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Journal of Lung, Pulmonary & Respiratory Research

Review Article
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Osimertinib in EGFR-Mutated NSCLC: benefits beyond disease-free survival and overall survival

Volume 12 Issue 2 - 2025

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Received: November 5, 2025 | **Published:** November 18, 2025

Abstract

Osimertinib, a third-generation tyrosine kinase inhibitor (TKI), has transformed the management of EGFR mutated non–small cell lung cancer (NSCLC). Although clinical trials have demonstrated substantial benefits in disease-free survival (DFS) and overall survival (OS), these traditional endpoints do not fully capture the true clinical and functional impact of the treatment. Beyond survival curves, there are meaningful benefits, including neuroprotection, functional preservation, and improved quality of life, that remain invisible to conventional metrics but are crucial to the real-world patient experience. This review synthesizes evidence from phase II and III studies, highlighting the significant reduction in brain metastases, decreased need for neurotoxic interventions, and prolonged time free from functional deterioration. Additionally, it discusses how therapeutic crossover may mask important differences in OS curves, as many patients who receive late access to osimertinib survive but do so with sequelae that those treated earlier are able to avoid. Emerging combination strategies and the potential role of artificial intelligence in personalizing relapse prevention are also explored. Osimertinib should be regarded not only as an effective therapy but as a central pillar of a new therapeutic paradigm focused on endpoints that reflect not only how long patients live, but how well they live.

Keywords: Osimertinib, EGFR-mutated NSCLC, brain metastasis prevention, neuroprotection; quality of life, functional preservation, targeted therapy, crossover effect, artificial intelligence, combination strategies.

Introduction

In epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC), the third- generation tyrosine kinase inhibitor (TKI) osimertinib has revolutionized therapeutic approaches. Clinical trials have demonstrated substantial improvements in conventional metrics such as disease-free survival (DFS) and overall survival (OS) compared to previous treatments.[1,2]

For instance, in the ADAURA study—conducted in the adjuvant setting following surgery— osimertinib reduced the risk of death at five years by approximately 50% compared to placebo (5- year survival: 88% vs. 78%).[3]

However, beyond these quantitative outcomes, it is essential to recognize that the clinical benefits of osimertinib extend to dimensions not always reflected in traditional endpoints.[4]

The following analysis presents six evidence-based arguments supporting the use of osimertinib in patients with EGFR-mutated NSCLC. These address critical aspects including neuroprotection, quality of life, functional preservation, redefinition of clinical benefit criteria, the potential for therapeutic personalization through artificial intelligence, and evolution toward combination strategies.[5-10]

Methodological considerations

This narrative review synthesizes evidence from pivotal phase II and III clinical trials evaluating osimertinib in patients with EGFR-mutated non-small cell lung cancer across early-stage, locally advanced, and metastatic settings. The therapeutic impact described in this article is derived from trial-reported endpoints such as disease-free survival, progression-free survival, overall survival, and CNS metastasis-free survival, as defined in each original study. Diagnostic assessment of tumor burden and relapse was based on standard imaging (contrast-enhanced CT and/or brain MRI) and RECIST v1.1 criteria for response and progression, while staging followed the 8th edition TNM classification. Functional status was evaluated using the Eastern Cooperative Oncology Group (ECOG) performance status scale, and patient-reported outcomes were captured through validated instruments, including SF-36 and quality-adjusted measures such as QALY and Q-TWiST where available. By relying on these widely accepted diagnostic and prognostic systems, the review aims to provide a consistent framework for interpreting the clinical and functional benefits of osimertinib across the different disease stages and therapeutic contexts discussed.[11-17]

Neuroprotection: prevention of brain metastases

One of osimertinib's most distinctive advantages is its potent neuroprotective effect, attributed to its ability to cross the blood-brain barrier and act effectively within the central nervous system (CNS). This CNS efficacy is not incidental but represents a deliberate aspect of its preclinical design, which demonstrated high brain penetration and sustained intracranial activity.[16,18]

Patients with EGFR-mutated NSCLC present a considerably higher risk of developing brain metastases, with a three-year cumulative incidence ranging from 29% to 60%, compared to 22% to 28% in those with wild-type EGFR.[5] While first-generation EGFR-TKIs showed limited CNS penetration,[5] osimertinib was specifically designed to achieve high cerebral exposure and has demonstrated substantial reduction of this risk.

