Erlotinib versus vinorelbine plus cisplatin as adjuvant therapy in Chinese patients with stage IIIA *EGFR* mutation-positive non-small-cell lung cancer (EVAN): a randomised, open-label, phase 2 trial

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Summary

Background Adjuvant chemotherapy after radical resection of stage IIIA non-small-cell lung cancer (NSCLC) has quite poor outcomes. We aimed to investigate whether adjuvant erlotinib therapy improves 2-year disease-free survival compared with chemotherapy in epidermal growth factor receptor (*EGFR*) mutation-positive stage IIIA NSCLC.

Methods In this randomised, open-label, phase 2 trial, eligible patients aged 18–75 years who had undergone complete (R0) resection of histologically or pathologically confirmed stage IIIA *EGFR* mutation-positive NSCLC and had not received any previous anticancer therapies were enrolled. Patients were randomly assigned (1:1) to receive either adjuvant erlotinib (150 mg once daily administered orally) or vinorelbine and cisplatin chemotherapy (four cycles of vinorelbine [25 mg/m² intravenously on days 1 and 8 of each 21-day cycle] plus cisplatin [75 mg/m² intravenously on day 1 of each 21-day cycle]). Randomisation was done by Simon's minimisation with a random element and was stratified by *EGFR* activating mutation type (exon 19 *vs* 21), histology (adenocarcinoma *vs* non-adenocarcinoma), and smoking status (smoker *vs* non-smoker). The primary endpoint in the unblinded intention-to-treat analysis was 2-year disease-free survival. This ongoing study is registered with ClinicalTrials.gov, number NCT01683175.

Findings Between Sept 8, 2012, and May 21, 2015, 102 patients from 16 centres across China were enrolled and randomly assigned to receive erlotinib (n=51) or chemotherapy (n=51). Median follow-up was 33·0 months (IQR 17·8–43·1). 2-year disease-free survival was 81·4% (95% CI 69·6–93·1) in the erlotinib group and 44·6% (26·9–62·4) in the chemotherapy group (relative risk 1·823 [95% CI 1·194–2·784; p=0·0054). The difference in 2-year disease-free survival between the groups was 36·7% (95% CI 15·5–58·0; p=0·0007). Adverse events of any grade occurred in 29 (58%) of 50 patients in the erlotinib group and 28 (65%) of 43 patients in the chemotherapy group. Grade 3 or worse adverse events occurred in six (12%) of 50 patients in the erlotinib group versus 11 (26%) of 43 in the chemotherapy group; the most common of these in the erlotinib group was rash (in two [4%] of 50 patients) and in the chemotherapy group were decreased neutrophil count (in seven [16%] of 43 patients) and myelosuppression (in four [9%]). No treatment-related deaths were reported.

Interpretation Adjuvant erlotinib improved 2-year disease-free survival in patients with *EGFR* mutation-positive stage IIIA NSCLC compared with chemotherapy, with a better tolerability profile. This study suggests that tyrosine kinase inhibitors could have a potentially important role as adjuvant therapy in *EGFR* mutation-positive stage IIIA NSCLC. However, this trial was a phase 2 study. Mature overall survival data are also needed. Ongoing studies will hopefully confirm the role of adjuvant EGFR tyrosine kinase inhibitor therapy in patients with NSCLC.

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Introduction

Surgery, where possible, remains the mainstay of treatment in patients with early-stage (I–IIIA) non-small-cell lung cancer (NSCLC).[1,2] However, recent systematic reviews and meta-analyses suggested no or only minimal benefit of adjuvant chemotherapy on overall survival, 5-year survival, and disease-free survival after complete resection in patients with early-stage NSCLC.[3–5] Comparison of these analyses suggests that the benefits of adjuvant chemotherapy have plateaued during the past two decades, with no additional gains in overall survival in this period. Adjuvant chemotherapy is also associated with substantial treatment-related toxicity, which might necessitate dose reductions, delays, or treatment discontinuation. Such events can have detrimental effects on patient wellbeing or clinical outcomes.[6] Therefore, although adjuvant chemotherapy might confer a survival benefit in some patients with stage I–IIIA NSCLC, further survival improvements should be sought through

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Research in context

Evidence before this study

At the time we began to write this report, we searched MEDLINE and PubMed for reports published in English between Jan 1, 2004, and July 1, 2017, using the search terms "resected NSCLC", "EGFR TKI", and "adjuvant". Our search found extensive published evidence to show that adjuvant chemotherapy conferred a small improvement in disease-free survival after complete resection of non-small-cell lung cancer (NSCLC). A meta-analysis published in 2008 indicated that adjuvant cisplatin-based chemotherapy increased 5-year survival by 5·4% compared with resection alone and disease-free survival by 5·8% compared with resection alone. In a more recent meta-analysis published in 2015, adjuvant chemotherapy increased disease-free survival by just 4·0% relative to resection alone. Comparison of these findings suggests that there has been no substantial improvement in the outcomes of adjuvant chemotherapy in patients with NSCLC in the past two decades. Epidermal growth factor receptor (EGFR) has a crucial pathogenic role in NSCLC, and clinical trials in the early 2000s showed that EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib improved progression-free survival in patients with NSCLC. By 2010, evidence was emerging to suggest that EGFR TKIs might also be effective as an adjuvant therapy after resection of stage IA–IIIA NSCLC. However, clinical trials underway or nearing completion at the time were mainly done in white patients with broad patient, disease, and treatment characteristics. Therefore, we planned this phase 2 trial to investigate whether or not adjuvant therapy with erlotinib was more effective and better tolerated than chemotherapy in a selected population of Chinese patients with *EGFR* mutation-positive, stage IIIA NSCLC who underwent complete (R0) resection. At the time of writing this report, the results of a phase 3 trial (ADJUVANT) in China were published and showed that adjuvant gefitinib, another EGFR TKI, increased disease-free survival compared with adjuvant chemotherapy in patients with stage II–IIIA NSCLC.

Added value of this study

To our knowledge, this is the first phase 2 clinical trial to suggest that adjuvant therapy with erlotinib might improve disease-free survival compared with adjuvant chemotherapy (vinorelbine and cisplatin) in patients with completely resected (R0), *EGFR* mutation-positive, stage IIIA NSCLC.

