Sains Malaysiana 54(8)(2025): 2021-2032
http://doi.org/10.17576/jsm-2025-5408-12

EGFR-Directed Tyrosine Kinase Inhibitors for Non-Small Cell Lung Cancer

(Perencat Tirosina Kinase EGFR Terarah untuk Kanser Paru-paru Bukan Sel Kecil)

FATIN NUR ELYANA MOHD SIDEK[1], MUHAMMAD KUMAYL ABDULWAHAB[1,*], RASHIDI DZUL KEFLEE[2], MOHAMMED ABDULLAH ALSHAWSH[3,4], SUZITA MOHD NOOR[5], ZARIF MOHAMED SOFIAN[6] & AZHAR ARIFFIN[1]

[1]*Department of Chemistry, Faculty of Science, Universiti Malaya, 50603 Kuala Lumpur, Malaysia*
[2]*Department of Molecular Medicine, Faculty of Medicine, Universiti Malaya, 50603 Kuala Lumpur, Malaysia*
[3]*Department of Pharmacology, Faculty of Medicine, Universiti Malaya, 50603 Kuala Lumpur, Malaysia*
[4]*School of Clinical Sciences, Faculty of Medicine, Nursing and Health Sciences, Monash University, 246 Clayton Road, Clayton, VIC, 3168, Australia*
[5]*Department of Biomedical Science, Faculty of Medicine, Universiti Malaya, 50603 Kuala Lumpur, Malaysia*
[6]*Department of Pharmaceutical Technology, Faculty of Pharmacy, Universiti Malaya, 50603 Kuala Lumpur, Malaysia*

Received: 2 September 2024/Accepted: 18 June 2025

ABSTRACT

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases and remains a leading cause of cancer-related deaths globally. While conventional chemotherapy has provided modest benefits, its toxicity and limited efficacy have underscored the need for more precise treatments. The identification of epidermal growth factor receptor (EGFR) mutations has transformed the therapeutic landscape, with EGFR tyrosine kinase inhibitors (EGFR-TKIs) significantly improving progression-free and overall survival in EGFR-mutant NSCLC. However, resistance mechanisms, such as T790M and C797S mutations have led to the development of successive generations of EGFR-TKIs. Fourth-generation inhibitors and combination therapies targeting bypass pathways now offer renewed hope for overcoming resistance. Nonetheless, the high cost and limited accessibility of these targeted therapies remain critical barriers, particularly in low- and middle-income countries. This review highlights the evolution of EGFR-TKIs, key resistance challenges, and economic considerations, emphasizing the need for equitable access to advance NSCLC treatment globally.

Keywords: EGFR; NSCLC; tyrosine-kinase inhibitors

ABSTRAK

Kanser paru-paru bukan sel kecil (NSCLC) menyumbang kira-kira 85% daripada semua kes kanser paru-paru dan kekal sebagai punca utama kematian berkaitan kanser di seluruh dunia. Walaupun kemoterapi konvensional telah memberikan faedah yang sederhana, ketoksikan dan keberkesanannya yang terhad telah menekankan keperluan untuk rawatan yang lebih tepat. Pengenalpastian mutasi reseptor faktor pertumbuhan epidermis (EGFR) telah mengubah landskap terapeutik dengan perencat tirosina kinase EGFR (EGFR-TKIs) dengan ketara meningkatkan kelangsungan hidup bebas perkembangan dan keseluruhan dalam NSCLC mutan EGFR. Walau bagaimanapun, mekanisme rintangan, seperti mutasi T790M dan C797S, telah membawa kepada pembangunan generasi berturut-turut EGFR-TKI. Perencat generasi keempat dan terapi gabungan yang menyasarkan laluan pintasan kini menawarkan harapan baharu untuk mengatasi rintangan. Namun begitu, kos tinggi dan akses terhad bagi terapi yang disasarkan ini kekal sebagai halangan kritikal, terutamanya di negara berpendapatan rendah dan sederhana. Kertas ini menyerlahkan evolusi EGFR-TKI, cabaran rintangan utama dan pertimbangan ekonomi, menekankan keperluan untuk akses yang saksama untuk memajukan rawatan NSCLC secara global.

Kata kunci: EGFR; NSCLC; perencat tirosina kinase

INTRODUCTION

Lung cancer remains the top cause of cancer-related deaths globally, with approximately 1.8 million deaths in 2020 (Sung et al. 2021). Non-small cell lung cancer (NSCLC) comprises 85% of cases, with adenocarcinoma as the most prevalent subtype (Thai et al. 2021). Unfortunately, late-stage diagnoses limit treatment options and survival rates (Araki et al. 2023). Precision medicine has transformed NSCLC therapy, especially through EGFR tyrosine kinase inhibitors (TKIs), which improve progression-free and overall survival (Graham et al. 2017; Wee & Wang 2017). EGFR mutations primarily exon 19 deletions and L858R are common in East Asians and non-smokers. First-generation TKIs (gefitinib, erlotinib) offered initial

success, but resistance, especially via the T790M mutation, developed within months (Santarpia et al. 2017). Second-generation inhibitors (afatinib, dacomitinib) addressed some resistance but were hindered by toxicity.

Third-generation TKIs like osimertinib specifically targeted T790M with better tolerance (Wu et al. 2020). Yet, the emergence of the C797S mutation prompted the development of fourth-generation inhibitors, such as BLU-945 and BDTX-1535, which target compound mutations and show preclinical promise against brain metastases (Corvaja et al. 2024). Combination strategies such as osimertinib with MET inhibitors like savolitinib are under clinical evaluation (TATTON: NCT02143466; SAVANNAH: NCT03778229) and may overcome bypass resistance. Ongoing efforts focus on integrating EGFR-TKIs with chemotherapy, antiangiogenic agents, and immunotherapies to delay resistance and improve outcomes (Fu et al. 2022; Su & Sun 2024). However, high costs and limited access, especially in low- and middle-income countries, remain a challenge. Strategies such as pricing reforms and assistance programs are vital for equitable treatment access. Continued innovation in fourth-generation inhibitors and combination regimens holds promise for improving survival and treatment durability in EGFR-mutant NSCLC.

EGFR-TYROSINE KINASE INHIBITORS (EGFR-TKIs)

EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR)

EGFR, a receptor tyrosine kinase first identified in the 1970s, is critical for regulating cell proliferation, differentiation, and survival (King Jr., Carpenter & Cohen 1980). Upon ligand binding such as EGF or TGF-α, EGFR dimerizes and autophosphorylates, triggering key downstream signaling pathways including Ras/MAPK, PI3K/Akt, JAK/STAT, PLCγ/PKC, and STAT, which govern oncogenic processes (Wieduwilt & Moasser 2008). In NSCLC, constitutively active EGFR signaling is primarily driven by activating mutations, with exon 19 deletions (ex19del) and exon 21 L858R mutations accounting for 85-90% of EGFR activation (Graham et al. 2017). These mutations enable ligand-independent activation of EGFR, promoting unchecked tumor growth and making EGFR an ideal target for tyrosine kinase inhibitors (Yun et al. 2007). EGFR-mutant tumors often exhibit oncogene addiction, showing high dependence on EGFR signaling and, consequently, high sensitivity to TKIs (Wieduwilt & Moasser 2008).

However, resistance remains a major therapeutic obstacle. The T790M mutation increases ATP-binding affinity, reducing the efficacy of first-generation TKIs (Kobayashi et al. 2005), while the C797S mutation compromises third-generation inhibitors like osimertinib (Santarpia et al. 2017). Additional resistance arises from bypass mechanisms, such as MET amplification, HER2 overexpression, and epithelial-mesenchymal transition (EMT), which activate alternative survival pathways (Engelman et al. 2007). To monitor and counteract resistance, advanced tools like circulating tumor DNA (ctDNA) analysis and droplet digital PCR (ddPCR) offer real-time mutation tracking, enabling timely treatment adjustments (Sundaresan et al. 2016). EGFR mutations are especially common in East Asians, non-smokers, and females, with rates surpassing 40%, and are associated with enhanced progression-free survival under EGFR-TKIs (Graham et al. 2017; Wu et al. 2020). Nonetheless, acquired resistance underscores the ongoing need for next-generation inhibitors and combinatorial strategies (Corvaja et al. 2024; Fu et al. 2022).