As shown in Figure 1, the cumulative incidence of brain metastases at 3 years is substantially lower in patients treated with osimertinib compared with earlier-generation TKIs, reinforcing its CNS- protective effect.

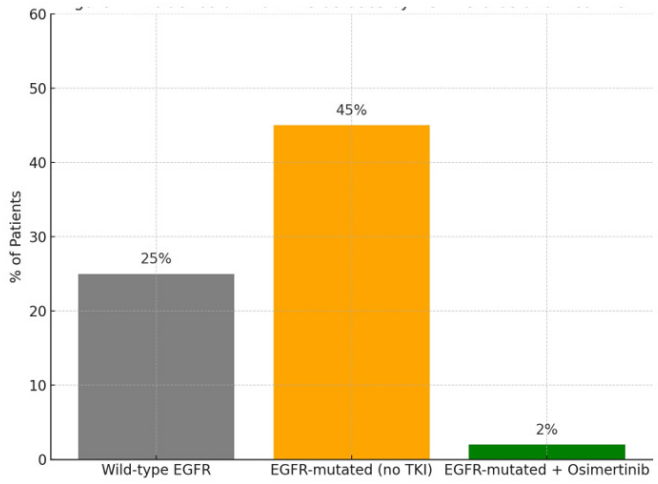

Figure 1 Estimated cumulative incidence of brain metastases at 3 years according to EGFR mutational status and treatment received.

In the FLAURA study—conducted in the metastatic setting as first-line treatment—Osimertinib reduced CNS progression rates by 52% compared to gefitinib or erlotinib (CNS event incidence: 6% vs. 15%),[1] suggesting significant preventive effects against new brain metastases. Similarly, in the ADAURA trial—in the adjuvant setting—only 1% to 2% of patients treated with osimertinib experienced CNS recurrence, compared to 10-11% in the placebo group.[3,7] This difference translated to an 82% relative reduction in the risk of brain metastases or death attributable to adjuvant treatment.[3]

This benefit was also consistent in the LAURA study, involving patients with locally advanced disease (unresectable stage III), where osimertinib reduced brain metastasis incidence (8% vs. 23%) and decreased the risk of CNS progression or death by 76% compared to placebo.[2]

This benefit carries significant clinical implications by reducing the need for treatments such as brain radiotherapy, which entail neurocognitive deterioration and quality of life impairment.[17,18] Consequently, osimertinib is currently the treatment of choice in international guidelines for patients with EGFR-mutated NSCLC at risk of or presenting with brain metastases.[1,28]

Given that the CNS is a frequent sanctuary site for relapse in EGFR+ NSCLC and that brain metastases carry high morbidity,[6] osimertinib's ability to prevent brain dissemination offers tangible clinical benefit: fewer patients develop neurological symptoms, seizures, or require brain radiotherapy due to this proactive neuroprotection.

Quality of life improvement and symptom control

Beyond prolonging life, osimertinib significantly improves the quality of that survival by offering a well-tolerated targeted therapy capable of alleviating symptoms and avoiding frequent toxicities associated with other options. Unlike cytotoxic chemotherapy, this oral TKI allows many patients to continue their daily activities without significant interruptions.

Even compared to first-generation EGFR inhibitors, osimertinib presents lower off-target toxicity, with reduced rates of severe skin reactions and diarrhea relative to gefitinib or erlotinib,[1] translating to a more comfortable therapeutic experience for patients.

In the FLAURA study, patients treated first-line with osimertinib maintained global quality of life at least equivalent to that observed with standard TKIs, without deterioration in health scores.[1] Moreover, clinically significant improvement in respiratory symptoms such as cough and chest pain was recorded from the first week of treatment and sustained for more than nine months.[1] These benefits were achieved while osimertinib doubled the median progression-free survival, reinforcing that efficacy and quality of life are not mutually exclusive but complementary objectives.

