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Review

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Expert consensus on the diagnosis and treatment of EGFR gene mutation non-small cell lung cancer

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Abstract

Background: Epidermal growth factor receptor (EGFR) mutations are the most clinically actionable oncogenic drivers in Asian patients with non-small-cell lung cancer (NSCLC). The therapeutic landscape has rapidly evolved from single-agent EGFR tyrosine kinase inhibitors (TKIs) to risk-adapted first-line intensification, perioperative and stage III targeted strategies, and mechanism-directed treatment after acquired resistance.

Methods: A multidisciplinary expert panel reviewed high-level evidence from peer-reviewed publications and major oncology meetings from 2024 to 2026 (ASCO, ESMO, WCLC *etc.*), with emphasis on clinical applicability in China. Recommendations were formulated according to molecular subtype, disease stage, metastatic pattern, resistance mechanism, drug accessibility, safety and multidisciplinary decision-making. Consensus statements were developed via a modified Delphi process in alignment with IOMJ submission requirements.

Results: Third-generation EGFR-TKIs remain the preferred backbone for EGFR exon 19 deletion and L858R-mutant advanced NSCLC. First-line intensified strategies, including osimertinib plus platinum-pemetrexed chemotherapy, aumolertinib plus chemotherapy, and amivantamab plus lazertinib, may be considered for selected high-risk patients. Osimertinib consolidation after definitive chemoradiotherapy has established a standard strategy for unresectable stage III EGFR-mutated NSCLC. For EGFR exon 20 insertion mutations, amivantamab plus chemotherapy and emerging selective oral TKIs have changed the therapeutic paradigm. After EGFR-TKI resistance, repeat molecular profiling is recommended to guide mesenchymal-epithelial transition factor (MET)-directed combinations, next-generation TKIs, antibody-drug conjugates, bispecific antibodies or chemotherapy-based regimens.

Conclusions: This consensus provides a practical framework for diagnosis, molecular testing, treatment selection, resistance management and toxicity control in EGFR-mutated NSCLC in China.

Keywords: EGFR-mutated NSCLC, osimertinib, targeted therapy, resistance mechanisms, consensus

INTRODUCTION

Advances in genomic testing have paved the way for precise, individualized treatment of patients with advanced non-small cell lung cancer (NSCLC)[1,2]. With the accumulation of evidence, treatment for advanced epidermal growth factor receptor (EGFR)-mutated NSCLC has shifted from chemotherapy to

tyrosine kinase inhibitors (TKIs), resulting in substantial improvements in survival and quality of life[3,4]. However, because of resistance mechanisms and treatment-related adverse events, most patients receiving first- or second-generation EGFR-TKIs do not achieve a progression-free survival (PFS) longer than 14 months, and PFS is even shorter in patients with brain metastases[5-8]. The third-generation EGFR-TKI osimertinib has been approved for advanced NSCLC with EGFR mutations, including acquired T790M, and as postoperative adjuvant therapy for EGFR mutation-driven NSCLC[9-11]. With continued advances in molecular testing, uncommon subtypes such as EGFR E709X, G719X, S768I, L861Q, and exon 20 insertion mutations have received increasing attention. The efficacy and appropriate populations for third-generation EGFR-TKIs in selected non-classical EGFR mutations are being actively investigated, and selective small-molecule inhibitors, bispecific antibodies, and combination strategies for EGFR exon 20 insertion mutations have also made important progress; nevertheless, substantial unmet clinical needs remain[12-14]. In patients with EGFR-mutated disease, therapeutic selection with an EGFR-TKI may eliminate target-sensitive clones and subsequently lead to more complex resistance alterations[15,16]. To delay or overcome resistance, EGFR-TKIs have been explored in combination with antiangiogenic agents or chemotherapy. In parallel, novel immunotherapy-based approaches and antibody-drug conjugates (ADCs) are being rapidly developed, providing new possibilities for addressing treatment resistance.

ECLUNG YOUNG (Yangtze River Delta Lung Cancer Cooperation Group [East China LUng caNcer Group, ECLUNG; Youth Committee]) developed this expert consensus on the clinical diagnosis and treatment of EGFR-mutated NSCLC by integrating the characteristics of drug development and clinical practice in the EGFR field in China. The consensus addresses: (1) classification and accurate identification of common EGFR mutations and their molecular and protein features; (2) selection, quality control, and standardized reporting of molecular testing methods; (3) general treatment strategies for patients with advanced and early-stage EGFR-mutated NSCLC; (4) management of special populations with EGFR-mutated disease; and (5) treatment strategies after resistance to EGFR-TKIs. The aim is to provide standardized guidance for diagnostic and therapeutic pathways and clinical decision-making in EGFR-mutated NSCLC.

SCOPE AND METHODOLOGY OF CONSENSUS DEVELOPMENT

This consensus applies to patients with pathologically confirmed or highly suspected NSCLC who require EGFR molecular testing, targeted therapy, perioperative therapy, management of locally advanced disease or special metastatic sites, or treatment decisions after resistance. Evidence sources should include randomized phase III trials, prospective phase II studies, real-world studies, systematic reviews, regulatory review documents, and abstracts from major scientific meetings. Meeting abstracts should be used only as updated evidence or to indicate research directions, whereas formal recommendations should preferentially rely on peer-reviewed full publications and regulatory labels.

Levels of evidence were categorized as follows: 1A, multiple randomized controlled trials, meta-analyses, or at least one high-quality phase III randomized controlled trial (RCT) demonstrating an overall survival (OS) benefit; 1B, a single high-quality phase III RCT with a positive primary endpoint, with OS immature or assessed as a secondary endpoint; 2A, consistent findings from prospective phase II studies, prespecified subgroup analyses, high-quality real-world studies, or systematic reviews; 2B, retrospective studies, small prospective studies, single-arm studies, or cohort studies; and 3, case reports, expert opinion, translational research, structural biology, or preclinical evidence.

The strength of recommendations was classified as "strong recommendation," "recommendation," "may be considered," or "not recommended for routine use." When differences exist in efficacy evidence,

accessibility, reimbursement, or approved indications, the applicable population and boundaries of evidence should be specified after the recommendation to avoid presenting exploratory regimens as standards of care.

STRUCTURE, BIOLOGICAL FUNCTIONS, AND ONCOGENIC MECHANISMS OF EGFR

The EGFR gene is located on chromosome 7p11.2, spans approximately 200 kb, and encodes EGFR, a transmembrane glycoprotein with receptor tyrosine kinase activity that plays a critical regulatory role in cell growth, proliferation, differentiation, survival, and migration[17,18]. Under normal conditions, ligand binding promotes formation of an active EGFR homodimer and ATP binding, which subsequently activates downstream signaling pathways, including MAPK and mTOR, and ultimately promotes cellular proliferation, differentiation, and migration[19,20]. EGFR contains three major functional domains: an extracellular ligand-binding domain, a transmembrane domain, and an intracellular tyrosine kinase domain. Highly conserved regions include: (1) the N-terminal lobe (N-lobe), in which the GSGSFG motif within the ATP phosphate-binding loop (P-loop) binds the gamma-phosphate group; (2) the alphaC helix (alphaC-helix), which contains binding sites for the alpha- and beta-phosphate groups and plays a key role in conformational change and autophosphorylation; and (3) the C-terminal lobe (C-lobe), in which the 20-30-amino-acid activation loop (A-loop) constitutes the catalytic center of the tyrosine kinase and the DFG motif is directly related to enzymatic activity[21].

The EGFR kinase domain is encoded by exons 18-24, whereas EGFR mutations in NSCLC occur predominantly in exons 18-21[1,22,23] [Figure 1]. Exon 18 alterations account for approximately 3%-5% of all EGFR mutations and include point mutations and deletion/insertion variants. G719X is the most common point mutation, and E709_T710delinsX is the most common deletion variant[22,24]. Among EGFR alterations, exon 19 deletion (19del) is one of the most common subtypes, with a frequency of approximately 44%, followed by exon 21 L858R and other mutations[25-27]. More than 54 exon 19 deletion variants have been identified, including large deletions, deletions accompanied by point mutations, and deletion-insertion variants[26,28]. EGFR exon 20 insertion (ex20ins) mutations are the next most frequent EGFR subtype after the classical mutations ex19del and L858R and are generally mutually exclusive with other oncogenic drivers[29]. EGFR exon 20 encodes amino acids E762-K823, including the alphaC helix formed by E762-M766 and the loop formed by A767-C775. A767-P772 is designated the proximal loop region, whereas H773-C775 is designated the distal loop region[30]. Overall, EGFR ex20ins variants show marked molecular heterogeneity, with a characteristic long-tail distribution of subtype frequencies[29]. EGFR ex20ins mutations are characterized by in-frame insertions and/or duplications between codons 761 and 775 near the alphaC helix, resulting in activation of EGFR signaling. According to insertion site and amino acid sequence, more than 100 EGFR ex20ins subtypes have been identified. Approximately 10% occur at the C terminus of the alphaC helix (761-766), whereas approximately 90% occur in the post-alphaC-helix loop domain. Insertions within the loop domain can be further classified as proximal-loop insertions (767-772), accounting for 66%-72% of EGFR ex20ins mutations, and distal-loop insertions (773-775), accounting for 27%-28%[27,31]. Conventional EGFR-TKIs are effective only in a very small subset of variants (approximately 5.1% of EGFR ex20ins mutations) and have limited efficacy against most other subtypes[32,33]. The structural diagram is shown in Figure 2.

EGFR kinase domain duplication (EGFR-KDD) refers to tandem duplication of the EGFR exon 18-25, exon 17-25, or exon 14-26 region. The duplicated kinase domains form an intramolecular dimer that activates downstream MAPK and mTOR signaling, thereby promoting tumor-cell proliferation, differentiation, and migration[34,35]. EGFR-KDD occurs in approximately 0.07% of lung cancers and is sensitive to EGFR-TKIs such as afatinib and icotinib[34,36]. EGFR fusions occur in 0.05%-0.13% of lung cancers and include

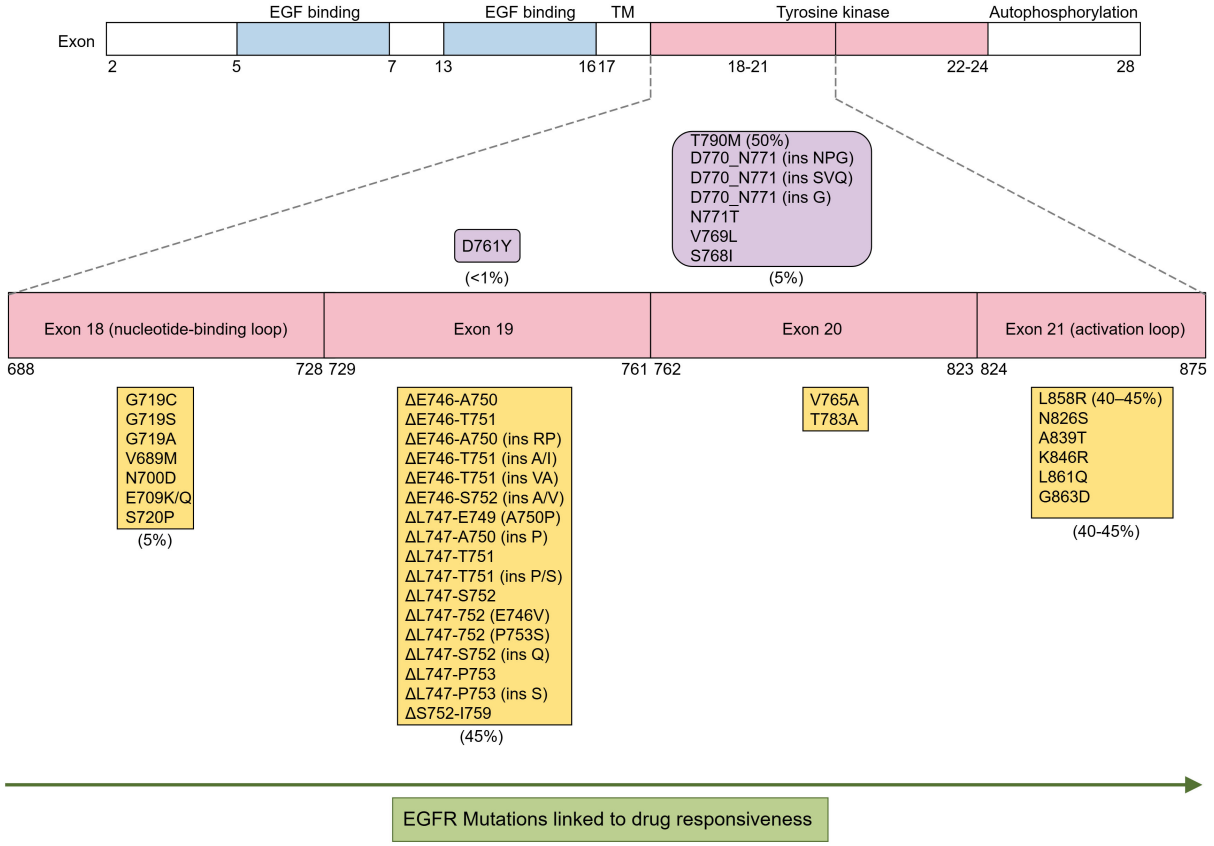


Figure 1. Schematic structure of the EGFR gene. EGFR: Epidermal growth factor receptor.

