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REVIEW

Research progress and challenges in the treatment of oncogene-addicted non-small cell lung cancer

Hanyi Li[1,2]*, Xuanguang Li[1,2]*, Tong Li[1,2]*, Fan Ren[1,2], Haochuan Yu[1,2], Dianxun Fu[3], Zuoqing Song[1,2], Song Xu[1,2]

[1]Department of Lung Cancer Surgery, Tianjin Medical University General Hospital, Tianjin 300052, China; [2]Tianjin Key Laboratory of Lung Cancer Metastasis and Tumor Microenvironment, Lung Cancer Institute, Tianjin Medical University General Hospital, Tianjin 300052, China; [3]Department of Radiology, Tianjin Key Laboratory of Functional Imaging, Tianjin Medical University General Hospital, Tianjin 300052, China

ABSTRACT Over the past 2 decades, remarkable advancements in the screening, diagnosis, and treatment of non-small cell lung cancer (NSCLC) have led to improved patient outcomes. For the treatment of NSCLC with actionable gene mutations, tyrosine kinase inhibitors developed against EGFR, ALK, RET, BRAF, ROS1, NTRK, MET, and KRAS, exhibit substantial antitumor activity and have been incorporated into standard treatment regimens. Additionally, numerous novel therapies, including immunotherapy and antibody-drug conjugate therapy, have been found to benefit patients with NSCLC. This review summarizes current advancements in targeted therapy for NSCLC, according to a systematic search of the PubMed database and synthesis of cutting-edge findings presented at the 2024 American Society of Clinical Oncology Annual Meeting and 2024 World Conference on Lung Cancer.

KEYWORDS Non-small cell lung cancer; actionable gene mutation; acquired resistance; consolidation therapy; tyrosine kinase inhibitors

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide[1]. According to the 2022 national cancer statistics from the National Cancer Center of China, lung cancer accounts for the most new cases and deaths among patients with malignant tumors. In 2022, of the 4.8247 million new cancer cases in China, 1.0606 million were attributed to lung cancer[2]. Because clinical symptoms typically appear late in the disease course, most patients with lung cancer are diagnosed in advanced stages. The 5-year survival rate of patients with stage I lung cancer exceeds 70%, whereas patients with stage IA1 (T1a ≤ 1 cm) lung cancer have a survival rate as high as 92%[3]. In contrast, the 5-year survival rate of patients with advanced non-small cell lung cancer (NSCLC) is markedly lower. Hence, to increase the survival rate of patients, early screening, diagnosis, and treatment of lung cancer are essential. Recent advances in precision targeted therapy have notably enhanced NSCLC treatment. This review is aimed at systematically synthesizing current advancements and recent research findings in targeted therapy for NSCLC in 2024.

Mutational landscape of NSCLC

In recent years, advances in next-generation sequencing have uncovered the remarkable molecular heterogeneity of NSCLC, and revealed a wide spectrum of driver mutations that govern tumor initiation, therapeutic responses, and the evolution of resistance. The most frequently altered oncogenes include epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), kirsten rat sarcoma viral oncogene homolog (KRAS), c-ros oncogene 1 (ROS1), rearranged during transfection (RET), MET proto-oncogene, receptor tyrosine kinase (MET), v-raf murine sarcoma viral oncogene homolog B1 (BRAF), human epidermal growth factor receptor 2 (HER2), neurotrophic tropomyosin receptor kinase (NTRK), and fibroblast growth factor receptor (FGFR). Among them, mutations in EGFR, primarily exon 19 deletions and L858R substitutions, are highly prevalent in Asian

*These authors contributed equally to this work.
Correspondence to: Zuoqing Song and Song Xu
E-mail: thoracic_expert@aliyun.com and xusong198@hotmail.com
ORCID ID: https://orcid.org/0000-0001-6153-387X
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patients (as many as 50%–60%) and predict strong sensitivity to EGFR tyrosine kinase inhibitors (TKIs). Nonetheless, acquired resistance through secondary mutations such as T790M and C797S remains a major clinical challenge[4]. ALK rearrangements, particularly EML4–ALK fusions, occur in 3–7% of NSCLC cases, particularly in younger, non-smoking individuals with adenocarcinoma histology, and are highly responsive to next-generation inhibitors such as alectinib and lorlatinib[5,6]. KRAS mutations, most notably the G12C variant, are predominant in Western populations (25%–30%) and have recently become targetable with covalent inhibitors such as sotorasib and adagrasib[7,8]. Although less common, ROS1 and RET fusions and MET exon 14 skipping mutations are highly actionable subgroups against which multiple agents (including repotrectinib, selpercatinib, and capmatinib) have shown robust clinical efficacy[9,10].

Beyond these canonical alterations, rare but targetable events are increasingly emerging. These include HER2 exon 20 insertions, BRAF V600E mutations, NTRK gene fusions, and FGFR abnormalities. Many of these alterations are amenable to treatment with novel TKIs or antibody–drug conjugates (ADCs; e.g., trastuzumab deruxtecan)[11,12]. Importantly, NSCLC frequently bears co-occurring mutations (such as TP53, STK11, and KEAP1) that modulate the therapeutic response and prognostic outcomes. For instance, concurrent TP53 mutations have been associated with diminished survival in EGFR-mutant NSCLC, whereas STK11/KEAP1 co-mutations have been associated with primary resistance to immune checkpoint inhibitors in KRAS-mutant tumors[13]. The most common mechanisms of resistance to targeted therapies in NSCLC, and the current strategies to overcome them, are summarized in **Table 1**. The following sections further discuss each therapeutic target in detail, highlighting representative agents and the most recent clinical trial data.

EGFR-TKIs

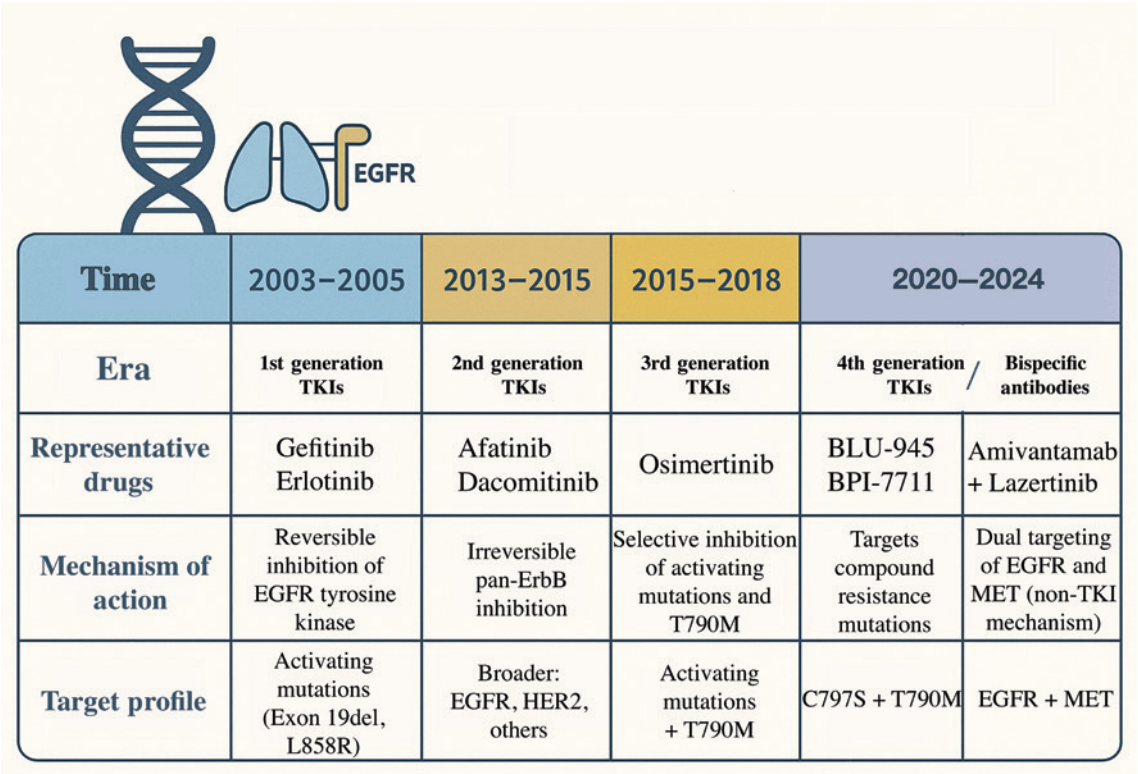
Progress in EGFR drug development

EGFR is a transmembrane protein with cytoplasmic kinase activity that transmits growth factor signals from the extracellular to the intracellular environment. EGFR gene mutations are the most prevalent driver mutations in NSCLC and affect as many as 60% of Asian patients with advanced NSCLC[14]. EGFR-TKIs have driven substantial advancements in the precision treatment of NSCLC (representative drugs summarized in **Figure 1**). Since the approval of the first-generation

