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REVIEW ARTICLE

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Systemic treatment of *EGFR*-mutated non-small cell lung cancer

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ABSTRACT

Lung cancer, particularly non-small cell lung cancer (NSCLC), remains a significant global health challenge, responsible for a substantial portion of cancer-related deaths. This review focuses on the pivotal role of epidermal growth factor receptor gene (EGFR) mutations in NSCLC, exploring their prevalence, diagnostic methods, and implications for targeted therapy. Common mutations in *EGFR*, constituting approximately 90% of all mutations, are associated with better prognosis and predict favourable response to EGFR tyrosine kinase inhibitors. Meanwhile, the remaining 10–15% comprise atypical mutations, including uncommon exon 18 mutations, exon 20 insertions, de novo T790M mutations, compound mutations, and others. The frequency of uncommon mutations has recently increased, posing challenges due to their largely unknown biological and clinical implications. The review underscores the necessity of summarizing recent scientific discoveries in *EGFR* mutations to enhance our understanding of their diverse nature and optimize targeted therapeutic approaches in NSCLC patients.

Keywords: lung cancer, EGFR, targeted treatment, tyrosine kinase inhibitor, review

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Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide. According to GLOBOCAN, in 2020 lung cancer was diagnosed in 2.2 million people (11.4% of all cancers) and caused 1.8 million deaths (18% of cancer deaths) [1]. Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancer cases. The disease is diagnosed mostly in an advanced stage when treatment cannot be curative. Currently, systemic treatment of NSCLC is based on histological and molecular features. Apart from Kirsten rat sarcoma viral oncogene homolog (*KRAS*) — found in approximately 25% of NSCLC cases — somatic mutations in the epidermal growth factor receptor gene (*EGFR*) are one of the most frequently observed driving mutations in NSCLC (11–14% of patients in Poland) [2]. The common *EGFR* mutations are positive predictive factors for EGFR tyrosine kinase inhibitor (EGFR-TKI) therapy. For several years, such treatment has been the standard of care in patients with incurable locally advanced or metastatic non-squamous NSCLC harboring activating *EGFR* mutations. Improvement in diagnostic tools influenced knowledge about the diversity of *EGFR* mutations and differences in effectiveness of EGFR-TKIs in patients with specific genetic abnormalities. Therefore, it is necessary to summarize recent scientific discoveries in this field.

EGFR mutations

The epidermal growth factor receptor is a member of the human epidermal growth factor receptor (HER) family of transmembrane receptors with tyrosine kinase activity triggered in response to extracellular ligands.

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Its activation initiates complex intracellular cascades that lead to proliferation, activation of neoangiogenesis, dissemination, and inhibition of apoptosis. As a result, EGFR became a target of molecularly-driven therapy.

The epidermal growth factor receptor gene encoding the EGFR receptor is located on the short arm of chromosome 7 (7p11.2) and contains 28 exons. Exons 18–24 encode the tyrosine kinase domain of the receptor. The vast majority of somatic *EGFR* mutations occurring in exons from 18 to 21 are well-established, actionable, oncogenic drivers, as they lead to ligand-independent constitutive activation of EGFR [3, 4]. The frequency of *EGFR* mutations differs depending on ethnicity — they are present in approximately 10% of Caucasian NSCLC cases [5] — mostly in young patients, females, non-smokers, and those with adenocarcinoma. In Asia, the frequency reaches 60% in adenocarcinoma [6]. The *EGFR* mutations are very rare (approximately 1%) in squamous-cell lung cancer; therefore screening for *EGFR* mutations is mostly restricted to patients with non-squamous histology including subtype not otherwise specified (NOS).

Multiple tyrosine kinase inhibitors have been developed to inhibit the activating signal induced by EGFR ligand binding. Originally, TKIs were used regardless of *EGFR* gene status but their activity in unselected patients was disappointing. Soon, activating mutations of *EGFR* were established as the sole predictive factor for TKIs. As EGFR-TKI therapy is the standard of care for NSCLC patients, detection of *EGFR*-activating mutations is obligatory in routine diagnostic procedures. Primarily, uniplex polymerase chain reaction (PCR) was used to amplify the predefined sequence of *EGFR*. Technological advances included genotyping with next-generation sequencing (NGS) and multiplex PCR assays. More sensitive techniques could simultaneously identify not only common but also many uncommon *EGFR* mutations and alterations in other genes [e.g. anaplastic lymphoma kinase (*ALK*), ROS proto-oncogene 1 (*ROS1*)], enabling comprehensive genetic testing. Nowadays, it is known that not only location but also a specific sequence of *EGFR* mutation that entails a change in EGFR structure can influence treatment effectiveness. That is why NGS-based strategies are preferred. Traditionally, *EGFR* mutations are examined in cancer tissue, but they also can be detected in liquid biopsy in blood (for patients unwilling or unable to undergo a tissue biopsy).

Common mutations

Approximately 90% of mutations — called common or classical mutations — are in-frame deletions in exon 19 (del19 — 40–50%) and point mutations in exon 21 leading to substitution of leucine for arginine in position 858 (L858R or sub21 — 30–40%). They lead to a change in EGFR protein, which results in increased catalytic activity. Such variants are predictors of the activity of first, second, and third-generation EGFR-TKIs [7]. Generally, del19 is related to a better prognosis after EGFR-TKI treatment than L858R [8].

Uncommon mutations

About 15% of *EGFR* mutations are termed atypical, uncommon, or rare, and are grouped into five categories:

1) major uncommon mutations — exon 18 G719X (2–3%), exon 20 S768I (1%), and exon 21 L861Q (1–2%);
2) exon 20 insertions (4–12%);
3) *de novo* T790M mutations (< 1–5%);
4) compound mutations;
5) other [3, 9, 10].

