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The "Romance of the Three Kingdoms" of EGFR-TKI Combination Therapy: Relationships Among Efficacy, Toxicity, and Resistance Mechanisms

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Abstract

Epidermal growth factor receptor (EGFR) mutations is one of the most significant driver genes in non-small cell lung cancer (NSCLC), particularly exhibiting a higher incidence among East Asian non-smokers with adenocarcinoma. The successful research and development of Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) has significantly improved the survival for this patient population. But primary and secondary resistance remain core challenges in clinical practice. To overcome drug resistance, enhance efficacy, and prolong patient survival, targeted combination therapy strategies have emerged and become a research focus. This review provides a systematic review of the latest clinical evidence for EGFR-TKI combination therapy with chemotherapy, anti-angiogenic agents, other signaling pathway inhibitors, immunotherapy, and emerging dual-target therapies (such as bispecific antibodies and antibody-drug conjugates). The results indicate that TKIs combined with chemotherapy or bispecific antibody drugs have become one of the key options for first-line treatment; Precision combinations targeting resistance mechanisms (such as MET) is the developmental direction for subsequent lines of therapy; while the combination of TKIs with immune checkpoint inhibitors requires cautious exploration. In the future, personalized combination strategies guided by dynamic molecular profiling, the development of novel drugs, and the optimization of treatment modalities will be key to further overcoming therapeutic bottlenecks.

Keywords: non-small cell lung cancer, EGFR, TKI, combination therapy, resistance, Amivantamab, ADC

1. Introduction

Lung cancer accounts for 18. 0% of all cancer deaths worldwide, ranking first; non-small cell lung cancer (NSCLC) accounts for 85% of lung cancer cases (BRAY F, LAVERSANNE M, SUNG H, et al., 2024). Among these, epidermal growth factor receptor (EGFR) mutations are the most common driver mutations in Asian populations, observed in approximately 40–50% of patients with lung adenocarcinoma. The successful development of EGFR tyrosine kinase inhibitors (TKIs) marked the dawn of the era of precision targeted therapy for NSCLC. As EGFR-TKIs have evolved through successive generations, their efficacy has gradually improved while associated adverse reactions have decreased, extending patients' median progression-free survival (PFS) to over 16 months and overall survival (OS) to more than 3 years (SORIA J C, OHE Y, VANSTEENKISTE J, et al., 2018). However, monotherapy with GFR-TKIs has limitations, as the therapeutic response often fails to improve further due to the development of resistance. Resistance is primarily categorized as primary resistance: approximately 10–30% of patients with EGFR mutations do not respond to initial treatment (SORIA J C, OHE Y, VANSTEENKISTE J, et al., 2018). Acquired resistance: After approximately 9–16 months of treatment,

nearly all patients develop resistance. The mechanisms underlying this resistance are complex and varied, including secondary EGFR mutations (such as T790M), bypass activation (such as MET or HER2 amplification), and histological transformation (such as transformation to small cell lung cancer) (WESTOVER D, ZUGAZAGOITIA J, CHO B C, et al., 2018). Consequently, combination therapy strategies—which aim to enhance tumor control through synergistic mechanisms and multi-target approaches that delay the development of resistance—have become a focal point of current clinical and basic research. This article systematically reviews key clinical research findings on various combination therapy strategies and outlines future directions for development.