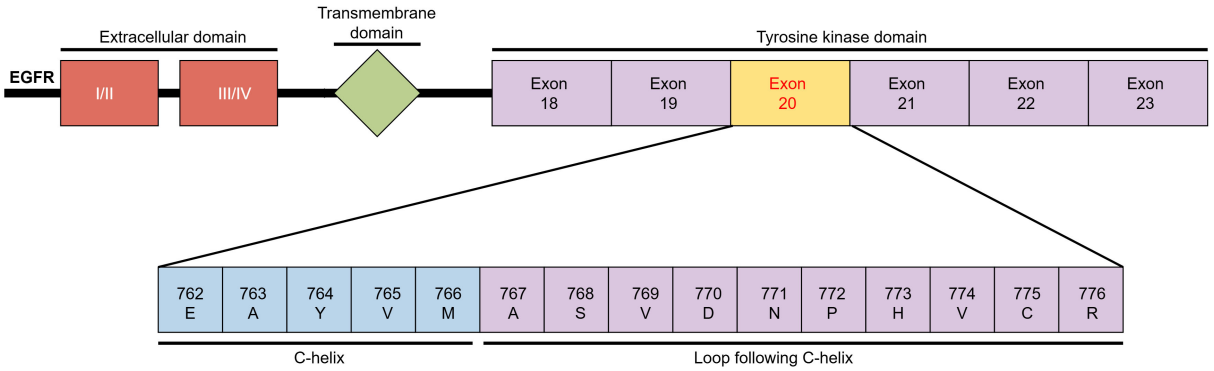


Figure 2. Structural diagram of EGFR exon 20 insertions. EGFR: Epidermal growth factor receptor.

EGFR-RAD51, EGFR-PURB, EGFR-SEPT14, EGFR-TNS3, EGFR-ZCCHC6, LINC01446-EGFR, EGFR-SEC61G, and KIF5B-EGFR. Patients may benefit from erlotinib, afatinib, icotinib, or gefitinib, with reported treatment durations ranging from 2 months to more than 36 months[37-40].

METHODS FOR DETECTING EGFR MUTATIONS

For advanced or recurrent NSCLC, tissue or cytology specimens are preferred for testing of EGFR and other oncogenic drivers. When tissue is unavailable or insufficient, peripheral-blood circulating tumor DNA (ctDNA) may be used as a supplementary specimen. In patients with leptomeningeal metastasis or central nervous system progression, cerebrospinal fluid ctDNA may better reflect the molecular characteristics of intracranial lesions than peripheral-blood ctDNA. At initial diagnosis, testing should

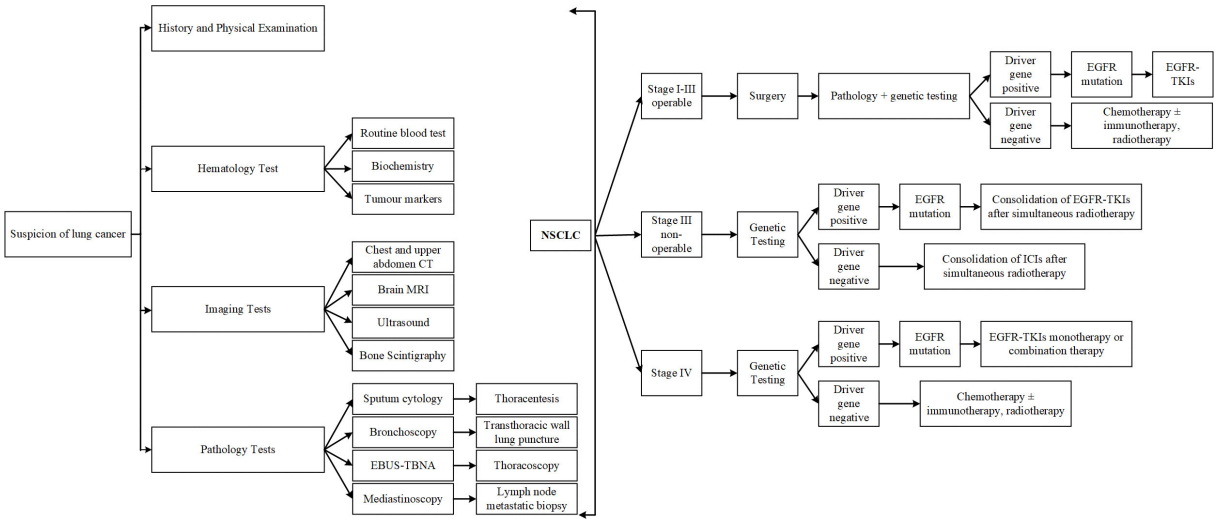


Figure 3. Diagnostic workflow. NSCLC: Non-small-cell lung cancer; EGFR: epidermal growth factor receptor; TKI: tyrosine kinase inhibitor; ICI: immune checkpoint inhibitor; EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration; CT: Computed tomography; MRI: Magnetic resonance imaging.

cover common sensitizing EGFR mutations, uncommon mutations, rare alterations, exon 20 insertions, compound mutations, and co-alterations that are actionable or may affect treatment selection, including mesenchymal-epithelial transition factor (MET) amplification, HER2, BRAF, ALK, ROS1, RET, NTRK, and KRAS. After progression on an EGFR-TKI, tissue rebiopsy or liquid biopsy should be performed whenever possible to distinguish EGFR-dependent resistance, bypass-pathway activation, histologic transformation, and progression without an identifiable actionable target. Methods for EGFR mutation testing are described below [Figure 3].

DNA-based NGS

Compared with conventional molecular testing methods, next-generation sequencing (NGS) offers clear technical advantages. NGS enables high-throughput sequencing in a single assay and has important applications in clinical diagnosis and treatment[41]. It provides high sensitivity and specificity and can identify genomic alterations in both tissue and liquid-biopsy specimens[42]. However, the accuracy of NGS is influenced by key factors including capture-probe coverage, sequencing depth, specimen quality, sequence complexity, and bioinformatic analysis. Given the increasing sensitivity, specificity, and clinical accessibility of DNA-based NGS, this method is generally recommended for identifying EGFR mutations in newly diagnosed patients and in patients with treatment resistance. When feasible, medium-to-large NGS panels covering major actionable drivers, resistance-associated genes, and key copy-number alterations should be prioritized. Panel selection should take into account the captured genomic region, sequencing depth, completeness of target coverage, analytical validation, reporting and interpretation capabilities, and clinical turnaround time.

RNA-based NGS

DNA sequencing by NGS is commonly used in clinical practice but may yield false-negative results for gene fusions. By comparison, RNA-based NGS can detect a broader range of fusion variants[43]. Because RNA-based fusion testing is not affected by intronic regions, it may identify fusion transcripts more accurately. Molecular testing for targeted therapy in NSCLC mainly includes point mutations, insertions/deletions, and gene fusions. In clinical practice, RNA-based methods have particular advantages for fusion detection. Considering the limited availability of tumor tissue in patients with advanced lung cancer, the need for timely treatment, and the cost of testing, it is recommended that a single NSCLC tissue specimen be assessed simultaneously by DNA-based NGS for point mutations and insertions/deletions and by RNA-based NGS for gene fusions.

PCR

PCR-based methods offer rapid turnaround, relatively low cost, and high sensitivity for known hotspot mutations. However, their detection range is constrained by primer and probe design, making them less suitable for identifying unknown mutations, complex insertions/deletions, fusions, or a broad spectrum of co-mutations[2]. Quantitative real-time PCR monitors the accumulation of amplification products in real time through fluorescent reagents incorporated into the reaction system. However, qPCR provides only relative quantification based on standard curves and reference materials and does not achieve precise absolute quantification. The amplification refractory mutation system (ARMS) uses mutation-specific primers to selectively amplify mutant target sequences and probes to detect amplification products on a real-time PCR platform, allowing highly specific and sensitive detection of rare mutations in sample DNA. Nevertheless, ARMS detects only predefined mutations and cannot identify novel or unknown variants[44]. Sanger sequencing uses primers designed for known mutation sites in disease-associated genes, followed by PCR amplification and direct sequencing[45]. A single mutation site can be amplified without sequencing all exons of the relevant gene; however, sensitivity is low, and low-frequency variants may be missed. From a cost-effectiveness perspective, PCR may be more favorable than NGS. Therefore, when financial resources are limited, NGS is not readily accessible, or specimen quantity is insufficient, routine EGFR testing by RT-PCR is recommended. Because testing methods differ in sensitivity, specificity, specimen requirements, turnaround time, and technical complexity, the method should be selected according to laboratory capabilities, specimen type and quantity, and clinical requirements.

Fluorescence *in situ* hybridization

Fluorescence *in situ* hybridization (FISH) can be used to detect and validate specific gene fusions, rearrangements, or amplification events. However, it relies on predefined probes, has limited coverage, and cannot comprehensively identify EGFR-related point mutations, insertions/deletions, complex rearrangements, or accompanying molecular alterations. For rare alterations such as EGFR fusions, FISH may be used as a supplementary validation method when NGS findings are equivocal or require further confirmation[37,46]. Because probe design, interpretation criteria, and positivity thresholds may vary among laboratories, and standardized criteria are lacking in some settings, FISH is not recommended as the preferred method for routine screening of EGFR-related alterations.

Immunohistochemistry

Although immunohistochemistry (IHC) is a cost-effective method, it is not suitable for detecting EGFR mutations[47]. Immunohistochemistry is mainly used to determine the molecular phenotype of a tumor; an EGFR 'positive' result generally indicates the presence of an EGFR mutation. However, EGFR mutation sites are concentrated in exons 18-21, and the specific mutation site must be identified to provide clearer guidance for the use of targeted therapy. Mutation-specific antibodies against EGFR exon 19 deletions and exon 21 L858R have been used for immunohistochemical detection of EGFR protein expression; although the specificity of each antibody is relatively high, some EGFR-mutated cases are not detected by these mutation-specific antibodies[48,49]. Studies have shown that EGFR expression by immunohistochemistry is unrelated to EGFR gene mutation status and cannot be used to select patients with NSCLC for treatment with EGFR tyrosine kinase inhibitors. Therefore, IHC is not recommended as the primary method for EGFR testing.

CONTENT REQUIREMENTS FOR EGFR NGS TEST REPORTS

This section was adapted from the 2024 ESMO recommendations on clinical reporting of genomic test results for solid cancers[50]. EGFR NGS reports should clearly document patient and specimen information, assay characteristics and performance, sample-specific quality-control metrics, genomic alterations using standardized nomenclature, clinical actionability, and relevant technical limitations to support accurate clinical interpretation.

QUALITY CONTROL FOR EGFR TESTING

This section was informed by the quality-control principles outlined in the 2024 ESMO Recommendations on clinical reporting of genomic test results for solid cancers and was further adapted to the complete workflow of EGFR molecular testing. Quality control should cover the pre-analytical, analytical, and post-analytical phases, including specimen adequacy and tumour-content assessment, assay validation, sample-specific performance metrics, appropriate internal controls, standardized interpretation and reporting, and participation in external quality-assessment programmes[50].