Implications of all the available evidence

Until now, options for adjuvant therapy in patients with *EGFR* mutation-positive, stage IIIA NSCLC have been scarce, and outcomes of chemotherapy are generally poor. In the past decade, interest in the options for adjuvant therapy in NSCLC has renewed. In particular, the expectation has emerged that patients with *EGFR* mutation-positive NSCLC are likely to show better outcomes with EGFR TKIs compared with conventional adjuvant chemotherapy. Several clinical trials have therefore investigated the use of EGFR TKIs as adjuvant therapy, but these trials enrolled broader patient populations than in this trial, including patients with less advanced disease (eg, stage I or II). We found that erlotinib extends disease-free survival in patients with high-risk (ie, stage III) NSCLC, which is consistent with trials in patients with less advanced NSCLC. Although overall survival data are still immature and require ongoing follow-up, the trajectories of the overall survival curves might indicate that erlotinib has a beneficial effect on overall survival, as well as on disease-free survival. Our trial further suggests clinical potential for adjuvant erlotinib therapy in stage IIIA NSCLC and also suggests that EGFR TKI therapy could be an appropriate adjuvant therapy in *EGFR* mutation-positive NSCLC; however, our trial is completed in only a small sized population. Ongoing studies, including ALCHEMIST-EGFR (NCT02193282) and WJOG6410L (UMIN000006252), are awaited to confirm the role of adjuvant EGFR-TKI therapy in the treatment of patients with high-risk NSCLC.

the use of alternative treatments with better tolerability than adjuvant chemotherapy. This aim is especially important in stage III NSCLC, which has a very poor prognosis and for which little consensus exists about options for adjuvant therapy.

Mutations in the epidermal growth factor receptor (*EGFR*) gene are observed in 10–15% of white patients with NSCLC[7,8] but are especially common in Asian patients; recent data revealed the presence of *EGFR* mutations in 49·3% of patients with locally advanced or metastatic NSCLC and adenocarcinoma histology in the Asia–Pacific cohort of the IGNITE study.[9]

Several EGFR tyrosine kinase inhibitors (TKIs), including erlotinib and gefitinib, have been approved for the treatment of patients with *EGFR* mutation-positive advanced NSCLC. Erlotinib has been approved worldwide (in 2011 in the European Union, in 2013 in the USA, and in 2017 in China) for use as a first-line treatment in this setting based on several clinical trials in Asian (eg, ENSURE[10] and OPTIMAL[11]) and predominantly white (EURTAC[12]) populations. These studies consistently showed that first-line erlotinib led to a greater improvement in progression-free survival compared with chemotherapy in patients with *EGFR* mutation-positive NSCLC.

Several clinical trials have investigated whether or not EGFR TKIs can be used in the adjuvant setting. The BR19 trial[13] was the first phase 3 study comparing an EGFR TKI (gefitinib) with placebo as adjuvant therapy in patients with completely resected stage IB–IIIA NSCLC. However, gefitinib did not show superiority over placebo in terms of either disease-free or overall survival. One contributing factor to this result might be the low proportion of patients with *EGFR*-activating mutations in the trial: of the 359 patients who underwent EGFR genotyping, only 15 had *EGFR* mutation-positive NSCLC. By contrast, in the RADIANT trial,[14] patients with completely resected stage IB–IIIA NSCLC expressing EGFR protein (as determined by immunohistochemistry, or with *EGFR*

gene amplification detected by fluorescence in-situ hybridisation) were randomly assigned to receive erlotinib or placebo for 2 years in a double-blind manner. This trial did not demonstrate a significant improvement in disease-free survival with erlotinib compared with placebo. However, in the *EGFR* mutation-positive subgroup of patients, which constituted only a small subset of the entire study population analysed post hoc, those receiving erlotinib did show a trend towards better disease-free survival compared with the placebo group.[14] In another single-arm trial (SELECT),[15] patients with *EGFR* mutation-positive stage IA–IIIA NSCLC received erlotinib after standard adjuvant chemotherapy, radiotherapy, or both; erlotinib showed a promising benefit in this setting with a 2-year disease-free survival of 89%.

Few studies have investigated whether or not EGFR TKIs might be suitable as an adjuvant therapy after complete resection in Chinese patients with intermediate-risk or high-risk NSCLC, despite the high prevalence of *EGFR*-activating mutations in this patient population.[9,16] The results of a phase 3 randomised controlled trial (ADJUVANT)[17] in Chinese patients with stage II–IIIA *EGFR* mutation-positive NSCLC were recently published and showed that once-daily gefitinib significantly improved median disease-free survival compared with chemotherapy (four cycles of vinorelbine plus cisplatin), without substantial differences in 3-year disease-free survival between the two treatment groups. However, at the time of planning the current study, no positive results from randomised trials of EGFR TKIs in an adjuvant setting had been reported, and the trials underway at the time (eg, the ADJUVANT study) enrolled broader patient populations, including patients with stage IA or II NSCLC. Therefore, for this trial, we decided to focus on patients with stage IIIA NSCLC in the hope of introducing an alternative to chemotherapy for these patients.

Here, we present the results of our randomised phase 2 EVAN trial comparing erlotinib with chemotherapy in Chinese patients with stage IIIA *EGFR* mutation-positive NSCLC.

Methods

Study design and participants

We did this multicentre, randomised, open-label, phase 2 trial in 16 centres (all hospitals) in China. Eligible patients were adults aged 18–75 years with histopathologically or cytologically confirmed *EGFR* mutation-positive stage IIIA NSCLC (defined according to the seventh edition of the TNM classification[18]) who had undergone complete resection (R0) up to 6 weeks before randomisation and who had not received any previous anticancer therapies. Only patients with a confirmed activating mutation in exon 19 (in-frame deletion; del19) or 21 (Leu858Arg point mutation) of the *EGFR* gene, as established by genetic tests were eligible. *EGFR* mutations were detected by direct sequencing using an amplification-refractory mutation polymerase chain reaction system (TaKaRa Biotechnology Co Ltd, Dalian, China). Additional inclusion criteria were Eastern Cooperative Oncology Group (ECOG) performance status 0–1, life expectancy of at least 12 weeks, and adequate haematological, liver, and kidney function. Resection was considered complete (R0) only if International Association for the Study of Lung Cancer criteria were met: free resection margins proved microscopically; systematic nodal dissection or lobe-specific systematic nodal dissection; no extracapsular nodal extension; and the highest mediastinal node removed must be negative.[19] Patients whose resections did not meet these criteria were excluded from the study. Patients were initially assessed and recruited in the study at each investigator centre. After central evaluation in Tianjin Medical University Cancer Institute (Tianjin Shi, China), patients who did not meet criteria of the R0 resection definition as mentioned in the protocol were excluded from the per-protocol analysis.

