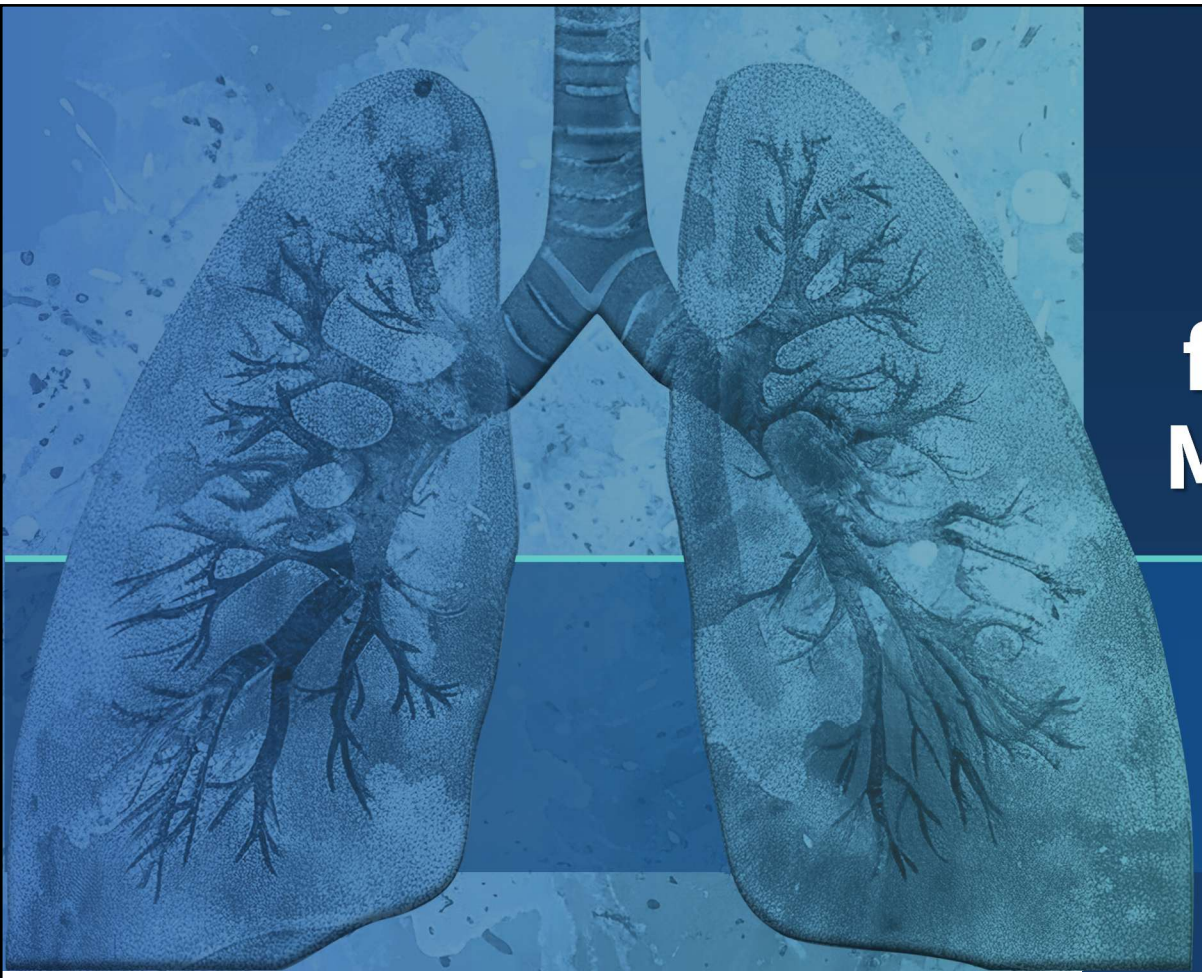

The Expanding Armamentarium for EGFR-Mutated Metastatic NSCLC:

Case-Driven Strategies for the Community-Based Clinician

Cornerstone Medical Education

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Presented by Cornerstone Medical Education and American Academy of CME.

Supported by an educational grant from Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC.

Presented by

Cornerstone Medical Education

AACME®
AMERICAN ACADEMY OF CME, INC.

Supported by an educational grant from Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC.

Faculty Information

Joshua K. Sabari, MD

Assistant Professor, Department of Medicine at NYU Grossman School of Medicine
Director, High Reliability Organization Initiatives, Perlmutter Cancer Center
NY Langone Health
New York, NY

Disclosures

Faculty Disclosures

- **Advisory Board/Consultant**
  - Genentech, Janssen, Jazz, Loxo@Lilly, Mirati Therapeutics (BMS), Pfizer, Regeneron, Revolution Medicines, Sanofi Genzyme, Takeda
- **Grant/Research Support**
  - Janssen, Loxo@Lilly, Mirati Therapeutics (BMS), Regeneron

Planner/Reviewer Disclosures

- **All other Planners and Reviewers have no relevant relationships to disclose.**
- **All relevant relationships have been mitigated.**

Please note, this activity will include discussion of off-label uses of approved agents and investigational data.

Accreditation and Credit Designation

In support of improving patient care, this activity has been planned and implemented by American Academy of CME, Inc. and Cornerstone Medical Education. American Academy of CME, Inc. is Jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Physicians:
American Academy of CME, Inc., designates this enduring material for a maximum of 1.0 *AMA PRA Category 1 Credits*™.

Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurse Practitioners and Nurses:
American Academy of CME, Inc., designates this educational activity for 1.0 ANCC contact hours (1.0 pharmacotherapeutic contact hours).

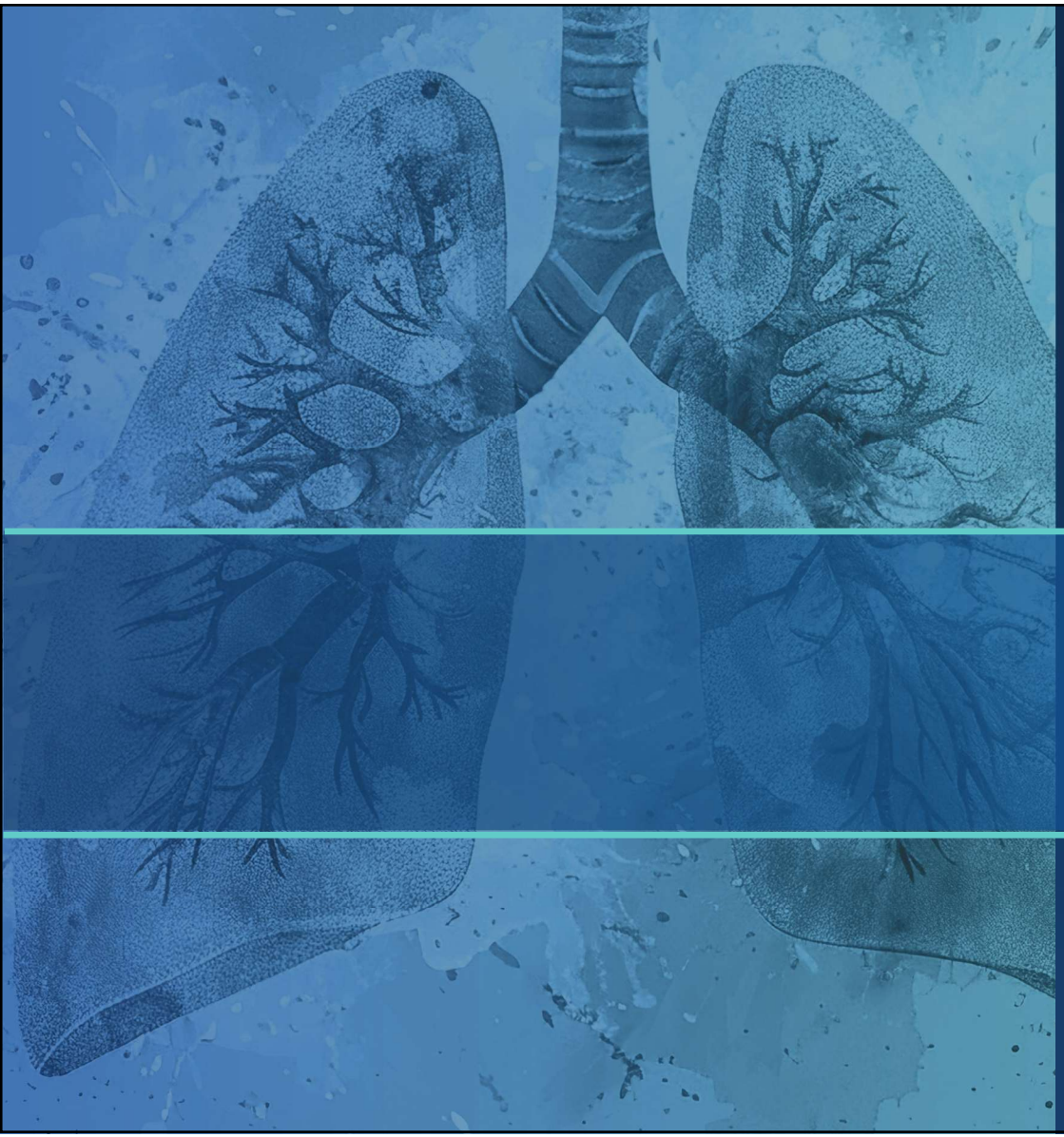
California: Provider approved by the California Board of Registered Nursing, Provider Number CEP16993 for 1.0 contact hours

Pharmacists:
This activity provides 1.0 ACPE contact hours (.10 CEUs) of continuing education credit. Universal Activity Number JA4008191-9999-25-016-H01-P, Knowledge.

Other Team Members:
Other members of the care team will receive a certificate of participation.

Learning Objectives

- Review the role of EGFR mutations in NSCLC tumorigenesis and appraise molecular testing guidelines to identify EGFR biomarkers that will ultimately guide targeted therapy decisions.
- Evaluate the established and evolving clinical trial evidentiary base for novel monoclonal antibodies (mAbs) and tyrosine kinase inhibitors (TKIs) in EGFR-mutated metastatic NSCLC (EGFRm mNSCLC), emphasizing the practice-changing potential of these agents in 1st and 2nd line treatment settings.
- Summarize the latest NCCN guideline recommendations for the treatment of EGFRm mNSCLC, with a specific focus on exon 19 deletions, exon 21 L858R substitutions, and exon 20 insertions.
- Work with your team to design individualized, evidence-driven treatment plans for patients with EGFRm mNSCLC, highlighting clinical nuances between available agents in 1st and 2nd line treatment.
- Apply the principles of shared decision making to real-world patient cases, focusing on the role of the interprofessional and interdisciplinary team in the mitigation and management of treatment-related adverse events for patients with EGFRm mNSCLC.



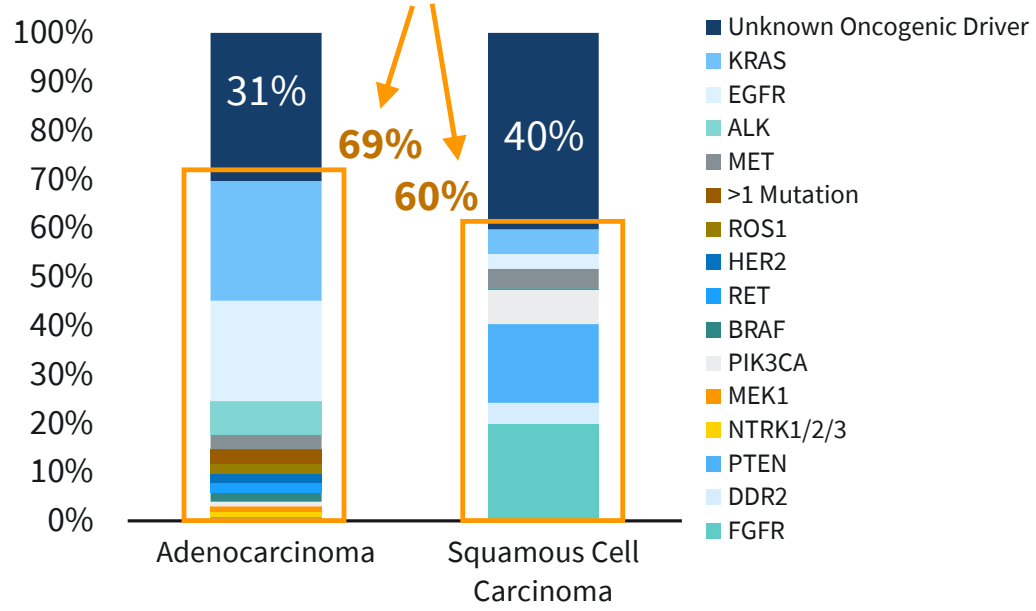
The Expanding Armamentarium for EGFR-Mutated Metastatic NSCLC:

