

Review

# Treatment Strategies for Non-Small Cell Lung Cancer with Common *EGFR* Mutations: A Review of the History of EGFR TKIs Approval and Emerging Data

Julian A. Marin-Acevedo <sup>1,†</sup> , Bruna Pellini <sup>2,3,\*,†</sup> , ErinMarie O. Kimbrough <sup>4</sup>, J. Kevin Hicks <sup>5</sup>   
and Alberto Chiappori <sup>2,3,\*</sup>

<sup>1</sup> Division of Medical Oncology, Indiana University Melvin and Bren Simon Comprehensive Cancer Center, Indianapolis, IN 46202, USA

<sup>2</sup> Department of Thoracic Oncology, Moffitt Cancer Center and Research Institute, Tampa, FL 33612, USA

<sup>3</sup> Department of Oncologic Sciences, Morsani College of Medicine, University of South Florida, Tampa, FL 33620, USA

<sup>4</sup> Division of Hematology and Oncology, Mayo Clinic, Jacksonville, FL 32224, USA

<sup>5</sup> Department of Individualized Cancer Management, Moffitt Cancer Center, Tampa, FL 33612, USA

\* Correspondence: bruna.pellini@moffitt.org (B.P.); alberto.chiappori@moffitt.org (A.C.); Tel.: +1-813-745-3050 or +1-813-449-8077 (B.P. & A.C.)

† These authors contributed equally to this work.

**Simple Summary:** The management of non-small cell lung cancer with a common *EGFR* mutation has evolved over the past decades. While frontline use of second- or third-generation EGFR tyrosine kinase inhibitors (TKIs) is preferred over first-generation EGFR-TKIs, choosing the ideal agent depends on multiple factors (drug availability, physician comfort, specific *EGFR* mutation, presence of brain metastasis, etc.). Furthermore, defining subsequent therapies at the time of progression will rely on numerous variables (extent of disease, frontline EGFR TKI generation used, mechanism of resistance, etc.). Consequently, defining an optimal sequencing strategy is both, crucial and challenging. In this review, we present a detailed summary of evidence supporting the use of EGFR TKIs with or without other therapeutic approaches, outline available options at the time of disease progression, summarize investigational strategies, and suggest an approach to therapeutic sequencing in patients with common *EGFR* mutations.

**Abstract:** The development of targeted therapies over the past two decades has led to a dramatic change in the management of *EGFR*-mutant non-small cell lung cancer (NSCLC). While there are currently five approved EGFR tyrosine kinase inhibitors (TKIs) for treating *EGFR*-mutant NSCLC in the first-line setting, therapy selection after progression on EGFR TKIs remains complex. Multiple groups are investigating novel therapies and drug combinations to determine the optimal therapy and treatment sequence for these patients. In this review, we summarize the landmark trials and history of the approval of EGFR TKIs, their efficacy and tolerability, and the role of these therapies in patients with central nervous system metastasis. We also briefly discuss the mechanisms of resistance to EGFR TKIs, ongoing attempts to overcome resistance and improve outcomes, and finalize by offering treatment sequencing recommendations.

**Keywords:** *EGFR* mutations; EGFR TKIs; non-small cell lung cancer; targeted therapies; therapy sequencing



**Citation:** Marin-Acevedo, J.A.; Pellini, B.; Kimbrough, E.O.; Hicks, J.K.; Chiappori, A. Treatment Strategies for Non-Small Cell Lung Cancer with Common *EGFR* Mutations: A Review of the History of EGFR TKIs Approval and Emerging Data. *Cancers* **2023**, *15*, 629. <https://doi.org/10.3390/cancers15030629>

Academic Editor: Sonia Molina-Pinelo

Received: 19 December 2022

Revised: 11 January 2023

Accepted: 13 January 2023

Published: 19 January 2023

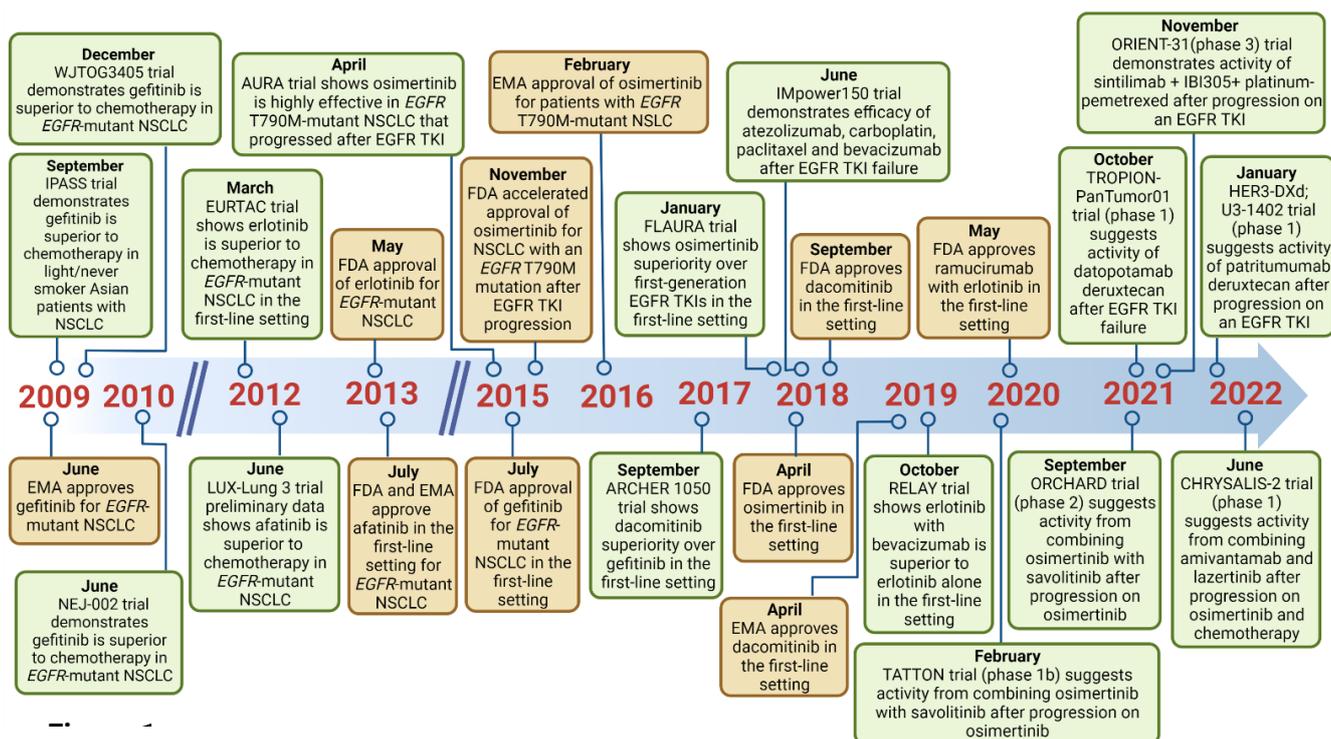


**Copyright:** © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

## 1. Introduction

Sensitizing mutations in the epidermal growth factor receptor (*EGFR*) gene are one of the most common targetable genomic alterations in non-small cell lung cancer (NSCLC). These can be found in ~15% of lung adenocarcinomas in the United States and 22–64% of lung adenocarcinoma in Asian patients [1,2]. In the past two decades, five EGFR tyrosine

kinase inhibitors (TKIs) have become commercially available for the management of advanced NSCLC with common *EGFR*-sensitizing mutations [i.e., *EGFR* exon 19 deletions or exon 21 mutations (L858R)]: erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib (Table 1; Figure 1) [3–9]. These drugs exhibit distinct activity and safety profiles and are divided into first- (e.g., erlotinib, gefitinib), second- (e.g., afatinib, dacomitinib), and third-generation (e.g., osimertinib) TKIs. The second- and third-generation TKIs, afatinib and osimertinib, have demonstrated extended activity against some uncommon *EGFR* mutations [e.g., T790M (osimertinib), G719X, L861Q, or S768I (afatinib and osimertinib)] [10–14].



**Figure 1.** Timeline depicting the publication of landmark trials on anti-*EGFR* TKIs, approval by the FDA and EMA, and publication of data pertaining novel therapies; EMA, European Medicines Agency; FDA, Food and Drugs Administration; TKIs, tyrosine kinase inhibitors. Created with BioRender.com, accessed on 8 January 2023.

The efficacy of the *EGFR* TKIs has improved with each new generation. First- and second-generation *EGFR* TKIs have superior response rates (RRs) and progression-free survival (PFS) compared to platinum-doublet chemotherapy (i.e., cisplatin or carboplatin combined with either gemcitabine, pemetrexed, paclitaxel, or docetaxel) [3–6,15]. Dacomitinib and osimertinib confer improved PFS and overall survival (OS) rates compared to the first-generation *EGFR* TKIs [7,8,16,17]. Afatinib confers superior PFS and OS compared to platinum-doublet chemotherapy but did not improve OS compared to first-generation *EGFR* TKIs [6,18,19]. While first-generation *EGFR* TKIs have been compared head-to-head with second- and third-generation TKIs and have proven to be less effective, second- and third-generation *EGFR* TKIs have not been compared head-to-head in a prospective clinical trial. Therefore, it is unclear if these drugs confer the same outcomes for patients.

Despite *EGFR* TKIs improved efficacy over chemotherapy, drug resistance eventually occurs [20]. A wide array of genomic pathways activation and transcriptional remodeling have been reported as mechanisms of resistance [20]. These findings have prompted investigation of novel combinations and therapeutics. In this review, we discuss the data to support the use of *EGFR* TKIs alone or in combination, describe developing therapies for resistant disease, and propose a treatment sequencing strategy based on the available data.

**Table 1.** Landmark Clinical Trials of EGFR TKIs as First-Line Therapy for Advanced NSCLC.

Drug(s)	Trial (NCT #)	Phase	Population Characteristics	Treatment Regimen /Cohorts	Outcomes	Side Effects	Rate of Discontinuation from Toxicity	FDA Approval Date
Erlotinib	EURTAC (NCT00446225)	III	N = 173 Stages IIIB/IV Adenocarcinoma only -Race: White (99%) -EGFR Mutations: ex19del and L858R -Asymptomatic brain metastases were allowed	Cohort A: Erlotinib 150 mg daily Cohort B: Platinum-based chemotherapy	ORR: 63.6% (A) vs. 17.8% (B) mPFS: 9.7 months (A) vs. 5.2 months (B) $p < 0.0001$ mOS: 19.3 months (A) vs. 19.5 months (B) $p = 0.87$	Overall grade $\geq 3$ AE: 45% (A) vs. 67% (B)	13% (A) vs. 23% (B)	14 May 2013
	IPASS (NCT00322452)	III	N = 1217 Stage IIIB/IV Adenocarcinoma only -Race: Asian (98%) -EGFR Mutations: ex19del, L858R, T790M, other -Excluded patients with untreated brain metastases	Cohort A: Gefitinib 250 mg daily Cohort B: Platinum-based chemotherapy	ORR: 84.8% (A) vs. 43.2% (B) mPFS: not reported; HR, 0.48 (95% CI, 0.34 to 0.67) for those with EGFR mutation mOS: 18.8 months (A) vs. 17.4 months (B) $p = 0.109$	Overall grade $\geq 3$ AE: not reported *	6.9% (A) vs. 13.6% (B)	
Gefitinib	NEJ-002 (N/A–Japan)	III	N = 230 Stage IIIB/IV NSCLC -Race: Asian/Japanese (100%) -EGFR Mutations: ex19del, L858R, and other (6.1%) -Asymptomatic brain metastases were allowed	Cohort A: Gefitinib 250 mg daily Cohort B: Platinum-based chemotherapy	ORR: 73.7% (A) vs. 30.7% (B) mPFS: 10.8 months (A) vs. 5.4 months (B) $p < 0.001$ mOS: 27.7 months (A) vs. 26.6 months (B) $p = 0.483$	Overall grade $\geq 3$ AE: 41.2% (A) vs. 71.7% (B)	Not reported	13 July 2015
	WJTOG3405 (N/A–Japan)	III	N = 118 Stage IIIB/IV NSCLC -Race: Asian/Japanese (100%) -EGFR Mutations: ex19del and L858R -Asymptomatic brain metastases were allowed	Cohort A: Gefitinib 250 mg daily Cohort B: Platinum-based chemotherapy	ORR: 62.1% (A) vs. 32.2% (B) mPFS: 9.2 months (A) vs. 6.3 months (B) $p < 0.0001$ mOS: 34.9 months (A) vs. 37.3 months (B) $p = 0.2070$	Overall grade $\geq 3$ AE: not reported *	Not Reported	

Table 1. Cont.

Drug(s)	Trial (NCT #)	Phase	Population Characteristics	Treatment Regimen /Cohorts	Outcomes	Side Effects	Rate of Discontinuation from Toxicity	FDA Approval Date
	IFUM (NCT01203917)	IV	N = 106 Stage IIIA/B/IV NSCLC -Race: White (100%) -EGFR Mutations: ex19del, L858R, T790M, S768I -Inclusion of brain metastatic disease not mentioned	Single-Arm: Gefitinib 250 mg daily	ORR: 69.8% mPFS: 9.7 months mOS: 19.2 months	Overall grade $\geq 3$ AE: 15%	7.5%	
	LUX-Lung 3 (NCT00949650)	III	N = 345 Stage IIIB/IV Adenocarcinoma only -Race: White (26.5%), Asian (71.7%), Other (1.7%) -EGFR Mutations: ex19del, L858R, Other (10.3%) -Asymptomatic stable brain metastases were allowed	Cohort A: Afatinib 40 mg daily Cohort B: Platinum-based chemotherapy	ORR: 56% (A) vs. 23% (B) mPFS: 11.1 months (A) vs. 6.9 months (B) $p = 0.0004$ mOS: 28.2 months (A) vs. 28.2 months (B) $p = 0.39$ mOS ex19del: 33.3 months (A) vs. 21.1 months (B) $p = 0.0015$ mOS L858R: 27.6 months (A) vs. 40.3 months (B) $p = 0.29$	Overall grade $\geq 3$ AE: 49% (A) vs. 48% (B)	8% (A) vs. 12% (B)	
Afatinib	LUX-Lung 6 (NCT01121393)	III	N = 364 Stage IIIB/IV Adenocarcinoma only -Race: Asian 100% -EGFR Mutations: ex19del, L858R, other (11%) -Asymptomatic, stable brain metastases were allowed	Cohort A: Afatinib 40 mg daily Cohort B: Platinum-based chemotherapy	ORR: 66.9% (A) vs. 23% (B) mPFS: 13.7 months (A) vs. 5.6 months (B) $p < 0.0001$ mOS: 23.1 months (A) vs. 23.5 months (B) $p = 0.61$ mOS ex19del: 31.4 months (A) vs. 18.4 months (B) $p = 0.023$ mOS L858R: 19.6 months (A) vs. 24.3 months (B) $p = 0.34$	Overall grade $\geq 3$ AE: 36% (A) vs. 60.2% (B)	5.9% (A) vs. 39.8% (B)	Approval for EGFR exon 19 deletions or exon 21 (L858R): 23 July 2013 Expansion of indication to all non-resistant EGFR mutations: 12 January 2018
	LUX-Lung 7	IIb	N = 319 Stage IIIB/IV Adenocarcinoma only -Race: Asian (59%), White (30%), Black (1%), not available (11%) -EGFR Mutations: ex19del and L858R -Active brain metastases (symptomatic or requiring treatment) excluded	Cohort A: Afatinib 40 mg daily with escalation to 50 mg daily if well tolerated after 4 weeks Cohort B: Gefitinib 250 mg daily	ORR: 70% (A) vs. 56% (B) mPFS: 11.0 months (A) vs. 10.9 months (B), HR 0.73 $p < 0.017$ mOS: 27.9 months (A) vs. 24.9 months (B) $p = 0.258$	Overall grade $\geq 3$ AE: 57% (A) vs. 52% (B)	6% (A) vs. 6% (B)	

Table 1. Cont.

