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SPECIAL ARTICLE

Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

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Available online 23 January 2023

Key words: ESCAT, ESMO Clinical Practice Guideline (CPG), ESMO-MCBS, oncogene-addicted metastatic non-small-cell lung cancer (mNSCLC), treatment, targeted therapy

INCIDENCE AND EPIDEMIOLOGY

Details on incidence and epidemiology are covered in the Supplementary Material Section 1, available at https://doi.org/10.1016/j.annonc.2022.12.009.

DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

Diagnostic procedures

Details on diagnostic procedures are covered in the Supplementary Material Section 2, available at https://doi.org/10.1016/j.annonc.2022.12.009. See Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2022.12.009 for a flow chart on diagnosis and testing biopsy/cytology samples in stage IV non-small-cell lung cancer (NSCLC).

Pathology and molecular biology

Biomarker testing is essential to identify subgroups of NSCLC with oncogenic drivers that can be therapeutically targeted. These drivers are mainly found in lung adenocarcinomas (LUADs). Demonstration of the specific molecular alteration is necessary to tailor treatment with the appropriate targeted therapy. The frequency of oncogenic drivers in NSCLC as well as general discussion of testing strategy and methodology, including the use of liquid biopsies, can be found in the Supplementary Material Section 3, available at https://doi.org/10.1016/j.annonc.2022.12.009.

Many parameters might determine which tests are required; pre-eminent amongst them is access to appropriate drugs.[1] Testing is mandatory for oncogenic drivers for which drugs are approved for routine usage. Broader testing may be used to support early drug access or clinical trials.[2,3] For personalised therapy approaches, European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of molecular Targets (ESCAT) classifications[4] need to be considered (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.12.009).

Clinically-relevant *EGFR* gene mutations in NSCLC include substitutions, deletions and insertions in exons 18-21 that activate the tyrosine kinase and variably confer sensitivity or resistance to available epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) or other drugs.[3,5] The most common alterations conferring sensitivity to first- to third-generation TKIs are the exon 21 L858R substitution and exon 19 deletion mutations. At a minimum when resources or material are limited, these mutations should be evaluated. The next most common alteration is a large group of exon 20 insertions mostly resistant to current EGFR TKIs but sensitive to some emerging agents (discussed in the treatment paragraph including *EGFR* exon 20 insertions). Other mutations, including in exon 18, variably sensitise, while some mutations confer resistance and may

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☆Note: Approved by the ESMO Guidelines Committee: February 2002, last update December 2022. This publication supersedes the previously published version—*Ann Oncol* 2018;29 (Suppl 4):iv192-iv237.

drive disease relapse. Complete sequencing of exons 18-21 by next-generation sequencing (NGS) is strongly recommended, to identify all possible sensitising mutations. Some allele-specific *EGFR* sequencing solutions do not provide complete coverage. EGFR FISH or immunohistochemistry (IHC) have no clinical utility and should not be tested.

Fusions (rearrangements) involving *ALK*, *ROS1*, *NTRK1-3* and *RET* genes are important oncogenic drivers in small groups of LUADs.[3,5] Each target has several TKIs available. Furthermore, *NRG1* fusions are a potential emerging target in LUADs. Oncogenic fusion proteins result in constitutive activation of the kinase and may increase fusion gene protein levels, allowing for screening of tumours for some of these fusions by IHC. Positive anaplastic lymphoma kinase (ALK) IHC with an appropriately validated assay may be used to prescribe ALK inhibitors. Cases positive by ROS1 or neurotrophic tyrosine receptor kinase (NTRK) IHC must be confirmed by a molecular method; this may also be preferred for ALK IHC-positive cases. Fusions can be detected by FISH, or multiplex RT—PCR panel assays, the latter requiring a tailored reaction for each potential fusion gene which makes this approach more complex. RNA-based NGS is preferred for identifying an expanding range of fusion genes. If NGS is used as the primary *NTRK* screening tool, IHC confirmation should be considered.[6]

Alterations in structure and/or expression of the *MET* gene drive oncogenesis in NSCLC.[3,5] High *MET* protein levels may be detected by IHC. Increased *MET* signalling may result from high gene copy number (GCN), either due to polysomy or true gene amplification. Detection is reliable by *in situ* hybridisation (ISH) techniques, but NGS or comparative genomic hybridisation may also identify cases. Definitions of high GCN vary and, in absence of current standardisation, confound existing data. *MET* exon 14 skipping mutations may be detected by DNA-based NGS, but RNA-based NGS may also identify additional cases missed by DNA sequencing.[7] *MET* amplification is an important resistance mechanism driving acquired resistance to EGFR (including osimertinib) and ALK inhibitors. Mesenchymal-epithelial transition (MET) kinase inhibitors are being investigated in several scenarios and approved in the *MET* exon 14 skipping setting.

KRAS mutations have become an important therapeutic target in LUADs and, unlike the other targets described here, are mostly smoking related.[5] Specific inhibitors for *KRAS* G12C mutations are now available. DNA sequencing and multiplex RT—PCR panel assays are the best approach to detection; most likely incorporated into NGS panels, as is the case for *BRAF* mutations. TKIs for *BRAF* V600E mutations are available. *HER2* exon 20 insertion mutations are rare in LUADs, but promising targeted drugs and antibody—drug conjugates are in development. Therefore, these mutations need to be covered with NGS panels.

Mutations coexisting with several of the above driver alterations may influence responses to targeted therapy and require additional treatment.[8] Comutations in *TP53* may be associated with lower efficacy of EGFR, ALK and ROS1 TKIs. Testing for comutations in an NGS panel may therefore become important.

Resistance to kinase inhibitors is almost inevitable and is variably due to the emergence of therapy-resistant tumour cell clones with target gene alteration, increased bypass pathway signalling and/or phenotypic transformation (small-cell, squamous-cell carcinoma or sarcomatoid carcinoma).[9] As treatments to target resistance mechanisms emerge, so does testing to detect each mechanism, and a need either for re-biopsy or, if appropriate, cell-free DNA (cfDNA) testing. Widespread use of osimertinib in the first line for *EGFR*-mutated NSCLC has decreased the importance of *EGFR* T790M detection but increases the need for identifying *MET* amplification as treatments for the latter are being evaluated.

Recommendations

- Adequate tissue material for histological diagnosis and molecular testing should be obtained to allow for individual treatment decisions [IV, A]. For recommended methods to obtain tissue, please refer to the ESMO Clinical Practice Guideline (CPG) on non-oncogene-addicted metastatic non-small-cell lung cancer (mNSCLC; available at: https://www.esmo.org/guidelines/guidelines-by-topic/lung-and-chest-tumours).[10]
- Pathological diagnosis should be made according to the 2021 World Health Organization classification of lung tumours [IV, A].
- Specific subtyping of all NSCLCs is necessary for therapeutic decision making and should be carried out wherever possible. IHC stains should be used to reduce the NSCLC-not otherwise specified rate to fewer than 10% of cases diagnosed [IV, A].
- The molecular tests below are recommended in patients with advanced non-squamous-cell carcinoma, and not recommended in patients with a confident diagnosis of squamous-cell carcinoma, except in unusual cases, e.g. young ($<$50 years) patients, never ($<$100 cigarettes in a lifetime)/former light smokers ($\leq$15 pack-years, all kinds of tobacco) or long-time ex-smokers (quit smoking $>$15 years ago, all kinds of tobacco) [IV, A].
- *EGFR* mutation status should be determined [I, A]. Test methodology should have adequate coverage of mutations in exons 18-21, including those associated with resistance to some therapies [III, A]. At a minimum, when resources or material are limited, the most common activating mutations (exon 19 deletion, exon 21 L858R point mutation) should be determined [I, A].
- The availability of TKIs effective against T790M-mutated recurrent disease makes T790M testing on disease relapse on first- or second-generation EGFR TKIs mandatory [I, A].
- Testing for *ALK* rearrangements should be carried out [I, A].
- Detection of the *ALK* translocation by FISH remains a standard, but IHC with high-performance ALK antibodies and validated assays may be used for screening [III, A] and have been accepted as an equivalent alternative to FISH for ALK testing.
- Testing for *ROS1* rearrangements should be carried out [II, A]. Detection of the *ROS1* translocation by FISH

remains a standard; IHC may be used as a screening approach [IV, A].
- *BRAF* V600 mutation status testing should be carried out [II, A].
- Testing for *NTRK* rearrangements should be carried out [II, A]. Screening for *NTRK* rearrangements may use IHC or NGS, with appropriate testing follow-up to validate a positive result [II, A].
- Testing for *MET* exon 14 skipping mutations, MET amplifications, *RET* rearrangements, *KRAS* G12C mutations and *HER2* mutations should be carried out [II, A].
- If available, multiplex platforms (NGS) for molecular testing are preferable [III, A].
- RNA-based NGS is preferred for identifying an expanding range of fusion genes [III, B]. Whichever testing modality is used, it is mandatory that adequate internal validation and quality control measures are in place and that laboratories participate in, and perform adequately in, external quality assurance schemes for each biomarker test [III, A].
- cfDNA (liquid biopsy) can be used to test for oncogenic drivers as well as resistance mutations, but all patients with a negative cfDNA blood test still require tissue biopsy [II, A].

STAGING AND RISK ASSESSMENT

Details on staging and risk assessment are covered in the Supplementary Material Section 4, available at https://doi.org/10.1016/j.annonc.2022.12.009.

Recommendations

- A complete history including a precise smoking history and comorbidities, weight loss, Eastern Cooperative Oncology Group performance status (ECOG PS) and physical examination must be recorded [IV, A].
- Laboratory standard tests including routine haematology, renal and hepatic functions and bone biochemistry tests are required. Other tests (e.g. lipid spectrum and creatine kinase levels) depend on toxicity of the targeted therapy that will be used [IV, A].
- An electrocardiogram is required if the targeted therapy can cause adverse cardiac events, including rhythmic modifications (e.g. long QT) [IV, A].
- Contrast-enhanced computed tomography (CT) scan of the chest and upper abdomen (including the liver and adrenal glands) should be carried out at diagnosis [IV, A].
- Imaging of the central nervous system (CNS) should be considered at diagnosis for all patients with metastatic disease [IV, B] and is required for patients with neurological symptoms or signs [IV, A]. If available, CNS imaging with gadolinium-enhanced magnetic resonance imaging (MRI) should be considered for all patients [IV, B].
- If bone metastases are clinically suspected, bone imaging is required [IV, B].
- Bone scintigraphy, ideally coupled with CT, can be used for detection of bone metastasis [IV, B]. [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG)—positron emission topography (PET)—CT is the most sensitive modality in detecting bone metastasis [III, B].
- FDG—PET—CT and brain imaging are recommended in patients suspected for oligometastatic disease [IV, A]. In the presence of a solitary metastatic site on imaging studies, efforts should be made to obtain a cytological or histological confirmation of stage IV disease [IV, A].
- For oligometastatic disease, mediastinal disease should be pathology proven if this potentially impacts the treatment plan [IV, A].
- NSCLC must be staged according to the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM (tumour—node—metastasis) 8th edition staging manual and must be grouped into the stage categories shown in Supplementary Tables S2 and S3, available at https://doi.org/10.1016/j.annonc.2022.12.009 [IV, A].
- Response evaluation is recommended after 8-12 weeks of treatment, using the same radiographic investigation that initially demonstrated the tumour lesions [IV, B]. Follow-up with a PET scan is not routinely recommended, due to its relatively low specificity despite a high sensitivity [IV, C].
- Measurements and response assessment should follow Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 [IV, A].[11] The clinical relevance of RECIST in evaluating the response remains debatable as patients can derive benefit from continuing the same TKI after RECIST v1.1 progression [III, A].