FIRST-GENERATION EGFR-TKIs

First-generation EGFR-TKIs, including gefitinib, erlotinib, and icotinib are reversible inhibitors that target common activating EGFR mutations such as exon 19 deletions (ex19del) and exon 21 L858R substitutions by competitively binding to the ATP-binding site, thereby inhibiting downstream signaling (Wieduwilt & Moasser 2008). Clinical trials like IPASS and OPTIMAL showed superior progression-free survival (PFS) for gefitinib and erlotinib compared to chemotherapy, confirming their efficacy in EGFR-mutant NSCLC (Mok et al. 2009; Wu et al. 2020). Icotinib, approved in China, also demonstrated comparable efficacy with fewer side effects (Tan et al. 2015). However, resistance typically arises within 6–10 months, most commonly due to the T790M mutation, which increases ATP affinity and reduces TKI binding. Initially thought to emerge post-treatment, T790M has also been detected in TKI-naive patients using high-sensitivity techniques, suggesting pre-existing resistant subclones (Su et al. 2012). The mutation often coexists with activating mutations and may contribute to tumor heterogeneity and progression (Kosaka et al. 2006).

Structurally, the T790M substitution creates steric hindrance in the ATP-binding pocket, further limiting inhibitor efficacy (Yun et al. 2008). Additionally, Activation-Induced Cytidine Deaminase (AICDA)-mediated cytosine deamination, promoted by NFκB activation, has been implicated in the mutation's development (El Kadi et al. 2018). T790M-positive tumors are associated with aggressive behavior and poorer outcomes, particularly when co-occurring with RB1/TP53 mutations, which may lead to EMT or small-cell transformation (Araki et al. 2023).

Detection of T790M through liquid biopsy methods (ctDNA, BEAMing, ddPCR, and NGS) enables early treatment switching to third-generation TKIs like osimertinib, which improve survival metrics (Hou et al. 2023; Ramalingam et al. 2018; Sundaresan et al. 2016). Beyond T790M, resistance also arises through MET amplification, HER2 alterations, and EMT, which activate alternative pathways like PI3K/AKT, MAPK, and STAT3, sustaining tumor survival and progression (Coleman et al. 2021; Santarpia et al. 2017). These mechanisms emphasize the importance of combination strategies targeting both EGFR and bypass pathways.

SECOND-GENERATION EGFR-TKIs

Second-generation EGFR-TKIs, including afatinib and dacomitinib, were developed to overcome resistance to first-generation inhibitors by forming irreversible covalent bonds with EGFR, enabling prolonged and broader inhibition. Both drugs also target multiple ErbB family members (HER1, HER2, HER4), expanding their efficacy across EGFR-driven tumors (Landi & Cappuzzo 2013). Despite this broader activity, acquired resistance such as the T790M mutation remains a challenge, and toxicity profiles are higher compared to first-generation agents (Takeda & Nakagawa 2019).

Afatinib approved by the FDA in 2013, showed significant improvements in progression-free survival (PFS) compared to chemotherapy, and first-generation (Sequist et al. 2013; Tu et al. 2018). Particularly, patients with exon 19 deletions and without brain metastases responded more favourably. However, toxicity is a concern with afatinib, especially grade 3–4 events such as diarrhea, rash, and stomatitis, prompting dose reductions (Tu et al. 2018). Dacomitinib approved in 2018 is another irreversible pan-HER inhibitor. In the ARCHER 1050 trial, it significantly outperformed gefitinib, achieving a PFS of 14.7 months versus 9.2 months ($p < 0.001$) (Ramalingam et al. 2018). Its broader inhibition of HER receptors contributed to more sustained EGFR suppression (Shirley 2018). Dacomitinib's tolerability is limited by high toxicity rates, including grade 3-4 diarrhea (47%), rash, and liver-related adverse events (Wang et al. 2022). Skin toxicities often necessitate dose modifications. Prophylactic strategies, such as the use of antibiotics and moisturizers, were shown to reduce severity but did not eliminate the need for dose adjustments (Iwasaku et al. 2023).

THIRD-GENERATION EGFR-TYROSINE KINASE INHIBITORS (EGFR-TKIs)

Third-generation EGFR-TKIs (osimertinib) received FDA approval in 2015 for metastatic T790M-positive NSCLC after prior EGFR-TKI failure. Osimertinib is a selective, irreversible inhibitor that targets both activating EGFR mutations and T790M by covalently binds to the CYS797 residue in the ATP-binding site, while sparing wild-type EGFR, thereby reducing off-target effects (Cross et al. 2014). In clinical trials, osimertinib demonstrated superior efficacy. The AURA3 trial showed it significantly improved PFS over chemotherapy in T790M-positive patients (10.1 vs. 4.4 months, HR = 0.30, $p < 0.001$), with a higher objective response rate (71% vs. 31%) (Wu et al. 2020). It was particularly effective against CNS metastases, extending PFS to 8.5 months compared to 4.2 months with chemotherapy.

Phase III trials have expanded osimertinib's indications across first-line, second-line, and adjuvant settings. The ADAURA trial confirmed osimertinib's role as an adjuvant therapy, improving disease-free survival (DFS) in patients with resected stage IB–IIIA while preserving health-related quality of life (Majem et al. 2022). A meta-analysis further supported its superiority over earlier TKIs and chemotherapy, reporting enhanced PFS (HR = 0.38), OS (HR = 0.66), and ORR (OR = 1.76), along with reduced toxicity (Huang et al. 2019). Osimertinib's safety profile is favorable, with fewer grade 3 or higher adverse events (23% vs. 47% with chemotherapy), and commonly reported side effects are generally manageable (Wu et al. 2020). Its high CNS activity and tolerability make it the preferred treatment option across therapy lines (Mok et al. 2017).

ACQUIRED MUTATIONS AMONG POST-OSIMERTINIB PATIENTS

Although osimertinib shows strong initial efficacy, resistance inevitably develops, leading to disease progression. These resistance mechanisms can be categorized into EGFR-dependent mutations and EGFR-independent bypass pathways (Mok et al. 2017). The C797S mutation is the most frequent EGFR-dependent resistance mechanism, impairing the covalent binding of osimertinib to the EGFR ATP-binding site. This mutation, especially when occurring alongside T790M, leads to cross-resistance against most EGFR-TKIs (Thress et al. 2015), creating a significant challenge in clinical management. Ercan et al. (2015) identified C797S, along with L718Q and L844V, as key resistance mutations that interfere with drug binding. Their findings highlight the urgent need for fourth-generation TKIs and dual inhibitor strategies to combat complex resistance profiles. Similarly, Zhang et al. (2018) reported that mutations L792H and G796R reduce osimertinib binding through structural alterations of EGFR, contributing to resistance in compound mutants such as L858R/T790M/L792H.

Beyond EGFR mutations, bypass signaling pathways drive resistance independently of EGFR inhibition. These include MET amplification, HER2 amplification, and PI3K/AKT/mTOR pathway activation (Goldberg et al. 2018). Planchard et al. (2018) emphasized molecular profiling and liquid biopsies as essential tools to detect resistance mutations early and guide adaptive therapeutic strategies. Their recommendations include combining EGFR-TKIs with MET or PI3K inhibitors to address bypass pathway activation and employing flexible treatment plans based on emerging resistance. Resistance also arises through epithelial-to-mesenchymal transition (EMT), which enhances tumor invasiveness, and small-cell lung cancer (SCLC) transformation, necessitating a shift to chemotherapy or immune checkpoint inhibitors (Goldberg et al. 2018).

FOURTH-GENERATION TYROSINE KINASE INHIBITORS (TKIs)

Fourth-generation EGFR-TKIs were developed to overcome resistance to third-generation inhibitors like osimertinib, particularly due to T790M and C797S mutations. These

inhibitors use covalent and non-covalent binding to enhance specificity, overcome steric hindrance, and spare wild-type EGFR, reducing adverse effects. BLU-945 targets T790M/C797S co-mutations with strong preclinical efficacy and is currently in the Phase I/II SYMPHONY trial (NCT04862780), being evaluated as monotherapy and in combination with osimertinib (Corvaja et al. 2024; Lim et al. 2024). JBJ-04-125-02 is an allosteric inhibitor designed for L858R/T790M/C797S mutations, and its derivative, JBJ-09-063, has shown synergy with osimertinib (Fu et al. 2022). BPI-361175 selectively inhibits single, double, and triple EGFR mutations, including brain metastases, with preclinical data showing potent tumor suppression, low toxicity, and blood-brain barrier (BBB) penetration (Liu et al. 2022).