The number of known uncommon *EGFR* mutations increased recently and exceeded 600. A majority of uncommon mutations have an unknown biological or clinical role. Dominant locations of atypical mutations are the P-loop (L718-V726) and C-terminal loop of the alpha C-helix (A767-G779); they account for 14% and 29% of atypical mutations, respectively [11].

Exon 20 insertions/duplications (ex20ins), similar to classic *EGFR* mutations, are more frequently found in never-smokers, females, and patients with adenocarcinoma. Although these mutations induce activation of the EGFR pathway, they are structurally and biologically distinct from classic mutations. In most cases, insertions do not affect the ATP-binding site leading to resistance to clinically achievable doses of EGFR-TKIs. Exon 20 mutations, grouped as in-frame insertions or duplications of 3–21 base pairs (1–7 amino acids), are heterogeneous with over 100 variants. About 90% of mutations affect the near-loop region (amino acid position A767-P772) and far-loop region (H773-C775) of the EGFR. The most common one is A767_V769dup [12, 13]. Approximately 10% of ex20ins are in the helix region (E761-M766) — the most common one, A763_Y764insFQEA (5–6% of all ex20ins), leads to structurally different EGFRs resulting in sensitivity to all three generations of EGFR-TKIs.

It is well known that tumors consist of genetically diverse cell populations. Also, in NSCLC with an *EGFR-driving* mutation, other genetic alterations are frequent. There are two sources of heterogeneity: co-occurring *EGFR* mutations (clonal and subclonal) and mutations in other genes [14].

In the Caucasian population, approximately 5–7% of *EGFR*-mutated patients harbor multiple *EGFR* mutations in the same tumor [15]. The rate of different mutations is especially high (30–50%) in cases with uncommon mutations [16–18]. Compound *EGFR*

mutations include the presence of at least two mutations: common plus common (10–20%), common plus uncommon (30–50%), uncommon plus uncommon (25–40%), or a complex mutation with *de novo* ex20 T790M compound (10–50%) [15]. In general, *EGFR* mutations are mutually exclusive to *KRAS* mutations and *ALK* or *ROS1* alterations. However, some cancer cells exhibit co-mutations in other genes. Somatic mutations in *TP53* (55–65%) and *RB1* (10%) occur early during tumor evolution [19]. Other mutations are also common in untreated *EGFR*-mutated patients, e.g. *CTNNB1* (5–10%) and *PI3KCA*/*PTEN* (8–12%) [19, 20]. Some of them (most data describe *TP53* co-mutations) are associated with inferior outcomes and an increased possibility of transformation to small-cell lung cancer (SCLC) [20, 21].

Structure-function classification

A vast majority of cited research used an exon-based classification of *EGFR* mutations. Since this simplistic categorization does not predict drug sensitivity, in 2021 Robichaux et al. [11] proposed structure-function-based classification. It considers spatial alterations in protein structure and accessibility of active areas for drug binding. It is composed of four groups:

1) classical-like mutations [distant from adenosine triphosphate (APT)-binding pocket, e.g. del19, L858R, and L861Q];
2) T790M-like mutations (located in the hydrophobic core);
3) insertions in exon 20 (the loop at the C-terminal end of alphaC-helix);
4) mutations on the interior surface of the ATP-binding pocket or C-terminal end of the alphaC-helix (P-loop and alphaC-helix compressing — PACC, e.g. G719X S768I).

EGFR tyrosine kinase inhibitors

There are three classes of EGFR inhibitors. The first generation involves reversible EGFR (wild-type and mutated) inhibitors: gefitinib, erlotinib, and icotinib (approved in China).

The second generation comprises irreversible inhibitors: afatinib and dacomitinib. These drugs not only covalently bind to the tyrosine kinase domain of EGFR but also to that of other HER family receptors.

The third generation — potent irreversible and brain-penetrant — osimertinib and lazertinib are highly selective for common *EGFR* mutations and T790M resistance mutations. Almonertinib and furmonertinib are registered in China.

Treatment

Early non-small cell lung cancer

Until 2022, there were no data on the effectiveness of EGFR-TKI therapy in improving overall survival (OS) in adjuvant settings.

The randomized phase II EVAN trial showed that two years of adjuvant erlotinib improved 2-year disease-free survival (DFS) compared to chemotherapy (CHT) — 81.4% *vs.* 44.6% [relative risk CHT *vs.* TKI 1.82; 95% confidence interval (CI) 1.19–2.78; p = 0.0054) in Chinese patients (n = 102) with resected stage IIIA *EGFR* mutated NSCLC [22]. Toxicity profile favored EGFR-TKIs. The 5-year survival rates were 84.4% in the TKI group and 51.1% in the CHT group [hazard ratio (HR) = 0.37; 95% CI 0.19–0.73; p = 0.003) [23]. Median OS reached 84.2 months and 61.1 months, respectively (HR = 0.32; 95% CI 0.15–0.67).

Six months of gefitinib after adjuvant CHT in stage III-N2 *EGFR* mutated NSCLC also improved DFS compared to CHT only, in a small (n = 60) phase II trial (HR = 0.37; 95% CI 0.16–0.85; p = 0.014) conducted in China [24]. The rates of 2-year DFS were 78.9% *vs.* 54.2%, respectively. However, the difference in OS was nonsignificant.

Two years of postoperative gefitinib in stage II–IIIA NSCLC with *EGFR* common mutations also resulted in a significantly reduced risk of recurrence or death compared to conventional CHT in phase III ADJUVANT-CTONG 1104 trial. Median DFS was 28.7 months for targeted therapy and 18 months for CHT (HR = 0.60; 95% CI 0.42–0.87; p = 0.0054) [25]. Interestingly, improvement in DFS did not entail an increase in OS. After a median follow-up of 80 months, despite the numerical advantage, there was no statistically significant difference in median OS — 75.5 months *vs.* 62.8 months (HR = 0.91; 95% CI 0.62–1.36; p = 0.674) [26].

