TKIs for NSCLC patients

Subjects: Oncology

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Lung cancer is the most common malignancy across the world. The new era in lung cancer treatments, especially this past decade, has yielded novel categories of targeted therapy for specific mutations and adjuvant therapy, both of which have led to improved survival rates.

lung cancer | adjuvant treatment | non-small-cell lung carcinoma (NSCLC) | epidermal growth factor receptor (EGFR) | tyrosine kinase inhibitor (TKI)

1. Introduction

Lung cancer is the leading cause of cancer-related deaths in the United States and poses a significant health care concern throughout the world [1]. Over 68% of patients are diagnosed after the age of 65 whereas less than 3% are diagnosed under the age of 45 years [2]. Non-small cell lung cancer (NSCLC) has the highest incidence of 85% among all lung cancers [3]. NSCLC includes any type of epithelial lung cancer apart from small-cell lung cancer and so is divided histologically into adenocarcinoma, squamous cell carcinoma (SCC), and large cell carcinoma [4]. As NSCLC is often insidious, patients can present with no symptoms until the disease is advanced, contributing to the poor prognosis of lung carcinoma [5]. Nearly 30% of patients with NSCLC have localized disease (stage I–IIIA) at the time of diagnosis and undergo curative surgery. Despite full tumor resection, many patients will experience systemic and/or local relapses, thereby succumbing to the disease. It is important to recognize that staging holds significance as to whether the tumor can be resected. Stages I and II are localized disease that can be resected without fear of the tumor having already metastasized whereas in stages IIIB and IV, resection is unfeasible. Stage IIIA is unique in that T3N0M0 is resectable whereas T3N2M0 is unresectable. Indeed, staging plays a role in determining the magnitude of the impact of the drug as a therapeutic. Several adjuvant therapies, including tyrosine kinase inhibitors (TKIs), chemotherapy, and immunotherapy, have been investigated as a means of improving survival outcomes for patients with fully resected NSCLC [6]. Currently, there is no consensus regarding optimal chemotherapy regimens for adjuvant treatment, especially when considering the added detail of specific tumor mutations. Clinical practice involves the combination of pharmaceutical agents such as cisplatin and second-generation chemotherapy drugs. Furthermore, the National Comprehensive Cancer Network guidelines lists options of chemotherapy regimens using cisplatin or carboplatin along with another drug, e.g., vinorelbine. Combinations of cisplatin with either etoposide (VP-16), gemcitabine, docetaxel, or pemetrexed (for adenocarcinoma) were also mentioned [7]. The most recent findings show that the combination of cisplatin plus vinorelbine is probably the best choice for adjuvant treatment [8][9].

Epidermal growth factor receptor (EGFR), also known as HER1, is a 170-kDa transmembrane receptor tyrosine kinase (RTK) found on the surface of epithelial cells and often overexpressed in malignancy [10]. Alterations in the EGFR gene have been found to be involved in cancer cell growth and tumor vascularization. EGFR mutations have been identified in up to 20% of all lung adenocarcinomas and there is a higher prevalence among females and non-smokers [11]. Patients with EGFR-mutant lung adenocarcinomas have a 70% response rate to first-line EGFR-TKI therapy, such as erlotinib, gefitinib, or afatinib [12]. TKI were previously used as supportive therapy for patients with NSCLC and, as shown in the chronological layout of the trials presented here, have since been used as monotherapy. There are five TKI currently available for the treatment of NSCLC in patients with EGFR-mutations, which are divided into three generations. The first generation includes erlotinib and gefitinib, the second generation dacomitinib and afatinib, and the third generation osimertinib. However, only osimertinib has been approved as adjuvant treatment for EGFR mutations in NSCLC [13]. Several clinical trials have shown improved efficacy, better outcomes in progression-free survival (PFS) and/or overall survival (OS) for several generations of TKI as compared to patients with EGFR-mutant lung adenocarcinoma who received chemotherapy as adjuvant treatment [14][15][16][17]. Additionally, these trials showed longer OS for patients with EGFR mutations compared to EGFR-wild type during the incidence of brain metastasis (patients were in stage I–III before brain metastasis) [18]. Given that there is propensity to acquired resistance, there is great need for continued advancements in therapeutic innovation, both in discovery and appropriate combinations.

NSCLC two-year survival rates have increased from 34% for diagnoses made in 2009–2010 to 42% for diagnoses made in 2015–2016 [3]. The new era of oncology treatments has included novel adjuvant therapy such as TKI in EGFR-mutant NSCLC. In this review paper we examine past, present and future therapies that have shown treatment efficacy for NSCLC patients with resected EGFR mutations such as those in exon 19 or 21 or the L858R substitution (**Table 1**).

