Adjuvant epidermal growth factor receptor tyrosine kinase inhibitors: are we actually ready?

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Comment on: Liang W, Cai K, Chen C, *et al.* Society for Translational Medicine consensus on postoperative management of EGFR-mutant lung cancer (2019 edition). Transl Lung Cancer Res 2019;8:1163-73.

Despite tremendous improvement in its clinical management, lung cancer is still the leading cause of cancer related death worldwide (1). It is usually diagnosed at advanced stage and only a minority of patients presents an early and potentially curable disease. However, with positive results of low-dose computed tomography (CT) screening in the high-risk population and with the improvement of diagnostic techniques, early diagnoses can hopefully increase in the near future (2). Therefore, defining the best curative treatment approach for this disease setting is of crucial relevance.

Liang and colleagues focused their attention on the subset of epidermal growth factor receptor (EGFR) positive patients cured with surgical resection and drew up a consensus on postoperative adjuvant targeted therapy management (3). As well known, EGFR mutations occur in the 10–15% of Caucasian patients and up to the 40% of Asian ones (4). EGFR testing is recommended in all patients with advanced non-squamous non-small cell lung cancer (NSCLC), but also in patients with pure squamous histology, especially if young and/or non-smokers. EGFR tyrosine kinase inhibitors (TKIs) represent the recommended first-line treatment in patients with advanced NSCLC bearing classic mutations (i.e., exon 19 in-frame deletions and exon 21-point mutations) (5). Several randomized trials have demonstrated, indeed, the superiority of oral treatment with EGFR TKIs compared to standard platinum-based chemotherapy for this subgroup of patients (4). In the consensus document, authors stated that also NSCLC patients who have undergone a radical resection need EGFR mutation profiling and that EGFR-TKIs can replace chemotherapy in patients candidate to adjuvant therapy after surgery, above all in patients who would probably not tolerate chemotherapy treatment, defining "at least 2 years" as the optimal treatment duration. In absence of direct comparisons, the reported adjuvant treatments are heterogeneous: chemotherapy, EGFR-TKI, chemotherapy plus EGFR-TKI (3).

Actually, several studies have evaluated the possibility of biological drugs as adjuvant therapy and the results are quite conflicting. What is clear is that, even in early stages, adjuvant treatment with EGFR TKIs could be effective only in those patients whose tumor expresses an EGFR activating mutation. Two are the phase III studies showing that erlotinib for 2 years or gefitinib for 1 year did not improve disease-free survival (DFS) [erlotinib: hazard ratio (HR) 0.90, 95% confidence interval (CI): 0.74–1.10, P=0.32; gefitinib: HR 1.28; 95% CI: 0.92–1.76; P=0.14] or overall survival (OS) (erlotinib: HR 1.13, 95% CI: 0.88–1.44, P=0.33; gefitinib: HR 1.24; 95% CI: 0.90–1.71; P=0.18) compared to placebo in radically resected NSCLC patients (stage IB–IIIA) and not selected

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for EGFR mutations (6,7). However, also in a molecular selected population, advantages seem limited only to DFS, which is a clear surrogate endpoint of efficacy especially in the adjuvant setting, and OS data remain immature. In two randomized trials, one phase II (the EVAN trial) and one phase III (the ADJUVANT study) conducted in Asian patients with EGFR-positive radically operated stage II–III NSCLC, a benefit in DFS was observed with erlotinib for 2 years (percentage of free disease patients: 81.4%, 95% CI: 69.6–93.1% versus 44.6%, 95% CI: 26.9–62.4%; P=0.0007) and with gefitinib for 2 years (28.7 versus 18.0 months, HR 0.60; 95% CI, 0.42–0.87, P=0.005), when compared to the adjuvant chemotherapy with cisplatin-vinorelbine (8,9). In both studies, the OS advantage could not be demonstrated. A phase II study conducted in patients with surgical-treated high-risk IIIA stage EGFR+ NSCLC reported an improvement in DFS (HR 0.37; 95% CI: 0.16–0.85; P=0.014), in the absence of OS benefit, with gefitinib for 6 months versus observation alone after adjuvant chemotherapy (10). Another phase II study, performed in resected patients with NSCLC (stage IB–IIIA) and activating EGFR mutation, did not report a significant increase in DFS with icotinib for 4–8 months versus the only observation after platinum-based adjuvant chemotherapy (11). Furthermore, Pennell et al. published a single-arm phase II trial of adjuvant erlotinib after surgery and consolidative chemo/radiotherapy in stage IA–IIIA NSCLC patients, reporting a 2-year DFS of 88% (no median DFS or OS reported) (12). A recent metanalysis confirmed that adjuvant TKIs reduce the risk of recurrence in EGFR mutant NSCLC patients without benefit in OS (13). Trials with OS as primary endpoint such as the ALCHEMIST-EGFR (NCT02193282) study, in which EGFR+ NSCLC patients are randomized to 2-year erlotinib or placebo after adjuvant chemotherapy, are still ongoing (14). The absence of OS improvement is a critical aspect in evaluating the benefit of a treatment with adjuvant intent. Pignon et al. in 2008 published the Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis that included individual data from 5 phase III studies, which randomized patients with stage I–IIIA NSCLC radically operated to receive cisplatin-based chemotherapy versus observation only (15). This meta-analysis reports a HR of 0.89 (95% CI: 0.82–0.96, P=0.005), which corresponds to an absolute 5-year survival benefit of 5.4%, in favor of adjuvant chemotherapy. Thus, in the absence of improved OS data for adjuvant EGFR TKIs compared to chemotherapy, at present, it seems reasonable to do not recommend routine molecular testing in the