MANAGEMENT OF ADVANCED AND METASTATIC DISEASE

See Figure 1 for a treatment algorithm after positive findings on molecular tests.

EGFR-mutated NSCLC

See Figure 2 for a treatment algorithm for patients with *EGFR*-activating mutations.

First-line EGFR TKIs for *EGFR* exon 19 deletion or exon 21 L858R. EGFR TKIs have become the standard first-line therapy for patients with a classical activating *EGFR* mutation (exon 19 deletion or exon 21 L858R) since the confirmation of the superiority of first-generation EGFR TKIs (gefitinib and erlotinib), over platinum-based doublet chemotherapy (ChT) in terms of tumour response rate, safety, quality of life and progression-free survival (PFS).[12,13] Second-generation EGFR TKIs (e.g. afatinib and dacomitinib) have a higher potency of EGFR inhibition via irreversible covalent binding and are pan-human epidermal growth factor receptor (HER) inhibitors. Afatinib compared with gefitinib improved PFS [hazard ratio (HR) 0.74, 95% confidence interval (CI) 0.57-0.95] but not overall survival (OS; HR 0.86, 95% CI 0.66-1.12) in the LUX-Lung 7 phase IIB randomised controlled trial (RCT) ($N = 319$).[14] In contrast, dacomitinib was superior to gefitinib in the ARCHER 1050 phase III RCT ($N = 452$) regarding PFS (HR 0.59, 95% CI 0.47-0.74) as well as OS, although the latter could not formally

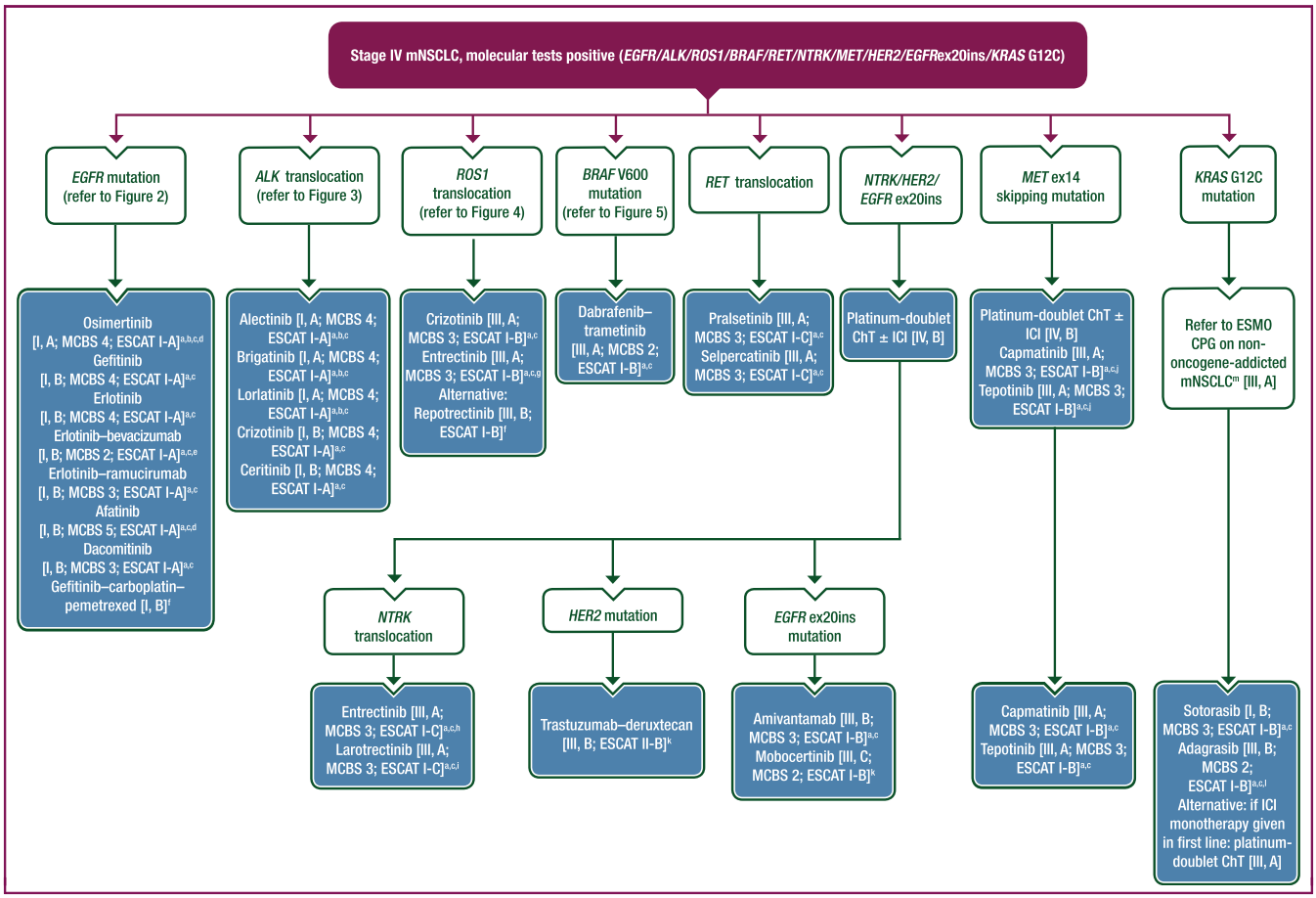

Figure 1. Treatment algorithm for stage IV mNSCLC after positive findings on molecular tests.
Purple: general categories or stratification; blue: systemic anticancer therapy.
ChT, chemotherapy; CPG, Clinical Practice Guideline; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; FDA, Food and Drug Administration; ICI, immune checkpoint inhibitor; MCBS, ESMO-Magnitude of Clinical Benefit Scale; mNSCLC, metastatic non-small-cell lung cancer.
[a]ESMO-MCBS v1.1[111] was used to calculate scores for new therapies/indications approved by the EMA or FDA. 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/esmo-mcbs-evaluation-forms).
[b]Preferred option(s).
[c]ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[4] See Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.12.009 for more information on ESCAT scores.
[d]Recommended treatment option for patients with a major uncommon, non-exon 20 insertion, sensitising *EGFR* mutation [III, B; ESMO-MCBS v1.1 score: 4 for afatinib; ESCAT: I-B].
[e]ESMO-MCBS v1.1 score for the combination of bevacizumab with gefitinib or erlotinib.
[f]Not EMA approved.
[g]Preferred over crizotinib in patients with brain metastases.
[h]If the patient has not been treated previously with a medicine that works in the same way as entrectinib.
[i]For patients who have no satisfactory alternative treatments.
[j]FDA approved; not EMA approved in first line.
[k]FDA approved; application for EMA approval withdrawn by the manufacturer.
[l]FDA approved; not EMA approved.
[m]A parallel ESMO CPG on non-oncogene-addicted mNSCLC is available at: https://www.esmo.org/guidelines/guidelines-by-topic/lung-and-chest-tumours.[10]

be tested due to hierarchical testing rules.[15,16] Compared with first-generation EGFR TKIs, second-generation TKIs are associated with more toxicities (acneiform rash, stomatitis, diarrhoea), leading to dose reduction. The third-generation EGFR TKIs also inhibit the resistant *EGFR* exon 20 T790M mutation. Osimertinib has the largest international approval while others are approved only in South Korea and China (e.g. lazertinib and almonertinib, respectively). Osimertinib was compared with first-generation EGFR TKIs in the FLAURA phase III RCT ($N = 556$), demonstrating a superior median PFS (mPFS) and median OS (mOS), with 18.9 versus 10.2 months (HR 0.46, 95% CI 0.37-0.57) and 38.6 versus 31.8 months (HR 0.80, 95% CI 0.64-1.00), respectively.[17,18] Blood—brain—barrier penetration is higher for osimertinib compared with first- and second-generation EGFR TKIs, resulting in CNS response rates >60%.[19] Of note, patients with stable CNS metastases were allowed in the LUX-Lung 7 and FLAURA trials, whereas all CNS metastases were excluded from the ARCHER 1050 trial.[14,15,17]

Serious adverse event (AE) rates are also lower for osimertinib.[15,17,20] These positive outcomes have established osimertinib as a preferable first-line treatment of patients with advanced *EGFR*-mutated NSCLC, especially for patients with CNS metastases. If osimertinib is not available in the first line, it