Exclusion criteria comprised: previous exposure to other targeted agents (eg, erlotinib, gefitinib, cetuximab, or trastuzumab) or chemotherapy; radiotherapy before or after surgery; poor gastrointestinal integrity or function; observation during surgery of extracapsular spread or fusion in lymph nodes; pathologically confirmed cancer involvement in all resected lymph nodes; history of previous malignancy in the past 5 years (except for disease cured by surgery alone with a disease-free interval of at least 5 years, cured basal cell carcinoma of the skin, or cured in-situ carcinoma of the uterine cervix); ocular inflammation; presence of any disorders or use of medications likely to affect the results of the study or increase the risk of treatment-related complications or result in contraindication of the study drugs; unstable systemic disease; and known hypersensitivity to the study drugs.

The trial adhered to the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by local institutional review boards and ethics committees at all participating centres. The synopsis of the study protocol is available in the appendix. All patients provided written informed consent to participate in the study.

See Online for appendix

Randomisation and masking

Eligible patients were randomly assigned in a 1:1 ratio to the two treatment groups. Randomisation was done using an interactive web-based response system (IWRS). Simon's minimisation method[20] was used for randomisation, with the stratification factors *EGFR* mutation type (exon 19 *vs* 21), histology (adenocarcinoma *vs* non-adenocarcinoma), and smoking status (smoker *vs* non-smoker). Non-smokers were defined as having never smoked, or having smoked up to a maximum of 100 cigarettes during their lifetime. An investigator logged onto the IWRS and requested the randomisation number and treatment for each patient. All treatments were administered in an unmasked manner; the

investigators, all study personnel, and all patients were aware of the treatment assignment.

Procedures

Eligible patients received either 2 years of erlotinib (150 mg once daily administered orally; erlotinib group) or four cycles (21 days per cycle) of vinorelbine (25 mg/m² intravenously on days 1 and 8 of each cycle) plus cisplatin (75 mg/m² intravenously on day 1 of each cycle; chemotherapy group). The treatments were to be discontinued in the event of relapse or unacceptable toxicity (according to the investigator's assessment) during the treatment period. After local or distant disease recurrence, patients in the chemotherapy group were offered standard therapy with an EGFR TKI in accordance with routine treatment of NSCLC in China.

Patients were to discontinue the study if erlotinib was interrupted or delayed by more than 2 weeks, or if the subsequent cycle of chemotherapy was delayed by more than 3 weeks. The chemotherapy dose could be increased or decreased by up to 10% from the planned dose. The erlotinib dose could be increased or decreased by 50 mg per day, but all patients could only receive a maximum 150 mg per day and minimum of 50 mg per day. Dose adjustments for toxicities were in accordance with the approved labels.

Disease recurrence was evaluated based on tumour assessments at follow-up visits, including chest CT at weeks 6 and 12 (equivalent to the start of cycle 3 and end of cycle 4), then every 3 months for the first 3 years after randomisation, and every 6 months in years 4 and 5 after randomisation; brain MRI every 6 months, or as indicated based on symptoms; and bone scans every 12 months, or as indicated based on symptoms.

All adverse events were to be recorded for up to 28 days after the last dose of study medication. Treatment-related serious adverse events were to be collected and reported even after the end of the study (with the end of the study defined as the point when the last patient completed the last visit). Adverse events were treated and followed up in accordance with the adverse event management protocol. Adverse drug reactions, serious adverse drug reactions, grade 3–4 adverse events, and serious adverse events were evaluated according to standard criteria. Interstitial lung disease was evaluated as an adverse event of special interest and was to be diagnosed based on patient symptoms and imaging findings (eg, CT scan).

Outcomes

The primary endpoint was 2-year disease-free survival. Secondary endpoints included median disease-free survival, overall survival, and safety. Disease-free survival was defined as time from the date of randomisation until first confirmation of disease recurrence or death from any cause. 2-year disease-free survival was defined as the proportion of patients alive and disease free at the 2-year timepoint. Overall survival was defined as the time from randomisation until death from any cause. We also planned to assess median disease-free survival in pre-specified subgroups of patients by smoking status, histology and gender.

Safety variables included clinical and laboratory adverse events, which were classified based on National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

The study protocol also stipulated that quality of life (Functional Assessment of Cancer Therapy-Lung; and Lung Cancer Symptom Scale) and tumour biomarkers would be secondary outcomes; however, these outcomes are not reported in this paper and will instead be reported in a separate publication.

Statistical analysis

The sample size was determined based on a projected hazard ratio (HR) for 2-year disease-free survival of 0·5 in favour of erlotinib, and considering 2-year disease-free survival of 74% for erlotinib and 48% for vinorelbine and cisplatin chemotherapy.[21–23] To achieve 80% power at a two-sided $\alpha=0\cdot2$ and an anticipated dropout rate of 15%, we planned to enrol 94 patients.

The primary endpoint of 2-year disease-free survival was estimated using the Kaplan–Meier method. The point estimates of 2-year disease-free survival in the erlotinib and chemotherapy groups were calculated using the Kaplan–Meier method, and SEs were calculated using the Greenwood formula. The difference between the treatment groups was estimated by the points estimates from the Kaplan–Meier method and the 95% CI was estimated by the pooled SE of the two treatments from the Greenwood formula. The 95% CIs for each treatment group were also constructed by the rate estimates and the SE estimates). The p value was calculated from the difference and the pooled SE between the groups, which were also used to calculate the 95% CIs. The relative risk (RR) and its 95% CI were derived from the log-transformation of survival function. An exploratory post-hoc analysis was done for 3-year disease-free survival; the Kaplan-Meier method was also used for this analysis.

2-year disease-free survival was analysed in the intention-to-treat population (all patients who were randomly assigned to a treatment group) and in the per-protocol population (all randomly assigned patients who received at least one dose of the study drug, who did not experience a major protocol violation, and who had at least one post-baseline tumour assessment). Any patients who discontinued from the study early and did not have any post-baseline tumour assessments were censored at the randomisation date.