Table 1 Summary of resistance mechanisms and strategies to overcome resistance to NSCLC targeted therapies

Target	Representative drugs	Resistance mechanisms	Strategies to overcome resistance
EGFR	Gefitinib, osimertinib	C797S mutation, MET amplification, HER2 amplification, EMT, SCLC transformation	4th-generation EGFR-TKIs, MET inhibitor combinations, ICI + VEGFR inhibitor combinations
ALK	Alectinib, lorlatinib	G1202R and L1196M mutations, insulin-like growth factor receptor 1R (IGF-1R) upregulation, neuroendocrine transformation, secondary mutations in ALK gene neuroendocrine transformation	Next-generation ALK inhibitors (e.g., TPX-0131), heat shock protein 90 (HSP90) inhibitors, epigenetic therapy combinations, combination therapies targeting co-occurring mutations (e.g., MEK inhibitors)
KRAS G12C	Sotorasib, adagrasib	Secondary KRAS mutations, EGFR/MET pathway activation, immune suppression in the tumor microenvironment	EGFR/MET inhibitors, combination therapy with ICIs (e.g., pembrolizumab or nivolumab), pan-KRAS inhibitors (e.g., RMC-6236), immune modulation (e.g., checkpoint blockade or T-cell reactivation)
ROS1	Crizotinib, entrectinib	G2032R mutation, brain metastasis, fusion variant heterogeneity	Lorlatinib or repotrectinib, taletrectinib
FGFR	Erdafitinib	Activation of MAPK or PI3K bypass pathways	Multi-targeted FGFR inhibitors (e.g., futibatinib)
HER2	Poziotinib, trastuzumab deruxtecan (T-DXd)	HER2 structural alterations, ADC efflux *via* extracellular vesicles, impaired internalization	ADC structure optimization, TKI + ADC combinations, bispecific antibodies (HER2 + EGFR)

ADC, antibody–drug conjugates; ICI, immune checkpoint inhibitor; TKI, tyrosine kinase inhibitor.



Time	2003–2005	2013–2015	2015–2018	2020–2024	
Era	1st generation TKIs	2nd generation TKIs	3rd generation TKIs	4th generation TKIs /	Bispecific antibodies
Representative drugs	Gefitinib Erlotinib	Afatinib Dacomitinib	Osimertinib	BLU-945 BPI-7711	Amivantamab + Lazertinib
Mechanism of action	Reversible inhibition of EGFR tyrosine kinase	Irreversible pan-ErbB inhibition	Selective inhibition of activating mutations and T790M	Targets compound resistance mutations	Dual targeting of EGFR and MET (non-TKI mechanism)
Target profile	Activating mutations (Exon 19del, L858R)	Broader: EGFR, HER2, others	Activating mutations + T790M	C797S + T790M	EGFR + MET

Figure 1 Evolution of EGFR-targeted therapies in non-small cell lung cancer (NSCLC). This figure summarizes the chronological development of EGFR tyrosine kinase inhibitors (TKIs) and bispecific antibodies from 2003 to 2024. The evolution is categorized into 5 therapeutic eras: • 1st generation TKIs (2003–2005): gefitinib and erlotinib reversibly inhibit EGFR tyrosine kinase, targeting primarily common activating mutations such as exon 19 deletion and L858R. • 2nd generation TKIs (2013–2015): afatinib and dacomitinib irreversibly inhibit the ErbB family, thus broadening the target spectrum to include EGFR, HER2, and others. • 3rd generation TKIs (2015–2018): osimertinib selectively inhibits both common activating mutations and the acquired resistance mutation T790M. • 4th generation TKIs (2020–2024): agents such as BLU-945 and BPI-7711 are designed to overcome compound resistance mutations, including C797S and T790M. • Bispecific antibodies (2020–2024): amivantamab in combination with lazertinib is a novel approach that co-targets EGFR and MET *via* non-TKI mechanisms, thus addressing broader resistance landscapes. Each row illustrates the representative agents, mechanisms of action, and target mutation profiles for each therapeutic generation, TKI, tyrosine kinase inhibitor.

reversible inhibitor, gefitinib, in 2003, EGFR-targeted therapy has undergone 4 successive generations of development characterized by progressive structural optimization and strategic adaptations to overcome acquired resistance mechanisms[15].

First-generation EGFR-TKIs, such as gefitinib, erlotinib, and icotinib, primarily target common activating mutations in EGFR, including exon 19 deletions and L858R substitutions. However, the emergence of acquired resistance, most notably the secondary T790M mutation, typically occurs within several months after treatment initiation[16]. Second-generation inhibitors, such as afatinib and dacomitinib, form irreversible covalent bonds with members of the ErbB receptor family, including HER2, thereby enhancing antitumor activity and expanding coverage to certain uncommon EGFR mutations. Despite these improvements, compared with first-generation drugs, their increased toxicity and inability to overcome T790M-mediated resistance limit their clinical utility. The third-generation agent osimertinib was specifically developed to address T790M-driven resistance. Because of its high selectivity and favorable central nervous system (CNS) penetration, osimertinib has become the current first-line standard of care for patients with EGFR-mutant NSCLC.

Mechanisms of EGFR resistance

The emergence of acquired resistance to EGFR TKIs in NSCLC encompasses 2 main mechanistic categories. The first involves EGFR-dependent resistance, characterized by secondary mutations within the EGFR gene—most notably the C797S substitution, which occurs in approximately 7%–14%

of patients and disrupts the covalent binding of osimertinib to the EGFR kinase domain. Less common tertiary mutations, such as L718Q and G724S, have also been identified and found to contribute to therapeutic escape. The second category comprises EGFR-independent resistance mechanisms, which are driven by the activation of bypass signaling pathways. These include MET amplification, HER2 amplification, mutations in PIK3CA and BRAF, the emergence of novel oncogenic fusions, and even histologic transformation, such as a switch from adenocarcinoma to small-cell lung cancer[4]. These resistance events typically result in disease progression within approximately 10 months after initiation of osimertinib therapy. To address this clinical challenge, the ORCHARD trial (NCT03944772), a phase II, non-randomized, platform study, is currently evaluating novel combination strategies in patients with advanced EGFR-mutant NSCLC who show progression on first-line osimertinib. This study included the first-in-human investigation of osimertinib in combination with datopotamab deruxtecan (Dato-DXd). Preliminary findings have suggested that this combination demonstrates encouraging antitumor activity and a manageable safety profile in patients bearing EGFR mutations who experience progression after frontline osimertinib treatment[17]. The SAVANNAH study has provided promising clinical evidence that patients with advanced EGFR-mutant NSCLC exhibit MET amplification and/or overexpression after disease progression on first-line osimertinib. In this trial, the combination of savolitinib (300 mg BID) and osimertinib was well tolerated and produced durable clinical responses, particularly in patients with high MET expression (IHC 3+ in ≥ 90% of tumor cells and/or fluorescence *in situ* hybridization-positive MET amplification ≥ 10 copies per cell)[18]. Similarly, in the FLOWERS study (CTONG2008), the combination of osimertinib with savolitinib significantly improved clinical outcomes and achieved an objective response rate (ORR) of 90.5%, in contrast to the 60.9% observed with osimertinib alone. The disease control rate (DCR) increased to 95% *vs.* 87%, and the median progression-free survival (PFS) was extended to approximately 19.6 months from 9.3 months. These findings support the biomarker-driven application of MET inhibition to overcome EGFR TKI resistance in this subset of patients. Although osimertinib, a third-generation EGFR-TKI, Significantly prolongs PFS and overall survival (OS) in patients with EGFR-mutant NSCLC, its clinical use remains limited by 3 major issues. First, the emergence of acquired resistance is highly heterogeneous, encompassing both EGFR-dependent and EGFR-independent mechanisms. Second, despite its CNS penetration, a risk of intracranial progression persists. Third, osimertinib is associated with notable adverse events, particularly interstitial lung disease (ILD) and cardiotoxicity. Future therapeutic strategies should prioritize precise identification of resistance mechanisms and the rational design of individualized combination regimens, such as those incorporating MET or HER3 inhibitors, to optimize patient outcomes.

Emerging therapeutic strategies after EGFR resistance

Clinical investigation of osimertinib in lung cancer is rapidly progressing toward 3 key directions: consolidation therapy, rational combination with other targeted agents, and the development of strategies to overcome acquired resistance mechanisms.

