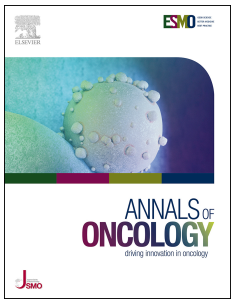

ESMO expert consensus statements on the management of *EGFR* mutant Non-Small Cell Lung Cancer

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SPECIAL ARTICLE

ESMO expert consensus statements on the management of *EGFR* mutant Non-Small Cell Lung Cancer

A. Passaro[1], N. Leighl[2§], F. Blackhall[3§], S. Popat[4§], K. Kerr[5§], M.J. Ahn[6], M.E. Arcila[7], O. Arrieta[8], D. Planchard[9], F. de Marinis[10], A.M. Dingemans[11], R. Dziadziuszko[12], C. Faivre-Finn[13], J. Feldman[14], E. Felip[15], G. Curigliano[16], R. Herbst[17], P.A. Jänne[18], T. John[19], T. Mitsudomi[20], T. Mok[21], N. Normanno[22], L. Paz-Ares[23], S. Ramalingam[24], L. Sequist[25], J. Vansteenkiste[26], I.I. Wistuba[27], J. Wolf[28], Y.L. Wu[29], S.R. Yang[30], J.C.H. Yang[31], Y. Yatabe[32], G. Pentheroudakis[33], S. Peters[34]

1. Division of Thoracic Oncology, European Institute of Oncology IRCCS, Milano, Italy
2. Division of Medical Oncology/Hematology, Princess Margaret Hospital Cancer Centre, Toronto, Ontario,
3. Division of Cancer Sciences, The University of Manchester, Manchester, United Kingdom; Department of Medical Oncology, The Christie National Health Service (NHS) Foundation Trust, Manchester, United Kingdom.
4. National Heart and Lung Institute, Imperial College, London, United Kingdom; Lung Unit, Royal Marsden Hospital, Fulham Road, London, United Kingdom; The Institute of Cancer Research, Fulham Road, London, United Kingdom.
5. Aberdeen Royal Infirmary, Aberdeen University Medical School, Aberdeen, Scotland
6. Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
7. Department of Pathology, Molecular Diagnostics Service, Memorial Sloan Kettering Cancer Center, New York, New York.
8. Thoracic Oncology Unit, Instituto Nacional de Cancerología, Mexico City, Mexico
9. Department of Medical Oncology, Gustave Roussy, Villejuif, France.
10. Division of Thoracic Oncology, European Institute of Oncology IRCCS, Milano, Italy
11. Department of Respiratory Medicine, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, The Netherlands.
12. Department of Oncology and Radiotherapy, Medical University of Gdańsk, Gdańsk, Poland
13. The University of Manchester, Manchester Academic Health Science Centre, The Christie NHS Foundation Trust, United Kingdom.
14. Lung Cancer Patient and Advocate, Co-Founder of EGFR Resisters Patient Group
15. Department of Medical Oncology, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona.
16. Department of Oncology and Hemato-Oncology, University of Milano, European Institute of Oncology IRCCS, Milano, Italy
17. Yale Comprehensive Cancer Center, Yale University School of Medicine, New Haven, Connecticut.
18. Lowe Center for Thoracic Oncology, Department of Medical Oncology, Dana-Farber Cancer
19. Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia.
20. Division of Thoracic Surgery, Department of Surgery, Kindai University Faculty of Medicine, Osaka-Sayama, Japan.
21. State Key Laboratory of Translational Oncology, Chinese University of Hong Kong, Shatin, Hong Kong Special Administrative Region, China.
22. Cell Biology and Biotherapy and Scientific Directorate, Istituto Nazionale Tumori, "Fondazione G.Pascale" IRCCS, Napoli, Italy
23. Lung Cancer Clinical Research Unit, and Complutense University, Madrid
24. Department of Hematology and Medical Oncology, Winship Cancer Institute, Atlanta, Georgia.
25. Department of Medicine, Massachusetts General Hospital, Boston, MA, USA.
26. Department of Respiratory Oncology, University Hospital KU Leuven, Leuven, Belgium.
27. Department of Translational Molecular Pathology, Unit 951, The University of Texas MD Anderson Cancer Center, Houston, TX, USA.
28. Lung Cancer Group Cologne, Department I for Internal Medicine and Center for Integrated Oncology Cologne/Bonn, University Hospital Cologne,Germany.
29. Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences, Guangdong, China.
30. Department of Pathology, Molecular Diagnostics Service, Memorial Sloan Kettering Cancer Center, New York, New York.
31. Department of Oncology, National Taiwan University Hospital and National Taiwan University Cancer Center, Taipei, Republic of China.
32. Department of Diagnostic Pathology, National Cancer Center Hospital, Tokyo, Japan.
33. Department of Medical Oncology, University of Ioannina, Ioannina, Epirus, Greece
34. Oncology Department - CHUV, Lausanne University, Lausanne, Switzerland.

§ These authors contributed equally

Corresponding author:

Dr Antonio Passaro,
Division of Thoracic Oncology,
European Institute of Oncology IRCCS
Via Giuseppe Ripamonti 435, 20141, Milan, Italy
Tel: +39-0257489826 Email: antonio.passaro@ieo.it Twitter: APassaroMD

Highlights

- A virtual consensus on the management of EGFR mutant NSCLC, was organised by the ESMO, including 34 experts from 18 countries
- The experts compiled recommendations with supporting evidence on controversial topics about the EGFR mutant lung cancer
- Recommendations formulated for tissue and biomarkers analyses; early, locally advanced and metastatic disease; miscellaneous

Abstract

The European Society for Medical Oncology (ESMO) held a virtual consensus-building process on *EGFR* mutant non-small cell lung cancer (NSCLC) in 2021. The consensus included a multidisciplinary panel of 34 leading experts in the management of lung cancer. The aim of the consensus was to develop recommendations on topics that are not covered in detail in the current ESMO Clinical Practice Guideline and where the available evidence is either limited or conflicting.

The main topics identified for discussion were (i) tissue and biomarkers analyses; (ii) Early and locally advanced disease; (iii) metastatic disease; (iv) clinical trial design, patient's perspective and miscellaneous.

The expert panel was divided into four working groups to address questions relating to one of the four topics outlined above. Relevant scientific literature was reviewed in advance. Recommendations were developed by the working groups and then presented to the entire panel for further discussion and amendment before voting.

This manuscript presents the recommendations developed, including findings from the expert panel discussions, consensus recommendations and a summary of evidence supporting each recommendation.

Keywords: consensus, lung cancer, treatment, testing, targeted therapy, *EGFR*

INTRODUCTION

The management of epidermal growth factor receptor (*EGFR)* mutant non-small cell lung cancer (NSCLC) has dramatically changed following the introduction of targeted therapy in the last fifteen years. However, despite these advances, evidence remains limited and/or conflicting in some specific areas where the optimal approach remains controversial, both in metastatic and early settings. In 2021, the European Society for Medical Oncology (ESMO) held a virtual consensus-building process on this topic to gain insights from a multidisciplinary group of experts and develop recommendations on controversial topics that cannot be adequately addressed in the current evidence-based ESMO Clinical Practice Guideline.

METHODS

The aim of this consensus-building process was to discuss controversial issues relating to the management of patients with *EGFR* mutant non-small cell lung cancer. The virtual meeting included a multidisciplinary panel of 32 leading experts from 16 countries and was chaired by A. Passaro and S. Peters. All experts were allocated to four different working groups. Each working group covered a specific subject area and was appointed a chair as follows:

1. Tissue and biomarkers analyses (Chair: K. Kerr)
2. Early and locally advanced disease (Chair: S. Popat)
3. Metastatic disease (Chair: N. Leighl)
4. Clinical Trial Design, patients' perspective, miscellaneous (Chair: F. Blackhall)

Planning, preparation and execution of the consensus process was conducted according to the ESMO standard operating procedures. No systematic literature search was undertaken. All recommendations compiled by the group were accompanied by a level of evidence and strength of recommendation based on the 'Infectious Diseases Society of America-United States Public Health Service Grading System' (supplementary Table S1). The final manuscript was reviewed and approved by all panel members.

RESULTS

TISSUE AND BIOMARKER ANALYSIS

1. Is there a need to accurately identify all *EGFR* mutations with clinical utility, covering those considered as common and atypical/uncommon?

STATEMENT: Broad screening of exons 18-21 for all mutations with established or potential clinical significance is recommended, preferably by NGS [ESCAT I-A] [I,A]

DISCUSSION: Comprehensive reflex biomarker testing, including *EGFR,* is recommended for all patients with a diagnosis of non-squamous non-small cell lung carcinomas (NSCLC), regardless of disease stage and should be initiated by the pathologist at the time of initial diagnosis.

The most common type of activating *EGFR* mutation is the in-frame deletion of exon 19 around the LREA motif (amino acids residues 747 to 750; ~45% of *EGFR* mutations), followed by p.L858R point mutation of exon 21 (~40% of *EGFR* mutations).[1]

Tumors with these activating mutations or less frequent mutations, defined as atypical/uncommon, such as insertions in exon 19, point mutations in exon 18 at position G719 (~3% of *EGFR* mutations), the exon 21 p.L861Q mutant (~2% of *EGFR* mutations), and the S768I mutation in exon 20 (~2% of *EGFR* mutations), showed variable sensitivity to EGFR tyrosine kinase inhibitors (TKIs).[2, 3]

On the other hand, most in-frame insertion mutations within exon 20 of *EGFR*, which accounts for (~4-10% of all *EGFR* mutations), and other uncommon mutations including exon 19 insertions, p.L747S, p.D761Y, p.T790M, and p.T854A confer resistance to EGFR TKIs.

