

LETTERS TO THE EDITOR

Early and locally advanced non-small-cell lung cancer: an update of the ESMO Clinical Practice Guidelines focusing on diagnosis, staging, systemic and local therapy



The following ESMO Clinical Practice Guideline has been recently updated with new treatment recommendations:

Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.¹

EUPDATE

View the ESMO eUpdate here: <https://www.esmo.org/guidelines/lung-and-chest-tumours/early-stage-and-locally-advanced-non-metastatic-non-small-cell-lung-cancer/eupdate-early-and-locally-advanced-non-small-cell-lung-cancer-nscl-treatment-recommendations2>.

PATHOLOGY/MOLECULAR BIOLOGY

Diagnosis

The original [Table 1](#) is updated.

STAGING AND RISK ASSESSMENT

Locoregional staging

The original [Figure 1](#) is updated.

TREATMENT OF EARLY STAGES (STAGES I-III A)

The original section 'Treatment of early stages (stages I-II)' is renamed 'Treatment of early stages (stages I-III A)'. The original recommendations are updated and a new treatment algorithm provided ([Figure 6](#)). The ESMO-MCBS table is updated to include osimertinib ([Table 6](#)).

Systemic therapy

Adjuvant treatment with targeted therapies

Adjuvant osimertinib for resected IB-III A NSCLC with EGFR exon 19 deletions or exon 21 L858R mutations.

Osimertinib is approved by both the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as adjuvant therapy after complete tumour resection in patients with stage IB-III A NSCLC whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations [I, A; European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: A].

Efficacy was demonstrated in a randomised, double-blind, placebo-controlled trial (ADAURA, NCT02511106) in patients with centrally confirmed EGFR exon 19 deletions or exon 21 L858R mutation-positive stage IB-III A NSCLC who had complete tumour resection, with or without prior adjuvant

chemotherapy (ChT).^{3,4} A total of 682 patients were randomised (1 : 1) to receive 3 years of osimertinib 80 mg orally once daily or placebo following recovery from surgery and standard adjuvant ChT, if given. The major efficacy outcome measure was disease-free survival (DFS) in patients with stage II-III A NSCLC determined by investigator assessment. With a median follow-up for the primary endpoint of 22.1 months in the osimertinib arm and 14.9 months in the placebo arm, the median DFS was not reached [(38.8 months-not evaluable (NE)) in patients on the osimertinib arm compared with 19.6 months (16.6-24.5 months) on the placebo arm [hazard ratio (HR) 0.17, 99.1% confidence interval (CI) 0.11-0.26, $P < 0.0001$]. DFS in the overall study population was a secondary efficacy outcome measure; the median was not reached (NE-NE) in patients on the osimertinib arm compared with 27.5 months (22.0-35.0 months) on the placebo arm (HR 0.20, 99.1% CI 0.14-0.30, $P < 0.0001$).^{3,4} The DFS benefit with osimertinib occurred in patients who received adjuvant ChT (HR 0.16, 95% CI 0.10-0.26), and among those who did not (HR 0.23, 95% CI 0.13-0.40), knowing that ChT administration was not a stratification factor and this decision was left to the investigator.³

The recommended osimertinib dose for adjuvant treatment of early-stage NSCLC is 80 mg orally once daily, with or without food, until disease recurrence, or unacceptable toxicity, or for up to 3 years.

Neoadjuvant or adjuvant immune checkpoint inhibitors

Unpublished data from phase III clinical trials have reported that in patients with stage IB-III A NSCLC, neoadjuvant immune checkpoint inhibitors (ICIs) plus ChT increases the rate of pathological complete response compared with ChT. Likewise, in the same setting, adjuvant ICI with anti-programmed death-ligand 1 (anti-PD-L1) leads to increased DFS versus best supportive care (BSC) for patients with PD-L1-positive tumours.