Median disease-free survival and overall survival were estimated using the Kaplan–Meier method. Disease-free and overall survival distributions between two groups were compared using log-rank tests. Log-rank tests were also used to compare disease-free survival distributions between the two groups for patients subdivided by

baseline factors. Prespecified subgroup analyses were done for the three stratification factors: smoking status, *EGFR* mutation type, and histology. Subgroup analyses for other baseline factors (sex, age, ECOG performance status, and T stage) were also done in a post-hoc manner.

Safety variables were analysed descriptively in terms of the number (percentage) of patients with adverse events (system organ class and preferred term), or as mean (SD) for laboratory variables. Safety outcomes were analysed in all patients who received at least one dose of the allocated study drug.

There were no interim analyses. The data cutoff date was June 15, 2017. All statistical analyses were done using SAS version 9.4.

This study is registered with ClinicalTrials.gov, number NCT01683175.

Role of the funding source

Shanghai Roche Pharmaceuticals Ltd funded this investigator-initiated trial, provided the study drugs, and funded medical writing support. Shanghai Roche Pharmaceuticals Ltd had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The National Key Research and Development Program of China funded data collection and analyses. All authors had access to all raw study data and made the final decision to submit the report for publication. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

Between Sept 8, 2012, and May 21, 2015, 290 patients were screened for eligibility, of whom 102 were enrolled and randomly assigned to receive erlotinib (n=51) or vinorelbine plus cisplatin chemotherapy (n=51); all 102 patients were included in the intention-to-treat analysis set (figure 1). One patient in the erlotinib group withdrew for personal reasons before receiving any study medication, and eight in the chemotherapy group did not receive any study medication. Of these eight patients, seven withdrew for personal reasons and one patient was found to have metastatic NSCLC before receiving the study medication. Major protocol deviations occurred in four patients in the erlotinib group (a lack of R0 resection in three patients and a lack of critical assessment in one patient) and 11 patients in the chemotherapy group, including the one patient with metastatic NSCLC who did not receive any study medication (figure 1).

The two groups were balanced in terms of baseline characteristics (table 1). About two-thirds of patients were female, and the median age of the patients was 58 years (IQR 51–66). 91 patients had adenocarcinoma and 11 had non-adenocarcinoma. An exon 19 deletion was found in 58 (57%) of 102 patients, an exon 21 Leu858Arg mutation in 43 (42%) patients, and one patient had both mutations

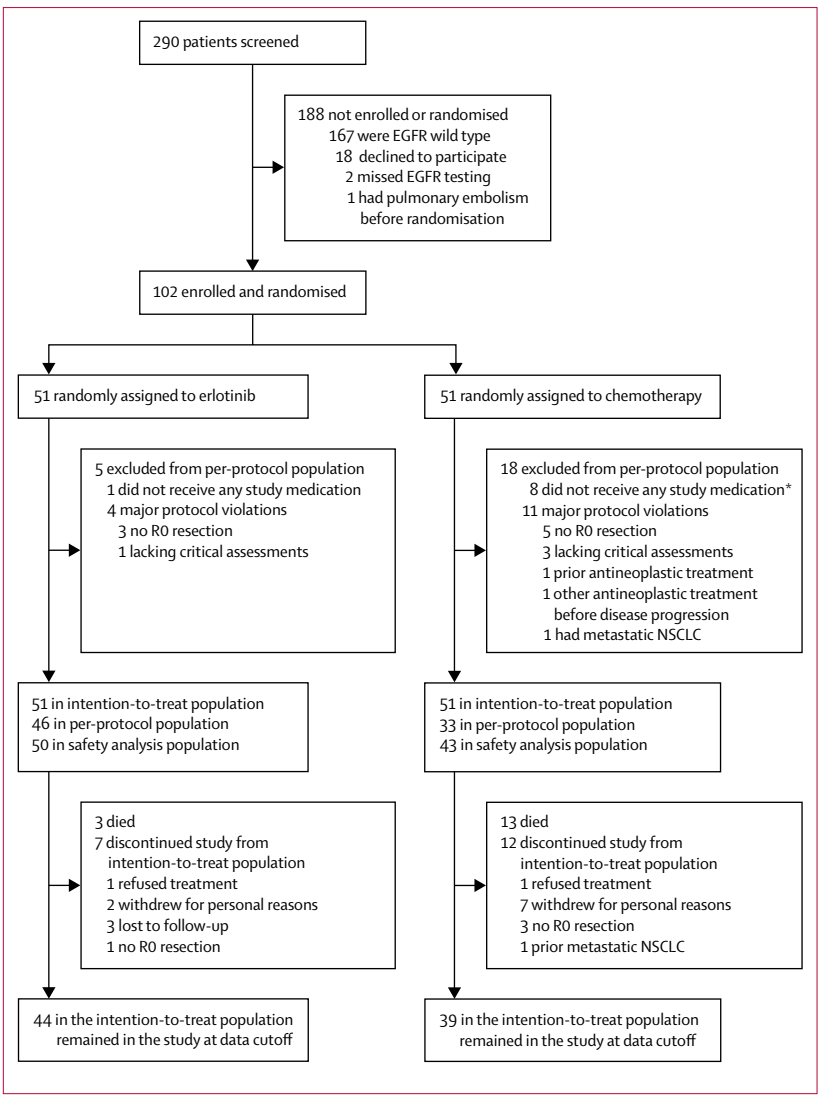

Figure 1: **Trial profile**
*Seven patients withdrew before receiving any study medication for personal reasons. One patient, who did not receive the study medication, had metastatic NSCLC, a major protocol deviation (this patient was also counted in the 11 major protocol violations in this group). EGFR=epidermal growth factor receptor. R0=complete resection. NSCLC=non-small-cell lung cancer.

(table 1). 99 patients had previously undergone lobectomy, and the remaining three patients had undergone pneumonectomy. The median duration of erlotinib therapy was 23·9 months (IQR 20·7–24·0). Erlotinib was administered for longer than 18 months in 39 (78%) of 50 patients, for 12–18 months in four (8%), for 6–12 months in one (2%) patient, and for less than 6 months in six (12%) patients. In the 43 patients in the chemotherapy group who started treatment, 32 (74%) completed four cycles of chemotherapy, four (9%) completed three cycles, one (2%) completed two cycles, and six (14%) completed one cycle.

2-year disease-free survival and median disease-free survival were measured after data cutoff on June 15, 2017.