Additional promising agents include BI-732, effective against Ex19del, L858R/C797S, and L858R/T790M/C797S mutations. Oral administration at 25 mg/kg in xenograft models resulted in tumor reduction and CNS activity (Corvaja et al. 2024; Lee et al. 2023). BDTX-1535 is a brain-penetrating, mutant-selective inhibitor with broad efficacy against both common and rare EGFR mutations, including L718X and A289V (Dardenne et al. 2024; Su & Sun 2024). TRX-221 is specifically designed to target C797S and T790M/C797S mutations with demonstrated CNS activity; preclinical studies show strong efficacy in both subcutaneous and intracranial tumor models, and it is currently in a Phase I/II trial (NCT06186076), although recruitment is pending (Lim et al. 2023).

Despite encouraging preclinical and early clinical data, these agents face challenges including toxicity, emerging resistance pathways, and limited long-term data. Combination therapies targeting MET and HER2 amplifications, and allosteric inhibitors to bypass structural resistance are actively being explored (Fu et al. 2022; Lim et al. 2024). Su and Sun (2024) call for the development of reversible, high-specificity EGFR-TKIs targeting compound mutations while maintaining tolerability. Integrative approaches combining immunotherapy and targeted agents are under investigation to enhance treatment durability (Corvaja et al. 2024).

EGFR-TKIs COMBINED WITH CHEMOTHERAPY

Combining EGFR-TKIs with chemotherapy has emerged as a strategy to enhance treatment efficacy and delay resistance in EGFR-mutated NSCLC. The NEJ009 trial demonstrated significant improvements in PFS, overall survival (OS), and objective response rate (ORR) with gefitinib plus carboplatin and pemetrexed versus gefitinib alone, albeit with increased manageable toxicities (Hosomi et al. 2020). However, the IMPRESS trial found no OS benefit when gefitinib was continued with chemotherapy after disease progression, indicating the importance of first-line combination rather than continuation beyond progression (Soria et al. 2015). Hou et al. (2023) (NCT01951469 trial) further reported improved intracranial and systemic PFS in patients with brain metastases treated with gefitinib plus chemotherapy, supporting its use in CNS involvement case. Meta-analyses by Xue et al. (2022) and Zhu et al. (2021) confirmed survival benefits of combining TKIs with platinum-based chemotherapy, with better balance of efficacy and tolerability in regimens including pemetrexed and carboplatin.

Recent data from the FLAURA2 trial reinforced the benefit of combining osimertinib with platinum-pemetrexed chemotherapy as a first-line regimen. The trial showed high ORR (87%), prolonged PFS (up to 3 years), and acceptable toxicity (Planchard et al. 2023). The OPAL study also supported this combination, reporting a 90.9% ORR and a median PFS of 31.0 months, with no treatment-related deaths (Saito et al. 2023). Ongoing trials such as COMPEL (NCT04765059) and EPONA (TORG 1938) are evaluating osimertinib continuation with chemotherapy in patients with disease progression, particularly focusing on maintaining CNS control and targeting resistant clones (Okuma et al. 2022; Sequist et al. 2021).

EGFR-TKIs COMBINED WITH ANTIANGIOGENIC THERAPY

Combining EGFR-TKIs with antiangiogenic agents provides a synergistic approach by simultaneously targeting tumor proliferation and angiogenesis, two key drivers of NSCLC progression and resistance. Antiangiogenic agents such as bevacizumab and ramucirumab inhibit the VEGF pathway, improving drug delivery and enhancing the efficacy of EGFR-TKIs through tumor vascular normalization (Masuda et al. 2017; Papini et al. 2021). The phase III RELAY trial demonstrated that erlotinib plus ramucirumab significantly prolonged PFS (19.4 vs. 12.4 months; HR = 0.59, $p < 0.0001$) and duration of response compared to erlotinib alone (Nakagawa et al. 2019). Similarly, the CTONG-1509 trial reported a PFS of 18.0 months with erlotinib and bevacizumab versus 11.3 months with erlotinib monotherapy (HR = 0.55, $p < 0.001$), with manageable toxicity (Zhou et al. 2019).

Osimertinib-based combinations have also been explored. The WJOG9717L trial showed a modest, non-significant PFS improvement with osimertinib plus bevacizumab (22.1 vs. 20.2 months; HR = 0.862; $p = 0.213$), and a higher incidence of grade ≥3 adverse events (Kenmotsu et al. 2022). Ongoing trials such as FLAIR and RAMOSE are investigating in specific patient populations, such as those with L858R mutations or treatment-naïve metastatic NSCLC (Saltos et al. 2021; Zhou et al. 2024). Preliminary data show manageable safety profiles, with efficacy outcomes still under evaluation. A meta-analysis by Dafni et al. (2022) suggests that smoking status may influence treatment efficacy. Smokers demonstrated significant PFS and OS benefits compared to non-smokers, indicating the potential utility of smoking status as a predictive biomarker.

EGFR-TKIs COMBINED WITH RADIOTHERAPY

Combining EGFR-TKIs with radiotherapy offers a synergistic strategy by inducing DNA damage and impairs repair pathways, effects that are amplified by EGFR-TKIs (Papini et al. 2021). This combination is promising for managing brain metastases, where EGFR-TKIs like osimertinib can penetrate the blood-brain barrier and enhance the efficacy of cranial irradiation. Clinically, a retrospective study by Kotek Sedef et al. (2021) showed that thoracic radiotherapy combined with EGFR-TKIs significantly improved overall survival (33 vs. 23 months; $p = 0.05$), particularly in patients with exon 19 deletions and those receiving higher biologically effective doses or stereotactic body radiotherapy (SBRT), which also offered superior local control.

A network meta-analysis by Xue et al. (2022) further reinforced the benefit of this approach, with a hazard ratio of 0.44 for PFS favoring the combination over TKI monotherapy (95% CI: 0.23-0.83). The benefit was particularly pronounced in patients with brain metastases. However, increased risks of adverse events such as pneumonitis and esophagitis were noted, underscoring the need for careful toxicity management and individualized treatment planning. The ongoing phase II NORTHSTAR trial is evaluating osimertinib with local consolidation therapy (LCT), including radiotherapy who developed T790M-mediated resistance (Elamin et al. 2018). Preliminary findings suggest that the addition of LCT to systemic therapy may delay progression and improve survival. The trial also incorporates exploratory biomarker analysis to guide personalized treatment strategies.

EGFR-TKIs COMBINED WITH IMMUNOTHERAPY

Combining EGFR-TKIs with immune checkpoint inhibitors (ICIs) offers a novel but complex strategy for enhancing immune responses in NSCLC. Preclinical data suggest EGFR activation upregulates PD-L1 expression, allowing immune evasion, while EGFR-TKIs may promote immunogenic apoptosis and facilitate T-cell recruitment (Chen et al. 2015; Suresh et al. 2018). However, EGFR-mutant NSCLC is typically associated with tumor mutation burden (TMB), leading to reduced responsiveness to immunotherapy. Clinical trials have yielded mixed results. The CAURAL trial (NCT02454933), assessing osimertinib with durvalumab, was terminated early due to high rates of interstitial lung disease, despite initial response activity (Yang et al. 2019). KEYNOTE-789 trial showed no significant survival benefit with pembrolizumab plus chemotherapy compared to chemotherapy alone in EGFR-TKI-resistant patients (Yang et al. 2024).

More promising results emerged from the IMpower150 and ATTLAS (KCSG-LU19-04) trials. IMpower150 reported improved PFS and OS in EGFR-mutant patients treated with atezolizumab plus bevacizumab and chemotherapy, especially in those with liver or brain metastases (Nogami et al. 2022). The ATTLAS trial further supported this combination, showing a PFS of 8.48 months and an ORR of 69.5%, albeit with increased toxicity (Park et al. 2024). Similarly, ORIENT-31 demonstrated improved PFS using sintilimab with chemotherapy after TKI failure, reinforcing the potential of combining ICIs with chemotherapy in this setting (Lu et al. 2023).

