



CHALLENGING CASES

Lung Cancer: EGFRm NSCLC

Prepared by: Cornerstone Specialty Network

Challenging Cases conducted: July 28, August 14, September 30, October 1, October 3, 2025

Participating Practices

Challenging Cases in...

Lung Cancer: EGFRm

**Program conducted:
July–October 2025**

Note: Aggregated results and high-level summary based on 4 practices and 1 live leadership exchange meeting (at least 25 HCPs) and do not necessarily reflect the views and opinions of the moderator or Cornerstone Specialty Network unless otherwise stated. Clinical data, NCCN Guidelines, and FDA approvals current at time of presentation.

- Utah Cancer Specialist (n=6) July 28, 2025
- Cancer Center of Kansas (n=6) August 14, 2025
- Singing River Cancer Center (n=5) September 30, 2025
- Northwestern Medicine (n=8) October 1, 2025
- Live Leadership Exchange Chicago October 3, 2025

Overall Program Impact and Future Considerations

Osimertinib remains the preferred 1L approach for EGFR-mutated NSCLC, with amivantamab-based combinations utilized after progression and repeat NGS guiding resistance-driven sequencing, though toxicity management and post-amivantamab strategy remain key real-world challenges

- Osimertinib (alone or with chemotherapy) is preferred in front-line EGFR-mutated NSCLC due to efficacy, tolerability, and CNS coverage; combination approaches are selectively reserved for higher disease burden
- Amivantamab-based regimens (commonly with carboplatin/pemetrexed) are the predominant choice following progression on osimertinib
- Repeat NGS and liquid biopsy on progression are widely utilized to characterize resistance and support clinical trial eligibility, despite sensitivity limitations and occasional tissue-liquid result discordance; tissue biopsy of metastatic lesion is done if accessible and safe
- Dermatologic reactions and infusion-related events with amivantamab are major adherence barriers; emphasizing the importance of early, practical management for rash, nausea, and other acute toxicities
- Decision-making is influenced not only by efficacy but by logistics such as biopsy access, testing turnaround time, and the need for clear guidance on post-amivantamab treatment strategy
- Dato-DXd will likely be utilized in the third line setting
- ***Recommended actions:*** provide real-world evidence for optimal sequencing after osimertinib failure, practical toxicity management for amivantamab, and efficient integration of repeat NGS to guide resistance-informed treatment decisions through Practice Patterns or Clinical Investigations

Challenging Cases in... Lung Cancer

EGFRm NSCLC

Patient case: untreated metastatic disease

- *What is the optimal first line therapy? Second line therapy? Third line therapy?*
- *Challenges with biopsy and testing?*
- *Sequencing considerations to provide the best outcomes for patients?*

