-line treatment of metastatic NSCC when added to cisplatin/pemetrexed [121], showed significant benefits when combined with cisplatin/gemcitabine in patients with SCC in the SQUIRE trial [122, 123] (ESMO MCBS score 1). However, a benefit from the addition of necitumumab to chemotherapy was not apparent for the small subgroup of patients with non-EGFR-expressing tumours. Thus, based on these results, and due to the limited clinical data, the addition of necitumumab to cisplatin and gemcitabine is an option for patients with EGFR-expressing SCC only. It should be noted that it has not been adopted as a standard treatment option in Europe and most Asian countries, and its use in NSCLC patients with SCC should be carefully evaluated [I, C; ESMO-MCBS score: 1]. Also, the combination of bevacizumab (anti-VEGF) with carboplatin and paclitaxel has been shown to improve survival in both Western and Asian patients with NSCC PS 0–1 NSCLC [124, 125] (ESMO MCBS score 2). Two meta-analyses also confirmed the superiority of bevacizumab platinum chemotherapy combinations over platinum combination therapy alone in NSCLC patients with NSCC [126, 127]. However, at the face-to-face meeting there was no consensus that bevacizumab could be used outside of combination with carboplatin and paclitaxel and therefore the Asian experts only accepted 'recommendation 5n' above with major reservation [A = 17% and C = 83%%].

Recommendation 6: maintenance

6a. Maintenance chemotherapy should be offered only to patients with PS 0–1 after first-line chemotherapy. Decisions about maintenance should consider histology, response to platinum-doublet chemotherapy and remaining

toxicity after first-line chemotherapy, PS and patient's preference [A = 83%%, C = 17%].

6b. In patients with NSCC and PS 0–1, pemetrexed switch maintenance should be considered in patients having disease control following four cycles of non-pemetrexed containing platinum-based chemotherapy [A = 100% and I, B]. Pemetrexed continuation maintenance should be considered in patients having disease control following four cycles of cisplatin-pemetrexed [A = 100% and I, A] ***or pemetrexed switch maintenance plus or minus bevacizumab****.*

6c. Continuation maintenance with gemcitabine is an option in NSCLC patients treated with four cycles of cisplatin-gemcitabine [A = 100% and I, C].

6d. Maintenance treatment with erlotinib is only recommended for NSCC patients with an EGFR sensitising mutation [A = 100% and II, B].

All 12 Asian experts agreed with and accepted completely [A = 100%] 'recommendations 6 b, c and d' after resolving the issues surrounding current practices in certain Asian countries identified in the pre-meeting surveys (see supplementary Table S4, available at *Annals of Oncology* online). The Japanese experts only accepted 'recommendation 6a' with major reservation.

As stated in the ESMO guidelines [24], decisions regarding maintenance therapy must take into account histology, residual toxicity after first-line chemotherapy, response to platinum doublets, PS and patient preference. 'Recommendations 6a, b, c and d' above are based on the data from several trials that have investigated the role of maintenance treatment in patients with good PS (0–1) either as 'continuation maintenance' (maintained use of an agent included in first-line treatment) or as 'switch maintenance' (introduction of a new agent) after four cycles of platinum-based chemotherapy. Randomised phase III trials of switch maintenance have reported improvements in PFS and overall survival for pemetrexed [118] and erlotinib [128] versus placebo, following four cycles of platinum-based therapy. This was confirmed for erlotinib in Asian patients from Korea, China and Malaysia, in a retrospective sub-group analysis of Asian patients enrolled in the SATURN trial both for the overall Asian patient population and for patients with EGFR IHC positive disease [129]. In the case of pemetrexed, the benefit was limited to those patients with NSCC. Furthermore, maintenance treatment with erlotinib is only recommended for NSCC patients with *EGFR*-sensitising mutations [III, B] [130]. Randomised trials investigating continuation maintenance have also shown an improvement in PFS and overall survival. The phase III PARAMOUNT trial of continuation maintenance with pemetrexed versus placebo after four induction cycles of cisplatin plus pemetrexed chemotherapy demonstrated a PFS and overall survival improvement in patients with a PS 0–1, which was confirmed at long-term follow-up [131, 132]. Continuation of pemetrexed following completion of four cycles of first-line cisplatin plus pemetrexed chemotherapy is, therefore, recommended in patients with NSCC, in the absence of progression after first-line chemotherapy and upon recovery from the toxicities of the previous treatment [I, A]. A phase III trial comparing maintenance bevacizumab, with or without pemetrexed, after first-line induction with bevacizumab, cisplatin and pemetrexed showed a benefit in PFS for the pemetrexed–bevacizumab combination but no improvement in overall survival [133]. Although, a trend towards improved overall survival was seen when analysing 58% of events for the 253 patients randomised in this trial [134]. In the PointBreak trial, which compared carboplatin plus paclitaxel plus bevacizumab followed by bevacizumab to carboplatin plus pemetrexed plus bevacizumab followed by pemetrexed plus bevacizumab in patients with NSCC, overall survival was comparable for both arms (HR, 1.00; 95% CI: 0.86–1.16; $P = 0.949$) [135]. Another phase III trial, showed that continuation maintenance with gemcitabine significantly reduced disease progression with a non-significant improvement in overall survival in patients with advanced NSCLC treated with four cycles of cisplatin/gemcitabine combination therapy first-line [I, C] [136].

Recommendation 7: patients with a PS of 2 and beyond

7a. In patients with PS 2, chemotherapy compared with BSC prolongs survival and improves QoL [A = 100% and I, A].

7b. Carboplatin-based combination therapy should be considered in eligible PS 2 patients [A = 100% and II, A].

7c. Single-agent chemotherapy with gemcitabine, vinorelbine, docetaxel [A = 100% and I, B] or pemetrexed (restricted to NSCC) [A = 100% and III, B] is an alternative treatment option.

7d. Poor PS (3–4) patients should be treated with BSC only [A = 100% and II, B], unless a molecularly targetable alteration is identified where treatment has minimal toxicity.

All 12 Asian experts agreed with and accepted completely [A = 100%] 'recommendations 7a, b, and c' in the pre-meeting surveys as shown in supplementary Table S5, available at *Annals of Oncology* online, and subsequently recommendation 7d after face-to-face discussion resolved the issues surrounding current practice in one Asian country.

These recommendations are based on the fact that chemotherapy has been shown to prolong survival and improve quality of life (QoL) in NSCLC patients with PS 2 when compared with BSC [I, A] [137, 138]. Furthermore, a recent meta-analysis of randomised trials comparing the efficacy and safety of platinum-based doublets versus single-agent regimens in the first-line therapy of PS 2 patients has shown platinum-based regimens to be superior in terms of response rate and survival despite an increase in toxicities (mainly haematological) [139]. Whilst, the superiority of carboplatin-based combinations over monotherapy in PS 2 patients has been demonstrated in two large phase III trials [138, 140], with an acceptable toxicity profile. Therefore, platinum-based (preferably carboplatin) doublets should be considered in eligible PS 2 patients [I, A]. Treatment with single-agent gemcitabine, vinorelbine, docetaxel [I, B], or pemetrexed (restricted to NSCC) [II, B] is an alternative option [140, 141].

To date, all the phase III studies involving immunotherapies that have reported data, have excluded patients with a PS ≥ 2. However, preliminary data from the CheckMate 153 trial involving 108 patients with advanced NSCLC and a PS of 2 treated with single-agent nivolumab reported improved treatment outcomes for non-squamous NSCLC patients [142]. In addition a European-based phase II safety trial (CheckMate 171), also involving patients treated with nivolumab, of whom 98/809 had a

PS of 2, has shown the safety for the patients with a PS of 2 to be comparable to that of the overall population [143]. Currently, the available data are insufficient to provide recommendations for the use of immune checkpoint inhibitors in PS 2 patients. Patients with a poor PS (3–4) should be offered BSC in the absence of known *EGFR* mutations, *ALK* or *ROS1* rearrangements or a *BRAF V600* mutation [III, B].

Recommendation 8: elderly patients

8a. Immunotherapy should be considered according to standard recommendations in elderly patients [A = 100% and IV, A].
8b. Carboplatin-based doublet chemotherapy should be provided to eligible patients aged ≥70 years with PS 0–2 and with adequate organ function [A = 100% and I, A].
8c. For those patients not eligible for doublet chemotherapy, single-agent chemotherapy remains the standard of care [A = 100% and I, B].

All 12 Asian experts agreed with and accepted completely [A = 100%] 'recommendations 8a, b, and c', in the pre-meeting surveys. This was based on historical data from phase III trials in European and Asian patients that established single-agent chemotherapy (docetaxel, vinorelbine or gemcitabine) as the standard of care first-line in patients with mNSCLC aged ≥70 years [141, 144], and from a more recent systematic review of randomised controlled trials that compared non-platinum single-agent therapy versus non-platinum combination therapy, or non-platinum therapy versus platinum combination therapy in patients >70 years of age with advanced NSCLC and showed platinum-based combination chemotherapy to be the preferred option for patients with a PS of 0–2 and adequate organ function [145]. However, platinum-based combination therapy is associated with an increase in treatment-related toxicities and its use needs to be balanced against the expected survival benefit. Concerns over treatment-related toxicity in elderly patients has led to the study of the use of the Comprehensive Geriatric Assessment (CGA) as a selection tool for treatment, based on a patient's fitness or frailty [146]. However, a multicentre, open-label, phase III trial, in elderly patients ≥70 years old with a PS of 0–2 and stage IV NSCLC randomly assigned between chemotherapy, on the basis of PS and age (standard arm: carboplatin-based doublet if PS ≤1 and age ≤75 years; docetaxel if PS =2 or age >75 years) and treatment allocation on the basis of CGA (CGA arm: carboplatin-based doublet for fit patients, docetaxel for vulnerable patients, and BSC for frail patients), showed treatment allocation on the basis of CGA to fail to improve treatment failure-free survival and overall survival, but to slightly reduce treatment-related toxicity [147]. Thus, a carboplatin-based doublet is the recommended treatment approach for elderly patients with a PS of 0-2 and adequate organ function [I, A], and for those patients not eligible for treatment with doublet chemotherapy, single-agent chemotherapy remains the standard of care [I, B].

Also, although to date, no studies dedicated to elderly patients have been reported, evidence is accumulating for the use of ICT mAbs in the treatment of elderly patients with advanced NSCLC, supported by subgroup analyses from randomised second-line trials in patients with NSCLC aged ≤65 years and >65 years showing equivalent efficacy [148–151] and no difference in toxicity [152]. Whilst, in a subgroup analysis of the KEYNOTE-024 trial there was no difference in the beneficial effect of pembrolizumab between patients aged ≤65 years and those aged >65 years of age (HR 0.61 versus 0.45) [64]. Similarly, in the CheckMate 026 trial, there was no difference in survival outcomes between patients treated with nivolumab aged ≤65 years when compared with >65 years [77]. Immunotherapy should therefore be considered for the treatment of elderly patients with mNSCLC. [III, A].

Recommendation 9: second-line treatment of patients with mNSCLC without a druggable oncogene driver

9a. Patients clinically or radiologically progressing after first-line therapy with a PS of 0–2 should be offered second-line therapy [A = 100% and I, A].
9b. PD-L1 testing is routinely recommended at diagnosis [A = 100% and I, A] to inform the use of pembrolizumab in the first-line setting or second-line setting.
9c. For patients with progression after first-line immunotherapy with pembrolizumab, platinum-based chemotherapy is recommended as a second-line treatment option [A = 100% and V, B].
9d. There is a general trend across each of the phase III studies in second-line (nivolumab, pembrolizumab and atezolizumab versus docetaxel) for enriched efficacy of anti-PD-1/PD-L1 agents in patients with higher PD-L1 expression compared with those with no/less PD-L1 expression. However, unselected patients may still have improved survival and tolerability with anti-PD-1/PD-L1 agents compared with docetaxel [A= 100% and I, A].
9e. PD-L1 and PD-1 inhibitors (nivolumab, pembrolizumab, and atezolizumab) are the treatment of choice for most patients with advanced, previously treated, PD-L1 ***inhibitor****-naive NSCLC, irrespective of PD-L1 expression [A= 100% and I, A].*
9f. In patients not suitable for immunotherapy, second-line chemotherapy is recommended. Comparable options as second-line therapy consist of pemetrexed, for NSCC only, or docetaxel, with a more favourable tolerability profile for pemetrexed [A = 100% and I, B].
9g. Treatment may be prolonged if disease is controlled and toxicity acceptable [A = 100% and II, B].
9h. Nintedanib/docetaxel is a treatment option in patients with adenocarcinoma, especially in those progressing within 9 months from the start of first-line chemotherapy with PS 0–2 [A = 83%, B = 17%% and II, B].
9i. Ramucirumab/docetaxel is a treatment option in patients with NSCLC progressing after first-line chemotherapy with PS 0–2 [A = 100% and I, B].
9j. Erlotinib represents a potential second-/third-line treatment option in particular for patients not suitable for immunotherapy or second-line chemotherapy in unknown EGFR status or EGFR WT tumours [D = 66%, E = 34%% and II, C].
9k. In ***platinum pretreated*** *patients with SCC unfit for chemotherapy or immunotherapy, afatinib is a potential*

option in patients with unknown EGFR status or EGFR WT patients with PS 0–2 [C = 100% and I, C].

All 12 Asian experts agreed with and accepted completely [A = 100%] 'recommendations 9a, b, c, f, g, h, and I' in the pre-meeting surveys (supplementary Table S6, available at *Annals of Oncology* online) and subsequently after discussion 'recommendations 9d and e', and the addition of the word inhibitor to 'recommendation 9e' see bold text above. Voting for 'recommendation 9h' was subsequently slightly changed with a vote of accepted with some reservation from one country (supplementary Table S13, available at *Annals of Oncology* online). The acceptance of these recommendations was based on the fact that currently three PD-1 or PD-L1 therapies (nivolumab, pembrolizumab and atezolizumab) are approved by the United States Food and Drug Administration (FDA) and the EMA for use in the second-line setting for the treatment of patients with NSCLC. Nivolumab and atezolizumab are approved or use in patients with advanced NSCLC irrespective of PD-L1 expression, while pembrolizumab is approved only in patients with PD-L1 expression $\geq$1%. Approval of nivolumab was based on the data from two phase III studies, CheckMate 017 [149] and CheckMate 057 [148] (ESMO MCBS score 5). In the CheckMate 017 trial, 272 patients with squamous NSCLC were randomised to receive either nivolumab or docetaxel, and overall survival was shown to be significantly better for those patients who received nivolumab (HR 0.59, 95% CI: 0.44–0.49, $P < 0.001$). In the CheckMate 057 trial, 582 patients with non-squamous NSCLC were randomised to receive either nivolumab or docetaxel and again overall survival was significantly better for those patients who received nivolumab (HR 0.73, 95% CI: 0.59–0.89, $P = 0.002$). Furthermore, a recent update of these studies has shown the 2-year overall survival results to favour nivolumab in both squamous (29% versus 16% with docetaxel) [I, A] and non-squamous NSCLC (23% versus 8% with docetaxel) [I, A]. Tolerability also favoured nivolumab, with 10% of patients experiencing grade 3–4 treatment-related adverse events (AEs) compared with 55% of patients receiving docetaxel.

Approval of pembrolizumab was based on the results of the KEYNOTE-010 trial which randomised 1034 patients with previously treated NSCLC and PD-L1 expression on at least 1% of tumour cells to receive either pembrolizumab or docetaxel [150, 153]. Overall survival was significantly longer for those patients receiving pembrolizumab (either 2 or 10 mg/kg) than for those receiving docetaxel (2 mg/kg, HR 0.72, 95% CI: 0.6–0.86; $P < 0.001$; 10 mg/kg, HR 0.60, 95% CI 0.49–0.72; $P < 0.001$), with a recently reported 2-year overall survival rates of 14.5% (2 mg/kg) versus 30.1% (10 mg/kg) [I, A]. Grade 3–5 treatment-related AEs were less common with pembrolizumab than with docetaxel (13%–16% versus 35%). There was no significant difference in the safety of pembrolizumab at doses of 2 or 10 mg/kg. Whilst, in the case of atezolizumab, the OAK trial, which evaluated 850 patients with advanced NSCLC previously treated with one or two prior lines of chemotherapy, randomised to receive either atezolizumab or docetaxel, showed atezolizumab to significantly improve overall survival (HR 0.73, 95% CI 0.62–0.87, $P < 0.001$) [151]. Tolerability was also better with atezolizumab, with 15% of patients experiencing a grade 3–4 treatment-related toxicity compared with 43% of those treated with docetaxel [I, A]. Thus, based on these trial data anti-PD-1/PD-L1 agents should be the treatment of choice for most patients with advanced, previously treated, PD-L1 inhibitor-naive NSCLC, irrespective of PD-L1 expression [I, A].

