Advances in Targeted Therapy for EGFR-mutated NSCLC Brain Metastasis

Jingxuan Pang * and Lewei Li

School of Clinical Medicine, Chengdu Medical College, Chengdu, China
Email: China.211171698@qq.com (J.P.); China.lillewei@outlook.com (L.L.)
*Corresponding author

***Abstract*—Lung cancer is one of the malignant tumors with the highest morbidity and mortality rates in the world, of which Non-Small Cell Lung Cancer (NSCLC) accounts for approximately 80%-85%. Epidermal Growth Factor Receptor (EGFR) mutations are prevalent in Asian NSCLC patients, and such patients are more prone to brain metastases. With the iterative development of EGFR-Tyrosine Kinase Inhibitors (EGFR-TKIs), significant progress has been made in therapeutic strategies for brain metastases from EGFR mutation-positive NSCLC. This paper systematically reviews the research advances in targeted therapy in this field. Based on the mechanism of impact, the intracranial activity and clinical application of the first-to fourth-generation EGFR-TKIs are elaborated in detail, and the R&D trends of the third-generation drugs and their resistance-related fourth-generation drugs are analyzed. The combination of targeted drugs with chemotherapy, radiotherapy, antiangiogenic therapy and other targeted drugs is also discussed in this paper. Furthermore, the paper presents the breakthrough of a new generation of high blood-brain barrier penetrating drugs. Finally, this paper proposes the prospects of transforming lung cancer brain metastases from terminal events to chronic diseases that can be managed for a long time by optimizing full-course management strategies.**

***Keywords*—non-small cell lung cancer, EGFR mutations, brain metastases, targeted therapy, EGFR-tyrosine kinase inhibitors, combination therapy, blood-brain barrier, drug resistance mechanism**

I. Introduction

Lung cancer is one of the malignant tumors with the highest morbidity and mortality in the world. The incidence and mortality of lung cancer in China rank first, with about 1,060,600 new cases (22.0%) and about 733,300 deaths (28.5%) in 2022 [1, 2]. Smoking is the main risk factor, but the ratio of non-smoking-related lung cancer is increasing, which is associated with air pollution, occupational exposure, and genetic susceptibility [3]. Non-Small Cell Lung Cancer (NSCLC) accounts for 80%–85% of cases, among which the Epidermal Growth Factor Receptor (EGFR) mutation rate is 30%–50% in Asian patients, which is much higher than that in Europe and America (10%–15%) [4].

EGFR mutations (such as exon 19 deletion, L858R) constitutively activate downstream signaling pathways, promote tumor proliferation and metastases [5], and become the key therapeutic target of NSCLC. Patients with positive EGFR mutations are more likely to develop CNS metastases [6]. Brain metastases refer to brain parenchymal metastases, and about 10%–15% are present at initial diagnosis and 26%–53% during the disease [7, 8]. EGFR mutants have a higher risk of brain metastasis (70% in some studies), which is the clinical focus and difficulty. Whereas the wild type is 15%–25% [9], it is related to mutations that upregulate VEGF and MMPs, enhancing blood-brain barrier penetration and brain microenvironment support [10].

EGFR-Tyrosine Kinase Inhibitors (EGFR-TKIs) improve patient prognosis, but there are still bottlenecks in the treatment of brain metastases. Specifically, the blood-brain barrier limits drug penetration; the cerebrospinal fluid/plasma concentration ratio of the first-generation drug is only 1%–5%; the third-generation osimertinib is 15%–25%; and some patients have poor efficacy [11]. Approximately 40% of patients develop acquired drug resistance after one or two years, with diverse mechanisms and difficulty in secondary biopsy [12]. Although combined radiotherapy improves local control, it may increase the risk of brain necrosis or cognitive impairment, and the best sequential strategy is unknown [13]. Clinical therapies mostly use brain metastasis as a subgroup analysis, with insufficient prospective large-scale studies and evidence-based evidence [14]. In the future, it is necessary to develop highly penetrating drugs, explore drug resistance mechanisms, and optimize multi-modal therapy. This paper reviews the research advances of targeted therapy of brain metastasis in EGFR-mutated NSCLC as follows, providing a clinical perspective.

- Targeted Therapeutic Mechanism

With the development of medicine, the first, second, and third generations of EGFR-TKIs have been applied in clinical practice in succession, and the fourth generation of

Manuscript received July 22, 2026; accepted August 28, 2026; published September 23, 2026.

TKIs is in the exploratory stage. In clinical practice, the first to third generations of EGFR-TKIs have brought more effective treatment options and improved survival likelihood for NSCLC patients. However, with the deepening of clinical use, drug resistance has become increasingly significant, and the treatment burden of NSCLC has further increased.

Fig. 1 presents the EGFR antibody-mediated targeting mechanism. EGFR monoclonal antibodies (such as cetuximab) block the binding of natural ligands (i.e., EGF or TGF-α) to receptors by competitively binding to the EGFR extracellular domain, thereby inhibiting receptor dimerization and abnormal activation of downstream signaling pathways [15].

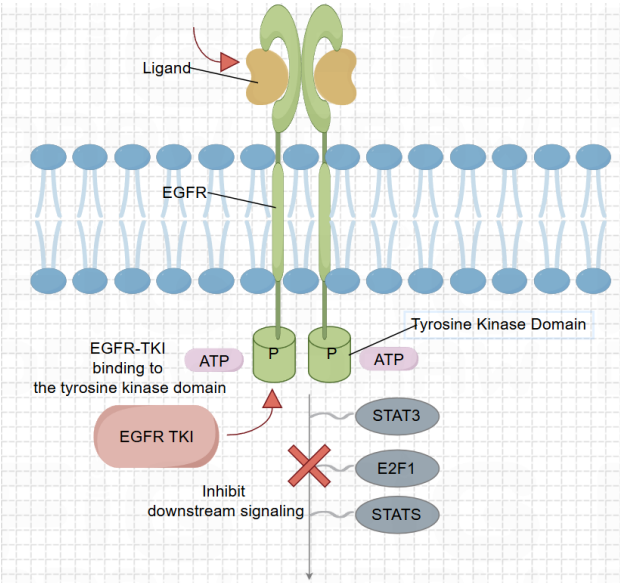

Fig. 1. EGFR Antibody-mediated targeting mechanism.

Fig. 2 presents the molecular mechanism of EGFR-TKI targeting. EGFR-TKI (i.e., osimertinib) inhibits kinase autophosphorylation and downstream signaling (i.e., MAPK and PI3K-AKT pathways) by binding to the ATP-binding site of the EGFR intracellular tyrosine kinase domain, and finally arrests tumor cell proliferation and survival [16].

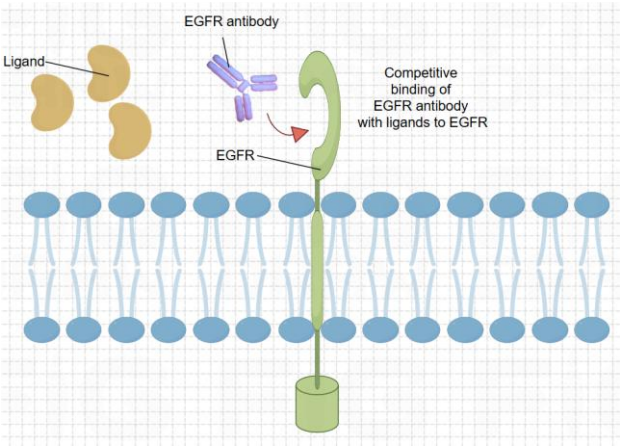

Fig. 2. EGFR targeted therapy mechanism.