CLINICAL TREATMENT OF EGFR-MUTATED NSCLC

Treatment of EGFR-mutated NSCLC should first be stratified according to disease stage. For patients with early-stage resectable disease, the main considerations are curative surgery, adjuvant EGFR-TKI therapy, and neoadjuvant strategies. For patients with unresectable stage III disease, the core strategy is osimertinib consolidation after definitive chemoradiotherapy. In advanced disease, single-agent or intensified first-line therapy should be selected according to EGFR mutation subtype, central nervous system (CNS) status, tumor burden, co-mutations, and patient preference. After progression, rebiopsy should be used to identify the dominant resistance mechanism and guide mechanism-directed therapy or systemic treatment with chemotherapy, ADCs, bispecific antibodies, and other approaches.

Common EGFR mutations

First-line EGFR-TKI monotherapy for advanced NSCLC with common EGFR mutations

For advanced NSCLC harboring EGFR 19del or L858R, single-agent EGFR-TKI remains the foundational first-line treatment for most patients. Multiple randomized controlled trials of first-line therapy for advanced EGFR-mutated NSCLC have demonstrated clear efficacy with first-generation EGFR-TKIs, including gefitinib, erlotinib, and icotinib[5,51,52]. Second-generation EGFR-TKIs provide greater efficacy than first-generation agents but are also associated with substantially more adverse events[8,53,54]. Studies of the third-generation EGFR-TKIs osimertinib, aumolertinib, furmonertinib, and befotertinib have each demonstrated superior efficacy compared with first-generation TKIs. In FLAURA, osimertinib significantly prolonged median PFS (18.9 months *vs.* 10.2 months, $P < 0.001$) and median OS (38.6 months *vs.* 31.8 months, $P = 0.046$) compared with a first-generation EGFR-TKI, although no clear OS difference was observed in the Asian subgroup[10,55]. The prospective real-world FLOURISH study provided additional data for Chinese patients with advanced EGFR-mutated NSCLC: at a median follow-up of 31.3 months, the median time to treatment discontinuation was 24.6 months, median real-world PFS was 19.4 months, and median OS was 41.0 months[56]. In AENEAS, aumolertinib significantly prolonged median PFS compared with gefitinib (19.3 months *vs.* 9.9 months, $P < 0.0001$) [57]. In FURLONG, first-line furmonertinib significantly prolonged median PFS compared with gefitinib (20.8 months *vs.* 11.1 months, $P < 0.0001$)[58]. Compared with icotinib, befotertinib also produced a superior median PFS (22.1 months *vs.* 13.8 months, $P < 0.0001$) [59]. Collectively, these data establish third-generation EGFR-TKIs as standard first-line therapy for advanced EGFR-mutated NSCLC. Data for EGFR-TKIs marketed in China are summarized in Table 1.

First-line combination therapy for advanced NSCLC with sensitizing EGFR mutations

The EGFR and VEGFR signaling pathways are closely interconnected and exhibit pathway cross-talk. Combining an EGFR-TKI with an antiangiogenic agent simultaneously inhibits EGFR and VEGFR signaling in tumor cells. The phase III RELAY, NEJ-026, CTONG1509, BEVERLY, and ACTIVE studies evaluated first-generation EGFR-TKIs combined with antiangiogenic therapy. These combinations significantly improved PFS compared with EGFR-TKI monotherapy, but the PFS benefit did not translate into an OS benefit[60-64]. In contrast, the clinical benefit of combining a third-generation EGFR-TKI with an antiangiogenic agent has been limited. In WJOG9717L, osimertinib plus bevacizumab did not provide a

Table 1. Key randomized controlled trials of first-line EGFR-TKI monotherapy for advanced NSCLC with common EGFR mutations

Study	Drugs	Study phase	Total number	Response rate (%)	mPFS (months)	HR (P)	mOS (months)	HR (P)
IPASS	Gefitinib *vs.* carboplatin + paclitaxel	Phase III	261	71.2 *vs.* 47.3	9.8 *vs.* 6.4	0.48 (P < 0.001)	21.6 *vs.* 21.9	1.00 (P = 0.99)
OPTIMAL	Erlotinib *vs.* carboplatin + paclitaxel	Phase III	165	83.0 *vs.* 36.0	13.1 *vs.* 4.6	0.16 (P < 0.0001)	22.8 *vs.* 27.2	1.19 (P = 0.27)
CONVINCE	Icotinib *vs.* carboplatin + paclitaxel	Phase III	285	NR	11.2 *vs.* 7.9	0.61 (P = 0.006)	30.5 *vs.* 32.1	(P = 0.885)
LUX-lung6	Afatinib *vs.* gemcitabine + cisplatin	Phase III	364	66.9 *vs.* 23.0	11.0 *vs.* 5.6	0.28 (P < 0.0001)	23.1 *vs.* 23.5	0.93 (P = 0.61)
ARCHER1050	Dacomitinib *vs.* Gefitinib	Phase III	452	75.0 *vs.* 70.0	14.7 *vs.* 9.2	0.59 (P < 0.0001)	34.1 *vs.* 26.8	0.76 (P = 0.0438)
CTONG 0901	Erlotinb *vs.* Gefitinib	Phase III	256	56.3 *vs.* 53.3	13.0 *vs.* 10.4	0.81 (P = 0.108)	22.9 *vs.* 20.1	0.84 (P = 0.25)
FLAURA	Osimertinib *vs.* Gefitinib/Erlotinib	Phase III	556	80.0 *vs.* 76.0	18.9 *vs.* 10.2	0.46 (P < 0.001)	38.6 *vs.* 31.8	0.799 (P = 0.0462)
AENEAS	Aumolertinib *vs.* Gefitinib	Phase III	429	74.0 *vs.* 72.0	19.3 *vs.* 9.9	0.46 (P < 0.0001)	NR	NR
FURLONG	Furmonertinib *vs.* Gefitinib	Phase III	357	89.0 *vs.* 84.0	20.8 *vs.* 11.1	0.44 (P < 0.0001)	NR	NR
IBIO-103	Befotertinib *vs.* Icotinib	Phase III	362	75.8 *vs.*78.3	22.1 *vs.* 13.8	0.49 (P < 0.0001)	NR	NR
LASER301	Lazertinib *vs.* gefitinib	Phase III	393	76.0 *vs.* 76.0	20.6 *vs.* 9.7	0.45 (P < 0.001)	NR	NR
REZOR	Rezivertinib *vs.* gefitinib	Phase III	369	NR	19.3 *vs.* 9.6	0.48 (P < 0.0001)	NR	NR

EGFR: Epidermal growth factor receptor; TKI: tyrosine kinase inhibitor; NSCLC: non-small-cell lung cancer; mPFS: median progression-free survival; mOS: median overall survival; HR: hazard ratio; NR: not reported.

statistically significant PFS benefit over osimertinib alone (22.1 months *vs.* 20.2 months, HR = 0.862, P = 0.213), and grade 3-4 adverse events were more frequent with combination therapy[65]. At present, there is no strong evidence supporting a synergistic or additive effect between antiangiogenic agents and EGFR-TKIs, particularly third-generation EGFR-TKIs. Subgroup analyses from several studies suggest that patients with exon 21 L858R, a smoking history, or TP53 co-mutations may derive greater benefit from antiangiogenic therapy plus an EGFR-TKI; therefore, appropriate patient selection may be required in future treatment strategies. Randomized trials of first-line EGFR-TKIs combined with antiangiogenic agents are summarized in Table 2.

Since the introduction of EGFR-TKIs, efforts to combine targeted therapy with chemotherapy have continued. The IMPRESS study showed no PFS benefit from continuing gefitinib after resistance to first-line gefitinib in patients with advanced EGFR-mutated NSCLC[66]. The AGAIN study suggested that adding platinum-doublet chemotherapy after a response to first-line EGFR-TKI therapy was associated with longer PFS but no OS benefit, regardless of whether patients received gefitinib or osimertinib. In first-line targeted therapy-chemotherapy combination studies, both NEJ-009 and FLAURA2 demonstrated superior efficacy with combination treatment and reported an OS benefit[67,68]. In FLAURA2, osimertinib plus platinum-pemetrexed significantly improved both PFS and OS compared with osimertinib alone in advanced EGFR-mutated NSCLC (P < 0.0001; P = 0.0280)[68]. The final OS analysis showed that osimertinib plus platinum-pemetrexed significantly prolonged OS compared with osimertinib alone, with median OS of 47.5 months *vs.* 37.6 months and an HR of 0.77, indicating that targeted therapy-chemotherapy combinations have progressed from a PFS-only benefit to an OS benefit[69]. AENEAS2 demonstrated that first-line aumolertinib

Table 2. Randomized controlled trials of first-line EGFR-TKI plus antiangiogenic therapy for advanced NSCLC with common EGFR mutations

Study	Drugs	Study phase	Total number	Response rate (%)	mPFS (months)	HR (P)	mOS (months)	HR (P)
RELAY	Erlotinib + Ramucirumab *vs.* Erlotinib	Phase III	449	76 *vs.* 75	19.4 *vs.* 12.4	0.59 (P < 0.001)	51.1 *vs.* 46.0	0.98 (P = 0.864)
NEJ-026	Erlotinib + Bevacizumab *vs.* Erlotinib	Phase III	228	72 *vs.* 74	16.9 *vs.* 13.3	0.605 (P = 0.016)	50.7 *vs.* 46.2	1.007 (P = 0.97)
ARTEMIS (CTONG1509)	Erlotinib + Bevacizumab *vs.* Erlotinib	Phase III	311	86.8 *vs.* 84.7	17.9 *vs.* 11.2	0.55 (P < 0.001)	36.2 *vs.* 31.6	0.92 (P = 0.581)
BEVERLY	Erlotinib + Bevacizumab *vs.* Erlotinib	Phase III	160	67.0 *vs.* 62.5	15.4 *vs.* 9.6	0.66 (P = 0.015)	33.3 *vs.* 22.8	0.72 (P = 0.132)
ACTIVE (CTONG1706)	Gefitinib + Apatinib *vs.* Gefitinib+ Placebo	Phase III	313	77.1 *vs.* 73.7	13.7 *vs.* 10.2	0.71 (P = 0.0189)	NR	NR
WJOG9717L	Bevacizumab + osimertinib *vs.* osimertinib	Phase II	122	82.0 *vs.* 86.0	22.1 *vs.* 20.2	0.862(P = 0.213)	NR	NR

EGFR: Epidermal growth factor receptor; TKI: tyrosine kinase inhibitor; NSCLC: non-small-cell lung cancer; mPFS: median progression-free survival; HR: hazard ratio; mOS: median overall survival; NR: not reported.

plus platinum-doublet chemotherapy significantly prolonged PFS compared with aumolertinib alone in advanced NSCLC with sensitizing EGFR mutations (28.9 months *vs.* 18.9 months, HR = 0.47), with consistent benefit across subgroups, and provided data from a Chinese-developed third-generation EGFR-TKI in a Chinese population[70]. MARIPOSA showed that amivantamab plus lazertinib prolonged median PFS by 7.1 months compared with osimertinib (23.7 months *vs.* 16.6 months, HR = 0.70)[71]. At a median follow-up of 37.8 months, median OS had not been reached in the combination group and was 36.7 months in the osimertinib group; the HR for death was 0.75 (95% CI, 0.61-0.92; P = 0.005). Three-year OS rates were 60% and 51%, respectively, and 42-month OS rates were 56% and 44%, respectively[72]. FLAURA2 and MARIPOSA both demonstrated a PFS benefit from adding other agents to an EGFR-TKI and introduced new first-line combination options for patients with EGFR-mutated disease. Although patients may derive clinical benefit in real-world practice, the complexity of NSCLC and the need for longitudinal disease management require further investigation of resistance mechanisms and population-specific efficacy and safety to optimize treatment strategies and improve prevention and management of potential adverse events. These studies provide new evidence for precise and individualized treatment of EGFR-mutated NSCLC. Key clinical trials of first-line EGFR-TKI-based combination strategies are summarized in Table 3.

First-line combination with SBRT or LCT in advanced EGFR-mutant NSCLC

The combination of targeted therapy and radiotherapy continues to be investigated in patients with advanced disease. A prospective randomized controlled trial (NCT03595644) enrolled 61 patients with stage IV EGFR-mutated NSCLC and assigned them to stereotactic body radiotherapy (SBRT) plus a TKI or a TKI alone. SBRT plus a TKI significantly delayed the emergence of acquired resistance and provided a clear PFS advantage (17.3 months *vs.* 9.0 months, P = 0.015), while also prolonging PFS and OS[73]. The study also suggested that irradiation of the primary tumor may be more beneficial than irradiation of metastatic lesions.