A recent multicenter, single-arm phase II study was conducted to investigate whether stereotactic ablative radiotherapy (SABR) administered to residual lesions at the time of best response to osimertinib might delay disease progression in patients with EGFR-mutant non-small cell lung cancer. The combination of osimertinib and SABR, compared with osimertinib monotherapy, significantly improved both PFS and OS. The median PFS and median OS of 32.3 months and 45 months, respectively, in the combination group indicated a substantial clinical benefit associated with the local ablative approach (**Table 2**). Therefore, this approach offers a promising and well-tolerated strategy for advanced EGFR-mutant NSCLC[19]. SABR in combination with immune checkpoint inhibitors (ICIs) enhances tumor antigen release, upregulates PD-L1 expression, and reprograms the tumor microenvironment, thus potentially amplifying ICI-induced antitumor T-cell responses[20]. However, the molecular mechanisms of SABR combined with EGFR-TKIs remain unclear. A meta-analysis has indicated that patients with NSCLC receiving thoracic radiotherapy combined with EGFR-TKIs have acceptable risk of severe treatment-related pneumonitis and rare fatal events. Nevertheless, the poor treatment tolerability of this combination warrants cautious clinical application[21]. In the phase III LAURA trial, in patients with unresectable stage III EGFR-mutant NSCLC who had completed definitive chemoradiotherapy, consolidation therapy with osimertinib significantly prolonged the PFS, from 5.6 months to 39.1 months; moreover, the median OS of 58.8 months in the updated data indicated substantially improved survival

Table 2 Recent or practice-changing clinical trials for EGFR mutation in NSCLC

Target	Drug	Population	Study	Outcome
EGFR	Osimertinib plus consolidative SABR	Advanced EGFR mutant (exon 19 or 21)	Multi-center single-arm phase 2 study	Median PFS 32.3 (osimertinib + SABR) *vs*. 18.9 (FLAURA) months; median OS 45 (osimertinib + SABR) *vs*. 38.6 (FLAURA) months
EGFR	Osimertinib after definitive CRT	Unresectable stage III EGFRm (Ex19del or L858R)	Phase 3 LAURA study	Median PFS 39.1 months (95% CI: 31.5, not calculable) (osimertinib) *vs*. 5.6 months (95% CI: 3.7–7.4) (PBO)
EGFR	Amivantamab + lazertinib	Advanced EGFR-mutant (Ex19del or L858R)	Phase 3 MARIPOSA study	Median PFS 39.1 months (95% CI: 19.1–27.7) (amivantamab + lazertinib) *vs*. 16.6 months (95% CI: 14.8–18.5) (osimertinib)
EGFR	Amivantamab + lazertinib	Atypical advanced EGFR mutation	CHRYSALIS-2 study	ORR 52% (95% CI: 42.0–62.0), median PFS 11.1 months (95% CI: 7.8–17.8); median TTD (14.0 *vs*. 3.2 months); 24-month OS (79% *vs*. 44%)
EGFR	Amivantamab + lazertinib	EGFR exon 19del/L858R/ atypical mutations with active BrM or LM	Phase 2 study	Systemic ORR 95% CI: RECIST 30%, 13–54% (BrM); 32%, 15%–55% (LM); Intracranial ORR (95% CI: RANO 40%, 20–64%) (BrM); 23%, 9%–46% (LM) Median time on treatment (range) 3.9 months (0.3–18.6 months) (BrM) 8.1 months (0–21.7 months) (LM)
EGFR	Adjuvant icotinib	EGFR-mutated, stage II-IIIA	Phase 3 trial	Median DFS 61.8 months (95% CI: 43.3–80.3) (12-month icotinib); 63.2 months (95% CI: 44.8–81.6) (6-month icotinib) *vs*. 23.7 months (95% CI: 16.5–30.9) (PBO)
EGFR	Ivonescimab combined with chemotherapy	Patients with EGFR mutation in whom EGFR-TKI treatment failed	Phase 3 trial	Median PFS 7.1 months (95% CI: 5.9–8.7) (ivonescimab + chemotherapy) *vs*. 4.8 months (95% CI: 4.2–5.6) (PBO + chemotherapy)
EGFR	Sunvozertinib	EGFR exon 20ins	WU-KONG1 Part B	Best ORR 53.3% (44.9% confirmed and 3.7% pending confirmation)

PBO, Placebo; RECIST, Response Evaluation Criteria in Solid Tumours; RANO, Response assessment in neuro-oncology; BrM, brain metastases; LM, leptomeningeal disease; CI, confidence interval; CRT, chemoradiotherapy; DFS, disease-free survival;TKI, tyrosine kinase inhibitor; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SABR, stereotactic ablative radiotherapy.

outcomes[22]. In parallel, the phase III FLAURA2 trial reported that, in a similar population, the combination of osimertinib with platinum–pemetrexed chemotherapy achieved a median PFS exceeding 2 years, thereby highlighting the potential of chemotherapy-based maintenance strategies in this setting[23].

Fourth-generation EGFR-TKIs achieve precise inhibition of the C797S resistance mutation through non-covalent allosteric modulation or ATP-competitive binding mechanisms. Sunvozertinib (DZD9008) is a highly selective, irreversible inhibitor of EGFR ex20ins mutations. The WU-KONG1 study showed that EGFR exon 20 insertion NSCLC patients who had received platinum-based pretreatment achieved a best overall response rate (ORR) of 53.3% (44.9% confirmed and 3.7% pending confirmation) and a 9-month survival rate of 57%. Compared with existing therapies, sunvozertinib has superior antitumor efficacy against EGFR mutant NSCLC[24]. Approximately 10% of EGFR-mutant NSCLCs bear mutations within exon 20 of EGFR (often insertions), which confer resistance to conventional EGFR-TKIs, because of the structural similarities between the ATP-binding pocket of EGFR ex20ins and wild-type EGFR[25]. The EGFR/MET bispecific antibody amivantamab has also demonstrated clinical efficacy in this population, achieving an ORR of 40% and a median PFS of 8.3 months[26]. More than 100 unique EGFR ex20ins variants have been identified in NSCLC, and different insertion positions correlate with variable therapeutic responses to EGFR-TKIs. Consequently, future drug development should prioritize agents capable of broadly targeting

these heterogeneous variants while maintaining favorable tolerability profiles. BDTX-1535, a fourth-generation EGFR inhibitor, has demonstrated clinically significant activity in patients with recurrent or refractory NSCLC, particularly those developing resistance to osimertinib. Preliminary phase 2 trial data (NCT05256290) have indicated robust efficacy across canonical EGFR mutations, non-canonical variants, and the C797S resistance mutation. In the evaluable cohort (n = 22), BDTX-1535 achieved an ORR of 36%, thus confirming broad activity against diverse EGFR-altered tumors. Notably, among osimertinib-resistant patients (n = 19) bearing C797S or exon 20 insertion mutations (e.g., PACC variants), the ORR reached 42%, and 5 patients exhibited a confirmed partial response (PR).

In addition, combination therapeutic strategies are continually expanding the clinical applicability of EGFR-TKIs. The bispecific EGFR-MET antibody amivantamab has shown promising potential in this context. This EGFR-MET bispecific antibody was approved by the Food and Drug Administration (FDA) in May 2021 for the second-line treatment of NSCLC bearing EGFR exon 20 insertion mutation. Previous studies have shown that chemotherapy combined with amivantamab as a first-line treatment for patients with advanced NSCLC with EGFR ex20ins mutation achieves better outcomes than chemotherapy alone[27]. The MARIPOSA phase 3 trial demonstrated that first-line treatment with amivantamab plus lazertinib (a brain-penetrating third-generation EGFR-TKI) is more effective than osimertinib and achieves greater antitumor activity despite resistance to initial treatment with osimertinib[28]. Amivantamab has also shown durable activity in patients with disease progression after treatment with afatinib[29]. The final OS analysis of MARIPOSA indicated a strong benefit of amivantamab plus lazertinib *vs*. osimertinib; a more than 12-month survival difference was observed with respect to the standard control arm treated with osimertinib. The hazard ratio was 0.75, and the median OS with osimertinib was 17 months[30]. Historically, patients with NSCLC with EGFR mutation and active brain or leptomeningeal metastases were often excluded from trials. However, a recent trial of amivantamab and lazertinib in these patients showed ORRs of 30% and 32% for brain metastases and leptomeningeal metastases, respectively. The intracranial ORRs (IC-ORRs) of 40% and 23% for brain metastases and leptomeningeal metastases, respectively, demonstrated meaningful clinical benefits in terms of treatment response and progression[31]. Subcutaneous administration of amivantamab is associated with improved patient tolerance; shorter administration times than required with intravenous administration; and longer PFS and OS[32].