Historically, combination chemotherapy regimens have failed to show any benefit over single-agent treatments in terms of overall survival, second-line [154]. However, single agents do improve disease-related symptoms and overall survival compared with BSC [154]. Docetaxel has shown improved efficacy compared with BSC in randomised trials [155, 156] with similar efficacy, but more favourable tolerability for the weekly schedule compared with the 3-weekly to weekly schedules of docetaxel [I, B] [157, 158]. Pemetrexed demonstrated comparable efficacy to docetaxel in a randomised phase III trial but with a more favourable toxicity profile [159]. Whilst, a retrospective analysis demonstrated the differential effect of histology with an improvement in the efficacy (overall survival) of pemetrexed compared with docetaxel seen in patients with non-squamous NSCLC (9.0 versus 8.3 months; HR 0.78; 95% CI 0.61–1.0; $P = 0.004$) [119]. Thus both docetaxel and pemetrexed (for NSCC only) represent confirmed second-line chemotherapy options, with comparable efficacy [I, B]. Second-line treatment duration should be individualised and prolongation of treatment is an option if disease is controlled and toxicity acceptable [24].

Chemotherapy combined with antiangiogenic agents has been investigated in patients with pretreated advanced NSCLC. Ramucirumab, an VEGF receptor 2 (VEGFR2) antibody, in combination with docetaxel, achieved superior PFS and overall survival when compared with docetaxel and placebo even in patients, who did not show any response to first-line chemotherapy, and regardless of tumour histology [160, 161] (ESMO MCBS score 1). Combination of the oral angiokinase inhibitor nintedanib with docetaxel, improved PFS compared with chemotherapy alone in the LUME-1 trial with a significant prolongation of overall survival observed in the group of patients with adenocarcinomas (median overall survival 12.6 versus 10.3 months; HR 0.82, 95% CI 0.7–0.99; $P = 0.0359$) [162]. Gastrointestinal events and transient elevation of liver enzymes were the AEs most frequently associated with nintedanib and again improved efficacy was seen in the poor prognosis patients with non-responding or rapidly progressing tumours [162, 163]. Combination of paclitaxel and bevacizumab is another treatment option based on the results of the ULTIMATE trial, which showed a prolongation of PFS for the combination of weekly paclitaxel and bi-weekly bevacizumab compared with docetaxel [164].

However, there was considerable discussion amongst the Asian experts regarding 'recommendation 9j' that proposes that erlotinib (an EGFR TKI) represents a potential second-/third-line treatment option, particularly for patients with either *EGFR* wild-type tumours or tumours of unknown *EGFR* mutation status not suitable for immunotherapy or second-line chemotherapy. The experts could only agree to reject with some reservation or completely 'recommendation 9j' [D = 66% and E = 34%%], based on the growing number of reports of the inferiority of EGFR TKIs, compared with chemotherapy, in the treatment of pre-treated patients with *EGFR* wild-type tumours [165]. In a meta-analysis summarising the results of six randomised trials in 900 patients, the PFS for *EGFR* TKIs was significantly inferior to that for chemotherapy in patients with *EGFR* wild-type tumours

(HR 1.37, 95% CI 1.20–1.56; $P < 0.00001$). However, these results did not translate into an OS difference (HR 1.02, 95% CI 0.87–12; $P = 0.81$) in a Chinese trial in patients with advanced *EGFR* wild-type NSCLC [166]. A European analysis has reported a significant improvement in PFS and overall survival for patients receiving second-line chemotherapy compared with second-line EGFR TKI therapy in patients ($n = 1278$) with pretreated NSCLC (PFS 4.3 versus 2.83 months, HR 0.66, 95% CI 0.57–0.77, OS 8.39 versus 4.99 months, HR 0.7, 95% CI 0.59–0.83; $P < 0.0001$) [167].

In patients with advanced SCC, afatinib has been shown to be superior to erlotinib in the LUX-Lung 8 trial, in terms of both PFS and overall survival (PFS 2.4 versus 1.9 months, HR 0.82, 95% CI 0.68–1.00; $P = 0.041$; OS 7.9 versus 6.8 months, HR 0.81, 95% CI 0.69–0.95; $P = 0.0077$) [168] (ESMO MCBS score 2). However, the Asian experts could only agree to accept with major reservation [C = 100%] 'recommendation 9k' that afatinib could be a therapeutic option in patients with advanced SCC [Eastern Cooperative Oncology Group (ECOG) PS 0–2] progressing on or after platinum-based chemotherapy, based on these data [I, C].

Thus, according to the ESMO 2018 Clinical Practice Guidelines for diagnosis, treatment and follow-up for mNSCLC [24], patients clinically or radiologically progressing after first-line therapy, should be offered second-line therapy irrespective of whether they have received maintenance treatment [I, A]. So far, no prospective trials have determined the best second-line therapy following failure of first-line treatment with pembrolizumab, but the preferred recommendation would be platinum-based chemotherapy according to the first-line trial results [64], as discussed above.

Recommendation 10: first-line treatment of *EGFR*-mutated NSCLC

10a. Patients with a tumour with a sensitising EGFR mutation should receive first-line EGFR TKIs including erlotinib, gefitinib or afatinib [I, A]. None of the three EGFR TKIs is consensually considered as a preferred option [III, C]. Dacomitinib will be added to the list when the drug is approved by regulatory agencies, the United States FDA and the EMA [A = 100% and I, A].

10b. First-line osimertinib is now considered one of the options for patients with a tumour with sensitising EGFR mutations [A = 100% and I, A].

10c. All patients should be considered for EGFR TKIs irrespective of clinical parameters, including PS, gender, tobacco exposure, histology and line of therapy [A = 100% and I, A].

10d. Erlotinib and bevacizumab represent a front-line treatment option in patients with EGFR-mutated tumours [A = 100% and II, A].

10e. Addition of carboplatin and pemetrexed to gefitinib represents a first-line option in patients with EGFR-mutated tumours [A = 100% and I, B].

10f. Patients who have radiological progression with ongoing clinical benefit may continue with EGFR TKIs [A = 100% and II, A].

10g. In EGFR-mutated NSCLC patients with localised distant progression and ongoing systemic control, continuation of treatment with an EGFR TKI in combination with local treatment of progressing metastatic sites may be considered [A = 100% and III, B].

All 12 Asian experts agreed with and accepted completely [A = 100%] 'recommendations 10a, b, d, e, f and g' in the pre-meeting surveys (supplementary Table S7, available at *Annals of Oncology* online) and subsequently after discussion recommendation 10c, based on the data presented at the end of this section. This acceptance of the ESMO recommendations was made based on the recognition that *EGFR* mutation status is a long-established [169, 170] predictive marker for the treatment of patients with NSCLC, as demonstrated by the results of phase III trials comparing first- (erlotinib and gefitinib) (ESMO MCBS score 4 for gefitinib and for erlotinib) and second-(afatinib) generation EGFR TKIs with standard platinum-based chemotherapy regimens (ESMO MCBS score 4) [171–176]. The benefit on PFS conferred by EGFR-TKI therapy was consistent across all the above studies and was independent of gender, age, smoking status and PS. The benefit on PFS conferred by EGFR TKI therapy was also observed in patients of Asian ethnicity [171, 175]. Notably none of the above studies demonstrated any benefit for EGFR TKI therapy over platinum-based therapy in terms of overall survival, probably due to the high level of treatment crossover. However, these data support the use of EGFR TKIs as the standard-of-care first-line in the treatment of Asian patients with *EGFR*-mutated NSCLC [I, A] (Figure 3). Asian patients with PS 3–4 may also be offered an EGFR TKI therapy as they are likely to receive a similar clinical benefit [II, A] [177], whilst Asian patients who have benefited from EGFR TKI therapy may continue to receive the same therapy beyond initial radiological progression as long as they are clinically stable [II, A] [178–180]. However, in the randomised, phase III, multicentre IMPRESS trial, conducted in 11 countries in Europe and the Asia-Pacific region, continuation of gefitinib plus chemotherapy after radiological disease progression on first-line gefitinib did not prolong PFS in patients receiving platinum-based doublet chemotherapy as subsequent-line therapy and platinum-based doublet chemotherapy remains the standard of care in this setting [181].

In terms of the choice of EGFR TKI (Figure 3), the randomised phase IIB Lux-Lung 7 trial, showed afatinib to significantly improve PFS and time to treatment failure in treatment-naive patients with *EGFR*-mutated NSCLC compared with gefitinib, with a manageable toxicity profile [182]. There was no significant benefit in overall survival [183]. The international, randomised, open-label, phase III ARCHER 1050 trial, randomly assigned patients with newly diagnosed advanced NSCLC and one *EGFR* mutation (exon 19 deletion or L858R) to receive dacomitinib or gefitinib until disease progression. Dacomitinib significantly improved PFS and overall survival compared with gefitinib in first-line treatment of patients with *EGFR*-mutation-positive NSCLC [184, 185] (FDA but not EMA approved and not yet approved in Asia). According to the ESMO guidelines erlotinib, gefitinib and afatinib are recommended as first-line therapy in patients with advanced NSCLC who have active sensitising *EGFR* mutations, regardless of their PS [I, A] (with no preference for any of the three agents over the others) [I, A]. However, both afatinib and dacomitinib are associated with a higher incidence of grade 3 skin and gastrointestinal toxicity, and a significant

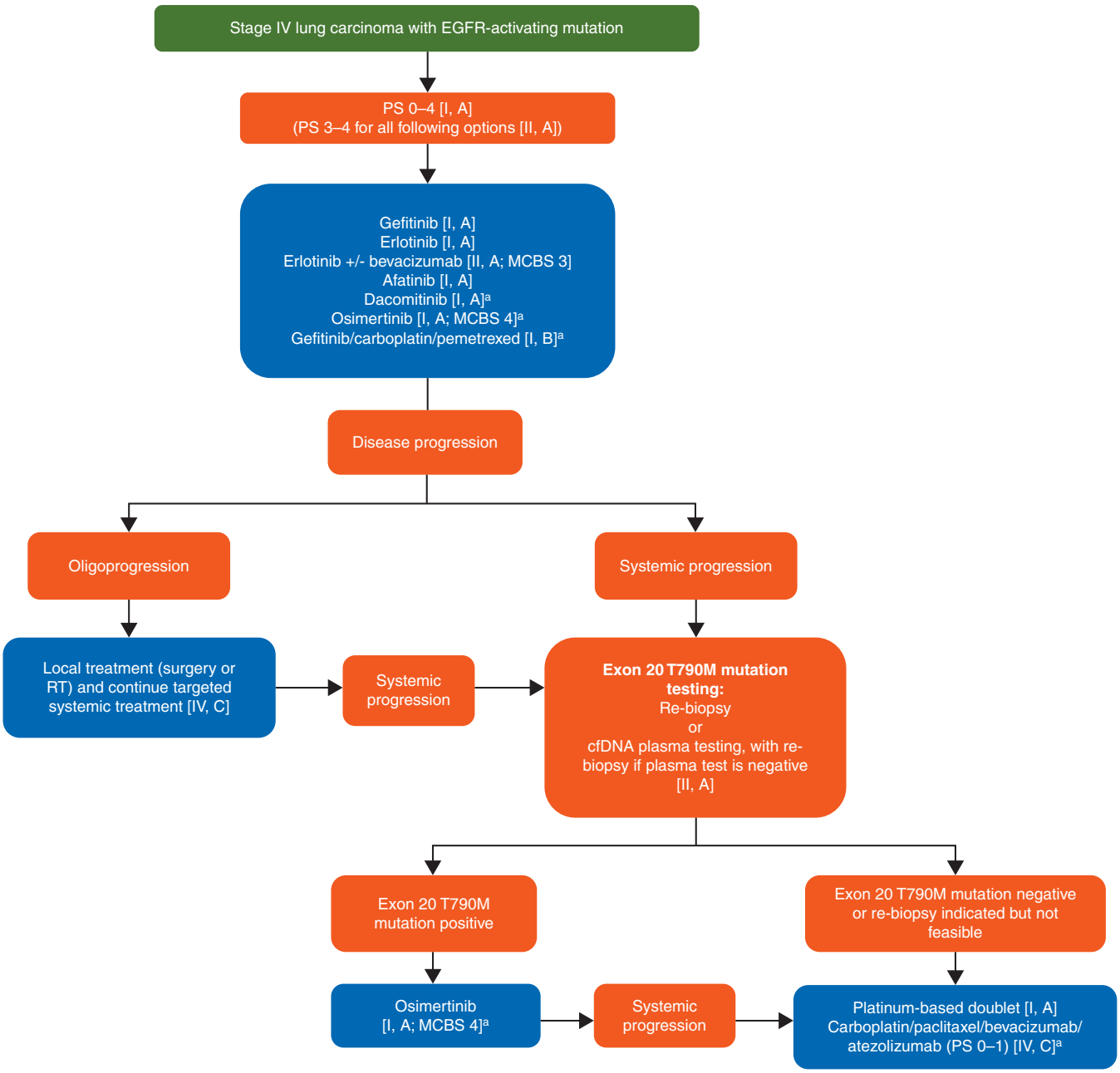

Figure 3. Treatment algorithm for stage IV lung carcinoma with an *EGFR*-activating mutation. [a]Depending on approval status and reimbursement. cfDNA, cell-free DNA; *EGFR*, epidermal growth factor receptor; MCBS, Magnitude of Clinical Benefit Scale; PS, performance status; RT, radiotherapy.

proportion of patients receiving these agents require a dose reduction. Osimertinib, a third generation EGFR TKI that targets both sensitising *EGFR* mutations and the resistant exon 20 *T790M* mutation [58], was compared with standard first-generation EGFR TKIs (gefitinib or erlotinib) in the phase III FLAURA trial [186]. Osimertinib showed a significant improvement in PFS compared with that of the standard EGFR-TKIs (PFS 18.9 versus 10.2 months; HR 0.46, 95% CI 0.37–0.57; $P < 0.0001$) in the first-line treatment of EGFR mutation-positive advanced NSCLC, with a similar safety profile and lower rates of serious AEs. Osimertinib can be considered one of the options for patients with sensitising *EGFR* mutation positive NSCLC (Figure 3 and Table 5).

A Japanese trial was the first to investigate EGFR-TKI therapy in combination with the antiangiogenic agent bevacizumab, versus erlotinib alone and demonstrated a significant difference in PFS (16.4 and 9.8 months, HR 0.52, 95% CI 0.35–0.76) [187]. Meanwhile comparison of bevacizumab plus erlotinib to erlotinib in the Japanese phase III NEJ026 first-line trial reports encouraging interim results with a significant benefit in terms of PFS for the combination therapy over elotinib alone (PFS 16.9 versus 13.3 months, HR 0.60, 95% CI 0.41–0.87), and updated

Table 5. Summary of drug approvals and reimbursement according to Asian country

Drugs	CSCO China		JSMO Japan		KSMO Korea		MOS Malaysia		SSO Singapore		TOS Taiwan		ESMO MCBS V1.1 [278, 279]
	Approval	Reimbursement	Approval	Reimbursement	Approval	Reimbursement	Approval	Reimbursement	Approval	Reimbursement	Approval	Reimbursement	
Pemetrexed 1st-line													4
Pemetrexed maintenance													ND
Pemetrexed 2nd-line													4
Gemcitabine													ND
Vinorelbine													ND
Nab-paclitaxel													ND
Docetaxel													ND
Cisplatin													ND
Carboplatin													ND
Bevacizumab													2
Ramucirumab													1
Nintedanib													ND
Cetuximab													ND
Necitumumab													1
Gefitinib													4
Erlotinib													4
Afatinib					*	*							4 or 2
Osimertinib													4
Crizotinib													4
Alectinib 1st-line													ND
Alectinib 2nd-line													ND
Ceritinib 1st-line													ND
Ceritinib 2nd-line													ND
Nivolumab 2nd-line													5
Pembrolizumab 1st-line													5
Atezolizumab			**								**		ND
Denozumab													ND
Zoledronic acid													ND

*First-line only, **Second-line only; ND, not done.

Approved or reimbursed

Partially reimbursed or with restriction

Not approved or reimbursed

data showed no benefit for overall survival (47 versus 47.4 months) [II, A] [188, 189]. A European phase II trial also evaluated the combination of erlotinib and bevacizumab, and determined it to be suitable as a front-line treatment option in patients with *EGFR*-mutated NSCLC [III, B]. In Europe, the use of the combination of erlotinib and bevacizumab has been approved by the EMA. Thus, erlotinib in combination with bevacizumab represents a front-line treatment option in patients *with EGFR*-mutated disease [II, B].

Whilst, the Japanese NEJ009 trial is the first phase III study to evaluate the efficacy of combination therapy with an EGFR-TKI (gefitinib) and a platinum doublet (carboplatin/pemetrexed) in untreated patients with advanced NSCLC with *EGFR* mutations [190]. Carboplatin/pemetrexed/gefitinib combination therapy demonstrated a significantly better PFS (20.9 versus 11.2 months, HR: 0.49, 95% CI 0.39–0.62) and overall survival (52.2 versus 38.8 months, HR: 0.69, 95% CI 0.52–0.92) when compared with gefitinib alone, as first-line therapy, but is not currently approved.

