Editorial Commentary

SELECTing adjuvant treatment in early stage epidermal growth factor receptor (EGFR)-positive non-small cell lung cancer

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In the last years, oncogene-driven lung cancer patients have witnessed an overwhelming progress in treatment options, especially in advanced setting of the disease (1). On the other hand, how to improve overall survival (OS) in epidermal growth factor receptor (EGFR)-positive (EGFR+) or ALK-rearranged early-stage lung cancer patients is unclear and whether tyrosine kinase inhibitors (TKI) play a role in the adjuvant setting is still matter of debate (2). Therefore, in this stage of non-small cell lung cancer (NSCLC), molecular analyses are not routinely performed. Different trials have been conducted involving EGFR+ early stage (I–IIIA) NSCLC patients, with the intent to demonstrate an improvement in patients' disease-free survival (DFS) and OS. The two first phase III trials in this setting, NCIC CTG BR19 and RADIANT, conducted before the validation of *EGFR* mutations' predictive role and enrolling, thus, unselected patients (or enriched for *EGFR* gene amplification and protein expression), failed to demonstrate any relevant role of gefitinib and erlotinib, respectively (3,4). Since then, the classical chemotherapeutic approach (cisplatin-based) remained the gold standard treatment also for these patients.

Later on, two other trials, enrolling only Chinese patients, have been conducted testing an investigational approach versus cisplatin-vinorelbine control arm. The EVAN study, a phase II trial evaluating a small number of only IIIA stage patients, reported an increase in 3-year DFS of 54% for erlotinib-treated patients versus 20%. However, these results couldn't be largely applied taking into account that IIIA stage is a high-risk population, Asian lung cancer patients retain particular clinic-pathological features, and the narrow number of participants weakened the results (5). The ADJUVANT/CTONG1104 phase III trial recently reported an improved median DFS of 28.7 months for gefitinib versus 18 months for chemotherapy. Even though these results shed light on the potential role of TKI as curative options for EGFR+ patients, DFS curves tend to converge at 36 months, denoting only a transient clinical benefit (6). Mature OS data will help the interpretation of study's results, strengthening the role of adjuvant TKI, particularly for patients that will receive EGFR inhibitors again at relapse. OS data from ongoing ALCHEMIST and ADAURA clinical studies, evaluating, the first, erlotinib for 2 years versus clinical observation and, the latter, osimertinib versus placebo for 3 years in complete resected patients, will inform properly in terms of long-term survival benefit (7,8).

In this scenario, Pennell *et al.* recently published results of the SELECT trial (9). In the phase II single-arm clinical study patients, surgically-treated for a stage IA–IIIA *EGFR*-mutated NSCLC, received, after chemotherapy and radiotherapy, erlotinib at 150 mg/die for 2 years. With a total number of 100 patients, the primary end-point of 2-year DFS has been met, reporting an 88% rate

compared to historical control of 76% (9). Median DFS and OS have not been reached and the estimated 5-year DFS and OS were 56% and 86%, respectively. Although around 70% of the patients concluded the entire course of 2 years treatment with erlotinib, a large number of patients (40%) required a first, and in a less extent a second dose reduction, due to clinically known erlotinib toxicities (i.e., rash, diarrhea, fatigue). Almost the entire number of patients experiencing a disease recurrence had stopped erlotinib, with a free disease interval of 25 months. These patients maintained *EGFR* canonical mutation at relapse, when a re-biopsy approach was feasible. The 65% of relapsed patients obtained a clinical benefit when erlotinib was re-administered for a medium period of 13 months, highlighting the feasibility of TKI re-treatment after adjuvant therapy.