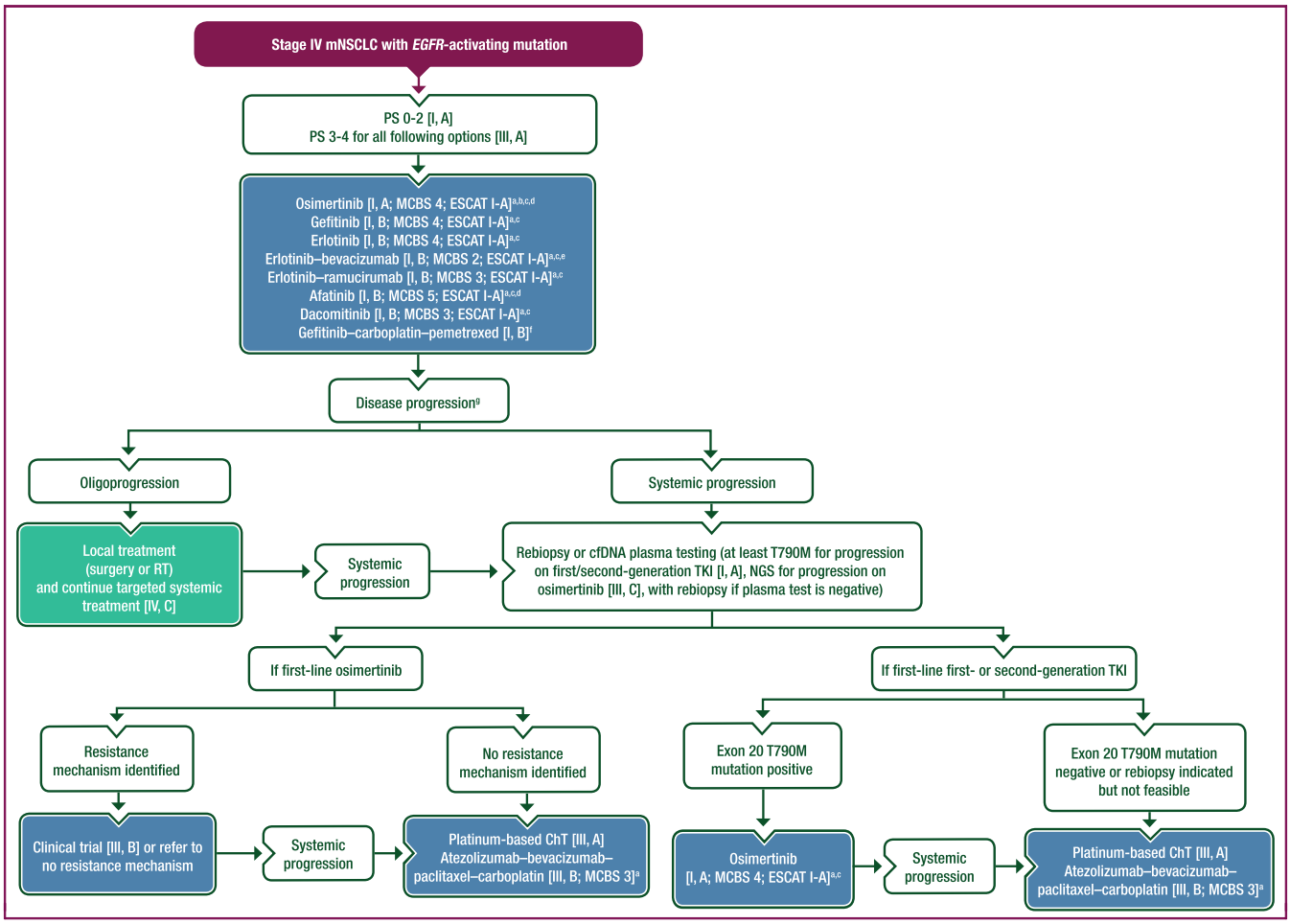

Figure 2. Treatment algorithm for stage IV mNSCLC with *EGFR*-activating mutation.
Purple: general categories or stratification; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.
cfDNA, cell-free DNA; ChT, chemotherapy; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; FDA, Food and Drug Administration; MCBS, ESMO-Magnitude of Clinical Benefit Scale; mNSCLC, metastatic non-small-cell lung cancer; NGS, next-generation sequencing; PS, performance status; RT, radiotherapy; TKI, tyrosine kinase inhibitor.
[a]ESMO-MCBS v1.1[111] was used to calculate scores for new therapies/indications approved by the EMA or FDA. 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/esmo-mcbs-evaluation-forms).
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[e]ESMO-MCBS v1.1 score for the combination of bevacizumab with gefitinib or erlotinib.
[f]Not EMA approved.
[g]Patients who have moderate radiological progression with ongoing clinical benefit may continue with EGFR TKIs [III, A].

is still acceptable to sequentially use first- or second-generation EGFR TKIs (e.g. erlotinib, gefitinib, afatinib and dacomitinib) followed by osimertinib, specifically for T790M-positive resistant disease (occurring in approximately half of the patients). Other first-line strategy options are combinations of EGFR TKIs and ChT [not European Medicines Agency (EMA) approved] or combination of EGFR TKIs and anti-angiogenics, which have shown significant improvement in PFS in phase III RCTs (e.g. erlotinib—bevacizumab and erlotinib—ramucirumab).[21-25] For anti-angiogenics, however, either no OS benefit was observed or OS data are not yet mature.[21-23] For ChT—gefitinib combinations, only superiority over first-generation EGFR TKIs has been demonstrated for OS,[24,25] whereas the benefit compared with osimertinib is not clear. Furthermore, with longer follow-up the OS benefit for ChT—gefitinib was not statistically significant anymore in the NEJ009 trial.[26] Moreover, toxicity, inconvenience for patients and costs increase with adding another treatment. Therefore, single-agent (third-generation) EGFR TKIs are still one standard first-line treatment.

First-line EGFR TKIs for uncommon *EGFR* mutations. Although the majority of activating *EGFR* mutations are exon 19 deletions or the exon 21 L858R point mutation, 10%-20% of patients present with an uncommon, non-exon 20 insertion mutation. In retrospective studies, first-generation EGFR TKIs result in a lower overall response rate (ORR) and PFS compared with exon 19 deletions or

exon 21 L858R.[27] In an analysis of several databases comprising also a pooled analysis of several Lux-Lung trials including major uncommon mutations, afatinib resulted in an ORR of 60% and a median time to treatment failure of 10.8 months.[28] Osimertinib resulted in an ORR of 53% and a mPFS of 8.2 months in a single-arm phase II study.[29] Therefore, afatinib and osimertinib can be considered for uncommon *EGFR* mutations.

Management of EGFR TKI resistance. Oligoprogression is discussed under 'Special populations, Oligometastases'.

The *EGFR* exon 20 T790M mutation is the most common cause of resistance to first- and second-generation EGFR TKIs, accounting for 50%-60% of cases. In the T790M setting, osimertinib was superior to platinum-doublet ChT in the AURA 3 phase III RCT ($N = 419$), with an mPFS of 10.1 versus 4.4 months (HR 0.30, 95% CI 0.23-0.41), respectively.[30] Therefore, the T790M status should be evaluated in all patients progressing on first- or second-generation EGFR TKIs, either on tissue or in plasma, as also those with T790M in plasma benefit.[31] Osimertinib should be given to those with a T790M-positive tumour, if not given in first line. As patients with a tumour negative for T790M obtain less benefit from osimertinib, platinum-based doublet ChT should be offered to these patients.[32]

With the increasing use of osimertinib either in first- or second-line therapy, management of resistance to osimertinib has become a major clinical issue. Resistance mechanisms are more diverse compared with first- and second-generation EGFR TKIs, and frequency of a certain genomic finding also depends on whether osimertinib is given in first or second line.[33] The most common genomic findings include *EGFR* exon 20 C797X mutation, *MET* amplification, *HER2* amplification and other non-*EGFR* pathway aberrations.[33] A number of novel approaches are being developed to manage osimertinib resistance. Preferably, patients progressing on osimertinib are enrolled in a clinical trial, if possible (extensively discussed in an ESMO expert consensus paper),[34] standard treatment is platinum-doublet ChT. Patients who have moderate asymptomatic radiological progression with ongoing clinical benefit may continue with EGFR TKIs.[35,36] It is advisable to test for resistance mechanisms when feasible, however, as tumour growth can become rapid with insufficient time to determine the resistance mechanism upon symptomatic progression.

The role of immunotherapy. Despite the tremendous success of immune checkpoint inhibitors (ICIs) in lung cancer, the role of ICIs in the management of advanced *EGFR*-mutated NSCLC remains controversial. These agents have a role in advanced-line settings after exhaustion of TKI treatment, preferably in combination with ChT and angiogenesis inhibition. The IMMUNOTARGET registry is a retrospective analysis on efficacy of single-agent ICIs in patients with driver oncogenes.[37] Tumour response in patients with *EGFR* mutations was 12% and mPFS and mOS were 2.1 and 10.0 months, respectively. In a subgroup analysis ($n = 91$ patients with a sensitising *EGFR* mutation of whom 78 were EGFR TKI-pretreated) of the IMpower150 phase III RCT, the combination of paclitaxel—carboplatin—bevacizumab—atezolizumab compared with paclitaxel—carboplatin—bevacizumab, showed longer mOS for the quadruplet: 29.4 versus 18.1 months (HR 0.60, 95% CI 0.31-1.14). Similar results were found for the group pretreated with EGFR TKIs.[38] Despite the limited sample size, this regimen has been widely adopted as a treatment option for patients with *EGFR* mutations after progression on EGFR TKIs. The phase III ORIENT-31 trial (sintilimab plus the bevacizumab biosimilar IBI305 plus pemetrexed—cisplatin versus sintilimab plus pemetrexed—cisplatin versus pemetrexed—cisplatin) in which Chinese patients with a sensitising *EGFR* mutation and progression on EGFR TKIs were enrolled ($N = 444$) supports the quadruplet regimen, as mPFS was significantly longer in the quadruplet versus the ChT-only arm: 6.9 versus 4.3 months (HR 0.46; 95% CI 0.34-0.64, $P < 0.001$). OS data are not mature yet.[39]

ALK-rearranged NSCLC

See Figure 3 for a treatment algorithm for patients with *ALK* translocations.

First-line treatment. Crizotinib, the first-in-class ALK TKI,[40] improved outcomes (PFS, ORR and quality of life) compared with platinum-based ChT for the initial treatment of patients with newly diagnosed *ALK*-rearranged NSCLC in the phase III PROFILE 1014 trial,[41] establishing first-line ALK TKIs as standard of care (SoC). Ceritinib, a second-generation ALK TKI, was also superior to ChT in the first-line setting.[42] Newer-generation ALK TKIs, however, have been shown in phase III RCTs to be superior to crizotinib in the first-line setting, including alectinib,[43] brigatinib,[44] ensartinib (not EMA approved)[45] and lorlatinib.[46] Alectinib, brigatinib and lorlatinib are preferred for initial treatment.

Alectinib. In the ALEX phase III RCT ($N = 303$), alectinib compared with crizotinib[43] resulted in a superior investigator-assessed mPFS (34.8 versus 10.9 months; HR 0.43, 95% CI 0.32-0.58).[47] Grade 3-5 toxicities were similar in frequency for alectinib versus crizotinib (52% versus 56%). AEs that occurred more frequently with alectinib included anaemia, myalgia, elevated bilirubin, weight gain and skin photosensitivity. CNS ORR and time to CNS progression were superior for alectinib.[48] mOS was not reached with alectinib versus 57.4 months with crizotinib (HR 0.67, 95% CI 0.46-0.98), and the 5-year OS rates were 63% and 46%, respectively,[47] establishing a benchmark for OS in this population. Two other first-line phase III trials [J-ALEX (Japan)[49] and ALESIA (Asia)[50]] reported similar outcomes.

Brigatinib. In the ALTA-1L phase III RCT ($N = 275$), brigatinib was compared with crizotinib. The 3-year PFS by blinded, independent central review was superior for brigatinib compared with crizotinib (43% versus 19%). mPFS was longer (24.0 versus 11.1 months; HR 0.48, 95% CI 0.35-0.66).[44] mOS was not reached in either group.

