Editorial Commentary

Postoperative management for non-small cell lung cancer harboring *EGFR* mutations

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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 (8). Patients were randomly assigned to receive another first-generation EGFR-TKI (erlotinib) 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

Table 1 Randomized controlled study of adjuvant EGFR-TKI for *EGFR*-mutated NSCLC

Study (reference)	Eligibility	Arm	No of *EGFR*-mutant	Effect of EGFR-TKI on DFS	Effect of EGFR-TKI on OS
EGFR-mutation-unselected					
BR.19 (Phase III) (7)	p-stage IB–IIIA	Gefitinib	7/251	HR =1.84 (0.44 to 7.73), P=0.40	HR =3.16 (0.61 to 16.45), P=0.15
		Placebo	8/252		
RADIANT (Phase III) (8)	p-stage IB–IIIA EGFR-positive*	Erlotinib	102/623	HR =0.61 (0.38 to 0.98)	HR =1.09 (0.55 to 2.16)
				mDFS, 46.4 m; 2 yr-DFS, 89%	
		Placebo	59/350	mDFS, 28.5 m; 2 yr-DFS, 72%	
EGFR-mutation-selected					
EVAN (Phase II) (9)	p-stage IIIA EGFR-mutant	Erlotinib	51	2 yr-DFS, 81.4%	
		VP	51	2 yr-DFS, 44.6%; HR =1.823 (1.194 to 2.784), P=0·0054	
CTONG1104 (Phase III) (10,11)	p-stage II–IIIA (N1–N2) EGFR-mutant	Gefitinib	111	HR =0.60 (0.42 to 0.87), P=0.0054	
				mDFS, 28.7 m; 3 yr-DFS, 34%	
		VP	111	mDFS, 18.0 m; 3 yr-DFS, 27%	

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.

assigned to receive a first-generation EGFR-TKI or chemotherapy (VP) (*Table 1*). The EVAN study is a randomized phase II study conducted for p-stage IIIA NSCLC harboring *EGFR*-mutations, and the primary endpoint was DFS at 2 years. At the median follow-up of 33 months, the 2-year DFS rate was higher in the erlotinib group (81.4%) than in the chemotherapy group (44.6%; P=0.0054) (9). The CTON1104 (ADJUVANT) study is a formal phase III study to compare the efficacy of adjuvant gefitinib treatment with that of adjuvant chemotherapy with VP. A total of 222 patients with completely resected p-stage II-IIIA (N1-2) NSCLC harboring *EGFR*-mutations were randomized. The primary endpoint of DFS was significantly longer in the gefitinib group (median DFS, 28.7 months) than in the VP group (18.0 months; P=0.0054) (10). Based on these results, Liang and coworkers have published the Society for Translational Medicine consensus on postoperative management of EGFR-mutant lung cancer (2019 edition) to support postoperative adjuvant treatment with an EGFR-TKI for completely resected p-stage II-IIIA NSCLC with activating *EGFR*-mutations as well as routine *EGFR*-testing after surgery for NSCLC (13).

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 year 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 2 Ongoing phase III randomized controlled study of adjuvant EGFR-TKI for *EGFR*-mutated NSCLC

Study	Eligibility	No of patients	Arm	Primary endpoint
IMPACT/WJOG6410L (JAPAN)	p-stage II–III	230	Gefitinib	DFS
			VP	
EVIDENCE/CCTC-1501 (China)	p-stage II–IIIA	320	Icotinib	DFS
			VP or PP (for Ad)	
ADAURA (International)	p-stage IB–IIIA, non-Sq	700	Osimertinib	DFS
			Placebo	
ALCHEMIST (A081105) (USA)	p-stage IB (≥4 cm)–IIIA	450	Erlotinib	OS
			Placebo	

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.

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 on-going 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

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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