2. EGFR-TKI Combined with Chemotherapy

Chemotherapy kills rapidly proliferating cancer cells by interfering with key processes of cell division. Its core mechanisms involve cytotoxic effects such as disrupting DNA structure and function, inhibiting nucleic acid (DNA/RNA) synthesis, and affecting microtubule function; it primarily acts on the cell cycle (particularly during the DNA synthesis and mitosis phases). This enables a synergistic mechanism in combination therapy: EGFR-TKIs target tumor cells that depend on the EGFR signaling pathway, while chemotherapy kills tumor cells that are resistant to EGFR-TKIs, thereby overcoming primary resistance caused by tumor heterogeneity. Current Phase III studies are exploring the value of combination chemotherapy. Results from the NEJ009 study show that gefitinib combined with pemetrexed and carboplatin significantly prolonged PFS (20. 9 months vs. 11. 9 months) and OS (50. 9 months vs. 38. 8 months) compared to gefitinib monotherapy, however, the incidence of Grade 3 or higher treatment-related adverse events (such as hematological toxicity) was higher in the combination group than in the gefitinib group (65. 3% vs. 31. 0%) (HOSOMI Y, MORITA S, SUGAWARA S, et al., 2020). Results from the FLAURA2 study showed that osimertinib in combination with pemetrexed and platinum-based chemotherapy significantly extended the investigator-assessed median PFS from 16. 7 months to 25. 5 months compared with osimertinib monotherapy, reducing the risk of disease progression or death by 38%. A benefit in PFS was also observed among patients with CNS metastases at baseline (24. 9 months vs. 13. 8 months) (PLANCHARD D, JäNNE P A, CHENG Y, et al., 2023). In terms of survival, the median overall survival was 47. 5 months in the osimertinib plus pemetrexed and platinum-based therapy group, compared with 37. 6 months in the osimertinib monotherapy group (P = 0. 02), representing a statistically significant difference; the hazard ratios (HRs) for patients with and without brain metastases at baseline were 0. 72 and 0. 77, respectively (JäNNE P A, PLANCHARD D, KOBAYASHI K, et al., 2026). For patients with the 19del and 21L858R mutations, the hazard ratio (HR) was 0. 76 in both cases. The incidence of Grade 3 or higher adverse events with combination therapy was five times higher than with EGFR-TKI monotherapy, primarily involving hematological (anemia and neutropenia), gastrointestinal (loss of appetite, mucositis, nausea, and vomiting), and fatigue/weakness (LANDRE T, ASSIé J B, CHOUAHNIA K, et al., 2024). This makes the regimen one of the first-line treatment options for advanced NSCLC with EGFR mutations. This combination strategy overcomes primary resistance caused by tumor heterogeneity, particularly in patients requiring rapid symptom relief. Related studies have also confirmed significant benefits in terms of PFS and OS. However, combination chemotherapy inevitably leads to cumulative toxicities, such as myelosuppression, nausea and vomiting, and fatigue (HOSOMI Y, MORITA S, SUGAWARA S, et al., 2020; PLANCHARD D, JäNNE P A, CHENG Y, et al., 2023), which may affect patients' quality of life and treatment adherence.

3. EGFR-TKIs in Combination with Anti-Angiogenic Agents

The vascular endothelial growth factor (VEGF) pathway plays a key role in tumor angiogenesis (OLSSON A K, DIMBERG A, KREUGER J, et al., 2006). Anti-angiogenic drugs (such as bevacizumab and anlotinib) can normalize tumor vasculature, reduce interstitial pressure, and improve drug delivery of TKIs (WILLETT C G, BOUCHER Y, DI TOMASO E, et al., 2004; VIALLARD C, LARRIVéE B., 2017). Results from the FL-ALTER (ZHOU H-Q, ZHANG Y-X, CHEN G, et al., 2024) study showed that gefitinib plus anlotinib provided a significant PFS benefit compared with gefitinib monotherapy (14. 8 months vs. 11. 2 months); in patients with brain metastases, gefitinib plus anlotinib extended median PFS by 5. 5 months (13. 8 months vs. 8. 3 months) compared with gefitinib monotherapy, reducing the risk of progression by 53% (HR = 0. 47). The gefitinib plus anlotinib group had a higher rate of Grade 3 or more severe adverse events (50% vs. 31%) compared with the gefitinib monotherapy group. The NEJ026 (SAITO H, FUKUHARA T, FURUYA N, et al., 2019) study results also confirmed the PFS advantage of erlotinib in combination with bevacizumab (16. 9 vs. 13. 3 months). However, the median overall survival did not show a significant benefit with erlotinib combined with bevacizumab compared to the erlotinib monotherapy group (50. 7 months vs. 46. 2 months; p = 0. 97) (KAWASHIMA Y, FUKUHARA T, SAITO H, et al., 2022). Regarding third-generation EGFR-TKIs, results from the WJOG9717L (KENMOTSU H, WAKUDA K, MORI K, et al., 2022) study showed that osimertinib combined with bevacizumab provided a PFS benefit compared to osimertinib monotherapy, but the difference was not statistically significant (22. 1 months vs. 20. 2 months, p = 0. 213). Afatinib combined with bevacizumab demonstrates some efficacy in the treatment of advanced EGFR-mutated non-small cell lung

cancer following osimertinib resistance, with median progression-free survival and overall survival of 2. 7 months and 9. 3 months, respectively (HATA A, KATAKAMI N, TAKASE N, et al., 2024). Further large-scale RCT studies are needed to confirm its true efficacy and safety. The combination of EGFR-TKIs and anti-angiogenic agents has been shown to significantly prolong PFS and is currently one of the effective treatment options. However, it was associated with a higher rate of Grade 3 or more severe adverse events, including bleeding (RR 1. 22, 95% CI: 0. 53–2. 79; P = 0. 64), hypertension (RR 1. 82, 95% CI: 0. 81–4. 09; P = 0. 15), and dyspnea (RR 1. 11, 95% CI: 0. 58–2. 14; P = 0. 75), particularly in cases of proteinuria (RR 4. 83, 95% CI: 1. 63–14. 31; P=0. 004) and diarrhea (RR 2. 37, 95% CI: 1. 29–4. 35; P=0. 005) (CHEN Z, JIANG S, LI X, et al., 2021). Patients should be closely monitored.