Table 3. First-line combination therapy with chemotherapy for advanced EGFR-mutant NSCLC

Study	Drugs	Study Phase	Total number	Response rate (%)	mPFS (months)	HR (P)	mOS (months)	HR (P)	Notes
NEJ-009	Gefitinib + Chemotherapy *vs.* Gefitinib	Phase III	345	84 *vs.* 67	20.9 *vs.* 11.9	0.49 ($P < 0.001$)	49.0 *vs.* 38.5	0.82 ($P = 0.127$)	
AGAIN	EGFR-TKI + intercalated platinum-pemetrexed chemotherapy *vs.* EGFR-TKI	Phase III	501	71.6 *vs.* 78	18.0 *vs.* 12.0	0.762 ($P = 0.003$)	48.0 *vs.* 48.0	0.985 ($P = 0.4496$)	
FLAURA 2	Osimertinib + Chemotherapy *vs.* Osimertinib	Phase III	557	83 *vs.* 76	25.5 *vs.* 16.7	0.62 ($P < 0.0001$)	47.5 *vs.* 37.6	0.77 ($P = 0.02$)	
MARIPOSA	Amivantamab + Lazertinib *vs.* Osimertinib	Phase III	858	86 *vs.* 85	23.7 *vs.* 16.6	0.70 ($P = 0.0002$)	NR *vs.* 36.7	0.75 ($P = 0.005$)	
AENEAS2	Aumolertinib + platinum-pemetrexed chemotherapy *vs.* aumolertinib	Phase III	624	93.2 *vs.* 87.3	28.9 *vs.* 18.9	0.47 ($P < 0.0001$)	NR	NR	
TOP	Osimertinib + Chemotherapy *vs.* Osimertinib	Phase III	294	82.9 *vs.* 71.6	34.0 *vs.* 15.6	0.44 ($P < 0.001$)	NR	NR	with concurrent TP53 mutation
ACROSS2	Aumolertinib + Chemotherapy *vs.* aumolertinib	Phase III	126	70.5 *vs.* 67.2	19.78 *vs.* 16.53	0.58 ($P = 0.0376$)	NR	NR	with ≥ 1 concomitant tumor-suppressor gene alteration

EGFR: Epidermal growth factor receptor; TKI: tyrosine kinase inhibitor; mPFS: median progression-free survival; HR: hazard ratio; mOS: median overall survival; NR: not reported.

Locally advanced lung cancer with sensitizing EGFR mutations

Approximately 30% of patients with non-small cell lung cancer present with stage III (locally advanced) disease. For patients with unresectable EGFR-mutated NSCLC, the current standard treatment is definitive concurrent chemoradiotherapy. The optimal consolidation treatment after concurrent chemoradiotherapy has historically remained uncertain. Based on data from the phase III PACIFIC study, durvalumab consolidation is the standard treatment for patients with unresectable stage III NSCLC without progression after chemoradiotherapy (CRT)[74,75]. However, a post hoc analysis of the EGFR-mutated subgroup in PACIFIC showed that patients with EGFR mutations did not benefit from durvalumab[76].

The early RECEL study evaluated the efficacy and safety of erlotinib plus radiotherapy *vs.* concurrent chemoradiotherapy in unresectable stage III NSCLC with sensitizing EGFR mutations. Median PFS was 27.86 months with erlotinib plus radiotherapy *vs.* 6.41 months with concurrent chemoradiotherapy, indicating that the combination with radiotherapy significantly prolonged PFS in this population[77]. The LAURA study established the evidence base for osimertinib consolidation after definitive chemoradiotherapy in unresectable stage III EGFR-mutated NSCLC. Osimertinib significantly prolonged PFS compared with placebo, with median PFS of 39.1 months versus 5.6 months, indicating that the PACIFIC paradigm should not be applied indiscriminately to patients with stage III EGFR-mutated disease[78]. Real-world studies have also explored consolidation after concurrent chemoradiotherapy in patients with unresectable stage III EGFR-mutated NSCLC. Outcomes were more favorable with osimertinib, with a 2-year PFS rate of 86% compared with 30% in the durvalumab group[79]. The ADVANCE study evaluated whether induction aumolertinib followed by thoracic radiotherapy with continued aumolertinib maintenance could replace conventional concurrent chemoradiotherapy in unresectable stage III NSCLC with sensitizing EGFR mutations. The final analysis presented at ASCO 2025

Table 4. Combined targeted therapy and radiotherapy

Study	Drugs	Study phase	Total number	Response rate (%)	mPFS (months)	HR (P)	mOS (months)	HR (P)
RECEL	Erlotinib + Radiation *vs.* Etoposide/Cisplatin + Radiation	Phase II	41	70 *vs.* 61.9	24.5 *vs.* 9.0	0.104 (P < 0.001)	NR	NR
PACIFIC (Post hoc analysis)	Durvalumab consolidation *vs.* placebo	Phase III	35	26.1 *vs.* 18.2	11.2 *vs.* 10.9	0.91	46.8 *vs.* 43.0	1.02
LAURA	cCRT/sCRT: Osimertinib *vs.* Placebo	Phase III	216	57 *vs.* 33	39.1 *vs.* 5.6	0.16 (P < 0.001)	58.8 *vs.* 54.0	0.67 (P = 0.14)
ADVANCE	Induction aumolertinib followed by concurrent aumolertinib-RT and maintenance aumolertinib *vs.* cCRT	Phase III	43	NR	34.0 *vs.* 7.8	0.15	NR	NR

EGFR: Epidermal growth factor receptor; TKI: tyrosine kinase inhibitor; mPFS: median progression-free survival; HR: hazard ratio; mOS: median overall survival; NR: not reported.

showed that, at a median follow-up of 25.5 months, median PFS was 34.0 months in the aumolertinib plus radiotherapy group *vs.* 7.8 months in the control group (HR 0.15, 95% CI 0.06-0.24) [80]. Taken together with current guidelines and available studies, concurrent chemoradiotherapy (cCRT) should remain the preferred standard treatment for unresectable stage III NSCLC with sensitizing EGFR mutations. EGFR-TKI consolidation after concurrent chemoradiotherapy and concurrent EGFR-TKI plus radiotherapy warrant attention and may represent important options, particularly for patients who decline or cannot tolerate chemotherapy. Key studies of radiotherapy-based treatment and consolidation strategies for locally advanced NSCLC are summarized in Table 4.

Perioperative treatment of early- and intermediate-stage NSCLC with sensitizing EGFR mutations

(1) Postoperative adjuvant therapy

An increasing body of clinical evidence has demonstrated the survival benefit and safety of adjuvant EGFR-TKI therapy in patients with EGFR-mutated NSCLC. Nevertheless, several important issues remain controversial, including the duration of postoperative adjuvant therapy, the relevant pathologic stages, and the role of chemotherapy in the adjuvant setting.

For patients with stage IA EGFR-mutated NSCLC who have undergone complete tumor resection, regular surveillance is currently recommended, and postoperative adjuvant therapy is not recommended. In ADAURA, after 3 years of adjuvant treatment in patients with completely resected stage IB-IIIA EGFR-mutated NSCLC, disease-free survival (DFS) was 65.8 months with osimertinib and 28.1 months with placebo (HR = 0.27, P < 0.0001), establishing 3 years of adjuvant osimertinib as a standard treatment[11,81]. In addition, as shown in Table 5, studies including ADJUVANT, IMPACT, and EVIDENCE demonstrated a significant DFS benefit with 2 years of postoperative adjuvant EGFR-TKI therapy in patients with completely resected stage II-IIIA EGFR-mutated lung cancer, although OS benefit data have not yet been reported[77,82-84]. The ICTAN study (NCT01996098), presented at ASCO 2024, evaluated the duration of adjuvant icotinib. DFS was 61.8 months with 12 months of icotinib, 63.2 months with 6 months of icotinib, and 23.7 months with observation; 12 months of icotinib provided no additional benefit over 6 months. For patients with early-stage, surgically eligible NSCLC harboring sensitizing EGFR mutations who undergo curative resection, adjuvant EGFR-TKI therapy is considered necessary. However, because the duration of adjuvant treatment in EGFR-mutated NSCLC ranges from 6 to 36 months and 12 months of icotinib did not provide additional benefit over 6 months, whether currently recommended treatment durations may constitute overtreatment requires further investigation. The ALCHEMIST/Alliance A081105 study reported at ASCO 2026 showed that adjuvant erlotinib improved DFS but not OS[85].

Table 5. Key randomized studies of adjuvant EGFR-TKIs in completely resected EGFR-mutated NSCLC

Study	Drugs	Study phase	Total number	Duration of treatment	mDFS (months)	HR (P)	mOS or 5-year OS rate	HR (P)
ADJUVANT	Gefitinib *vs.* Chemotherapy	Phase III	222	2 years	30.8 *vs.* 19.8	0.56 (*P* = 0.001)	75.5 *vs.* 62.8	0.92 (*P* = 0.674)
IMPACT	Gefitinib *vs.* Chemotherapy	Phase III	232	2 years	35.9 *vs.* 25.1	0.92 (*P* = 0.63)	78.0% *vs.* 74.6%	1.03 (*P* = 0.89)
EVIDENCE	Icotinib *vs.* Chemotherapy	Phase III	322	2 years	47.0 *vs.* 22.1	0.36 (*P* < 0.0001)	NR	NR
ADAURA	Osimertinib *vs.* Placebo	Phase III	682	3 years	65.8 *vs.* 28.1	0.27 (*P* < 0.0001)	88.0% *vs.* 78.0%	0.49 (*P* < 0.001)
ICTAN	Icotinib (12m) *vs.* Icotinib (6m) *vs.* Observation	Phase III	251	12 months or 6 months	61.8 *vs.* 63.2 *vs.* 23.7	6m *vs.* O: 0.41 (*P* = 0.000025) 12m *vs.* O: 0.40 (*P* = 0.000014) 12m *vs.* 6m: 0.97 (*P* = 0.89)	74.5% *vs.* 74.0% *vs.* 65.1%	6m *vs.* O: 0.41 0.56 (*P* = 0.041) 12m *vs.* O: 0.55 (*P* = 0.035) 12m *vs.* 6m: 1.00 (*P* = 0.99)

EGFR: Epidermal growth factor receptor; TKI: tyrosine kinase inhibitor; mDFS: median disease-free survival; mOS: Median overall survival; HR: Hazard ratio.

(2) Preoperative neoadjuvant therapy

Clinical studies of neoadjuvant targeted therapy are ongoing, and no definitive conclusions have yet been established. A single-arm phase II study (NCT01833572) demonstrated the feasibility of neoadjuvant gefitinib in patients with stage II-IIIA EGFR-mutated NSCLC. The objective response rate (ORR) was 54.5%, the major pathologic response (MPR) rate was 24.2%, and median DFS was 33.5 months, suggesting that preoperative EGFR-TKI therapy has a degree of feasibility and safety[86]. EMERGING-CTONG 1103 was a randomized phase II trial comparing neoadjuvant erlotinib with chemotherapy in patients with stage IIIA-N2 EGFR-mutated NSCLC. The primary endpoint of ORR was not met (54.1% with erlotinib and 34.3% with chemotherapy), although an improvement in median PFS was observed (21.5 months and 11.4 months, respectively)[87]; this did not translate into an OS benefit[88]. Neoadjuvant treatment with the third-generation EGFR-TKI osimertinib has also entered prospective evaluation. NCT03433469 was a multicenter, single-arm phase II study of neoadjuvant osimertinib in patients with resectable stage I-IIIA EGFR-mutated NSCLC. The MPR rate was approximately 15%, and the prespecified primary endpoint was not met; however, treatment was generally well tolerated, with no safety signal that substantially compromised surgery[89]. Multiple additional trials of preoperative neoadjuvant EGFR-TKI therapy, including NCT02824952 and NCT06018688, are ongoing.

Uncommon EGFR mutations

EGFR exon 20 insertion mutations

EGFR ex20ins is the third most common EGFR mutation subtype after the two common mutations, 19del and L858R, and accounts for approximately 12% of EGFR-mutated NSCLC. No clear difference in incidence has been identified between Eastern and Western populations, and the clinical characteristics are similar to those of common EGFR mutations[12,90].

