REVIEW ARTICLE

# ESMO 2025 and the Future of EGFR-Mutated NSCLC Sequencing: First-Line Choices That Keep the Next Line Alive

## *ESMO 2025 e o Futuro da Sequenciação Terapêutica no CPNPC com Mutação do EGFR: Opções de Primeira Linha que Preservam a Linha Terapêutica Subsequente*

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# ABSTRACT

The therapeutic landscape for *EGFR-mutated* non-small-cell lung cancer (NSCLC) has rapidly evolved with the advent of third-generation tyrosine kinase inhibitors (TKIs), bispecific antibodies, and antibody–drug conjugates (ADCs). Despite substantial improvements in first-line efficacy, a significant proportion of patients fail to reach targeted second-line therapies because of rapid clinical decline at progression. This concise review synthesizes evidence from phase II-III clinical trials and recent real-world data to evaluate how current first-line strategies influence the feasibility of subsequent therapies, with particular attention to central nervous system (CNS) risk, co-mutational biology, and treatment tolerability. Osimertinib monotherapy remains the global standard owing to its robust systemic and intracranial efficacy. The addition of chemotherapy, as shown in FLAURA2, further enhances first-line tumor control but may compromise salvage opportunities by reducing the likelihood of preserving actionable resistance. The amivantamab-lazertinib combination provides clear benefit in biomarker-defined high-risk disease but often limits the potential to reuse TKI-based approaches later in the course of treatment. Across studies, approximately 35%-40% of patients are unable to receive a targeted second-line regimen, and real-world survival after osimertinib failure is frequently restricted to 8-12 months. These data collectively suggest that the optimal first-line approach in *EGFR-mutated* NSCLC is not simply the regimen with the longest progression-free survival but rather the one that preserves access to subsequent effective therapies. Clinical decisions at diagnosis must therefore be made with downstream eligibility in mind, ensuring that patients remain candidates for HER3- and TROP2-directed ADCs and other emerging agents that are likely to shape survival beyond the first-line setting.



**Keywords:**
Carcinoma, Non-Small-Cell Lung/drug therapy; Carcinoma, Non-Small-Cell Lung/genetics; ErbB Receptors/genetics; Osimertinib

***Palavras-chave:***
*Carcinoma Pulmonar de Células não Pequenas/genética; Carcinoma Pulmonar de Células não Pequenas/tratamento farmacológico; Osimertinib; Receptores ErbB/genética*



# *RESUMO*

*O panorama terapêutico do cancro do pulmão de não pequenas células (CPNPC) com mutação do EGFR evoluiu rapidamente com a introdução dos inibidores da tirosina-cinase (ITC) de terceira geração, dos anticorpos biespecíficos e dos conjugados anticorpo–fármaco (ADC). Apesar dos ganhos substanciais de eficácia em primeira linha, uma proporção significativa de doentes não chega a receber terapêuticas alvo em segunda linha, frequentemente devido a deterioração clínica rápida no momento da progressão da doença.*

*Esta revisão concisa sintetiza a evidência proveniente de ensaios clínicos de fase II–III e de dados recentes de prática clínica real, analisando de que forma as estratégias atuais de primeira linha condicionam a viabilidade de terapêuticas subsequentes. A análise centra-se, em particular, no risco de envolvimento do sistema nervoso central (SNC), na biologia das co-mutações e na tolerabilidade cumulativa do tratamento.*

*A monoterapia com osimertinibe continua a ser o padrão global de tratamento devido à sua robusta eficácia sistémica e intracraniana. A associação de quimioterapia, conforme demonstrado no FLAURA2, permite um maior o controlo tumoral inicial, mas pode comprometer estratégias de recuperação, ao reduzir a probabilidade de emergência de mecanismos de resistência acionáveis.*

*De forma semelhante, a combinação amivantamab–lazertinib demonstra benefício clínico claro em subgrupos de alto risco definidos por biomarcadores, mas frequentemente limita a possibilidade de reutilização de abordagens baseadas em ITQ em linhas subsequentes.*

*De forma transversal aos estudos analisados, estima-se que cerca de 35%–40% dos doentes não consigam receber um regime alvo em segunda linha, sendo que a sobrevivência observada em contexto de prática clínica real após falência do osimertinib é frequentemente limitada a 8–12 meses. Em conjunto, estes dados sugerem que a estratégia ótima em primeira linha no CPNPC com mutações do EGFR não deve ser determinada exclusivamente pela sobrevivência livre de progressão, mas antes pela capacidade de preservar o acesso a terapêuticas eficazes ao longo da sequência terapêutica.*

*Assim, as decisões clínicas no momento do diagnóstico devem integrar uma perspetiva longitudinal, considerando a elegibilidade futura dos doentes para ADC dirigidos a HER3 e TROP2, bem como para outros agentes emergentes que provavelmente desempenharão um papel determinante na sobrevivência para além da primeira linha.*

**Key message:**
In *EGFR-mutated* NSCLC, survival is ultimately contingent on patients reaching the next line of active therapy; the optimal first-line choice is the one that preserves future targeted options rather than merely maximizing initial PFS.

