Recent advances and new insights in the management of early-stage epidermal growth factor receptor-mutated non-small-cell lung cancer

Miguel J Sotelo, José Luis García, Cesar Torres-Mattos, Héctor Milián, Carlos Carracedo, María Ángeles González-Ruiz, Xabier Mielgo-Rubio, Juan Carlos Trujillo-Reyes, Felipe Couñago

ORCID number: Miguel J Sotelo 0000-0002-8861-9355; José Luis García 0000-0002-0044-8265; Cesar Torres-Mattos 0000-0003-4030-0457; Héctor Milián 0000-0003-3870-3572; Carlos Carracedo 0000-0001-6071-7714; María Ángeles González-Ruiz 0000-0002-4616-9499; Xabier Mielgo-Rubio 0000-0002-0985-6150; Juan Carlos Trujillo-Reyes 0000-0002-3370-0869; Felipe Couñago 0000-0001-7233-0234.

Author contributions: Sotelo MJ performed the research and wrote the manuscript; Luis García J, Torres-Mattos C, Milián H, Carracedo C, González-Ruiz MA, Trujillo JC, Couñago F and Mielgo-Rubio X contributed critical review of the manuscript for important intellectual content and all authors approved the final version.

Conflict-of-interest statement: Dr. MIELGO-RUBIO reports personal fees and non-financial support from ROCHE, personal fees from ASTRA ZENECA, grants, personal fees and non-financial support from BMS, personal fees from MSD, personal fees from ABBOTT, personal fees from KIOWA-KIRIN, outside the submitted work. Rest of authors declares no conflict of interest.

Open-Access: This article is an open-access article that was

Miguel J Sotelo, Department of Medical Oncology, Hospital María Auxiliadora; Department of Medical Oncology, Centro Oncológico Aliada; Oncological Research Unit, Clínica San Gabriel, Lima 15801, Peru

José Luis García, Department of Thoracic Surgery, Hospital Universitario La Princesa; Department of Thoracic Surgery, MD Anderson Cancer Center; Department of Thoracic Surgery, Hospital HM, Madrid 28006, Spain

Cesar Torres-Mattos, Department of Medical Oncology, Hospital Nacional Guillermo Almenara; Oncological Research Unit, Clínica San Gabriel, Lima 15033, Peru

Héctor Milián, Department of Thoracic Surgery, Hospital Universitario La Princesa, Madrid 28006, Spain

Carlos Carracedo, Department of Medical Oncology, Centro Oncológico Aliada, Lima 15036, Peru

María Ángeles González-Ruiz, Department of Radiation Oncology, Hospital Universitario Virgen Macarena, Sevilla 41009, Spain

Xabier Mielgo-Rubio, Department of Oncology, Hospital Universitario Fundación Alcorcón, Alcorcón 28922, Madrid, Spain

Juan Carlos Trujillo-Reyes, Department of Thoracic Surgery, Hospital de la Santa Creu i Sant Pau, Barcelona 08041, Spain

Felipe Couñago, Department of Radiation Oncology, Hospital Universitario Quirónsalud Madrid; Hospital La Luz; Universidad Europea de Madrid, Madrid 28223, Spain

Corresponding author: Miguel J Sotelo, MD, PhD, Department of Medical Oncology, Hospital María Auxiliar; Department of Medical Oncology, Centro Oncológico Aliada; Oncological Research Unit, Clínica San Gabriel, Avda Miguel Iglesias 968, Lima 15801, Peru.

miguel.sotelo.lezama@gmail.com

Abstract

Patients with early-stage non-small-cell lung cancer (NSCLC) are candidates for curative surgery; however, despite multiple advances in lung cancer management, recurrence rates remain high. Adjuvant chemotherapy has been demonstrated to significantly prolong overall survival (OS), but this benefit is modest
and there is an urgent need for effective new therapies to provide a cure for more patients. The high efficacy of tyrosine kinase inhibitors (TKIs) against epidermal growth factor receptor-mutated (EGFR) in patients with advanced EGFR-mutated NSCLC has led to the evaluation of these agents in early stages of the disease. Multiple clinical trials have evaluated the safety and efficacy of EGFR TKIs as an adjuvant treatment, in patients with resected EGFR-mutated NSCLC, and shown that they significantly prolong disease-free survival (DFS), but this benefit does not translate to OS. Recently, an interim analysis of the ADAURA trial demonstrated that, surprisingly, osimertinib improved DFS. This led to the study being stopped early, leaving many unanswered questions about its potential effect on OS and its incorporation as a standard adjuvant treatment in this patient subgroup. These targeted agents are also being evaluated in locally-advanced disease, with promising results, although prospective studies with larger sample sizes are needed to confirm these results. In this article, we review the most relevant studies on the role of EGFR TKIs in the management of early-stage EGFR-mutated NSCLC.

Key Words: Non-small-cell lung cancer; Early stage; Epidermal growth factor receptor-mutated; Epidermal growth factor receptor-mutated-tyrosine kinase inhibitor; Adjuvant; Neoadjuvant

Core Tip: Epidermal growth factor receptor-mutated (EGFR) tyrosine kinase inhibitors (TKIs) have changed the natural history of advanced EGFR-mutated non-small-cell lung cancer (NSCLC). Multiple clinical trials conducted in the adjuvant setting have shown that EGFR TKIs prolong disease-free survival (DFS) but not overall survival (OS). Osimertinib demonstrated a surprising improvement in DFS in an interim analysis of the ADAURA study, which led to the study being stopped early, and left many unanswered questions about its potential effect on OS. Locally-advanced disease is also an attractive situation for assessment of the efficacy of these agents, with encouraging results so far. We discuss the recent advances in the management of early-stage EGFR-mutated NSCLC.

INTRODUCTION

Non-small-cell lung cancer (NSCLC) represents 85% of all lung cancers, and more than 50% of patients with NSCLC are diagnosed in advanced stages[1,2]. Only 25%-30% are diagnosed in early stages, making them candidates for curative surgical treatment[3-6]; however, more than 50% of these patients go on to have recurrence and die from the disease[3,6-9]. NSCLC has a high metastatic potential, even in early stages, and the aim of adjuvant treatment is to eradicate residual micrometastases[10]. Platinum-based adjuvant chemotherapy has been shown to prolong overall survival (OS), but with an absolute improvement in 5-year OS of only 4%[11,12]. Therefore, there is a need for new effective and minimally-toxic treatments to increase the cure rate.

Treatment with EGFR tyrosine kinase inhibitors (TKIs) in patients with metastatic EGFR-mutated NSCLC has been demonstrated to increase survival more than chemotherapy, changing the natural history of the disease in this subgroup of patients [13-17]. This has raised the question of whether a molecularly-targeted adjuvant treatment with EGFR TKIs could improve the modest benefit afforded by chemotherapy in patients with completely-resected EGFR-mutated NSCLC. Multiple EGFR...
TKIs have been assessed in this setting and have shown a significant benefit in disease-free survival (DFS) but not OS\cite{9,18-20}.

Unresectable and potentially-resectable locally-advanced disease are also attractive settings for evaluating the role of these agents. Multiple phase II clinical trials have shown encouraging results\cite{9,21-23}, although many questions remain to be answered.

In this review, we discuss the most relevant studies evaluating the role of EGFR TKIs in resectable, potentially-resectable, and unresectable locally-advanced NSCLC with EGFR-activating mutation.

**EGFR TKIS AS TREATMENT FOR RESECTABLE DISEASE**

EGFR mutations are the most common oncogenic drivers in NSCLC, occurring in 10-15\% of Caucasian patients\cite{24-26} and approximately 30\% of patients in Latin America\cite{27}, while in the Asian population the prevalence of EGFR mutations is significantly higher, around 50\%\cite{28,29}.

The presence of EGFR-activating mutations in patients with NSCLC confers high sensitivity to treatment with EGFR TKIs. In phase III clinical trials, multiple EGFR TKIs have shown dramatic, long-lasting responses that have translated to longer survival\cite{13-17,30-36}, never before seen in patients with advanced NSCLC treated with chemotherapy, positioning these targeted agents as the standard treatment in patients with advanced EGFR-mutated NSCLC.

The prevalence of EGFR mutations in NSCLC, the results observed in advanced disease, and the clinical need for new treatments to help cure more patients in early stages have led to the evaluation of EGFR TKIs as adjuvant therapy (Table 1).

