Targeted Molecular Treatments in Non-Small Cell Lung Cancer: A Clinical Guide for Oncologists

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Abstract: Targeted molecular treatments have changed the way non-small cell lung cancer (NSCLC) is managed. Epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), v-raf murine sarcoma viral oncogene homolog B1 (BRAF), and c-ros oncogene 1 (ROS1) mutations are now used to guide specific anti-cancer therapies to improve patient outcomes. New targeted molecular treatments are constantly being developed and evaluated as a means to improve efficacy, overcome resistance, or minimise toxicity. This review article summarises the current evidence for the efficacy, resistance mechanisms, and safety of targeted molecular treatments against specific mutations in NSCLC.

Keywords: personalized therapy; non-small cell; lung cancer; targeted therapy; mutation; rearrangement

1. Introduction

Worldwide, lung cancer is the most commonly diagnosed cancer and the leading cause of cancer mortality. It accounted for 1.8 million new cases in 2012 (12.9% of all cancers) and caused 1.6 million deaths (19.4% of all cancers) [1]. Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancer cases, and adenocarcinoma is the most frequent histological subtype, accounting for nearly 40% of all lung cancer cases [2]. Prior to the use of targeted therapy and immunotherapy, patients with advanced lung cancer had a poor prognosis. Platinum doublet chemotherapy, which was the standard of care for all patients with incurable locally advanced or metastatic NSCLC [3], achieved a response rate of 19%, and a median overall survival of 7.9 months [4]. Modern trials with targeted treatments have resulted in significantly better outcomes, with median overall survival now extending to around, or even beyond, two years in selected populations [5–8].

Specific mutations have been found to be prevalent in lung adenocarcinomas, some of which are predictors for response to targeted treatment. The most common mutations occur in kirsten rat sarcoma virus (KRAS, found in 24% of cases), epidermal growth factor receptor (EGFR, 17%), anaplastic lymphoma kinase (ALK, 3%), v-raf murine sarcoma viral oncogene homolog B1 (BRAF, 2%), and c-ros oncogene 1 (ROS1, 1–2%) [9,10]. We will explore the current evidence for targeted therapy for different mutations in NSCLC, with the aim of providing clinical guidance for oncologists treating NSCLC.

2. EGFR Mutation-Positive NSCLC

EGFR mutations were first described in lung adenocarcinomas in 2004 [11] and were rapidly recognised as a predictor for response to EGFR tyrosine kinase inhibitors (TKIs). The frequency of mutations in this gene varies based on phenotypic characteristics of patients. They occur more...
frequently in Asian non-smoking women, with an incidence up to 40% [12]. The most common EGFR mutations are exon 19 deletions and exon 21 L858R point mutations [9]. Together, these two mutations account for 90% of all EGFR mutations [13]. The remaining EGFR mutations consist of a range of rarer mutations (which can either be sensitising or non-sensitising with respect to EGFR TKIs), and include exon 18 insertions, G719X point mutations in exon 18 (1–4%), exon 20 mutations (2–5%), and complex mutations (1–2%) [14,15].

EGFR TKIs have been developed to treat EGFR mutation-positive lung cancers, and a list of these are included in Table 1.

Table 1. Tyrosine kinase inhibitors (TKIs) in non-small cell lung cancer. EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase.

|                     | First Generation | Second Generation | Third Generation |
|---------------------|------------------|-------------------|------------------|
| EGFR TKIs           | Gefinitib        | Afatinib          | Osimertinib      |
|                     | Erlotinib        | Dacomitinib       | Poziotinib       |
|                     | Icotinib         | Neratinib         |                  |
| ALK TKIs            | Crizotinib       | Ceritinib         | Lorlatinib       |
|                     |                  | Alectinib         | Entrectinib      |
|                     |                  | Brigatinib        | Ensartinib       |

2.1. Efficacy

Early studies investigated the efficacy of EGFR TKIs in a pre-treated population of unselected patients with advanced NSCLC. The BR.21 trial found a 30% improvement in overall survival in patients treated with erlotinib compared to placebo, with an absolute survival benefit of two months [16]. Other studies in unselected populations have not demonstrated a statistically significant overall survival benefit of using EGFR TKIs when compared to chemotherapy or placebo [17–20], in combination with chemotherapy [21,22], or as maintenance therapy after chemotherapy [23–28]. The role of erlotinib in EGFR wild-type NSCLC as maintenance therapy was most recently discounted in a phase III trial when erlotinib as maintenance treatment resulted in a median overall survival of 9.7 months compared to a median overall survival of 9.5 months when erlotinib was used on progression [29].

Although designed as a study to select patients based on phenotypic characteristics (ethnicity and smoking history), the Iressa Pan-Asia Study (IPASS) study was the first to demonstrate differential outcomes for patients treated with an EGFR TKI (gefitinib) based on the presence or absence of an activating EGFR mutation. These data were based on a subset analysis of patients, which demonstrated that the benefit of EGFR TKIs was exclusive to patients with an EGFR mutation [30]. Subsequently, trials have been performed investigating gefitinib, erlotinib, or icotinib in treatment-naïve patients selected for the presence of an activating EGFR mutation. The results of these trials are summarised in Table 2. Treatment with an EGFR TKI typically resulted in superior median progression-free survival (PFS) of 9–13 months when compared to platinum doublet chemotherapy, which had median PFS in the range of 4–6 months. Furthermore, the response rates were as high as 83% in patients on an EGFR TKI, compared to 36% in patients who received chemotherapy. Due to crossover between the study arms, none of these trials demonstrated a statistically significant improvement in overall survival, which can extend up to 38 months [5,6,30–37].
Table 2. Pivotal randomised controlled trials of Epidermal Growth Factor Receptor (EGFR) TKIs in patients with Stage IIIB/IV non-small cell lung cancer.

| Author, Year | Trial Name | Country | Population | Intervention | Control | Median Overall Survival (Months) | Median Progression-Free Survival (Months) | Response Rate |
|--------------|------------|---------|------------|--------------|---------|-------------------------------|---------------------------------------------|--------------|
| **First line treatment** | | | | | | | | |
| Mok, 2009 [30,31] | IPASS | East Asia | Non-smokers Phase III | Gefitinib 609 | Carboplatin and paclitaxel 608 | 18.6 vs. 17.3 HR 0.91 (0.76 to 1.10) | 5.7 vs. 5.8 HR 0.75 (0.65 to 0.85) | 43% vs. 32.2% |
| Mitsudomi, 2010 [5,32] | WJTOG3405 | Japan | EGFR mutation + | Gefitinib 86 | Carboplatin and docetaxel 86 | 38.4 vs. 37.5 HR 1.25 (0.88 to 1.78) | 9.2 vs. 6.3 HR 0.49 (0.34 to 0.71) | 62.1% vs. 32.2% |
| Maemondo, 2010 [33,38] | NEJ002 | Japan | EGFR mutation + | Gefitinib 115 | Carboplatin & paclitaxel 115 | 27.7 vs. 26.6 HR 0.89 (0.63 to 1.24) | 10.8 vs. 5.4 HR 0.32 (0.24 to 0.44) | 73.7% vs. 30.7% |
| Zhou, 2011 [34,35] | OPTIMAL/CTONG-0802 | China | EGFR mutation + | Erlotinib 82 | Carboplatin and gemcitabine 72 | 22.8 vs. 27.2 HR 1.19 (0.83 to 1.71) | 13.1 vs. 4.6 HR 0.37 (0.25 to 0.54) | 83% vs. 36% |
| Rosell, 2012 [36] | EURTAC | Europe | EGFR mutation + | Erlotinib 86 | Carboplatin and docetaxel or gemcitabine 87 | 19.3 vs. 19.5 | HR 1.04 (0.65 to 1.68) | 9.7 vs. 5.2 | 58% vs. 15% |
| Wu, 2015 [6] | ENSURE | Asia | EGFR mutation + | Erlotinib 110 | Carboplatin and gemcitabine 107 | 26.3 vs. 25.5 HR 0.91 (0.63 to 1.31) | 11.0 vs. 5.5 HR 0.34 (0.22 to 0.51) | 62.7% vs. 33.6% |
| Sequist, 2013 [7,39] | LUX-Lung 3 | International | EGFR mutation + | Afatinib 230 | Carboplatin and pemetrexed 212 | 23.1 vs. 23.5 HR 0.93 (0.72-1.22) | 11 vs. 5.6 HR 0.28 (0.20 to 0.39) | 66.9% vs. 23% |
| Wu, 2014 [7,40] | LUX-Lung 6 | Asia | EGFR mutation + | Afatinib 242 | Carboplatin and gemcitabine 222 | 27.9 vs. 24.5 HR 0.86 (0.66 to 1.12) | 11.0 vs. 10.9 HR 0.73 (0.57 to 0.95) | 70% vs. 56% |
| Park, 2016 [41] | LUX-Lung 7 | International | EGFR mutation + | Afatinib 160 | Gefitinib 159 | 34.1 vs. 26.8 HR 1.06 (0.84 to 1.34) | 14.7 vs. 9.2 HR 0.59 (0.47 to 0.74) | 75% vs. 72% |
| Wu, 2017 | ARCHER 1050 [43,44] | China | EGFR mutation + | Dacomitinib 227 | Gefitinib 225 | Data immature | Data immature | 64.8% vs. 33.8% |
| Shi, 2017 | CONVINCE [37] | China | EGFR mutation + | Icotinib 148 | Carboplatin and pemetrexed | Data immature | Data immature | 80% vs. 76% (NS) |
| Soria, 2018 [45] | FLAURA | International | EGFR mutation + | Osimertinib 279 | Gefitinib or erlotinib 277 | Data immature | Data immature | 80% vs. 76% (NS) |
| **Second line treatment** | | | | | | | | |
| Mok, 2017 [46] | AURA3 | International | T790M mutation + PD after EGFR TKI Phase III | Osimertinib 279 | Platinum and pemetrexed 140 | Data immature | Data immature | 10.1 vs. 4.4 HR 0.30 (0.23 to 0.41) | 71% vs. 31% |