II. Mechanisms of Targeted Therapy

A. Mechanism of Monotherapy with Targeted Therapy

With EGFR as an example, normal EGFR regulates cell growth and proliferation. After the Receptor Tyrosine Kinase (RTK) is activated in cancer cells, the intracellular domain of EGFR is self-phosphorylated, and the formed phosphotyrosine residues act as adaptor molecule docking points to induce downstream signaling, which results in uncontrolled cell proliferation and tumors [17]. Targeted drug therapy aims to design drugs genetically for defined oncogenic sites and selectively bind mutant sites to kill tumor cells without effect on surrounding normal tissues [18]. At present, clinical EGFR-targeting drugs are divided into antibodies and Tyrosine Kinase Inhibitors (TKIs). Antibody drugs competitively bind to EGFR with ligands, block ligand activation, inhibit EGFR dimer formation, and block downstream signaling pathways, thereby inhibiting tumorigenesis [15]. EGFR-TKIs competitively bind to the tyrosine kinase domain with ATP to prevent EGFR autophosphorylation, thus inhibiting the activation of downstream signaling pathways and achieving tumor inhibition [16].

B. Mechanism of Targeted Combination Therapy

In the treatment of brain metastases of EGFR-mutated NSCLC, targeted combination therapy demonstrates unique advantages. Its mechanisms mainly include synergistic inhibition of tumor growth, enhancement of blood-brain barrier penetration, and delay of drug resistance. In preclinical models, EGFR-TKI can increase radiation response by promoting radiation-induced apoptosis, inhibiting cell cycle, DNA damage repair, accelerating proliferation, and angiogenesis [19]. In addition, combination therapy can inhibit tumor heterogeneity and bring significant clinical benefits in patients with NSCLC who develop resistance mechanisms [20]. The combination of multiple means improves patient prognosis, and targeted combination therapy has been an innovative treatment worthy of further exploration in the future.

III. Clinical Targeted Therapy

Compared with traditional chemotherapy, due to the limitation of the Blood-Brain Barrier (BBB) and the blood-tumor barrier, it is difficult for drugs to reach effective intracranial concentrations. Thus, the treatment for brain metastasis is mainly local intervention. Currently, EGFR-TKIs have become the first-line treatment option for EGFR-mutant NSCLC [21].

A. EGFR-TKI Monotherapy

1) First-generation EGFR-TKIs

Commonly used first-generation EGFR-TKIs in clinical practice include icotinib, erlotinib, and gefitinib, which reversibly bind to the ATP-binding site of EGFR, block cell growth, and induce cell death. Gefitinib and erlotinib have been approved globally for EGFR-mutant NSCLC,

and icotinib has been approved in China [22].

A multicenter phase III study (BRAIN)onfirms a significant benefit of icotinib in intracranial therapy in patients with EGFR-mutant NSCLC and multiple BRAIN metastases [2]. These findings suggested that icotinib may be a better first-line treatment option for patients with brain metastases. To compare the differences in CNS control between the two drugs, Li Mengxia et al. conducted a retrospective study. It is observed that erlotinib presents a trend toward prolonging the median central nervous system Time-To-Progression (nTTP) in patients with EGFR-mutant Brain Metastases (BM) compared with gefitinib. For patients with pre-existing brain metastases prior to EGFR-TKI treatment, erlotinib as first-line treatment significantly prolongs the median nTTP (30 months vs 15.8 months, $p = 0.024$) [23]. For patients with brain metastases, several studies propose that [24–26] erlotinib has better central penetration in patients with EGFR mutations in BM. Meanwhile, several studies insist that gefitinib is effective in brain metastases [27–30]. These still need to be verified by prospective randomized controlled studies.

Although the first generation of TKI brings hope for survival to patients, most patients develop acquired drug resistance [31]. The most common and most studied is the T790M mutation, accounting for about 50%–60%.

2) Second-generation EGFR-TKIs

To overcome the acquired drug resistance of the first-generation EGFR-TKIs, researchers developed irreversible second-generation EGFR-TKIs (afatinib and dactinib), which can covalently bind with EGFR to enhance the long-lasting inhibitory effect.

Afatinib: According to two comprehensive clinical trials, LUX-Lung 3 [32] and LUX-Lung [33], the median CNS progression time is longer in the afatinib group than in the chemotherapy group in both trials (15.2 vs 5.7 months; 15.2 vs 7.3 months) [34]. The LUX-Lung 7 study indicates that the presence of baseline brain metastases fails to impair the therapeutic benefit of afatinib [35]. Subgroup analysis of clinical trial data also confirms that afatinib has therapeutic activity in EGFR mutation-positive NSCLC patients and is not affected by the presence of metastases [36, 37].

Dacotinib: A Phase II study in patients with EGFR mutations and brain metastases indicates that the intracranial ORR of dacotinib is 68.8% [38]. Another prospective Phase II clinical study confirms that dacotinib (iORR of 66.7% and median iPFS of 16.6 months) demonstrates strong systemic and intracranial efficacy with manageable adverse events in NSCLC patients with EGFR mutations and severe brain metastases, thus supporting its use as a first-line treatment [39].

Although the second-generation EGFR-TKIs can achieve longer-lasting efficacy through irreversible binding, they lack selectivity for EGFR; they inhibit mutant EGFR and wild-type EGFR, resulting in more adverse reactions and failure to significantly improve the drug resistance caused by the T790M mutation [40, 41].

3) Third-generation EGFR-TKIs

To address the poor selectivity, limited blood-brain barrier penetration, and T790M drug resistance of the first- and second-generation EGFR-TKIs, the researchers have developed third-generation EGFR-TKIs, mainly including osimertinib, ametinib, fumetinib, befortinib, lazetinib, etc.

Osimertinib: Osimertinib is a third-generation irreversible EGFR-TKI that stably binds to the C797 site, inhibits tyrosine kinase phosphorylation, induces tumor cell death, and has good blood-brain barrier penetration [11, 42–45]. The AURA3 study validates the efficacy of osimertinib on the central nervous system [10]. For patients with advanced NSCLC with T790M mutations and disease progression during first-line EGFR-TKI therapy (including patients with CNS metastasis), osimertinib is significantly better than platinum-containing chemotherapy (iPFS: 11.0 months vs. 4.2 months) [44]. According to the FLAURA study [10, 46], osimertinib has advantages in intracranial efficacy, and the 18-month PFS rates of patients with brain metastases are 58% and 40%, respectively [11]. These results suggest that osimertinib reduces the risk of CNS progression.

Ametinib: The AENEAS study shows that the first-line treatment of EGFR-mutated advanced NSCLC with ametinib improves CNS PFS and reduces the risk of CNS progression compared with gefitinib [47]. The ACHIEVE trial (which allows the inclusion of patients with neurological symptoms) indicates that high-dose ametinib has a median PFS of more than 20 months and an intracranial response rate of more than 85% in patients with EGFR-mutant NSCLC brain metastases [48].

Furmonertinib: Furmonertinib has been approved in China for the first-line treatment of advanced NSCLC with EGFR mutations [49]. It has high fat solubility (LogP = 4.77) as a non-P-gp substrate, and the active metabolite can “dual-channel into the brain”. Animal models indicate that the brain/plasma exposure ratio is better than that of osimertinib and ametinib [50]. A Phase IIb study (NCT03452592) is being conducted, enrolling numerous patients with metastases in the central nervous system (48%) and carrying EGFR L858R [51]. The results show its strong strength in the treatment and prevention of metastases in the central nervous system [51]. FURLONG (NCT03787992) preliminary results prove that fumetinib significantly prolongs CNS PFS compared to gefitinib (20.8 vs 9.8 months, $P = 0.0011$), with a CNS ORR of 91% and a DCR of 100% in patients with measurable CNS lesions [52].