# INTRODUCTION

Epidermal growth factor receptor-mutated (EGFRm) non-small cell lung cancer (NSCLC) is one of the most molecularly characterized and therapeutically advanced subsets of lung cancer.[1] Over the past decade, targeted therapies have evolved substantially, progressing from first-generation EGFR tyrosine kinase inhibitors (TKIs) to third-generation brain-penetrant agents that markedly improve progression-free survival (PFS) and quality of life. In the phase III FLAURA trial, first-line osimertinib increased median PFS from 10.2 to 18.9 months (HR 0.46) and median overall survival (OS) from 31.8 to 38.6 months compared with earlier TKIs.[2] Nevertheless, despite these substantial advances in the first-line setting, the clinical course of EGFRm NSCLC remains challenging because of inevitable disease progression, limited durability of response, and a persistent need for rational sequencing strategies.

The approval of osimertinib as a universal first-line standard has reshaped treatment paradigms but has also created a therapeutic bottleneck once resistance develops. Post-osimertinib management is heterogeneous and often suboptimal, with real-world data indicating that more than 35%-40% of patients do not receive second-line targeted therapy owing to rapid progression or declining performance status.[3] Until recently, therapeutic decisions after osimertinib relied almost exclusively on chemotherapy, which offers only incremental survival benefit at the cost of increased toxicity.

New-generation combinations, such as amivantamab plus lazertinib in the MARIPOSA trial, have challenged the long-standing "osimertinib-first" approach by improving PFS and delaying central nervous system (CNS) failure (median PFS ~23.7 *vs* ~16.6 months; HR 0.70).[4] However, these regimens introduce new uncertainties, including greater post-progression sequencing complexity, accessibility and economic constraints, infusion burden, and unknown implications for OS. Meanwhile, the advent of antibody–drug conjugates (ADCs), such as datopotamab deruxtecan and sacituzumab tirumotecan, as well as bispecific HER3-directed agents such as izalontamab and brenzictan, has initiated a new treatment era in which potent cytotoxic delivery may restore sensitivity beyond TKI resistance.

Because modern EGFRm NSCLC now encompasses multiple classes of active agents including TKIs, bispecific antibodies, immune checkpoint inhibitors (with limited value), VEGF-targeted strategies, and emerging ADCs the choice of first-line therapy increasingly determines the availability and effectiveness of all subsequent options. Notably, the addition of platinum-based chemotherapy to osimertinib in FLAURA2 further extended PFS from 16.7 to 25.5 months (HR 0.62) compared with osimertinib alone,[5] but again raises concerns about exhausting valuable later-line agents before clear OS benefits are established.

This short review aims to synthesize the most recent phase II-III data available up to October 2025, to quantify how first-line choices shape second-line opportunities and overall survival potential, and to propose a pragmatic sequencing model that reflects real-world clinical pressures.

# UPDATED TRIAL LANDSCAPE & SEQUENCING OUTCOMES

First-line therapy for *EGFR-mutated* NSCLC has traditionally prioritized maximizing progression-free survival (PFS) and delaying the onset of symptomatic disease. Osimertinib monotherapy, as shown in the FLAURA trial, achieved a median PFS of 18.9 months and a median overall survival (OS) of 38.6 months compared with earlier EGFR-TKIs and remains the globally accepted standard.[2] However, clinical deterioration after progression often prevents molecular reassessment or implementation of targeted second-line strategies, with real-world data indicating that more than one-third of patients do not receive directed salvage therapy following first-

line osimertinib.[3] This discrepancy between early tumor control and long-term treatment continuity underscores the need to evaluate first-line decisions in terms of their downstream consequences.

The integration of platinum-based chemotherapy with osimertinib in FLAURA2 extended median PFS to 25.5 months, representing the most robust front-line efficacy signal to date in EGFRm disease.[5] Nonetheless, more intensive suppression of tumor biology early in the disease course may reduce the likelihood of maintaining a targetable resistance profile at progression, thereby constraining the feasibility of subsequent precision therapies. In this context, initial gains must be carefully weighed against the risk of limiting later therapeutic flexibility.