HR: hazard ratio; NS: not significant; PD: progressive disease. IPASS: Iressa Pan-Asia Study; WJTOG: West Japan Thoracic Oncology Group; NEJ: North East Japan Study Group; CTONG: Chinese Thoracic Oncology Group; EURTAC: European Randomised Trial of Tarceva vs Chemotherapy. All trials used consistent dosing of gefitinib 250 mg, erlotinib 150 mg, afatinib 40 mg daily, dacomitinib 45 mg daily, icotinib 125 mg three times a day, and osimertinib 80 mg daily.
The question of whether there are meaningful differences between first-generation TKIs has been addressed in three small studies. In these studies, no significant differences between erlotinib and gefitinib were observed, although there were some differences in the pattern of side effects [47–49]. The benefits of EGFR TKIs observed with *EGFR* mutation-positive cancers does not translate to patients who have high *EGFR* expression identified using immunohistochemistry or increased *EGFR* copy number detected by fluorescence in situ hybridization [31,50].

In an effort to improve further outcomes for these patients, second-generation EGFR TKIs have been developed. Afatinib and dacomitinib were both designed to bind covalently to the mutated EGFR protein. Additionally, these agents are pan-HER inhibitors and block activation of other members of the *EGFR/HER* family. These agents result in superior PFS compared to chemotherapy in treatment-naïve patients with *EGFR*-mutated tumours [7,39,40,43]. There are only limited data comparing second- and first-generation agents to each other. In a randomised phase II study, Lux Lung 7, afatinib and gefitinib were compared as first-line therapy for treatment-naïve patients. Afatinib was found to have a statistically significant PFS benefit; however, the absolute benefit was small (0.1 months) [41,42] and there seems to be little meaningful efficacy difference between the agents. The recently published overall survival data for the phase III trial of dacomitinib compared to gefitinib did show a statistically significant improvement in median overall survival (34.1 vs. 26.8 months). Despite these results, the clinical use of dacomitinib is likely to be limited by the FLAURA trial (discussed in the next paragraph), especially given the toxicity profile of dacomitinib [44].

Osimertinib, a third-generation irreversible EGFR TKI, has greater efficacy than the first- and second-generation agents. FLAURA, a randomised study comparing first-line osimertinib to erlotinib or gefitinib, showed that, despite similar response rates, patients treated with osimertinib had better PFS (18.9 months vs. 10.2 months). In patients who had stable central nervous system (CNS) metastases at time of trial enrolment, osimertinib also had a superior PFS to the first-generation EGFR TKIs (15.2 months vs. 9.6 months). Overall survival data from this study are currently immature [45].

There are no prospective studies investigating the efficacy of EGFR TKIs in patients with uncommon *EGFR* mutations. Observational data with small sample sizes do indicate activity of first-generation EGFR TKIs in some of the rarer *EGFR* mutations; however, the response rates may be lower compared to patients with common *EGFR* mutations [14]. In vitro data has demonstrated that cells with exon 18 mutations had better responses to second-generation EGFR TKIs such as afatinib and neratinib compared to first- or third-generation EGFR TKIs [51]. Ad hoc analyses of trial data showed a greater benefit of afatinib in patients with point mutations and duplications in exons 18–21, with a disease control rate of 84%, median PFS of 10.7 months, and median overall survival of 19 months. Meanwhile, patients who had de novo T790M mutations or exon 20 insertions had lower response rates (15% and 9%, respectively), shorter median PFS (2.9 months and 2.7 months), and shorter overall survival (14.9 months and 9.2 months) [52]. The resistance to EGFR TKIs and the poorer prognosis associated with exon 20 mutations was also seen in a retrospective analysis of 20 patients by Noronha et al. [53]. A phase II study of poziotinib in patients with *EGFR* exon 20 mutant advanced NSCLC is currently recruiting, with early results suggesting activity [54]. Without phase III evidence to support a different approach, EGFR TKIs are still the recommended first-line option for patients with uncommon but activating *EGFR* mutations.

Although several studies have been conducted in the adjuvant setting, only one trial has been completed where patient selection was prospectively based on the presence of an activating *EGFR* mutation. Consequently, interpretation of results is difficult. Based on the available data, EGFR TKIs may improve PFS, though the data for overall survival remains immature [55–57]. A phase III trial of adjuvant osimertinib in *EGFR* mutation-positive patients is currently recruiting, with results expected in late 2021 [58]. EGFR TKIs have yet to be implemented into routine clinical practice in this setting.
2.2. Resistance

Primary resistance, where the best response achieved is progressive disease, is a relatively rare occurrence, and is noted in 4–10% of EGFR mutation-positive NSCLC treated with an EGFR TKI [30,32–34,36,39–41,43,45]. Acquired resistance, where progressive disease develops after a period of objective response or stability, will eventually occur in all patients treated with an EGFR TKI. The most common resistance mechanisms are the T790M mutation (49–62%), c-MET amplification (5–22%), human epidermal growth factor receptor 2 (HER2) amplification (12%), epithelial–mesenchymal transition (20%), and small cell lung cancer transformation (3–14%) [59–64].

Continuation of a first- or second-generation EGFR TKI after progression on these agents has not been shown to improve outcomes [65,66]. However, osimertinib has demonstrated activity against the exon 20 T790M mutation, which occurs when threonine at position 790 is replaced by methionine [67]. This substitution leads to increased ATP affinity, cell proliferation and survival, and, ultimately, resistance to first generation TKIs [68,69]. AURA3 compared treatment with osimertinib to standard platinum doublet chemotherapy in patients with secondary T790M mutation after progression with a first-generation EGFR TKI. Osimertinib resulted in better PFS (10.1 vs. 4.4 months) and higher response rates (70% vs. 30%). A PFS benefit in patients with stable CNS metastases was also seen with osimertinib (8.5 months vs. 4.2 months) [46].

2.3. Toxicity

The adverse events of the first-generation EGFR TKIs are often Grade 1 or Grade 2 and are less likely to cause dose reductions (~20%) or drug discontinuation (~6%) compared to chemotherapy. The most common adverse events of any grade are rash or acne (66–80%), diarrhoea (25–55%) and elevated liver transaminases, particularly of alanine aminotransferase (37–55%). Most of the Grade 3 to Grade 5 adverse events occur in <6% of patients, with the exception of elevated transaminases which can occur in up to 26% of patients. The rates of pneumonitis are uncommon, in order of 1–5% [6,30,33,34,36]. There are subtle differences in the pattern of toxicity between erlotinib and gefitinib. Erlotinib is more likely to cause rash or diarrhoea, while gefitinib is more likely to cause liver function abnormalities [49]. However, these differences have little meaningful clinical impact.