In the adjuvant setting, a phase III trial confirmed that self-reported global health is maintained during osimertinib treatment: after up to 96 weeks of therapy, physical and mental scores on the SF-36 questionnaire remained stable and without clinically relevant differences compared to placebo.[7] This supports that even three years of adjuvant treatment do not compromise patient wellbeing—a key finding when evaluating prolonged treatment strategies.

In summary, osimertinib's favorable tolerability profile—with fewer grade ≥3 adverse events than previous TKIs (1)—combined with its sustained capacity to control tumor symptoms, translates to superior quality of life: patients not only live longer but feel better, with fewer interruptions due to toxicity or progression.

This superior tolerability profile is illustrated in Figure 2, where osimertinib demonstrates fewer clinically meaningful adverse events and improved symptomatic control compared with first- generation EGFR-TKIs.

Preservation of neurological function and functional status

Prevention of brain metastases with osimertinib not only improves statistics but preserves neurological integrity and patient autonomy—functional impacts of enormous clinical value. Development of intracranial metastases frequently entails relevant neurological deficits—such as motor alterations, cognitive deterioration, or seizures—and necessitates aggressive local treatments (neurosurgery, brain radiotherapy) that often further deteriorate brain function.

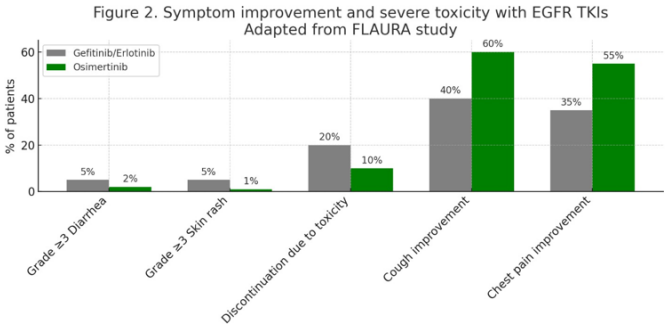

Figure 2 Comparison of toxicity profile and symptomatic control between osimertinib and first- generation TKIs.

Multiple studies have documented that CNS metastases cause significant deterioration in cognitive function and quality of life.[6] Furthermore, interventions like whole brain radiotherapy (WBRT) can amplify this damage: in a randomized trial, adding WBRT after radiosurgery caused cognitive deterioration in 92% of patients at 3 months, compared to 64% in the group without WBRT, without survival benefit and with marked negative impact on quality of life.[17,18] Preventing patients from reaching this situation is crucial.

By keeping the brain free of metastases, osimertinib reduces the need for WBRT and other neurotoxic therapies, protecting long-term cognitive function. For example, in ADAURA, only 1% of patients treated with osimertinib required intervention for brain metastases, compared to ~10% in the placebo group.[3] This implies that the vast majority of patients on

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osimertinib remained without neurological symptoms or exposure to potentially neurotoxic treatments.

Consequently, these patients preserve their general functional status (ECOG 0-1) for longer periods, without the deterioration associated with CNS progression. This effect is also reflected in prolonged time to requiring subsequent therapies: in the FLAURA study, patients on osimertinib took almost twice as long to need a new line of treatment compared to gefitinib/erlotinib (25.9 vs. 13.4 months),[1] suggesting a more extended period of active life without clinically disabling relapses.

This functional impact is not theoretical. In a recent prospective study, at three months from brain metastases diagnosis, 45% of patients presented clinically significant deterioration of their functional independence, measured by the Barthel index. Additionally, they reported marked increases in fatigue, motor dysfunction, somnolence, and pain, along with abrupt deterioration in multiple quality of life domains (physical, emotional, and social functions). Most notably, this functional decline did not correlate closely with survival, reinforcing the limitations of OS as the sole criterion for clinical evaluation.[6]

This phenomenon was clearly illustrated in the LAURA study. While median DFS was more than three times superior with osimertinib compared to placebo (39.1 vs. 5.6 months), overall survival had not yet shown statistically significant differences at the time of analysis.[2] This might lead one to think that initiating osimertinib at relapse would provide the same benefit as starting it from the beginning. However, 84% of patients in the placebo arm who progressed were rescued with osimertinib, and even so, many debuted with CNS progression.

