



SEOM clinical guidelines for the treatment of non-small cell lung cancer (2018)

M. Majem¹ · O. Juan² · A. Insa³ · N. Reguart⁴ · J. M. Trigo⁵ · E. Carcereny⁶ · R. García-Campelo⁷ · Y. García⁸ · M. Guirado⁹ · M. Provencio¹⁰

Received: 22 October 2018 / Accepted: 29 October 2018 / Published online: 17 November 2018
© The Author(s) 2018

Abstract

Non-small cell lung cancer (NSCLC) accounts for up to 85% of all lung cancers. The last few years have seen the development of a new staging system, diagnostic procedures such as liquid biopsy, treatments like immunotherapy, as well as deeper molecular knowledge; so, more options can be offered to patients with driver mutations. Groups with specific treatments account for around 25% and demonstrate significant increases in overall survival, and in some subgroups, it is important to evaluate each treatment alternative in accordance with scientific evidence, and even more so with immunotherapy. New treatments similarly mean that we must reconsider what should be done in oligometastatic disease where local treatment attains greater value.

Keywords NSCLC · Chemotherapy · Immunotherapy · Targeted therapies · Radiotherapy

✉ M. Majem
mmajem@santpau.cat

O. Juan
ojjuanv@seom.org

A. Insa
amelia_insa@ono.com

N. Reguart
NREGUART@clinic.cat

J. M. Trigo
jmtrigo@seom.org

E. Carcereny
ecarcereny@iconcologia.net

R. García-Campelo
MA.Rosario.Garcia.Campelo@sergas.es

Y. García
ygarcia.tauli.cat@gmail.com

M. Guirado
mariaspalux@hotmail.com

M. Provencio
mprovencio.hpth@salud.madrid.org

² Medical Oncology Department, Hospital Universitari i Politècnic La Fe, Valencia, Spain

³ Medical Oncology Department, Hospital Clínico Universitario de Valencia, Valencia, Spain

⁴ Medical Oncology Department, Hospital Clínic, IDIBAPS, Universitat de Barcelona, Barcelona, Spain

⁵ Medical Oncology Department, Hospital Universitario Virgen de la Victoria, Málaga, Spain

⁶ Medical Oncology Department, Institut Català d'Oncologia Badalona-Hospital Germans Trias i Pujol, Badalona, Spain

⁷ Medical Oncology Department, Complejo Hospitalario Universitario A Coruña, Coruña, Spain

⁸ Medical Oncology Department, Institut d'Investigació i Innovació Parc Taulí I3PT, Universitat Autònoma de Barcelona, Parc Taulí Hospital Universitari, Sabadell, Spain

⁹ Medical Oncology Department, Hospital General Universitario de Elche, Elche, Spain

¹⁰ Medical Oncology Department, Hospital Universitario Puerta de Hierro-Majadahonda, Universidad Autónoma de Madrid, Madrid, Spain

¹ Medical Oncology Department, Hospital de la Santa Creu i Sant Pau, Sant Antoni Maria Claret 167, 08025 Barcelona, Spain

Methodology

Relevant studies published in peer review journals were used for the guideline elaboration. The Infectious Diseases Society of America grading system was used to assign levels of evidence and grades of recommendation.

Diagnosis

Diagnosis: pathology and molecular testing

The pathological diagnosis of non-small cell lung cancer (NSCLC) should be made according to the World Health Organization (WHO) classification [1]. The International Association for the Study of Lung Cancer (IASLC) provided adenocarcinoma classification as well as key recommendations for the management of small biopsies and cytology [2]. For therapeutic implications, specific subtyping of NSCLC is strongly recommended whenever possible. Limited diagnostic workup is also recommended to preserve as much tissue as possible for further molecular assessments.

The Spanish Society of Medical Oncology and the Spanish Society of Pathology published evidence-based recommendations for molecular testing in lung cancer [3]. Genetic profiling of NSCLC advanced disease is recommended in daily clinical practice by both ESMO [4] and ASCO [5] guidelines, as it has demonstrated to have an impact on patients' outcomes (I,A). New molecular guidelines recommend to include upfront ROS-1 testing along with EGFR and ALK in stage IV non-SCC and endorse to include other additional genes such as BRAF, MET, HER2, KRAS and RET for laboratories that perform next-generation sequencing (NGS) testing [5]. Immunohistochemistry can be considered as an alternative to fluorescence in situ hybridization for ALK and/or ROS1 testing.

In EGFR mutant patients progressing on first- or second-generation EGFR TKI, the detection of EGFR T790M secondary resistance mutations in tumor tissue is recommended (I,A). Liquid biopsies or molecular DNA profiling in blood (ctDNA) is currently accepted as a good surrogate for EGFR testing in tissue (II,A), enabling clinicians to collect samples in a non-invasive approach [6, 7].

All patients with advanced NSCLC should, at baseline, have their tissue assessed for programmed cell death 1 ligand (PD-L1) expression by IHC test for selecting patients for anti-programmed death 1 (PD-1) or anti-PD-L1 treatment [8].

Disease staging

In NSCLC, the following staging work-up is highly recommended:

- Clinical history, including smoking and family history; physical examination, performance status (PS) and weight loss should be assessed.
- Blood test, including hematology, renal and hepatic function.
- Bronchoscopy.
- Chest and upper abdomen (including liver and adrenal glands) computerized tomography (CT).
- Brain CT or magnetic resonance imaging (MRI) is recommended for patients undergoing radical treatment, in patients with EGFR mutation or ALK translocation or if there are neurological symptoms in the physical examination.
- Bone scan is recommended if there is bone pain, high serum calcium or high alkaline phosphatase.
In patients undergoing potentially radical treatment, additional recommendations should be considered:
- Whole-body FDG-positron emission tomography (PET-CT).
- Pulmonary function tests.
- Ergospirometry if the pulmonary function tests are not normal.
- Chest MRI in Pancoast tumour.
- Invasive mediastinal staging, endobronchial ultrasound-guided fine-needle aspiration and/or endoscopic ultrasound-guided fine-needle aspiration are recommended in patients with suspected mediastinal or hilar lymph nodes (LNs) in the PET-CT. For patients with suspected LNs on PET-CT and negative EBUS/EUS results, an additional mediastinoscopy is recommended. In patients with no suspected LN on the PET-CT, invasive mediastinal staging is also recommended in patients with enlarged mediastinal LNs (≥ 1.5 cm), in tumors ≥ 3 cm and/or in patients with central tumors.
- Histological and cytological confirmation is strongly recommended in the presence of pleural/pericardial effusion or isolated metastatic site.

Staging system

During the 16th World Congress of Lung Cancer, the International Association for the Study of Lung Cancer (IASLC) proposed the TNM 8th edition that was accepted by the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) [9]. The TNM 8th edition is effective since January 2017 (Table 1). The most striking changes in the TNM 8th edition are the further subdividing and detailing of both T and M stages, although the consequences for therapeutic approach are not yet obvious in all situations.

Table 1 TNM classification 8th edition

Stage	T	N	M
Occult	TX	N0	M0
0	Tis	N0	M0
IA1	T1a(mi)/T1a	N0	M0
IA2	T1b	N0	M0
IA3	T1c	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIB	T1a-T2b	N1	M0
	T3	N0	M0
IIIA	T1a-T2b	N2	M0
	T3	N1	M0
	T4	N0/N1	M0
IIIB	T1a-T2b	N3	M0
	T3/T4	N2	M0
IIIC	T3/T4	N3	M0
IVA	Any T	Any N	M1a/M1b
IVB	Any T	Any N	M1c

Stage I–II

A multidisciplinary tumor board evaluation of NSCLC patients with stage I–II disease is strongly recommended, even non-surgical patients. It has to include a preoperative cardiopulmonary assessment.