Second-generation EGFR TKIs such as afatinib are more likely to result in adverse events when compared to chemotherapy or first-generation EGFR TKIs. Adverse events that are Grade 3 or higher occur in up to 49% of patients and include severe diarrhoea (up to 15%) and rash (up to 16%) [7,41]. In most studies, these have been successfully managed with dose reductions, and consequently the rate of discontinuation of drug as a result of toxicity is comparable to first-generation EGFR TKIs (6–10%) [41,43].

Meanwhile, osimertinib has been shown to have a better toxicity compared to first-generation EGFR TKIs, with a lower frequency and lower severity of adverse events of rash and transaminase elevations [45].

3. ALK-Positive NSCLC

ALK rearrangements were first identified in 2007 [70]. Although a single rearrangement with echinoderm microtubule-associated protein-like 4 (EML4) was initially identified, it has become apparent that there are several variants based on the location of the rearrangement. These variants may have prognostic significance with differences in outcome noted between them [71].

ALK rearrangements are more common in younger patients who have never smoked, or who have a light smoking history [72]. The commonly used ALK TKIs are listed in Table 1, and the pivotal randomised controlled trials for ALK TKIs are listed in Table 3.
3.1. Efficacy

Crizotinib was initially developed as a mesenchymal-to-epithelial transition (MET) inhibitor. However, during phase I trials it became apparent that it had substantial activity against ALK-rearranged tumours [73]. It was the first ALK TKI to show a clinically significant benefit in ALK-positive NSCLC, when it was evaluated in the second-line setting compared to chemotherapy. Patients treated with crizotinib had a median PFS of 7.7 months compared to 3.0 months with chemotherapy [8]. Data from this study resulted in crizotinib becoming a standard treatment in this group of patients.

Subsequently, ALK TKIs have been evaluated in the first-line setting. Crizotinib was compared to standard platinum doublet chemotherapy in the PROFILE 1014 study, with better PFS and higher response rates observed for crizotinib than for chemotherapy [74]. A study with the same design but using ceritinib resulted in similar outcomes [75]. Both crizotinib and ceritinib have shown activity in stable CNS metastases compared to chemotherapy, with median PFS of 9.0 months with crizotinib (vs. 4.0 months) and 10.7 months with ceritinib (vs. 6.7 months) [75,76].

Most recently, alectinib has been compared to crizotinib in the first-line setting in the ALEX study. In this study, alectinib had superior efficacy, with the median PFS not reached in the alectinib arm and 11.1 months in the crizotinib arm. Alectinib does have meaningful CNS activity compared to crizotinib. In patients treated with alectinib, the cumulative rate of CNS metastases was markedly reduced (9.4% vs. 41.4%), and, in patients with known CNS metastases at time of trial enrolment, the response rates were higher (59% vs. 26%) [77].

Ensartinib, a third-generation ALK TKI, had response rates of 66% and a median PFS 9.2 months in an early phase I/II trial. Recruitment is currently ongoing for a first-line phase III trial of ensartinib compared to crizotinib in ALK-positive NSCLC [78].

In parallel with trials of EGFR TKIs, these studies have all allowed crossover of patients. Consequently, it has not been possible to demonstrate improvements in overall survival.

3.2. Resistance

Acquired resistance usually occurs within the first two years of ALK TKI treatment and can occur due to acquired point mutations in ALK, or due to bypass track activation via activation of EGFR or amplification of CKIT. The most common resistance mutation is L1196M, though there are often multiple resistance mutations that occur concurrently [72].

Alectinib and ceritinib have been studied in phase III trials in the second line setting after resistance to crizotinib. They had superior efficacy when compared to chemotherapy with response rates between 35–40%, a median PFS of approximately 9 months, and evidence of efficacy in patients with known CNS metastases [79,80]. Phase II trials investigating brigatinib and lorlatinib show response rates up to 65% in patients with and without CNS metastases [81,82]. A phase II trial for entrectinib, a pan-tropomyosin receptor kinase (TRK), -ROS1, and -ALK TKI, is currently underway for mutation-positive patients with solid tumours after promising phase I data [83].

Using in vitro data on cell lines, Gainor et al. demonstrated that the activity of second-line therapy is influenced by the specific resistant mutation that occurs, as shown in Table 4 [84]. Sequential ALK TKI can also lead to the development of compound ALK mutations that may suggest resistance to specific ALK TKIs [85], thus highlighting the importance of patient selection and treatment sequencing when determining the optimal management pathway for each patient.
Table 3. Pivotal randomised controlled trials of Anaplastic Lymphoma Kinase (ALK) TKIs in patients with Stage IIIB/IV non-small cell lung cancer.

| Author, Year | Trial Name | Country | Population | Intervention | Control | Median Overall Survival (Months) | HR (95% CI) | Median Progression Free Survival (Months) | HR (95% CI) | Response Rate |
|--------------|------------|---------|------------|--------------|---------|-------------------------------|-------------|--------------------------------|-------------|--------------|
| First line treatment |
| Solomon, 2014 [74] | PROFILE 1014 | International | ALK-positive | Crizotinib 172 | Platinum and pemetrexed 171 | NR vs. NR | 0.82 (0.54 to 1.26), NS | 10.9 vs. 7.0 | 0.45 (0.35 to 0.60) | 74% vs. 45% |
| Soria, 2017 [75] | ASCEND-4 | International | ALK-positive | Ceritinib 189 | Platinum and pemetrexed 187 | NR vs. 26.2 | 0.73 (0.50 to 1.08), NS | 16.6 vs. 8.1 | 0.55 (0.42 to 0.73) | 72.5% vs. 26.7% |
| Peters, 2017 [77] | ALEX | International | ALK-positive | Alectinib 600 mg BD 152 | Crizotinib 151 | HR 0.76 (0.48 to 1.20), NS | NR vs. NR | 0.47 (0.34 to 0.65) | 82.9% vs. 75.5% |
| Second line treatment |
| Shaw, 2013 [8] | PROFILE 1007 | International | ALK-positive | Crizotinib 173 | Pemetrexed or docetaxel 174 | Data immature | 20.3 vs. 22.8 | 1.02 (0.68 to 1.54), NS | 7.7 vs. 3.0 | 0.49 (0.37 to 0.64) | 65% vs. 20% |
| Kim, 2017 [81] | International | ALK-positive | PD after chemotherapy | Brigatinib 90 mg daily 112 | Brigatinib 180 mg daily 110 | Not reported | 9.2 vs. 15.6 | 0.55 (0.35 to 0.86) | 45% vs. 54% |
| Hida, 2017 [86] | J-ALEX | Japan | ALK-positive | Alectinib 300 mg BD 103 | Crizotinib 104 | Data immature | NR vs. 10.2 | HR 0.34 (0.17 to 0.71) | 92% vs. 79% |
| Shaw, 2017 [79] | ASCEND-5 | International | ALK-positive | Ceritinib 115 | Pemetrexed or docetaxel 116 | Data immature | 1.0 (0.67 to 1.49), NS | 5.4 vs. 1.6 | HR 0.49 (0.36 to 0.67) | 39% vs. 7% |
| Novello, 2017 [80] | ALUR | International | ALK-positive | Alectinib 600 mg BD 117 | Pemetrexed or docetaxel | Not reported | 9.6 vs. 1.4 | 0.15 (0.08 to 0.29) | 36.1% vs. 11.4% |

HR: hazard ratio; NS: not significant; PD: progressive disease. All trials with crizotinib and ceritinib used consistent dosing at 250 mg BD and 750 mg daily, respectively.
Table 4. Spectrum of activity of different Anaplastic Lymphoma Kinase (ALK) tyrosine kinase inhibitors for different resistance mutations, as studied by Gainor et al. using in vitro data on cell lines [84].

| ALK Mutation | Crizotinib | Ceritinib | Alectinib | Brigatinib | Lorlatinib |
|--------------|-----------|-----------|-----------|------------|------------|
| V1           | S         | S         | S         | S          | S          |
| C1156Y       | I         | S         | S         | S          | S          |
| I1171N       | I         | S         | R         | S          | S          |
| I1171S       | I         | S         | I         | S          | S          |
| I1171T       | I         | S         | S         | S          | S          |
| F1174C       | I         | S         | S         | S          | S          |
| L1196M       | R         | S         | I         | S          | S          |
| L1198F       | S         | I         | S         | S          | S          |
| G1202R       | R         | I         | R         | I          | S          |
| G1202del     | I         | I         | I         | I          | S          |
| D1203N       | I         | S         | S         | S          | S          |
| E1210K       | S         | S         | S         | S          | S          |
| G1269A       | I         | S         | S         | No data    | S          |
| D1203N + F1174C | R   | R         | I         | I          | I          |
| D1203N + E1210K | I     | I         | I         | I          | S          |

* R: resistant; S: sensitive; I: intermediate.