Initially, studies were carried out in a population that was not selected for the presence of EGFR mutations. Based on the rationale that high EGFR expression in NSCLC confers aggressiveness and poor response to chemotherapy, Goss et al\cite{37} conducted the phase III trial BR19, which compared gefitinib for 2 yr vs placebo in 503 patients with resected stage IB-IIIA NSCLC, and found no differences in DFS or OS between the two arms. There were only 15 patients with EGFR mutations, and no benefit was observed for gefitinib in this small subgroup, either in DFS [hazard ratio (HR): 1.84, 95\% confidence interval (CI): 0.44-7.73; \( P = 0.395 \)], or OS (HR 3.16, 95\%CI: 0.61-16.45; \( P = 0.15 \))\cite{37}. Similarly, the phase III trial RADIANT evaluated erlotinib for 2 yr vs placebo, after completion of standard adjuvant treatment, in 973 patients with resected stage IB-IIIA NSCLC with EGFR expression/amplification. There were no significant differences in DFS or OS between the two arms. However, when the data from the 161 patients with EGFR-activating mutations were analysed, DFS was better with erlotinib (46.4 vs 28.5 mo; HR: 0.61, 95\%CI: 0.384-0.981; \( P = 0.039 \)), but this did not reach statistical significance due to the hierarchical analysis established in the study design. The 2-year DFS was 75\% and 54\% for erlotinib and placebo, respectively\cite{38}.

Although there was a marked difference between the two study arms in patients with EGFR mutation, it should be noted that certain imbalances in the patient characteristics may have influenced these results (more patients with stage IB in the erlotinib arm; in the placebo arm, more patients were in stage IIIA and 44\% of patients did not receive previous adjuvant chemotherapy).

Following the discovery that the presence of EGFR mutation favours response to EGFR TKIs, multiple trials have been performed to evaluate these agents as adjuvant treatment in patients with EGFR mutations. SELECT was a phase II single-arm trial that included 100 patients with resected stage IA-IIIA EGFR-mutated NSCLC, who, after completing standard adjuvant treatment, received erlotinib for 2 years. The 2-year DFS was 88\%, which was significantly higher than the 76\% observed in historic controls (\( P = 0.0047 \)). The 5-year DFS and OS were 56\% and 86\%, respectively. It is important to mention that of the 40 patients who had disease recurrence, this occurred during treatment in only 4; in the other 36 it occurred after stopping erlotinib\cite{39}. In the phase III trial ADJUVANT/CTONG1104, 222 patients with resected stage II-IIIA EGFR-mutated NSCLC were randomly assigned to receive gefitinib for 2 yr or cisplatin plus vinorelbine for 4 cycles. With a median follow-up of 36.5 mo, the median DFS was significantly longer with gefitinib than with cisplatin plus vinorelbine (28.7 vs 18 mo; HR: 0.60, 95\%CI: 0.42-0.87; \( P = 0.0054 \))\cite{40}. However, with longer follow-up, no statistically significant difference was observed between the two arms for 3-year DFS (39.6\% vs 32.5\%; \( P = 0.316 \)), 5-year DFS (22.6\% vs 23.2\%; \( P = 0.928 \)), or OS (75.5\% vs 62.8\%; HR: 0.92, 95\%CI: 0.62-1.36; \( P = 0.674 \))\cite{41}. Likewise, Tada et al conducted the phase III IMPACT study, which included 234 patients with resected stage II-III EGFR-mutated NSCLC randomized to receive gefitinib for 2 yr or cisplatin plus vinorelbine...
Table 1: Clinical trials of adjuvant epidermal growth factor receptor-mutated tyrosine kinase inhibitors in epidermal growth factor receptor-mutated non-small-cell lung cancer

| Clinical trial                  | Type of trial | Sample size | Primary outcome | Stage | Treatment                  | Previous adjuvant chemotherapy | TKI Duration | DFS | OS |
|--------------------------------|---------------|-------------|-----------------|------|----------------------------|--------------------------------|--------------|-----|-----|
| BR19, Goss et al[37]           | Phase III     | 503 (15 with EGFR mutation) | OS      | IB-IIIA | Gefitinib vs placebo | Yes (17% in gefitinib arm and 17% in placebo arm) | 2 yr         | HR 1.84; $P = 0.395$ | HR: 3.16; $P = 0.15$ |
| RADIANT, Kelly et al[38]       | Phase III     | 973 (161 with EGFR mutation) | DFS (ITT population) | IB-IIIA | Erlotinib vs placebo | Yes (45.1% in erlotinib arm and 55.9% in placebo arm) | 2 yr         | 46.4 vs 28.5 mo; HR: 0.61; $P = 0.039^1$ | Median OS NR in both arms; HR: 1.08; $P < 0.001$ |
| SELECT, Pennell et al[39]      | Phase II      | 100         | 2-yr DFS        | IA-IIIA | Erlotinib        | Yes (not reported)                          | 2 yr         | Median DFS NR; 2-yr DFS 88%; 3-yr DFS 56% | Median OS NR, 5-yr OS 86% |
| ADJUVANT/CTONG1104, Zhong et al[40,41] | Phase III     | 222         | DFS             | II-IIIA | Gefitinib vs cisplatin-vinorelbine | No                            | 2 yr         | 28.7 vs 18 mo; HR: 0.60; $P = 0.0054$ | 75.5 vs 62.8 mo; HR: 0.92; $P = 0.674$ |
| IMPACT, Tada et al[42]         | Phase III     | 234         | DFS             | II-III  | Gefitinib vs cisplatin-vinorelbine | No                            | 2 yr         | 36 vs 25.2 mo; HR: 0.92; $P = 0.63$ | Median OS NR in both arms; HR: 1.03; $P = 0.89$ |
| EVAN, Yue et al[43]            | Phase II      | 102         | 2-yr DFS        | IIIA   | Erlotinib        | No                            | 2 yr         | 42.4 vs 21 mo; HR: 0.268; $P < 0.0001$ | Median OS NR in both arms; HR: 0.165; $P = 0.0013$ |
| Neal et al[44]                 | Phase II      | 46          | 2-yr DFS        | IA-IIIA | Afatinib 3 mo vs 2 yr | Yes (52% in 3-mo arm and 45% in 2-yr arm) | 3 mo vs 2 yr | 42.8 vs 58.6 mo | Median OS NR in both arms |
| ADAURA, Wu et al[45]           | Phase III     | 682         | DFS in stages II-IIIA | IB-IIIA | Osimertinib vs placebo | Yes (60% in both arms) | 3 yr         | Stages II-IIIA: NR vs 19.6 mo; HR: 0.17; $P < 0.001$ | Median OS NR in both arms (immature OS data) |

$^1$Results in EGFR-mutated population. EGFR: Epidermal growth factor receptor; DFS: Disease-free survival; HR: Hazard ratio; ITT: Intention to treat; NR: Not reached; OS: Overall survival; TKI: Tyrosine kinase inhibitor.

The results were recently reported, with no differences observed in DFS (36 vs 25.2 mo; HR: 0.92; 95% CI: 0.67-1.28; $P = 0.63$) or OS (median not reached in either arm; HR: 1.03, 95% CI: 0.65-1.65; $P = 0.89$) between the two arms[42]. The ADJUVANT/CTONG1104 and IMPACT trials, with similar designs, showed an initial separation of the DFS curves, which overlap around 48 mo, suggesting that adjuvant treatment with EGFR TKIs only delays relapse.

The lack of results demonstrating a benefit in OS and the heterogeneous populations (stages IA-IIIA) included in the various clinical trials prompted the phase II
randomised trial EVAN, which evaluated erlotinib for 2 yr vs cisplatin plus vinorelbine for 4 cycles, as an adjuvant treatment, in a specific population of 102 patients with resected stage IIIA EGFR-mutated NSCLC who had received no previous treatment[43]. The median DFS was significantly longer with erlotinib than with chemotherapy (42.4 vs 21 mo; HR: 0.268, 95%CI: 0.136-0.531; \( P < 0.0001 \)). Both 2-year DFS (81.4% vs 44.6%; \( P = 0.0054 \)), and 3-year DFS (54.2% vs 19.8%; \( P = 0.0460 \)) were significantly higher with erlotinib. However, this study had several limitations, including the small sample size and the high percentage of patients (35%) in the chemotherapy-therapy arm who did not meet the per protocol population criteria (8 patients who did not receive chemotherapy and 11 major protocol deviations), which could have influenced the difference in DFS between the two study arms. Furthermore, in this study, PET scan was not performed as part of screening; this, in addition to the patients with stage IIIA having a high probability of micrometastatic disease[10], means that a percentage of patients, rather than an adjuvant treatment, could have been receiving treatment for advanced disease—a situation in which it is already known that EGFR TKIs are superior to chemotherapy. Afatinib, the second-generation EGFR TKI, which was the first to demonstrate a benefit in OS in patients with advanced EGFR-mutated NSCLC[13], was also assessed as an adjuvant, in a phase II clinical trial comparing afatinib for 2 yr vs afatinib for 3 mo, in 46 patients with resected stage I-A IIIA EGFR-mutated NSCLC, who had previously received standard adjuvant treatment. The 2-year DFS was numerically higher with 2 yr of afatinib than with 3 mo (81% vs 70%; \( P = 0.55 \)), but this difference did not reach statistical significance, although it must be recognised that certain limitations of the study such as the small sample size and low percentage of patients who completed treatment in the 2-year group (41%) could have influenced the lack of statistical significance[44].