Similarly, another phase III trial (IMPACT) with a similar design showed no improvement with adjuvant gefitinib, either in terms of DFS (HR = 0.92; 95% CI 0.67–1.28; p = 0.63) or OS (HR = 1.03; 95% CI 0.65–1.65; p = 0.89) [27]. The reason for the difference in DFS results between those trials is unknown.

The main objective of the phase III ADAURA study was to evaluate DFS improvement with osimertinib given for 3 years as adjuvant treatment in completely resected stage II–IIIA NSCLC that harbors del19 or L858R *EGFR* mutations (alone or in combination with another *EGFR* mutation). The secondary endpoints included DFS in patients with stage IB–IIIA and OS [28]. The study involved patients regardless of whether they received postoperative CHT or not. After approximately 2 years, the study was unblinded, and the results of the interim analysis were published. Among patients

with stage II–IIIA NSCLC who were treated with osimertinib, 90% have not experienced disease recurrence or death. In the placebo group, 2-year DFS reached 44% with a median of 19.6 months (HR = 0.17; 99.06% CI 0.11–0.26; p < 0.001). In the overall population (stage IB–IIIA), the results were similar — 2-year DFS was 89% in the osimertinib group and 52% in the control group (HR = 0.20; 99.12% CI 0.14–0.30; p < 0.001). The benefit was seen consistently across subgroups irrespective of stages (stage I — HR = 0.39, stage II — HR = 0.17, stage IIIA — HR = 0.12) and previous adjuvant CHT (HR = 0.16 for those who received CHT and HR = 0.23 for those who had not). Also, a significant reduction in the risk of central nervous system (CNS) relapse or death was observed in patients treated with osimertinib. The percentage of patients who lived without CNS relapse reached 98% in the osimertinib group compared to 85% in the placebo group (HR = 0.18). In updated analysis of the primary endpoint, median DFS was longer for osimertinib than for placebo (65.8 *vs.* 21.9 months), which corresponded with a 77% reduction in the risk of disease recurrence or death (95% CI 0.18–0.30) [29]. Results of the final OS analysis were published in 2023. Among patients with stage II to IIIA adjuvant osimertinib provided a benefit in the 5-year OS rate (85% in the osimertinib arm and 73% in the control arm — 0.49; 95.03% CI 0.33–0.73; p < 0.001). Similar results were observed in the overall population — 5-year OS rates were 88% *vs.* 78%, respectively (HR = 0.49; 95.03% CI 0.34–0.7; p < 0.001) [30]. The results were consistent with the stage and use of adjuvant chemotherapy.

Advanced non-small cell lung cancer — common mutations (del19, L858R)

Tyrosine kinase inhibitor monotherapy — first-generation tyrosine kinase inhibitors

For a long time, first-generation EGFR-TKIs were well-established first-line standard treatment in NSCLC patients with common *EGFR* mutations. They demonstrated longer progression-free survival (PFS) and higher objective response rate (ORR) compared to standard platinum-based CHT in multiple phase III trials. The safety profile and quality of life favored TKI therapy over CHT. However, improvement in OS has not been shown probably due to the design of trials that allowed crossover (with rates exceeding 65% in most trials) [31, 32].

Tyrosine kinase inhibitor monotherapy — second-generation tyrosine kinase inhibitors

Afatinib is the only EGFR-TKI, with some data suggesting a possible improvement in OS over first-line CHT in patients with del19. Despite no impact on OS shown in two phase III trials, in preplanned analyses of LUX-LUNG 3 and LUX-LUNG 6 (both with crossover) that were conducted in NSCLC patients with *EGFR* mutation, OS seemed to be longer in patients with del19 (HR — 0.4–0.64), but, on the other hand, it seemed to be worse in those with L858R (HR — 1.22–1.3), so this suggestion should be interpreted with great caution [8].

Although afatinib showed superiority over gefitinib in PFS in the phase III LUX-LUNG 7 trial (median PFS 11 months for second-generation and 10.9 months for first-generation TKIs; HR = 0.73; p = 0.017) the difference in OS, which was a co-primary endpoint, was not statistically significant (median OS 27.9 months for afatinib and 24.5 months for gefitinib; HR = 0.86; 95% CI 0.66–1.22) [33].

In the phase III ARCHER-1050 study, dacomitinib was compared with gefitinib. Again, second-generation TKIs demonstrated higher effectiveness than first-generation TKIs — median PFS reached 14.7 months for dacomitinib and 9.2 months for gefitinib (HR = 0.59; 95% CI 0.47–0.74; p < 0.001). However, there was no difference in ORR (75% and 72%, respectively). Due to the statistical design of the trial, negative ORR results did not allow for formal testing of OS data. Median OS in the dacomitinib arm was 34.1 months compared with 26.8 months in the gefitinib arm (HR = 0.76; 95% CI 0.59–0.94; nominal p = 0.044). Dacomitinib was more toxic than gefitinib [34, 35].

Tyrosine kinase inhibitor monotherapy — third-generation tyrosine kinase inhibitors

In the FLAURA trial, osimertinib was compared with first-generation EGFR-TKIs in patients with common *EGFR* mutations. The trial allowed crossover to osimertinib after erlotinib or gefitinib failure if *EGFR* exon 20 T790M resistance mutation was detected. The primary endpoint — PFS — was improved in the osimertinib arm compared to the control arm (median 18.9 *vs.* 10.2 months; HR = 0.46; 95% CI 0.37–0.57; p < 0.001) [36]. Objective response rates were similar in both arms (80% *vs.* 76%; p = 0.24). However, OS was marginally improved by osimertinib (median OS 38.6 *vs.* 31.8 months; HR = 0.80; 95.05% CI 0.64–1.0; p = 0.046) [37]. A subgroup analysis suggested that the OS improvement was observed mainly in non-Asians (HR = 0.54; 95% CI 0.38–0.77) and in those with exon 19 deletion (HR = 0.68; 95% CI 0.51–0.9). There was no clear benefit from osimertinib either in Asians (HR = 1.0; 95% CI 0.75–1.32) or in patients with exon 21 L858R mutations (HR = 1.0; 95% CI 0.71–1.4). The safety profile of the third-generation EGFR-TKIs was better than that of erlotinib/gefitinib (grade ≥ 3 adverse events 34% *vs.* 45%).