3.3. Toxicity

The most common toxicities of any grade due to crizotinib or ceritinib are diarrhoea (up to 85%), nausea (up to 69%), vomiting (up to 66%), constipation (up to 43%), and raised liver transaminases (up to 53%). Crizotinib is also associated with visual disorders such as visual impairment, photophobia, or blurred vision (71%), oedema (49%), and upper respiratory tract infections (32%) [74,75]. Alectinib is associated with hyperbilirubinaemia but has lower overall rates of gastrointestinal adverse events compared to the other ALK TKIs [77]. The main toxicities from lorlatinib are hypercholesterolaemia and hypertriglyceridaemia [82].

4. ROS1-Positive NSCLC

ROS1 rearrangements are more likely to be present in younger, non-smoking Asian patients [10]. There are no TKIs that have been designed to specifically target ROS1. However, in early clinical trials, it became apparent that ALK TKIs had activity in ROS1-positive patients. Crizotinib had a response rate of 71.7% and a median PFS of 15.9 months in a phase II trial of 127 patients [87]. Ceritinib had a response rate of 62% and a median PFS of 9.3 months in a phase II trial of 32 patients, though the median PFS improved to 19.3 months in patients who were treatment-naïve [88]. Finally, a phase I trial of lorlatinib included 12 ROS1-positive patients and achieved a response rate of 50% with a median PFS of 7 months [82]. Importantly, the ALK inhibitor alectinib, which has a structure that is distinct from the other agents mentioned above, is not active in ROS1-mutated tumours [89].

5. BRAF Mutation-Positive NSCLC

BRAF V600E mutations have been noted in several tumour types, most notably melanoma. They may also occur in <5% of NSCLC and are often associated with poor response to platinum-based chemotherapy. The availability of RAF inhibitors has led to their evaluation in NSCLC, although the rarity of the mutation means that the data is limited to phase II trials. Dabrafenib in monotherapy resulted in a response rate of 33%, median PFS of 5.5 months and median overall survival of 12.7 months [90]. In keeping with the experience in melanoma, the addition of the Mitogen-activated protein kinase (MEK) inhibitor trametinib resulted in better outcomes (response rates of 64% and a median PFS of 10.9 months) [91]. These agents have regulatory approval for use in NSCLC from the Food and Drug Administration (FDA) and the European Medicines Agency.
Toxicity

The most common adverse event from dabrafenib and trametinib was pyrexia, which occurred in 64% of patients. Other toxicities such as nausea, diarrhoea, fatigue, peripheral oedema, vomiting, dry skin, anorexia, and headache each occurred in 25–36% patients [91].

6. KRAS Mutation-Positive NSCLC

KRAS mutations are the most common mutation found in NSCLC. They often occur at codon 12, and can rarely occur at codon 13 and 61 [92]. They are mutually exclusive with EGFR mutations and ALK translocations in almost all cases [93]. KRAS mutations are more common in smokers, and also convey a poorer prognosis [94,95].

There are no targeted treatments that have a clinically meaningful benefit in patients with KRAS mutations. While MEK inhibitors such as selumetinib and trametinib held promise in early research, benefit could not be demonstrated in larger trials in patients with advanced NSCLC. A phase III trial of second-line selumetinib and docetaxel compared to docetaxel alone showed no difference in PFS (3.9 months vs. 2.8 months) and no difference in median overall survival (8.7 months vs. 7.9 months) [96]. A phase II trial of second-line trametinib compared to docetaxel alone showed no difference in median PFS (12 weeks vs. 11 weeks) with a response rate of 12% in both arms [97].

7. Other Mutations in NSCLC

There are other less common mutations that have been investigated as potential drug targets. Mutations in the mesenchymal-to-epithelial transition (MET) gene that cause exon 14 skipping occur in 3% of non-squamous NSCLC, and are more likely in older patients [98]. Patients with MET mutations who never received MET inhibitor therapy had a poor prognosis (median overall survival 8.1 months), which was worse if there was concurrent MET amplification (median overall survival 5.2 months). Treatment with a MET inhibitor extended the median overall survival to 24.6 months [99]. Early trials have suggested an antitumour effect of crizotinib in patients with MET exon 14-altered NSCLC, and in patients with MET amplification [100,101]. Other MET TKIs, such as capmatinib, tepotinib, salvolitinib, cabozantinib, glesatinib, and merestinib, are currently being investigated for patients with MET mutations.

RET rearrangements occur in 1–2% of patients with NSCLC [102,103]. Vandetanib, lenvatinib, and cabozantinib, which are multitargeted kinase inhibitors, have demonstrated antitumour effect in RET-positive NSCLC in phase II trials with response rates ranging from 16% to 53% [104–107]. Alectinib has also shown promising pre-clinical evidence against RET-positive NSCLC [89].

HER2 mutations occur in 1–6% of patients with NSCLC [108–110] and are more common in never-smokers. Gender or ethnicity did not affect incidence of the HER2 mutations [109]. Retrospective studies have shown responses to HER2-targeted therapies including trastuzumab, neratinib, afatinib, lapatinib, and trastuzumab emtansine [108,111]. Phase II trials have confirmed anti-cancer activity with trastuzumab emtansine and afatinib in patients with HER2-mutated NSCLC [112,113]. A further phase II trial investigating the benefit of afatinib is underway. In HER2-amplified NSCLC, phase II trials have shown no clinical benefit of trastuzumab monotherapy, trastuzumab with chemotherapy, trastuzumab emtansine, or pertuzumab [114–117].

8. Conclusions

Targeted molecular therapies have revolutionised the management of advanced NSCLC and have become the international standard of care for patients with driver mutations. Individualised patient care has never been so important. The optimal sequencing of TKIs to provide the best outcomes for our patients is unknown, especially in the immunotherapy era of oncology. An improved understanding of molecular resistance will guide the development of new treatments and assist with decision-making about treatment selection.
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References

1. Ferlay, J.; Soerjomataram, I.; Dikshit, R.; Eser, S.; Mathers, C.; Rebelo, M.; Parkin, D.M.; Forman, D.; Bray, F. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int. J. Cancer* **2015**, *136*, E359–E386. [CrossRef] [PubMed]

2. De la Cruz, C.S.; Tanoue, L.T.; Matthay, R.A. Lung cancer: Epidemiology, etiology, and prevention. *Clin. Chest Med.* **2011**, *32*, 605–644. [CrossRef] [PubMed]

3. Rajeswaran, A.; Trojan, A.; Burnand, B.; Giannelli, M. Efficacy and side effects of cisplatin- and carboplatin-based doublet chemotherapeutic regimens versus non-platinum-based doublet chemotherapeutic regimens as first line treatment of metastatic non-small cell lung carcinoma: A systematic review of randomized controlled trials. *Lung Cancer* **2008**, *59*, 1–11. [CrossRef] [PubMed]

4. Schiller, J.H.; Harrington, D.; Belani, C.P.; Langer, C.; Sandler, A.; Krook, J.; Zhu, J.; Johnson, D.H. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N. Engl. J. Med.* **2002**, *346*, 92–98. [CrossRef] [PubMed]

