
Review Paper

Adjuvant Treatment with Tyrosine Kinase Inhibitors in Epidermal Growth Factor Receptor mutated Non-Small-Cell Lung Carcinoma Patients, Past, Present and Future

Walid Shalata ^{1*}, Binil Mathew Jacob ² and Abed Agbarya ³.

¹ The Legacy Heritage Oncology Center & Dr. Larry Norton Institute, Soroka Medical Center & Ben-Gurion University, Beer-Sheva, Israel.

² Medical School for International Health, Ben-Gurion University of the Negev, Beer-Sheva, Israel

³ Oncology Department, Bnai Zion Medical Centre, Haifa, Israel.

* Correspondence: walid.shalata@gmail.com ; Tel: +972 (0)54 2967100

Simple Summary: This review article details the progress of lung cancer treatments for a subtype known as non-small cell lung cancer with a special mutation of epidermal growth factor receptor. We are including past trials that involve exclusively chemotherapy, present trials that explore the use of drugs known as tyrosine kinase inhibitors, as well as ongoing trials that consider an interplay between these two. Finally, we propose some areas of future research given the implications of the current studies, namely regarding metastasis to the brain and central nervous system.

Abstract: 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. In the present study, we review the changes and development of treatments, with a special focus on adjuvant therapy using tyrosine kinase inhibitors (TKIs) administered to non-small-cell lung carcinoma patients who had a complete resection of the tumor harboring a mutated epidermal growth factor receptor. The clinical trials are dating from the past (chemotherapy trials), present (TKIs) and future (ongoing trials).

Keywords: 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 is divided histologically into adenocarcinoma, squamous cell carcinoma (SCC), and large cell carcinoma[4]. 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 1-3) 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. 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 of optimal chemotherapy regimens for adjuvant treatment. 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 regimen 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]. Most reviewers concluded 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]. There are five EGFR-TKI treatment drugs currently available for EGFR-mutant lung cancer, which are divided into 3 generations: 1st generation (erlotinib and gefitinib), 2nd generation (dacomitinib and afatinib) and 3rd 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[14–17]. 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].

NSCLC 2-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 EGFR mutations (Table 1).

Table 1. Reviewed clinical trials of adjuvant therapy for completely resected EGFR-mutated NSCLC

	Past	Past	Present ^a
Treatment	Chemotherapy without TKI (n=7)	TKI with or without chemotherapy (n=5)	TKI (n=3)
Trial Name ^b	ALPI ¹⁸ IALT ¹⁹ BLT ²⁰ CALGB 9633 ²¹ JBR – 10 ²² ANITA ²³ MAGRIT ²⁴	Pemtrexed+carboplatin+gefitinib ²⁸ EVAN ²⁹ ADJUVANT ¹⁵ SELECT ¹⁶ ADAURA ¹⁴	ALCHEMIST ³⁰ EMERGING ³¹ Afatinib ³²

^a Present clinical trials include ongoing and studies pending future results.

^b Superscript number indicates Reference.

Total number of reviewed clinical trials n=15

Abbreviations: EGFR, epidermal growth factor receptor; NSCLC, non-small-cell lung cancer; TKI, tyrosine kinase inhibitor.

2. Past clinical trials that included adjuvant chemotherapy (AC) without EGFR-TKI in patients with completely resected EGFR mutated NSCLC