Drug(s)	Trial (NCT #)	Phase	Population Characteristics	Treatment Regimen /Cohorts	Outcomes	Side Effects	Rate of Discontinuation from Toxicity	FDA Approval Date
Dacomitinib	ARCHER 1050 (NCT01774721)	III	N = 452 Stage IIIB/IV NSCLC -Race: Asian (75%), Black (<1%), White (25%) -EGFR Mutations: ex19del, L858R -Brain or leptomeningeal metastases excluded	Cohort A: Dacomitinib 45 mg daily Cohort B: Gefitinib 250 mg daily	ORR: 75% (A) vs. 72% (B) mPFS: 14.7 months (A) vs. 9.2 months (B) $p < 0.0001$ mOS: 34.1 months (A) vs. 26.8 months (B) $p = 0.438$	Overall grade $\geq 3$ AE: 63% (A) vs. 41% (B)	10% (A) vs. 7% (B)	27 September 2018
Osimertinib	FLAURA (NCT02296125)	III	N = 556 Stage IIIB/IV NSCLC -Race: Asian (62%), White (36%), Other (1%) -EGFR Mutations: ex19del, L858R -Asymptomatic, stable brain metastases were allowed	Cohort A: Osimertinib 80 mg daily Cohort B: Gefitinib 250 mg daily or Erlotinib 150 mg daily	ORR: 80% (A) vs. 76% (B) mPFS: 18.9 months (A) vs. 10.2 months (B) $p < 0.001$ mOS: 38.6 months (A) vs. 31.8 months (B) $p = 0.046$	Overall grade $\geq 3$ AE: 42% (A) vs. 47% (B)	15% (A) vs. 18% (B)	18 April 2018
Erlotinib + ramucirumab	RELAY (NCT02411448)	III	N = 449 Stage IV NSCLC -Race: Asian (77%), White (22.3%), Other (1%) -EGFR Mutations: ex19del, L858R -Brain or leptomeningeal metastases excluded	Cohort A: Erlotinib 150 mg daily + ramucirumab 10 mg/kg once every 2 weeks Cohort B: Erlotinib 150 mg daily + placebo once every 2 weeks	ORR: 76% (A) vs. 75% (B) mPFS: 19.4 months (A) vs. 12.4 month $p \leq 0.0001$ mOS: Not available	Overall grade $\geq 3$ AE: 72% (A) vs. 54% (B)	13% (A) vs. 11% (B)	29 May 2020

\* Only individual grade  $\geq 3$  AEs are reported; Abbreviations: AEs, adverse events; FDA, Food and Drug Administration; mPFS, median progression-free survival; mOS, median overall survival; ORR, overall response rate; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

## 2. Exploring the Use of EGFR TKIs

### 2.1. EGFR TKIs versus Platinum-Doublet Chemotherapy

In July 2002, gefitinib became the first EGFR TKI to be approved in the world, specifically in Japan, for advanced NSCLC [21]. Two years later, erlotinib was approved in the US for unselected patients with advanced NSCLC [22,23]. Nine years later it was approved in the first-line setting for the treatment of advanced NSCLC with an *EGFR* exon 19 del (ex19del) or L858R mutation based on findings of the EURTAC study [3,24]. This phase 3 trial demonstrated improvement in RR (64% vs. 18%) and PFS (9.7 months vs. 5.2 months;  $p < 0.0001$ ) in the intention-to-treat patient population when compared to a platinum-doublet [3]. Erlotinib was better tolerated, and its use was associated with less serious adverse events (AEs) (6% vs. 20%) (Table 1) [3].

In 2009, the European Medicines Agency (EMA) approved gefitinib for the treatment of advanced *EGFR*-mutant NSCLC based on the phase 3 clinical trial IPASS [4,25]. Gefitinib showed improved RR (43% vs. 32%) and OS (18.8 vs. 17.4 months;  $p = 0.109$ ) compared to chemotherapy in a population of light/never-smokers East Asians patients with advanced pulmonary adenocarcinoma [4,26]. Subgroup and post-hoc analyses of this study confirmed that gefitinib conferred a superior RR for all patients with *EGFR*-mutant NSCLC (71% vs. 47%). Specifically, the RR was 85% vs. 43% for patients with ex19del and 61% vs. 53% for the ones with L858R mutations [4,26]. Following IPASS, several landmark trials have confirmed the superiority of gefitinib over platinum-doublet in the first-line setting for patients with *EGFR*-mutant NSCLC in East Asian (NEJ-002, WJTOG3405) and White patients (IFUM) (Table 1) [27–31]. In 2015, the U.S. Food and Drugs administration (FDA) approved gefitinib for first-line treatment of metastatic NSCLC [32].

Afatinib was the first second-generation EGFR TKI approved by the FDA in 2013 [33]. It demonstrated improved PFS and RR compared to chemotherapy in the LUX-Lung 3 (PFS 11 vs. 7 months,  $p = 0.0004$ ; RR 56% vs. 23%) and the LUX-Lung 6 (PFS 14 vs. 6 months,  $p < 0.0001$ ; RR 67% vs. 23%) clinical trials [5,6,9,34]. Interestingly, in both trials the OS benefit from afatinib was seen among patients with *EGFR* ex19del mutations but not in those with L858R mutations (Table 1) [6]. Up to 49% of patients receiving afatinib developed serious toxicities, however, cessation of treatment due to side effects was more common among those receiving chemotherapy [5,6,9]. According to the retrospective RealGiDo study, afatinib can be dose-reduced to improve tolerability without affecting efficacy [35].

Osimertinib was initially approved for patients with *EGFR* T790M mutant-NSCLC who had progressed on or after EGFR TKI therapy [36]. The phase 3 AURA3 trial demonstrated improved RR (71% vs. 31%) and median PFS (10.1 vs. 4.4 months;  $p < 0.001$ ) in those receiving osimertinib vs. platinum-based chemotherapy [37]. In this study, osimertinib also demonstrated activity against asymptomatic central nervous system (CNS) metastasis while showcasing a safe toxicity profile. Only 23% of patients experienced serious AEs compared to 47% of patients in the chemotherapy group. Osimertinib was only discontinued in 7% of patients [37]. While there was a trend towards improved OS with osimertinib (26.2 vs. 22.5 months), this difference did not reach statistical significance ( $p = 0.277$ ) [38].

### 2.2. Second- and Third-Generation EGFR TKIs versus First-Generation EGFR TKIs

The phase 2b LUX-Lung 7 clinical trial evaluated the use of afatinib vs. gefitinib in treatment-naïve patients with advanced *EGFR*-mutant NSCLC [19]. Afatinib conferred longer PFS (11 vs. 10.9 months;  $p = 0.017$ ) and time-to-treatment failure (13.7 vs. 11.5 months;  $p = 0.0073$ ) [19]. There were no differences in OS. The rate of toxicities and discontinuation of therapy were also similar (Table 1) [18,19]. In contrast, a real-world study showed that afatinib improved PFS and 1-year OS rates (16.4 months,  $p = 0.005$ ; 78.2%;  $p = 0.004$ ) compared to gefitinib (10.3 months and 69.1%) and erlotinib (12.1 months and 71.6%) [39].

Dacomitinib was approved in 2018 based on the phase 3 ARCHER 1050 trial [8,40,41]. In this study, first-line dacomitinib resulted in improved PFS (15 vs. 9 months;  $p < 0.0001$ ) and OS (34 vs. 27 months;  $p = 0.438$ ) compared to gefitinib [8,16]. The toxicities and rate of therapy discontinuation were similar in both groups (Table 1) [8,16].

Osimertinib was approved for the first-line treatment of *EGFR*-mutant NSCLC in 2018 based on results of the phase 3 FLAURA trial [7,36]. In this study, osimertinib demonstrated similar RR (80% vs. 76%) and disease control rate (DCR: 97% vs. 92%) to first-generation *EGFR* TKIs, but longer PFS (19 vs. 10 months;  $p < 0.001$ ) and OS (39 vs. 32 months;  $p = 0.046$ ) [7,17]. It was also better tolerated than gefitinib or erlotinib (Table 1) [7,17]. Based on these combined findings, osimertinib, afatinib and dacomitinib are preferred over first-generation *EGFR* TKIs in the front-line setting.

### 2.3. Second-Generation *EGFR* TKIs Following First-Generation *EGFR* TKI Failure

The phase 2 LUX-Lung 4 trial evaluated the use of afatinib in patients who progressed after treatment with erlotinib or gefitinib [42]. The RR was 8% and the PFS was 4.4 months. Approximately 37% of patients experienced a grade  $\geq 3$  toxicity and 29% of patients discontinued afatinib due to serious AEs [42]. Given the limited clinical efficacy, afatinib is not used in this setting.

### 2.4. Third-Generation *EGFR* TKIs Following First and Second-Generation *EGFR* TKI Failure

The phase 1/2 AURA trial evaluated the use of osimertinib after progression on gefitinib or erlotinib. The DCR and PFS were 84% and 8.2 months for all-comers, and 95% and 9.6 months for those with a T790M mutation, respectively [43]. The phase 2 AURA2 trial evaluated osimertinib in patients with *EGFR* T790M, who progressed on any first- or second-generation TKI. The DCR was 92%, RR was 70%, and PFS was 9.9 months. Approximately 34% of patients experienced a grade  $\geq 3$  toxicity but only 5% discontinued osimertinib due to an AE [44].

The GioTag observational study evaluated the role of sequencing osimertinib after afatinib failure in patients with *EGFR* T790M mutations [45]. The OS was 37.6 months for all-comers, 41.6 months for those with co-existing *EGFR* del19ex mutation, and 44.8 months for Asian patients [45]. A retrospective study from South Korea also demonstrated a role for sequencing osimertinib after afatinib among those with *EGFR* T790M-mutant NSCLC [46]. In this analysis, the median time on treatment for patients who received osimertinib was 20.8 months while the 2- and 3-year OS rates were 86% and 69%, respectively [46]. Therefore, osimertinib is recommended for patients with *EGFR* T790M-mutant NSCLC who progress after a first- or second-generation TKI.

### 2.5. *EGFR* TKIs in Combination with Anti-Vascular Endothelial Growth Factors

Combination therapies targeting the vascular endothelial growth factor (VEGF), or the VEGF receptor (VEGFR), and *EGFR* have been studied [47]. The phase 3 NEJ026 trial evaluated erlotinib +/- bevacizumab in Japanese patients with advanced *EGFR*-mutant NSCLC [48]. Erlotinib plus bevacizumab resulted in improved PFS (16.9 vs. 13.3 months;  $p = 0.016$ ) without increasing toxicity rates [48]. Similarly, the phase 3 RELAY trial evaluating erlotinib +/- ramucirumab demonstrated an improved PFS in those receiving combination therapy (19 vs. 12 months;  $p < 0.0001$ ) [49]. Grade  $\geq 3$  toxicities and treatment discontinuation, however, were more common in the combination therapy group (Table 1) [49]. While the median OS data is not yet available, there were no differences at 1 and 2 years between the two treatment groups [49].

Afatinib plus bevacizumab were evaluated in a phase 1 clinical trial in Japan achieving a RR of 81% [50]. Similarly, in an observational study from Taiwan using the same combination therapy the RR was 88%, the PFS was 24 months, and the OS was 46 months [51].

Osimertinib in combination with anti-VEGF has also been investigated. A phase 1/2 trial (NCT02803203) evaluated first-line osimertinib with bevacizumab [52]. The RR was 80% and the PFS was 19 months [52]. Approximately 31% of patients discontinued bevacizumab due to toxicity [52]. This combination was also evaluated in Japanese (WJOG 8715L) and European (BOOSTER) patients with *EGFR* T790M-mutant NSCLC who developed disease progression after a first- or second-generation *EGFR* TKI [53,54]. These phase 2 trials failed to demonstrate an improvement in PFS compared to osimertinib alone

(14 vs. 9 months;  $p = 0.20$  in the WJOG 8715L Trial, and 15 vs. 12 months;  $p = 0.83$  in the BOOSTER Trial) [53,54]. Combination therapy resulted in a significantly shorter time to treatment failure (8 vs. 11 months;  $p = 0.0074$ ) and an increased incidence of grade  $\geq 3$  toxicities (47% vs. 18%) [54]. Another phase 2 trial (WJOG9717L) evaluated the use of osimertinib with bevacizumab in patients with common *EGFR* mutations [55]. The median PFS was similar to osimertinib alone (22.1 vs. 20.2 months; HR 0.862  $p = 0.213$ ), while the rate of grade  $\geq 3$  toxicities was higher in the combination group (56% vs. 48%) [55]. These combined findings suggest osimertinib plus bevacizumab does not improve outcomes and increases toxicities.

Currently, there are several ongoing studies evaluating bevacizumab or ramucirumab with second- or third-generation *EGFR* TKIs in the frontline setting ([Clinicaltrials.gov](https://clinicaltrials.gov): NCT04575415, NCT04148898, NCT03909334, NCT02971501, NCT04181060, accessed on 9 January 2023). The results of these studies are awaited and may affect current treatment paradigms.

## 2.6. *EGFR* TKIs in Combination with Chemotherapy

The use of *EGFR* TKIs with chemotherapy has been investigated in retrospective and prospective studies [56–61]. Although the results of these studies are mixed, some suggest that combination therapy may be more beneficial in selected treatment-naïve patients [56–61].

Erlotinib plus chemotherapy was evaluated as first-line therapy in patients with advanced/metastatic NSCLC with or without common *EGFR* mutation in the phase 2 trial CALGB 30406 [56]. This study included 66 patients with a common *EGFR* mutation. Of these, 33 received erlotinib monotherapy and 33 received erlotinib with paclitaxel and carboplatin. There were no significant differences in PFS for all-comers between the two treatment groups (PFS = 5.0 vs. 6.6 months;  $p = 0.1988$ ) [56]. The phase 3 IMPRESS trial evaluated chemotherapy +/- gefitinib after disease progression on gefitinib [57]. The PFS was 5.4 months in both groups, however, more toxicities were seen in the combination arm [57]. Two phase 3 trials, one in India (CTRI/2016/08/007149) and one in Japan (NEJ009), evaluated gefitinib in combination with chemotherapy versus gefitinib alone in treatment-naïve patients [58,59]. The combination arms resulted in improved RR, longer PFS and OS. However, grade  $\geq 3$  toxicities were more frequent in the combination arms [58,59].