Osimertinib, a third-generation EGFR TKI, was evaluated as first-line treatment for EGFR-mutated NSCLC in the phase III trial FLAURA, showing longer survival and greater central nervous system (CNS) efficacy than erlotinib or gefitinib[15,16]. The high efficacy demonstrated by this agent in advanced disease and the lack of robust results supporting the use of EGFR TKIs as adjuvant treatment led Wu et al to conduct the phase III trial ADAURA. This included 682 patients with resected stage IB-IIIA EGFR-mutated NSCLC, who, after completing standard adjuvant chemotherapy, were randomly assigned to receive osimertinib or placebo for 3 yr. The primary outcome of the study was DFS in patients in stages II-III A. After an interim analysis that was not planned as part of the protocol, the independent monitoring committee recommended unblinding of the study, due to evidence of a clear benefit in favour of osimertinib. In patients with stage II-III A disease, osimertinib markedly improved DFS (not reached vs 19.6 mo; HR: 0.17, 99.06%CI: 0.11-0.26; \( P < 0.001 \)) in comparison with placebo, the 2-year DFS being 90% and 44%, respectively. These results were consistent in the total population (median not reached vs 27.5 mo; 2-year DFS 89% vs 52%; HR: 0.20, 99.12%CI: 0.14-0.30; \( P < 0.001 \)), and a reduction was also observed in risk of CNS recurrence or death (HR 0.18, 95%CI: 0.10-0.33) [45].

While the benefit observed with osimertinib in terms of DFS was striking, many questions were raised regarding whether these results, with a median follow-up of 22 mo in an adjuvant trial, were sufficient to position osimertinib as a standard treatment in this situation. Recently, Zhong et al[41] published the updated data from the ADJUVANT/CTONG1104 trial, confirming a benefit in DFS, but which ultimately did not translate to an OS benefit. In addition, multiple meta-analyses have analysed the role of EGFR TKIs as adjuvant treatment in patients with NSCLC with an EGFR-activating mutation, showing a benefit in DFS but not OS[46-48].

Although, overall, the trials with first- and second-generation TKIs showed a benefit in DFS, the high number of recurrences after stopping adjuvant treatment with EGFR TKIs in the different studies was striking. In the ADJUVANT/CTONG1104 trial, the difference in DFS observed between the two arms was smaller with a longer follow-up [41], while in the SELECT trial, 90% of recurrences occurred after stopping erlotinib [39]. These findings suggest that adjuvant treatment with EGFR TKIs delays recurrence but does not prevent it, and therefore does not appear to be able to change the natural history of the disease by curing more patients.

Although multiple studies have evaluated the role of EGFR TKIs as adjuvant therapy, the question of whether previous adjuvant chemotherapy is necessary remains unanswered. An indirect comparison of the DFS results from RADIANT, SELECT, and the phase II afatinib trial with those from the ADJUVANT/CTONG1104 trial suggests that giving an EGFR TKI after standard adjuvant treatment provides a greater benefit in DFS than giving an EGFR TKI as a sole adjuvant treatment[18]. In the ADAURA trial, 60% of patients in the osimertinib arm received adjuvant chemotherapy, which could have led to a greater benefit in the experimental arm, and the
lack of adjuvant chemotherapy in 40% of the control arm patients could have led to a more marked difference between the two arms.

It should be borne in mind that EGFR TKIs given for a prolonged period cause toxicity[38,39,44,45], which can negatively affect quality of life in patients who are considered disease-free. If we were to treat all patients with resected EGFR-mutated NSCLC with adjuvant EGFR TKIs, we would be over-treating a group of patients that may already be cured, meaning we would not be adding any benefit and only worsening their quality of life.

Another point under discussion is the response to EGFR TKIs in patients with recurrence after receiving adjuvant therapy. In the SELECT study, only one patient with recurrence during erlotinib treatment was found to have a T790M mutation, and 65% of patients with recurrence were retreated with erlotinib, reaching a median treatment duration of 13 mo[39]. Likewise, in the ADJUVANT/CTONG1104 trial, 36.8% of patients with recurrence in the gefitinib arm were treated with EGFR TKIs, achieving a response rate of 46.4%[41]. While the results available so far suggest that adjuvant treatment with EGFR TKIs does not appear to affect sensitivity to these agents in patients with recurrence, there is still insufficient evidence and we cannot draw definitive conclusions regarding the potential development of resistance to these agents.

Targeted treatments and immunotherapy have been shown to significantly prolong OS in advanced NSCLC; however, high prices make access difficult, so many patients cannot benefit from these agents. Osimertinib is a very expensive drug and the ADAURA study proposed a prolonged treatment, so it is reasonable to demand a strong benefit in OS that justifies its use, especially as there would be a group of patients receiving adjuvant osimertinib who may already be cured and would therefore be overtreated at the expense of toxicity and a very high economic cost[19,49,50].

Finally, a significant improvement in DFS that does not translate to a significant improvement in OS has been a constant finding in adjuvant studies of EGFR TKIs, which raises the issue of whether DFS is a suitable primary outcome in adjuvant studies[19]. Although, in the past, DFS was considered a surrogate for OS in NSCLC [51], this is only applicable for chemotherapy[50], and nowadays, in the era of targeted therapies, with more treatment options available, there is a greater probability that OS will be affected by subsequent treatments, as has been seen in multiple studies with EGFR TKIs in patients with advanced disease[52]. One possible explanation for the lack of OS benefit in adjuvant studies is that, in patients in the control arm, treatment with EGFR TKIs at the time of recurrence could have attenuated a potential benefit in OS, if present[20]. This makes us question whether we really should treat all these patients with adjuvant EGFR TKIs, if treating only patients with recurrence would achieve the same results. We must await the OS results from the ADAURA trial, but it is likely that these will be affected by the early termination of the study[19], and that we will never know if this dramatic benefit in DFS translates to a higher patient cure rate. Currently, the phase III trial ALCHEMIST (A081105) is underway, which compares erlotinib for 2 yr vs placebo, in patients with completely-resected stage IB-IIIA EGFR-mutated NSCLC, after standard adjuvant treatment. The primary outcome of this study is OS[53], and it could give us more information on the role of EGFR TKIs in this setting.

**EGFR TKIS AS TREATMENT FOR POTENTIALLY-RESECTABLE LOCALLY-ADVANCED DISEASE**

Locally-advanced NSCLC is associated with a poor prognosis[54]. Although such patients are treated with curative intent, the 5-year OS rates are low. In this situation, pathological complete response (pCR) after a preoperative treatment has been correlated with OS[55]. However, neoadjuvant chemotherapy achieves pCR rates that range from 0-16%[56]. Currently, ongoing research aims to translate the benefits from targeted therapy and immunotherapy to potentially-resectable disease.

Neoadjuvant immunotherapy, with or without chemotherapy, is being assessed in multiple clinical trials, with promising results[57,58]. Provencio et al carried out the phase II clinical trial NADIM, in which a surprising pCR of 63% was reported with chemotherapy plus nivolumab[59].

EGFR TKIs are also being assessed for use as neoadjuvant treatment in NSCLC (Table 2). Zhong et al[41] carried out a small phase II trial in which they assessed the feasibility of giving neoadjuvant treatment guided by EGFR status, in 24 patients with stage IIIA NSCLC. Patients with mutated EGFR received erlotinib for 42 d, while
patients with native EGFR received carboplatin plus gemcitabine for 3 cycles. Although the response rate (RR) was numerically higher with erlotinib (58.3% vs 25%; \( P = 0.18 \)), there was no increase in the N2 pCR (16.7% vs 25%; \( P = 0.64 \)) or in OS (14.5 vs 28.1 mo; \( P = 0.201 \)) [60]. A different phase II single-arm trial included 25 patients with stage III A EGFR-mutated NSCLC treated with neoadjuvant erlotinib for 56 d, observing a RR of 42.1%, with a resectability rate of 68.4%. On pathology, 50% partial responses were reported, but no complete response [61]. Similarly, Xiong et al conducted a phase II clinical trial in patients with stage III A NSCLC, in which they compared neoadjuvant treatment with erlotinib for 4-7 wk (15 patients with EGFR mutation) and cisplatin-based doublet chemotherapy for 2 cycles (16 patients without EGFR mutation), observing a RR (67% vs 19%) and an OS (51 vs 20.9 mo) that were numerically higher in the patients treated with erlotinib. The pathological response was higher in the erlotinib group (67% vs 38%), although this difference was not statistically significant and there was no pCR in this group [62]. Finally, the phase II trial EMERGING-CTONG 1103 included 72 patients with stage III A EGFR-mutated NSCLC, randomly assigned to erlotinib (42 d neoadjuvant and 12 mo adjuvant) vs cisplatin plus gemcitabine (2 cycles neoadjuvant and 2 cycles adjuvant). There were no significant differences in RR (54.1% vs 34.3%; \( P = 0.092 \)) or OS (45.8 vs 39.2 mo; HR: 0.77, 95% CI: 0.41-1.45; \( P = 0.417 \)), and pCR was not observed in either arm [63]. Final analysis of OS was recently reported, with similar results (42.2 vs 36.9 mo; HR: 0.83; 95% CI: 0.47-1.47; \( P = 0.513 \)) [64].