	Erlotinib group (n=51)	Chemotherapy group (n=51)
Age, years	59 (50–66)	57 (51–61)
Gender		
Male	17 (33%)	20 (39%)
Female	34 (67%)	31 (61%)
EGFR mutation type		
Exon 19 deletion	30 (59%)	28 (55%)
Exon 21 Leu858Arg	21 (41%)	22 (43%)
Both mutations	..	1 (2%)
Histology		
Adenocarcinoma	46 (90%)	45 (88%)
Non-adenocarcinoma	5 (10%)	6 (12%)
Smoking status		
Smoker	13 (25%)	12 (24%)
Non-smoker	38 (75%)	39 (76%)
ECOG performance status		
0	21 (41%)	22 (43%)
1	29 (57%)	28 (55%)
Missing	1 (2%)	1 (2%)
T stage		
1	18 (35%)	21 (41%)
2	27 (53%)	26 (51%)
3	4 (8%)	4 (8%)
4	2 (4%)	0
N stage		
0	2 (4%)	0
1	1 (2%)	0
2	48 (94%)	51 (100%)
Type of resection		
Lobectomy	49 (96%)	50 (98%)
Pneumonectomy	2 (4%)	1 (2%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group.

Table 1: **Baseline characteristics**

Median follow-up in the intention-to-treat population was 33·0 months (IQR 17·8–43·1). At data cutoff, in the intention-to-treat population, 16 (31%) of 51 patients in the erlotinib group and 22 (43%) of 51 patients in the chemotherapy group had disease progression or had died. In the intention-to-treat population, 2-year disease-free survival was significantly better in the erlotinib group than in the chemotherapy group (81·4% [95% CI 69·6–93·1] *vs* 44·6% [26·9–62·4]; RR 1·823 [95% CI 1·194–2·784; p=0·0054; figure 2A). The difference in 2-year disease-free survival between the groups was 36·7% (SE 10·86; 95% CI 15·5–58·0; p=0·0007). Median disease-free survival was also longer in the erlotinib group than in the chemotherapy group (42·4 months [95% CI 31·7–not reached] *vs* 21·0 months [12·3–32·4], HR 0·268 [95% CI 0·136–0·531]; log-rank p<0·0001; stratified log-rank p=0·0003). In an exploratory post-hoc analysis, the 3-year disease-free survival was also significantly better in the erlotinib group than in the chemotherapy group (54·2% [95% CI 35·1–73·4] *vs* 19·8% [1·5–38·1]; RR 2·735 [95% CI 1·018–7·347]; p=0·0460). The difference in 3-year disease-free survival between the groups was 34·41% (SE 13·51; 95% CI 7·93–60·89; p=0·0190).

Similar results were observed in the per-protocol population (figure 2B). At data cutoff, disease recurrence or death occurred in 16 (35%) of 46 patients in the erlotinib group and 18 (55%) of 33 patients in the chemotherapy group. In the per-protocol population, 2-year disease-free survival was 80·4% (95% CI 68·1–92·2) in the erlotinib group *vs* 47·5% (28·6–66·7) in the chemotherapy group (RR 1·691 [95% CI 1·099–2·601]; p=0·0168) and 3-year disease-free survival was 51·4% (95% CI 31·5–71·3) *vs* 25·0% (3·5–46·5; RR 2·061 [95% CI 0·801–5·301]; p=0·1336); both favoured the erlotinib group. The difference in 2-year disease-free survival between the groups was 32·85% (SE 11·60; 95% CI 10·12–55·58; p=0·0046) and the difference in 3-year disease-free survival between the groups was 26·47% (SE 14·95; –2·83 to 55·78; p=0·0766). Median disease-free survival in the per-protocol population was longer in the erlotinib group than in the chemotherapy group (42·4 months [95% CI 30·23–not reached] *vs* 21·2 months [14·9–34·6]; HR 0·327 [95% CI 0·160–0·669]; log-rank p=0·0016; stratified log-rank p=0·0063).

In prespecified subgroups of patients based on stratification factors, disease-free survival in the intention-to-treat population favoured erlotinib in non-smokers, patients with *EGFR* mutation type exon 19, and patients with adenocarcinoma (figure 3), whereas there were no significant differences between erlotinib and chemotherapy in patients who were smokers, those with *EGFR* mutation type exon 21, and patients with non-adenocarcinoma. Figure 3 also shows disease-free survival results in subgroups of patients divided by non-stratification factors.

The Kaplan–Meier plots of overall survival are shown in figure 4. At data cutoff, 41 (80%) of 51 patients in the erlotinib group versus 26 (51%) of 51 in the chemotherapy group were still alive, three (6%) versus 13 (26%) had died, and seven (14%) versus 12 (24%) had discontinued the study. The HR for overall survival was 0·165 (95% CI 0·047–0·579) in favour of erlotinib (log-rank p=0·0013; stratified log-rank p=0·0017). Although the median overall survival had not been reached in either group at data cutoff, the overall survival curve maintained a higher trajectory in the erlotinib group than in the chemotherapy group throughout the trial, consistent with the disease-free survival curves (figure 4).

Safety analyses were done in the safety analysis population, which included 50 patients in the erlotinib group and 43 patients in the chemotherapy group who received at least one dose of the allocated study drug. Adverse events of any grade occurred in 29 (58%) of 50 patients in the erlotinib group and 28 (65%) of 43 in the chemotherapy group.

Grade 3 or worse adverse events occurred in six (12%) of 50 patients in the erlotinib group versus 11 (26%) of 43 in the chemotherapy group (table 2). Serious adverse events occurred in six (12%) versus seven (16%) patients, and serious adverse drug reactions occurred in four (8%) versus seven (16%) patients, respectively. No adverse events resulting in death occurred in either group. In the erlotinib group, six (12%) of 50 patients experienced an adverse event leading to a dose reduction or interruption and four (8%) of 50 experienced an adverse event leading to treatment discontinuation. In the chemotherapy group, 13 (30%) of 43 had an adverse event leading to a dose reduction or interruption and three (7%) had an adverse event leading to treatment discontinuation.