Despite encouraging results of the SELECT study, some critical issues emerge. One major point concerns treatment-related toxicities, requiring multiple dose reductions (40% of patients), in absence of solid randomized efficacy data of lower doses of erlotinib or therapy discontinuation (11% of the studied population). The cumulative toxicity of such a long treatment in a particular setting, as the adjuvant one, jeopardizes patients' compliance and the achievement of effective dose intensity. Symptoms and quality of life monitoring, actually not investigated in the SELECT trial, acquires crucial value in this setting, in which financial costs and duration of adverse events during the whole timeframe of treatment (i.e., 24 months) are hardly comparable to those of the shorter standard chemotherapy strategy (3 months) (10). Moreover, the SELECT trial is a phase II single arm study without untreated control data and the population involved is heterogeneous (patients with resected stage IA to IIIA), including subjects at higher risk of disease recurrence (i.e., N1–N2) and patients for whom adjuvant therapy is not recommended in clinical practice (i.e., stage I) (11). Undoubtedly, more selected data are needed to better understand which patients actually would benefit the most from adjuvant targeted therapy. Moreover, lacking of OS data, that play a crucial role in the perspective of a treatment algorithm aimed at eliminating the microscopic residual disease, undermines study's relevance. The median OS, in fact, is one of the secondary objectives and has not been reached yet. On the other hand, the primary endpoint—DFS—representing a surrogate measure of efficacy, is not affected by following treatment choices or by eventual crossover and seems to have, however, a quite right association with OS results in the adjuvant setting (12).

How long the treatment has to be protracted is another matter of debate. In the SELECT trial few recurrences (4%) occurred during targeted therapy, whereas a major rate was found in patients that interrupted it precociously. Thirty-six of the 40 patients with recurrent cancer had completed erlotinib treatment, and most of them were sensitive to the re-challenge with the TKI. These data seem to support the feasibility of a standard sequential treatment approach at time of relapse (13). The biological mechanism underpinning this disease behavior is not perfectly understood; it seems that cancer proliferation, suppressed by the TKI, arises again when the treatment is suspended. The most supported hypothesis is that targeted therapies are able to inhibit cancer growth during their administration but are inefficient to eradicate the microscopic disease. In this scenario, the evaluation of the minimal residual disease could guide the identification of patients who really benefit of targeted therapy in the adjuvant setting and patients who would receive more advantages from a targeted treatment at relapse (14). Moreover, it could help to define how long should be extended the adjuvant treatment in order to maximize the long-term impact. Lastly, understanding the right balance between different treatments' impacts on the disease—chemotherapy and radiotherapy, with their eradicative and immunogenic roles, and TKIs with their growth-suppressing properties—could help to find a strategy to improve clinical outcome and identify early mechanisms of resistance.

It is noteworthy that osimertinib turned out to be widely superior to first generation TKIs among EGFR+ patients in the advanced setting, making SELECT results potentially outdated (15). Relevant information about the type of adjuvant TKI and the correct duration (in terms of years) will derive from ongoing trials, such as ALCHEMIST and ADAURA. Furthermore, a change in this direction would revolutionize the diagnostic approach to NSCLC patients, expanding the molecular characterization to the early stage disease, currently not recommended in clinical practice (11).

Nevertheless, several positive considerations are due. The 2-year DFS of 88% is an important result that overtakes historical data in this setting (16). The combination of chemotherapy, radiotherapy if indicated, and TKIs and their potential synergistic effect could represent a potential future therapeutic alternative in postoperative management. TKI-restricted strategy, however, represents a

promising option, particularly for patients unfit for standard chemotherapeutic regimen, expanding, in this way, the population eligible for adjuvant therapy. In the coming years, due to increasing data supporting the utilization of screening procedures, the percentage of early stage NSCLC patients could rise and new personalized and efficient strategies are needed. More solid data on the potential predictive role of *EGFR* mutation in the precocious setting represent a crucial prerequisite for further developments in this direction. Even if deeper analyses are essential, these studies, such as the SELECT trial, provide new precious information in the adjuvant setting, paving the way toward a more effective postoperative treatment strategy for every single patient affected by NSCLC. The availability of more potent and well-tolerated inhibitors and the opportunity to molecularly sub-stratify even oncogene-addicted patients (e.g., high-risk with EGFR+/TP53+ lung cancers) could represent a relevant chance to address the best treatment to the right patient, not only delaying disease recurrence but also altering its natural history.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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