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REVIEW ARTICLE

Targeted therapy resistance in EGFR-mutant non-small cell lung cancer: Roles of MET, Trop-2-directed antibody–drug conjugates, and molecular monitoring

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Abstract

Introduction: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have substantially improved outcomes in patients with EGFR-mutant non-small cell lung cancer (NSCLC), but acquired resistance remains a major barrier to durable disease control.

Objective: This narrative review summarizes the major mechanisms of EGFR-TKI resistance and evaluates the roles of mesenchymal–epithelial transition factor (MET)-targeted therapy, trophoblast cell-surface antigen 2 (Trop-2)-directed antibody–drug conjugates (ADCs), and molecular monitoring in post-resistance management.

Methods: Relevant randomized controlled trials, translational studies, and consensus guidelines on targeted therapy resistance in NSCLC were identified from PubMed and Web of Science, with emphasis on recent high-quality evidence and seminal studies.

Results: EGFR-TKI resistance arises through on-target EGFR alterations, bypass pathway activation, histologic transformation, and non-genetic adaptation. *MET* amplification is a clinically relevant bypass mechanism, particularly after third-generation EGFR-TKI exposure, and may support combined EGFR/MET inhibition when confirmed using assay-specific criteria. Trop-2-directed ADCs provide a non-genotype-dependent treatment option for patients with heterogeneous or non-actionable resistance, although Trop-2 expression is not yet a validated universal predictive biomarker. Plasma circulating tumor DNA can facilitate rapid detection of emerging resistance, but negative or discordant plasma findings should be interpreted together with tissue biopsy, disease distribution, and the possibility of histologic transformation. Minimal residual disease assessment remains investigational for treatment-guided decision-making.

Conclusion: Post-EGFR-TKI management should follow a mechanism-guided framework integrating progression pattern, tissue and plasma reassessment, biomarker-specific interpretation, matched therapy, and longitudinal molecular monitoring. Prospective studies are needed to standardize testing thresholds and optimize treatment sequencing.

Keywords: Non-small cell lung cancer; Targeted therapy; Epidermal growth factor receptor; Mesenchymal–epithelial transition factor; Trophoblast cell-surface antigen 2; Resistance mechanisms

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1. Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 80–85% of all lung cancer cases and remains one of the leading causes of cancer-related mortality worldwide.[1] Although surgery, radiotherapy, and platinum-based chemotherapy remain important treatment modalities, many patients are still diagnosed at an advanced stage or eventually experience disease recurrence, resulting in unsatisfactory long-term outcomes.[2] This clinical reality has prompted a gradual shift in research focus from traditional treatment paradigms to the in-depth characterization of tumor molecular biology. The evolution of cancer therapy from conventional chemotherapy toward precision oncology has been extensively reviewed elsewhere.[3]

With the rapid development of high-throughput sequencing and molecular pathology technologies, the treatment paradigm for NSCLC has progressively shifted from traditional histological subtyping to an era of precision medicine centered on driver genes.[4] Among these molecular events, epidermal growth factor receptor (EGFR) mutations are among the most established actionable drivers in NSCLC, whereas mesenchymal–epithelial transition factor (MET) amplification may function either as a primary oncogenic alteration or as an important bypass mechanism of acquired resistance to EGFR tyrosine kinase inhibitors (TKIs). In contrast, trophoblast cell-surface antigen 2 (Trop-2) is not a classical driver gene but is increasingly recognized as a therapeutically exploitable cell-surface antigen for antibody–drug conjugates (ADCs) in advanced or treatment-resistant NSCLC.[5-7] Small-molecule TKIs and ADCs directed against these key targets have significantly improved the progression-free survival and overall survival of patients with specific molecular subtypes, thereby establishing the core role of targeted therapy in the comprehensive treatment landscape of NSCLC.[8,9]

Although targeted therapies provide substantial initial clinical benefit, acquired resistance remains a major barrier to durable disease control. Resistance evolution is characterized by marked spatial and temporal heterogeneity and may involve on-target secondary alterations, activation of bypass signaling pathways, histologic or phenotypic transformation, and tumor microenvironmental remodeling. Common resistance mechanisms following EGFR-TKI therapy include secondary *EGFR* mutations (such as T790M, C797S), activation of bypass signaling pathways (such as *MET* amplification), and alterations in tumor biological behavior (transformation to small cell lung cancer).[10] Furthermore, patients with certain rare mutation subtypes or coexisting multiple molecular aberrations still lack highly effective and standardized treatment strategies, which remains a challenge in current clinical practice. In recent years, next-generation EGFR-TKIs have expanded into adjuvant therapy and the treatment of uncommon mutations. In parallel, MET-targeted therapies have shown promising activity in *MET* amplification-driven disease, and Trop-2-directed ADCs have emerged as potential options in TKI-resistant populations. Together, these advances have broadened the therapeutic landscape of NSCLC.[11-13]

Advances in precision medicine are reshaping treatment decisions for NSCLC. The dynamic monitoring of circulating tumor DNA (ctDNA) and minimal residual disease (MRD) assessments has made it possible to identify emerging resistance and molecular relapse earlier. These approaches may also support treatment adjustments based on real-time molecular changes.[14,15] Against this backdrop, seamlessly integrating molecular monitoring results with targeted therapy strategies to achieve truly individualized treatment has emerged as a crucial direction for current research. To provide a comprehensive synthesis, relevant literature was primarily retrieved from PubMed and Web of Science, focusing on high-quality clinical trials and peer-reviewed translational studies published predominantly within the last five years. Based on these premises, this narrative review summarizes recent advances in EGFR-, MET-, and Trop-2-directed therapies in NSCLC, with particular emphasis on resistance evolution, mechanism-based post-resistance treatment strategies, and the potential integration of ctDNA- and MRD-based molecular monitoring into individualized therapeutic decision-making.[5,6,11,13] Our objective is to develop a conceptual framework that integrates the diverse pathways involved in the evolutionary trajectory of NSCLC resistance. This framework aims to synthesize key clinical evidence, elucidate primary resistance mechanisms, and assess the potential utility of molecular monitoring, thereby serving as a crucial reference for optimizing individualized treatment strategies following resistance. In contrast to previous reviews that have examined EGFR, MET, or Trop-2 as discrete therapeutic targets, this review seeks to incorporate these targets within a resistance-evolution framework. This framework connects driver inhibition, suppression of bypass resistance, ADC-based post-resistance therapy, and dynamic molecular monitoring.

In clinical practice, therapeutic resistance in NSCLC rarely follows a linear or single-mechanism pattern. Instead, resistance frequently emerges through the coexistence and dynamic competition of multiple subclones. For example, an EGFR-mutant tumor initially dependent on EGFR signaling may later acquire secondary EGFR alterations,

activate MET-mediated bypass signaling, undergo phenotypic transformation, or lose dependence on a single actionable driver.[16] Under such circumstances, post-progression treatment decisions cannot rely only on the molecular status at baseline. Rather, they require repeated reassessment of the evolving tumor genome and biological phenotype.