Case-Driven Strategies for the Community-Based Clinician

Why Biomarkers Matter

Examining the Empiric Role of Molecular Testing in *EGFR*-mutated NSCLC

Lung Adenocarcinoma and Squamous Cell Carcinoma Biomarker Frequency

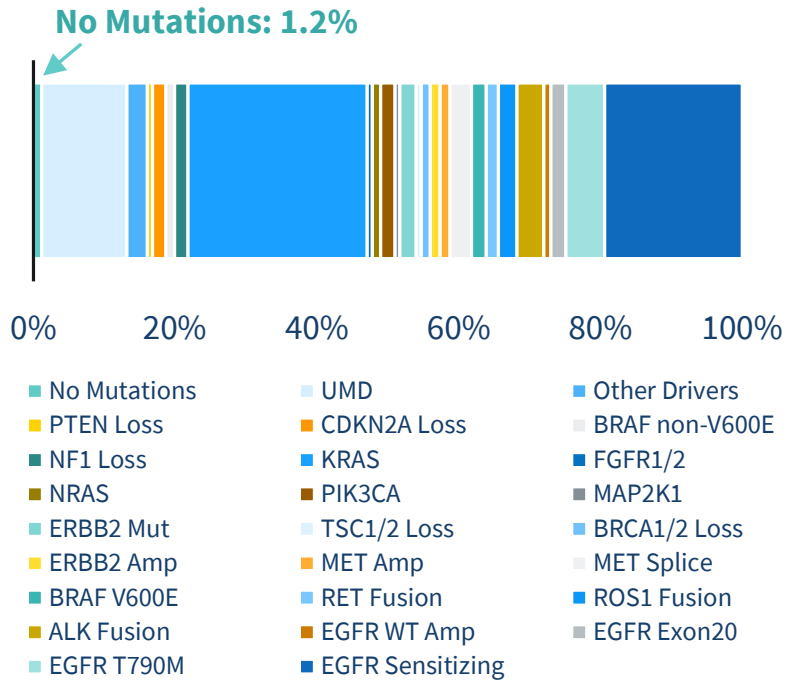


PD-L1 Expression in NSCLC Tumor Cells

Actionable for Immune Checkpoint Inhibitor Monotherapy

Kurzrock R, et al. *Cancer Metastasis Rev.* 2024.

Molecular Revolution: Targeted Therapy



Jordan EJ, et al. *Cancer Discov.* 2017; NCCN Guidelines for NSCLC, Version 8.2025.

Molecular Revolution: Targeted Therapy

MOLECULAR AND BIOMARKER-DIRECTED THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]

***EGFR* Exon 19 Deletion or Exon 21 L858R**
- First-line therapy
  - Afatinib[1]
  - Erlotinib[2]
  - Dacomitinib[3]
  - Gefitinib[4,5]
  - Osimertinib[6]
  - Osimertinib + pemetrexed + (cisplatin or carboplatin) (nonsquamous)[7]
  - Erlotinib + ramucirumab[8]
  - Erlotinib + bevacizumab[c] (nonsquamous)[9]
  - Amivantamab-vmjw + lazertinib[10]
- Subsequent therapy
  - Osimertinib[11]
  - Amivantamab-vmjw + carboplatin + pemetrexed (nonsquamous)[12]
  - Datopotamab deruxtecan-dlnk (nonsquamous)[13]

***EGFR* S768I, L861Q, and/or G719X**
- First-line therapy
  - Afatinib[1,14]
  - Erlotinib[2]
  - Dacomitinib[3]
  - Gefitinib[4,5]
  - Osimertinib[6,15]
- Subsequent therapy
  - Osimertinib[11]

***EGFR* Exon 20 Insertion Mutation**
- First-line therapy
  - Amivantamab-vmjw + carboplatin + pemetrexed (nonsquamous)[16]
- Subsequent therapy
  - Amivantamab-vmjw[17]
  - Sunvozertinib[18]

***KRAS* G12C Mutation[d]**
- Subsequent therapy
  - Sotorasib[19]
  - Adagrasib[20]

***ALK* Rearrangement**
- First-line therapy
  - Alectinib[21,22]
  - Brigatinib[23]
  - Ceritinib[24]
  - Crizotinib[21,25]
  - Ensartinib[26]
  - Lorlatinib[27]
- Subsequent therapy
  - Alectinib[28,29]
  - Brigatinib[30]
  - Ceritinib[31]
  - Ensartinib[32]
  - Lorlatinib[33]

***ROS1* Rearrangement**
- First-line therapy
  - Crizotinib[34]
  - Entrectinib[35]
  - Repotrectinib[36]
  - Taletrectinib[37]
- Subsequent therapy
  - Lorlatinib[38]
  - Entrectinib[35]
  - Repotrectinib[36]
  - Taletrectinib[37]

***BRAF* V600E Mutation**
- First-line therapy
  - Dabrafenib/trametinib[39]
  - Encorafenib/binimetinib[40]
  - Dabrafenib[41]
  - Vemurafenib
- Subsequent therapy
  - Dabrafenib/trametinib[41,42]
  - Encorafenib/binimetinib[40]

***NTRK1/2/3* Gene Fusion**
- First-line/Subsequent therapy
  - Larotrectinib[43]
  - Entrectinib[44]
  - Repotrectinib[45]

***MET* Exon 14 Skipping Mutation[d]**
- First-line therapy/Subsequent therapy
  - Capmatinib[46]
  - Crizotinib[47]
  - Tepotinib[48]

***RET* Rearrangement**
- First-line therapy
  - Selpercatinib[49]
  - Pralsetinib[50]
- Subsequent therapy
  - Cabozantinib[51,52]

***ERBB2 (HER2)* Mutation**
- Subsequent therapy
  - Fam-trastuzumab deruxtecan-nxki[d,53]
  - Ado-trastuzumab emtansine[d,54]
  - Zongertinib[55]

***NRG1* Gene Fusion**
- Subsequent therapy
  - Zenocutuzumab-zbco[56]

HER2-positive IHC 3+
- Subsequent therapy
  - Fam-trastuzumab deruxtecan-nxki[57]

c-Met/MET (≥50% IHC 3+ and *EGFR* wild-type)
- Subsequent therapy
  - Telisotuzumab vedotin-tllv (nonsquamous)[58]

PD-L1 ≥50% First-Line Therapy

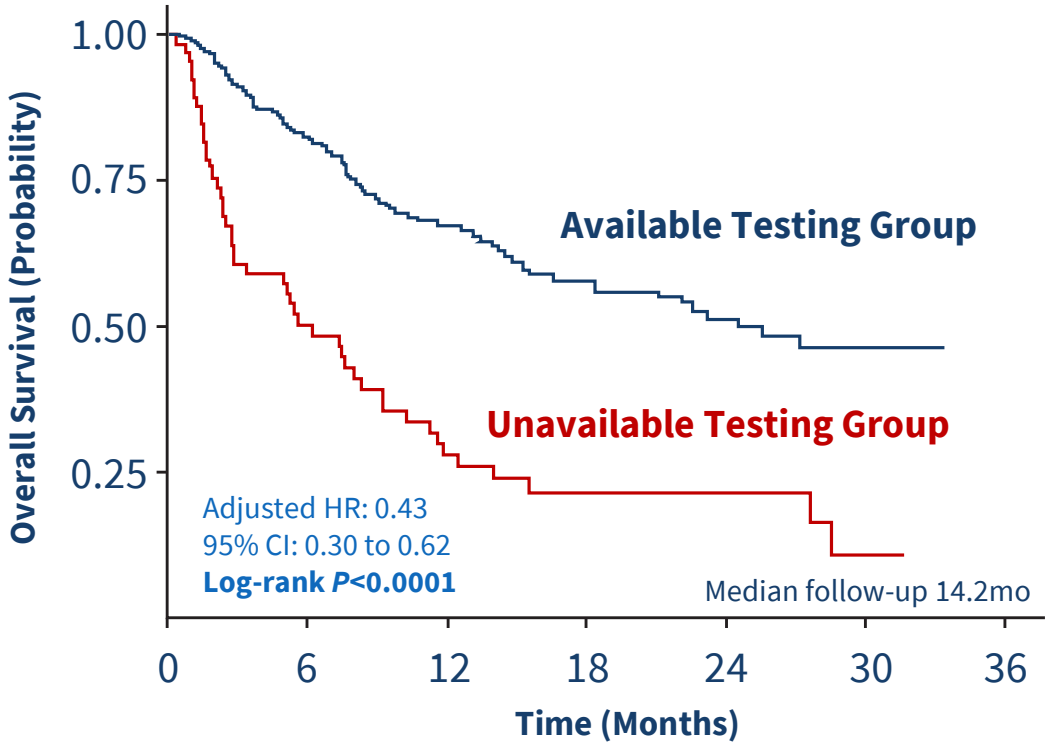
PD-L1 ≥1%–49% First-Line Therapy

Jordan EJ, et al. *Cancer Discov.* 2017; NCCN Guidelines for NSCLC, Version 8.2025.

Importance of Biomarker Testing: OS Benefit in NSCLC

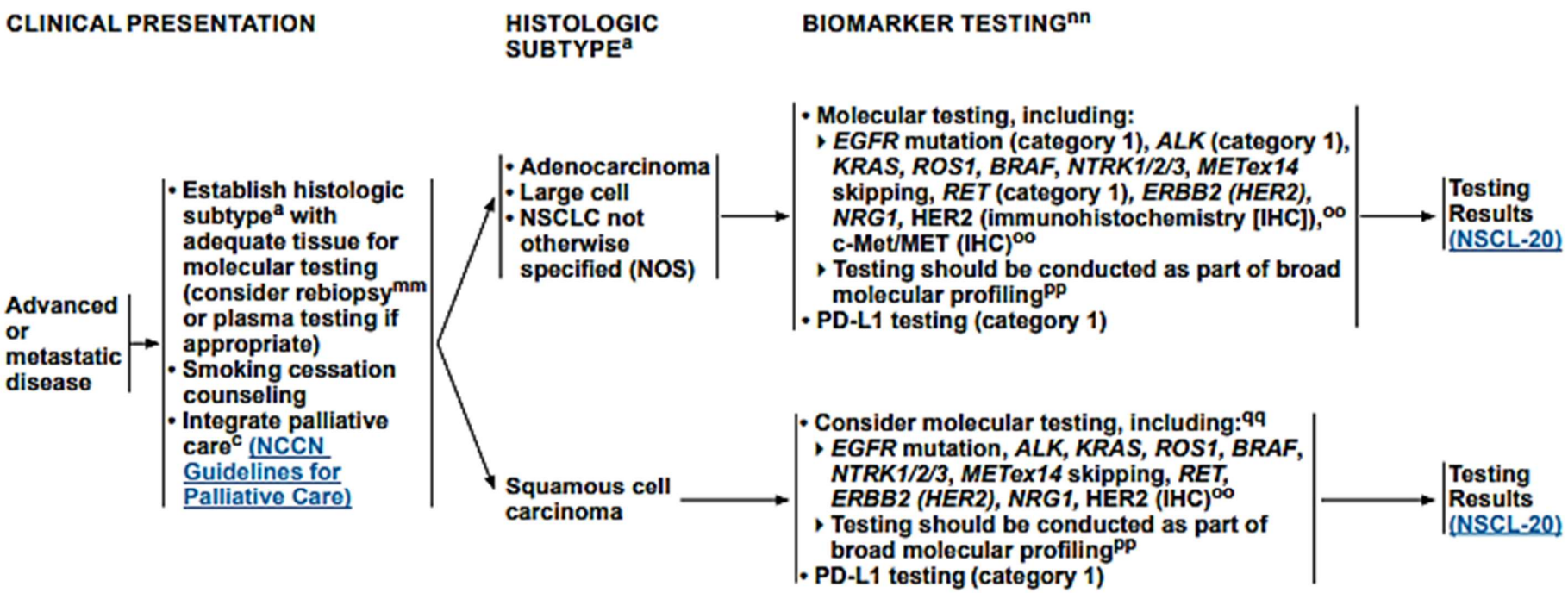
- Patients should **NOT be initiated on therapy** (except in emergent cases) **until results of biomarker testing are available**

Overall survival based on availability of results ***before first-line therapy*** in 236 mNSq NSCLC pts.



Aggarwal C, et al. *JCO Precis Oncol.* 2023.