The small sample sizes and heterogeneity of these phase II trials do not allow us to draw definitive conclusions regarding efficacy. There was a remarkable lack of pCR in these studies; in addition, the response rates appear to be lower than those observed with EGFR TKIs as first-line treatment [31, 33, 34, 36], which could be due to the short preoperative treatment duration in these trials. Although neoadjuvant treatment with these agents appears feasible, there remain many unanswered questions, such as the risk of disease flare after stopping EGFR TKI treatment [65]; randomised trials with larger sample sizes are needed to provide more data on the safety and efficacy of these agents in potentially-resectable disease. Currently underway is the phase III clinical trial NeoADAURA (ClinicalTrials.gov number, NCT04351555), which compares osimertinib for 9 wk with or without chemotherapy for 3 cycles vs chemotherapy alone for 3 cycles, as neoadjuvant treatment, in patients with stage II-IIIB EGFR-mutated NSCLC, followed by adjuvant osimertinib for 3 yr. This trial could provide more information on the optimal duration of preoperative treatment, the role of chemotherapy in this scenario, and the need for adjuvant treatment.
**Table 3 Clinical trials of pidermal growth factor receptor tyrosine kinase inhibitors in the management of unresectable pidermal growth factor receptor-mutated non-small-cell lung cancer**

| Clinical trial                     | Type of study | Sample size | Primary outcome | Stage       | Treatment                                                                 | TKI duration | RR          | PFS         | OS          |
|-----------------------------------|---------------|-------------|-----------------|-------------|---------------------------------------------------------------------------|--------------|-------------|-------------|-------------|
| RECEL, Xing et al[70]             | Phase II      | 40          | PFS             | III         | Erlotinib + RT vs cisplatin-etoposide + RT                               | 2 yr         | 70% vs 61.9%; P = 0.744 | 24.5 vs 9 mo; HR: 0.104; P < 0.001 | Not reported |
| Lee et al[71]                     | Phase II      | 59 (12 with EGFR mutation) | RR, toxicity and OS | III         | EGFR mutation: erlotinib x 3 → erlotinib+RT → erlotinib x 6 vs erlotinib x 3 → cisplatin-irinotecan+RT Native/unknown EGFR: cisplatin-irinotecan x 3 → cisplatin-irinotecan+RT → cisplatin-irinotecan x 3 | 33 wk        | EGFR mutation: 71.4% vs 80% Native/unknown EGFR: 70% vs 73.9% Native/unknown EGFR: 9 vs 12.3 mo | EGFR mutation: 39.3 vs 31.2 mo Mutated vs native EGFR: 74.8 vs 25.3 mo, P = 0.034 |
| LOGIK0902/OLCSG0905, Saeki et al[73] | Phase II     | 20          | 2-yr OS         | III         | Gefitinib cisplatin-docetaxel+RT                                         | 8 wk         | 85%          | 2-yr PFS 36.9% | 2-yr OS 90% |

HR: Hazard ratio; OS: Overall survival; PFS: Progression-free survival; RR: Response rate; RT: Radiotherapy; TKI: Tyrosine kinase inhibitors.

**EGFR TKIS AS TREATMENT FOR UNRESECTABLE LOCALLY-ADVANCED DISEASE**

The phase III PACIFIC trial demonstrated that maintenance with durvalumab after chemoradiotherapy, in patients with unresectable stage III NSCLC, significantly prolonged DFS and OS[66,67], positioning it as the standard treatment for these patients. Despite the good outcomes with this treatment strategy, approximately 44% of patients had progression and died from the disease[67]. Therefore, there is a need for new biomarker-guided therapies that would allow us to appropriately select the best treatment for each patient.

The PACIFIC trial subgroup analysis suggests that patients with EGFR mutation may benefit less from chemoradiotherapy followed by durvalumab[66]. This is probably due to the biology of EGFR-mutated NSCLC, which is associated with a higher risk of metastasis, meaning these patients obtain a greater benefit from local treatment such as chemoradiotherapy[68,69]. Thus, the optimal treatment in this patient subgroup is unknown.

Preclinical studies suggest that EGFR TKIs have a radiosensitizing effect[21,22]. This has prompted several clinical trials to evaluate the role of these targeted agents in unresectable locally-advanced disease (Table 3). The phase II trial RECEL compared erlotinib (for 2 yr) or cisplatin plus etoposide, concomitantly with radiotherapy in 40 patients with unresectable stage III EGFR-mutated NSCLC, and demonstrated that erlotinib plus radiotherapy significantly prolonged DFS (24.5 vs 9 mo; HR: 0.104, 95%CI: 0.028-0.389; P < 0.001) compared to chemoradiotherapy[70]. A different phase II study by Lee et al included 59 patients with unresectable stage III NSCLC, of whom
12 had an EGFR-activating mutation. Patients with mutated EGFR were randomised to erlotinib for 3 cycles, followed by erlotinib plus radiotherapy, followed by erlotinib for 6 cycles, vs erlotinib for 3 cycles followed by chemoradiotherapy with cisplatin plus irinotecan; patients with native/unknown EGFR status were randomised to cisplatin plus irinotecan for 3 cycles before or after chemoradiotherapy with cisplatin plus irinotecan. Patients with mutated EGFR had a significantly longer OS (74.8 vs 25.3 mo, P = 0.034) than patients with native EGFR. Gefitinib has also been assessed, in the phase II trial LOGIK0902/OLC8905[72], which included 20 patients with unresectable stage III EGFR-mutated NSCLC who were treated with gefitinib for 8 wk followed by chemoradiotherapy with cisplatin plus docetaxel, and found a RR of 85%, a 2-year DFS rate of 36.9%, and a 2-year OS of 90%[73].

Although these phase II studies show encouraging results, they must be confirmed in phase III clinical trials. Currently, the phase III LAURA trial is underway, comparing osimertinib until progression vs placebo, as maintenance treatment after standard chemoradiotherapy[74].

CONCLUSION

Adjuvant treatment with first- and second-generation EGFR TKIs, in patients with resected EGFR-mutated NSCLC, has demonstrated a benefit in DFS, which does not translate to OS. Surprisingly, in the ADAURA trial, the third-generation EGFR TKI osimertinib prolonged DFS in these patients; however, certain limitations of the design of this study and its early termination based on a benefit in DFS only, raise questions about its use as a standard adjuvant treatment. The OS data from the ADAURA trial and the results of the ALCHEMIST trial will confirm if EGFR TKIs have a role as adjuvant treatment.

These targeted therapies are also undergoing evaluation in potentially-resectable and unresectable locally-advanced disease, with encouraging results; however, we must await the results of the phase III trials NeoADAURA and LAURA, which should provide more data on the safety and efficacy of EGFR TKIs in these situations.