Surgery

For stage I–II NSCLC patients and no medical contraindications to surgery, surgical resection remains the treatment of choice, yielding the best potential choice of cure for these patients (IB).

The type of surgery resection depends on the extension of the disease, the location of the tumor and the preoperative evaluation:

- In stage I–II medically fit NSCLC patients, lobectomy or anatomic pulmonary resection is recommended rather than sublobar resection (I,B). Systematic mediastinal lymph node dissection is recommended over selective sampling lymph node dissection for accurate pathologic staging [10] (IB). For stage II patients undergoing anatomic resection, mediastinal lymph node dissection may provide additional survival benefit over sampling [11] (II,B).
- A sublobar resection (anatomical segmentectomy) is recommended over nonsurgical therapy for patients who cannot tolerate a lobar resection due to decreased pulmonary function or comorbid disease (I,B).

- For patients with a stage I predominantly ground glass opacity with lesion ≤ 1 cm, sublobar resection with negative margins is suggested over lobectomy (I,B).
- Reresection is recommended for patients with positive margins in resected stage I–II NSCLC patients. If it is not possible, postoperative radiotherapy may be considered [12].

Adjuvant therapy

Overall survival (OS) benefit of adjuvant treatment is limited to cisplatin-based chemotherapy in completely resected fit stage II–III patients [13].

- Four cycles of cisplatin-based chemotherapy following complete resection in stage II NSCLC patients remain the standard of care in adjuvant setting, offering a 5% OS benefit [13] (I,A).
- Stage I (7th TNM edition) NSCLC patients do not benefit from adjuvant therapy except those patients with tumors > 4 cm [5, 14] (I,C).
- In elderly fit patients, adjuvant platinum-based chemotherapy should be considered.
- Postoperative radiotherapy (PORT) is not indicated in completely resected stage I–II NSCLC patients [15] (I,A–II,A).

Neoadjuvant therapy

Preoperative chemotherapy has the potential role to reduce tumor size, increase operability, and eliminate micrometastases. A meta-analysis with 15 randomized trials showed a significant benefit of preoperative chemotherapy on OS (representing an absolute survival improvement of 5% at 5 years [16]). Although neoadjuvant chemotherapy has similar impact on OS than adjuvant chemotherapy, more conclusive evidence favors adjuvant treatment (I,B).

Stereotactic ablative radiotherapy (SART)

SART is recommended for medically inoperable NSCLC patients with node negative tumors ≤ 5 cm (2C). Several non-randomized studies suggest that SART might be a suitable option for operable patients older than 75 years [17] (II,C).

Other adjuvant treatments

Adjuvant EGFR TKI in patients with EGFR mutation has not demonstrated a survival benefit yet. Several trials in patients with EGFR mutations or ALK translocations in adjuvant setting are ongoing [18].

Stage III

Stage III NSCLC is a heterogeneous and complex disease that has been classified into different subgroups: resectable, potentially resectable and unresectable locally advanced NSCLC. Treatment decision should be taken by an experienced multidisciplinary team (Fig. 1).

Resectable and potentially resectable NSCLC

- In patients with R0 resected stage III NSCLC, 4 cycles of adjuvant platinum-based chemotherapy should be given (preferably cisplatin doublet) [19] (I,A).
- In patients with pathological N2 NSCLC, PORT appears to improve OS in non-randomized analysis, and it is usually administered after adjuvant chemotherapy (II,A).
- In patients with potentially resectable disease, the optimal treatment strategy remains unclear. Several phase III trials and a meta-analysis showed that induction therapy followed by surgery might be better than surgery alone [20]. Surgery has been compared to radiotherapy in patients with tumor response after induction chemotherapy, without differences in overall survival [21]. Surgery was also compared to radiotherapy after induction chemoradiotherapy in the Lung Intergroup Trial 0139 showing better progression-free survival in the surgery arm, with no differences in OS except in the unplanned analysis in the subset of patients who underwent lobectomy [22]. The optimal chemotherapy regimen has not been established in randomized trials, although cisplatin-based chemotherapy is recommended.
- In case of superior sulcus (Pancoast) tumors, concurrent chemoradiation followed by surgery is the preferred option [23] (Table 2).

Unresectable NSCLC

Unresectable LA-NSCLC includes stage IIIA N2 (bulky and/or multiple nodal involvement), stage IIIB and IIIC.

- Concurrent chemoradiotherapy is the treatment of choice for medically fit patients (I,A). Several randomized clinical trials and a meta-analysis have shown a higher 5-year survival rates favoring this strategy over sequential approaches [24].
- Cisplatin-based combinations are recommended for medically fit patients (usually with etoposide or vinorelbine) [24].
- Radiotherapy is usually given at a dose of 60–66 Gy in 30–33 fractions over 6–7 weeks. Higher doses are not recommended outside of clinical trials [25].
- If concurrent chemoradiotherapy is not feasible due to poor performance status, comorbidities, and/or unfit patients, a sequential approach is a reasonable option [26].
- There is no role for prophylactic cranial irradiation in stage III (II,A).
- In patients with no progressive disease after concurrent chemoradiotherapy, consolidation treatment with Durvalumab for 1 year has shown to improve progression-free survival (PFS) and OS (I,A) [27–29]. The European Medical Agency has recently approved consolidation with Durvalumab in patients with PD-L1 expression $\geq 1\%$ based on an unplanned post hoc analysis.