Necessary Biomarker Testing for Lung Cancer

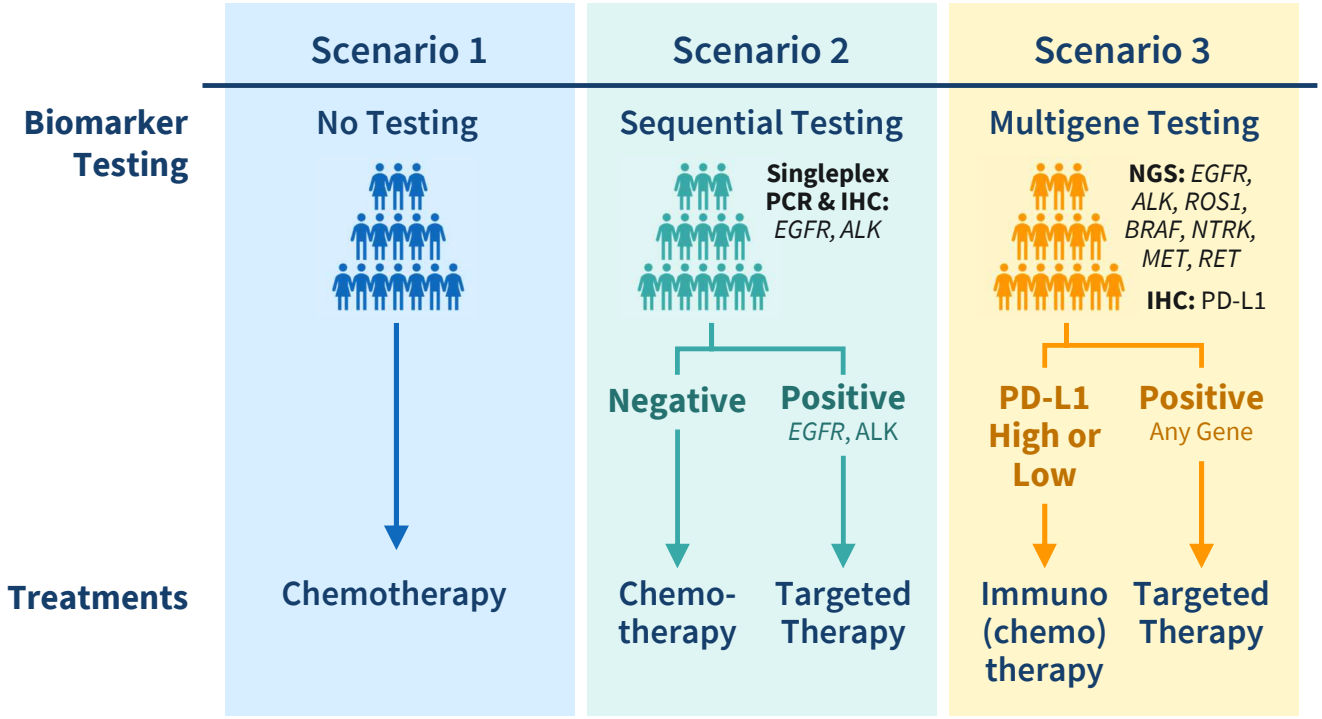


NCCN Guidelines for NSCLC, Version 8.2025.

Sequential Single-gene vs. Comprehensive Multi-gene Testing

- **Broad molecular profiling** via next-generation sequencing (NGS) is guideline recommended.

Comprehensive NGS panel testing has been shown to be more efficient and cost-effective with quicker time to results.



Hofmarcher T, et al. *Front Med.* 2023; Pennell NA, et al. *JCO Precis Oncol*. 2019.

Tissue vs ctDNA (Liquid) Biopsy

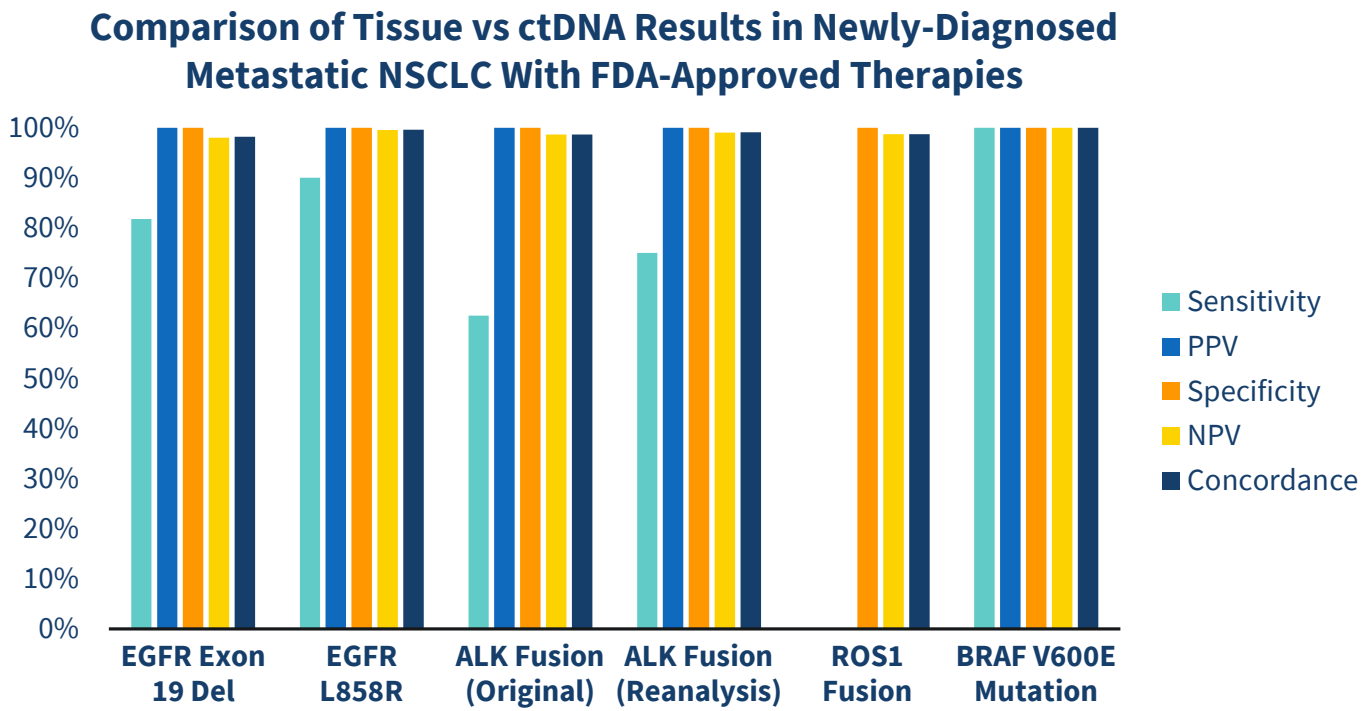
	Advantages	Disadvantages
 **Tissue Biopsy**	• Pathology information • Assessment of DNA and non-DNA biomarkers • PD-L1 assessment	• Longer TAT • Limited tissue quantities • Invasive • At PD, re-biopsy not always feasible • Tumor heterogeneity
 **Liquid Biopsy** (ctDNA)	• High concordance rate • Rapid TAT • Minimally invasive • Repeatable over time • Better capture tumor heterogeneity and clonal evolution	• Non-DNA biomarkers not evaluable • Increased costs if used concurrently with tissue testing • False negatives

PD: progressive disease;
TAT: turnaround time

Rolfo C, et al. *J Thorac Oncol*. 2021.

NILE (Non-invasive vs Invasive Lung Evaluation) Study

- Newly diagnosed advanced NSCLC (n = 282)
- Designed to test concordance between tissue & ctDNA (liquid) biopsy biomarker detection



Leighl NB, et al. *Clin Cancer Res*. 2019.

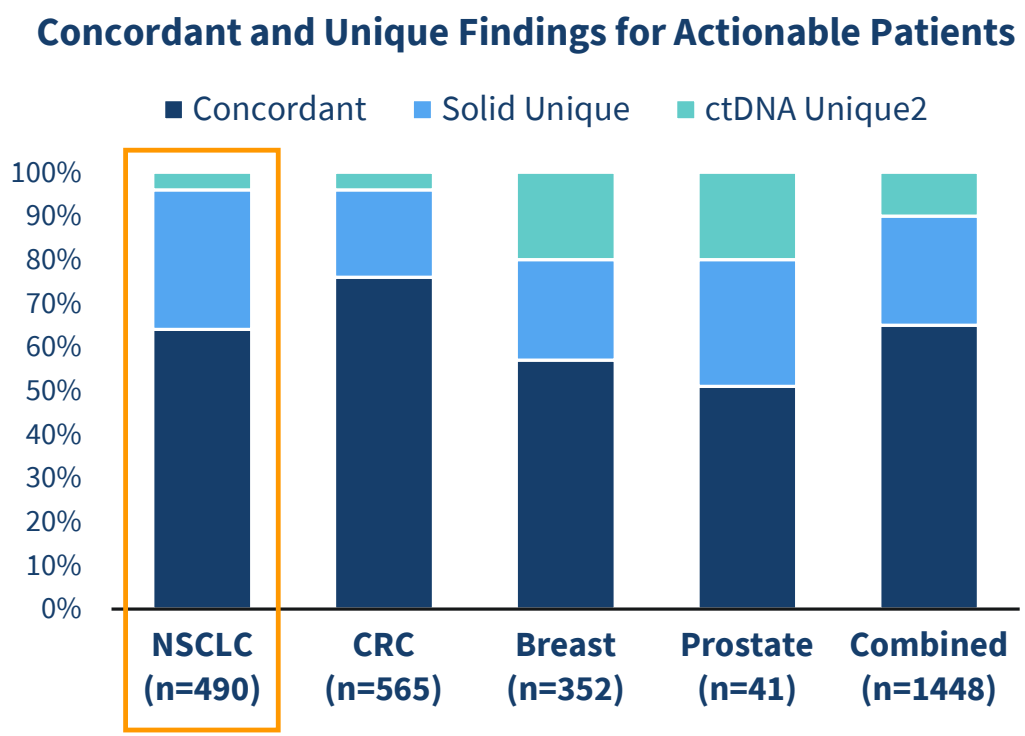
Guidelines: Concurrent vs Sequential Biomarker Testing in NSCLC

NCCN®[1]	Both ctDNA and tissue testing have appreciable false negative rates, supporting the complementarity of these approaches, and ***data support complementary testing to reduce turnaround time and increase yield of targetable alteration detection***
ESMO®[2]	In treatment-naive NSCLC, **ctDNA can be considered complementary or alternative to tissue NGS for biomarker evaluation.** If available, tissue testing with such assays remains the gold standard compared with ctDNA, although any tissue assay can be limited by low tumour cellularity or quality
ASCO/IASLC®[3]	Although tissue-based testing remains the gold standard for tumor genotyping for many cancer patients, because of technical and biologic limitations of ctDNA analysis, **cfDNA analysis can be used either sequentially, when tumor tissue is insufficient/inadequate for testing, or concurrently, when tissue is scant or of uncertain adequacy for genotyping**

[1]NCCN Guidelines for NSCLC, Version 8.2025; [2]Pascual J, et al. *Ann Oncol*. 2022; [3]https://www.iaslc.org/iaslc-atlas-molecular-testing-targeted-therapy-lung-cancer.

Concurrent NGS Testing Increases Detection Rates

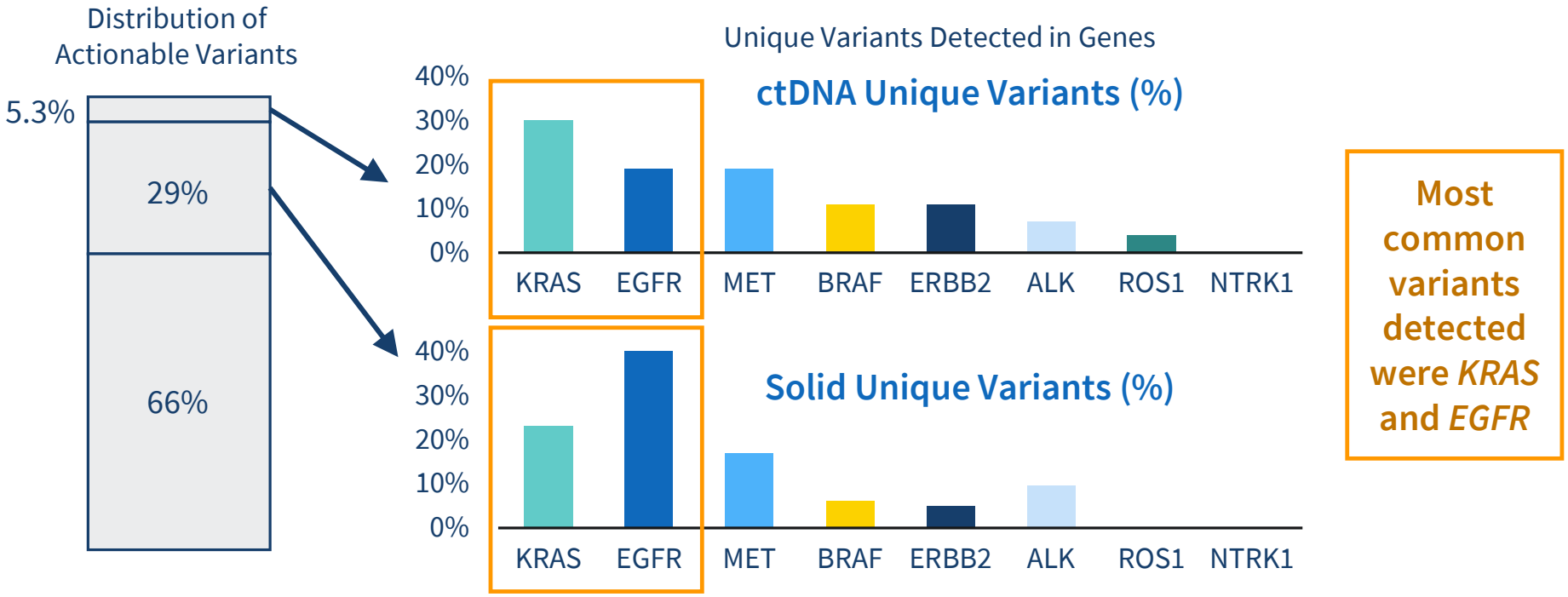
- N = 3209 pts (May 2020 - December 2022)
- Patients had stage IV NSCLC, Breast, Prostate, or CRC
- Tissue and plasma ctDNA tested for genomic profiling
- Biopsies and blood draws must have occurred within 30 days



Iams WT, et al. *JAMA Netw Open.* 2024.