Benefit was seen across subgroups particularly in patients with brain metastases. AEs that occurred at a higher

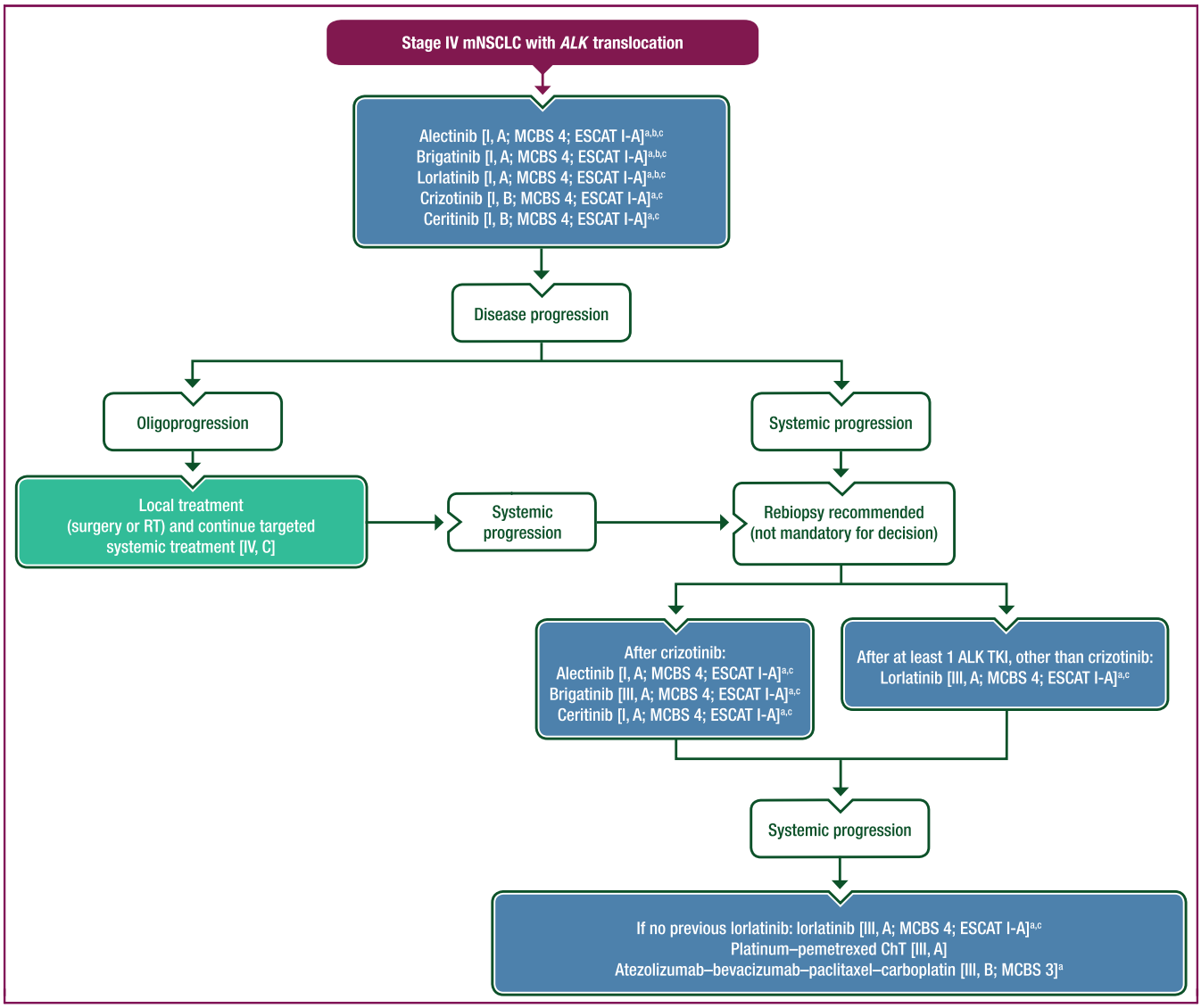

Figure 3. Treatment algorithm for stage IV mNSCLC with *ALK* translocation.
Purple: general categories or stratification; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.
ALK, anaplastic lymphoma kinase; ChT, chemotherapy; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; FDA, Food and Drug Administration; MCBS, ESMO-Magnitude of Clinical Benefit Scale; mNSCLC, metastatic non-small-cell lung cancer; RT, radiotherapy; TKI, tyrosine kinase inhibitor.
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[c]ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[4] See Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.12.009 for more information on ESCAT scores.

incidence with brigatinib included increased creatine kinase levels, cough and hypertension. Interstitial lung disease (ILD)/pneumonitis occurred in 4% of patients.

Ensartinib (not EMA approved). The eXalt3 phase III RCT ($N = 290$) comparing ensartinib with crizotinib demonstrated improved mPFS with ensartinib (25.8 versus 12.7 months; HR 0.51, 95% CI 0.35-0.72).[45] Rash, elevated transaminases and pruritis were the most common AEs.

Lorlatinib. In the CROWN phase III RCT ($N = 296$) lorlatinib resulted in a significantly longer independently-determined mPFS than crizotinib [not reached (NR) versus 9.3 months; HR 0.28, 95% CI 0.19-0.41].[46] Intracranial ORR and time to intracranial progression were superior for lorlatinib. The most common AEs of any grade with lorlatinib were hyperlipidaemia, oedema, increased weight, peripheral neuropathy and cognitive effects. Lorlatinib was associated with more grade 3-4 AEs (mainly altered lipid levels) than crizotinib (72% versus 56%).

Of note, there have not been direct comparisons between the newer-generation ALK TKIs. The choice of drug will be influenced by factors including the extent of CNS

disease, patient preference and the need to manage the distinct toxicity profiles seen with these drugs.

Beyond first-line treatment. Oligoprogression is discussed under 'Special populations, Oligometastases'.

Progression on crizotinib. For patients who have had initial therapy with crizotinib, treatment with newer-generation inhibitors has shown efficacy intracranially and extracranially.

In the ASCEND-5 phase III RCT ($N = 231$), ceritinib was superior to single-agent ChT (PFS HR 0.49, 95% CI 0.36-0.67) in patients with progression on crizotinib and platinum-doublet ChT.[51]

In the ALUR phase III RCT ($n = 107$), alectinib was superior to single-agent ChT (docetaxel or pemetrexed) in patients previously treated with platinum-based doublet ChT and crizotinib (PFS HR 0.32, 95% CI 0.17-0.59).[52] Grade $\geq$3 AEs were less frequent (27% versus 41%) and CNS efficacy was also improved with alectinib.

Activity of brigatinib in patients previously treated with crizotinib was confirmed in a phase II study where a 90 mg dose lead-in for 7 days followed by 180 mg was compared with 90 mg daily.[53] Improved results were seen with the 180 mg dosing compared with the 90 mg dosing, with mPFS of 16.7 months and intracranial ORR of 67%.

Although lorlatinib is active in patients progressing on crizotinib, with an ORR of 69%, intracranial ORR of 68% and mPFS not reached,[54] the EMA approval for lorlatinib post-crizotinib also requires prior second-generation TKI treatment.[55]

Progression on a second-generation ALK TKI. Lorlatinib has shown activity in a phase I-II study[54] in patients treated with prior second-generation TKIs. In patients treated with two or three prior ALK TKIs (with or without previous ChT), ORR was 39%, mPFS was 6.9 months and intracranial ORR was 53%. Although response rates were higher in patients who had identified *ALK* mutations, lorlatinib remained active even in patients who did not have identified mutations. Brigatinib has also been reported to have activity in patients progressing on alectinib in two single-arm studies with response rates of 34%-40%.[56,57] Re-biopsy of progressing tumour tissue or plasma cfDNA analysis may identify resistance mutations or alternative mechanisms of resistance assisting selection of subsequent therapies.

Following progression on lorlatinib, ChT with a platinum–pemetrexed-based combination is recommended. The additional value of ICIs is uncertain as *ALK*-positive NSCLC has been excluded from most ICI trials with the exception of IMpower150 where benefit was observed in a small subgroup including *ALK*-positive NSCLC.[58]

Treatment of ROS1-rearranged NSCLC

See Figure 4 for a treatment algorithm for patients with *ROS1* translocations.

Crizotinib was the first approved TKI for the treatment of *ROS1*-rearranged advanced NSCLC, based on the results of the *ROS1* expansion cohort of the PROFILE 1001 phase I study ($N = 53$), which included treatment-naive patients and those who had received prior ChT. ORR was 72% and mPFS and mOS were 19.3 and 51.4 months, respectively. Four-year survival rate was 51%.[59] Based on these results, single-agent crizotinib is recommended in the first-line setting in this patient population. If patients have received crizotinib in the first-line setting, then they may be offered platinum-based ChT in the second-line setting.

Entrectinib is a newer-generation ROS1 and NTRK TKI. In an updated analysis of three ongoing phase I or II trials (ALKA-372-001, STARTRK-1 and STARTRK-2), including 161 patients with *ROS1*-rearranged advanced NSCLC (60 treatment-naive, two previously treated with crizotinib), ORR was 67%, mPFS was 15.7 months and mOS was not reached. For the patients with baseline CNS metastases ($n = 24$), intracranial ORR was 79%, mPFS was 12 months and mOS was 28.3 months.[60] Entrectinib received Food and Drug Administration (FDA) approval (2019)[61] and EMA conditional marketing authorisation (2020)[62] for the treatment of *ROS1*-rearranged NSCLC not previously treated with ROS1 inhibitors. Entrectinib, if available, based on these results, is preferred over crizotinib in patients with brain metastases.

Ceritinib was tested in a single-arm phase II study ($N = 32$); ORR was 62%, mPFS was 19.3 months for crizotinib-naive patients (the two crizotinib-pretreated patients died or withdrew before first response evaluation) and mOS was 24 months.[63]

Lorlatinib also targets *ROS1* with preclinical activity against most known resistance mutations in the gene, and was evaluated in an open-label, single-arm, phase I-II trial ($N = 69$, 40 patients had received crizotinib as their only previous TKI, 8 had previously received a non-crizotinib ROS1 TKI or two or more ROS1 TKIs). ORR was 62% in TKI-naive patients and 35% in crizotinib-pretreated patients. Intracranial ORR was 64% (7/11) and 50% (12/24) in TKI-naive and crizotinib-pretreated patients, respectively. The median duration of response (mDoR) was 25.3 and 13.8 months for the TKI-naive and crizotinib-pretreated patients, respectively.[64] Both ceritinib and lorlatinib are not approved by the EMA.

Repotrectinib, a novel newer-generation ROS1/tropomyosin receptor tyrosine kinase (TRK)/ALK TKI, showed promising activity in the early phase TRIDENT-1 trial.[65] Repotrectinib received FDA breakthrough designation for the treatment of *ROS1*-positive treatment-naive as well as TKI-pretreated NSCLC.

BRAF mutations

See Figure 5 for a treatment algorithm for patients with *BRAF* V600 mutations.