Befotertinib: Befotertinib is a highly selective third-generation EGFR-TKI that penetrates the blood-brain barrier. According to a first-line study of (IBIO-103) [NCT04206072] [53], befortinib significantly improves intracranial PFS (24.9 vs 15.2 months) and intracranial ORR (92.3% vs 55.6%) in patients with brain metastases compared with icotinib [53]. In the second-line study of IBIO-102 [NCT038611566], patients with brain metastases have a median OS of 23.0 months [54]. Based on the above studies, befortinib has been approved in China for the first-and second-line treatment of

EGFR-mutant NSCLC [55].

Lazetinib: Lazetinib (YH25448, JNJ-73841937) is an oral and highly effective brain tissue-penetrating EGFR TKI [53]. Analysis in LASE201 [NCT03046992] [56] and LASER301 [NCT04248829] [57] indicate a clinically meaningful therapeutic benefit of lazetinib in patients with CNS metastases (median PFS: 20.6 vs 9.7 months, HR 0.45) [57]. The comprehensive analysis shows that the median iPFS in the iFAS population is 27.7 months, and the iORR in the cEFR population is 92% [58]. A phase II study proves that patients with CNS progression following prior EGFR-TKI therapy have an intracranial ORR of 55% with razetinib, a median iPFS of 15.8 months, and a cerebrospinal fluid permeation rate of 46.2% [56, 59].

Although osimertinib has a high response rate to T790M mutations, acquired drug resistance is still inevitable, and the main mechanisms include the C797S mutation, the C-MET amplification, small cell lung cancer transformation, and downstream gene activation [40]. This is a key clinical challenge that requires a new solution.

4) Fourth-generation EGFR-TKI

The R&D of fourth-generation EGFR-TKIs aims to overcome resistance to third-generation drugs, especially for resistance mechanisms such as the C797S mutation and the T790M/C797S co-mutation. Current drug candidates in the clinical stage include BDTX-1535, JIN-A02, etc. BDTX-1535 (NCT05256290) [60] achieved an overall response rate of 50% in phase I studies and easily crossed the blood-brain barrier [61, 62], which provides hope for patients with brain metastases. The oral presentation data of JIN-A02 (Phase I/II, NCT05394831) at the 2025 ASCO Annual Meeting indicate that JIN-A02 exhibits clear intracranial activity in patients after EGFR-TKI resistance and is the most direct clinical evidence of brain metastasis in the current four-generation TKI [63]. BBT-207 (NCT05920135) is under development and exhibits intracranial antitumor activity in preclinical data at the 2023 American Association for Cancer Research (AACR) Annual Meeting [64]. Fourth-generation EGFR-TKI drugs have shown potential in both preclinical and early clinical data. In the future, attention should be paid to their long-term safety, combination therapy, and ability to cover rare mutations.

5) New-generation EGFR-TKI

Zorifertinib (AZD3759) is the first oral EGFR-TKI specifically designed for the treatment of advanced non-small cell lung cancer with central nervous system metastases, which can completely penetrate the blood-brain barrier [65]. EVEREST is a phase 3 randomized controlled trial in patients with EGFR mutation-positive NSCLC with central nervous system metastases [66]. Compared with the first-generation EGFR-TKI, zolitinib alone can achieve a high response rate of intracranial lesions. The drug is recommended by the *China Driver Gene-Positive NSCLC Brain Metastasis Clinical Diagnosis and Treatment Guidelines (2025 Edition)* in December 2024 as one of the preferred regimens for initial targeted therapy of EGFR classical mutation NSCLC brain metastasis (Class 2A) [67].

B. Targeted Combination Therapy

At present, due to the diverse resistance mechanisms of third-generation EGFR-TKIs, the combination of different small-molecule inhibitors is one of the strategies to overcome targeted resistance. Targeted combination therapy has become the main research direction for clinical EGFR mutation-positive advanced NSCLC.

1) Targeted combination chemotherapy

Chemotherapy drugs can destroy the tumor microenvironment, normalize tumor blood vessels, and improve the penetration of TKI drugs in tumor tissue. Besides, it can cooperate with TKI to inhibit tumor cell growth through the regulation of the cell cycle [19]. According to the results of a phase III clinical trial (FLAURA2), for patients with advanced NSCLC with EGFR mutations, osimertinib combined with chemotherapy significantly prolongs overall survival compared with osimertinib monotherapy, and in patients with baseline CNS metastases, the combination therapy reduces the risk of CNS progression or death by 42% [53, 68, 69]. The GAP BRAIN Phase III trial in Chinain dicates that gefitinib in combination with chemotherapy significantly prolongs intracranial progression-free survival (15.6 vs. 9.1 months) compared with monotherapy in patients with NSCLC with EGFR mutations and BRAIN metastases [27].

2) Targeted combination radiotherapy

When targeted drugs are combined with radiotherapy, radiotherapy destroys the structural integrity of the blood-brain barrier and promotes more targeted drugs to enter brain metastases. Meanwhile, targeted drugs can interfere with the DNA damage repair of tumor cells after radiotherapy and enhance radiotherapy sensitivity. The two complement each other [70]. A meta-analysis pooling treatment response and toxicity from 18 studies found that for patients with NSCLC brain metastases. WBRT + EGFR-TKIs improve treatment response rates and one-year survival without increasing treatment toxicity except for rash [71]. A retrospective analysis proposes that combined Stereotactic Radiotherapy (SRT) in patients with brain metastases significantly improves iPFS and prolongs OS regardless of whether patients receive third-generation EGFR-TKI therapy [72]. Another retrospective multi-institutional analysis indicates that in patients with EGFR-mutant NSCLC with brain metastases, EGFR-TKI therapy combined with SRS can prolong OS [73]. In addition, studies of three-generations EGFR-TKI in combination with SRS are ongoing (NCT03535363, NCT03769103, NCT03497767).

3) Targeted combination immunization

Targeted combination immunization strategies in clinical practice have not shown clear benefits, and the risk of toxicity is increased [74–76]. In patients with brain metastases after EGFR-TKI resistance, the results of the HARMONi-A study (NCT05184712) indicate that the combination of evocizumab (PD-1/VEGF dual antibody) with chemotherapy significantly improves intracranial

progression-free survival (5.75 months vs. 4.14 months) [77]. In addition, the final analysis results of the HARMONi global phase III study (NCT06396065) were announced at the 2025 WCLC, and evocizumab combined with chemotherapy significantly improves PFS in patients with NSCLC after EGFR-TKI resistance (HR = 0.52) [78]. A new treatment option is provided for patients with brain metastases after EGFR-TKI resistance.

4) Targeted therapy combined with anti-angiogenic agents (VEGR)

In EGFR-mutant NSCLC patients with brain metastases, the combination of EGFR-TKIs and anti-angiogenic agents exert synergistic effects, primarily through dual modulation of both tumor cells and the tumor microenvironment [79, 80].

Bevacizumab is a recombinant anti-Vascular Endothelial Growth Factor (VEGF) monoclonal antibody that targets the VEGF signaling pathway, thus inhibiting angiogenesis and tumor growth [81]. The subgroup analysis of the ARTEMIS (CTONG1509) study indicates that erlotinib in combination with bevacizumab significantly prolongs PFS compared with erlotinib alone in patients with asymptomatic brain metastases (17.9 months vs. 11.1 months) [82]. Two meta-analyses [79, 83] confirm this result. Multiple studies of osimertinib in combination with bevacizumab fail to show superior efficacy over the single agent for third-generation TKIs (WJOG-8715L [84], WJOG-9717L [85], BOOSTER [86]). However, osimertinib in combination with ramurumab has potential, with the JVDL study (40% baseline brain metastases) and the RAMOSE trial (46% baseline brain metastases) showing that the intracranial efficacy of the combination regimen deserves validation [87, 88].

