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First-Line Treatment Strategies in NSCLC—Where Evidence Meets Patient Needs

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Executive Summary

The current standard of care for first-line treatment of EGFR-mutated, advanced NSCLC is osimertinib, a third-generation tyrosine kinase inhibitor (TKI) that has demonstrated superior efficacy over first-generation EGFR TKIs. Despite its benefits, challenges with osimertinib remain; particularly the emergence of resistance. This has driven the development and approval of novel combination regimens that offer increased effectiveness over osimertinib monotherapy but also present increased toxicity. These new options complicate clinical decision-making, as clinicians must evaluate an expanding body of data and multiple treatment choices to determine the best approach for each patient. In this evolving landscape, decisions that incorporate the latest clinical evidence alongside patient goals and preferences are more essential than ever. To deliver optimal, personalized treatment, clinicians need to stay updated on emerging data and consider both tumor-related and patient-specific factors.

A discussion-based educational format can help bridge gaps in care for EGFR-mutated, locally advanced, or metastatic NSCLC by encouraging clinicians to critically evaluate treatment options and approaches. This format fosters a deeper understanding of complex cases and the impact of treatment decisions on patients' lives, leading to more informed and personalized decision-making.

ALIGNMENT TABLE: SUMMARY OF NEEDS, GAPS, DATA, AND INTENDED OUTCOMES

Gap 1: As emerging data challenges the current standard of care, clinicians may lack the necessary tools and knowledge to effectively differentiate and evaluate first-line treatment options for EGFR-mutated, locally-advanced or metastatic NSCLC, making it difficult to develop personalized treatment plans that align with each patient's unique clinical profile.	
Educational Need	For effective treatment personalization and sequencing, clinicians require education on integrating up-to-date data from approved first-line treatments for EGFR-mutated, locally-advanced or metastatic NSCLC, enabling them to apply treatment strategies tailored to each patient's unique needs.
Learning Objective(s) (As a result of participation in this activity, learners will be able to:)	COMPARE available first-line treatment options for EGFR-mutated, locally-advanced or metastatic NSCLC based on the most recent clinical data and patient's unique characteristics.
Desired Outcomes (Learners will demonstrate:)	(Level 4: Competence) • Competence in applying evidence-based strategies to develop personalized treatment plans for EGFR-mutated, locally-advanced or metastatic NSCLC, ensuring individualized decision-making.
Gap #2: As new therapies emerge and challenge the current standard, clinicians may lack the necessary tools and strategies to effectively individualize treatment decision and utilize shared decision making with their patients regarding the evolving first-line treatment options for EGFR-mutated NSCLC, leading to treatment decisions that might not align with patient-specific goals.	
Educational Need	For proper shared decision-making, clinicians need strategies to effectively assess and discuss patient preferences and treatment outcomes, ensuring that first-line treatment decisions for EGFR-mutated, locally-advanced or metastatic NSCLC combine the most up-to-date clinical data, as well as patients goals.
Learning Objective(s) (As a result of participation in this activity, learners will be able to:)	APPLY appropriate strategies for engaging patients with EGFR-mutated locally-advanced or metastatic NSCLC in shared decision-making to align first-line treatment choices with their specific goals and preferences.

Desired Outcomes (Learners will demonstrate:)	Level 4: Competence • Competence in applying strategies for assessing patient preferences and facilitating shared decision-making when considering first-line treatment for EGFR-mutated, locally-advanced or metastatic NSCLC.

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Narrative

Introduction:

Around a third of non-small cell lung cancer (NSCLC) patients have sensitizing mutations in the epidermal growth factor receptor (EGFR).[1] Treating EGFR-mutated NSCLC is challenging because patients often develop resistance to targeted therapies and respond poorly to treatments like immunotherapy, which are effective for other NSCLC types.[2,3] This underscores the need for a personalized approach to treatment.