In summary, clinical research targeting EGFR in lung cancer is rapidly advancing along 3 key trajectories: consolidation therapy, combinatorial targeted strategies, and the development of approaches to overcome resistance mechanisms. These ongoing trials not only highlight differential therapeutic efficacy across diverse pathological contexts but also provide a critical foundation for the advancement of precision and individualized treatment in lung cancer.

ALK-TKIs

Progress in ALK-targeted drug development

Despite continuing optimization of EGFR-targeted therapies, substantial progress has been made in sequential treatment strategies for ALK rearrangements, the second most prevalent driver alteration in NSCLC (occurring in 3%–7% of cases). Similarly to EGFR inhibition, the generational evolution of ALK TKIs, from crizotinib to lorlatinib, has significantly extended the median treatment duration mPFS, from 10 to 60 months. However, the resistance mechanisms fundamentally diverge: EGFR resistance is mediated primarily by acquired secondary mutations (e.g., T790M/C797S), whereas ALK resistance involves predominantly bypass signaling reactivation (e.g., through EGFR or KIT pathways)[33]. ALK rearrangements are a critical therapeutic target in NSCLC, particularly among younger, never-smoking patients with adenocarcinoma histology. Several critical clinical trials have markedly reshaped the therapeutic landscape of ALK-positive NSCLC, and new data support deeper, longer-lasting, and more CNS-penetrant responses.

Current clinical trials of ALK-targeted drugs

The long-term results of the CROWN phase III trial continue to indicate that lorlatinib is the most potent ALK inhibitor in the frontline setting. In treatment-naïve patients with advanced ALK-positive NSCLC, lorlatinib achieved a median PFS that remains unreached after 5 years of follow-up, whereas crizotinib achieved a median PFS of 9.1 months [hazard ratio (HR) 0.19]. The 5-year PFS rate reached 60%, and durable intracranial disease control was observed, with a CNS PFS

HR of 0.06, thus establishing lorlatinib as a new benchmark in ALK-directed therapy[34]. In the early-stage setting, the ALINA trial indicated that alectinib, when used as adjuvant therapy in completely resected stage IB–IIIA ALK-positive NSCLC, compared with platinum-based chemotherapy, achieved a 76% lower risk of disease recurrence or death (HR 0.24, $P < 0.0001$). These results mark a major milestone in the use of ALK-TKIs in the curative-intent setting and highlight the expanding role of molecularly targeted adjuvant therapy[35]. Beyond approved agents, new-generation ALK inhibitors have shown encouraging activity in patients with refractory or CNS-involved disease. Ensartinib received FDA approval in late 2024 for use in patients with advanced ALK-rearranged NSCLC, thereby offering a viable alternative for cancers progressing on earlier-generation TKIs. Meanwhile, the investigational agent NVL-655, which is currently being evaluated in the ALKOVE-1 phase I/II study, demonstrated an ORR of 39% in heavily pretreated patients, and intracranial responses were observed. NVL-655 has since received FDA Breakthrough Therapy Designation, and a phase III head-to-head trial against alectinib (ALKAZAR) is underway[36]. Similarly, zidesamtinib, being explored in the ARROS-1 trial, is under investigation for activity in both ALK- and ROS1-rearranged NSCLC, and updated efficacy data are anticipated in late 2025.

Collectively, these advances underscore a maturing era in ALK-targeted therapy, defined by durable first-line disease control, a shift toward early-stage curative application, and next-generation inhibitors aimed at overcoming resistance and CNS progression. As the therapeutic paradigm continues to evolve, biomarker-driven stratification and CNS-directed efficacy remain essential considerations in optimizing outcomes for patients with ALK-rearranged NSCLC.

KRAS inhibitors

Progress in KRAS-targeted drug development

In contrast to the structured, iterative advancements in ALK-targeted therapy, the breakthrough targeting of KRAS, which was historically considered an intractable oncoprotein, signifies a new era in precision oncology for NSCLC. KRAS G12C inhibitors (e.g., adagrasib) achieve selective inhibition through covalent binding to the mutant cysteine residue. Notably, therapeutic strategies for ALK and KRAS exhibit mechanistic complementarity: KRAS pathway activation frequently emerges as a bypass resistance mechanism after ALK inhibition, whereas ALK fusions may drive resistance to KRAS inhibitors, thereby providing a rationale for cross-target therapeutic sequencing. KRAS is among the most frequently mutated oncogenes in all human malignancies, and KRAS mutations are observed in approximately 1 in 7 cases. These mutations are particularly common in lung adenocarcinoma and are found in approximately 25% of cases[37,38]. Previous studies have indicated notable geographical variations in the KRAS G12C mutation rate in advanced NSCLC: America, 8.9%–19.5%; Europe, 9.3%–18.4%; Latin America, 6.9%–9.0%; and Asia, 1.4%–4.3%[7]. Among the various KRAS mutants, KRAS G12C is the most common mutation and represents approximately 40% of KRAS mutations. A total of 10%–13% of advanced non-squamous NSCLC cases are attributed to this mutation. Immunotherapy (IO) is the first-line treatment for KRAS mutation-carrying NSCLC, and combining IO with targeted therapy may enhance treatment efficacy.

Current clinical trials of KRAS-targeted therapies

Olomorasib (LY3537982), a second-generation inhibitor targeting GDP-bound KRAS G12C, has shown significant efficacy against NSCLC. Burns et al. have reported that olomorasib (50 or 100 mg BID) combined with pembrolizumab achieved good safety and antitumor activity in patients with advanced NSCLC bearing KRAS G12C mutation, with an antitumor response rate of 77% and favorable preliminary PFS regardless of PD-L1 expression[39] (**Table 3**). An updated phase I/II study of olomorasib in patients with advanced solid tumors with the KRAS G12C mutation has indicated an ORR of 35% for non-colorectal solid tumors and 41% for NSCLC. Another study has shown that olomorasib has a favorable safety profile even in patients with prior intolerance to KRAS G12C inhibitors[40].

Fulzerasib (GFH925), the first KRAS G12C inhibitor developed in China, has shown notable efficacy as a monotherapy in previously treated patients with NSCLC. A study examining fulzerasib and cetuximab combination therapy in previously untreated patients with advanced NSCLC with the KRAS G12C mutation showed an ORR of 81.8% and a disease control rate of 100%. Among patients with brain metastases, the ORR was 70%. The preliminary data, with 88% of patients still under treatment and a median follow-up of 5.1 months,

Table 3 Treatment advances in TKIs for KRAS G12C mutant NSCLC

Target	Trial ID/reference	Intervention	Population	Key outcomes (reported with 95% CI)	Key safety data (grade ≥ 3)
KRAS G12C	NCT04956640 2024 ASCO. 8510	Olomorasib + pembrolizumab	Advanced KRAS G12C mutation	ORR: 77% (64–87) mPFS: 9.0 months (7.0–NE) DOR: 10.2 months (6.4–NE)	Diarrhea: 16%
KRAS G12C	NCT0495664 2024 ASCO. 3007	Olomorasib	Advanced solid tumors KRAS G12C mutation	NSCLC mPFS: 9.0 months (3.0–NE) CRC DCR: 84% (75–91) Non-CRC DCR: 90% (82–95)	TRAEs: 5%
KRAS G12C	NCT05756153 2024 ASCO. 8511	Fulzerasib (GFH925) + cetuximab	Untreated advanced KRAS G12C mutation	ORR: 80% (56–94) DCR: 100% (83–100) mPFS: 8.7 months (5.6–11.2)	TRAEs: 18.5%
KRAS G12C	NCT04685135 2024 ASCO. 8509	Adagrasib	Locally advanced or metastatic KRAS G12C mutation	mPFS: 5.49 months (4.15–7.0) *vs.* 3.84 months (2.76–4.86) ORR: 31.9% (27–38) *vs.* 9.2% (5–15)	TRAEs: 47.0%
KRAS G12C	NCT05920356 2024 ASCO. 8512	Sotorasib + carboplatin and pemetrexed	Advanced KRAS G12C mutation	ORR: 65% (47–80) mPFS: 10.8 months (5.4–NE) PD-L1 < 1% mPFS: 11.9 months (5.3–NE)	TRAEs: 52%
KRAS G12C + SHP2	NCT05288205 2024 ASCO. 3008	KRAS G12C inhibitor (glecirasib, JAB-21822) + SHP2 inhibitor (JAB-3312)	KRAS G12C mutation	ORR: 77.8% (58–91) DCR: 92.6% (76–99) 12-month PFS: 53.7% (34–69)	TRAEs: 41.9%

ASCO, American Society of Clinical Oncology; CI, confidence interval; DOR, duration of response; DCR, disease control rate; NSCLC, non-small cell lung cancer; ORR, overall response rate; PFS, progression-free survival.

suggest that the combination of fulzerasib with cetuximab is a promising first-line treatment for NSCLC with the KRAS G12C mutation[41].