4. EGFR-TKIs in Combination with Other Signaling Pathway Inhibitors (to Target Bypass Activation)

Combination MET inhibitors: MET amplification is one of the most common mechanisms of resistance to EGFR-TKIs, particularly osimertinib (approximately 15–20%) (LEONETTI A, SHARMA S, MINARI R, et al., 2019), this is targeted therapy following the resolution of acquired resistance. The SAVANNAH Phase II study demonstrated that, in patients with osimertinib resistance and high levels of MET amplification or overexpression, the objective response rate (ORR) for the combination of osimertinib and cevotinib reached 32%, with a median progression-free survival (PFS) of 5. 3 months (YANG J C, CHEN Y M, BATRA U, et al., 2025). Tepotinib in combination with gefitinib has also demonstrated activity in the first-line treatment of patients with MET-amplified EGFR mutations (WU Y L, CHENG Y, ZHOU J, et al., 2020), Median PFS: 16. 6 months vs. 4. 2 months; median OS: 37. 3 months vs. 13. 1 months. Several Phase III studies are currently underway to further evaluate the efficacy and safety of EGFR-TKIs in combination with MET inhibitors.

Combination with HER2 inhibitors: HER2 amplification or mutation is also one of the mechanisms of resistance (LEONETTI A, SHARMA S, MINARI R, et al., 2019). The antibody-drug conjugate (ADC) Trastuzumab Deruxtecan has demonstrated groundbreaking efficacy in patients with HER2-mutated non-small cell lung cancer (NSCLC), including those who have previously received EGFR-TKI therapy, with an objective response rate of 55%, a median progression-free survival of 8. 2 months, and a median overall survival of 17. 8 months (LI B T, SMIT E F, GOTO Y, et al., 2022), which offers a new treatment option for these drug-resistant patients. Combination therapy with MEK/AXL inhibitors: For cases involving persistent activation of the downstream RAS/RAF/MEK pathway or AXL activation associated with epithelial-mesenchymal transition (EMT) (TANIGUCHI H, YAMADA T, WANG R, et al., 2019), clinical trial results for combination therapy with trametinib and dabrafenib showed objective response rates and disease control rates of 61. 5% and 92. 3%, respectively. The median PFS was 13. 5 months (WENG C D, LIU K J, JIN S, et al., 2024), while this combination strategy demonstrated a favorable disease control rate, its true efficacy and safety still require further validation.

5. EGFR-TKI Combined with Immunotherapy

TKI-induced tumor cell death can release antigens and enhance immunogenicity, while immune checkpoint inhibitors (ICIs) can lift T-cell suppression; the two may act synergistically (CHEN G, HUANG A C, ZHANG W, et al., 2018). However, clinical practice faces serious challenges. A collaborative Phase 1 study, the CAURAL trial, reported an increased incidence of interstitial lung disease (ILD)-like events in the osimertinib plus durvalumab group in the independent Phase Ib TARTON trial (NCT02143466), with an overall incidence of ILD/pneumonitis as high as 38%, including 13% of Grade 3 or higher events. (OXNARD G R, YANG J C, YU H, et al., 2020) Recruitment for CAURAL has ended early (YANG J C, SHEPHERD F A, KIM D W, et al., 2019). The combination of EGFR-TKIs and ICIs (PD-1/PD-L1 inhibitors) carries a significant risk of additive toxicity; in particular, the incidence of interstitial pneumonia is significantly higher than with either agent alone. Five out of seven patients (71. 4%) receiving pembrolizumab plus gefitinib experienced Grade 3 or 4 hepatotoxicity, leading to permanent discontinuation of treatment in four patients. (YANG J C, GADGEEL S M, SEQUIST L V, et al., 2019) The final analysis of the IMpower150 (SOCINSKI M A, NISHIO M, JOTTE R M, et al., 2021) clinical trial showed that atezolizumab in combination with bevacizumab and chemotherapy (ABCP) continued to demonstrate an overall survival (OS) benefit in patients with EGFR-mutated NSCLC, with a median OS of 19.5 months—a significant improvement over chemotherapy alone. The first interim results from the ORIENT-31 (LU S, WU L, JIAN H, et al., 2022) trial further confirm that the combination of sintilimab with the bevacizumab biosimilar IBI305 and chemotherapy significantly improves PFS (6. 9 vs. 4. 3 months, HR 0. 46) in patients whose disease has progressed on EGFR-TKIs. However, it was associated with an increased incidence of immune-related adverse events (irAEs) (relative risk: 2. 02, 95% CI: 1. 45–2. 81, p < 0. 0001) and grade 3–5 adverse events (irAEs, RR: 2. 02, 95% CI: 1. 03–3. 98, p = 0. 04) (CHEN X, ZHAO J, ZHANG W, et al., 2025). The above clinical trials indicate that first-line concurrent combination therapy with EGFR-TKIs and ICIs does more harm than good in most patients. However, combination immunotherapy demonstrates some efficacy following resistance to EGFR-TKIs. Immunotherapy may be used as sequential therapy for