Patient case: untreated metastatic disease

Patient History

55-year-old female with 5 pack year smoking history

4-month history of cough and SOB

Other medical history includes DM on metformin, otherwise healthy

Recent history of hemoptysis

Diagnosis

CXR: Right upper lobe mass

CT CAP: 4 cm spiculated mass RUL, bilateral mediastinal nodes, **2 liver mets**

MRI: head negative

Biopsy of liver:
Adenocarcinoma, moderately differentiated,
*TTF-1 +

NGS: EGFR Exon 19 deletion, PD-L1 80%, TMB 8

*thyroid transcription factor -1

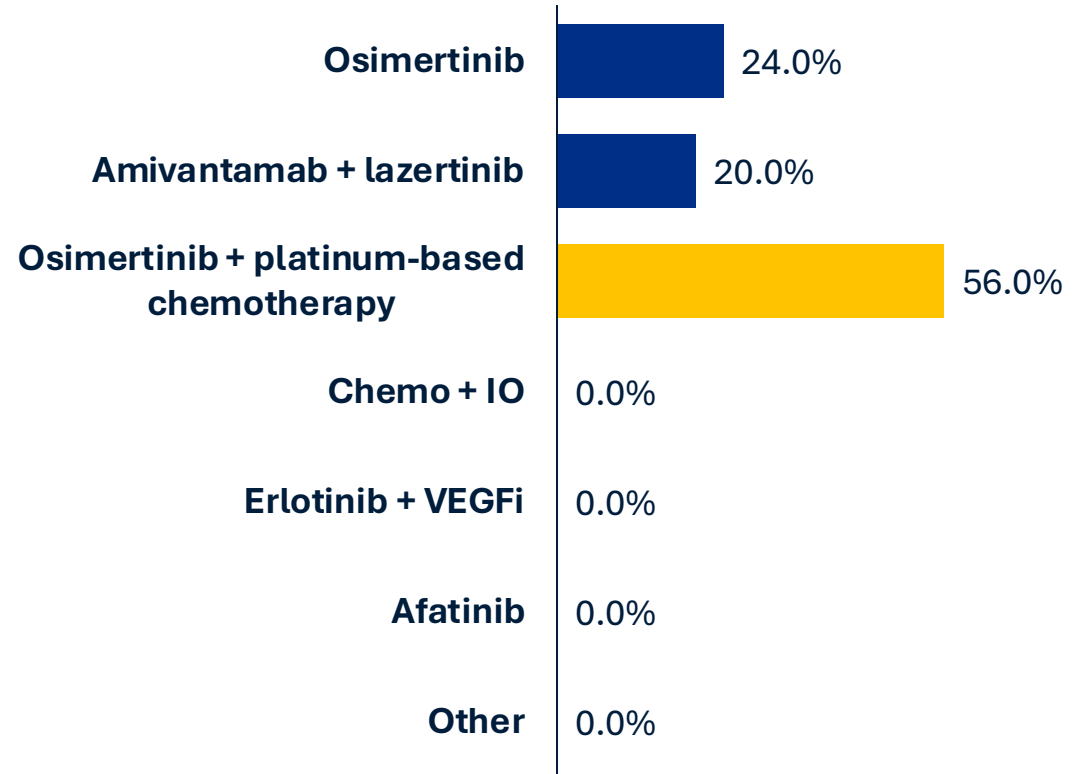
What first-line treatment do you recommend?





ARS Results from HCP Participants

What first-line treatment do you recommend for NSCLC EGFR Exon 19 del?