Adverse events that occurred in 10% or more patients in either group are shown in table 3 by system organ class and preferred term, with a complete list in appendix pp 2–4. Skin and subcutaneous disorders were the most common types of adverse events in the erlotinib group, occurring in 23 (46%) of 50 patients, and most of these adverse events were rash, which occurred in 18 (36%) of 50 patients. Gastrointestinal disorders occurred in 12 (24%) of 50 patients, with diarrhoea being the most common (in ten [20%] of 50 patients; table 3). There were no cases of vomiting in the erlotinib group. Infections and infectious diseases occurred in seven (14%) of 50 patients in the erlotinib group. The most common adverse events in the chemotherapy group were gastrointestinal disorders (14 [33%] of 43 patients), including vomiting (12 [28%]and nausea (seven [16%]), and laboratory abnormalities in 17 [40%] of 43 patients, including decreased neutrophil count (14 [33%]) and white blood cell count (eight [19%]), which were expected considering the adverse events commonly associated with vinorelbine and cisplatin chemotherapy.

The most common grade 3 or worse adverse event in the erlotinib group was rash, which occurred in two (4%) of 50 patients (table 2). The most common grade 3 or worse adverse events in the chemotherapy group were decreased neutrophil count in seven (16%) of 43 patients, and myelosuppression (haematological toxicity including low white blood cell count, neutrophil count, anaemia, or decreased platelets) in four (9%) patients; vomiting and decreased white blood cell count occurred in one (2%) patient each (table 2). Most of these grade 3 or worse adverse events were also recorded as serious adverse events or serious drug-related adverse events (appendix p 1). Notably, no clinically relevant changes in laboratory variables for blood cell counts (white blood cells, neutrophils, or platelets), liver enzymes (alanine aminotransferase or aspartate aminotransferase), and renal function markers (serum creatinine or creatinine clearance) were recorded in the erlotinib group.

Interstitial lung disease occurred in one (2%) of 50 patients in the erlotinib group. This patient was a 60-year-old woman who started erlotinib in May, 2013, and was diagnosed with interstitial pneumonia in March, 2015. The adverse event was classified as grade 3, required hospital admission, and resulted in permanent discontinuation of erlotinib. A CT scan in April, 2015, showed non-clinically significant chest abnormalities and no other abnormalities. Another CT scan in May, 2017, indicated reduced pneumonia and relief of cough, suggesting resolution of the interstitial lung disease without detrimental effects on the patient's quality of life. The patient died in July, 2017, due to cancer progression.

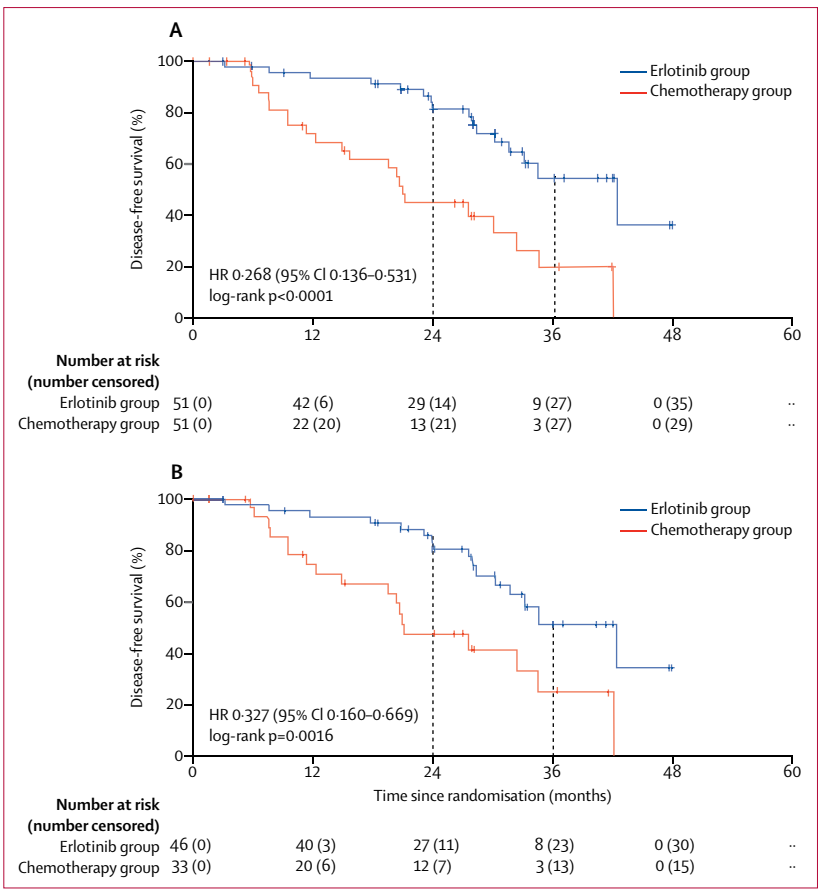

Figure 2: **Kaplan–Meier plots of disease-free survival in the (A) intention-to-treat and (B) per-protocol populations**

Tick marks represent censored patients. HR=hazard ratio.

Discussion

The results of this phase 2 trial show that adjuvant erlotinib improved 2-year disease-free survival compared with standard-of-care adjuvant chemotherapy in patients with completely resected (R0), *EGFR* mutation-positive stage IIIA NSCLC.

Several results have been reported from studies in the adjuvant setting of EGFR TKIs in stage IA–IIIA NSCLC. Most studies were unable to demonstrate a significant benefit for TKIs, possibly due to inappropriate patient population selection (ie, no EGFR mutation selection, and not including stage IIIA patients only)[13,14] or early

