# Is there a role for first generation TKIs in adjuvant setting of EGFR mutated early NSCLC?

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*Comment on:* Yue D, Xu S, Wang Q, *et al.* Updated Overall Survival and Exploratory Analysis From Randomized, Phase II EVAN Study of Erlotinib Versus Vinorelbine Plus Cisplatin Adjuvant Therapy in Stage IIIA Epidermal Growth Factor Receptor+ Non-Small-Cell Lung Cancer. J Clin Oncol 2022;40:3912-7.

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In terms of cancer- related mortality, it is clear that lung cancer is the leading cause of death in men and the second in women. Non-small cell lung cancer (NSCLC) accounts for the vast majority of cases (85%) and only one of three patients is a candidate for curative treatment with complete surgery at the time of diagnosis (1).

Considering the risk of recurrence and metastasis after surgery, adjuvant chemotherapy with cisplatin has been established as the standard of care for patients with completely resected stage II and III NSCLC. This choice is also highly recommended for patients with adverse features stage IB disease. This approach provides a 5-year overall survival (OS) benefit of 5.4% compared to no systemic treatment (2).

Given the demonstrated effectiveness of EGFR (epidermal growth factor receptor) tyrosine kinase inhibitors (TKIs) in metastatic setting of NSCLC, their utility in the adjuvant setting has been explored over last years. Therefore, there are some meta-analyses and several randomized controlled trials that have supported that an adjuvant strategy with EGFR-TKIs may improve disease-free survival (DFS) in patients with early-stage NSCLC. However, no significant superiority has been demonstrated in any of the available studies. This has been interpreted as secondary to the immaturity of OS data due to insufficient follow-up period (3-11). Recently, despite these findings, the third generation EGFR-TKI osimertinib, has been approved for the adjuvant treatment of completely excised NSCLC based on improvement in DFS and is the current gold standard of therapy in this setting (12).

In the article that generated this comment, Yue *et al.* provided an update on overall survival and exploratory analysis from the randomized, phase II EVAN trial of erlotinib versus vinorelbine plus cisplatin adjuvant therapy in stage IIIA EGFR expressing non-small cell lung cancer (13). The study included patients between the ages of 18 and 75 years who had had undergone complete resection (R0) of histologically or pathologically confirmed stage IIIA EGFR mutation-positive NSCLC and who had not received prior antitumor therapy. Patients were randomly assigned t(1:1) to receive adjuvant erlotinib (150 mg orally diary) or chemotherapy with vinorelbine and cisplatin (four cycles). The primary endpoint was 2-year disease-free survival. 102 patients from 16 centers across China were include, N2 was present in 94% and 100% of patients in the erlotinib and chemotherapy arms respectively. At baseline, after a median

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follow-up of 33.0 months, 2-year disease-free survival was 81.4% (95% CI: 69.6–93.1%) for patients in the erlotinib group and 44.6% (26.9–62.4%) for patients in the chemotherapy group (relative risk 1.823; 95% CI: 1.194–2.784; P=0.0054). Adverse events of any grade occurred in 29 (58%) of 50 patients in the erlotinib cohort and in 28 (65%) of 43 patients in the chemotherapy cohort. Grade 3 or higher adverse events occurred in 6 (12%) of the 50 patients in the erlotinib arm compared to 11 (26%) of the 43 patients in the chemotherapy arm. No treatment-related deaths were reported (9). Based on these findings, the authors conclude that adjuvant treatment with erlotinib in patients with EGFR mutation-positive stage IIIA NSCLC resulted in superior 2-year disease-free compared with chemotherapy, with a better tolerability profile.

In recently published OS update and exploratory analysis, the median follow-up in the erlotinib and chemotherapy arms was 54.8 and 63.9 months, respectively. With erlotinib, 5-year DFS was 48.2% (95% CI: 29.4–64.7%) and 46.2% (95% CI: 27.6–62.9%) in the intention-to-treat and per-protocol populations, respectively. Median OS was 84.2 months with erlotinib versus 61.1 months with chemotherapy (hazard ratio, 0.318; 95% CI: 0.151–0.670). The 5-year survival rates were 84.8% with erlotinib and 51.1% with chemotherapy. In addition, prevalent genes with variants co-occurring at baseline in the whole-exome sequencing analysis were *TP53*, *MUC16*, *FAM104B*, *KMT5A*, and *DNAH9*. In the erlotinib cohort, a single nucleotide polymorphism mutation in UBXN11 was associated with significantly worse DFS (P=0.01) (13).