DUAL-TARGET APPROACHES: MET AND MEK INHIBITORS

Resistance to EGFR-TKIs often arises through activation of bypass pathways such as MET amplification and the RAS/RAF/MEK/ERK signaling cascade. These pathways can promote tumor survival and continued proliferation despite EGFR inhibition (Qin et al. 2023). Dual-target strategies combining EGFR-TKIs with inhibitors of MET or MEK have emerged as promising approaches to overcome resistance mechanisms. The TATTON trial (NCT02143466) evaluated osimertinib with the MET inhibitor savolitinib and reported an ORR of 64% and a median PFS of 9.1 months (Ahn et al. 2022; Oxnard et al. 2020). While combining osimertinib with the MEK inhibitor selumetinib (a MEK1/2 inhibitor) also showed tumor suppression, it was associated with increased toxicity. A third arm with durvalumab faced safety concerns due to interstitial lung disease, leading to discontinuation of these combination. The SAVANNAH trial further explored osimertinib and savolitinib in MET-amplified patients post-osimertinib progression. Early results showed promising antitumor activity, supporting biomarker-guided treatment. Stratification based on MET expression helped identify patients more likely to benefit from dual inhibition (Ahn et al. 2022). Study by Luo et al. (2021) combined erlotinib with trametinib (a MEK inhibitor) showed overall efficacy was limited (4% ORR, 1.8 months PFS), although patients with BRAF fusions showed benefit, suggesting a role for selective biomarker-driven strategies. Toxicities, such as rash, diarrhea, and fatigue, were common, reinforcing the importance of optimizing safety.

TOXICITY PROFILES OF COMBINATION THERAPIES

Combination therapies involving EGFR inhibitors and other agents, such as antiangiogenics, immune checkpoint inhibitors, and chemotherapy, have shown promise in improving outcomes. However, these combinations are often associated with distinct toxicity profiles that necessitate careful management. This summary serves as a practical guide for clinicians to anticipate, monitor, and mitigate adverse events associated with these therapies (Table 1), ensuring patient safety and treatment efficacy. The detailed data from trials emphasize the need for proactive symptom management and biomarker-driven approaches to personalize therapy.

SELECTION CRITERIA IN COMBINATION THERAPIES

The selection of combination therapies for EGFR-mutant NSCLC is guided by a comprehensive understanding of

resistance mechanisms, molecular profiles, and predictive biomarkers. Treatment strategies are personalized based on genetic alterations such as MET amplification, HER2 overexpression, and bypass signaling pathways that confer resistance to EGFR-TKIs. For instance, combining VEGF inhibitors like bevacizumab with EGFR-TKIs benefits patients with high VEGF expression by normalizing tumor vasculature and enhancing drug delivery (Araki et al. 2023). Chemotherapy, particularly platinum-based agents or pemetrexed, is often combined with EGFR-TKIs in cases of acquired resistance to co-target downstream pathways like PI3K/AKT, as demonstrated by the NEJ009 trial, which showed improved PFS and OS with concurrent gefitinib and chemotherapy.

Immunotherapy combinations, though promising, require strict patient selection using markers such as PD-L1 to mitigate toxicity and limited efficacy. For patients with resistance to osimertinib, combination approaches using MET inhibitors like savolitinib or platinum-based chemotherapy are employed when MET amplification is detected (Araki et al. 2023). Additionally, novel therapies such as antibody-drug conjugates (ADCs) and EGFR-MET bispecific antibodies are emerging for cases with complex resistance mutations like C797S or MET amplification, highlighting the importance of biomarker-guided and sequencing-informed strategies to improve clinical outcomes (Araki et al. 2023).

ECONOMIC IMPACT AND STRATEGIES FOR ACCESSIBILITY OF EGFR-TKIs

The cost-effectiveness and accessibility of EGFR-TKIs vary widely across regions due to differences in healthcare infrastructure and economic conditions. While high-HDI countries report high availability of EGFR testing and erlotinib (98%), access remains limited in lower-income nations (57%) due to affordability and infrastructure challenges (Carbonnaux et al. 2016). Only 42.6% of the global population, mostly in wealthier regions, benefits from free or low-cost testing. Economic evaluations support EGFR testing's cost-effectiveness, as shown in Japan (ICER $32,500/QALY), Mexico ($3,630–$4,917

TABLE 1. Toxicity profiles of combination therapies

Combination therapy	Trial reference	Profile of main toxicities	References
Gefitinib + Carboplatin + Pemetrexed	NEJ009	Grade ≥: Hematologic (65.3%), Non-hematologic (31.0%), Treatment-related death (0.6%)	(Hosomi et al. 2020)
Gefitinib + Cisplatin + Pemetrexed	IMPRESS	Grade ≥3: Leukopenia (2%), Decreased neutrophil count (4%), Asthenia (2%)	(Soria et al. 2015)
Gefitinib + Pemetrexed + Platinum	GAP BRAIN	Grade 3: Alanine aminotransferase level increase (11.3%), Neutropenia (7.5%), and Nausea (7.5%)	(Hou et al. 2023)
Osimertinib + Platinum-Pemetrexed	FLAURA2	Serious adverse events (37%), Grade ≥3 adverse events (50%)	(Planchard et al. 2023)
	OPAL	Grade ≥3: Neutrophil count decreased (44.8%), Anemia (22.4%), Platelet count decreased (20.9%)	(Saito et al. 2023)
Ramucirumab + Erlotinib	RELAY	Grade ≥3: Hypertension (24%), Dermatitis acneiform (15%), Diarrhea (7%). One treatment-related death (pulmonary hemorrhage)	(Nakagawa et al. 2019)
Bevacizumab + Erlotinib	CTONG 1509	Grade ≥3: Hypertension, Proteinuria, Rash	(Zhou et al. 2019)
Osimertinib + Bevacizumab	WJOG9717L	Hypertension (Grade 3 ≥: 7%), Paronychia (Grade 3: 7%), Proteinuria (any grade: 54%)	(Kenmotsu et al. 2022)
	FLAIR	Hypertension (Grade 3: 16.6%), Proteinuria (any grade: 33%), Diarrhea (any grade: 27.7%)	(Zhou et al. 2024)
Osimertinib + Ramucirumab	RAMOSE	Hypertension (Grade 3: 7.1%), Rash (Grade 3: 4.2%), Neutropenia (Grade 3: 2.8%)	(Saltos et al. 2021)
Osimertinib + Durvalumab	CAURAL	ILD (3%) reported as Grade 2. Diarrhea (50%) and Rash (67%) reported	(Yang et al. 2019)
Atezolizumab + Bevacizumab + Carboplatin + Paclitaxel	ATTLAS	Grade ≥3 toxicities: Hypertension (2.0%), Proteinuria (1.3%), Neutropenia (5.3%). Treatment-related deaths: Pneumonia (2 cases), Cerebral embolic infarction (1 case)	(Park et al. 2024)

per progression-free month), and China ($22,973/QALY with assistance programs) (Arrieta et al. 2016; Narita et al. 2015; You et al. 2019). However, osimertinib remains cost-ineffective in countries like the US and China unless prices drop significantly, with the Netherlands requiring a 30% reduction to meet thresholds. To improve access, strategies such as local drug production, inclusion in the WHO Essential Medicines List, national reimbursement schemes, expanded diagnostics, biosimilars, and price negotiations are being adopted. Broad policy reform and collaboration across sectors are essential for equitable global access to EGFR-TKIs (Carbonnaux et al. 2016).

CONCLUSION

The advent of EGFR-targeted therapies has revolutionized the treatment landscape for NSCLC, significantly improving PFS and OS for patients with EGFR mutations. However, the persistent challenge of acquired resistance driven by mutations like T790M and C797S or alternative signaling pathways has spurred the evolution of EGFR-TKIs from first- and second-generation agents to third-generation drugs like osimertinib, and now to emerging fourth-generation inhibitors. These advancements, along with promising combination therapies involving chemotherapy, immunotherapy, and antiangiogenic agents, reflect a paradigm shift toward long-term disease control. Moving forward, the future of NSCLC treatment lies in the refinement of these approaches, integration of biomarker-driven strategies, and the resolution of economic and accessibility barriers, paving the way for EGFR-TKIs to transform NSCLC from a lethal diagnosis into a manageable or potentially curable condition.