Combination therapy with bispecific antibodies offers an alternative strategy. Amivantamab plus lazertinib in the MARIPOSA trial improved PFS to approximately 23.7 months in biomarker-defined high-risk disease and demonstrated encouraging intracranial control.[4] Yet this approach complicates sequencing: progression after dual EGFR targeting may preclude the reuse of TKI-based therapy, leaving chemotherapy or antibody-drug conjugates (ADCs) as the main salvage options. Economic and logistical constraints further limit the real-world scalability of this regimen to high-resource settings.

Mechanistic studies reinforce these concerns. Resistance to osimertinib is biologically heterogeneous and often lacks a clearly druggable driver, explaining why only a minority of patients transition to a successful targeted second-line approach.[6] At the same time, immune checkpoint inhibitors have limited activity in *EGFR-mutated* NSCLC, with low response rates and short-lived benefit, contributing little to sequencing recovery.[7] For now, effective second-line therapy relies heavily on maintaining performance status and preserving eligibility for ADCs.

As disease progresses beyond first-line therapy, survival outcomes increasingly depend on timely access to active salvage treatments. After osimertinib failure, median survival in real-world practice may be reduced to 8-12 months,[8] and treatment intensity frequently declines. Even when second-line or later therapies are delivered, observational cohorts demonstrate diminished tolerability and limited continuity of care.[9] Meanwhile, newer ADCs targeting HER3 or TROP2 can provide clinically meaningful disease control, but their benefit is contingent on patients surviving long enough and remaining fit enough to receive them.[10]

Taken together, emerging evidence suggests that first-line success should be judged not only by PFS gains but also by the capacity to maintain patient eligibility for subsequent therapies. Sequencing in *EGFR-mutated* NSCLC must therefore become proactive rather than reactive. A regimen that delivers strong early responses yet leaves no viable salvage pathway may ultimately compromise overall survival. The central strategic question is no longer "Which first-line option is strongest?" but "Which first-line decision best preserves the viability of subsequent treatments?"

## SEQUENCING ALGORITHM AND CLINICAL IMPLEMENTATION

The therapeutic efficacy of first-line treatment in EGFR-mutated NSCLC depends not only on initial tumor control but also on its ability to preserve a viable strategy at the time of progression. The sequencing algorithm depicted in Fig. 1 is built around long-term navigability: it integrates baseline tumor biology, central nervous system (CNS) involvement, co-mutational risk, and the likelihood of maintaining eligibility for salvage therapy. Clinical deterioration after progression on first-line osimertinib frequently limits access to subsequent targeted options. Real-world analyses indicate that many patients never reach a molecularly guided salvage line because of rapid functional decline or the absence of actionable resistance alterations.[11] This limitation affects overall survival more profoundly than modest differences in initial PFS, making sequencing success heavily dependent on decisions taken at diagnosis.

Within this framework, three broad therapeutic groups require distinct strategies. Patients with exon 19 deletion tumors usually derive durable systemic and intracranial benefit from first-line osimertinib while preserving a therapeutic reserve for later phases.[1,2] Patients with substantial CNS involvement carry a high risk of neurological progression and may benefit from intensified control with platinum-based chemotherapy plus osimertinib to stabilize intracranial disease.[5] By contrast, patients with biologically aggressive tumors such as L858R disease or TP53 co-mutated profiles exhibit faster resistance evolution, supporting early intensification with amivantamab plus lazertinib in selected high-risk settings.[12]

Progression remains the critical inflection point in this algorithm. Resistance to osimertinib is biologically heterogeneous and frequently lacks clearly targetable alterations.[13] Immune checkpoint inhibitors rarely restore durable disease control once EGFR-TKI resistance has emerged, with response rates that are

low and short-lived.[7] Patients who maintain performance status and CNS stability are far more likely to receive HER3- or TROP2-directed antibody-drug conjugates capable of re-establishing disease control.[14,15]

Accordingly, sequencing decisions must actively protect future opportunities. Preservation of performance status, routine molecular testing using plasma and tissue, regular brain imaging, and early symptom-driven interventions are essential to avoid losing access to active therapies. A first-line regimen that delivers impressive early responses but closes off therapeutic pathways at progression may ultimately compromise survival despite apparently superior short-term outcomes. The central question in *EGFR-mutated* NSCLC has therefore shifted from "Which first-line option yields the longest PFS?" to "Which first-line strategy best sustains the continuum of effective care across multiple lines of therapy?"