The LUX-Lung 5 trial evaluated afatinib plus chemotherapy vs. single agent chemotherapy in patients with advanced *EGFR*-mutant NSCLC who had progressed after treatment with first-generation *EGFR* TKI, chemotherapy, and afatinib [60]. In this phase 3 clinical trial, afatinib plus chemotherapy resulted in improved RR (32.1% vs. 13.2%;  $p = 0.005$ ) and PFS (5.6 vs. 2.8 months;  $p = 0.003$ ), however, there was no difference in OS between the two groups [60]. The incidence of grade  $\geq 3$  toxicities was higher in the combination group [60].

A retrospective study evaluated osimertinib plus chemotherapy in the third-line setting or beyond [61]. The median duration of treatment was 6.1 months, and the median OS was 10.4 months (95% CI 7.0–13.2 months). According to the authors, the OS was slightly inferior compared to the AURA3 trial likely reflecting that their populations was more heavily pre-treated than AURA3 [61]. Approximately 27% of patients developed grade  $\geq 3$  toxicities. The rate of osimertinib discontinuation was 2% [61]. Currently, the use of osimertinib in combination with chemotherapy is being investigated as first-line therapy in *EGFR*-mutant NSCLC in the phase 3 FLAURA2 trial (NCT04035486) and in patients with detectable *EGFR* mutations in ctDNA in two phase 2 studies (NCT04410796, NCT05281406). Preliminary data from FLAURA2 suggests that the combination is well tolerated and safe [62].

## 2.7. *EGFR* TKIs in Combination with Immunotherapy

The use of first-generation *EGFR* TKIs in combination with immune checkpoint inhibitors (ICIs) has been investigated in three phase 1 clinical trials in patients with *EGFR*-

mutant NSCLC [63–65]. While response to therapy appeared promising, grade  $\geq 3$  toxicities were seen in more than 40% of patients and therapy was discontinued in 35% of patients [63–65].

Osimertinib was combined with durvalumab in one arm of the phase 1b TATTON trial [66]. The RR was 43% with this combination, however, the treatment arm was terminated because of increased reports of interstitial lung disease (ILD) [66]. The phase 3 CAURAL trial evaluated osimertinib with or without durvalumab in patients with *EGFR* T790M mutations who had received prior EGFR TKI [67]. The RR was 80% and no grade  $\geq 3$  toxicities were seen among the first 14 treated patients. However, recruitment was terminated due to the high rates of ILD reported in the TATTON trial [66,67]. While the combination of EGFR TKIs with ICIs appeared promising, the incidence and severity of AEs seems prohibitive.

### 3. Mechanisms of Resistance to EGFR TKIs

Cancer cells may develop innate or acquired resistance to EGFR TKI therapy (Table 2). Primary resistance occurs from coexisting uncommon *EGFR* mutations, mutations in genes other than *EGFR*, or heterogeneity to TKI response [68]. Acquired resistance is defined as progression on an EGFR TKI in a patient with a common *EGFR* mutation that achieved significant or durable ( $\geq 6$  months) clinical response [69]. Acquired resistance mechanisms are further subclassified as *EGFR*-dependent and -independent, but these can coexist and overlap [70,71].

**Table 2.** Mechanisms of Resistance to EGFR-TKI.

Classification	Sub-Classification	Examples
Primary	Coexisting Activating Mutations/fusions	Uncommon <i>EGFR</i> Mutations: <i>EGFR</i> Exon 20 insertions or duplications, de novo <i>EGFR</i> T790M Other: <i>MET</i> amplifications, <i>ALK</i> fusions/ <i>EML4-ALK</i> fusions
	Heterogeneity in TKI Response	Cellular apoptotic machinery heterogeneity/Baseline BIM protein expression differences
Secondary/ Acquired	<i>EGFR</i> -Dependent	<i>EGFR</i> T790M (“gatekeeper” mutation) Non-T790M <i>EGFR</i> Mutations: D761Y, S768I, V769L, C797X, L792X, G719A, G769X, L718Q, or G724S
	<i>EGFR</i> -Independent	Bypass Mechanisms: (A) Genetic alterations: <i>MET</i> exon 14 skipping mutation, <i>ERBB2/HER2</i> mutations/amplification, <i>HER3</i> upregulation, <i>RET</i> or <i>FGFR3</i> fusions, <i>PIK3CA/BRAF/KRAS</i> mutations (B) Immune escape: PD-L1 upregulation Histologic Transformation: (A) Small Cell Lung Cancer (B) EMT

Abbreviations: EMT: Epithelial-to-mesenchymal transformation; PD-L1: Programmed Death-Ligand 1; TKI, tyrosine kinase inhibitor.

*EGFR*-dependent mechanisms lead to an increase in EGFR kinase activity. The most common is the development of the *EGFR* T790M mutation (“gatekeeper”) which accounts for 25–50% of cases of treatment failure after first- and second-generation EGFR TKIs [7,68,70,72–79]. The *EGFR* C797X mutations are also commonly seen. Specifically, the *EGFR* C797S mutation accounts for ~7–8% of cases of osimertinib resistance when used as first-line therapy and 10–26% of cases when used as second-line therapy [80,81]. Other mutations like *EGFR* L792X, G769X, L718Q, G719A, G724S, or exon 18 variants D761Y, S768I, V769L are less common [77–80,82,83].

*EGFR*-independent mechanisms include bypass mechanisms and histologic/phenotypic transformation [70,71,81,84–89]. EGFR proteins, as members of the ERBB/HER family, normally interact with other ERBB/HER family members to create dimers that phosphorylate

and activate downstream signaling pathways [20]. Bypass mechanisms may be a result of *ERBB2/HER2* mutations/amplifications that form EGFR/HER2 dimers or active HER2 molecules with downstream activating effects [20]. *MET* amplifications can promote persistent HER3 tyrosine kinase activity with downstream activation [20]. Other bypass mechanisms of resistance may result from *PIK3CA*, *BRAF*, *KRAS*, and *MET* exon 14 skipping mutations, as well as *RET* and *FGFR3* fusions [84–88]. Upregulation of PD-L1 leading to immune escape has also been described [90]. Histologic transformation to small cell lung cancer (SCLC) occurs in 3–14% of NSCLC patients treated with EGFR TKIs [70,71,81,89]. It has been suggested that initial biopsies may fail to capture pre-existing SCLC and that treatment with EGFR TKIs results in regression of the NSCLC component while allowing the SCLC component to progress [91]. Patients with concurrent *EGFR/RB1/TP53* mutations seem to be at a particularly high risk of undergoing SCLC histologic transformation [92]. Epithelial-to-mesenchymal transition (EMT) is another mechanism of resistance affecting ~5% of EGFR-TKI resistant tumors [71]. EMT occurs following genetic changes in cancer cells that allow them to transition from having an epithelial to having a mesenchymal phenotype. This transition enables cancer cells to migrate, invade surrounding tissue, and become resistant to therapy [71,93,94].

#### 4. Therapy Following EGFR TKI

The therapy choice after progression on EGFR TKIs varies according to symptoms, metastatic burden, mechanism of resistance, and the class of EGFR TKI used in the front-line setting. In patients who are initially treated with first- or second-generation EGFR TKIs and develop an *EGFR* T790M mutation, osimertinib is preferred over chemotherapy [37,38,44,61,95]. Patients who develop asymptomatic disease progression or oligoprogression (3 to 5 new metastasis) while on an EGFR TKI, but do not acquire an *EGFR* T790M mutation, should continue treatment with the same EGFR TKI plus local palliative therapy (surgery or radiation) to sites of active disease [96–98]. For symptomatic patients with multiple new metastases after an EGFR TKI without an *EGFR* T790M mutation, a change in systemic therapy is recommended (Table 3) [98–103]. The use of first- or second-generation TKIs after progression on osimertinib is not recommended given the poor disease control and short PFS [104].

Chemoimmunotherapy is considered the standard of care for patients with advanced NSCLC, but studies have often excluded patients with *EGFR* mutations [99–101]. The phase 3 trials IMpower130, IMpower150, and ORIENT-31, included patients with *EGFR*-mutant NSCLC after progression on EGFR TKIs [102,105–107]. IMpower150 evaluated the combination of carboplatin, paclitaxel, atezolizumab, and bevacizumab. This combination resulted in a trend towards improved RR (71% vs. 42%), PFS (10 vs. 7 months; HR 0.61–95% CI 0.36–1.03), and OS (26 vs. 20 months; HR 0.91–95% CI 0.53–1.59) compared to chemotherapy plus bevacizumab alone among patients with *EGFR*-mutant NSCLC; however, the differences were not statistically significant [105,106]. Further, there was no significant improvement in RR, PFS, or OS in the those receiving chemoimmunotherapy versus chemotherapy plus bevacizumab (Table 3) [106]. Similar results were seen in the IMpower130 trial, where the addition of immunotherapy to chemotherapy did not result in improved PFS or OS among patients with *EGFR*-mutant NSCLC [102]. The ORIENT-31 trial evaluated the combination of an anti-PD-1 agent (sintilimab), an anti-VEGF agent (IBI305), and chemotherapy in *EGFR*-mutant NSCLC after EGFR TKI failure [107]. Preliminary results demonstrated an improvement in PFS with chemoimmunotherapy plus anti-VEGF vs. chemotherapy alone (6.9 vs. 4.3 months;  $p < 0.0001$ ). This improvement was also seen with the use of chemoimmunotherapy compared to chemotherapy alone (5.6 vs. 4.3 months;  $p < 0.0584$ ) [107]. The safety and efficacy of chemoimmunotherapy in *EGFR*-mutant NSCLC is being assessed in ongoing phase 2 and 3 trials (NCT03786692, Checkmate 722–NCT02864251).

Table 3. Strategies to Overcome TKI Resistance.

Strategy	Drugs	Supporting Clinical Trial	Population	Intervention	ORR	PFS	OS
3rd Generation TKIs	Osimertinib	AURA 3	Stages IIIB/IV Adenocarcinoma EGFR T790M after failure to 1st or 2nd generation TKIs N = 419	Cohort A: Osimertinib 80 mg daily Cohort B: Pemetrexed 500 mg/m <sup>2</sup> with either carboplatin AUC 5 or cisplatin 75 mg/m <sup>2</sup> every 3 weeks	71% (A) vs. 31% (B) <i>p</i> < 0.001	10.1 months (A) vs. 4.4 months (B), HR 0.30 <i>p</i> < 0.001	26.8 months (A) vs. 22.5 months (B) <i>p</i> = 0.277
Chemo-Immunotherapy +/- anti-VEGF therapy	Atezolizumab +/- Bevacizumab	IMpower150	Stage IV non-squamous NSCLC. Those with EGFR mutations should have received and progressed or had unacceptable toxicities while on TKI N = 124/1202 EGFR positive	Cohort A: ABCP: Atezolizumab 1200 mg, bevacizumab 15 mg/Kg, carboplatin AUC 6, paclitaxel 200 mg/m <sup>2</sup> every 3 weeks Cohort B: ACP: Atezolizumab 1200 mg, carboplatin AUC 6, paclitaxel 200 mg/m <sup>2</sup> every 3 weeks Cohort C: BCP: Bevacizumab 15 mg/Kg, carboplatin AUC 6, paclitaxel 200 mg/m <sup>2</sup> every 3 weeks	70.6% (A) vs. 35.6% (B) vs. 41.9% (C)	10.2 months (A) vs. 6.9 months (C) HR 0.61 CI 0.36–1.03 6.9 months (B) vs. 6.9 months (C), HR 1.14 CI 0.73–1.78	26.1 months (A) vs. 20.3 months (C), HR 0.91 CI 0.53–1.59 21.4 months (B) vs. 20.3 months (C), HR 1.16 CI 0.71–1.89
		IMpower130	Stage IV non-squamous NSCLC. Those with EGFR mutations should have received and progressed or had unacceptable toxicities while on TKI N = 44/724 with EGFR or ALK genomic aberrations	Cohort A: Atezolizumab 1200 mg, carboplatin AUC 6, and nab-paclitaxel 100 mg/m <sup>2</sup> every 3 weeks Cohort B: Carboplatin AUC 6, and nab-paclitaxel 100 mg/m <sup>2</sup> every 3 weeks	EGFR-cohort not reported	7.0 months (A) vs. 6.0 months (B), HR 0.75 CI 0.36–1.54	14.4 months (A) vs. 10.0 months (B), HR 0.98 CI 0.41–2.31

Table 3. Cont.

Strategy	Drugs	Supporting Clinical Trial	Population	Intervention	ORR	PFS	OS
	Sintilimab +/- IBI305	ORIENT-31	EGFR-mutant non-squamous NSCLC who had progressed after EGFR TKI N = 444	Cohort A: Sintilimab 200 mg, IBI305 15 mg/Kg, cisplatin 75 mg/m <sup>2</sup> , pemetrexed 500 mg/m <sup>2</sup> every 3 weeks Cohort B: Sintilimab 200 mg, placebo, cisplatin 75 mg/m <sup>2</sup> , pemetrexed 500 mg/m <sup>2</sup> every 3 weeks Cohort C: Placebo, cisplatin 75 mg/m <sup>2</sup> , pemetrexed 500 mg/m <sup>2</sup> every 3 weeks	43.9% (A) vs. 33.1% (B) vs. 25.2% (C)	6.9 months (A) vs. 4.3 months (C) HR 0.464 <i>p</i> < 0.0001 5.6 months (B) vs. 4.3 months (C) HR 0.726 <i>p</i> = 0.0584	NA
Immunotherapy	Pembrolizumab	KEYNOTE-001	Advanced NSCLC N = 78/550 with common EGFR mutations	Pembrolizumab 2 or 10 mg/Kg every 3 weeks, or 10 mg/Kg every 2 weeks	7.7% (all), 20% PD-L1 ≥50%, 8.7% PD-L1 1–49%, 0% <1%	NA	NA
	Durvalumab	ATLANTIC	Advanced NSCLC and disease progression after ≥2 systemic therapies N = 111/444 with EGFR or ALK mutations	Durvalumab 10 mg/Kg every 2 weeks	3.6% (PD-L1 <25%) vs. 12.2% PD-L1 ≥25%	1.9 months (PD-L1 <25%) vs. 1.9 months (PD-L1 ≥25%)	9.9 months (PD-L1 <25%) vs. 13.3 months (PD-L1 ≥25%)
c-MET Agents		ORCHARD (Experimental Module 1)	Metastatic NSCLC with EGFR and MET alterations after progression on first line osimertinib N = 20	Osimertinib 80 mg daily with savolitinib 300 or 600 mg daily	41%	NA	NA

Table 3. Cont.