EGFR-mutated non-small cell lung cancer after resistance to EGFR-TKIs.

6. Dual-Target Combination Therapy

Amivantamab: A bispecific antibody whose core mechanism of action involves simultaneously targeting two key driver pathways: the epidermal growth factor receptor (EGFR) and the c-MET pathway. It exerts potent antitumor activity through a dual synergistic mechanism and has demonstrated unique advantages, particularly in overcoming resistance to EGFR-TKIs. The CHRYSALIS (PARK K, HAURA E B, LEIGHL N B, et al., 2021) study demonstrated sustained efficacy in patients who had developed resistance to osimertinib and whose disease had progressed despite chemotherapy. The Phase III MARIPOSA (ROSENFELD R., 2025) study demonstrated that, in first-line treatment, the combination of Amivantamab and the third-generation TKI lazertinib significantly prolonged PFS (23. 7 vs. 16. 6 months) compared to osimertinib monotherapy, and is expected to become a new option for first-line treatment. This drug also demonstrates some efficacy against EGFR exon 20 insertion mutations (YUN J, LEE S H, KIM S Y, et al., 2020), but it is associated with an increased incidence of adverse reactions; the combination group reported a higher rate of Grade 3 or higher adverse events (75% vs. 43%).

Ivonescimab: a bispecific antibody targeting PD-1 and VEGF. Results from the AK112-201 (ZHAO Y, CHEN G, CHEN J, et al., 2023) study demonstrate outstanding efficacy when combined with chemotherapy: an ORR as high as 50% and an mPFS of 8. 2 months, significantly outperforming historical controls treated with chemotherapy alone (ORR of approximately 20–30% and mPFS of approximately 4–5 months). Monotherapy demonstrated activity: the ORR reached 26. 7% and mPFS reached 7. 1 months, far exceeding the response rates of less than 10% observed with traditional PD-1 monotherapy in similar patient populations, confirming the advantages of its bispecific antibody design.

7. Challenges

EGFR-TKIs represent a major milestone in precision targeted therapy for non-small cell lung cancer (NSCLC). First-generation TKIs (gefitinib and erlotinib) effectively inhibit classic EGFR mutations, significantly improving objective response rates (60%–70%) and progression-free survival (PFS) compared to chemotherapy. Additionally, their side effects (such as rash and diarrhea) are generally easier to manage than those of chemotherapy, thereby improving patients' quality of life. With the continuous development and advancement of TKIs, disease control rates have steadily improved for patients with advanced EGFR-mutated NSCLC. However, most patients experience disease progression approximately 9–16 months after receiving monotherapy with an EGFR-TKI. The mechanisms of resistance are complex and diverse, including on-target mutations (such as the T790M mutation following TKI treatment), bypass activation (such as MET or HER2 amplification), and histological transformation (such as progression to small cell lung cancer). The shift from single-agent targeted therapy to combination targeted therapy aims to delay the development of drug resistance through the synergistic action of multiple mechanisms. To overcome the limitations of single-agent therapy, various combination strategies have been explored and have shown promise; however, significant challenges remain. Combination therapy is associated with a broader range of more severe adverse reactions and places higher demands on patients' physical condition. Tumor heterogeneity results in complex and variable mechanisms of drug resistance. The greatest challenge lies in using liquid biopsy (ctDNA) for real-time dynamic monitoring to identify the most effective combination therapy for patients at the optimal time, thereby avoiding "blind combination therapy." Financial burden and drug accessibility: Many novel combination therapies (particularly bispecific antibodies and ADCs) are prohibitively expensive, limiting their clinical application.