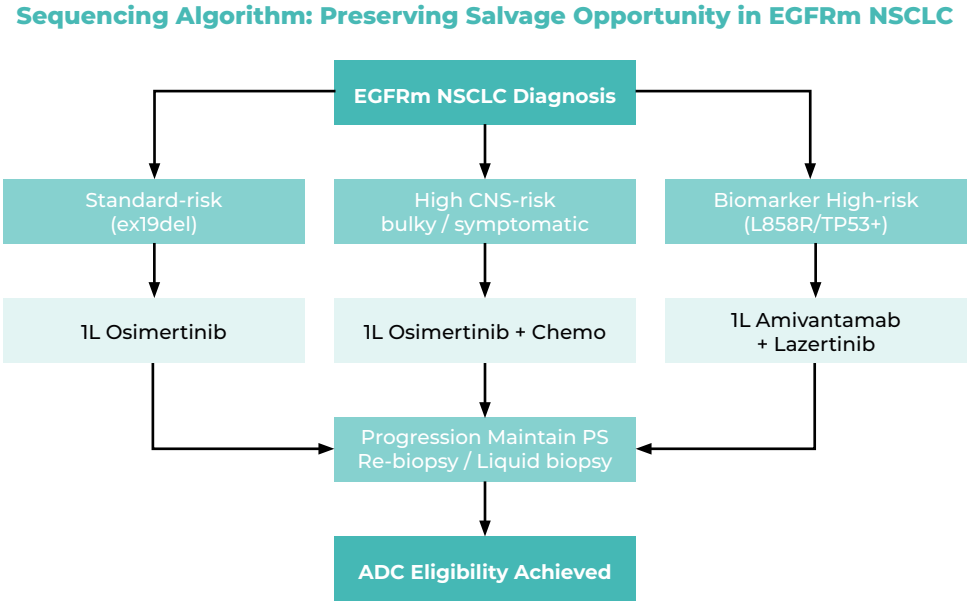


**Figure 1** Risk-adapted first-line strategy in EGFR-mutant NSCLC aiming to secure ADC eligibility at progression.

# ENHANCED & EXTENDED VERSION

Following progression on first-line osimertinib, the therapeutic trajectory becomes notably heterogeneous and is often clinically constrained. Continuation of EGFR blockade with platinum-based chemotherapy remains a prevalent strategy, particularly in patients with central nervous system (CNS) control and preserved performance status. This approach can serve as a temporary bridge to the next active treatment class, although overall survival gains are inconsistent and largely contingent on the timing of intervention and the underlying resistance biology.[16] As depicted in the algorithm structure in Fig. 1, patients who maintain good functional reserve at this stage continue to have multiple salvage opportunities, whereas early functional decline markedly narrows the feasible treatment window.

The acquisition of EGFR T790M remains the most clinically actionable resistance pathway, enabling rechallenge with osimertinib in rare cases where the mutation reappears or was not initially detected.[16] However, this scenario is becoming increasingly uncommon in the era of third-generation TKIs, prompting greater reliance on antibody-based strategies as the disease evolves.[17] This shift reflects a broader transition in the field: resistance is no longer primarily a single-gene event but a network-level adaptation involving MET, HER3, MAPK signaling, cell-state plasticity, and stromal influences.

Once clearly targetable resistance mechanisms are lost,

bispecific monoclonal antibodies such as amivantamab have demonstrated significant antitumor activity by addressing both receptor-specific and bypass resistance pathways.[18] In line with this, treatment paradigms are moving toward dual-axis suppression of ligand-dependent and ligand-independent signaling, with the aim of delaying exhaustion of molecular rescue routes. HER3-directed antibody-drug conjugates, including patritumab deruxtecan, have shown robust responses even in heavily pretreated patients, restoring disease control after multiple prior therapies.[19] Their benefit, however, is strongly dependent on patients maintaining adequate organ function and neurologic stability long enough to reach this therapeutic slot.

TROP2-targeted ADCs are emerging as a rational salvage option for patients without other biologically privileged targets. By leveraging tumor-selective cytotoxic delivery, these agents may re-expand therapeutic possibilities in settings where conventional treatment options are rapidly diminishing.[20] The clinical implication is clear: salvage intent requires survival, and survival at this stage depends as much on supportive measures and timely treatment transitions as on the intrinsic potency of any given drug.