The recent phase III IMpower-010 trial assessed the role of adjuvant atezolizumab 1200 mg every 3 weeks for 16 cycles versus BSC in completely resected stage IB-III A NSCLC patients following recovery from surgery and standard adjuvant cisplatin-based ChT.⁵ In hierarchical testing, atezolizumab significantly improved the DFS versus BSC in PD-L1-expressing tumour cells $\geq 1\%$ (SP263 assay) stage II-III A NSCLC [median DFS not reached versus 35.3 months, (HR 0.66, 95% CI 0.50-0.88, $P = 0.0039$)], as well as in all randomised stage II-III A tumours [median DFS 42.3 versus 35.3 months, (HR 0.79, 95% CI 0.64-0.96, $P = 0.0205$)]. Finally, in the intention-to-treat population, DFS did not cross significance boundary [HR 0.81, 95% CI 0.67-0.99, $P = 0.04$].⁵ Atezolizumab, however, does not have EMA approval in this setting yet.

The primary analysis population from the three-arm CheckMate 816 trial reported that nivolumab plus platinum-based ChT for 3 cycles as neoadjuvant strategy in patients with stage IB-III A NSCLC significantly improved the

Table 1. Work-up for diagnosis and staging

	Mandatory	Optional
General	Medical history ^a Physical examination ^a Assessing comorbidity PS	
Imaging	CT thorax and upper abdomen ^a PET-CT ^a MRI brain ^c	X-ray thorax ^b Bone scintigraphy Contrast-enhanced CT brain
Laboratory	Blood cell counts Renal function Liver enzymes	Bone parameters ^d
Cardiopulmonary function	FVC, FEV1, DLCO ECG If indicated: CPET	Ejection fraction, CAG
Tissue procurement	Bronchoscopy ^{e,d} EBUS/EUS mediastinal nodes ^a CT-guided biopsy	Mediastinoscopy
Genomic profiling	EGFR mutation status	ALK fusion status
Other biomarkers	PD-L1 expression (for unresectable NSCLC)	PD-L1 expression (for completely resected NSCLC)

CAG, coronary angiography; CPET, cardiopulmonary exercise testing; CT, computed tomography; DLCO, diffusing capacity of the lungs for carbon monoxide; EBUS, endoscopic bronchial ultrasound; ECG, electrocardiogram; EUS, endoscopic ultrasound; FEV1, forced expiratory volume in 1 second; FVC, forced expiratory vital capacity; MRI, magnetic resonance imaging; NSCLC, non-small-cell lung cancer; PD-L1, programmed death-ligand 1; PET-CT, positron emission tomography computed tomography; PS, performance status.

^a Tests needed for clinical staging.

^b X-ray could be used as a first test in case of suspicious of lung cancer. However, a CT scan is recommended for those patients with risk factors or high clinical suspicion and a negative X-ray.

^c See text.

^d Optional, at physician's discretion upon suspicion. Bone scan or PET-CT to be carried out in case of suspicion for bone metastases.

^e Depending on site and size of tumour with biopsy/aspiration/brush/washing.

primary endpoint of pathological complete responses compared with ChT alone [24.0% versus 2.2%, odds ratio 13.94, 99% CI 3.49-55.75, $P < 0.0001$]. This benefit was consistent across disease stages, histologies, tumour mutational burden and PD-L1 expression levels.⁶ There are no data yet, however, on outcome with this strategy from this phase III trial. Therefore, in stage IB-IIIa NSCLC, the immune strategy in the (neo)adjuvant setting using ICIs $\pm$ CT is not yet standard. Several large phase III clinical trials are still ongoing with immune strategy in the (neo)adjuvant stage IB-IIIa clinical scenario.

Post-operative radiotherapy

The original recommendations are updated.

Recommendations

Adjuvant ChT

- Adjuvant ChT should be offered to patients with resected TNM (tumour—node—metastasis) 8th edition stage IIB and III NSCLC [I, A] and can be considered in patients with T2bN0, stage IIA resected primary tumour >4 cm [II, B]. Pre-existing comorbidity, time from surgery and post-operative recovery need to be taken into account

in this decision taken in a multidisciplinary tumour board [V, A].