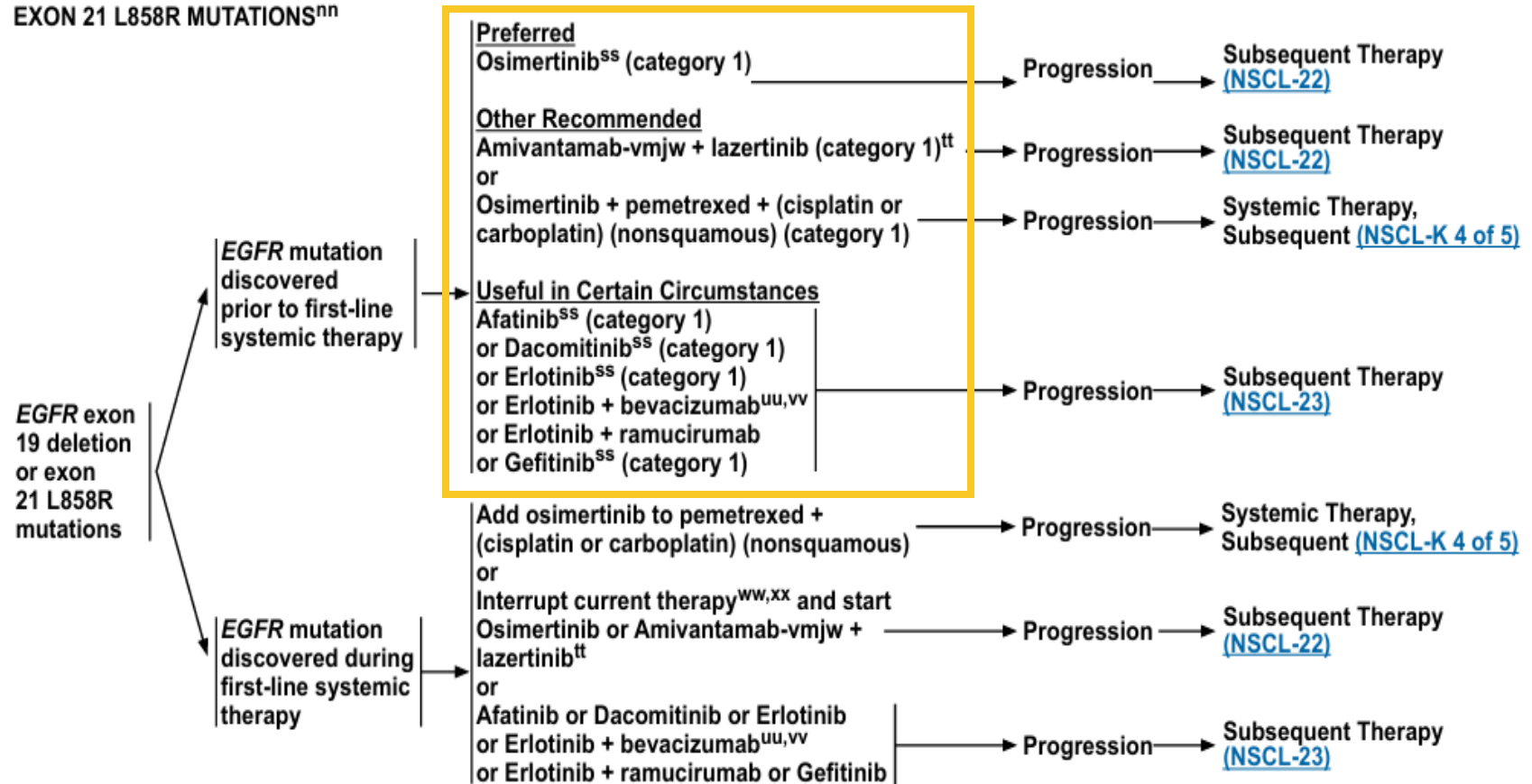


How do you view preferred vs other recommended vs useful in certain circumstances if all category 1?

Impact on treatment decision...payers, pathways?

EGFR EXON 19 DELETION OR EXON 21 L858R MUTATIONSⁿⁿ

FIRST-LINE THERAPY^{rr}



Approvals and Updates

RYBREVANT® (Amivantamab)

- As a **single agent** for adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has **progressed on or after platinum-based chemotherapy**
- In **combination with carboplatin and pemetrexed** for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test
- **August 19, 2024: In combination with lazertinib for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations, as detected by an FDA-approved test (MARIPOSA)**
- **September 19, 2024: In combination with carboplatin and pemetrexed for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations, whose disease has progressed on or after treatment with an EGFR tyrosine kinase inhibitor (MARIPOSA-2)**

TAGRISO® (Osimertinib)

- The **first-line** treatment of adult patients with metastatic NSCLC whose tumors have **EGFR exon 19 deletions or exon 21 L858R mutations**, as detected by an FDA-approved test
- The treatment of adult patients with **metastatic EGFR T790M mutation-positive NSCLC**, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy
- **February 19, 2024: In combination with pemetrexed and platinum-based chemotherapy, for the 1L treatment of adult patients with locally advanced or metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test (FLAURA-2)**

- **PALOMA-3:** Phase 3 study evaluating the pharmacokinetics (PK), efficacy and safety of **subcutaneous amivantamab** (administered via manual injection) combined with lazertinib compared to IV amivantamab and LAZCLUZE™ (lazertinib) in patients with EGFR-mutated advanced or metastatic NSCLC after progression on osimertinib and chemotherapy.
 - **December 16, 2024:** FDA issued CRL as part of a standard pre-approval inspection at a manufacturing facility

- *Subcutaneous amivantamab with lazertinib demonstrated non-inferior efficacy and decreased infusion-related reactions compared to IV amivantamab with lazertinib*

1L Treatments: Mariposa and Flaura2

| | MARIPOSA (Amivantamab) | | | FLAURA2 (Osimertinib) | |
|----------------------------|--|--|---------------------------|--|---|
| Inclusion Criteria | Locally advanced or metastatic NSCLC <u>Treatment-naïve</u> for advanced disease with EGFR Ex19del or L858R; ECOG PS 0 or 1; Asymptomatic or previously treated and stable CNS mets permitted | | | Phase 3, open-label trial <u>Treatment-naïve</u> patients with advanced nonsquamous NSCLC With EGFR exon 19 deletion or L858R mutation; WHO PS 0/1; Stable CNS mets permitted | |
| N | 1074 | | | 557 | |
| Study design | Amivantamab + Lazertinib (n=429) | Osimertinib (n=429) | Lazertinib (n=216) | Osimertinib + Platinum chemotherapy (n = 279) | Osimertinib (n = 278) |
| Median PFS, months | 23.7 | 16.6 | 18.5 | 25.5 | 16.7 |
| | HR: 0.70 (0.58-0.85) P < 0.001 | | | HR: 0.62 (0.49-0.79) P < 0.0001 | |
| Median OS, months | <i>Presented at ELCC25, 37.8 months follow-up</i> Not reached | 36.7 | | <i>Press release July 21, 2025, indicated positive final OS results; yet to be presented</i> NE | 36.7 |
| | HR: 0.75 (0.61-0.92) P < 0.005 | | | HR: 0.75 (0.57-0.97) | |
| ORR % | 78% | 73% | --- | 83% | 76% |
| Median DoR, months | 25.8 | 16.8 | --- | 24.0 | 15.3 |
| Intracranial ORR, % | 68% (n=180) | <i>With CNS mets at baseline</i> Exploratory analysis 69% (n=187) | | 73% (n=118) | <i>With measurable and nonmeasurable CNS mets at baseline</i> 69% (n=104) |
| Reference | N Engl J Med 2024;391:1486-98. ELCC25 | | | N Engl J Med 2023;389:1935-48 | |