This raises a critical warning: relying on subsequent "rescue" may mean losing irreversible functional opportunities. Although OS curves may appear similar, patients who relapse with brain metastases, functional deterioration, or neurological symptoms have not lived equally. They have lived with more sequelae, more interventions, more symptoms, and less autonomy. The quality of time lived matters as much as its duration. Therefore, the decision to administer osimertinib from early stages not only aims to prolong life but to preserve it in its fullest and most functional form, without ceding ground to neurological deterioration that may be preventable.

Osimertinib markedly improved progression-free survival and reduced early CNS relapse compared with placebo, while overall survival at 36 months remained similar between groups at the time of analysis. Importantly, many of the patients represented in the placebo arm's OS curve have experienced CNS relapse and may be living with neurological morbidity that remains invisible to conventional survival endpoints.

Novel clinical benefit metrics: beyond DFS and OS

The impact of osimertinib in patients with EGFR-mutated NSCLC exceeds what conventional metrics such as progression-free survival (PFS) or overall survival (OS) reflect. In the ADAURA, LAURA, and FLAURA studies, the benefit in PFS was substantially superior to that observed in OS, with curves separating early and markedly (HR 0.16 to 0.46), while OS curves tend to converge (HR 0.49 to 0.81).[1–3] This phenomenon is explained, in part, by extensive use of osimertinib in subsequent lines, prolonged post-progression survival, and the dilutive effect of sequential treatments.

As depicted in Figure 3, progression-free survival and CNS relapse differ markedly between treatment arms, even though overall survival appears similar at the time of analysis. This apparent convergence in OS is largely influenced by the high rate of crossover in the placebo arm—with 81% of patients who experienced BICR-confirmed progression subsequently receiving osimertinib—which dilutes the observable survival difference. Many of these patients, despite remaining alive within the OS curve, have already developed CNS progression and may be living with neurological sequelae and treatment-related burden that conventional survival endpoints fail to capture. In contrast, osimertinib provides prolonged symptom-free intervals, lower CNS morbidity, and a qualitatively superior trajectory of lived experience.

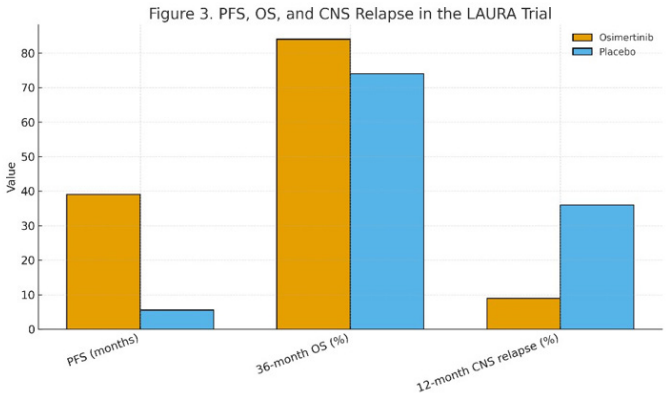

Figure 3 PFS, Overall Survival, and CNS Relapse in the LAURA Trial.

As analyzed in the previous section, this "statistical paradox" may conceal significant clinical realities. The LAURA study offers an eloquent example: although no statistically significant differences in OS were observed at the time of analysis, 84% of patients in the placebo arm were rescued with osimertinib and, even so, many debuted with CNS progression.[2] That is, they lived a similar time but with clearly inferior functional prognosis. A single brain relapse can trigger a cascade of adverse events—seizures, cognitive deterioration, loss of autonomy—that are rarely reflected in OS curves but profoundly impact quality of life and eligibility for future therapies.