8. Future Research Approaches and Directions

Future breakthroughs will depend on a shift in treatment strategies toward "precision, personalization, and dynamism." Precision and personalized treatment are based on "one-to-one" therapy guided by dynamic molecular subtyping: Future treatment decisions will rely heavily on repeated biopsies (tissue or liquid biopsies) conducted "during treatment" and "after resistance develops." By monitoring for the early emergence of resistance via ctDNA, combination regimens can be adjusted in a timely manner. Optimizing treatment modalities and sequences: Exploring optimal treatment sequences (e. g., "first-line combination therapy" vs. "sequential monotherapy followed by precision combination therapy") to achieve the best balance between efficacy and toxicity. The revolution in novel drugs and exploration of mechanisms: In-depth exploration of bispecific antibodies and antibody-drug conjugates (ADCs): This is currently the most groundbreaking area of research. Future research will not be limited to new targets (such as TROP2 and B7-H3); it will also need to explore combinations of novel ADCs and bispecific antibodies, as well as how to shift the timing of treatment to the first-line setting or even the adjuvant/neoadjuvant stages. Drug development to overcome specific resistance mechanisms: Development of fourth-generation EGFR-TKIs targeting grade 3 mutations, such as C797S, that arise following resistance to osimertinib. In summary, the treatment of EGFR-mutated NSCLC has evolved from an era of precise but short-lived efficacy with single-agent TKIs to a new era of long-term disease control

centered on combination therapy. Through the continuous emergence of innovative drugs and optimized treatment strategies, the ultimate goal is to transform advanced EGFR-mutated NSCLC into a chronic disease that can be effectively managed over the long term.

9. Conclusion

Targeted therapy for EGFR-mutated NSCLC has evolved from the era of monotherapy to a new era of combination therapy. Currently, TKI-chemotherapy combinations or TKI-bispecific antibody combinations have become standard options in first-line treatment. Precision combination therapies targeting mechanisms of acquired resistance (such as those targeting MET), as well as novel dual-target therapies represented by bispecific antibodies and ADCs, show great potential for breaking through the bottlenecks in second-line treatment. However, the combination of TKIs and immunotherapy must be approached with extreme caution. Individualized combination therapy strategies guided by real-time molecular monitoring, combined with a growing number of innovative drugs, are expected to further prolong survival in patients with EGFR-mutated NSCLC and ultimately achieve the goal of long-term disease control.

Table 1.

Strategy	Advantages/Mechanism of Action	Side Effects and Adverse Reactions	Representative research/evidence
TKI+ chemotherapy	Chemotherapy kills tumor cells that are resistant to EGFR-TKIs	Cumulative toxicity: Myelosuppression, nausea and vomiting, and fatigue are significantly increased, affecting quality of life and treatment adherence.	FLAURA2 Study: Median PFS of 25. 5 months with osimertinib plus chemotherapy versus 19. 0 months with osimertinib monotherapy; median OS extended from 37. 6 months to 47. 5 months.
TKI+ anti-angiogenic agents	Inhibit the VEGF pathway, normalize tumor vasculature, and improve drug delivery.	Specific toxicities: hypertension, proteinuria, risk of bleeding (hemoptysis), thromboembolic events, gastrointestinal perforation.	RELAY Study: Median PFS was 19. 4 months for erlotinib plus ramucirumab versus 12. 4 months for erlotinib monotherapy.
TKI+ other targeted therapies (to address bypass pathways)	Overcoming acquired resistance, such as that associated with specific resistance mechanisms like MET amplification	Therapeutic efficacy is highly dependent on precise biomarkers; new mechanisms of resistance may emerge.	MET amplification: Osimertinib + Sevotinib, ORR 32%.
Bispecific antibody	Simultaneously block multiple targets or signaling pathways	such as rash, hypoalbuminemia, risk of venous thromboembolism, and high cost associated with Amivantamab	MARIPOSA: Amivantamab (EGFR/MET bispecific antibody) + lazertinib vs osimertinib demonstrated a significant prolongation of PFS (23. 7 vs 16. 6 months) and reduced the risk of acquired C797S mutations and MET amplification by 5-fold and 4-fold, respectively.
TKI+ immunotherapy	Boost the immune system	The incidence of serious adverse reactions, such as interstitial pneumonia and hepatotoxicity, increased significantly, leading to the early termination of several studies. The efficacy remains unclear.	TATTON and CAURAL, and the incidence of Grade 3–5 adverse events was higher in the combined group.

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