Anlotinib is an oral small molecule multi-target anti-angiogenic drug, which has the dual effects of anti-tumor angiogenesis and inhibiting tumor cell growth [89]. The post hoc analysis of the ALTER0303 study (NCT02388919) proves that anlotinib alone can benefit patients with advanced NSCLC with brain metastases [90]. At the 2023 IASLC World Lung Cancer Progress (WCLC), the latest data from the AWLAYS study (amertinib + anlotinib) and a phase II clinical study (NCT04978753) that include only patients with brain metastases confirm the intracranial efficacy of amertinib plus anlotinib, providing a highly effective and chemotherapy-free treatment option for patients with brain metastases [91]. The AUTOMAN study (osimertinib + anlotinib) likewise observes a trend in efficacy in the brain metastasis subgroup consistent with the overall population [92]. Preliminary data from another ATTENTION study (ametinib + apatinib) present an ORR of 100% in the brain metastasis subgroup (60% in the monotherapy group, P=0.04). However, we still need to note that the toxicity brought by the combination of anlotinib and a third-generation EGFR-TKI is not negligible [93].

5) Dual-targeted combination therapy

a) EGFR-TKI in combination with EGFR-TKI

The first and third generations of EGFR-TKIs have complementary resistance mechanisms. The first generation of TKI is effective against the C797S mutation without T790M [94], while the third generation of TKI can overcome the T790M mutation [95]. On this basis, the FOCUS-I study explored the efficacy of fumetinib in combination with icotinib in the first-line treatment of EGFR-mutant NSCLC [96]. The results indicate that the combined protocol is particularly prominent in brain metastasis control (median iPFS: 24.2 months), and the safety is manageable [96], which still needs to be validated in a Phase III study. However, it ushers in a promising direction for the treatment of EGFR-mutant NSCLC, especially the “dual-targeted combination” strategy.

b) EGFR-TKI + EGFR/MET bispecific antibody

Amilvantamab (JNJ-61186372) is a bispecific antibody targeting EGFR and MET, which can exert anti-tumor effects through direct inhibition of signaling pathways [97] and Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) [98]. Its combined regimen with third-generation TKI lazetinib exhibits outstanding intracranial activity in EGFR-mutant NSCLC. In the Phase III MARIPOSA study [99], first-line use of amivantamab in combination with lazetinib versus osimertinib alone significantly prolongs PFS and OS, with more significant benefit in the brain metastasis subgroup (3-year intracranial PFS rate 36% vs 18%) [100]. CHRYSALIS-2 (NCT04077463) (Cohort A) [101] studies also confirm its exact intracranial activity. In second-line therapy, the MARIPOSA-2 study indicates that amivastumab in combination with chemotherapy ± razetinib significantly prolongs intracranial PFS in patients who progress after osimertinib resistance [102].

c) EGFR-TKI in combination with MET inhibitor

Targeting EGFR-TKI resistance caused by secondary MET amplification, MET inhibitor in combination with EGFR-TKI is an effective treatment [103]. The SAVANNAH study shows that in patients with EGFR-mutant NSCLC with high MET amplification/overexpression, osimertinib combined with savoltinib significantly improves ORR and PFS compared with monotherapy, and demonstrates the potential of preventing new CNS lesions in patients without baseline brain metastases [104]. The INSIGHT 2 study evaluates terpotinib in combination with Osimertinib, with a 79.2% intracranial disease control rate in patients with brain metastases present at baseline [105].

IV. Discussion

With the widespread application of the third-generation EGFR-TKIs, the treatment of EGFR-mutated NSCLC brain metastases has entered an era of precision and individualization. Based on existing evidence-based medical evidence, the evaluation of different treatment strategies needs to comprehensively consider intracranial

efficacy, systemic control, toxicity spectrum, and patient quality of life [67].

A. Clinical Evaluation and Selection of Different Intetrgenerational TKIs

For patients with newly treated EGFR classical mutation (19del/L858R) with brain metastasis, the third generation EGFR-TKIs have become standard treatment for their excellent intracranial activity. The FLAURA study [10, 46] confirms a complete Response Rate (CR) of 41% with osimertinib alone in patients with brain metastases. The AENEAS study indicates that ametinib compared with gefitinib significantly prolongs CNS Progression-Free Survival (PFS) (29.0 months vs. 8.3 months) [47]. However, for patients who have developed T790M resistance mutations after using first- and second-generation TKIs, switching to third-generation drugs such as osimertinib remains the preferred strategy [67]. Notably, for the EGFR 21L858R mutation subgroup, studies suggest that the combination of a third-generation TKI with chemotherapy may bring better benefits, and prospective trials need to be conducted in the future [106].

B. Applicable Boundary of Combination Therapy Modalities

Combination therapy increases the toxicity burden while improving efficacy. The FLAURA2 [45] study demonstrates that although osimertinib combined with chemotherapy reduces the risk of CNS progression by 42%, the incidence of grade ≥3 adverse events is as high as 64% (29% in the single-agent group). The MARIPOSA study [53] also confirms that while evantumab in combination with lazetinib significantly improves PFS in patients with brain metastases, venous thromboembolic events increase (40% vs 11%) [99]. Thus, for patients with high tumor burden, symptomatic disease, or poor prognosis (e.g., L858R mutation, multiple brain metastases), intensive regimens may be preferred. For asymptomatic and small-volume brain metastases, the third-generation TKI monotherapy is still the fundamental option for both efficacy and safety [106].

C. Optimization of Treatment Sequence Strategies

With the continuous optimization of first-line treatment strategies, the selection of initial treatment options directly affects the management path after subsequent drug resistance. The "Z + 3" model (first-line zolitinib sequential third-generation TKI) proposed by the EVEREST study achieves a median overall survival (OS) of 37.3 months, providing insights for the whole-course management of patients with brain metastases [66]. In response to bypass resistance mechanisms such as MET amplification, TATTON and SAVANNAH studies confirm that osimertinib combined with savoltinib can overcome drug resistance and demonstrate the potential of preventing new CNS lesions in patients without baseline brain metastases [104, 107, 108]. It is suggested that accurate sequencing based on the drug resistance mechanism is the key to prolonging survival.

D. Current Treatment Status and New Drug Development

Current treatment strategies for EGFR-mutated NSCLC brain metastases have shifted from a single-agent sequential model with intergenerational drug change as the core to combination therapy characterized by multi-mechanism synergy.

Zolitinib, as the world's first EGFR-TKI approved for brain metastasis from lung cancer, overcomes the physical barrier with its 100% blood-brain barrier penetration rate [65]. The EVEREST study indicates that the median intracranial progression-free survival of first-line treatment with zolitinib is 15.2 months [66], which is expected to become a new foundation of first-line treatment. Idotinib (TY-9591) is a deuterated derivative of osimertinib [109]. The interim analysis of its pivotal phase II ESAONA study (NCT05948813) proves that in patients with EGFR mutations and brain metastases, the iORR of the idotinib group is significantly better than that of the osimertinib group (91.0% vs. 75.2%) [110]. At present, the new drug marketing application of idotinib has been accepted by the National Medical Products Administration (NMPA) of China in February 2026 and included in the priority review procedure. It is intended to be used for the first-line treatment of locally advanced or metastatic NSCLC with EGFR-sensitive mutations (19del/L858R) and central nervous system metastases [110, 111]. Evantuzumab in combination with lazetinib presents clinically meaningful benefits in patients with active brain metastases [112]. When it comes to ADC, a phase II trial (NCT07343479) of Sacituzumab Tirumotecan (sac-TMT) combined with third-generation TKI±radiotherapy in patients with brain metastases after failure of EGFR-TKI treatment is being conducted, providing a new direction for overcoming drug resistance [113].

The combination of targeted therapy with traditional Chinese medicine has been explored in clinical practice. Many studies suggest that Chinese medicines such as astragalus and ginseng may play an auxiliary role by regulating the immune microenvironment and reducing the adverse reactions of targeted drugs [114–117], but high-quality evidence-based medical evidence is still needed. In addition, fourth-generation TKIs such as BI-4732 exhibit strong antitumor activity and low blood-brain barrier efflux rate in preclinical intracranial models. For C797S resistance mutations, early clinical trials are expected [118].