REFERENCES

1. Langer CJ, Besse B, Gualberto A, Brambilla E, Soria JC. The evolving role of histology in the management of advanced non-small-cell lung cancer. J Clin Oncol 2010; 28: 5311-5320 [PMID: 21079145 DOI: 10.1200/JCO.2010.28.8126]
2. Bradbury P, Sivajohananthan D, Chan A, Kalkarni S, Ung Y, Ellis PM. Postoperative Adjuvant Systemic Therapy in Completely Resected Non-Small-Cell Lung Cancer: A Systematic Review. Clin Lung Cancer 2017; 18: 259-273.e8 [PMID: 28162945 DOI: 10.1016/j.cllc.2016.07.002]
3. Wakelee H, Chhatwani L. Adjuvant chemotherapy for resected non-small cell lung cancer. Semin Thorac Cardiovasc Surg 2008; 20: 198-203 [PMID: 19038728 DOI: 10.1053/j.semtcvs.2008.09.001]
4. Molina JR, Yang P, Cossivi SD, Schild SE, Adjei AA. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc 2008; 83: 584-594 [PMID: 18452692 DOI: 10.4065/83.5.584]
5. Le Chevalier T. Adjuvant chemotherapy for resectable non-small-cell lung cancer: where is it going? Ann Oncol 2010; 21 Suppl 7: vii196-vii198 [PMID: 20943614 DOI: 10.1093/annonc/mdq376]
6. Heon S, Johnson BE. Adjuvant chemotherapy for surgically resected non-small cell lung cancer. J Thorac Cardiovasc Surg 2012; 144: S39-S42 [PMID: 22502967 DOI: 10.1016/j.jtcvs.2012.03.039]
7. Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, Postmus PE, Rusch V, Sobin L; International Association for the Study of Lung Cancer International Staging Committee; Participating Institutions. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. J Thorac Oncol 2007; 2: 706-714 [PMID: 17762336 DOI: 10.1097/JTO.0b013e31812f3c1a]
8. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, Dunant A, Torri V, Rosell R, Seymour L, Sprio SG, Rolland E, Fossati R, Aubert D, Ding K, Waller D, Le Chevalier T; LACE Collaborative Group. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008; 26: 3552-3559 [PMID: 18506026 DOI: 10.1200/JCO.2007.13.9030]
9. Friedlaender A, Addio A, Russo A, Gregoric V, Cortinovis D, Rolfo CD. Targeted Therapies in Early Stage NSCLC: Hype or Hope? Int J Mol Sci 2020; 21 [PMID: 32878298 DOI: 10.3390/ijms21173629]
10. Deng XF, Jiang L, Liu QX, Zhou D, Hou B, Cui K, Min JX, Dai JG. Lymph node micrometastases are associated with disease recurrence and poor survival for early-stage non-small cell lung cancer patients: a meta-analysis. J Cardiothorac Surg 2016; 11: 28 [PMID: 26883746 DOI: ]
Recent advances of early EGFR-mutated NSCLC’s management

11 NSCLC Meta-analyses Collaborative Group. Arriagada R, Auperin A, Burdett S, Higgins JP, Johnson DH, Le Chevalier T, Le Peuchoux C, Parmar MK, Pignon JP, Souhami RL, Stephens RJ, Stewart LA, Tierney JF, Tribodet H, van Meerbeeck J. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet 2010; 375: 1267-1277 [PMID: 20338627 DOI: 10.1016/S0140-6736(10)6059-1]

12 Burdett S, Pignon JP, Tierney J, Tribodet H, Stewart L, Le Peuchoux C, Auperin A, Le Chevalier T, Stephens RJ, Arriagada R, Higgins JP, Johnson DH, Van Meerbeeck J, Parmar MK, Souhami RL, Bergman B, Douillard JY, Dunant A, Endo C, Girling D, Kato H, Keller SM, Kimura H, Kuuttila A, Kodama K, Komaki R, Kris MG, Lad T, Mineo T, Piantadosi S, Rosell R, Scaglotti G, Seymour LK, Shepherd FA, Sylvester R, Tada H, Tanaka F, Torri V, Waller D, Liang Y; Non-Small Cell Lung Cancer Collaborative Group. Adjuvant chemotherapy for resected early-stage non-small cell lung cancer. Cochrane Database Syst Rev 2015; CD011430 [PMID: 25730344 DOI: 10.1002/14651858.CD011430]

13 Yang JC, Wu YL, Schuler M, Sebastian M, Popat S, Yamamoto N, Zhou C, Hu CP, O’Byrne K, Feng J, Lu S, Huang Y, Greater SL, Lee KY, Tsai CM, Gorbonova V, Hirsh V, Bennouna J, Orlov S, Mok T, Boyer M, Su WC, Lee KH, Kato T, Massey D, Shahidi M, Zazulina V, Sequist LV. Afatinib vs cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LU-Lung 3 and LU-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. Lancet Oncol 2015; 16: 141-151 [PMID: 25589191 DOI: 10.1016/S1470-2045(14)71173-8]

14 Wu YL, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S, Tsuji F, Linke R, Rosell R, Corral J, Migliorino MR, Pluzanski A, Shao EL, Wang T, White JL, Nadanaciva S, Sandin R, Mok TS. Dacomitinib vs gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. Lancet Oncol 2017; 18: 1454-1466 [PMID: 28955802 DOI: 10.1016/S1470-2045(17)30608-3]

15 Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, Dechaphukhul A, Imamura F, Nogami N, Kurata T, Okamoto I, Zhou C, Cho BC, Cheng Y, Cho EK, Voon PJ, Planchar D, Su WC, Gray JE, Lee SM, Hodges R, Marotti M, Rukazenkov Y, Ramalingam SS; FLAURA Investigators. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2018; 378: 113-125 [PMID: 29151359 DOI: 10.1056/NEJMoa1713137]

16 Ramalingam SS, Vansteenkiste J, Planchar D, Cho BC, Gray JE, Ohe Y, Zhou C, Reungwetwattana T, Cheng Y, Chewaskulyong B, Shah R, Cobo M, Lee KH, Cheepe P, Tiseo M, John T, Lin MC, Imamura F, Kurata T, Todd A, Hodges R, Saggese M, Rukazenkov Y, Soria JC; FLAURA Investigators. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. N Engl J Med 2020; 382: 41-50 [PMID: 31751012 DOI: 10.1056/NEJMoa1913662]

17 Mok TS, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S, Chawla A, Rosell R, Corral J, Migliorino MR, Pluzanski A, Noonan K, Tang Y, Pastel M, Wilner KD, Wu YL. Updated Overall Survival in a Randomized Study Comparing Dacomitinib with Gefitinib as First-Line Treatment in Patients with Advanced Non-Small-Cell Lung Cancer and EGFR-Activating Mutations. Drugs 2021; 81: 257-266 [PMID: 33331989 DOI: 10.21037/drugs-2021-04-144]

18 Gridelli C, Casaluce F. The adjuvant regimen for resected EGFR mutated patients: the "same-for-all" or not? Ann Transl Med 2020; 8: 1195 [PMID: 33241044 DOI: 10.21037/atm-20-3170]

19 Ghyawali B, West HJ. Lessons From ADAURA on Adjuvant Cancer Drug Trials: Evidence, Ethics, and Economics. J Clin Oncol 2021; 39: 175-177 [PMID: 33275490 DOI: 10.1200/JCO.20.01762]

20 Waqar SN, Govindan R. Adjuvant Therapy With EGFR Tyrosine Kinase Inhibitors: Tempering Great Expectations With Realism. J Clin Oncol 2021; 39: 697-700 [PMID: 33417483 DOI: 10.1200/JCO.20.03297]

21 Singhie EK, Gay CM. Narrative review of the emerging role of molecular biomarkers in guiding the definitive management of unresectable non-small cell lung cancer. Transl Lung Cancer Res 2020; 9: 2051-2058 [PMID: 33029625 DOI: 10.21037/tlcr-20-330]

22 Jiang L, Meng X, Zhao X, Xing L, Yu J. Perspective on treatment for unresectable locally advanced non-small cell lung cancer with oncogene-driven mutation: a narrative review. Transl Lung Cancer Res 2020; 9: 2137-2144 [PMID: 32909632 DOI: 10.21037/tlcr-20-722]

23 Gong J, Zhang L. Tyrosine kinase inhibitors as induction therapy in nonsmall-cell lung cancer. Curr Opin Oncol 2021; 33: 55-58 [PMID: 33165003 DOI: 10.1097/CCO.0000000000000696]

24 Kris MG, Johnson BE, Berry LD, Kwiakowski DJ, Iafrite AJ, Wistuba II, Varella-Garcia M, Franklin WA, Aronson SL, Su PF, Shyr Y, Camidge DR, Sequist LV, Glisson BS, Khuri FR, Garon EB, Pao W, Rudin C, Schiller J, Haura EB, Sejinski M, Shiri K, Chen H, Giaccone G, Ladanyi M, Kugler K, Minna JD, Bunn PA. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. JAMA 2014; 311: 1998-2006 [PMID: 24846037 DOI: 10.1001/jama.2014.3741]

25 Matikas A, Mistriotis D, Georgoulas V, Kotsakis A. Current and Future Approaches in the Management of Non-Small-Cell Lung Cancer Patients With Resistance to EGFR TKIs. Clin Lung Cancer 2015; 16: 252-261 [PMID: 25700775 DOI: 10.1016/j.clcc.2014.12.013]