Highlights of Prescribing Information 1L Treatments: Amivantamab, Osimertinib

| | RYBREVANT® (Amivantamab) | | | TAGRISSO® (Osimertinib) | | |
|---------------------------------|--|---|--|--|--|--|
| Black box warnings | None | | | None | | |
| Contraindications | None | | | None | | |
| Warnings And Precautions | <ul style="list-style-type: none"> • Infusion-Related Reactions (IRR) • Interstitial Lung Disease (ILD)/Pneumonitis • Venous Thromboembolic (VTE) Events with Concomitant Use with Lazertinib • Dermatologic Adverse Reactions • Ocular Toxicity • Embryo-Fetal Toxicity | | | <ul style="list-style-type: none"> • Interstitial Lung Disease (ILD)/Pneumonitis • QTc Interval Prolongation • Cardiomyopathy • Keratitis • Erythema Multiforme Major, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis • Cutaneous Vasculitis • Aplastic Anemia • Embryo-Fetal Toxicity | | |
| Adverse reactions | With Lazertinib (>20%) Rash, nail toxicity, infusion-related reaction, musculoskeletal pain, stomatitis, edema, VTE, paresthesia, fatigue, diarrhea, constipation, COVID-19, hemorrhage, dry skin, decreased appetite, pruritus, nausea, and ocular toxicity | With Chemo (>20%) Rash, nail toxicity, infusion-related reaction, fatigue, nausea, stomatitis, constipation, edema, decreased appetite, musculoskeletal pain, vomiting, and COVID-19 | Single Agent (>20%) Rash, IRR, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, and vomiting | Single Agent (>20%) Leukopenia, lymphopenia, thrombocytopenia, anemia, diarrhea, rash, musculoskeletal pain, neutropenia, nail toxicity, dry skin, stomatitis, and fatigue | Following platinum-based chemoradiation therapy (>20%) Lymphopenia, leukopenia, ILD/pneumonitis, thrombocytopenia, neutropenia, rash, diarrhea, nail toxicity, musculoskeletal pain, cough and COVID-19 | With Chemo (>20%) Leukopenia, thrombocytopenia, neutropenia, lymphopenia, rash, diarrhea, stomatitis, nail toxicity, dry skin, and increased blood creatinine |
| Drug Interactions | None | | | Strong CYP3A Inducers | | |
| Specific Populations | Avoid in: Lactation | | | Avoid in: Lactation | | |

