Editorial

Critical points in the management of *EGFR*-mutated non-small cell lung cancer

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The success of epidermal growth factor receptor (*EGFR*)-targeted therapy has opened the era of precision medicine in lung cancer. High response rates and prolonged disease control reported with tyrosine kinase inhibitors (TKIs) than conventional chemotherapy have dramatically changed the clinical prospects of stage IV non-small cell lung cancer (NSCLC) harboring *EGFR*-activating mutations. Their potential role and effectiveness in other setting—adjuvant and neoadjuvant—is currently the new goal to define.

In clinical practice, an accurate molecular diagnosis and staging of malignancy remains crucial, especially for *EGFR*-mutant NSCLC patients, considering the subsequent impact on their treatment management. Firstly, the use of low-dose computed tomography (CT) in early screening has increased number of patients with pulmonary nodules. In case of ground-glass opacity lesions, the location of the tumor through finger touch aloe is more difficult to identify, and secondly, positron emission tomography (PET)-CT easily makes false negatives. There are several methods for nodule localization, including CT-guided markings (blue dye, hookwire, others)—with their logistic problematic, involving pain and pneumothorax—and alternative method of pleural dye marking using radial endobronchial ultrasound and virtual bronchoscopy before performing sublobar pulmonary resection (1).

Another more interesting scenario included some patients having confused radiological picture of multiple bilateral lung lesions without other sites of disease, where synchronous multiple primary lung cancers rather than contralateral metastases are the hardest diagnose to do. Clearly, pathological specimen obtained from both lesions is the best histopathological and molecular examination. Where not feasible for both nodules, and in presence of one of those diagnosed as "oncogenic-addicted" tumor, the use of targeted therapy as "neoadjuvant" choice could be one tool to help differentiate diagnoses of synchronous primary versus metastatic disease, as reported in a case report. A short course of 8 weeks gefitinib as neoadjuvant treatment significantly reduced size of left lung lesion, leading to radical surgical resection, without mortality or major morbidity presented, and confirming the presence of common exon 21 L858R point mutation. The

synchronous contralateral lung lesion—who's not decreased during gefitinib therapy—was subsequently resected also, confirming the absence of *EGFR* sensitizing mutations, and consequently suggesting the initial diagnosis of bilateral synchronous primary lesions (2).

However, the role of neoadjuvant *EGFR*-targeted therapy remains unclear, lacking data from prospective phase III clinical trials. As reported in a pooled analysis, a short-term of median 42 days neoadjuvant *EGFR*-TKI therapy could be a feasible treatment modality for patients with resectable or potentially resectable *EGFR*-mutant NSCLC, with 80% of surgical resection rates and more than 60% of R0 rates, despite not so high downstaging and pathological complete response rates (14% and 0%, respectively), probably due to spatial heterogeneity within and between tumors (3). With aim to search other neoadjuvant targeted therapy regimen, the feasibility of chemotherapy combined with *EGFR*-TKI was suggested by the strong overall response rates (ORRs) and progression-free survival (PFS) reported with gefitinib plus chemotherapy as first-line in two clinical trials (4,5).

Based on impressive results of ADAURA trial, a single arm phase II trial (NCT03433469) is ongoing to evaluate the efficacy of osimertinib as a neoadjuvant therapy for patients with surgically resectable (stage I–IIIA) *EGFR*-mutant NSCLC, and a phase III trial neoADAURA (NCT04351555) is designed to compare neoadjuvant osimertinib, with or without chemotherapy, and chemotherapy alone for resectable NSCLC (NCT04351555). Data from these ongoing trials will prospectively confirm whether and what type of *EGFR*-TKI neoadjuvant treatment can improve survival of *EGFR*-mutated patients.

So, the best timing of *EGFR*-TKI administration for patients with resectable *EGFR*-mutated NSCLC remain the open question, as well as it remains unclear whether preoperative or postoperative administration of *EGFR*-TKI or both is more effective for those patients. Several randomized clinical trials provided strong evidence for adjuvant *EGFR*-TKI therapy, significantly improving disease-free survival (DFS) compared with adjuvant chemotherapy or placebo for patients with postoperative stage II–III NSCLC with *EGFR*-sensitive mutations (6-8).