V. Outlook and Conclusions

The treatment of EGFR-mutated NSCLC brain metastasis is shifting to an active intervention system with risk stratification as the core. With the launch of exclusive drugs for metastasis such as zolitinib [65] and idotinib [109], and the optimization of combination regimens such as osimertinib and evantumab, more patients will be given the hope of long-term survival. Future breakthroughs should focus on in-depth analysis of the brain metastasis microenvironment, promoting the

clinical translation of fourth-generation TKI and novel drug delivery systems, which establish a drug resistance early warning and intervention model based on dynamic monitoring [112, 119]. It is expected that, driven by precision medicine and multidisciplinary collaboration, brain metastasis from lung cancer will be transformed from an end event with poor prognosis to a chronic disease that can be managed for a long time.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

J.P. and L.L. jointly conceived this review. J.P. served as the first author and corresponding author, led the overall structuring and organization of this review, performed the literature search and screening, carried out data extraction and organization, prepared all main text tables and figures, wrote the original draft, and was responsible for manuscript submission, revision, and correspondence. L.L. contributed to the literature search and screening, participated in data extraction and interpretation, contributed to the compilation and verification of the supplementary table, and critically revised the manuscript for important intellectual content. Both authors contributed to the final editing and approved the final version.

References

[1] R. S. Zheng *et al*., "Cancer incidence and mortality in China, 2022," *Chinese Journal of Oncology*, vol. 46, no. 3, pp. 221–231, 2024. (in Chinese)

[2] J. J. Yang *et al*., "Icotinib versus whole-brain irradiation in patients with EGFR-mutant non-small-cell lung cancer and multiple brain metastases (BRAIN): A multicentre, phase 3, open-label, parallel, randomised controlled trial," *Lancet Respir. Med*., vol. 5, no. 9, pp. 707–716, 2017.

[3] B. C. Bade and C. S. Dela Cruz, "Lung cancer 2020: Epidemiology, etiology, and prevention," *Clin. Chest Med*., vol. 41, no. 1, pp. 1–24, 2020.

[4] Y. Shi *et al*., "A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER)," *J. Thorac. Oncol*., vol. 9, no. 2, pp. 154–162, 2014.

[5] W. H. Hsu *et al*., "Overview of current systemic management of EGFR-mutant NSCLC," *Ann. Oncol.*, vol. 29, no. suppl_1, pp. i3–i9, 2018.

[6] T. Iuchi *et al*., "Frequency of brain metastases in non-small-cell lung cancer, and their association with epidermal growth factor receptor mutations," *Int. J. Clin. Oncol.*, vol. 20, no. 4, pp. 674–679, 2015.

[7] J. S. Barnholtz-Sloan *et al.*, "Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System," *J. Clin. Oncol*., vol. 22, no. 14, pp. 2865–2872, 2004.

[8] D. London *et al.*, "The incidence and predictors of new brain metastases in patients with non-small cell lung cancer following discontinuation of systemic therapy," *J. Neurosurg*., vol. 137, no. 2, pp. 544–554, 2022.

[9] X. Li *et al*., "Optimal initial time point of local radiotherapy for unresectable lung adenocarcinoma: A retrospective analysis on overall arrangement of local radiotherapy in advanced lung adenocarcinoma," *Front. Oncol*., vol. 12, 793190, 2022.

[10] P. W. Sperduto *et al*., "Estimating survival in patients with lung cancer and brain metastases: An update of the graded prognostic assessment for lung cancer using molecular markers (Lung-molGPA)," *JAMA Oncol*., vol. 3, no. 6, pp. 827–831, 2017.

[11] T. Reungwetwattana *et al*., "CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer," *J. Clin. Oncol*., vol. 36, no. 33, pp. 3290–3297, 2018.

[12] T. Jiang *et al*., "A consensus on the role of osimertinib in non-small cell lung cancer from the AME Lung Cancer Collaborative Group," *J. Thorac. Dis*., vol. 10, no. 7, pp. 3909–3921, 2018.

[13] W. J. Magnuson *et al*., "Management of brain metastases in tyrosine kinase inhibitor-naïve epidermal growth factor receptor-mutant non-small-cell lung cancer: A retrospective multi-institutional analysis," *J. Clin. Oncol*., vol. 35, no. 10, pp. 1070–1077, 2017.

[14] A. Passaro *et al*., "Recent advances on the role of EGFR tyrosine kinase inhibitors in the management of NSCLC with uncommon, non exon 20 insertions, EGFR mutations," *J. Thorac. Oncol.*, vol. 16, no. 5, pp. 764–773, 2021.

[15] G. Lurje and H. J. Lenz, "EGFR signaling and drug discovery," *Oncology*, vol. 77, no. 6, pp. 400–410, 2009.

[16] R. Rosell and N. Karachaliou, "Large-scale screening for somatic mutations in lung cancer," *Lancet*, vol. 387, no. 10026, pp. 1354–1356, 2016.

[17] J. Wu and Z. Lin, "Non-small cell lung cancer targeted therapy: Drugs and mechanisms of drug resistance," *Int. J. Mol. Sci.*, vol. 23, no. 23, 2022.

[18] S. Ashique *et al.*, "Targeted drug delivery: Trends and perspectives," *Curr. Drug Deliv*., vol. 18, no. 10, pp. 1435–1455, 2021.

[19] W. J. Kelly, N. J. Shah, and D. S. Subramaniam, "Management of brain metastases in epidermal growth factor receptor mutant non-small-cell lung cancer," *Front. Oncol*., vol. 8, 208, 2018.

[20] J. Chmielecki *et al.*, "Analysis of acquired resistance mechanisms to osimertinib in patients with EGFR-mutated advanced non-small cell lung cancer from the AURA3 trial," *Nat. Commun.*, vol. 14, no. 1, 1071, 2023.

[21] R. Rosell *et al.*, "Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial," *Lancet Oncol*., vol. 13, no. 3, pp. 239–246, 2012.

[22] N. Karachaliou *et al*., "EGFR first- and second-generation TKIs-there is still place for them in EGFR-mutant NSCLC patients," *Transl. Cancer Res*., vol. 8, no. Suppl 1, pp. S23–S47, 2019.

[23] M. X. Li *et al*., "Central nervous system progression in advanced non-small cell lung cancer patients with EGFR mutations in response to first-line treatment with two EGFR-TKIs, gefitinib and erlotinib: a comparative study," *BMC Cancer*, vol. 17, no. 1, 245, 2017.

[24] Y. Togashi *et al*., "Cerebrospinal fluid concentration of gefitinib and erlotinib in patients with non-small cell lung cancer," *Cancer Chemother. Pharmacol*., vol. 70, no. 3, pp. 399–405, 2012.

[25] G. Y. Chen *et al.*, "Determining plasma and cerebrospinal fluid concentrations of EGFR-TKI in lung cancer patients," *Anal. Biochem*., vol. 669, p. 115115, 2023.

[26] E. Lee *et al*., "Erlotinib versus gefitinib for control of leptomeningeal carcinomatosis in non-small-cell lung cancer," *J. Thorac. Oncol.*, vol. 8, no. 8, pp. 1069–1074, 2013.

[27] X. Hou *et al.*, "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 Netw. Open*, vol. 6, no. 2, e2255050, 2023.

[28] C. Wu *et al*., "Gefitinib in the treatment of advanced non-small cell lung cancer with brain metastasis," *Chinese Journal of Oncology*, vol. 29, no. 12, pp. 943–945, 2007. (in Chinese)

[29] C. Wu *et al*., "Gefitinib as palliative therapy for lung adenocarcinoma metastatic to the brain," *Lung Cancer*, vol. 57, no. 3, pp. 359–364, 2007.