Considering the need to identify mutations affecting *EGFR* and other targetable genes, parallel testing with a comprehensive next-generation sequencing (NGS) panel, rather than single-gene *EGFR* testing, using tissue - or plasma/blood if tumor tissue is not available - is recommended. The use of NGS makes efficient sample use, improves timely access to results, bypasses delays for ordering follow-up testing, and can be cost-effective if enough targets are included. Considering the clinical application of NGS to examine tumors in NSCLC, rare *EGFR* mutations of unknown biological and clinical significance are encountered in clinical practice.

Interestingly, distinct response rates to EGFR TKIs are reported even for mutations at the same location within the genomic DNA. Compound mutations are defined as double or multiple independent mutations of the EGFR tyrosine kinase domain, in which the EGFR TKI sensitizing or other mutation is identified together with a mutation of unknown clinical significance. Advances in tumor genotyping methodology provide a higher probability of identifying atypical and compound mutations in the EGFR tyrosine kinase domain in ~20% of the same tumor sample. More attention and collaborative efforts are required to elucidate these rare compound mutations' biological and clinical significance.

Level of consensus: 96.8% (30) agree; 3.2% (1) abstain. Total: 31 voters

2: What is the role of tissue rebiopsy at disease progression in patients on TKI therapy for *EGFR* mutant NSCLC?

STATEMENT: In all patients with *EGFR*-mutant NSCLC who are progressing on TKI therapy, a tissue rebiopsy is recommended (when feasible) to assess for actionable mechanisms of resistance and potential histologic transformation [I,A].

DISCUSSION: Nearly all *EGFR*-mutated NSCLC patients eventually develop resistance to TKI therapy.[4] There are three main mechanisms of acquired resistance that are important for clinical practice:

i. On-target resistance involving *EGFR*
ii. Off-target resistance through activation of bypass oncogenic pathways
iii. Histologic transformation.

Characterization of these resistance mechanisms at progression can reveal actionable insights for selecting subsequent treatments and clinical trials.

EGFR T790M is a classic example of on-target resistance that occurs in approximately 50% of patients with disease progression on first-generation TKIs. Detection of this mutation is critical as third-generation TKIs such as osimertinib can overcome T790M-mediated resistance.[5] In the past few years, the landscape of on-target resistance has been transformed by the increasing use of osimertinib for T790M-positive tumors and the growing adoption of osimertinib as the preferred first-line TKI. Consequently, instead of the single predominant variant T790M, there is a wide spectrum of acquired *EGFR* mutations (e.g., p.C797X, p.G724S, p.L718Q, p.L792H, p.G769R, etc.) that confer resistance to osimertinib in smaller subsets of patients.[6-8] While these variants do not drive standard-of-care treatments at this time, screening for these mutations may guide clinical trials that are exploring the efficacy of older TKIs and novel EGFR inhibitors for each specific genotypes.[9]

MET amplification represents the most common mechanism of off-target resistance, occurring in up to 24% of patients progressing on osimertinib.[10] In this population, combination therapy using MET and EGFR TKI is emerging as an effective therapeutic option.[11] Other infrequent but potentially druggable mechanisms of off-target resistance include *ERBB2* amplification, *BRAF* mutations, *MET* exon 14 skipping mutations, and oncogenic fusions involving *RET*, *ALK*, *ROS1*, *BRAF*, *FGFR3*, and *NTRK1*.[9, 12, 13] Altogether, these divergent pathways underscore the need for comprehensive molecular profiling.

Histologic transformation affects approximately 15% of patients at disease progression and highlights the importance of tissue analysis.[14, 15] It is well-recognized that a subset of lung adenocarcinomas can transform into small cell lung cancer (SCLC) under selective pressure from TKI therapy, potentially driven by p53 and Rb inactivation[15]. Similar to de novo SCLC, but to a lesser extent, these tumors are sensitive to platinum/etoposide chemotherapy.[16] While the clinical implications of squamous cell transformation are less clear, these patients may benefit from histology-specific treatments. Sarcomatoid transformation can also occur through epithelial-to-mesenchymal transition and is associated with poor outcomes.[17]

In patients with disease progression who require a change in systemic therapy, a tissue biopsy is recommended to assess all actionable resistance mechanisms. In addition to histologic evaluation for transformation, DNA/RNA-based NGS using comprehensive gene panels should be preferred, given the heterogeneity of resistance patterns.
DNA/RNA-based NGS for fusion detection is recommended. While DNA-based NGS can be validated for mutations, amplifications, and fusions in key genes associated with resistance, some fusions can be missed [18]. If NGS is not available, mutational testing for *EGFR* T790M and FISH for *MET* amplification should be performed at a minimum for patients on early-generation TKIs. For patients on osimertinib, there is anecdotal evidence that FISH may detect higher rates of *MET* amplification than NGS-based methods. Given that resistant cells are often subclonal, utilising molecular assays with high analytical sensitivity is important.[19] When tissue sampling is not feasible, a liquid biopsy may represent a viable alternative despite its inability to capture histologic transformation and limited sensitivity for amplifications and fusions.[20, 21]

Level of consensus: 100% (31) agree. Total: 31 voters

3: What is the role of cfDNA testing in the context of genomic profiling upfront and at disease progression on EGFR TKI therapy?

STATEMENT: cfDNA testing is of value and recommended, if no tissue is available, to identify the *EGFR* alterations and some resistance mechanisms, both in primary diagnostic and resistance setting [I,A].

DISCUSSION: In patients with suspected NSCLC, a biopsy sample is essential for histological diagnosis and evaluation of biomarkers. If the tissue sample is not sufficient, inadequate or missing, cfDNA analysis represents a possible alternative for the evaluation of *EGFR* mutations.[1, 21, 22] Technologies capable of identifying all *EGFR* mutations in exons 18-21 should be used for cfDNA analysis.[22] Any negative results should be interpreted with caution due to the possibility of false negatives determined by the limited sensitivity of the cfDNA test. In fact, about 25% of NSCLC patients are defined "non-shedder", as their tumors release low amounts of DNA, below the sensitivity limits of currently available technologies.[23] In patients with EGFR-mutant NSCLC progressing after TKI treatment, cfDNA testing can identify mechanisms of resistance.[24, 25] In particular, in patients progressing on 1st or 2nd generation TKIs the identification of the p.T790M variant might suggest sensitivity to 3rd generation TKIs. EGFR mutant patients recurring on TKI treatment usually maintain the sensitizing mutation. As a consequence, those cases in which both the sensitizing and the resistance mutations are not detected, are likely to have too low levels of ctDNA in plasma and they should be considered as non-informative, rather than negative.[26] A low variant allelic frequency (VAF) of the sensitizing EGFR mutation is also associated with a high rate of false negative T790M test.[27] Therefore, in patients with negative or low VAF EGFR sensitizing mutation, a tissue biopsy is recommended.

cfDNA analysis offers a potential advantage over tissue analysis in better representing the tumor heterogeneity typical of progressive disease.[28] However, some resistance mechanisms to EGFR TKI, including small-cell lung cancer (SCLC) transformation, squamous-cell transformation and epithelial-to-mesenchymal transition (EMT), can only be identified through tissue analysis.[1, 12] – while MET amplification and oncogenic fusion diagnostic remains challenging using cfDNA. Therefore, cfDNA and tumor tissue analyses provide complementary information on TKI resistance mechanisms.

Increasing evidence suggests that cfDNA testing allows monitoring response to treatment and predicting relapse in EGFR mutant NSCLC patients on treatment with EGFR TKI.[22] However, the clinical utility of an early diagnosis of progression has not yet been demonstrated in randomized clinical trials with adequate cohorts of patients.[29] Therefore, the monitoring of the response to treatment with EGFR TKI should be restricted to clinical trials or cases selected by tumor boards for peculiar clinical-pathological characteristics, such as rare EGFR mutations that may not respond to treatment with TKI.

Level of consensus: 90.3% (28) agree; 9.7% (3) disagree. Total: 31 voters

4: Should we perform EGFR and PD-L1 testing simultaneously or sequentially?

STATEMENT: PD-L1 testing should be performed at the same time as *EGFR* (and other biomarkers) to allow expeditious triaging in case where a targetable genetic alteration is not identified. [I,A]

DISCUSSION: Immune checkpoint inhibitors (ICIs), given as a single agent or in combination with platinum-based chemotherapy, are a standard treatment for advanced or metastatic lung cancer, in patients with *EGFR* or *ALK*-wildtype NSCLC. Clinical trials evidence suggests that *EGFR* or *ALK*-positive tumors rarely derive sufficient responses to ICI treatments.[30-32] Pooled analyses reported lower response rates of *EGFR* and ALK-positive tumors, reflected in shorter progression-free survival.[33, 34] Furthermore, a phase II trial of pembrolizumab in EGFR-TKI naive patients with advanced *EGFR* mutant NSCLC failed to show sufficient responses even in the subset with high PD-L1 expression.[35]

In addition, ICI treatments are associated with increased risk of adverse effects in patients who subsequently or concomitantly receive a TKI, and the incidence is particularly high in cases using the third-generation TKI.[36, 37] This adverse effect develops regardless of concomitant and sequential use of such agents. Of particular interest, the CAURAL trial, a phase III trial which compared combined durvalumab and osimertinib versus osimertinib monotherapy, was terminated prematurely due to the increased incidence of interstitial lung disease-like events in the osimertinib plus durvalumab arm from the separate phase Ib TATTON trial [38]. .[39]

Given the lower clinical benefit and higher potential for adverse reactions, the current treatment guidelines do not recommend ICI treatments in *EGFR* or *ALK*-positive tumors.[40-42] Although EGFR mutated tumors often have negative or low PD-L1 expression, some may show higher expression, yet clinical response to ICI tends to be poor.[31, 43-46] Therefore, simultaneous testing of PD-L1 and molecular testing of *EGFR* is recommended to select the appropriate therapy.