Table 1. Reviewed clinical trials of adjuvant therapy for past trials that were uncharacterized for EGFR, past and present trials involving TKI with or without chemotherapy in completely resected EGFR-mutated NSCLC.

Treatment	Chemotherapy Uncharacterized for EGFR-TKI (*n* = 7)	TKI with or without Chemotherapy (*n* = 5)	TKI [a] (*n* = 3)
Trial Name [b]	ALPI [18] IALT [19] BLT [20] CALGB 9633 [21] JBR-10 [22] ANITA [23] MAGRIT [24]	Pemtrexed + carboplatin + gefitinib [25] EVAN [26] ADJUVANT [15] SELECT [16] ADAURA [14]	ALCHEMIST [27] EMERGING [28] Afatinib [29]

2. EGFR-TKI Used in Clinical Trials for NSCLC Adjuvant Therapy

2.1. Erlotinib

Erlotinib is a derivative of quinazoline classified as an antineoplastic agent. It is a first generation TKI medication treatment for NSCLC tumors with EGFR mutations, exon 19 deletion (ex19del), or exon 21 point mutation (L858R). Erlotinib exerts its antagonist ability by competing with adenosine triphosphate (ATP) on the catalytic site of the EGFR located at the intracellular part [30]. Through reversible binding, erlotinib inhibits the phosphorylation of EGFR, thus disabling the signal transduction pathway and blocking proliferative cellular reactions leading to reduced carcinogenesis process related to activation of EGFR. This targeted therapy drug is orally administered. The Food & Drug Administration (FDA) approved erlotinib for NSCLC on 18 November 2004 and has, since 18 October 2016, restricted its use in lung cancer as a first line treatment to metastatic NSCLC with the EGFR mutations listed above. It remains first-line treatment for locally advanced, unresectable, or metastatic pancreatic cancer when combined with gemcitabine [31].

2.2. Gefitinib

Gefitinib is an anilinoquinazoline compound possessing antineoplastic properties. This drug belongs to first generation therapy of TKI NSCLC harboring EGFR exon 19 or exon 21 (L858R) mutation. Gefitinib specifically inhibits the catalytic activity of several tyrosine kinases among them EGFR. It is considered as an antagonist of EGFR and could cause an inhibition of tyrosine kinase-dependent tumor growth [25]. The drug is able to bind in a competitive way to the ATP domain of the tyrosine kinase part on EGFR, hence blocking the autophosphorylation of the receptor, and as a consequence inhibiting the signal transduction downstream cellular mechanism. Gefitinib actions include the induction of cell cycle arrest and restricting angiogenesis. It is given through oral administration. The FDA approved gefitinib for advanced NSCLC progressing beyond platinum doublet chemotherapy and docetaxel on 5 May 2003 and, since 13 July 2015, it has been expanded for use as a first line treatment in metastatic NSCLC with the EGFR mutations listed above [26].

2.3. Osimertinib

Osimertinib is a third generation EGFR inhibitor which can selectively bind in an irreversible way. It is indicated for patients suffering NSCLC as an antagonist agent with antitumoral capability. This TKI binds covalently to mutated EGFR in exon 19, exon 21 L858R, as well as to exon 20 T790M. Therefore, it may prevent cell signaling cascade mediated by EGFR activation [27]. Osimertinib potentially may inhibit neoplasm growth in EGFR-overexpressing tumor cells and induce cell death. This medication is orally available. Approval for osimertinib by the FDA came first on 13 November 2015 for use as adjuvant therapy after tumor resection in adult patients with NSCLC with the above EGFR mutations, but this was expanded on 18 April 2018 for use as a first line therapy in metastatic NSCLC with the EGFR mutations listed above [28].

3. Past Clinical Trials That Included Adjuvant Therapy Using EGFR-TKI in Patients with Completely Resected EGFR Mutated NSCLC

3.1. Pemetrexed-Carboplatin Adjuvant Chemotherapy with/without Gefitinib Trial

In this phase II study, 60 patients with resected NSCLC bearing EGFR mutations, exon 19 deletion or L858R, were enrolled [29]. Participants with stage IIIA were randomized to a combination of pemetrexed and carboplatin, for four cycles, followed with or without gefitinib for six months. The results showed longer PFS among those who received chemotherapy + gefitinib (median, 39.8 months) than among those who received only chemotherapy (27.0 months) (HR, 0.369; 95% CI, 0.161–0.847; $p = 0.014$). Two-year DFS rate was 78.9% in the AC treatment group with TKI vs. 54.2% without TKI. Two-year OS was 92.4% in the AC treatment arm with TKI vs. 77.4% in control arm without TKI (HR, 0.37; 95% CI 0.12–1.11, $p = 0.076$). OS was also longer for chemotherapy + gefitinib arm (median, 41.6 months) than chemotherapy alone (32.6 months, $p = 0.066$) (**Table 2**).