Strategy	Drugs	Supporting Clinical Trial	Population	Intervention	ORR	PFS	OS
		TATTON	Locally advanced or metastatic NSCLC with <i>EGFR</i> mutation and <i>MET</i> amplification after progression on <i>EGFR</i> TKIs Cohort B1: Previously treated with 3rd generation TKI N = 69 Cohort B2: No 3rd previous generation TKI T790M negative N = 51 Cohort B3: No 3rd previous generation TKI T790M positive N = 18 Cohort D: No previous 3rd generation TKI T790M negative N = 42	Cohort B: Osimertinib 80 mg daily with savolitinib 300 mg (if $\leq 55$ Kg) or 600 mg daily Cohort D: Osimertinib 80 mg daily with savolitinib 300 mg daily	All B: 48% B1: 30% B2: 65% B3: 67% D: 64%	All B: 7.6 months B1: 5.4 months B2: 9.0 months B3: 11.0 months D: 9.1 months	NA
		CHRYSALIS	Metastatic or unresectable NSCLC with <i>EGFR</i> mutation who progressed on osimertinib and were chemotherapy naïve N = 166 (121 cohort A, 45 cohort B)	Cohort A: Amivantamab 1050 mg (1400 mg for patients $\geq 80$ kg) weekly Cohort B: Amivantamab 1050 mg (1400 mg for patients $\geq 80$ kg) weekly with lazertinib 240 mg daily	Cohort A: 19% Cohort B: 36%	NA Cohort A median DOR: 5.9 months Cohort B median DOR: 9.6 months	NA

Table 3. Cont.

Strategy	Drugs	Supporting Clinical Trial	Population	Intervention	ORR	PFS	OS
		CHRYSALIS 2	Advanced or metastatic NSCLC with <i>EGFR</i> exon 19 deletion or L858R that progressed after osimertinib (1st or 2nd line) and platinum-based chemotherapy N = 162	Amivantamab 1050 mg (1400 mg if $\geq 80$ Kg) with lazertinib 240 mg daily	36%	NA DOR: not reached	NA
ADC		NCT03260491	Locally advanced or metastatic <i>EGFR</i> -mutant NSCLC who fail prior TKI N = 57 Prior osimertinib and platinum-based chemotherapy: N = 44	HER3-DXd (pertuzumab deruxtecan) 5.6 mg/kg every 3 weeks	All: 39% Prior osimertinib and platinum chemotherapy: 39%	All: 8.2 months Prior osimertinib and platinum chemotherapy: 8.2 months	NA
		TROPION-PanTumor 01	Advanced or metastatic NSCLC with Actionable Mutations who failed TKI and chemotherapy N = 34 <i>EGFR</i> -mutant: N = 29, 65% after osimertinib	Datopotamab deruxtecan 4 mg/Kg, 6 mg/Kg, or 8 mg/Kg	35%	NA Median DOR: 9.5 months	NA

Abbreviations: ADC, Antibody Drug Conjugate; AEs, adverse events; AUC, area under the curve; DOR, duration of response; NA, not available; NSCLC, non-small cell lung cancer; OS, overall survival; ORR, overall response rate; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

Expression of PD-L1 seems to play a role in response to immunotherapy alone in *EGFR*-mutant NSCLC [108–110]. A subgroup analysis in the KEYNOTE-001 trial suggested that patients with common *EGFR* mutations and PD-L1  $\geq 50\%$  had better RR with pembrolizumab than those with PD-L1  $< 1\%$  [108]. Similarly, the phase 2 ATLANTIC trial evaluating the use of durvalumab after  $\geq 2$  lines of therapy in those with *EGFR*-mutant NSCLC, demonstrated that patients with PD-L1  $\geq 25\%$  had improved RR (12% vs. 4%) and OS (13.3 vs. 9.9 months) compared to those with PD-L1  $< 25\%$  [109,110].

### 5. Novel EGFR TKIs and Targeted Therapies

Savolitinib, an oral TKI against c-MET, was combined with osimertinib in patients with *EGFR*-mutant NSCLC with *MET* amplifications/mutations after progression on osimertinib in the phase 2 trial ORCHARD [111]. The RR was 41% among the 17 evaluable patients, while PFS and OS was not reported [111]. The phase 1b TATTON trial evaluated the combination of osimertinib and savolitinib in patients who had progressed on osimertinib. Combination therapy resulted in a RR of 30% and a PFS of 5.4 months [112]. INSIGHT-2 is an ongoing phase 2 trial evaluating tepotinib (*MET* inhibitor) plus osimertinib in patients with *MET* amplification after progression on osimertinib (NCT03940703).

The phase 1 CHRYSALIS trial investigated amivantamab (bi-specific antibody against *EGFR* and *MET*) +/- lazertinib (third-generation *EGFR* TKI) in patients with *EGFR*-mutant NSCLC who progressed on osimertinib [113]. Preliminary results demonstrated a RR of 19% in the monotherapy group and 36% in those receiving combination therapy [113]. The phase 1 CHRYSALIS-2 trial evaluated amivantamab plus lazertinib in patients with *EGFR*-mutant NSCLC who progressed on osimertinib and platinum-based chemotherapy. Among the 50 evaluable patients, the RR was 36%, the median duration of response was not reached, and grade  $\geq 3$  toxicities mainly included infusion reactions, dermatitis, and hypoalbuminemia [114]. The amivantamab plus lazertinib combination has been moved to phase 3 investigation under the MARIPOSA trial. The latter is comparing frontline amivantamab plus lazertinib versus osimertinib alone in treatment-naïve patients with advanced NSCLC with common *EGFR* mutations (NCT04487080) [115].

Patritumumab deruxtecan, an anti-HER3 antibody-drug conjugate (ADC), was investigated in a phase 1 clinical trial (U3-1402) in patients with *EGFR*-mutant NSCLC who progressed on *EGFR* TKI [116]. The RR was 39% and the PFS was 8.2 months [116]. The phase 2 HERTHENA-Lung01 trial is underway to confirm these findings (NCT04619004).

Datopotamab deruxtecan, an ADC directed against Trop-2, was investigated in the phase 1 TROPION-PanTumor01 trial in patients with advanced NSCLC with an actionable mutation (including *EGFR*) who had previously progressed after treatment with a TKI and chemotherapy [117]. The RR was 35% and the median duration of response was 9.5 months [117]. The phase 3 TROPION-Lung01 trial is underway to confirm these findings (NCT04656652).

### 6. Special Considerations: Brain, Liver, and Bone Metastases

Retrospective data suggest that the metastatic pattern does not differ among patients with *EGFR*-mutant NSCLC compared to those without *EGFR* mutations [118]. Approximately 25% of patients with advanced *EGFR*-mutant NSCLC have brain metastases at the time of diagnosis and ~50% develop these within 3 years [119]. The management of brain metastasis may be challenging depending on the location and the number of lesions. Therefore, it is important to select an *EGFR* TKI with good CNS coverage. Unfortunately, many *EGFR* TKIs trials excluded patients with brain metastases [4,8,28,49]. A retrospective study assessing first-generation *EGFR* TKIs demonstrated that up to 12% of patients receiving first-line erlotinib and 18–30% of patients receiving first-line gefitinib developed CNS disease progression [120]. Findings from a retrospective Japanese study suggest that patients treated with erlotinib had a lower chance of developing CNS metastasis than those treated with gefitinib (4.8% vs. 24.5%;  $p = 0.04$ ) [121].

The LUX-Lung 3 and LUX-Lung 6 trials included patients with asymptomatic brain metastases but did not report the rates of CNS progression [5,9]. This was reported in a cohort study in Taiwan [122]. Approximately 18% (N = 47) of patients treated with front-line afatinib developed CNS progression [122]. Among patients without known CNS metastasis, 11% developed brain metastases, while 33% of patients with known brain metastases had CNS disease progression [122]. The ARCHER 1050 study excluded patients with brain metastasis, however, 0.44% of patient treated with dacomitinib and 4.9% receiving gefitinib developed CNS disease [8,123]. In a series of 14 patients with brain metastases treated with first-line dacomitinib, nearly 86% had improvement of their CNS disease suggesting dacomitinib has CNS activity [124]. The CNS activity of dacomitinib is currently under investigation (NCT04675008).

The FLAURA trial allowed the enrollment of patients with neurologically stable CNS metastasis [7]. Approximately 6% of patients treated with osimertinib had progressive CNS disease versus 15% of patients treated with erlotinib or gefitinib [7]. In patients without known or treated CNS disease, 3% of patients on osimertinib and 7% receiving standard EGFR TKI developed CNS disease [125]. The CNS PFS was longer in those receiving osimertinib compared to standard EGFR TKI (median CNS PFS, not reached vs. 13.9 months; HR, 0.18;  $p = 0.014$ ) [125]. The CNS RR in those with known brain metastases receiving osimertinib was better than in those receiving standard EGFR TKI (91% vs. 68%) [7,126].

Combination therapy may provide improved control of CNS disease. The RELAY study evaluating erlotinib +/- ramucirumab also excluded patients with brain metastases. In this study, however, only two patients (0.9%) treated with erlotinib plus ramucirumab developed CNS metastasis versus eight patients (3.6%) in the placebo plus erlotinib group [49]. It is unclear which approach between second-, third-generation EGFR TKIs, or combination anti-EGFR/VEGF therapy will result in better CNS outcomes. Osimertinib, however, remains the agent with the strongest evidence supporting its use in prevention and treatment of CNS metastasis.

Liver metastases affect 14–17% of patients with *EGFR*-mutant NSCLC [118,127]. This incidence is similar to that seen among *EGFR* wild-type NSCLC, suggesting *EGFR* mutations do not confer a higher risk for developing liver metastasis [128]. Although the treatment of patients with liver metastasis does not usually differ from patients without liver involvement, outcomes tend to be worse when liver metastases are present, even with the use of *EGFR* TKIs like osimertinib [128–130].

In contrast to liver, bone metastases occur more commonly in *EGFR*-mutant (40–54%) than in *EGFR* wild-type NSCLC (32%) [118,131]. Bone metastases seem to be associated with a lower risk of death among patients with *EGFR*-mutant NSCLC [132]. Furthermore, patients with *EGFR* mutations and bone metastases appear to have better OS than those without *EGFR* mutations and bone metastasis [132]. Retrospective data suggest that the use of osimertinib is associated with better clinical outcomes than the use of first- or second-generation *EGFR* TKIs in patients with this metastatic pattern [130]. Finally, the addition of bisphosphonates to therapy not only prevents skeletal complications but also seems to enhance the effect of *EGFR* TKIs and improve PFS [132].

## 7. Treatment Sequencing: A Suggested Approach

The ideal sequencing of *EGFR* TKIs and other therapies for patients with *EGFR*-mutant NSCLC remains uncertain. While osimertinib is often incorporated in the treatment of *EGFR*-mutant NSCLC, the timing of its incorporation remains unclear. The FLAURA trial demonstrated that frontline osimertinib conferred an advantage in PFS and OS when compared to first-generation *EGFR* TKIs [7]. After first- and second-generation TKI failure due to an acquired T790M mutation, osimertinib also improved outcomes compared to chemotherapy (AURA3 trial) [37]. However, it is unknown whether front-line osimertinib use results in more durable response than sequencing *EGFR* TKIs as in the AURA 1-3 trials [133–135].

Many experts advocate for the use of osimertinib in the front-line setting due to its better tolerability than first- and second-generation EGFR TKIs [134,135], and superior outcomes compared to first-generation EGFR TKIs [5,7,9,134]. However, other experts favor the use of osimertinib after progression on a first- or second-generation EGFR TKI to delay the use of chemotherapy [136,137]. The latter approach has some limitations. At the time of progression on first- or second-generation EGFR TKI, mutation analysis should be pursued, but testing for *EGFR* and other acquired mutations at progression may not be feasible or readily available [138,139]. According to the Flatiron Health database, evaluating a predominately US-based population, only 30% of patients were tested for *EGFR* mutations following progression on a first- or second-generation EGFR TKI [139]. Sequencing strategies also assume that patients who progress develop a T790M mutation. This mutation, however, only occurs in 25–50% of patients treated with a first- or second-generation EGFR TKIs [7,68,70,72–79]. A simulation study comparing first-line osimertinib to alternative EGFR TKI sequencing strategies suggests an improvement in PFS among those receiving osimertinib in the first-line setting regardless of the presence of a T790M mutation [135].

Sequencing EGFR TKIs also assumes patients will be fit to receive subsequent therapies, however, ~30% of patients will not be eligible for second-line treatment [139–141]. In the FLAURA trial, 35% of patients receiving first-generation EGFR TKIs did not receive second-line therapy [17]. A small retrospective real-world study conducted in three certified lung cancer centers in Germany also found that 30% of patients treated with front-line first- or second-generation EGFR TKIs did not receive second-line therapy due to poor performance status, CNS metastasis, rapid disease progression, or death [138]. Additionally, studies in the United States revealed that 28–30% of patients treated with frontline first- or second-generation EGFR TKI did not receive subsequent therapies [139,141]. Among those who received subsequent treatment, only 23% to 25% received osimertinib [139,141].

As it is difficult to predict the mechanisms of resistance and performance status at the time of disease progression, using upfront osimertinib over sequencing strategies may provide the patients the best outcomes for all-comers. If osimertinib is not available, a second-generation EGFR TKI is also a good choice, especially for those with uncommon *EGFR* mutations. The prospective APPLE study is evaluating the optimal strategy for osimertinib use (upfront vs. sequential) (NCT02856893) and hopefully will inform future EGFR TKIs sequencing.

The choice of upfront EGFR TKI may also be affected by the specific *EGFR* mutation. For example, in the LUX-Lung 3 and 6 trials, a subgroup analysis revealed superior OS in patients with *EGFR* ex19del receiving afatinib compared to chemotherapy [6]. However, there was no significant difference in OS in patients with L858R mutations receiving afatinib or chemotherapy [6]. In the FLAURA trial, patients receiving osimertinib who had an ex19del had improved OS compared to patients with L858R mutations [17]. In the ARCHER 1050 study, however, patients receiving dacomitinib who had L858R mutations only had a trend toward superior OS compared to patients with ex19del [16]. These combined findings suggest that ex19del mutations are associated with better prognosis.

The presence of CNS metastasis may also dictate the choice of front-line therapy. Osimertinib and afatinib are the only EGFR TKIs that have been evaluated in prospective trials in patients with CNS disease on presentation [5,7,9]. Osimertinib demonstrated superior CNS DCR and PFS compared to first-generation EGFR TKIs [7,121,125,126]. While there is no direct comparison with second-generation EGFR TKIs, preclinical data suggest that osimertinib provides improved CNS penetration compared to afatinib [142]. Approximately 11% of patients receiving front-line afatinib developed CNS metastases, while only 3% receiving front-line osimertinib developed CNS metastasis in the FLAURA trial [122,125].