2.1. The Adjuvant Lung Project Italy Trial (ALPI)

The ALPI was an AC trial reporting participation of 1,209 patients[19]. The prospective study included NSCLC cases diagnosed at stages I to IIIA, who were randomized to chemotherapy arm of mitomycin, vindesine, and cisplatin (MVP) for three cycles or no treatment. Resection involved lobectomy or pneumonectomy, although more limited types were allowed. Relevant lymph nodes were removed also. The 71 participating centers (Italian as well as 5 from the European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group) were permitted adjuvant radiotherapy to their discretion; for the MVP treatment arm, this was initiated 3 to 5 weeks after last cycle while for the control arm, this was initiated at 4 to 6 weeks after surgery. At 64.5 months of median follow-up there were no differences in overall survival, hazard ratio (HR) 0.96, 95% confidence interval (CI), 0.81-1.13, $P=0.59$ or PFS (HR 0.89, 95% CI, 0.76-1.03, $P=0.13$) between the arms in this study (Table 2). Hematologic toxicity was the most frequently observed adverse effect; other adverse effects included grade 2 and 3 acute pneumonitis, grade 4 pneumonitis and grade 4 esophagitis. Both treatment and control arms showed >40% of patients with brain relapse (Table 3).

2.2. International Adjuvant Lung Cancer Trial (IALT)

The IALT has provided the most evidence for AC in this setting to date[20]. There were 1,867 patients with completely resected NSCLC classified as stages I to IIIA in this prospective study that compiled data from multiple participating centers. Each center had license to determine the dose of cisplatin, the drug combined alongside and policy for postoperative radiotherapy. Patients were randomly assigned to the chemotherapy arm, with cisplatin being administered to 74% of them. Three or four courses of cisplatin-based chemotherapy were used, along with either etoposide, vinorelbine, vinblastine, or vindesine. The results showed that the AC arms had a higher survival rate than the observation arm [44.5% vs. 40.4% at 5 years, HR for death 0.86 (95% CI, 0.76-0.98, $P<0.03$)] and

exhibited better PFS [39.4 vs. 34.3 at 5 years HR 0.83 (95% CI, 0.74-0.94, $P<0.003$)]. This trial was successful in demonstrating better survival by cisplatin-based adjuvant treatment (Table 2). 22.6% of patients presented with at least one instance of grade 4 toxic effect, including neutropenia, thrombocytopenia and vomiting as the significant effects, which were consistently found in over 1% of patients (Table 3).

2.3. The Big Lung Trial (BLT)

The Big Lung Trial was a negative trial that failed to observe survival benefits for patients with stage I to III NSCLC with resection[21]. Only 381 patients were selected, so presumably the study did not meet quality standards especially given the various stratifications in therapeutic delivery. Preoperative chemotherapy was given to 3% of the patients, and 5% from both treatment arms did not achieve complete resections. Multiple cisplatin-based chemotherapy schemes were devised (e.g., cisplatin + vindesine, mitomycin + ifosfamide + cisplatin, mitomycin + vinblastine + cisplatin or vinorelbine + cisplatin) for use as the treatment arm, which was compared to the control arm that did not receive chemotherapy. Further, the patients were staggered into different categories of treatment schedules where 13% of patients did not receive scheduled chemotherapy, instead receiving radiotherapy, 21% receiving either one or two cycles of chemotherapy and 64% receiving all three cycles of the assorted therapy schemes. There was no benefit for chemotherapy protocol in terms of survival (HR 1.02; 95% CI, 0.77-1.35, $P=0.90$) (Table 2). 30% developed grade 3 and 4 toxicity, mainly hematologic, nausea/vomiting and neutropenic fever. Additionally, 6 patients were reported dead by treatment-related toxicity (Table 3).

2.4. Cancer and Leukemia Group B (CALGB) 9633 Trial

This study recruited 344 stage IB patients with resected NSCLC[22]. Participants were randomized and assigned to two arms. The first arm received four cycles of paclitaxel with carboplatin chemotherapy while the second arm served as control under observation. 57% received four cycles at full dose while 86% received all four cycles. Survival was not significantly different HR 0.83 (95% CI, 0.64-1.08), $P=0.125$). Median survival times were 95 and 78 months in AC arm vs. observation. DFS was without statistically significant difference (HR, 0.80; 90% CI, 0.62-1.02; $p=0.065$). Median DFS was 89 and 56 months in AC and observation arm. However, for patients who had tumors ≥ 4 cm in diameter, there was a significant survival difference for the doublet chemotherapy agents (HR 0.69; 95% CI, 0.48-0.99, $P=0.043$). OS analysis showed 31% lowered risk of death. Median survival time was 99 months in AC vs. 77 months in control arm. DFS was improved significantly by 31% in AC (HR, 0.69; 90% CI, 0.49-0.97; $p=0.035$). Median DFS was 96 months in AC vs 63 month in control group for those patients with tumors ≥ 4 cm however there was no difference in DFS for patients with smaller tumors (Table 2). 35% of patients developed grade 3 and 4 toxicity, predominantly neutropenia, and no treatment-related toxic deaths were recorded (Table 3).