Concurrent NGS Testing Increases Detection Rates

Actionable Variants Detected in Non–Small Cell Lung Cancer (NSCLC) Cohort

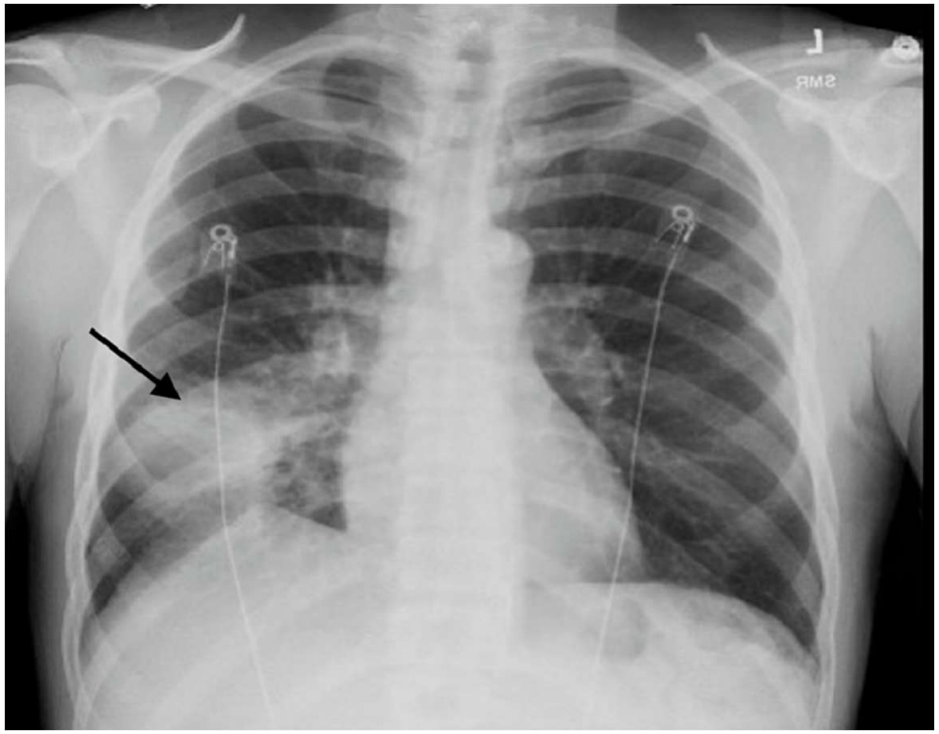


Most common variants detected were *KRAS* and *EGFR*

Iams WT, et al. *JAMA Netw Open.* 2024.

Patient Case #1:

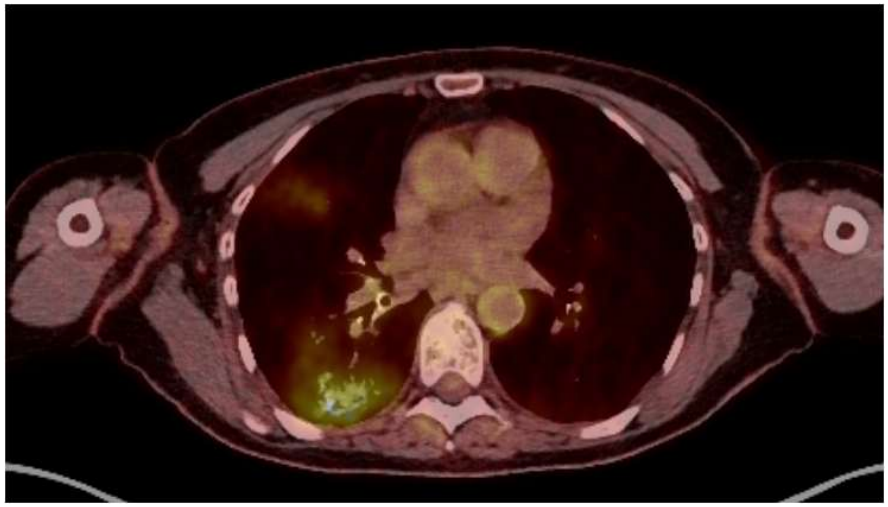
- 47-year-old woman, lifetime never smoking history, presented for elective gastric sleeve evaluation
- Past medical history:
  - Hypertension
  - Obesity
  - Obstructive sleep apnea
- Active, employed as an executive assistant, ECOG 0
- Preoperative CXR for clearance revealed a **right lower lobe mass**

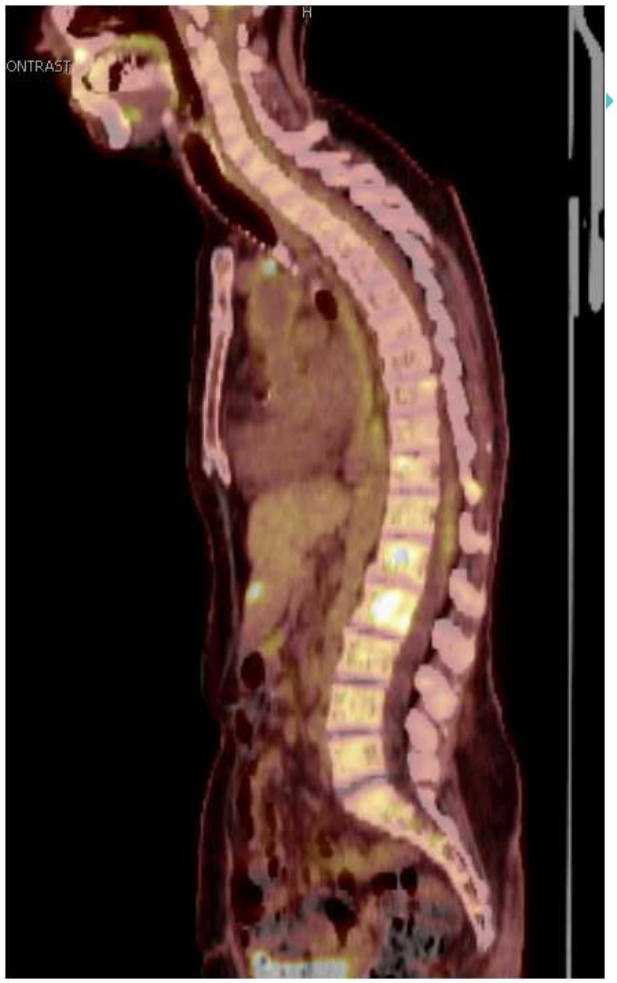


Images courtesy of Dr. Sabari.

Staging Evaluation

- **CT Chest:** mass in the right lower lobe, measuring 5.0 x 3.4cm
- **PET/CT:** Right lower lobe mass was FDG avid, bilateral mediastinal and right hilar adenopathy as well as diffuse axial skeletal bone metastases including spine (vertebral body)





Images courtesy of Dr. Sabari.

Staging Evaluation

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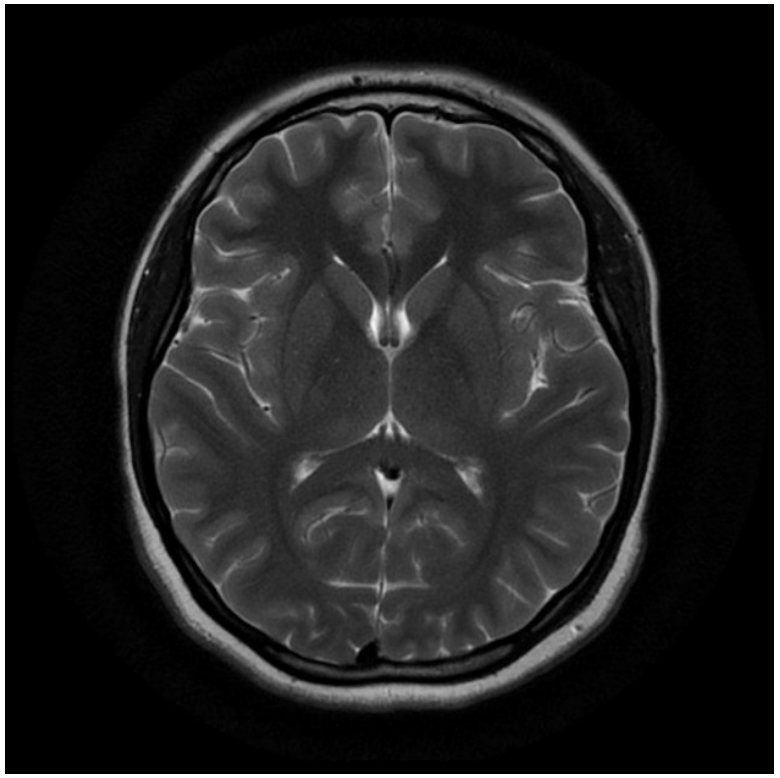
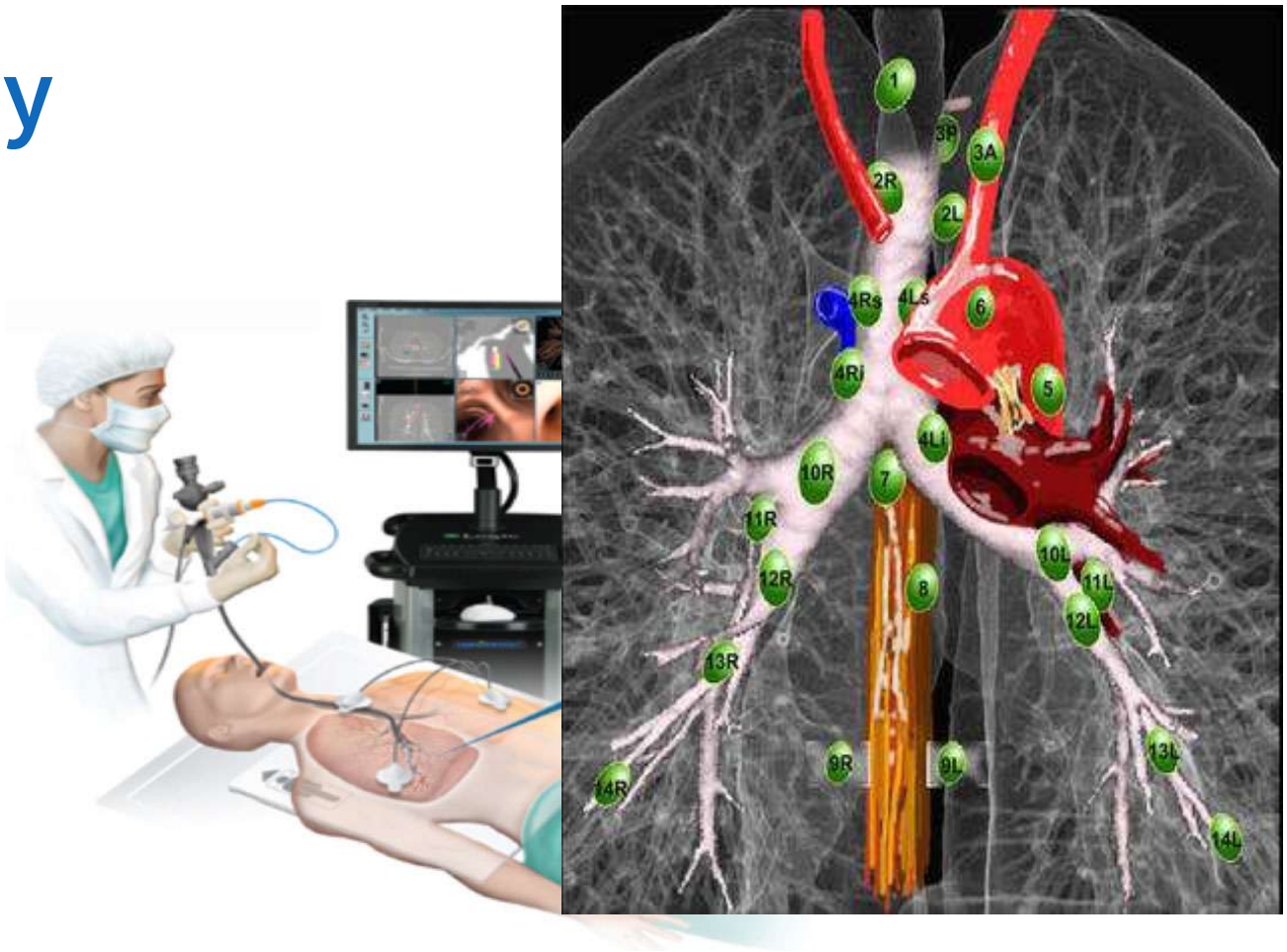
- **PET/CT:** Right lower lobe mass was FDG avid, bilateral mediastinal and right hilar adenopathy as well as diffuse axial skeletal bone metastases including spine (vertebral body)
- **MRI:** brain without evidence of intracranial metastasis



Images courtesy of Dr. Sabari.