For these reasons, it becomes necessary to expand how we measure clinical benefit. Trials like ADAURA already incorporated composite endpoints such as CNS metastasis-free survival, which showed an 82% reduction in the risk of brain recurrence or death with osimertinib (HR 0.18).[3] This metric directly reflects time lived without brain lesions—a more tangible parameter for patients and physicians than global DFS.

Additionally, indicators such as Quality-Adjusted Life Years (QALY) or Quality-adjusted Time Without Symptoms or Toxicity (Q-TWiST) integrate quantity and quality of life into a single value. Given osimertinib's low toxicity profile and sustained efficacy, it is expected to provide superior Q- TWiST compared to chemotherapy or other TKIs.[8] Indeed, the importance of formally evaluating this quality-adjusted time in patients treated with osimertinib has been emphasized.[8]

Finally, other metrics such as functional deterioration-free survival or time to symptomatic progression could help better capture the clinical impact of avoiding disabling relapses. Using these new patient-centered measures—functional preservation, locoregional and metastatic control, and sustained quality of life—osimertinib's advantage becomes even more evident: it not only prolongs life but extends the time of useful, full, and disease-free meaningful life.[19]

Personalized prevention through artificial intelligence

Finally, osimertinib use is enhanced when integrated with modern artificial intelligence (AI) tools that enable personalized prevention of relapses according to each patient's individual risk. AI, through machine

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learning algorithms and analysis of clinical/radiological big data, can identify subtle patterns associated with higher probability of brain metastases or relapse in certain locations.

Recent studies have developed machine learning models capable of predicting brain metastasis risk in NSCLC patients based on their clinical characteristics and initial imaging.[20,21] These tools achieved classification of high-risk patients for developing CNS metastases with ~70% sensitivity, distinguishing, for example, that patients with EGFR+ adenocarcinoma and certain factors (female sex, lymphatic invasion, etc.) have greater propensity to metastasize to the brain.[22-25]

How does this translate to benefit? First, it enables proactive surveillance: patients identified as high-risk can undergo closer neuroradiological follow-ups (e.g., periodic MRI), detecting very early subclinical metastases for timely treatment. Moreover, in the near future, these models could help select who benefits most from preventive strategies like adjuvant osimertinib, considering that resistance patterns and efficacy vary significantly according to EGFR mutation subtype and TKI generation used.[26]

For example, in resected early stages, the presence of certain molecular signals (persistent positive circulating tumor DNA, according to another genomic AI tool) or high-risk characteristics could guide intensification or prolongation of osimertinib treatment in those who need it most, personalizing optimal adjuvant therapy duration.

Additionally, AI in imaging (radiomics) is already being investigated to predict intracranial response to osimertinib in patients with brain metastases, which could early indicate whether local therapy should be escalated.[24]

In summary, integration of intelligent algorithms allows taking osimertinib efficacy to the next level: personalized prevention, where each EGFR-mutated patient receives appropriate preventive treatment for the necessary time, avoiding both overtreatment in low-risk cases and catastrophic relapses in high-risk cases. This synergy between osimertinib and AI promises to maximize individual clinical benefit, ensuring the right patient receives the right therapy at the right time.[25]

Evolution toward combination strategies: the future of targeted therapy

The therapeutic paradigm in EGFR-mutated NSCLC is rapidly evolving from Osimertinib monotherapy toward combination strategies that promise to amplify the previously described benefits. This transition seeks not only to improve traditional efficacy metrics but to enhance the qualitative aspects of survival we have analyzed: neuroprotection, functional preservation, and sustained quality of life.[27]

Osimertinib plus chemotherapy: redefining the first-line standard

The FLAURA2 study marked a milestone by demonstrating that the combination of osimertinib with platinum/pemetrexed followed by maintenance with osimertinib/pemetrexed significantly outperformed osimertinib monotherapy in patients with advanced EGFR-mutated NSCLC. Overall survival results showed an HR of 0.75 (95% CI 0.57-0.97), with median OS not yet reached in the combination arm versus 36.7 months with monotherapy.[4] Beyond these numbers, the combination maintained osimertinib's favorable safety profile, preserving the quality of life that characterizes this targeted therapy, while the significant prolongation of progression-free survival (median >2years regardless of pemetrexed maintenance duration) suggests more extended periods of active and functional life.[28]