2.5. JBR-10 Trial

In this study, 482 patients diagnosed with NSCLC who had complete tumor resection, were recruited[23]. Randomization arms were observation or AC. Four cycles of vinorelbine with cisplatin chemotherapy were administered. 45% of the patients were at stage IB and 55% were at stage II (T3N0 patients were excluded). AC extended OS in treatment arm vs. control arm 94 vs. 73 months, (HR for death, 0.69 $P=0.04$), significantly increased PFS, [HR for recurrence, 0.60 (95% CI, 0.45-0.79, $P<0.001$)]. Survival at 5 years was for AC 69% (95% CI 62-75) vs. 54% (95%CI 48-61) ($p=0.03$) as compared to observation. PFS at 5 years was 61% for AC (95%CI 54-68%) vs. 49% in the observation arm (95%CI 42-55%) $p=0.08$. The subgroup analysis showed no survival benefit for patients with stage IB ($P=0.79$). Nevertheless, for patients with stage II the chemotherapy arm showed significant benefit with a median survival of 80 months compared to 41 months for the observation arm [HR 0.59 (95% CI, 0.42-

0.85, $P=0.004$)] (Table 2). Grade 3 or 4 neutropenia was the most common adverse effect with 73% of patients developing it from chemotherapy. Other notable grade 3 or 4 adverse effects included anemia (7% of patients), fatigue (15%), nausea (10%), anorexia (10%), vomiting (7%), constipation (3%), sensory neuropathy 2%, motor neurotoxicity 3%, hearing loss 2%, febrile neutropenia following colony-stimulating factor administration (7%) and thrombocytopenia (1%). There were two toxicity related deaths (Table 3).

2.6. Adjuvant Navelbine International Trialist Association (ANITA) Trial

840 patients who underwent complete NSCLC resection were recruited to this study[24]. Patients with stage I to IIIA were randomized to a combination of cisplatin plus vinorelbine for four courses vs. observation. 36% of patients had stage IB, 24% stage II and 39% had stage IIIA disease. The 101 participating centers across 14 countries were given the prerogative to determine whether postoperative radiation therapy (PORT) should be used: 24% of patients in the AC arm received PORT compared to 33% in the control arm. Interestingly, compliance to treatment was higher for cisplatin compared to vinorelbine. The results showed that the chemotherapy arm significantly improved median survival of 65.7 (95% CI 47.9-88.5) vs. 43.7 months. OS of an 8.6% improvement at 5 years [HR 0.80 (95% CI, 0.66-0.96, $P=0.02$)] and 8.4% at 7 years (Table 2). 92% patients developed neutropenia, febrile neutropenia was found in 7% and seven toxicity related deaths occurred (Table 3).

2.7. MAGRIT Trial

In the MAGRIT trial, 12,820 patients with resected MAGE-A3 expressing NSCLC were recruited[25]. 33% of these presented with exclusively MAGE-A3 positive tumor. Patients, from 443 centers across 43 countries, with stage I to IIIA were either given adjuvant chemotherapy or not before being randomized and assigned to two arms. The first arm (AC) received 13 intramuscular injections of recMAGE-A3 with AS15 immunostimulant (MAGE-A3 immunotherapeutic) vs. the second arm of placebo for 27 months. In patients with MAGE-A3-positive surgically resected NSCLC, adjuvant treatment with the MAGE-A3 immunotherapeutic did not improve disease-free survival when compared to placebo, which showed 60.5 months (95% CI 57.2-not reached) for the MAGE-A3 arm and 57.9 months (55.7-not reached) for the placebo group (HR 1.02, 95% CI 0.89-1.18; $p=0.74$). The use of the MAGE-A3 immunotherapeutic for use in NSCLC has stopped because of the findings showing no differences between MAGE-A3 immunotherapeutic in comparison to placebo (Table 2). Both arms expressed similar frequency of grade 3 or worse adverse events such as infection/infestation, vascular disorders and neoplasm (Table 3).