Tissue Biopsy

- Bronchoscopy/ EBUS guided biopsy of the dominant right lower lobe mass and mediastinal lymph nodes



Images courtesy of Dr. Sabari.

Tissue Biopsy

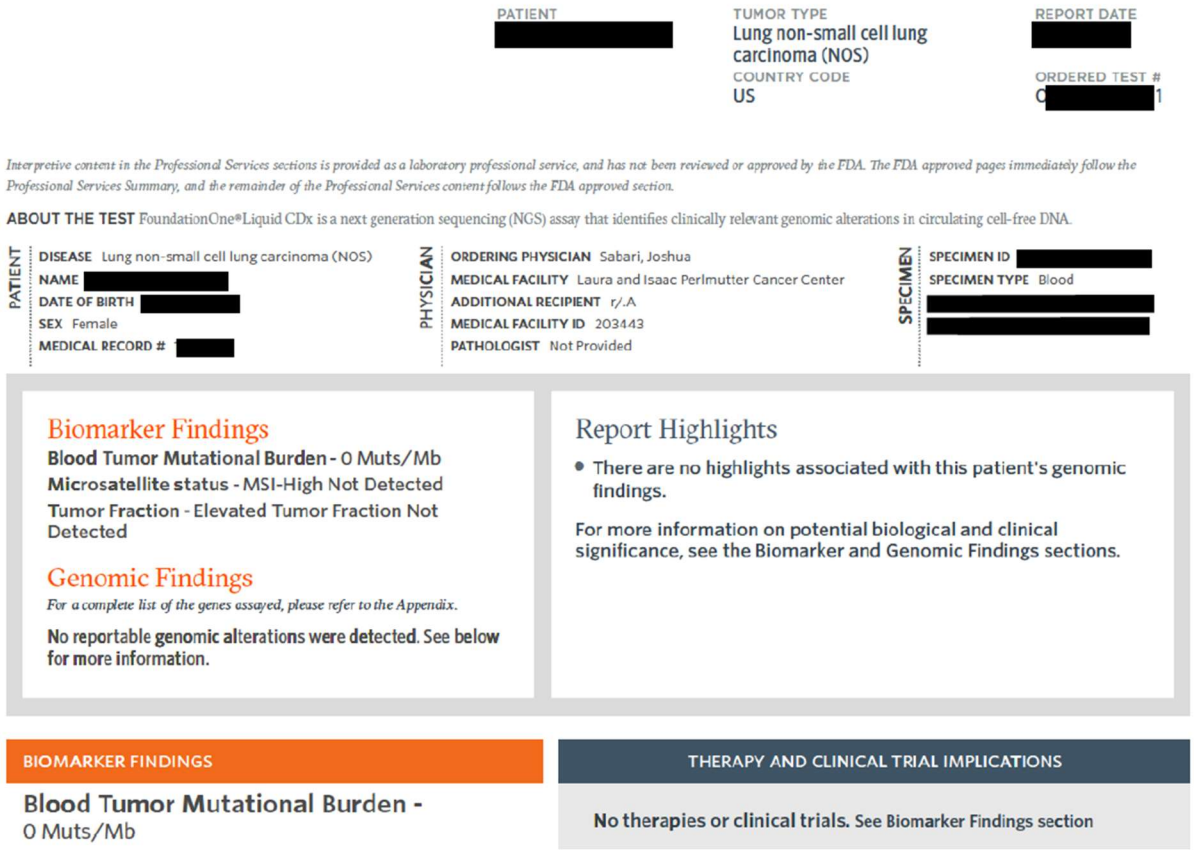
- Bronchoscopy/ EBUS guided biopsy of the dominant right lower lobe mass and mediastinal lymph nodes

PATHOLOGY

- Poorly differentiated adenocarcinoma, favor NSCLC
- IHC positive for TTF1, Napsin A; negative for p40 and p63
- PD-L1 expression <1%

Next Generation Sequencing

Plasma NGS



PATIENT [redacted]

TUMOR TYPE
Lung non-small cell lung carcinoma (NOS)
COUNTRY CODE
US

REPORT DATE [redacted]

ORDERED TEST # [redacted]

Interpretive content in the Professional Services sections is provided as a laboratory professional service, and has not been reviewed or approved by the FDA. The FDA approved pages immediately follow the Professional Services Summary, and the remainder of the Professional Services content follows the FDA approved section.

ABOUT THE TEST FoundationOne®Liquid CDx is a next generation sequencing (NGS) assay that identifies clinically relevant genomic alterations in circulating cell-free DNA.

PATIENT
DISEASE Lung non-small cell lung carcinoma (NOS)
NAME [redacted]
DATE OF BIRTH [redacted]
SEX Female
MEDICAL RECORD # [redacted]

PHYSICIAN
ORDERING PHYSICIAN Sabari, Joshua
MEDICAL FACILITY Laura and Isaac Perlmutter Cancer Center
ADDITIONAL RECIPIENT r/.A
MEDICAL FACILITY ID 203443
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN ID [redacted]
SPECIMEN TYPE Blood
[redacted]

Biomarker Findings

Blood Tumor Mutational Burden - 0 Muts/Mb
Microsatellite status - MSI-High Not Detected
Tumor Fraction - Elevated Tumor Fraction Not Detected

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

No reportable genomic alterations were detected. See below for more information.

Report Highlights

- There are no highlights associated with this patient's genomic findings.

For more information on potential biological and clinical significance, see the Biomarker and Genomic Findings sections.

BIOMARKER FINDINGS

Blood Tumor Mutational Burden -
0 Muts/Mb

THERAPY AND CLINICAL TRIAL IMPLICATIONS

No therapies or clinical trials. See Biomarker Findings section

Next Generation Sequencing

Plasma NGS

PATIENT [redacted]

TUMOR TYPE
Lung non-small cell lung carcinoma (NOS)
COUNTRY CODE
US

REPORT DATE [redacted]

ORDERED TEST # [redacted]

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0 Muts/Mb

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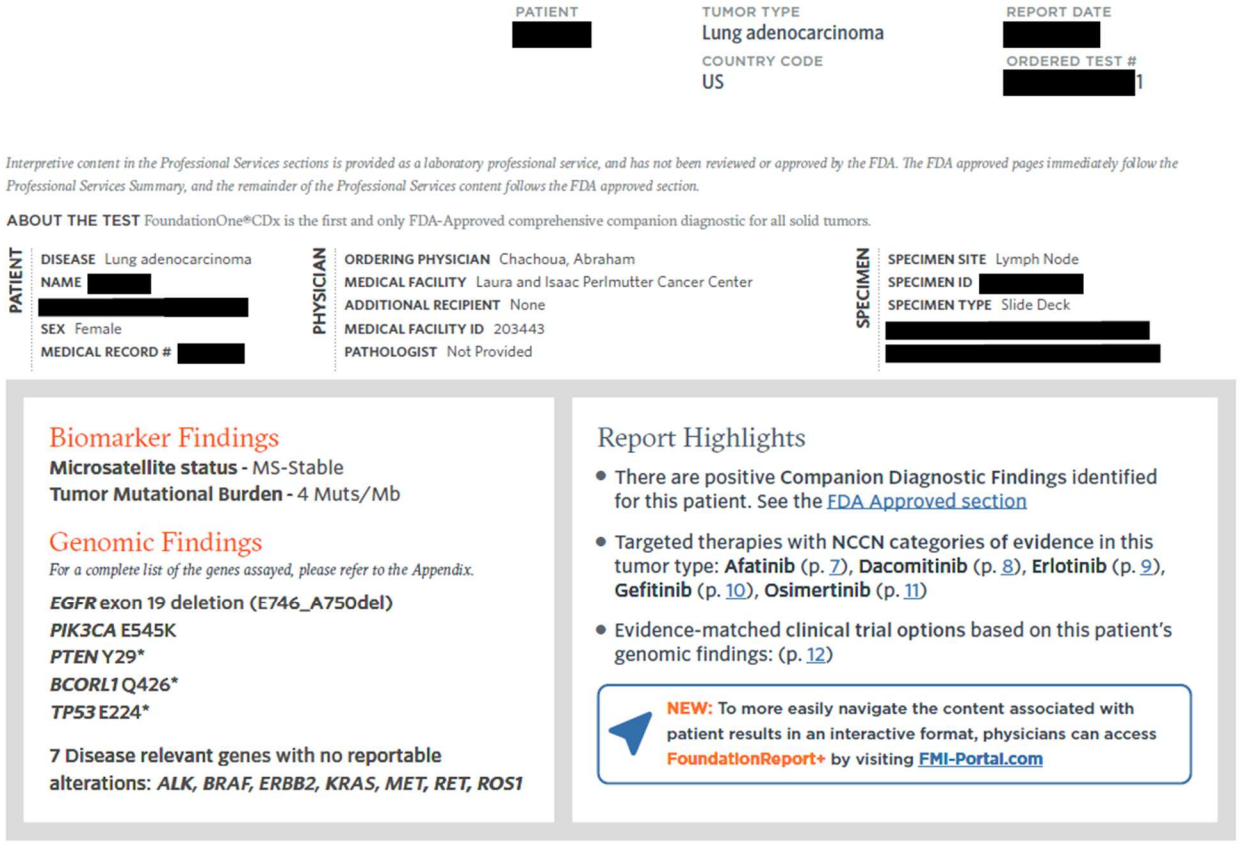
No therapies or clinical trials. See Biomarker Findings section

Next Generation Sequencing

Tissue NGS



PATIENT [redacted]

TUMOR TYPE
Lung adenocarcinoma
COUNTRY CODE
US

REPORT DATE [redacted]
ORDERED TEST # [redacted]1

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ABOUT THE TEST FoundationOne®CDx is the first and only FDA-Approved comprehensive companion diagnostic for all solid tumors.

PATIENT
DISEASE Lung adenocarcinoma
NAME [redacted]
SEX Female
MEDICAL RECORD # [redacted]

PHYSICIAN
ORDERING PHYSICIAN Chachoua, Abraham
MEDICAL FACILITY Laura and Isaac Perlmutter Cancer Center
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 203443
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN SITE Lymph Node
SPECIMEN ID [redacted]
SPECIMEN TYPE Slide Deck
[redacted]

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 4 Muts/Mb

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

EGFR **exon 19 deletion (E746_A750del)**
PIK3CA **E545K**
PTEN **Y29***
BCORL1 **Q426***
TP53 **E224***

7 Disease relevant genes with no reportable alterations: *ALK, BRAF, ERBB2, KRAS, MET, RET, ROS1*

Report Highlights

- There are positive **Companion Diagnostic Findings** identified for this patient. See the FDA Approved section
- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Afatinib** (p. 7), **Dacomitinib** (p. 8), **Erlotinib** (p. 9), **Gefitinib** (p. 10), **Osimertinib** (p. 11)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 12)

NEW: To more easily navigate the content associated with patient results in an interactive format, physicians can access **FoundationReport+** by visiting **FMI-Portal.com**

Next Generation Sequencing

Tissue NGS

PATIENT [redacted]

TUMOR TYPE
Lung adenocarcinoma

COUNTRY CODE
US

REPORT DATE [redacted]

ORDERED TEST # [redacted]1

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SEX Female
MEDICAL RECORD # [redacted]

PHYSICIAN
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MEDICAL FACILITY Laura and Isaac Perlmutter Cancer Center
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 203443
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN SITE Lymph Node
SPECIMEN ID [redacted]
SPECIMEN TYPE Slide Deck
[redacted]

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BCORL1 Q426*
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Next Generation Sequencing

Tissue NGS

PATIENT [redacted]

TUMOR TYPE
Lung adenocarcinoma

COUNTRY CODE
US

REPORT DATE [redacted]

ORDERED TEST # [redacted]1

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MEDICAL RECORD # [redacted]

PHYSICIAN
ORDERING PHYSICIAN Chachoua, Abraham
MEDICAL FACILITY Laura and Isaac Perlmutter Cancer Center
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 203443
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN SITE Lymph Node
SPECIMEN ID [redacted]
SPECIMEN TYPE Slide Deck
[redacted]

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 4 Muts/Mb

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

EGFR **exon 19 deletion (E746_A750del)**
PIK3CA **E545K**
PTEN **Y29***
[redacted]
TP53 **E224***