- For adjuvant ChT, a two-drug combination with cisplatin is preferable [I, A]. In randomised studies, the attempted cumulative cisplatin dose was up to 300 mg/m², delivered in 3 to 4 cycles.
- When cisplatin administration is not feasible, carboplatin is an accepted alternative [IV, B].
- Although the most frequently studied regimen is cisplatin-vinorelbine, other combinations such as cisplatin and gemcitabine, or docetaxel or pemetrexed (only in adenocarcinoma tumours) could be also feasible [II, B].
- Carboplatin and paclitaxel is a potential ChT option for T2bN0, stage IIA resected primary tumour >4 cm [IV, B].

Adjuvant treatment with targeted therapies

- Osimertinib is indicated for the adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIa NSCLC whose tumours have EGFR exon 19 deletions or exon 21 L858R substitution mutations [I, A; ESMO-MCBS v1.1 score: A].

Post-operative radiotherapy

- Post-operative radiotherapy (PORT) in completely resected early-stage I-IIIa NSCLC is not recommended [I, E].
- In case of microscopic residual tumour (R1) resection (positive resection margin, chest wall), PORT should be considered [IV, B].
- Even if such patients were not included in randomised, clinical trials, adjuvant ChT should be considered in patients with R1 resection of stage IIA-IIB-III disease [V, A].
- In case both ChT and radiotherapy (RT) are administered post-R1 surgery, RT may be administered before ChT [V, C].

TREATMENT OF LOCALLY ADVANCED STAGE (STAGE III)

The original recommendations are updated and a new treatment algorithm provided (see Figure 6). The ESMO-MCBS table is updated for durvalumab (see Table 6).

Resectable locally advanced NSCLC

PORT after resected stage III NSCLC. PORT should not be used in patients with NSCLC following complete R0 resection and after (neo)adjuvant ChT, as no statistically significant difference in 3-year DFS was shown in a randomised, controlled trial.

The large randomised, controlled LungART trial presented at ESMO 2020 explored the role of modern mediastinal PORT in patients with completely resected NSCLC with histo/cytologically proven N2 nodal involvement. The study randomised 501 patients with completely resected stage IIIa N2 NSCLC to PORT (54 Gy in 27-30 fractions or no PORT). Safety analysis was carried out in 487 patients.⁷ LungART is the only large, adequately-powered, high-quality, randomised trial in the modern era to be completed in these patients. The trial selected a well-defined, high-risk