Activating *BRAF* mutations are alternative oncogenic drivers in NSCLC that are generally mutually exclusive with *EGFR* mutations and *ALK* and *ROS1* rearrangements. In a vemurafenib basket trial ($N = 62$ *BRAF* V600-mutated NSCLC), ORR was 38% in previously untreated patients ($n = 8$) and 37% in previously treated patients ($n = 54$).[66,67] In the AcSé vemurafenib trial, no responses were observed in patients with NSCLC and a non-*BRAF* V600 mutation

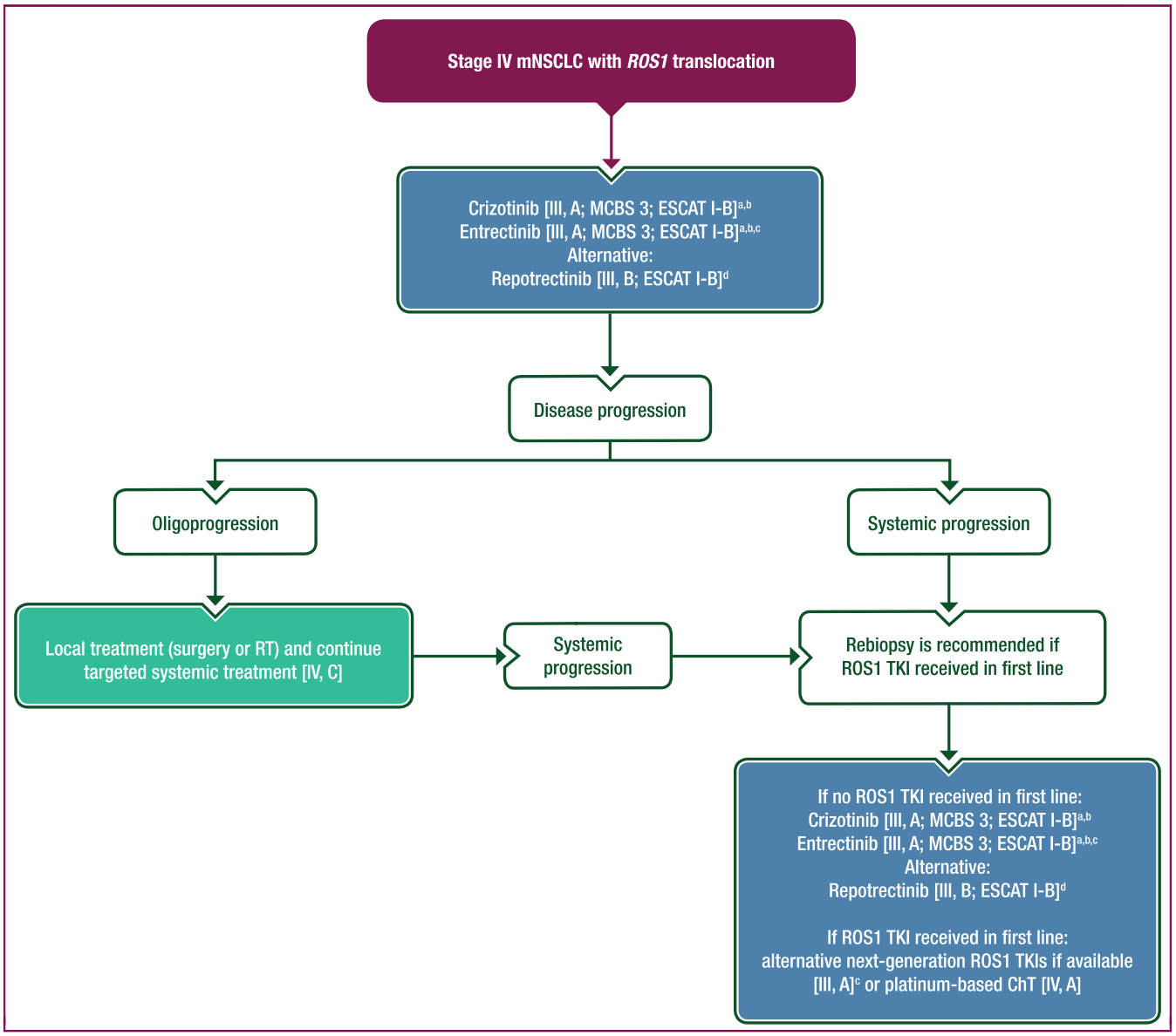

Figure 4. Treatment algorithm for stage IV mNSCLC with *ROS1* translocation.
Purple: general categories or stratification; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.
ChT, chemotherapy; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; FDA, Food and Drug Administration; MCBS, ESMO-Magnitude of Clinical Benefit Scale; mNSCLC, metastatic non-small-cell lung cancer; RT, radiotherapy; TKI, tyrosine kinase inhibitor.
[a]ESMO-MCBS v1.1[111] was used to calculate scores for new therapies/indications approved by the EMA or FDA. 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/esmo-mcbs-evaluation-forms).
[b]ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[4] See Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.12.009 for more information on ESCAT scores.
[c]Preferred over crizotinib in patients with brain metastases.
[d]Not EMA approved.

($n = 17$). ORR was 45%, mDoR 6.4 months, mPFS 5.2 months and mOS 10.0 months in the *BRAF* V600 cohort ($n = 101$).[68]

A prospective, multicentre, multicohort phase II study (BRF113928) of dabrafenib monotherapy (cohort A, $n = 78$), or combination therapy with a MEK inhibitor (trametinib) beyond first line (cohort B, $n = 57$) or in first line (cohort C, $n = 36$) in patients with *BRAF* V600E-mutated mNSCLC was reported. With dabrafenib monotherapy, the ORR was 33% and mPFS and mDoR were 5.5 and 9.6 months, respectively.[69] With the combination of dabrafenib—trametinib in pretreated patients, the ORR was 68% (54.8-80.1) and mPFS and mDoR were 10.2 months (95% CI 6.9-16.7 months) and 9.8 months (95% CI 6.9-18.3 months), respectively.[70] With combination dabrafenib—trametinib therapy in treatment-naive patients, the ORR was 64% (46%-79%) and mPFS and mDoR were 10.8 months (95% CI 7.0-14.5 months) and 10.2 months (95% CI 8.3-15.2 months), respectively.[70] In

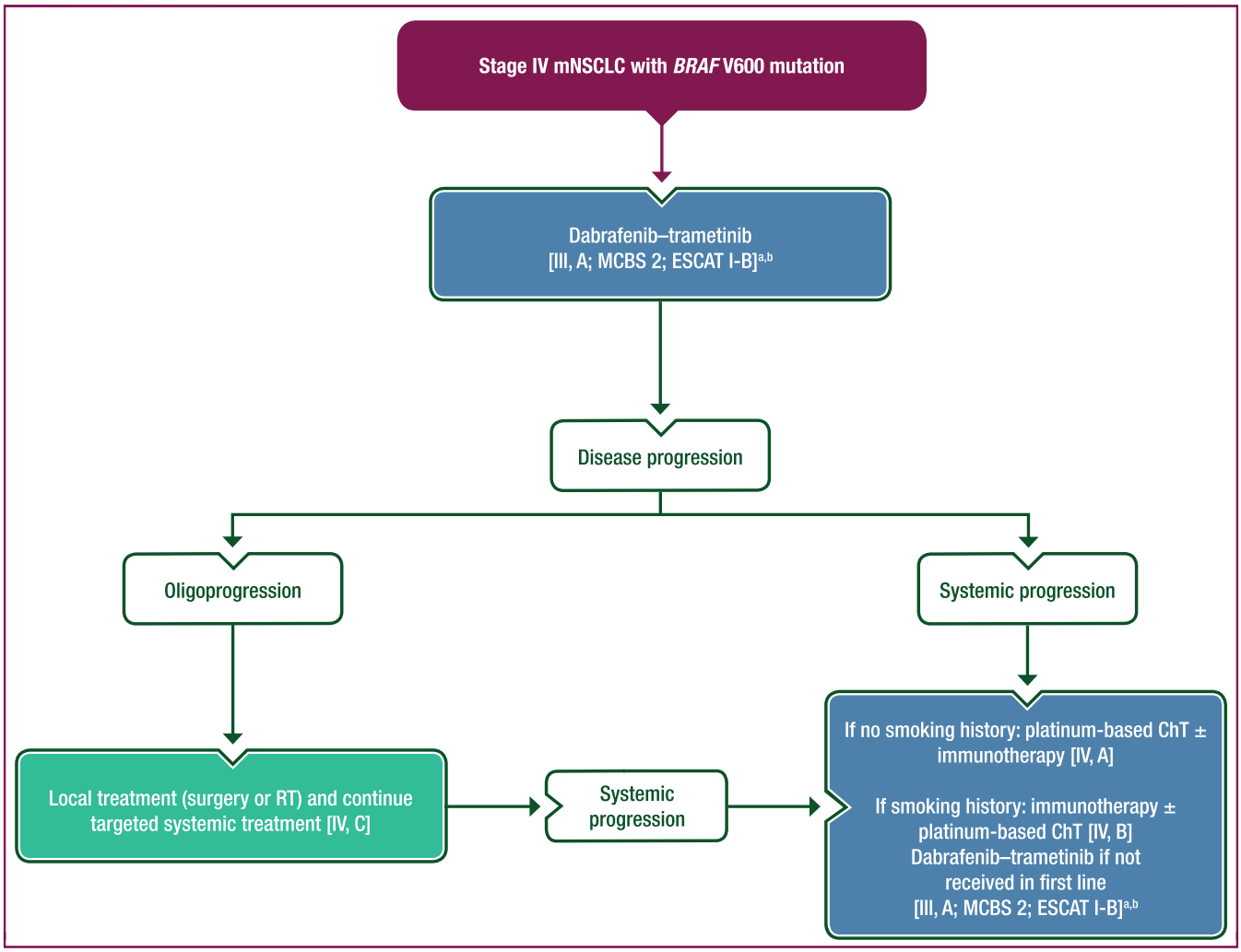

Figure 5. Treatment algorithm for stage IV mNSCLC with *BRAF* V600 mutation.
Purple: general categories or stratification; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.
ChT, chemotherapy, EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; FDA, Food and Drug Administration; MCBS, ESMO-Magnitude of Clinical Benefit Scale; mNSCLC, metastatic non-small-cell lung cancer; RT, radiotherapy.
[a]ESMO-MCBS v1.1[111] was used to calculate scores for new therapies/indications approved by the EMA or FDA. 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/esmo-mcbs-evaluation-forms).
[b]ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[4] See Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.12.009 for more information on ESCAT scores.

pretreated and treatment-naive patients, respectively, the mOS was 18.2 months (95% CI 14.3-28.6 months; 4- and 5-year survival rates: 34% and 22%, respectively) and 17.3 months (95% CI 12.3-40.2 months; 4- and 5-year survival rates: 26% and 19%, respectively).[70] These results represent a clinically significant improvement over both single-agent dabrafenib and conventional ChT. Dabrafenib in combination with trametinib is recommended for the treatment of patients with *BRAF* V600-mutated advanced or metastatic NSCLC (trial only enrolled V600E-positive patients). Very few data on the benefit of single-agent ICI in the *BRAF*-mutated population are available. Results of the international IMMUNOTARGET study (43 patients with *BRAF*-mutated, 40% V600E) showed poor outcomes in *BRAF*-mutated patients, with an ORR of 24% and a mPFS of 3.1 months.[37] Consistent with this, another retrospective study investigating the efficacy of single-agent ICI in oncogene-addicted mNSCLC, confirmed that patients with *BRAF* V600-mutated ($n = 28$ patients) showed a response rate of 26%.[71]

RET fusions

Selpercatinib, a rearranged during transfection (RET)-selective inhibitor, was evaluated in the LIBRETTO-001 phase I-II study in patients with *RET*-rearranged NSCLC.[72] The ORR was 64% (95% CI 54% to 73%) in 105 platinum-pretreated patients and 85% (95% CI 70% to 94%) in 39 treatment-naive patients. The mDoR was 17.5 months in pretreated and NR for treatment-naive patients. Pralsetinib, another RET-selective inhibitor, was evaluated in the ARROW study;[73] the ORR was 59% (95% CI 50% to 67%) in 136 platinum-pretreated patients and 72% (95% CI 60% to 82%) in 75 treatment-naive patients. The mDoR was NR in

treatment-naive patients and 22.3 months for pretreated patients. Importantly, both agents are associated with high intracranial response rates.[73,74] Treatment with selpercatinib or pralsetinib (for both: EMA indication is for those not previously treated with a RET inhibitor)[75,76] is recommended in patients with *RET* fusion-positive NSCLC.