5. Yoshioka, H.; Mitsudomi, T.; Morita, S.; Yatabe, Y.; Negoro, S.; Okamoto, I.; Seto, T.; Satouchi, M.; Tada, H.; Hirashima, T.; et al. Final overall survival results of WJTOG 3405, a randomized phase 3 trial comparing gefitinib (G) with cisplatin plus docetaxel (CD) as the first-line treatment for patients with non-small cell lung cancer (NSCLC) harboring mutations of the epidermal growth factor receptor (EGFR). *J. Clin. Oncol.* **2014**, *32* (Suppl. 15), 8117. [CrossRef]

6. 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] [PubMed]

7. Yang, J.C.-H.; 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 non-small-cell lung cancer: Analyses from the phase III, randomized, open-label, ENSURE study. *J. Clin. Oncol.* **2014**, *32* (Suppl. 15), 8117. [CrossRef]

8. Shaw, A.T.; Kim, D.-W.; Nakagawa, K.; Seto, T.; Crino, L.; Ahn, M.-J.; De Pas, T.; Besse, B.; Solomon, B.J.; Blackhall, F.; et al. Crizotinib versus chemotherapy in patients with advanced ALK-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]

9. Kris, M.G.; Johnson, B.E.; Berry, L.D.; Kwiatkowski, D.J.; Iafrate, A.J.; Wistuba, I.I.; Varella-Garcia, M.; Franklin, W.A.; Aronson, S.L.; Su, P.-F.; et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. *JAMA* **2014**, *311*, 1998–2006. [CrossRef] [PubMed]

10. Bergethon, K.; Shaw, A.T.; Ou, S.-H.I.; Katayama, R.; Lovly, C.M.; McDonald, N.T.; Massion, P.P.; Siwak-Tapp, C.; Gonzalez, A.; Fang, R.; et al. ROS1 rearrangements define a unique molecular class of lung cancers. *J. Clin. Oncol.* **2012**, *30*, 863–870. [CrossRef] [PubMed]

11. Lynch, T.J.; Bell, D.W.; Sordella, R.; Gurubhagavatula, S.; Okimoto, R.A.; Brannigan, B.W.; Harris, P.L.; Haserlat, S.M.; Supko, J.G.; Haluska, F.G.; et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non–small-cell lung cancer to gefitinib. *N. Engl. J. Med.* **2004**, *350*, 2129–2139. [CrossRef] [PubMed]

12. Yatabe, Y.; Kerr, K.M.; Utomo, A.; Rajadurai, P.; Tran, V.K.; Du, X.; Chou, Y.; Enriquez, M.L.D.; Lee, G.K.; Iqbal, J.; et al. EGFR mutation testing practices within the Asia Pacific region: Results of a multicenter diagnostic survey. *J. Thorac. Oncol.* **2015**, *10*, 438–445. [CrossRef] [PubMed]

13. Li, A.R.; Chitalle, D.; Riely, G.; Pao, W.; Miller, V.A.; Zakowski, M.F.; Rusch, V.; Kris, M.G.; Ladanyi, M. EGFR mutations in lung adenocarcinomas: Clinical testing experience and relationship to EGFR gene copy number and immunohistochemical expression. *J. Mol. Diagn.* **2008**, *10*, 242–248. [CrossRef] [PubMed]
14. Beau-Faller, M.; Prim, N.; Ruppert, A.-M.; Nanni-Metéllus, I.; Lacave, R.; Lacroix, L.; Escande, F.; Lizard, S.; Pretet, J.-L.; Rouquette, I.; et al. Rare EGFR exon 18 and exon 20 mutations in non-small-cell lung cancer on 10 117 patients: A multicentre observational study by the French ERMETIC-IFCT network. Ann. Oncol. 2013, 25, 126–131. [CrossRef] [PubMed]

15. Shi, Y.; Au, J.S.-K.; Thongprasert, S.; Srinivasan, S.; Tsai, C.-M.; Khoa, M.T.; Heeroma, K.; Itoh, Y.; Cornielio, 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]

16. Shepherd, F.A.; Pereira, J.R.; 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]

17. Kim, E.S.; Hirsh, V.; Mok, T.; Socinski, M.A.; Gervais, R.; Wu, Y.-L.; Li, L.-Y.; Watkins, C.L.; Sellers, M.V.; Lowe, E.S.; et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): A randomised phase III trial. Lancet 2008, 372, 1809–1818. [CrossRef]

18. Ciuleanu, T.; Stelmakh, L.; Cicenas, S.; Miliauskas, S.; Grigorescu, A.C.; Hillenbach, C.; Johannsdottir, H.K.; Klughammer, B.; Gonzalez, E.E. Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): A randomised multicentre, open-label, phase 3 study. Lancet Oncol. 2012, 13, 300–308. [CrossRef]

19. Miller, V.A.; Hirsh, V.; Cadranel, J.; Chen, Y.-M.; Park, K.; Kim, S.-W.; Zhou, C.; Su, W.-C.; Wang, M.; Sun, Y.; et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): A phase 2b/3 randomised trial. Lancet Oncol. 2012, 13, 528–538. [CrossRef]

20. Ellis, P.M.; Shepherd, F.A.; Millward, M.; Perrone, F.; Seymour, L.; Liu, G.; Sun, S.; Cho, B.C.; Morabito, A.; Leigh, N.B.; et al. Dacomitinib compared with placebo in pretreated patients with advanced or metastatic non-small-cell lung cancer (NCIC CTG BR.26): A double-blind, randomised, phase 3 trial. Lancet Oncol. 2014, 15, 1379–1388. [CrossRef]

21. Herbst, R.S.; Prager, D.; Hermann, R.; Fehrenbacher, L.; Johnson, B.E.; Sandler, A.; Kris, M.G.; Tran, H.T.; Klein, P.; Li, X.; et al. TRIBUTE: A phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. J. Clin. Oncol. 2005, 23, 5892–5899. [CrossRef] [PubMed]

22. Wu, Y.-L.; Lee, J.S.; Thongprasert, S.; Yu, C.-J.; Zhang, L.; Ladra, G.; Srimuninnimit, V.; Sriuranpong, V.; Sandoval-Tan, J.; Zhu, Y.; et al. Intercalated combination of chemotherapy and erlotinib for patients with advanced stage non-small-cell lung cancer (FASTACT-2): A randomised, double-blind trial. Lancet Oncol. 2013, 14, 777–786. [CrossRef]

23. Takeda, K.; Hida, T.; Sato, T.; Ando, M.; Seto, T.; Satouchi, M.; Ichinose, Y.; Katakami, N.; Yamamoto, N.; Kudoh, S.; et al. Randomized phase III trial of platinum-doublet chemotherapy followed by gefitinib compared with continued platinum-doublet chemotherapy in Japanese patients with advanced non-small-cell lung cancer: Results of a west Japan thoracic oncology group trial (WJTOG0203). J. Clin. Oncol. 2010, 28, 753–760. [CrossRef] [PubMed]

24. Cappuzzo, F.; Ciuleanu, T.; Stelmakh, L.; Cicenas, S.; Szczesna, A.; Juhasz, E.; Esteban, E.; Molinier, O.; Brugger, W.; Melezinek, I.; et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: A multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol. 2010, 11, 521–529. [CrossRef]

25. Coudert, B.; Ciuleanu, T.; Park, K.; Wu, Y.L.; Giaccone, G.; Brugger, W.; Gopalanakrishna, P.; Cappuzzo, F. Survival benefit with erlotinib maintenance therapy in patients with advanced non-small-cell lung cancer (NSCLC) according to response to first-line chemotherapy. Ann. Oncol. 2012, 23, 388–394. [CrossRef] [PubMed]