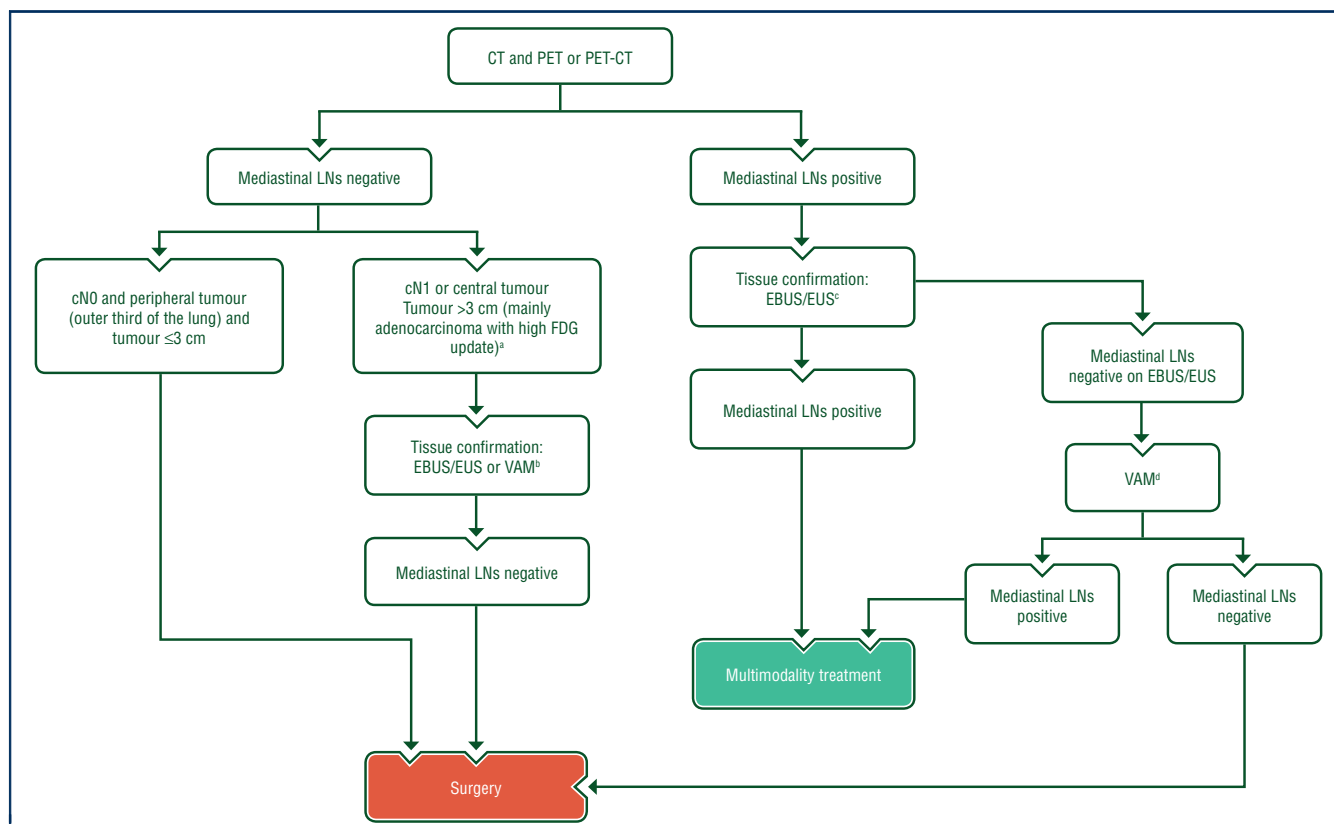


Figure 1. Suggested algorithm for locoregional lymph node staging in patients with non-metastatic NSCLC.

Red: surgery; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.

CT, computed tomography; EBUS, endoscopic bronchial ultrasound; EUS, endoscopic ultrasound; FDG, fluorodeoxyglucose; LN, lymph node; NPV, negative predictive value; NSCLC, non-small-cell lung cancer; PET, positron emission tomography; VAM, video-assisted mediastinoscopy.

^a In tumours > 3 cm (mainly in adenocarcinoma with high FDG uptake), invasive staging should be considered.

^b Depending on local expertise to adhere to minimal requirements for staging.

^c Endoscopic techniques are minimally invasive and are the first choice if local expertise with EBUS/EUS needle aspiration is available.

^d Due to its higher NPV, in case of PET-positive or CT-detected mediastinal LN enlargement, negative endoscopic staging (EBUS or EUS) and high clinical suspicion with availability of VAM, nodal dissection or biopsy is recommended.

Adapted with permission from De Leyn et al.²

patient population (52% of patients had ≥ 2 N2 nodal stations involved), 91% of whom had undergone positron emission tomography (PET) scans, and 95% of whom had undergone systemic ChT. The quality of surgery carried out was clearly specified and also reviewed centrally by a surgical committee.

At a median follow-up of 4.8 years, the DFS HR reported in the trial was 0.85 (95% CI 0.67–1.07, $P = 0.16$), with median DFS times of 30.5 months for PORT and 22.8 months without PORT. Three-year DFS rates were 47.1% and 43.8% with and without PORT, respectively. There was also no evidence that PORT improved overall survival (OS), with 3-year OS rates of 66.5% and 68.5% with and without PORT, respectively. Not only did PORT fail to provide a survival benefit, but it may actually be harmful for patients, with an incidence of late grade 3–4 cardiopulmonary toxicity twice that in patients without PORT (10.8% versus 4.9%).