Several additional oncogenic drivers which can be targeted by specific targeted therapies

For the oncogenic drivers discussed below, there are currently no EMA approved first-line targeted agents. For *MET* exon 14 skipping mutations, capmatinib and tepotinib are approved by the FDA but not the EMA in first line. If no first-line targeted options are available, treatments for non-oncogene-addicted tumours are often extrapolated to those with an oncogenic driver. ICIs with or without ChT are the SoC first-line treatment of patients with non-oncogene-addicted mNSCLC.[10] Except for *KRAS*, however, data regarding efficacy of ICI monotherapy are very limited for these drivers (and if available, efficacy is limited).[37] Even fewer data are available for ChT—ICI. A non-smoking history is associated with lower ICI efficacy.[77] Therefore, for the drivers discussed in this paragraph, unless otherwise stated, platinum-doublet ChT with or without ICI is recommended as first-line therapy, and ICI monotherapy is not recommended.

***MET* exon 14 skipping mutations and *MET* amplifications.** Two type Ib MET inhibitors have gained regulatory approval for patients with *MET* exon 14 skipping mutations; capmatinib and tepotinib.[78,79] Among the *MET* exon 14-positive patients treated with capmatinib in the GEOMETRY study, the ORR was 41% (95% CI 29% to 53%) in 69 pretreated patients and 68% (95% CI 48% to 84%) in 28 treatment-naive patients; the mDoR was 9.7 months (95% CI 5.6-13.0 months) and 12.6 months (95% CI 5.5 months to NR), respectively.[80] Among patients with high *MET* amplification (≥10 copies), ORR was 29% (95% CI 19% to 41%) in previously treated patients and 40% (95% CI 16% to 68%) in treatment-naive patients.[80] Among the 152 patients with a *MET* exon 14 skipping mutation who received tepotinib in the VISION study, where enrolment was either based on tissue or liquid biopsy results, the ORR was 45% (95% CI 37% to 53%), with an mDoR of 11.1 months (95% CI 8.4-18.5 months) and mPFS of 8.9 months (95% CI 8.2-11.2 months) in the combined biopsy group.[81] According to the EMA labels, both agents can be recommended following prior treatment with immunotherapy and/or platinum-based ChT in patients with *MET* exon 14 skipping mutations.[78,79] Both agents have a first-line label according to the FDA. Capmatinib can be given to patients with high *MET* amplification (≥10 GCN) following prior treatment with immunotherapy and/or platinum-based ChT, but is neither EMA nor FDA approved.

***HER2* exon 20 mutations.** Several pan-HER TKIs, including afatinib, dacomitinib and neratinib, have been studied in small phase II studies with disappointing results, although some genotypes retain sensitivity.[82] Poziotinib resulted in an ORR of 28% (95% CI 19% to 38%), a mPFS of 5.5 months (95% CI 3.9-5.8 months) and mDoR of 5.1 months (95% CI 4.2-5.5 months) in a phase II trial enrolling pretreated patients with *HER2*-mutated NSCLC ($n = 90$).[83] The antibody—drug conjugates directed against *HER2* have generated more positive results. Trastuzumab—emtansine was evaluated in a basket study including 18 pretreated patients with *HER2*-mutated LUAD.[84] The ORR was 44% (95% CI 22% to 69%). Trastuzumab—deruxtecan was evaluated in the DESTINY LUNG01 study enrolling 91 *HER2*-mutated pretreated NSCLC patients.[85] The ORR was 55% (95% CI 44% to 65%) and mDoR was 9.3 months (95% CI 5.7-14.7 months). Of concern is drug-related ILD that occurred in 26% of patients and resulted in the death of two patients. Trastuzumab—deruxtecan (FDA approved), if available, can be recommended for patients following prior first-line therapy but is not EMA approved.

***NTRK* fusions.** Based on basket trials including a small number of *NTRK* fusion-positive NSCLC patients, larotrectinib and entrectinib have gained regulatory approval in the European Union. Due to the rarity of this alteration (<0.1%), both agents have been evaluated in basket trials containing small numbers of NSCLC patients, all pretreated. The ORR for entrectinib among 22 NSCLC patients (total 121 patients) enrolled in three ongoing phase I-II studies was 64% with a mPFS of 14.9 months and mDoR of 19.9 months.[86] Pooled results from two trials evaluating larotrectinib reported an ORR of 73% (95% CI 45% to 92%) for patients with NSCLC ($n = 20$, 15 evaluable). mDOR, mPFS and mOS were 33.9 months (95% CI 5.6-33.9 months), 35.4 months (95% CI 5.3-35.4 months) and 40.7 months (95% CI 17.2 months to NR), respectively.[87] Both agents are recommended to treat patients with *NTRK* fusion-positive NSCLC who have no satisfactory alternative treatments.

***KRAS* G12C mutations.** *KRAS* is the most frequently mutated oncogene in NSCLC, and *KRAS* G12C is the most frequent mutation. For *KRAS* G12C-mutated NSCLC it is recommended to follow the first-line treatment algorithms in the ESMO CPG on non-oncogene-addicted mNSCLC.[10] Platinum-doublet ChT can be given as a second-line option to patients treated in the first line with monotherapy ICI. The Kirsten rat sarcoma virus (KRAS) G12C-specific inhibitor sotorasib has completed phase III testing in platinum- and ICI-pretreated patients.[88] In the CodeBreak200 trial ($N = 345$), sotorasib was superior to docetaxel: mPFS was 5.6 versus 4.5 months (HR 0.66; 95% CI 0.51-0.86, $P = 0.002$). No difference in mOS was shown, but the study was not powered for OS. Grade ≥3 treatment-related AEs occurred less frequently in the sotorasib arm (33.1% versus 40.4%). Sotorasib is therefore recommended for treatment of *KRAS* G12C-mutated NSCLC failing prior therapy. Adagrasib, which is approved by the FDA but not the EMA, is another KRAS G12C inhibitor. In a registrational phase II cohort, ORR was 43% (95% CI 33.5% to 52.6%) in 112 assessable patients. mDoR was 8.5 months (95% CI 6.2-13.8 months) and mPFS was 6.5 months (95% CI 4.7-8.4 months).[89]

***EGFR* exon 20 insertions.** *EGFR* exon 20 insertions confer limited sensitivity to EGFR TKIs and ICIs. Therefore, the

preferred first-line treatment is platinum-doublet ChT. Amivantamab, a bispecific antibody targeting *EGFR* and *MET*, is approved by both the EMA and FDA for patients with tumours progressing on platinum-doublet ChT.[90,91] In a phase I study ($n = 81$), ORR was 40% with an mDoR of 11.1 months and an mPFS of 8.3 months.[92] Amivantamab can be recommended for treatment of *EGFR* exon 20 insertion-mutated NSCLC failing prior therapy. Mobocertinib, an EGFR TKI, showed activity in a phase I-II trial in patients with previously treated NSCLC ($n = 114$ platinum-pretreated), with an independent review committee-assessed ORR of 28%, an mDoR of 17.5 months and a mPFS of 7.3 months.[93] Mobocertinib is FDA but not EMA approved.[94]

Special populations

PS2 and beyond. Some of the randomised phase III TKI trials allowed entry to patients with PS2 (4%-14% of patients). If subgroups analyses were presented for patients with PS2, a benefit of the TKI was generally seen in this patient population.[95] Although the data are limited for patients with PS >2, TKIs should be given to patients with a poor PS due to the cancer, as ORR is high and toxicity is manageable. Most trial data regarding poor PS is derived from EGFR and ALK TKI trials. In all trials, toxicity was mild, ORR high and most patients improved in PS.[96-98] It is reasonable to assume that efficacy data can be extrapolated to other oncogenic drivers.

Elderly. In all randomised phase III EGFR and ALK TKI trials, elderly patients (defined as ≥65 years) were enrolled and comprised 10%-50% of the total patient population. Elderly patients derive the same, or even more benefit compared with younger patients; a PFS HR was generally lower in the elderly patient population.[95] In a pooled analysis of phase II and III gefitinib trials, a PFS benefit for gefitinib versus ChT was found for patients aged ≥70 years ($N = 71$).[99] Only limited trial data exist for patients aged ≥75 years, but these patients seem to derive the same benefit.[100,101]

Oligometastases. Reliable data on the incidence of synchronous oligometastatic disease in patients with oncogene-addicted mNSCLC do not exist. In a retrospective series ($N = 266$), 38% of patients with metastatic LUAD and an *EGFR* mutation, treated with first-generation TKIs, developed oligoprogression during TKI treatment.[102]

Data regarding the role of local ablative therapy (LAT) for oligometastatic oncogene-addicted mNSCLC are scarce, mainly available for *EGFR*-mutated NSCLC, and mostly derived from retrospective series, subgroup analysis of phase II RCTs and one phase III RCT. A retrospective series evaluating patients with oligometastatic or oligoprogressive LUAD and an oncogenic driver (mainly *EGFR*) suggests that the addition of LAT improves OS and PFS compared with TKI treatment alone.[103]

Two small single-arm phase II trials also suggest that LAT improves survival.[104,105] In the phase II trial of Gomez et al.,[106] enrolling patients with synchronous oligometastatic NSCLC without progression on systemic therapy, patients with an *EGFR* mutation or *ALK* rearrangement were allowed ($n = 8$ out of 49 enrolled patients). The presence of an oncogenic driver was associated with a reduced risk of death but due to small numbers, no subgroup analyses according to the addition of LAT could be carried out.

One open-label phase III RCT (SINDAS) reported interim results for patients with oligometastatic LUAD ($N = 133$, five or fewer metastases) and an *EGFR* mutation; patients with brain metastases were excluded.[107] The addition of radiotherapy (RT) (25-40 Gy in 5 fractions to all involved disease sites) to first-generation EGFR TKIs significantly improved mPFS and mOS, [20.2 versus 12.5 months, (HR 0.68, $P < 0.001$) and 25.5 versus 17.4 months, (HR 0.68, $P < 0.001$), respectively]. Despite the PFS and OS advantages, a high screen-failure rate (78%) combined with a non-typical group of patients with *EGFR* mutations (brain metastases excluded and ∼70% of all metastases being bone metastases) does not allow extrapolation of the results to routine clinical practice.

There are fewer prospective data available for patients with oligoprogressive disease on TKI treatment. For recommendations regarding oligoprogression in the brain, please refer to the European Association of Neuro-Oncology (EANO)—ESMO CPG on brain metastases from solid tumours for recommendations.[108] Based on a prematurely-closed, single-arm phase II trial it is suggested that patients with oligoprogression on erlotinib can benefit from LAT as mPFS after LAT was 6 months.[109] Retrospective data also suggest a survival benefit of LAT for oligoprogressive lesions with the continuation of the TKI.[103] Prospective trials are ongoing.