Recommendation 11: second-line treatment of *EGFR*-mutated NSCLC

11a. EGFR TKI should be stopped at the time when a patient starts chemotherapy for treatment of TKI resistance [A = 100% and I, A].

11b. All tumours with clinical evidence of EGFR TKI resistance, not previously treated with osimertinib, should be tested for the presence of an EGFR exon 20 T790M mutation [A = 100% and I, A].

11c. Liquid biopsy can be used as the initial test for the detection of a T790M mutation, and if tests are negative, a re-biopsy should be attempted if feasible [A = 100% and II, A].

11d. Osimertinib is the standard therapy for patients whose tumours have tested positive for T790M either in liquid biopsy or re-biopsy, if not received previously [A = 100% and I, A].

11e. In EGFR-mutated NSCLC with CNS disease, osimertinib is highly active and may be considered as a therapeutic option [A = 100%].

11f. Platinum-based doublet is the standard therapy for patients whose tumour is tested T790M negative in either re-biopsy or in liquid biopsy (only when re-biopsy is not feasible) [A = 100% and I, A].
*11g. Combination of atezolizumab and bevacizumab with carboplatin and paclitaxel **might** be considered as a therapeutic option in patients with EGFR-mutated tumours, PS 0–1, in absence of contraindications to use of immunotherapy after targeted therapies has been exploited [A = 100% and **IV, C,** after discussion].*

All 12 Asian experts agreed with and accepted completely [A = 100%] 'recommendations 11a, b, c, d and f' in the pre-meeting survey (supplementary Table S8, available at *Annals of Oncology* online) and subsequently after discussion 'recommendations 11e and g'. In the case of 'recommendation 11e' the word **highly** was removed from the statement 'osimertinib is **highly** active'. In the case of 'recommendation 11g' the level of evidence was revised to **IV, C** as there was no specific trial addressing this treatment approach second-line and should was changed to **might** (see bold text above).

Almost all patients who benefit from EGFR TKIs will develop clinical resistance and progress after 9–12 months of treatment. Various mechanisms of resistance to first-generation TKIs have been described [164]. The most common mechanism of resistance (49%–60% of cases) involves the acquisition of *EGFR* exon 20 *T790M* mutations [191]. However, a number of third-generation EGFR TKIs are designed to specifically target the *EGFR T790M* mutation [23]. To date, the only approved treatment of mNSCLC patients with tumour *EGFR T790M* mutations is osimertinib, based on data from the randomised phase III AURA 3 trial, in 419 patients, that compared osimertinib with pemetrexed-platinum in patients with proven *EGFR T790M* mutations at the time of their progression on first-/second-generation EGFR-TKI therapies [53] (Figure 3). The ORRs were 71% and 31%, for osimertinib and pemetrexed-platinum, respectively [odds ratio (OR) 5.39, 95% CI 3.46–8.48; $P < 0.001$]. The primary end point (PFS) was also significantly different (10.2 versus 4.4 months; HR 0.30, 95% CI 0.23–0.41; $P < 0.0001$). Also, among the 144 patients with metastases to the CNS, the median duration of PFS was longer among patients receiving osimertinib than among those receiving pemetrexed-platinum therapy (8.5 versus 4.2 months; HR 0.32; 95% CI 0.21–0.49). In addition, the proportion of patients with AEs of grade 3 or higher was lower in those patients receiving osimertinib (23%) than those receiving pemetrexed/platinum therapy (47%) [53]. This study indicates that all patients with clinical resistance to first-/second-generation EGFR TKIs should be tested for the presence of the *EGFR T790M* mutation, and that osimertinib should be offered as standard treatment of patients who have *EGFR T790M* mutation-positive disease [I, A] [24] (ESMO MCBS score of 4).

In patients with resistance to EGFR TKI therapy in the absence of a tumour *EGFR T790M* mutation, the mechanisms of resistance can include *MET* gene amplification, *PIK3CA* alterations, *KRAS* mutations and small cell transformation. Thus, as per the ESMO Guidelines [24], the current recommended standard of care for these patients is a platinum-based doublet, based on the data from the IMPRESS trial [181]. Results of the IMpower 150 trial (see Recommendation 5, **first-line treatment of NSCLC without a druggable oncogene driver**) [102], which included data on patients with *EGFR* or *ALK* genetic alterations, support the use of a combination of atezolizumab (anti-PD-L1) and bevacizumab with carboplatin and paclitaxel as a therapeutic option in patients with non-squamous mNSCLC, and a PS of 0–1, in the absence of contraindications to the use of immunotherapy and may be an option also in the second-line setting [IV, C] (Figure 3). However, following the meeting in Guangzhou, two publications [192, 193] reported a lack of efficacy for ICT mAbs as single-agents second-line, in TKI naive, PD-L1+, *EGFR*-mutant patients with advanced NSCLC, including those with PD-L1 expression ≥50%. These data suggest that these agents may not be an appropriate therapeutic choice in this setting.

Recommendation 12: first-line treatment of *ALK*-rearranged NSCLC

12a. Patients with ALK-rearranged NSCLC should receive first-line treatment with an ALK TKI, including crizotinib [A = 100% and I, A], ceritinib [A = 100% and I, B] and alectinib [A = 100% and I, A].
12b. Alectinib is associated with a longer PFS and lower toxicity than crizotinib and showed activity against CNS disease in previously untreated patients with ALK-positive NSCLC [A = 100% and I, A].
*12c. In patients with CNS involvement front-line use of ALK TKIs is effective, and alectinib [III, A] or ceritinib [IV, B] are recommended [A = 100%]. **Ceritinib represents a better treatment strategy than chemotherapy [I, B] and presumably crizotinib [IV, B]; alectinib represents a better treatment option than crizotinib [I, A]; brigatinib represents a better treatment option than crizotinib [I, B].***
12d. In ALK-rearranged NSCLC patients with localised distant progression and ongoing systemic control, continuation of treatment with ALK TKI in combination with local treatment of the progressing metastatic sites may be considered [A = 100% and III, B].

All 12 Asian experts agreed with and accepted completely [A = 100%] 'recommendations 12a, b, c and d in the pre-meeting survey based on the data below.

The antitumour activity of the dual ALK and MET TKI crizotinib was initially demonstrated in two multicentre, single-arm studies, in NSCLC patients harbouring an *ALK* rearrangement [194, 195]. Subsequently, the phase III PROFILE 1014 and 1029 trials, comparing crizotinib with platinum–pemetrexed (without maintenance pemetrexed) as first-line treatment in *ALK*-rearranged advanced NSCLC, demonstrated a significantly longer PFSs and higher ORRs for patients treated with crizotinib than for those treated with chemotherapy [196, 197]. As a consequence, first-line treatment with crizotinib is a treatment option for patients with *ALK*-rearranged NSCLC [I, A] (EMA approved in first-line, ESMO MCBS score 4). The second-generation ALK inhibitors ceritinib and alectinib have also shown robust antitumour efficacy, along with intracranial activity, in patients with *ALK*-rearranged NSCLC in the ASCEND [198, 199] and J-ALEX [200] trials. Indeed the head-to-head Japanese phase III J-ALEX trial comparing alectinib with crizotinib, showed alectinib to be superior to crizotinib as an initial treatment with an HR for PFS

of 0.34 (95% CI 0.17–0.70; $P < 0.0001$). A similar head-to-head global trial of alectinib and crizotinib (the ALEX trial) in *ALK*-rearranged treatment-naïve patients also showed investigator assessed PFS to be significantly longer for alectinib than for crizotinib (PFS 34.8 versus 10.9 months; HR: 0.43, 95% CI 0.32–0.58) [201, 202]. In patients with baseline CNS metastases, PFS was 27.7 months for alectinib versus 7.4 months for crizotinib (HR 0.35, 95% CI 0.22–0.56) [201]. Also, grade 3–5 AEs were less frequent with alectinib (41% versus 50% with crizotinib). In a phase III trial (ALTA 1) in patients with *ALK*-positive mNSCLC who had not previously received an ALK inhibitor, superior efficacy against systemic and intracranial disease and a significantly longer PFS was observed for those patients who received the ALK-inhibitor brigatinib than for those who received crizotinib [203]. Thus, front-line use of ALK TKIs is effective in patients with *ALK*-rearranged NSCLC including those with CNS involvement (Figure 4), and additional text has been added to 'recommendation 12c above', and in Table 2. The EMA has approved alectinib for use in first and later-lines and ceritinib in second-line in following crizotinib failure, for patients with *ALK* translocated NSCLC, and brigatinib has recently received favourable opinion for approval from the EMA for use second-line post crizotinib (see below).

Recommendation 13: second-line treatment of *ALK*-rearranged NSCLC

13a. Ceritinib and alectinib are recommended in patients with ALK-positive advanced NSCLC who progress on treatment with or are intolerant to crizotinib [A = 100% and I, A].

13b. In patients with ALK-positive NSCLC progressing on crizotinib with CNS progression, treatment should be a next-generation ALK TKI such as alectinib or ceritinib [A = 100% and I, A].

13c. In patients who progress after a second-generation ALK TKI, the next-generation ALK inhibitors such, as brigatinib or lorlatinib, are an option if available [A = 100% and III, C]. If not pemetrexed and cisplatin should be considered.

13d. Assessment of the molecular mechanisms of resistance could also have an impact in the decision-making process [A = 100% after discussion].

13e. The optimal sequencing of ALK-targeted agents remains to be established.

13f. Combination of atezolizumab and bevacizumab with carboplatin and paclitaxel ***might*** *be considered as a therapeutic option in patients with ALK-mutated tumour, PS 0–1, in the absence of contraindications to use of*

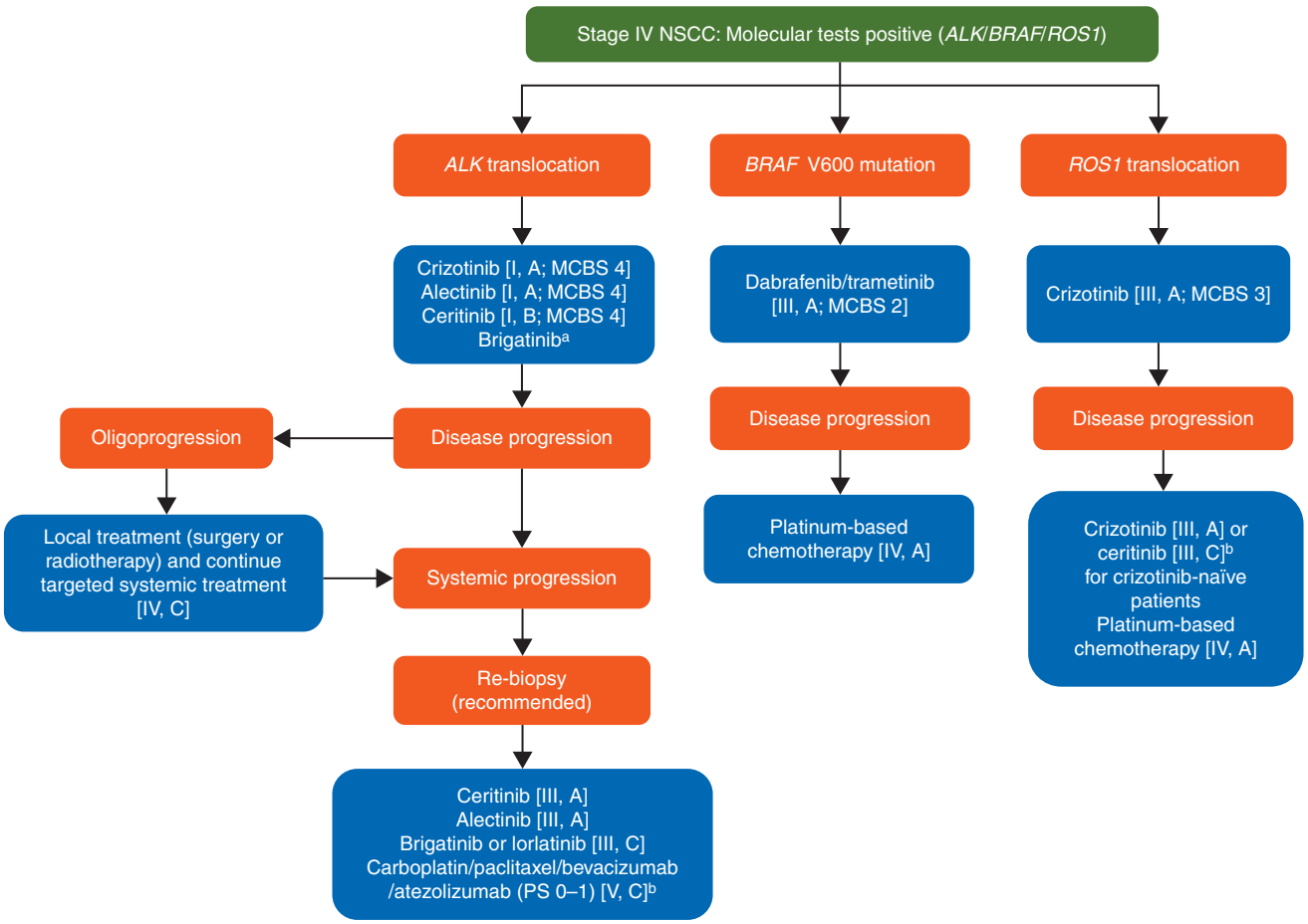

Figure 4. Treatment algorithm for stage IV lung NSCC positive for *ALK/BRAF/ROS1* alterations. [a]Not approved for first-line treatment. [b]Depending on approval status and reimbursement. *ALK*, anaplastic lymphoma kinase; MCBS, Magnitude of Clinical Benefit Scale; NSCC, non-squamous cell carcinoma; PS, performance status.

*immunotherapy after targeted therapies has been exploited [A = 100% and **V, C**].*

All 12 Asian experts agreed with and accepted completely [A = 100%] 'recommendations 13a, b, c, and e' in the pre-meeting survey (supplementary Table S9, available at *Annals of Oncology* online) and subsequently after discussion 'recommendations 13d and f'. In the case of 'recommendation 13 f' the level of evidence was revised to **V, C** as there was no specific trial addressing this treatment approach second-line and the word should change to **might** (see bold text above) and supplementary Table S13, available at *Annals of Oncology* online and Table 2.

Crizotinib was shown to be superior to second-line chemotherapy (either pemetrexed or docetaxel) in TKI-naïve patients with previously treated *ALK*-rearranged NSCLC in the phase III PROFILE 1007 trial, in terms of ORR and PFS [204]. Whilst, ceritinib (ASCEND-5 trial) [205] and alectinib (ALUR trial) [206] have both been shown to significantly improve mPFS compared with chemotherapy (5.4 months, 95% CI 4.1–6.9 for ceritinib versus 1.6 months, 95% CI 1.4–2.8 for chemotherapy; HR 0.49, 95% CI 0.36–0.6; $P < 0.0001$ and 9.6 months, 95% CI 6.9–12.2 for alectinib versus 1.4 months, 95% CI 1.3–1.6 for chemotherapy (HR 0.15, 95% CI 0.08–0.29; $P < 0.001$) in patients with ALK-positive NSCLC previously treated with crizotinib and chemotherapy. These data, support the use of ceritinib and alectinib in patients with *ALK*-positive advanced NSCLC who progress on treatment with, or are intolerant to, crizotinib [I, A] (Figure 4). Their use is also proposed in *ALK*-rearranged NSCLC patients progressing on crizotinib with CNS progression [I, A]. The next-generation ALK inhibitors, such as brigatinib or lorlatinib, target a wider range of *ALK*-resistance mutations, and sequential therapy with these ALK inhibitors is the preferred treatment approach in crizotinib-resistant and/or second-generation-resistant populations based on the results of the ALTA trial evaluating brigatinib in crizotinib-resistant *ALK*-rearranged NSCLC patients [207], and a phase I study with lorlatinib in *ALK*-rearranged patients pretreated with one, two or more ALK TKIs, including patients with CNS metastases at baseline (intracranial ORR 42%) [208]. However, brigatinib has been shown to have limited clinical activity in alectinib-refractory ALK-positive mNSCLC [209]. Thus, studies are needed to establish biomarkers of response to brigatinib and to identify effective therapeutic options for alectinib-resistant ALK-positive NSCLC patients. A phase II study of brigatinib after first-line ceritinib or alectinib [NCT03535740], is ongoing. A phase II study of lorlatinib in patients with *ALK*- or *ROS1*-rearanged NSCLC at the recommended phase II dose has demonstrated a 69% response rate in crizotinib-pre-treated patients, and a 39% RR in patients who had received previous treatment with two or more ALK TKIs. In patients previously treated with one or more second-generation ALK TKIs, a higher proportion of patients harbouring a secondary *ALK* mutation responded to treatment with lorlatinib compared with those without detectable *ALK* mutations [210]. However, data suggest that the sequential use of ALK TKIs can encourage the emergence of other *ALK* mutations [211]. At the present time, brigatinib has received a favourable opinion for approval by the EMA for use in crizotinib-resistant, ALK+ patients, and the approval for lorlatinib is pending. As reported above, results of the IMpower 150 trial (which included patients with *EGFR* or *ALK* genetic alterations) [102], support the use of a combination of atezolizumab (anti-PD-L1) and bevacizumab with carboplatin and paclitaxel as a therapeutic option first-line in patients with non-squamous mNSCLC and a PS of 0–1, in the absence of contraindications to the use of immunotherapy, and may be an option also in the second-line setting in patients with *ALK*-rearranged NSCLC [**V, C**].