Current recommendations in China suggest that first-line treatment for EGFR ex20ins-mutated NSCLC should follow the approach used for locally advanced or metastatic NSCLC without an actionable driver, namely chemotherapy with or without bevacizumab, or an immune checkpoint inhibitor with or without

chemotherapy. Mobocertinib (TAK-788), the first targeted agent developed for EGFR ex20ins, was evaluated in the phase I/II EXCLAIM study in patients with EGFR ex20ins-mutated NSCLC that progressed during or after platinum-based chemotherapy. The ORR was 28%, median PFS was 7.3 months, median OS was 20.2 months, and safety was manageable[91]. However, EXCLAIM-2, which compared first-line mobocertinib monotherapy with platinum-based chemotherapy in locally advanced or metastatic EGFR ex20ins-mutated NSCLC, was terminated after failing to meet its primary endpoint, and the marketing authorization was subsequently to be withdrawn. Several targeted therapies for EGFR ex20ins have now entered phase III clinical development. PAPILLON was the pivotal phase III trial of first-line therapy for EGFR exon 20 insertion mutations. Amivantamab plus chemotherapy significantly improved PFS compared with chemotherapy, with median PFS of 11.4 and 6.7 months, respectively (HR = 0.40, $P < 0.001$), and also reduced the risk of death (HR= 0.67)[14]. In the Chinese phase II single-arm WU-KONG6 study, sunvozertinib produced an ORR of 61% in EGFR 20ins-mutated disease and received accelerated approval from the US FDA in 2025 for metastatic EGFR exon20ins NSCLC that had progressed after platinum-based chemotherapy[92]. WU-KONG28 further evaluated sunvozertinib in the first-line setting. In treatment-naive patients with advanced non-squamous NSCLC harboring EGFR exon20ins, sunvozertinib monotherapy significantly prolonged PFS compared with platinum-pemetrexed chemotherapy, with median PFS of 10.3 months *vs.* 7.5 months (HR = 0.65); ORRs were 58.9% and 31.1%, and median durations of response (DORs) were 11.2 and 7.1 months, respectively[93]. In a phase II single-arm study of poziotinib for 20ins mutations (NCT03066206), the overall ORR among 50 patients was 32%, and median PFS was 5.5 months[94]. Third-generation EGFR-TKIs have also been explored. In POSITION20, double-dose osimertinib produced an overall ORR of 28% and median PFS of 6.8 months[95]. ECOG-ACRIN 5162 likewise demonstrated activity of double-dose osimertinib in 20ins-mutated disease, with an overall ORR of 25% and median PFS of 9.7 months [96]. The AFACET study (NCT03727724) evaluated afatinib plus cetuximab in patients with advanced EGFR ex20ins-mutated disease; the overall ORR was 43%, the confirmed ORR was 32%, and median PFS was 5.5 months[97]. Given the limitations of the available efficacy data, the effectiveness of afatinib plus cetuximab requires further investigation and validation. Detailed data are provided in Table 6. A phase Ib trial of JMT101 (becotarug) plus osimertinib in EGFR ex20ins NSCLC reported a confirmed ORR of 36.4% and median PFS of 8.2 months. Among patients refractory to platinum therapy, the confirmed ORR was 34.0%, median PFS was 9.2 months, and median DOR was 13.3 months[98]. In addition, the phase III study NCT06380348 is evaluating the efficacy and safety of first-line JMT101 plus osimertinib versus cisplatin plus pemetrexed in advanced NSCLC harboring EGFR ex20ins. Multiple agents and novel compounds are currently being investigated in first- and later-line settings for EGFR ex20ins-mutated NSCLC. Clinicians should continue to follow the emerging evidence to support standardized management of this molecular subtype. Key clinical studies of systemic therapies for advanced NSCLC harboring EGFR exon 20 insertion mutations are summarized in Table 7.

G719X, S768I, L861Q, and E709X mutations

Approximately 7%-23% of patients with NSCLC harbor non-classical EGFR mutations, including G719X, L861Q, S768I, and exon 20 insertion mutations[99]. The traditional classification of uncommon mutations according to exon location does not fully explain differences in sensitivity to EGFR-TKIs among molecular subtypes. Using genomic data from 16,715 patients with EGFR-mutated NSCLC, three-dimensional structural modeling, and drug-sensitivity experiments, Robichaux *et al.* classified EGFR mutations into structural-functional subgroups, including classical-like, T790M-like, exon 20 loop insertion, and P-loop and alphaC-helix compressing (PACC) mutations[1]. EGFR exon 20 insertion mutations generally respond poorly to EGFR-TKIs, whereas patients with G719X, L861Q, or S768I tend to have better outcomes. Studies have shown that approximately 30% of patients with G719X-mutated NSCLC also harbor E709X. E709X may mediate primary resistance to third-generation EGFR-TKIs in patients with G719X-mutated NSCLC, whereas NSCLC harboring compound E709X/G719X mutations remains sensitive to afatinib[100]. A small

Table 6. Treatment of uncommon EGFR mutations

Study	Drugs	Study Phase	Total number	EGFR mutation type	Response rate (%)	mPFS (months)	mOS (months)
ACHILLES	Afatinib *vs.* Chemotherapy	Phase III	109	G719X/L861Q/S768I /E709X/Others	61.4 *vs.* 47.1	10.6 *vs.* 5.7	NR
LUX-Lung2/3/6	Afatinib	Phase III Post-hoc analysis	75	G719X/L861Q/S768I	71.0	10.7	19.4
UNICORN	Osimertinib	Phase II	40	G719X/L861Q/S768I	55.0	9.4	NR
KCSG-LU 15-09	Osimertinib	Phase II	36	G719X/L861Q/S768I ex20ins/T790M	50	8.2	27.0
LU21-16	Lazertinib	Phase II	34	G719X/L861Q/S768I/ex18del	50	10.8	NR
AIM	Aumolertinib	Phase II	17	G719X/L861Q/S768I/others	47.1	11.8	NR
ChiCTR2000029058	Mefatinib	Phase II	21	G719X/L861Q/S768I	85.71	20.6	NR
CHRYSALIS-2 Cohort C	Amivantamab + lazertinib	Phase I/Ib	105	G719X/L861Q/S768I	52	11.1	NR

EGFR: Epidermal growth factor receptor; mPFS: median progression-free survival; mOS: median overall survival; NR: not reported.

Table 7. Key clinical studies of systemic therapies for advanced NSCLC harboring EGFR exon 20 insertion mutations

	Study	Drugs	Study phase	Total number	Response rate (%)	mPFS (months)	mOS (months)
First-line	PAPILLON	Amivantamab + Chemotherapy *vs.* Chemotherapy	Phase III	308	73 *vs.* 47	11.4 *vs.* 6.7	NR *vs.* 24.4
	WU-KONG28	Sunvozertinib *vs.* carboplatin-pemetrexed	Phase III	324	58.9 *vs.* 31.1	10.3 *vs.* 7.5	NR
Later-line	WU-KONG6	Sunvozertinib	Phase II	97	61	NR	NR
	CHRYSALIS	Amivantamab	Phase I	81	40	8.3	22.8
	REZILIENT1	Zipalertinib	Phase I/II	244	35.2	NR	NR
	ZENITH20 cohort 1	Poziotinib	Phase II	115	14.8	4.2	NR
	POSITION20	Osimertinib (160mg)	Phase II	25	28	6.8	15.2
	ECOG-ACRIN 5162	Osimertinib (160mg)	Phase II	20	25	9.7	NR
	AFACET	Afatinib + cetuximab	Phase II	37	32	5.5	NR

EGFR: Epidermal growth factor receptor; mPFS: Median progression-free survival; mOS: Median overall survival; NR: not reported.

study of 15 patients reported an ORR of 33.3% in the overall cohort. Among all patients with exon 18 E709X mutations, median PFS was 10.9 months and median OS was not reached. No significant difference was observed between second- and third-generation TKIs (PFS: 13.5 months *vs.* 10.9 months; OS: 17.1 months *vs.* not reached), suggesting that patients with exon 18 E709X-mutated NSCLC may benefit from second- or third-generation EGFR-TKIs[101]. No drug has been developed specifically for non-classical EGFR mutations, and the available evidence largely comes from clinical studies of first-, second-, and third-generation EGFR-TKIs. A subgroup analysis of the phase III NEJ-002 trial of the first-generation TKI gefitinib showed low sensitivity in tumors with G719X or L861Q, with a response rate of only 20%[102]. A post hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6 showed that afatinib achieved an ORR of 71% and median PFS of 10.7 months in non-classical EGFR mutations (G719X/L861Q/S768I)[103]. On this basis, the US FDA approved afatinib for uncommon mutations in exons 18-21, including G719X, S768I, and L861Q. In the recent ACHILLES study, median PFS was significantly longer with afatinib than with chemotherapy (10.6 months *vs.* 5.7 months; HR = 0.422, $P = 0.0007$), further demonstrating the activity of afatinib in uncommon mutations[104]. Two phase II studies of osimertinib also demonstrated activity in

patients with non-classical EGFR mutations[105,106]. The third-generation EGFR-TKI lazertinib achieved an ORR of 50.0%, a disease control rate (DCR) of 88.9%, and median PFS of 10.8 months in Korean patients with non-classical EGFR mutations[107]. In a single-arm phase II study of first-line mefatinib in advanced NSCLC with rare EGFR mutations, 21 patients achieved an ORR of 85.71% and median PFS of 20.6 months[108]. In another clinical study of the third-generation TKI aumolertinib in non-classical mutations (NCT04785742), updated results presented at WCLC 2023 showed an overall ORR of 47.1%, DCR of 100%, and median PFS of 11.8 months[109]. Beyond conventional EGFR-TKIs, cohort C of CHRYSALIS-2 showed high antitumor activity with amivantamab plus lazertinib in advanced NSCLC harboring non-classical EGFR mutations, including G719X, L861Q, S768I, and compound mutations. In the full publication, the overall ORR was 52%, median DOR was 14.1 months, and median PFS was 11.1 months. In the treatment-naive subgroup, ORR was 57% and median PFS was 19.5 months, suggesting a stronger efficacy signal in previously untreated patients[110]. The updated first-line subgroup analysis presented at ASCO 2026 further reported a median OS of approximately 41.0 months[111].

Current advances in non-classical EGFR-mutated NSCLC indicate that targeted agents are playing an increasingly important role. Additional studies and multidimensional comparisons are needed to define optimal strategies for advanced, early-stage, and locally advanced non-classical EGFR-mutated NSCLC. More refined classification of mutation subtypes and corresponding precision treatment will be essential to establish a comprehensive precision-treatment framework for this population.

EGFR and other co-mutations

Coexisting dual or multiple driver mutations

EGFR-mutated non-small cell lung cancer was previously considered a tumor driven by a single oncogene, in which blockade of the activated driver could selectively eliminate tumor cells. However, some patients still respond poorly to EGFR-TKI monotherapy, and co-mutations identified in treatment-naive tumors can likewise contribute to primary resistance. One study reported that 22% of patients had multiple EGFR mutations or co-mutations[112]. These alterations can be broadly classified into three categories: first, multiple alterations within the EGFR pathway itself; second, EGFR mutations accompanied by bypass-pathway activation, such as c-MET amplification, HER2 mutation, or PI3K mutation; and third, activation of downstream EGFR signaling pathways, including MAPK, PTEN, and PI3K/AKT. Activating alterations in these downstream pathways may coexist with EGFR mutations and affect the efficacy of EGFR-targeted therapy[113]. At present, evidence is insufficient to determine precisely which co-mutations alter the biological behavior of EGFR-mutated NSCLC or the efficacy of targeted therapy. Nevertheless, tumors with a more homogeneous EGFR-driven molecular profile generally respond better, whereas more numerous and heterogeneous co-mutations or a higher tumor mutational burden (TMB) are generally associated with poorer efficacy.