Level of consensus: 100% (31) agree. Total: 31 voters

5: Is there a need to extend testing recommendations for *EGFR* mutations from advanced stage disease to those patients with radically resected non-squamous NSCLC?

STATEMENT: Yes, the introduction of EGFR TKI therapy into the post-resection adjuvant setting requires testing for this patient group [I,A].

DISCUSSION: Approximately 20-30% of patients with newly diagnosed lung cancer present with localized disease (stage I-III). Unfortunately, outcomes of surgery with curative intent remain poor with 5-year survival rates ranging between 40-80%, despite the use of adjuvant chemotherapy.[47] Additionally, the high rate of clinically relevant toxicities and adverse events associated with chemotherapy, further compromise treatment adherence and lead to worse outcomes.

The use of targeted therapies in the adjuvant setting is being explored for various molecular subsets of lung cancer. In December 2020, the FDA approved osimertinib as the first adjuvant treatment for patients with stage IB, II and IIIA NSCLC with complete tumour resection harbouring *EGFR* mutations.

This approval was based on the results from the phase III ADAURA trial, which demonstrated that adjuvant targeted therapy in this setting was associated with significantly improved disease-free survival.[48] A total of 682 patients with resected stage IB-IIIA (7th American Joint Committee on Cancer TNM edition) and whose tumours harboured EGFR mutations (*EGFR* exon 19 deletions or exon 21 p.L858R point mutation) were included in the study and were randomized to receive osimertinib or placebo (1:1 ratio), with or without standard adjuvant chemotherapy according to investigator's choice. Targeted treatment reduced the risk of disease or death in high risk patients (stage II to IIIA disease) by 83% (HR, 0.17; 99.06% CI, 0.11-0.26; P < .001) compared with the placebo group. While overall survival data are still maturing, at 24 months, 90% of the Osimertinib cohort remained alive and disease-free (95% CI, 84%-93%), compared with 44% of the placebo group. In addition to the survival benefit, patients on the treatment arm also experienced less central nervous system disease progression.

Based on the above data, it is therefore recommended that testing for *EGFR* mutations be expanded to encompass those patients with radically resected non-squamous NSCLC. Although, at present, osimertinib is approved for treatment of only the most common sensitizing *EGFR* mutations (exon 19 deletions and the p.L858R mutation in exon 21), upfront broad genotyping for *EGFR* mutations, as well as other drivers, might be considered to facilitate other potential treatment decisions and management of recurrence samples.

Level of consensus: 96.8% (30) agree; 3.2% (1) disagree. Total: 31 voters

6: What is the biological background and therapeutic relevance of *EGFR* exon 20 insertion mutations?

STATEMENT: *EGFR* exon20 insertion mutations are activating for EGFR kinase signalling and are of therapeutic relevance as specific targeted therapies are emerging for this group of mutations [I,A].

DISCUSSION: *EGFR* exon20 insertion mutations are a large, diverse family of alterations occurring within residues 761-775 coding for the C-helix of the EGFR protein (761-766) and the loop following the C-helix (767-775).[49] These mutations constitutively activate the EGFR pathway and occur in mutual exclusivity with other driver mutations. They are found in the same demographic population as the other classical *EGFR* mutations.[50] Tumours with these mutations show co-existing molecular features similar to those with classical *EGFR* mutations, including a low TMB.[51]

Early reports underestimated their prevalence (2-6% of all *EGFR* mutations), probably due to methodological factors.[49, 52] More recently, comprehensive hybrid capture NGS found Exon20ins accounted for 12% of all *EGFR* mutations identified,[51] implying prevalence similar to *BRAF, ROS1* and even *ALK* alterations in the same test population on non-squamous NSCLC.

In a surgical series, resection of tumours with exon20ins mutations was associated with poorer DFS compared to those with classical mutations, but OS was the same for both groups.[53] In patients with advanced disease, prognosis was poorer than for patients with classically mutated disease, presumably due to primary resistance to EGFR TKI therapy; prognosis was similar to wild type cases also treated with chemotherapy.[54] Like classically *EGFR* mutated NSCLC, these tumours are relatively resistant to immunotherapy.

A few mutations occurring in the C-helix coding residues, such as A763_Y764insFQEA, actually might confer partial sensitivity to currently available EGFR TKIs.[55] Osimertinib shows wider, but limited activity against exon20ins mutations[56]. However, renewed interest in these mutations, in general, is driven by activity data for poziotinib, mobocertinib and the bispecific monoclonal antibody amivantamab.[53, 57, 58]

This emerging therapeutic option makes testing for *EGFR* exon 20 insertions essential. Given the high heterogeneity of mutations in this region, and differences in response depending on the mutation, n NGS assay should be prioritized for exon20ins analysis to allow broader detection and characterization. Some commercial allele-specific PCR testing solutions have limited or no coverage of *EGFR* exon 20 insertions. Sizing assays can be used for broad screening of insertions. However, while this provides broad binary detection (presence or absence of mutation), only the size of the insertion is provided without sequence characterization. A practical and sensitive sequencing solution covering all four kinase domain exons, including exon20, should be favored, as well as characterisation and reporting of all mutations found.

Level of consensus: 100 % (31) agree. Total: 31 voters

7: Is it necessary to test for and report co-mutations occurring with *EGFR* mutation in advanced stage NSCLC?

STATEMENT: The co-mutational landscape found with *EGFR* mutation in advanced NSCLC may be a poor prognostic indicator and may predict relative resistance to EGFR TKIs.
Investigating the presence of co-occurring alterations can be performed, but is not required, in absence of direct therapeutic implications [I,A].

DISCUSSION: Emerging literature raises the prospect of refining treatment options for *EGFR* mutated NSCLC, based on the co-mutational landscape, but there is no consensus on the clinical impact of the reported findings, or on how treatment decisions might be changed.
The mutations most frequently reported in conjunction with *EGFR* mutations are *TP53* (40-65% of cases), *NKX2-1* (12-17%), *PIK3CA* (9-12%), *RB1* (~ 10%), *CTNNB1* (5-9%) and *CDK4* (7-10%).[59] Other mutations reported, especially in relation to patient outcomes, include *PTEN, ATM, IDH1, KRAS, KEAP1-NFE2L2* pathway alterations, *BRCA1, NOTCH1, FAT1* and *ABCB1*, as well as *ERBB2* and *MET* amplifications. *TP53* and *RB1* mutations appear to be associated with a higher TMB. Literature is inconclusive regarding the prognostic significance of these findings in the absence of therapy in surgically resected disease.

The most frequently studied and the commonest co-occurring mutation is *TP53*, which tends to be truncal rather than subclonal. Co-occurring *TP53* mutation might result in poorer outcomes on EGFR TKI therapy [59-62] but this remains a matter of debate.[63-65] Reports suggesting that the classification of *TP53* mutations (disruptive/non-disruptive, pathogenic/non-pathogenic, *Exon8* vs *non-Exon8*) might have an impact have been refuted and showed that all *TP53* mutations appeared to confer similar resistance to EGFR TKIs.[62] Coexisting *TP53* and *RB1* mutations may predict a greater risk of SCLC transformation at relapse. Various other co-existing molecular alterations have been reported in association with apparent resistance to EGFR TKIs, but these lack consistency and the studies are quite heterogeneous.
Currently there is insufficient evidence to make a robust recommendation for co-mutational testing. More data are required in order to inform prospective clinical studies. With the rapidly expanding adoption of broad panel NGS testing, pathologists and oncologists will encounter co-existing mutations and possibly other changes, in their patients with *EGFR* mutations. Recording such data, in conjunction with clinical outcomes, will be of value in helping our understanding of this issue.

Level of consensus: 93.5% (29) agree; 6.5% (2) disagree. Total: 31 voters

EARLY AND LOCALLY ADVANCED

1: What is the role of adjuvant osimertinib for common *EGFR* mutated, stage IB-IIIA R0 resected NSCLC?

STATEMENT: To date, the use of Osimertinib for three years, is recommended as adjuvant therapy in patients with resected, stage IB-IIIA (7th TNM) NSCLC harbouring *EGFR* mutations.
The impressive improvement of disease-free survival (DFS) including better CNS control, should ideally be supported by overall survival and/or quality of life benefit upon mature follow up [I,A].