[30] T. Iuchi *et al*., "Phase II trial of gefitinib alone without radiation therapy for Japanese patients with brain metastases from EGFR-mutant lung adenocarcinoma," *Lung Cancer*, vol. 82, no. 2, pp. 282–287, 2013.

[31] N. Karachaliou *et al.*, "Characterising acquired resistance to erlotinib in non-small cell lung cancer patients," *Expert Rev. Respir. Med*., vol. 13, no. 10, pp. 1019–1028, 2019.

[32] L. V. Sequist *et al*., "Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with

EGFR mutations," *J. Clin. Oncol*., vol. 31, no. 27, pp. 3327–3334, 2013.
[33] Y. L. Wu *et al*., "Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial," *Lancet Oncol.*, vol. 15, no. 2, pp. 213–222, 2014.
[34] M. Schuler *et al.*, "First-line afatinib versus chemotherapy in patients with non-small cell lung cancer and common epidermal growth factor receptor gene mutations and brain metastases," *J. Thorac. Oncol*., vol. 11, no. 3, pp. 380–390, 2016.
[35] K. Park *et al.*, "Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial," *Lancet Oncol*., vol. 17, no. 5, pp. 577–589, 2016.
[36] D. E. Dawe, J. N. Greenspoon, and P. M. Ellis, "Brain metastases in non-small-cell lung cancer," *Clin. Lung Cancer*, vol. 15, no. 4, pp. 249–257, 2014.
[37] G. Metro *et al*., "Pharmacotherapeutic options for treating brain metastases in non-small cell lung cancer," *Expert Opin. Pharmacother.*, vol. 16, no. 17, pp. 2601–2613, 2015.
[38] H. A. Jung *et al.*, "Dacomitinib in EGFR-mutant non-small-cell lung cancer with brain metastasis: a single-arm, phase II study," *ESMO Open*, vol. 8, no. 6, 102068, 2023.
[39] Y. Yu *et al*., "Dacomitinib in the treatment of EGFR-mutated non-small cell lung cancer with brain metastases: an open-label, multicenter, phase II study," *Lung Cancer*, vol. 207, 108710, 2025.
[40] X. Liu *et al*., "Epidermal growth factor receptor (EGFR): A rising star in the era of precision medicine of lung cancer," *Oncotarget*, vol. 8, no. 30, pp. 50209–50220, 2017.
[41] K. Lee *et al.*, "Repeat biopsy procedures and T790M rates after afatinib, gefitinib, or erlotinib therapy in patients with lung cancer," *Lung Cancer*, vol. 130, pp. 87–92, 2019.
[42] D. A. Cross *et al*., "AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer," *Cancer Discov*., vol. 4, no. 9, pp. 1046–1061, 2014.
[43] T. S. Mok *et al.*, "Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer," *N. Engl. J. Med*., vol. 376, no. 7, pp. 629–640, 2017.
[44] Y. L. Wu *et al*., "CNS efficacy of osimertinib in patients with T790M-positive advanced non-small-cell lung cancer: Data from a randomized phase III trial (AURA3)," *J. Clin. Oncol*., vol. 36, no. 26, pp. 2702–2709, 2018.
[45] P. A. Jänne *et al*., "CNS efficacy of osimertinib with or without chemotherapy in epidermal growth factor receptor-mutated advanced non-small-cell lung cancer," *J. Clin. Oncol*., vol. 42, no. 7, pp. 808–820, 2024.
[46] Y. Cheng *et al.*, "Osimertinib versus comparator EGFR TKI as first-line treatment for EGFR-mutated advanced NSCLC: FLAURA China, a randomized study," *Target Oncol*., vol. 16, no. 2, pp. 165–176, 2021.
[47] S. Lu et al., "Central nervous system efficacy of aumolertinib versus gefitinib in patients with untreated, EGFR-mutated, advanced non-small cell lung cancer: data from a randomized phase III trial (AENEAS)," *Cancer Commun. (Lond.)*, vol. 44, no. 9, pp. 1005–1017, 2024.
[48] H. Li *et al.*, "High-dose aumolertinib for untreated EGFR-variant non-small cell lung cancer with brain metastases: The ACHIEVE phase 2 nonrandomized clinical trial," *JAMA Oncol*., vol. 11, no. 8, pp. 900–908, 2025.
[49] Y. Xie *et al.*, "Furmonertinib in uncommon EGFR-mutated non-small cell lung cancer with central nervous system metastases: A retrospective cohort study," *Int. J. Cancer*, vol. 157, no. 5, pp. 954–963, 2025.
[50] R. Qi *et al*., "Efficacy and safety of re-challenging 160 mg furmonertinib for advanced NSCLC after resistance to third-generation EGFR-TKIs targeted agents: A real-world study," *Lung Cancer*, vol. 184, 107346, 2023.
[51] Y. Shi *et al*., "Efficacy, safety, and genetic analysis of furmonertinib (AST2818) in patients with EGFR T790M mutated non-small-cell lung cancer: a phase 2b, multicentre, single-arm, open-label study," *Lancet Respir. Med*., vol. 9, no. 8, pp. 829–839, 2021.
[52] Y. Shi *et al*., "Central nervous system efficacy of furmonertinib (AST2818) versus gefitinib as first-line treatment for EGFR-mutated NSCLC: Results from the FURLONG study," *J. Thorac. Oncol*., vol. 17, no. 11, pp. 1297–1305, 2022.
[53] S. Lu *et al*., "Befotertinib (D-0316) versus icotinib as first-line therapy for patients with EGFR-mutated locally advanced or metastatic non-small-cell lung cancer: a multicentre, open-label, randomised phase 3 study," *Lancet Respir. Med*., vol. 11, no. 10, pp. 905–915, 2023.
[54] S. Lu *et al*., "Befotertinib for patients with pretreated EGFR T790M mutated locally advanced or metastatic NSCLC: Final overall survival results from a phase 2 trial," *Lung Cancer*, vol. 195, 107901, 2024.
[55] H. A. Blair, "Befotertinib: First approval," *Drugs*, vol. 83, no. 15, pp. 1433–1437, 2023.
[56] B. C. Cho *et al*., "A phase 1/2 study of lazertinib 240 mg in patients with advanced EGFR T790M-positive NSCLC after previous EGFR tyrosine kinase inhibitors," *J. Thorac. Oncol.*, vol. 17, no. 4, pp. 558–567, 2022.
[57] R. A. Soo *et al*., "Central nervous system outcomes of lazertinib versus gefitinib in EGFR-mutated advanced NSCLC: A LASER301 subset analysis," *J. Thorac. Oncol.*, vol. 18, no. 12, pp. 1756–1766, 2023.
[58] J. C. Yang *et al*., "Central nervous system outcomes of lazertinib treatment in EGFR-mutated advanced NSCLC: Pooled analysis from LASER201 and LASER301," *Clin. Lung Cancer*, vol. 26, no. 8, pp. 642–650.e6, 2025.
[59] M. H. Hong *et al*., "Lazertinib in EGFR-variant non-small cell lung cancer with CNS failure to prior EGFR tyrosine kinase inhibitors: A nonrandomized controlled trial," *JAMA Oncol*., vol. 10, no. 10, pp. 1342–1351, 2024.
[60] E. Dardenne *et al*., "Abstract 1229: BDTX-1535: A MasterKey EGFR inhibitor targeting classical and non-classical oncogenic driver mutations and the C797S acquired resistance mutation to address the evolving molecular landscape of EGFR mutant NSCLC," *Cancer Res.*, vol. 84, no. 6_Supplement, pp. 1229–1229, 2024.
[61] W. C. M. Dempke and K. Fenchel, "Targeting C797S mutations and beyond in non-small cell lung cancer-a mini-review," *Transl. Cancer Res*., vol. 13, no. 11, pp. 6540–6549, 2024.
[62] "BDTX-1535 goes after osimertinib resistance," *Cancer Discov*., vol. 11, no. 12, pp. 2952–2953, 2021.
[63] S. M. Lim *et al.*, "Phase 1/2 clinical trial of JIN-A02, a 4th generation EGFR-TKI, in patients with 3rd generation EGFR-TKI resistance in EGFR mutated advanced/metastatic Non-Small Cell Lung Cancer (NSCLC)," *J. Clin. Oncol*., vol. 42, no. 16_suppl, pp. TPS8658–TPS8658, 2024.
[64] C. Su and S. Y. Sun, "Fourth-generation epidermal growth factor receptor-tyrosine kinases inhibitors: hope and challenges," *Transl. Cancer Res*., vol. 13, no. 8, pp. 3929–3934, 2024.
[65] K. Li *et al*., "Long-term survival of a patient with Epidermal Growth Factor Receptor (EGFR)-mutant Non-Small Cell Lung Cancer (NSCLC) and untreated multiple brain metastases treated with zorifertinib: A case report," *Thorac. Cancer*, vol. 15, no. 16, pp. 1325–1329, 2024.
[66] Q. Zhou *et al*., "First-line zorifertinib for EGFR-mutant non-small cell lung cancer with central nervous system metastases: The phase 3 EVEREST trial," *Med*, vol. 6, no. 1, 100513, 2025.
[67] X. Zhi *et al*., "Clinical diagnosis and treatment guidelines for brain metastases in driver gene-positive non-small cell lung cancer in China (2025 edition)," *Chinese Journal of Lung Cancer*, vol. 28, no. 1, pp. 1–21, 2025. (in Chinese)
[68] P. A. Jänne *et al*., "Survival with osimertinib plus chemotherapy in EGFR-mutated advanced NSCLC," *N. Engl. J. Med*., vol. 394, no. 1, pp. 27–38, 2026.
[69] D. Planchard *et al*., "Osimertinib with or without chemotherapy in EGFR-mutated advanced NSCLC," *N. Engl. J. Med.*, vol. 389, no. 21, pp. 1935–1948, 2023.
[70] A. Wrona, R. Dziadziuszko, and J. Jassem, "Combining radiotherapy with targeted therapies in non-small cell lung cancer: focus on anti-EGFR, anti-ALK and anti-angiogenic agents," *Transl. Lung Cancer Res*., vol. 10, no. 4, pp. 2032–2047, 2021.
[71] K. Zhou *et al*., "Efficacy and safety of WBRT+EGFR-TKI versus WBRT only in the treatment of NSCLC patients with brain metastasis: An updated meta-analysis," *Thorac. Cancer*, vol. 13, no. 4, pp. 563–570, 2022.
[72] K. Pan *et al*., "Efficacy analysis of brain radiotherapy in EGFR mutation non-small cell lung cancer with brain metastasis: a retrospective study," *Discov. Oncol.*, vol. 16, no. 1, 488, 2025.