TP53 and other adverse-prognostic co-mutations

TP53 is one of the most frequently mutated tumor-suppressor genes, and TP53 mutations occur in more than half of all patients with cancer and are often associated with poor prognosis[114]. TP53 alterations are highly heterogeneous; any mutation site or variant type that causes loss or reduction of TP53 function may contribute to tumorigenesis, making direct development of TP53-targeted drugs particularly challenging[114]. In the BENEFIT study, patients with TP53 mutations had shorter PFS and OS than those with wild-type TP53, and patients with mutations in TP53 exons 6 or 7 had even poorer PFS and OS[115]. A meta-analysis confirmed that OS was worse in patients with TP53 mutations than in those with wild-type TP53 (HR = 1.73, 95% CI: 1.22-2.44, $P = 0.002$)[116]. In subgroup analyses, PFS was poorer among patients receiving EGFR-TKI therapy, although the ORR analysis did not confirm this finding. Because no mutation-specific

targeted therapy is available for TP53, whether combination therapy is the optimal approach for EGFR/TP53 co-mutated disease, and which combination can substantially improve survival, remain to be determined. EGFR-TKIs combined with antiangiogenic agents or chemotherapy have shown a degree of activity in patients with EGFR/TP53 co-mutations. ACTIVE demonstrated that apatinib plus gefitinib improved PFS in patients with EGFR/TP53 co-mutated disease[64]. RELAY showed encouraging efficacy with an EGFR-TKI plus antiangiogenic therapy in this population. Compared with erlotinib alone, ramucirumab plus erlotinib significantly improved PFS in patients with EGFR-mutated NSCLC and concurrent TP53 mutations[117]. ALTER-L004 showed that icotinib plus anlotinib improved ORR and DCR in patients with EGFR/TP53 co-mutations[118]. These findings suggest that targeted therapy plus an antiangiogenic agent may become a new option for EGFR/TP53 co-mutated disease and warrants continued investigation. In a subgroup analysis of MARIPOSA, median PFS among patients with TP53 co-mutations was 18.2 months with amivantamab plus lazertinib and 12.9 months with osimertinib (HR = 0.65, $P = 0.003$)[71,119]. The TOP study presented at ELCC 2026 focused on patients with advanced NSCLC harboring sensitizing EGFR mutations and concurrent TP53 mutations. Compared with osimertinib alone, first-line osimertinib plus carboplatin and pemetrexed followed by maintenance osimertinib plus pemetrexed significantly prolonged PFS, with median PFS of 34.0 months *vs.* 15.6 months (HR = 0.44, $P < 0.001$); ORR and DOR were also improved. OS data remain immature, although the interim analysis showed a trend toward an OS benefit with combination therapy[120]. In ACROSS2, among patients with EGFR mutations and co-alterations in tumor-suppressor genes, aumolertinib plus chemotherapy significantly prolonged PFS compared with aumolertinib alone, with median PFS of 19.78 months *vs.* 16.53 months (HR = 0.58)[121]. Several retrospective studies have likewise shown a more pronounced PFS benefit with an EGFR-TKI plus chemotherapy than with EGFR-TKI monotherapy in EGFR/TP53 co-mutated NSCLC[122-124].

Special populations

Brain metastases

Brain metastases develop in approximately 25%-40% of patients with NSCLC. The incidence is higher in EGFR-mutated than in EGFR-wild-type NSCLC and may reach approximately 40%-60% among patients with EGFR mutations. One major challenge in treating brain metastases is the blood-brain barrier (BBB), which restricts drug penetration into the CNS. Most TKIs are substrates of P-glycoprotein or breast cancer resistance protein (BCRP) and are therefore subject to efflux at the BBB, limiting intracranial activity[125,126]. In addition, brain metastases have greater genomic instability than the primary lung tumor and harbor more copy-number variations (CNVs)[127].

For patients with asymptomatic brain metastases from EGFR-mutated NSCLC, third-generation EGFR-TKIs are preferred. Compared with first-generation TKIs, third-generation agents more effectively reduce the risk of intracranial disease progression. Reported CNS PFS with aumolertinib and furmonertinib was 29.0 months[128] and 20.8 months[129], respectively. Studies and regulatory review data for befotertinib also indicate intracranial disease-control activity in patients with baseline CNS metastases[59]. In patients without baseline CNS metastases, first-line treatment with a third-generation EGFR-TKI may prevent or delay the development of CNS metastases. The newer-generation EGFR inhibitor AZD3759 (zorifertinib) has also shown favorable activity in patients with brain metastases. In clinical studies comparing AZD3759 with gefitinib or erlotinib in EGFR-mutated NSCLC with CNS metastases, AZD3759 demonstrated superior CNS efficacy[130,131]. Intensified targeted therapy is another important area of investigation. ACHIEVE showed that high-dose aumolertinib as first-line therapy in treatment-naive patients with brain metastases produced a high intracranial response rate and prolonged intracranial disease control[132]. GASTO-1063 suggested that aumolertinib plus anlotinib may further improve intracranial PFS[133]. Patients with symptomatic brain metastases and stable extracranial disease should receive active local therapy, including

surgical resection, stereotactic radiotherapy (SRT), or SRT combined with whole-brain radiotherapy (WBRT).

Leptomeningeal metastasis

Leptomeningeal metastasis (LM) is one of the most serious complications of advanced non-small cell lung cancer, with an incidence of up to 10% in advanced NSCLC harboring EGFR or ALK alterations. Diagnosis of brain or leptomeningeal metastasis from lung cancer should integrate three key elements: neurologic function, cranial imaging, and cerebrospinal fluid cytology. Once the diagnosis is established, graded prognostic assessment (GPA) is recommended for risk classification[134]. For response assessment, the combined use of RECIST and RANO-BM criteria is more appropriate, and intracranial and systemic response assessments should be applied together[135]. EGFR-TKIs are recommended as first-line treatment for EGFR-mutated NSCLC with LM. The BLOOM study evaluated osimertinib in patients with LM after failure of prior EGFR-TKI therapy and reported a median PFS of 8.6 months and median OS of 11 months[136]. Commonly used cytotoxic agents have limited penetration across the BBB; however, because the BBB may be disrupted to some extent in patients with LM, systemic chemotherapy may still help improve outcomes, although the benefit is limited. Intrathecal administration is the most commonly used method for delivering chemotherapy directly to LM, particularly in non-nodular and non-mass-forming disease. Pemetrexed is a safe and effective intrathecal chemotherapy agent. In ChiCTR1800016615, intrathecal pemetrexed at 50 mg achieved a response rate of 84.6% with acceptable tolerability in patients with EGFR-positive NSCLC and LM that had progressed after EGFR-TKI therapy[137]. Therefore, an EGFR-TKI combined with intrathecal therapy may provide additional benefit for patients with LM.

Liver metastases

The liver is a common site of metastasis from lung cancer. Approximately 13.4%-22% of patients with NSCLC develop liver metastases during the disease course, and prognosis is very poor, with a mean survival of only 5-6 months in the natural history. Retrospective studies have shown that PFS and OS are significantly shorter in patients with liver metastases than in those without liver involvement[138,139]. A retrospective analysis of 388 patients receiving an EGFR-TKI as first-line therapy found that PFS among patients with liver metastases was not better with osimertinib than with gefitinib/erlotinib (7.4 months *vs.* 7.1 months) or afatinib (7.4 months *vs.* 5.6 months)[138]. In a MARIPOSA subgroup analysis of patients with baseline liver metastases, median PFS was 18.2 months with amivantamab plus lazertinib and 11.0 months with osimertinib (HR = 0.58, $P = 0.017$)[140]. Local treatment options for liver metastases may include interventional hepatic therapy, radiofrequency ablation, radioactive seed implantation, precision radiotherapy, and argon-helium cryoablation. Local treatment of hepatic lesions should be integrated with systemic therapy, including chemotherapy, immunotherapy, or targeted therapy. Overall, amivantamab plus lazertinib provided substantial benefit in this population with a pronounced unmet need and produced a greater reduction in the risk of progression or death than that observed in the overall population. Most single-modality treatments have limitations and suboptimal long-term efficacy, whereas multimodality treatment may improve outcomes. Further studies are needed to optimize patient selection, define the best treatment strategy, and better characterize treatment-related toxicity.

Bone metastases

Lung cancer is among the solid tumors most likely to metastasize to bone. Bone metastases not only impair daily functioning but may also cause skeletal-related events, including bone pain, pathologic fracture, spinal cord or nerve compression, and disturbances of calcium and phosphate homeostasis[141]. The generally accepted diagnostic criteria for bone metastasis include a clinically confirmed diagnosis of lung cancer together with a positive bone biopsy or definitive imaging evidence of bone metastasis. Imaging is used to

identify the sites of bone involvement and assess whether pathologic fracture and/or spinal cord compression is present; when necessary, it may also guide biopsy. Systemic therapy is the mainstay of treatment, while appropriate local treatment can improve control of bone-metastasis-related symptoms. Surgery, radiotherapy, bisphosphonates, and inhibitors of bone resorption may be used to optimize management[142-144]. The main goals of surgery are to relieve pain, reduce or prevent impairment of musculoskeletal function and complications related to spinal cord compression, prevent or treat pathologic fractures, and improve quality of life, thereby potentially prolonging survival indirectly[145]. External-beam radiotherapy is a standard treatment for uncomplicated bone metastases. For uncomplicated painful bone metastases, the American Society for Radiation Oncology (ASTRO) and the European Society for Medical Oncology (ESMO) consider a single 8-Gy fraction to provide pain relief comparable to commonly used multifraction regimens, with potential advantages in convenience and cost-effectiveness[146]. Bisphosphonates reduce bone resorption and increase mineralization by inhibiting osteoclast activity, thereby limiting osteolytic lesions caused by tumor metastases, relieving bone pain, and reducing hypercalcemia and other skeletal-related events associated with bone metastases[147].

Older patients

Although malignancies are common in older adults, older patients remain markedly underrepresented in clinical studies conducted in China and internationally[148]. Recommended tools for geriatric assessment include the instrumental activities of daily living (IADL) scale and activities of daily living (ADL) scale for functional status; the Charlson comorbidity index (CCI) or Cumulative Illness Rating Scale-Geriatric (CIRS-G) for comorbidity; the Mini-Mental State Examination (MMSE) for cognitive status; the Geriatric Depression Scale (GDS) for depression screening; assessment of geriatric syndromes such as falls; and evaluation of nutritional status through measures such as weight change[149]. The G-8 screening tool may also help assess mortality risk in older patients with lung cancer[150]. Polypharmacy is common in older patients with lung cancer. Drug-drug interactions and hepatic and renal function should be carefully considered, and anticancer drug doses should be individualized. First-line EGFR-TKI therapy is recommended for older patients with advanced NSCLC harboring sensitizing EGFR mutations, as survival benefits are similar to those in the overall population, and even very old patients may benefit. In phase III registration trials of the third-generation EGFR-TKIs osimertinib, aumolertinib, or furmonertinib, age-based subgroup analyses showed similar outcomes in patients aged ≥ 65 years and those aged < 65 years[55,57-59]. When an EGFR-TKI is combined with chemotherapy or an antiangiogenic agent, however, the patient's physical condition should guide selection of cytotoxic drugs and treatment regimens, and adverse events should be monitored carefully[151,152].

Patients with chronic obstructive pulmonary disease

Approximately 65% of patients with lung cancer have concomitant chronic obstructive pulmonary disease (COPD), and 50.2% of patients with NSCLC have COPD[153]. A 30-year study showed that, among patients with lung cancer and severe COPD, the risk of COPD-related death increased significantly with increasing Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade and could even exceed the risk of death from lung cancer itself[154]. The presence of COPD is also an important determinant of postoperative survival in patients with early-stage NSCLC. A retrospective analysis using a Cox regression model to evaluate the association between diagnosed COPD and survival in NSCLC found that the 5-year OS rate after surgery was significantly lower in patients with COPD than in those without COPD (54.4% *vs.* 69.0%, $P = 0.0002$)[155]. In advanced NSCLC, simultaneous treatment of COPD and lung cancer is an important determinant of outcome and is associated with significantly longer OS. A retrospective study of patients with NSCLC receiving chemotherapy assessed the association between pharmacologic treatment of COPD and OS. Median OS was significantly longer when lung cancer and COPD were treated concurrently (16.7

months *vs.* 8.2 months, $P = 0.023$), indicating that COPD treatment is an important prognostic factor in patients with concomitant lung cancer and COPD[156]. A database study of patients with NSCLC in Taiwan, China, found that among patients treated with EGFR-TKIs, those with concomitant COPD had shorter PFS and OS than those without COPD (mPFS: 0.62 *vs.* 0.69, $P < 0.001$; mOS: 2.28 *vs.* 2.04, $P < 0.001$)[157]. Therefore, a comprehensive assessment and management strategy for COPD should be established alongside lung-cancer treatment to improve patient outcomes.