Fig. 1 Treatment algorithm for Stage III

Treatment Algorithm for Stage III

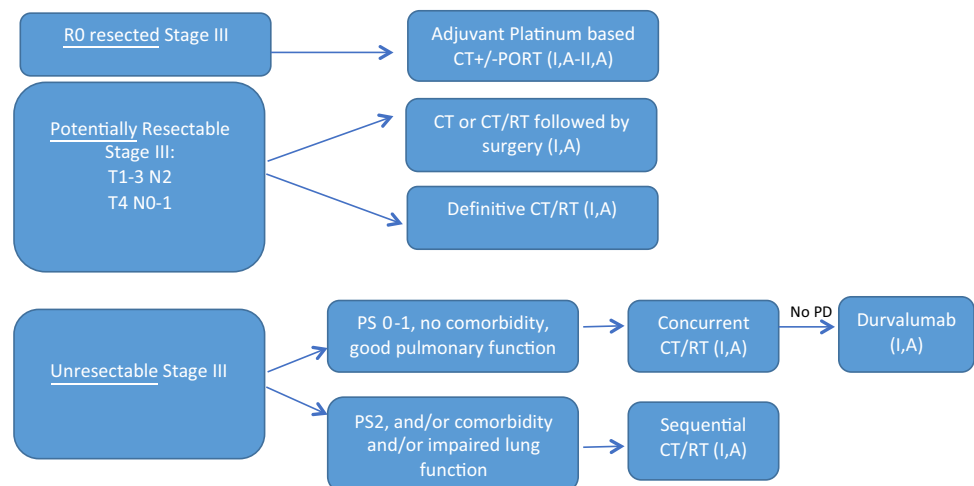


Table 2 Summary of recommendations

Diagnosis	WHO classification for pathological diagnosis is required and also IASLC classification of adenocarcinoma For therapeutic implications, specific subtyping of NSCLC is strongly recommended Molecular testing in stage IV non-SCC should include EGFR mutations, ALK and ROS-1 translocations by a validated technique In patients progressing to first or second generation EGFR TKI determination of EGFR T790M in plasma or tissue should be performed PD-L1 expression should be test to all patients with advanced NSCLC at baseline
Staging	Comprehensive evaluation must include thorax and upper abdomen CT More extensive evaluations are recommended if a radical approach is considered Stage disease must be classified using the TNM 8th edition
Stage I–II	Patients should be evaluated in a multidisciplinary tumor board
Medically fit for surgery	Lobectomy or anatomic pulmonary resection plus systematic mediastinal lymph node dissection
Medically inoperable, node negative NSCLC tumours ≤ 5 cm	SART
Adjuvant chemotherapy (four cycles of cisplatin-based chemotherapy)	Recommended in stage II Not recommended in stage I 7th TNM edition (except T > 4 cm)
Post operative radiotherapy (PORT)	Not indicated in completely resected stage I–II
Stage III	Treatment decision should be taken by an experienced multidisciplinary team
Completely resected	Adjuvant chemotherapy (four cycles of adjuvant cisplatin-based chemotherapy) \pm PORT
Potentially resectable	Resection followed by adjuvant chemotherapy Induction chemotherapy or chemoradiotherapy followed by surgery
Unresectable stage III	Medically fit: concurrent chemoradiotherapy with cisplatin-based chemotherapy Sequential chemoradiotherapy if concurrent treatment is not feasible PCI is not indicated Durvalumab if no progressive disease after concurrent chemoradiotherapy
Stage IV	
Stage IV without driver mutations	
First line	
PD-L1 $\geq 50\%$	Pembrolizumab Note: Combination of immunotherapy plus standard chemotherapy may be considered
PD-L1 < 50% or unknown	Platinum-based chemotherapy based on tumor histology:
Squamous cell carcinoma (SCC)	Platinum-based doublets (4, up to 6 cycles) Immunotherapy (atezolizumab or pembrolizumab) and carboplatin plus paclitaxel or nab-paclitaxel ^(#)
Non-squamous-cell carcinoma (non-SCC)	Platinum-based doublet: Cisplatin/pemetrexed has more efficacy and less toxicity than cisplatin/gemcitabine Bevacizumab added to a platinum doublet, if there are no contraindications Pemetrexed maintenance Immunotherapy (atezolizumab ^(#) or pembrolizumab) plus standard chemotherapy
Elderly	Comprehensive geriatric assessment is highly recommended
Fit patients	Decision according to histology and PD-L1 expression levels
Unfit or comorbidities	Single agent chemotherapy
PS 2	Combination therapy Single-agent therapy Best supportive care
PS 3–4	Best supportive care

Table 2 (continued)

Second line	
PS 0–2	
If no prior immunotherapy	Pembrolizumab (PD-L1 $\geq 1\%$), nivolumab or atezolizumab
If prior immunotherapy	Platinum doublets
If contraindication for immunotherapy	Docetaxel–nintedanib (non-SCC) Docetaxel (SCC, non-SCC) Pemetrexed (non-SCC)
If prior immunotherapy alone	Platinum doublets
If prior immunotherapy + CT	Docetaxel–nintedanib (non-SCC) Docetaxel (SCC, non-SCC) Pemetrexed (non-SCC)
PS 3–4	Best supportive care
Stage IV with driver mutations	
EGFR mutation	
First-line EGFR TKI	Erlotinib, gefitinib, afatinib, dacomitinib ^(#) , osimertinib
Brain metastasis	Osimertinib
After EGFR TKI progression	
Clinical benefit maintained or oligoprogressive disease	Continuation with the EGFR TKI
T790 M positive	Osimertinib (if not previously given)
T790 M negative	Platinum-based chemotherapy
ALK mutation	
First-line ALK TKI	Alectinib, brigatinib ^(#) , crizotinib or ceritinib
Progression to crizotinib	Ceritinib, alectinib or brigatinib ^(#)
Brain metastasis	Alectinib, brigatinib ^(#) or lorlatinib ^(#)
Other genetic alterations	
ROS-1	Crizotinib
B-RAF ^{v600}	Dabrafenib plus trametinib
Oligometastatic disease	Systemic therapy and local ablative strategies Local ablative strategies and TKI-continuation if clinical benefit is still retained (if actionable mutation)
Follow-up	Smoking cessation counseling
Curative intent	
Surgery	Medical history, physical examination and spiral chest CT scan every 6–12 months for 2 years and annually thereafter
SART	Medical history, physical examination and spiral chest CT scan every 6 months for 3 years and annually thereafter PET–CT \pm biopsy if recurrence is suspected
Advanced disease	Early palliative care Evaluation of response every 6–12 weeks

(#) Not EMA approved

Stage IV

Stage IV without driver mutations (Fig. 2)

First-line therapy

- For stage IV, PS 0–1 NSCLC patients without driver mutations whose tumors express PD-L1 at levels of 50%

or greater (tumor proportion score (TPS) $\geq 50\%$), pembrolizumab is recommended in the absence of contraindications to use immunotherapy [30] (I,A).

- For patients with low (TPS $< 50\%$) or unknown PD-L1 expression, chemotherapy with platinum doublets should be considered in all stage IV PS 0–1 NSCLCs without driver mutations (I,A). Data have shown that platinum combination therapy increases OS and improves quality

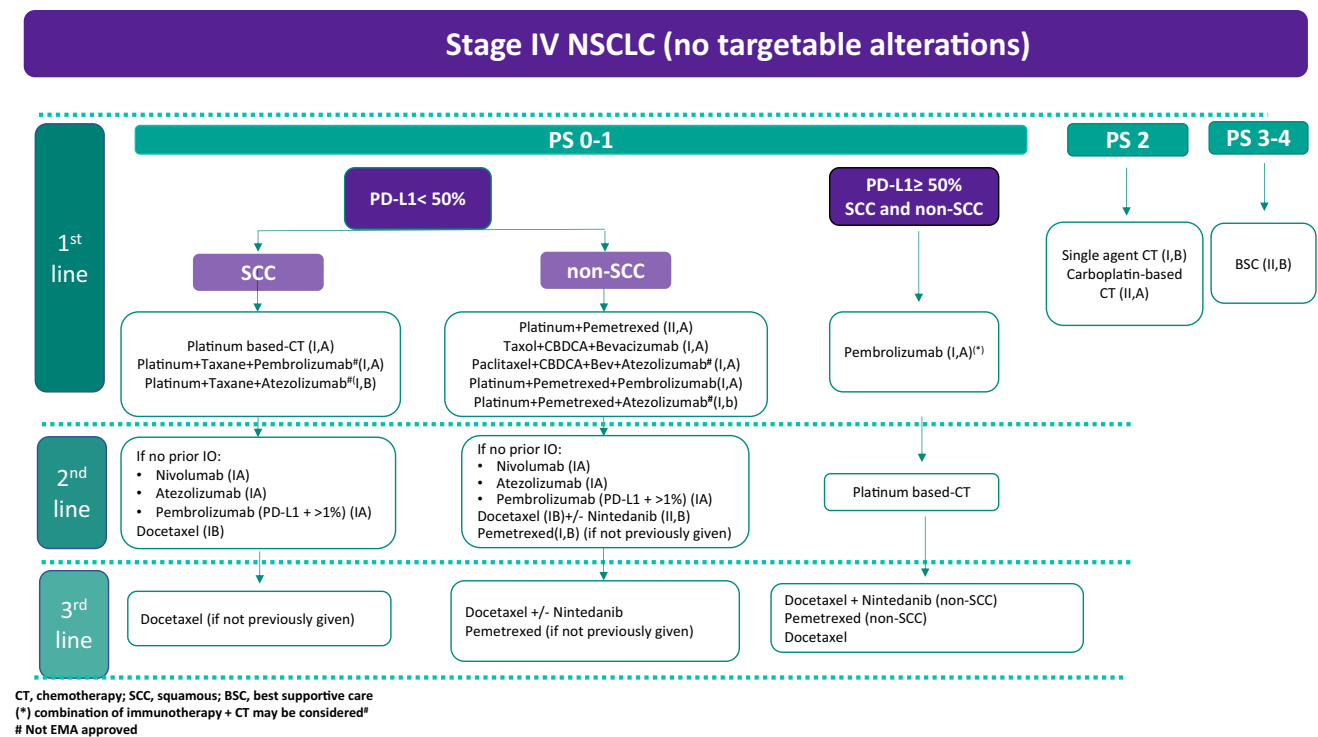


Fig. 2 Treatment algorithm for Stage IV with no targetable alterations

of life (QoL) compared to supportive care, single-agent cisplatin or other monotherapy [31–34].