This survival information derived from the EVAN trial is valuable because it is the first data of OS improvement in the adjuvant setting with EGFR-TKIs in NSCL.

However, to better evaluate these findings, it is important to consider the design and results of the others Phase III (ADJUVANT-CTONG1104, ADAURA and RADIANT) and Phase II (SELECT) trials (*Table 1*) (7-11,14).

The first study, SELECT phase II trial of adjuvant erlotinib, included patients ranging with stage IA to IIIA [7th edition of the American Joint Committee on Cancer (AJCC) staging system]. Erlotinib was administered for 2 years after standard adjuvant chemotherapy with or without radiotherapy. Data from 100 patients were analyzed; of these, 13% were in stage IA, 32% in stage IB, 11% in stage IIA, 16% in stage IIB, and 28% in stage IIIA. Forty percent of patients required a dose reduction of erlotinib to 100 mg and 16% to 50 mg. Median follow-up was 5.2 years, and 2-year DFS was 88% (96% in stage I, 78% in stage II and 91% in stage III). Malignancy recurrence occurred in 40 patients, with four patients relapsing while receiving erlotinib. The median time to relapse was 25 months after discontinuation of erlotinib. Among patients with relapse who underwent repeat biopsy (n=24; 60%), the T790M mutation was detected in one patient. Most patients with relapse were rechallenged with erlotinib (n=26; 65%) for a median of 13 months. Brain-only metastases accounted for 20% of recurrences (8).

The second study, the phase III ADJUVANT-CTONG1104 trial compared gefitinib with vinorelbine plus cisplatin as adjuvant treatment for stage II–IIIA (N1-N2) EGFR-mutated NSCLC. 222 patients were randomly assigned in a 1:1 ratio to receive adjuvant gefitinib for 24 months or cisplatin and vinorelbine for four cycles. The primary endpoint was DFS. At baseline, after at a median follow-up of 36.5 months, median disease-free survival (DFS) was better with gefitinib compared to chemotherapy [28.7 *vs.* 18 months, hazard ratio (HR), 0.60; 95% CI: 0.42–0.87; P=0.0054] (14). A subsequent data update, with a median follow-up of 80 months, confirmed the improvement in DFS with gefitinib versus chemotherapy (30.8 *vs.* 19.8 months, HR, 0.56; 95% CI: 0.40–0.79; P=0.001). However, gefitinib did not improve OS. Post-progression therapy was administered in 68.4% and 73.6% of patients receiving gefitinib and chemotherapy, respectively. Additional targeted therapy made a significant contribution to OS (HR, 0.23; 95% CI: 0.14–0.38) compared to no retreatment (10).

The third study, the phase III RADIANT trial of adjuvant erlotinib versus placebo in patients with stage IB–IIIA NSCLC, was conducted in patients with totally resected stage IB to IIIA NSCLC whose tumors expressed EGFR protein by immunohistochemistry or EGFR amplification by fluorescence *in situ* hybridization. Patients were allocated 2:1 to erlotinib or placebo for 2 years. The primary endpoint was disease-free survival (DFS); secondary endpoints were overall survival (OS) and DFS and OS in patients with tumors harboring activating EGFR mutations (EGFRm-positive). A total of 973 patients were included. There were no statistically significant differences in DFS (median, 50.5 months for erlotinib and 48.2 months for placebo; hazard ratio, 0.90; 95% CI: 0.74–1.10; P=0.324). Among the 161 patients (16.5%) in the EGFRm-positive subgroup, DFS was superior with erlotinib (median, 46.4 *vs.* 28.5 months; hazard ratio, 0.61; 95% CI: 0.38–0.98; P=0.039), but this was not found to be significant. OS data were immature.