Addressing specific resistance mechanisms

Resistance to osimertinib, inevitable in most patients, has driven the development of combinations targeting specific molecular mechanisms. The SAVANNAH trial explored the combination of osimertinib with savolitinib (MET inhibitor) in patients with MET overexpression and/or amplification after progression on first-line osimertinib. Results showed an objective response rate of 56% with a median progression-free survival of 7.4 months, offering an effective therapeutic option that allows patients to remain on targeted treatment, avoiding premature transition to cytotoxic chemotherapy with its implications for functional deterioration and quality of life.[29]

In parallel, the ORCHARD study evaluated the combination of osimertinib with datopotamab deruxtecan (Dato-DXd), a TROP2-directed antibody-drug conjugate, after progression on osimertinib. The combination demonstrated response rates of 36-43% depending on dose, with a median progression-free survival of 11.7 months for the 6 mg/kg dose, significantly extending time free from symptomatic progression compared to traditional salvage options.[30]

The era of upfront combinations: amivantamab plus Lazertinib The recent approval of amivantamab plus lazertinib as a first-line option in the NCCN 2025 guidelines represents another paradigmatic advance. This combination of bispecific antibody (EGFR/MET) plus third-generation TKI offers a preventive strategy against multiple resistance mechanisms from treatment initiation. Results from the MARIPOSA trial in patients with advanced EGFR-mutated NSCLC show significant improvements in progression-free survival compared to osimertinib alone, suggesting that this approach not only improves efficacy but could reduce the incidence of specific resistance patterns, potentially prolonging progression-free periods and maintaining patients in optimal functional status for longer.[31]

Implications for future therapeutic sequences

These developments raise fundamental questions about optimal treatment sequencing: should osimertinib be used as a "backbone" in upfront combinations or should combinations be reserved for later lines? The answer likely lies in personalization based on specific biomarkers and individual risk profiles. The artificial intelligence algorithms we mentioned previously become particularly relevant here, as they could identify which patients benefit most from intensive strategies from the outset versus sequential approaches, optimizing not only survival but the quality of time lived.

Preserving qualitative benefits in the combination era

It is crucial that, in the pursuit of greater efficacy, new combination strategies maintain the qualitative benefits that distinguish osimertinib: neuroprotection, functional preservation, and sustained quality of life. Preliminary data suggest that well-tolerated combinations achieve this balance, extending periods of active life without significantly compromising patient wellbeing. However, it will be fundamental that future trials systematically incorporate patient-centered endpoints—time free from functional deterioration, cognitive preservation, quality-adjusted life—to comprehensively evaluate the benefit of these more complex strategies.

The paradox of traditional endpoints in the combination era

However, it is paradoxical that despite these revolutionary therapeutic advances, clinical benefit assessment remains anchored in traditional metrics of progression-free survival and overall survival. The

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FLAURA2, SAVANNAH, and ORCHARD trials continue to prioritize these endpoints, relegating to secondary or exploratory analyses the dimensions that truly matter in patients' daily lives: time free from disabling neurological symptoms, preservation of cognitive autonomy, or ability to maintain family and work roles.[4,29-30] This disconnect between the sophistication of our therapies and the simplicity of our evaluation metrics represents a missed opportunity to capture the true value of these combinations.

While we develop increasingly complex strategies to combat molecular resistance, we maintain a surprisingly reductionist view of clinical benefit. The "hidden endpoints" we have explored in this analysis—proactive neuroprotection, functional preservation, sustained quality of life—should be systematically incorporated into the design of these combination trials, recognizing that therapeutic success in a chronic disease like EGFR-mutated NSCLC is measured not solely in months of survival, but in the quality and fullness of life preserved during those months. The future challenge lies in evolving our evaluation criteria at the same pace that our therapies evolve.