[73] M. He *et al.*, "Effects of EGFR-TKIs combined with intracranial radiotherapy in EGFR-mutant non-small cell lung cancer patients with brain metastases: a retrospective multi-institutional analysis," *Radiat. Oncol*., vol. 20, no. 1, 6, 2025.
[74] Y. Li *et al*., "Osimertinib exacerbates immune checkpoint inhibitor-related severe adverse events by activating the IL-6/JAK/STAT3 pathway in macrophages," *Cancer Biol. Med*., vol. 21, no. 12, pp. 1156–1170, 2024.
[75] N. Wiest *et al*., "Role of immune checkpoint inhibitor therapy in advanced EGFR-mutant non-small cell lung cancer," *Front. Oncol*., vol. 11, 751209, 2021.
[76] N. Okada *et al*., "Effect of pre-treatment with EGFR-TKIs on immune checkpoint inhibitor-associated interstitial lung disease in lung cancer patients: Analysis using a Japanese claims database," *Int. J. Clin. Pharmacol. Ther.*, vol. 62, no. 2, pp. 69–76, 2024.
[77] W. Fang *et al*., "Ivonescimab plus chemotherapy in non-small cell lung cancer with EGFR variant: A randomized clinical trial," *JAMA*, vol. 332, no. 7, pp. 561–570, 2024.
[78] J. W. Goldman *et al*., "PL02.12 Ivonescimab vs placebo plus chemo, phase 3 in patients with EGFR+ NSCLC progressed with 3rd gen EGFR-TKI treatment: HARMONi," *J. Thorac. Oncol*., vol. 20, no. 10, pp. S2–S3, 2025.
[79] Y. Pan and Q. Gu, "Efficacy and safety of targeted therapy combined with anti-angiogenesis treatment in brain metastases of non-small cell lung cancer: a systematic review and meta-analysis," *Lung Cancer*, vol. 203, 108532, 2025.
[80] P. H. Feng *et al*., "Bevacizumab reduces S100A9-positive MDSCs linked to intracranial control in patients with EGFR-mutant lung adenocarcinoma," *J. Thorac. Oncol*., vol. 13, no. 7, pp. 958–967, 2018.
[81] A. Sandler *et al*., "Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer," *N. Engl. J. Med.*, vol. 355, no. 24, pp. 2542–2550, 2006.
[82] X. Le *et al*., "ARTEMIS highlights VEGF inhibitors as effective partners for EGFR TKIs in EGFR mutant NSCLC," *Cancer Cell*, vol. 39, no. 9, pp. 1178–1180, 2021.
[83] R. Li *et al*., "Bevacizumab plus erlotinib versus erlotinib alone for advanced EGFR-mutant non-small cell lung cancer: a meta-analysis of randomized clinical trials," *Eur. J. Med. Res.*, vol. 28, no. 1, 302, 2023.
[84] H. Akamatsu *et al.*, "Phase I/II study of osimertinib with bevacizumab in EGFR-mutated, T790M-positive patients with progressed EGFR-TKIs: West Japan Oncology Group 8715L (WJOG8715L)," *Clin. Lung Cancer*, vol. 20, no. 4, pp. e492–e494, 2019.
[85] H. Kenmotsu *et al*., "Randomized phase 2 study of osimertinib plus bevacizumab versus osimertinib for untreated patients with nonsquamous NSCLC harboring EGFR mutations: WJOG9717L study," *J. Thorac. Oncol*., vol. 17, no. 9, pp. 1098–1108, 2022.
[86] R. A. Soo *et al.*, "A randomised phase II study of osimertinib and bevacizumab versus osimertinib alone as second-line targeted treatment in advanced NSCLC with confirmed EGFR and acquired T790M mutations: the European Thoracic Oncology Platform (ETOP 10-16) BOOSTER trial," *Ann. Oncol*., vol. 33, no. 2, pp. 181–192, 2022.
[87] H. A. Yu *et al*., "Phase I study of the efficacy and safety of ramucirumab in combination with osimertinib in advanced T790M-positive EGFR-mutant non-small cell lung cancer," *Clin. Cancer Res*., vol. 27, no. 4, pp. 992–1002, 2021.
[88] X. Le *et al*., "A multicenter open-label randomized phase II study of osimertinib with and without ramucirumab in tyrosine kinase inhibitor-naïve EGFR-mutant metastatic non-small cell lung cancer (RAMOSE trial)," *J. Clin. Oncol*., vol. 43, no. 4, pp. 403–411, 2025.
[89] Y. Y. Syed, "Anlotinib: First global approval," *Drugs*, vol. 78, no. 10, pp. 1057–1062, 2018.
[90] S. Jiang *et al*., "The impact of anlotinib on brain metastases of non-small cell lung cancer: Post hoc analysis of a phase III randomized control trial (ALTER0303)," *Oncologist*, vol. 25, no. 5, pp. e870–e874, 2020.
[91] C. H. Z. Y. W. J. *et al*., "Updated data of ALWAYS study: A phase II trial of aumolertinib plus anlotinib as first-line therapy for EGFR-mutant non-small cell lung cancer," in *Proc. Int. Assoc. Study Lung Cancer (IASLC) 2023 World Conf. Lung Cancer (WCLC)*, Singapore, 2023.
[92] B. Yan *et al*., "Osimertinib combined with anlotinib as first-line treatment in advanced or metastatic NSCLC patients with EGFR mutation: a prospective, single arm, exploratory study," *Lung Cancer*, vol. 205, 108627, 2025.
[93] T. Li *et al*., "A pilot study of anlotinib with third-generation epidermal growth factor receptor tyrosine kinase inhibitors in untreated EGFR-mutant patients with advanced non-small cell lung cancer," *Transl. Lung Cancer Res*., vol. 12, no. 6, pp. 1256–1263, 2023.
[94] J. H. Starrett *et al*., "Drug sensitivity and allele specificity of first-line osimertinib resistance EGFR mutations," *Cancer Res*., vol. 80, no. 10, pp. 2017–2030, 2020.
[95] J. Remon *et al.*, "Osimertinib and other third-generation EGFR TKI in EGFR-mutant NSCLC patients," *Ann. Oncol*., vol. 29, no. suppl_1, pp. i20–i27, 2018.
[96] C. S. o. C. O. (CSCO), "FOCUS-I study: A phase II trial of furmonertinib plus icotinib as first-line therapy in patients with EGFR-mutant advanced non-small cell lung cancer," in *Proc. 28th Annu. Meeting Chinese Soc. Clin. Oncol. (CSCO)*, China, 2025.
[97] D. Brazel and M. Nagasaka, "The development of amivantamab for the treatment of non-small cell lung cancer," *Respir. Res*., vol. 24, no. 1, 256, 2023.
[98] K. D. Grugan *et al*., "Fc-mediated activity of EGFR x c-Met bispecific antibody JNJ-61186372 enhanced killing of lung cancer cells," *MAbs*, vol. 9, no. 1, pp. 114–126, 2017.
[99] J. C. Yang *et al*., "Overall survival with amivantamab-lazertinib in EGFR-mutated advanced NSCLC," *N. Engl. J. Med*., vol. 393, no. 17, pp. 1681–1693, 2025.
[100] J. C. Yang, "Overall survival benefit from amivantamab plus lazertinib in the prespecified subgroup with brain metastases: Updated results from the phase 3 MARIPOSA study," in *Proc. European Lung Cancer Congr. (ELCC) 2025*, Barcelona, Spain, 2025.
[101] B. Besse *et al*., "Amivantamab plus lazertinib in patients with EGFR-mutant NSCLC after progression on osimertinib and platinum-based chemotherapy: Results from CHRYSALIS-2 cohort A," *J. Thorac. Oncol*., vol. 20, no. 5, pp. 651–664, 2025.
[102] A. Passaro *et al*., "Amivantamab plus chemotherapy with and without lazertinib in EGFR-mutant advanced NSCLC after disease progression on osimertinib: primary results from the phase III MARIPOSA-2 study," *Ann. Oncol*., vol. 35, no. 1, pp. 77–90, 2024.
[103] E. R. York *et al.*, "Tolerable and effective combination of full-dose crizotinib and osimertinib targeting MET amplification sequentially emerging after T790M positivity in EGFR-mutant non-small cell lung cancer," *J. Thorac. Oncol*., vol. 12, no. 7, pp. e85–e88, 2017.
[104] B. P. Levy *et al*., "Efficacy and CNS results from a randomized subset of the phase 2 SAVANNAH study comparing savolitinib (savo) + osimertinib (osi) combination with savo + placebo (PBO)," *J. Clin. Oncol*., vol. 43, no. 16_suppl, pp. 8513–8513, 2025.
[105] Y. L. Wu *et al*., "Tepotinib plus osimertinib in patients with EGFR-mutated non-small-cell lung cancer with MET amplification following progression on first-line osimertinib (INSIGHT 2): a multicentre, open-label, phase 2 trial," *Lancet Oncol.*, vol. 25, no. 8, pp. 989–1002, 2024.
[106] P. Abdayem, C. Parisi, and D. Planchard, "First line and treatment sequencing in EGFR-mutated metastatic NSCLC: What is right for which patient?" *Drugs*, vol. 86, no. 3, pp. 335–357, 2026.
[107] R. J. Hartmaier *et al*., "Osimertinib + savolitinib to overcome acquired MET-mediated resistance in epidermal growth factor receptor-mutated, MET-amplified non-small cell lung cancer: TATTON," *Cancer Discov.*, vol. 13, no. 1, pp. 98–113, 2023.
[108] B. P. Levy, F. de Marinis, L. Bonanno et al., "Efficacy and CNS results from a randomized subset of the phase 2 SAVANNAH study comparing savolitinib (savo) + osimertinib (osi) combination with savo + placebo (PBO)," *J. Clin. Oncol.*, vol. 43, no. 16_suppl, 8513, 2025. doi: 10.1200/JCO.2025.43.16_suppl.8513
[109] C. J. Park, M. S. Li, and S. I. Ou, "Old wine in new bottles? Deuterium switch (replacing hydrogen with deuterium) comes to thoracic oncology as deuterated lorlatinib (deulorlatinib, TGRX-326) and deuterated osimertinib (asandeutertinib, TY-9591) in ALK+ NSCLC and EGFR+ NSCLC, respectively," *J. Thorac. Oncol*., vol. 20, no. 6, pp. 708–713, 2025.
[110] Y. Shi *et al.*, "Efficacy and safety of asandeutertinib versus osimertinib as first-line treatment in EGFR-mutated NSCLC patients with brain metastases: Interim analysis of an open-label, multicenter, randomized, pivotal phase II study (ESAONA)," *J. Clin. Oncol*., vol. 44, 2026.