The treatment landscape advanced with the approval of EGFR-targeted therapies, particularly tyrosine kinase inhibitors (TKIs).[3,4] For locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitutions, the first-line standard is osimertinib, a third-generation TKI approved in 2018 based on the phase 3 FLAURA trial results.[2,5]

Despite its superior survival rates, challenges remain with osimertinib treatment, primarily the emergence of resistance and the limited efficacy of subsequent therapies due to heterogeneous resistance mechanisms.[7,8] These shortcomings have driven the development of combination regimens aimed at preventing the emergence of resistance.[9]

In the past year, the FDA approved two combination therapies for the first-line treatment of adults with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations.[10,11] These combinations are also listed as additional options in the NCCN guidelines, Version 11.2024 beside osimertinib monotherapy, which is the preferred treatment.[2]

- Osimertinib in combination with platinum-based chemotherapy was approved on February 16, 2024 based on the results of the phase 3 FLAURA 2 trial.[10] The trial demonstrated a statistically significant improvement in median PFS for the combination when compared to osimertinib alone (25.5 vs 16.7 months).[10,12] Although the OS results are still immature, no trend toward OS detriment has been observed, with further analysis ongoing.[12]
- Amivantamab in combination with lazertinib was approved on August 19, 2024 based on the results of the phase 3 MARIPOSA trial.[11] The trial demonstrated a statistically significant improvement in PFS for the combination when compared to osimertinib alone (23.7 vs 16.6).[13,14] While the OS results are still immature, the trial showed a favorable and improving trend in OS for amivantamab-lazertinib after approximately 3 years follow up.[15]

While the recently approved combinations have shown benefits in PFS, clinicians highlight the importance of seeing these improved outcomes translated to a prolonged OS.[8,16,17] These consideration is especially relevant given that the combinations are associated with increased toxicity.[8,17] The combination of amivantamab and lazertinib was associated with a higher risk of venous thromboembolic events and infusion-related reactions.[13,14] The combination of osimertinib with platinum-based chemotherapy was associated with higher incidence of hematologic toxicities when compared to osimertinib monotherapy.[12] Additionally, the combination regimens require intravenous administration, which is less practical and can be a barrier to treatment.

"We've been reluctant to automatically embrace these new approaches in the absence of OS benefit, and that has not been reported yet, although there are hints that it might be

there. So far, we are seeing PFS benefit, response rate benefit, and some CNS benefit, but at the cost of heightened toxicity and tremendous inconvenience."

Corey J. Langer, MD
Director, Thoracic Oncology
Professor of Medicine (Hematology-Oncology)
Hospital of the University of Pennsylvania

Clinicians need to carefully consider which patients might gain the most from up-front combination therapies, as opposed to starting with osimertinib monotherapy and optimizing treatment sequencing over time. They must also determine how to integrate this evolving body of data into treatment plans that align with each patient's individual goals.

Gap 1: As emerging data challenge the current standard of care, clinicians may lack the necessary tools and knowledge to effectively differentiate and evaluate first-line treatment options for EGFR-mutated, locally-advanced or metastatic NSCLC, making it difficult to develop personalized treatment plans that align with each patient's unique clinical profile.

To select the most appropriate front-line treatment, clinicians must consider a range of disease-related, molecular, and patient-centered factors.[8] Staying current with emerging data and new approvals is equally essential, as these developments can shift the balance of treatment options and influence clinical decision-making and patient preferences.[8,17]

When evaluating emerging data that may influence first-line treatment decisions for EGFR-mutated, locally advanced, or metastatic NSCLC, several considerations emerge:

- Updated outcomes: If the benefits in PFS observed in the FLAURA 2 and MARIPOSA trials translate into improvements in OS, clinicians may be more inclined to adopt these combination therapies.[8,17]
- The impact on quality of life: The extent to which side effects affect patients' daily lives can significantly influence therapy selection, particularly as real-world patients often experience more intense and frequent side effects than those reported in clinical trials.[18,19] As patient advocate Jill Feldman said ***"Nowhere in the real world are patients hand-picked, closely monitored, or so well cared for as they are in clinical trials."***[19]
- Mode of administration: Currently, both chemotherapy and amivantamab require intravenous administration. However, amivantamab may receive approval for subcutaneous administration in the coming months. Findings from the PALOMA-3 trial indicated that subcutaneous amivantamab was non-inferior to intravenous administration, with an associated increase in overall survival (65% of patients alive at 12 months in the subcutaneous group compared to 51% in the intravenous group) and fewer infusion-related reactions and venous thromboembolic events.[20,21] Additionally, injection time was significantly reduced from 5 hours for intravenous administration to under 5 minutes for the subcutaneous option. According to Dr Corey Langer, the Director of Thoracic Oncology and Professor of Medicine at PennMedicine, the subcutaneous presentation might "***make amivantamab a lot more attractive to give … it might be only a matter of time until we convert all intravenous amivantamab to subcutaneous.***"[17]

The current changes in the landscape of EGFR-mutated, locally-advanced, or metastatic NSCLC underscore the need for clinicians to stay up-to-date on the latest evidence for first-line treatment and to integrate this data into decision-making. However, this is not always the case. An observational study reported that 29.2% of patients who received timely biomarker test results did not receive the appropriate targeted therapy recommended based on those results.[22] The authors speculated that factors such as outdated clinical information and lagging awareness of targeted treatment options may have contributed to this practice gap.