Recommendation 14: patients with *ROS1*-rearranged NSCLC

14a. Crizotinib is recommended in the first-line setting in patients with stage IV NSCLC with ROS1 rearrangement, because it has shown results indicating improved response rate and duration of response [A = 100% and III, A].

14b. In patients with ROS1-positive NSCLC, who have not received crizotinib in the first-line setting, single-agent crizotinib may be offered as second-line therapy [A = 100% and III, A].

14c. Ceritinib might be considered in crizotinib-naïve patients but is currently not approved by the EMA [A = 100% and III, C].

14d. If patients have received crizotinib in the first-line setting, then they may be offered platinum-based chemotherapy therapy in the second-line setting [A = 100% and IV, A].

All 12 Asian experts agreed with and accepted completely [A = 100%] 'recommendations 14a, b, c, and d in the pre-meeting surveys. This was based on data on 50 patients with *ROS1*-rearranged NSCLC included in the PROFILE 1001 trial [212], which reported an ORR for crizotinib of 72%, a disease control rate of 90% and a median PFS of 19.2 months. A small prospective French phase II trial [213] and a retrospective subgroup analysis of the EUROS1 trial [214] of crizotinib for patients with *ROS1*-rearranged NSCLC, reported mPFSs of 10.0 and 9.1 months, and ORRs of 72% and 80%, respectively. In an Asian phase II study of crizotinib in 127 patients with *ROS1*-rearranged lung cancer, the mPFS was 13.4 months [215]. Thus, single-agent crizotinib is recommended in the first-line setting or second-line in patients with stage IV NSCLC with an *ROS1* rearrangement [III, A]. In a Korean phase II study, 32 patients with *ROS1*-rearranged advanced NSCLC were treated with ceritinib [216]. Among crizotinib-naïve patients, the ORR was 67%, with a disease control rate of 87%. Ceritinib might be an option for crizotinib-naïve patients but is currently not approved by the EMA [III, C].

Recommendation 15: patients with *BRAF*-mutated NSCLC

15a. Patients with stage IV NSCLC with a BRAF V600 mutation should be exposed in first or second line to BRAF/MEK inhibition using dabrafenib/trametinib [A = 100% and III, A].

15b. If patients have received BRAF/MEK inhibition in the first-line setting, then they may be offered platinum-based chemotherapy in the second-line setting [A = 100% and IV, A].

All 12 Asian experts agreed with and accepted completely [A = 100%] 'recommendations 15a and b', in the pre-meeting surveys.

The *BRAF V600E* mutation is observed in 1%–2% of lung adenocarcinomas [217–219], particularly in those patients with a history of smoking. The activity of the *BRAF* inhibitors vemurafenib, dabrafenib and sorafenib was confirmed in a European retrospective cohort study in patients with *BRAF*-mutant lung adenocarcinoma [220]. Overall survival with first-line therapy was 25.3 months for patients with V600E mutant disease and 11.8 months for patients with non-V600E mutant disease. Thirty-one patients received one BRAF inhibitor, and four received a second inhibitor. The ORR for patients receiving BRAF therapy was 53%, and the disease control rate was 85%. In a vemurafenib basket trial (VE-BASKET), a total of 19 NSCLC patients were assessable for response. Overall, one patient was treatment-naïve and 50% and 45% of patients had received one or two or more lines of therapy before inclusion in the study, respectively. The ORR, PFS and overall survival were 42%, 7.3 months and not yet reached, respectively [221]. A multicohort phase II study of dabrafenib monotherapy (cohort A), or combination therapy with a MEK inhibitor (trametinib) (cohort B, beyond first-line and cohort C in first-line treatment) in patients with *BRAF V600E*-mutant metastatic NSCLC reported an ORR of 33%, and a mPFS and median duration of response of 5.5 and 9.6 months, respectively, for patients receiving dabrafenib monotherapy [222]. In pretreated patients receiving the combination of dabrafenib and trametinib the ORR was 66% and mPFS and median duration of response (mDoR) were 10.2 and 9.8 months, respectively [223, 224]. In treatment-naïve patients receiving a combination of dabrafenib and trametinib therapy the ORR was 64% and mPFS and mDoR were 10.9 and 10.4 months, respectively [225]. As a consequence, the EMA and FDA have approved dabrafenib in combination with trametinib for the treatment of patients with *BRAF V600*-mutation-positive advanced or mNSCLC. BRAF/MEK inhibition using dabrafenib with trametinib is also recommended in patients with BRAF inhibitor-naïve, stage IV NSCLC with a *BRAF V600E* mutation [III, A] (Figure 4).

Recommendation 16: patients with NSCLC with other druggable oncogene drivers

16a. Phase II trials suggest a clinically meaningful benefit using multitargeted agents with anti-RET activity in patients with RET rearranged NSCLC. However, these studies are small and subject to selection bias and results on benefit heterogeneous [A = 100% and III, C].

16b. Targeting RET is not currently routinely recommended and recruitment into open trials is encouraged [A = 100% and III, C].

16c. Targeting MET amplification is not currently routinely recommended and recruitment into open trials is encouraged [A = 100% and III, C].

16d. Targeting MET exon14 variants (while evidence of benefit is stronger) is not currently routinely recommended and recruitment into open trials is encouraged [A = 100% and III, C].

16e. Crizotinib has demonstrated potential clinical efficacy for MET exon14 variant NSCLC that needs to be confirmed [A = 100% and III, C].

16f. Given the paucity of robust data, targeting HER2 dysregulation is not currently recommended and recruitment into open trials is encouraged [A = 100% and III, C].

16g. Targeting NRTK fusions is not currently recommended and recruitment into open trials is encouraged [A = 100% and III, C].

All 12 Asian experts agreed with and accepted completely [A = 100%] 'recommendations 16a–g', in the pre-meeting surveys.

Recommendation 17: role of radiation therapy (RT) in stage IV NSCLC

17a. RT can achieve symptom control for a variety of clinical scenarios including haemoptysis, symptomatic airway obstruction, painful chest wall disease and bone metastasis, superior vena cava syndrome, soft tissue or neural invasion [A = 100% and II, B].

17b. Administration of high dose RT does not result in greater levels of palliation [A = 100% and II, B].

17c. External beam radiation therapy (EBRT) alone is more effective for palliation than endobronchial brachytherapy (EBB) alone [A = 100% and II, B].

17d. For patients previously treated by EBRT who are symptomatic from recurrent endobronchial central obstruction, EBB may be considered in selected cases [A = 100% and III, C].

17e. Neurological symptoms from spinal compression can be relieved by early RT [A = 100% and II, B].

All 12 Asian experts agreed with and accepted completely [A = 100%] 'recommendations 17a–e', in the pre-meeting surveys. This was based on the well-established role of EBRT in the symptom control of metastases, such as painful chest wall disease, painful bone metastasis, superior vena cava syndrome, soft tissue or neural invasion [23]. Thirty to 40 percent of patients with NSCLC will develop bone metastases. A recent systematic review of palliative EBRT regimens for patients with thoracic symptoms from NSCLC includes data from 14 randomised controlled trials involving 3576 patients [226]. Also, as described previously, EBRT is also indicated in cases of haemoptysis, symptomatic airway obstruction and sometimes following surgery for CNS metastases and bone metastases [23]. The data on the optimal timing of thoracic RT and systemic therapy in patients with stage IV NSCLC are sparse. Furthermore, to date, there is no evidence that the concurrent administration of chemotherapy, targeted agents or immunotherapy with palliative RT is beneficial in this group of patients [24].

EBB is another method that can be used for the palliation of thoracic symptoms. The effectiveness of EBB compared with EBRT or other alternative endoluminal treatments was assessed in a Cochrane systematic review [227], which concluded that EBRT alone was more effective for palliation than EBB alone [II, B]. However, for patients previously treated by EBRT who are symptomatic from recurrent endobronchial central obstruction, EBB may be considered in selected cases [III, C] [24].

Recommendation 18: brain metastases

18a. Whole brain radiation therapy (WBRT) should not be offered in recursive positioning analysis (RPA) class III patients in view of the dismal prognosis [I, E]; only BSC is recommended [A = 100%].
18b. WBRT can be considered in selected patients, contingent on prognostic factors of better survival [A = 100% and II, C].
18c. Hippocampus avoidance WBRT is not currently recommended as a standard treatment [A = 100% and III, C].
18d. In the case of a single metastasis, stereotactic radiation surgery (SRS) alone, or resection, is the recommended treatment in patients with RPA class I–II [A=100% and III, B].
18e. Postoperative WBRT or SRS is recommended after surgical resection [I, A].
18f. SRS alone, without WBRT but with close MRI brain imaging follow-up, is an alternative strategy [A=100% and III, B].
18g. For two to four metastases, SRS alone is recommended in RPA class I–II patients [III, B].
18h. For patients with symptomatic brain metastases and/or oedema, dexamethasone or an equivalent dose of another corticosteroid is recommended [A = 100% and III, A].
*18i. In patients with detected asymptomatic CNS metastases at presentation, systemic therapy with deferred RT **can** be considered due to similar intracranial and extracranial responses [B = 83%, C = 17% and II, **C**].*
18j. In patients with a druggable oncogene driver (e.g. EGFR, ALK) and clinically asymptomatic brain metastases, next-generation TKIs may restore control of brain disease and delay cranial RT [A = 100% and II, B].
18k. In patients undergoing immune-checkpoint inhibitor therapy, limited data support safety in patients with small volume untreated CNS metastases [A = 100% and III, B].

All 12 Asian experts agreed with and accepted completely [A = 100%] 'recommendations 18b–h and j and k', in the pre-meeting surveys (see supplementary Table S10, available at *Annals of Oncology* online) and 'recommendation 18a' after discussion at the face-to-face meeting. For 'recommendation 18i' the level of evidence was changed from IIB to II**C** and the word should changed to **can** (see bold text above). Ultimately, the recommendation was accepted by five countries with some reservation [B = 83%] and one country with major reservation [C = 17%], due to the limited available data.

CNS metastases are frequently identified in patients with NSCLC, predominantly in patients with adenocarcinomas. Approximately 30%–64% of patients with mNSCLC have CNS metastases.

As described previously [23], the treatment of patients with brain metastases and no driver mutations is based on prognosis estimated using the Radiation Therapy Oncology Group RPA [228]. Radiation therapy is not recommended for RPA class III patients (who have a Karnofsky index of ≤70%) based on their dismal prognosis (median survival is generally <2 months). The role of WBRT in unselected patients has been questioned by data following the results of phase III non-inferiority QUARTZ trial, in which patients were randomised to receive either BSC including dexamethasone plus WBRT (20 Gy in five daily fractions) or the same BSC without WBRT [229] which reported no difference between the treatment arms in terms of symptom relief, steroid use, overall survival, QoL or quality-adjusted life years, confirming no benefit for WBRT in the RPA class III subset [I, A]. A signal for WBRT benefit was seen for younger patients with better Karnofsky indices and either controlled primary or no-extracranial disease. WBRT can therefore be considered for patients with prognostic factors for better survival such as driver mutations [III, C]. The most frequent WBRT schedules are 20 Gy in 5 fractions or 30 Gy in 10 fractions, with no difference in outcome [I, A] [230]. For most patients with symptomatic brain metastases and/or significant oedema, dexamethasone or equivalent corticosteroid is recommended [III, A] [231]. Tapering of the dose and, if possible, cessation after RT, are recommended. In patients with asymptomatic brain metastases corticosteroid use is not recommended. WBRT-induced tumour shrinkage has been shown to correlate with better survival and preservation of neurocognitive function (NCF) [232]. Also, tumour progression was shown to adversely affect NCF more than WBRT, identifying enhancement of radiation response as being important in these patients. Neuroprotective agents have not demonstrated a convincing role in this setting and are not recommended for routine use [II, C], although a small phase III trial of memantine (RTOG 0614) suggested a benefit [233]. Hippocampus avoidance WBRT is probably safe [234], but is still undergoing trial evaluation and is not currently recommended [III, C].

In the case of patients with single brain metastases surgical resection can be considered [235–237], and postoperative WBRT or SRS is generally recommended [I, A] [238]. SRS alone is a treatment strategy in the case of RPA class I and II patients with a limited number of metastases [III, B] [239–241]. In fact, SRS has increasingly become the favoured treatment modality due to the fact that it is less toxic than WBRT. However, there is no randomised trial comparing SRS alone with WBRT. A survival advantage in favour of WBRT plus SRS has been demonstrated when compared with WBRT, but only in patients with a single brain metastasis [254]. The majority of studies evaluating WBRT as an adjunct to SRS or neurosurgery have shown a decline in cognitive function in the combined arm [242, 243]. SRS alone with close follow-up, without WBRT consolidation, is therefore a recommended strategy [III, B]. SRS of the surgical cavity in patients who have had complete resection of one to three brain metastases has been shown to lower the incidence of local recurrence when compared with observation alone [24, 244].

Although it is generally accepted that SRS should be considered for the treatment of patients with ≤4 brain metastases, a prospective observational study from Japan challenged this view [245]. The study enrolled 1194 eligible patients (76% had lung cancer) with one to ten newly diagnosed brain metastases, longest diameter <3 cm, largest tumour <10 ml in volume and a total cumulative volume of ≤15 ml, and showed the overall survival outcome to be the same for patients with 2–4 metastases and those with 5–10 metastases, treated with SRS. This study therefore suggested the use of tumour volume and absolute size rather than the number of metastases as treatment criteria. In most countries, SRS is now based on total tumour volume rather than numbers of metastases, as the risk of radionecrosis increases with tumour volume [III, C] [242]. In patients undergoing SRS, radionecrosis is a challenging complication to manage.

In patients with asymptomatic brain metastases who have not yet received prior systemic therapy (i.e. chemotherapy, TKIs), treatment with upfront systemic therapy and deferred RT should be considered, with trial data suggesting similar intracranial and extra-cranial ORRs [II, B] [246, 247]. In a phase III Asian trial in patients with *EGFR*-mutant NSCLC and multiple brain metastases, icotinib (an EGFR-TKI) was associated with significantly longer intracranial PFS than whole brain irradiation plus chemotherapy, indicating that EGFR TKIs might be a better first-line therapeutic option for this patient population [248]. In patients suitable for first-line ICT mAb therapy, CNS metastases are generally mandated to have been treated before therapy in most available clinical trials. Evidence of intracranial responses has been demonstrated in smaller series and across diseases, but evidence remains limited regarding the safety and efficacy of immunotherapy in patients with small volume, untreated, NSCLC CNS metastases [III, B] [249].

Between 44% and 60% of mNSCLC patients with a druggable oncogene driver (e.g. *EGFR, ALK*), develop brain metastases during the course of their disease [250, 251]. For these patients, the evidence suggests that the use of CNS-penetrant next-generation TKIs (e.g. osimertinib, alectinib, ceritinib, brigatinib) may restore control of brain disease, thereby potentially delaying cranial RT [II, A] [186, 199, 202]. Also, next-generation TKIs may also reduce the incidence of new CNS metastases thereby significantly postponing the time to until patients need CNS RT [184].

Recommendation 19: LM carcinomatosis

19a. A high index of suspicion should be borne for leptomeningeal involvement especially in patients with druggable oncogenic drivers having TKI treatment [V]. CSF sampling is diagnostic of leptomeningeal disease (LMD) but limited by low sensitivity, albeit with high specificity [IV] [A = 100%]

19b. Patients with druggable oncogenic drivers and LMD can be treated with CNS-penetrant next-generation TKIs [A = 100% and III, B].

19c. Intra-CSF pharmacotherapy can be considered contingent on clinical factors [A = 100% and V, C].

All 12 Asian experts agreed with and accepted completely [A = 100%] 'recommendations 19a and b' in the pre-meeting surveys (see supplementary Table S11, available at *Annals of Oncology* online) and recommendations 19c after discussion at the face-to-face meeting, and based on the data presented below.

LMD is a deadly complication of solid tumours and is associated with a poor prognosis. Of the patients with NSCLC who present with CNS metastases (30%–64%), 4%–7% present with LMD [252]. The incidence and prevalence of LMD is increasing due to screening for brain metastases, better imaging modalities, as well as a prolongation of patient survival in those with CNS metastases.