7 Disease relevant genes with no reportable alterations: *ALK, BRAF, ERBB2, KRAS, MET, RET, ROS1*

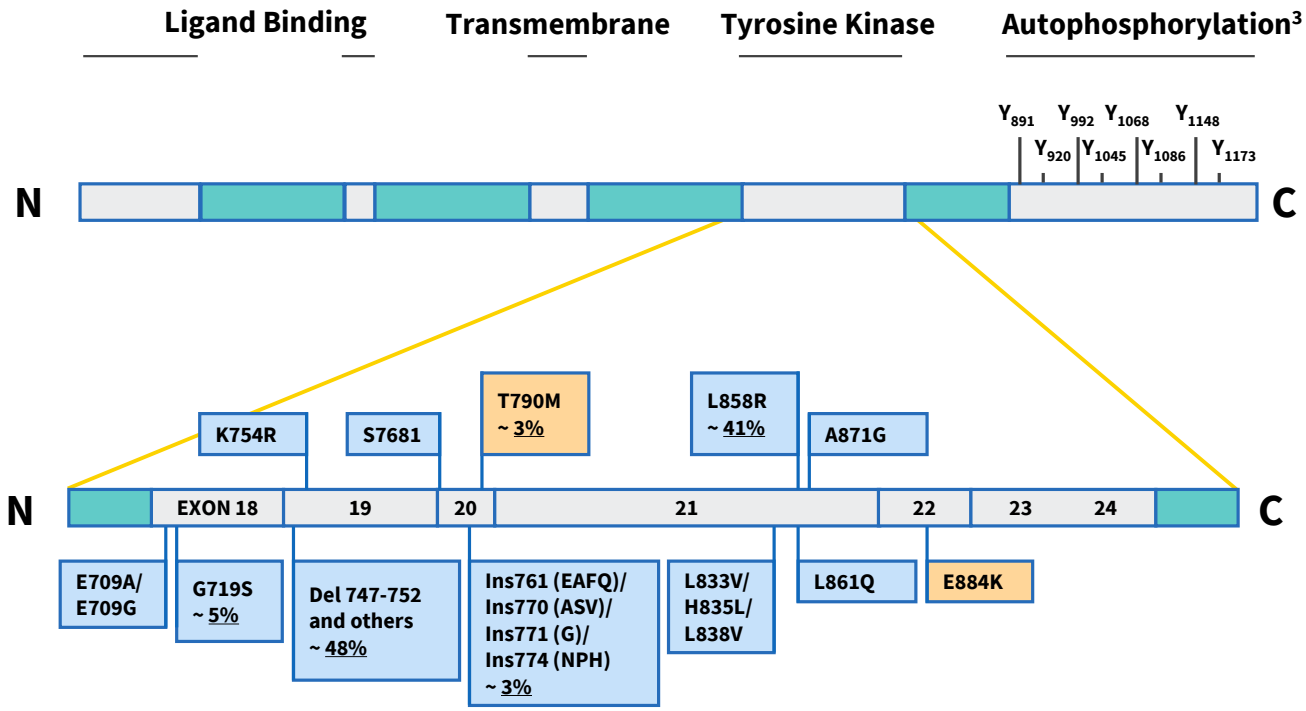
Report Highlights

- There are positive **Companion Diagnostic Findings** identified for this patient. See the FDA Approved section
- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Afatinib** (p. 7), **Dacomitinib** (p. 8), **Erlotinib** (p. 9), **Gefitinib** (p. 10), **Osimertinib** (p. 11)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 12)

NEW: To more easily navigate the content associated with patient results in an interactive format, physicians can access **FoundationReport+** by visiting **FMI-Portal.com**

EGFR Kinase Domain Mutations

- Encoded by exons 18–24[1]
- Mutation detection generally focused on 18–21[1]
- Sequencing has identified >600 described *EGFR* variants.[1,2]

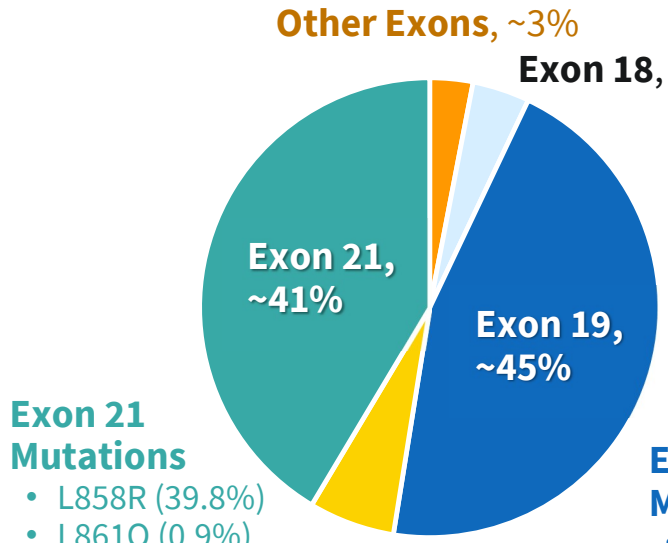


[1]Passaro A. *J Thorac Oncol*. 2021; [2]https://cancer.sanger.ac.uk; [3]Irmer D. *Oncogene*. 2007.

EGFR Mutations in NSCLC

- The most common mutations are exon 19 deletions and L858R mutation in exon 21[1,2]
  - Detected in ~85% of all mutation cases
  - Clinically relevant as patients respond to *EGFR* tyrosine TKIs
- Exon 20 insertions are the third most common *EGFR* subtype[3,4]
  - SOC is amivantamab plus platinum-based chemotherapy
  - Prognosis is poorer compared to common *EGFR* mutations

Frequency of *EGFR* Mutations[1]



Exon 21 Mutations
- L858R (39.8%)
- L861Q (0.9%)

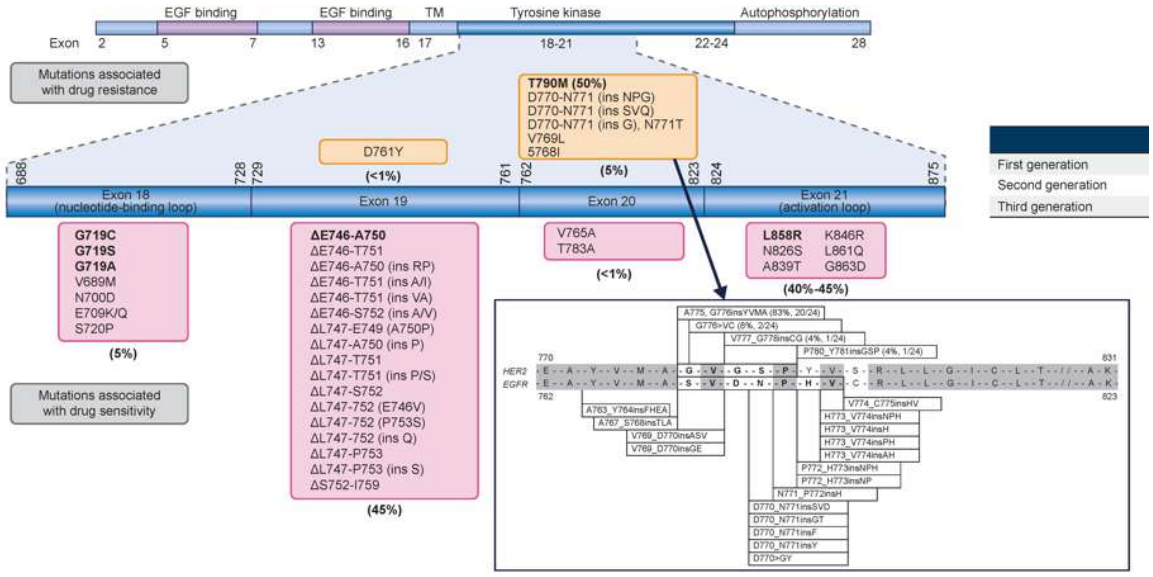
Exon 19 Mutations
- Del 19 (44.8%)
- Ins 19 (0.6%)

[1]Kobayashi Y, et al. *Cancer Sci*. 2016; [2]Girard N, et al. WCLC Annual Meeting 2021: Abstract 3390; [3]Remon J, et al. *Cancer Treat Rev*. 2020; [4]NCCN Guidelines for NSCLC, Version 8.2025.

Molecular Testing

Guidelines (NCCN) recommend **broad molecular profiling** (NGS panels).

- **Comprehensive Profiling (NGS)**
  - Best for detecting rare variants and complex alterations in multiple genes in a single assay
- **PCR-based Assays**
  - Fewer alterations assayed
  - Can detect most common variants (L858R, ex19 del)
  - Fast TAT, less DNA required

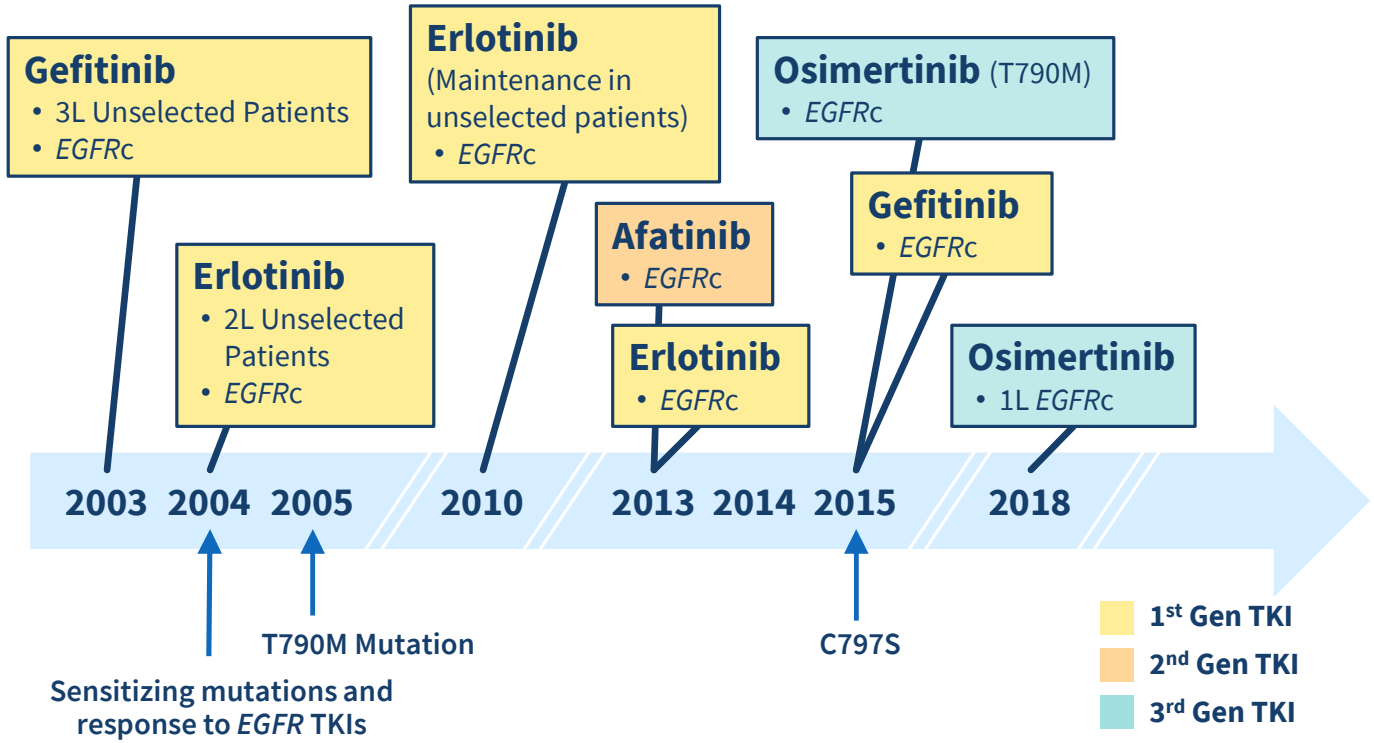


NCCN Guidelines for NSCLC, Version 8.2025; Pirker R, et al. *J Thorac Oncol*. 2010.

What would you consider as first-line treatment?