Adagrasib, an effective covalent inhibitor of KRAS G12C, is characterized by a long half-life (23 h), dose-dependent pharmacokinetics, and favorable brain penetration. In the phase III KRYSTAL-12 trial, adagrasib exhibited superior PFS and ORR to docetaxel (DOCE) in previously treated patients with locally advanced or metastatic NSCLC bearing the KRAS G12C mutation, who had previously received platinum-containing chemotherapy and were receiving anti-PD-(L)1 therapy concurrently or sequentially[42]. On the basis of groundbreaking data from the KRYSTAL-12 study, the 2025 NCCN guidelines designate adagrasib as the preferred second-line regimen for KRAS G12C mutant NSCLC. With increasing use of biomarker testing (although current global testing rates are below 40%), significantly more patients are anticipated to benefit from this therapy. Adagrasib's clinical outcomes not only validate the feasibility of KRAS-targeted therapy but also mark the advent of a new era in precision oncology for lung cancer. Accumulating real-world evidence and breakthroughs in combination strategies suggest that this agent might represent a landmark advancement in cancer therapeutics. For patients, timely molecular profiling and clinical trial participation are critical pathways for accessing cutting-edge treatments.

Sotorasib, a highly selective, specific, and irreversible KRAS G12C inhibitor, is recommended in NCCN guidelines as a subsequent treatment option for patients with KRAS G12C mutant NSCLC who have undergone platinum-based chemotherapy (with or without IO combination therapy)[43]. The CodeBreaK 101 trial evaluated sotorasib in combination with carboplatin and pemetrexed for patients with advanced NSCLC bearing the KRAS G12C mutation. This combination showed favorable efficacy and durability in treatment-naive, PD-L1-negative, advanced KRAS G12C mutant NSCLC, and manageable safety profiles[44].

The KRAS G12D mutation, a critical oncogenic driver in multiple malignancies, is particularly prevalent in pancreatic

Table 4 Treatment advances in ADC therapy for NSCLC

Medicine	Linker/payload	Trial (reg. No.)	Phase and population	Median PFS	Median OS	HR (95% CI)	ORR (%)	≥ Grade 3 TEAEs
Sacituzumab govitecan (TROP2)	CL2A cleavable linker, SN-38 payload; DAR ≈ 7.6:1	EVOKE-01 (NCT05089734)	Phase III; mNSCLC post-platinum + PD-(L)1	4.1 *vs.* 3.9 months	11.1 *vs.* 9.8 months	OS HR 0.84 (0.68–1.04); PFS HR 0.92 (0.77–1.11)	NR	66.6% *vs.* 75.7%; discontinuations 9.8% *vs.* 16.7%
Dato-DXd (TROP2)	Cleavable tetrapeptide linker, DXd payload; DAR 4:1	TROPION -Lung01 (NCT04656652)	Phase III; pretreated advanced NSCLC	4.4 *vs.* 3.7 months	12.9 *vs.* 11.8 months	PFS HR 0.75 (0.62–0.91); OS HR 0.94 (0.78–1.14)	26.4% *vs.* 12.8%	25.6% *vs.* 42.1%; ILD 8.8% *vs.* 4.1%
Sigvotatug vedotin [Integrin beta-6 (IB)]	Likely MMAE payload *via* protease-cleavable linker	SGNB6A-001 (phase I)	Advanced solid tumors incl. NSCLC	NR	NR	NR	19.5% overall; 32.5% taxane-naïve	Manageable
Patritumab deruxtecan (HER3)	Tetrapeptide cleavable linker, topoisomerase I payload	HERTHENA -Lung02 (NCT05338970)	Phase III; EGFRm NSCLC post-EGFR-TKI	5.8 *vs.* 5.4 months	16.0 *vs.* 15.9 months	PFS HR 0.77 (0.63–0.94); OS HR 0.98 (0.79–1.22)	35.2% *vs.* 25.3%	57.9% *vs.* 46.1%; ILD 5.2%; TRAE deaths 1.4%
Iza-bren (EGFR × HER3)	Tetrapeptide cleavable linker, novel topoisomerase I payload Ed-04	NCT05194982 (phase Ib)	Driver-altered NSCLC incl. EGFR exon20ins	NR	NR	NR	PR 85.7% (6/7 EGFR-ex20ins)	NR
Telisotuzumab vedotin (c-MET)	MMAE payload *via* protease cleavable linker	Mid-phase (FDA accelerated approval May 2025)	c-MET-high NSCLC post-treatment	NR	NR	NR	ORR 28.6% overall; 34.6% in c-MET-high	NR

CI, confidence interval; FDA, Food and Drug Administration; HR, hazard ratio; ILD, interstitial lung disease; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

ductal adenocarcinoma (36%), colorectal carcinoma (12%), and lung adenocarcinoma (4%). Although no targeted therapies are currently approved for KRAS G12D-driven cancers, several investigational agents have achieved promising preclinical and clinical progress and might potentially offer therapeutic breakthroughs. HRS-4642 has emerged as a novel small-molecule inhibitor exhibiting high selectivity for KRAS G12D. Preclinical studies have revealed its ability to specifically suppress KRAS G12D protein activity, thereby inhibiting tumor cell proliferation and survival through sustained blockade of KRAS signaling pathways. This compound is currently undergoing phase I/II clinical evaluation and has demonstrated favorable pharmacokinetic profiles, with prolonged plasma and tumor tissue retention in xenograft models[45]. MRTX1133, a non-covalent inhibitor, demonstrates nanomolar-level affinity for KRAS G12D with > 1,000-fold selectivity over wild-type KRAS. Preclinical evaluations in 25 human-derived tumor models have demonstrated > 30% tumor regression in 44% of cases, particularly in pancreatic cancer models (73% response rate). Structural analyses have confirmed its dual binding to both inactive and active KRAS G12D conformations[46]. Additional investigational compounds in preclinical development include RMC-9805, TH-Z835, and BI-2852, which use diverse targeting strategies such as covalent inhibition and allosteric modulation. These advancements collectively address the urgent clinical need for KRAS G12D-targeted therapies, particularly in pancreatic cancer, in which this mutation predominates (40%–45% incidence). Current clinical trials are focusing on second-line or later settings for locally advanced or metastatic solid tumors, and emerging combination strategies are exploring synergies between KRAS inhibitors and proteasome-targeting agents. Although therapeutic validation awaits the completion of ongoing clinical trials, these developments mark substantial progress in overcoming historical challenges associated with KRAS targetability.

Despite these advancements, therapies based on new KRAS inhibitors face major challenges because of the rapid development of acquired resistance. The use of KRAS inhibitors in combination with other upstream or downstream signaling pathway inhibitors such as SHP2 and CDK4/6 has facilitated considerable progress in overcoming resistance. Increased HER2 copy number has been identified as a mechanism of resistance, which can be mitigated by co-targeting SHP2[47]. Combination therapy with KRAS G12C inhibitors (glecirasib and JAB-21822) and SHP2 inhibitors (JAB-3312) has shown manageable safety and broad ORR and PFS when used as a first-line treatment for NSCLC with the KRAS p.G12C mutation[48].

In addition, recent studies have suggested that oncogenic KRAS mutations are closely associated with glycolysis and glutamine metabolism. Oncogenic KRAS-mutant tumors strongly rely on aerobic glycolysis (the Warburg effect) for energy production, even under oxygen-rich conditions[49]. MEK/ERK inhibitors targeting the glycolysis pathway have shown therapeutic potential[50]. Concurrent use of glycolysis inhibitors with ICIs might counteract lactate-mediated immunosuppression, thereby restoring antitumor immunity[51]. Glutamine is the primary carbon/nitrogen source for biosynthesis of mitochondrial metabolites, amino acids, nucleotides, and fatty acids, which are essential for proliferation and redox homeostasis. Oncogenic KRAS mutations amplify glutamine uptake and conversion to glutamate *via* glutaminase, thereby fueling tricarboxylic acid cycle intermediates for ATP generation and biomass production[50]. The SLC7A11-mediated glutamine/cysteine antiporter is a druggable target. Sulfasalazine, an SLC7A11 inhibitor, selectively eliminates KRAS-mutant cancer cells *in vitro* and suppresses tumor growth *in vivo*[52].