The clinical significance of integrating EGFR, MET, Trop-2, and molecular monitoring lies in establishing a dynamic treatment decision-making framework for acquired resistance to targeted therapies in NSCLC. Within this framework, EGFR inhibition represents the foundation of targeted treatment for driver-positive NSCLC; MET inhibition addresses one of the most clinically relevant bypass resistance mechanisms; Trop-2-directed ADCs provide therapeutic options for patients with heterogeneous or non-actionable resistance; and ctDNA/MRD monitoring enables dynamic detection of molecular recurrence and emerging resistance before overt clinical progression.[17] To inform this framework, relevant randomized controlled trials, translational studies, and consensus recommendations were identified through PubMed and Web of Science, emphasizing high-quality recent evidence and landmark studies that have defined current understanding of resistance mechanisms and treatment strategies. This paper aims to summarize the evolving landscape of targeted therapy resistance and discuss emerging precision approaches for optimizing sequential therapeutic strategies in NSCLC.[18,19]

2. Latest research progress in targeted therapy for core targets

2.1. *EGFR* mutation target: Clinical breakthroughs in adjuvant therapy and rare mutations

EGFR mutations are the most common driver gene alterations in NSCLC, among which exon 19 deletions (19del) and the exon 21 L858R point mutation account for approximately 80% of all *EGFR* mutations.[20] With the continuous development of third-generation EGFR-TKIs, their clinical value across different treatment stages of EGFR-mutant NSCLC has been gradually validated.[11]

The therapeutic role of EGFR-TKIs has evolved from the management of advanced metastatic disease to a broader disease-course strategy covering early-stage postoperative recurrence prevention, first-line systemic therapy, central nervous system disease control, and subsequent treatment after acquired resistance.[11,21] This expansion reflects not only the improved potency and selectivity of newer-generation EGFR-TKIs but also the increasing recognition that EGFR-mutant NSCLC should be managed as a molecularly defined disease throughout its entire clinical trajectory. In early-stage disease, the major objective of EGFR-TKI therapy is to reduce micrometastatic relapse after complete resection. In advanced disease, the treatment goal is prolonged systemic and intracranial disease control while maintaining quality of life. In uncommon EGFR-mutant disease, therapeutic selection is more complex because sensitivity to EGFR inhibition varies substantially according to the exact mutation subtype and molecular conformation.

From this perspective, *EGFR* mutation status should not be interpreted simply as positive or negative. Classical sensitizing mutations, major uncommon mutations, exon 20 insertions, compound mutations, and resistance-associated secondary mutations represent biologically and clinically distinct entities. This distinction is particularly important when evaluating clinical trial results, because the efficacy observed in classical EGFR-mutant populations cannot be directly extrapolated to all rare mutation subgroups.[22]

In the adjuvant setting, a multicenter, randomized, controlled phase III trial demonstrated that the third-generation EGFR-TKI aumolertinib significantly improved disease-free survival in patients with resected EGFR-mutant NSCLC harboring EGFR-sensitizing mutations.[23] Notably, among patients undergoing MRD testing, molecular clearance after adjuvant EGFR-TKI therapy may provide additional prognostic information. However, whether MRD status should directly guide treatment escalation, de-escalation, or treatment duration remains to be validated in prospective studies.[24] The integration of MRD assessment into adjuvant EGFR-TKI therapy is clinically attractive but remains methodologically challenging. A persistently positive MRD result after surgery may indicate the presence of residual microscopic disease and a higher probability of subsequent relapse, whereas MRD clearance during adjuvant therapy may reflect effective suppression of residual tumor clones.[25] Nevertheless, several unresolved questions constrain the prompt clinical application of these findings. The optimal management strategy for MRD-positive patients—whether it involves extended EGFR-TKI therapy, enhanced systemic treatment, or increased surveillance—remains indeterminate. Conversely, the safety of treatment de-escalation in MRD-negative patients, without adversely affecting long-term survival outcomes, has yet to be ascertained. Furthermore, variations in assay sensitivity, timing of sample collection, the use of tumor-informed versus tumor-naïve platforms, and the inherent biological heterogeneity of ctDNA shedding may affect the accuracy and reliability of MRD interpretation.[26] Therefore, MRD should currently be regarded as a promising risk-stratification tool rather than a definitive

basis for modifying adjuvant EGFR-TKI treatment outside prospective clinical trials.[4]

For uncommon *EGFR* mutations, therapeutic sensitivity varies substantially across mutation subtypes. Major uncommon mutations, such as G719X, L861Q, and S768I, may retain sensitivity to selected EGFR-TKIs, whereas EGFR exon 20 insertion mutations generally show limited sensitivity to conventional first- to third-generation EGFR-TKIs. Therefore, treatment strategies should be discussed according to specific mutation categories rather than grouped under a broad definition of "rare *EGFR* mutations."[27] In patients with locally advanced or metastatic NSCLC harboring classical EGFR-sensitizing mutations, limertinib demonstrated prolonged progression-free survival compared with gefitinib in the first-line setting. Its reported intracranial activity also suggests potential value for patients with concurrent brain metastases.[28,29] Overall, these findings support the expanding role of third-generation EGFR-TKIs across selected clinical settings, including adjuvant therapy, first-line treatment for classical EGFR-sensitizing mutations, and carefully defined uncommon mutation subgroups.

2.2. *MET* amplification target: Clinical progress of selective inhibitors

MET amplification may act as a primary oncogenic driver in a subset of NSCLC and is also a well-recognized bypass mechanism of acquired resistance to EGFR-TKIs. However, its clinical interpretation remains challenging because detection platforms and positivity thresholds differ across studies, including fluorescence *in situ* hybridization (FISH), next-generation sequencing (NGS)-based copy-number assessment, and *MET*/centrosomal protein 7 (CEP7) ratio-based criteria.[30]

Unlike point mutations, *MET* amplification is a quantitative and context-dependent biomarker.[30] Its predictive value may be influenced by absolute gene copy number, *MET*/CEP7 ratio, tumor purity, focality of amplification, and the presence of chromosome 7 polysomy.[31] High-level focal *MET* amplification is more likely to represent a true oncogenic driver or dominant resistance mechanism, whereas low-level copy-number gain may reflect genomic instability or coexist with other resistance alterations.[32] This distinction is clinically relevant because patients with high-level *MET* amplification may derive greater benefit from MET-directed therapy, while those with low-level or heterogeneous amplification may show less durable responses.