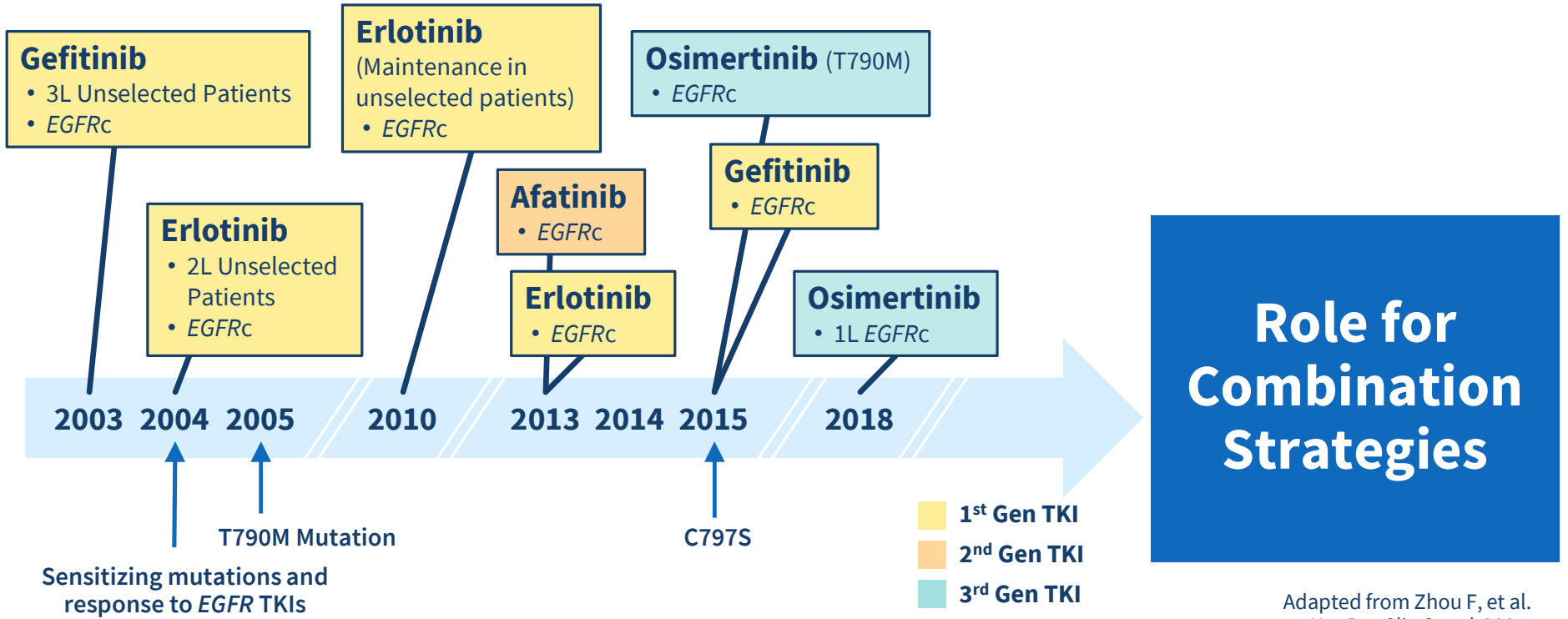
1. Osimertinib
2. Osimertinib + Carboplatin + Pemetrexed
3. Amivantamab + Lazertinib
4. Amivantamab + Chemotherapy
5. Carboplatin + Pemetrexed + Pembrolizumab
6. Carboplatin + Pemetrexed + Bevacizumab
7. Erlotinib

The Arrival of a New Targeted Therapy Paradigm in *EGFR*-mutated Metastatic NSCLC



Adapted from Zhou F, et al. *Nat Rev Clin Oncol*. 2025.

The Arrival of a New Targeted Therapy Paradigm in *EGFR*-mutated Metastatic NSCLC

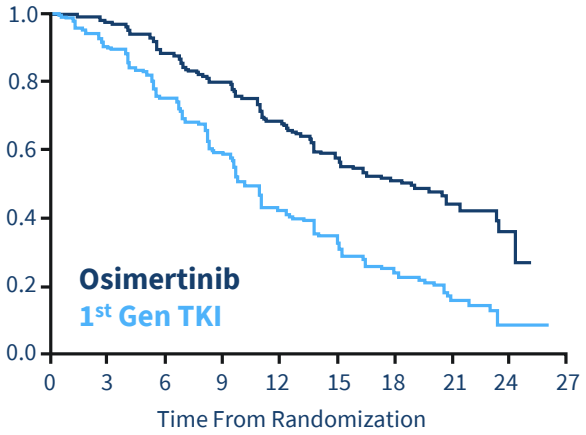


Role for Combination Strategies

Adapted from Zhou F, et al. *Nat Rev Clin Oncol*. 2025.

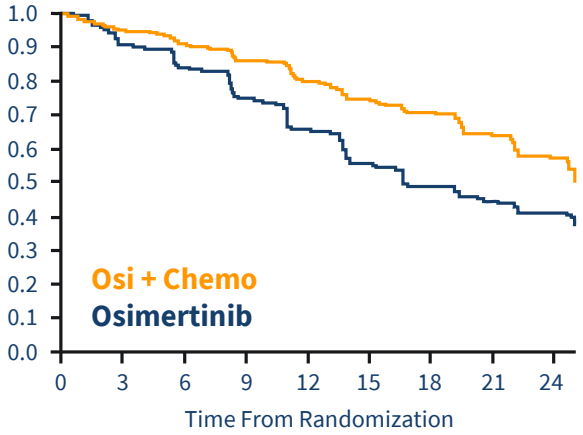
Options for 1L Treatment for *EGFR*+ NSCLC

FLAURA
Osi Mono



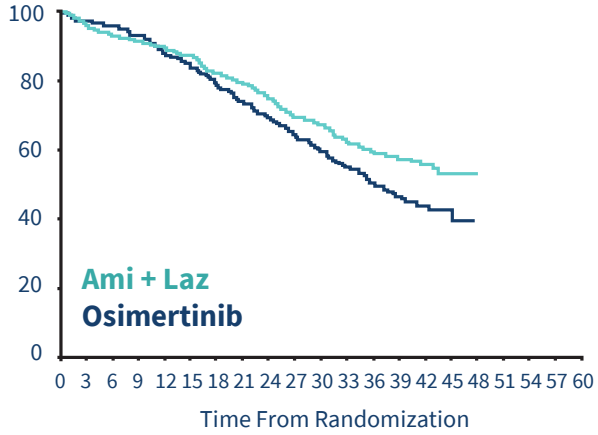
Progression-Free Survival		**Overall Survival**	
Osimertinib	18.9 mo	Osimertinib	38.6 mo
1st Gen TKI	10.2 mo	1st Gen TKI	31.8 mo

FLAURA 2
Osi + Chemo



Progression-Free Survival	
Osi + Chemo	25.5 mo
Osimertinib	16.7 mo

MARIPOSA
Ami + Lazertinib

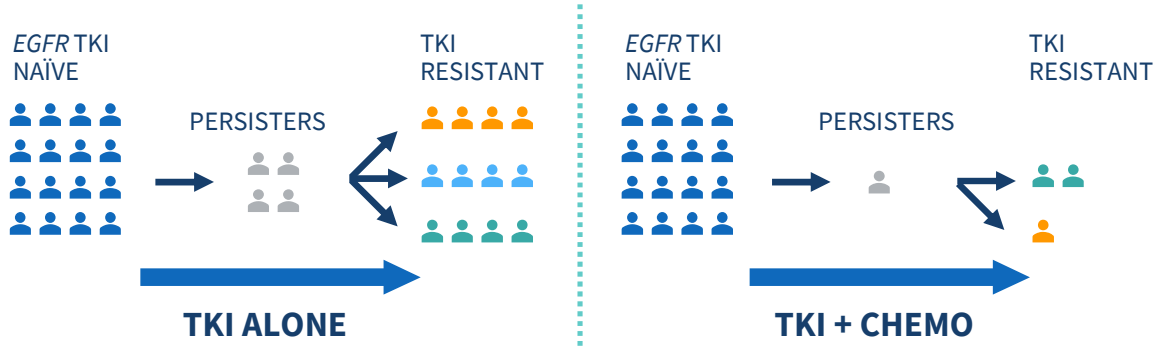


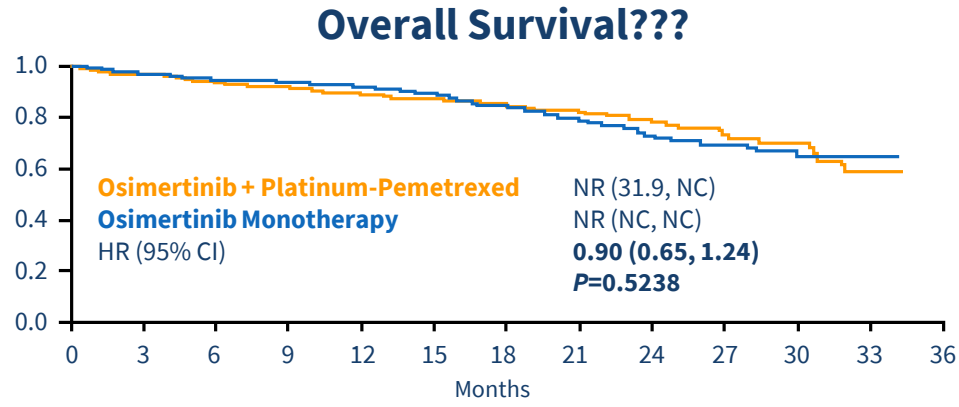
Progression-Free Survival		**Overall Survival**	
Ami + Laz	23.7 mo	Ami + Laz	NR
Osimertinib	16.6 mo	Osimertinib	36.7 mo

Soria JC, et al. *N Engl J Med*. 2018; Planchard D, et al. *N Engl J Med*. 2023; Cho BC, et al. *N Engl J Med*. 2024.

First-line Combination Therapies – Benefit

- To combine two active therapies, there needs to be clear improvement in PFS more than the sum of sequencing OR improvement in overall survival.
- Combination studies demonstrated improved PFS above additive sequencing suggesting further eradication of persister subclones changes natural history
- Allow more patients to receive both therapies (2L drop off of treatment ~30%)



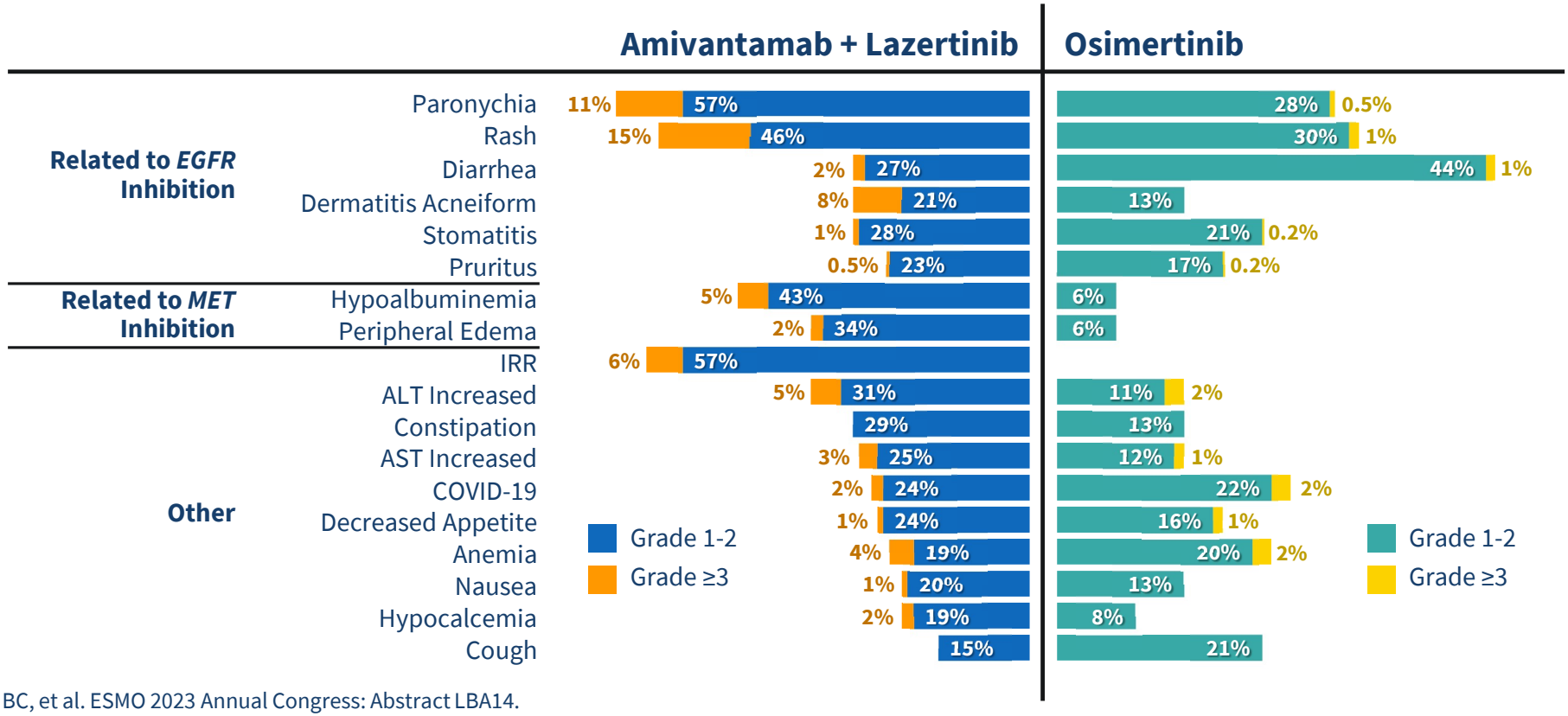


Janne P, et al. WCLC Annual Meeting 2023: Abstract PL03.13.