Patient case: untreated metastatic disease

Patient History

55-year-old female with 5 pack year smoking history

4-month history of cough and SOB

Other medical history includes diabetes mellitus on metformin, otherwise healthy

Recent history of hemoptysis

Diagnosis

CXR: Right upper lobe mass

CT CAP: 4 cm spiculated mass RUL, bilateral mediastinal nodes, **2 liver mets**

MRI: head negative

Biopsy of liver:
Adenocarcinoma, moderately differentiated, TTF-1 +

NGS: EGFR Exon 19 deletion, PD-L1 80%, TMB 8

Treatment/Progression

Patient had an excellent response to osimertinib + chemo

15 months after initiation, new liver lesions and several bone lesions

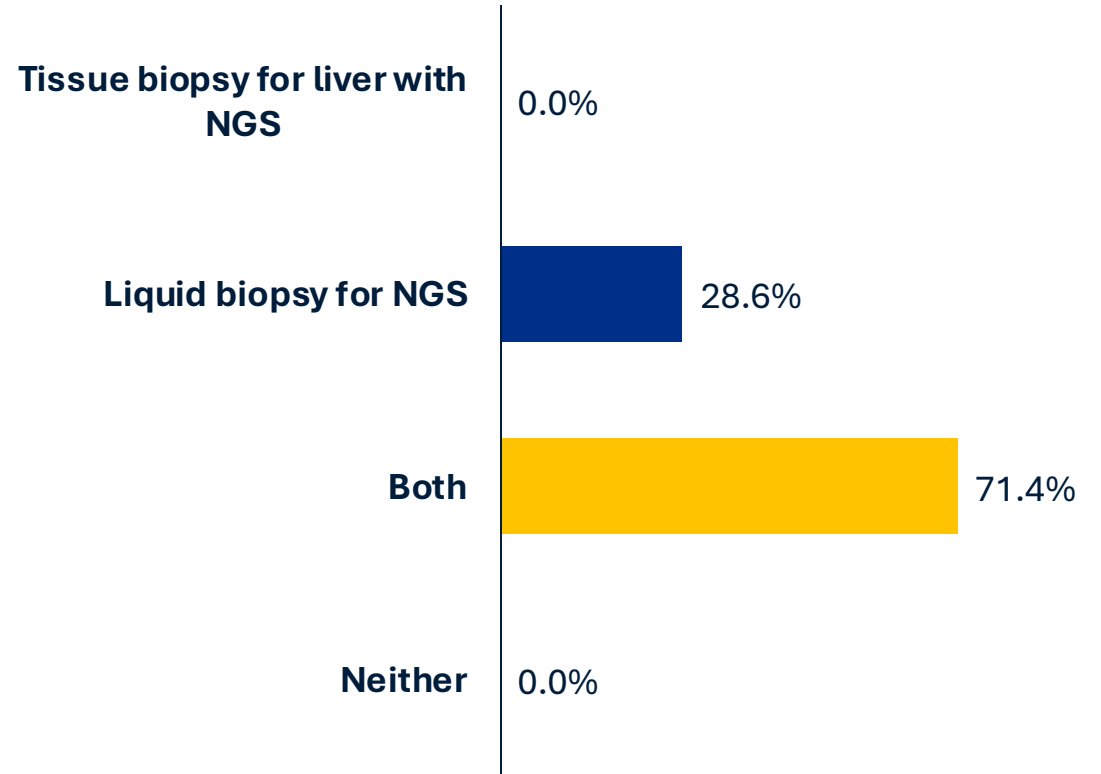
MRI: head negative

ECOG PS remains excellent



ARS Results from HCP Participants

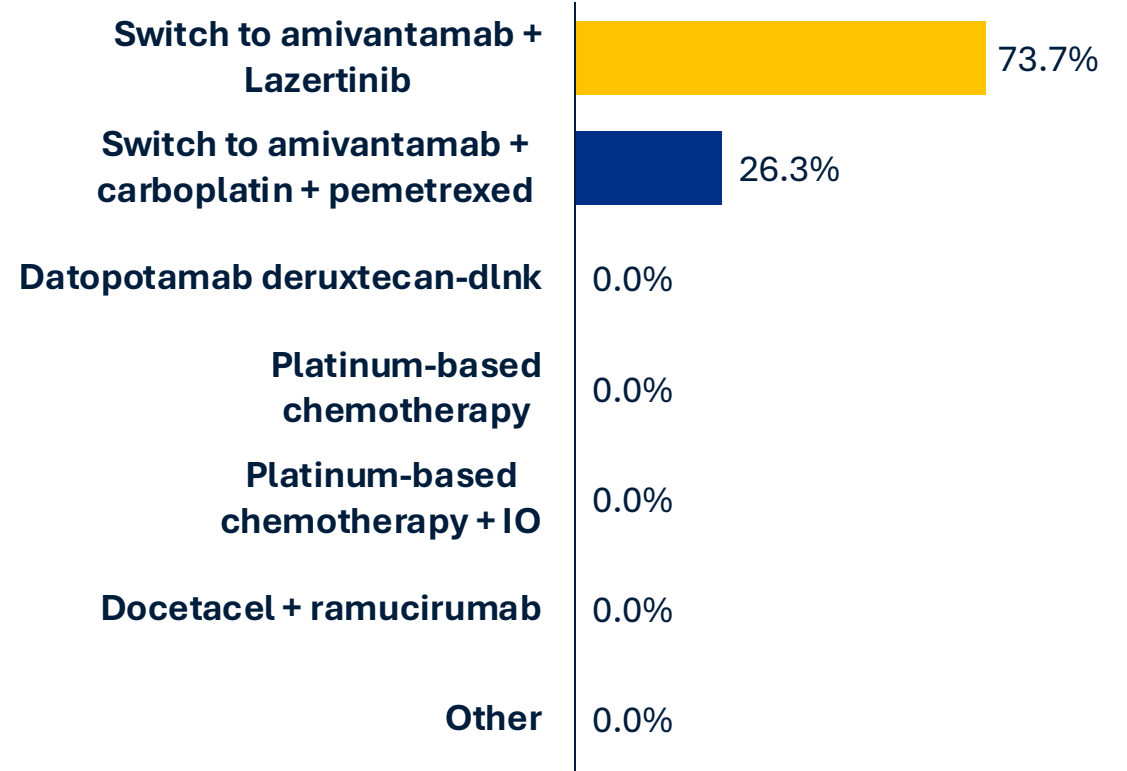
What additional diagnostic testing would you do if tumor progression?