ACKNOWLEDGEMENTS

The work is supported financially by the Ministry of Higher Education, Malaysia via Fundamental Research Grant Scheme (FRGS/1/2022/STG04/UM/02/1) and Universiti Malaya via Universiti Malaya Impact Oriented Interdisciplinary Research Grant (IIRG001C-2022FNW). During the preparation of this work, we used ChatGPT to detect language errors and improve clarity. After using this tool/service, we reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

REFERENCES

Ahn, M-J., De Marinis, F., Bonanno, L., Cho, B.C., Kim, T-M., Cheng, S., Novello, S., Proto, C., Kim, S-W., Lee, J.S., Metro, G., Yang, J.C., Xu, W., Hartmaier, R., Telaranta-Keerie, A., Poole, L. & Sequist, L. 2022. EP08. 02-140 MET biomarker-based preliminary efficacy analysis in SAVANNAH: savolitinib+ osimertinib in EGFRm NSCLC post-osimertinib. *Journal of Thoracic Oncology* 17(9): S469-S470.

Araki, T., Kanda, S., Horinouchi, H. & Ohe, Y. 2023. Current treatment strategies for EGFR-mutated non-small cell lung cancer: from first line to beyond osimertinib resistance. *Japanese Journal of Clinical Oncology* 53(7): 547-561.

Arrieta, O., Anaya, P., Morales-Oyarvide, V., Ramírez-Tirado, L.A. & Polanco, A.C. 2016. Cost-effectiveness analysis of EGFR mutation testing in patients with non-small cell lung cancer (NSCLC) with gefitinib or carboplatin–paclitaxel. *The European Journal of Health Economics* 17(7): 855-863.

Carbonnaux, M., Souquet, P.J., Meert, A.P., Scherpereel, A., Peters, M. & Couraud, S. 2016. Inequalities in lung cancer: A world of EGFR. *European Respiratory Journal* 47(5): 1502-1509.

Chen, N., Fang, W., Zhan, J., Hong, S., Tang, Y., Kang, S., Zhang, Y., He, X., Zhou, T., Qin, T., Huang, Y., Yi, X. & Zhang, L. 2015. Upregulation of PD-L1 by EGFR activation mediates the immune escape in EGFR-driven NSCLC: Implication for optional immune targeted therapy for NSCLC patients with EGFR mutation. *Journal of Thoracic Oncology* 10(6): 910-923.

Coleman, N., Hong, L., Zhang, J., Heymach, J., Hong, D. & Le, X. 2021. Beyond epidermal growth factor receptor: MET amplification as a general resistance driver to targeted therapy in oncogene-driven non-small-cell lung cancer. *ESMO Open* 6(6): 100319.

Corvaja, C., Passaro, A., Attili, I., Aliaga, P.T., Spitaleri, G., Signore, E.D. & de Marinis, F. 2024. Advancements in fourth-generation EGFR TKIs in EGFR-mutant NSCLC: Bridging biological insights and therapeutic development. *Cancer Treatment Reviews* 130: 102824.

Cross, D.A., Ashton, S.E., Ghiorghiu, S., Eberlein, C., Nebhan, C.A., Spitzler, P.J., Orme, J.P., Finlay, M.R., Ward, R.A., Mellor, M.J., Hughes, G., Rahi, A., Jacobs, V.N., Red Brewer, M., Ichihara, E., Sun, J., Jin, H., Ballard, P., Al-Kadhimi, K., Rowlinson, R., Klinowska, T., Richmond, G.H., Cantarini, M., Kim, D.W., Ranson, M.R. & Pao, W. 2014. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. *Cancer Discovery* 4(9): 1046-1061.

Dafni, U., Soo, R.A., Peters, S., Tsourti, Z., Zygoura, P., Vervita, K., Han, J.Y., De Castro, J., Coate, L., Früh, M., Hashemi, S.M.S., Nadal, E., Carcereny, E., Sala, M.A., Bernabé, R., Provencio, M., Cuffe, S., Roschitzki-Voser, H., Ruepp, B., Rosell, R. & Stahel, R.A. 2022. Impact of smoking status on the relative efficacy of the EGFR TKI/angiogenesis inhibitor combination therapy in advanced NSCLC - A systematic review and meta-analysis. *ESMO Open* 7(3): 100507.

Dardenne, E., O'Connor, M., Nilsson, M., He, J., Yu, X., Heymach, J.V., Le, X. & Buck, E. 2024. BDTX-1535: A MasterKey EGFR inhibitor targeting classical and non-classical oncogenic driver mutations and the C797S resistance mutation to address the evolving molecular landscape of EGFR mutant NSCLC. *Cancer Research* 84(6): 1229.

El Kadi, N., Wang, L., Davis, A., Korkaya, H., Cooke, A., Vadnala, V., Brown, N.A., Betz, B.L., Cascalho, M., Kalemkerian, G.P. & Hassan, K.A. 2018. The EGFR T790M mutation is acquired through AICDA-mediated deamination of 5-methylcytosine following TKI treatment in lung cancer. *Cancer Research* 78(24): 6728-6735.

Elamin, Y.Y., Antonoff, M., Blakely, C., Baggstorm, M., Bivona, T., Le, X., Louie, A.V., Doebele, R.C., Rusthoven, C., Lee, P., Govindan, R., Swisher, S.G., Papadimitrakopoulou, V.A., Heymach, J.V. & Gomez, D.R. 2018. Randomized phase II trial of osimertinib with or without local consolidation therapy (LCT) for patients with EGFR-mutant metastatic NSCLC (NORTHSTAR). *Annals of Oncology* 29(Supp. 8): VIII547.

Engelman, J.A., Zejnullahu, K., Gale, C.M., Lifshits, E., Gonzales, A.J., Shimamura, T., Zhao, F., Vincent, P.W., Naumov, G.N., Bradner, J.E., Althaus, I.W., Gandhi, L., Shapiro, G.I., Nelson, J.M., Heymach, J.V., Meyerson, M., Wong, K.K. & Jänne, P.A. 2007. PF00299804, an irreversible pan-ERBB inhibitor, is effective in lung cancer models with EGFR and ERBB2 mutations that are resistant to gefitinib. *Cancer Research* 67(24): 11924-11932.

Ercan, D., Choi, H.G., Yun, C.H., Capelletti, M., Xie, T., Eck, M.J., Gray, N.S. & Jänne, P.A. 2015. EGFR mutations and resistance to irreversible pyrimidine-based EGFR inhibitors. *Clinical Cancer Research* 21(17): 3913-3923.

Fu, K., Xie, F., Wang, F. & Fu, L. 2022. Therapeutic strategies for EGFR-mutated non-small cell lung cancer patients with osimertinib resistance. *Journal of Hematology & Oncology* 15(1): 173.

Goldberg, M.E., Montesion, M., Young, L., Suh, J., Greenbowe, J., Kennedy, M., Giaccone, G., Akerley, W.L., Dowlati, A., Creelan, B.C., Hicks, J.K., Hesketh, P.J., Kelly, K.L. Riess, J.W., Miller, V.A., Stephens, P.J., Frampton, G.M., Ali, S., Gregg, J.P. & Albacker, L.A. 2018. Multiple configurations of EGFR exon 20 resistance mutations after first-and third-generation EGFR TKI treatment affect treatment options in NSCLC. *PLoS ONE* 13(11): e0208097.

Graham, R.P., Treece, A.L., Lindeman, N.I., Vasalos, P., Shan, M., Jennings, L.J. & Rimm, D.L. 2017. Worldwide frequency of commonly detected EGFR mutations. *Archives of Pathology & Laboratory Medicine* 142(2): 163-167.

Hosomi, Y., Morita, S., Sugawara, S., Kato, T., Fukuhara, T., Gemma, A., Takahashi, K., Fujita, Y., Harada, T., Minato, K., Takamura, K., Hagiwara, K., Kobayashi, K., Nukiwa, T., Inoue, A.; North-East Japan Study Group. 2020. Gefitinib alone versus gefitinib plus chemotherapy for non–small-cell lung cancer with mutated epidermal growth factor receptor: NEJ009 study. *Journal of Clinical Oncology* 38(2): 115-123.

Hou, X., Li, M., Wu, G., Feng, W., Su, J., Jiang, H., Jiang, G., Chen, J., Zhang, B., You, Z., Liu, Q. & Chen, L. 2023. Gefitinib plus chemotherapy vs gefitinib alone in untreated EGFR-mutant non–small cell lung cancer in patients with brain metastases: The GAP BRAIN open-label, randomized, multicenter, phase 3 study. *JAMA Network Open* 6(2): e2255050.