Focusing on the ADAURA trial, patients with resected stage IB–IIIA lung cancer harboring common *EGFR* mutations were randomized 1:1 to osimertinib or placebo for a maximum of 3 years after radical surgery with or without adjuvant chemotherapy, based on the standard of care. Notably, the question of ADAURA was not to interrogate the role of adjuvant chemotherapy, because the randomization or stratification not allows it. Osimertinib kept its beneficial effect and plays its role in DFS, with or without adjuvant chemotherapy [hazard ratio (HR) DFS: 0.16 and 0.23, respectively]. As expected, the benefits of adding osimertinib to the treatment are larger when risk of relapse was higher, going to HR DFS of 0.12 from stage III to lower HR of 0.5 for stage IB. Data on survival are still not mature, and, notably, all preliminary data are from unplanned interim analysis. Looking at curves, the first impression was that resected *EGFR*-mutated lung cancer patients fast progressed, suggesting the prognostic impact of these mutations. Second, the DFS rate in control arm is around 44% at 2 years, quite low comparing to 60% of LACE trial's meta-analysis (9), probably due to better correct staging and complete resection criteria. The use of next generation sequencing (NGS) for identify early-stage high-risk patients (for example *EGFR*-positive patients with concurrent *TP53* positive mutation) is highly debated, considering high costs and international guidelines. For instance, some molecular profile (*TP53* mutations alone or with co-occurrence of *RB1* mutations) or the lack of plasma clearance of mutant *EGFR* could guide the clinician to identify whose patients will not be longer responders to an *EGFR*-TKIs therapy and, consequently whose patients might be eligible to front-line or early combinatorial approaches. In the future scenario of precision medicine, the organoid is a new *in vitro* personalized pre-clinical model of drug sensitive test, and it should improve knowledge on biological alteration in early setting (10). To date, there is no role in clinical practice for any kind of drug sensitivity test, but it will be the next step of precision cancer medicine.

About stage IV *EGFR*-mutated disease, the use of first-generation (gefitinib and erlotinib) and second-generation (afatinib and dacomitinib) *EGFR*-TKIs as first-line setting significantly improved response rates and PFS compared with standard chemotherapy, as reported in pivotal phase III clinical trials (11-15). More recently, the third-generation *EGFR*-TKI osimertinib showed higher efficacy, prolonging of 8 months median PFS (18.9 versus 10.2 months) and above all, significantly improving overall survival (38.6 versus 31.8 months) (16,17). However, the acquired resistance to *EGFR*-TKIs inevitably occurs, resulting in disease progression. The type and the relative incidence of resistance mechanism was influenced by the specific *EGFR*-TKI used, differing in on-target (*EGFR*-dependent) and off-target (*EGFR*-independent) mechanisms. Patients receiving first- or second-generation *EGFR*-TKIs predominantly

develop *EGFR*-dependent resistance, while it occurs only in 10–15% of patients treated with osimertinib (17).