Patients with LMD may present with non-specific neurological symptoms (headaches, nausea, vomiting) as well as discrete signs related to the CNS area involved (gait difficulties, cranial nerve palsies). Diagnosis may involve cerebrospinal MRI with contrast enhancement, ideally before cerebral spinal fluid (CSF) intervention. CSF sampling with cytological assessment, is diagnostic [IV, A]. The prognosis for patients with NSCLC LMD is poor, and the treatment aim is to prolong survival coupled with an acceptable QoL. Patients with druggable oncogenic drivers may derive benefit from a CNS-penetrant next-generation TKI as per those with brain metastases [III, B], as described previously for icotinib under 'recommendation 18' above [248], and in a recent review [253], Also, investigation of afatinib versus platinum-based chemotherapy first-line in *EGFR*-mutation-positive patients with NSCLC and brain metastases supported the clinical activity of afatinib in this setting [254]. The specific and strong CNS activity of osimertinib might also suggest its use in this context (IV, C) [53, 186]. Chemotherapy may have activity both extra-cranially and intra-cranially, and possibly in the context of LMD [IV, C], and bevacizumab may have a role [IV, C] [255, 256]. Intra-CSF pharmacotherapy may be considered via repeated lumbar punctures, a reservoir, or a ventricular device, although consideration should be given to patient factors, e.g. PS, extra-cranial control and likely benefit [V, C]. No randomised data exist to support the role of RT for LMD. In exceptional cases, focal RT can be considered for circumscribed, notably symptomatic, lesions [V, C].

Recommendation 20: treatment of OMD

20a. Stage IV patients with one to three synchronous metastases at diagnosis may experience long-term DFS following systemic therapy and local consolidative therapy (LCT) (high-dose RT or surgery) [A = 100% and II, B]. Because of the limited evidence, these patients should be discussed within a multidisciplinary tumour board [A = 100% and II, B], and inclusion in clinical trials is preferred.

20b. Although operative risk is low and long-term survival may be obtained, current evidence for surgery in OMD is limited, and the relative contribution of surgery versus RT as local treatment modality has not yet been established.

20c. Stage IV patients with limited metachronous metastases may be treated with radical local therapy (high-dose RT or surgery) and may achieve long-term DFS [A = 100% and IV, C]. However, this is based mainly on retrospective data and inclusion in clinical trials is preferred.

20d. Stage IV patients with driver mutations, with oligoprogression while on molecular-targeted therapy, may be treated with a radical local treatment (high-dose RT or surgery) and may experience long-term DFS [A = 100% and IV, C]. However, this is based mainly on retrospective data and inclusion in clinical trials is preferred.

20e. Solitary lesions in the contralateral lung should, in most cases, be treated with curative-intent therapy, ***unless contraindicated*** *[A = 100% and IV, B].*

All 12 Asian experts agreed with and accepted completely [A = 100%] 'recommendations 20a–d' in the pre-meeting surveys (see supplementary Table S12, available at *Annals of Oncology* online) and 'recommendations 20e' after discussion at the face-to-face meeting and rewording of the recommendation to remove the wording 'considered as synchronous secondary primary tumours and if possible' after 'should be', and the addition of '**unless contraindicated**' (see also bold text above) after 'therapy', based on the data presented below.

Long-term disease control, or even cure, can be achieved in some subgroups of patients with OMD after aggressive local

treatment of distant metastases with surgery or high-dose RT [257]. However, almost all the published clinical trials investigating local treatment of OMD, in patients with NSCLC, have limited inclusion to patients with ≤5 metastases. In addition, the vast majority of the trials included patients with ≤3 metastases and in an individual patient meta-analysis, almost 90% of the patients had a single metastasis [257]. Some studies also limited the number of organs in which these metastases are present [258].

Oligometastases can be either synchronous or metachronous [259] and their biology may differ, as suggested by the fact that patients with metachronous oligometastases have a better prognosis [257]. In patients receiving systemic therapy (mainly in tumours with driver mutations treated with TKIs), the term oligoprogression can be also applied in the case of the progression of a limited number of metastatic lesions, when all the other lesions remain stable.

The specific approach to the treatment of oligometastases in the brain has been discussed above ('recommendation 18'). However, another subgroup requiring discussion is that of patients with a solitary lesion in the contralateral lung. The International Association for the Study of Lung Cancer (IASLC) Staging and Prognostic Factors Committee carried out a systematic literature review, aimed at distinguishing a second primary from a metastasis in patients who have more than one pulmonary nodule [86]. This review concluded that few features are definitive, with many commonly used factors being suggestive, carrying a substantial risk of misclassification as the majority of second primary lung tumours are of the same histology. For these cases, the IASLC recommended a careful review by a multidisciplinary tumour board, and pursuit of radical therapy, such as that for a synchronous secondary primary tumour, when possible. Both surgery [259, 260] and SRS [261, 262] have been shown to generate patients who are long-term survivors, in this setting [IV, B].

A systematic literature review showed surgery to be the most common treatment approach for both the primary tumour ($n = 635$, 83.9%) and metastases ($n = 339$, 62.3%). Predictive factors for overall survival were synchronous versus metachronous metastases ($P < 0.001$), N-stage ($P = 0.002$) and adenocarcinoma histology ($P = 0.036$) [257]. Whilst, RPA for risk groups identified a good prognosis (low-risk) group presenting with metachronous metastases (5-year overall survival 48%), an intermediate-risk group presenting with synchronous metastases and N0 disease (5-year overall survival 36%) and, finally, a high-risk group presenting with synchronous metastases and intrathoracic N1/N2 disease (5-year overall survival 14%). However, it should be noted that the positive outcomes in these patients might not be due solely to treatment, but also to patient selection or other biases [263].

Stage IV patients with limited synchronous metastases at diagnosis may experience long-term disease-free survival (DFS) following systemic therapy and local consolidated therapy (LCT) such as high-dose RT including stereotactic ablative body RT (SABR) or surgery [III, B]. Five phase II trials evaluating LCT in patients with NSCLC and synchronous oligometastases have been published. Three small, single-arm studies generally showed durable PFS in a subgroup of patients [264–266], whilst two randomised phase II studies were stopped early after interim analysis. The first of these phase II studies randomised mNSCLC patients with ≤3 metastases, without progression after first-line systemic therapy (n=49), between consolidative therapy [(chemo) RT or surgery] with or without maintenance or maintenance treatment alone and showed a significant difference in PFS time between the two groups [PFS 11.9 months in the LCT (surgery) group versus 3.9 months in the maintenance group; HR=0.35, $P = 0.005$] [267]. The second phase II study randomised patients with ≤5 metastatic sites between maintenance chemotherapy alone and SABR followed by maintenance chemotherapy ($n = 29$) [268]. So far, there are no published data on the impact of LCT on overall survival and long-term toxicity. Stage IV NSCLC patients with limited metachronous metastases may be treated using radical local treatment such as high-dose Rt or surgery, as some patients may experience long-term DFS [IV, B]. However, this is based mainly on retrospective data. There is also a paucity of prospective data to support this treatment approach in patients with driver mutations who present with oligoprogression on molecular-targeted therapies [IV, C]. Furthermore, there are little data on the safety of combining SABR with molecularly targeted agents.

Some recommendations for the implementation of standard-of-care, and advanced imaging modalities for identifying and following up patients with OMD, have been published by the European Organisation for Research and Treatment of Cancer (EORTC) imaging group [269]. In the synchronous, metachronous and oligoprogressive disease settings, inclusion of patients in clinical trials is preferred because of the limited evidence available.

Recommendation 21: bone metastases

21a. Zoledronic acid reduces SREs (pathological fracture, radiation/surgery to bone or spinal cord compression) and is recommended in stage IV bone metastatic disease [A = 100% and II, B].
21b. Denosumab shows a trend towards superiority to zoledronic acid in lung cancer in terms of SRE prevention [A = 100% and II, B].
21c. In the case of uncomplicated painful bone metastases, single fraction EBRT is the recommended treatment on the basis of non-inferiority to multiple fraction RT [A = 100% and I, A].

All 12 Asian experts agreed with and accepted completely [A = 100%] 'recommendations 21a–c' in the pre-meeting surveys, based on the data discussed in the paragraph below.

Bone metastases occur in 30%–40% of patients with NSCLC, and it may be reasonable to evaluate bone disease at diagnosis. In general, the treatment approach is to palliate symptoms and prevent complications. Palliative RT is highly effective and usually achieves rapid pain relief. Both standard EBRT and SABR can be used to palliate painful, uncomplicated bone pain. Systematic reviews of palliative RT trials of patients with bone metastases have shown single- and multiple-fraction regimens to provide equal pain relief. However, retreatment rates were significantly higher for those patients receiving single-fraction treatment [I, A] [270, 271].

The bisphosphonate zoledronic acid has been shown to reduce skeletal-related events (SREs) (pathological fracture, radiation or

surgery to bone, or spinal cord compression) in patients with NSCLC [II, B] [272, 291]. Denosumab, a monoclonal antibody that slows the breakdown of bone, has shown a trend towards superiority over zoledronic acid in advanced solid tumours in terms of SRE prevention [II, B] [273, 292], and in a large phase III trial, denosumab was associated with improved overall survival in a subgroup of 702 patients with mNSCLC [274]. In a phase III trial of denosumab versus zoledronic acid in patients with advanced cancers (44% NSCLC), denosumab significantly delayed the time to first on-study SRE compared with zoledronic acid. Denosumab also reduced the time period over which pain interfered with daily life (used as surrogate for QoL) and worsening pain interference in patients with no/mild baseline pain [275]. Zoledronic acid or denosumab are thus recommended in selected patients (life expectancy >3 months at high risk of SREs) with advanced lung cancer with bone metastases [I, B].

Recommendation 22: the role of minimally invasive procedures in patients with stage IV NSCLC

22a. In the case of symptomatic major airway obstruction or post-obstructive infection, endoscopy debulking by laser, cryotherapy or stent placement may be helpful [A = 100% and III, C].
22b. Endoscopy is useful in the diagnosis and treatment (endobronchial or for guiding endovascular embolisation) of haemoptysis [A = 100% and III, C].
22c. Vascular stenting might be useful in NSCLC-related superior vena cava compression [A = 100% and II, B].

All 12 Asian experts agreed with and accepted completely [A = 100%] 'recommendations 22a–c in the pre-meeting surveys.

Endoscopy has a role to play in palliative care, notably in the case of symptomatic major airway obstruction or post-obstructive infection, where endoscopic debulking by laser, cryotherapy or stent placement may be helpful [III, C] [23]. Endoscopy is useful in the diagnosis and treatment (endobronchial or by guiding endovascular embolisation) of haemoptysis [III, C]. Vascular stenting is useful in NSCLC-related superior vena cava compression [III, B] [23].

Recommendation 23: palliative care in patients with stage IV NSCLC

23. Early palliative care intervention is recommended, in parallel with standard oncological care [A = 100% and I, A].

All 12 Asian experts agreed with and accepted completely [A = 100%] 'recommendation 23' in the pre-meeting survey.

Early palliative care intervention is recommended, in parallel with standard oncological care [I, A], with evidence demonstrating that palliative care interventions significantly improve QoL (ESMO MCBS score 4). Two randomised trials evaluating the impact of introducing specialised, early, palliative care after diagnosis of stage IV NSCLC on patient QoL in ambulatory patients were able to show improvements in QoL and mood [276], and in one trial, a reduction in aggressive treatment and an improvement in overall survival [277].

Recommendation 24: follow-up in patients with stage IV NSCLC

24. Close follow-up, at least every 6–12 weeks to allow for early initiation of second-line therapy, is advised, but should depend on individual retreatment options [A = 100% and III, B].

All 12 Asian experts agreed with and accepted completely [A = 100%] 'recommendation 24' in the pre-meeting survey.

Due to the aggressive nature of this disease, generally close follow-up, at least every 6–12 weeks after first-line therapy, is advised to allow for early initiation of second-line therapy but should also depend on individual retreatment options [III, B].

Conclusions

The results of the voting by the Asian experts both before and after the face-to-face meeting in Guangzhou showed high concordance (supplementary Table S1–S13, available at *Annals of Oncology* online) with the ESMO recommendations for the treatment of patients with mNSCLC published as part of the 2016 'ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up' for mNSCLC [23], and the July 2018 update of these guidelines [24]. In terms of level of agreement, there were no votes of less than an A (accept completely) following the face-to-face discussions, except for 'recommendations 3l [B = 100%], 5c [B = 100%] and n [C = 100%], 6a [A = 83%, C = 7%], 9j [D = 100%] and k [C = 100%], and 18i' [B = 83%, C = 17%] (supplementary Table S13, available at *Annals of Oncology* online).

Thus, these guidelines can be considered to be consensus guidelines for the treatment of patients with mNSCLC in Asia, with ≥80% of experts voting to accept completely or accept with reservation a specific recommendation except for 'recommendations 5n (overall vote C), 9j (overall vote D) and 9K (overall vote C). As mentioned previously, the levels of agreement provided by each of the Asian experts were based on the available 'scientific' evidence, and were independent of the approval and reimbursement status of certain drugs (including biologics) in their individual countries. A summary of the approval and reimbursement status of the recommended drugs, as of July 2018, is presented for each participating country in Table 5 and will obviously impact on some of the treatment strategies that can be adopted by certain countries.

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References

1. Torre LA, Bray F, Siegel RL et al. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65(2): 87–108.
2. Pakzad R, Mohammadian-Hafshejani A, Ghoncheh M et al. The incidence and mortality of lung cancer and their relationship to development in Asia. Transl Lung Cancer Res 2015; 4(6): 763–774.
3. World Cancer Report. http://www.iarc.fr/en/media-centre/iarcnews/2018/wcr.php (November 2018, date last accessed).
4. IARC. Cancer incidence, mortality and prevalence worldwide GLOBOCAN 2012. http://gco.iarc.fr (September 2018, date last accessed).
5. Bray F, Ferlay J, Soerjomataram I et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68(16): 394–424.
6. "IASLC 2015 Statement on Tobacco Control and Smoking Cessation" in Edition; https://www.iaslc.org/sites/default/files/wysiwyg-assets/News/iaslc_2015_tobacco_statement_long.pdf (7 September 2015, date last accessed).
7. Li Q, Hsia J, Yang G. Prevalence of smoking in China in 2010. N Engl J Med 2011; 364(25): 2469–2470.
8. Koplan J, Eriksen M. Smoking cessation for Chinese men and prevention for women. Lancet 2015; 386(10002): 1422–1423.
9. Chen W, Zheng R, Baade PD et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016; 66(2): 115–132.
10. Park JY, Jang SH. Epidemiology of lung cancer in Korea: recent trends. Tuberc Respir Dis (Seoul) 2016; 79(2): 58–69.
11. Foundation for the Promotion of Cancer Research; Cancer Statistics in Japan 2015. https://ganjoho.jp/data/reg_stat/statistics/brochure/2015/cancer_statistics_2015.pdf201 (September 2018, date last accessed).
12. Eldridge L. The Japanese lung cancer smoking paradox. Verywell health 2018; https://www.verywellhealth.com/the-japanese-lung-cancer-smoking-paradox-2248990 (November 2018, date last accessed).
13. Funatogawa I, Funatogawa T, Yano E. Trends in smoking and lung cancer mortality in Japan, by birth cohort, 1949-2010. Bull World Health Organ 2013; 91(5): 332–340.
14. Nakaji S, Yoshioka Y, Mashiko T et al. Explanations for the smoking paradox in Japan. Eur J Epidemiol 2003; 18(5): 381–383.
15. Planchard D, Besse B. Lung cancer in never-smokers. Eur Respir J 2015; 45(5): 1214–1217.
16. Wakelee HA, Chang ET, Gomez SL et al. Lung cancer incidence in never smokers. J Clin Oncol 2007; 25(5): 472–478.
17. Toh CK, Gao F, Lim WT et al. Never-smokers with lung cancer: epidemiologic evidence of a distinct disease entity. JCO 2006; 24(15): 2245–2251.
18. Kang H, Park C-W, Kim W et al. Never-smoker lung cancer is increasing. J Lung Cancer 2012; 11(2): 89–93.
19. Couraud S, Souquet PJ, Paris C et al. BioCAST/IFCT-1002: epidemiological and molecular features of lung cancer in never-smokers. Eur Respir J 2015; 45(5): 1403–1414.
20. Ha SY, Choi SJ, Cho JH et al. Lung cancer in never-smoker Asian females is driven by oncogenic mutations, most often involving EGFR. Oncotarget 2015; 6(7): 5465–5474.
21. Society JLC. Lung Cancer Practice Guidelines Version 1.1; https://www.haigan.gr.jp/modules/guideline/index.php?content_id=3 2017 (October 2018, date last accessed).
22. Zhou Q, Wu YL. Developing CSCO lung cancer practice guidelines stratified by resource availability and treatment value. JGO 2017; 3(4): 285–288.