DISCUSSION: Adjuvant therapy in patients with resected NSCLC is administered in order to improve cure rates, often measured by 5-year OS. The latter has been proven for adjuvant cisplatin-based chemotherapy in stage IB and IIIA (7th TNM), which therefore is our current standard approach [66]. At present, it remains uncertain whether the use of adjuvant TKIs in completely resected *EGFR* mutated NSCLC will lead to improvement in cure rates. In two previous randomized trials on adjuvant use of first generation EGFR-TKIs, the DFS benefit was not translated in OS differences (see below). The ADAURA trial compared 3 years of adjuvant osimertinib versus placebo in patients with completely resected stage IB-IIIA NSCLC with a common *EGFR* mutation[48]. Adjuvant chemotherapy was administered if indicated in standard care, but use was lower than could be expected in a predominantly stage II-IIIA population. An early analysis of DFS (maturity 33%) showed an impressive difference for osimertinib versus placebo in stage II/IIIA (HR 0.17), and with even less maturity (7%), a similar HR of 0.18 for central nervous system (CNS) DFS. Further follow-up is needed to determine if ADAURA will improve overall survival. Several elements differ from previous adjuvant TKI trials, including the use of osimertinib subsequent CNS disease control [67], the longer duration of TKI in ADAURA (3 instead of 2 years), and the much more prominent impact observed on DFS.

Level of consensus: 93.5% (29) agree; 6.5% (2) abstain. Total: 31 voters

2: Are there any roles for the first or second-generation EGFR-TKIs as adjuvant therapy for surgically resected, stage II-III, *EGFR* mutation-positive NSCLC?

STATEMENT: There is no solid evidence to use 1st or 2nd generation EGFR-TKI as adjuvant treatment for surgically resected *EGFR*-mutant NSCLC [I,A].

DISCUSSION: Different phase III clinical trials evaluated the use of first-generation EGFR TKIs (erlotinib and gefitinib) in resected *EGFR*-mutant lung cancer, failing to demonstrate a significant survival benefit [68, 69].
In particular, the phase III RADIANT, investigating the role of adjuvant erlotinib for 2 years, reported a DFS benefit in the *EGFR* mutation-positive subgroup, which was not statistically significant (HR, 0.61; *P* = .039) [69].
In addition, three different randomized phase III studies, evaluated the role of postoperative gefitinib in patients with resected NSCLC, selected by common *EGFR* mutation: the CTONG-1104 and the IMPACT compared the EGFR TKI with standard cisplatin/vinorelbine; while the BR.19, that closed prematurely, evaluated the use of gefitinib for 2 years compared with placebo, with or without prior adjuvant chemotherapy or radiotherapy. The CTONG-1104 study was positive for DFS (HR 0.56, P=.001) but negative for OS (HR 0.92, P=.674)[70]. The IMPACT study was negative for DFS (HR 0.92, P=0.63) and OS (HR 1.03, P=0.89)[71].
These two studies showed a similar trend, characterized by an initial DFS advantage that disappeared about two years after the end of TKI administration, without any difference in OS.
Considering these efficacy results, the use of non-third generation EGFR TKI is not recommended in adjuvant setting.

Level of consensus: 90.3% (28) agree; 6.5% (2) disagree; 3.2% (1) abstain. Total: 31 voters

3: How should patients with completely resected *EGFR* mutated NSCLC be followed up?

STATEMENT: Patients should be followed up as per the current ESMO guideline on early-stage NSCLC. Considering that patients with *EGFR* mutated NSCLC have a higher risk for development of CNS metastases, 6-monthly brain imaging (MRI preferred) should be added during the follow-up [I,A].

DISCUSSION: The current ESMO guideline, not tailored according to predictive biomarkers and relative risk of relapse, suggests a follow-up after radical therapy every 6 months with preferably contrast-enhanced chest/upper abdomen CT scan for 2 years; thereafter an annual visit with (low-dose) chest CT to detect second primary tumours[66]. In particular, for *EGFR* mutant resected lung disease, a frequent clinical and imaging follow-up, every 4-6 months, could be considered, also after the first two years after the surgery. As *EGFR* mutated NSCLC carcinomas have a higher propensity towards the development of CNS metastases [72], it may be reasonable to add dedicated CNS imaging, even in asymptomatic patients, notably aiming at an early change of treatment strategy including the use of SRS.

Level of consensus: 93.5% (29) agree; 6.5% (2) abstain. Total: 31 voters

4: Should patients with *EGFR* mutated NSCLC surgically resected stage Ib – IIIa NSCLC receive adjuvant chemotherapy?

STATEMENT: Adjuvant chemotherapy is strongly recommended for patients who undergo resection of *EGFR*-mutant stage Ib-IIIa (7th TNM) NSCLC with good performance status, regardless of the addition of TKI treatment. Adjuvant chemotherapy may be considered for high-risk, margin-negative, stage Ib disease (7th American Joint Committee on Cancer TNM edition) with good performance status [I,A].

DISCUSSION: Adjuvant chemotherapy for stage Ib-IIIa (7th TNM) NSCLC is considered a standard of care according to the high level of evidence from many randomized trials and meta-analyses[73]. In the ADAURA trial, approximately 60% of patients received adjuvant chemotherapy by physician discretion, with balance between osimertinib and control arms. Although the benefit of osimertinib was observed regardless of chemotherapy, the HR for 2 year-disease free survival was higher in patients who received adjuvant chemotherapy compared to those who did not (HR; 0.16 vs 0.23), suggesting an incremental effect of chemotherapy to adjuvant osimertinib [48, 74]. More importantly, the need for adjuvant chemotherapy was not addressed by the trial design and not stratified for, rendering any conclusion about its utility in that setting impossible. Other studies of first-generation EGFR TKIs did not administer adjuvant chemotherapy to both arms but only EGFR TKIs in the experimental arm, with chemotherapy given only in the control arm, resulting in limitations in interpretation for the role of adjuvant chemotherapy[70]. A similar approach can be recommended for patients with stage Ib disease and candidates for adjuvant EGFR TKIs.

Level of consensus: 93.5% (29) agree; 3.2% (1) disagree; 3.2 % (1) abstain. Total: 31 voters

5: What is the role of adjuvant osimertinib for *EGFR* mutated early stage resected NSCLC patients who do not meet the ADAURA inclusion criteria?

STATEMENT: While there is no data specifically addressing this population, osimertinib may be considered as adjuvant therapy in patients with EGFR mutant NSCLC via extrapolation from the ADAURA data, in cases of resection less than a lobectomy, or residual tumor, including where radiotherapy is indicated. A tailored approach is required for patients with sensitive *EGFR* uncommon mutations [II,C].

DISCUSSION: In the ADAURA trial, as per study protocol, only patients treated with lobectomy or pneumonectomy, were enrolled. To date, when considering the multiple types of more limited lung cancer surgery undertaken to achieve complete surgical resection, adjuvant osimertinib may be indicated for all patients that undergo radical lung cancer surgery, including those treated with segmentectomy, wedge and sleeve resection, even if obtained through a high effective and less invasive thoracic surgery, including video-assisted thoracoscopic surgery (VATS) and robotic approaches[75].
In case of lung cancer surgery, with positive pathological margins, IE microscopic (R1), macroscopic (R2) and uncertain R(un), multidisciplinary evaluation for post-resection local treatment (re-resection vs radiation therapy) is highly indicated. While the role of chemotherapy is strongly established there, a consensus is still lacking regarding post-operative adjuvant radiation therapy, which has shown discrepant trials results in patients with positive margins[76-78]. It is however most often recommended in guidelines and delivered in this clinical scenario.
Considering that patients with microscopic (R1) or macroscopic (R2) positive resection margins are at high risk or relapse, in this setting, the use of adjuvant osimertinib, might be considered, for patients with stage IB to IIIA.
Conversely, for patients with resected stage IA1-3 (8^{th} TNM; T ≤1 to 3 cm) (not enrolled in the ADAURA trial) using adjuvant osimertinib, is not indicated. Indeed, in the ADAURA trial, patients with resected stage IB achieved a significant lower benefit, compared with those with stage II-IIIa when treated with adjuvant osimertinib (DFS HR 0.39 vs 0.17)[48].
For patients with sensitive *EGFR* uncommon mutations, using osimertinib as adjuvant options should be tailored evaluated according to each different alteration. Indeed, based on the data reported in the metastatic setting, osimertinib could be discussed as adjuvant treatment for patients with p.L861Q, p.S7681, p.G719X, p.L747P and complex mutations, including compound mutations with common alterations (Exon 19 deletions or p.L858R). Alternatively, for patients with E709X alone or in combination and S768I in combination with non-common alterations, the use of osimertinib cannot be recommended based on current efficacy data[2, 3].

Level of consensus: 90.3% (28) agree; 6.5% (2) disagree; 3.2% (1) abstain. Total: 31 voters

6: What is the role of adjuvant osimertinib for patients with *EGFR* mutated, early stage resected NSCLC who fall within ADAURA eligibility criteria but with clinical concern for osimertinib tolerance?

STATEMENT: Patients who are potentially eligible for adjuvant osimertinib on the basis of *EGFR* genotype, surgical resection and pathological stage (ADAURA eligible), but with clinical concern for tolerance such as old age, comorbidities such as interstitial lung disease, inadequate full recovery post-surgery, ECOG performance status ≥2, cardiac compromise, or history of malignancy, may be considered for adjuvant osimertinib on a case-by-case basis. Every effort should be implemented towards optimizing comorbidities and performing additional safety monitoring, taking into account the personalized risk of adverse events balanced against potential for improved disease-free survival coupled to unknown overall survival impact [II,C].

