What We Have Learned From Adjuvant Therapy for Resected EGFR-Mutant Non–Small-Cell Lung Cancer

Si-Yang Liu, MD; Jia-Tao Zhang, MD; and Yi-Long Wu, MD

Since 2017, when the ADJUVANT-CTONG1104 (Gefitinib Versus Vinorelbine/Platinum as Adjuvant Treatment in Stage II-IIIA(N1-N2) NSCLC With EGFR Mutation) trial first reported the positive disease-free survival (DFS) for adjuvant treatment with gefitinib compared with chemotherapy in resected EGFR-mutant non–small-cell lung cancer (NSCLC), several trials such as the EVAN (Erlotinib in Post Radical Operation NSCLC Patients With EGFR Mutation), EVIDENCE (Icotinib as Adjuvant Therapy Compared With Standard Chemotherapy in Stage II-IIIA NSCLC With EGFR-mutation), and SELECT (Surgery for Early Lung Cancer With Post- operative Erlotinib) trials have presented similar DFS results with various first-generation tyrosine kinase inhibitors (TKIs). In the article accompanying this editorial, Tada et al reported the DFS and overall survival (OS) results from the similarly designed IMPACT trial conducted in Japan. The IMPACT study was an open-label, randomized phase III trial that evaluated the efficacy of adjuvant gefitinib versus cisplatin plus vinorelbine (cis/vin) chemotherapy in resectable stage II-III NSCLC patients with EGFR exon 19 deletions or exon 21 L858R mutations. After a median follow-up of 70 months, the median PFS was 35.9 months in the gefitinib group and 25.1 months in the cis/vin group. The 5-year OS rates were 78.0% and 74.6%, respectively. No significant differences in DFS or OS were observed between the adjuvant gefitinib and cis/vin arms.

The IMPACT study has been the only negative randomized trial in which the targeted population was based on selecting the EGFR mutation. Some interesting phenomena have been noted from these phase III trials, including the IMPACT, CTONG1104, and EVIDENCE trials. First, all three trials were designed as head-to-head comparisons between epidermal growth factor receptor–tyrosine kinase inhibitor (EGFR-TKI) and doublet chemotherapy, which is different from the ADAURA (Osimertinib Versus Placebo in Resected EGFR-Mutated NSCLC With or Without Adjuvant Chemotherapy) and ALCHEMIST (Erlotinib in Treating Patients With Stage IB-IIIA NSCLC Completely Removed by Surgery) trials. This design makes it possible that, if similar DFS and OS are observed in both groups, adjuvant EGFR-TKIs might be an alternative in selected patients, although it was not a noninferiority design.

Second, the first-generation EGFR-TKI in the adjuvant setting had a similar trend on the Kaplan-Meier (KM) curves for DFS. The advantage of adjuvant targeted therapy persisted during the medication period, and the survival benefit lasted almost 2 years after the treatment cessation. Then, KM curves began to converge, indicating that the adjuvant first-generation TKI delayed disease recurrence during drug exposure and that the medication duration might be correlated with the curative effect. Third, brain metastases were the predominant failure pattern and remain an obstacle for the adjuvant first-generation EGFR-TKI treatment.

Another important issue is the role of adjuvant chemotherapy in resected EGFR-mutant NSCLC in the precision medicine era. The ADAURA study, which was the first international phase III randomized placebo-controlled clinical trial, evaluated the third-generation TKI osimertinib in a 3-year adjuvant setting where adjuvant chemotherapy was not mandated. In the primary efficacy population (stage II-IIIA NSCLC), the median DFS for osimertinib was not reached yet versus 19.6 months for the placebo arm, with a hazard ratio of 0.17 (95% CI, 0.12 to 0.23; \( P < .0001 \)). In exploratory analyses to evaluate the recipients of adjuvant chemotherapy, a clinically meaningful DFS benefit with adjuvant osimertinib was observed in patients across all stages with and without adjuvant chemotherapy (DFS hazard ratios of 0.16 and 0.23, respectively). The US Food and Drug Administration (FDA) considered that the adjuvant chemotherapy recipients did not reveal a substantial difference in the efficacy or safety results.

On the basis of these data, the FDA granted osimertinib as adjuvant targeted therapy for EGFR-mutated NSCLCs regardless of adjuvant chemotherapy on December 18, 2020. Taken together, adjuvant chemotherapy might not be necessary for EGFR-mutant patients in the adjuvant setting.