The treatment of KRAS-mutant NSCLC has transitioned from being historically considered "undruggable" into a precision-targeted therapeutic era. G12C inhibitors, particularly when administered through combination regimens incorporating ICIs or chemotherapy, have demonstrated significant survival benefits in clinical practice. Future research must prioritize the development of targeted agents for non-G12C subtypes, strategies to overcome resistance mechanisms, and biomarker-guided individualized treatment approaches. Emerging combination therapies and novel drug technologies have substantial promise for addressing current therapeutic limitations and may potentially offer more durable clinical outcomes. Continued advancements in clinical trial data will be crucial to validate the safety and efficacy of these innovative therapeutic modalities.

ROS1-TKIs

In 1980, Balduzzi et al. identified the ROS1 gene in the RNA of avian myeloblastosis virus UR2[53]. Crizotinib demonstrated significant antitumor activity in patients with advanced NSCLC with ROS1 rearrangement and was the first TKI approved by the FDA and the European Medicines Agency

for this indication[54,55]. However, because of drug resistance, most patients experience relapse over time. In the phase III CROWN trial, lorlatinib doubled the 1-year PFS rate and inhibited the progression of brain metastases. Although ROS1 rearrangements are rare, they represent a significant therapeutic target for advanced NSCLC[56].

Mature data from the TRIDENT-1 study have been reported for repotrectinib, a compact macrocyclic inhibitor. In TKI-naïve ROS1 fusion-positive NSCLC, the ORR reached 79%, and the median PFS of 35.7 months. In pretreated patients, the ORR remained clinically meaningful, at 38%, and the median PFS was 9.0 months[57]. Taletrectinib, a next-generation, CNS-active, selective ROS1-TKI, showed initial efficacy in patients with crizotinib-refractory ROS1+ NSCLC[58]. The TRUST-I study (NCT04395677) reported an ORR of 91% (95% CI: 83–95) and an IC-ORR of 88% (7/8 patients; 95% CI: 47–100) in treatment-naïve patients. In TKI-pretreated patients, the ORR was 52% (95% CI: 40–65), and the IC-ORR was 75% (12/16 patients; 95% CI: 48–93). Among 12 patients with the G2032R mutation, 8 (67%; 95% CI: 35–90) responded to treatment. Extended follow-up confirmed that taletrectinib maintained high and durable overall responses, robust intracranial activity, and efficacy against the G2032R mutation, with a favorable safety profile and a low rate of neurological adverse events[59].

The resistance mechanisms to ROS1-TKIs are notably complex, involving bypass signaling activation such as MET amplification and KRAS mutations, which may circumvent ROS1 inhibition, or small cell lung cancer transformation in some patients, thus leading to TKI failure. Furthermore, ROS1 fusion detection relies on RNA sequencing or fluorescence *in situ* hybridization techniques, which require advanced expertise and have limited availability in primary care hospitals. The diversity of fusion partners might also influence TKI efficacy; moreover, the lack of targeted research in this area poses substantial challenges for ROS1-TKI therapy. However, advancements in technology are driving a paradigm shift from single target approaches to multidimensional precision strategies. The development of highly selective inhibitors, exploration of combination therapeutic strategies, and enhanced management of CNS metastases hold promise for transitioning ROS1 fusion-positive NSCLC toward a chronic disease management model. Concurrently, innovations in detection technologies and international collaboration are expected to accelerate the establishment of personalized treatment frameworks and to extend survival benefits for patients with rare mutations. Collectively, these data highlight a rapidly evolving landscape for ROS1+ NSCLC, marked by superior systemic and CNS efficacy, favorable tolerability, and expanding treatment options beyond first-generation agents. Continued maturation of critical trials, including ARROS-1 and TRUST-II, is expected to further refine the sequencing and personalization of ROS1-targeted therapy.

FGFR-TKIs

FGFR is a tyrosine kinase receptor that plays crucial roles in various biological processes and comprises 5 homologous members (FGFR1–5)[60]. Dysregulation of FGFR signaling has been implicated in several diseases, notably tumorigenesis and cancer progression[61,62]. Erdafitinib, an oral selective pan-FGFR-TKI, effectively targets FGFR1–4 and exhibits significant antitumor activity[63]. In a study in patients with metastatic urothelial carcinoma and FGFR alterations who were previously treated with anti-PD-1 or anti-PD-L1 therapy, erdafitinib treatment, compared with chemotherapy, markedly improved OS (12.1 months *vs*. 7.8 months; HR for death: 0.64; 95% CI: 0.47–0.88; $P = 0.005$). Additionally, the median PFS was longer in the erdafitinib group than the chemotherapy group (5.6 months *vs*. 2.7 months; HR for progression or death: 0.58; 95% CI: 0.44–0.78)[64]. Bahleda et al. have reported that erdafitinib is well tolerated and shows preliminary clinical activity in advanced solid tumors with FGFR pathway alterations, including notable responses in urothelial carcinoma and cholangiocarcinoma[65]. The RAGNAR study involved patients with advanced or metastatic NSCLC who showed specific FGFR1–4 alterations and had experienced disease progression after standard therapies. Patients with other targetable alterations, such as EGFR, ALK, and ROS1, were excluded. Recent results from that study have indicated that erdafitinib demonstrated clinically relevant activity in this cohort[66].

HER2-TKIs

HER2 is a receptor tyrosine kinase encoded by the ERBB2 oncogene on chromosome 17 (17q21)[67]. Effective treatment options for patients with NSCLC with HER2 mutations have historically been limited, and no approved targeted therapies are currently available in China. This scarcity might be attributable to the rare occurrence of HER2 protein overexpression or amplification in NSCLC, and the small sample sizes in studies

that yielded inconclusive results[68,69]. Zongertinib, a novel TKI, selectively binds the tyrosine kinase domain of HER2. Recent clinical trials have shown that zongertinib is effective in patients with NSCLC with HER2 alterations, including gene mutations, rearrangements, amplifications, or overexpression, thus particularly benefiting patients with HER2 mutations[70,71]. This groundbreaking drug offers new hope for patients with advanced lung cancer with HER2 mutation. BAY 2927088, a potent, oral, reversible HER2 TKI, has demonstrated manageable safety and antitumor activity in patients with advanced NSCLC bearing activating HER2 mutations. The SOHO-01 study enrolled patients with advanced HER2-mutant NSCLC that progressed after ≥ 1 prior systemic regimen and were either HER2-targeting therapy-naïve (cohort D) or had received prior HER2-targeting ADC therapy (cohort E). As of October 14, 2024, 44 (cohort D) and 34 (cohort E) patients had received treatment. The baseline characteristics included median ages of 62.0 (D) and 62.5 (E) years; 63.6% (D) and 61.8% (E) women; 70.5% (D) and 64.7% (E) never-smokers; and 54.5% (D) and 76.5% (E) patients with ≥ 2 prior lines of therapy. Notably, 82.4% of cohort E had received trastuzumab deruxtecan. The efficacy outcomes (investigator-assessed) were as follows:

- Objective response rate: 70.5% (cohort D) vs. 35.3% (cohort E)
- Disease control rate (response or stable disease ≥ 12 weeks): 81.8% (D) vs. 52.9% (E)
- Median duration of response: 8.7 months (D) vs. 9.5 months (E)

BAY 2927088 elicited durable responses in patients refractory to HER2-targeted therapy and in those with prior HER2-targeting ADC exposure[72].

Advances in ADC therapy

Current clinical trials of ADCs

When conventional targeted therapies encounter resistance limitations, ADCs offer alternative strategies through their target-specific payload delivery mechanism. In recent years, ADCs have emerged as a promising therapeutic modality in NSCLC. ADCs combine tumor antigen specificity with potent cytotoxic payloads, thereby enabling selective elimination of malignant cells. Several novel ADCs have recently demonstrated encouraging clinical efficacy in biomarker-defined NSCLC subgroups, with promising safety profiles (**Table 4**).

Sacituzumab govitecan (SG), a trop-2-directed ADC, is conjugated with the topoisomerase I inhibitor SN-38 *via* a cleavable linker (CL2A)[73], and achieves an average drug-antibody ratio of approximately 7.6[74]. For patients with metastatic NSCLC who show progression after platinum-based chemotherapy and PD-(L)1 therapy, DOCE remains the standard treatment, although the outcomes are suboptimal. In the updated EVOKE-01 study, compared with DOCE administered at 75 mg/m^2 on day 1 every 21 days, SG administered at 10 mg/kg through intravenous infusion on days 1 and 8 did not achieve a significant primary endpoint but demonstrated a survival advantage and better tolerance. SG had a low incidence of high-grade treatment-emergent adverse events (TEAEs) and TEAEs leading to discontinuation[75].