Another important issue is whether *MET* amplification occurs as a *de novo* driver alteration or as an acquired bypass mechanism after EGFR-TKI exposure. In the former situation, selective MET inhibitor monotherapy may be a rational treatment approach in biomarker-selected patients. In contrast, when *MET* amplification emerges after EGFR-TKI therapy in EGFR-mutant NSCLC, continued EGFR pathway suppression combined with *MET* inhibition may be biologically more appropriate, because the original EGFR-dependent clone and the *MET*-amplified resistant clone may coexist. Therefore, the clinical interpretation of *MET* amplification should integrate treatment history, coexisting genomic alterations, amplification level, and the spatial-temporal pattern of disease progression.

Recently, the selective MET inhibitor vebreltinib demonstrated antitumor activity in a phase II clinical study of *MET* amplification-driven advanced NSCLC.[33] These findings underscore the therapeutic significance of MET inhibition in patients selected based on specific biomarkers. However, the clinical positioning of MET inhibitor monotherapy relative to EGFR/MET dual inhibition should be evaluated based on whether *MET* amplification constitutes a primary driver event or an acquired mechanism of bypass resistance.

In addition, molecular monitoring technologies for efficacy evaluation and prognostic assessment are attracting increasing attention. In MET-amplified disease, molecular monitoring may help clarify whether *MET* amplification represents a dominant resistance clone or only one component of a heterogeneous resistance landscape. Previous studies have indicated that low baseline ctDNA levels, early ctDNA clearance during treatment, and the absence of co-mutations are associated with longer progression-free survival.[34,35] These findings suggest that dynamic molecular monitoring holds promise as a crucial tool for predicting efficacy and optimizing treatment in patients with *MET* amplification. Importantly, *MET* amplification should not be interpreted in isolation. Coexisting EGFR secondary mutations, human epidermal growth factor receptor 2 (HER2) amplification, cell-cycle pathway alterations, or histologic transformation may reduce the efficacy of MET-directed therapy, highlighting the need for comprehensive molecular profiling at progression.

2.3. Trophoblast cell-surface antigen 2 target: Therapeutic value of antibody–drug conjugates after drug resistance

Trophoblast cell-surface antigen 2 is expressed in a substantial proportion of NSCLC and has been associated with aggressive tumor biology and treatment resistance in selected contexts. However, its role as a predictive biomarker for Trop-2-directed ADCs remains incompletely established.[36] Trop-2-directed ADCs consist

of a monoclonal antibody against Trop-2, a chemical linker, and a cytotoxic payload.

Unlike EGFR and MET, Trop-2 does not function primarily as a classical oncogenic driver in NSCLC. Its therapeutic relevance stems mainly from its cell-surface expression and suitability as an antigen for targeted cytotoxic drug delivery. This distinction is important because Trop-2-directed ADCs are not designed to block a single dominant signaling pathway. Instead, they combine antigen recognition with intracellular release of a cytotoxic payload, thereby producing antitumor activity even in tumors with heterogeneous resistance mechanisms. The bystander effect may further enhance activity in tumors with uneven antigen expression, although excessive payload diffusion may also contribute to off-target toxicity. Therefore, Trop-2-directed ADCs occupy a unique therapeutic position between targeted therapy and chemotherapy.

After binding to Trop-2-expressing tumor cells, these agents deliver cytotoxic drugs intracellularly and may exert bystander killing effects, thereby providing a therapeutic strategy for complex resistance contexts that is less dependent on a single oncogenic driver pathway.[13]

OptiTROP-Lung04 is a multicenter randomized controlled trial that enrolled 376 patients with advanced NSCLC harboring EGFR-sensitizing mutations who experienced disease progression following EGFR-TKI therapy. The study compared the efficacy of sacituzumab tirumotecan monotherapy against pemetrexed combined with platinum-based chemotherapy. The results demonstrated that sacituzumab tirumotecan significantly prolonged the median progression-free survival of patients (8.3 months vs. 4.3 months, hazard ratio = 0.49), and also showed a distinct advantage in overall survival (hazard ratio = 0.60, p = 0.001).[37] Regarding efficacy indicators, the ORR in the sacituzumab tirumotecan group reached 60.6%, which was significantly higher than the 43.1% observed in the chemotherapy group, and the duration of response was also substantially extended.[38]

Sacituzumab tirumotecan demonstrated consistent efficacy across subgroups, including those previously treated with multiple EGFR-TKIs and those with brain or liver metastases.[37] Concurrently, its incidence of grade 3 or higher hematological adverse events was lower than that of the chemotherapy group, leading to improved patient quality of life. Nevertheless, the toxicity profiles of Trop-2-directed ADCs may vary according to payload type, linker stability, and drug-to-antibody ratio.[39] Clinical application therefore requires careful monitoring for hematologic toxicity, stomatitis, gastrointestinal adverse events, and interstitial lung disease, particularly in heavily pretreated patients or those with baseline pulmonary impairment. The aforementioned results indicate that, provided these toxicities are meticulously managed, Trop-2-targeted ADCs represent a valuable therapeutic option in patients who have failed EGFR-TKI therapy, offering a new alternative for post-resistance treatment strategies (Table 1).[37] The findings indicate that sacituzumab tirumotecan could serve as a clinically significant later-line treatment option for EGFR-mutant NSCLC following the failure of EGFR-TKI therapy, especially in cases where no clearly actionable resistance alterations are identified or where multiple resistance mechanisms are present. However, its optimal sequencing in relation to platinum-based chemotherapy, EGFR/MET dual inhibition, and other ADCs has yet to be determined.

3. Resistance mechanisms after EGFR-TKI therapy and mechanism-based treatment strategies

3.1. Molecular and biological mechanisms of targeted therapy resistance

Resistance mechanisms in NSCLC targeted therapy are highly heterogeneous and dynamically evolving. Resistance may be present before treatment as primary resistance or may emerge under therapeutic selective pressure as acquired resistance. These two forms are not mutually exclusive and may coexist within spatially heterogeneous tumor subclones.[40,41] From a molecular biology perspective, currently identified resistance mechanisms can be broadly classified into four categories: on-target resistance, such as secondary *EGFR* mutations; off-target or bypass resistance, such as MET or HER2 amplification; lineage plasticity and histologic transformation, including transformation to small-cell lung cancer (SCLC) or squamous cell carcinoma; and non-genetic mechanisms, including epithelial–mesenchymal transition and tumor microenvironmental remodeling.[5,42,43] In EGFR-TKI therapy, secondary mutations in the *EGFR* gene remain the most classical mechanism of acquired resistance. Among them, the T790M mutation was once the primary cause of resistance to first- and second-generation EGFR-TKIs. However, with the widespread application of third-generation EGFR-TKIs, the C797S mutation has gradually emerged as a new core resistance event.[16,44] The allelic configuration of C797S is clinically relevant. When C797S and T790M occur in trans, combined first- and third-generation EGFR-TKI therapy may retain activity in selected cases. In contrast, when these mutations occur in cis, this strategy is generally ineffective, highlighting the importance of allelic-level molecular characterization.[45,46] Beyond alterations in the target itself, the activation of