Consequently, PORT cannot be recommended for patients with completely resected stage I–III N2 NSCLC. Its potential utility for locoregional disease control in resected stage III N2 disease (decrease of the rate of mediastinal relapse by 50%) is offset by the risk of over-added cardiopulmonary toxicity. Further analysis is needed to determine

whether certain patients, in particular, could benefit. For patients with incompletely resected R1 stage III NSCLC, PORT should be considered, with thorough assessment in a multidisciplinary tumour board.

Unresectable locally advanced NSCLC

The phase III PACIFIC trial randomised (2 : 1) 713 patients with unresectable, locally-advanced NSCLC without disease progression within the first 42 days after concurrent chemoradiotherapy, to consolidative durvalumab for 1 year or placebo.⁸ After a median follow-up of 34.2 months, the median OS for durvalumab was reached (47.5 months versus 29.1 months for placebo, HR 0.72, 95% CI 0.59–0.89), and the estimated 5-year OS rates were 42.9% versus 33.4% for durvalumab versus placebo, respectively. The median PFS was 16.9 months for durvalumab and 5.6 months for placebo (HR 0.55, 95% CI 0.45–0.68) with a 5-year PFS rate of 33.1% versus 19.0%, respectively.⁸

A *post hoc* exploratory analysis of the mature survival data requested by licensing European authorities observed that the benefit with durvalumab was not evident in patients with PD-L1 expression < 1%. The significance of this observation is disputed.⁹