26 Barlesi F, Mazieres J, Merlio JP, Debievre D, Mosser J, Lena H, Ouafik L, Besse B, Rouquette I, Westeel E, Escande F, Monnet I, Lemoine A, Veillon R, Blons H, Audigier-Valette C, Bringuey PP, Lamy R, Beau-Faller M, Pujol JL, Sabourin JC, Penault-Llorca F, Denis MG, Lantuejoul S, Morin F, Tran Q, Missy P, Langlais A, Milleron B, Cadranel J, Soria JC, Zalcman G; Biomarkers France contributors. Routine molecular profiling of patients with advanced non-small-cell lung cancer: results of a 1-year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT). Lancet

DOI: 10.1186/s13019-016-0427-x

Sotelo MJ et al. Recent advances of early EGFR-mutated NSCLC’s management
Sotelo MJ et al. Recent advances of early EGFR-mutated NSCLC’s management

2016; 387: 1415-1426 [PMID: 26777916 DOI: 10.1016/S0140-6736(16)00004-0]

27 Reaz LE, Cardona AF, Santos ES, Cateo H, Rolfo C, Lopes G, Barrios C, Mas LA, Vallejos C, Zatarain-Barrón ZL, Caglelic V, Arrieta O. The burden of lung cancer in Latin-America and challenges in the access to genomic profiling, immunotherapy and targeted treatments. *Lung Cancer* 2018; 119: 7-13 [PMID: 29657535 DOI: 10.1016/j.lungcan.2018.02.014]

28 Shi Y, Au JS, Thongprasert S, Srinivasan S, Tsai CM, Khoa MT, Heeroma K, Itoh Y, Cornelio G, Yang PC. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). *J Thorac Oncol* 2014; 9: 154-162 [PMID: 24419411 DOI: 10.1097/JTO.0000000000000103]

29 Han B, Tjulandin S, Hagiwara K, Normanno N, Wulandari L, Laktionov K, Hudoyo A, He Y, Zhang YP, Wang MZ, Liu CY, Ratcliffe M, McCormack R, Reck M. EGFR mutation prevalence in Asia-Pacific and Russian patients with advanced NSCLC of adenocarcinoma and non-adenocarcinoma histology: The IGNITE study. *Lung Cancer* 2017; 113: 37-44 [PMID: 29110846 DOI: 10.1016/j.lungcan.2017.08.021]

30 Sequist LV, Yang JC, Yamamoto N, O’Byrne K, Hirsh V, Mok T, Geater SL, Orlov S, Tsai CM, Beyer M, Su WC, Bennouna J, Kato T, Gorbunova V, Lee KH, Shah R, Massey D, Zazzalina V, Shahidi M, Schuler M. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol* 2013; 31: 3327-3334 [PMID: 23816960 DOI: 10.1200/JCO.2012.44.2806]

31 Wu YL, Zhou C, Hu CP, Feng J, Lu S, Huang Y, Li W, Hou M, Shi JH, Lee KY, Xu CR, Massey D, Kim M, Shi Y, Geater SL. Afatinib vs cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol* 2014; 15: 213-222 [PMID: 24439229 DOI: 10.1016/S1470-2045(13)70604-1]

32 Mitsudomi T, Morita S, Yatabe Y, Nogoro S, Okamoto I, Tsutsumi T, Seto T, Satouchi M, Tada H, Hirashima T, Asami K, Katakami N, Takada M, Yoshioha K, Shibata K, Kudoh S, Shimizu E, Saito H, Toyooka S, Nakagawa K, Fukusuka M; West Japan Oncology Group. Gefitinib vs cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol* 2010; 11: 121-128 [PMID: 20022809 DOI: 10.1016/S1470-2045(09)70364-X]

33 Fukukwa M, Wu YL, Thongprasert S, Sunpaweravong P, Leong SS, Sriruampong V, Chao TY, Nakagawa K, Chu DT, Saijo N, Duffield EL, Rukazenkov Y, Speake G, Jiang H, Armour AA, To KF, Yang JC, Mok TS. biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib vs carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). *J Clin Oncol* 2011; 29: 2866-2874 [PMID: 21670455 DOI: 10.1200/JCO.2010.33.4235]

34 Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, Zhang S, Wang J, Zhou S, Ren S, Lu S, Zheng L, Hu C, Luo Y, Chen L, Ye M, Huang J, Zhi X, Zhang Y, Xiu Q, Ma J, You C. Erlotinib vs chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2011; 12: 735-742 [PMID: 21783417 DOI: 10.1016/S1470-2045(11)70184-X]

35 Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, Palermo R, Garcia-Gomez C, Pallares C, Sanchez JM, Porta R, Cobo M, Garrido P, Longo F, Moran T, Insa A, De Marinis F, Corre R, Bover I, Almio I, Dassini E, de Castro J, Milella M, Reguart N, Altavilla G, jetnicki U, Proncovich M, Moreno I, Terrasa J, Muñoz-Langa J, Valdivia J, Isla D, Domine M, Molinier O, Mazieres J, Baine N, Garcia-Campello R, Robinet G, Rodriguez-Abruña D, Lopez-Vivancos G, Gabbia V, Ferrera-Delgado L, Bombaron P, Bernabe R, Bearn A, Artal C, Cortesi E, Rolfo C, Sanchez-Ronco M, Drozdowickij A, Queralt C, de Aguirre I, Ramirez JL, Sanchez JJ, Molina MA, Taron M, Paz-Ares LM. Spanish Lung Cancer Group in collaboration with Groupe Francais de Pneumo-Cancérologie and Associazione Italiana Oncologia Toracica. Erlotinib vs standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012; 13: 239-246 [PMID: 22285168 DOI: 10.1016/S1470-2045(11)70393-X]

36 Inoue A, Kobayashi K, Maenomoto M, Sugawara S, Oizumi S, Isobe H, Gemma A, Harada M, Yoshizawa H, Kinoshita I, Fujita Y, Okinaga S, Hirano H, Yoshimori K, Harada T, Saito Y, Hagisawa K, Morita S, Nukiwa T, North-East Japan Study Group. Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemosensitive non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). *Ann Oncol* 2013; 24: 54-59 [PMID: 22967997 DOI: 10.1093/annonc/mds214]

37 Goss GD, O’Callaghan C, Lorimer I, Tsao MS, Masters GA, Jett J, Edelman MJ, Lilienbaum R, Choy H, Khuri F, Pisters K, Gandara D, Kernstine K, Butts C, Noble J, Hensign TA, Rowland K, Schiller J, Ding K, Shepherd FA. Gefitinib vs placebo in completely resected non-small-cell lung cancer: results of the NCIC CTG BR19 study. *J Clin Oncol* 2013; 31: 3320-3326 [PMID: 23980901 DOI: 10.1200/JCO.2013.51.1816]

38 Kelly K, Altorki NK, Eberhardt WE, OBrien ME, Spigel DR, Crino L, Tsai CM, Kim JH, Cho EK, Hoffman PC, Orlov SV, Serwatowski P, Wang J, Foley MA, Horan JD, Shepherd FA. Adjuvant Erlotinib Versus Placebo in Patients With Stage IB-IIIA Non-Small-Cell Lung Cancer (RADIANT): A Randomized, Double-Blind, Phase III Trial. *J Clin Oncol* 2015; 33: 4007-4014 [PMID: 26324372 DOI: 10.1200/JCO.2015.61.8918]
Penell NA, Neal JW, Chaft JE, Azzoli CG, Jänne PA, Govindan R, Evans TL, Costa DB, Wakelee HA, Heint RS, Shapiro MA, Muzikansky A, Murthy S, Lanuti M, Rusch VW, Kris MG, Sequist LV. SELECT: A Phase II Trial of Adjuvant Erlotinib in Patients With Resected Epidermal Growth Factor Receptor-Mutant Non-Small-Cell Lung Cancer. J Clin Oncol 2019; 37: 97-104 [PMID: 30444685 DOI: 10.1200/JCO.18.00131]

Zhong WZ, Wang Q, Mao WM, Xu ST, Wu L, Shen Y, Liu YY, Chen C, Cheng Y, Xu L, Wang J, Fei K, Li XF, Li J1, Huang C, Liu ZD, Xu S, Chen KN, Xu SD, Liu LX, Yu P, Wang BH, Ma HT, Yan HH, Yang XN, Zhou Q, Wu YL. ADJUVANT investigators. Gefitinib vs vinorelbine plus cisplatin as adjuvant treatment for stage II-IIIA (N1-N2) EGFR-mutant NSCLC (ADJUVANT/CTONG1104): a randomised, open-label, phase 3 study. Lancet Oncol 2018; 19: 139-148 [PMID: 29174310 DOI: 10.1016/S1470-2045(17)30729-5]

