



# Society for Translational Medicine consensus (2019 edition) shows an option for postoperative management of EGFR-mutant lung cancer

Tatsuya Nagano, Motoko Tachihara, Daisuke Hazama, Yoshihiro Nishimura

Division of Respiratory Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

*Correspondence to:* Tatsuya Nagano, MD, PhD. Division of Respiratory Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, 7-5-1, Kusunoki-Cho, Chuo-ku, Kobe, 650-0017, Japan. Email: [tnagano@med.kobe-u.ac.jp](mailto:tnagano@med.kobe-u.ac.jp).

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A consensus and guidelines about postoperative management of non-small cell lung cancer (NSCLC) with EGFR mutation have been published primarily by Chinese thoracic surgeons and oncologists (1). Since EGFR mutations are detected in 38.4% of lung cancers in Asia (95% CI, 36.5% to 40.3%) (China, 38.4%; Japan, 36.6%; Korea, 32.4%) (2), this consensus will have a particular meaning for lung cancer management in Asia. In this editorial commentary, we would like to outline the background leading to this consensus and share our personal opinion.

The first randomized phase III trial comparing gefitinib 250 mg/day for 2 years as adjuvant therapy with placebo for patients who were completely resected NSCLC (stage IB-IIIa) was conducted in Japan (3). However, the trial was stopped after the randomization of 38 patients, since interstitial lung disease (ILD) were increasingly observed in Japan. Another phase III trial comparing gefitinib 250 mg/day for 2 years as adjuvant therapy with placebo for patients who were completely resected NSCLC (stage IB-IIIa) (the NCIC CTG BR19 study) did not show an overall survival (OS) (HR, 1.24; 95% CI, 0.94 to 1.64;  $P=0.14$ ) or disease-free survival (DFS) benefit (HR, 1.22; 95% CI, 0.93 to 1.61;  $P=0.15$ ) (4). Although this trial did not limit patients to those with EGFR mutations, subgroup analyses of this trial did not show OS (HR, 3.16; 95% CI, 0.61 to 16.45;  $P=0.15$ ) or DFS benefit (HR, 1.84; 95% CI, 0.44 to 7.73;  $P=0.395$ ) from gefitinib,

even for the 15 patients with NSCLC with EGFR mutation. In addition, a phase III trial comparing adjuvant erlotinib 150 mg/day with placebo for 2 years for patients with completely resected NSCLC (stage IB-IIIa) (the RADIANT study) did not show a DFS benefit (HR, 0.90; 95% CI, 0.74 to 1.10;  $P=0.324$ ), with DFS as the primary endpoint (5). Unlike the NCIC CTG BR19 study, the RADIANT study showed a DFS benefit (HR, 0.61; 95% CI, 0.38 to 0.98;  $P=0.039$ ) from erlotinib for 161 patients with EGFR-mutant NSCLC. However, the RADIANT study also did not show an OS benefit for either the total population (HR, 1.13; 95% CI, 0.88 to 1.45) or patients with EGFR-mutant NSCLC (HR, 1.09; 95% CI, 0.55 to 2.16). Therefore, the Japan Lung Cancer Society decided that adjuvant EGFR tyrosine kinase inhibitors (TKIs) were not recommended for the treatment of completely resected NSCLC with EGFR mutation (stage IB-IIIa) in 2018 (strength of recommendation: 1; level of evidence C, according to Minds guideline 2014).

On the other hand, the recent phase III trial comparing adjuvant gefitinib 250 mg/day for 2 years with vinorelbine plus cisplatin for patients who were completely resected NSCLC with EGFR mutation [stage II-IIIa (N1-N2)] in China (the ADJUVANT/CTONG 1104 study) showed a DFS benefit (HR, 0.60; 95% CI, 0.42 to 0.87;  $P=0.0054$ ), with DFS as the primary endpoint (6). In this trial, serious adverse events were observed in 7% of adjuvant gefitinib

arm and 23% of adjuvant vinorelbine plus cisplatin arm, and ILD did not occur in gefitinib arm. Furthermore, another phase II trial comparing adjuvant erlotinib 150 mg/day with vinorelbine plus cisplatin for patients who were completely resected NSCLC with EGFR mutation (stage IIIA) in China (EVAN study) showed a DFS benefit (relative risk, 1.823; 95% CI, 1.194 to 2.784;  $P=0.0054$ ) (7). These two Chinese studies showed a DFS benefit, but it is noteworthy that an OS benefit with adjuvant EGFR TKIs has not been reported. Currently, a new phase III trial comparing adjuvant osimertinib with placebo for patients who were completely resected NSCLC with EGFR mutation (stage IB-IIIa) (the ADAURA study) is recruiting patients (60% of patients recruited from Asia countries), and the results will be opened in the third quarter of 2021 (8). The primary endpoint of the ADAURA study is DFS, and secondary endpoints include the DFS rate at 2, 3, and 5 years, OS, the OS rate at 5 years, and safety and tolerability. Since a phase III study comparing osimertinib with gefitinib or erlotinib (the FLAURA study) showed an OS benefit (HR, 0.46; 95% CI, 0.37 to 0.57;  $P<0.001$ ) from osimertinib (9) and patients receive osimertinib for 3 years in the ADAURA study, prolonged DFS is expected. However, to cure EGFR-mutant NSCLC, an EGFR TKI alone may not be sufficient, since even EGFR-mutant NSCLC has heterogeneity. The recent phase III trial comparing gefitinib 250 mg/day with gefitinib concurrently combined with carboplatin plus pemetrexed for patients with newly diagnosed EGFR-mutant NSCLC (stage IIIB-IV or postoperative relapse) in Japan (the NEJ009 study) showed an OS benefit (HR, 0.722; 95% CI, 0.55 to 0.95;  $P=0.021$ ), with OS as the primary endpoint (10). This NEJ009 study may provide clues for improving the cure rate of adjuvant therapy.

Thus, unless OS improvement is proven, EGFR TKIs as adjuvants are not yet recommended internationally. However, since medical conditions vary from country to country, adjuvant EGFR TKIs may be a possible option in some conditions in which relapse testing is not regularly available or access to treatment is restricted.

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