- Meta-analyses have shown higher response rates (RRs) and a slightly longer OS for cisplatin combinations than for carboplatin combinations [35] (I,B). Carboplatin can be recommended if any contraindication for cisplatin exists.
- Non-platinum regimens have reported lower efficacy than platinum regimens [36] (I,A).
- Recently, results from several phase III trials have shown a significant benefit in terms of efficacy for the addition of immunotherapy to platinum-based chemotherapy regardless of the PD-L1 status [37–41] (I,A-I,B).
- Cisplatin-based combinations and some modalities of treatment will be selected based on tumor histology:

- The expected toxicity profile should contribute to the selection of the chemotherapy regimen. The nab-paclitaxel/carboplatin regimen has shown in a phase III trial to have higher RRs (with a larger impact in SCC) than paclitaxel/carboplatin and less neurotoxicity (I,B) [45].
- Recently, two randomized phase III trials have shown that the addition of immunotherapy (atezolizumab or pembrolizumab) to standard first-line chemotherapy (carboplatin plus paclitaxel or nab-paclitaxel) in SCC, results in significantly longer PFS with atezolizumab (I,B) [38] and OS and PFS with pembrolizumab (I,A) [40] than chemotherapy alone, regardless of PD-L1 expression. It is important to underline that these combinations were not approved by the European Medical Agency when this guideline was submitted.

For squamous cell lung cancer (SCC)

- For PS 0–1 SCC patients, without major comorbidities and with low (TPS < 50%) or unknown PD-L1, platinum-based doublets with the addition of a third-generation cytotoxic agent (gemcitabine, vinorelbine, taxanes) are recommended (I,A). The different combinations have shown comparable efficacy [42].
- Four cycles are recommended, up to a maximum of six cycles in selected cases [43, 44] (I,A).

For non-squamous cell lung cancer (Non-SCC)

- Any platinum-based doublets with a third-generation agent can be used in non-SCC patients with low (TPS < 50%) or unknown PD-L1 [42] (I,A).
- Pemetrexed-based combination chemotherapy represents a therapeutic option. This regimen showed a slight but significant survival benefit compared with gemcitabine or docetaxel-based combinations (results coming from a

meta-analysis and a preplanned subgroup analysis of a randomized phase III trial [46, 47] (II,A).

- Bevacizumab/paclitaxel/carboplatin combination chemotherapy followed by maintenance bevacizumab has shown improvement in OS in two randomized clinical trials and, therefore, it can be offered to patients with advanced PS 0–1 non-SCC and no contraindications for antiangiogenic treatment [6, 48] (I,A).
- Maintenance therapy can be considered in those PS 0–1 patients with at least stable disease and who have recovered from residual toxicity after first-line chemotherapy:
 - Pemetrexed switch maintenance could be considered after four cycles of non-pemetrexed platinum-based chemotherapy [49] (I,B).
 - Pemetrexed continuation maintenance should be considered in patients having disease control after four courses of pemetrexed platinum-based chemotherapy [50] (I,A).
- Recently, three randomized phase III trials have shown that the addition of immunotherapy (pembrolizumab or atezolizumab) to standard first-line chemotherapy (pemetrexed platinum-based combination or bevacizumab plus chemotherapy) in non-SCC resulted in significantly longer OS \pm PFS than chemotherapy alone, regardless of PD-L1 expression [37, 39, 41]. It is important to underline that pembrolizumab with pemetrexed and platinum-based chemotherapy was the only combination approved by the European Medical Agency when this guideline was submitted.

Second-line therapy

Patients clinically or radiologically progressing after first-line therapy, with a PS 0–1 and appropriate PS 2, should be offered second-line treatment (I,A). Second-line treatment should be individualized and treatment duration should be subject to tolerability and clinical benefit.

- In patients with metastatic non-SCC and SCC who have not received prior immunotherapy, and with no contraindications, single-agent pembrolizumab (PD-L1 TPS \geq 1%), nivolumab or atezolizumab is recommended (I,A). This recommendation is based on data from the main Phase III trials, showing significant improvements in OS and tolerability of immunotherapy agents when compared to single-agent docetaxel [51–54].
- Nintedanib added to docetaxel has demonstrated a significant OS benefit as compared with docetaxel alone in previously treated stage IV, PS 0–1 adenocarcinoma,

particularly in those patients progressing within 9 months after start of first-line therapy [55] (II,B).

- Docetaxel, or pemetrexed have demonstrated improvement in terms of OS and QoL (I,B) and are recommended for those patients with contraindications to immunotherapy or nintedanib combination therapy (non-SCC) [56, 57].
- In patients who have received an immune checkpoint inhibitor as first-line therapy, platinum doublets are recommended (I,B).
- For those patients who have received first-line conventional chemotherapy and immune therapy, single agent, docetaxel, pemetrexed (non-SCC) or docetaxel plus nintedanib (non-SCC) could be considered (IIB).
- There is no sufficient evidence to recommend the use of cytotoxic drugs as fourth-line therapy or beyond; patients should be considered to be included in clinical trials, and continued best supportive care.

Elderly and PS2

Age should not be considered as a decisive factor for treatment selection, and Comprehensive Geriatric Assessment would help to ascertain the true biological status [58].

- For those elderly fit patients with PS 0–1 and adequate organ function, first-line treatment decision should be based according to histology and PD-L1 expression levels [59] (I,B). Single agent chemotherapy (vinorelbine, gemcitabine, docetaxel) is recommended for those with comorbidities or unfit patients [60] (IB).
- For patients with PS 2, chemotherapy prolongs OS compared to best supportive care (BSC) [61] (I,B). In an individualized-based decision, combination therapy, single-agent therapy, or palliative therapy alone may be used for PS 2 patients. In the first-line setting, platinum-based doublets (preferably carboplatin) have superior efficacy to monotherapy, despite higher toxicity rates [62, 63] (II,A).
- Unfit patients with PS 3–4 should not receive active treatment regardless of age because no benefit has been demonstrated. Supportive care is recommended (II,B).