Zhong WZ, Wang Q, Mao WM, Xu ST, Wu L, Wei YC, Liu YY, Chen C, Cheng Y, Yin R, Yang F, Ren SX, Li XF, Li J, Huang C, Liu ZD, Xu S, Chen KN, Xu SD, Liu LX, Yu P, Wang BH, Ma HT, Yang JJ, Yan HH, Yang XN, Zhou SY, Qiu YL. Gefitinib Versus Vinorelbine Plus Cisplatin as Adjuvant Treatment for Stage II-IIIA (N1-N2) EGFR-Mutant NSCLC: Final Overall Survival Analysis of CTONG1104 Phase III Trial. J Clin Oncol 2021; 39: 713-722 [PMID: 33332190 DOI: 10.1200/JCO.20.01820]

Tada H, Mutsudomi T, Yamanaka T, Sugio K, Tsusboi M, Okamoto I, Iwamoto Y, Sakakura N, Sugawara S, Atagi S, Takahashi Y, Hayashi H, Okada M, Yoshikawa H, Inokawa H, Takahashi K, Higashiyama M, Yoshino I, Nakagawa K. West J Oncology Group. Adjuvant gefitinib vs cisplatin/vinorelbine in Japanese patients with completely resected, EGFR-mutated, stage II-IIIA non-small cell lung cancer (IMPACT, WJOG6410L). A randomised phase 3 trial. J Clin Oncol 2021; 39: 8501 [DOI: 10.1200/JCO.2021.39.15_suppl.8501]

Yue D, Xu S, Wang Q, Li X, Shen Y, Zhao H, Chen C, Mao W, Liu W, Liu J, Zhang L, Ma H, Li Q, Yang Y, Liu Y, Chen H, Wang C. Erlotinib vs 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. Lancet Respir Med 2018; 6: 863-873 [PMID: 30150014 DOI: 10.1016/S2213-2600(18)30277-7]

Neal JW, Costa DB, Muzikansky A, Shragger JB, Lanuti M, Huang J, Ramachandran KJ, Rangachari D, Huberman MS, Pietrowska Z, Kris MG, Azzoli CG, Sequist L V., Chaft JE. Randomized Phase II Study of 3 mo or 2 yr of Adjuvant Afatinib in Patients With Surgically Resected Stage I-II EGFR-Mutant Non-Small-Cell Lung Cancer. JCO Precis Oncol 2021; (8): 325-332 [DOI: 10.1200/PO.20.00301]

Wu YL, Tsusboi M, He J, John T, Grohe C, Majem M, Goldman JW, Laktionov K, Kim SW, Kato T, Hu HV, Lu S, Lee KY, Akewanyo C, Yu CJ, de Marinis F, Bonanno I, Dome H, Shepherd FA, Zeng L, Hodge R, Atsou A, Rukazkenov Y, Herbist RS. ADAURA Investigators. Osimertinib in Resected EGFR-Mutant Non-Small-Cell Lung Cancer. N Engl J Med 2020; 383: 1711-1723 [PMID: 32955177 DOI: 10.1056/NEJMoa2027071]

Wu JX, He Q, Ye F, Zhou QX, Chen HJ, Sun L, Wu H. EGFR-TKI-based vs non-EGFR-TKI-based adjuvant therapy in resected non-small-cell lung cancer with EGFR mutations: a meta-analysis of randomized controlled trials. Onco Targets Ther 2018; 11: 6803-6810 [PMID: 30439313 DOI: 10.2147/OTT.S174593]

Cheng H, Li JX, Wang XJ, Chen ZW, Wang RQ, Zhong HC, Wu TC, Cao QD. A meta-analysis of adjuvant EGFR-TKIs for patients with resected non-small cell lung cancer. Lung Cancer 2019; 137: 7-13 [PMID: 31520922 DOI: 10.1016/j.lungcan.2019.08.002]

Raphael J, Vincent M, Boldt G, Shah PS, Rodrigues G, Blanchette P. Adjuvant Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (TKIs) in Resected Non-Small-Cell Lung Cancer (NSCLC): A Systematic Review and Meta-analysis. Am J Clin Oncol 2019; 42: 440-445 [PMID: 30913991 DOI: 10.1097/COC.0000000000000533]

West HJ, Gyawali B. Why Not Adore ADAURA? vs7: 677-678 [PMID: 33538783 DOI: 10.1001/jamaoncol.2020.6752]

Upreti D. Osimertinib Should Not Yet Be Considered the Standard of Care for EGFR-Mutant NSCLC in the Adjuvant Setting. J Thorac Oncol 2021; 16: 371-374 [PMID: 3634721 DOI: 10.1016/j.jtho.2020.12.003]

Mauguen P, Pignon JP, Burdett S, Domerg C, Fisher D, Paulus R, Mandrekar SJ, Belani CP, Shepherd FA, Eisen T, Pang H, Collette L, Sause WT, Dahlberg SE, Crawford F, O'Brien M, Schild SE, Parmar M, Tierney JF, Le Pechoux C, Michiels S. Surrogate Lung Project Collaborative Group. Surrogate endpoints for overall survival in chemotherapy and radiotherapy trials in operable and locally advanced lung cancer: a re-analysis of meta-analyses of individual patients' data. Lancet Oncol 2013; 14: 619-626 [PMID: 23680111 DOI: 10.1016/S1470-2045(13)70158-X]

Langer CJ. Epidermal growth factor receptor inhibition in mutation-positive non-small-cell lung cancer: is afatinib better or simply newer? J Clin Oncol 2013; 31: 3363-3366 [PMID: 23980079 DOI: 10.1200/JCO.2013.49.8782]

Govindan R, Mandrekar SJ, Gerber DE, Oxnard GR, Dahlberg SE, Chaft J, Malik S, Mooney M, Abrams JS, Jänne PA, Gandara DR, Ramalingam SS, Vokes EE. Alchemists Trials: A Golden Opportunity to Transform Outcomes in Early-Stage Non-Small-Cell Lung Cancer. Clin Cancer Res 2015; 21: 5439-5444 [PMID: 26672084 DOI: 10.1158/1078-0432.CCR-15-0354]

Chansky K, Detterbeck FC, Nicholson AG, Rusch VW, Vallières E, Groome P, Kennedy C, Krasnik M, Peake M, Shemanski L, Bolejack V, Crowley JJ, Asamura H, Rami-Porta R, IASLC Staging and
Sotelo MJ et al. Recent advances of early EGFR-mutated NSCLC’s management

Prognostic Factors Committee, Advisory Boards, and Participating Institutions. The IASLC Lung Cancer Staging Project: External Validation of the Revision of the TNM Stage Groupings in the Eighth Edition of the TNM Classification of Lung Cancer. *J Thorac Oncol* 2017; 12: 1109-1121 [PMID: 28641257 DOI: 10.1016/j.jtho.2017.04.011]

**Pataer A.** Kalhorn N, Correa AM, Raso MG, Erasmus JJ, Kim ES, Behrens C, Lee JJ, Roth JA, Stewart DJ, Vapoorciyan AA, Wistuba II, Swisher SG; University of Texas MD Anderson Lung Cancer Collaborative Research Group. Histopathologic response criteria predict survival of patients with resected lung cancer after neoadjuvant chemotherapy. *J Thorac Oncol* 2012; 7: 823-832 [PMID: 22481232 DOI: 10.1097/JTO.0b013e318247f04a]

**Hellmann MD.** Chaft JE, William WN Jr, Rusch V, Pisters KM, Kalhorn N, Pataer A, Travis WD, Swisher SG, Kris MG; University of Texas MD Anderson Lung Cancer Collaborative Group. Pathological response after neoadjuvant chemotherapy in resectable non-small-cell lung cancers: proposal for the use of major pathological response as a surrogate endpoint. *Lancet Oncol* 2014; 15: e42-e50 [PMID: 24384493 DOI: 10.1016/S1470-2045(13)70334-6]

**Broderick SR.** Bott MJ. Neoadjuvant immunotherapy in patients with resectable non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2019; 158: 1471-1474 [PMID: 31628313 DOI: 10.1016/j.jtcvs.2019.06.114]

**Yi C, He Y, Xia H, Zhang H, Zhang P.** Review and perspective on adjuvant and neoadjuvant immunotherapies in NSCLC. *Onco Targets Ther* 2019; 12: 7329-7336 [PMID: 31564915 DOI: 10.2147/OTT.S218321]