Educational activities targeted at addressing this gap could improve decision-making practices across the multidisciplinary lung cancer care team, leading to better patient outcomes. Published data form and educational activity on advanced NSCLC showed that clinician knowledge of patient selection and management strategies increased from 34% at baseline to 86% after taking part in the activity, with 88% of participants indicating they would apply this knowledge in clinical practice to enhance patient care.[22]

Gap #2: As new therapies emerge and challenge the current standard, clinicians may lack the necessary tools and strategies to effectively individualize treatment decision and utilize shared decision making with their patients regarding the evolving first-line treatment options for EGFR-mutated NSCLC, leading to treatment decisions that might not align with patient-specific goals.

Shared-decision making (SDM) is a patient-centered process in which healthcare providers engage patients and caregivers in discussions about the diagnosis, prognosis, and available treatments, leading to decisions that balance patient preferences, values, and individual circumstances with clinical expertise.[23] Different studies support the need for increasing SDM to align treatment decisions with patient values and preferences, especially when multiple treatment options with no clear preference are available.[24,25] This highlights the importance of incorporating SDM conversations and tools to the first-line treatment for EGFR-mutated, locally advanced or metastatic NSCLC space as new approvals challenge the current standard of care.[8]

Even though clinicians acknowledge the value of SDM, they also report various barriers to its implementation.[26,27] Qualitative studies assessing the perception of SDM among clinicians report barriers that span from time constraints and limited resources to complexity in patient communication and challenges in balancing patient autonomy with clinical guidelines.[23,26,27]

This last challenge can be particularly significant if clinicians approach the SDM process with implicit bias, viewing SDM as a potential risk when patients' choices conflict with clinical guidelines or recommendations.[27] While it is crucial for patients to receive evidence-based treatment, it is equally important to recognize that only patients can fully understand the personal implications that a given treatment may have on their lives.[8,19]

“Our lives are complicated, and what survival means is unique to each patient. […] The context in which people live must be considered." […] Tolerable is relative. Intolerable is more than side effects, it's about functioning and being able to do what you enjoy doing. […] Quality of life is also unique to each patient. A young parent may be willing to tolerate severe long-term side effects to spend as much time with their young children as possible, whereas someone who plays the piano and gardens wants to make sure treatment won't affect their ability to do those activities."[19]

Jill Feldman

Patient advocate
Stage 4, EGFR-positive lung cancer survivor since 2009
Co-founder of EGFR Resisters

Additionally, some clinicians may have a limited view of SDM, perceiving it as merely presenting options and answering questions, rather than as a collaborative process where both parties acknowledge and respect each other's role and expertise.[23]

"We (patient and caregiver) would be presented with the information from the provider. He allowed us to ask questions. And, the questions weren't necessarily answered with the information that we needed to feel like we were empowered".[23]

Anonymous late-stage NSCLC patient.

Educational activities that equip clinicians treating EGFR-mutated, locally advanced, or metastatic NSCLC with the skills and tools for SDM may help them tailor treatment plans that align with patient preferences and provide optimal clinical benefits. Studies on the impact of SDM education at the undergraduate level report positive impacts on provider skills, confidence, and attitudes.[28,29] Additionally, a CME/CE and quality improvement initiative at community hospitals led to a 22.2% increase in appropriate targeted therapy for NSCLC patients (from 77.8% to 100%) and found that 46% of clinicians intended to improve communication and care coordination, directly supporting SDM in practice.[25]

Conclusions:

Patients with EGFR-mutated, locally advanced, or metastatic NSCLC now have multiple first-line treatment options. While this expands choices, it also complicates decision-making, as clinicians must evaluate each option's efficacy, safety, and alignment with patient preferences amidst rapidly emerging data. In this context, educational activities that keep clinicians current with the latest clinical data, support the assessment of various treatment factors, and enhance their ability to engage patients in SDM are crucial. These resources help ensure that treatment decisions integrate clinical evidence and patient-specific goals for optimal outcomes.

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