26. Johnson, B.E.; Kabbabinar, F.; Fehrenbacher, L.; Hainsworth, J.; Kasubhai, S.; Kressel, B.; Lin, C.-Y.; Marsland, T.; Patel, T.; Polikoff, J.; et al. ATLAS: Randomized, double-blind, placebo-controlled, phase IIIIB trial comparing bevacizumab therapy with or without erlotinib, after completion of chemotherapy, with bevacizumab for first-line treatment of advanced non-small-cell lung cancer. J. Clin. Oncol. 2013, 31, 3926–3934. [CrossRef] [PubMed]
27. Zhang, L.; Ma, S.; Song, X.; Han, B.; Cheng, Y.; Huang, C.; Yang, S.; Liu, X.; Liu, Y.; Lu, S.; et al. Gefitinib versus placebo as maintenance therapy in patients with locally advanced or metastatic non-small-cell lung cancer (INFORM; C-TONG 0804): A multicentre, double-blind randomised phase 3 trial. *Lancet Oncol.* 2012, 13, 466–475. [CrossRef]  
28. Zhao, H.; Fan, Y.; Ma, S.; Song, X.; Han, B.; Cheng, Y.; Huang, C.; Yang, S.; Liu, X.; Liu, Y.; et al. Final overall survival results from a phase III, randomized, placebo-controlled, parallel-group study of gefitinib versus placebo as maintenance therapy in patients with locally advanced or metastatic non-small-cell lung cancer (INFORM; C-TONG 0804). *J. Thorac. Oncol.* 2015, 10, 655–664. [CrossRef] [PubMed]  
29. Cicénasa, S.; Geater, S.L.; Petrov, P.; Hotko, Y.; Hooper, G.; Xia, F.; Mudie, N.; Wu, Y.-L. Maintenance erlotinib versus erlotinib at disease progression in patients with advanced non-small-cell lung cancer who have not progressed following platinum-based chemotherapy (UNO study). *Lung Cancer* 2016, 102, 30–37. [CrossRef] [PubMed]  
30. 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] [PubMed]  
31. Fukuoka, M.; Wu, Y.-L.; Thongprasert, S.; Sunpaweravong, P.; Leong, S.-S.; Srisuranpong, 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] [PubMed]  
32. 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]  
33. 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] [PubMed]  
34. Zhou, C.; Wu, Y.-L.; Chen, G.; Feng, J.; Liu, X.-Q.; Wang, C.; Zhang, S.; Wang, J.; Zhou, S.; Ren, S.; et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): A multicentre, open-label, randomised phase 3 study. *Lancet Oncol.* 2011, 12, 735–742. [CrossRef]  
35. Zhou, C.; Wu, Y.L.; Chen, G.; Feng, J.; Liu, X.Q.; Wang, C.; Zhang, S.; Wang, J.; Zhou, S.; Ren, S.; et al. Final overall survival results from a randomised, phase III study of erlotinib versus chemotherapy as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer (OPTIMAL, CTONG-0802). *Ann. Oncol.* 2015, 26, 1877–1883. [CrossRef] [PubMed]  
36. 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]  
37. Shi, Y.K.; Wang, L.; Han, B.H.; Li, W.; Yu, P.; Liu, Y.P.; Ding, C.M.; Song, X.; Ma, Z.Y.; Ren, X.L.; et al. First-line icotinib versus cisplatin/pemetrexed plus pemetrexed maintenance therapy for patients with advanced EGFR mutation-positive lung adenocarcinoma (CONVINCE): A phase 3, open-label, randomized study. *Ann. Oncol.* 2017, 28, 2443–2450. [CrossRef] [PubMed]  
38. 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-naive non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). *Ann. Oncol.* 2013, 24, 54–59. [CrossRef] [PubMed]  
39. Sequist, L.V.; Yang, J.C.-H.; 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] [PubMed]
40. 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]

41. 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]

42. 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] [PubMed]

43. 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]

44. 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] [PubMed]

45. 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] [PubMed]

46. 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.M.E.; et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N. Engl. J. Med.* 2017, 369, 629–640. [CrossRef] [PubMed]

47. Kim, S.T.; Uhm, J.E.; Lee, J.; Sun, J.-M.; Sohn, I.; Kim, S.W.; Jung, S.-H.; Park, Y.H.; Ahn, J.S.; Park, K.; et al. Randomized phase II study of gefitinib versus erlotinib in patients with advanced non-small-cell lung cancer who failed previous chemotherapy. *Lung Cancer* 2012, 75, 82–88. [CrossRef] [PubMed]

48. Yang, J.J.; Zhou, Q.; Yan, H.H.; Zhang, X.C.; Chen, H.J.; Tu, H.Y.; Wang, Z.; Xu, C.R.; Su, J.; Wang, B.C.; et al. A phase III randomised controlled trial of erlotinib vs gefitinib in advanced non-small cell lung cancer with EGFR mutations. *Br. J. Cancer* 2017, 116, 568–574. [CrossRef] [PubMed]

49. Urata, Y.; Katakami, N.; Morita, S.; Kaji, R.; Yoshioka, H.; Seto, T.; Satouchi, M.; Iwamoto, Y.; Kanehara, M.; Fujimoto, D.; et al. Randomized phase III study comparing gefitinib with erlotinib in patients with previously treated advanced lung adenocarcinoma: WJOG 5108L. *J. Clin. Oncol.* 2016, 34, 3248–3257. [CrossRef] [PubMed]

50. Hirsch, F.R.; Kabbinavar, F.; Eisen, T.; Martins, R.; Schnell, F.M.; Dziadziuszko, R.; Richardson, K.; Richardson, F.; Wacker, B.; Sternberg, D.W.; et al. A randomized, phase II, biomarker-selected study comparing erlotinib to erlotinib intercalated with chemotherapy in first-line therapy for advanced non-small-cell lung cancer. *J. Clin. Oncol.* 2011, 29, 3567–3573. [CrossRef] [PubMed]

51. Kobayashi, Y.; Togashi, Y.; Yatabe, Y.; Gondi, M.; Loo, S.; Kato, K.; Suda, K.; Tomizawa, K.; et al. EGFR exon 18 mutations in lung cancer: Molecular predictors of augmented sensitivity to afatinib or neratinib as compared with first- or third-Generation TKIs. *Clin. Cancer Res.* 2015, 2015, 5305–5313. [CrossRef] [PubMed]

52. Yang, J.C.-H.; Sequist, L.V.; Geater, S.L.; Tsai, C.-M.; Mok, T.S.K.; Schuler, M.; Yamamoto, N.; Yu, C.-J.; Ou, S.-H.J.; 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]

53. Noronha, V.; Choughule, A.; Patil, V.M.; Joshi, A.; Kumar, R.; Philip, D.S.J.; Banavali, S.; Dutt, A.; Kumar, P. Epidermal growth factor receptor exon 20 mutation in lung cancer: Types, incidence, clinical features and impact on treatment. *Onco Targets Ther.* 2017, 10, 2903–2908. [CrossRef] [PubMed]

54. Elamin, Y.; Robichaux, J.; Heymach, J. Preliminary results of a phase II study of poziotinib in EGFR exon 20 mutant advanced NSCLC. *J. Thorac. Oncol.* 2017, 12, S1536. [CrossRef]
55. Goss, G.D.; O'Callaghan, C.; Lorimer, I.; Tsao, M.-S.; Masters, G.A.; Jett, J.; Edelman, M.J.; Lilienbaum, R.; Choy, H.; Khuri, F.; et al. Gefitinib versus placebo in completely resected non-small-cell lung cancer: Results of the NCIC CTG BR19 study. *J. Clin. Oncol.* **2013**, *31*, 3320–3326. [CrossRef] [PubMed]

56. Kelly, K.; Altorki, N.K.; Eberhardt, W.E.E.; O'Brien, M.E.R.; Spigel, D.R.; Crino, L.; Tsai, C.-M.; Janjigian, Y.Y.; Cho, E.K.; Hoffman, P.C.; et al. Adjuvant erlotinib versus placebo in patients with stage IB-IIIA non-small-cell lung cancer (RADIANT): A randomized, double-blind, phase III trial. *J. Clin. Oncol.* **2015**, *33*, 4007–4014. [CrossRef] [PubMed]

57. Zhong, W.-Z.; Wang, Q.; Mao, W.-M.; Xu, S.-T.; Wu, L.; Shen, Y.; Liu, Y.-Y.; Chen, C.; Cheng, Y.; Xu, L.; et al. Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II-IIIA (N1–N2) EGFR-mutant NSCLC (ADJUVANT/CTONG1104): A randomised, open-label, phase 3 study. *Lancet Oncol.* **2018**, *19*, 139–148. [CrossRef]