There are no data to show higher effectiveness of osimertinib over second-generation TKIs. A retrospective analysis conducted in Japan (n = 554) suggested higher efficacy of afatinib compared to osimertinib in analysis of OS adjusted by the propensity score (median 36.2 *vs.* 25.1 months; HR = 1.47; 95% CI 1.07–2.02; p = 0.018), but no significant difference was observed in the primary endpoint, time to discontinuation of any TKI (HR = 1.146; 95% CI 0.93–1.41). In a subgroup analysis, afatinib showed a trend towards longer OS compared to osimertinib in patients with L858R mutation; conversely, in patients with brain metastases, osimertinib was the preferred drug [38].

A pooled retrospective analysis of LUX-Lung 3, 6, and 7 trials demonstrated that median OS was not reached after 4.7 years of follow-up in patients treated with sequential afatinib and osimertinib [39]. Additionally, the median time on osimertinib in any treatment line was 20.2 months, which was similar to this observed in the FLAURA trial. In the global (68% of patients declaring non-Asian ethnicity) Gio-Tag retrospective study in 204 patients treated in the first line with afatinib followed by osimertinib (with proven T790M acquired resistance mutation) such sequential strategy was found to be attractive. The median time to treatment failure (TTF) with afatinib in the first and osimertinib in the second line was 28.1 months. Median OS reached 41.3 months, and the 2-year OS rate was 80%. The results were even better in patients with del19 (median TTF 30.6 months, median OS 45.7 months) [40].

The limitation of the two aforementioned analyses is the absence of patients without acquired T790M mutation or individuals who did not receive a second line of treatment.

Lazertinib — another third-generation EGFR-TKI — was compared with gefitinib in the phase III LASER301 trial that included 393 patients with previously untreated *EGFR*-mutated advanced NSCLC [41]. Only del19 or L858R mutations were allowed. PFS (primary endpoint) was significantly longer (median 20.6 months) in the lazertinib group than in the control group (median 9.7 months; HR = 0.45; 95% CI 0.34–0.58; p < 0.001). Objective response rates were similar in both groups and reached 76%. Also, 18-month OS rates did not differ significantly (80% *vs.* 72%; HR = 0.74; 95% CI 0.51–1.08; p = 0.116), but these data were immature. Adverse events were reported with similar frequency in both arms.

In the phase III MARIPOSA trial lazertinib in combination with amivantamab — bispecific anti-EGFR and anti-MET antibody (arm A) — was compared with osimertinib monotherapy (arm B) in first-line treatment of *EGFR* mutated (del19/L858R) NSCLC. There was also arm C with lazertinib monotherapy; however, these results have not been reported yet. The primary and secondary endpoint results were shown at the European Society for Medical Oncology (ESMO) congress in 2023 [42]. The median PFS rate, the primary endpoint, was 23.7 months in arm A and 16.6 in arm B (HR = 0.70; 95% CI 0.58–0.85; p < 0.001). There was no difference in ORR (86% and 85%, respectively). Interim OS results revealed no difference — HR = 0.70; 95% CI 0.61–1.05; p = 0.11. Experimental treatment resulted in higher toxicity — the rate of grade 3–5 adverse effects was 75% and 43%, respectively.

Almonertinib and furmonertinib improved PFS compared to gefitinib only in trials conducted in China [43, 44].

Tyrosine kinase inhibitors combined with antiangiogenic agents

Several studies, mostly conducted in Asia (Tab. 1), yielded similar results. A combination of a first-generation EGFR-TKI with an antiangiogenic agent improved PFS (HR 0.54–0.6) but not OS, with the possible exception of the RELAY trial as its final OS data have not been published yet [45–47]. The toxicity of such therapy was higher than monotherapy with EGFR-TKIs. Nevertheless, the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) approved the combination of bevacizumab or ramucirumab with EGFR-TKIs as an option in the first-line treatment for NSCLC with activating *EGFR* mutations. On the other hand, such a strategy was not effective when osimertinib (in the first or second line) or afatinib were combined with bevacizumab [48–50].

A meta-analysis of 12 phase II and III randomized trials suggested that addition of an antiangiogenic drug to the first-generation EGFR-TKI might serve as an alternative to osimertinib [51]. In an indirect comparison, there were no differences between the efficacy of these strategies in men, ever-smokers, or patients with L858R mutation. Conversely, osimertinib was superior in females, never-smokers, patients with ex19del, and those with metastases to the central nervous system (CNS).

