European Society of Medical Oncology (ESMO) guidelines for oncogene-addicted metastatic non-small cell lung cancer (NSCLC): a personalized treatment for each patient

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In the last years, the better knowledge of target mutations in non-small cell lung cancer (NSCLC) has changed the prognosis of patients with advanced or metastatic disease. After the emergence of the first targeted treatments, clinical studies have shown that the survival of patients with a molecular alteration has radically changed (1,2). These targeted therapies have been reflected in previous clinical guidelines, which included alterations such as the epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and ROS proto-oncogene 1 (ROS1). However, with the standardization of next generation sequencing (NGS) and a better understanding of the physiopathology of NSCLC, new alterations have emerged as biomarkers and treatment targets (3). Nowadays, NSCLC has been subdivided into different entities, with different prognosis, evolution, and options of treatment. There is a big difference between the response to treatments, pathogenesis, and development of an oncogene-addicted NSCLC versus a wild-type NSCLC. Although immune checkpoint inhibitors (ICIs) have changed the prognosis of NSCLC, it seems that response is worse in some patients with oncogene-addicted mutations (4), which may be explained by factors such as absence of tobacco consumption which may cause a mutational signature with a decreased number of neoantigens and less clonal expansion (5). Another problem is that each oncogene is associated with different patient characteristics, molecular profile, and evolution. This heterogenicity has led to classify each alteration as differentiated types of disease. For instance, most of this oncogene alterations are associated with Asiatic never-smoker younger women and exposure to radon gas (6,7). With this impending need to classify all this knowledge and "types of disease" into the clinical practice by the main worldwide oncology societies, different guidelines have been developed. One of the most important and recently updated are the European Society of Medical Oncology (ESMO) guidelines for Oncogene Addicted NSCLC (3).

With this update, compared to the previous generic metastatic NSCLC treatment guidelines, ESMO has prepared two different guidelines separating oncogene addicted and non-oncogene addicted treatments, therefore increasing the personalization of the treatment options depending on the tumour molecular profile. The first

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major update can be found in the beginning, where ESMO recommends tests that should be done to all patients. In previous guidelines there were doubts of whether to recommend wide screening tests such as NGS or to test particular mutations through individual methods like EGFR, ALK and ROS1 exclusively. In the current guidelines (3), after the appearance of many target drugs against a great number of mutations, the recommendation has been upgraded to suggest that all non-squamous NSCLC, and squamous NSCLC with certain characteristics (e.g., young and never smoker patients) should be evaluated with the NGS technique (grade IIIA of evidence). Moreover, it includes the liquid biopsy as a diagnostic possibility (grade IIA of evidence), although it has not yet overcome the tissue analysis. This point is important since, due to the reduction in price of the technique, it is sometimes more expensive to do multiple single mutations, than to proceed straight away with NGS. Recently, a cost-effectiveness analysis which compares NGS to single-gene tests (8), showed that NGS improved the detection of actionable biomarkers by 74.4%, improved the proportion of patients receiving biomarker-driven therapy by 11.9%, and decreased the proportion of patients with biomarker-positive disease receiving non-biomarker-driven therapy by 40.5%. The incremental cost-effectiveness ratio for NGS-directed therapy was $148,786 compared with single-gene tests. Nevertheless, doubts have emerged regarding NGS in some settings: as different articles point out, RNA-sequencing has many problems such as incapacity to detect alterations due to limited tissue, the impact of formalin fixation or ubiquitous RNA degradation enzymes (9,10). A clinical setting where this has been observed is in the detection of the mesenchymal epithelial transition (MET) factor amplification (METamp) resistance alteration after osimertinib use in the INSIGHT-2 trial (11), where patients were pre-screened with NGS and fluorescence in situ hybridization (FISH) analysis to find the mutation: about 50% of patients had METamp detected with FISH while only 11.7% of patients were detected by NGS. Regarding the penetrance of NGS in the clinical practice, although in the last 10 years most of the hospitals have preferred to do single-gene tests, there has recently been a tendency to switch to NGS. In a recent published study about the tests used to diagnose molecular alterations in Spanish hospitals, starting from 2020, when different molecular alterations had new investigational targeted therapies, NGS increased from about 1% in previous years to 5–10% of patients (12). When future data becomes published, we are sure that the percentage will exponentially increase. The conclusion of the analysis is that NGS is a cost-effective therapy for advanced/metastatic non-squamous NSCLC and needs to be implemented in the clinical practice. Nonetheless, some alterations, particularly those detected with RNA-sequencing, should be analysed with techniques that yield a better detection rate.