[111] Tyk Medicines, Inc., "TYK Medicines' new drug for lung cancer brain metastasis, asandeutertinib, has marketing application accepted and granted priority review," TYK Medicines Official Website, 2026.
[112] H. Yu, "CNS metastases in EGFR-mutant lung cancers: Biology, treatment opportunities, and current challenges," 2025.
[113] M. Sharma *et al*., "Brain metastases from non-small cell lung cancer: molecular subtypes and emerging CNS-directed precision therapies," *Front. Oncol*., vol. 16, 1717432, 2026.
[114] Z. Wang *et al.*, "An update on Chinese herbal medicines as adjuvant treatment of anticancer therapeutics," *Biosci. Trends*, vol. 12, no. 3, pp. 220–239, 2018.
[115] L. Chen *et al*., "Strategies for enhancing non-small cell lung cancer treatment: Integrating Chinese herbal medicines with epidermal growth factor receptor-tyrosine kinase inhibitors therapy," *Eur. J. Pharmacol.*, vol. 980, 176871, 2024.
[116] Y. Lu *et al*., "Chinese herbal medicine combined with first-generation EGFR-TKIs in treatment of advanced non-small cell lung cancer with EGFR sensitizing mutation: A systematic review and meta-analysis," *Front. Pharmacol*., vol. 12, 698371, 2021.
[117] X. Song *et al*., "Challenges of EGFR-TKIs in NSCLC and the potential role of herbs and active compounds: From mechanism to clinical practice," *Front. Pharmacol.*, vol. 14, 1090500, 2023.
[118] E. J. Lee *et al*., "Discovery of a novel potent EGFR inhibitor against EGFR activating mutations and on-target resistance in NSCLC," *Clin. Cancer Res.*, vol. 30, no. 8, pp. 1582–1594, 2024.
[119] T. Ding, Y. Xie, and M. Ding, "Therapeutic progress in leptomeningeal metastasis from EGFR mutant non-small cell lung cancer: a clinical medicine review," *J. Cancer Res. Clin. Oncol*., vol. 152, no. 1, 38, 2026.