## 8. Conclusions

Studies have demonstrated that the use of frontline second- and third-generation is preferred over first-generation EGFR TKIs in patients with *EGFR*-mutant NSCLC. Only

osimertinib and dacomitinib have prospective data demonstrating improved PFS and OS over first-generation EGFR TKIs [16,17]. While there are no prospective studies to support an OS benefit of afatinib compared to first-generation EGFR TKIs, real-world evidence does suggest this benefit. Afatinib, osimertinib, and dacomitinib have not been compared head-to-head, therefore there is no strong evidence to support one over the other in the front-line setting. The use of erlotinib plus ramucirumab has also demonstrated good activity compared to erlotinib alone. However, OS data is lacking and patients with CNS metastasis were not included in this study. Furthermore, this approach is more costly and burdensome for patients as it involves infusions every 2 weeks.

When selecting a sequencing strategy for EGFR there are several aspects to consider, including CNS disease at presentation, the type of *EGFR* mutation at presentation, access to specific drugs, access to genomic testing at the time of progression, mechanisms of resistance, clinical performance status at progression, and provider level of comfort.

Evidence suggests osimertinib has better CNS penetration than afatinib and may provide better clinical outcomes in patients with bone metastasis, therefore we recommend it over other EGFR TKIs in patients with CNS or bone involvement. On the other hand, for patients with uncommon *EGFR* mutations, although osimertinib is an alternative, afatinib is the most extensively studied drug and the only one approved for this patient population [5,10,34,143].

When progression occurs and EGFR TKI therapy has been exhausted, a preferred therapeutic option is the use of chemoimmunotherapy with bevacizumab or the combination of chemotherapy plus bevacizumab, over chemotherapy alone. For patients who cannot receive an antiangiogenic agent, chemotherapy +/- EGFR TKI continuation should be considered. Immunotherapy alone could be another therapeutic option for selected patients with high PD-L1 levels (e.g.,  $\geq 25\%$ ) [109,110].

Finally, novel agents and drug combinations have shown promising results in early phase trials (Table 3). Ongoing studies evaluating the ideal sequencing and combination strategies to improve outcomes and overcome EGFR TKI resistance will hopefully inform the optimal treatment sequencing strategy (NCT04811001, NCT04413201, NCT04105153, NCT04035486, NCT03909334 and NCT02789345). Results of these studies are anxiously awaited.

**Author Contributions:** Conceptualization, J.A.M.-A. and B.P.; methodology, J.A.M.-A. and B.P.; investigation, J.A.M.-A. and B.P.; writing—original draft preparation, J.A.M.-A. and B.P.; writing—review and editing, J.A.M.-A., B.P., E.O.K., J.K.H. and A.C.; visualization, J.A.M.-A., B.P., J.K.H. and A.C.; supervision, B.P. and A.C. All authors have read and agreed to the published version of the manuscript.

**Funding:** No funding was received for the conduct of this research.

**Acknowledgments:** Figure 1 was created using [BioRender.com](https://BioRender.com), accessed on 8 January 2023.

**Conflicts of Interest:** Pellini receives research support from Bristol Myers Squibb (to the institution), has received speaker honoraria from BioAscend, Merck, MJH Life Science, Play to Know AG, Grupo Pardini, Foundation Medicine, and has done consulting/advisory board work with Guidepoint, Guardant Health, Illumina, Regeneron, and AstraZeneca. B.P. reports funding from the Bristol Myers Squibb Foundation/the Robert A. Winn Diversity in Clinical Trials Awards Program, outside of the submitted work. Chiappori receives Research support from Bristol Myers Squibb, AstraZeneca, and Novartis. He has received speaker, consultant and/or advisor honoraria from Blueprint, Takeda, Genentech, Pfizer, Merck, Astra Zeneca, Janssen and Jazz. Hicks received research support from OneOme. Marin-Acevedo and Kimbrough disclose no conflicts.

## References

1. D'Angelo, S.P.; Pietanza, M.C.; Johnson, M.L.; Riely, G.J.; Miller, V.A.; Sima, C.S.; Zakowski, M.F.; Rusch, V.W.; Ladanyi, M.; Kris, M.G. Incidence of EGFR exon 19 deletions and L858R in tumor specimens from men and cigarette smokers with lung adenocarcinomas. *J. Clin. Oncol.* **2011**, *29*, 2066–2070. [[CrossRef](#)] [[PubMed](#)]
2. Shi, Y.; Au, J.S.; Thongprasert, S.; Srinivasan, S.; Tsai, C.M.; Khoa, M.T.; Heeroma, K.; Itoh, Y.; Cornelio, G.; Yang, P.C. 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. [[CrossRef](#)] [[PubMed](#)]

3. Rosell, R.; Carcereny, E.; Gervais, R.; Vergnenegre, A.; Massuti, B.; Felip, E.; Palmero, R.; Garcia-Gomez, R.; Pallares, C.; Sanchez, J.M.; et al. Erlotinib versus 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. [CrossRef] [PubMed]
4. Mok, T.S.; Wu, Y.L.; Thongprasert, S.; Yang, C.H.; Chu, D.T.; Saijo, N.; Sunpaweravong, P.; Han, B.; Margono, B.; Ichinose, Y.; et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N. Engl. J. Med.* **2009**, *361*, 947–957. [CrossRef]
5. Wu, Y.L.; Zhou, C.; Hu, C.P.; Feng, J.; Lu, S.; Huang, Y.; Li, W.; Hou, M.; Shi, J.H.; Lee, K.Y.; et al. Afatinib versus 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. [CrossRef]
6. Yang, J.C.; Wu, Y.L.; Schuler, M.; Sebastian, M.; Popat, S.; Yamamoto, N.; Zhou, C.; Hu, C.P.; O’Byrne, K.; Feng, J.; et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): Analysis of overall survival data from two randomised, phase 3 trials. *Lancet Oncol.* **2015**, *16*, 141–151. [CrossRef]
7. Soria, J.C.; Ohe, Y.; Vansteenkiste, J.; Reungwetwattana, T.; Chewaskulyong, B.; Lee, K.H.; Dechaphunkul, A.; Imamura, F.; Nogami, N.; Kurata, T.; et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. *N. Engl. J. Med.* **2018**, *378*, 113–125. [CrossRef]
8. Wu, Y.L.; Cheng, Y.; Zhou, X.; Lee, K.H.; Nakagawa, K.; Niho, S.; Tsuji, F.; Linke, R.; Rosell, R.; Corral, J.; et al. Dacomitinib versus 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. [CrossRef]
9. Sequist, L.V.; Yang, J.C.; Yamamoto, N.; O’Byrne, K.; Hirsh, V.; Mok, T.; Geater, S.L.; Orlov, S.; Tsai, C.M.; Boyer, M.; et al. 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. [CrossRef]
10. Yang, J.C.; Schuler, M.; Popat, S.; Miura, S.; Heeke, S.; Park, K.; Marten, A.; Kim, E.S. Afatinib for the Treatment of NSCLC Harboring Uncommon EGFR Mutations: A Database of 693 Cases. *J. Thorac. Oncol.* **2020**, *15*, 803–815. [CrossRef]
11. Yang, J.C.; Schuler, M.; Popat, S.; Miura, S.; Park, K.; Passaro, A.; De Marinis, F.; Solca, F.; Marten, A.; Kim, E.S. Afatinib for the Treatment of Non-Small Cell Lung Cancer Harboring Uncommon EGFR Mutations: An Updated Database of 1023 Cases Brief Report. *Front. Oncol.* **2022**, *12*, 834704. [CrossRef] [PubMed]
12. Passaro, A.; Mok, T.; Peters, S.; Popat, S.; Ahn, M.J.; De Marinis, F. Recent Advances on the Role of EGFR Tyrosine Kinase Inhibitors in the Management of NSCLC with Uncommon, Non Exon 20 Insertions, EGFR Mutations. *J. Thorac. Oncol.* **2021**, *16*, 764–773. [CrossRef]
13. Cho, J.H.; Lim, S.H.; An, H.J.; Kim, K.H.; Park, K.U.; Kang, E.J.; Choi, Y.H.; Ahn, M.S.; Lee, M.H.; Sun, J.M.; et al. Osimertinib for Patients with Non-Small-Cell Lung Cancer Harboring Uncommon EGFR Mutations: A Multicenter, Open-Label, Phase II Trial (KCSG-LU15-09). *J. Clin. Oncol.* **2020**, *38*, 488–495. [CrossRef] [PubMed]
14. Song, C.; Yang, X. Osimertinib-Centered Therapy Against Uncommon Epidermal Growth Factor Receptor-Mutated Non-Small-Cell Lung Cancer—A Mini Review. *Front. Oncol.* **2022**, *12*, 834585. [CrossRef] [PubMed]
15. Wu, Y.L.; Zhou, C.; Liam, C.K.; Wu, G.; Liu, X.; Zhong, Z.; Lu, S.; Cheng, Y.; Han, B.; Chen, L.; et al. First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: Analyses from the phase III, randomized, open-label, ENSURE study. *Ann. Oncol.* **2015**, *26*, 1883–1889. [CrossRef]
16. Mok, T.S.; Cheng, Y.; Zhou, X.; Lee, K.H.; Nakagawa, K.; Niho, S.; Lee, M.; Linke, R.; Rosell, R.; Corral, J.; et al. Improvement in Overall Survival in a Randomized Study That Compared Dacomitinib with Gefitinib in Patients with Advanced Non-Small-Cell Lung Cancer and EGFR-Activating Mutations. *J. Clin. Oncol.* **2018**, *36*, 2244–2250. [CrossRef]
17. Ramalingam, S.S.; Vansteenkiste, J.; Planchard, D.; Cho, B.C.; Gray, J.E.; Ohe, Y.; Zhou, C.; Reungwetwattana, T.; Cheng, Y.; Chewaskulyong, B.; et al. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. *N. Engl. J. Med.* **2020**, *382*, 41–50. [CrossRef]
18. Paz-Ares, L.; Tan, E.H.; O’Byrne, K.; Zhang, L.; Hirsh, V.; Boyer, M.; Yang, J.C.; Mok, T.; Lee, K.H.; Lu, S.; et al. Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: Overall survival data from the phase IIb LUX-Lung 7 trial. *Ann. Oncol.* **2017**, *28*, 270–277. [CrossRef]
19. Park, K.; Tan, E.-H.; O’Byrne, K.; Zhang, L.; Boyer, M.; Mok, T.; Hirsh, V.; Yang, J.C.-H.; Lee, K.H.; Lu, S.; et al. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): A phase 2B, open-label, randomised controlled trial. *Lancet Oncol.* **2016**, *17*, 577–589. [CrossRef]
20. Morgillo, F.; Della Corte, C.M.; Fasano, M.; Ciardiello, F. Mechanisms of resistance to EGFR-targeted drugs: Lung cancer. *ESMO Open* **2016**, *1*, e000060. [CrossRef]
21. Hama, R.; Sakaguchi, K. The Gefitinib Story. Available online: <https://npjip.org/english/The-gefitinib-story.pdf> (accessed on 3 January 2023).
22. Shepherd, F.A.; Rodrigues Pereira, J.; Ciuleanu, T.; Tan, E.H.; Hirsh, V.; Thongprasert, S.; Campos, D.; Maoleekoonpiroj, S.; Smylie, M.; Martins, R.; et al. Erlotinib in previously treated non-small-cell lung cancer. *N. Engl. J. Med.* **2005**, *353*, 123–132. [CrossRef] [PubMed]
23. Cohen, M.H.; Johnson, J.R.; Chen, Y.F.; Sridhara, R.; Pazdur, R. FDA drug approval summary: Erlotinib (Tarceva) tablets. *Oncologist* **2005**, *10*, 461–466. [CrossRef] [PubMed]

24. Drugs.com. Tarceva FDA Approval History. Available online: <https://www.drugs.com/history/tarceva.html> (accessed on 11 April 2021).
25. Kazandjian, D.; Blumenthal, G.M.; Yuan, W.; He, K.; Keegan, P.; Pazdur, R. FDA Approval of Gefitinib for the Treatment of Patients with Metastatic EGFR Mutation-Positive Non-Small Cell Lung Cancer. *Clin. Cancer Res.* **2016**, *22*, 1307–1312. [[CrossRef](#)] [[PubMed](#)]
26. Fukuoka, M.; Wu, Y.L.; Thongprasert, S.; Sunpaweravong, P.; Leong, S.S.; Sriuranpong, V.; Chao, T.Y.; Nakagawa, K.; Chu, D.T.; Saijo, N.; et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). *J. Clin. Oncol.* **2011**, *29*, 2866–2874. [[CrossRef](#)]
27. Inoue, A.; Kobayashi, K.; Maemondo, M.; Sugawara, S.; Oizumi, S.; Isobe, H.; Gemma, A.; Harada, M.; Yoshizawa, H.; Kinoshita, I.; et al. Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naïve non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). *Ann. Oncol.* **2013**, *24*, 54–59. [[CrossRef](#)]
28. Mitsudomi, T.; Morita, S.; Yatabe, Y.; Negoro, S.; Okamoto, I.; Tsurutani, J.; Seto, T.; Satouchi, M.; Tada, H.; Hirashima, T.; et al. Gefitinib versus 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. [[CrossRef](#)]
29. Yoshioka, H.; Shimokawa, M.; Seto, T.; Morita, S.; Yatabe, Y.; Okamoto, I.; Tsurutani, J.; Satouchi, M.; Hirashima, T.; Atagi, S.; et al. Final overall survival results of WJTOG3405, a randomized phase III trial comparing gefitinib versus cisplatin with docetaxel as the first-line treatment for patients with stage IIIB/IV or postoperative recurrent EGFR mutation-positive non-small-cell lung cancer. *Ann. Oncol.* **2019**, *30*, 1978–1984. [[CrossRef](#)]
30. Douillard, J.Y.; Ostoros, G.; Cobo, M.; Ciuleanu, T.; McCormack, R.; Webster, A.; Milenkova, T. First-line gefitinib in Caucasian EGFR mutation-positive NSCLC patients: A phase-IV, open-label, single-arm study. *Br. J. Cancer* **2014**, *110*, 55–62. [[CrossRef](#)]
31. Maemondo, M.; Inoue, A.; Kobayashi, K.; Sugawara, S.; Oizumi, S.; Isobe, H.; Gemma, A.; Harada, M.; Yoshizawa, H.; Kinoshita, I.; et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N. Engl. J. Med.* **2010**, *362*, 2380–2388. [[CrossRef](#)]
32. Drugs.com. Iressa FDA Approval History. Available online: <https://www.drugs.com/history/iressa.html> (accessed on 1 September 2022).
33. Drugs.com. Gilotrif FDA Approval History. Available online: <https://www.drugs.com/newdrugs/fda-approves-gilotrif-late-stage-non-small-cell-lung-cancer-3851.html> (accessed on 11 April 2022).
34. Yang, J.C.; Sequist, L.V.; Geater, S.L.; Tsai, C.M.; Mok, T.S.; Schuler, M.; Yamamoto, N.; Yu, C.J.; Ou, S.H.; Zhou, C.; et al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: A combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. *Lancet Oncol.* **2015**, *16*, 830–838. [[CrossRef](#)]
35. Halmos, B.; Tan, E.H.; Soo, R.A.; Cadranel, J.; Lee, M.K.; Foucher, P.; Hsia, T.C.; Hochmair, M.; Griesinger, F.; Hida, T.; et al. Impact of afatinib dose modification on safety and effectiveness in patients with EGFR mutation-positive advanced NSCLC: Results from a global real-world study (RealGiDo). *Lung Cancer J. IASLC* **2019**, *127*, 103–111. [[CrossRef](#)] [[PubMed](#)]
36. Drugs.com. Tagrisso FDA Approval History. Available online: <https://www.drugs.com/history/tagrisso.html> (accessed on 13 April 2021).
37. Mok, T.S.; Wu, Y.L.; Ahn, M.J.; Garassino, M.C.; Kim, H.R.; Ramalingam, S.S.; Shepherd, F.A.; He, Y.; Akamatsu, H.; Theelen, W.S.; et al. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. *N. Engl. J. Med.* **2017**, *376*, 629–640. [[CrossRef](#)] [[PubMed](#)]
38. Papadimitrakopoulou, V.A.; Mok, T.S.; Han, J.Y.; Ahn, M.J.; Delmonte, A.; Ramalingam, S.S.; Kim, S.W.; Shepherd, F.A.; Laskin, J.; He, Y.; et al. Osimertinib versus platinum-pemetrexed for patients with EGFR T790M advanced NSCLC and progression on a prior EGFR-tyrosine kinase inhibitor: AURA3 overall survival analysis. *Ann. Oncol.* **2020**, *31*, 1536–1544. [[CrossRef](#)] [[PubMed](#)]
39. Pluzanski, A.; Krzakowski, M.; Kowalski, D.; Dziadziuszko, R. Real-world clinical outcomes of first-generation and second-generation epidermal growth factor receptor tyrosine kinase inhibitors in a large cohort of European non-small-cell lung cancer patients. *ESMO Open* **2020**, *5*, e001011. [[CrossRef](#)] [[PubMed](#)]
40. Drugs.com. Vizimpro FDA Approval History. Available online: <https://www.drugs.com/history/vizimpro.html> (accessed on 13 April 2021).
41. US Food and Drug Administration. FDA Approves Dacomitinib for Metastatic Non-Small Cell Lung Cancer. Available online: <https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-dacomitinib-metastatic-non-small-cell-lung-cancer-0> (accessed on 1 September 2022).
42. Katakami, N.; Atagi, S.; Goto, K.; Hida, T.; Horai, T.; Inoue, A.; Ichinose, Y.; Kobayashi, K.; Takeda, K.; Kiura, K.; et al. LUX-Lung 4: A phase II trial of afatinib in patients with advanced non-small-cell lung cancer who progressed during prior treatment with erlotinib, gefitinib, or both. *J. Clin. Oncol.* **2013**, *31*, 3335–3341. [[CrossRef](#)] [[PubMed](#)]
43. Janne, P.A.; Yang, J.C.; Kim, D.W.; Planchard, D.; Ohe, Y.; Ramalingam, S.S.; Ahn, M.J.; Kim, S.W.; Su, W.C.; Horn, L.; et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N. Engl. J. Med.* **2015**, *372*, 1689–1699. [[CrossRef](#)]
44. Goss, G.; Tsai, C.M.; Shepherd, F.A.; Bazhenova, L.; Lee, J.S.; Chang, G.C.; Crino, L.; Satouchi, M.; Chu, Q.; Hida, T.; et al. Osimertinib for pretreated EGFR Thr790Met-positive advanced non-small-cell lung cancer (AURA2): A multicentre, open-label, single-arm, phase 2 study. *Lancet Oncol.* **2016**, *17*, 1643–1652. [[CrossRef](#)]