Moving to the treatment of patients with molecular alterations, the greatest strength of the guidelines is how everything is organized for each mutation, and how there are recommendations for each line of treatment. In the EGFR setting we can find osimertinib as the preferred drug for the first line based on the FLAURA trial, which showed a good central nervous system (CNS) penetrance, median progression-free survival (PFS) of 18.9 months [95% confidence interval (CI): 15.2–21.4], and median overall survival (OS) of 38.6 months (95% CI: 34.5–41.8) (13). FLAURA efficacy and safety data supports the use of osimertinib *vs.* gefitinib and erlotinib in first-line setting. However, no direct comparison was done against second generation EGFR tyrosine-kinase inhibitors (TKI), but the safety profile of osimertinib seems to support it as preferred option. The positioning of osimertinib as first-line therapy has changed the resistance profile, with a preponderance of METamp or other secondary targetable alterations, therefore recommending the re-biopsy at the time of progression (14). Although there is currently not a single therapy approved after osimertinib resistance, many clinical trials are ongoing with agents such as savolitinib or tepotinib, and patients should be referred to reference hospitals since they seem promising options. The next controversy revolves around what to do after the targeted therapy options have been exhausted. Three clinical trials, two of which are cited in the ESMO guidelines (3), have tested the ICI approach: IMpower150 (15), ORIENT-31 (16) and KEYNOTE-789 (17), which compare chemotherapy plus an ICI *vs.* chemotherapy alone. The IMpower150 (15) showed benefit in the scarce number of patients included, but the trial was biased in patients with targetable alterations since they were removed from the main analysis after an amendment, so even though the ESMO guidelines (3) recommend it as an option, there are some doubts regarding the benefit for these patients. In fact, two other trials go against ICI use: the ORIENT-31 (16) and the KEYNOTE-789 (17). Although the primary median PFS analysis of ORIENT-31 (16) was positive, there is no median OS difference between the ICI cohort and the control group. KEYNOTE-789 (17) was negative

for the main endpoints. Taken altogether there is not enough data to support the use of ICIs in this setting since it does not seem to offer benefit over chemotherapy alone, while there is a risk of immune side effects or hyperprogression. Moreover, although evidence is scarce, ICIs do not usually have a good prognosis in patients with other targeted mutations such as ALK (4). In this population, small cohorts in different clinical trials have tried to assess TKI or chemotherapy combinations with conflicting results. Some mutations such as v-Raf murine sarcoma viral oncogene homolog B1 (BRAF) or Kirsten rat sarcoma (KRAS) have conflicting data with a potential benefit of ICIs use. Particularly in KRAS patients, which have ongoing phase II and III trials with ICI combinations, and where ICIs are still considered as a first-line standard of care (4). In other patients with rarer mutations like rearranged during transfection (RET) or human epidermal growth factor receptor 2 (HER2) data is even scarcer, and no recommendation can be given (4). Future trials such as the phase III DESTINY-LUNG04 may offer more data since it randomized patients to either receive Trastuzumab-deruxtecan or carboplatin-pemetrexed-pembrolizumab. Future clinical trials on combination therapies and biomarkers for ICI therapy based on specific characteristics of oncogene-addicted NSCLC need to be conducted.

Other settings have been radically updated to include all the current developments. Regarding ALK, the first line has multiple options with second and third generation ITKs. The most recent addition is lorlatinib, a third generation TKI which shows great CNS penetrance, prolonged median PFS and OS. In fact, in the CROWN phase III trial (18), which compared lorlatinib *vs.* crizotinib, the hazard ratio (HR) for time to intracranial progression was 0.02 (95% CI: 0.002–0.14) in patients without CNS disease at diagnosis, while 0.10 (95% CI: 0.04–0.27) in patients with CNS disease at baseline. The ESMO guidelines (3) cannot recommend third generation TKI over second generation since they have not been directly compared, and the side effects profile of each TKI should be assessed in each case. Considering the HR for CNS progression seen with the use of drugs like osimertinib or lorlatinib a new controversy has recently emerged: should patients be monitored with CNS tests during treatment, or should they only be done when neurologic symptoms appear? Future trials should assess whether CNS scans are cost-effective and if they impact in the survival of patients, since patients already spend an important amount of time in the hospital, which is a huge burden for the quality of life. If we can reduce the number of scans the patient has to undertake during their disease, it would alleviate part of the burden. Another controversial point is the efficacy of these drugs in brain metastases and how they should be managed in the inclusion/exclusion criteria of clinical trials. Regarding this topic, the Food and Drug Administration (FDA) has done specific recommendations for the inclusion of patients with brain metastases in clinical trials with the aim of clarifying this setting (19).

