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Contents

Monthly Volume 12 Number 10 October 24, 2021

World Journal of Clinical Oncology

Monthly Volume 12 Number 10 October 24, 2021

Contents

CASE REPORT

World Journal of Clinical Oncology

Monthly Volume 12 Number 10 October 24, 2021

Contents

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MINIREVIEWS

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

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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

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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.

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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[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[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[24-26] and approximately 30% of patients in Latin America [27], while in the Asian population the prevalence of EGFR mutations is significantly higher, around 50%[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[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* [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; $P = 0.15$)[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[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[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; $P = 0.0054$)[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 mo; HR: 0.92, 95%CI: 0.62-1.36; $P = 0.674$)[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; $P = 0.395$[1]	HR: 3.16; $P = 0.15$[1]
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)[1]	2 yr	46.4 *vs* 28.5 mo; HR: 0.61; $P = 0.039$[1]	Median OS NR in both arms; HR: 1.09; $P < 0.001$[1]
SELECT, Pennell *et al*[39]	Phase II	100	2-yr DFS	IA-IIIA	Erlotinib	Yes (not reported)	2 yr	Mean DFS NR; 2-yr DFS 88%; 5-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; $P = 0.0054$ 3-yr DFS 39.6% *vs* 32.5%; $P = 0.316$ 5-yr DFS 22.6% *vs* 23.2%; $P = 0.928$	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 *vs* cisplatin-vinorelbine	No	2 yr	42.4 *vs* 21 mo; HR: 0.268; $P < 0.0001$ 2-yr DFS 81.4% *vs* 44.6%; $P = 0.0054$ 3-yr DFS 54.2% *vs* 19.8%; $P = 0.0460$	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 2-yr DFS 81% *vs* 70%; $P = 0.55$	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; $P < 0.001$ 2-yr DFS 90% *vs* 44%ITT: NR *vs* 27.5 mo; HR: 0.20; $P < 0.001$ 2-yr DFS 89% *vs* 52%	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.

for 4 cycles. 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 chemo-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 IA-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-IIIA. 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-IIIA 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.

Neodjuvant 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

Table 2 Clinical trials of neoadjuvant epidermal growth factor receptor tyrosine kinase inhibitors in epidermal growth factor receptor-mutated non-small-cell lung cancer

Clinical trial	Study type	Sample size	Primary outcome	Stage	Treatment	TKI duration	RR	R0 resectability rate	PR	OS
Zhong *et al*[60]	Phase II	24 (12 with EGFR mutation)	RR	IIIA	Erlotinib (patients with EGFR mutation) *vs* carboplatin-gemcitabine (patients with native EGFR)	42 d	58.3% *vs* 25%; *P* = 0.18	50% *vs* 71.4; *P* = 0.59	16.7% *vs* 25%; *P* = 0.64	14.5 *vs* 28.1 mo; *P* = 0.201
Xiong *et al*[61]	Phase II	25	Resectability rate	IIIA	Erlotinib	56 d	42.1%	68.4%	50%	51.6 mo
Xiong *et al*[62]	Phase II	31 (15 with EGFR mutation)	Resectability rate	IIIA	Erlotinib *vs* cisplatin-based chemotherapy	4-7 wk	67% *vs* 19%	80% *vs* 50%	67% *vs* 38%	51 *vs* 20.9 mo
EMERGING-CTONG 1103, Zhong *et al*[63], Wu *et al*[64]	Phase II	72	RR	IIIA	Erlotinib *vs* cisplatin-gemcitabine	42 d (12 mo after surgery)	54.1% *vs* 34.3%; *P* = 0.092	73% *vs* 63%	MPR: 9.7% *vs* 0%	42.2 *vs* 36.9 mo; HR: 0.83; *P* = 0.513

EGFR: Epidermal growth factor receptor; HR: Hazard ratio; MPR: Major pathological response; OS: Overall survival; PR: Pathological response; RR: Response rate; TKI: Tyrosine kinase inhibitor.

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 IIIA 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 IIIA 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 IIIA 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 unresectable	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 unresectable	EGFR mutation: erlotinib x 3 → erlotinib+RT → erlotinib x 6 *vs* erlotinib x 3 → cisplatin-irinotecan+RT Native/unknown EGFR: cisplatin-irinotecan × 3 → cisplatin-irinotecan+RT *vs* cisplatin-irinotecan+RT → cisplatin-irinotecan x 3	33 wk	EGFR mutation: 71.4% *vs* 80% Native/unknown EGFR: 70% *vs* 73.9%	EGFR mutation: 11.6 *vs* 8.1 mo Native/unknown EGFR: 9 *vs* 12.3 mo	EGFR mutation: 39.3 *vs* 31.2 mo Native/unknown EGFR: 16.3 *vs* 25.3 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 unresectable	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[71]. Gefitinib has also been assessed, in the phase II trial LOGIK0902/OLCSG0905[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.

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