Stage IV with driver mutations (Fig. 3)

EGFR mutation

First-line setting

- EGFR TKIs (gefitinib, erlotinib, afatinib) have shown superior PFS, RR, toxicity profile and QoL for EGFR TKIs as first-line treatment compared with platinum-

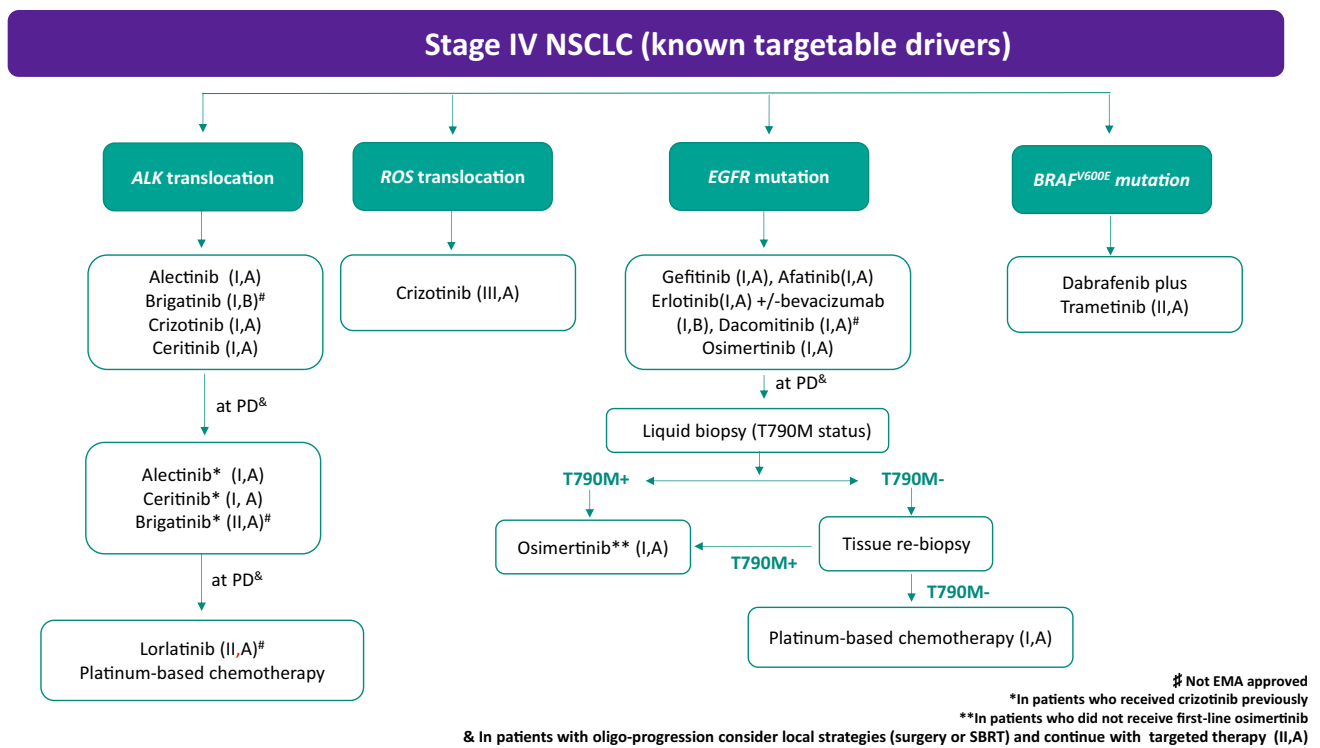


Fig. 3 Treatment algorithm for Stage IV with known targetable drivers

based doublets (I,A) [64, 65]. Only a prespecified subanalysis showed a significant improvement in OS favoring afatinib in patients with Del19 mutations [65].

- Patients with PS 3–4 may also be offered an EGFR TKI, as they are likely to receive a similar clinical benefit to patients with good PS (III,A).
- Results from direct comparison of first-, second- and third-generation EGFR TKIs in previously untreated patients have been reported. Although a benefit in terms of PFS has been demonstrated for third-generation TKIs osimertinib (I,A) and dacomitinib (I,A) [66–68], to date only dacomitinib has shown a significant OS advantage (I,A) [69]. However, grade 3–4 treatment-related adverse events were significantly higher with dacomitinib. OS data from the FLAURA trial comparing osimertinib versus standard of care are still immature [67].
- An exploratory data on brain disease suggest that the probability of experiencing a progression on central nervous system (CNS) was lower with osimertinib and provided a higher intracranial activity (II,B) [70].
- Combinations of bevacizumab and erlotinib were also explored in the first-line setting demonstrating a significant increase in PFS but only a slight trend of OS improvement with the combination [71–73] (I,B).
- Combination of pemetrexed-carboplatin and gefitinib has demonstrated a significant increase in PFS and OS in japanese population [74] (I,B).

After EGFR TKI progression

- Patients might benefit of continuation with the EGFR TKI, especially if clinical benefit is maintained from a sustained EGFR oncogenic blockade [7] or if there is an oligoprogressive disease treatable with local strategies (SART or surgery) (II,A) [75].
- EGFR Exon 20, T790 M mutation, is the main mechanism of acquired resistance after first- or second-generation EGFR TKIs [76]. Osimertinib has demonstrated greater efficacy over platinum-based chemotherapy (I,A) [77].
- For patients with systemic symptomatic progression in whom T790 M cannot be detected or who have progressed to osimertinib, platinum-based chemotherapy remains the standard of care (II,A). The combination of atezolizumab plus bevacizumab plus chemotherapy has demonstrated a significant PFS benefit in the subgroup of patients with EGFR mutation (III,A) [50].
- Continuation of EGFR TKI with platinum-based chemotherapy does not impact on PFS nor on OS [78] (I,A).

ALK translocation

First-line setting

- First-line treatment with ALK TKIs is the preferred treatment (I,A). Crizotinib and ceritinib have shown a

significant statistical improvement in terms of PFS and RR compared with chemotherapy in randomized phase III trials (I,A) [79, 80].

- Alectinib (I,A) and brigatinib (I,B) have shown a significant improvement in PFS versus crizotinib and, therefore, are the preferred first-line options. Grade 3–5 adverse events were higher for patients treated with crizotinib [81, 82]. It is important to underline that brigatinib was not approved by the European Medical Agency when this guideline was submitted.
- Chemotherapy is indicated (III,B) in patients whose ALK results are not available and urgent systemic treatment is required. Treatment plan should be reassured when genotypic results were available.
- For patients who received chemotherapy in the first-line, crizotinib should be recommended as second-line treatment (I,A) [83]. Alectinib and ceritinib should also be considered, although no specific trials have been conducted.

After ALK TKI progression

- For patients who develop resistance or are intolerant to crizotinib, ceritinib (IA), alectinib (IA) or brigatinib (IIA) can be recommended. Ceritinib and alectinib have shown a significant improvement in median PFS and less adverse events than chemotherapy. Brigatinib has shown a favorable PFS in a crizotinib-refractory ALK-positive phase II trial [84–86].
- Lorlatinib has shown activity in patients who have progressed on next-generation ALK TKI (ceritinib, alectinib or brigatinib) [87] (II,A).
- Ensartinib and entrectinib have also been demonstrated activity in previously treated patients in early phase trials [88, 89].
- For patients with systemic symptomatic progression to ALK TKI, platinum-based chemotherapy remains the standard of care (II,A). The combination of atezolizumab plus bevacizumab plus chemotherapy has demonstrated a significant PFS benefit (III,B) [50].

Brain metastases

- Alectinib, brigatinib and lorlatinib have shown greater activity in CNS disease. In the ALEX trial, fewer patients treated with alectinib (12%) had CNS progression than crizotinib (45%). In the ALTA-1 trial, intracranial RR was 78% for brigatinib versus 29% for crizotinib [82].
- For asymptomatic or patients who became asymptomatic with steroids, brain-penetrable ALK TKIs may be used and local treatments may be deferred (I,B).