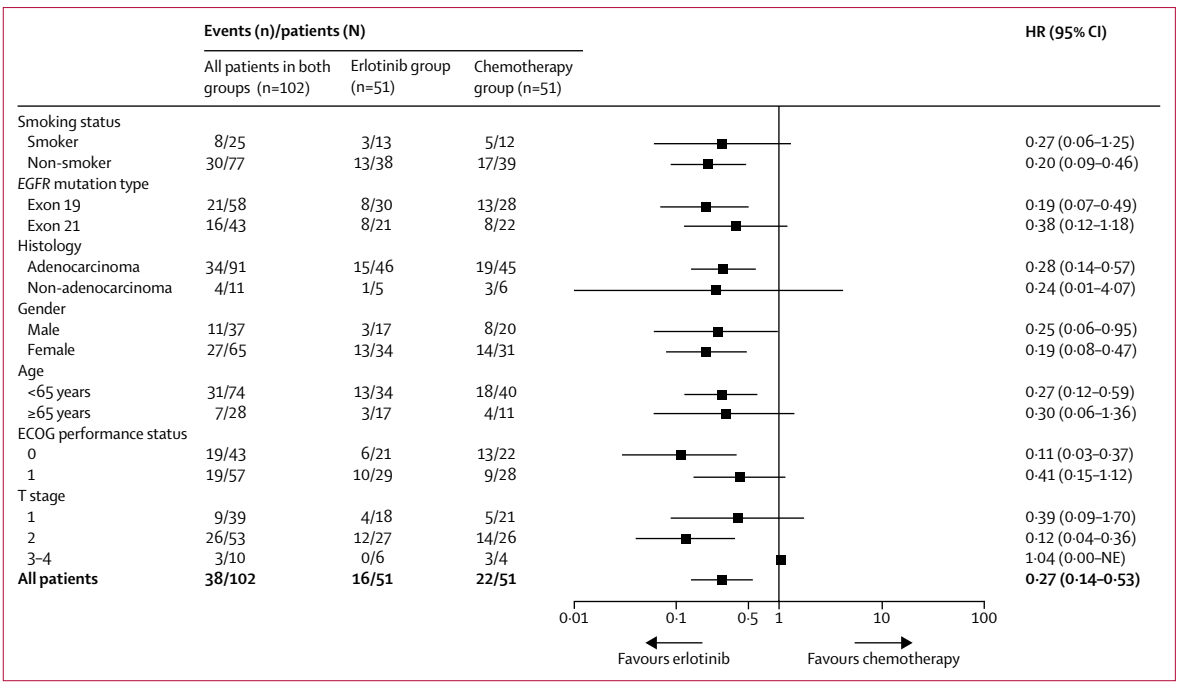

Figure 3: **Disease-free survival in patient subgroups (intention-to-treat population)**
Subgroups were either prespecified (smoking status, *EGFR* mutation type, and histology) or chosen in a post-hoc manner (gender, age, ECOG performance status, and T stage). HR=hazard ratio. ECOG=Eastern Cooperative Oncology Group. NE=not estimable.

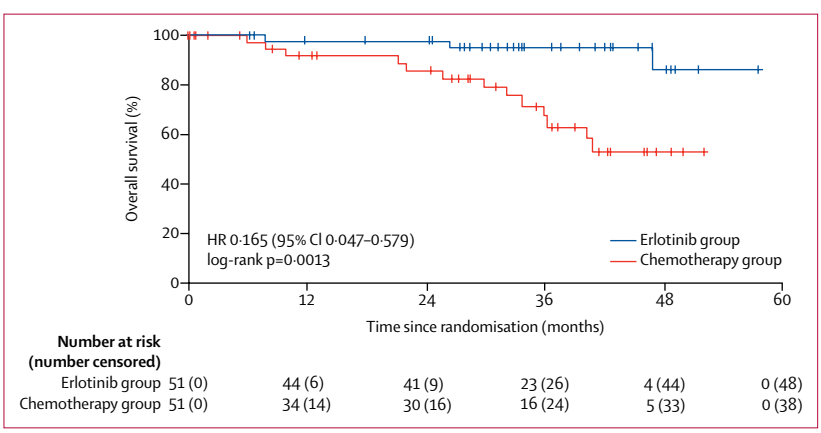

Figure 4: **Kaplan–Meier plot of overall survival (intention-to-treat population)**
Median overall survival was not reached in either group. Tick marks represent censored patients. HR=hazard ratio.

trial termination with no benefit.[13] The phase 2, single-arm SELECT trial suggested a possible benefit for erlotinib in the adjuvant treatment of patients with stage IA–IIIA NSCLC with or without radiotherapy.[15]

Recently, the ADJUVANT trial showed that gefitinib improved disease-free survival in Chinese patients with *EGFR* mutation-positive stage II–IIIA NSCLC.[17] 3-year disease-free survival in the intention-to-treat populations was 34·0% (95% CI 25·0–45·0) in the gefitinib group and 27·0% (16·0–38·0) in the chemotherapy group (HR 0·74, 95% CI 0·42–1·32; p=0·37).[17] In our trial, 3-year disease-free survival was 54·2% (95% CI 35·1–73·4) in the erlotinib group versus 19·8% (1·5–38·1) in the chemotherapy group (RR 2·735 [95% CI 1·018–7·347], p=0·0460). Thus, there was an apparently larger difference in 3-year disease-free survival between EGFR TKI-treated patients versus chemotherapy-treated patients in our trial relative to the ADJUVANT study. One possible explanation is that the patients in our study had more advanced NSCLC (all patients had stage IIIA disease). Patients with stage IIIA–N2 disease are more advanced, have poorer outcomes, and are more likely to experience recurrence.[24] However, the major limitations of interstudy comparison should not be overlooked, and the difference in 3-year disease-free survival might be attributable to the large CIs associated with the small patient series in our study.

The optimum treatment algorithm for adjuvant therapy for NSCLC is unknown. In two phase 2 studies that involved adjuvant chemotherapy followed by EGFR TKI therapy with gefitinib[25] or erlotinib,[15] both schedules produced encouraging 2-year disease-free survival rates of around 80%, which were similar to the 2-year disease-free survival of 81·4% in our study. Moreover, in the roughly 50% of patients treated with adjuvant chemotherapy in the RADIANT trial,[14] 2-year disease-free survival was 75% in patients with *EGFR* mutations population. Thus, all these studies show the efficacy of additional EGFR TKI therapy after surgery, with or without chemotherapy. Similar to the ADJUVANT study,[17] the EVAN study was also a head-to-head comparison of EGFR TKI therapy with adjuvant chemotherapy, and has shown that EGFR TKI therapy

might be a viable alternative to chemotherapy in the adjuvant setting.

Previous meta-analyses have suggested that adjuvant chemotherapy increases 5-year overall survival by about 5% compared with surgery alone in patients with resectable NSCLC.[5] Despite improvements in disease-free survival, EGFR TKIs versus chemotherapy have not substantially improved overall survival when used as adjuvant therapy in patients with high-risk NSCLC, and no previous studies have reported clear benefits for adjuvant erlotinib therapy on overall survival. In our trial, mortality seemed to be lower in the erlotinib group than in the chemotherapy group. However, overall survival data are extremely preliminary, since only three overall survival events occurred in the erlotinib group; these data must therefore be interpreted cautiously.