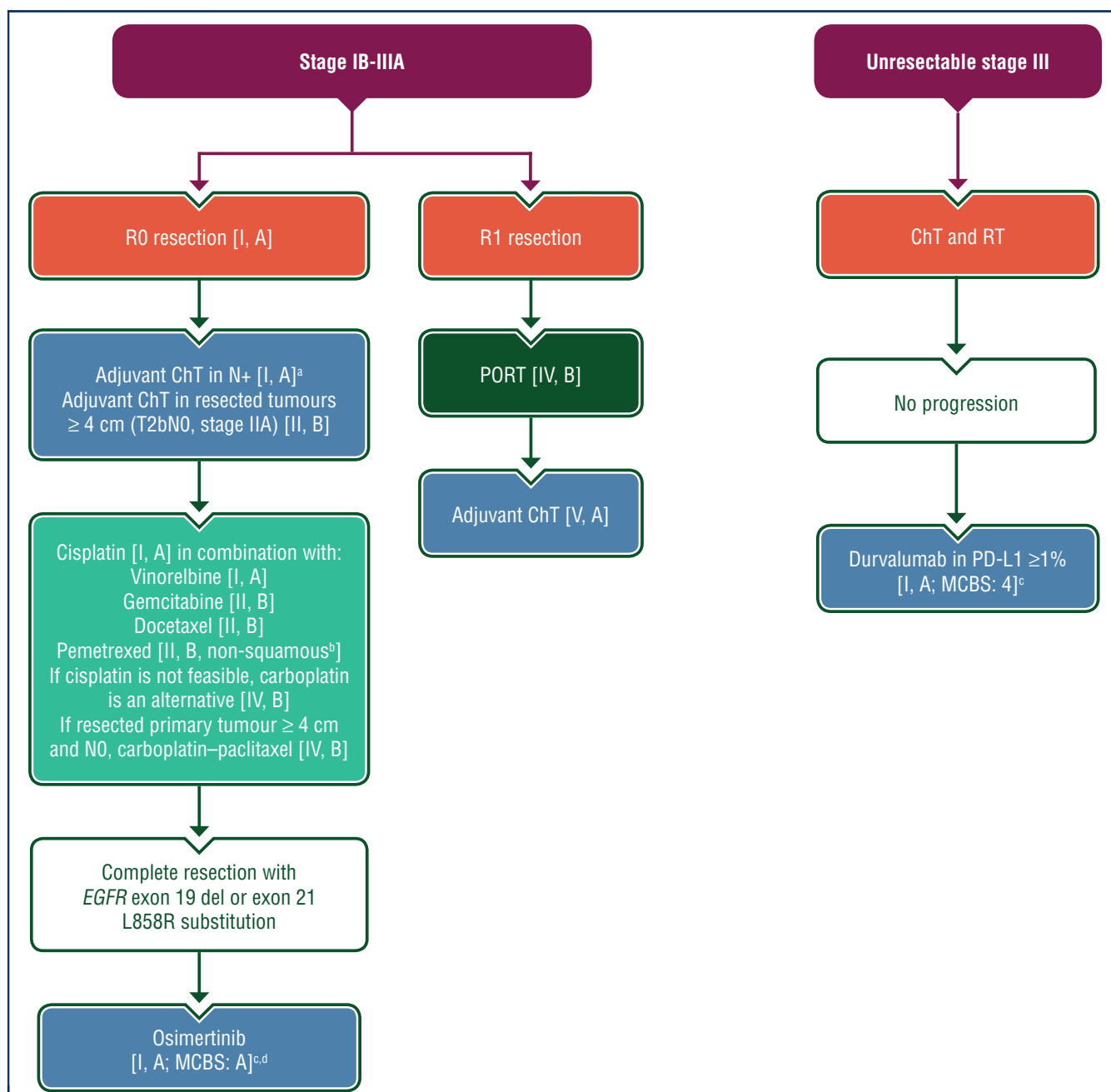


Figure 6. Systemic treatment algorithm for early-stage (stage IB-IIIa) and unresectable locally advanced (stage III) NSCLC.

For resection criterion, check Figure 2. Purple: general categories or stratification (symptom); red: surgery; dark green: radiotherapy; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.

ChT, chemotherapy; ESMO, European Society for Medical Oncology; MCBS, Magnitude of Clinical Benefit Scale; N+, node-positive; PD-L1, programmed death-ligand 1; PORT, post-operative radiotherapy; RT, radiotherapy.

^a For stage IB, adjuvant ChT in primary tumours ≥ 4 cm [II, B].

^b Only in adenocarcinoma tumours.

^c ESMO-MCBS v1.1 score for new therapy/indication approved by the EMA since 1 January 2016 and the Food and Drug Administration (FDA) since 1 January 2020. The score has been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (<https://www.esmo.org/guidelines/esmo-mcbs/scale-evaluation-forms-v1.0-v1.1/scale-evaluation-forms-v1.1>).

^d Primary endpoint of ADAURA trial was DFS in stage II-IIIa according to 7th TNM (T > 5 cm or N+). Adjuvant osimertinib in stage IB (3 cm < T ≤ 5 cm) was a secondary endpoint. Stage was a stratification factor. Therefore, indication for osimertinib in T ≤ 5 cm N0 will follow local recommendations/physician's discretion [I, B].

Recommendations

PORT after resected stage III NSCLC

- PORT is not beneficial for patients with completely resected stage III N2 NSCLC [I, E] and should only be considered in the setting of residual microscopic or macroscopic disease [IV, B].

Unresectable locally advanced NSCLC

- The consolidation administration of the ICI durvalumab within 1-42 days after the end of concurrent chemoradiotherapy has demonstrated a survival benefit in unresectable stage III NSCLC and is recommended in patients whose disease has not progressed following platinum-

Table 6. ESMO-MCBS table for new therapies/indications in early and locally advanced NSCLC

