Editorial

Multidisciplinary and real life data: practical management of *epidermal growth factor receptor* (*EGFR*) mutant non-small cell lung cancer (NSCLC)

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Comment on: 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.

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.

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.

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.

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.

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The identification of key genetic events driving lung tumor growth and metastatic spread led to postulate the concept of oncogene addiction (1). According to this model, cancer cells are highly dependent on the function of a main driver oncogene and its inhibition by a selective targeted agent translates into a marked antitumor activity. This is the case of the epidermal growth factor receptor (*EGFR*) and its activating mutations, mainly represented by deletion in exon 19 or the *L858R* substitution in exon 21, in which EGFR tyrosine kinase inhibitors (TKIs) dramatically changed the natural history of disease (2,3). These drugs, initially tested in metastatic and pretreated disease, then replaced platinum doublet chemotherapy in front-line setting. More recently, a large phase III trial placed osimertinib, a third-generation EGFR TKI, as adjuvant treatment in surgically resected non-small cell lung cancer (NSCLC) harboring classical *EGFR* mutations (4). Indeed, the *EGFR* mutated disease still represents the paradigm of precision medicine, in which a personalized approach is required irrespective of disease stage.

In its "International Multidisciplinary Team (iMDT) corner", the *Journal of Thoracic Disease* published 5 case reports (5-9), focusing on practical management of *EGFR* mutant NSCLC patients in different settings, including early stage, locally advanced and EGFR TKI-resistant disease. Importantly, all cases highlighted the growing role of multidisciplinary team in the decision making process and depict real life management of such conditions.

Du *et al.* (5) published the case of a young woman with bilateral lung synchronous lesions who responded to neoadjuvant gefitinib. In detail, the patient, after receiving diagnosis of lung adenocarcinoma exon *21 L858R EGFR* mutated, was treated with gefitinib for 8 weeks before surgical resection. Gefitinib significantly reduced the left nodule and then, a left lower lobectomy with mediastinal lymphadenectomy was performed, confirming the initial diagnosis of limited stage adenocarcinoma (ypT1cN0M0). The patient continued gefitinib and three months later she underwent a right lower lobe wedge resection with diagnosis of invasive adenocarcinoma (ypT1bN0M0).

Molecular tests showed the *KIF5B-RET* fusion, whereas *EGFR* was wild type. The authors concluded that EGFR-TKI as neoadjuvant therapy is an interesting and evolving treatment option. Currently, in locally advanced disease, no EGFR-TKIs has been approved. In this context, the ongoing phase III NeoADAURA study (NCT04351555) aim to evaluate the efficacy and the safety of neoadjuvant osimertinib as monotherapy or in combination with chemotherapy versus chemotherapy alone in patients with resectable and mutated NSCLC (10). In unresectable stage III NSCLC patients who do not progress after definitive chemoradiation, 1-year maintenance with durvalumab is the standard of care according to PACIFIC trial results (11); however, only 6% of participants had an activating *EGFR* mutations and the impact produced by durvalumab in such population is not defined. Moreover, literature data suggested a limited benefit for immunotherapy in *EGFR* mutation positive NSCLC (12,13). The phase III randomized, placebo-controlled, LAURA (NCT03521154) is evaluating the efficacy and safety of osimertinib following curative chemoradiation in patients with stage III unresectable *EGFR* mutation-positive NSCLC (14).

The case by Du *et al.* (5) is the starting point for a necessary consideration: the multidisciplinary care (MTD) is widely recommended as best practice for lung cancer, above all in the context of an extreme complexity such as the *EGFR* mutated disease. The available data showed that inclusion of MDTs has been associated with positive consequences in multiple aspects of patients' management, including survival benefit. For example, radical local therapy combined with osimertinib continuation should be considered for patients progressed on osimertinib, when the progression occurs without actionable biomarkers emergence and except those who developed extensive progression: in this setting, sharing the case in a multidisciplinary team is recommended (15). Recently, The Spanish Lung Cancer Group promoted a review focused on quality indicators to the best care of lung cancer patients: the authors concluded that time, resources, leadership, recording of activity and administrative support are the main factors for the success of MDTs (16). In order to ensure the continuity of the cases presentation during the COVID-19 pandemic, the successful experience of transition to virtual thoracic tumor board can be also used to overcome the problem of distance barriers presented in many hospital centers (17). To improve survival in patients with *EGFR* mutations, new therapies targeting different resistance mechanisms are being developed: in this context, MDTs also facilitate the access to clinical trials and real world data. The introduction of next-generation sequencing (NGS) in clinical practice has opened new opportunities for precision oncology. However, the systematic interpretation of NGS data, aiming to translate molecular alterations into clinical indications, highlighted some critical issues, and many medical centers have instituted the molecular tumor boards (MTBs) with the aim to discuss all potential therapeutic strategies based on identification of actionable mutations and, if possible, to refer the patients to open clinical trials. In 2020 Koopman and colleagues published an interesting retrospective analysis of 110 NSCLC cases with suggested treatment of complex genomic alterations and corresponding treatment outcomes for targeted therapy. The MTB recommended targeted therapy for 59 of 110 NSCLC cases with complex molecular profiles: 24 within a clinical trial, 15 in accordance with guidelines and 20 off label. The authors concluded that the adherence to the MTB recommendation resulted in a positive clinical response in the majority of patients with metastatic NSCLC (objective response rate of 67%, median PFS of 6.3 months and OS of 10.4 months) (18).