45. Hochmair, M.J.; Morabito, A.; Hao, D.; Yang, C.T.; Soo, R.A.; Yang, J.C.; Gucaalp, R.; Halmos, B.; Marten, A.; Cufer, T. Sequential afatinib and osimertinib in patients with EGFR mutation-positive non-small-cell lung cancer: Final analysis of the GioTag study. *Future Oncol.* **2020**, *16*, 2799–2808. [[CrossRef](#)]
46. Kim, T.; Jang, T.W.; Choi, C.M.; Kim, M.H.; Lee, S.Y.; Park, C.K.; Chang, Y.S.; Lee, K.Y.; Kim, S.J.; Yang, S.H.; et al. Sequential treatment of afatinib and osimertinib or other regimens in patients with advanced non-small-cell lung cancer harboring EGFR mutations: Results from a real-world study in South Korea. *Cancer Med.* **2021**, *10*, 5809–5822. [[CrossRef](#)]
47. Byers, L.A.; Heymach, J.V. Dual targeting of the vascular endothelial growth factor and epidermal growth factor receptor pathways: Rationale and clinical applications for non-small-cell lung cancer. *Clin. Lung Cancer* **2007**, *8* (Suppl. 2), S79–S85. [[CrossRef](#)]
48. Saito, H.; Fukuhara, T.; Furuya, N.; Watanabe, K.; Sugawara, S.; Iwasawa, S.; Tsunozuka, Y.; Yamaguchi, O.; Okada, M.; Yoshimori, K.; et al. Erlotinib plus bevacizumab versus erlotinib alone in patients with EGFR-positive advanced non-squamous non-small-cell lung cancer (NEJ026): Interim analysis of an open-label, randomised, multicentre, phase 3 trial. *Lancet Oncol.* **2019**, *20*, 625–635. [[CrossRef](#)] [[PubMed](#)]
49. Nakagawa, K.; Garon, E.B.; Seto, T.; Nishio, M.; Ponce Aix, S.; Paz-Ares, L.; Chiu, C.H.; Park, K.; Novello, S.; Nadal, E.; et al. Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* **2019**, *20*, 1655–1669. [[CrossRef](#)] [[PubMed](#)]
50. Ninomiya, T.; Nogami, N.; Kozuki, T.; Harada, D.; Kubo, T.; Ohashi, K.; Kuyama, S.; Kudo, K.; Bessho, A.; Fukamatsu, N.; et al. A phase I trial of afatinib and bevacizumab in chemo-naive patients with advanced non-small-cell lung cancer harboring EGFR mutations: Okayama Lung Cancer Study Group Trial 1404. *Lung Cancer J. IASLC* **2018**, *115*, 103–108. [[CrossRef](#)] [[PubMed](#)]
51. Hsu, P.C.; Huang, C.Y.; Wang, C.C.; Kuo, S.C.; Chu, C.H.; Tung, P.H.; Huang, A.C.; Wang, C.L.; Chiu, L.C.; Fang, Y.F.; et al. The Combination of Afatinib and Bevacizumab in Untreated EGFR-Mutated Advanced Lung Adenocarcinoma: A Multicenter Observational Study. *Pharmaceuticals* **2020**, *13*, 331. [[CrossRef](#)] [[PubMed](#)]
52. Yu, H.A.; Schoenfeld, A.J.; Makhnin, A.; Kim, R.; Rizvi, H.; Tsui, D.; Falcon, C.; Houck-Loomis, B.; Meng, F.; Yang, J.L.; et al. Effect of Osimertinib and Bevacizumab on Progression-Free Survival for Patients with Metastatic EGFR-Mutant Lung Cancers: A Phase 1/2 Single-Group Open-Label Trial. *JAMA Oncol.* **2020**, *6*, 1048–1054. [[CrossRef](#)] [[PubMed](#)]
53. Akamatsu, H.; Toi, Y.; Hayashi, H.; Fujimoto, D.; Tachihara, M.; Furuya, N.; Otani, S.; Shimizu, J.; Katakami, N.; Azuma, K.; et al. Efficacy of Osimertinib Plus Bevacizumab vs Osimertinib in Patients with EGFR T790M-Mutated Non-Small Cell Lung Cancer Previously Treated with Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor: West Japan Oncology Group 8715L Phase 2 Randomized Clinical Trial. *JAMA Oncol.* **2021**, *7*, 386–394. [[CrossRef](#)]
54. Soo, R.A.; Han, J.Y.; Dafni, U.; Cho, B.C.; Yeo, C.M.; Nadal, E.; Carcereny, E.; de Castro, J.; Sala, M.A.; Bernabe, R.; et al. A randomised phase II study of osimertinib and bevacizumab versus osimertinib alone as second-line targeted treatment in advanced NSCLC with confirmed EGFR and acquired T790M mutations: The European Thoracic Oncology Platform (ETOP 10-16) BOOSTER trial. *Ann. Oncol.* **2022**, *33*, 181–192. [[CrossRef](#)]
55. Kenmotsu, H.; Wakuda, K.; Mori, K.; Kato, T.; Sugawara, S.; Kirita, K.; Yoneshima, Y.; Azuma, K.; Nishino, K.; Teraoka, S.; et al. Randomized Phase 2 Study of Osimertinib Plus Bevacizumab Versus Osimertinib for Untreated Patients with Nonsquamous NSCLC Harboring EGFR Mutations: WJOG9717L Study. *J. Thorac. Oncol.* **2022**, *17*, 1098–1108. [[CrossRef](#)]
56. Janne, P.A.; Wang, X.; Socinski, M.A.; Crawford, J.; Stinchcombe, T.E.; Gu, L.; Capelletti, M.; Edelman, M.J.; Villalona-Calero, M.A.; Kratzke, R.; et al. Randomized phase II trial of erlotinib alone or with carboplatin and paclitaxel in patients who were never or light former smokers with advanced lung adenocarcinoma: CALGB 30406 trial. *J. Clin. Oncol.* **2012**, *30*, 2063–2069. [[CrossRef](#)]
57. Soria, J.C.; Wu, Y.L.; Nakagawa, K.; Kim, S.W.; Yang, J.J.; Ahn, M.J.; Wang, J.; Yang, J.C.; Lu, Y.; Atagi, S.; et al. Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): A phase 3 randomised trial. *Lancet Oncol.* **2015**, *16*, 990–998. [[CrossRef](#)]
58. Noronha, V.; Patil, V.M.; Joshi, A.; Menon, N.; Chougule, A.; Mahajan, A.; Janu, A.; Purandare, N.; Kumar, R.; More, S.; et al. Gefitinib Versus Gefitinib Plus Pemetrexed and Carboplatin Chemotherapy in EGFR-Mutated Lung Cancer. *J. Clin. Oncol.* **2020**, *38*, 124–136. [[CrossRef](#)] [[PubMed](#)]
59. Hosomi, Y.; Morita, S.; Sugawara, S.; Kato, T.; Fukuhara, T.; Gemma, A.; Takahashi, K.; Fujita, Y.; Harada, T.; Minato, K.; et al. Gefitinib Alone Versus Gefitinib Plus Chemotherapy for Non-Small-Cell Lung Cancer with Mutated Epidermal Growth Factor Receptor: NEJ009 Study. *J. Clin. Oncol.* **2020**, *38*, 115–123. [[CrossRef](#)] [[PubMed](#)]
60. Schuler, M.; Yang, J.C.; Park, K.; Kim, J.H.; Bennouna, J.; Chen, Y.M.; Chouaid, C.; De Marinis, F.; Feng, J.F.; Grossi, F.; et al. Afatinib beyond progression in patients with non-small-cell lung cancer following chemotherapy, erlotinib/gefitinib and afatinib: Phase III randomized LUX-Lung 5 trial. *Ann. Oncol.* **2016**, *27*, 417–423. [[CrossRef](#)] [[PubMed](#)]
61. White, M.N.; Piotrowska, Z.; Stirling, K.; Liu, S.V.; Banwait, M.K.; Cunanan, K.; Sequist, L.V.; Wakelee, H.A.; Hausrath, D.; Neal, J.W. Combining Osimertinib with Chemotherapy in EGFR-Mutant NSCLC at Progression. *Clin. Lung Cancer* **2021**, *22*, 201–209. [[CrossRef](#)] [[PubMed](#)]
62. Planchard, D.; Feng, P.H.; Karaseva, N.; Kim, S.W.; Kim, T.M.; Lee, C.K.; Poltoratskiy, A.; Yanagitani, N.; Powar, S.; Huang, X.; et al. 1401P Osimertinib plus platinum/pemetrexed in newly-diagnosed EGFR mutation (EGFRm)-positive advanced NSCLC: Safety run-in results from the FLAURA2 study. *Ann. Oncol.* **2020**, *31*, S888. [[CrossRef](#)]