After osimertinib administration as front-line setting, no evidence of T790M mutation emerged at resistance from plasma genotyping, as expected (17). Interestingly, the tumor escape mechanisms after first-line osimertinib are still not clear, with data by analysis of circulating tumor DNA (ctDNA) from the FLAURA trial. Approximately 30% of resistance to third-generation *EGFR*-TKI is mediated by acquisition of *EGFR* C797S, independently from the presence or not of *EGFR* T790M mutation, and whit different incidence rates according to the treatment setting. Rare tertiary *EGFR* mutation involves exon 18, including the L718Q, identified in 8% of osimertinib-resistant Chinese NSCLC patients (18). The rapid identification of specific resistance mechanisms emerged as crucial for the management of *EGFR*-mutant NSCLC. As described in a Chinese patient progressed after 9 months of icotinib, the identification of T790M mutation by NGS-based ctDNA genetic testing leads to osimertinib administration, but without response. This failure was retrospectively explained by comprehensive NGS of surgical specimen, identifying high rates of *EGFR* L718Q mutations and high copy number of *EGFR* amplification. At this point, the choice of platinum chemotherapy doublets with aim to "clear" the composition of the heterogeneous tumor mass achieved about 5 months of PFS and significant response to osimertinib re-challenge. This effective treatment strategy emphasizes the need to constantly look for the variable mutational status during the history of "*EGFR*-targetable diseases". Blood-based tumor analyses, known as liquid biopsy, are an attractive opportunity, minimally invasive and accessible than tissue biopsy. As reported by Luo (19), the Achilles heel for the detection of *EGFR* mutations on ctDNA is lower sensitivity (67.4%) despite its great specificity (93.5%). Sensitivity depends on the ability to detect ctDNA, considering their variable levels from less than 0.1% to over 10% and depending on several factors (disease burden, treatment response, stage, cellular turnover). From all analytical methods, broad NGS assays are the best alternative—and preferred if available—to detect all potentially actionable mutations by liquid biopsy. Despite high specificity, the sensitivity of plasma NGS-based techniques is lower across different platforms, mainly due to the absence of tumor shedding in 15–20% of patients, their inferior sensitivity to detecting gene amplification compared with fluorescence *in situ* hybridization and their failure to detect histologic transformation (20). On other hands, the plasma NGS evaluation has the potentiality to capture tumor heterogeneity and clonality. Nowadays, plasma NGS analysis produced most of available data on resistance to osimertinib, although comparisons between tissue and plasma samples are limited in this setting. The phase II MERLOSE trial will evaluate the concordance between ctDNA and tissue data at the occurrence of osimertinib resistance. Interestingly, the APPLE trial will clarify the role of dynamic monitoring of ctDNA in clinical practice, with aim to compare the initiation of treatment of *EGFR* T790M based on cfDNA versus radiological evidence of disease progression. Monitoring *EGFR* mutation status through ctDNA, could help identify patients at higher risk for disease relapse and overall worse prognosis after a radical surgery, as currently under investigation in the ADAURA trial. The knowledge of the different alterations associated with *EGFR* resistance and the interplay with the different lines of therapy will help to guide clinical decisions, with anticipation and eventual circumvention of disease progression. Currently, platinum-based chemotherapy is the only approved regimen for patients progressed to osimertinib. Less explored is the role of an osimertinib re-challenge after occurred osimertinib resistance in absence of *EGFR* T790M-mutation. The rationale behind re-challenging with an *EGFR*-TKI after intervening chemotherapy is based on the consideration that chemotherapy may eradicate the clones responsible for clinical resistance to a given *EGFR*-TKI, and regrowth of *EGFR*-TKI-sensitive cells can occur, whit a potential re-sensitization of the tumor to the inhibitor. The tumor molecular profile after intervening chemotherapy has a critical role for propose an *EGFR*-TKI re-challenge. So, mutational profiling for treatment monitoring remains crucial for guide subsequent treatment—including the *EGFR*-TKI re-challenges.

In the absence of a specific resistance mechanism, biomarker-driven approaches are not feasible. The worst impact inevitably falls on those patients progressed after first- or second-generation *EGFR*-TKI, where the T790M mutation is not only a mechanism of resistance, but also needs for osimertinib prescription. Unfortunately, less than 25% of patients eventually received osimertinib after acquiring resistance to the older-generation *EGFR*-TKI, as prospectively reported in the REMEDY trial, highlighting the relevance of this information and the necessary to obtain (21). Delaying use of osimertinib may affect the prognosis of patients. Retrospective trial suggested that the timing of treatment, but not the timing of re-biopsy,

influenced the outcome of osimertinib treatment, with longer PFS in those patients who received osimertinib directly after confirmation of the T790M mutation by re-biopsy than those with intercalated treatment between re-biopsy and osimertinib (22). As reported by Zheng, the refuse of biopsy at first progression, delayed the use of osimertinib, resulting in earlier disease progression. Early biopsy for detecting T790M mutation in progressed NSCLC patients is strongly recommended, with liquid biopsy like blood or pleural effusion (or cerebrospinal fluid based liquid biopsy for brain site disease) as alternative for clinic (23).

For resectable *EGFR*-TKI resistant NSCLC patients, salvage surgery may be an option after multidisciplinary team (MDT) discussion. Despite no confirmed evidence for its efficiency, it could provide sample for gene detection, and in cases with solitary lung metastasis, may be indicated for differentiating metachronous primary lung cancer (24).

Notably, after standard thoracic surgery, postoperative infections constituted 14–16% after lung resection. However, large-scale infection of the thoracic wall resulting from pleural empyema, is extremely rare among post-lobectomy patients. Several newly-developed techniques, including NGS, can help identify the causative microorganism, especially in those case with unknown pathogen and consequent ineffective antibiotic/antifungal treatment (25).