Huang, L., Huang, H., Zhou, X.P., Liu, J.F., Li, C.R., Fang, M. & Wu, J.R. 2019. Osimertinib or EGFR-TKIs/chemotherapy in patients with EGFR-mutated advanced nonsmall cell lung cancer: A meta-analysis. *Medicine (Baltimore)* 98(43): e17705.

Iwasaku, M., Uchino, J., Chibana, K., Tanzawa, S., Yamada, T., Tobino, K., Uchida, Y., Kijima, T., Nakatomi, K., Izumi, M., Tamiya, N., Kimura, H., Fujita, M., Honda, R., Takumi, C., Yamada, T., Kaneko, Y., Kiyomi, F. & Takayama, K. 2023. Prophylactic treatment of dacomitinib-induced skin toxicities in epidermal growth factor receptor-mutated non–small-cell lung cancer: A multicenter, Phase II trial. *Cancer Medicine* 12(14): 15117-15127.

Kenmotsu, H., Wakuda, K., Mori, K., Kato, T., Sugawara, S., Kirita, K., Yoneshima, Y., Azuma, K., Nishino, K., Teraoka, S., Shukuya, T., Masuda, K., Hayashi, H., Toyozawa, R., Miura, S., Fujimoto, D., Nakagawa, K., Yamamoto, N. & Takahashi, T. 2022. Randomized phase 2 study of osimertinib plus bevacizumab versus osimertinib for untreated patients with nonsquamous NSCLC harboring EGFR mutations: WJOG9717L study. *Journal of Thoracic Oncology* 17(9): 1098-1108.

King Jr., L.E., Carpenter, G. & Cohen, S. 1980. Characterization by electrophoresis of epidermal growth factor stimulated phosphorylation using A-431 membranes. *Biochemistry* 19(7): 1524-1528.

Kobayashi, S., Boggon, T.J., Dayaram, T., Jänne, P.A., Kocher, O., Meyerson, M., Johnson, B.E., Eck, M.J., Tenen, D.G. & Halmos, B. 2005. EGFR mutation and resistance of non–small-cell lung cancer to gefitinib. *New England Journal of Medicine* 352(8): 786-792.

Kosaka, T., Yatabe, Y., Endoh, H., Yoshida, K., Hida, T., Tsuboi, M., Tada, H., Kuwano, H. & Mitsudomi, T. 2006. Analysis of epidermal growth factor receptor gene mutation in patients with non–small cell lung cancer and acquired resistance to gefitinib. *Clinical Cancer Research* 12(19): 5764-5769.

Kotek Sedef, A., Akkus Yildirim, B., Topkan, E. & Taner Sumbul, A. 2021. Upfront thoracic radiotherapy to primary lesion improves outcomes in patients with stage IV non-small cell lung cancer harboring EGFR mutations. *J. BUON* 26(4): 1446-1452.

Landi, L. & Cappuzzo, F. 2013. Irreversible EGFR-TKIs: Dreaming perfection. *Translational Lung Cancer Research* 2(1): 40-49.

Lee, E.J., Lee, J., Oh, S.Y., Lee, Y.W., Kim, J.Y., Choi, S-J., Park, S., Yu, M.R., Kim, J.H., Pyo, K-H., Lee, J.B., Hong, M.H., Lim, S.M., Baum, A., Woelflingseder, L., Engelhardt, H., Petronczki, M., Solca, F., Yun, M.R. & Cho, B.C. 2023. BI-732, a novel fourth-generation EGFR-TKI, demonstrates promising activities against the C797S-mediated EGFR-TKI resistance. *Cancer Research* 83(7_ Suppl.): 4476.

Lim, S., Choi, S., Lee, J., Kim, S., Choi, E., Lee, S., Chun, K. & Lee, K. 2023. 2357P TRX-221, a 4th generation, mutant-selective, and CNS-active EGFR inhibitor with robust antitumor activity in osimertinib-resistant tumor models harboring C797S mutation. *Annals of Oncology* 34(Supplement 2): S1198.

Lim, S.M., Schalm, S.S., Lee, E.J., Park, S., Conti, C., Millet, Y.A., Woessner, R., Zhang, Z., Tavera-Mendoza, L.E., Stevison, F., Albayya, F., Dineen, T.A., Hsieh, J., Oh, S.Y., Zalutskaya, A., Rotow, J., Goto, K., Lee, D.H., Yun, M.R. & Cho, B.C. 2024. BLU-945, a potent and selective next-generation EGFR TKI, has antitumor activity in models of osimertinib-resistant non-small-cell lung cancer. *Therapeutic Advances in Medical Oncology* 16: 17588359241280689.

Liu, L., Qiu, C., Liu, X., Lian, Y., Chen, H., Song, X., Du, G., Guo, J., Yan, D., Lan, H., Ding, L. & Wang, J. 2022. BPI-361175, a 4th generation EGFR-TKI for the treatment of non-small cell lung cancer (NSCLC). *Cancer Research* 82(12_Supplement): 5462.

Lu, S., Wu, L., Jian, H., Cheng, Y., Wang, Q., Fang, J., Wang, Z., Hu, Y., Han, L., Sun, M., Miao, L., Ding, C., Cui, J., Wang, K., Li, B., Li, X., Ye, F., Liu, A., Pan, Y., Cang, S., Zhou, H., Sun, X., Shen, Y., Wang, S., Zhang, W. & He, Y. 2023. Sintilimab plus chemotherapy for patients with EGFR-mutated non-squamous non-small-cell lung cancer with disease progression after EGFR tyrosine-kinase inhibitor therapy (ORIENT-31): Second interim analysis from a double-blind, randomised, placebo-controlled, phase 3 trial. *The Lancet Respiratory Medicine* 11(7): 624-636.

Luo, J., Makhnin, A., Tobi, Y., Ahn, L., Hayes, S.A., Iqbal, A., Ng, K., Arcila, M.E., Riely, G.J., Kris, M.G. & Yu, H.A. 2021. Erlotinib and trametinib in patients with *EGFR*-mutant lung adenocarcinoma and acquired resistance to a prior tyrosine kinase inhibitor. *JCO Precision Oncology* 5: PO.20.00315.

Majem, M., Goldman, J.W., John, T., Grohe, C., Laktionov, K., Kim, S.W., Kato, T., Vu, H.V., Lu, S., Li, S., Lee, K.Y., Akewanlop, C., Yu, C.J., de Marinis, F., Bonanno, L., Domine, M., Shepherd, F.A., Atagi, S., Zeng, L., Kulkarni, D., Medic, N., Tsuboi, M., Herbst, R.S. & Wu, Y.L. 2022. Health-related quality of life outcomes in patients with resected epidermal growth factor receptor–mutated non–small cell lung cancer who received adjuvant osimertinib in the phase III ADAURA trial. *Clinical Cancer Research* 28(11): 2286-2296.

Masuda, C., Yanagisawa, M., Yorozu, K., Kurasawa, M., Furugaki, K., Ishikura, N., Iwai, T., Sugimoto, M. & Yamamoto, K. 2017. Bevacizumab counteracts VEGF-dependent resistance to erlotinib in an EGFR-mutated NSCLC xenograft model. *International Journal of Oncology* 51(2): 425-434.

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., Lee, C.K., Sebastian, M., Templeton, A., Mann, H., Marotti, M., Ghiorghiu, S., Papadimitrakopoulou, V.A.; AURA3 Investigators. 2017. Osimertinib or platinum–pemetrexed in EGFR T790M–positive lung cancer. *New England Journal of Medicine* 376(7): 629-640.

Mok, T.S., Wu, Y.L., Thongprasert, S., Yang, C.H., Chu, D.T., Saijo, N., Sunpaweravong, P., Han, B., Margono, B., Ichinose, Y., Nishiwaki, Y., Ohe, Y., Yang, J.J., Chewaskulyong, B., Jiang, H., Duffield, E.L., Watkins, C.L., Armour, A.A. & Fukuoka, M. 2009. Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. *New England Journal of Medicine* 361(10): 947-957.

Nakagawa, K., Garon, E.B., Seto, T., Nishio, M., Ponce Aix, S., Paz-Ares, L., Chiu, C.H., Park, K., Novello, S., Nadal, E., Imamura, F., Yoh, K., Shih, J.Y., Au, K.H., Moro-Sibilot, D., Enatsu, S., Zimmermann, A., Frimodt-Moller, B., Visseren-Grul, C. & Reck, M. 2019. Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): A randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Oncology* 20(12): 1655-1669.