ROS-1 and other rare targetable genetic alterations

- Crizotinib is indicated for the treatment of *ROS-1*-positive advanced NSCLC based on the results of a single-arm trial in 50 patients [90] (III,A).
- Dabrafenib–Trametinib is indicated for the treatment of advanced NSCLC BRAF^{V600E} mutation based on results from non-comparative studies in pretreated or naïve patients [91, 92] (II,A).
- New investigational drugs have shown activity in early clinical trials targeting oncogenic drivers such as crizotinib, tepotinib or capmatinib (MET amplified, MET^{e14} mutation), LOXO-292 and BLU-667 (RET), entrectinib (NTRK, ROS, ALK fusions), LOXO-101 or larotrectinib (NTRK fusions) [93] and ado-trastuzumab emtansine (HER2 mutations). However, none of these targeted drugs have an official regulatory approval by EMA except the orphan drug designation of LOXO-101 in NTRK fusion tumors.

Oligometastatic NSCLC

The oligometastatic state consists of patients with metastasis limited in number and location. The number of metastases ranges from a single metastatic lesion to a single organ with multiple metastases or to multiple lesions in multiple organs. The most accepted number of metastatic lesions is up to five and, most important, these should be suitable to radical treatment by local therapy: surgical resection, SART or both. The oligometastatic disease comprises four different settings [94]:

1. Metastatic lesions limited in number and location at diagnosis, all the lesions including the primary tumor are suitable to radical therapy.
2. Multiple metastases that are transformed into an oligometastatic disease after systemic treatment due to response, and all lesions can be managed with radical intent.
3. The primary tumor and most areas of metastatic disease remain controlled, but one or a limited number of metastases progress while systemic therapy.
4. Oligorecurrence occurs in patients treated with curative intent and metachronously present 1–5 metastatic lesions suitable to ablative therapy.
 - Patients with oligometastatic disease at diagnosis should be treated with systemic therapy and local consolidative ablative therapy (LAT) to primary and all metastatic sites. Two phase II studies

showed that LAT after systemic therapy increased PFS vs no further local treatment [95, 96] (I,A).

- Patients with actionable mutations receiving targeted therapies who progress on isolated site can be treated with LAT [75, 97] (II,A).

Management and follow-up

- Smoking cessation counseling is encouraged in any stage as it leads to superior treatment outcomes since smoking may impact on drugs' bioavailability (II,A).
- There is not an established consensus regarding the most optimal follow-up in patients with NSCLC. However, due to the inherent aggressiveness of the disease, a close follow-up is advised.

Follow up in patients after curative treatment:

- NSCLC patients treated with radical intent must be followed to identify treatment-related complications, detection of treatable relapse or occurrence of second primary lung cancer (III,A).
- In patients with curative surgery, a close follow-up visit including medical history, physical examination and chest CT is recommended every 6–12 months for the first 2 years and annually thereafter (III,B).
- For patients treated with SART with radical intent, CT scans every 6 months for 3 years are recommended and annually thereafter (III,B). PET-CT ± biopsy is endorsed when recurrence is suspected based on chest CT To discriminate from focal fibrosis (III,B).
- Routine surveillance with blood test, FDG-PET imaging or another radiological assessment is not endorsed (II,D).

Follow up in patients with advanced disease:

- Early palliative care is strongly recommended [98] (I,A).
- Evaluation of response is recommended every 6–12 weeks after therapy initiation, using the same baseline radiographic method. The frequency of the radiologic assessment can be tailored for patients benefiting long time on targeted agents (III,B).
- For patients eligible for successive lines that respond to first-line treatment, it is advisable to undergo clinical and/or radiological evaluation 6 weeks after finishing treatment and then every 6–12 weeks to enable second-line therapy to commence promptly (III,B).

Compliance with ethical standards

Conflict of interest MM reports personal fees from AstraZeneca, Roche, Lilly, Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim,

Novartis, Tesaro, outside the submitted work. OJ reports grants from Astra Zeneca and personal fees from Astra Zeneca, BMS, MSD, ROCHE, Boehringer Ingelheim, Lilly outside the submitted work. MP reports grants from BMS, Roche and personal fees from BMS, MSD, ROCHE, Pierre Fabre, Novartis; Takeda, Lilly, Pfizer outside the submitted work. NR reports advisory Board/Consultancy/Speaker honoraria from MSD, Bristol-Myers, Roche, Boehringer Ingelheim, Guardant Health, Pfizer, Abbie, Ipsen, Novartis, Astra-Zeneca, Lilly, Takeda outside the submitted work; Research Funding from Pfizer, NanoString Technology, and Institutional financial interests related to clinical trials and patient recruitment. GC reports non-financial support from Millennium Pharmaceuticals, Inc., during the conduct of the study; personal fees from ARIAD, AstraZeneca, Roche, Pfizer, BMS, Boehringer Ingelheim, MSD outside the submitted work. YG reports personal fees from Roche, Boehringer-Ingelheim, Lilly, MSD, Pfizer, BMS outside the submitted work. JMT reports personal fees from Roche, Boehringer-Ingelheim, BMS, Astra Zeneca, MerckSerono outside the submitted work. AI, EC, MG, have not reported any potential conflicts of interest.

Ethical approval The current study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent No informed consent was necessary for this guideline.

Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

1. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, et al. The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. *J Thorac Oncol.* 2015;10(9):1243–60.
2. Lindeman NI, Cagle PT, Aisner DL, Arcila ME, Beasley MB, Bernicker EH, et al. 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. *J Mol Diagn.* 2018;20(2):129–59.
3. Felip E, Concha A, de Castro J, Gomez-Roman J, Garrido P, Ramirez J, et al. Biomarker testing in advanced non-small-cell lung cancer: a national consensus of the Spanish Society of Pathology and the Spanish Society of Medical Oncology. *Clin Transl Oncol.* 2015;17(2):103–12.
4. Novello S, Barlesi F, Califano R, Cufer T, Ekman S, Levra MG, et al. Metastatic non-small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2016;27(suppl 5):v1–27.
5. Kalemkerian GP, Narula N, Kennedy EB, Biermann WA, Donington J, Leighl NB, 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):911–9.
6. Yang JC, Sequist LV, Geater SL, Tsai CM, Mok TS, Schuler M, et al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. *Lancet Oncol.* 2015;16(7):830–8.
 7. Park K, Yu CJ, Kim SW, Lin MC, Sriuranpong V, Tsai CM, 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):305–12.
 8. Adam J, Le Stang N, Rouquette I, Cazes A, Badoual C, Pinot-Roussel H, et al. Multicenter harmonization study for PD-L1 IHC testing in non-small-cell lung cancer. *Ann Oncol.* 2018;29(4):953–8.
 9. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol.* 2016;11(1):39–51.
 10. El-Sherif A, Gooding WE, Santos R, Pettiford B, Ferson PF, Fernando HC, et al. Outcomes of sublobar resection versus lobectomy for stage I non-small cell lung cancer: a 13-year analysis. *Ann Thorac Surg.* 2006;82(2):408–15 (**discussion 15-6**).
 11. Blackmon SH, Cooke DT, Whyte R, Miller D, Cerfolio R, Farjah F, et al. The Society of Thoracic Surgeons expert consensus statement: a tool kit to assist thoracic surgeons seeking privileging to use new technology and perform advanced procedures in general thoracic surgery. *Ann Thorac Surg.* 2016;101(3):1230–7.
 12. Wang EH, Corso CD, Rutter CE, Park HS, Chen AB, Kim AW, et al. Postoperative radiation therapy is associated with improved overall survival in incompletely resected stage II and III non-small-cell lung cancer. *J Clin Oncol.* 2015;33(25):2727–34.
 13. Burdett S, Pignon JP, Tierney J, Tribodet H, Stewart L, Le Pechoux C, et al. Adjuvant chemotherapy for resected early-stage non-small cell lung cancer. *Cochrane Database Syst Rev.* 2015. <https://doi.org/10.1002/14651858.CD011430>.
 14. Strauss GM, Herndon JE 2nd, Maddaus MA, Johnstone DW, Johnson EA, Harpole DH, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the cancer and leukemia group B, radiation therapy oncology group, and north central cancer treatment group study groups. *J Clin Oncol.* 2008;26(31):5043–51.
 15. Group NM-aC, Arriagada R, Auperin A, Burdett S, Higgins JP, Johnson DH, et al. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. *Lancet.* 2010;375(9722):1267–77.
 16. Group NM-aC. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. *Lancet.* 2014;383(9928):1561–71.
 17. Videtic GMM, Donington J, Giuliani M, Heinzerling J, Karas TZ, Kelsey CR, et al. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: executive summary of an ASTRO evidence-based guideline. *Pract Radiat Oncol.* 2017;7(5):295–301.
 18. Zhong WZ, Wang Q, Mao WM, Xu ST, Wu L, Shen Y, et al. Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II-IIIa (N1-N2) EGFR-mutant NSCLC (ADJUVANT/CTONG1104): a randomised, open-label, phase 3 study. *Lancet Oncol.* 2018;19(1):139–48.
 19. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE collaborative group. *J Clin Oncol.* 2008;26(21):3552–9.
 20. Burdett SS, Stewart LA, Ryzewska L. Chemotherapy and surgery versus surgery alone in non-small cell lung cancer. *Cochrane Database Syst Rev.* 2007. <https://doi.org/10.1002/14651858.CD006157.pub2>.
 21. van Meerbeeck JP, Kramer GW, Van Schil PE, Legrand C, Smit EF, Schramel F, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. *J Natl Cancer Inst.* 2007;99(6):442–50.
 22. Albain KS, Swann RS, Rusch VW, Turrisi AT 3rd, Shepherd FA, Smith C, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet.* 2009;374(9687):379–86.
 23. Rusch VW, Giroux DJ, Kraut MJ, Crowley J, Hazuka M, Winton T, et al. Induction chemoradiation and surgical resection for superior sulcus non-small-cell lung carcinomas: long-term results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). *J Clin Oncol.* 2007;25(3):313–8.
 24. Auperin A, Le Pechoux C, Rolland E, Curran WJ, Furuse K, Fournel P, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol.* 2010;28(13):2181–90.
 25. Bradley JD, R Komaki, Masters G, Blumenschein G, Schild S. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol.* 2015;16(2):187–99.
 26. Pritchard RS, Anthony SP. Chemotherapy plus radiotherapy compared with radiotherapy alone in the treatment of locally advanced, unresectable, non-small-cell lung cancer. A meta-analysis. *Ann Intern Med.* 1996;125(9):723–9.
 27. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *New Engl J Med.* 2017;377(20):1919–29.
 28. Antonia SJ, Ouzguroglu M. Durvalumab in stage III non-small-cell lung cancer. *New Engl J Med.* 2018;378(9):869–70.
 29. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *New Engl J Med.* 2018. <https://doi.org/10.1056/nejmoa1809697> (**Epub ahead of print**).
 30. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Czoszi T, Fulop A, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *New Engl J Med.* 2016;375(19):1823–33.
 31. Group NM-AC. 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(28):4617–25.
 32. Lilenbaum RC, Herndon JE 2nd, List MA, Desch C, Watson DM, Miller AA, et al. Single-agent versus combination chemotherapy in advanced non-small-cell lung cancer: the cancer and leukemia group B (study 9730). *J Clin Oncol.* 2005;23(1):190–6.
 33. Sandler AB, Nemunaitis J, Denham C, von Pawel J, Cormier Y, Gatzemeier U, et al. Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol.* 2000;18(1):122–30.
 34. Wozniak AJ, Crowley JJ, Balcerzak SP, Weiss GR, Spiridonidis CH, Baker LH, et al. Randomized trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small-cell lung cancer: a Southwest Oncology Group study. *J Clin Oncol.* 1998;16(7):2459–65.