DISCUSSION: ADAURA recruited patients with ECOG Performance Status 0-1 and aged ≥18 with no upper limit. Patients were required to have fully recovered from surgery and were randomized no more than 10 weeks post-surgery (if adjuvant chemotherapy was not given) and no more than 26 weeks post-surgery (if undergoing chemotherapy)[48]. Patients were excluded with typical osimertinib exclusions: enteral comorbidities limiting drug absorption (e.g. vomiting, or prior gastrointestinal surgery limiting drug absorption), uncontrolled active infection e.g. viral hepatitis, cardiac comorbidities (mean resting corrected QT interval (QTc) >470 msec, clinically important abnormalities in rhythm, conduction, or morphology of resting ECG, factors that increase the risk of QTc prolongation or risk of arrhythmic events, or unexplained sudden death under 40 years of age in first-degree relatives or any concomitant medication known to prolong the QT interval), pulmonary comorbidities (past medical history of interstitial lung disease (ILD), drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD), inadequate organ function[48]. With regard to cardio-toxicity, osimertinib increases the QTc interval in a dose-dependent manner and interacts medications acting similarly.[79] Patients with baseline cardiac compromise may be at increased risk of cardiac adverse events and efforts to minimize QTc by changing concurrent medications at baseline are strongly encouraged, alongside regular cardiac monitoring as recommended for metastatic patients.[80] Hence, in patients with baseline cardiac compromise, benefits of osimertinib should be carefully balanced against potential risks and additional safety monitoring is recommended.

Patients randomized to osimertinib were age 30-86 with a median age of 64. Disease-free survival (DFS) multivariable analysis demonstrated marked superiority for osimertinib in both those aged <65 years (HR= 0.16, 95%CI:0.09-0.26) and those ≥65 years (HR=0.22, 95%CI:0.13-0.36), suggesting no obvious efficacy difference by age. Any safety effect by age is unknown as elderly-specific analyses are not yet published. Therefore, whilst no particular efficacy concerns are expected for elderly patients, additional adverse events cannot be fully excluded. Hence, consideration should be given to additional safety monitoring of elderly patients on an individualized basis, especially as this population has increased co-morbidities and concomitant medication usage.

Osimertinib has previously been shown to be associated with low ILD rates, with FLAURA reporting 4% ILD events[81], and slightly higher rates reported in the real world ASTRIS study (ILD/pneumonitis-like events in 1%),[82] and higher still in a Japanese real-world series (ILD identified in 6.5% with 3.51 odds ratio in patients with prior ILD).[83] In ADAURA, where ILD was an exclusion, ILD events were reported in 3% of the osimertinib group (2% at grade 1 and 1% at grade 2) versus none in the control arm. Hence, osimertinib is a relative or absolute contraindication in patients with baseline ILD, and risks should be weighed against potential benefits.

ADAURA mandated randomization either 10 weeks or 26 weeks post-surgery contingent on chemotherapy use after full recovery after surgery. The efficacy benefit of commencing osimertinib beyond these timeframes and safety in patients without full recovery from surgery remains uncertain and benefits of osimertinib should be carefully balanced against potential risks.

Thus, in patients with baseline co-morbidities and/or modifiable concomitant medication, efforts should be made to optimize co-morbidities and change concomitant medication to minimize risk of osimertinib adverse events. Osimertinib should be considered on an individualized basis as part of shared decision-making, noting that some co-morbidities may represent an absolute osimertinib contraindication (e.g. severe baseline ILD). Safety assessments should be performed more frequently than routine to monitor the risk:benefit ratio.

Level of consensus: 87.0% (27) agree; 6.5% (2) disagree; 6.5% (2) abstain. Total: 31 voters

7: What is the role of EGFR TKIs for patients with EGFR mutated early-stage NSCLC undergoing stereotactic body radiation therapy (SBRT) instead of surgery?

STATEMENT: In early-stage *EGFR*-mutated NSCLC patients, the concurrent or sequential treatment with EGFR TKI and SBRT is currently not recommended [III,C].

DISCUSSION: The use of SBRT for T1/T2-N0-M0 NSCLC remains an important treatment option, particularly for medically inoperable NSCLC patients, patients with high risk of surgical complications, and those who do not consent for surgical procedures. In a large group of molecularly unselected early NSCLC patients treated with SBRT with long follow-up, 5-year local relapse rate was 10.5%, regional relapse rate was 12.7%, and distant relapse rate was 19.9%.[84] A high risk of death from comorbidities constitutes an important competing risk in this population. Limited data exist on outcomes of SBRT in patients with early-stage *EGFR* mutant NSCLC. One retrospective study suggested a higher risk of out-of-field relapse,[85] although another study did not confirm this association.[86] There is no published study assessing the impact of EGFR TKI on outcome of EGFR mutation positive NSCLC radically treated with SBRT, therefore the addition of EGFR TKI to patients undergoing radical SBRT is not recommended

Level of consensus: 87.1% (27) agree; 9.7% (3) disagree; 3.2% (1) abstain. Total: 31 voters

8: What is the role of neoadjuvant EGFR TKI for patients with operable stage IA-IIIA NSCLC or borderline operable e.g. T3/T4 disease?

STATEMENT: There is currently no data to support neoadjuvant EGFR TKI for NSCLC in operable or borderline operable cases [II,C].

DISCUSSION: Data from the ADAURA trial[48] has resulted in the approval of osimertinib in stage IB-IIIA *EGFR* mutation positive NSCLC as adjuvant therapy. Based on these data it seems reasonable to explore this in the neoadjuvant setting. The NeoADAURA trial is currently ongoing and will evaluate the efficacy and safety of neoadjuvant osimertinib, as monotherapy or in combination with platinum-based chemotherapy vs chemotherapy alone, in patients with *EGFR* mutation-positive resectable stage II–IIIB NSCLC.[87] Neoadjuvant followed by adjuvant erlotinib versus neoadjuvant and adjuvant cisplatin-gemcitabine chemotherapy has been previously evaluated in a randomized phase 2 trial in *EGFR* mutant stage IIIA-N2 NSCLC performed in China.[88] A PFS benefit for erlotinib was observed (HR=0.39; 95% CI 0.23-0.67, P=0.001) driven by adjuvant erlotinib. However, the primary end point of a significant improvement in ORR for neoadjuvant erlotinib therapy versus chemotherapy was not met.
Nowadays, based on these evidences, the use of neoadjuvant EGFR TKI is note recommended outside of clinical trials.

Level of consensus: 87.1% (27) agree; 9.7% (3) disagree; 3.2% (1) abstain. Total: 31 voters

9: In patients with *EGFR* mutant inoperable stage III NSCLC, undergoing curative-intent chemo-radiotherapy, what is the role of consolidation immune-checkpoint inhibitor therapy?

STATEMENT: In *EGFR*-positive disease, the use of consolidation immune-checkpoint inhibitor therapy after curative-intent chemo-radiotherapy (CT-RT), is not recommended [I,C].

DISCUSSION: The standard management of stage III inoperable patients changed in 2017 as a result of the publication of the PACIFIC trial comparing durvalumab versus placebo in unresectable, stage III NSCLC without disease progression after concurrent CT-RT.[89] Recently updated results confirm significant and durable improvements in both PFS and OS endpoints with estimated 4-year OS rates of 49.6% vs. 36.3%, and 4-year PFS rates of 35.3% vs 19.5% respectively for durvalumab versus placebo in the intention-to-treat population. [90] Durvalumab is the only immune-checkpoint inhibitor currently approved by FDA and EMA in this setting.

PACIFIC was designed as an all-comers study, therefore was not designed to evaluate clinical outcomes based on biomarkers such as EGFR mutation status.

Most pre-specified sub-groups derived a PFS and OS benefit from durvalumab in the PACIFIC trial. PFS or OS magnitude of benefit results were reported to be reduced in 43 patients with EGFR mutations enrolled in the study [PFS-HR 0.84 (95% CI: 0.40–1.75); OS-HR 0.97 (95% CI: 0.40–2.33)] [91] However, it should be noted that the exploratory nature of the analysis and the small size of this subgroup prevent definitive conclusions. In addition in a post-hoc analysis of the PACIFIC trial, patients with PD-L1<1% did not derive a survival benefit with durvalumab, and patients with driver mutations are known to more likely have low rates of PD-L1 expression and CD8+ tumor-infiltrating lymphocytes.[92] These data remain highly controversial in regards to the PFS benefit In PD-L1 negative cases and in view of the imbalanced patient groups, as well as the OS overperformance of patients in the PD-L1 negative control arm. Another small multi-institutional retrospective analysis of 37 patients with *EGFR* mutation treated with concurrent CT-RT with or without durvalumab consolidation did not show a significant difference in PFS between the two groups.[93] In addition, the patients treated with durvalumab experienced a high frequency of severe immune related adverse events. Of note, out of 24 patients who completed CT-RT without durvalumab, 16 completed CT-RT alone and 8 completed CT-RT with induction or consolidation EGFR TKIs.

Level of consensus: 90.3% (28) agree; 9.7% (3) abstain. Total: 31 voters

10: In patients with inoperable stage III *EGFR*-mutant NSCLC, what is the role of TKIs, pre-, post-, during RT?

STATEMENT: Currently, there is no role for EGFR TKIs, pre-, during or post RT in EGFR mutant inoperable stage 3 NSCLC [III,C].