ROS1 has gained new options besides crizotinib like entrectinib, a newer generation ROS1/neurotrophic receptor tyrosine kinase (NTRK) TKI, and repotrectinib, a ROS1/ALK/tropomyosin receptor kinase (TRK) drug. As it is the case of lorlatinib in ALK disease, although the drugs have not been compared, pooled data of phase I/II trials of entrectinib (20) ALKA-372-001, STARTRK-1 and STARTRK-2 show a good CNS penetrance with an intracranial overall response rate (ORR) of 79%, which suggests that entrectinib is a good option, particularly in cases with CNS disease. Recommendations over BRAF V600E patients have not changed since there has not been any novelty after the phase II BRF113928 trial report (21) before the publication of the ESMO guidelines (3). However, in the recent American Association of Clinical Oncology (ASCO) congress, another BRAF-mitogen-activated protein kinase (MEK) combination was reported with the phase II PHAROS trial (22), which employed encorafenib-binimetinib with encouraging results: among 59 treatment naïve patients with metastatic NSCLC, the ORR was 75% with a median PFS not reached (NR) after a median duration of follow-up of 18.2 months.

Starting from this point, the guidelines expand a wide range of possibilities for multiple targets that did not have any recommendation in the previous guidelines. (I) MET exon 14 skipping mutations have two options with the approval of capmatinib and tepotinib in the second line setting based on the data reported in the GEOMETRY phase II trial (23) and the VISION phase II trial (24). (II) After past failures, patients with a HER2 alteration have a promising option with the development of trastuzumab-deruxtecan based on the results of the DESTINY-LUNG01 trial (25). Currently, it is being tested in the first and second line in the DESTINY-LUNG02 and 04 trials. (III) EGFR exon 20 insertions, previously considered as a resistant alteration, have two promising options with the development of amivantamab and mobocertinib, which are being tested in the first and second line setting as well. (IV) KRAS G12C, one of the most frequently detected

alterations, has been difficult to target, and preliminary data is not as good as with other molecular alterations. Only sotorasib has a European Medicines Agency (EMA) approval as a second line therapy based on the results of the CodeBreak200 phase III trial (26), which randomized 345 patients to either receive sotorasib or docetaxel. Sotorasib was superior with a median PFS of 5.6 months (95% CI: 4.3–7.8) *vs.* 4.5 months (95% CI: 3–5.7), but there was not a difference in OS. New drugs like adagrasib and different investigational combinations like the addition of ICIs to the TKI are currently being tested. (V) Although very infrequent, basket trials of NTRK-targeting drugs like larotrectinib and entrectinib and RET-targeting drugs like selpercatinib and pralsetinib show good results in patients with NSCLC and are presently recommended as an option for these patients.

One of the most important topics which supposes a challenge for clinicians and is addressed in the ESMO guidelines (3) is how to manage special populations. As expected, there is a recommendation to use most of the referred drugs in patients with a bad performance status since the toxicity is manageable and the ORR is high (27,28). This data comes from EGFR and ALK TKI trials but can be expanded to other patients. Similarly, although limited trial data is available for patients aged ≥75 years, considering the good balance of ORR with scarce toxicity, there is a recommendation to use targeted therapy in these patients as well. Lastly, although the data available is not robust, there is a recommendation to continue with a targeted therapy when the patient has an oligoprogression and proceed with local therapy for that location. These recommendations are valid and strengthen the guidelines, although more robust data should be obtained. One special setting which is not individually assessed in the ESMO oncogene-addicted guidelines (3) is the brain metastases population. Readers are instead referred to the "European Association of Neuro-Oncology (EANO)–ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours" (29) which were published in 2021. With the emergence of newer generation drugs, the CNS penetrance is higher, and the risk of CNS progression has been lowered. The EANO-ESMO brain metastases guidelines offer insightful information regarding the staging and management of different clinical situations, but would require an update, considering the evolution in the targeted therapy field. There is a recommendation to employ upfront targeted therapy for EGFR, ALK and ROS1 patients, but only TKIs are mentioned, and although other mutations are briefly assessed, antibodies or antibody-drug conjugates are not mentioned. Moreover, many controversies such as the monitoring strategies in these patients are not individually assessed. An updated brain metastases guideline with a deeper analysis of the oncogene-addicted metastatic NSCLC setting should be undertaken.

Taken altogether, the oncogene addicted NSCLC ESMO guidelines present updated information regarding the latest breakthrough drugs for each molecular entity, and good algorithms to individually optimize the treatment for each patient, including special populations. However, some controversies should be assessed in future clinical trials. We propose that future trials should assess NGS weakness in specific settings, and special populations which are underrepresented in clinical trials. However, the setting which should be better explored after first line targeted therapy has been optimized is the management of each oncogene beyond progression: trials should assess if a tumour reanalysis should be done to offer directed therapy (such as the EGFR-MET combination therapies beyond osimertinib in patients with MET amplification) or if generic chemotherapy is the better approach.

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