The IMPACT and CTONG1104 trials were two representative phase III trials that reported OS results with more than a 5-year follow-up. Although negative OS data were reported, the 5-year OS rate of 78.0% reported by the IMPACT, and 53.2% reported by the CTONG1104 trial were the best in this era when only adjuvant chemotherapy without EGFR-TKI was available in each...
THE TAKEAWAY

In the article that accompanies this editorial (Tada et al5), adjuvant gefitinib presented no significant survival benefits compared with adjuvant chemotherapy for postoperative *EGFR*-mutant non–small-cell lung cancer. This negative evidence for adjuvant first-generation tyrosine kinase inhibitor indicates the importance of drug choice and duration of therapy in this setting.

Moreover, after the official approval of adjuvant osimertinib, what is the role of first-generation *EGFR*-TKIs in the adjuvant setting? (Fig 1). The following questions need to be answered. First, whether prolonging the duration of the adjuvant first-generation TKI would bring significant survival benefits needs further investigation. Similar to the CTONG1104, EVIDENCE, and IMPACT trials, the KM curves showed an interesting spindle type. The curves gradually became close to each other after the drug cessation, indicating that prolonging the drug exposure time might delay the recurrence time and even prolong OS. Second, in the subsequent treatment analysis after disease relapse, the recurrent patients who had the opportunity to rechallenge TKIs achieved improved OS. Thus, elucidating the resistance mechanisms after adjuvant TKI administration is essential to precisely select subsequent treatments. It is worthy of further exploration whether the sequential treatment model of the adjuvant first-generation TKI followed by osimertinib after relapse would be a better treatment opinion. Moreover, when osimertinib is not

![FIG 1. Role of first-generation EGFR-TKI. DFS, disease-free survival; EGFR-TKI, epidermal growth factor receptor–tyrosine kinase inhibitor; HR, hazard ratio; OS, overall survival; TKI, tyrosine kinase inhibitor.](image-url)
accessible in certain districts, the first-generation EGFR-TKI would be a great option as well.

Adjuvant treatment decisions should focus on exploring the pragmatic treatment paradigm. A precisely beneficial population and how to set up the length of treatment should be considered seriously to keep the promise of an augmented cure for resectable NSCLC.

The intratumoral heterogeneity of the EGFR mutation alone may not be sufficient to identify the advantaged group. Identifying clonal targetable comutations from baseline specimens and during cancer evolution might help clinicians select the resistant subclones that might benefit from chemotherapy, Wu et al reported a comprehensive genomic result from the CTONG1104 trial that EGFR-mutated patients with RB1 alterations might benefit from adjuvant chemotherapy instead of TKI.

Furthermore, in the pursuit of curing operable EGFR-mutant NSCLC, the existing findings centered around the understanding that adjuvant EGFR-TKIs mainly suppress tumor growth during treatment other than eliminating the microscopic disease completely. Hence, dynamic minimal residual disease (MRD) detection through circulating tumor DNA capture might be a promising way to define beneficial populations, the best time to initiate the adjuvant TKI, and optimal duration. Serial postoperative MRD positivity could predict an unfavorable DFS, precedence radiographic progression, and help clinicians tailor adjuvant treatment to treat patients with a high risk of recurrence and award MRD-negative patients a drug holiday. Herein integrating MRD detection into a prospective study design could improve the clinical utility of this approach, eg, the MERMAID trial (A Phase III Study of Adjuvant Durvalumab plus Chemotherapy in Resected NSCLC patients with MRD+ post-surgery).

The IMPACT trial might not be able to impact the clinical practice in the adjuvant setting for EGFR-mutant NSCLC right now. Instead, this negative evidence reminds us to carefully consider the role of the first-generation TKI in the adjuvant setting, such as the best sequential treatment strategy of the first-generation and third-generation TKIs, the medical duration, the resistant mechanisms, and subsequent treatments after disease relapse. Molecular subtyping and MRD detection might be the potential ways to break through the current dilemma and maximize the survival benefits.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Yi-Long Wu
Honoraria: AstraZeneca, Lilly, Roche, Pfizer, Boehringer Ingelheim, MSD Oncology, Bristol Myers Squibb, China, Hengrui Pharmaceutical
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