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EDITORIAL

# Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors As Adjuvant Therapy in Completely Resected Non–Small-Cell Lung Cancer

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More than 10 years ago, the role of adjuvant chemotherapy in early stage non–small-cell lung cancer (NSCLC) was definitively established for stage II and III disease,[1-6] whereas subset analyses suggested a benefit in patients with large IB tumors.[7] Currently, any attempt to improve results of cisplatin-based chemotherapy by means of pharmacogenomics approaches has failed, and results of additional studies are eagerly awaited.[8-10]

In the article that accompanies this editorial, Kelly et al[11] report the mature data of the RADIANT trial. It is noteworthy that only 51% of subjects in the erlotinib arm and 57% in the placebo arm received adjuvant chemotherapy. This situation was quite likely related to the relevant proportion of enrolled patients with stage IB disease for which the value of adjuvant chemotherapy is still debatable in the absence of prospective data for large IB tumors.

No statistically significant difference was shown in disease-free survival (DFS), which was the primary endpoint of the study, whereas a trend suggestive of improved outcomes with erlotinib was demonstrated in the subgroup of patients (16.5%) with an epidermal growth factor receptor (EGFR) –sensitizing mutation. EGFR mutation status was not among the stratification factors. In addition, an imbalance was observed in some patients' characteristics, such as performance status, in the comparison of the control arm in the EGFR mutant subgroup with the intention-to-treat population. Therefore, no definitive conclusion can be drawn.

The choice of DFS as the primary endpoint deserves comment. Although the correlation between progression-free survival (PFS) and overall survival (OS) has been demonstrated for advanced NSCLC, in the recognition of PFS as an acceptable surrogate endpoint for OS,[12] the same information is not available for the early-disease setting. For adjuvant studies, OS remains the preferred primary endpoint, and DFS may be considered only if a futility-based interim analysis is planned to drive continuation of the trial or not.

The selection of patients was based on fluorescence in situ hybridization and EGFR immunohistochemistry, which are less sensitive tests for biomarkers than mutation testing. In the IPASS (Iressa Pan-Asia Study) trial, it was shown that the PFS benefit in patients with EGFR high copy number was entirely driven by the mutation-positive subgroup. In the era of personalized therapy, it is challenging to appropriately design a clinical trial that will preserve overtime the validity of the study hypothesis, especially in the adjuvant setting, where prolonged follow-up is needed. On another note, the recent revision of the lung cancer staging system with significant changes in stage allocation, and with further changes anticipated, represents an additional layer of complexity in the data interpretation.

Given the existing evidence, one reasonable clinical question could be, "Should all patients with resected adenocarcinoma be tested for EGFR mutation?" The College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology expert consensus opinion,[13] endorsed by the American Society of Clinical Oncology,[14] encourages EGFR and anaplastic lymphoma kinase testing at diagnosis for all patients with early-stage adenocarcinoma. The benefit of this approach is that it enables rapid initiation of treatment in patients who experience a recurrence because molecular information is immediately available. This also favors their enrollment onto clinical trials, and a definitive trial to evaluate erlotinib and crizotinib in molecularly selected patients is planned in the United States (ALCHEMIST trial; NCT02201992, NCT02193282). Other randomized trials are ongoing in China (ADJUVANT; CTONG 1104) and Japan (IMPACT; WJOG6401L) in patients with completely resected IIIA-II/N2-N1 NSCLC with EGFR mutation who are randomly assigned to receive gefitinib versus a combination of vinorelbine plus platinum as adjuvant treatment. The disadvantage is the extra cost incurred by molecular testing of patients with early-stage disease who do not experience a relapse, as well as the possibility that the molecular profile could change at the time of relapse.

At the present time, the role of targeted agents as adjuvant therapies remains largely unknown. Patients with sensitizing mutations might derive more benefit from adjuvant chemotherapy,[15] and chemotherapy may reduce the frequency of EGFR sensitizing mutations, suggesting a preferred response of EGFR mutated subclones to chemotherapy.[16] In a Japanese phase III study, investigators administered adjuvant gefitinib or placebo for 2 years to patients with completely resected NSCLC in stage IB to IIIA for 4 to 6 weeks after surgery until recurrence or withdrawal. Recruitment was stopped after 38 patients were randomly assigned; this was because of interstitial lung disease.[17] In another phase III study,[18] researchers compared gefitinib with placebo after cisplatin-based chemotherapy. This study was prematurely closed as consequence of the negative

outcomes of other phase III studies,[19,20] but no advantage was detected in few enrolled patients with EGFR mutant tumors.[21]

The onset of acquired resistant mutations could be a concern because they have been frequently observed in EGFR-mutant, advanced NSCLC treated with EGFR tyrosine kinase inhibitors (TKIs). In a retrospective study, T790 resistant mutations were more common in cancers that recurred while patients were receiving an adjuvant EGFR TKI than in cancers that recurred after the EGFR TKI was stopped (67% *v* 0%). Patients who had a recurrence after the EGFR TKI was stopped were treated again, with significant clinical benefit. In a large, prospective phase II study, patients with completely resected EGFR mutant tumors received erlotinib for 2 years after completion of adjuvant chemotherapy. In this trial, 63% of patients with recurrence underwent repeat biopsy; in only one case was a T790M resistance mutation detected, and the recurrent cases were still sensitive to EGFR TKIs.

The optimal duration of adjuvant therapy with EGFR TKIs remains a matter of debate. So far, in all adjuvant studies to test EGFR TKIs, the planned duration of therapy has been 2 years, but no statement can be made in this context. Despite the favorable toxicity profile of EGFR TKIs, no robust data are available for long-time exposure, and it is unknown how the duration of therapy might correlate with efficacy in this setting. Data from long-term survivors with advanced NSCLC treated with EGFR TKIs indicate a good quality of life and safety, even after $>3$ years of treatment.[22] In the RADIANT study, the median duration of treatment was only 11.9 months for erlotinib-treated patients, and the rate of grade $\geq 3$ rash, diarrhea, and dosage reductions and interruptions were significantly higher in the experimental arm. Overall, the safety profile did not differ among EGFR-mutant NSCLCs. These findings should be carefully considered in the plans for future studies involving patients who might potentially be cured with surgery plus adjuvant chemotherapy.

In summary, this study represents an additional piece of research that aims to define the best approach in patients with completely resected NSCLC and to define the role of EGFR TKIs in this setting. The authors should be praised for their foresight in designing this type of trial nearly 10 years ago. The efficacy of adjuvant EGFR TKIs in patients with mutations must be further investigated in well-designed randomized trials, such as the already-recruiting ALCHEMIST study or the randomized phase III clinical trials in EGFR mutation–positive patients initiated in China (ADJUVANT; CTONG 1104) and Japan (IMPACT; WJOG6401L).

## AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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