Sacituzumab tirumotecan (SKB264), which is attached to belotecan derivative targeting topoisomerase I *via* a novel linker, is being tested in the OptiTROP-Lung01 study. This nonrandomized phase II trial, presented at the 2024 American society of clinical oncology (ASCO) annual meeting, evaluated the efficacy and safety of SKB264 in combination with the PD-L1 inhibitor KL-A167 as the first-line treatment for locally advanced or metastatic NSCLC negative for driver genes. The results showed favorable efficacy and manageable safety profiles[76]. As China's first domestically developed anti-TROP2 ADC, SKB264 might become the first TROP2 ADC approved for EGFR-positive patients.

Dato-DXd, another ADC, comprises a humanized anti-TROP2 IgG1 monoclonal antibody linked to 4 DXd molecules through a cleavable peptide linker. In the phase III TROPION-Lung01 study, Dato-DXd, compared with DOCE, significantly improved PFS in previously treated patients with advanced NSCLC[77]. Recent research has confirmed the efficacy and safety of this ADC, thus potentially establishing it as a new standard for subsequent therapy after immune-targeted resistance in patients with advanced NSCLC. The phase II ICARUS-LUNG01 study evaluated the efficacy, safety, and biomarker correlates of response/resistance to Dato-DXd in patients with previously treated advanced NSCLC. The ORR was 26% in the overall population. Enhanced clinical benefit was observed in the non-squamous NSCLC subgroup, which achieved an ORR of 30.5% and mPFS of 4.8 months. Exploratory biomarker analyses demonstrated clinical activity across varying TROP2 expression levels, as quantified by histochemical score. The TROP2 expression level was associated with the PFS benefit of Dato-DXd treatment. Further analysis

suggested that activation of DNA repair pathways (ATM and BRCA1 upregulation) and immunosuppressive signatures (e.g., TGF-β signaling) might contribute to acquired resistance[77]. This study has provided valuable insights into biomarker-driven strategies for ADC development in thoracic oncology.

Sigvotatug vedotin (SGN-B6A) targets integrin β6 with engineered specificity that prevents binding to other integrins, thereby enhancing tumor selectivity. The 2024 ASCO annual meeting presented updated phase I trial results, which showed confirmed ORRs of 19.5% overall and 32.5% in patients without prior taxane therapy[78]. The phase 1 SGNB6A-001 trial evaluated the safety of sitravatinib plus pembrolizumab in patients with advanced solid tumors. Among 8 response-evaluable patients with head and neck cancer, 2 achieved a confirmed complete response, and 1 achieved a confirmed PR, thus yielding a confirmed ORR of 37.5%. Sigvotatug vedotin plus pembrolizumab demonstrated a manageable safety profile and encouraging preliminary efficacy signals[79]. Sigvotatug vedotin continues to demonstrate strong antitumor activity and manageable safety, and a critical phase III trial assessing its efficacy as a second-line or third-line therapy for NSCLC is ongoing.

Patritumab deruxtecan (HER3-DXd), a novel antibody-drug conjugate comprising a fully human anti-HER3 monoclonal antibody linked to a topoisomerase I inhibitor payload *via* a stable, tetrapeptide-based cleavable linker, has demonstrated superior clinical outcomes to platinum-based chemotherapy (PBC) in the global phase 3 HERTHENA-Lung02 trial (NCT05338970). This randomized study enrolled patients with advanced/metastatic EGFR-mutated (Ex19del or L858R) NSCLC that progressed after third-generation EGFR TKI therapy. The PFS rate (95% CI) with HER3-DXd *vs*. PBC was 0.50 (0.44–0.56) *vs*. 0.38 (0.32–0.44) at 6 months; 0.29 (0.23–0.35) *vs*. 0.19 (0.14–0.25) at 9 months; and 0.18 (0.12–0.25) *vs*. 0.05 (0.01–0.13) at 12 months. The ORR (95% CI) was 35.2% (29.7%–40.9%) with HER3-DXd *vs*. 25.3% (20.4%–30.6%) with PBC. The median DOR (95% CI) was 5.7 (5.1–7.3) months with HER3-DXd *vs*. 5.4 (4.1–5.6) months with PBC[80].

Iza-bren (BL-B01D1), a first-in-class bispecific ADC, combines an EGFR × HER3-targeting antibody with a novel topoisomerase I inhibitor payload (Ed-04) *via* a stable, tetrapeptide-based cleavable linker. In the phase 1b module of the NCT05194982 trial, which enrolled patients with driver-altered NSCLC bearing non-canonical EGFR-TKI-sensitizing mutations, multiple expansion cohorts were stratified according to prespecified genomic alterations. These alterations included EGFR exon 20 insertions; atypical EGFR mutations; and alterations in HER2, ALK, ROS1, BRAF (V600E and other variants), KRAS (G12C and other variants), SMARCA4, MET (exon 14), RET, and NTRK. As of December 5, 2024, 73 genomic alteration-positive patients with NSCLC were enrolled. Among 7 patients with EGFR exon 20 insertion mutations, 6 (85.7%) achieved confirmed partial responses[81].

Finally, telisotuzumab vedotin (Emrelis), a novel MET-targeted MMAE ADC, was granted FDA accelerated approval in May 2025 for previously treated, c-MET–high non-squamous NSCLC. The approval was based on a mid-phase clinical study, in which the overall ORR was 28.6%, and an ORR of 34.6% was observed specifically in patients with high c-MET expression[82].

Limitations of ADCs

Although ADCs achieve potent anti-tumor activity through precise delivery of cytotoxic payloads, their efficacy might be limited by tumor heterogeneity and activation of bypass signaling pathways. For instance, in EGFR-TKI-resistant patients, bypass mechanisms such as MET amplification or KRAS mutations might compromise the targeted effects of ADCs. Additionally, the intricate drug design of ADCs, requiring coordinated optimization of 3 core components (antibody, linker, and payload), poses multifaceted challenges in NSCLC treatment. However, advancements in technological innovation and interdisciplinary collaboration hold promise for refining the precision and individualized application of ADCs. These developments are expected to reshape the therapeutic paradigm for advanced lung cancer, and to offer broader clinical benefits through enhanced targeting strategies and optimized therapeutic windows.

Immunotherapy efficacy

The poor efficacy of immunotherapy in oncogene-driven tumors is attributed to several underlying mechanisms. First, tumors bearing driver mutations such as EGFR or ALK often exhibit a low tumor mutational burden[83], thus limiting the generation of neoantigens, decreasing tumor immunogenicity, and ultimately weakening the immune system's ability to recognize and eliminate tumor cells. Second, activation of oncogenic

pathways contributes to the formation of an immunosuppressive tumor microenvironment by downregulating MHC expression and promoting the infiltration of tumor-associated macrophages and regulatory T cells, which inhibit tumor-specific immune responses. In addition, although some EGFR-mutant tumors express PD-L1, this expression is typically driven by oncogenic signaling rather than adaptive immune escape, thus leading to a poor response to ICIs. Furthermore, because resistance mutations such as T790M are often accompanied by enhanced expression of anti-apoptotic and immunosuppressive factors, the efficacy of ICIs is further diminished[84].

In contrast, combining VEGFR inhibitors with immunotherapy offers a mechanistic rationale for overcoming these limitations. VEGF/VEGFR inhibition can normalize the abnormal tumor vasculature, thereby improving immune cell infiltration by facilitating T cell trafficking into tumors. It also suppresses the accumulation of immunosuppressive cells such as regulatory T cells and myeloid-derived suppressor cells, while promoting the maturation of dendritic cells and enhancing antigen presentation. Moreover, VEGF blockade can act synergistically with ICIs by alleviating immune suppression and enhancing the activation of $CD8^+$ T cells, thereby effectively transforming "cold" tumors into "hot" tumors[85].

Because of the consistent background of low immunogenicity, immunosuppressive microenvironment, and non-adaptive PD-L1 expression in oncogene-driven tumors, single-agent ICIs are often insufficient. However, the addition of VEGFR inhibitors might reshape the tumor microenvironment and improve immunotherapy responses. Recent phase II/III trials and biomarker studies, such as those involving VEGF-A, have shown that triple combination therapy (ICI + VEGFR inhibitor + chemotherapy) provides significant clinical benefits in patients with NSCLC with EGFR or ALK mutations. In the future, biomarker-guided randomized controlled trials, along with mechanistic validation and toxicity management, will be critical to establish this combination as a new therapeutic standard for oncogene-driven NSCLC.