Narita, Y., Matsushima, Y., Shiroiwa, T., Chiba, K., Nakanishi, Y., Kurokawa, T. & Urushihara, H. 2015. Cost-effectiveness analysis of EGFR mutation testing and gefitinib as first-line therapy for non-small cell lung cancer. *Lung Cancer* 90(1): 71-77.

Nogami, N, Barlesi, F, Socinski, M.A., Reck, M., Thomas, C.A., Cappuzzo, F., Mok, T.S.K., Finley, G., Aerts, J.G., Orlandi, F., Moro-Sibilot, D., Jotte, R.M., Stroyakovskiy, D., Villaruz, L.C., Rodríguez-Abreu, D., Wan-Teck Lim, D., Merritt, D., Coleman, S., Lee, A., Shankar, G., Yu, W., Bara, I. & Nishio, M. 2022. IMpower150 final exploratory analyses for atezolizumab plus bevacizumab and chemotherapy in key NSCLC patient subgroups with EGFR mutations or metastases in the liver or brain. *Journal of Thoracic Oncology* 17(2): 309-323.

Okuma, Y., Nomura, S., Ninomiya, K., Yamaguchi, H., Murakami, S., Kogure, Y., Harada, D., Okishio, K., Okamoto, H. & Goto, Y. 2022. 1186TiP EPONA, efficacy of osimertinib with platinum and pemetrexed in EGFR mutant non-small cell lung cancer patients bearing CNS metastasis, and have systemic progression but stable intracranial disease on osimertinib resistance (TORG 1938). *Annals of Oncology* 33(Suppl. 7): S1090-S1091.

Oxnard, G.R., Yang, J.C., Yu, H., Kim, S.W., Saka, H., Horn, L., Goto, K., Ohe, Y., Mann, H., Thress, K.S., Frigault, M.M., Vishwanathan, K., Ghiorghiu, D., Ramalingam, S.S. & Ahn, M.J. 2020. TATTON: A multi-arm, phase Ib trial of osimertinib combined with selumetinib, savolitinib, or durvalumab in EGFR-mutant lung cancer. *Annals of Oncology* 31(4): 507-516.

Papini, F., Sundaresan, J., Leonetti, A., Tiseo, M., Rolfo, C., Peters, G.J. & Giovannetti, E. 2021. Hype or hope–Can combination therapies with third-generation EGFR-TKIs help overcome acquired resistance and improve outcomes in EGFR-mutant advanced/metastatic NSCLC? *Critical Reviews in Oncology/Hematology* 166: 103454.

Park, S., Kim, T.M., Han, J.Y., Lee, G.W., Shim, B.Y., Lee, Y.G., Kim, S.W., Kim, I.H., Lee, S., Kim, Y.J., Park, J.H., Park, S.G., Lee, K.H., Kang, E.J., Kim, J.W., Shin, S.H., Ock, C.Y., Nam, B.H., Lee, J., Jung, H.A., Sun, J.M., Lee, S.H., Ahn, J.S. & Ahn, M.J. 2024. Phase III, randomized study of atezolizumab plus bevacizumab and chemotherapy in patients with EGFR-or *ALK*-rearranged or translocated non–small-cell lung cancer (ATTLAS, KCSG-LU19-04). *Journal of Clinical Oncology* 42(11): 1241-1251.

Planchard, D., Poltoratskiy, A., Kim, S-W., Kim, T.M., Yanagitani, N., Kagamu, H., Feng, P-H., Hughes, B., Yang, T-Y., Yang, J.C-H., Lee, C.K., Karaseva, N., Mitchell, P., Tambo, Y., Armenteros Monterroso, E., Todd, A., Sahasrabudhe, A., Jänne, P.A. & Kobayashi, K. 2023. 568P First-line (1L) osimertinib+ platinum-pemetrexed in EGFR-mutated (EGFRm) advanced NSCLC: Updated FLAURA2 safety run-in (SRI) results. *Annals of Oncology* 34(Suppl. 4): S1692-S1693.

Planchard, D., Popat, S., Kerr, K., Novello, S., Smit, E.F., Faivre-Finn, C., Mok, T.S., Reck, M., Van Schil, P.E., Hellmann, M.D., Peters, S.; ESMO Guidelines Committee. 2018. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 29(Suppl 4): iv192-iv237. Erratum in: *Ann. Oncol.* 2019 30(5): 863-870.

Qin, K., Hong, L., Zhang, J. & Le, X. 2023. MET amplification as a resistance driver to TKI therapies in lung cancer: Clinical challenges and opportunities. *Cancers* 15(3): 612.

Ramalingam, S.S., Yang, J.C., Lee, C.K., Kurata, T., Kim, D.W., John, T., Nogami, N., Ohe, Y., Mann, H., Rukazenkov, Y., Ghiorghiu, S., Stetson, D., Markovets, A., Barrett, J.C., Thress, K.S. & Jänne, P.A. 2018. Osimertinib as first-line treatment of EGFR mutation–positive advanced non–small-cell lung cancer. *Journal of Clinical Oncology* 36(9): 841-849.

Saito, R., Sugawara, S., Ko, R., Azuma, K., Morita, R., Maemondo, M., Oizumi, S., Takahashi, K., Kagamu, H., Tsubata, Y., Seike, M., Kikuchi, T., Okamoto, I., Satoshi, M., Asahina, H., Tanaka, K., Sugio, K. & Kobayashi, K. 2023. Phase 2 study of osimertinib in combination with platinum and pemetrexed in patients with previously untreated EGFR-mutated advanced non-squamous non-small cell lung cancer: The OPAL Study. *European Journal of Cancer* 185: 83-93.

Saltos, A., Baik, C., Sanborn, R.E., Shum, E., Kim, C., Hall, R., Fidler, M.J., Shu, C.A., Otterson, G., Patel, J., Wong, K., Hanna, N., Gray, J., Heymach, J. & Le, X. 2021. P76.62 RAMOSE: An open-label randomized phase II study of osimertinib with or without ramucirumab in TKI-naïve EGFR-mutant metastatic NSCLC. *Journal of Thoracic Oncology* 16(3 Suppl.): S614.

Santarpia, M., Liguori, A., Karachaliou, N., Gonzalez-Cao, M., Daffinà, M.G., D'Aveni, A., Marabello, G., Altavilla, G. & Rosell, R. 2017. Osimertinib in the treatment of non-small-cell lung cancer: design, development and place in therapy. *Lung Cancer (Auckl)* 8: 109-125.

Sequist, L.V., Peled, N., Tufman, A., Servidio, L., Li, J., Taylor, R. & Zhao, J. 2021. P47.11 COMPEL: Chemotherapy with/without osimertinib in patients with EGFRm advanced NSCLC and progression on first-line osimertinib. *Journal of Thoracic Oncology* 16(10 Suppl.): S1101.

Sequist, L.V., Yang, J.C., Yamamoto, N., O'Byrne, K., Hirsh, V., Mok, T., Geater, S.L., Orlov, S., Tsai, C.M., Boyer, M., Su, W.C., Bennouna, J., Kato, T., Gorbunova, V., Lee, K.H., Shah, R., Massey, D., Zazulina, V., Shahidi, M. & Schuler, M. 2013. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *Journal of Clinical Oncology* 31(27): 3327-3334.

Shirley, M. 2018. Dacomitinib: First global approval. *Drugs* 78(18): 1947-1953.

Soria, J.C., Wu, Y.L., Nakagawa, K., Kim, S.W., Yang, J.J., Ahn, M.J., Wang, J., Yang, J.C., Lu, Y., Atagi, S., Ponce, S., Lee, D.H., Liu, Y., Yoh, K., Zhou, J.Y., Shi, X., Webster, A., Jiang, H. & Mok, T.S. 2015. 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. *The Lancet Oncology* 16(8): 990-998.

Su, C. & Sun, S.Y. 2024. Fourth-generation epidermal growth factor receptor-tyrosine kinases inhibitors: hope and challenges. *Translational Cancer Research* 13(8): 3929-3934.

Su, K.Y., Chen, H.Y., Li, K.C., Kuo, M.L., Yang, J.C., Chan, W.K., Ho, B.C., Chang, G.C., Shih, J.Y., Yu, S.L. & Yang, P.C. 2012. Pretreatment epidermal growth factor receptor (EGFR) T790M mutation predicts shorter EGFR tyrosine kinase inhibitor response duration in patients with non–small-cell lung cancer. *Journal of Clinical Oncology* 30(4): 433-440.