58. Wu, Y.-L.; Herbst, R.S.; Mann, H.; Rukazenkov, Y.; Marotti, M.; Tsuboi, M. ADAURA: Phase III, double-blind, randomized study of osimertinib versus placebo in EGFR mutation-positive early stage NSCLC after complete surgical resection. *Clin. Lung Cancer* **2018**, *19*, e533–e536. [CrossRef] [PubMed]

59. Sequist, L.V.; Watanabe, B.A.; Dias-Santagata, D.; Digumarthy, S.; Turke, A.B.; Fidias, P.; Bergheton, K.; Shaw, A.T.; Gettinger, S.; Casper, A.K.; et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci. Transl. Med.* **2011**, *3*, 75ra26. [CrossRef] [PubMed]

60. Arcila, M.E.; Oxnard, G.R.; Nafa, K.; Riely, G.J.; Solomon, S.B.; Zakowski, M.F.; Kris, M.G.; Pao, W.; Miller, V.A.; Ladanyi, M. Rebiopsy of lung cancer patients with acquired resistance to EGFR inhibitors and enhanced detection of the T790M mutation using a locked nucleic acid-based assay. *Clin. Cancer Res.* **2011**, *17*, 1169–1180. [CrossRef] [PubMed]

61. Yu, H.A.; Arcila, M.E.; Rekhtman, N.; Sima, C.S.; Zakowski, M.F.; Pao, W.; Kris, M.G.; 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] [PubMed]

62. Engelman, J.A.; Zejnullahu, K.; Mitsudomi, T.; Song, Y.; Hyland, C.; Park, J.O.; Lindeman, N.; Gale, C.-M.; Zhao, X.; Christensen, J.; et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science* **2007**, *316*, 1039–1043. [CrossRef] [PubMed]

63. Takezawa, K.; Pirazzoli, V.; Arcila, M.E.; Nebhan, C.A.; Song, X.; de Stanchina, E.; Ohashi, K.; Janjigian, Y.Y.; Spitzler, P.J.; Melnick, M.A.; et al. HER2 amplification: A potential mechanism of acquired resistance to EGFR inhibition in EGFR-mutant lung cancers that lack the second-site EGFR790M mutation. *Cancer Discov.* **2012**, *2*, 922–933. [CrossRef] [PubMed]

64. Zhang, Z.; Lee, J.C.; Lin, L.; Olivas, V.; Au, V.; LaFramboise, T.; Abdel-Rahman, M.; Wang, X.; Levine, A.D.; Rho, J.K.; et al. Activation of the AXL kinase causes resistance to EGFR-targeted therapy in lung cancer. *Nat. Genet.* **2012**, *44*, 852–860. [CrossRef] [PubMed]

65. Soria, J.-C.; Wu, Y.-L.; Nakagawa, K.; Kim, S.-W.; Yang, J.-J.; Ahn, M.-J.; Wang, J.; Yang, J.C.-H.; Lu, Y.; Ataghi, 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]

66. Mok, T.S.K.; Kim, S.-W.; Wu, Y.-L.; Nakagawa, K.; Yang, J.-J.; Ahn, M.-J.; Wang, J.; Yang, J.C.-H.; Lu, Y.; Ataghi, S.; et al. Gefitinib plus chemotherapy versus chemotherapy in epidermal growth factor receptor mutation-positive non-small-cell lung cancer resistant to first-line gefitinib (IMPRESS): Overall survival and biomarker analyses. *J. Clin. Oncol.* **2017**, *35*, 4027–4034. [CrossRef] [PubMed]

67. Pao, W.; Miller, V.A.; Politi, K.A.; Riely, G.J.; Somwar, R.; Zakowski, M.F.; Kris, M.G.; Varmus, H. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. *PloS Med.* **2005**, *2*, e73. [CrossRef] [PubMed]

68. Song, S.; Jacobson, K.N.; McDermott, K.M.; Reddy, S.P.; Cress, A.E.; Tang, H.; Dudek, S.M.; Black, S.M.; Garcia, J.G.N.; Makino, A.; et al. ATP promotes cell survival via regulation of cytosolic [Ca^{2+}] and Bcl-2/Bax ratio in lung cancer cells. *Am. J. Physiol. Cell Physiol.* **2016**, *310*, C99–C114. [CrossRef] [PubMed]

69. Yun, C.-H.; Mengwasser, K.E.; Toms, A.V.; Woo, M.S.; Greulich, H.; Wong, K.-K.; Meyer, 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]
86. Hida, T.; Nokihara, H.; Kondo, M.; Kim, Y.H.; Azuma, K.; Seto, T.; Takiguchi, Y.; Nishio, M.; Yoshioka, H.; Imamura, F.; et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): An open-label, randomised phase 3 trial. *Lancet* 2017, 390, 29–39. [CrossRef]

87. Wu, Y.-L.; Yang, C.-H.; Kim, D.-W.; Lu, S.; Zhou, J.; Seto, T.; Yang, J.-J.; Yamamoto, N.; Ahn, M.-J.; Takahashi, T.; et al. Phase II study of crizotinib in East Asian patients with ROS1-positive advanced non-small cell lung cancer. *J. Clin. Oncol.* 2018, 36, 1405–1411. [CrossRef] [PubMed]

88. Lim, S.M.; Kim, H.R.; Lee, J.-S.; Lee, K.H.; Lee, Y.-G.; Min, Y.J.; Cho, E.K.; Lee, S.S.; Kim, B.-S.; Choi, M.Y.; et al. Open-label, multicentre, phase II study of ceritinib in patients with non-small-cell lung cancer harboring ROS1 rearrangement. *J. Clin. Oncol.* 2017, 35, 2613–2618. [CrossRef] [PubMed]

89. Kodama, T.; Tsukaguchi, T.; Satoh, Y.; Yoshida, M.; Watanabe, Y.; Kondoh, O.; Sakamoto, H. Alectinib shows potent antitumor activity against RET-rearranged non-small cell lung cancer. *Mol. Cancer Ther.* 2014, 13, 2910–2918. [CrossRef] [PubMed]

90. Bos, J.L. Ras oncogenes in human cancer: A review. *Cancer Res.* 1989, 49, 4682–4689. [PubMed]

91. Gainor, J.F.; Varghese, A.M.; Ou, S.-H.I.; Kabraji, S.; Awad, M.M.; Katayama, R.; Pawlak, A.; Mino-Kenudson, M.; Yeap, B.Y.; Riely, G.J.; et al. ALK rearrangements are mutually exclusive with mutations in EGFR or KRAS: An analysis of 1,683 patients with non-small cell lung cancer. *Clin. Cancer Res.* 2013, 19, 4273–4281. [CrossRef] [PubMed]

92. Ahrendt, S.A.; Decker, P.A.; Alawi, E.A.; Zhu, Y.Y.R.; Sanchez-Cespedes, M.; Yang, S.C.; Haasler, G.B.; Kajdacsy-Balla, A.; Demeure, M.J.; Sidransky, D. Cigarette smoking is strongly associated with mutation of the K-ras gene in patients with primary adenocarcinoma of the lung. *Cancer* 2001, 92, 1525–1530. [CrossRef]

93. Jänne, P.A.; van den Heuvel, M.M.; Barlesi, F.; Souquet, P.-J.; Smit, E.F.; Groen, H.J.M.; Kelly, R.J.; et al. ALK rearrangements are mutually exclusive with mutations in EGFR or KRAS: An analysis of 1,683 patients with non-small cell lung cancer. *Clin. Cancer Res.* 2013, 19, 4273–4281. [CrossRef] [PubMed]

94. Blumenschein, G.R.J.; Smit, E.F.; Planchard, D.; Cadranel, J.; De Pas, T.; Dunphy, F.; Udup, K.; Ahn, M.-J.; Hanna, N.H.; et al. A randomized phase II study of the MEK1/MEK2 inhibitor trametinib compared with docetaxel in KRAS-mutant advanced non-small-cell lung cancer. *J. Clin. Oncol.* 2016, 34, 721–730. [CrossRef] [PubMed]