**Table 1** Trials of tyrosine kinase inhibitors (TKIs) in adjuvant setting of non small cell lung cancer EGFR mutated

| Study | Stage | N/Population | EXPERIMENTAL ARM | Control arm | Primary endpoint | Results |
|---|---|---|---|---|---|---|
| EVAN Phase II | III A, N2 in 94% and 100% of erlotinib and chemotherapy arms respectively. | 102/100% Asian | Erlotinib for 3 years | Standard chemotherapy | 2-year DFS | DFS: 42.2 months in erlotinib *vs.* 21.2 months in chemotherapy arm P<0.0063 HR 0.327<br>5 years OS: 84.8% erlotinib *vs.* 51.1% chemotherapy, P=0.015, HR 0.318<br>Adverse events: all grades in 29 (58%) of 50 patients receiving erlotinib and in 28 (65%) of 43 patients with chemotherapy |
| SELECT single-arm, open-label Phase II | IA to IIIA | 100/White 72/100; Asian 17/100 | Erlotinib for 2 years at the end of standard adjuvant chemotherapy +/− radiotherapy | Not applicable | 2-year DFS | DFS: 88% (96% stage I, 78% stage II, 91% stage III). 40% of patients decrease erlotinib dose to 100 mg and 16% to 50 mg |
| ADJUVANT-CTONG1104 Phase III | II–IIIA (N1-2) | 222/100% Asian | Gefitinib for 2 years | Standard chemotherapy | DFS | DFS: 30.8 months in gefitinib *vs.* 19.8 months in chemotherapy, P=0.001, HR 0.56<br>5 years OS: 53.2% gefitinib *vs.* 51.2% chemotherapy, P=0.674, HR 0.92<br>Post-progression therapy in 68.4% and 73.6% of patients gefitinib and chemotherapy<br>Further targeted therapy *vs.* no retreatment OS (HR 0.23; 95% CI: 0.14–0.38) |

**Table 1** (*continued*)

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| Study | Stage | N/Population | EXPERIMENTAL ARM | Control arm | Primary endpoint | Results |
|---|---|---|---|---|---|---|
| ADAURA Phase III | IB to IIIA: 32% IB, 34% II, 34% IIIA | 682: 64% Asian; 36% no Asian | Osimertinib for 3 years +/− standard chemotherapy | Placebo +/− standard chemotherapy | DFS stage II to IIIA | DFS at 2 years 89% in osimertinib *vs.* 52% in placebo arm; HR 0.20; 99% CI: 0.14–0.30) |
| | | | | | | At 24 months, 98% of patients in osimertinib *vs.* 85% in placebo arm free of central nervous system (CNS) disease (overall HR of disease recurrence or death 0.18; 95% CI: 0.10–0.33). OS immature |
| | | | | | | In patients with stage II and IIIA disease, 2-year DFS 90% and 44% (HR 0.17; 95% CI: 0.11–0.26) |
| | | | | | | Serious adverse events in 16% of patients. osimertinib dose reductions 9% and discontinuation 11% |
| | | | | | | DFS update: 4-year DFS rate 70% for osimertinib and 29% for placebo |
| | | | | | | DFS HR overall population was 0.27 (95% CI: 0.21–0.34); 4-yr DFS rate was 73% for osimertinib and 38% for placebo |
| | | | | | | HR for CNS DFS in stage II–IIIA was 0.24 (95% CI: 0.14–0.42) |
| | | | | | | Long-term safety data of osimertinib was consistent with primary analysis |
| | | | | | | Osimertinib received approval by the U.S. Food and Drug Administration (FDA) as adjuvant treatment for resected EGFR-mutated NSCLC on December 18, 2020 |
| RADIANT Phase II | IB-IIIA expressing EGFR+ by immunohistochemistry or EGFR amplification by fluorescence *in situ* hybridization | 973: ITT population (80% white, 17% Asian; EGFRm population (56% white, 42% Asian) | Erlotinib for 2 years | Placebo | DFS | DFS (median, 50.5 *vs.* 48.2; HR 0.90; 95% CI: 0.74–1.10; P=0.324) |
| | | | | | | 161 patients (16.5%) in the EGFRm-positive subset, DFS (median, 46.4 *vs.* 28.5 months; HR 0.61; 95% CI: 0.38–0.98; P=0.039). OS immature |
| | | | | | | Brain metastases in 37.1% of relapsed patients |
| | | | | | | Frequency of dose reductions in erlotinib arm was 46% |

DFS, disease-free survival; OS, overall survival; HR, hazard ratio; yr, year.

Brain metastases were of concern in 37.1% of patients who relapsed. The frequency of dose reductions in the erlotinib arm was 46% (7).

