The discovery of activating mutations in the epidermal growth factor receptor (EGFR) gene has become a “game-changer” in the treatment of non-small cell lung cancer (NSCLC) (1,2). Several randomized controlled studies (RCTs) showed that tyrosine kinase inhibitors (TKIs) of EGFR provided a superior survival benefit over platinum-based chemotherapy for advanced NSCLC harboring activating EGFR mutations such as deletions in the exon 19 (Del19) and a point mutation in the exon 21 (L858R). Today, systemic treatment with an EGFR-TKI has become a standard treatment of care for advanced EGFR-mutated NSCLC (3). In addition, routine EGFR-testing is recommended in daily clinical practice before starting first-line systemic treatment for patients with advanced non-squamous NSCLC, as activating EGFR-mutations are frequently found in non-squamous NSCLC.

For patients with early-stage NSCLC, surgery is the optimal treatment for the cure. After complete resection, adjuvant platinum-doublet chemotherapy such as vinorelbine plus cisplatin (VP) is recommended for pathologic stage (p-stage) II-III patients based on accumulating clinical evidence shown in several RCTs. However, postoperative adjuvant platinum-doublet chemotherapy has provided only a modest survival benefit of 5–10% improvement in 5-year overall survival rate (4-6). Here, the most important clinical question is whether adjuvant treatment with an EGFR-TKI may provide a superior clinical benefit over that with platinum-doublet chemotherapy for completely resected EGFR-mutated NSCLC. In other words, even for EGFR-mutated patients, platinum-doublet chemotherapy remains the recommended regimen in postoperative adjuvant setting, or systemic treatment with an EGFR-TKI may replace it? To address the question, several RCTs of adjuvant EGFR-TKI treatment have been conducted (Table 1). In an early study (BR.19), all patients with completely resected p-stage IB-IIIA NSCLC were eligible regardless of EGFR-status, and a total of 503 patients were randomly assigned to receive a first-generation EGFR-TKI (gefitinib) or placebo for 2 years (7). Exploratory analyses of only 15 patients with EGFR-mutations demonstrated no survival benefit from gefitinib [hazard ratio (HR), 1.84 for disease-free survival (DFS) and 3.16 for overall survival (OS)]. In another early study (RADIANT), p-stage IB-IIIA NSCLC patients either with EGFR-protein expression-positive by immunohistochemistry or with EGFR-gene amplification-positive by fluorescence in situ hybridization were eligible regardless of EGFR-status, and a total of 503 patients were randomly assigned to receive a first-generation EGFR-TKI (gefitinib) or placebo for 2 years. Among 161 patients with EGFR-mutations, DFS seemed in favor of the erlotinib group whereas the DFS benefit was not statistically significant. In recent randomized studies reported from China (9-12), only EGFR-mutated patients were enrolled, and were
I strongly make an objection against the recommendations. The goal of adjuvant treatment for resected NSCLC patients is to increase the proportion of patient with “cure”, whereas the goal of systemic treatment for advanced un-resectable NSCLC is prolongation of overall survival time. To justify the use of an EGFR-TKI in postoperative adjuvant setting, a significant increase in the proportion of cured patients or those who survived 5 years or longer should be demonstrated in a randomized phase III study. The CTONG1104 study is the only phase III study showing a significant DFS benefit with adjuvant EGFR-TKI treatment for completely resected EGFR-mutated NSCLC. However, in a post hoc analysis of the study, postoperative recurrence was lower in the gefitinib group than in the VP group during early postoperative period (0–21 months after surgery), but recurrence in the gefitinib group has constantly increased at a constant rate 12 months post-surgery (11). These results may indicate that adjuvant treatment with EGFR-TKI do not improve the proportion of cured patients but only delay development of tumor recurrence. For advanced EGFR-mutated NSCLC, systemic treatment with an EGFR-TKI may provide a significant survival benefit, but may not lead to cure in most patients. In postoperative adjuvant setting, elimination of all tumor cells in minimal residual tumor (MRD) may not be achieved with an EGFR-TKI, which is essential to increase

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Eligibility</th>
<th>Arm</th>
<th>No of EGFR-mutant</th>
<th>Effect of EGFR-TKI on DFS</th>
<th>Effect of EGFR-TKI on OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR-mutation-unselected</td>
<td>p-stage IB–IIIA</td>
<td>Gefitinib</td>
<td>7/251</td>
<td>HR =1.84 (0.44 to 7.73), P=0.40</td>
<td>HR =3.16 (0.61 to 16.45), P=0.15</td>
</tr>
<tr>
<td>(Phase III) (7)</td>
<td>Placebo</td>
<td>8/252</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RADIANT</td>
<td>p-stage IB–IIIA</td>
<td>Erlotinib</td>
<td>102/623</td>
<td>HR =0.61 (0.38 to 0.98)</td>
<td>HR =1.09 (0.55 to 2.16)</td>
</tr>
<tr>
<td>(Phase III) (8)</td>
<td>EGFR-positive*</td>
<td>Placebo</td>
<td>59/350</td>
<td>mDFS, 46.4 m; 2 yr-DFS, 89%</td>
<td>mDFS, 28.5 m; 2 yr-DFS, 72%</td>
</tr>
<tr>
<td>EGFR-mutation-selected</td>
<td>p-stage IIIA</td>
<td>Erlotinib</td>
<td>51</td>
<td>2 yr-DFS, 81.4%</td>
<td></td>
</tr>
<tr>
<td>(Phase II) (9)</td>
<td>EGFR-mutant</td>
<td>VP</td>
<td>51</td>
<td>2 yr-DFS, 44.6%; HR =1.823 (1.194 to 2.784), P=0.0054</td>
<td></td>
</tr>
<tr>
<td>CTONG1104</td>
<td>p-stage II–IIIA</td>
<td>Gefitinib</td>
<td>111</td>
<td>HR =0.60 (0.42 to 0.87), P=0.0054</td>
<td>mDFS, 28.7 m; 3 yr-DFS, 34%</td>
</tr>
<tr>
<td>(Phase III) (10,11)</td>
<td>(N1–N2)</td>
<td>EGFR-mutant</td>
<td>111</td>
<td>mDFS, 18.0 m; 3 yr-DFS, 27%</td>
<td></td>
</tr>
</tbody>
</table>