95. Drilon, A.E.; Camidge, D.R.; Ignatius Ou, S.-H.; Hall, D.; Shivdasani, P.; Heng, J.C.; Dahlberg, S.E.; Janne, P.A.; Verma, S.; et al. MET exon 14 mutations in non–small-cell lung cancer are associated with advanced stage and stage-dependent MET genomic amplification and c-Met overexpression. *J. Clin. Oncol.* 2016, 34, 721–730. [CrossRef] [PubMed]

96. Awad, M.M.; Leonardi, G.C.; Kravets, S.; Dahlberg, S.E.; Drilon, A.E.; Noonan, S.; Camidge, D.R.; Ignatius Ou, S.-H.; Botelho, D.; Gadgeel, S.M.; et al. Impact of MET inhibitors on survival among patients (pts) with MET exon 14 mutant (METdel14) non-small cell lung cancer (NSCLC). *J. Clin. Oncol.* 2017, 35, 8511. [CrossRef]

97. Drilon, A.E.; Camidge, D.R.; Ignatius Ou, S.-H.; Clark, J.W.; Socinski, M.A.; Weiss, J.; Riely, G.J.; Winter, M.; Wang, S.C.; Monti, K.; et al. Efficacy and safety of crizotinib in patients (pts) with advanced MET exon 14- altered non-small cell lung cancer (NSCLC). *J. Clin. Oncol.* 2016, 34, 108. [CrossRef]
101. Camidge, D.R.; Ignatius Ou, S.-H.; Shapiro, G.I.; Otterson, G.A.; Villaruz, L.C.; Villalona-Calero, M.A.; Iafrate, A.J.; Varella-Garcia, M.; Dacic, S.; Cardarella, S.; et al. Efficacy and safety of crizotinib in patients with advanced c-MET-amplified non-small cell lung cancer (NSCLC). *J. Clin. Oncol.* 2014, 32, 8001. [CrossRef] [PubMed]

102. Pan, Y.; Zhang, Y.; Li, Y.; Hu, H.; Wang, L.; Li, H.; Wang, R.; Ye, T.; Luo, X.; Zhang, Y.; et al. ALK, ROS1 and RET fusions in 1139 lung adenocarcinomas: A comprehensive study of common and pattern-specific clinicopathologic, histologic and cytologic features. *Lung Cancer* 2014, 84, 121–126. [CrossRef] [PubMed]

103. Lipson, D.; Capelletti, M.; Yelensky, R.; Otto, G.; Parker, A.; Jarosz, M.; Curran, J.A.; Balasubramanian, S.; Bloom, T.; Brennan, K.W.; et al. Identification of new ALK and RET gene fusions from colorectal and lung cancer biopsies. *Nat. Med.* 2012, 18, 382–384. [CrossRef] [PubMed]

104. Drilon, A.; Rekhtman, N.; Arcila, M.; Wang, L.; Ni, A.; Albano, M.; Van Voorthuysen, M.; Somwar, R.; Smith, R.S.; Montecalvo, J.; et al. Cabozantinib in patients with advanced RET-rearranged non-small-cell lung cancer: An open-label, single-centre, phase 2, single-arm trial. *Lancet Oncol.* 2016, 17, 1653–1660. [CrossRef]

105. Lee, S.-H.; Lee, J.-K.; Ahn, M.-J.; Kim, D.-W.; Sun, J.-M.; Keam, B.; Kim, T.M.; Heo, D.S.; Ahn, J.S.; Choi, Y.-L.; et al. Vandetanib in pretreated patients with advanced non-small cell lung cancer-harboring RET rearrangement: A phase II clinical trial. *Ann. Oncol.* 2017, 28, 292–297. [CrossRef] [PubMed]

106. Yoh, K.; Seto, T.; Satouchi, M.; Nishio, M.; Yamamoto, N.; Murakami, H.; Nomura, M.; Matsumoto, S.; Kohno, T.; Tsuta, K.; et al. Vandetanib in patients with previously treated RET-rearranged advanced non-small-cell lung cancer (LURET): An open-label, multicentre phase 2 trial. *Lancet Respir. Med.* 2016, 5, 42–50. [CrossRef] [PubMed]

107. Velcheti, V.; Hida, T.; Reckamp, K.L.; Yang, J.C.; Nokihara, H.; Sachdev, P.; Feit, K.; Kubota, T.; Nakada, T.; Dutucu, C.E.; et al. Phase 2 study of lenvatinib (LN) in patients (Pts) with RET fusion-positive adenocarcinoma of the lung. *Ann. Oncol.* 2016, 27 (Suppl. 6), 1204PD. [CrossRef] [PubMed]

108. Mazieres, J.; Peters, S.; Lepage, B.; Cortot, A.B.; Barlesi, F.; Beau-Faller, M.; Besse, B.; Blons, H.; Mansuet-Lupo, A.; Urban, T.; et al. Lung cancer that harbors an HER2 mutation: Epidemiologic characteristics and therapeutic perspectives. *J. Clin. Oncol.* 2013, 31, 1997–2003. [CrossRef] [PubMed]

109. Arcila, M.E.; Chaft, J.E.; Nafa, K.; Roy-Chowdhuri, S.; Lau, C.; Zaidinski, M.; Zakowski, M.F.; Kris, M.G.; Ladanyi, M. Prevalence, clinicopathologic associations and molecular spectrum of ERBB2 (HER2) tyrosine kinase mutations in lung adenocarcinoma. *Clin. Cancer Res.* 2012, 18, 4910–4918. [CrossRef] [PubMed]

110. Shigematsu, H.; Takahashi, T.; Nomura, M.; Majmudar, K.; Suzuki, M.; Lee, H.; Wistuba, I.I.; Fong, K.M.; Toyooka, S.; Shimizu, N.; et al. Somatic mutations of the HER2 kinase domain in lung adenocarcinomas. *Cancer Res.* 2005, 65, 1642–1646. [CrossRef] [PubMed]

111. Lai, W.-C.V.; Lebas, L.; Milla, J.; Barnes, T.A.; Gautschi, O.; Peters, S.; Ferrara, R.; Ni, A.; Sabari, J.K.; Clarke, S.J.; et al. Afatinib in patients with metastatic HER2-mutant lung cancers: Results from a phase II basket trial. *J. Clin. Oncol.* 2017, 35 (Suppl. 15), 9071. [CrossRef] [PubMed]

112. De Greve, J.; Moran, T.; Graas, M.-P.; Galdermans, D.; Vuylsteke, P.; Canon, J.-L.; Chand, V.K.; Fu, Y.; Massey, D.; Vansteenkiste, J. Phase II study of afatinib, an irreversible ErbB family blocker, in demographically and genotypically defined non-small-cell lung cancer (NSCLC) patients. *J. Clin. Oncol.* 2013, 31 (Suppl. 15), 8063. [CrossRef] [PubMed]

113. Li, B.T.; Shen, R.; Buonocore, D.; Olah, Z.T.; Ni, A.; Ginsberg, M.S.; Ulaner, G.; Weber, W.; Ladanyi, M.; Won, H.H.; et al. Ado-trastuzumab emtansine in patients with HER2 mutant lung cancers: An international multicenter study. *J. Clin. Oncol.* 2017, 35 (Suppl. 15), 9071. [CrossRef] [PubMed]
116. Hotta, K.; Aoe, K.; Kozuki, T.; Ohashi, K.; Ninomiya, K.; Ichihara, E.; Kubo, T.; Ninomiya, T.; Chikamori, K.; Harada, D.; et al. A phase II study of trastuzumab emtansine in HER2-positive non–small cell lung cancer. *J. Thorac. Oncol.* **2018**, *13*, 273–279. [CrossRef] [PubMed]

117. Herbst, R.S.; Davies, A.M.; Natale, R.B.; Dang, T.P.; Schiller, J.H.; Garland, L.L.; Miller, V.A.; Mendelson, D.; Van den Abbeele, A.D.; Melenevsky, Y.; et al. Efficacy and safety of single-agent pertuzumab, a human epidermal receptor dimerization inhibitor, in patients with non–small cell lung cancer. *Clin. Cancer Res.* **2007**, *13*, 6175–6181. [CrossRef] [PubMed]