DISCUSSION: Retrospective data suggested that patients with *EGFR* mutant inoperable stage III NSCLC treated with concurrent chemo-radiotherapy (CTRT) have superior local, but inferior distant control following platinum-based CTRT compared with those who have *EGFR* wild-type disease.[94-96] Such clinical evidence, together with preclinical models suggesting an enhancement of response to RT, provide a rationale for the evaluation of EGFR TKIs in this setting. However, to date there is no evidence showing a benefit in terms of patient outcome with the addition of EGFR TKIs, pre-, post-, during CTRT or RT alone.

In the pre-CTRT setting, RTOG 1306 was a randomized phase II study comparing induction TKI to no induction treatment prior to concurrent CTRT in stage III NSCLC patients with EGFR mutations or ALK rearrangements (NCT01822496). The study closed early due to poor accrual in 2018 and has not been published.

The benefit of the administration of EGFR TKIs concurrently with RT or CTRT in stage III NSCLC patients with *EGFR* mutations has not been demonstrated in randomised studies. The data available in this setting come from single-arm prospective studies, which only included a small proportion of patients with *EGFR* mutations, therefore precluding robust recommendations in this setting.[97, 98]

In the post CTRT setting, SWOG 0023 investigated maintenance gefitinib vs. placebo in molecularly unselected patients with stage III NSCLC, who had responded to concurrent CTRT and consolidation docetaxel.[99] The study reported a worse median survival in the gefitinib arm (23 and 35 months respectively; P = 0.013).

In contrast, the LAURA Phase III trial (NCT03521154) is currently recruiting, to assess the efficacy of osimertinib following chemoradiation in patients. with stage III unresectable NSCLC.

Finally, there is no evidence supporting the exclusive role of TKIs in *EGFR* mutant inoperable radically treatable stage 3 NSCLC.

Level of consensus: 90.3% (30) agree; 6.5% (2) disagree; 3.2% (1) abstain. Total: 31 voters

11: What is the optimal treatment of patients with *EGFR*-mutant recurrent disease that occurs during or after adjuvant osimertinib administration?

STATEMENT: Prospective dataset on this clinical situation is limited. Data suggests that if recurrent disease occurs after the completion of adjuvant osimertinib, the recurrence is more likely to be responsive to osimertinib re-challenge and hence we recommend consideration of a repeat course of osimertinib. However, if recurrent disease occurs while the patient is on adjuvant osimertinib, we recommend cessation of adjuvant osimertinib and rebiopsy of the recurrent disease to guide next treatment as there may be a detectable mechanism of osimertinib resistance. Locally-ablative therapy may be considered for oligo-recurrence [I,A].

DISCUSSION: If recurrent disease is detected after completion of adjuvant osimertinib, then based on extrapolation from limited prior data from the SELECT study and from single institution reports, both of which employed first-generation EGFR TKIs, the biology of the recurrence may be favorable to rechallenge with osimertinib.[100, 101] In the absence of prospective data using osimertinib, our current recommendation is to consider a repeat course of osimertinib for such patients.
If recurrence occurs while the patient is in the midst of adjuvant osimertinib, then the biology is likely similar to progression on osimertinib in the advanced disease setting. Locally ablative options could be considered for oligorecurrence. Acquired resistance to osimertinib in general appears to be more heterogeneous compared to earlier EGFR TKIs and there doesn't appear to be a common or dominant mechanism of resistance. A repeat biopsy could be helpful in guiding next steps for such a patient.[14] The two most actionable findings on repeat biopsy are acquired *MET* amplification (which may be treated with a combination of an EGFR and a MET TKI)[11] and SCLC transformation (which may be treated with carboplatin and etoposide)[16]. Note that SCLC transformation is only possible to detect with a tissue biopsy and is not detectable on a liquid biopsy.
In absence of a targetable mechanism of resistance, refers to statement 3D.

Level of consensus: 96.8% (30) agree; 3.2% (1) abstain. Total: 31 voters

METASTATIC DISEASE (figure 1 & 2)

1. What is the optimal first-line therapy for patients with common *EGFR* mutations?

STATEMENT: First-line third-generation EGFR TKI such as osimertinib is considered the preferred option for patients with a tumour with common *EGFR* mutations [I,A].

DISCUSSION: Treatment with a third-generation EGFR TKI in 2021 is the preferred frontline option in case of a common sensitizing mutation (exon 19 deletions or p.L858R) diagnosed in advanced NSCLC. [102] Second-generation inhibitors, such as afatinib and dacomitinib, may provide a modest progression-free survival advantage over the first generation (erlotinib or gefitinib) TKIS, however at the price of a higher toxicity. [103, 104] Osimertinib is the most commonly used third-generation inhibitor and the first to have demonstrated a significant prolongation of PFS and OS compared to treatment with first-generation EGFR-TKIs, with a more favorable safety profile. Although PFS benefit was observed in all predefined subgroups, the magnitude of OS benefit was less pronounced among Asian patients and those with an p.L858R mutation.[67, 81] However, the panel considers this should not restrict the use of osimertinib in first-line therapy for these patients subgroups. Beyond osimertinib, other third-generation inhibitors are being developed such as almonertinib (now aumolertinib), lazertinib, alflutinib, rezivertinib, ASK120069, SH-1028, D-0316, and abivertinib. Some of these agents are approved in Asian countries like lazertinib (approved in the Republic of Korea) and almonertinib (approved in China) for the treatment of patients with *EGFR* p.T790M resistance mutation-positive NSCLC.[105, 106] . In the absence of access to third-generation EGFR TKI, patients should receive first- or second-generation EGFR TKI.
New combination strategies have shown interesting results frontline, but have not been adopted as standards. Adding VEGF inhibitors to the standard 1st generation TKIs has been shown to prolong PFS but not OS.[107-110] The combination of chemotherapy with gefitinib resulted in improved OS compared to gefitinib as first-line therapy in two randomized trials from Asia. However, this approach has not been compared to the use of a third-generation EGFR TKI as initial therapy. A similar randomized trial using a backbone of osimertinib is underway (FLAURA2 - NCT04035486).[111, 112]

Level of consensus: 96.8% (30) agree; 3.2% (1) abstain. Total: 31 voters

2. What is the optimal management of patients with central nervous system (CNS) disease and/or with leptomeningeal involvement?

STATEMENT: Third generation EGFR TKI should be prioritized for those patients with CNS metastasis, including leptomeningeal disease, as initial therapy. The benefit of radiotherapy in addition to EGFR TKI is not supported by prospective controlled trials data. For those with intracranial progression despite osimertinib 80 mg, delivery of local stereotactic radiation, avoiding WBRT, with the continuation of standard dose osimertinib is standard, while increasing the osimertinib dose to 160 mg can be considered if accessible. Patients who present with leptomeningeal disease may benefit from osimertinib at a preferred dose of 160 mg, if available [II,A].

DISCUSSION: Osimertinib is the preferred agent for common *EGFR* mutant with CNS metastasis. Previously, gefitinib, erlotinib and afatinib all demonstrated intracranial responses in patients with brain metastasis, despite their relatively low CNS penetration. In the FLAURA trial, osimertinib demonstrated a better CNS control over gefitinib or erlotinib in patients with brain metastases and delayed the emergence of brain metastases in patients without CNS cancer location.[113] Lazertinib also showed a potent CNS activity.[106] AZD3759 has shown excellent CNS penetration and good CNS activity in a phase 1 study. [114, 115]

Radiotherapy plays a major role in NSCLC patients with brain metastases. [116, 117] Whether early or delayed brain radiotherapy is preferrable for *EGFR* mutant lung cancer patients remains a matter of debate. A retrospective study has shown that use of upfront TKI, and deferral of radiotherapy might be associated with inferior OS. SRS followed by TKI resulted in the longest OS, as compared to immediate WBRT. Of note, avoiding toxicities including the potential neurocognitive sequelae of WBRT is a priority in that disease entity, characterized by a long survival duration,

A randomized study challenging the timing for RT in the era of osimertinib might help refining treatment algorithms, while initiating osimertinib treatment as the first intervention in patients with brain metastasis is routinely advocated for in most centers.

Patients with leptomeningeal metastasis have a very poor outcome. Very few patients are diagnosed with leptomeningeal metastasis at the time of diagnosis.[118, 119] Most studies only used MRI to establish such a diagnosis. Pulse high dose erlotinib has been shown effective for some patients in small studies,[120] all performed before the global registration of Osimertinib. Osimertinib 80 mg was shown to be effective for EGFR TKI naïve patients.[121] However, a single-arm study in EGFR TKI-treated patients with cytology proven leptomeningeal carcinomatous demonstrated good anticancer activity with osimertinib 160 mg (BLOOM study).[122] Osimertinib 160 mg has been accepted in many countries as a standard of care for this condition. The addition of radiotherapy to patients with leptomeningeal metastasis remains unclear.[123] However, many patients in the BLOOM study also received brain radiotherapy.

Level of consensus: 90.3% (28) agree; 9.7 % (3) abstain. Total: 31 voters

3. What is the optimal management post osimertinib failure?

Subsequent management will depend upon patient and disease characteristics, genomic findings and access to treatment or clinical trials.