Tyrosine kinase inhibitors combined with chemotherapy

Historically, the combination of EGFR-TKIs and CHT has shown greater effectiveness than CHT alone in *EGFR*-mutated NSCLC. In the *EGFR*-positive subpopulation of the randomized phase III FASTACT-2 trial conducted in Asia, erlotinib added to a platinum doublet with gemcitabine improved PFS (median 16.8 *vs.* 6.9 months; HR = 0.25, 95% CI 0.16–0.39; p < 0.001) and OS (median 31.4 *vs.* 20.6 months; HR = 0.48; 95% CI 0.27–0.84; p = 0.009) compared to CHT alone, without compromising tolerance [52]. Data from two phase III trials (conducted in Japan and India) evaluated effectiveness of gefitinib and platinum-based

Table 1. Main results of clinical trials that compared combination strategies [EGFR tyrosine kinase inhibitors (EGFR-TKIs) + antiangiogenic agent/ chemotherapy (CHT)] to EGFR-TKI monotherapy

Experimental arm	Study/phase	PFS — HR (median PFS)	OS — HR (median OS)
Erlotinib + ramucirumab	RELAY/III	0.59 (19.4 *vs.* 12.4 mo)	ND
Erlotinib + bevacizumab	NEJ026/III	0.60 (16.9 *vs.* 13.3 mo)	1.0 (NS)
	BEVERLY/III	0.6 (15.4 *vs.* 9.7 mo)	0.7 (NS)
	ARTEMIS – CTONG1509/III	0.55 (17.9 *vs.* 11.2 mo)	0.92 (NS)
Afatinib + bevacizumab	AfaBev-CS/II	0.87 (NS)	ND
Osimertinib + bevacizumab	WJOG9717L/II	0.86 (NS)	0.97 (NS)
	BOOSTER/II	0.96 (NS)	1.03 (NS)
Gefitinib + platinum-based CHT	NEJ009/III	0.49 (20.9 *vs.* 11.2 mo)	0.72 (50.9 *vs.* 38.8 mo)
	CTRI/2016/08/007149/III	0.51 (16 *vs.* 8 mo)	0.45 (NR *vs.* 17 mo)
Osimertinib + platinum-based CHT	FLAURA2/III	0.62 (25.5 *vs.* 16.7 mo)	ND

HR — hazard ratio; mo — months; ND — no data; NS — not significant; OS — overall survival; PFS — progression-free survival

CHT as a first-line treatment for NSCLC with activating *EGFR* mutations. Both studies showed better efficacy of the combination of EGFR-TKI with CHT compared to gefitinib in terms of PFS and OS (Tab. 1). However, in an update of the NEJ009 trial, a numerical improvement in OS was reported, but it lost its significance (primary p-value 0.021, updated 0.13) [53, 54]. Combined treatment induces higher toxicity than TKI monotherapy.

Wang et al. [55] published a meta-analysis of phase II and phase III trials. The authors found a positive impact of gefitinib and CHT combination on OS (HR = 0.57; 95% CI 0.37–0.89), PFS (HR = 0.52; 95% CI 0.39–0.70), and ORR [odds ratio (OR) = 1.91; 95% CI 1.44–2.55], albeit with higher toxicity [55]. The OS benefit was not observed in patients with common mutations.

The FLAURA2 study investigated a combination of osimertinib and platinum-based CHT in *EGFR*-mutated (del19/L858R) NSCLC [56]. The combination of osimertinib with CHT showed a significant benefit in PFS over osimertinib alone (HR = 0.62; 95% CI 0.49–0.79; $p < 0.0001$). Similar results were observed in patients with brain metastases — median PFS was 24.9 months in the combination arm *vs.* 13.8 months in the TKI monotherapy arm. Overall survival data were not mature. As anticipated, adverse events were more common and severe in the combination group.

Tyrosine kinase inhibitors combined with immunotherapy

The effectiveness of EGFR-TKI combination with immune checkpoint inhibitors has not been reported yet. Some early trials showed high toxicity rates [57–60], others demonstrated an acceptable safety profile with promising efficacy [61]. Unfortunately, a phase III trial — CAURAL — was stopped due to safety concerns.

Next lines of treatment

After first- or second-generation tyrosine kinase inhibitors

Even though many patients respond to first- or second-generation EGFR-TKIs, the majority have disease progression because of acquired resistance. In approximately 60% of cases, resistance is mediated by T790M mutation in position 790 in exon 20 *EGFR* resulting in substitution of threonine with methionine [62]. Other resistance mechanisms consist of hepatocyte growth factor receptor (*MET*) gene amplification (5%), human epidermal growth factor receptor-2 (*HER2*) amplification (5–10%), histological transformation to small-cell lung cancer (2–10%), epithelial-mesenchymal transition (EMT) (2–10%), *BRAF* mutations (1%), and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) mutations or amplifications (2%) [45, 63].

Osimertinib was designed to be active against the T790M mutation. In a phase III AURA3 study, osimertinib was compared with platinum-based CHT in patients who progressed on first-line EGFR-TKI (94% erlotinib or gefitinib, 4% afatinib) with confirmed T790M mutation evaluated in tumor sample or circulating tumor DNA (ctDNA). The trial allowed crossover. Those who developed disease progression during CHT could receive osimertinib. Osimertinib improved PFS (primary endpoint) compared to CHT — median 10.1 *vs.* 4.4 months (HR = 0.30; 95% CI 0.23–0.41; $p < 0.001$). In patients with CNS metastases, the effect was even better (HR = 0.32; 95% CI 0.21–0.49). There was no difference in OS — the median reached 26.8 months in the osimertinib arm and 22.5 months in the CHT arm (HR = 0.87; 95% CI 0.67–1.12). In additional analysis, corrected for crossover effect, osimertinib

appeared to be more effective (median OS 26.8 months) than CHT alone (15.9 months) (HR = 0.54). The response rate was higher with osimertinib (71%) than with CHT (31%) (OR = 5.39; p < 0.001). Safety profile favored TKIs, with 9% of grade 3 adverse events compared to 34% in the CHT arm [64].

In patients without T790M substitution, second-line treatment with platinum-based CHT is recommended. Continuation of the TKI with the addition of CHT was less effective than CHT alone in the unselected population of the IMPRESS trial (HR for OS = 1.44; 95% CI 1.07–1.94; p = 0.016) [34]. In a subgroup of patients with T790M, HR for OS = 1.15 (95% CI 0.68–1.94). Second-line therapy with the third-generation EGFR-TKI — osimertinib — resulted in an ORR of 28%, with median PFS reaching 5.1 months and median OS 13.4 months in the single-arm phase II trial TREM [65].