Therapy	Durvalumab
Disease setting	Consolidation therapy in patients with stage III NSCLC who did not have disease progression after ≥ 2 cycles of platinum-based CRT
Trial	A study of durvalumab as consolidation therapy in patients with locally advanced, unresectable NSCLC (stage III) who have not progressed following definitive, platinum-based, concurrent chemoradiation therapy (PACIFIC) ¹⁰⁻¹⁴ Phase III NCT02125461
Control (median)	Placebo PFS ITT across all PD-L1 categories control: 5.6 months OS control: 29.1 months 2-year OS control: 55.3% 4-year OS control: 36.3%
Absolute survival gain	PFS ITT across all PD-L1 categories gain: 11.6 months OS gain: 18.4 months 2-year OS gain: 11% 4-year OS gain: 13.3%
HR (95% CI)	PFS HR: 0.55 (0.44-0.67) OS HR: 0.71 (0.57-0.88)
QoL/toxicity	No benefit observed
ESMO-MCBS score ^a	4 ^b (Form 2a)
Therapy	Osimertinib — 3 years
Disease setting	Adjuvant treatment after tumour resection <i>EGFR</i> exon 19 deletions or exon 21 (L858R) mutation
Trial	A study of osimertinib versus placebo in patients with <i>EGFR</i> mutation positive stage IB-IIIa NSCLC following complete tumour resection with or without adjuvant chemotherapy (ADAURA) ¹⁵ Phase III NCT02511106
Control (median)	Placebo 2-year DFS control: 52% ^d
Absolute survival gain	2-year DFS gain: 37% ^d
HR (95% CI)	DFS HR: 0.20 (0.14-0.30) ^{c,d}
QoL/toxicity	
ESMO-MCBS score ^a	A ^d (Form 1)

CI, confidence interval; CRT, chemoradiotherapy; DFS, disease-free survival; *EGFR*, epidermal growth factor receptor; EMA, European Medicines Agency; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; FDA, Food and Drug Administration; HR, hazard ratio; ITT, intention to treat; NSCLC, non-small-cell lung cancer; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; QoL, quality of life.

^a ESMO-MCBS v1.1.¹⁵ The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (<https://www.esmo.org/guidelines/esmo-mcbs/scale-evaluation-forms-v1.0-v1.1/scale-evaluation-forms-v1.1>).

^b EMA approval is limited to PD-L1 $>1\%$, based on *post hoc* subgroup analysis indicating lack of benefit for patients with PD-L1 $<1\%$ ¹³; FDA approval is based on ITT and is irrespective of PD-L1.

^c HR with 99.12% CI.

^d Approval was based on all patient data (including stage Ib), which was a secondary outcome (statistically significant after hierarchical testing).

based chemoradiotherapy [I, A] in the intention-to-treat population across all PD-L1 categories and in patients whose tumours express PD-L1 on tumour cells (as per the EMA-approved indication) [I, A; ESMO-MCBS v1.1 score: 4].

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

The original recommendations are updated.

Recommendations

- NSCLC patients treated with radical intent should be followed for treatment-related complications, detection of treatable relapse or occurrence of second primary lung cancer. Multidisciplinary team assessment is required for feasibility check for treatment of locoregional relapse [III, A].
- Surveillance every 6 months for 2 years with a visit including history, physical examination and contrast-enhanced volume chest and abdominal CT scan at least at 12 and 24 months is recommended, with optional [¹⁸F]2-fluoro-2-deoxy-D-glucose-PET if required, and thereafter an annual visit including history, physical examination and chest/upper abdominal CT scan in order to detect second primary tumours [III, B].

J. Remon^{1,†}, J.-C. Soria^{2,†} & S. Peters,³ on behalf of the ESMO Guidelines Committee*

¹Department of Medical Oncology, Centro Integral Oncológico Clara Campal (HM-CIOCC), Hospital HM Nou Delfos, HM Hospitales, Barcelona, Spain;

²University Paris-Saclay and Gustave Roussy Cancer Campus, Villejuif, France;

³Department of Oncology, Centre Hospitalier Universitaire Vaudois, Lausanne University, Lausanne, Switzerland (*E-mail: clinicalguidelines@esmo.org).

†These authors contributed equally.