23. Novello S, Barlesi F, Califano R et al. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016; 27(Suppl 5): v1–v27.
24. Planchard D, Popat S, Kerr K et al. Metastatic non-small cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018; 29: 1v192–iv237.
25. Yoshino T, Arnold D, Taniguchi H et al. Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: a JSMO-ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS. Ann Oncol 2018; 29(1): 44–70.
26. Dykewicz CA. Centers for Disease Control and Prevention, Infectious Diseases Society of America, American Society of Blood and Marrow Transplantation. Summary of the Guidelines for Preventing Opportunistic Infections among Hematopoietic Stem Cell Transplant Recipients. Clin Infect Dis 2001; 33: 139–144.
27. Forrest LM, McMillan DC, McArdle CS, Dunlop DJ. An evaluation of the impact of a multidisciplinary team, in a single centre, on treatment and survival in patients with inoperable non-small-cell lung cancer. Br J Cancer 2005; 93(9): 977–978.
28. Freeman RK, Van Woerkom JM, Vyverberg A, Ascioti AJ. The effect of a multidisciplinary thoracic malignancy conference on the treatment of patients with lung cancer. Eur J Cardiothorac Surg 2010; 38(1): 1–5.
29. Protack CD, Blasberg JD, Liu J et al. The impact of decreasing variability in surgical care through a structured multi-disciplinary thoracic oncology program. J Clin Pathways 2017; 3: 40–45.
30. Schmidt HM, Roberts JM, Bodnar AM et al. Thoracic multidisciplinary tumor board routinely impacts therapeutic plans in patients with lung and esophageal cancer: a prospective cohort study. Ann Thorac Surg 2015; 99(5): 1719–1724.
31. Ost DE, Ernst A, Lei X et al. Diagnostic yield and complications of bronchoscopy for peripheral lung lesions. Results of the AQuIRE Registry. Am J Respir Crit Care Med 2016; 193(1): 68–77.
32. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013; 143(5): e142S–e165S.
33. van der Drift MA, van der Wilt GJ, Thunnissen FB, Janssen JP. A prospective study of the timing and cost-effectiveness of bronchial washing during bronchoscopy for pulmonary malignant tumors. Chest 2005; 128(1): 394–400.
34. Herth F, Becker HD, Ernst A. Conventional vs endobronchial ultrasound-guided transbronchial needle aspiration: a randomized trial. Chest 2004; 125(1): 322–325.
35. Paone G, Nicastri E, Lucantoni G et al. Endobronchial ultrasound-driven biopsy in the diagnosis of peripheral lung lesions. Chest 2005; 128(5): 3551–3557.
36. Adams K, Shah PL, Edmonds L, Lim E. Test performance of endobronchial ultrasound and transbronchial needle aspiration biopsy for mediastinal staging in patients with lung cancer: systematic review and meta-analysis. Thorax 2009; 64(9): 757–762.
37. Nakajima T, Kimura H, Takeuchi K et al. Treatment of lung cancer with an ALK inhibitor after EML4-ALK fusion gene detection using endobronchial ultrasound-guided transbronchial needle aspiration. J Thorac Oncol 2010; 5(12): 2041–2043.
38. Nakajima T, Yasufuku K, Nakagawara A et al. Multigene mutation analysis of metastatic lymph nodes in non-small cell lung cancer diagnosed by endobronchial ultrasound-guided transbronchial needle aspiration. Chest 2011; 140(5): 1319–1324.
39. Rekhtman N, Brandt SM, Sigel CS et al. Suitability of thoracic cytology for new therapeutic paradigms in non-small cell lung carcinoma: high accuracy of tumor subtyping and feasibility of EGFR and KRAS molecular testing. J Thorac Oncol 2011; 6(3): 451–458.
40. Sakairi Y, Nakajima T, Yasufuku K et al. EML4-ALK fusion gene assessment using metastatic lymph node samples obtained by endobronchial ultrasound-guided transbronchial needle aspiration. Clin Cancer Res 2010; 16(20): 4938–4945.
41. Chan EY, Gaur P, Ge Y et al. Management of the solitary pulmonary nodule. Arch Pathol Lab Med 2017; 141(7): 927–931.
42. Choi SH, Chae EJ, Kim JE et al. Percutaneous CT-guided aspiration and core biopsy of pulmonary nodules smaller than 1 cm: analysis of outcomes of 305 procedures from a tertiary referral center. AJR Am J Roentgenol 2013; 201(5): 964–970.
43. Fontaine-Delaruelle C, Souquet PJ, Gamondes D et al. Negative predictive value of transthoracic core-needle biopsy: a multicenter study. Chest 2015; 148(2): 472–480.
44. Lee SM, Park CM, Lee KH et al. C-arm cone-beam CT-guided percutaneous transthoracic needle biopsy of lung nodules: clinical experience in 1108 patients. Radiology 2014; 271(1): 291–300.
45. Takeshita J, Masago K, Kato R et al. CT-guided fine-needle aspiration and core needle biopsies of pulmonary lesions: a single-center experience with 750 biopsies in Japan. AJR Am J Roentgenol 2015; 204(1): 29–34.
46. Travis WD, Brambilla E, Burke AP et al. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart, 4th edition. Lyon: IARC Press 2015.
47. Travis WD, Brambilla E, Noguchi M et al. International association for the study of lung cancer/American Thoracic Society/European Respiratory Society International multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011; 6(2): 244–285.
48. Travis WD, Brambilla E, Noguchi M et al. Diagnosis of lung cancer in small biopsies and cytology: implications of the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification. Arch Pathol Lab Med 2013; 137(5): 668–684.
49. Kerr KM, Bubendorf L, Edelman MJ et al. Second ESMO consensus conference on lung cancer: pathology and molecular biomarkers for non-small-cell lung cancer. Ann Oncol 2014; 25(9): 1681–1690.
50. Lindeman N, Cagle P, Aisner D. Updated molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors: guideline from the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. Arch Pathol Lab Med 2018.
51. Kalemkerian GP, Narula N, Kennedy EB et al. Molecular testing guideline for the selection of patients with lung cancer for treatment with targeted tyrosine kinase inhibitors: American Society of Clinical Oncology Endorsement of the College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology Clinical Practice Guideline Update. J Clin Oncol 2018; 36(9): 911–919.
52. Lindeman NI, Cagle PT, Beasley MB et al. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. J Thorac Oncol 2013; 8: 823–859.
53. Mok TS, Wu YL, Ahn MJ et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med 2017; 376(7): 629–640.
54. Zhang YL, Yuan JQ, Wang KF et al. The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. Oncotarget 2016; 7(48): 78985–78993.
55. Liam CK, Leow HR, How SH et al. Epidermal growth factor receptor mutations in non- small cell lung cancers in a multiethnic Malaysian patient population. Asian Pac J Cancer Prev 2014; 15(1): 321–326.
56. Bareschino MA, Schettino C, Rossi A et al. Treatment of advanced non small cell lung cancer. J Thorac Dis 2011; 3(2): 122–133.
57. Oxnard GR, Miller VA, Robson ME et al. Screening for germline EGFR T790M mutations through lung cancer genotyping. J Thorac Oncol 2012; 7(6): 1049–1052.
58. Cross DA, Ashton SE, Ghiorghiu S et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. Cancer Discov 2014; 4(9): 1046–1061.

59. Mok T, Wu YL, Lee JS et al. Detection and dynamic changes of EGFR mutations from circulating tumor DNA as a predictor of survival outcomes in NSCLC patients treated with first-line intercalated erlotinib and chemotherapy. Clin Cancer Res 2015; 21(14): 3196–3203.
60. van der Wekken AJ, Pelgrim RT, Hart N et al. Dichotomous ALK-IHC is a better predictor for ALK inhibition outcome than traditional ALK-FISH in advanced non-small cell lung cancer. Clin Cancer Res 2017; 23(15): 4251–4258.
61. Gainor JF, Dardaei L, Yoda S et al. Molecular mechanisms of resistance to first- and second-generation ALK inhibitors in ALK-rearranged lung cancer. Cancer Discov 2016; 6(10): 1118–1133.
62. Chen YF, Hsieh MS, Wu SG et al. Clinical and the prognostic characteristics of lung adenocarcinoma patients with ROS1 fusion in comparison with other driver mutations in East Asian populations. J Thorac Oncol 2014; 9(8): 1171–1179.
63. Wu Y-L, Yang JC-H, Kim D-W et al. Phase II Study of Crizotinib in East Asian Patients With ROS1-Positive Advanced Non-Small-Cell Lung Cancer. JCO 2018; 36(14): 1405–1411.
64. Reck M, Rodriguez-Abreu D, Robinson AG et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 2016; 375(19): 1823–1833.
65. Lopes G, Wu Y-L, Kudaba I et al. Pembrolizumab (pembro) versus paltinum-based chemotherapy (chemo) as first-line therapy for advanced/metastatic NSCLC with PD-L1 tumor proportion score (TPS) ≥1%: open-label, phase 3 KEYNOTE-042 study. JCO 2018; 36(Suppl 18): LBA4.
66. Kerr KM, Hirsch FR. Programmed death ligand-1 immunohistochemistry: friend or foe? Arch Pathol Lab Med 2016; 140(4): 326–331.
67. Hirsch FR, McElhinny A, Stanforth D et al. PD-L1 immunohistochemistry assays for lung cancer: results from phase 1 of the Blueprint PD-L1 IHC assay comparison project. J Thorac Oncol 2017; 12(2): 208–222.
68. Ratcliffe MJ, Sharpe A, Midha A et al. Agreement between programmed cell death ligand-1 diagnostic assays across multiple protein expression cutoffs in non-small cell lung cancer. Clin Cancer Res 2017; 23(14): 3585–3591.
69. Rimm DL, Han G, Taube JM et al. A prospective, multi-institutional, pathologist-based assessment of 4 immunohistochemistry assays for PD-L1 expression in non-small cell lung cancer. JAMA Oncol 2017; 3(8): 1051–1058.
70. Adam J, Le Stang N, Rouquette I et al. Multicenter French harmonization study for PD-L1 IHC testing in non-small cell lung cancer. Ann Oncol 2018; 29(4): 953–958.
71. Soo RA, Lim SM, Syn NL et al. Immune checkpoint inhibitors in epidermal growth factor receptor mutant non-small cell lung cancer: current controversies and future directions. Lung Cancer 2018; 115: 12–20.
72. Chen N, Fang W, Zhan J et al. Upregulation of PD-L1 by EGFR activation mediates the immune escape in EGFR-driven NSCLC: implication for optional immune targeted therapy for NSCLC patients with EGFR mutation. J Thorac Oncol 2015; 10(6): 910–923.
73. Han JJ, Kim DW, Koh J et al. Change in PD-L1 expression after acquiring resistance to gefitinib in EGFR-mutant non-small-cell lung cancer. Clin Lung Cancer 2016; 17: 263-270.e2.
74. Liu SY, Dong ZY, Wu SP et al. Clinical relevance of PD-L1 expression and CD8+ T cells infiltration in patients with EGFR-mutated and ALK-rearranged lung cancer. Lung Cancer 2018; 125: 86–92.
75. Dong ZY, Zhong WZ, Zhang XC et al. Potential predictive value of TP53 and KRAS mutation status for response to PD-1 blockade immunotherapy in lung adenocarcinoma. Clin Cancer Res 2017; 23(12): 3012–3024.
76. Hellmann MD, Ciuleanu TE, Pluzanski A et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med 2018; 378(22): 2093–2104.
77. Carbone DP, Reck M, Paz-Ares L et al. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. N Engl J Med 2017; 376(25): 2415–2426.
78. Rizvi H, Sanchez-Vega F, La K et al. Molecular determinants of response to anti-programmed cell death (PD)-1 and anti-programmed death-ligand (PD-L)-ligand 1 blockade in patients with non-small-cell lung cancer profiled with targeted next-generation sequencing. J Clin Oncol 2018; 36(7): 633–641.
79. Rizvi NA, Hellmann MD, Snyder A et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 2015; 348(6230): 124–128.
80. Gandara DR, Kowanetz M, Mok TSK et al. Blood-based biomarkers for cancer immunotherapy: tumor mutational burden in blood (bTMB) is associated with improved atezolizumab (atezo) efficacy in 2L1 NSCLC (POPLAR and OAK). Ann Oncol 2017; 28(Suppl 5): v460–v496.
81. Velcheti V, Kim ES, Mekhail T et al. Prospective clinical evaluation of blood-based tumor mutational burden (bTMB) as a predictive biomarker of Atezolizumab (Atezo) in 1L non-small cell lung cancer (NSCLC): interim B-FIRST results. JCO 2018; 36(Suppl 15); 12001.
82. Grunnet M, Sorensen JB. Carcinoembryonic antigen (CEA) as tumor marker in lung cancer. Lung Cancer 2012; 76(2): 138–143.
83. Kuhn MJ, Hammer GM, Swenson LC et al. MRI evaluation of "solitary" brain metastases with triple-dose gadoteridol: comparison with contrast-enhanced CT and conventional-dose gadopentetate dimeglumine MRI studies in the same patients. Comput Med Imaging Graph 1994; 18(5): 391–399.
84. Wu Y, Li P, Zhang H et al. Diagnostic value of fluorine 18 fluorodeoxyglucose positron emission tomography/computed tomography for the detection of metastases in non-small-cell lung cancer patients. Int J Cancer 2013; 132(2): E37–E47.
85. Brierley JD, M.K G, Wittekind CE, TNM Classification of Malignant Tumours, 8th edition. Hoboken, USA: Wiley-Blackwell; 2016.
86. Detterbeck FC, Franklin WA, Nicholson AG et al. The IASLC Lung Cancer Staging Project: background data and proposed criteria to distinguish separate primary lung cancers from metastatic foci in patients with two lung tumors in the forthcoming eighth edition of the TNM classification for lung cancer. J Thorac Oncol 2016; 11(5): 651–665.
87. Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45(2): 228–247.
88. Bohnsack O, Hoos A, Ludajic K. Adaptation of the immune related response criteria: IRRECIST. Ann Oncol 2014; 25(Suppl 4): iv369.
89. Wolchok JD, Hoos A, O'Day S et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009; 15(23): 7412–7420.
90. Seymour L, Bogaerts J, Perrone A et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 2017; 18(3): e143–e152.
91. Hodi FS, Ballinger M, Lyons B et al. Immune-modified response evaluation criteria in solid tumors (imRECIST): refining guidelines to assess the clinical benefit of cancer immunotherapy. J Clin Oncol 2018; 36(9): 850–858.
92. Gandara DR, Pawel JV, Sullivan RN et al. Impact of atezolizumab (atezo) treatment beyond disease progression (TBP) in advanced NSCLC: results from the randomized phase III OAK study. JCO 2017; 35(Suppl 15): 9001.
93. Tazdait M, Mezquita L, Lahmar J et al. Patterns of responses in metastatic NSCLC during PD-1 or PDL-1 inhibitor therapy: comparison of RECIST 1.1, irRECIST and iRECIST criteria. Eur J Cancer 2018; 88: 38–47.
94. Mazieres J, Fehrenbacher L, Rittmeyer A et al. Non-classical response measured by immune-modified RECIST and post-progression treatment effects of atezolizumab in 2L/3L NSCLC: results from the randomized phase II study POPLAR. JCO 2016; 34(Suppl 15): 9032.
95. Kazandjian DG, Blumenthal GM, Khozin S et al. Characterization of patients treated with a programmed cell death protein 1 inhibitor (anti-PD-1) past RECIST progression from a metastatic non-small cell lung cancer (mNSCLC) trial. JCO 2016; 34(Suppl 15): 3000.
96. Ung KA, Campbell BA, Duplan D et al. Impact of the lung oncology multidisciplinary team meetings on the management of patients with cancer. Asia Pac J Clin Oncol 2016; 12(2): e298–e304.