Table 1. Key molecular targets and representative precision therapeutic strategies in NSCLC

Molecular target	Alteration	Representative therapy	Indicated population	Major clinical implication	References
EGFR	Exon 19 deletion/L858R	Aumolertinib	Patients with resected EGFR-mutant NSCLC in the adjuvant setting	Phase 3 evidence supports improved disease-free survival in resected EGFR-mutant NSCLC	23
EGFR	Major uncommon mutations (e.g., G719X, L861Q, S768I)	Aumolertinib	Patients with advanced NSCLC harboring uncommon *EGFR* mutations	Preclinical and early clinical evidence suggest antitumor activity in selected uncommon EGFR-mutant NSCLC	27
EGFR	EGFR-sensitising mutations	Limertinib	Patients with locally advanced or metastatic EGFR-mutant NSCLC receiving first-line treatment	Phase 3 evidence supports prolonged progression-free survival versus gefitinib in the first-line setting.	28
MET	Amplification	Vebreltinib	Patients with advanced *MET* amplification-driven NSCLC	Phase II data support antitumor activity in biomarker-selected patients, although clinical positioning continues to evolve	33
Trop-2	Trop-2 overexpression	Trop-2-directed ADCs	Previously treated patients with advanced NSCLC	Trop-2-directed ADCs have shown clinical activity in selected populations; however, the predictive value of Trop-2 expression remains to be fully established.	7,39
Trop-2	EGFR-TKI-resistant EGFR-mutant disease	Sacituzumab tirumotecan (sac-TMT)	Patients with locally advanced or metastatic EGFR-mutant non-squamous NSCLC after EGFR-TKI failure	Randomized phase III evidence supports sac-TMT as an effective later-line option, with improved progression-free survival and overall survival versus platinum-pemetrexed chemotherapy.	37

Notes: The therapies listed are representative examples and do not imply class-wide efficacy or uniform regulatory approval across jurisdictions; *MET* amplification, MET exon 14 skipping, and MET protein overexpression are biologically and clinically distinct biomarkers and should not be used interchangeably; Trop-2 expression is not currently a universally validated predictive biomarker for selecting Trop-2-directed antibody–drug conjugates; clinical evidence and regulatory status should be interpreted according to the specific agent, biomarker definition, study population, treatment setting, and jurisdiction.

Abbreviations: ADC: Antibody–drug conjugate; EGFR: Epidermal growth factor receptor; MET: Mesenchymal–epithelial transition factor; NSCLC: Non-small cell lung cancer; Sac-TMT: Sacituzumab tirumotecan; TKI: Tyrosine kinase inhibitor; Trop-2: Trophoblast cell-surface antigen 2.

bypass signaling pathways also plays a critical role in the resistance process. *MET* amplification is among the most clinically relevant bypass mechanisms after EGFR-TKI therapy. By activating downstream phosphoinositide 3-kinase/protein kinase B, mitogen-activated protein kinase, and related survival pathways independently of EGFR signaling, *MET* amplification allows tumor cells to maintain proliferative and anti-apoptotic signaling despite persistent EGFR inhibition.[45,47,48] Additionally, molecular events such as HER2 amplification, *BRAF* mutations, and *PIK3CA* mutations can also mediate similar resistance processes in a subset of patients. Furthermore, oncogenic fusions (e.g., *ALK*, *RET*) and cell cycle gene alterations (e.g., *CDK4*/*CDK6* amplification) have emerged as highly relevant off-target bypass mechanisms driving third-generation TKI resistance, necessitating comprehensive NGS upon progression.[49]

At a higher level of tumor biological alterations, phenotypic transformation has increasingly garnered attention. A proportion of EGFR-mutant NSCLC can transform into SCLC or squamous cell carcinoma phenotypes following TKI therapy. This resistance pattern is clinically challenging because it is often associated with rapid disease progression, reduced dependence on the original EGFR signaling pathway, and limited responsiveness to subsequent targeted therapy. Therefore, tissue re-biopsy should be considered when clinical progression is inconsistent with the expected pattern

of molecular resistance.[50-52] Furthermore, epithelial–mesenchymal transition is also believed to be closely associated with the resistance phenotype and enhanced invasiveness (Figure 1).[53,54]

3.2. Mechanism-based therapeutic strategies for resistance

A mechanism-based framework has gradually emerged for different resistance patterns. For resistance mediated by *EGFR* C797S and related on-target *al*terations, fourth-generation EGFR-TKIs are being developed to overcome resistance while preserving activity against activating *EGFR* mutations. However, most agents remain investigational, and their efficacy, safety, optimal sequencing, and activity against compound *EGFR* mutations require further clinical validation.[55] Although related drugs are still in clinical research, preliminary data suggest this strategy has potential in specific molecular contexts. In addition, for patients with C797S and T790M in a *trans* configuration, the strategy of combining first- and third-generation