Table 2. Past clinical trials that included adjuvant therapy without EGFR-TKI in patients with completely resected EGFR mutated NSCLC.

Trial name	Date published	Participants (n)	NSCLC Stage	Treatment arm	Control arm	Outcome
The Adjuvant Lung Project (ALPI)	2003 October	1,209	I to IIIA	Mitomycin, vindesine and cisplatin	No treatment	No differences found
International Adjuvant Lung Cancer Trial (IALT)	2004 January	1,867	I to IIIA	Cisplatin-based with either etoposide, vinorelbine, vinblastine, or vindesine	Observation	AC arm: significantly higher survival rate and PFS
The Big Lung Trial (BLT)	2004 July	381	I to IIIA	Cisplatin-based: Cisplatin+vindesine Mitomycin+ifosfamide+cisplatin, Mitomycin+vinblastine+cisplatin, Or vinorelbine+cisplatin	No treatment	No survival benefit found
CALGB 9633 trial	2008 September	344	IB	Paclitaxel+ Carboplatin	Observation	AC arm: significantly improved survival of patients with tumors ≥ 4 cm
JBR-10 trial	2005 June	482	IB to II	Vinorelbine+ Cisplatin	Observation	Chemotherapy significantly prolonged OS, PFS
Adjuvant Navelbine International Trialist Association (ANITA)	2006 August	840	I to IIIA	Vinorelbine+ Cisplatin	Observation	Chemotherapy significantly improved median survival
MAGRIT trial	2016 June	12820	IB to IIIA	1. AC followed by MAGE-A3 2. No AC followed by MAGE-A3	Placebo	1. Found no differences between arms 2. Found no differences between arms in survival

Abbreviations: NSCLC, non-small-cell lung cancer; AC, adjuvant chemotherapy; PFS, progression-free survival; CALGB, Cancer and Leukemia Group B; OS, overall survival.

Reported adverse events (AE) of past clinical trials that included adjuvant therapy without EGFR-TKI in patients with completely resected EGFR mutated NSCLC are listed in Table 3.

Table 3. Adverse events (AE) reported in past clinical trials that included adjuvant therapy without EGFR-TKI in patients with completely resected EGFR mutated NSCLC.

Trial	Chemotherapy arm	Control arm
The Adjuvant Lung Project (ALPI)	Grade 3 neutropenia in 16% of patients Grade 4 neutropenia in 12% of patients >40% of patients had brain relapse	>40% of patients had brain relapse
International Adjuvant Lung Cancer Trial (IALT)	Grade 4 toxicity in 23% of patients Approximately 1% deaths induced by toxic effects	NR
The Big Lung Trial (BLT)	Grade 3 and 4 toxicities in approximately 30% of the patients	NR
CALGB 9633 trial	Grade 3-4 neutropenia in 35% of patients. 34% required dose reduction	NR
JBR-10 trial	Grade 3-4 neutropenia in 73% of patients 32% required hospitalization 0.8% deaths related to toxicity	NR
Adjuvant Navelbine International Trialist Association (ANITA)	Neutropenia toxicity in 92% of patients 9% febrile neutropenia 2% deaths related to toxicity	NR
MAGRIT trial	Grade ≥ 3 AE 2% of infections and infestations, 2% of vascular disorders, 2% of neoplasm	Grade ≥ 3 3% of infections and infestations 3% of vascular disorders 2% of neoplasm

Abbreviation: AE, adverse events; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; NSCLC, non-small-cell lung cancer; NR, not reported.