Finally, the phase III ADAURA study, evaluated 682 patients with NSCLC and confirmed EGFR mutation, AJCC stage IB to IIIA, some of whom received chemotherapy. Adjuvant osimertinib was compared to placebo and was administered until relapse for up to three years. The primary endpoint was disease-free survival for patients with stage II to IIIA NSCLC. 32% of patients had stage IB, 34% stage II and 34% stage IIIA disease. This study demonstrated an increase in DFS rates at 2 years (89 *vs.* 52%; HR 0.20; 99% CI: 0.14–0.30). At 24 months, 98% of patients in the osimertinib arm and 85% in the placebo remained free of central nervous system (CNS) disease (overall HR for disease recurrence or death 0.18; 95% CI: 0.10–0.33). OS data were immature at this time. In patients with stage II to IIIA disease, 2-year DFS rates were 90% and 44%, respectively (HR 0.17; 95% CI: 0.11–0.26). Serious adverse events were reported in 16% of patients. Dose reductions were required by 9% of patients and discontinuation in 11% (11) The findings of this trial supported for the approval of osimertinib by the U.S. Food and Drug Administration (FDA) for the adjuvant treatment of resected EGFR-mutated NSCLC (12). Recently, an updated exploratory analysis from the ADAURA trial reported that the DFS HR was 0.23 (95% CI: 0.18–0.30); the 4-year DFS rate was 70% for osimertinib and 29% for placebo. In the overall population, the DFS HR was 0.27 (95% CI: 0.21–0.34); the 4-year DFS rate was 73% for osimertinib and 38% for placebo. Local/regional and distant recurrence occurred in fewer patients treated with osimertinib. The HR for CNS DFS in stage II-IIIA was 0.24 (95% CI: 0.14–0.42). The long-term safety data for osimertinib were consistent with the safety profile observed in the primary analysis (15).

After reviewing each trial separately, it is clear that there are important differences in design (phase II and III trials), selection criteria (variability in stage from IA to IIIA, receiving or no receiving adjuvant chemotherapy prior to EGFR-TKIs, presence of EGFR mutation *vs.* amplification) and therefore in the patient populations included. Another important aspect is the optimal duration of adjuvant treatment, since the available information suggests that 2 years of continuous treatment with TKIs would be sufficient, whereas osimertinib, the only agent approved in the adjuvant setting, was administered for 3 years, in the ADAURA trial.

The EVAN study included only stage IIIA patients, with a sample size of 94 patients, which is a larger number of patients in this stage compared to the other available studies in the adjuvant setting of EGFR-mutated NSCLC. For this reason, it is highly likely, as Yue *et al.* hypothesized, that the survival benefit in the study population could be explained by the fact that specifically stage IIIA patients are more likely to relapse compared to other early stages. This finding must be interpreted carefully because it may be secondary to a bias in the selection of the population.

In clinical practice, cost should not be the determining factor in the choice of oncology treatment. In the situation of choosing the type of EGFR-TKIs, the most important considerations are the toxicity profile, the emergence of resistance and the frequency of brain relapse, scenarios in which erlotinib has clear disadvantages and economic reasons do not sufficiently support not treating patients with osimertinib, which has demonstrated increased survival and adequate tolerability on a continuous basis over the follow-up time in clinical trials.

In order to consider changing the current standard of treatment, it would be relevant to have information within a clinical trial on comparisons of relapse patterns and frequency of development of resistance mutations during adjuvant treatment with the different EGFR-TKIs available. These data could be useful in making a better selection of the type of EGFR-TKI.

Unanswered questions remain regarding the benefits of adjuvant EGFR-TKIs for these patients with earlier stages of NSCLC, especially those with stage IB. Furthermore, it is relevant to obtain more data about the usefulness of EGFR-TKI treatment after progression and the role of biomarkers to identify patients at high risk of relapse after surgery and to develop new treatment strategies and prevent the emergence of resistant disease. The whole-exome sequencing analysis performed in EVAN trial, noted that in erlotinib group, a single-nucleotide polymorphism mutation in UBXN11 was associated with significantly worse DFS, it would be of interest to obtain the same information from the others EGFR-TKIs to guide treatment selection.

In conclusion, the answer to the question of whether first-generation TKIs have a role in the adjuvant setting of EGFR mutated NSCLC is NOT.

Osimertinib has been shown to increase survival over time and has a better toxicity profile than the other EGFR-TKIs. In addition, it has greater central nervous system (CNS) penetration and a lower frequency of recurrence with brain metastases compared to first-generation EGFR-

TKIs such as erlotinib and gefitinib (8-10). The EVAN trial results support that erlotinib could be considered for treatment in the adjuvant setting for patients with stage IIIA R0 EGFR mutated NSCLC. However, limitations in generalizing these results to the whole population include that the study was conducted in a single type of population (Chinese) and in patients with advanced stage disease (IIIA).

Thus, with the exception of economic aspects, which are important but not sufficient, it is difficult to find a valid rationale for the use of first-generation EGFR-TKIs in the adjuvant setting of EGFR mutated NSCLC with the available data.

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