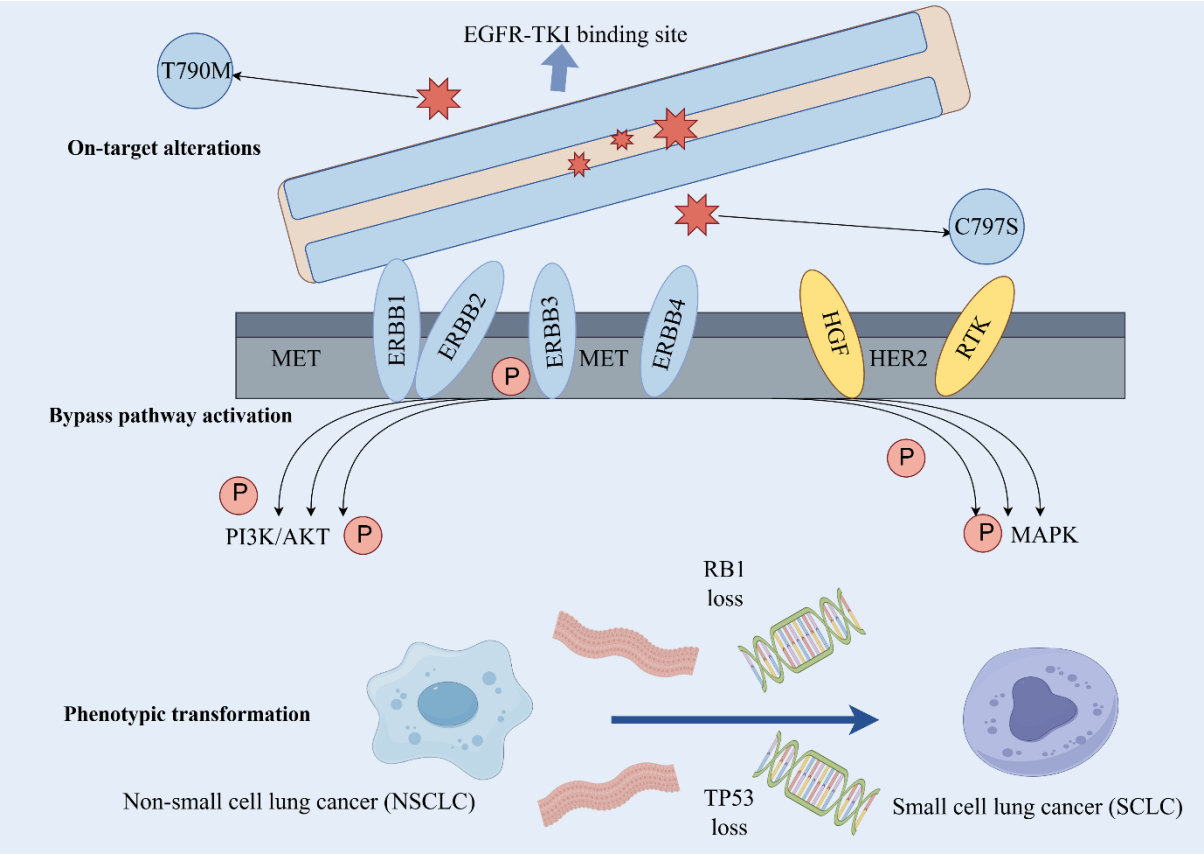


Figure 1. Mechanism-guided assessment, treatment, and longitudinal monitoring of acquired EGFR-TKI resistance in EGFR-mutant NSCLC. This figure illustrates an integrated framework connecting acquired resistance mechanisms, molecular and histologic reassessment, mechanism-guided treatment, and longitudinal monitoring after EGFR-TKI progression. Resistance mechanisms are classified into four categories: on-target EGFR alterations; off-target or bypass pathway activation, including acquired *MET* amplification and HER2 (*ERBB2*) amplification; lineage plasticity and histologic transformation; and non-genetic adaptive mechanisms, including epithelial–mesenchymal transition, drug-tolerant persister states, and tumor-microenvironmental remodeling. At progression, plasma ctDNA testing and tissue biopsy provide complementary information. Tissue biopsy is required when plasma findings are negative or discordant and whenever histologic transformation is suspected. Treatment is selected according to the dominant resistance mechanism and the strength of supporting evidence. Options include investigational next-generation EGFR inhibitors for selected on-target *al*terations, EGFR/MET dual inhibition for confirmed acquired *MET* amplification, histology-directed treatment for transformation, and chemotherapy, drug-specific ADCs, or clinical trials when no actionable mechanism is identified. Serial ctDNA monitoring should be integrated with radiographic and clinical assessment to evaluate clonal evolution.
Abbreviations: ADCs: Antibody–drug conjugates; ctDNA: Circulating tumor DNA; EGFR: Epidermal growth factor receptor; HER2: Human epidermal growth factor receptor 2; MET: Mesenchymal–epithelial transition factor; NSCLC: Non-small cell lung cancer; TKI: Tyrosine kinase inhibitor. This figure was drawn using Figdraw (Export ID: IUTRO42cab; Version 2.0, Home for Researchers, China).

EGFR-TKIs has demonstrated certain efficacy in some studies, although its applicable population and long-term benefits require further validation.[56,57]

In bypass activation-related resistance, target combination inhibition strategies have become a major focus of current research. In resistance mechanisms driven by MET amplification, combining MET inhibitors with EGFR-TKIs has shown synergistic antitumor activity in multiple clinical studies, significantly improving disease control and progression-free survival.[58] This strategy provides a clear molecular rationale for resolving acquired resistance to EGFR-TKIs, and also underscores the importance of dynamic molecular testing before and during treatment.[59]

For patients lacking clearly targetable molecular aberrations or those with multiple resistance mechanisms, ADCs offer a relatively "mechanism-independent" therapeutic approach.[37] ADC drugs targeting Trop-2, via antigen-mediated intracellular delivery of cytotoxic agents, have shown clinically meaningful activity in patients following EGFR-TKI progression. This effect is not significantly influenced by specific *EGFR* mutation types or bypass activation status, thereby providing a novel option for treatment in complex resistance contexts.[37]

Regarding resistance related to phenotypic transformation, treatment strategies historically borrowed from standard chemotherapy regimens for SCLC. However, patients typically exhibit limited and transient responses to traditional platinum-etoposide and immunotherapy. Recently, a paradigm shift has occurred with the development of delta-like canonical Notch ligand 3 (DLL3)-targeted bispecific T-cell engagers (e.g., tarlatamab), which have demonstrated remarkable and durable clinical activity in previously treated *de novo* SCLC.[60] However, applying these DLL3-directed therapies in EGFR-mutant SCLC transformation remains complex. Recent real-world multi-institutional data suggest that clinical responses to tarlatamab in transformed SCLC may be substantially lower than those observed in *de novo* SCLC, highlighting the distinct underlying biology and intense treatment refractoriness of the transformation phenotype.[61] Future studies should further elucidate the molecular drivers of phenotypic transformation to identify additional novel therapeutic targets (Table 2). Clinically, treatment after EGFR-TKI progression should follow a mechanism-guided algorithm. Tissue re-biopsy and/or plasma-based NGS should first be performed to identify actionable resistance alterations. Patients with *MET* amplification may be considered for EGFR/MET dual inhibition; those with *EGFR* C797S or compound *EGFR* mutations may be eligible for investigational next-generation EGFR inhibitors; patients with histologic transformation require pathology-confirmed treatment adaptation; and those without actionable alterations may be considered for chemotherapy, ADCs, or clinical trials.