Sundaresan, T.K., Sequist, L.V., Heymach, J.V., Riely, G.J., Jänne, P.A., Koch, W.H., Sullivan, J.P., Fox, D.B., Maher, R., Muzikansky, A., Webb, A., Tran, H.T., Giri, U., Fleisher, M., Yu, H.A., Wei, W., Johnson, B.E., Barber, T.A., Walsh, J.R., Engelman, J.A., Stott, S.L., Kapur, R., Maheswaran, S., Toner, M. & Haber, D.A. 2016. Detection of T790M, the acquired resistance EGFR mutation, by tumor biopsy versus noninvasive blood-based analyses. *Clinical Cancer Research* 22(5): 1103-1110.

Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A. & Bray, F. 2020. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians* 71(3): 209-249.

Suresh, K., Naidoo, J., Lin, C.T. & Danoff, S. 2018. Immune checkpoint immunotherapy for non-small cell lung cancer: Benefits and pulmonary toxicities. *Chest* 154(6): 1416-1423.

Takeda, M. & Nakagawa, K. 2019. First-and second-generation EGFR-TKIs are all replaced to osimertinib in chemo-naive EGFR mutation-positive non-small cell lung cancer? *International Journal of Molecular Sciences* 20(1): 146.

Tan, F., Shi, Y., Wang, Y., Ding, L., Yuan, X. & Sun, Y. 2015. Icotinib, a selective EGF receptor tyrosine kinase inhibitor, for the treatment of non-small-cell lung cancer. *Future Oncology* 11(3): 385-397.

Thai, A.A., Solomon, B.J., Sequist, L.V., Gainor, J.F. & Heist, R.S. 2021. Lung cancer. *Lancet* 398: 535-554.

Thress, K.S., Paweletz, C.P., Felip, E., Cho, B.C., Stetson, D., Dougherty, B., Lai, Z., Markovets, A., Vivancos, A., Kuang, Y., Ercan, D., Matthews, S.E., Cantarini, M., Barrett, J.C., Jänne, P.A. & Oxnard, G.R. 2015. Acquired EGFR C797S mutation mediates resistance to AZD9291 in non–small cell lung cancer harboring EGFR T790M. *Nature Medicine* 21(6): 560-562.

Tu, C.Y., Chen, C.M., Liao, W.C., Wu, B.R., Chen, C.Y., Chen, W.C., Hsia, T.C., Cheng, W.C. & Chen, C.H. 2018. Comparison of the effects of the three major tyrosine kinase inhibitors as first-line therapy for non-small-cell lung cancer harboring epidermal growth factor receptor mutations. *Oncotarget* 9(36): 24237-24247.

Wang, X., Huang, A., Lu, Y., Gao, S., Hu, W. & Cheng, H. 2022. Drug-induced liver injury associated with dacomitinib: A case report. *Frontiers in Oncology* 12: 979462.

Wee, P. & Wang, Z. 2017. Epidermal growth factor receptor cell proliferation signaling pathways. *Cancers* 9(5): 52.

Wieduwilt, M.J. & Moasser, M. 2008. The epidermal growth factor receptor family: Biology driving targeted therapeutics. *Cellular and Molecular Life Sciences* 65(10): 1566-1584.

Wu, Y.L., Tsuboi, M., He, J., John, T., Grohe, C., Majem, M., Goldman, J.W., Laktionov, K., Kim, S-W., Kato, T., Vu, H-V., Lu, S., Lee, K.Y., Akewanlop, C., Yu, C-J., de Marinis, F., Bonanno, L., Domine, M., Shepherd, F.A., Zeng, L., Hodge, R., Atasoy, A., Rukazenkov, Y. & Herbst, R.S.; ADAURA Investigators. 2020. Osimertinib in resected EGFR-mutated non–small-cell lung cancer. *New England Journal of Medicine* 383(18): 1711-1723.

Xue, J., Li, B., Wang, Y., Huang, Z., Liu, X., Guo, C., Zheng, Z., Liang, N., Le, X. & Li, S. 2022. Efficacy and safety of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor combination therapy as first-line treatment for patients with advanced *EGFR*-mutated, non-small cell lung cancer: A systematic review and bayesian network meta-analysis. *Cancers* 14(19): 4894.

Yang, J.C., Lee, D.H., Lee, J.S., Fan, Y., de Marinis, F., Iwama, E., Inoue, T., Rodríguez-Cid, J., Zhang, L., Yang, C.T., de la Mora Jimenez, E., Zhou, J., Pérol, M., Lee, K.H., Vicente, D., Ichihara, E., Riely, G.J., Luo, Y., Chirovsky, D., Pietanza, M.C., Bhagwati, N. & Lu, S. 2024. Phase III KEYNOTE-789 study of pemetrexed and platinum with or without pembrolizumab for tyrosine kinase inhibitor–resistant, *EGFR*–mutant, metastatic nonsquamous non–small cell lung cancer. *Journal of Clinical Oncology* 42(34): 4029-4039.

Yang, J.C., Shepherd, F.A., Kim, D.W., Lee, G.W., Lee, J.S., Chang, G.C., Lee, S.S., Wei, Y.F., Lee, Y.G., Laus, G., Collins, B., Pisetzky, F. & Horn, L. 2019. Osimertinib plus durvalumab versus osimertinib monotherapy in EGFR T790M–positive NSCLC following previous EGFR TKI therapy: CAURAL brief report. *Journal of Thoracic Oncology* 14(5): 933-939.

You, R., Liu, J., Wu, D.B., Qian, X., Lyu, B., Zhang, Y. & Luo, N. 2019. Cost-effectiveness analysis of EGFR mutation testing and afatinib versus gemcitabine-cisplatin as first-line therapy for advanced non-small-cell lung cancer in China. *Cancer Management and Research* 11: 10239-10248.

Yun, C.H., Mengwasser, K.E., Toms, A.V., Woo, M.S., Greulich, H., Wong, K.K., Meyerson, M. & Eck, M.J. 2008. The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. *Proceedings of the National Academy of Sciences* 105(6): 2070-2075.

Yun, C.H., Boggon, T.J., Li, Y., Woo, M.S., Greulich, H., Meyerson, M. & Eck, M.J. 2007. Structures of lung cancer-derived EGFR mutants and inhibitor complexes: mechanism of activation and insights into differential inhibitor sensitivity. *Cancer Cell* 11(3): 217-227.

Zhang, B., Xu, J., Zhang, X., Gu, P., Wang, H., Wang, S., Qian, J., Qiao, R., Zhang, Y., Yang, W., Qian, F., Zhou, Y., Lu, J., Zhang, L. & Han, B. 2018. Coexistence of sensitive and resistant epidermal growth factor receptor (EGFR) mutations in pretreatment non-small cell lung cancer (NSCLC) patients: First or third generation tyrosine kinase inhibitors (TKIs)? *Lung Cancer* 117: 27-31.

Zhou, Q., Li, J., Cang, S-D., Lin, J-X., Tu, H-Y., Du, Y., Qin, J-W., Liang, X-H., Yu, Y., Lan, H-T., Shi, H-Q., Hua, D., Liu, S-Y.M. & Wu, Y-L. 2024. FLAIR: A phase II, open label, randomized study of osimertinib plus bevacizumab versus osimertinib in recurrent or metastatic treatment-naïve NSCLC patients harboring *EGFR* 21L858R mutation. *Clinical Lung Cancer* 26(2): 152-157.e1.

Zhou, Q., Wu, Y-L., Cheng, Y., Liu, Y., Chen, G., Cui, J., Yang, N., Song, Y., Li, X-L., Lu, S., Zhou, J., Ma, Z., Yu, S-Y., Huang, C. & Shu, Y. 2019. CTONG 1509: Phase III study of bevacizumab with or without erlotinib in untreated Chinese patients with advanced EGFR-mutated NSCLC. *Annals of Oncology* 30(5): v603.

Zhu, C.M., Lian, X.Y., Zhang, H.Y., Bai, L., Yun, W.J., Zhao, R.H. & Li, Q.S. 2021. EGFR tyrosine kinase inhibitors alone or in combination with chemotherapy for non-small-cell lung cancer with EGFR mutations: A meta-analysis of randomized controlled trials. *Journal of Cancer Research and Therapeutics* 17(3): 664-670.

*Corresponding author; email: kumaylabdul@um.edu.my