97. Baser S, Shannon VR, Eapen GA et al. Smoking cessation after diagnosis of lung cancer is associated with a beneficial effect on performance status. Chest 2006; 130(6): 1784–1790.
98. Hughes AN, O'Brien ME, Petty WJ et al. Overcoming CYP1A1/1A2 mediated induction of metabolism by escalating erlotinib dose in current smokers. J Clin Oncol 2009; 27(8): 1220–1226.
99. Brahmer J, Rodríguez-Abreu D, Robinson A et al. OA 17.06 updated analysis of KEYNOTE-024: pembrolizumab vs platinum-based chemotherapy for advanced NSCLC With PD-L1 TPS ≥50%. J Thorac Oncol 12: S1793–S1794.
100. Gandhi L, Rodriguez-Abreu D, Gadgeel S et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 2018; 378(22): 2078–2092.
101. Paz-Ares LG, Luft AV, Vicente D et al. Pembrolizumab plus chemotherapy for squamous non-small cell lung cancer. NEJM 2018; 379(21): 2040–2051.
102. Socinski MA, Jotte RM, Cappuzzo F et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med 2018; 378(24): 2288–2301.
103. Jotte R, Cappuzzo F, Vynnychenko I et al. IMpower131: primary PFS and safety analysis of a randomized phase III study ofaAtezolizumab + carboplatin + paclitaxel or nab-paclitaxel vs carcboplatin + nab-paclitaxel as 1L therapy in advanced squamous NSCLC. JCO 2018; 36(Suppl 18): LBA9000.
104. Papadimitrakopoulou V, Cobo M, Bordon R et al. IMPOWER132 PFS and safety results with 1L atezolizumab + carboplatin/cisplatin + pemetrexed in stage IV non-squamous NSCLC. IASLC 19th World Congress of Lung Cancer 2018, Toronto, Canada; Abstr OA05.07.
105. Cappuzzo F. Impower130: progression-free survival (PFS) and safety analysis from a randomized phase 3 study of carboplatin + nab-paclitaxel (CnP) with or without atezolizumab (atezo) as first-line (1L) therapy in advanced non-squamous NSCLC. Ann Oncol 2018; LBA 53.
106. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group. BMJ 1995; 311: 899–909.
107. NSCLC Meta-Analyses Collaborative Group. Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: a systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. J Clin Oncol 2008; 26: 4617–4625.
108. Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy and supportive care versus supportive care alone for advanced non-small cell lung cancer. Cochrane Database Syst Rev 2010; CD007309.
109. Delbaldo C, Michiels S, Syz N et al. Benefits of adding a drug to a single-agent or a 2-agent chemotherapy regimen in advanced non-small-cell lung cancer: a meta-analysis. JAMA 2004; 292(4): 470–484.
110. Pujol JL, Barlesi F, Daures JP. Should chemotherapy combinations for advanced non-small cell lung cancer be platinum-based? A meta-analysis of phase III randomized trials. Lung Cancer 2006; 51(3): 335–345.
111. Park JO, Kim SW, Ahn JS et al. Phase III trial of two versus four additional cycles in patients who are nonprogressive after two cycles of platinum-based chemotherapy in non small-cell lung cancer. JCO 2007; 25(33): 5233–5239.
112. Rossi A, Chiodini P, Sun JM et al. Six versus fewer planned cycles of first-line platinum-based chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual patient data. Lancet Oncol 2014; 15(11): 1254–1262.
113. Grossi F, Aita M, Defferrari C et al. Impact of third-generation drugs on the activity of first-line chemotherapy in advanced non-small cell lung cancer: a meta-analytical approach. Oncologist 2009; 14(5): 497–510.
114. Schiller JH, Harrington D, Belani CP et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002; 346(2): 92–98.
115. de Castria TB, da Silva EM, Gois AF, Riera R. Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer. Cochrane Database Syst Rev 2013; CD009256.
116. Li M, Zhang Q, Fu P et al. Pemetrexed plus platinum as the first-line treatment option for advanced non-small cell lung cancer: a meta-analysis of randomized controlled trials. PLoS One 2012; 7(5): e37229.
117. Scagliotti GV, Parikh P, von Pawel J et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. JCO 2008; 26(21): 3543–3551.
118. Ciuleanu T, Brodowicz T, Zielinski C et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet 2009; 374(9699): 1432–1440.
119. Scagliotti G, Hanna N, Fossella F et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two phase III studies. Oncologist 2009; 14(3): 253–263.
120. Socinski MA, Bondarenko I, Karaseva NA et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. JCO 2012; 30(17): 2055–2062.
121. Paz-Ares L, Mezger J, Ciuleanu TE et al. Necitumumab plus pemetrexed and cisplatin as first-line therapy in patients with stage IV non-squamous non-small-cell lung cancer (INSPIRE): an open-label, randomised, controlled phase 3 study. Lancet Oncol 2015; 16(3): 328–337.
122. Paz-Ares L, Socinski MA, Shahidi J et al. Correlation of EGFR-expression with safety and efficacy outcomes in SQUIRE: a randomized, multicenter, open-label, phase III study of gemcitabine-cisplatin plus necitumumab versus gemcitabine-cisplatin alone in the first-line treatment of patients with stage IV squamous non-small-cell lung cancer. Ann Oncol 2016; 27: 1573–1579.
123. Thatcher N, Hirsch FR, Luft AV et al. Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomised, controlled phase 3 trial. Lancet Oncol 2015; 16(7): 763–774.
124. Sandler A, Gray R, Perry MC et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006; 355(24): 2542–2550.
125. Zhou C, Wu YL, Chen G et al. BEYOND: a randomized, double-blind, placebo-controlled, multicenter, phase III study of first-line carboplatin/paclitaxel plus bevacizumab or placebo in Chinese patients with advanced or recurrent nonsquamous non-small-cell lung cancer. JCO 2015; 33(19): 2197–2204.
126. Lima AB, Macedo LT, Sasse AD. Addition of bevacizumab to chemotherapy in advanced non-small cell lung cancer: a systematic review and meta-analysis. PLoS One 2011; 6(8): e22681.
127. Soria JC, Mauguen A, Reck M et al. Systematic review and meta-analysis of randomised, phase II/III trials adding bevacizumab to platinum-based chemotherapy as first-line treatment in patients with advanced non-small-cell lung cancer. Ann Oncol 2013; 24(1): 20–30.
128. Cappuzzo F, Ciuleanu T, Stelmakh L et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol 2010; 11(6): 521–529.
129. Wu Y-L, Kim J-H, Park K et al. Efficacy and safety of maintenance erlotinib in Asian patients with advanced non-small-cell lung cancer: a subanalysis of the phase III, randomized SATURN study. Lung Cancer 2012; 77(2): 339–345.
130. Cicenas S, Geater SL, Petrov P et al. Maintenance erlotinib versus erlotinib at disease progression in patients with advanced non-small-cell lung cancer who have not progressed following platinum-based chemotherapy (IUNO study). Lung Cancer 2016; 102: 30–37.
131. Paz-Ares L, de Marinis F, Dediu M et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. Lancet Oncol 2012; 13: 247–255.

132. Paz-Ares LG, de Marinis F, Dediu M et al. PARAMOUNT: final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. JCO 2013; 31(23): 2895–2902.
133. Barlesi F, Scherpereel A, Rittmeyer A et al. Randomized phase III trial of maintenance bevacizumab with or without pemetrexed after first-line induction with bevacizumab, cisplatin, and pemetrexed in advanced nonsquamous non-small-cell lung cancer: aVAPERL (MO22089). J Clin Oncol 2013; 31(24): 3004–3011.
134. Barlesi F, Scherpereel A, Gorbunova V et al. Maintenance bevacizumab-pemetrexed after first-line cisplatin-pemetrexed-bevacizumab for advanced nonsquamous nonsmall-cell lung cancer: updated survival analysis of the AVAPERL (MO22089) randomized phase III trial. Ann Oncol 2014; 25(5): 1044–1052.
135. Patel JD, Socinski MA, Garon EB et al. PointBreak: a randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer. J Clin Oncol 2013; 31(34): 4349–4357.
136. Pérol M, Chouaid C, Pérol D et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 2012; 30: 3516–3524.
137. Gridelli C, Ardizzoni A, Le CT et al. Treatment of advanced non-small-cell lung cancer patients with ECOG performance status 2: results of an European Experts Panel. Ann Oncol 2004; 15(3): 419–426.
138. Quoix E, Zalcman G, Oster JP et al. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: iFCT-0501 randomised, phase 3 trial. Lancet 2011; 378(9796): 1079–1088.
139. Bronte G, Rolfo C, Passiglia F et al. What can platinum offer yet in the treatment of PS2 NSCLC patients? A systematic review and meta-analysis. Crit Rev Oncol Hematol 2015; 95(3): 306–317.
140. Zukin M, Barrios CH, Pereira JR et al. Randomized phase III trial of single-agent pemetrexed versus carboplatin and pemetrexed in patients with advanced non-small-cell lung cancer and Eastern Cooperative Oncology Group performance status of 2. JCO 2013; 31(23): 2849–2853.
141. Gridelli C, Perrone F, Gallo C et al. Chemotherapy for elderly patients with advanced non-small-cell lung cancer: the Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. J Natl Cancer Inst 2003; 95(5): 362–372.
142. Spigel D, Schwartzberg L, Waterhouse D et al. P3.02c-026 is nivolumab safe and effective in elderly and PS2 patients with non-small cell lung cancer (NSCLC)? Results of CheckMate 153. J Thorac Oncol 2017; 12(1): S1287–S1288.
143. Popat S, Ardizzoni A, Ciuleanu T et al. 1303PDNivolumab in previously treated patients with metastatic squamous NSCLC: results of a European single-arm, phase 2 trial (CheckMate 171) including patients aged $\geq$70 years and with poor performance status. Ann Oncol 2017; 28: mdx380.006.
144. Kudoh S, Takeda K, Nakagawa K et al. Phase III study of docetaxel compared with vinorelbine in elderly patients with advanced non-small-cell lung cancer: results of the West Japan Thoracic Oncology Group Trial (WJTOG 9904). JCO 2006; 24(22): 3657–3663.
145. Santos FN, de Castria TB, Cruz MR, Riera R. Chemotherapy for advanced non-small cell lung cancer in the elderly population. Cochrane Database Syst Rev 2015; CD010463.
146. Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. J Clin Oncol 2007; 25(14): 1824–1831.
147. Corre R, Greillier L, Le CH et al. Use of a comprehensive geriatric assessment for the management of elderly patients with advanced non-small-cell lung cancer: the phase III randomized ESOGIA-GFPC-GECP 08-02 Study. JCO 2016; 34(13): 1476–1483.
148. Borghaei H, Paz-Ares L, Horn L et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 2015; 373(17): 1627–1639.
149. Brahmer J, Reckamp KL, Baas P et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 2015; 373(2): 123–135.
150. Herbst RS, Baas P, Kim DW et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016; 387(10027): 1540–1550.
151. Rittmeyer A, Barlesi F, Waterkamp D et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017; 389(10066): 255–265.
152. Ferrara R, Mezquita L, Auclin E et al. Immunosenescence and immune checkpoint inhibitors in non-small cell lung cancer patients: does age really matter? Cancer Treat Rev 2017; 60: 60–68.
153. Herbst R, Garon E, Kim D-W et al. OA03.07 KEYNOTE-010: durable clinical benefit in patients with previously treated, PD-L1-expressing NSCLC who completed pembrolizumab. J Thorac Oncol 2017; 12(1): S254–S255.
154. Di Maio M, Chiodini P, Georgoulias V et al. Meta-analysis of single-agent chemotherapy compared with combination chemotherapy as second-line treatment of advanced non-small-cell lung cancer. JCO 2009; 27(11): 1836–1843.
155. Fossella FV, DeVore R, Kerr RN et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000; 18(12): 2354–2362.
156. Shepherd FA, Dancey J, Ramlau R et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. JCO 2000; 18(10): 2095–2103.
157. Gridelli C, Gallo C, Di Maio M et al. A randomised clinical trial of two docetaxel regimens (weekly vs 3 week) in the second-line treatment of non-small-cell lung cancer. The DISTAL 01 study. Br J Cancer 2004; 91(12): 1996. 2004.
158. Schuette W, Nagel S, Blankenburg T et al. Phase III study of second-line chemotherapy for advanced non-small-cell lung cancer with weekly compared with 3-weekly docetaxel. J Clin Oncol 2005; 23(33): 8389–8395.
159. Hanna N, Shepherd FA, Fossella FV et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004; 22: 1589–1597.
160. Garon EB, Ciuleanu TE, Arrieta O et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet 2014; 384(9944): 665–673.
161. Reck M, Paz-Ares L, Bidoli P et al. Outcomes in patients with aggressive or refractory disease from REVEL: a randomized phase III study of docetaxel with ramucirumab or placebo for second-line treatment of stage IV non-small-cell lung cancer. Lung Cancer 2017; 112: 181–187.
162. Reck M, Kaiser R, Mellemgaard A et al. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. Lancet Oncol 2014; 15(2): 143–155.
163. Novello S, Kaiser R, Mellemgaard A et al. Analysis of patient-reported outcomes from the LUME-Lung 1 trial: a randomised, double-blind, placebo-controlled, phase III study of second-line nintedanib in patients with advanced non-small cell lung cancer. Eur J Cancer 2015; 51(3): 317–326.
164. Cortot AB, Audigier-Valette C, Molinier O et al. Weekly paclitaxel plus bevacizumab versus docetaxel as second or third-line treatment in advanced non-squamous non-small cell lung cancer (NSCLC): results

from the phase III study IFCT-1103 ULTIMATE. JCO 2016; 34(Suppl 15): 9005–9005.
165. Garassino MC, Martelli O, Broggini M et al. Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial. Lancet Oncol 2013; 14(10): 981–988.
166. Zhao N, Zhang XC, Yan HH et al. Efficacy of epidermal growth factor receptor inhibitors versus chemotherapy as second-line treatment in advanced non-small-cell lung cancer with wild-type EGFR: a meta-analysis of randomized controlled clinical trials. Lung Cancer 2014; 85(1): 66–73.
167. Tomasini P, Brosseau S, Mazieres J et al. EGFR tyrosine kinase inhibitors versus chemotherapy in EGFR wild-type pre-treated advanced non-small cell lung cancer in daily practice. Eur Respir J 2017; 50.
168. Soria JC, Felip E, Cobo M et al. Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial. Lancet Oncol 2015; 16(8): 897–907.
169. Lynch TJ, Bell DW, Sordella R et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004; 350(21): 2129–2139.
170. Paez JG, Janne PA, Lee JC et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004; 304(5676): 1497–1500.
171. Han JY, Park K, Kim SW et al. First-SIGNAL: first-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. JCO 2012; 30(10): 1122–1128.
172. Maemondo M, Inoue A, Kobayashi K et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010; 362(25): 2380–2388.
173. Mok TS, Wu YL, Thongprasert S et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009; 361(10): 947–957.
174. Rosell R, Carcereny E, Gervais R et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012; 13(3): 239–246.
175. Sequist LV, Yang JC, Yamamoto N et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. JCO 2013; 31(27): 3327–3334.
176. Wu YL, Zhou C, Hu CP et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol 2014; 15(2): 213–222.
177. Inoue A, Kobayashi K, Usui K et al. First-line gefitinib for patients with advanced non-small-cell lung cancer harboring epidermal growth factor receptor mutations without indication for chemotherapy. JCO 2009; 27(9): 1394–1400.
178. Park K, Yu CJ, Kim SW et al. First-line erlotinib therapy until and beyond response evaluation criteria in solid tumors progression in Asian patients with epidermal growth factor receptor mutation-positive non-small-cell lung cancer: the ASPIRATION Study. JAMA Oncol 2016; 2(3): 305–312.
179. Yang JJ, Chen HJ, Yan HH et al. Clinical modes of EGFR tyrosine kinase inhibitor failure and subsequent management in advanced non-small cell lung cancer. Lung Cancer 2013; 79(1): 33–39.
180. Lim SW, Park S, Kim Y et al. Continuation of gefitinib beyond progression in patients with EGFR mutation-positive non-small-cell lung cancer: a phase II single-arm trial. Lung Cancer 2018; 124: 293–297.
181. Soria JC, Wu YL, Nakagawa K et al. Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial. Lancet Oncol 2015; 16(8): 990–998.
182. Park K, Tan EH, O'Byrne K et al. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. Lancet Oncol 2016; 17(5): 577–589.
183. Paz-Ares L, Tan EH, O'Byrne K et al. Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial. Ann Oncol 2017; 28(2): 270–277.
184. Wu YL, Cheng Y, Zhou X et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. Lancet Oncol 2017; 18(11): 1454–1466.
185. Mok TS, Cheng Y, Zhou X et al. Improvement in overall survival in a randomized study that compared dacomitinib with gefitinib in patients with advanced non-small-cell lung cancer and EGFR-activating mutations. JCO 2018; 36(22): 2244–2250.
186. Soria JC, Ohe Y, Vansteenkiste J et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med 2018; 378(2): 113–125.
187. Seto T, Kato T, Nishio M et al. Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): an open-label, randomised, multicentre, phase 2 study. Lancet Oncol 2014; 15(11): 1236–1244.
188. Furuya N, Fukuhara T, Saito H et al. Phase III study comparing bevacizumab plus erlotinib to erlotinib in patients with untreated NSCLC harbouring activation EGFR mutations: nEJ026. JCO 2018; 36(Suppl 15): 9006.
189. Yamamoto N, Seto T, Nishio M et al. Erlotinib plus bevacizumab (EB) versus erlotinib alone (E) as first-line treatment for advanced EGFR mutation-positive non-squamous non-small cell lung cancer (NSCLC): survival follow-up results of JO25567. J Clin Oncol 2018; 36(Suppl 15): 2007.
190. Nakamura A, Inoue A, Morita S et al. Phase III study comparing gefitinib monotherapy (G) to combination therapy with gefitinib, carboplatin and pemetrexed (GCP) for untreated patients (pts) with advanced non-small cell lung cancer (NSCLC) with EGFR mutations (NEJ009). JCO 2018; 36(Suppl 15): 9005.
191. Yu HA, Arcila ME, Rekhtman N et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. Clin Cancer Res 2013; 19(8): 2240–2247.
192. Garassino MC, Gelibter AJ, Grossi F et al. Italian nivolumab expanded access program in nonsquamous non-small cell lung cancer patients: results in never-smokers and EGFR-mutant patients. J Thorac Oncol 2018; 13(8): 1146–1155.
193. Lisberg A, Cummings A, Goldman JW et al. A phase II study of pembrolizumab in EGFR-mutant, PD-L1+, tyrosine kinase inhibitor naive patients with advanced NSCLC. J Thorac Oncol 2018; 13(8): 1138–1145.
194. Camidge DR, Bang YJ, Kwak EL et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet Oncol 2012; 13(10): 1011–1019.
195. Shaw AT, Yeap BY, Solomon BJ et al. Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer harbouring ALK gene rearrangement: a retrospective analysis. Lancet Oncol 2011; 12(11): 1004–1012.
196. Solomon BJ, Mok T, Kim DW et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 2014; 371(23): 2167–2177.
197. Wu YL, Lu S, Lu Y et al. Results of PROFILE 1029, a phase III comparison of first-line crizotinib versus chemotherapy in East Asian patients with ALK-positive advanced non-small cell lung cancer. J Thorac Oncol 2018; 13(10): 1539–1548.
198. Cho BC, Kim DW, Bearz A et al. ASCEND-8: a randomized phase 1 study of ceritinib, 450 mg or 600 mg, taken with a low-fat meal versus 750 mg in fasted state in patients with anaplastic lymphoma kinase (ALK)-rearranged metastatic non-small cell lung cancer (NSCLC). J Thorac Oncol 2017; 12(9): 1357–1367.