Patients with diabetes mellitus

Diabetes mellitus (DM) is a common underlying disease among patients with cancer. The hyperglycemic environment caused by diabetes may also affect the activity of tumor suppressor genes, thereby increasing the risk of cancer. In patients with cancer complicated by diabetes, persistently poor glycemic control can readily induce multiple complications and worsen prognosis[158]. Patients with lung cancer who are receiving glucose-lowering medications should also maintain awareness of glycemic prevention and control. Studies have shown that impaired glycemic status adversely affects survival in patients with advanced NSCLC, whereas appropriate glycemic control (HbA1c ≤ 6.6%) may improve OS[159]. Metformin is the preferred first-line glucose-lowering agent for type 2 diabetes and also has antitumor effects; accordingly, increasing attention has been paid to its potential antitumor activity[160,161]. A meta-analysis showed that patients receiving metformin plus an EGFR-TKI had longer PFS than those receiving an EGFR-TKI alone (HR 0.84; $P = 0.004$)[162]. Another meta-analysis showed that metformin treatment significantly improved survival in patients with lung cancer; after stratification by histologic subtype, the HRs for OS in undifferentiated carcinoma, NSCLC, and SCLC were 0.78, 0.73, and 0.51, respectively[163]. Therefore, in patients with lung cancer and concomitant diabetes who have no contraindication to metformin, metformin may be preferentially used as adjunctive therapy. The common adverse effects of metformin are primarily gastrointestinal and usually occur early during treatment; gradual dose escalation or switching to an extended-release formulation is effective in reducing these adverse effects. When metformin is combined with an EGFR-TKI, an EGFR-TKI with a favorable adverse-effect profile should be selected.

MECHANISMS OF RESISTANCE TO EGFR-TKIS

First- to third-generation TKIs

A targeted agent directed against a specific genomic alteration generally addresses a defined mutation subtype, and resistance mechanisms differ among generations of EGFR-TKIs. Resistance to EGFR-TKIs can be classified as EGFR-dependent or EGFR-independent. In patients treated with first- or second-generation EGFR-TKIs, EGFR-dependent resistance predominates, and the most common mechanism is T790M, which accounts for approximately 50% of cases[15,164]. Resistance mechanisms also differ between first-line and second-line use of third-generation EGFR-TKIs. Major mechanisms of resistance to third-generation EGFR-TKIs include C797S mutation, MET amplification, HER2 amplification, small-cell lung cancer transformation (10%), and alterations in downstream EGFR signaling, including KRAS, BRAF, PIK3CA, and the RAS/RAF/MEK/ERK pathway[165-168]. After resistance to a third-generation agent, the mechanism remains unknown in approximately 50% of patients, who may require chemotherapy or immunotherapy.

Primary resistance

Primary resistance to an EGFR-TKI refers to lack of response to initial therapy because of the biological or genetic characteristics of the tumor, or to disease progression within 3 months of starting an EGFR-TKI without evidence of an objective response[169]. The mechanisms of primary resistance remain incompletely understood. Based on available studies, potential mechanisms include EGFR variants with low sensitivity to EGFR-TKIs, such as L861Q, G719X, S768I, L747P, Ex19ins, Ex20ins, and de novo T790M; co-mutations

involving TP53, RB1, MET, KRAS, NRAS, SMAD4, PIK3CA, CTNNB1, DDR2, ERBB4, FGFR1, or FGFR3; high PD-L1 expression; and phenotypic transformation of non-squamous NSCLC to small-cell lung cancer or squamous cell carcinoma[169-172]. These findings indicate that the mechanisms of primary resistance may be more complex than those of acquired resistance, and no superior strategy has yet been established. Guidelines recommend chemotherapy plus antiangiogenic therapy or chemoimmunotherapy after first- or second-line progression. In clinical practice, chemotherapy or antiangiogenic therapy is often added to the original EGFR-TKI and may help overcome primary resistance. The POISE study (NCT03567642), presented at ASCO 2024, enrolled 11 patients with NSCLC harboring sensitizing EGFR mutations together with TP53 and RB1 mutations. After 9 weeks of induction osimertinib, patients received four cycles of etoposide plus cisplatin or carboplatin, followed by osimertinib monotherapy until disease progression. Median PFS was 15.6 months, and median OS was 17.9 months[173]. In RELAY, the HR for erlotinib plus ramucirumab was 0.59, and PFS was 19.4 months with the combination *vs.* 12.4 months with monotherapy, suggesting that dual inhibition of VEGF and EGFR pathways may delay resistance[60].

Acquired resistance

Acquired resistance refers to disease progression during continued treatment after the tumor was initially sensitive to therapy, the patient achieved a response (partial response [PR] or complete response [CR]), or clinical benefit was maintained for ≥ 6 months, without intervening systemic therapy[174]. Common resistance mechanisms are summarized below.

T790M mutation

Rebiopsy after resistance to first- or second-generation EGFR-TKIs shows that T790M accounts for approximately 50% of resistance mechanisms[175]. Rebiopsy is currently required after failure of a first- or second-generation EGFR-TKI. If T790M is detected, treatment with a third-generation EGFR-TKI, such as osimertinib or aumolertinib, is recommended; if T790M is not detected, chemotherapy is recommended. In the phase III AURA3 study, PFS with osimertinib in patients with T790M-mutated disease was 10.1 months[176,177]. In the AENEAS study of aumolertinib for T790M-mutated disease progressing after a first-generation EGFR-TKI, median PFS was 12.4 months and median OS was 30.2 months[178]. In a phase IIb study of furmonertinib in advanced EGFR T790M-mutated NSCLC, PFS was 9.6 months[179]. In a study of befotertinib for T790M-positive disease, median PFS was 16.6 months and median OS was 31.5 months[180]. Thus, third-generation TKIs can substantially prolong survival in patients who acquire T790M after progression on a first- or second-generation EGFR-TKI.

C797S mutation

C797S is a missense mutation in the EGFR tyrosine kinase domain that prevents third-generation EGFR-TKIs from forming a covalent bond within the ATP-binding domain of the EGFR kinase, thereby impairing drug activity[166]. After second-line osimertinib, T790M and C797S commonly coexist, making subsequent treatment more complex. Concurrent T790M and C797S can occur in cis or in trans. Available studies indicate that tumors with T790M/C797S in trans are resistant to third-generation TKIs but sensitive to combined first- and third-generation TKIs; therefore, osimertinib plus a first-generation EGFR-TKI may be considered[181]. In contrast, tumors with T790M/C797S in cis are insensitive to first- and second-generation EGFR-TKIs and may require chemotherapy or brigatinib plus cetuximab[181,182]. Fourth-generation EGFR-TKIs targeting C797S and compound resistance mutations remain in early clinical development and include DZD6008, BLU-945, BLU-701, BBT-176, and JIN-A02[183]. Current evidence is derived mainly from phase I/II dose-escalation studies, expansion cohorts, or meeting abstracts and is insufficient to support routine clinical use; enrollment in clinical trials should be prioritized.

MET amplification

MET amplification is a common mechanism of resistance to EGFR-TKIs[166], and multiple clinical studies have evaluated MET-directed strategies. In the phase Ib TATTON study, osimertinib plus savolitinib produced a median PFS of 9.0-11 months in patients with MET amplification after resistance to a first- or second-generation EGFR-TKI, regardless of T790M status[184]. In the INSIGHT study of tepotinib plus gefitinib, among patients with MET amplification, tepotinib plus gefitinib improved PFS (16.6 months *vs.* 4.2 months [HR = 0.13]), OS (37.3 months *vs.* 13.1 months [HR = 0.10]), ORR (66.7% *vs.* 42.9%), and DOR (19.9 months *vs.* 2.8 months) compared with chemotherapy and was well tolerated[165]. For patients who develop MET amplification or MET overexpression after first-line osimertinib without a dominant resistance mechanism such as small-cell transformation, osimertinib plus savolitinib has shown better disease control than chemotherapy in studies including SACHI and SAVANNAH and represents an important mechanism-directed option[185,186].

BRAF V600E mutation

BRAF mutations are uncommon in NSCLC, with an incidence of approximately 1.5%-3.5%; BRAF V600E is the most frequent subtype[187,188]. BRAF is a component of the MAPK pathway downstream of EGFR, and acquired BRAF alterations are infrequent in patients previously treated with an EGFR-TKI. For patients who progress after a third-generation EGFR-TKI, combination strategies are commonly used, including a first-generation EGFR-TKI, an anti-EGFR antibody, or a targeted agent directed against the corresponding resistance alteration[189]. In 2019, Huang et al. reported in the Journal of Thoracic Oncology a patient with EGFR-mutated NSCLC who acquired BRAF V600E after progression on osimertinib. The patient continued osimertinib and received the BRAF inhibitor dabrafenib plus the MEK inhibitor trametinib, achieving stable disease; PFS exceeded 7.4 months at the time of publication[190].

HER2 alterations

HER2 alterations are oncogenic drivers in NSCLC and also represent an important mechanism of acquired resistance to EGFR-TKIs. Among HER-family proteins, HER2 has the greatest catalytic kinase activity[191], and its phosphorylation activates downstream PI3K-AKT, MAPK, and ERK/MET-MAPK signaling[192,193]. HER2 alterations in NSCLC mainly include amplification and mutation, both of which can activate HER2 signaling[194]. HER2 amplification is more common after resistance to first-line first-generation EGFR-TKIs, such as erlotinib or gefitinib, than after third-generation EGFR-TKIs and occurs in approximately 10% of cases[15]. A single-arm phase II study evaluated trastuzumab plus paclitaxel in patients with HER2-expressing NSCLC after progression on an EGFR-TKI. The overall ORR was 46%, and all four patients with HER2 amplification (> 10 copies/nucleus) achieved a response[195]. Trastuzumab emtansine (T-DM1) is an ADC comprising an anti-HER2 antibody, a non-cleavable linker, and a cytotoxic payload. A phase II study of T-DM1 in patients previously treated with an EGFR-TKI observed partial responses in 4 patients with HER2 immunohistochemistry (IHC) 3+ tumors, with an ORR of 20%[196]. Another phase II study in 18 heavily pretreated patients with HER2-mutated lung cancer reported an ORR of 44% and median PFS of 5 months with T-DM1[197]. Trastuzumab deruxtecan (T-DXd), another ADC, has also shown favorable antitumor activity in HER2-expressing or HER2-mutated NSCLC. In the phase II DESTINY-Lung01 study, T-DXd achieved a confirmed ORR of 55% and median PFS of 8.2 months in patients with HER2-mutated NSCLC previously treated with current standard therapies[198].

TREATMENTS AFTER RESISTANCE TO EGFR-TKIS

Antibody-drug conjugates

An antibody-drug conjugate (ADC) links a monoclonal antibody to a cytotoxic drug through a linker, enabling precise delivery of the payload to antigen-expressing tumor cells, targeted killing of specific cancer

cells, and reduced toxicity to normal tissues[199]. Sacituzumab govitecan (Trodelvy), datopotamab deruxtecan (Dato-DXd), and sacituzumab tirumotecan (SKB264) have shown activity in clinical studies. EVOKE-1 was a phase III trial of second-line sacituzumab govitecan in patients with NSCLC that had progressed after platinum-based chemotherapy and immunotherapy, or in patients with actionable driver alterations who had progressed after targeted therapy. Results presented at ASCO 2024 showed OS of 11.1 months with sacituzumab govitecan *vs.* 9.8 months with docetaxel, representing a numerical benefit that did not reach statistical significance[200]. TROPION-LUNG01 enrolled patients whose disease had progressed after immunotherapy or after at least one line of targeted therapy. In patients with non-squamous NSCLC, median OS was 14.6 months with Dato-DXd *vs.* 12.3 months with docetaxel[201]. TROPION-Lung05 was a phase II study of Dato-DXd in NSCLC with actionable genomic alterations, and the ORR in the EGFR-mutated subgroup was approximately 43.6%[202]. In KL264-01, second-line sacituzumab tirumotecan (SKB264/sac-TMT), a TROP2-directed ADC, achieved an overall ORR of 40% and median PFS of 6.2 months in advanced NSCLC; in the EGFR-mutated subgroup, ORR was 55% and median PFS was 11.1 months[203]. OptiTROP-Lung04 compared sac-TMT monotherapy with pemetrexed plus platinum in EGFR-mutated non-squamous NSCLC after progression on an EGFR-TKI; sac-TMT significantly improved progression-free and overall survival outcomes compared with platinum-based chemotherapy[204]. HERTHENA-Lung01 showed that in patients with EGFR-mutated NSCLC that had progressed after an EGFR-TKI and platinum-based chemotherapy, patritumab deruxtecan (HER3-DXd) achieved a confirmed ORR of 29.8%, median DOR of 6.4 months, median PFS of 5.5 months, and median OS of 11.9 months[205]. However, HERTHENA-Lung02 did not demonstrate a statistically significant OS benefit. Telisotuzumab vedotin (Teliso-V) is a c-Met-directed ADC. In an independent central review, Teliso-V plus osimertinib achieved an ORR of 50.0% and median PFS of 7.4 months[206]. In 2025, Teliso-V received accelerated FDA approval for previously treated non-squamous NSCLC with high c-Met protein overexpression. In addition, a phase I trial of the EGFR-directed ADC CPO301 in advanced or metastatic lung cancer with EGFR mutation or amplification is ongoing [NCT05948865].