ARS Results from HCP Participants

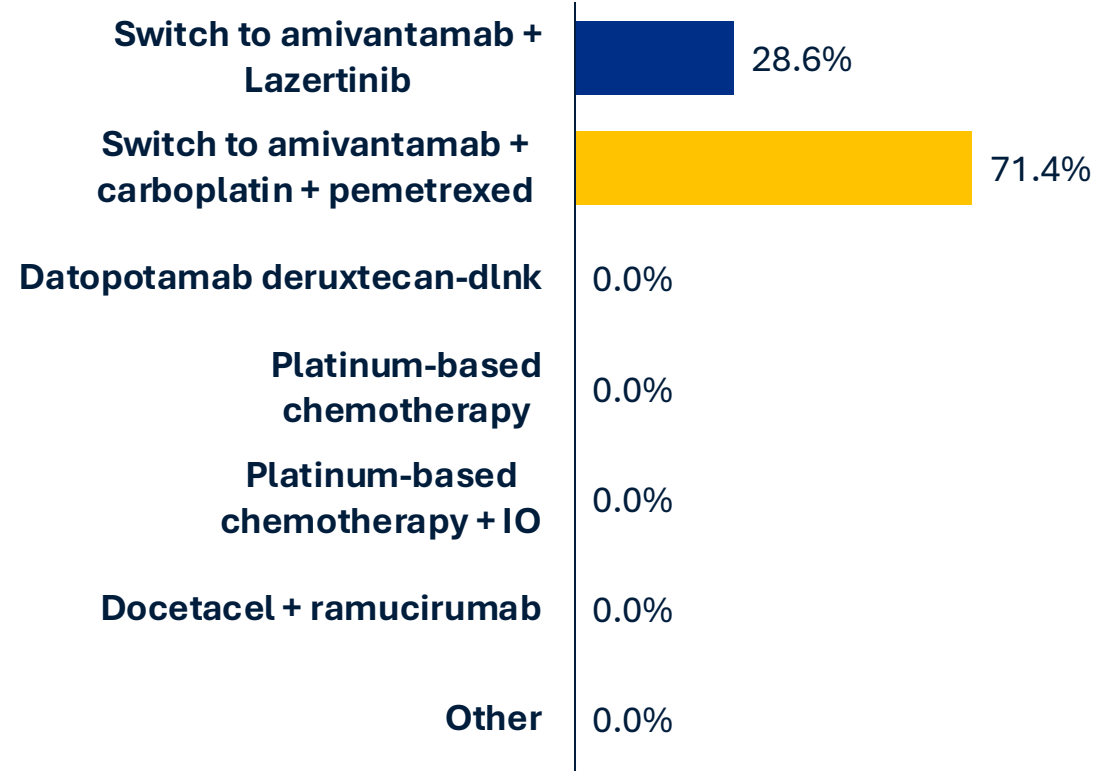
What is your choice of second line therapy on first progression with liver and bone mets?





ARS Results from HCP Participants

What is your choice of second line systemic therapy if progression with brain mets?