Three cases focused on acquired resistance (6-8). Song and coll. described the clinical course of a man affected by *EGFR* exon 21 mutated advanced NSCLC who received front line icotinib (6). After 9 months, his disease progressed by acquiring the gatekeeper *T790M* mutation, but unfortunately the patient did not respond to osimertinib. To better understand this therapeutic failure, an NGS analysis was performed showing a rare *EGFR* mutation (*L718Q*) associated with an *EGFR* amplification. Notably, *T790M* was not detected. At that time, patient was offered standard platinum doublet chemotherapy, with evidence of short-term response. However, chemotherapy restored the *EGFR* dependence, as a novel molecular test showed the re-appearance of the *T790M* and re-challenge osimertinib was promptly given, delaying progression of approximately five months. Zheng *et al.* (7) reported the story of a woman who had brain and pulmonary relapse 4 years after lobectomy for a stage I *EGFR* mutant adenocarcinoma. This patient received three lines of treatment with different EGFR-TKIs (gefitinib first line, anlotinib second line, and osimertinib third line). Treatment decision was based on the molecular portrait of the disease at time of progression and, similarly to the previous report, her cancer remained in some way addicted to *EGFR* and EGFR inhibition lasted for more than three years. In the context of oncogene addiction, we are used to classify mechanisms of acquired resistance into two main categories. The first one includes target

dependent (on-target) mechanisms, in which the disease continue to be addicted to the original driver, while the second one includes non-target (or off-target) mechanisms, in which alternative gene alterations drive tumor growth (3). Intuitively, outside/beyond clinical trials, continuing EGFR inhibition with a different agent could be a suitable option in the first scenario. In addition, persistence of EGFR dependence seems to translate into a more indolent clinical course, characterized by oligo-progression in pre-existing sites of disease or appearance of small new lesions, thus offering the possibility to combine local ablative strategy (19). In this perspective, Zang *et al.* (8) integrated salvage surgery to systemic treatment (8). Particularly, this patient stayed on gefitinib for more than 2 years and progressed by developing a single lung lesion. After multidisciplinary discussion, patient underwent wedge resection and continued the same therapy for additional 10 months. Interestingly, molecular analysis performed on metastatic lesion tested positive for the acquired *T790M EGFR* mutation and at intracranial failure patient received osimertinib, obtaining a tumor control lasting for 12 months.

Nevertheless, since osimertinib was approved for first-line treatment, the frequency and spectrum of *EGFR*-mutant NSCLC resistance mechanisms has changed. Activation of alternative pathway, such as *MET* amplification, occur at the highest frequency, followed by *RAS-RAF-MAPK* alterations, *RET* fusions, and others as well as histologic transformation such as small cell and neuroendocrine differentiation (3). Currently, no targeted treatment combinations is approved for these resistance mechanisms and second-line therapy mainly consists of platinum-based chemotherapy. To complicate this scenario, a growing amount of studies have reported the role of co-occurring genomic alterations, mainly in tumor suppressor genes, in modulating both the efficacy and pattern of resistance to targeted agents in *EGFR* addicted NSCLC (20).

Jia *et al.* (9), discussed the case of a past smoker man who underwent surgical resection of his lung adenocarcinoma (T1aN0M0) and relapsed after three years. At the time of recurrence, an NGS analysis was performed in primary and secondary lesions with evidence of the classical *EGFR* mutation in exon 21 (*L858R*) coupled with a mutation of the *TP53* gene (*R110L*); interestingly, in the site of recurrence (lymph nodes), an additional mutation in the *CDKN2A* gene (*H83Y*) was reported. In order to identify the optimal front-line treatment, different EGFR-TKIs was tested in patient-derived organoids cultures, with evidence of a better tumor growth inhibition with osimertinib. Based on this findings, patient received the drug, progressing after 9 months. Optimal treatment of *EGFR* and *TP53* mutant NSCLC patients is a matter of debate irrespective of disease stage (21). From a practical point of view, presence of mutated *TP53* does not impact on the current treatment algorithm and based on current evidences, patients diagnosed with pathological stage IA do not require any adjuvant treatment even if *EGFR* and *TP53* mutations co-exist. Similarly, in metastatic setting, the same molecular status does not alter therapeutic choice and EGFR-TKI such as osimertinib remains the preferred front-line option. However, as *TP53* mutation negatively affect prognosis, patients harboring dual *EGFR/TP53* mutations deserve a more intensive follow-up or tumor assessment according to the stage of disease.

In conclusion, the *EGFR* mutated disease, the paradigm of precision medicine, requires a personalized treatment regardless of the stage; a multidisciplinary team, a board of certified professionals from different specialization settings, plays a fundamental role in the make decisions about the best clinical pathway of each NSCLC *EGFR* mutated patient.

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