Chemotherapy with or without immunotherapy

For patients with widespread progression after resistance to a third-generation EGFR-TKI, a change in systemic therapy is recommended. CSCO guidelines recommend platinum-doublet chemotherapy with or without bevacizumab. Depending on the resistance mechanism and available evidence, mechanism-matched targeted therapy plus chemotherapy or immunotherapy plus chemotherapy may be considered. In FLAURA2, first-line osimertinib plus platinum-based chemotherapy achieved a median PFS of 25.5 months compared with 16.7 months for osimertinib alone in advanced NSCLC with sensitizing EGFR mutations (HR = 0.62), representing a 38% reduction in the risk of disease progression or death[68]. Based on these results and clinical practice, osimertinib plus chemotherapy may provide a potential reference strategy after resistance to EGFR-TKI monotherapy. ORIENT-31 showed that both a four-drug combination and immunotherapy plus chemotherapy significantly prolonged median PFS compared with platinum-doublet chemotherapy in patients with EGFR-mutated disease; however, interim results released in 2023 showed no statistically significant OS difference among the three groups[207]. Immune checkpoint inhibitor monotherapy has generally shown limited efficacy after EGFR-TKI resistance. Several studies, including ORIENT-31, NEJ043, and IMpower150, have provided preliminary evidence for immune checkpoint inhibition plus antiangiogenic therapy and chemotherapy in this setting[208-210]. For patients with an unknown resistance mechanism after a third-generation EGFR-TKI, immunotherapy-based combination treatment may represent a potential option, but the optimal regimen, selection of patients most likely to benefit, and safety require further study. For patients with widespread progression after resistance to EGFR-TKIs and no effective targeted option, immune checkpoint inhibitors are recommended.

Bispecific antibody therapy

The PD-1/PD-L1 axis and VEGF-mediated immunosuppression commonly coexist in the tumor microenvironment. Ivonescimab is a novel tetravalent antibody designed to accumulate in the tumor microenvironment and more effectively block the independent but complementary PD-1 and VEGF pathways, thereby enhancing immune-cell-mediated tumor killing[211]. Compared with separate anti-PD-1 and anti-VEGF agents, ivonescimab provides dual targeting within a single molecule. HARMONi-A enrolled patients with advanced non-squamous EGFR-mutated NSCLC after failure of an EGFR-TKI and compared ivonescimab plus pemetrexed and carboplatin with placebo plus pemetrexed and carboplatin. Median PFS was 7.06 months *vs.* 4.8 months, respectively. Grade ≥ 3 adverse events occurred in 61.5% and 49.1% of patients, respectively; most were attributed to chemotherapy, whereas rates of grade ≥ 3 VEGF-related and immune-related adverse events were 3.1% and 6.2%, respectively[212]. The final analysis showed that ivonescimab plus chemotherapy significantly improved OS, with median OS of 16.8 months versus 14.1 months (HR 0.74, $P = 0.02$) and 30-month OS rates of 29.1% versus 18.4%; grade ≥ 3 treatment-emergent adverse events occurred in 67.1% *vs.* 54.7%[213]. For patients with EGFR-mutated NSCLC who develop osimertinib resistance associated with MET amplification, amivantamab provides an additional treatment option[214]. Studies of other bispecific approaches, including PD-L1/CTLA-4 blockade (KN046-202), are ongoing.

MANAGEMENT OF ADVERSE EFFECTS

EGFR-TKIs are generally well tolerated, and adverse events are usually mild. Common toxicities include cutaneous, gastrointestinal, and pulmonary adverse events[215]. Cutaneous toxicity mainly includes rash, acneiform rash, and paronychia. These events may be reduced by preventive measures such as skin moisturization and topical or oral medications. Severe skin reactions may require interruption of TKI therapy, followed by dose-reduced rechallenge after improvement. Gastrointestinal toxicity most commonly manifests as diarrhea, which is frequent, and some patients also develop hepatotoxicity. Diarrhea can be managed with symptomatic treatment and dose adjustment, whereas hepatotoxicity requires close monitoring of liver function and timely modification of treatment. Pulmonary toxicity is among the most serious adverse events associated with EGFR-TKIs and may present as interstitial lung disease (ILD) or pulmonary fibrosis. The incidence is low: reported ILD rates with gefitinib, erlotinib, afatinib, and osimertinib are 1.3%-2.2%, 0.6%-1.5%, 0.2%-0.6%, and 3.0%, respectively[208-210]. In the AENEAS study, the overall incidence of ILD with aumolertinib was 0.9%. Once pulmonary toxicity occurs, however, it may lead to severe consequences or death. Management includes interruption of the TKI and corticosteroid therapy, with permanent discontinuation when necessary.

The frequency and severity of adverse events differ among generations of EGFR-TKIs. A previous meta-analysis showed that afatinib was more likely than gefitinib or erlotinib to cause rash and diarrhea[216], whereas gefitinib was more strongly associated with an increased risk of elevated liver enzymes[215]. Third-generation EGFR-TKIs, including osimertinib and aumolertinib, generally have favorable safety and tolerability, but characteristic toxicities still require attention, including rash, diarrhea, paronychia, elevated liver enzymes, interstitial lung disease or drug-induced pneumonitis, QT-interval prolongation, cardiac dysfunction, and laboratory abnormalities. In AENEAS, creatine kinase elevation occurred in 35.5% of patients receiving aumolertinib, compared with 9.3% in the gefitinib control group[57]. Clinicians should therefore monitor for unexplained myalgia or muscle weakness and closely assess serum creatine phosphokinase, myoglobin, hepatic and renal function, and potassium. Persistently abnormal results require prompt medical evaluation. Concomitant use of drugs that increase creatine phosphokinase, such as statins, should be avoided.

Overall, adverse events associated with EGFR-TKIs are preventable and manageable. Early recognition and intervention are essential. Oncologists should implement comprehensive preventive and therapeutic measures, including lifestyle modification and pharmacologic intervention, to minimize the impact of toxicity. Patient education and structured follow-up are also important for improving treatment adherence and quality of life.

SUMMARY AND PERSPECTIVES

EGFR mutations are the most common oncogenic drivers in NSCLC, and EGFR-TKIs have become standard first-line therapy for advanced EGFR-positive NSCLC. With continued research, additional third-generation EGFR-TKIs, such as befotertinib and rezivertinib, have emerged and demonstrated substantial efficacy and prolonged PFS in the first-line setting. Fourth-generation EGFR-TKIs have now entered clinical investigation. Despite major advances in the clinical application of EGFR-TKIs, benefit remains limited for some rare mutations, and treatment resistance continues to be a major challenge. More precise risk stratification based on minimal residual disease (MRD) assessment or dynamic ctDNA monitoring may support individualized treatment, earlier detection of resistance, and timely adjustment of therapeutic strategies. Refining the population most likely to benefit from EGFR-TKIs, improving safety management, and overcoming resistance will remain major clinical priorities. The key consensus recommendations on molecular testing, treatment selection, and resistance management, together with their recommendation levels, are summarized in Table 8. This expert consensus will continue to follow emerging evidence, promote standardized diagnosis and treatment of EGFR-mutated NSCLC, and ultimately improve survival and quality of life for patients with lung cancer.

Table 8. Consensus on the diagnosis and treatment of EGFR gene mutation non-small cell lung cancer in China

	Consensus number	Key points	Recommendation level
Detection time point	Consensus 1	EGFR mutation testing is recommended for patients with NSCLC in whom molecular results may influence treatment decisions, particularly those with advanced non-squamous NSCLC or tumors containing an adenocarcinoma component	Strong recommendation
	Consensus 2	Comprehensive molecular testing covering EGFR and other actionable driver alterations, including ALK, ROS1, BRAF, KRAS, HER2, and others, is recommended whenever feasible, rather than relying solely on sequential single-gene testing	Strong recommendation
Detection method	Consensus 3	DNA-based NGS is the preferred method for EGFR mutation testing. When NGS is unavailable, validated RT-PCR assays may be used for hotspot mutations. FISH is not recommended for routine EGFR mutation screening, but may serve as a supplementary validation method in selected circumstances	Recommendation
Detection strategy	Consensus 4	Tumor tissue or cytology specimens are preferred for EGFR mutation testing. If tissue is unavailable or insufficient, plasma ctDNA may be used in advanced NSCLC; pleural effusion or cerebrospinal fluid may also be considered in selected patients	Strong recommendation
	Consensus 5	Laboratories performing EGFR testing should participate in regular external quality assessment programs and maintain validated internal quality-control procedures, such as PQCC, CAP, CLIA, or equivalent quality systems	Strong recommendation
Treatment strategy	Consensus 6	For patients with advanced NSCLC harboring sensitizing EGFR mutations, including exon 19 deletion or L858R, single-agent EGFR-TKI remains the therapeutic backbone. For selected high-risk patients, intensified first-line strategies may be preferentially discussed, including osimertinib plus chemotherapy, aumolertinib plus chemotherapy, or amivantamab plus lazertinib	Strong recommendation
	Consensus 7	For completely resected stage IB-IIIA NSCLC harboring sensitizing EGFR mutations such as exon 19 deletion or L858R, adjuvant osimertinib is recommended. In stage II-IIIA disease, adjuvant icotinib may also be considered where appropriate in China	Strong recommendation
	Consensus 8	For patients with advanced NSCLC harboring EGFR exon 20 insertion mutations, platinum-pemetrexed chemotherapy and evidence-supported amivantamab plus chemotherapy may be prioritized in the first-line setting. In later lines, sunvozertinib or other investigational agents may be selected according to regulatory approval, drug accessibility, and the specific insertion-site subtype	Recommendation

Consensus 9	For advanced NSCLC harboring uncommon EGFR mutations such as G719X, S768I, or L861Q, EGFR-TKI treatment may be considered. Afatinib has the strongest supporting evidence, while osimertinib or aumolertinib may also be considered in selected patients.	Recommendation
Consensus 10	For patients with disease progression after EGFR-TKI therapy, repeat NGS-based molecular testing is recommended to identify resistance mechanisms and guide subsequent targeted therapy, combination treatment, or enrollment in appropriate clinical trials	Strong recommendation
Consensus 11	For patients who develop acquired EGFR T790M after first- or second-generation EGFR-TKI treatment, third-generation EGFR-TKIs are recommended. Representative agents include osimertinib, aumolertinib, furmonertinib, and befotertinib	Strong recommendation
Consensus 12	For patients without an actionable resistance mechanism after EGFR-TKI failure, platinum-pemetrexed chemotherapy remains the backbone. Immune checkpoint inhibitor monotherapy is not recommended routinely. In fit patients with non-squamous disease and no contraindications, immunotherapy plus anti-angiogenic therapy and chemotherapy, or bispecific antibody plus chemotherapy, may be considered according to accessibility in China. ADCs and bispecific antibodies should preferably be used within approved indications or clinical trials	Recommendation; Not recommended for routine use for ICI monotherapy

EGFR: Epidermal growth factor receptor; NSCLC: non-small-cell lung cancer; ALK: anaplastic lymphoma kinase; ROS1: c-ros oncogene 1; BRAF: v-raf murine sarcoma viral oncogene homologue B1; KRAS: Kirsten rat sarcoma viral oncogene; HER2: Human epidermal growth factor receptor 2; TKI: tyrosine kinase inhibitor; NGS: next-generation sequencing; RT-PCR: reverse transcription-polymerase chain reaction.

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Authors' contributions

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Conflicts of interest

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Ethical approval and consent to participate

Not applicable

Consent for publication

Not applicable

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