3.3. The role of precision monitoring in resistance management

With the widespread application of targeted therapies in NSCLC, resistance management has gradually shifted from relying solely on radiographic and clinical symptom evaluations to a precision monitoring paradigm that integrates molecular-level information. Conventional radiographic assessment remains indispensable for evaluating tumor burden, but it may not capture early

Table 2. Mechanism-guided interpretation and therapeutic options after EGFR-TKI progression

Resistance category	Specific alteration or phenotype	Required confirmation and clinical setting	Representative management strategy	Evidence status	Key clinical implication and limitation	References
On-target *EGFR* alteration	Acquired *EGFR* T790M	Tissue- or plasma-confirmed T790M after progression on a first- or second-generation EGFR-TKI; tissue testing should be considered when plasma is negative, and the result would alter treatment	Osimertinib	Established/ approved in this biomarker-defined setting	Randomized phase III evidence supports osimertinib over platinum–pemetrexed in T790M-positive disease after prior first-line EGFR-TKI therapy. This evidence should not be directly extrapolated to resistance after first-line osimertinib.	49,62

(*Cont'd...*)

Table 2. (*Continued*)

Resistance category	Specific alteration or phenotype	Required confirmation and clinical setting	Representative management strategy	Evidence status	Key clinical implication and limitation	References
On-target *EGFR* alteration	C797S or complex/compound *EGFR* alterations	Comprehensive NGS; allelic phasing should be considered when C797S and T790M coexist, and the cis/trans configuration would affect treatment selection	Investigational fourth-generation EGFR inhibitors or genotype-selected clinical trials	Investigational; phase I/II or early clinical evidence	Fourth-generation EGFR inhibitors remain under clinical investigation. Combined first- and third-generation EGFR inhibition may be considered only in highly selected trans-configured cases and is not a standard treatment.	63,64
Off-target or bypass pathway activation	Acquired *MET* amplification	Report assay platform, absolute gene copy number, *MET*/CEP7 ratio when available, amplification focality, and study-specific threshold; confirm plasma-only copy-number findings when feasible	Continued EGFR inhibition combined with a selective MET inhibitor	Phase II study-supported; investigational or jurisdiction-specific	EGFR/MET dual inhibition has demonstrated clinical activity in study-defined acquired MET-mediated resistance. *MET* amplification must be distinguished from *MET* exon 14 skipping, MET protein overexpression, chromosome 7 polysomy, and nonspecific low-level copy-number gain.	65
Off-target or bypass pathway activation	HER2 amplification; acquired *ALK* or *RET* fusion; selected *BRAF*, *PIK3CA*, or cell-cycle pathway alterations	Comprehensive genomic profiling and alteration-specific confirmation when the result would change treatment	Alteration-matched therapy or biomarker-selected clinical trial	Early clinical or investigational evidence	These alterations are relatively uncommon and may be subclonal. No universal "EGFR–HER2 dual inhibition" standard has been established for acquired HER2-amplified resistance. Treatment should be based on alteration-specific evidence.	66
Lineage plasticity and histologic transformation	Transformation to small-cell lung cancer or squamous cell carcinoma	Tissue re-biopsy and pathological confirmation are required	Histology-directed treatment; platinum–etoposide is commonly used for SCLC transformation; DLL3-directed therapy should preferably be evaluated in an appropriate clinical trial	Histology-directed chemotherapy: established practice; DLL3-directed therapy in transformed disease: early/retrospective evidence	Plasma genomic testing cannot confirm histologic transformation. Evidence for tarlatamab in *de novo* SCLC should not be directly extrapolated to EGFR-mutant transformed SCLC.	60,61,67

(*Cont'd...*)

Table 2. (*Continued*)

Resistance category	Specific alteration or phenotype	Required confirmation and clinical setting	Representative management strategy	Evidence status	Key clinical implication and limitation	References
Non-genetic adaptive resistance	Epithelial–mesenchymal transition, drug-tolerant persister states, transcriptional reprogramming, or microenvironmental remodeling	Pathological or translational assessment; no standardized clinical diagnostic threshold	Platinum-based chemotherapy or clinical-trial enrollment	Preclinical or early translational evidence; no validated mechanism-specific standard	EMT is a phenotypic resistance mechanism rather than a molecular target. "Targeting EMT pathways" should not be presented as an established clinical treatment.	53,68
No dominant actionable mechanism or multiclonal resistance	No sufficiently validated actionable alteration, or coexistence of several competing resistance mechanisms	Integrate progression pattern, tissue and plasma genomic results, and histology when indicated	Platinum-based chemotherapy, a drug-specific ADC supported in the relevant setting, or clinical-trial enrollment	Treatment-specific evidence; phase III evidence exists for selected ADCs, but class-wide conclusions are inappropriate	Trop-2 expression is not a universally validated predictive biomarker. Trop-2-directed ADC selection should be based on drug-specific trial evidence, prior treatment, toxicity, and regulatory availability rather than "high Trop-2 expression" alone.	39

Notes: "Established," "study-supported," "investigational," and "early evidence" refer to the strength and clinical context of the available evidence and do not imply identical regulatory approval across jurisdictions; regulatory status should be verified according to the region and manuscript submission date; *MET* amplification, MET exon 14 skipping, and MET protein overexpression are biologically and clinically distinct and should not be used interchangeably; Trop-2 expression is not currently a universally validated predictive biomarker for selecting Trop-2-directed ADC therapy.

Abbreviations: ADC: Antibody–drug conjugate; DLL3: Delta-like canonical Notch ligand 3; EGFR: Epidermal growth factor receptor; EMT: Epithelial–mesenchymal transition factor; HER2: Human epidermal growth factor receptor 2; MET: Mesenchymal–epithelial transition factor; NGS: Next-generation sequencing; NSCLC: Non-small cell lung cancer; SCLC: Small-cell lung cancer; TKI: Tyrosine kinase inhibitor; Trop-2: Trophoblast cell-surface antigen 2.

molecular evolution during targeted therapy. Resistant subclones can emerge before measurable radiographic progression, creating a temporal gap between molecular relapse and imaging-defined disease progression.[69] Therefore, monitoring tools capable of dynamically reflecting changes in the molecular characteristics of tumors have become key instruments for optimizing resistance management and treatment decision-making.

Nevertheless, ctDNA findings should always be interpreted in clinical context. A positive plasma result may help rapidly identify actionable resistance mechanisms, but a negative result does not exclude molecular progression. Tumors with low shedding, isolated brain metastases, pleural-only disease, or small-volume intrathoracic recurrence may release insufficient ctDNA into the bloodstream. In such cases, tissue re-biopsy remains important, especially when histologic transformation is suspected. In addition, clonal hematopoiesis may generate false-positive variants unrelated to the tumor, particularly in genes such as *TP53* or other hematologic-associated alterations. Therefore, ctDNA should complement rather than fully replace tissue-based molecular and pathological assessment. However, false-negative results may occur in patients with low tumor DNA shedding, isolated central nervous system progression, or limited intrathoracic disease.[17] Therefore, negative plasma results should not replace tissue biopsy when clinical suspicion of progression remains high.[70] In early-stage and locally advanced NSCLC, MRD assessment is emerging as a promising tool for relapse risk stratification after curative-intent therapy. Nevertheless, standardized assays, optimal sampling intervals, clinically meaningful thresholds, and MRD-guided treatment strategies remain under active investigation (Figure 2).[71]