***3A)* What is the optimal management in patients with on-target *EGFR* alterations following osimertinib treatment?**

STATEMENT: In clinical practice, the use of standard platinum chemotherapy should be considered the standard of care. Alternative on-target therapies, including TKI, monoclonal antibody (mAb) and antibody-drug conjugates (ADC), should be considered as preferred therapeutic options upon the development of a new *EGFR* mutation following osimertinib treatment, in the context of clinical trials [II,B].

DISCUSSION: The development of an on-target *EGFR* mutation as a mechanism of resistance to first-line osimertinib occurs in ~15 % of patients. These mutations include p.C797S (most common), p.L718Q, p.L792F, and p.G796S.[6, 124] As osimertinib is structurally diverse from prior generation inhibitors, these mutations do not impart resistance to prior generation EGFR TKIs and clinical efficacy has been observed when treatment has been switched to an earlier generation inhibitor.[125]

Following the development of resistance to second-line osimertinib (i.e. in the presence of *EGFR* p.T790M), on-target mechanisms of resistance are detected in ~25% of patients. Only when the osimertinib resistance mutation occurs in a different allele than the T790M mutation (trans), there can be some benefit of the addition of a first-generation EGFR TKI.[126-128] However, in most cases (>95%), the osimertinib resistance mutation occurs in cis with p.T790M.[6] In the phase 1/2, clinical efficacy has been observed with amivantamab when administered alone or in combination with the EGFR TKI Lazertinib [129, 130] and patritumab deruxtecan. [131]

Level of consensus: 83.8% (26) agree, 9.7% (3) disagree, 6.5% (2) abstain. Total: 31 voters

3B) What is the optimal management in patients with emergent targetable alterations beyond EGFR?

STATEMENT: Mechanisms of acquired osimertinib resistance include targetable alterations such as in particular *MET* amplification and *HER2* amplification.
Although platinum chemotherapy is still the standard of care in this setting, strategies targeting specific mechanisms of resistance are showing promising results, and patients with osimertinib-resistant tumors, should be prioritized for access to molecularly-driven clinical trials with specific agents targeting resistance alterations [II,B].

DISCUSSION: *MET* amplification is the most frequent off-target mechanism of resistance to osimertinib (10-15%). Clinical trials are showing promising results for combining MET-inhibitors with osimertinib upon development of resistance.
In EGFR-mutant patients previously treated with a third-generation EGFR-TKI and *MET* amplification, the combination of osimertinib and savolitinib achieved a 30% response rate.[6, 11] Tepotinib is being assessed in combination with osimertinib in *EGFR*-mutated, MET-amplified, locally advanced or metastatic NSCLC with acquired resistance to osimertinib (INSIGHT 2 study, NCT03940703).
The combination of capmatinib with gefitinib showed encouraging clinical activity in patients with *EGFR*-mutant and MET-dysregulated NSCLC. [132] Based on the results, to date the combination of capmatinib with osimertinib is under investigation in *EGFR*-mutant patients resistant to prior EGFR-TKI, whose tumors are T790M negative and harbor *MET* amplification (GEOMETRY-E, NCT04816214).
Other investigational therapeutics targeting the *EGFR*-resistant pathway include the use of monoclonal antibodies (mAbs) and antibody-drug conjugate, alone or in combination with EGFR TKis.
In particular, the combination of amivantamab and lazertinib achieves responses in 36% of patients who progressed on osimertinib. *EGFR* and *MET*-based biomarkers of resistance identified a subgroup of patients who are more likely to respond to amivantamab and lazertinib.[130, 133, 134]. In the same resistant setting, the use of the ADC patritumab deruxtecan (HER3-DXd) showed an interesting antitumor activity (ORR by BICT was 39%) across various EGFR TKI resistance mechanisms (i.e. *EGFR* C797S, *MET* or *HER2* amplification, and *BRAF* fusion).[131]
In addition, patients with acquired *ALK* fusion after osimertinib progression benefited from the combination of EGFR and ALK-TKIs in reported clinical cases.[6, 133]
For patients with an acquired *RET* fusion as a mechanism of resistance, the addition of selpercatinib to osimertinib is feasible, with evidence of radiographic responses and potential durable benefit.[13, 135]

Level of consensus: 90.3% (28) agree; 9.7% (3) disagree. Total: 31 voters

3C) What is the optimal management in patients with evidence of histologic transformation?

STATEMENT: Chemotherapy with platinum-etoposide is recommended for patients with evidence of small cell transformation, after standard EGFR TKI therapy. Whether osimertinib should be continued with chemotherapy is unknown. Patients with other histologic transformation should receive histology-appropriate chemotherapy (e.g. squamous cell carcinoma).
The use of immunotherapy in this clinical scenario should be evaluated in clinical trials [IV,B].

DISCUSSION: Histologic transformation to small cell neuroendocrine carcinoma has been described in 3-10% of patients with acquired resistance to EGFR kinase inhibitors and even *de novo* in patients with *EGFR* mutant lung cancer.[4, 16, 136-138] Recently, transformation to other pathologic subtypes such as squamous carcinoma has been described in up to 15% of patients with acquired resistance to osimertinib.[14] The diagnosis of histologic transformation requires assessment of tumor tissue, e.g. from re-biopsy. Concomitant mutations in *TP53, Rb1* and *PIK3CA* are prevalent, and may be detected at baseline prior to evidence of histologic transformation.[16, 137, 138] The risk of small cell transformation may be higher in patients with complete inactivation of P53 and Rb1, as well as genomic aberrations such as hypermutated APOBEC signatures.[137, 138] Marcoux *et al* have reported a median time from diagnosis to small cell transformation of 17.8 months, with a median time of 15.8 months since EGFR TKI initiation.[16] Median survival from the time of transformation is 10.9 months. Systemic treatment with etoposide/platinum is associated with a response rate of 54%, and activity with taxanes as a single agent or combination therapy has been reported. Local therapy should be used as clinically indicated. The value of continuing EGFR TKI therapy with chemotherapy is unknown and is being explored [NCT03567642]. Combinations of checkpoint and PARP inhibitor is currently being evaluated [NCT04538378].

Level of consensus: 90.3% (28) agree; 3.2% (1) disagree; 6.5% (2) abstain. Total: 31 voters

3D) What is the optimal management in patients post-osimertinib progression with no targetable alterations?

STATEMENT: For patients with slow disease progression and no deterioration in clinical symptoms, osimertinib may be continued until symptomatic or significant progression. Clinical trials should be prioritized in this setting. Although the optimal management remains to be defined, the standard systemic treatment for osimertinib-resistant patients, remains platinum-based chemotherapy with or without bevacizumab.
The combination of atezolizumab and bevacizumab plus platinum-based chemotherapy could be considered as alternative option. The use of platinum-based chemotherapy plus immune checkpoint inhibitor has not been established yet, and is currently assessed in randomized phase 3 trials for this specific clinical scenario. For patients with oligoprogression, including in the CNS, local therapy such as radiation or surgery could be considered with continuation of Osimertinib [II,B].

DISCUSSION: The tumor response rate with platinum-based chemotherapy in patients with *EGFR* mutation positive lung cancer after failing first line EGFR TKI is about 30%, and median PFS is estimated between 5-6 months.[139, 140] At least two ongoing randomized phase III studies, namely CheckMate-722 and KEYNOTE-789, will address the role of immunotherapy in combination with chemotherapy in this patient group [141, 142].
In a small subgroup of patients (n = 58) with classical *EGFR* mutations enrolled in the phase III IMpower-150, the combination of atezolizumab plus bevacizumab and platinum-based chemotherapy (ABPC; n = 26) showed an OS improvement (HR = 0.60; 95% CI: 0.31–1.14), compared to standard bevacizumab plus carboplatin and paclitaxel (BCP; n = 32). This improvement was confirmed, although less pronounced in the TKI pretreated patients (n = 22 vs 32, respectively for. ABPC and BCP) (HR 0.74; 95% CI: 0.38–1.46) (data cutoff September 13, 2019; median follow-up, 39.3 months) [143]. Recently, in the same setting, were presented the first interim analysis (median follow up of 9.8 months) of the double-blind phase III ORIENT-31 trial, conducted in China. In this trial, evaluating 444 randomized patients, the combination of sintilimab plus biosimilar bevacizumab and chemotherapy showed a trend towards PFS benefit compared to standard chemotherapy (mPFS 6.9 vs 4.3 months; HR 0.46 CI 95%: 0.33–0.63; p<0.0001)
The option to continue osimertinib in combination with systemic chemotherapy at osimertinib progression remains empirical. Data from the IMPRESS study demonstrate no evidence of improvement in PFS and OS with continuation of gefitinib in combination with chemotherapy at gefitinib progression.[139] However, given the different EGFR TKI profile, we may not extrapolate data with gefitinib apply to osimertinib resistance scenario. Indeed, osimertinib is active at the CNS level, and therefore, for patients with known and non-progressive CNS metastasis on osimertinib, it might be reasonable to consider maintaining osimertinib with chemotherapy. However, such an approach should be further validated in prospective studies. For patients with both CNS and non-CNS progression on osimertinib, local radiotherapy to CNS metastasis and chemotherapy are the preferred options.

Level of consensus: 93.6% (29) agree; 3.2% (1) disagree; 3.2% (1) abstain. Total: 31 voters

4. What is the role of EGFR TKI re-challenge?

STATEMENT: EGFR TKI rechallenge could be considered in patients with disease progression (including in CNS) who have been off EGFR TKI for at least 6 months and do not have evidence of targetable *EGFR* resistance mechanisms, in absence of molecular-driven clinical-trial availability [III,C].