Currently, there are a lack of prospective data evaluating the use of a specific LAT (RT versus surgery). The role of minimally-invasive thoracic surgery, in particular with the use of modern technologies (robotic systems), is also becoming the new standard in pretreated complex surgical cases due to benefits compared with traditional open approaches.

Patients with synchronous or oligoprogressive, oncogene-driven mNSCLC should be discussed by the multidisciplinary tumour board (MTB) and, if possible, enrolled in a clinical trial.

Brain metastases. Therapeutic strategies for patients with brain metastases are discussed in the EANO—ESMO CPG on brain metastases from solid tumours.[108]

Bone metastases. Therapeutic strategies for patients with bone metastases are discussed in the ESMO CPG on bone health in cancer.[110]

Role of RT in stage IV

Details and recommendations on the role of RT are covered in the ESMO CPG on non-oncogene-addicted mNSCLC.[10]

Role of surgery in stage IV

Details and recommendations on the role of surgery are covered in the ESMO CPG on non-oncogene-addicted mNSCLC.[10]

Role of minimally-invasive procedures in stage IV

Details on the role of minimally-invasive procedures and recommendations are covered in the ESMO CPG on non-oncogene-addicted mNSCLC.[10]

Recommendations

EGFR-mutated NSCLC

- All patients with a sensitising *EGFR* mutation should receive first-line EGFR TKIs irrespective of clinical parameters including PS, gender, tobacco exposure and histology [I, A].
- Osimertinib is the preferable first-line treatment option for patients with a classical activating *EGFR* mutation (exon 19 deletion or exon 21 L858R), especially for patients with CNS metastases [I, A; ESMO-Magnitude of Clinical Benefit (ESMO-MCBS) v1.1 score: 4; ESCAT: I-A].
- Erlotinib, gefitinib, afatinib and dacomitinib are other first-line single-agent treatment options [erlotinib and gefitinib: I, B; ESMO-MCBS v1.1 score: 4; ESCAT: I-A; afatinib: I, B; ESMO-MCBS v1.1 score: 5; ESCAT: I-A; dacomitinib: I, B; ESMO-MCBS v1.1 score: 3; ESCAT: I-A].
- Another first-line option is gefitinib combined with carboplatin—pemetrexed [I, B; not EMA approved].
- EGFR TKIs combined with anti-angiogenic therapy are additional first-line treatment options, including erlotinib—bevacizumab [I, B; ESMO-MCBS v1.1 score: 2; ESCAT: I-A; EMA approved, not FDA approved] or erlotinib—ramucirumab [I, B; ESMO-MCBS v1.1 score: 3; ESCAT: I-A].
- Considering toxicity, cost increases with adding additional treatments and patient inconvenience, single-agent EGFR TKIs are still a standard first-line treatment [I, A; ESCAT: I-A].
- Afatinib or osimertinib is a recommended treatment option for patients with a major uncommon, non-exon 20 insertion, sensitising *EGFR* mutation [III, B; ESMO-MCBS v1.1 score: 4 for afatinib; ESCAT: I-B].
- Patients who have moderate radiological progression with ongoing clinical benefit may continue with EGFR TKIs [III, A].
- Upon resistance to first-line first- or second-generation EGFR TKIs, patients should be tested for the presence of the *EGFR* exon 20 T790M mutation from plasma cfDNA and/or tumour re-biopsy [I, A].
- Patients with T790M-positive resistance should receive osimertinib as second-line therapy [I, A; ESMO-MCBS v 1.1 score: 4; ESCAT: I-A], whereas T790M-negative resistance should be treated with platinum-based ChT [III, A].
- Genomic analysis by NGS (tissue, or cfDNA followed by tissue if no target is found with cfDNA) should be made available to a patient who develops resistance to osimertinib [III, C].
- Platinum-doublet ChT is the SoC upon progression on osimertinib [III, A]. Clinical trial enrolment is encouraged, especially if a targetable resistance mechanism is identified [III, B].
- The combination of atezolizumab—bevacizumab—paclitaxel—carboplatin may be considered as a treatment option for patients with EGFR TKI failure, PS 0-1 and no contraindication for ICIs [III, B; ESMO-MCBS v1.1 score: 3].
- Single-agent ICIs may be considered as a treatment option only after progression on EGFR TKIs and ChT [IV, C].

ALK-rearranged NSCLC

- Patients should be treated in the first-line setting with alectinib, brigatinib or lorlatinib [I, A; ESMO-MCBS v1.1 score: 4; ESCAT: I-A]. These options are preferred over crizotinib or ceritinib [I, B; ESMO-MCBS v1.1 score: 4; ESCAT: I-A].
- Alectinib is recommended in patients who progress on treatment with, or are intolerant to, crizotinib [I, A; ESMO-MCBS v1.1 score: 4; ESCAT: I-A].
- Brigatinib and ceritinib represent additional treatment options at crizotinib resistance [brigatinib: III, A; ESMO-MCBS v1.1 score: 4; ESCAT: I-A; ceritinib: I, A; ESMO-MCBS v1.1 score: 4; ESCAT: I-A].
- In patients who progress after a second-generation ALK TKI, the newer-generation ALK inhibitor lorlatinib is an option [III, A; ESMO-MCBS v1.1 score: 4; ESCAT: I-A].
- Following progression on lorlatinib, ChT with a platinum—pemetrexed-based combination is recommended [III, A].
- Following progression on lorlatinib, atezolizumab—bevacizumab—paclitaxel—carboplatin can be considered [III, B; ESMO-MCBS v1.1 score: 3].

Treatment of *ROS1*-rearranged NSCLC

- Crizotinib or entrectinib is recommended in the first-line setting [III, A; ESMO-MCBS v1.1 score: 3; ESCAT: I-B].
- Entrectinib, if available, is preferred over crizotinib in patients with brain metastases [III, A; ESMO-MCBS v1.1 score: 3; ESCAT: I-B].
- Repotrectinib, if available, is an option in the first-line setting but is not EMA approved [III, B; ESCAT: I-B].
- If patients have received crizotinib in the first-line setting, they may be offered a newer-generation TKI if available [III, A] (no EMA approval) or platinum-based ChT in the second-line setting [IV, A].

BRAF mutations

- BRAF—MEK inhibition using dabrafenib—trametinib is recommended [III, A; ESMO-MCBS v1.1 score: 2; ESCAT: I-B].
- If patients have received BRAF—MEK inhibition in the first-line setting, they may be offered platinum-based ChT with or without immunotherapy in the second-line setting, if they do not have a smoking history [IV, A]. For patients with a smoking history, immunotherapy with or without ChT should be considered as per the ESMO CPG on non-oncogene-addicted mNSCLC [IV, B].[10]

RET fusions

- Treatment with selpercatinib or pralsetinib is recommended as first-line therapy for patients with *RET* fusion-

positive NSCLC [III, A; ESMO-MCBS v1.1 score: 3; ESCAT: I-C].

Other oncogenic drivers for which targeted therapy is available

- Platinum-doublet ChT with or without ICIs is recommended as first-line therapy for patients with a *MET* amplification, *NTRK* gene fusion, *HER2* mutation and *EGFR* exon 20 mutation [IV, B].
- Capmatinib and tepotinib in first line [III, A; ESMO-MCBS v1.1 score: 3; ESCAT: I-B; FDA approved, not EMA approved] or in second line [III, A; ESMO-MCBS v1.1 score: 3; ESCAT: I-B] are recommended in patients with a *MET* exon 14 skipping mutation.
- If no MET TKI is available in the first line, platinum-doublet ChT with or without ICIs is recommended as first-line therapy for patients with a *MET* exon 14 skipping mutation [IV, B].
- In patients with *HER2* exon 20 mutations, trastuzumab—deruxtecan, if available, is recommended for patients following prior first-line therapy but is not EMA approved [III, B; ESCAT: II-B].
- Larotrectinib and entrectinib are recommended for patients with NSCLC and an *NTRK* gene fusion and who have no satisfactory treatment options [III, A; ESMO-MCBS v1.1 score: 3; ESCAT: I-C].
- For *KRAS* G12C-mutated NSCLC, it is recommended to follow the first-line treatment algorithms in the ESMO CPG on non-oncogene-addicted mNSCLC [III, A].[10]
- Platinum-doublet ChT can be given to patients with *KRAS* G12C-mutated NSCLC and progression on first-line monotherapy ICI [III, A].
- Sotorasib is recommended for treatment of *KRAS* G12C-mutated NSCLC failing prior therapy [I, B; ESMO-MCBS v1.1 score: 3; ESCAT: I-B].
- Adagrasib is recommended for treatment of *KRAS* G12C-mutated NSCLC failing prior therapy [III, B; ESMO-MCBS v1.1 score: 2; ESCAT: I-B; FDA approved, not EMA approved].
- Amivantamab is recommended for treatment of *EGFR* exon 20 insertion-mutated NSCLC failing prior therapy [III, B; ESMO-MCBS v1.1 score: 3; ESCAT: I-B].
- Mobocertinib can be given as treatment of *EGFR* exon 20 insertion-mutated NSCLC failing prior therapy [III, C; ESMO-MCBS v1.1 score: 2; ESCAT: I-B; FDA approved, not EMA approved].

Special populations

- TKIs should be given to patients with PS $\geq$2 and an oncogenic driver [III, A].
- TKIs should be given to elderly patients [II, A].
- Patients with oligometastatic disease at diagnosis may experience long-term PFS following systemic therapy and LAT (high-dose RT or surgery) [II, B], but due to limited evidence, inclusion in clinical trials is preferred.
- Patients with advanced NSCLC and a driver mutation, with oligoprogression while on molecular-targeted therapy, may benefit from LAT (high-dose RT or surgery) including improved long-term disease-free survival, but data are limited and inclusion in clinical trials is preferred.

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

Details on follow-up, long-term implications and survivorship, as well as palliative care in stage IV NSCLC are covered in the Supplementary Material Section 5, available at https://doi.org/10.1016/j.annonc.2022.12.009.

Recommendations

Follow-up, long-term implications and survivorship

- Follow-up every 8-12 weeks should be carried out if there is an option for a next line of therapy [IV, A].
- Psychosocial support should be offered if needed [IV, A].
- Smoking cessation should be encouraged [IV, A].

Palliative care in stage IV

- Early palliative care intervention is recommended, in parallel with standard oncological care [I, A].

METHODOLOGY

This CPG was developed in accordance with the ESMO standard operating procedures for CPG development (https://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. A table of ESCAT scores is included in Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.12.009. ESCAT scores have been defined by the authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[4] A table of ESMO-MCBS scores included in Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2022.12.009. ESMO-MCBS v1.1[111] was used to calculate scores for new therapies/indications approved by the EMA or FDA (https://www.esmo.org/Guidelines/ESMO-MCBS). The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee. The FDA/EMA or other regulatory body approval status of new therapies/indications is reported at the time of writing this CPG. Levels of evidence and grades of recommendation have been applied using the system shown in Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2022.12.009.[112] Statements without grading were considered justified standard clinical practice by the authors. For future updates to this CPG, including Living Guidelines, please see the ESMO Guidelines website at https://www.esmo.org/guidelines/guidelines-by-topic/lung-and-chest-tumours.