Many factors can affect overall survival results, and several considerations might also be important in clinical practice. Whether or not a longer treatment duration might lead to improved overall survival results remains unknown. The treatment duration in EVAN was 23·9 months, which was consistent with that reported in SELECT[15] (20·0 months) and ADJUVANT[17] (21·9 months), but longer than that in RADIANT[14] (11·9 months). The optimal duration of adjuvant therapy warrants further investigation and, indeed, disease relapse can occur during or after adjuvant EGFR TKI therapy. Treatment considerations after relapse will be of great importance. Whether or not EGFR TKIs can be used as first-line therapy and whether treatment should be changed to other drugs are major questions that need to be addressed. In the SELECT study,[13,15] 63% of 24 patients with recurrence underwent repeat biopsy, and only one patient had the *T790M* mutation; overall, 71% of patients with recurrence had rechallenge with erlotinib. At the data cutoff in our trial, overall survival data were immature; we are now endeavouring to continue follow-up to collect additional information for further analysis.

The type and grade of adverse events recorded in our trial are consistent with the known safety profiles of erlotinib and chemotherapy.[11,12] Rash and diarrhoea were the most common adverse events in the erlotinib group, whereas haematological adverse events, vomiting, and nausea were the most common events in the chemotherapy group. Our study demonstrated that erlotinib treatment for 2 years was safe and tolerable. Another important consideration and one which, based on findings from the ADJUVANT trial,[17] now warrants further investigation, is the potential impact of 24 months of erlotinib or EGFR TKI therapy versus that of 3 months of chemotherapy on patient quality of life.

One patient in the erlotinib group had interstitial lung disease nearly 2 years after starting treatment. This grade 3 adverse event required admission to hospital and permanent discontinuation of erlotinib, but the lung disease resolved thereafter. Although interstitial lung disease is quite a rare adverse event, it is potentially fatal. One meta-analysis suggested that interstitial lung disease occurs in 1·2% of patients treated with erlotinib or gefitinib and is fatal in 22·8% of cases.[26] Interstitial lung disease should be managed by supportive therapy and discontinuation of the EGFR TKI.[27] Re-introduction of an EGFR TKI may be possible in such cases,[28] but further studies are needed to confirm this possibility.

Some limitations to consider when interpreting our results are the relatively small sample size, even though the study was sufficiently powered for the primary endpoint, and the limited potential for generalisability or extrapolation of our results to non-Asian populations

	Erlotinib group (n=50)		Chemotherapy group (n=43)	
	Events	Patients	Events	Patients
Any grade ≥3 adverse event	8	6 (12%)	16	11 (26%)
Neutrophil count decreased	0	0	9	7 (16%)
Myelosuppression	0	0	4	4 (9%)
Rash	2	2 (4%)	0	0
Interstitial lung disease*	1	1 (2%)	0	0
Platelet count decreased	1	1 (2%)	0	0
Acne-like dermatitis	1	1 (2%)	0	0
Diarrhoea	1	1 (2%)	0	0
Cholelithiasis	1	1 (2%)	0	0
Mediastinal tumour	1	1 (2%)	0	0
White blood cell count decreased	0	0	1	1 (2%)
Vomiting	0	0	1	1 (2%)
Fatigue	0	0	1	1 (2%)

Data are n or n (%). *Interstitial lung disease was also recorded as an adverse event of special interest.

Table 2: **Grade 3 or worse adverse events**

	Erlotinib group (n=50)		Chemotherapy group (n=43)	
	Events	Patients	Events	Patients
At least one adverse event	120	29 (58%)	84	28 (65%)
Skin and subcutaneous tissue disorders	42	23 (46%)	0	0
Rash	27	18 (36%)	0	0
Gastrointestinal disorders	24	12 (24%)	40	14 (33%)
Vomiting	0	0	25	12 (28%)
Diarrhoea	12	10 (20%)	0	0
Nausea	3	3 (6%)	15	7 (16%)
Infections and infectious diseases*	15	7 (14%)	0	0
Laboratory abnormalities	4	3 (6%)	34	17 (40%)
Neutrophil count decreased	0	0	17	14 (33%)
White blood cell count decreased	0	0	12	8 (19%)
Respiratory, chest, and mediastinal diseases*	10	5 (10%)	1	1 (2%)
Blood and lymphatic system disorders	0	0	7	5 (12%)
Myelosuppression	0	0	7	5 (11·6)

Data are n or n (%). The table shows adverse events that occurred in ≥10% of patients in either group. *There were no individual adverse events within these categories in ≥10% of patients in either group. See appendix pp 2–4 for the full list of adverse events.

Table 3: **Adverse events (by system organ class)**

with NSCLC. Our results must also be interpreted with caution in view of the fact that this was a phase 2 study focusing on treatment of stage IIIA NSCLC with immature overall survival data. Additionally, more patients in the chemotherapy group than in the erlotinib group did not receive treatment, probably owing to a lower willingness of patients to undergo chemotherapy, as well as the number of major protocol violations (four in the erlotinib group *vs* 11 in the chemotherapy group), which reduced the number of patients in the per-protocol population. A major contributor to these protocol violations and the reduced size of the per-protocol population was that after central evaluation of patients recruited in each study site, eight cases did not meet the criteria for R0 resection. Nevertheless, results in the per-protocol population were consistent with those in the intention-to-treat population. Among other limitations, although the overall survival curve maintained a higher trajectory in the erlotinib than chemotherapy group throughout the EVAN trial, no other trial has shown an overall survival advantage for EGFR TKI therapy in this setting. Loss to follow-up was a limitation for the overall survival data in our study; however, survival follow-up is ongoing, and more extensive follow-up data will be available for subsequent analyses.

In conclusion, erlotinib improved 2-year disease-free survival compared with chemotherapy in patients receiving adjuvant therapy after complete resection of stage IIIA NSCLC. We also found that erlotinib was better tolerated than chemotherapy, with fewer adverse events requiring dose reductions or interruptions and fewer grade 3 or worse adverse events. However, mature data for overall survival, and complete follow-up, are needed. Ongoing studies, including ALCHEMIST-EGFR (NCT02193282) and WJOG6410L (UMIN000006252), are awaited to confirm the role of adjuvant EGFR TKI therapy in patients with NSCLC.

Contributors

All authors made substantial contributions to acquisition of data and critical revision of the manuscript for important intellectual content; CW and DY made substantial contributions to conception and design of the study and were responsible for data analysis.

Declaration of interests

DY has served as an advisor for Roche and AstraZeneca. CW has served as an adviser for Roche and AstraZeneca and has received research funding from Roche, AstraZeneca, Bristol-Myers Squibb, and Eli Lilly. The other authors declare no competing interests.

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