63. Creelan, B.C.; Yeh, T.C.; Kim, S.W.; Nogami, N.; Kim, D.W.; Chow, L.Q.M.; Kanda, S.; Taylor, R.; Tang, W.; Tang, M.; et al. A Phase 1 study of gefitinib combined with durvalumab in EGFR TKI-naïve patients with EGFR mutation-positive locally advanced/metastatic non-small-cell lung cancer. *Br. J. Cancer* **2021**, *124*, 383–390. [[CrossRef](#)]
64. Gettinger, S.; Hellmann, M.D.; Chow, L.Q.M.; Borghaei, H.; Antonia, S.; Brahmer, J.R.; Goldman, J.W.; Gerber, D.E.; Juergens, R.A.; Shepherd, F.A.; et al. Nivolumab Plus Erlotinib in Patients with EGFR-Mutant Advanced NSCLC. *J. Thorac. Oncol.* **2018**, *13*, 1363–1372. [[CrossRef](#)]
65. Rudin, C.; Cervantes, A.; Dowlati, A.; Besse, B.; Ma, B.; Costa, D.; Schmid, P.; Heist, R.; Villaflor, V.; Sarkar, I.; et al. MA15.02 Long-Term Safety and Clinical Activity Results from a Phase Ib Study of Erlotinib Plus Atezolizumab in Advanced NSCLC. *J. Thorac. Oncol.* **2018**, *13*, S407. [[CrossRef](#)]
66. Oxnard, G.R.; Yang, J.C.; Yu, H.; Kim, S.W.; Saka, H.; Horn, L.; Goto, K.; Ohe, Y.; Mann, H.; Thress, K.S.; et al. TATTON: A multi-arm, phase Ib trial of osimertinib combined with selumetinib, savolitinib, or durvalumab in EGFR-mutant lung cancer. *Ann. Oncol.* **2020**, *31*, 507–516. [[CrossRef](#)]
67. Yang, J.C.; Shepherd, F.A.; Kim, D.W.; Lee, G.W.; Lee, J.S.; Chang, G.C.; Lee, S.S.; Wei, Y.F.; Lee, Y.G.; Laus, G.; et al. Osimertinib Plus Durvalumab versus Osimertinib Monotherapy in EGFR T790M-Positive NSCLC following Previous EGFR TKI Therapy: CAURAL Brief Report. *J. Thorac. Oncol.* **2019**, *14*, 933–939. [[CrossRef](#)]
68. Gainor, J.F.; Shaw, A.T. Emerging paradigms in the development of resistance to tyrosine kinase inhibitors in lung cancer. *J. Clin. Oncol.* **2013**, *31*, 3987–3996. [[CrossRef](#)] [[PubMed](#)]
69. Jackman, D.; Pao, W.; Riely, G.J.; Engelman, J.A.; Kris, M.G.; Janne, P.A.; Lynch, T.; Johnson, B.E.; Miller, V.A. Clinical definition of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. *J. Clin. Oncol.* **2010**, *28*, 357–360. [[CrossRef](#)] [[PubMed](#)]
70. Yu, H.A.; Arcila, M.E.; Rekhman, N.; Sima, C.S.; Zakowski, M.F.; Pao, W.; Kris, M.G.; Miller, V.A.; Ladanyi, M.; Riely, G.J. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin. Cancer Res.* **2013**, *19*, 2240–2247. [[CrossRef](#)]
71. Sequist, L.V.; Waltman, B.A.; Dias-Santagata, D.; Digumarthy, S.; Turke, A.B.; Fidias, P.; Bergethon, K.; Shaw, A.T.; Gettinger, S.; Cosper, A.K.; et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci. Transl. Med.* **2011**, *3*, 75ra26. [[CrossRef](#)]
72. Yun, C.H.; Mengwasser, K.E.; Toms, A.V.; Woo, M.S.; Greulich, H.; Wong, K.K.; Meyerson, M.; Eck, M.J. The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 2070–2075. [[CrossRef](#)] [[PubMed](#)]
73. Toyooka, S.; Kiura, K.; Mitsudomi, T. EGFR mutation and response of lung cancer to gefitinib. *N. Engl. J. Med.* **2005**, *352*, 2136. [[CrossRef](#)]
74. Tanaka, K.; Nosaki, K.; Otsubo, K.; Azuma, K.; Sakata, S.; Ouchi, H.; Morinaga, R.; Wataya, H.; Fujii, A.; Nakagaki, N.; et al. Acquisition of the T790M resistance mutation during afatinib treatment in EGFR tyrosine kinase inhibitor-naïve patients with non-small cell lung cancer harboring EGFR mutations. *Oncotarget* **2017**, *8*, 68123–68130. [[CrossRef](#)]
75. Kobayashi, S.; Boggon, T.J.; Dayaram, T.; Janne, P.A.; Kocher, O.; Meyerson, M.; Johnson, B.E.; Eck, M.J.; Tenen, D.G.; Halmos, B. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. *N. Engl. J. Med.* **2005**, *352*, 786–792. [[CrossRef](#)]
76. Wu, S.G.; Liu, Y.N.; Tsai, M.F.; Chang, Y.L.; Yu, C.J.; Yang, P.C.; Yang, J.C.; Wen, Y.F.; Shih, J.Y. The mechanism of acquired resistance to irreversible EGFR tyrosine kinase inhibitor-afatinib in lung adenocarcinoma patients. *Oncotarget* **2016**, *7*, 12404–12413. [[CrossRef](#)]
77. Jotte, R.M.; Spigel, D.R. Advances in molecular-based personalized non-small-cell lung cancer therapy: Targeting epidermal growth factor receptor and mechanisms of resistance. *Cancer Med.* **2015**, *4*, 1621–1632. [[CrossRef](#)]
78. Balak, M.N.; Gong, Y.; Riely, G.J.; Somwar, R.; Li, A.R.; Zakowski, M.F.; Chiang, A.; Yang, G.; Ouerfelli, O.; Kris, M.G.; et al. Novel D761Y and common secondary T790M mutations in epidermal growth factor receptor-mutant lung adenocarcinomas with acquired resistance to kinase inhibitors. *Clin. Cancer Res.* **2006**, *12*, 6494–6501. [[CrossRef](#)] [[PubMed](#)]
79. Zhang, H.; Shao, Y.W.; Xia, Y. Responsiveness to Full-Dose Afatinib in a Patient with Lung Adenocarcinoma Harboring EGFR S768I and V769L Mutations. *J. Thorac. Oncol.* **2019**, *14*, e25–e27. [[CrossRef](#)] [[PubMed](#)]
80. Leonetti, A.; Sharma, S.; Minari, R.; Perego, P.; Giovannetti, E.; Tiseo, M. Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. *Br. J. Cancer* **2019**, *121*, 725–737. [[CrossRef](#)]
81. Schoenfeld, A.J.; Yu, H.A. The Evolving Landscape of Resistance to Osimertinib. *J. Thorac. Oncol.* **2020**, *15*, 18–21. [[CrossRef](#)]
82. Thress, K.S.; Pawelczak, C.P.; Felip, E.; Cho, B.C.; Stetson, D.; Dougherty, B.; Lai, Z.; Markovets, A.; Vivancos, A.; Kuang, Y.; et al. Acquired EGFR C797S mutation mediates resistance to AZD9291 in non-small cell lung cancer harboring EGFR T790M. *Nat. Med.* **2015**, *21*, 560–562. [[CrossRef](#)]
83. Ou, S.I.; Cui, J.; Schrock, A.B.; Goldberg, M.E.; Zhu, V.W.; Albacker, L.; Stephens, P.J.; Miller, V.A.; Ali, S.M. Emergence of novel and dominant acquired EGFR solvent-front mutations at Gly796 (G796S/R) together with C797S/R and L792F/H mutations in one EGFR (L858R/T790M) NSCLC patient who progressed on osimertinib. *Lung Cancer J. IASLC* **2017**, *108*, 228–231. [[CrossRef](#)] [[PubMed](#)]
84. Le, X.; Puri, S.; Negrao, M.V.; Nilsson, M.B.; Robichaux, J.; Boyle, T.; Hicks, J.K.; Lovinger, K.L.; Roarty, E.; Rinsurongkawong, W.; et al. Landscape of EGFR-Dependent and -Independent Resistance Mechanisms to Osimertinib and Continuation Therapy Beyond Progression in EGFR-Mutant NSCLC. *Clin. Cancer Res.* **2018**, *24*, 6195–6203. [[CrossRef](#)]

85. Ricordel, C.; Friboulet, L.; Facchinetti, F.; Soria, J.C. Molecular mechanisms of acquired resistance to third-generation EGFR-TKIs in EGFR T790M-mutant lung cancer. *Ann. Oncol.* **2019**, *30*, 858. [[CrossRef](#)]
86. Suzawa, K.; Offin, M.; Schoenfeld, A.J.; Plodkowski, A.J.; Odintsov, I.; Lu, D.; Lockwood, W.W.; Arcila, M.E.; Rudin, C.M.; Drilon, A.; et al. Acquired MET Exon 14 Alteration Drives Secondary Resistance to Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor in EGFR-Mutated Lung Cancer. *JCO Precis. Oncol.* **2019**, *3*, 19. [[CrossRef](#)]
87. Romaniello, D.; Marrocco, I.; Belugali Nataraj, N.; Ferrer, I.; Drago-Garcia, D.; Vaknin, I.; Oren, R.; Lindzen, M.; Ghosh, S.; Kreitman, M.; et al. Targeting HER3, a Catalytically Defective Receptor Tyrosine Kinase, Prevents Resistance of Lung Cancer to a Third-Generation EGFR Kinase Inhibitor. *Cancers* **2020**, *12*, 2394. [[CrossRef](#)]
88. Shields, M.D.; Hicks, J.K.; Boyle, T.A.; Haura, E.B.; Creelan, B.C. Selpercatinib Overcomes CCDC6-RET-Mediated Resistance to Osimertinib. *J. Thorac. Oncol.* **2021**, *16*, e15–e17. [[CrossRef](#)] [[PubMed](#)]
89. Marcoux, N.; Gettinger, S.N.; O’Kane, G.; Arbour, K.C.; Neal, J.W.; Husain, H.; Evans, T.L.; Brahmer, J.R.; Muzikansky, A.; Bonomi, P.D.; et al. EGFR-Mutant Adenocarcinomas That Transform to Small-Cell Lung Cancer and Other Neuroendocrine Carcinomas: Clinical Outcomes. *J. Clin. Oncol.* **2019**, *37*, 278–285. [[CrossRef](#)] [[PubMed](#)]
90. Chen, N.; Fang, W.; Zhan, J.; Hong, S.; Tang, Y.; Kang, S.; Zhang, Y.; He, X.; Zhou, T.; Qin, T.; et al. Upregulation of PD-L1 by EGFR Activation Mediates the Immune Escape in EGFR-Driven NSCLC: Implication for Optional Immune Targeted Therapy for NSCLC Patients with EGFR Mutation. *J. Thorac. Oncol.* **2015**, *10*, 910–923. [[CrossRef](#)] [[PubMed](#)]
91. Suda, K.; Murakami, I.; Sakai, K.; Mizuuchi, H.; Shimizu, S.; Sato, K.; Tomizawa, K.; Tomida, S.; Yatabe, Y.; Nishio, K.; et al. Small cell lung cancer transformation and T790M mutation: Complimentary roles in acquired resistance to kinase inhibitors in lung cancer. *Sci. Rep.* **2015**, *5*, 14447. [[CrossRef](#)] [[PubMed](#)]
92. Offin, M.; Chan, J.M.; Tenet, M.; Rizvi, H.A.; Shen, R.; Riely, G.J.; Rekhman, N.; Daneshbod, Y.; Quintanal-Villalonga, A.; Penson, A.; et al. Concurrent RB1 and TP53 Alterations Define a Subset of EGFR-Mutant Lung Cancers at risk for Histologic Transformation and Inferior Clinical Outcomes. *J. Thorac. Oncol.* **2019**, *14*, 1784–1793. [[CrossRef](#)] [[PubMed](#)]
93. Raouf, S.; Mulford, I.J.; Frisco-Cabanos, H.; Nangia, V.; Timonina, D.; Labrot, E.; Hafeez, N.; Bilton, S.J.; Drier, Y.; Ji, F.; et al. Targeting FGFR overcomes EMT-mediated resistance in EGFR mutant non-small cell lung cancer. *Oncogene* **2019**, *38*, 6399–6413. [[CrossRef](#)]
94. Tulchinsky, E.; Demidov, O.; Kriajevska, M.; Barlev, N.A.; Imyanitov, E. EMT: A mechanism for escape from EGFR-targeted therapy in lung cancer. *Biochim. Biophys. Acta Rev. Cancer* **2019**, *1871*, 29–39. [[CrossRef](#)]
95. John, T.; Akamatsu, H.; Delmonte, A.; Su, W.C.; Lee, J.S.; Chang, G.C.; Huang, X.; Jenkins, S.; Wu, Y.L. EGFR mutation analysis for prospective patient selection in AURA3 phase III trial of osimertinib versus platinum-pemetrexed in patients with EGFR T790M-positive advanced non-small-cell lung cancer. *Lung Cancer J. IASLC* **2018**, *126*, 133–138. [[CrossRef](#)]
96. Yap, T.A.; Macklin-Doherty, A.; Papat, S. Continuing EGFR inhibition beyond progression in advanced non-small cell lung cancer. *Eur. J. Cancer* **2017**, *70*, 12–21. [[CrossRef](#)] [[PubMed](#)]
97. Goto, Y.; Tanai, C.; Yoh, K.; Hosomi, Y.; Sakai, H.; Kato, T.; Kaburagi, T.; Nishio, M.; Kim, Y.H.; Inoue, A.; et al. Continuing EGFR-TKI beyond radiological progression in patients with advanced or recurrent, EGFR mutation-positive non-small-cell lung cancer: An observational study. *ESMO Open* **2017**, *2*, e000214. [[CrossRef](#)] [[PubMed](#)]
98. NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) 2021, Version 4.2021—March 3, 2021. *J. Natl. Compr. Cancer Netw. JNCCN* **2021**, *2*, 94–123.
99. Gandhi, L.; Rodriguez-Abreu, D.; Gadgeel, S.; Esteban, E.; Felip, E.; De Angelis, F.; Domine, M.; Clingan, P.; Hochmair, M.J.; Powell, S.F.; et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *N. Engl. J. Med.* **2018**, *378*, 2078–2092. [[CrossRef](#)] [[PubMed](#)]
100. Paz-Ares, L.; Ciuleanu, T.E.; Cobo, M.; Schenker, M.; Zurawski, B.; Menezes, J.; Richardet, E.; Bennouna, J.; Felip, E.; Juan-Vidal, O.; et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): An international, randomised, open-label, phase 3 trial. *Lancet Oncol.* **2021**, *22*, 198–211. [[CrossRef](#)] [[PubMed](#)]
101. Paz-Ares, L.; Luft, A.; Vicente, D.; Tafreshi, A.; Gumus, M.; Mazieres, J.; Hermes, B.; Cay Senler, F.; Csoszi, T.; Fulop, A.; et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. *N. Engl. J. Med.* **2018**, *379*, 2040–2051. [[CrossRef](#)]
102. West, H.; McCleod, M.; Hussein, M.; Morabito, A.; Rittmeyer, A.; Conter, H.J.; Kopp, H.G.; Daniel, D.; McCune, S.; Mekhail, T.; et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): A multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* **2019**, *20*, 924–937. [[CrossRef](#)]
103. Socinski, M.A.; Jotte, R.M.; Cappuzzo, F.; Orlandi, F.; Stroyakovskiy, D.; Nogami, N.; Rodriguez-Abreu, D.; Moro-Sibilot, D.; Thomas, C.A.; Barlesi, F.; et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. *N. Engl. J. Med.* **2018**, *378*, 2288–2301. [[CrossRef](#)]
104. Choudhury, N.J.; Makhnin, A.; Tobi, Y.Y.; Daly, R.M.; Preeshagul, I.R.; Iqbal, A.N.; Ahn, L.S.; Hayes, S.A.; Heller, G.; Kris, M.G.; et al. Pilot Study of Dacomitinib for Patients with Metastatic EGFR-Mutant Lung Cancers with Disease Progression After Initial Treatment with Osimertinib. *JCO Precis. Oncol.* **2021**, *5*, 695–700. [[CrossRef](#)]
105. Nogami, N.; Barlesi, F.; Socinski, M.A.; Reck, M.; Thomas, C.A.; Cappuzzo, F.; Mok, T.S.K.; Finley, G.; Aerts, J.G.; Orlandi, F.; et al. IMpower150 Final Exploratory Analyses for Atezolizumab Plus Bevacizumab and Chemotherapy in Key NSCLC Patient Subgroups with EGFR Mutations or Metastases in the Liver or Brain. *J. Thorac. Oncol.* **2022**, *17*, 309–323. [[CrossRef](#)]