3. EGFR-TKI used in clinical trials for NSCLC adjuvant therapy

3.1. Erlotinib

Erlotinib is a derivative of quinazoline classified as an antineoplastic agent. It is a 1st 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[26]. 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 November 18, 2004 and has since October 18, 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[27].)

3.2. Gefitinib

Gefitinib is an anilinoquinazoline compound possessing antineoplastic properties. This drug belongs to 1st 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[28]. 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 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 May 5, 2003 and has since July 13, 2015 been expanded for use as a first line treatment in metastatic NSCLC with the EGFR mutations listed above[29].

3.3. Osimertinib

Osimertinib is a 3rd 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[30]. 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 November 13, 2015 for use as adjuvant therapy after tumor resection in adult patients with NSCLC with the above EGFR mutations, but was then expanded on April 18, 2018 for use as a first line therapy in metastatic NSCLC with the EGFR mutations listed above[31].

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

4.1. 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[32]. 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; $P=0.014$). 2-year DFS rate was 78.9% in the AC treatment group with TKI vs. 54.2% without TKI. 2-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 4).

4.2. EVAN

102 patients with resected NSCLC harboring EGFR exon 19 deletion or L858R mutation were recruited[33]. 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 2-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 4).

4.3. 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 2 years. The results showed prolonged 2-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 OS final results analysis [16] (Table 4).

4.4. SELECT Trial

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 2 years. The results showed 2-year course was achieved in 69% of patients. DFS at 2 years was 88%. Patients' median follow-up was 5.2 years. At 5-year 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 13-month median duration (Table 4).

4.5. 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 3 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 2 years. Overall HR for disease recurrence or death, 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 4).

Table 4. Past clinical trials that included adjuvant therapy using EGFR-TKI in patients with completely resected EGFR mutated* NSCLC.

Trial	Publication Date	Participants (n)	NSCLC Stage*	Treatment arm	Control arm	TKI Duration	Outcome
Pemetrexed+ carboplatin AC with or without gefitinib (Phase II)	2014 March	60	IIIA	Pemetrexed+ carboplatin followed with gefitinib	Pemetrexed + carboplatin	6 months	Improved median PFS in pemetrexed + carboplatin + gefitinib arm vs. pemetrexed + carboplatin arm 2-year DFS 78.9% in AC with TKI vs. 54.2% in AC without TKI
EVAN (Phase II)	2018 August	102	IIIA	Erlotinib	Vinorelbine + cisplatin	2 years (median)	2-yr higher rate of DFS with TKI vs. chemotherapy 2-year DFS 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)
ADJUVANT - CTONG1104 (Phase III)	2017 November	222	II to IIIA	Gefitinib	Vinorelbine + cisplatin	2 years	Longer median DFS with TKI vs. chemotherapy. OS without significant difference 2-year median DFS 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)
SELECT (Phase II)	2018 November	100	IA to IIIA	Erlotinib (single arm, after AC)		2 years	Improved 2-yr DFS with TKI. 4% recurrence during erlotinib treatment. Recurrences after stopping erlotinib were rechallenged having 13 months median duration. 5-yr OS: 86%.
ADAURA (Phase III)	2020 September	682	IB to IIIA	Osimertinib	Placebo	3 years	Higher disease-free rate at 24 months in the osimertinib arm than in the placebo arm. Lower overall HR for disease recurrence or death 2-year DFS 89% o (95% CI, 85–92) in osimertinib arm vs 52% (95% CI, 46–58) in placebo arm (p=?)

Abbreviations NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor; AC, adjuvant chemotherapy; HR, hazard ratio, DFS, disease-free survival, OS, overall survival.

*EGFR mutations, Exon 19 deletion or exon 21 point mutation L858R, confirmed for all patients

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 5.

Table 5. Adverse Events reported for clinical trials that included adjuvant therapy using EGFR-TKI in patients with completely resected EGFR mutated NSCLC.