Post-osimertinib treatment

Until 2023, the standard of care for patients who progressed on osimertinib or first/second generation TKIs and who were negative for T790M mutation was platinum-based CHT. Continuation of osimertinib with addition of immunotherapy failed to improve survival but increased toxicity [66].

Lazertinib plus amivantamab

A combination of lazertinib with amivantamab showed encouraging efficacy in the phase I CHYSALIS study. Of 45 patients who relapsed after osimertinib and had not received CHT (cohort E) 36% had ORR, but median PFS was only 4.9 months [67]. In updated results from Cohort A of the CHRYSALIS-2 trial that enrolled patients who progressed on osimertinib and platinum-based CHT (n = 50) combination of lazertinib with amivantamab resulted in similar results (ORR = 36%) [68]. In the phase III MARIPOSA-2 study, 657 patients who progressed on osimertinib received a combination of amivantamab and lazertinib with CHT (carboplatin plus pemetrexed), a combination of amivantamab and CHT or CHT alone in a 2:2:1 ratio [69]. There were two primary endpoints evaluating PFS in both experimental arms versus the CHT arm. Primary results were published in 2024. The combination of amivantamab with lazertinib and CHT remarkably improved PFS compared to the control arm — median PFS was 8.3 months *vs.* 4.2 months (HR = 0.44; 95% CI 0.35–0.56; p < 0.001). Similarly, the amivantamab and CHT treatment arms showed improved PFS (median 6.3 months) compared to CHT alone (HR = 0.48; 95% CI 0.36–0.64; p < 0.001). The ORRs were higher (p < 0.001 for both comparisons) in both experimental arms (63% for amivantamab–lazertinib–CHT and 64% for amivantamab–CHT) than in the CHT alone arm (36%). Interim OS analysis failed to reveal statistically significant differences. Moreover, the toxicity of the combined therapy was very high — in the amivantamab plus lazertinib plus CHT arm, grade 3–5 toxic events were reported in 92% of patients, serious adverse events in 52%; 35% of patients discontinued at least one of the drugs.

Immunotherapy

Single-agent immunotherapy is not effective in *EGFR*-mutated NSCLC, even in further lines of treatment. In a meta-analysis of trials comparing immune checkpoint inhibitors (ICIs) with docetaxel (OAK, CheckMate 057, KEYNOTE 010, POPLAR; n = 38) in NSCLC patients pretreated with platinum-based CHT, there was no improvement in OS (HR = 1.11; 95% CI 0.8–1.53) [70]. Thus, single-agent ICI can be considered only in patients with no other treatment options available.

The combination of pembrolizumab and platinum-based CHT (KEYNOTE-789 phase III trial) in patients pretreated with EGFR-TKI was not superior to CHT alone — HR for PFS = 0.8 (95% CI 0.65–0.97); HR for OS = 0.84 (95% CI 0.69–1.02) [71]. In another phase III trial, nivolumab combined with CHT in patients who progressed after 1–2 lines of EGFR-TKIs failed to improve PFS (HR = 0.75; 99.5% CI 0.56–1.0) or OS (HR = 0.82; 99.5% CI 0.61–1.1) compared with CHT [72]. In a phase II trial, the combination of toripalimab (anti-PD-1 antibody) with CHT in patients who failed EGFR-TKI treatment resulted in an ORR of 50%, median PFS of 7 months, and median OS of 23.5 months [73].

The combination of ICIs with antiangiogenic agents and CHT after progression on TKIs has been a matter of debate since the exploratory analysis of the IMPOWER-150 trial was published. In a population of patients with sensitizing *EGFR* mutations, combination therapy with atezolizumab, bevacizumab, and CHT (ABCP, n = 26) showed encouraging improvement in OS compared to the bevacizumab and CHT arms (BCP, n = 32) — median OS 29.4 months *vs.* 18.1 months (HR = 0.60; 95% CI 0.31–1.14), respectively. In those who received previous EGFR-TKI therapy, the results were similar — median OS 27.8 months in the ABCP arm (n = 22) and 18.1 months in the BCP arm (n = 28) (HR = 0.74; 95% CI 0.38–1.46). There were no differences in OS between the atezolizumab with CHT (ACP) and BCP arms (HR = 1.0 in all patients with sensitizing mutation and 1.01 in EGFR-TKI pretreated) [74]. Although the study was not powered to evaluate the effectiveness of ABCP combination in the subgroup of patients with *EGFR* mutations, it resulted in the EMA registration of atezolizumab with bevacizumab and platinum-based combination in EGFR-TKI pretreated patients.

The first phase III study that documented improved effectiveness of the combination of an ICI with an antiangiogenic agent and CHT compared to CHT alone

was the ORIENT-31 trial [75]. The therapy with sintilimab (anti-PD-1 antibody) and IBI305 (bevacizumab biosimilar) plus CHT showed PFS and ORR benefits compared to CHT alone. Median PFS was 6.9 months in the combination arm and 4.3 months (HR = 0.75; 95% CI 0.337–0.639; p < 0.0001) in the CHT alone arm. The ORR rates were 44% and 25%, respectively. Additionally, the combination of sintilimab with CHT improved PFS compared to CHT alone (HR = 0.72; 95% CI 0.55–0.94; p = 0.016). Median PFS was 5.5 months for the combination arm and 4.5 months for the CHT alone arm. No significant differences in OS were observed — median OS was 21.1 months for sintilimab plus IBI305 plus CHT (crossover adjusted HR = 0.97), 20.5 months for sintilimab plus CHT (crossover adjusted HR = 0.98), and 19.2 months for CHT alone [76].