106. Reck, M.; Mok, T.S.K.; Nishio, M.; Jotte, R.M.; Cappuzzo, F.; Orlandi, F.; Stroyakovskiy, D.; Nogami, N.; Rodriguez-Abreu, D.; Moro-Sibilot, D.; et al. Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): Key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial. *Lancet Respir. Med.* **2019**, *7*, 387–401. [[CrossRef](#)]
107. Lu, S.; Wu, L.; Jian, H.; Cheng, Y.; Wang, Q.; Fang, J.; Wang, Z.; Hu, Y.; Sun, M.; Han, L.; et al. VP9-2021: ORIENT-31: Phase III study of sintilimab with or without IBI305 plus chemotherapy in patients with EGFR mutated nonsquamous NSCLC who progressed after EGFR-TKI therapy. *Ann. Oncol.* **2022**, *33*, 112–113. [[CrossRef](#)]
108. Hellmann, M.D.; Garon, E.B.; Gandhi, L.; Hui, R.; Zhang, J.; Rangwala, R.; Rizvi, N.A. MINI03.05 Efficacy of Pembrolizumab in Key Subgroups of Patients with Advanced NSCLC. *J. Thorac. Oncol.* **2015**, *10*, S261–S406. [[CrossRef](#)]
109. Garassino, M.C.; Cho, B.C.; Kim, J.H.; Mazieres, J.; Vansteenkiste, J.; Lena, H.; Jaime, J.C.; Gray, J.E.; Powderly, J.; Chouaid, C.; et al. Final overall survival and safety update for durvalumab in third- or later-line advanced NSCLC: The phase II ATLANTIC study. *Lung Cancer J. IASLC* **2020**, *147*, 137–142. [[CrossRef](#)] [[PubMed](#)]
110. Garassino, M.C.; Cho, B.-C.; Kim, J.-H.; Mazières, J.; Vansteenkiste, J.; Lena, H.; Corral Jaime, J.; Gray, J.E.; Powderly, J.; Chouaid, C.; et al. Durvalumab as third-line or later treatment for advanced non-small-cell lung cancer (ATLANTIC): An open-label, single-arm, phase 2 study. *Lancet Oncol.* **2018**, *19*, 521–536. [[CrossRef](#)] [[PubMed](#)]
111. Yu, H.A.; Ambrose, H.; Baik, C.; Cho, B.C.; Cocco, E.; Goldberg, S.B.; Goldman, J.W.; Kraljevic, S.; De Langen, A.J.; Okamoto, I.; et al. 1239P ORCHARD osimertinib + savolitinib interim analysis: A biomarker-directed phase II platform study in patients (pts) with advanced non-small cell lung cancer (NSCLC) whose disease has progressed on first-line (1L) osimertinib. *Ann. Oncol.* **2021**, *32*, S978–S979. [[CrossRef](#)]
112. Sequist, L.V.; Han, J.Y.; Ahn, M.J.; Cho, B.C.; Yu, H.; Kim, S.W.; Yang, J.C.; Lee, J.S.; Su, W.C.; Kowalski, D.; et al. Osimertinib plus savolitinib in patients with EGFR mutation-positive, MET-amplified, non-small-cell lung cancer after progression on EGFR tyrosine kinase inhibitors: Interim results from a multicentre, open-label, phase 1b study. *Lancet Oncol.* **2020**, *21*, 373–386. [[CrossRef](#)]
113. Leighl, N.B.; Shu, C.A.; Minchom, A.; Felip, E.; Cousin, S.; Cho, B.C.; Park, K.; Han, J.Y.; Boyer, M.; Lee, C.K.; et al. 1192MO Amivantamab monotherapy and in combination with lazertinib in post-osimertinib EGFR-mutant NSCLC: Analysis from the CHRYSALIS study. *Ann. Oncol.* **2021**, *32*, S951–S952. [[CrossRef](#)]
114. Shu, C.A.; Goto, K.; Ohe, Y.; Besse, B.; Lee, S.-H.; Wang, Y.; Griesinger, F.; Yang, J.C.-H.; Felip, E.; Sanborn, R.E.; et al. Amivantamab and lazertinib in patients with EGFR-mutant non-small cell lung (NSCLC) after progression on osimertinib and platinum-based chemotherapy: Updated results from CHRYSALIS-2. *J. Clin. Oncol.* **2022**, *40*, 9006. [[CrossRef](#)]
115. Cho, B.C.; Felip, E.; Hayashi, H.; Thomas, M.; Lu, S.; Besse, B.; Sun, T.; Martinez, M.; Sethi, S.N.; Shreeve, S.M.; et al. MARIPOSA: Phase 3 study of first-line amivantamab + lazertinib versus osimertinib in EGFR-mutant non-small-cell lung cancer. *Future Oncol.* **2022**, *18*, 639–647. [[CrossRef](#)]
116. Janne, P.A.; Baik, C.; Su, W.C.; Johnson, M.L.; Hayashi, H.; Nishio, M.; Kim, D.W.; Koczywas, M.; Gold, K.A.; Steuer, C.E.; et al. Efficacy and Safety of Patritumab Deruxtecan (HER3-DXd) in EGFR Inhibitor-Resistant, EGFR-Mutated Non-Small Cell Lung Cancer. *Cancer Discov.* **2022**, *12*, 74–89. [[CrossRef](#)]
117. Garon, E.B.; Johnson, M.L.; Lisberg, A.E.; Spira, A.; Yamamoto, N.; Heist, R.S.; Sands, J.M.; Yoh, K.; Meric-Bernstam, F.; Kitazono, S.; et al. LBA49 Efficacy of datopotamab deruxtecan (Dato-DXd) in patients (pts) with advanced/metastatic (adv/met) non-small cell lung cancer (NSCLC) and actionable genomic alterations (AGAs): Preliminary results from the phase I TROPION-PanTumor01 study. *Ann. Oncol.* **2021**, *32*, S1326–S1327. [[CrossRef](#)]
118. Beypinar, I.; Demir, H.; Araz, M.; Uysal, M. The relationship between EGFR mutation and metastasis pattern in lung adenocarcinoma. *J. Oncol. Sci.* **2019**, *5*, 65–69. [[CrossRef](#)]
119. Rangachari, D.; Yamaguchi, N.; VanderLaan, P.A.; Folch, E.; Mahadevan, A.; Floyd, S.R.; Uhlmann, E.J.; Wong, E.T.; Dahlberg, S.E.; Huberman, M.S.; et al. Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small-cell lung cancers. *Lung Cancer J. IASLC* **2015**, *88*, 108–111. [[CrossRef](#)] [[PubMed](#)]
120. Aiko, N.; Shimokawa, T.; Miyazaki, K.; Misumi, Y.; Agemi, Y.; Ishii, M.; Nakamura, Y.; Yamanaka, T.; Okamoto, H. Comparison of the efficacies of first-generation epidermal growth factor receptor tyrosine kinase inhibitors for brain metastasis in patients with advanced non-small-cell lung cancer harboring EGFR mutations. *BMC Cancer* **2018**, *18*, 1012. [[CrossRef](#)] [[PubMed](#)]
121. Yoshida, K.; Kanda, S.; Shiraiishi, H.; Goto, K.; Itahashi, K.; Goto, Y.; Horinouchi, H.; Fujiwara, Y.; Nokihara, H.; Yamamoto, N.; et al. Difference in central nerve system metastasis during gefitinib or erlotinib therapy in patients with EGFR-mutated non-small cell lung cancer: A retrospective study. *J. Thorac. Dis.* **2019**, *11*, 1347–1354. [[CrossRef](#)]
122. Liang, S.K.; Lee, M.R.; Liao, W.Y.; Ho, C.C.; Ko, J.C.; Shih, J.Y. Prognostic factors of afatinib as a first-line therapy for advanced EGFR mutation-positive lung adenocarcinoma: A real-world, large cohort study. *Oncotarget* **2018**, *9*, 23749–23760. [[CrossRef](#)]
123. Bergonzini, C.; Leonetti, A.; Tiseo, M.; Giovannetti, E.; Peters, G.J. Is there a role for dacomitinib, a second-generation irreversible inhibitor of the epidermal-growth factor receptor tyrosine kinase, in advanced non-small cell lung cancer? *Expert Opin. Pharmacother.* **2020**, *21*, 1287–1298. [[CrossRef](#)]
124. Peng, W.; Pu, X.; Jiang, M.; Wang, J.; Li, J.; Li, K.; Xu, Y.; Xu, F.; Chen, B.; Wang, Q.; et al. Dacomitinib induces objective responses in metastatic brain lesions of patients with EGFR-mutant non-small-cell lung cancer: A brief report. *Lung Cancer J. IASLC* **2021**, *152*, 66–70. [[CrossRef](#)]

125. Reungwetwattana, T.; Nakagawa, K.; Cho, B.C.; Cobo, M.; Cho, E.K.; Bertolini, A.; Bohnet, S.; Zhou, C.; Lee, K.H.; Nogami, N.; et al. CNS Response to Osimertinib Versus Standard Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Patients with Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. *J. Clin. Oncol.* **2018**, *36*, 3290. [CrossRef]
126. Wu, Y.L.; Ahn, M.J.; Garassino, M.C.; Han, J.Y.; Katakami, N.; Kim, H.R.; Hodge, R.; Kaur, P.; Brown, A.P.; Ghiorghiu, D.; et al. CNS Efficacy of Osimertinib in Patients with T790M-Positive Advanced Non-Small-Cell Lung Cancer: Data From a Randomized Phase III Trial (AURA3). *J. Clin. Oncol.* **2018**, *36*, 2702–2709. [CrossRef]
127. Castanon, E.; Rolfo, C.; Vinal, D.; Lopez, I.; Fusco, J.P.; Santisteban, M.; Martin, P.; Zubiri, L.; Echeveste, J.I.; Gil-Bazo, I. Impact of epidermal growth factor receptor (EGFR) activating mutations and their targeted treatment in the prognosis of stage IV non-small cell lung cancer (NSCLC) patients harboring liver metastasis. *J. Transl. Med.* **2015**, *13*, 257. [CrossRef]
128. Jiang, T.; Cheng, R.; Zhang, G.; Su, C.; Zhao, C.; Li, X.; Zhang, J.; Wu, F.; Chen, X.; Gao, G.; et al. Characterization of Liver Metastasis and Its Effect on Targeted Therapy in EGFR-mutant NSCLC: A Multicenter Study. *Clin. Lung Cancer* **2017**, *18*, 631–639.e632. [CrossRef] [PubMed]
129. Walia, P.; Zhan, L.; Schmid, S.; Brown, M.C.; Khan, K.; Garcia, M.; Chowdhury, M.; Herman, J.; Sabouhanian, A.; Strom, E.; et al. P59.17 EGFR Mutation Status, Liver Metastasis, and Overall Survival in Advanced Lung Adenocarcinoma Patients. *J. Thorac. Oncol.* **2021**, *16*, S1154–S1155. [CrossRef]
130. Gen, S.; Tanaka, I.; Morise, M.; Koyama, J.; Kodama, Y.; Matsui, A.; Miyazawa, A.; Hase, T.; Hibino, Y.; Yokoyama, T.; et al. Clinical efficacy of osimertinib in EGFR-mutant non-small cell lung cancer with distant metastasis. *BMC Cancer* **2022**, *22*, 654. [CrossRef] [PubMed]
131. Kuijpers, C.; Hendriks, L.E.L.; Derks, J.L.; Dingemans, A.C.; Van Lindert, A.S.R.; Van den Heuvel, M.M.; Damhuis, R.A.; Willems, S.M. Association of molecular status and metastatic organs at diagnosis in patients with stage IV non-squamous non-small cell lung cancer. *Lung Cancer J. IASLC* **2018**, *121*, 76–81. [CrossRef]
132. Zhang, G.; Cheng, R.; Zhang, Z.; Jiang, T.; Ren, S.; Ma, Z.; Zhao, S.; Zhou, C.; Zhang, J. Bisphosphonates enhance antitumor effect of EGFR-TKIs in patients with advanced EGFR mutant NSCLC and bone metastases. *Sci. Rep.* **2017**, *7*, 42979. [CrossRef]
133. Remon, J.; Lopes, G. Upfront osimertinib—Winner takes it all? *Nat. Rev. Clin. Oncol.* **2020**, *17*, 202–203. [CrossRef]
134. Passiglia, F.; Raez, L.E.; Rolfo, C. Moving osimertinib to first-line: The right “strategy” in the chessboard of epidermal growth factor receptor-mutated non-small cell lung cancer? *J. Thorac. Dis.* **2018**, *10*, S1076–S1080. [CrossRef]
135. Haratake, N.; Misumi, T.; Yamanaka, T.; Seto, T. Optimizing Sequential Treatment with EGFR Tyrosine Kinase Inhibitor with a Simulation of the T790M Mutation Rate in EGFR-Mutated Lung Cancer. *J. Thorac. Oncol.* **2020**, *1*, 100085. [CrossRef]
136. Hirsh, V.; Singh, J. Optimal sequencing strategies in the treatment of EGFR mutation-positive non-small cell lung cancer: Clinical benefits and cost-effectiveness. *Am. J. Health Syst. Pharm.* **2020**, *77*, 1466–1476. [CrossRef]
137. Girard, N. Optimizing outcomes and treatment sequences in EGFR mutation-positive non-small-cell lung cancer: Recent updates. *Future Oncol.* **2019**, *15*, 2983–2997. [CrossRef]
138. Roeper, J.; Falk, M.; Schatz, S.; Tiemann, M.; Sackmann, S.; Ukena, D.; Wessler, C.; Wiest, G.; Heukamp, L.; Friesinger, F. Risk of Not Receiving 2nd Line Therapy is High in EGFR mt+ pts: Real World Data of Certified Lung Cancer Centers on Treatment Sequence in EGFR mt+ pts. *J. Thorac. Oncol.* **2018**, *13*, S494–S495. [CrossRef]
139. Chiang, A.; Fernandes, A.; Pavilack, M.; Wu, J.; Laliberte, F.; Duh, M.S.; Chehab, N.; Subramanian, J. Real World Biomarker Testing and Treatment Patterns in Patients with Advanced NSCLC Receiving EGFR-TKIs. *J. Thorac. Oncol.* **2018**, *13*, S410–S411. [CrossRef]
140. Cuppens, K.; Lodewyckx, L.; Demedts, I.; Decoster, L.; Colinet, B.; Deschepper, K.; Janssens, A.; Galdermans, D.; Pieters, T.; Group, R.S. Real-World Treatment Patterns, Epidermal Growth Factor Receptor (EGFR) Testing and Outcomes in EGFR-Mutated Advanced Non-small Cell Lung Cancer Patients in Belgium: Results from the REVEAL Study. *Drugs Real World Outcomes* **2021**, *8*, 141–152. [CrossRef]
141. Gray, J.E.; Thakrar, B.; Sun, P.; Maclachlan, S.; Chehab, N.; Potter, D. Treatment (tx) patterns in patients (pts) with lung cancer starting 1st or 2nd generation (1G/2G) EGFR-TKI: A US insurance claims database analysis. *Ann. Oncol.* **2018**, *29*, 156–157. [CrossRef]
142. Ballard, P.; Yates, J.W.; Yang, Z.; Kim, D.W.; Yang, J.C.; Cantarini, M.; Pickup, K.; Jordan, A.; Hickey, M.; Grist, M.; et al. Preclinical Comparison of Osimertinib with Other EGFR-TKIs in EGFR-Mutant NSCLC Brain Metastases Models, and Early Evidence of Clinical Brain Metastases Activity. *Clin. Cancer Res.* **2016**, *22*, 5130–5140. [CrossRef] [PubMed]
143. US Food and Drug Administration. FDA Broadens Afatinib Indication to Previously Untreated, Metastatic NSCLC with Other Non-Resistant EGFR Mutations. Available online: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-broadens-afatinib-indication-previously-untreated-metastatic-nsclc-other-non-resistant-egfr#:~:text=FDA%20initially%20approved%20afatinib%20in,progressing%20after%20platinum%2Dbased%20chemotherapy> (accessed on 1 September 2022).

**Disclaimer/Publisher’s Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.