Trial	Adverse Events TKI arm	Adverse Events Control arm
Pemetrexed-carboplatin adjuvant chemotherapy with/without gefitinib (Phase II)	Approximately 43% of the patients who had both AC and gefitinib also had a rash	NR
EVAN (Phase II)	Grade ≥ 3 , in 12% of patients Rash in 4% of patients.	Grade ≥ 3 , in 11% of patients decreased neutrophil count 16% of patients. Myelosuppression: 9% of patients.
ADJUVANT - CTONG1104 (Phase III)	Grade ≥ 3 , 2% of patients had raised alanine aminotransferase 2% of patients had raised aspartate aminotransferase Serious AE in 7% of patients	Grade ≥ 3 Neutropenia in 34% of patients Leucopenia in 16% of patients vomiting in 8% of patients. Serious AE in 23% of patients
SELECT (Phase II)	Erlotinib dose reduction: 40% of patients. Second dose reduction of erlotinib: 16% of patients. Grades 1-3 A: rash, diarrhea, dry skin, fatigue, nausea/vomiting, nail changes, pruritis, stomatitis, and transaminitis. Recurrence 40% of patients No grade 4 or 5 AE.	Not relevant
ADAURA (Phase III)	98% of patients reported AE Interstitial lung disease in 3% of patients. \leq grade 3 AE; diarrhea, paronychia, stomatitis, upper respiratory tract infection and decreased appetite. Dose reduction Grade ≥ 3 AE reported in 20% of patients	89% of patients reported AE Grade ≥ 3 AE reported in 13% of patients

Abbreviations AE, Adverse events, TKI, tyrosine kinase inhibitor NR, not reported.

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

5.1. 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[34]. 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 2 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, 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 6 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).

5.2. EMERGING Trial

EMERGING Trial, recruited 72 patients with resected NSCLC to this investigation [32]. 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 1 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 3 years. Post-surgery care for up to 2 years comprised of chest computerized tomography (CT) scan, abdominal ultrasound every 3 months, brain MRI bi-annually and bone scan once a year. Study results are expected to be published on December 2022 (Table 6).

5.3. Adjuvant Afatinib Trial

95 patients with resected NSCLC were enrolled[35]. Inclusion criteria were diagnosis of stage I to III NSCLC harboring EGFR mutations. Participants were randomized to short course (3 months) afatinib vs. long course (2 years) afatinib. Patients were followed up every 6 months for three years and then once in the fourth year. Chest CT scan, blood tests, performance status and physical exam were conducted at these follow ups. Study results are estimated for November 2021 (Table 6).

Table 6. Ongoing clinical trials that include adjuvant therapy with EGFR-TKI in patients with completely resected EGFR mutated NSCLC

Abbreviations: EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor, NSCLC, non-small cell lung cancer

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

6. Discussion

Non-small cell lung cancer accounts for the majority of all lung cancers, which are the leading cause of cancer-related deaths in the United States[3]. Traditionally, the disease has poor prognosis due to late onset of symptoms and curative resection is often complicated by systemic or local relapse[5]. Adjuvant therapies, including TKIs, chemotherapy and immunotherapy, have been shown to improve survival outcomes. New research continues to increase the number of options for treatment. A particularly promising avenue of study involves the mutations of epidermal growth factor receptor in NSCLC as they can be better targeted by the generations of TKIs. Presently, drugs of the first TKI generation, erlotinib and gefitinib along with the third-generation agent, osimertinib have been approved for clinical use as adjuvant treatment due to their better efficacy, improved outcomes in PFS and/or OS[14–17].