Available online 1 September 2021

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<https://doi.org/10.1016/j.annonc.2021.08.1994>

ACKNOWLEDGEMENTS

The ESMO Guidelines Committee acknowledges and thanks the following people who have acted as reviewers for this update: Rolf Stahel (ESMO Guidelines Steering Committee) and Marina Garassino (ESMO Faculty, metastatic NSCLC). George Pentheroudakis (Chief Medical Officer of ESMO) provided coordination and writing support. Catherine Evans, Richard Lutz and Jennifer Lamarre (ESMO staff) provided editing support. Nathan Cherny, Chair of the ESMO-MCBS Working Group, Urani Dafni ESMO-MCBS Working Group Member/Frontier Science Foundation Hellas and Giota Zygoura of Frontier Science Foundation Hellas provided review and validation of the ESMO-MCBS scores. Nicola Latino (ESMO Scientific Affairs staff) provided coordination and support of the ESMO-MCBS scores and Angela Corstorphine of Kstorfin Medical Communications Ltd. provided medical writing and editing support in the preparation of the ESMO-MCBS table; this support was funded by ESMO.

FUNDING

No external funding has been received for the preparation of these guidelines. Production costs have been covered by ESMO from central funds.

DISCLOSURE

JCS reports that he is on the Board of directors for Hookipa Pharma, a former full-time employee of AstraZeneca from September 2017 to December 2019 and has shares in Relay Therapeutics and Gritstone Bio. JR reports receipt of honoraria to institute for consultancy, advisory boards and/or lectures from AstraZeneca, Bristol Myers Squibb (BMS), Boehringer Ingelheim, Merck Sharp & Dohme (MSD), OSE-Immunotherapeutics, Pfizer, Roche. SP reports consultation/advisory roles for AbbVie, Amgen, AstraZeneca, Bayer, BeiGene, Biocartis, BioInvent, Blueprint Medicines, Boehringer Ingelheim, BMS, Clovis, Daiichi Sankyo, Debiopharm, Eli Lilly, Elsevier, F. Hoffmann-La Roche/Genentech, Foundation Medicine, Illumina, Incyte, IQVIA, Janssen, Medscape, MSD, Merck Serono, Merrimack, Mirati, Novartis, PharmaMar, Phosphatin Therapeutics, Pfizer, Regeneron, Sanofi, Seattle Genetics, Takeda, Vaccibody; talk in a company's organised public event: AstraZeneca, Boehringer Ingelheim, BMS, e-cancer, Eli Lilly, F. Hoffmann-La Roche/Genentech, Illumina, Medscape, MSD, Novartis, PER, Pfizer, Prime, RTP, Sanofi, Takeda; receipt of grants/research support as (sub) investigator in trials (institutional financial support for clinical trials) sponsored by Amgen, AstraZeneca, Biodesix, Boehringer Ingelheim, BMS, Clovis, F. Hoffmann-La Roche/Genentech, GlaxoSmithKline, Illumina, Lilly, MSD, Merck Serono, Mirati, Novartis, Pfizer, Phosphatin Therapeutics.

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Detection of additional occult malignancy through profiling of ctDNA in late-stage cancer patients



Next-generation sequencing (NGS) of circulating tumor DNA (ctDNA) is an increasingly used method for the genomic profiling of cancer. This approach has several advantages in comparison with NGS of tissue biopsies: non-invasive, easily accessible, and representative of the entire tumor burden present within the patient.¹ ctDNA assays may also detect genetic aberrations arising from other sources, such as alterations of clonal hematopoiesis of indeterminate origin (CHIP).²

Here, we report three cases of patients who underwent genomic profiling of cancer by NGS of ctDNA and for whom the analysis of the results allowed the detection of an additional occult malignancy.

From December 2020 to June 2021, 1086 patients underwent NGS of ctDNA by using the FoundationOne® Liquid Assay³ at Gustave Roussy (Villejuif, France). Five (0.46%) of them had a suspicion of a second cancer based on the analysis of ctDNA sequencing. Three of them underwent further investigations which confirmed the presence of a second malignancy and are presented below.

CASE 1

Patient #1 was a 73-year-old Caucasian male who presented in February 2020 with thoracic pain. Diagnostic work-up