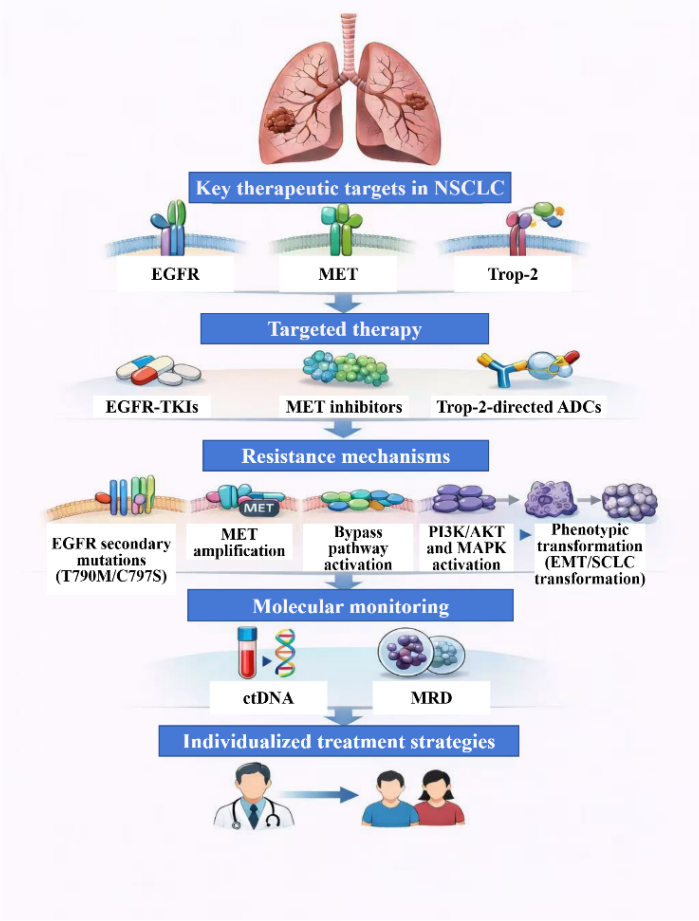


Figure 2. Integrated framework of core therapeutic targets, resistance mechanisms, and molecular monitoring in non-small cell lung cancer. This figure delineates the complex landscape of precision therapy for NSCLC, structured around three principal therapeutic targets—EGFR, MET, and Trop-2—and their associated treatment modalities, predominant resistance mechanisms, and the significance of molecular monitoring in tailoring individualized treatment strategies. The figure is organized as follows: The upper panel highlights the three primary therapeutic targets (EGFR, MET, and Trop-2) that are currently actionable in clinical settings for NSCLC. Below each target, the respective therapeutic strategies are depicted: EGFR-targeted therapy employing EGFR TKIs, MET-targeted therapy utilizing MET inhibitors, and Trop-2-directed ADCs. The central section provides an overview of the major resistance mechanisms that may develop during or post-treatment. For EGFR-TKIs, resistance can manifest through secondary *EGFR* mutations (e.g., T790M, C797S), activation of bypass pathways (e.g., *MET* amplification), and phenotypic alterations (e.g., epithelial–mesenchymal transition or transformation to small-cell lung cancer). In the context of MET-targeted therapy, resistance may occur via bypass activation through the PI3K/AKT and MAPK pathways. Abbreviations: ADC: Antibody–drug conjugate; AKT: Protein kinase B; ctDNA: Circulating tumor DNA; EGFR: Epidermal growth factor receptor; EMT: Epithelial–mesenchymal transition factor; MAPK: Mitogen-activated protein kinase; MET: Mesenchymal–epithelial transition factor; MRD: Minimal residual disease; NGS: Next-generation sequencing; NSCLC: Non-small cell lung cancer; PI3K: Phosphoinositide 3-kinase; SCLC: Small-cell lung cancer; TKI: Tyrosine kinase inhibitor; Trop-2: Trophoblast cell-surface antigen 2.

4. Discussion

The major challenge in contemporary NSCLC targeted therapy is no longer limited to identifying actionable drivers at diagnosis, but increasingly lies in managing molecular evolution under therapeutic pressure. EGFR-, MET-, and Trop-2-directed strategies represent different but interconnected dimensions of this process: driver inhibition, bypass resistance suppression, and post-resistance cytotoxic delivery.[72] Future research must continue to deepen across multiple dimensions—including the development of novel targets, the management of resistance mechanisms, the application of precision biomarkers, and the optimization of treatment for special populations—to further propel the targeted therapy of NSCLC toward a more precise and individualized direction.[73]

From a clinical decision-making perspective, treatment after EGFR-TKI progression should begin with

classifying the progression pattern. Patients with limited oligoprogression may benefit from local therapy while continuing the original EGFR-TKI, especially when most disease sites remain controlled. In contrast, patients with systemic progression require comprehensive reassessment of resistance mechanisms. Plasma ctDNA testing can serve as an initial noninvasive approach, but tissue biopsy should be considered when plasma testing is negative, when transformation is clinically suspected, or when a progressing lesion is accessible.

After molecular reassessment, treatment should be selected according to the dominant resistance pattern. Patients with *MET* amplification may be candidates for EGFR/MET dual inhibition. Patients with *EGFR* C797S or complex EGFR compound mutations should preferably be considered for investigational next-generation EGFR inhibitors or genotype-specific clinical trials.[16] Patients with histologic transformation require pathology-confirmed treatment adaptation, usually shifting away from standard EGFR-TKI-based strategies. For patients without actionable resistance alterations, or those with multiple heterogeneous mechanisms, platinum-based chemotherapy, Trop-2-directed ADCs, or clinical trial enrollment may be reasonable options.[8] This stepwise framework highlights that post-resistance therapy should not be chosen solely according to treatment line, but according to the biological mechanism driving progression.