35. Ardizzoni A, Boni L, Tiseo M, Fossella FV, Schiller JH, Paesmans M, et al. Cisplatin- versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: an individual patient data meta-analysis. *J Natl Cancer Inst.* 2007;99(11):847–57.
36. D'Addario G, Pintilie M, Leighl NB, Feld R, Cerny T, Shepherd FA. Platinum-based versus non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a meta-analysis of the published literature. *J Clin Oncol.* 2005;23(13):2926–36.
37. Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *New Engl J Med.* 2018;378(22):2078–92.
38. Jotte RM, Cappuzzo F, Vynnychenko I, Stroyakovskiy D, Rodriguez-Abreu D, Hussein MA, et al. Mpower131: primary PFS and safety analysis of a randomized phase III study of atezolizumab + carboplatin + paclitaxel or nab-paclitaxel vs carboplatin + nab-paclitaxel as 1L therapy in advanced squamous NSCLC. In: Cannistra SA, editor. 2018 ASCO Annual Meeting; 2018; Chicago: Journal of Clinical Oncology; 2018. p. LBA9000.
39. Papadimitrakopoulou VA, Cobo M, Bordonni R, Dubray-Longeras P, Szalai Z, Ursol G, et al. IMpower132:PFS and safety results with 1L atezolizumab + carboplatin +pemetrexed in stage IV non-squamous NSCLC. IASLC 19th World Conference on Lung Cancer; Toronto, Canada2018. p. OA05.7.
40. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gumus M, Mazieres J, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *New Engl J Med.* 2018. <https://doi.org/10.1056/nejmoa1810865> (Epub ahead of print).
41. Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *New Engl J Med.* 2018;378(24):2288–301.
42. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *New Engl J Med.* 2002;346(2):92–8.
43. Park JO, Kim SW, Ahn JS, Suh C, Lee JS, Jang 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. *J Clin Oncol.* 2007;25(33):5233–9.
44. Rossi A, Chiodini P, Sun JM, O'Brien ME, von Plessen C, Barata F, 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):1254–62.
45. Socinski MA, Bondarenko I, Karaseva NA, Makhson AM, Vynnychenko I, Okamoto I, 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. *J Clin Oncol.* 2012;30(17):2055–62.
46. Li M, Zhang Q, Fu P, Li P, Peng A, Zhang G, 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.
47. Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol.* 2008;26(21):3543–51.
48. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *New Engl J Med.* 2006;355(24):2542–50.
49. Ciuleanu T, Brodowicz T, Zielinski C, Kim JH, Krzakowski M, Laack E, 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):1432–40.
50. Paz-Ares LG, de Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, 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. *J Clin Oncol.* 2013;31(23):2895–902.
51. Herbst RS, Baas P, Kim DW, Felip E, Perez-Gracia JL, Han JY, 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):1540–50.
52. Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *New Engl J Med.* 2015;373(2):123–35.
53. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *New Engl J Med.* 2015;373(17):1627–39.
54. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, 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):255–65.
55. Reck M, Kaiser R, Mellemaard A, Douillard JY, Orlov S, Krzakowski M, 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):143–55.
56. Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, 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. *J Clin Oncol.* 2000;18(10):2095–103.
57. Hanna N, Shepherd FA, Fossella FV, Pereira JR, De Marinis F, von Pawel J, 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(9):1589–97.
58. Molina-Garrido MJ, Guillen-Ponce C, Blanco R, Saldana J, Feliu J, Antonio M, et al. Delphi consensus of an expert committee in oncogeriatrics regarding comprehensive geriatric assessment in seniors with cancer in Spain. *J Geriatr Oncol.* 2018;9(4):337–45.
59. Quoix E, Zalcman G, Oster JP, Westeel V, Pichon E, Lavole A, 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):1079–88.
60. Gridelli C, Perrone F, Gallo C, Cigolari S, Rossi A, Piantedosi F, 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):362–72.
61. Gridelli C, Ardizzoni A, Le Chevalier T, Manegold C, Perrone F, Thatcher N, 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):419–26.
62. Lilenbaum R, Villafior VM, Langer C, O'Byrne K, O'Brien M, Ross HJ, et al. Single-agent versus combination chemotherapy in patients with advanced non-small cell lung cancer and a performance status of 2: prognostic factors and treatment selection based on two large randomized clinical trials. *J Thorac Oncol.* 2009;4(7):869–74.
63. Zukin M, Barrios CH, Pereira JR, Ribeiro Rde A, Beato CA, do Nascimento YN, 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. *J Clin Oncol*. 2013;31(23):2849–53.
64. Lee CK, Davies L, Wu YL, Mitsudomi T, Inoue A, Rosell R, et al. Gefitinib or erlotinib vs chemotherapy for EGFR mutation-positive lung cancer: individual patient data meta-analysis of overall survival. *J Natl Cancer Inst*. 2017. <https://doi.org/10.1093/jnci/djw279>.
 65. Yang JC, Wu YL, Schuler M, Sebastian M, Papat S, Yamamoto N, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. *Lancet Oncol*. 2015;16(2):141–51.
 66. Paz-Ares L, Tan EH, O'Byrne K, Zhang L, Hirsh V, Boyer M, 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):270–7.
 67. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *New Engl J Med*. 2018;378(2):113–25.
 68. Wu YL, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S, 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):1454–66.
 69. Mok TS, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S, 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. *J Clin Oncol*. 2018;36(22):2244–50.
 70. Reungwetwattana T, Nakagawa K, Cho BC, Cobo M, Cho EK, Bertolini A, et al. CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer. *J Clin Oncol*. 2018. <https://doi.org/10.1200/JCO.2018.78.3118>.
 71. Rosell R, Dafni U, Felip E, Curioni-Fontecedro A, Gautschi O, Peters S, et al. Erlotinib and bevacizumab in patients with advanced non-small-cell lung cancer and activating EGFR mutations (BELIEF): an international, multicentre, single-arm, phase 2 trial. *Lancet Respir Med*. 2017;5(5):435–44.
 72. Seto T, Kato T, Nishio M, Goto K, Atagi S, Hosomi Y, 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):1236–44.
 73. Yamamoto N, Nishio M, Goto K, Okamoto I, Yamanaka T, Tanaka 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* 36. 2018. https://doi.org/10.1200/JCO.2018.36.15_suppl.9007.
 74. Nakamura A, Inoue A, Morita S, Hosomi Y, Kato T, Fukuhara T, 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). *J Clin Oncol*. 2018. https://doi.org/10.1200/JCO.2018.36.15_suppl.9005.
 75. Weickhardt AJ, Scheier B, Burke JM, Gan G, Lu X, Bunn PA Jr, et al. Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer. *J Thorac Oncol*. 2012;7(12):1807–14.
 76. Yu HA, Arcila ME, Rekhtman N, Sima CS, Zakowski MF, Pao W, 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):2240–7.
 77. Mok TS, Wu YL, Ahn MJ, Garassino MC, Kim HR, Ramalingam SS, et al. Osimertinib or platinum-pemetrexed in EGFR T790 M-positive lung cancer. *New Engl J Med*. 2017;376(7):629–40.
 78. Mok TSK, Kim SW, Wu YL, Nakagawa K, Yang JJ, Ahn MJ, et al. Gefitinib plus chemotherapy versus chemotherapy in epidermal growth factor receptor mutation-positive non-small-cell lung cancer resistant to first-line gefitinib (IMPRESS): overall survival and biomarker analyses. *J Clin Oncol*. 2017;35(36):4027–34.
 79. Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *New Engl J Med*. 2014;371(23):2167–77.
 80. Soria JC, Tan DSW, Chiari R, Wu YL, Paz-Ares L, Wolf J, 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):917–29.
 81. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *New Engl J Med*. 2017;377(9):829–38.
 82. Camidge, Kim HR, Ahn MJ, Yang JC, Han JY, Lee JS, et al. Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer. *New Engl J Med*. 2018. <https://doi.org/10.1056/nejmoa1810171> (Epub ahead of print).
 83. Shaw AT, Kim DW, Nakagawa K, Seto T, Crino L, Ahn MJ, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *New Engl J Med*. 2013;368(25):2385–94.
 84. Shaw AT, Kim TM, Crino L, Gridelli C, Kiura K, Liu G, 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):874–86.
 85. Novello S, Mazieres J, Oh IJ, de Castro J, Migliorino MR, Helland A, et al. Alectinib versus chemotherapy in crizotinib-pretreated anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer: results from the phase III ALUR study. *Ann Oncol*. 2018;29(6):1409–16.
 86. Kim DW, Tiseo M, Ahn MJ, Reckamp KL, Hansen KH, Kim SW, et al. Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small-cell lung cancer: a randomized, multicenter phase II trial. *J Clin Oncol*. 2017;35(22):2490–8.
 87. Shaw AT, Felip E, Bauer TM, Besse B, Navarro A, Postel-Vinay S, 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):1590–9.
 88. Drlon A, Siena S, Ou SI, Patel M, Ahn MJ, Lee J, et al. Safety and antitumor activity of the multitargeted pan-TRK, ROS1, and ALK inhibitor entrectinib: combined results from two phase I trials (ALKA-372-001 and STARTRK-1). *Cancer Discov*. 2017;7(4):400–9.
 89. Horn L, Infante JR, Reckamp KL, Blumenschein GR, Leal TA, Waqar SN, et al. Ensartinib (X-396) in ALK-positive non-small cell lung cancer: results from a first-in-human phase I/II, multicenter study. *Clin Cancer Res*. 2018;24(12):2771–9.
 90. Shaw AT, Ou SH, Bang YJ, Camidge DR, Solomon BJ, Salgia R, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *New Engl J Med*. 2014;371(21):1963–71.
 91. Planchard D, Smit EF, Groen HJM, Mazieres J, Besse B, Helland A, 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):1307–16.
92. Planchard D, Besse B, Groen HJM, Souquet PJ, Quoix E, Baik CS, 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):984–93.
93. Drilon A, Laetsch TW, Kummar S, DuBois SG, Lassen UN, Demetri GD, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *New Engl J Med.* 2018;378(8):731–9.
94. Juan O, Popat S. Ablative therapy for oligometastatic non-small cell lung cancer. *Clin Lung Cancer.* 2017;18(6):595–606.
95. Gomez DR, Blumenschein GR Jr, Lee JJ, Hernandez M, Ye R, Camidge DR, 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):1672–82.
96. Iyengar P, Wardak Z, Gerber DE, Tumati V, Ahn C, Hughes RS, et al. Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: a phase 2 randomized clinical trial. *JAMA Oncol.* 2018;4(1):e173501.
97. Ou SH, Janne PA, Bartlett CH, Tang Y, Kim DW, Otterson GA, et al. Clinical benefit of continuing ALK inhibition with crizotinib beyond initial disease progression in patients with advanced ALK-positive NSCLC. *Ann Oncol.* 2014;25(2):415–22.
98. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *New Engl J Med.* 2010;363(8):733–42.