**Provenco M, Nadal E, Insa A, García-Campeiro MR, Casal-Rubio J, Dómine M, Majem M, Rodríguez-Abreu D, Martínez-Martí A, De Castro Carpeño J, Cobo M, López Vivanco G, Del Barco E, Bernabé Caro R, Viñolas N, Barneto Aranda I, Viteri S, Pereira E, Royuela A, Casarrubios M, Salas Antón C, Parra ER, Wistuba I, Calvo V, Laza-Brivtiesca R, Romero A, Massuti B, Cruz-Bermúdez A. Neoadjuvant chemoradiation and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2020; 21: 1413-1422 [PMID: 32979984 DOI: 10.1016/S1470-2045(20)30453-8]

**Zhong W, Yang X, Yan H, Zhang X, Su J, Chen Z, Liao R, Nie Q, Dong S, Zhou Q, Yang J, Tu H, Wu YL.** Phase II study of biomarker-guided neoadjuvant treatment strategy for IIIA-N2 non-small cell lung cancer based on epidermal growth factor receptor mutation status. *J Hematol Oncol* 2015; 8: 54 [PMID: 25981169 DOI: 10.1186/s13045-015-0151-3]

**Xiong L, Li R, Sun J, Lou Y, Zhang W, Bai H, Wang H, Shen J, Jing B, Shi C, Zhong H, Gu A, Jiang L, Shi J, Fang W, Zhao H, Zhang J, Wang J, Ye J, Han B.** Erlotinib as Neoadjuvant Therapy in Stage IIIA (N2) EGFR Mutation-Positive Non-Small Cell Lung Cancer: A Prospective, Single-Arm, Phase II Study. *OncoEvol* 2019; 24: 157-e64 [PMID: 30158288 DOI: 10.1634/theoncologist.2018-0120]

**Xiong L, Lou Y, Bai H, Li R, Xia J, Fang W, Zhang J, Han-Zhang H, Lizardo A, Li B, Gu A, Han B.** Efficacy of erlotinib as neoadjuvant regimen in EGFR-mutant locally advanced non-small cell lung cancer patients. *J Int Med Res* 2020; 48: 300060519887275 [PMID: 31885349 DOI: 10.1177/0300060519887275]

**Zhong WZ, Chen KN, Chen C, Gu CD, Wang J, Yang XN, Mao WM, Wang Q, Qiao GB, Cheng Y, Xu L, Wang CL, Chen MW, Kang X, Yan W, Yan HH, Liao RQ, Yang JJ, Zhang XC, Zhou Q, Wu YL.** Erlotinib Versus Gemcitabine Plus Cisplatin as Neoadjuvant Treatment of Stage IIIA-N2 EGFR-Mutant Non-Small-Cell Lung Cancer (EMERGING-CTONG1103): A Randomized Phase II Study. *Clin Oncol* 2019; 37: 2235-2245 [PMID: 31194613 DOI: 10.1016/J.CONC.2019.00775]

**Wu Y-L, Zhong W, Chen K-N, Chen C, Yang F, Yang X-N, Gu C, Mao W, Wang Q, Qiao G-B, Cheng Y, Xu L, Wang C, Chen M, Yan H-H, Liao R-Q, Zhang X, Yang J, Liu S-Y, Zhou Q, The EMERGING Investigators.** CTONG1103: Final overall survival analysis of the randomized phase 2 trial of erlotinib vs gemcitabine plus cisplatin as neoadjuvant treatment of stage IIIA-N2 EGFR-mutant non-small cell lung cancer. *J Clin Oncol* 2021; 39: 8502 [DOI: 10.1200/JCO.2021.39_suppl.8502]

**Chaft JE, Oxnard GR, Sima CS, Kris MG, Miller VA, Riely GJ.** Disease flare after tyrosine kinase inhibitor discontinuation in patients with EGFR-mutant lung cancer and acquired resistance to erlotinib or gefitinib: implications for clinical trial design. *Clin Cancer Res* 2011; 17: 6298-6303 [PMID: 21356766 DOI: 10.1158/1078-0432.CCR-11-1468]

**Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, Yokoi T, Chiappori A, Lee KH, de Wit M, Cho BC, Bouruba M, Quantin X, Tokito T, Mekhaiil T, Planched D, Kim YC, Karapetis CS, Hirer S, Ostoros G, Kubota K, Gray JE, Paz-Ares L, de Castro Carpeño J, Wadsworth C, Melillo G, Jiang H, Huang Y, Dennis PA, Özgüroğlu M; PACIFIC Investigators.** Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. *N Engl J Med* 2017; 377: 1919-1929 [PMID: 28885881 DOI: 10.1056/NEJMoa1709937]

**Gray JE, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, Kuraata T, Chiappori A, Lee KH, Cho BC, Planched D, Paz-Ares L, Faivre-Finn C, Vansteenkiste JF, Spigel DR, Wadsworth C, Taboada M, Dennis PA, Özgüroğlu M, Antonia SJ.** Three-Year Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC-Update from PACIFIC. *J Thorac Oncol* 2020; 15: 288-293 [PMID: 31622733 DOI: 10.1016/j.jtho.2019.10.002]

**Tanaka K, Hida T, Oya Y, Oguri T, Yoshida T, Shinmizu J, Horio Y, Hata A, Kaji R, Fujita S, Sekido Y, Kodaira T, Kokubo M, Katakami N, Yatabe Y.** EGFR Mutation Impact on Definitive Concurrent Chemoradiation Therapy for Inoperable Stage III Adenocarcinoma. *J Thorac Oncol* 2015; 10: 1720-1725 [PMID: 26743835 DOI: 10.1097/JTO.0000000000000675]
Nakamura M, Kageyama SI, Niho S, Okumura M, Hojo H, Motegi A, Nakamura N, Zenda S, Yoh K, Goto K, Akimoto T. Impact of EGFR Mutation and ALK Translocation on Recurrence Pattern After Definitive Chemoradiotherapy for Inoperable Stage III Non-squamous Non-small-cell Lung Cancer. *Clin Lung Cancer* 2019; 20: e256-e264 [PMID: 30926356 DOI: 10.1016/j.cllc.2019.02.021]

Xing L, Wu G, Wang L, Li J, Wang J, Yuan Z, Chen M, Xu Y, Fu X, Zhu Z, Lu Y, Han C, Xia T, Xie C, Li G, Ma S, Lu B, Lin Q, Zhu G, Qu B, Zhu W, Yu J. Erlotinib Versus Etoposide/Cisplatin With Radiation Therapy in Unresectable Stage III Epidermal Growth Factor Receptor Mutation-Positive Non-Small-Cell Lung Cancer: A Multicenter, Randomized, Open-Label, Phase 2 Trial. *Int J Radiat Oncol Biol Phys* 2021; 109: 1349-1358 [PMID: 33220395 DOI: 10.1016/j.ijrobp.2020.11.026]

Lee Y, Han JY, Moon SH, Nam BH, Lim KY, Lee GK, Kim HT, Yun T, An HJ, Lee JS. Incorporating Erlotinib or Irinotecan Plus Cisplatin into Chemoradiotherapy for Stage III Non-small Cell Lung Cancer According to EGFR Mutation Status. *Cancer Res Treat* 2017; 49: 981-989 [PMID: 28111430 DOI: 10.4143/crt.2016.522]

Hotta K, Sasaki J, Saeki S, Takigawa N, Katsui K, Takayama N, Nogami N, Shiyoama Y, Bessho A, Kishimoto J, Tanimoto M, Kiura K, Ichinose Y. Gefitinib Combined With Standard Chemoradiotherapy in EGFR-Mutant Locally Advanced Non-Small-Cell Lung Cancer: The LOGIK0902/OLCSG0905 Intergroup Study Protocol. *Clin Lung Cancer* 2016; 17: 75-79 [PMID: 26387039 DOI: 10.1016/j.cllc.2015.08.004]

Saeki S, Hotta K, Yamaguchi M, Harada D, Bessho A, Tanaka K, Inoue K, Gembka K, Ichihara E, Kishimoto J, Sasaki T, Shiyoama Y, Katsui K, Sasaki J, Kiura K, Sugio K. Induction gefitinib followed by standard chemoradiotherapy in locally advanced (LA) non-small-cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) activating mutations: The LOGIK0902/OLCSG0905 intergroup phase II study. *Ann Oncol* 2019; ix153 [DOI: 10.1093/annonc/mdz436]

Lu S, Casarini I, Kato T, Cobo M, Özgüroğlu M, Hodge R, van der Gronde T, Saggsse M, Ramalingam SS. Osimertinib Maintenance After Definitive Chemoradiation in Patients With Unresectable EGFR Mutation Positive Stage III Non-small-cell Lung Cancer: LAURA Trial in Progress. *Clin Lung Cancer* 2021 [PMID: 33558193 DOI: 10.1016/j.cllc.2020.11.004]