ACKNOWLEDGEMENTS

Manuscript editing support was provided by Richard Lutz, Fraser Simpson, Claire Bramley, Catherine Evans, Jennifer Lamarre and Guy Atchison (ESMO Guidelines staff); this support was funded by ESMO. Nathan Cherny, Chair of the ESMO-MCBS Working Group, Urania Dafni 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 KMC provided medical writing and editing support in the preparation of the ESMO-MCBS table; this support was funded by ESMO. Dr Jordi Remón Masip (on behalf of the ESMO Translational Research and Precision Medicine Working Group) and Dr Svetlana Jezdic (ESMO Medical Affairs Advisor) provided validation support for ESCAT scores. Matt Hellmann provided initial writing support during the conception of this guideline.

FUNDING

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

DISCLOSURE

LEH reports personal fees as an invited speaker from Benecke, Medtalks and VJOncology; personal fees for participation in mentorship programme funded by AstraZeneca; personal fees for travel support from Roche; personal fees as member of the committee that revised the Dutch guidelines on NSCLC, brain metastases and leptomeningeal metastases; fees paid to her institution for an educational webinar from Janssen; fees paid to her institution for advisory board membership from Amgen, Bristol-Myers Squibb (BMS), Boehringer Ingelheim, Janssen, Lilly, Merck, Merck Sharp & Dohme (MSD), Novartis, Pfizer, Roche and Takeda; fees paid to her institution as an invited speaker from AstraZeneca, Bayer, high5oncology, Lilly and MSD; fees paid to her institution for interview sessions from Roche; fees paid to her institution for podcast appearance from Takeda; institutional research grants from AstraZeneca, Boehringer Ingelheim, Roche, Takeda, Pfizer and Merck; institutional funding as a local principal investigator (PI) from AbbVie, AstraZeneca, Blueprint Medicines, Gilead, GlaxoSmithKline (GSK), Merck Serono, Mirati, MSD, Novartis, Roche and Takeda; non-remunerated roles as chair for metastatic NSCLC of the lung cancer group for European Organisation for Research and Treatment of Cancer (EORTC) and as the secretary of the studies foundation for Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose (NVALT).

KK reports personal fees as an invited speaker from Amgen, AstraZeneca, Boehringer Ingelheim, BMS, Eli Lilly, Medscape, Merck Serono, MSD, Novartis, Pfizer, Prime Oncology, Roche and Roche Diagnostics/Ventana; personal fees for consultancy and advisory board membership from AbbVie, Amgen, AstraZeneca, Bayer, Debiopharm, Diaceutics, Janssen, Merck Serono, MSD, Novartis, Pfizer, Regeneron, Roche and Roche Diagnostics/Ventana; non-remunerated roles as the past Pathology Committee Chair for International Association for the Study of Lung Cancer (IASLC) and member of the UK Lung Cancer Consortium.

JM reports fees paid to her institution as an invited speaker from AstraZeneca, Boehringer Ingelheim, BMS, MSD and Roche; fees paid to her institution for expert testimony from AstraZeneca, Boehringer Ingelheim and MSD; fees paid to her institution for travel expenses from Ipsen.

TSM reports personal fees as an invited speaker from AbbVie, ACEA Pharma, Alpha Biopharma, Amgen, Amoy Diagnostics, BeiGene, Boehringer Ingelheim, BMS, Daiichi Sankyo, Daz Group, Eli Lilly, Fishawack Facilitate, InMed Medical Communication, Janssen, Jiahui Holdings Co., LiangYiHui Healthcare, Lucene Health Inc., Lunit USA, Inc., MD Health, Medscape/WebMD, Merck Serono, MIRXES, MSD, Novartis, OrigiMed, PeerVoice, PER, Permanyer SL, Pfizer, Prime Oncology, Research to Practice, Roche, Sanofi-Aventis, Shanghai BeBirds Translation & Consulting Co., Taiho Pharmaceutical Co., Takeda and Touch Medical Media; personal fees for advisory board membership from AbbVie, ACEA Pharma, Alpha Biopharma, Amgen, Amoy Diagnostics, BeiGene, Berry Oncology, Blueprint Medicines, Boehringer Ingelheim, BMS, C4 Therapeutics, Cirina Ltd, Covidien LP, CStone Pharma, Curio Science, D3 Bio Ltd, Da Volterra, Daiichi Sankyo, Eisai, Eli Lilly, Fishawack Facilitate, G1 Therapeutics, Gilead Sciences, Gritstone Oncology, Guardant Health, Hengrui, Ignyta, Incyte, Inivata, IQVIA, Janssen, Lakeshore Biotech, Loxo Oncology, Lucene Health Inc., Lunit USA, Inc., Medscape/WebMD, Merck Serono, Mirati Therapeutics, MiRXES, MoreHealth, MSD, Novartis, OrigiMed, OSE Immunotherapeutics, Pfizer, Puma Tech, Qiming Development, Roche, Roche/Genentech, Sanofi-Aventis, SFJ Pharmaceutical Ltd, Synergy Research, Takeda, Tigermed, Vertex Pharmaceuticals, Virtus Medical and Yuhan; personal fees as the Chairman for ACT Genomics-Sanomics Group; personal fees as a member of the board of directors from AstraZeneca and HutchMed; holds stocks/shares from AstraZeneca, Aurora Tele-Oncology, Biolidics Ltd, HutchMed and Sanomics Ltd.; institutional funding from AstraZeneca, BMS, Clovis Oncology, G1 Therapeutics, Merck Serono, MSD, Novartis, Pfizer, Roche, SFJ Pharmaceuticals, Takeda and XCovery; non-remunerated roles as an invited speaker with AstraZeneca, Aurora Tele-Oncology, Lunit USA, Inc. and Sanomics Ltd and for an advisory role with geneDecode; non-remunerated leadership roles with American Society of Clinical Oncology (ASCO), Asian Thoracic Oncology Research Group (ATORG), Chinese Lung Cancer Research Foundation Limited (CLCRF), Chinese Society of Clinical Oncology (CSCO), Hong Kong Cancer Fund (HKCF), Hong Kong Cancer Therapy Society (HKCTS), IASLC and St. Stephen's College & Prep School (Hong Kong).

UN reports fees paid to her institution as an invited speaker from MSD; fees paid to her institution for advisory board membership and a writing engagement from AstraZeneca; institutional funding as a coordinating PI for Bayer; non-remunerated roles as a PI for clinical trials funded by Deutsche Krebshilfe and as a member of the board of directors and vice-chair of 'Strahlenschutzkommission' from the German Commission on Radiological Protection.

AP reports personal fees as an invited speaker from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Mundipharma

and Takeda; personal fees for advisory board membership from AstraZeneca, Boehringer Ingelheim, BMS, Eli Lilly, Janssen, MSD, Pfizer and Roche; non-remunerated activities with Italian Association of Medical Oncology (AIOM) as member of the Scientific Committee for lung cancer guidelines.

SP reports personal fees for an editorial role as an Associate Editor for Annals of Oncology; fees paid to her institution as an invited speaker from AstraZeneca, BMS, Boehringer Ingelheim, ecancer, Eli Lilly, Fishawack, Illumina, Imedex, Medscape, Mirati, MSD, Novartis, OncologyEducation, Physician's Education Resource (PER), Pfizer, Partnerships in International Medical Education (PRIME), RMEI Medical Education, LLC (RMEI), Roche/Genentech, Research To Practice (RTP), Sanofi and Takeda; fees paid to her institution for advisory board membership from AbbVie, Amgen, Arcus, AstraZeneca, Bayer, BeiGene, Bio Invent, Biocartis, Blueprint Medicines, BMS, Boehringer Ingelheim, Daiichi Sankyo, Debiopharm, Eli Lilly, F-Star, Foundation Medicine, Genzyme, Gilead, GSK, Illumina, Incyte, IQVIA, iTeos, Janssen, Merck Serono, Mirati, MSD, Novartis, Novocure, Pfizer, PharmaMar, Phosplatin Therapeutics, Regeneron, Roche/Genentech, Sanofi, Seattle Genetics, Takeda and Vaccibody; institutional funding as a steering committee member from AstraZeneca, BeiGene, BMS, iTeos, Mirati, MSD, PharmaMar, Phosplatin Therapeutics and Roche/Genentech; institutional funding as a coordinating PI from AstraZeneca; institutional funding as a trial chair from GSK and Roche/Genentech; non-remunerated role as President and Council Member for the Ballet Béjart Lausanne Foundation; non-remunerated leadership roles as President of ESMO (2020-2022), Vice- President of Swiss Academy of Multidisciplinary Oncology (SAMO), Vice-President of Lung Group for Swiss Group for Clinical Cancer Research (SAKK); non-remunerated role as PI involved in academic trials for European Thoracic Oncology Platform (ETOP)/EORTC/SAKK; non-remunerated role as Council Member and Scientific Committee Chair for ETOP/International Breast Cancer Study Group (IBCSG) Partners member of American Association of Cancer Research (AACR), ASCO, Association Suisse des médecines-assistant(e)s et chef(fe)s de Clinique (ASMAC)/Verband Schweizerischer Assistenz- und Oberärztinnen und- ärzte (VSAO), Fédération des médecins suisses (FMH) and IASLC.

DP reports personal fees as an invited speaker from AbbVie, AstraZeneca, Janssen, Novartis, Peer CME, Pfizer, priME Oncology and Samsung; personal fees for advisory board membership from AbbVie, AstraZeneca, BMS, Celgene, Daiichi Sankyo, Janssen, Merck, Novartis, Pfizer, Roche and Samsung; institutional funding as a PI from AbbVie, AstraZeneca, BMS, Daiichi Sankyo, Janssen, Merck, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi and Sanofi-Aventis.

ES reports personal fees as an invited speaker from Boehringer Ingelheim and Daiichi Sankyo; personal fees for advisory board membership from Merck Serono; fees paid to his institution for advisory board membership from AstraZeneca, BMS, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Janssen, MSD, Roche, Sanofi and Takeda; institutional funding as a local PI from AstraZeneca, Genmab, Gilead and Pfizer.

BJS reports personal fees as an invited speaker from AstraZeneca, Pfizer and Roche/Genentech; personal fees for advisory board membership from Amgen and Roche/Genentech; fees paid to his institution for advisory board membership from AstraZeneca, BMS, Merck and Novartis; fees paid to his institution for steering committee membership from Novartis, Pfizer and Roche/Genentech; personal fees as a member of the board of directors from Cancer Council Victoria and Thoracic Oncology Group of Australasia; personal fees as a consultant from Peter MacCallum Cancer Centre; royalties from UpToDate.

GV reports personal fees as an invited speaker and for advisory board membership from Roche; personal fees as a consultant from Ab Medica; institutional funding as a PI from Fondazione AIRC per la ricerca sul cancro ETS (AIRC) and the Italian Ministry of Health.

MR reports personal fees as an invited speaker from Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Lilly, Merck, MSD, Novartis, Roche and Sanofi; personal fees for advisory board membership from Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Mirati, MSD, Pfizer, Roche and Sanofi.

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