The future of EGFR-mutated NSCLC is shaping toward a personalized therapeutic ecosystem where osimertinib, as a cornerstone, is strategically combined with other agents according to individual molecular and clinical profiles, maximizing not only life duration but its quality and fullness.

Conclusions

Osimertinib has emerged as a transformative treatment in EGFR-mutated NSCLC, not only for prolonging DFS and OS, but for protecting critical organs, keeping patients free from disabling metastases, and preserving their quality of life and daily function. Current evidence convincingly demonstrates that a patient receiving osimertinib is, on average, living longer and better than with previous alternatives: remaining without recurrence (especially without brain metastases) for longer periods, avoiding in many cases aggressive treatments like WBRT with their cognitive sequelae, better controlling respiratory and systemic symptoms, and not suffering greater detriment in wellbeing during treatment.

The evolution toward combination strategies further amplifies these benefits. Whether combined upfront with chemotherapy, or sequentially with targeted agents like savolitinib or antibody-drug conjugates like datopotamab deruxtecan, osimertinib serves as the cornerstone of an evolving therapeutic ecosystem that promises not just incremental survival gains, but sustained preservation of the qualitative aspects that define meaningful survival.

Furthermore, the scientific community is recognizing these benefits through new clinical parameters more centered on the patient (such as brain metastasis-free time, QALY, and Q-TWiST), which help quantify what matters in the patient's daily life and not just in population statistics.

Looking toward the future, incorporation of artificial intelligence and precision medicine augurs that we will be able to further optimize osimertinib use, selecting those who benefit most from specific combinations and anticipating relapse.

All the above reinforces the central message: patients truly benefit from receiving osimertinib. In practical terms for the specialist, this means that by offering osimertinib—whether as monotherapy or as the backbone of combination strategies—we are not only offering additional months of life, but additional years of active, productive life free from significant disease, definitively changing the natural history of EGFR-mutated NSCLC in the patient's favor.

Ultimately, this analysis invites us to transcend traditional evaluation based solely on progression- free survival and overall survival. The paradox highlighted by the combination era—where therapeutic sophistication outpaces our evaluation metrics—underscores the urgent need to develop a more comprehensive perspective that recognizes and values the "hidden endpoints" that truly matter to our patients: preservation of cognitive autonomy, the ability to maintain family and work roles, time lived without disabling neurological symptoms, and the possibility of aging with dignity without premature deterioration associated with brain metastases or severe toxicities.

Importantly, the apparent similarity in overall survival in ADAURA must be interpreted in the context of an exceptionally high crossover rate in the placebo arm—where 81% of patients with BICR-confirmed progression ultimately received osimertinib. This markedly dilutes observable survival differences and conceals a clinically meaningful reality: many of these patients, although alive in OS curves, had already developed CNS progression and may now be living with neurological sequelae and a substantial long-term treatment burden not captured by conventional survival endpoints. This observation not only reframes how OS should be interpreted, but also generates a key hypothesis: that early, uninterrupted access to osimertinib may prevent not merely death, but years lived with irreversible CNS morbidity—an outcome of profound clinical and human significance.

In the context of EGFR-mutated NSCLC, where many patients will live with their disease for years as a manageable chronic condition, these qualitative aspects of survival acquire clinical relevance comparable—and sometimes superior—to traditional quantitative metrics. The future challenge lies not only in developing more effective combinations but in systematically incorporating these "invisible" but fundamental dimensions into our decision-making and trial design, recognizing that true therapeutic success is measured not only in months gained, but in the quality and fullness of life preserved.

Acknowledgments

The authors acknowledge the use of Claude 4 artificial intelligence for syntax optimization and idiomatic language support in preparing this manuscript for publication.

Conflict of interest

The author states that he has no conflict of interest.

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Citation: Casarini I, Cantón ED. Osimertinib in EGFR-Mutated NSCLC: benefits beyond disease-free survival and overall survival. *J Lung Pulm Respir Res*. 2025;12(2):42–47. DOI: 10.15406/jlprr.2025.12.00332