199. Soria JC, Tan DSW, Chiari R et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. Lancet 2017; 389(10072): 917–929.
200. Hida T, Nokihara H, Kondo M et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. Lancet 2017; 390(10089): 29–39.
201. Camidge DR, Peters S, Mok T et al. Updated efficacy and safety data from the global phase III ALEX study of alectinib (ALC)vs crzotinib(CZ) in untreated advanced ALK+ NSCLC. JCO 2018; 36; Abstr 9043.
202. Peters S, Camidge DR, Shaw AT et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. N Engl J Med 2017; 377(9): 829–838.
203. Camidge DR, Kim HR, Ahn MJ et al. Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer. N Engl J Med 2018.
204. Shaw AT, Kim DW, Nakagawa K et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013; 368(25): 2385–2394.
205. Shaw AT, Kim TM, Crino L et al. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2017; 18(7): 874–886.
206. Novello S, Mazieres J, Oh IJ et al. 1299O_PRPrimary results from the phase III ALUR study of alectinib versus chemotherapy in previously treated ALK+ non-small-cell lung cancer (NSCLC). Ann Oncol 2017; 28(Suppl 5): mdx440.058.
207. Kim DW, Tiseo M, Ahn MJ et al. Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small-cell lung cancer: a randomized, multicenter phase II trial. JCO 2017; 35(22): 2490–2498.
208. Shaw AT, Felip E, Bauer TM et al. Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial. Lancet Oncol 2017; 18(12): 1590–1599.
209. Lin JJ, Zhu VW, Schoenfeld AJ et al. Brigatinib in patients with alectinib-refractory ALK-positive NSCLC. J Thorac Oncol 2018; 13(10): 1530–1538.
210. Shaw A, Martini JF, Bauer T et al. Efficacy of lorlatinib in patients (ptd) with advanced ALK-positive non-small cell lung cancer (NSCLC) and ALK kinase domain mutations. Proceedings of the AACR Meeting, Chicago, USA. Cancer Res 2018; 78(13) (Suppl).
211. Yoda S, Lin JJ, Lawrence MS et al. Sequential ALK inhibitors can select for lorlatinib-resistant compound ALK mutations in ALK-positive lung cancer. Cancer Discov 2018; 8(6): 714–729.
212. Shaw AT, Ou SH, Bang YJ et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. N Engl J Med 2014; 371(21): 1963–1971.
213. Moro-Sibilot D, Faivre L, Zalcman G et al. Crizotinib in patients with advanced ROS1-rearranged non-small cell lung cancer (NSCLC). Preliminary results of the ACSé Phase II Trial. J Clin Oncol 2015; 33: 8065–8065.
214. Mazieres J, Zalcman G, Crino L et al. Crizotinib therapy for advanced lung adenocarcinoma and a ROS1 rearrangement: results from the EUROS1 cohort. J Clin Oncol 2015; 33(9): 992–999.
215. Goto K, Yang JC-H, Kim D-W et al. Phase II study of crizotinib in east Asian patients (pts) with ROS1-positive advanced non-small cell lung cancer (NSCLC). JCO 2016; 34(Suppl 15): 9022–9022.
216. Lim SM, Kim HR, Lee JS et al. Open-label, multicenter, phase II study of ceritinib in patients with non-small-cell lung cancer harboring ROS1 rearrangement. J Clin Oncol 2017; 35(23): 2613–2618.
217. Barlesi F, Mazieres J, Merlio JP et al. Routine molecular profiling of patients with advanced non-small-cell lung cancer: results of a 1-year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT). Lancet 2016; 387(10026): 1415–1426.
218. Kris MG, Johnson BE, Berry LD et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. JAMA 2014; 311(19): 1998–2006.
219. Paik PK, Arcila ME, Fara M et al. Clinical characteristics of patients with lung adenocarcinomas harboring BRAF mutations. JCO 2011; 29(15): 2046–2051.
220. Gautschi O, Milia J, Cabarrou B et al. Targeted therapy for patients with BRAF-mutant lung cancer: results from the European EURAF cohort. J Thorac Oncol 2015; 10(10): 1451–1457.
221. Hyman DM, Puzanov I, Subbiah V et al. Vemurafenib in multiple non-melanoma cancers with BRAF V600 mutations. N Engl J Med 2015; 373(8): 726–736.
222. Planchard D, Kim TM, Mazieres J et al. Dabrafenib in patients with BRAF(V600E)-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial. Lancet Oncol 2016; 17(5): 642–650.
223. Planchard D, Besse B, Groen HJM et al. Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. Lancet Oncol 2016; 17(7): 984–993.
224. Planchard D, Besse B, Kim TM et al. Updated survival of patients (pts) with previously treated BRAF V600E–mutant advanced non-small cell lung cancer (NSCLC) who received dabrafenib (D) or D + trametinib (T) in the phase II BRF113928 study. JCO 2017; 35(Suppl 15): 9075.
225. Planchard D, Smit EF, Groen HJM et al. Dabrafenib plus trametinib in patients with previously untreated BRAF(V600E)-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. Lancet Oncol 2017; 18(10): 1307–1316.
226. Stevens R, Macbeth F, Toy E et al. Palliative radiotherapy regimens for patients with thoracic symptoms from non-small cell lung cancer. Cochrane Database Syst Rev 2015; 1: CD002143.
227. Reveiz L, Rueda JR, Cardona AF. Palliative endobronchial brachytherapy for non-small cell lung cancer. Cochrane Database Syst Rev 2012; 12: CD004284.
228. Sperduto PW, Kased N, Roberge D et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. JCO 2012; 30(4): 419–425.
229. Mulvenna P, Nankivell M, Barton R et al. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. Lancet 2016; 388(10055): 2004–2014.
230. Tsao MN, Lloyd N, Wong RK et al. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. Cochrane Database Syst Rev 2012; CD003869.
231. Vecht CJ, Hovestadt A, Verbiest HB et al. Dose-effect relationship of dexamethasone on Karnofsky performance in metastatic brain tumors: a randomized study of doses of 4, 8, and 16 mg per day. Neurology 1994; 44(4): 675–680.
232. Li J, Bentzen SM, Renschler M, Mehta MP. Regression after whole-brain radiation therapy for brain metastases correlates with survival and improved neurocognitive function. JCO 2007; 25(10): 1260–1266.
233. Brown PD, Pugh S, Laack NN et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. Neuro Oncol 2013; 15(10): 1429–1437.
234. Gondi V, Pugh SL, Tome WA et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. JCO 2014; 32(34): 3810–3816.
235. Mintz AH, Kestle J, Rathbone MP et al. A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis. Cancer 1996; 78(7): 1470–1476.
236. Patchell RA, Tibbs PA, Walsh JW et al. A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 1990; 322(8): 494–500.
237. Vecht CJ, Haaxma-Reiche H, Noordijk EM et al. Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? Ann Neurol 1993; 33(6): 583–590.

238. Patchell RA, Tibbs PA, Regine WF et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA 1998; 280: 1485–1489.
239. Aoyama H, Shirato H, Tago M et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA 2006; 295(21): 2483–2491.
240. Kocher M, Soffietti R, Abacioglu U et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. JCO 2011; 29(2): 134–141.
241. Sahgal A, Aoyama H, Kocher M et al. Phase 3 trials of stereotactic radiosurgery with or without whole-brain radiation therapy for 1 to 4 brain metastases: individual patient data meta-analysis. Int J Radiat Oncol Biol Phys 2015; 91(4): 710–717.
242. Ernst-Stecken A, Ganslandt O, Lambrecht U et al. Phase II trial of hypofractionated stereotactic radiotherapy for brain metastases: results and toxicity. Radiother Oncol 2006; 81(1): 18–24.
243. Patil CG, Pricola K, Sarmiento JM et al. Whole brain radiation therapy (WBRT) alone versus WBRT and radiosurgery for the treatment of brain metastases. Cochrane Database Syst Rev 2012; CD006121.
244. Mahajan A, Ahmed S, McAleer MF et al. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. Lancet Oncol 2017; 18(8): 1040–1048.
245. Yamamoto M, Serizawa T, Higuchi Y et al. A multi-institutional prospective observational study of stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901 study update): irradiation-related complications and long-term maintenance of mini-mental state examination scores. Int J Radiat Oncol Biol Phys 2017; 99(1): 31–40.
246. Lim SH, Lee JY, Lee MY et al. A randomized phase III trial of stereotactic radiosurgery (SRS) versus observation for patients with asymptomatic cerebral oligo-metastases in non-small-cell lung cancer. Ann Oncol 2015; 26(4): 762–768.
247. Robinet G, Thomas P, Breton JL et al. Results of a phase III study of early versus delayed whole brain radiotherapy with concurrent cisplatin and vinorelbine combination in inoperable brain metastasis of non-small-cell lung cancer: Groupe Francais de Pneumo-Cancerologie (GFPC) Protocol 95-1. Ann Oncol 2001; 12(1): 59–67.
248. Yang JJ, Zhou C, Huang Y et al. Icotinib versus whole-brain irradiation in patients with EGFR-mutant non-small-cell lung cancer and multiple brain metastases (BRAIN): a multicentre, phase 3, open-label, parallel, randomised controlled trial. Lancet Respir Med 2017; 5(9): 707–716.
249. Goldberg SB, Gettinger SN, Mahajan A et al. Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. Lancet Oncol 2016; 17(7): 976–983.
250. Baik CS, Chamberlain MC, Chow LQ. Targeted therapy for brain metastases in EGFR-mutated and ALK-rearranged non-small-cell lung cancer. J Thorac Oncol 2015; 10(9): 1268–1278.
251. Rangachari D, Yamaguchi N, VanderLaan PA et al. Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small-cell lung cancers. Lung Cancer 2015; 88(1): 108–111.
252. Nayar G, Ejikeme T, Chongsathidkiet P et al. Leptomeningeal disease: current diagnostic and therapeutic strategies. Oncotarget 2017; 8: 73312–73328.
253. Morin-Ben Abdallah S, Wong A. Brain metastases in non-small cell lung cancer: aretyrosine kinase inhibitors and checkpoint inhibitors now viable options? Curr Oncol 2018; 25: 103–S114.
254. Schuler M, Wu YL, Hirsh V et al. First-line afatinib versus chemotherapy in patients with non-small cell lung cancer and common epidermal growth factor receptor gene mutations and brain metastases. J Thorac Oncol 2016; 11(3): 380–390.
255. Besse B, Le Moulec S, Mazieres J et al. Bevacizumab in patients with nonsquamous non-small cell lung cancer and asymptomatic, untreated brain metastases (BRAIN): a nonrandomized, phase II study. Clin Cancer Res 2015; 21(8): 1896–1903.
256. Zimmermann S, Dziadziuszko R, Peters S. Indications and limitations of chemotherapy and targeted agents in non-small cell lung cancer brain metastases. Cancer Treat Rev 2014; 40(6): 716–722.
257. Ashworth AB, Senan S, Palma DA et al. An individual patient data metaanalysis of outcomes and prognostic factors after treatment of oligometastatic non-small-cell lung cancer. Clin Lung Cancer 2014; 15(5): 346–355.
258. Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol 1995; 13(1): 8–10.
259. Kozower BD, Larner JM, Detterbeck FC, Jones DR. Special treatment issues in non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013; 143(Suppl 5): e369S.
260. Tonnies M, Pfannschmidt J, Bauer TT et al. Metastasectomy for synchronous solitary non-small cell lung cancer metastases. Ann Thorac Surg 2014; 98(1): 249–256.
261. Chang JY, Liu YH, Zhu Z et al. Stereotactic ablative radiotherapy: a potentially curable approach to early stage multiple primary lung cancer. Cancer 2013; 119(18): 3402–3410.
262. Griffioen GH, Lagerwaard FJ, Haasbeek CJ et al. Treatment of multiple primary lung cancers using stereotactic radiotherapy, either with or without surgery. Radiother Oncol 2013; 107(3): 403–408.
263. Palma DA, Salama JK, Lo SS et al. The oligometastatic state—separating truth from wishful thinking. Nat Rev Clin Oncol 2014; 11(9): 549–557.
264. Collen C, Christian N, Schallier D et al. Phase II study of stereotactic body radiotherapy to primary tumor and metastatic locations in oligometastatic nonsmall-cell lung cancer patients. Ann Oncol 2014; 25(10): 1954–1959.
265. De Ruysscher D, Wanders R, van Baardwijk A et al. Radical treatment of non-small-cell lung cancer patients with synchronous oligometastases: long-term results of a prospective phase II trial (Nct01282450). J Thorac Oncol 2012; 7(10): 1547–1555.
266. Downey RJ, Ng KK, Kris MG et al. A phase II trial of chemotherapy and surgery for non-small cell lung cancer patients with a synchronous solitary metastasis. Lung Cancer 2002; 38(2): 193–197.
267. Gomez DR, Blumenschein GR Jr, Lee JJ et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. Lancet Oncol 2016; 17(12): 1672–1682.
268. Iyengar P, Wardak Z, Gerber DE et al. Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: a phase 2 randomized clinical trial. JAMA Oncol 2018; 4(1): e173501.
269. deSouza NM, Liu Y, Chiti A et al. Strategies and technical challenges for imaging oligometastatic disease: recommendations from the European Organisation for research and treatment of cancer imaging group. Eur J Cancer 2018; 91: 153–163.
270. Chow E, Zeng L, Salvo N et al. Update on the systematic review of palliative radiotherapy trials for bone metastases. Clin Oncol (R Coll Radiol) 2012; 24(2): 112–124.
271. Sze WM, Shelley M, Held I, Mason M. Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy—a systematic review of the randomised trials. Cochrane Database Syst Rev 2004; CD004721.
272. Rosen LS, Gordon D, Tchekmedyian NS et al. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: a randomized, phase III, double-blind, placebo-controlled trial. Cancer 2004; 100(12): 2613–2621.
273. Henry DH, Costa L, Goldwasser F et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. J Clin Oncol 2011; 29(9): 1125–1132.
274. Scagliotti GV, Hirsh V, Siena S et al. Overall survival improvement in patients with lung cancer and bone metastases treated with denosumab

versus zoledronic acid: subgroup analysis from a randomized phase 3 study. J Thorac Oncol 2012; 7(12): 1823–1829.
275. Henry D, Vadhan-Raj S, Hirsh V et al. Delaying skeletal-related events in a randomized phase 3 study of denosumab versus zoledronic acid in patients with advanced cancer: an analysis of data from patients with solid tumors. Support Care Cancer 2014; 22(3): 679–687.
276. Temel JS, Greer JA, Muzikansky A et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010; 363(8): 733–742.
277. Temel JS, Greer JA, El-Jawahri A et al. Effects of early integrated palliative care in patients with lung and GI cancer: a randomized clinical trial. JCO 2017; 35(8): 834–841.
278. Cherny NI, Dafni U, Bogaerts J et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Ann Oncol 2017; 28(10): 2340–2366.
279. Dafni U, Karlis D, Pedeli X et al. Detailed statistical assessment of the characteristics of the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) threshold rules. ESMO Open 2017; 2(4): e000216.