adjuvant setting, unless functional to the inclusion in clinical trials. Targeted therapies, with or without chemotherapy, cannot be recommended in the adjuvant treatment of NSCLC outside of experimental protocols (5).

Another element of concern for strong positive recommendations for adjuvant TKIs is related to the heterogeneity of trials, design, selected population and duration of treatment. The definition of a timeframe of 2-year treatment after surgical resection, as reported by authors, seems quite empiric. Thus, even if targeted therapies are usually more tolerated than chemotherapy, is important to underline that can be characterized by adverse events such as skin, gastrointestinal toxicities or fatigue for the entire duration of treatment (2 years versus 3 months of chemotherapy), potentially requiring dose reduction, treatment interruption and impairing patient compliance: actually in clinical trials up to one-third of patients did not complete the two years pre-planned treatment. Also, in the case of more tolerable treatment, as 3rd generation TKI, the risk of relevant toxicities exists (e.g., lung interstitial disease), although low.

In the consensus document, authors propose to follow-up EGFR+ patients with annual brain magnetic resonance imaging (MRI) and bone scan, additionally to conventional CT, because of the higher risk of recurrence for this patients' subset (3). The European Society for Medical Oncology (ESMO) recommend the brain staging with MRI for all patients in stage III (16). For the other disease stages international recommendations are quite heterogeneous. The National Comprehensive Cancer Network (NCCN) recommends brain MRI in all patients with early or locally advanced NSCLC, excluding stage IA (5); the National Institute for Health and Care Excellence (NICE) recommends brain CT in stage II and brain MRI for people with stage III NSCLC who are having a treatment with curative intent (17); on the other hand the American College of Chest Physicians (ACCP) limits the indication to stage III and IV and in case of symptomatic patients (18). As well-known, NSCLC patients with EGFR mutations appear to have a higher incidence (50–60%) of brain metastasis (19), therefore appears reasonable to implement brain-imaging follow up for their early detection. However, considering the absence of improvements in OS, solid prospective data are needed before recommending an intensive follow up strategy. Bone scintigraphy is considered optional in the imaging work-up for diagnosis and staging by ESMO guidelines (16) and current data are still weak to implement its execution in case

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of asymptomatic patients.

Which should be the hypothetical best TKI to be used in the adjuvant setting is another element of uncertainty. Liang *et al.* in the consensus emphasize the role of osimertinib as the best option; nevertheless, available data of 3rd generation TKI usage in EGFR+ patients are, currently, limited to stage IV patients with EGFR mutations (exon 19 deletion of L858R allele), for whom is preferable in respect to 1st generation TKI, as elucidated in the FLAURA trial. Updated OS data reported a gain of 6.8 months of survival when osimertinib is administered upfront (HR for death, 0.80; 95.05% CI: 0.64–1.00; P=0.046) (20). For these reasons is plausible to consider its role at relapse for EGFR+ patients initially treated with surgery, but no evidence exists preferring the administration of osimertinib, rather than other EGFR TKI, in the adjuvant setting. The results of ongoing trial ADAURA (NCT02511106), expected in the third quarter of 2021, will give us relevant insights about the role of adjuvant osimertinib in terms of DFS—as primary endpoint—OS and health-related quality of life, as secondary endpoints (21).

Furthermore, unfortunately, we still ignore the precise biological mechanism at the basis of adjuvant EGFR targeting. We cannot exclude flare reactions with TKIs suspension, potentially caused by the reactivation of the microscopic disease that targeted therapies are unable to completely eradicate (22). And, more clinically relevant, we have no tools to forecast the biological evolution of EGFR+ neoplastic cells under drug pressure. If the rate of T790M emergence during adjuvant treatment with 1st generation TKI seems low (12), we do not have any ideas whether treatment with more potent TKI might spur the development of more aggressive clones, difficult to be treated after; recent data shed light on relevant alternative mechanisms of resistance, such as histotype transition and off-target alterations that should be taken into account when an adjuvant treatment is selected (23).

Finally, the position paper on the postoperative management of EGFR-mutated NSCLC patients highlights a relevant aspect in thoracic oncology, adjuvant targeted treatments for EGFR+ patients, which will acquire even more significance in the next future of improved screening and early detection. However, the only availability of PFS data and the need of larger studies in not-Asiatic population put emphasis on the importance of having more solid and numerous data before recommending the use of EGFR-TKIs in the adjuvant setting of our daily clinical practice.

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