Table 2. Past clinical trials that included adjuvant therapy using EGFR-TKI in patients with completely resected EGFR mutated * NSCLC.

Outcome: 2-Year Median DFS	TKI Duration	Control Arm	Treatment Arm	NSCLC Stage *	Participants (*n*)	Publication Date	Trial
78.9% (95% CI N/A) in AC with TKI vs. 54.2% (95% CI N/A) in AC without TKI (*p* value N/A)	6 months	Pemetrexed + carboplatin	Pemetrexed + carboplatin followed with gefitinib	IIIA	60	2014 March	Pemetrexed + carboplatin AC with or without gefitinib (Phase II)
81.4% (95% CI 69.6–93.1) in erlotinib arm vs 44.6% (95% CI 26.9–62.4) in chemotherapy arm (*p* = 0.0054)	2 years (median)	Vinorelbine + cisplatin	Erlotinib	IIIA	102	2018 August	EVAN (Phase II)
28.7 months with TKI (95% CI, 24.94–32.46) vs. 18 months with chemotherapy combination (95% CI, 13.59–22.34) (*p* = 0.005)	2 years	Vinorelbine + cisplatin	Gefitinib	II to IIIA	222	2017 November	ADJUVANT - CTONG1104 (Phase III)

Outcome: 2-Year Median DFS	TKI Duration	Control Arm	Treatment Arm	NSCLC Stage *	Participants (*n*)	Publication Date	Trial
88% in erlotinib arm (95% CI N/A)	2 years		Erlotinib (single arm, after AC)	IA to IIIA	100	2018 November	SELECT (Phase II)
89% (95% CI, 85–92) in osimertinib arm vs 52% (95% CI, 46–58) in placebo arm (*p* value N/A)	3 years	Placebo	Osimertinib	IB to IIIA	682	2020 September	ADAURA (Phase III)

ruited [32]. Patients diagnosed at stage IIIA were randomized to a combination of vinorelbine and cisplatin, for four cycles vs. erlotinib (until disease progression). The results showed two-year DFS of 81.4% (95% CI 69.6–93.1) in the erlotinib arm and 44.6% (95% CI 26.9–62.4) in the chemotherapy arm (relative risk 1.823 95% CI 1.194–2.784; $p = 0.0054$) (**Table 2**).

3.3. ADJUVANT Trial (CTONG 1104)

This phase III study enrolled 222 patients with EGFR confirmed mutations (exon 19 deletion or L858R) in resected NSCLC [16]. Patients with stage II to IIIA were randomized to receive gefitinib or a combination of vinorelbine and cisplatin, for four cycles vs. gefitinib for two years. The results showed prolonged two-year median DFS of 28.7 months with TKI (95% CI, 24.94–32.46) vs. 18 months with chemotherapy combination (95% CI, 13.59–22.34), HR,0.60, (95% CI, 0.42–0.87, $p = 0.005$). No significant differences were found for the analysis of OS final results [16] (**Table 2**).

3.4. SELECT Trial

Briefly, 100 patients with resected NSCLC bearing mutant EGFR, were recruited to this study [17]. Participants diagnosed with stage IB to IIIA, after AC with or without radiotherapy, were randomized to a single arm of erlotinib for up to two years. The results showed two-year course was achieved in 69% of patients. DFS at two years was 88%. Patients' median follow-up was 5.2 years. At five years, DFS was 56% (95% CI, 45–66%) and OS was 86% (95% CI, 77–92%). Recurrence of the disease was found in four patients while receiving therapy with erlotinib, and in 36 patients who concluded erlotinib treatment, having 25 months as median time to recurrence. Retreatment with erlotinib in 65% of the recurrent patients had a 13-month median duration (**Table 2**).

3.5. ADAURA Trial

In this phase III study, 682 patients with resected NSCLC, carrying EGFR-mutation (Ex19del or L858R) were recruited [14]. Participants with stage IB to IIIA after AC were randomized to osimertinib vs. placebo for three years. Results showed 89% of patients were disease-free (95% CI, 85–92) in the osimertinib arm and 52% (95% CI, 46–58) in the placebo arm at two years. Overall HR for disease recurrence or death of 0.20 (99.12% CI, 0.14–0.30; $p <$

0.001) can be translated into 80% lower risk for disease recurrence or death, thereby extending DFS in osimertinib arm vs. placebo. Furthermore, results were significant in showing that, at 24 months, 98% of the patients were alive without central nervous system (CNS) disease after receiving osimertinib vs. 85% of patients who received placebo. Overall HR for CNS disease recurrence or death, 0.18; (95% CI, 0.10–0.33) means that 82% decreased risk of CNS disease recurrence or death in the osimertinib arm (**Table 2**).

Adverse events reported in the clinical trials involving adjuvant therapy using EGFR-TKI in patients with completely resected NSCLC harboring EGFR-mutations are summarized in **Table 3**.