MARIPOSA-2 is the first randomized trial to investigate combination therapy after progression to osimertinib

September 19, 2024:

FDA approved **Amivantamab in combination with carboplatin and pemetrexed** for the

treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations, whose disease has progressed on or after treatment with an EGFR tyrosine kinase inhibitor (MARIPOSA-2)



| | MARIPOSA-2 | | |
|--|--|----------------------------|---|
| Inclusion Criteria | Randomized, open-label, multicenter, Phase 3 trial Locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations Progressive disease on or after receiving osimertinib Asymptomatic or previously treated and stable intracranial metastases permitted | | |
| N | 131 | 263 | 263 |
| Study design | Amivantamab in combination with carboplatin and pemetrexed | Carboplatin and pemetrexed | Amivantamab plus carboplatin and pemetrexed with Lazertinib |
| Median PFS, months | Median follow-up of 8.7 months, 6.3 months 4.2 months 8.3 months HR: 0.48 P < 0.001 HR: 0.44 P < 0.001 | | |
| Median OS, months | Prespecified second interim OS analysis at a median follow-up of 18.1 months, ESMO 2024 17.7 months 15.3 months --- HR: 0.73 (0.54-0.99) P=0.039 | | |
| ORR % | 64% | 36% | 63% |
| Median Intracranial PFS, months | 12.5 | 8.3 | 12.8 |
| Reference | Ann Oncol. 2024 Jan;35(1):77-90. | | |

| CHRYSALIS-2 |
|--|
| Open-label, two-part, phase 1/1b study Cohort A, evaluated the combination of amivantamab and lazertinib in patients with EGFR Ex19del- or L858R-mutated NSCLC with disease progression on or after osimertinib and platinum-based chemotherapy. |
| 162 |
| Amivantamab plus Lazertinib 39 (24%) had previously received first-line osimertinib followed by platinum-based chemotherapy and 67 (41%) had received osimertinib as a second-line treatment (after a previous first- or second-generation EGFR TKI) followed by platinum-based chemotherapy |
| Median follow-up of 12.3 months Median PFS by BICR: 4.5 months |
| Investigator vs BICR assessed ORR: 28% (95% CI: 22–36) vs 35% (27–42) |
| Investigator vs BICR assessed Median DoR: 8.4 months vs 8.3 months |
| Median OS: 14.8 months |
| J Thorac Oncol. 2025;20:651-664 |

Unmet need...

- Immunotherapy alone has no benefit in EGFR-mutant NSCLC, and the combination with chemotherapy failed to meet its primary endpoint in the KEYNOTE-789 and CheckMate-722 studies

- Phase III **KEYNOTE-789** Study of Pemetrexed and Platinum With or Without Pembrolizumab for Tyrosine Kinase Inhibitor–Resistant, EGFR–Mutant, Metastatic Nonsquamous Non-Small Cell Lung Cancer → **no benefit**
- *Nivolumab Plus Chemotherapy in Epidermal Growth Factor Receptor–Mutated Metastatic Non–Small-Cell Lung Cancer After Disease Progression on Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors: Final Results of CheckMate-722* → **no benefit**

On June 23, 2025, the FDA granted accelerated approval to datopotamab deruxtecan-dlnk (Datroway, Daiichi Sankyo, Inc.) for adults with locally advanced or metastatic epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC) who have received prior EGFR-directed therapy and platinum-based chemotherapy.



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 7.2025
Non-Small Cell Lung Cancer

July 10, 2025

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[Discussion](#)

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE – SUBSEQUENT^{d,l}

| ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 0–2) | SQUAMOUS CELL CARCINOMA (PS 0–2) |
|--|---|
| <p>Preferred (no previous IO): Systemic immune checkpoint inhibitors^e</p> <ul style="list-style-type: none"> • Nivolumab^w (category 1) • Pembrolizumab^x (category 1) • Atezolizumab^f (category 1) <p>Preferred (EGFR exon 19 deletion or L858R):</p> <ul style="list-style-type: none"> • Datopotamab deruxtecan-dlnk <p>Other Recommended (no previous IO or previous IO):^y</p> <ul style="list-style-type: none"> • Docetaxel • Pemetrexed • Gemcitabine • Ramucirumab/docetaxel • Albumin-bound paclitaxel • Fam-trastuzumab deruxtecan-nxki (HER2 IHC 3+) • Telisotuzumab vedotin-tilv (c-Met/MET ≥50% IHC 3+ and EGFR wild-type) | <p>Preferred (no previous IO): Systemic immune checkpoint inhibitors^e</p> <ul style="list-style-type: none"> • Nivolumab^w (category 1) • Pembrolizumab^x (category 1) • Atezolizumab^f (category 1) <p>Other Recommended (no previous IO or previous IO):^y</p> <ul style="list-style-type: none"> • Docetaxel • Gemcitabine • Ramucirumab/docetaxel • Albumin-bound paclitaxel • Fam-trastuzumab deruxtecan-nxki (HER2 IHC 3+) |
| ADENOCARCINOMA, LARGE CELL, NSCLC NOS, SQUAMOUS CELL CARCINOMA (PS 3–4) Best supportive care (NCCN Guidelines for Palliative Care) | |