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; NSCLC, non-small-cell lung cancer; DFS, disease-free survival; OS, overall survival; HR, hazard ratio; p-stage, pathologic stage; mDFS, median disease-free survival; 2-yr DFS, 2-year disease-free survival rate; VP, vinorelbine plus cisplatin. *EGFR protein expression by immunohistochemistry or EGFR amplification by fluorescence in situ hybridization.
the proportion of cured patients. In addition, an EGFR-TKI is active not only for advanced unresectable EGFR-mutated NSCLC, but also for tumor with postoperative recurrence. In fact, the WJTOG3405 study comparing first-line treatment with gefitinib versus chemotherapy [cisplatin plus docetaxel (DP)], a subset analysis showed that the progression-free survival (PFS) was longer in the gefitinib group (13.7 versus 8.1 months) among patients with postoperative recurrence (14), suggesting that EGFR-mutated patients who underwent complete resection were effectively treated with an EGFR-TKI at the time of tumor recurrence. In addition, adjuvant EGFR-TKI treatment may cause postoperative recurrence with resistance to an EGFR-TKI. In advanced NSCLC with activating EGFR-mutations, first-line treatment with a first-generation EGFR-TKI usually achieves a significant tumor shrinkage, but most patients experience tumor progression through development of resistant tumor caused by resistant EGFR-mutations such as T790M and other mechanisms within one year after the initiation of treatment (15). Osimertinib, a third-generation EGFR-TKI can overcome the T790M resistance (16,17), but may induce a variety of complicated resistance mechanisms such as activation of bypass signaling pathways and transformation to small cell carcinoma (18,19). When EGFR-TKI-resistant postoperative tumor recurrence may develop in patients who received adjuvant EGFR-TKI treatment, no effective treatment other than platinum-doublet chemotherapy is currently available. Accordingly, adjuvant treatment with an EGFR-TKI is not recommended for completely resected NSCLC with EGFR-mutations in daily clinical practice, as no RCT showed a significant OS benefit with prophylactic use of an EGFR-TKI before tumor recurrence. I have a concern about ongoing large-scale RCTs of adjuvant EGFR-TKI treatment, as most of them was conducted to evaluate DFS as the primary endpoint (Table 2).

More importantly, a careful attention should be paid to implementation of adjuvant treatment following complete resection, because a certain percentage of patients will be cured without any adjuvant treatment. In fact, RCTs of adjuvant chemotherapy showed that 5-year survival rates for completely resected p-stage II–IIIA NSCLC were 30–50% in the surgery-alone group (4). For such patients who will be cured without adjuvant treatment, adjuvant EGFR-TKI treatment is unnecessary in principle, and is potentially harmful as is associated with several adverse events including lethal interstitial lung disease. To reduce the potential risk of adjuvant EGFR-TKI treatment for potentially curable patients, biomarker-oriented selection of patients who truly need adjuvant treatment due to a higher risk of postoperative recurrence is a promising approach. Among several biomarkers, circulating tumor DNA (ctDNA) is a potentially useful marker not only in predicting postoperative recurrence but also in monitoring therapeutic effect of adjuvant treatment. Today, osimertinib, has become the preferred EGFR-TKI in first-line treatment for advanced EGFR-mutated NSCLC, as is associated with a superior survival benefit (PFS and OS) and toxicity profile over a first-generation EGFR-TKI (gefitinib or erlotinib) (20,21). However, prophylactic use of osimertinib in postoperative adjuvant setting may induce a variety of EGFR-TKI-resistant mechanisms, as is demonstrated in

<table>
<thead>
<tr>
<th>Study</th>
<th>Eligibility</th>
<th>No of patients</th>
<th>Arm</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPACT/WJOG6410L (JAPAN)</td>
<td>p-stage II–III</td>
<td>230</td>
<td>Gefitinib</td>
<td>DFS</td>
</tr>
<tr>
<td>EVIDENCE/CCTC-1501 (China)</td>
<td>p-stage II–IIIA</td>
<td>320</td>
<td>Icotinib</td>
<td>DFS</td>
</tr>
<tr>
<td>ADAURA (International)</td>
<td>p-stage IB–IIIA, non-Sq</td>
<td>700</td>
<td>Osimertinib</td>
<td>DFS</td>
</tr>
<tr>
<td>ALCHEMIST (A081105) (USA)</td>
<td>p-stage IB (≥4 cm)–IIIA</td>
<td>450</td>
<td>Erlotinib</td>
<td>OS</td>
</tr>
</tbody>
</table>

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; DFS, disease-free survival; OS, overall survival; VP, vinorelbine plus cisplatin; PP, pemetrexed plus cisplatin.
systemic treatment for advanced NSCLC (18,19). The optimal selection of agent in postoperative adjuvant setting as well as the optimal selection of patients may be the key to achieve the optimal risk-benefit balance with adjuvant EGFR-TKI treatment for EGFR-mutated NSCLC patients.

In conclusion, the current clinical evidence may not support the use of adjuvant EGFR-TKI treatment for completely resected EGFR-mutated NSCLC, because only a significant prolongation of DFS after surgery was achieved. On-going RCTs may reveal whether adjuvant EGFR-TKI treatment can improve the postoperative prognosis (Table 2).

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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