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References

1. Wang G, Lin Y, Zheng L, et al. A new method for accurately localizing and resecting pulmonary nodules. J Thorac Dis 2020;12:4973-84.
2. Du W, Zhao Y, Xuan Y, et al. Different efficacy in the non-small cell lung cancer patient with bilateral synchronous lesions treated with neoadjuvant gefitinib therapy: a case report. J Thorac Dis 2020;12:1582-7.
3. Sun L, Guo YJ, Song J, et al. Neoadjuvant EGFR-TKI Therapy for EGFR-Mutant NSCLC: A Systematic Review and Pooled Analysis of Five Prospective Clinical Trials. Front Oncol 2020;10:586596.
4. Hosomi Y, Morita S, Sugawara S, et al. Gefitinib Alone Versus Gefitinib Plus Chemotherapy for Non-Small-Cell Lung Cancer With Mutated Epidermal Growth Factor Receptor: NEJ009 Study. J Clin Oncol 2020;38:115-23.
5. Noronha V, Patil VM, Joshi A, et al. Gefitinib Versus Gefitinib Plus Pemetrexed and Carboplatin Chemotherapy in EGFR-Mutated Lung Cancer. J Clin Oncol 2020;38:124-36.
6. Zhong WZ, Wang Q, Mao WM, et al. Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II-IIIA (N1-N2) EGFR-mutant NSCLC (ADJUVANT/CTONG1104): a randomised, open-label, phase 3 study. Lancet Oncol 2018;19:139-48.
7. Yue D, Xu S, Wang Q, et al. Erlotinib versus vinorelbine plus cisplatin as adjuvant therapy in Chinese patients with stage IIIA EGFR mutation-positive non-small-cell lung cancer (EVAN): a randomised, open-label, phase 2 trial. Lancet Respir Med 2018;6:863-73.
8. Wu YL, Tsuboi M, He J, et al. Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer. N Engl J

Med 2020;383:1711-23.
9. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008;26:3552-9.
10. Jia Z, Wang Y, Cao L, et al. First-line treatment selection with organoids of an EGFRm + TP53m stage IA1 patient with early metastatic recurrence after radical surgery and follow-up. J Thorac Dis 2020;12:3764-73.
11. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57.
12. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13:239-46.
13. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31:3327-34.
14. Wu YL, Cheng Y, Zhou X, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. Lancet Oncol 2017;18:1454-66.
15. Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol 2014;15:213-22.
16. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:113-25.
17. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. N Engl J Med 2020;382:41-50.
18. Song Y, Jia Z, Wang Y, et al. Potential treatment strategy for the rare osimertinib resistant mutation EGFR L718Q. J Thorac Dis 2020;12:2771-80.
19. Luo J, Shen L, Zheng D. Diagnostic value of circulating free DNA for the detection of EGFR mutation status in NSCLC: a systematic review and meta-analysis. Sci Rep 2014;4:6269.
20. Malapelle U, Mayo de-Las-Casas C, Rocco D, et al. Development of a gene panel for next-generation sequencing of clinically relevant mutations in cell-free DNA from cancer patients. Br J Cancer 2017;116:802-10.
21. Kanai K, Yamamoto N, Nogami N, et al. 141PD A prospective study of molecular testing status in the EGFR mutation positive NSCLC patients with disease progression during EGFR TKI treatment (REMEDY study). J Thorac Oncol 2018;13:S82-3.
22. Tseng JS, Yang TY, Chen KC, et al. Intercalated Treatment Following Rebiopsy Is Associated with a Shorter Progression-Free Survival of Osimertinib Treatment. Cancer Res Treat 2018;50:1164-74.
23. Zheng Y, Zhou M, Arulananda S, et al. Management of non-small cell lung cancer with resistance to epidermal growth factor receptor tyrosine kinase inhibitor: case discussion. J Thorac Dis 2020;12:159-64.
24. Zang J, Horinouchi H, Hanaoka J, et al. The role of salvage surgery in the treatment of a gefitinib-resistant non-small cell lung cancer patient: a case report. J Thorac Dis 2021;13:4554-9.
25. Dai J, Greiffenstein P, Petrella F, et al. Treatment of a lung lobectomy patient with severe post-surgical infection in the anterior thoracic wall by multiple debridement and drainage procedures: a case report. J Thorac Dis 2020;12:7481-7.

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