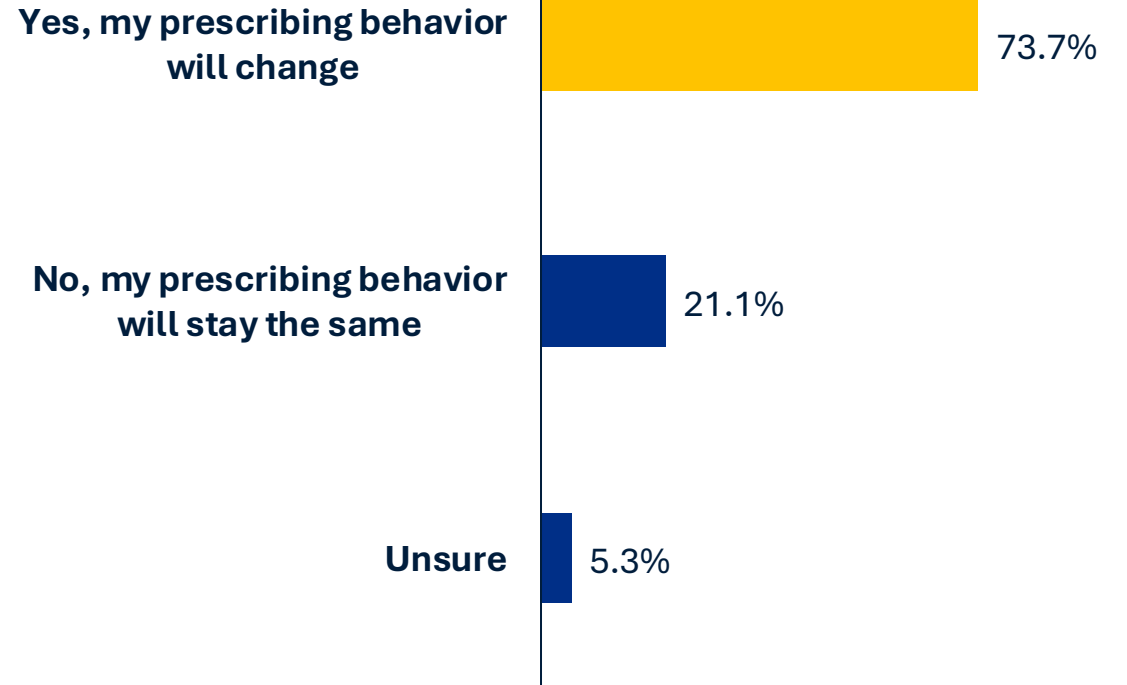
SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE – PROGRESSION^{d,l}

| ADENOCARCINOMA, LARGE CELL, NSCLC NOS ^{e,y} | SQUAMOUS CELL CARCINOMA ^{e,y} |
|--|--|
| <ul style="list-style-type: none"> • Options for PS 0–2: nivolumab,^w pembrolizumab, atezolizumab^f; datopotamab deruxtecan-dlnk (EGFR exon 19 deletion or L858R); fam-trastuzumab deruxtecan-nxki (HER2 IHC 3+); telisotuzumab vedotin-tilv (c-Met/MET ≥50% IHC 3+ and EGFR wild-type), docetaxel (category 2B); pemetrexed (category 2B); gemcitabine (category 2B); ramucirumab/docetaxel (category 2B); or albumin-bound paclitaxel (category 2B) • PS 3–4: Best supportive care • Options for further progression are best supportive care or clinical trial. | <ul style="list-style-type: none"> • Options for PS 0–2: nivolumab,^w pembrolizumab, atezolizumab^f; fam-trastuzumab deruxtecan-nxki (HER2 IHC 3+); docetaxel (category 2B); gemcitabine (category 2B); ramucirumab/docetaxel (category 2B); or albumin-bound paclitaxel (category 2B) • PS 3–4: Best supportive care • Options for further progression are best supportive care or clinical trial. |



ARS Results from HCP Participants

Will the challenging case discussed impact your prescribing behavior for patients with EGFRm NSCLC?



Key Takeaways

Lung Cancer

Patient case: untreated metastatic disease

- *Testing and retesting drives treatment strategies*
- *Awareness of clinical trial data provides new treatment options for patients*
- *New FDA approvals and NCCN Guidelines will play a pivotal role in directing treatment pathways*