Ultimately, the success of post-osimertinib therapy is determined less by the drug class itself and more by the patient's ability to remain eligible long enough to receive the next effective agent. Preserving clinical stability particularly neurological function and performance status becomes the decisive factor for survival once patients enter post-progression care. As emphasized in Fig. 1, the respiratory and neurologic trajectories between first and second line dictate whether patients actually arrive at the point where high-value agents can be deployed. Modern sequencing success therefore rests on foundational choices made at diagnosis, where each decision must not only address the present disease state but also safeguard access to future life-extending therapies.

## STRATEGIC INTERPRETATION & FUTURE DIRECTIONS

Sequencing success in *EGFR-mutated* NSCLC depends on sustaining both biological control and clinical eligibility across multiple lines of therapy. Progression on EGFR-TKIs is driven by diverse and evolving mechanisms, many of which lack an immediately actionable resistance target.[21] This heterogeneity makes it essential to preserve therapeutic reserve from the time of diagnosis, ensuring that patients survive long enough and remain fit enough to benefit from later-line targeted approaches.

The emergence of potent antibody-drug conjugates (ADCs) and bispecific targeting strategies has expanded salvage opportunities, particularly when progression remains biologically structured and performance status is preserved. TROP2-directed agents, including sacituzumab-based and next-generation ADCs, show activity in post-TKI settings and represent a rapidly maturing therapeutic class.[22] In parallel, amivantamab is gaining broader integration as a bispecific EGFR/MET strategy, not only after exon 20 insertion progression but also increasingly as an option in the post-osimertinib setting.[23] Determining whether dual EGFR targeting should be sequenced before or after chemotherapy has therefore become a central and unresolved clinical question.

Resistance evolution after osimertinib is shaped by competing selection dynamics, including bypass pathway activation, phenotypic transformation, and multigene interactions.[24] These patterns underscore that optimal first-line regimens must preserve the possibility of identifying a druggable escape route later on, rather than suppressing the disease so profoundly that actionable biology has vanished by the time progression is recognized.

Real-world data consistently show that patients who reach later-line therapies particularly HER3- and TROP2-targeting ADCs can regain durable disease control.[25] However, access to these agents declines sharply when clinical deterioration occurs before formal progression assessment or when extensive prior chemotherapy further erodes tolerance.[26] Accordingly, timely imaging, plasma-based molecular tracking, proactive CNS surveillance, and early symptom-guided interventions are not ancillary measures; they are survival-critical components of a sequencing strategy.

Strategic therapy planning must therefore shift from a linear "best first-line drug" mindset to a longitudinal framework in which each decision is evaluated by what it preserves. The overarching goal is to ensure that patients arrive at the next innovation still capable of receiving it. In *EGFR-mutated* NSCLC, the most successful first-line choice is not merely the most potent upfront, but the one that most reliably safeguards the next effective option.

# CONCLUSİON

Recent advancements in targeted and antibody-based therapies have markedly improved the prognosis of patients with EGFR-mutated NSCLC. However, survival outcomes remain suboptimal because a substantial proportion of patients never reach a biologically informed second-line treatment. As discussed in this review, disease progression is not merely a chronological event but a decisive clinical and biological juncture that determines whether patients can access the expanding array of HER3- and TROP2-targeted therapies or are instead relegated to cytotoxic regimens with limited tolerability. Accordingly, the efficacy of first-line therapy should not be judged solely on early tumor-control metrics such as response rate or progression-free survival.

Achieving optimal treatment sequencing requires a paradigm shift toward preserving long-term therapeutic optionality. Maintenance of performance status, routine molecular monitoring through tissue and plasma-based assays, and systematic CNS surveillance are essential to enable the timely detection and characterization of progression. Equally important is the recognition that the biological footprint of first-line regimens extends beyond initial tumor shrinkage: therapies that suppress or eradicate tumor biology so profoundly that no actionable resistance can emerge may unintentionally narrow the landscape of effective salvage options that could otherwise offer meaningful survival gains.

Ultimately, the most effective treatment strategy for EGFR-mutated NSCLC is not defined by the longest initial progression-free interval, but by its capacity to maintain access to future lines of active therapy. As more potent combinations and ADCs move into earlier treatment lines, sequencing strategies must be consciously designed around continuity ensuring that patients remain clinically and biologically eligible for innovative therapies throughout the entire course of their disease.

**Consent for Publication**

Intellectual and clinical content. AHÖ approved the final version and is fully accountable for all aspects of the work.

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