DISCUSSION: The mainstay of treatment for patients who develop disease progression after osimertinib is systemic chemotherapy. Several novel approaches, including combination regimens based on osimertinib, are currently under development. The salvage approaches seek to leverage knowledge of the underlying resistance mechanism to utilize rational combination therapies. Presently, the relatively limited number of treatment options for salvage therapy defines the interrogation about rechallenging patients with osimertinib. Re-introduction of EGFR TKI after being off therapy has resulted in modest responses and clinical benefit. [144, 145] Majority of the available evidence regarding rechallenge was obtained prior to the introduction of third generation EGFR TKIs in the clinic. We recommend tumor biopsy and/or liquid biopsy in the setting of acquired resistance to osimertinib as the first step.[146] If a specific resistance mechanism is not identified, or when a resistance mechanism with no known treatment options is present, rechallenging with osimertinib further down the course of therapy is appropriate. The likelihood of benefit from re-introduction of osimertinib is greater when the interval from prior exposure to the TKI therapy is > 6 months. The standard dose of 80 mg/d is appropriate in this situation. Rechallenging is also appropriate in the situation of progression of brain metastasis in a patient who has been off EGFR TKI therapy.[147] Prospective studies are needed to quantify the benefit or re-introduction of osimertinib in various clinical situations.

Level of consensus: 90.3% (28) agree; 3.3% (1) disagree; 6.4% (2). abstain Total: 31 voters

5. What is the role of immune checkpoint inhibitors strategy in patients with *EGFR* mutant lung cancer?

STATEMENT: Immune checkpoint inhibitors as monotherapy are not recommended, before other standard therapeutic options are exhausted, regardless the PD-L1 expression, due to their limited efficacy and increased risk of toxicity predisposition with subsequent TKI treatment. These facts, as well as potential toxicities while sequencing IO followed by osimertinib, emphasize the need of obtaining genomic testing results prior to starting immunotherapy-based treatment in newly diagnosed NSCLC patients with advanced disease [II,B].

DISCUSSION: Patients with *EGFR*-mutant NSCLC show limited benefit from immune checkpoint inhibitors [30, 33, 34, 92, 148-157]. Exploratory analysis of phase III trials and pooled analyses in pretreated patients have demonstrated modest efficacy of single agent PD-1/PD-L1, significantly reduced as compared to WT NSCLC patients. Interestingly, responses may vary according to the mutation type (uncommon > p.L858R > exon 19 deletions) and potentially PD-L1 expression.[30, 32, 158] A front-line trial of pembrolizumab in patients with high PD-L1 rumor expression required early discontinuation (11 patients) due to lack of efficacy.[35] Of note, hyperprogressive (HPD) disease with checkpoint inhibitors has been more frequently hypothesized in patients with *EGFR* mutant lung cancer (20%). [159, 160]

Several immunotherapy combinations have been tested in patients with *EGFR* mutant disease. Although some combinations of TKI plus PD-1/PD-L1 inhibitors (e.g. atezolizumab or nivolumab plus erlotinib) have reasonable safety profiles and favorable efficacy, others (e.g. durvalumab plus gefitinib or osimertinib) resulted in increased toxicity including pneumonitis (38% of patients in the durvalumab plus osimertinib TATTON trial cohort).[39, 161] Interestingly, relevant toxicities have also been reported with TKIs in clinical practice when given after initial immunotherapy, possibly due to the long half-life of ICIs compounds.[162]

Level of consensus: 90.3% (28) agree; 9.7 % (3) abstain. Total: 31 voters

6. What is the optimal management for patients with *EGFR* exon 20 insertions mutant lung cancer?

STATEMENT: Platinum-based chemotherapy should be offered as first-line therapy, preferably without checkpoint inhibitors due to the potential risk of toxicity with later lines of targeted therapy. After platinum failure, targeted agents such as amivantamab or mobocertinib, should be considered as second-line therapy [II,B].

DISCUSSION: *EGFR* exon 20 insertions are non-classical *EGFR* mutations that are known to be resistant to standard EGFR TKIs.[163, 164] The disruption of the key protein structure at the α–C helix lowers the affinity for EGFR TKIs, with an inhibitory activity similar to the *EGFR* wild type population. The first line management should be similar to systemic treatment of *EGFR* wild type lung cancer until new data prove otherwise. However, the role of first line single agent immunotherapy is uncertain and should not be prioritized, as both KEYNOTE 024 and KEYNOTE 042 have intentionally excluded patients with any type of *EGFR* mutations, often without a history of smoking.[165, 166] The cornerstone of treatment should be platinum-based chemotherapy. Arguably, it is feasible to add immunotherapy to chemotherapy as per KEYNOTE 189 or IMpower 150 trial regimens, but due to the lack of comparative study, it is unclear if the combination of chemotherapy and immunotherapy is better than chemotherapy alone. [140, 167]
Recently, amivantamab, a bi-specific monoclonal antibody targeting both *EGFR* and *MET*, and mobocertinib, a selective oral TKI targeting *EGFR* and *HER2* exon 20 insertion mutations, were approved by the US FDA for use in patients with *EGFR* exon 20 insertion mutant lung cancer after first line chemotherapy fails. To date, the role of these two new agents is under investigation in phase 3 clinical trials, in first-line setting.

Level of consensus: 83.9% (26) agree; 6.5% (2) disagree; 9.6% (3). abstain Total: 31 voters

7. What is the optimal management for patients with uncommon sensitizing *EGFR* mutations?

STATEMENT: Afatinib and osimertinib should be considered as monotherapy, based on a tailored approach including all emerging data, for the treatment of patients with major uncommon sensitizing *EGFR* mutations (p.G719X, p.L861Q, p.S768I) or compound mutations,
The use of chemotherapy could be considered where a strength of recommendation in favor of TKI is limited or missing [II,B]

DISCUSSION: Afatinib is the only EGFR TKI currently approved for 3 types of uncommon *EGFR* mutations (p.G718X, p.S768I and p.L861Q) by US FDA. The approval was based on pooled prospective individual patient data from 3 trials, Lux-Lung2, Lux-Lung-3 and Lux-Lung-6.[168]
The PFS and RR of the EGFR TKI naïve patients with these uncommon *EGFR* mutations were similar to patients with the two common sensitizing *EGFR* mutations when treated with afatinib at 40mg per day. [169-173] On the other hand, the PFS in patients with these uncommon mutations treated with gefitinib was much shorter. [174]
In addition, the efficacy of osimertinib in patients with uncommon alterations, was confirmed, although on a limited dataset, in different small studies showing that osimertinib was active in particular in the major uncommon alterations (G719X, L861Q and S768I) and can be considered as an alternative tratment.[175]
Standard chemotherapy with platinum and pemetrexed should be considered as first line therapy for patients with uncommon or atypical *EGFR* mutations without prior evidence of anticancer activity of EGFR TKIs. The addition of immune checkpoint inhibitors is controversial since these patients were excluded in most first line randomized studies of checkpoint inhibitors.

Level of consensus: 90.5% (29) agree; 3.2% (1) disagree; 3.2% (1) abstain Total: 31 voters

8. If a patient's tumor has concurrent targetable alterations in addition to an *EGFR* mutation, which treatment should be offered?

STATEMENT: In presence of two or more concomitant targetable alterations, the use of specific TKI should be evaluated after a comprehensive NGS analysis to identify the potential dominant clone. In case of confirmed co-presence of different alterations, the use of platinum based-chemotherapy with or without TKI, should be prioritized [IV,C].

DISCUSSION: Different studies suggested that *EGFR* mutations and other major oncogenic driver alterations (e.g., *ALK*, *ROS1*, *RAS*, *MET*) are generally mutually exclusive; however, thanks to the evolving role of molecular testing, co-occurring alterations have been reported which may impact response to targeted therapies.[176, 177]
In patients with EGFR mutations plus co-occurring alterations, EGFR TKI has a generally good response rate, but outcomes seem inferior to what would be expected in patients with either alteration alone.[178-180]
Intratumoral heterogeneity has been reported suggesting that co-occurring mutations arise in different tumor cells, reinforcing the importance of trying to understand which signaling pathway is the dominant one to guide the selection of TKI in clinical practice (e.g. sensitivity of assays might suggest tumor mutation burden). It seemed that first-line EGFR TKI is a reasonable regimen for most of the subgroup (with the limitation of small retrospective series). In case of primary resistance, it may be advisable to target the co-alteration pathway (monotherapy or polytherapy strategies). The role of combination of TKIs in co-mutated patients in the available studies is not straightforward, thus further studies are needed. At resistance, a re-biopsy (tissue/ctDNA) for the detection of acquired resistance mechanisms would be recommended to select the appropriate therapeutic regimen for these patients.
The presence of concurrent genomic alterations at resistance supports a combinatorial treatment strategies as initial therapy, specifically in a molecularly defined cohort of patients with evidence of pre-existing *MET* amplification (e.g. trials ongoing with a selective inhibitor of the MET receptor like capmatinib, tepotinib or savolitinib or EGFR/MET bispecific antibody like amivantamab and EGFR TKIs).[6, 181]

Level of consensus: 87.1% (27) agree; 3.2% (1) disagree; 9.7% (3). abstain Total: 31 voters

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