Table 3. Adverse Events reported for clinical trials that included adjuvant therapy using EGFR-TKI in patients with completely resected EGFR mutated NSCLC.

Adverse Events Control Arm	Adverse Events TKI Arm	Trial
NR	Approximately 43% of the patients who received both AC and gefitinib developed a rash	Pemetrexed-carboplatin adjuvant chemotherapy with/without gefitinib (Phase II)
Grade ≥ 3, in 11% of patients decreased neutrophil count 16% of patients. Myelosuppression: 9% of patients.	Grade ≥ 3, in 12% of patients Rash in 4% of patients.	EVAN (Phase II)
Grade ≥ 3 Neutropenia in 34% of patients Leucopenia in 16% of patients Vomiting in 8% of patients. Serious AE in 23% of patients	Grade ≥ 3: 2% of patients with elevated alanine aminotransferase and 2% of patients with elevated aspartate aminotransferase Serious AE in 7% of patients	ADJUVANT—CTONG1104 (Phase III)
Not relevant	No grade 4 or 5 AE. Grades 1–3A: rash, diarrhea, dry skin, fatigue, nausea/vomiting, nail changes, pruritis, stomatitis, and transaminitis. Recurrence occurred in 40% of patients 40% of patients required dose reduction of erlotinib, while 16% of patients required second dose reduction	SELECT (Phase II)
89% of patients reported AE	Grade ≥3 AE reported in 20% of patients: diarrhea, paronychia, stomatitis, upper respiratory tract infection and decreased appetite.	ADAURA (Phase III)

Adverse Events Control Arm	Adverse Events TKI Arm	Trial
Grade ≥3 AE reported in 13% of patients	98% of patients reported AE Interstitial lung disease in 3% of patients	

Mutated NSCLC

4.1. Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST Trial)

In this phase III study, 450 patients with resected NSCLC are estimated to be enrolled [33]. Inclusion criteria are diagnosis of stage IB to IIIA with confirmed EGFR exon 19 or L858R mutations. Participants are randomized to two pairs of blinded and unblinded arms to erlotinib vs. placebo for up to two years. The primary objective of the trial is to examine if adjuvant therapy with erlotinib has an improved OS while secondary objectives consider better DFS, the safety profile of erlotinib, and the use of circulating EGFR mutations in cell-free plasma DNA as a prognostic marker. After treatment, patients will be followed up every six months for four years and then once a year for the next six years. Study outcomes are anticipated to be released on October 2026 (**Table 6**).

Table 4. Ongoing clinical trials that include adjuvant therapy with EGFR-TKI in patients with completely resected EGFR mutated NSCLC.

Estimated Study Completion Date	Study Start Date	TKI Duration (years)	EGFR Mutation	Control Arms	TKI Arms	NSCLC Stage	Estimated Enrollment (*n*)	Trial
October 2026	August 2014	2	In exon 19 or L858R confirmed for all patients	Placebo	Erlotinib	IB to IIIA	450	ALCHEMIST [A081105] (Phase III)
December 2022	April 2011	1	In Exon 19 or 21	Gemcitabine/cisplatin (2 cycles) as neoadjuvant and adjuvant (2 cycles)	Erlotinib as neoadjuvant (42 days) and adjuvant (1 year)	IIIA	72	EMERGING (Phase II)
November 2021	January 2013	2	EGFR Mutations	Afatinib for 2 years	Afatinib for 3 months	I to III	92	Adjuvant Afatinib (Phase III)

4.2. EMERGING Trial

The EMERGING Trial recruited 72 patients with resected NSCLC to this investigation [29]. Participants with stage IIIA-N2 NSCLC bearing EGFR mutation in exon 19 or 21 were randomized to erlotinib vs. combination of gemcitabine plus cisplatin. Erlotinib is first given as neoadjuvant for 42 days followed by one year as adjuvant

therapy. Gemcitabine and cisplatin are given for two cycles of neoadjuvant therapy followed by a further two cycles of adjuvant therapy. The outcomes of the research include PFS and OS at three years. Post-surgery care for up to two years comprised of chest computerized tomography (CT) scan, abdominal ultrasound every three months, brain MRI bi-annually and bone scan once a year. Study results are expected to be published on December 2022 (**Table 6**).

4.3. Adjuvant Afatinib Trial

Briefly, 95 patients with resected NSCLC were enrolled [34]. Inclusion criteria were diagnosis of stage I to III NSCLC harboring EGFR mutations. Participants were randomized to short course (three months) afatinib vs. long course (two years) afatinib. Patients were followed up every six months for three years and then once in the fourth year. Chest CT scan, blood tests, performance status, and a physical exam were conducted at these follow ups. Study results are estimated for November 2021 (**Table 6**).

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