Past studies involving adjuvant chemotherapy have had mixed results. They played an innovative role to provide clinical data and document the efficacy of different treatments including cisplatin, carboplatin, paclitaxel, vindesine, vinorelbine, vinoblastine, etoposide, ifosfamide, and mitomycin. While the ALPI, BLT and later MAGRIT (involving immunotherapy subsequent to AC) were negative trials, the IALT, CALGB 9633, JBR-10 and ANITA trials demonstrated improvements in progression-free survival, disease-free survival, and overall survival. Other trials not included in this review have suggested efficacy of additional chemotherapeutics such as uracil/tegafur though these therapies have as yet not been approved for commercial use in North America or Europe[36]. The survival benefits accrued by AC is dependent on staging and tumor size, however the lack of attunement to gene markers and mutations leaves the therapeutic strategy lagging in the modern era of personalized medicine.

In the setting of non-EGFR mutant resected NSCLC and subsequent AC, one notable ongoing study has been IMpower010 which is similarly examining the efficacy and safety of drug, in this case

the anti-PD-L1 monoclonal antibody atezolizumab, compared to best supportive care (BSC) following AC in resected NSCLC[37]. IMpower010 is the first phase III global study using an immune checkpoint inhibitor to show statistically significant DFS benefit vs BSC for patients with stage IB to IIIA. Comparable to the permethrexed-carboplatin-gefitinib, EVAN and ADJUVANT – CTONG 1104 trials, there has been ongoing interest in identifying whether the use of TKI or other non-chemotherapeutic can produce improved survival rates with lowered adverse events across all forms of NSCLC. All three of these studies have shown improvements in DFS while adverse events were comparable between TKI plus AC and AC alone. Notably the ADJUVANT – CTONG 1104 trial showed a decrease in serious adverse effects (7% vs 23%). This will continue to be an area of investigation both for the use of TKI in EGFR-mutant NSCLC as well as non-EGFR mutant NSCLC.

Osimertinib, a third-generation adjuvant TKI therapy plays an innovative role as novel treatment strategy [14]. Osimertinib trial findings in ADAURA demonstrated increased efficacy such as significantly longer DFS in patients administered with this oral TKI in comparison to patients who received placebo. Previous studies have successfully shown long disease-free survival statistics for patients taking adjuvant erlotinib and gefitinib for a range of disease staging from IA to IIIA[16,17] However these patients are still susceptible to relapses that target CNS metastasis. The role of EGFR mutations, including but not limited to exon 19 deletion, as a predictor for such brain metastasis may be considered[18]. Osimertinib's irreversible binding to EGFR and potentially antineoplastic effects in curtailing tumor cell proliferation and tumor vascularization should be further explored.

The National Institute of Health's National Library of Medicine displays three ongoing studies involving erlotinib and afatinib which will yield better insight into the utility of these TKI drugs as adjuvant therapy in prolonging lifespan in patients who have been surgically resected for EGFR-mutant NSCLC across stages IA-III A[34,35,38]. These investigations will detail greater knowledge on safety profile for erlotinib and examine the question of afatinib approval across both short and long course treatments. There is a scope for future studies assessing efficacy and survival outcomes in dacomitinib, comparisons between TKI and cisplatin + vinorelbine as an adjuvant therapy, and further elucidation of brain and other metastasis site incidence.

7. Conclusions

Innovative pharmaceutical research of the 21st century has managed to develop modern drugs aiming at specific mutated proteins which are expressed in malignant tumors. These anticancer medications have benefited the clinical oncology field in prescribing TKI adjuvant therapy regimen to EGFR-mutated NSCLC resected patients. The advanced generation agents comply with targeted treatment patient-tailored approach, acting to extend life through higher efficacy, longer progression-free survival and improved overall survival of NSCLC patients. Prospect investigational trials are imperative in efforts to overcome the challenges posed by third-generation EGFR-TKI resistance and discovery of new mutations.

Author Contributions:

Conceptualization, W.S. and A.A.; software, W.S. and B.M.J.; formal analysis, W.S.; investigation, W.S. and B.M.J.; writing – original draft preparation, W.S. and B.M.J.; writing – review and editing,

W.S. and A.A.; visualization, W.S. and A.A.; supervision, W.S. and A.A.; project administration, W.S. and A.A. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

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