Uncommon mutations

Major uncommon mutations (exon 8 G719X, exon 20 S768I, exon 21 L861Q)

The efficacy of EGFR-TKIs in patients with uncommon mutations is unclear. A retrospective analysis showed that in first-line treatment TKIs are more effective than CHT (PFS HR = 0.53; 95% CI 0.30–0.93; p = 0.028) [17].

In general, first-generation EGFR-TKIs are less effective in tumors with G719X, S768I, or L861Q mutations than in tumors with common mutations. Data from post-hoc analysis of the NEJ002 trial showed 20% ORR with gefitinib therapy in patients with rare mutations (G719X or L861Q) in comparison with 76% in individuals with common mutations (p = 0.017). Median PFS was 2.2 months and 11.4 months, respectively [77]. Additionally, OS was shorter — median OS reached 12 months in those with uncommon *EGFR* mutations *vs.* 28.4 months in those with common *EGFR* mutations. Similar results were reported in a prospective study conducted in Taiwan involving a population of 161 patients with major uncommon *EGFR* mutations. Patients were treated with erlotinib or gefitinib, and ORR was lower than in the control group of patients with common *EGFR* mutations (42% *vs.* 67%; p < 0.001). Consequently, median PFS (7.7 *vs.* 11.4 months respectively; p < 0.001) and OS (in first-line 24 *vs.* 29.7 months; p < 0.001) were decreased [78]. There were non-significant differences in PFS between patients with G719X or L861Q mutations. In the COSMIC database, ORR on first-generation TKIs ranged from 32 to 42% [79].

In a post-hoc analysis of LUX-Lung 2, 3, and 6 trials, patients with rare *EGFR* mutations achieved ORR of 71% on treatment with afatinib. Median PFS and OS reached 10.7 months, and 19.4 months, respectively [8]. Similar results were obtained in an aggregated analysis of 305 patients treated with afatinib — ORR ranged from 58 to 71%, median TTF from 11 to 16 months [16].

In a phase II study conducted in Korea treatment with osimertinib resulted in an ORR of 50% in 36 patients with rare mutations, median PFS of 8.2 months, and a median duration of response (DOR) of 11.2 months [80]. The results were confirmed in a prospective phase II trial performed in the USA (n = 17) — ORR of 47%, median PFS 10.5 months, and median OS 13.8 months [81]. In the retrospective UNICORN analysis of 44 cases with solitary rare mutation (mixed mutations were excluded), ORR on first-line therapy with a third-generation TKI was 60% and median PFS was 8.6 months [18]. The largest retrospective review of osimertinib effectiveness in this group of patients was published by Ji J et al. [20]. Fifty patients with at least one atypical mutation, excluding concurrent common mutations or T790M, treated with osimertinib in the USA were identified. Twenty patients received TKI in the first line — after exclusion of patients with ex20ins, ORR reached 47% and the median time to treatment discontinuation (TTD) was 14.2 months [20].

It is still uncertain which EGFR-TKI demonstrates higher effectiveness in selected uncommon mutations. Preclinical data are inconsistent — on the one hand, patients with L861Q seem to respond similarly to TKI as del19/L858R, on the other G719X seems to be related to inferior outcomes to osimertinib compared to afatinib (Tab. 2 and 3). This phenomenon could be explained by the structural subgroups classification proposed by Robichaux et al. [11].

Exon 20 insertions (ex20ins)

Due to the heterogeneity of ex20ins and diverse functional effects, it is impossible to provide simple recommendations for the entire group. First- and second-generation EGFR-TKIs are widely considered ineffective in most patients with ex20ins — ORRs drop below 27% and median PFS is 1–4 months. Interestingly, in unselected patients with exon 20 insertions, regular dose osimertinib (80 mg daily) failed to show effectiveness [82]. An increased dose (160 mg/day) slightly improved ORR to 25-28% and median PFS to 7–10 months [83, 84]. However, some insertions (A763, M766, N771, and V769) showed sensitivity to afatinib with an ORR > 50% and the median TTF from 8 to 39 months [16]. Specific ex20ins (p.A763_Y764insFQEA) that accounts for 5–6% of all ex20ins — is associated with sensitivity to all generations of EGFR-TKIs.

Because of the limited activity of TKIs in patients with ex20ins, platinum-based chemotherapy is the current standard of care in the first-line treatment with 19–44% of ORR and median PFS of 6.4–7.1 months in retrospective studies [85–87]. The role of ICIs added to

Table 2. Efficacy of tyrosine kinase inhibitors (TKIs) in first-line setting in TKI-naive patients with G719X mutation

G719X	Yang et al. [16] (afatinib) n = 194	Villaruz et al. [81] (osimertinib) n = 7	Bar et al. [18] (osimertinib) n = 16	Ji et al. [20] (osimertinib) n = 4
ORR	61%	43%	53%	33%
Outcome, median	TTF 14.2 mo	PFS 5.6 mo	PFS 8.6 mo	TTD 5.8 mo

mo — months; ORR — objective response rate; PFS — progression-free survival; TTD — time to treatment discontinuation; TTF — time to treatment failure

Table 3. Efficacy of tyrosine kinase inhibitors (TKIs) in first-line setting in TKI-naive patients with L861Q mutation

L861Q	Yang et al. [16] (afatinib) n = 109	Villaruz et al. [81] (osimertinib) n = 6	Bar et al. [18] (osimertinib) n = 11	Ji et al. [20] (osimertinib) n = 10
ORR	58%	50%	78%	40%
Outcome, median	TTF 11.5 mo.	PFS 10.5 mo	PFS 15.7 mo	TTD 19.3 mo

mo — months; ORR — objective response rate; PFS — progression-free survival; TTD — time to treatment discontinuation; TTF — time to treatment failure

CHT or used in monotherapy is uncertain — in small groups of patients with ex20ins, ICIs seem to be more effective than in classic *EGFR* mutations [88].