In addition to well-characterized bypass mechanisms such as *MET* amplification, rare oncogenic fusions, including *ALK* rearrangements, have emerged as clinically significant drivers of acquired resistance to EGFR-TKIs in a subset of patients. An illustrative case report documented that an acquired *EML4-ALK* fusion, specifically Variant 3a/b, mediated resistance to osimertinib in a patient with *EGFR* L858R-positive NSCLC, underscoring that even uncommon fusion events can dominate the resistance phenotype under therapeutic pressure. This observation underscores the necessity for comprehensive NGS at the time of disease progression, as the identification of such fusions may redirect treatment toward alternative targeted strategies, such as *ALK* inhibition, in patients who might otherwise be considered to have "non-actionable" resistance. Nevertheless, the true frequency, clonal architecture, and optimal management of *ALK* fusion-mediated resistance remain largely unknown. Prospective molecular profiling and collaborative case registries are essential to determine whether routine screening for these rare events translates into meaningful clinical benefit and to define their potential impact on treatment paradigms.[74]

Despite the introduction of a mechanism-guided framework, its implementation in routine clinical practice is impeded by several unresolved operational challenges that are not comprehensively addressed in the current literature. Firstly, *MET* amplification, recognized as one of the most actionable bypass mechanisms, lacks a universally accepted assay-specific threshold for patient selection. Various studies have utilized different cutoffs, such as a FISH *MET*/CEP7 ratio of ≥2.0 or an NGS-based copy number of ≥5, without direct comparative analysis of these criteria in prospective head-to-head trials. As a result, clinicians face uncertainty when interpreting a "positive" *MET* amplification result, particularly when the reported level falls within an ambiguous range. We propose that, until standardized criteria are established, treatment decisions should be based on thresholds validated in the pivotal trial of the specific MET inhibitor being considered (e.g., FISH gene copy number ≥10 or NGS-derived copy number ≥ 10 for savolitinib-based combinations), and that low-level amplification should not automatically guide therapy outside of clinical trials. Secondly, the optimal sequencing of post-resistance therapies remains unclear.

First, exploring novel molecular targets and combination treatment strategies remains a core direction for future research. Although relatively mature treatment systems have been established for classic targets such as EGFR and MET, efficacy remains limited for certain mutation subtypes (*KRAS* G12C, *BRAF* V600E).[75,76] In addition, the coexistence of multiple resistance mechanisms suggests that single-target inhibition is often insufficient to achieve durable control.[6] Therefore, combined inhibition strategies centered on key signaling pathways—such as EGFR/MET dual-target inhibition, or the rational combination of targeted therapy with anti-angiogenic therapy or immunotherapy—hold promise for delaying the onset of resistance through synergistic effects. However, their optimal combination modalities, sequencing of administration, and toxicity management still require further clarification through prospective clinical studies.[77,78]

Second, biomarker-guided precision treatment decision-making needs further refinement. Dynamic monitoring of ctDNA and MRD assessment provide vital tools for predicting targeted-therapy efficacy and identifying early resistance. Nevertheless, their detection thresholds, timing, and clinical decision-making criteria remain largely unstandardized. More importantly, the routine clinical utility of ctDNA is hindered by biological limitations, including low tumor DNA shedding (particularly in intrathoracic-only progression), interference from clonal hematopoiesis of indeterminate potential leading to false positives, and the inherent spatial heterogeneity of resistance clones that may cause

discordance between tissue and plasma genotyping.[69,71] Future research should incorporate large-scale prospective cohorts to validate the predictive value of ctDNA clearance, specific mutational profile changes, and Trop-2 expression across different treatment stages. Such efforts may facilitate the transition of molecular monitoring from an adjunctive tool to a basis for therapeutic decision-making.[79]

Furthermore, the further optimization of post-resistance treatment strategies remains an urgent clinical issue to be resolved. ADCs have demonstrated clinically meaningful activity in EGFR-TKI-resistant NSCLC, but several questions remain unresolved. These include whether Trop-2 expression can reliably predict benefit, how ADCs should be sequenced with chemotherapy or targeted combinations, and whether specific resistance mechanisms influence ADC sensitivity. Differences in payload, linker design, bystander effect, and toxicity profiles should also be considered when comparing ADC agents.[37,39] However, due to differences in target selection, drug payloads, and toxicity profiles among various ADC drugs, their optimal timing of application and sequential or combination modalities with other treatments still require more clinical data for support. Additionally, for specific resistance mechanisms such as phenotypic transformation (transformation to small cell lung cancer), effective targeted approaches are currently lacking. An in-depth elucidation of the relevant molecular mechanisms may provide a breakthrough for developing novel treatment strategies.[51,67]

Finally, the systematic evaluation of special populations and real-world treatment outcomes also warrants attention. Special populations require more dedicated evidence. Patients with brain metastases need therapies with reliable intracranial activity; patients with liver metastases often have aggressive disease biology and poorer prognosis; and elderly patients or those with comorbidities may have reduced tolerance to combination therapy or ADC-related toxicity. Prospective subgroup analyses and real-world studies are therefore necessary to refine individualized treatment strategies.[80,81] Future efforts should strengthen real-world studies and prospective subgroup analyses to evaluate the efficacy, safety, and impact on quality of life of targeted drugs in these populations, thereby providing more generalizable evidence for individualized dose adjustments and optimized treatment strategies.

Overall, the future development of targeted therapy for NSCLC will rely on the deep integration of basic research and clinical practice. By continuously advancing the research and development of drugs for novel targets, refining the molecular biomarker system, and optimizing combination and sequential treatment strategies, it is expected to further break through the bottleneck of drug resistance, maximize therapeutic benefits, and propel the NSCLC management paradigm toward a true transformation into precision medicine.

5. Conclusion

In recent years, with the continuous refinement of molecular subtyping and the constant emergence of innovative drugs, targeted therapy for NSCLC has entered a new phase of precision and multidimensional development. Treatment strategies revolving around key molecular targets such as EGFR, MET, and Trop-2 have not only significantly prolonged survival in specific populations but also progressively formed a more comprehensive therapeutic paradigm across disease stages (adjuvant therapy, advanced-stage therapy, and post-resistance therapy). Third-generation EGFR-TKIs have demonstrated encouraging efficacy in the adjuvant therapy of patients with EGFR-sensitizing mutations and in rare mutation subtypes, providing new evidence-based rationales for early recurrence risk management and treatment of special populations.[11,12,24]

Meanwhile, as *MET* amplification represents a crucial driver event and resistance mechanism, successful application of its targeted inhibitors has filled previous treatment gaps, marking significant progress in strategies targeting bypass activation resistance.[6] Furthermore, ADCs targeting Trop-2 have achieved dual benefits in both progression-free survival and overall survival among patients who experienced EGFR-TKI treatment failure, thereby expanding the available options for post-resistance therapies.[37]

Despite these remarkable advancements, targeted therapy for NSCLC still faces multiple challenges, including complex resistance mechanisms, the coexistence of multiple molecular aberrations, and the current limitations of predictive biomarkers. Future research should focus on developing novel targets, optimizing multi-target combined inhibition strategies, and establishing dynamic monitoring systems based on ctDNA and MRD to support earlier and more precise treatment decisions.[24,82] Concurrently, the safety and efficacy of treatments in special populations—such as elderly patients and those with brain or liver metastases—urgently require validation through additional prospective studies.

In summary, ongoing advancements in targeted drug development, coupled with the enhanced integration of molecular biomarkers and precision-monitoring technologies, have the potential to significantly enhance the long-term efficacy of targeted therapies in NSCLC. These developments may ultimately improve both survival

rates and quality of life for patients.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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