Conclusions

Current research in NSCLC treatment has achieved significant advancements in precision targeting and IO, including promising developments in targeting rare mutations and ADCs. These approaches contribute to continuing progress in lung cancer treatment by offering diverse and effective precision treatment options. Although substantial progress has been made in pharmacological therapies for NSCLC, multiple challenges persist. For instance, the mechanisms of drug resistance have become increasingly complex. Although EGFR-TKIs, such as osimertinib, have significantly extended PFS in patients, acquired resistance remains a critical issue. Tumor heterogeneity drives bypass activation (e.g., MET amplification) or dysregulation of downstream signaling pathways (e.g., RAS-MAPK), and some patients exhibit primary resistance even during initial treatment. Although third-generation agents can overcome T790M mutations, they remain ineffective against emerging mutations such as C797S. The diversity of genetic mutations poses major limitations on the therapeutic options for NSCLC. More than a dozen driver gene mutations (e.g., EGFR, ALK, ROS1, KRAS, and RET) have been identified in NSCLC; however, the development of targeted agents for rare mutations (e.g., HER2 alterations and MET exon14 skipping mutations) remains delayed. For example, in KRAS G12C, although inhibitors such as D-1553 have entered clinical trials, their ORRs have remained below 40%, and optimized combination regimens have yet to achieve clinical maturity. The tumor microenvironment and drug delivery barriers, particularly the inadequate blood-brain barrier penetration ability, substantially constrain the therapeutic efficacy against CNS metastases. Although osimertinib decreases the risk of CNS progression by 84%, its efficacy against established brain metastases remains limited. Furthermore, the immunosuppressive microenvironment mediated by tumor stromal cells might attenuate the therapeutic effects of targeted agents. Finally, current precision detection systems require further refinement. The predictive value of existing biomarkers (e.g., PD-L1, tumor mutational burden) remains controversial, and the sensitivity of liquid biopsy techniques (e.g., ctDNA analysis) in early-stage patients is limited to 60–70%. Furthermore, the lack of standardization in genetic testing protocols might lead to the exclusion of some patients who could potentially benefit from targeted therapies. The current development of fourth-generation TKIs and dual-target inhibitors has shown breakthroughs in targeting rare mutations, and the temporal therapeutic paradigm for NSCLC is undergoing substantial innovation. Integrated models that dynamically monitor ctDNA mutational burden and features of the immune microenvironment (e.g., tumor-infiltrating lymphocyte infiltration levels) enable more accurate prediction of treatment response. Artificial-intelligence-driven radiomics analysis technologies can now

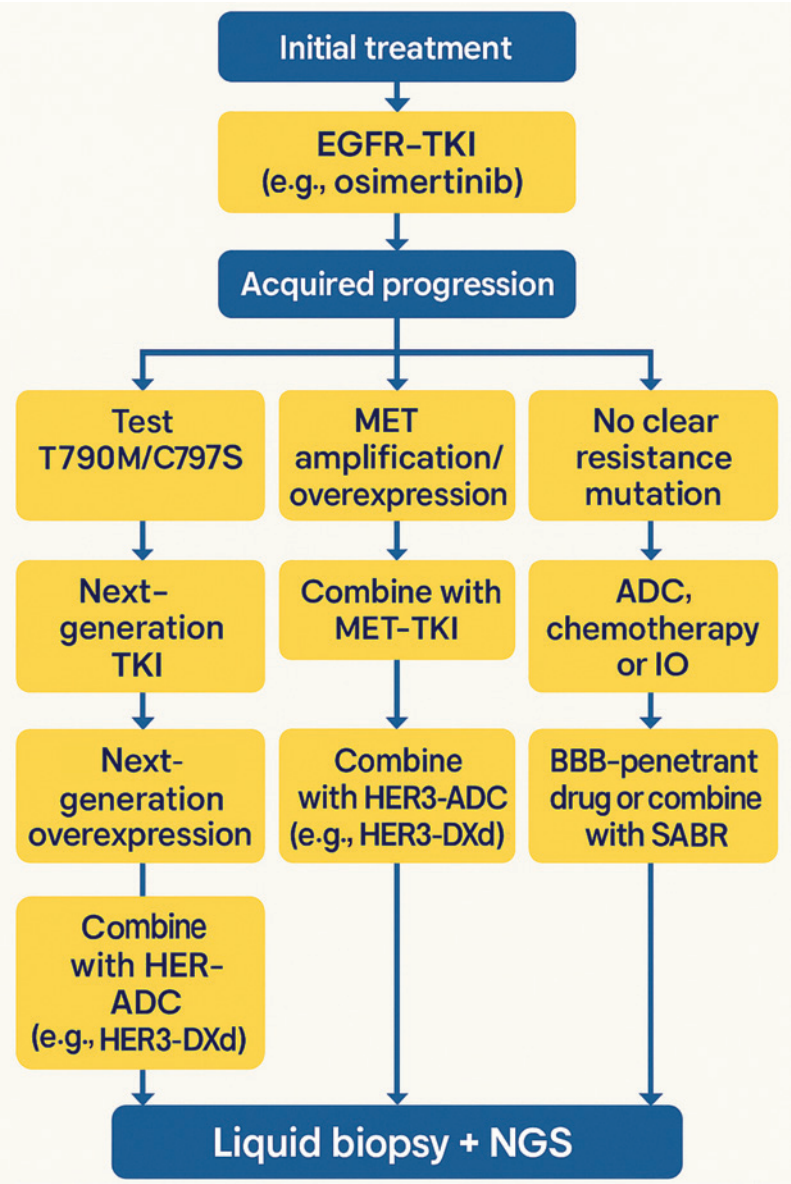


Figure 2 Sequential therapy strategies in oncogene-driven NSCLC. This figure illustrates a proposed therapeutic decision-making pathway for patients with NSCLC who develop acquired resistance after initial EGFR-TKI treatment (e.g., osimertinib). After disease progression: • If T790M or C797S resistance mutations are identified, treatment may proceed with next-generation EGFR-TKIs or HER family–directed therapies (e.g., HER3-directed antibody–drug conjugates such as HER3-DXd). • If MET amplification or overexpression is detected, combination therapy with a MET-TKI and HER3-ADC (e.g., HER3-DXd) is suggested. • If no clear resistance mechanism is found, therapeutic options include ADCs, chemotherapy, IO, or brain-penetrant agents if CNS metastases are present, possibly in combination with SABR. All pathways converge on the recommendation for liquid biopsy and NGS to guide molecular profiling and personalized treatment strategies. ADCs, antibody–drug conjugates; CNS, central nervous system; IO, immunotherapy; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; SABR, stereotactic ablative radiotherapy; TKI, tyrosine kinase inhibitor.

predict EGFR mutation status *via* pretreatment CT imaging with 85% accuracy. Artificial intelligence is poised to be deeply integrated into clinical decision-making systems, by generating personalized therapeutic regimens through real-time analysis of genomic, radiomic, and clinical datasets. According to current evidence, the following sequential treatment principles are recommended for driver-gene-positive NSCLC (**Figure 2**).

- Targeted therapy prioritization: patients with actionable driver mutations (e.G., Egfr mutations or alk fusions) should receive matched tkis as the first-line treatment (e.G., Third-generation egfr-tki osimertinib for egfr-sensitizing mutations, or lorlatinib for alk-positive disease).
- Resistance-stratified management: After the development of resistance:
  i. For on-target acquired mutations (e.g., EGFR T790M), substitute next-generation TKIs targeting the resistance mechanism (e.g., osimertinib).
  ii. For bypass signaling activation (e.g., MET amplification), implement dual-pathway inhibition (e.g., EGFR/MET bispecific antibodies).
- Cross-mechanism transition: When TKI failure occurs without actionable resistance targets, shift to mechanism-agnostic approaches—prioritizing ADCs (e.g., HER2-directed ADCs) or ICI-based combinations.
- Longitudinal biomarker surveillance: In this framework, dynamic monitoring *via* ctDNA next-generation sequencing is integral, to track genomic evolution and precisely guide intervention timing throughout the therapeutic sequence.

Furthermore, establishing cross-institutional clinical data-sharing platforms to combine real-world evidence with randomized controlled trials will be critical for optimizing therapeutic strategies. Despite persistent challenges in NSCLC management, the field is anticipated to transition from a "chronic disease management" paradigm toward achieving "functional cure" objectives within the next decade.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceptualized, analyzed, and wrote the manuscript: Hanyi Li, Xuanguang Li.
Contributed data or analysis tools: Xuanguang Li, Tong Li.
Performed the analysis: Fan Ren, Haochuan Yu, Dianxun Fu.
Contributed funding acquisition and resources: Song Xu, Zuoqing Song.

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