Novel treatment options in patients with ex20ins

Both the FDA and EMA approved amivantamab for the treatment of patients with ex20ins after CHT failure. In a subgroup of 81 patients from the multicohort phase I/II CHYSALIS trial, ORR reached 40% with median PFS of 8.3 months [89].

The combination of amivantamab and CHT was compared with CHT in the first-line treatment in the phase III PAPILLON study. The primary results were presented at the ESMO congress in 2023. Median PFS was prolonged in the combination arm (11.4 months) compared to CHT alone (6.7 months) with a 60% reduction in the relative risk of progression or death (HR = 0.395; 95% CI 0.30–0.53; $p < 0.0001$) [90]. Objective responses were also more common in the combination arm — 73% *vs.* 47%, respectively (OR = 3.0; $p < 0.0001$). An interim analysis failed to show OS improvement but the rate of crossover to amivantamab after CHT failure was high (66%).

Mobocertinib is a selective TKI targeting *EGFR* ex20ins that was temporarily approved by the FDA as a second-line treatment following platinum-based CHT. In a pooled analysis of 114 patients in the EXCLAIM phase I/II study, ORR reached 28%, and median PFS was 7.3 months [91]. In October 2023, mobocertinib lost FDA approval due to the failure of the EXLAIM-2 trial to reach pre-specified endpoints. Takeda published information that the trial comparing mobocertinib with CHT in the first-line setting first-line had been discontinued.

Other promising TKIs tested in early-phase trials are:
- poziotinib — pan-HER TKI — ORR = 32% [92];
- sunvozertinib — selective irreversible EGFR ex20ins TKI — ORR = 39% [93];
- TAS6417/CLN-081 — irreversible EGFR-TKI — ORR = 38% [94].

De novo T790M

As mentioned earlier, osimertinib was designed to be active against sensitive *EGFR* mutations and T790M resistance mutations. Additionally, it has shown activity in tumors with *de novo* T790M mutations. In a retrospective analysis of 9 patients, an objective response was observed in 4 of them, and median PFS was 12.7 months [18]. On the other hand, afatinib appeared to be less effective, providing unsatisfactory ORR ranging from 9 to 24% [8, 18, 59].

Compound mutations

Data regarding the effectiveness of EGFR-TKIs in patients with compound/complex *EGFR* mutations are limited and mostly based on retrospective analyses. Although *in vitro* studies showed reduced activity of first-generation EGFR-TKIs, it can be concluded that individuals with complex mutations, involving at least two common mutations or a combination of common and uncommon mutations, exhibit similar results with EGFR-TKIs as patients with single del19/L858R mutations [15, 17, 18]. Generally, EGFR-TKI therapy is more effective in compound mutations, when at least one variant is common, compared to complex uncommon mutations [18]. A subgroup with at least two uncommon mutations should be treated with second or third-generation TKIs, as the response rates were

higher than with first-generation TKIs [59, 95, 96]. Patients with complex mutations including *de novo* T790M would not obtain benefit from first- or second-generation TKIs; however, osimertinib seemed to maintain its activity [18].

Other uncommon mutations

Available clinical data suggest that first-generation TKIs are ineffective in patients harboring other uncommon mutations. However, ORR was observed in 64% of patients with E709X or L747X mutations treated with afatinib, with a median TTF of 11 months [16].

Conclusions

Tyrosine kinase inhibitors became the standard of care in *EGFR*-mutated NSCLC. However, this clinical utilization cannot be simplified due to heterogeneity of *EGFR* mutations. Research and ongoing clinical trials are crucial for gaining a better understanding of the effectiveness of different TKIs in the context of uncommon *EGFR* mutations and TKI treatment resistance. However, due to the rarity of such variants large randomized trials might be difficult to conduct. Personalized medicine approaches, incorporating molecular profiling and targeted therapies based on the specific mutation profile of each patient, are increasingly being explored and address these challenges to some extent. Medical oncologists should stay updated on the latest research findings and clinical guidelines to make informed decisions about the treatment of patients with uncommon *EGFR* mutations.

Article Information and Declarations

Author contributions

R.Ł.C: conceptualization, writing — original draft; E.K.W., A.T., A.M.H.: writing — review and editing; P.J.P: conceptualization, writing — original draft and review, supervision.

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Conflict of interest

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Supplementary material

Recent research reports — 14.06.2024.

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Supplementary material

Recent research reports — 14.06.2024

A post-hoc subgroup analysis of the PACIFIC trial suggested that durvalumab following chemoradiotherapy did not improve progression-free survival (PFS) [hazard ratio (HR) = 0.91; 95% confidence interval (CI) 0.39–2.13] or overall survival (OS) (HR = 1.02; 95% CI 0.39–2.63) in patients with *EGFR* mutations [1]. In a prospective phase III LAURA trial, osimertinib or placebo was used as a maintenance treatment until disease progression in 216 patients with unresectable stage III *EGFR* mutated (*del19* or *L858R)* non-small cell lung cancer (NSCLC) without progression during or after chemoradiotherapy. The protocol allowed crossover to osimertinib in patients who received placebo and experienced disease progression. The first data from the LAURA trial were presented in June 2024 during the American Society of Clinical Oncology meeting and simultaneously published in the *New England Journal of Medicine*. The primary endpoint, PFS, was met — osimertinib demonstrated statistically significant improvement compared to placebo. Median PFS was 39.1 months with osimertinib and 5.6 with placebo (HR = 0.16; 95% CI 0.1–0.24; $p < 0.001$) [2]. Overall survival data were not mature. Anti-EGFR treatment was related to higher rates of adverse events (AE) of grade 3 or higher — 35% with osimertinib and 12% with placebo. The most common AE was radiation pneumonitis — reported in 48% (46% G1–2) of patients exposed to osimertinib and 38% (all G1–2) of those receiving placebo.

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