First-line Combination Therapies – Cost

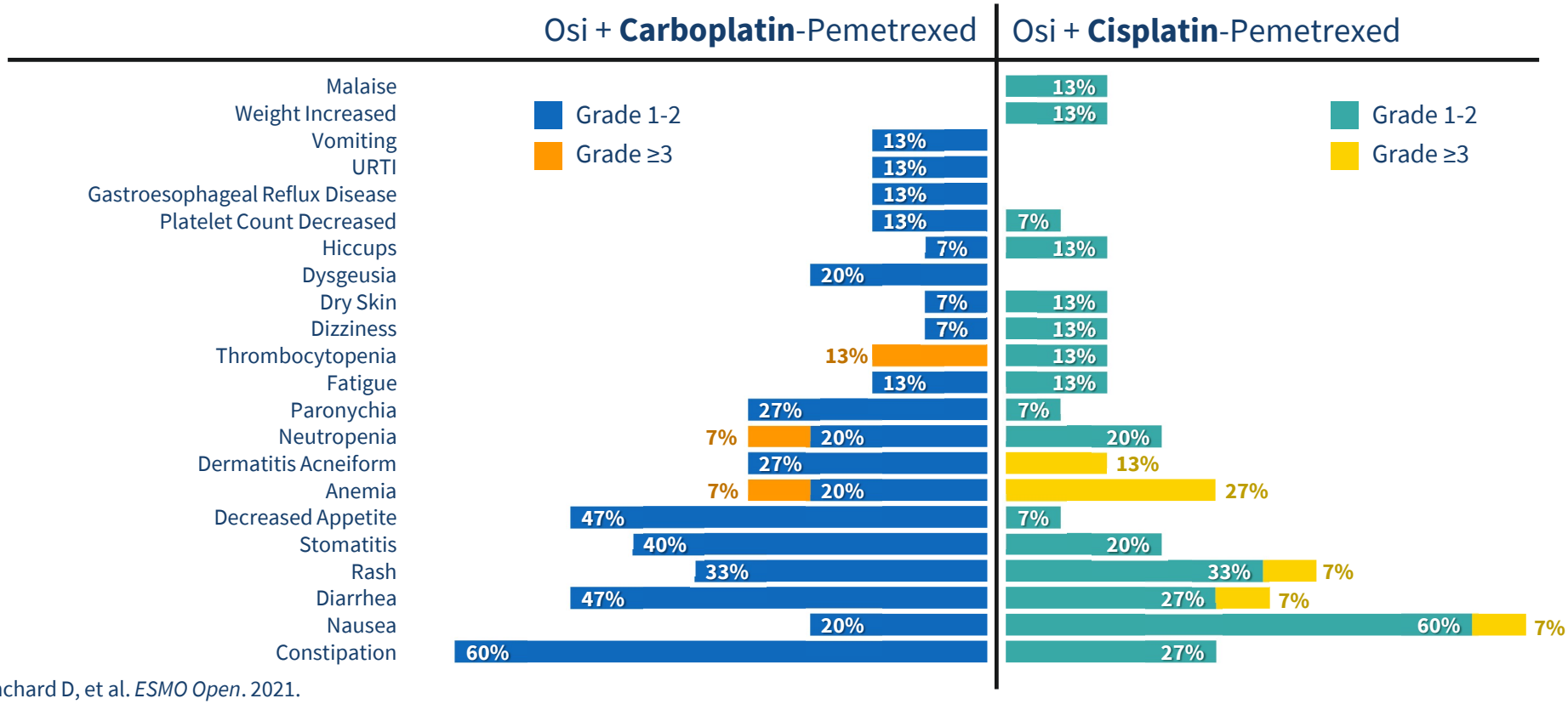
- **Toxicity:** more toxicity and for longer
- **Quality of life:** intravenous therapy every 2-3 weeks
- Financial cost to patient and healthcare system
- **Over-treatment:**
  - Significant heterogeneity in response to osimertinib
  - Many would do well with osimertinib monotherapy

Safety Profiles: Amivantamab + Lazertinib



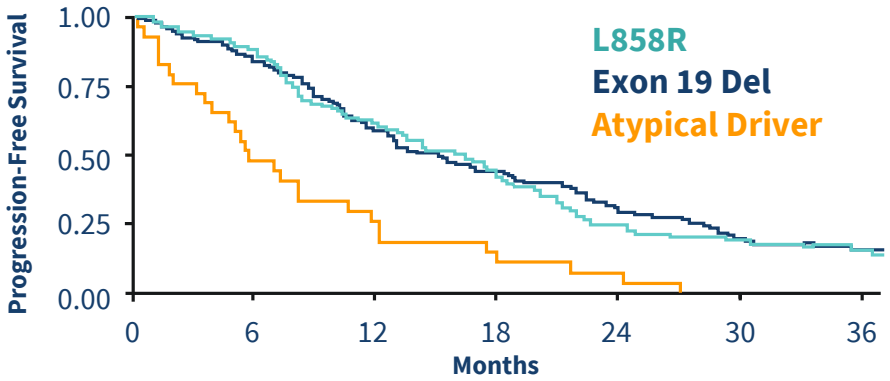
Cho BC, et al. ESMO 2023 Annual Congress: Abstract LBA14.

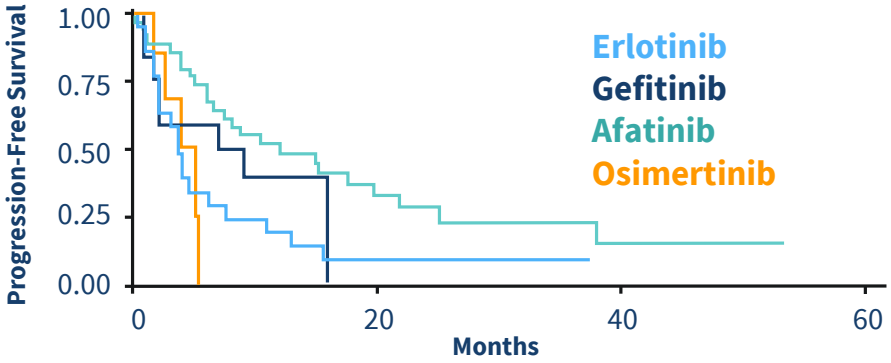
Safety Profiles: Osimertinib + Chemo



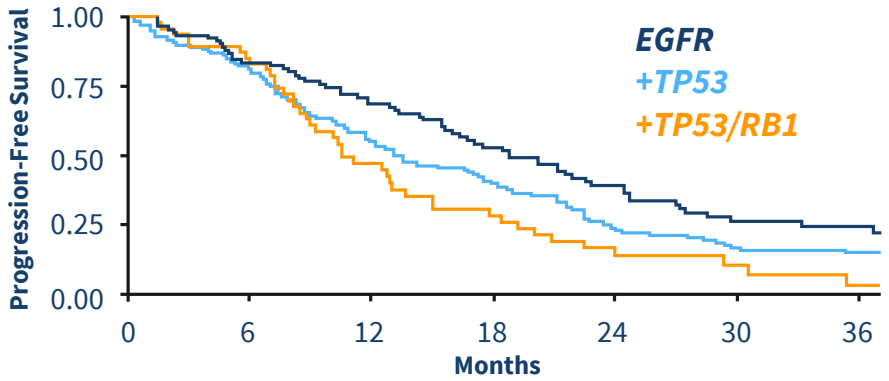
Planchard D, et al. *ESMO Open*. 2021.

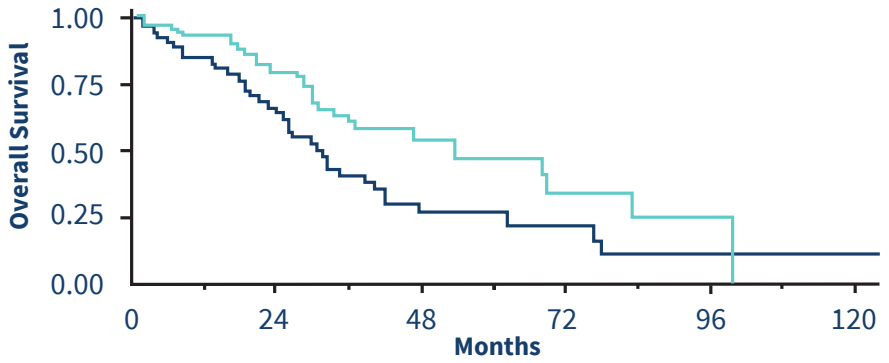
EGFR Mutation Subtype





Co-Mutations





Choudhury NJ, et al. *J Thorac Oncol*. 2023; Janning M, et al. *Ann Oncol*. 2022; Bar J, et al. *J Thorac Oncol*. 2023; Aggarwal C, et al. *JCO Precis Oncol*. 2018.

First-Line Therapy for Locally Advanced or Metastatic *EGFR* + NSCLC

Combination Strategies

FLAURA 2
Osimertinib + Platinum-based Chemotherapy

MARIPOSA
Amivantamab + Lazertinib

Phase 3 FLAURA2: Osimertinib With or Without Chemotherapy in 1L *EGFR*m Advanced NSCLC

Safety Run-in Period (N = 30)
Published in ESMO Open, 2021

Patient with untreated locally advanced/metastatic *EGFR*m NSCLC

Key Inclusion Criteria:

- Aged ≥ 18 years (Japan: ≥ 20 years)
- Pathologically confirmed non-squamous NSCLC
- EX19del/L858R (local/central test)
- WHO PS 0/1
- No prior systemic therapy for advanced NSCLC
- Stable CNS metastases were allowed*
- Brain scans at baseline (MRI/CT)

Stratification by:

- **Race** (Chinese Asian/non-Chinese Asian/non-Asian)
- ***EGFR*m** (local/central test)
- **WHO PS** (0/1)

Randomization 1:1 (N = 557)

Osimertinib 80 mg (QD) + **Pemetrexed** 500 mg/m^2 + **Carboplatin** AuC5 or **Cisplatin** 75 mg/m^2 (Q3W for 4 cycles for platinum-based treatments)

Maintenance **Osimertinib** 80 mg (QD) + **Pemetrexed** (Q3W)†

Osimertinib 80 mg (QD)

Follow-up:
RECIST 1.1 assessment at 6 and 12 weeks, then every 12 weeks until RECIST 1.1 defined radiological disease progression or other withdrawal criteria were met

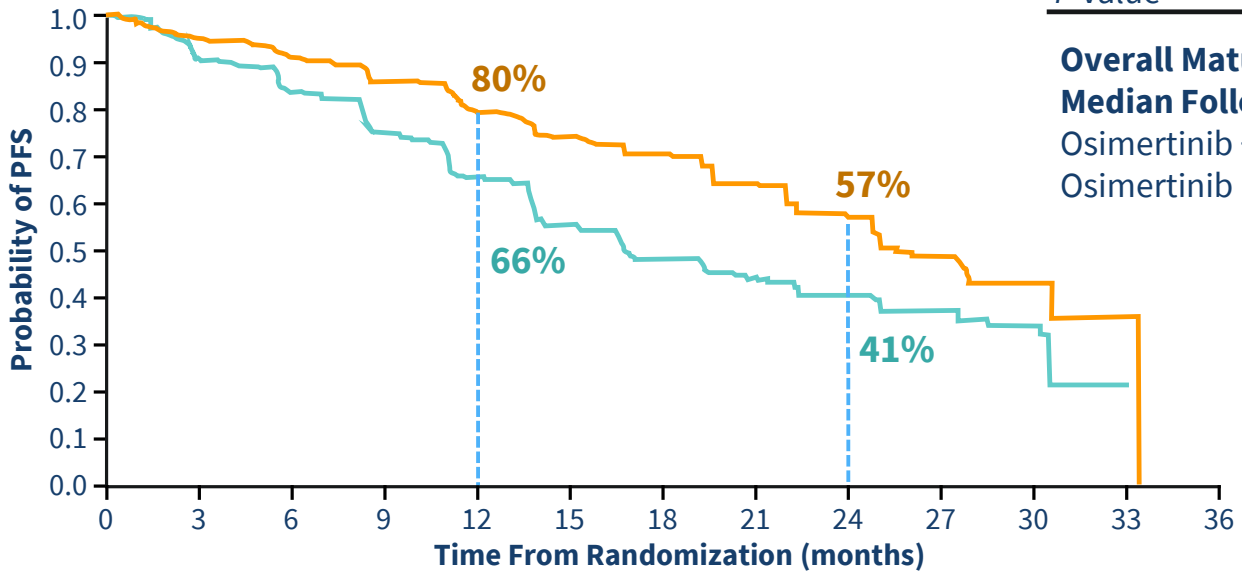
- **Primary endpoint**: PFS by investigator assessment per RECIST 1.1‡§
  - **Sensitivity analysis**: PFS by BICR assessment per RECIST 1.1
- **Secondary endpoints**: OS, ORR, DoR, DCR, HRQoL, safety (AEs by CTCAE v5) and PFS2‡

*Not requiring steroids for at least two weeks. †Pemetrexed maintenance continued until a discontinuation criterion was met. ‡Efficacy analyses in the full analysis set, defined as all patients randomized to study treatment regardless of the treatment actually received and safety analyses in the safety analysis set, defined as all randomized patients who received ≥ 1 dose of study treatment–one patient who was randomized to osimertinib plus platinum-pemetrexed received only osimertinib and was therefore included in the osimertinib monotherapy safety analysis set. §The study provided 90% power to demonstrate a statistically significant difference in PFS assuming HR = 0.68 at 5% two-sided significance level.

Janne P, et al. WCLC Annual Meeting 2023: Abstract PL03.13; Planchard D, et al. *N Engl J Med*. 2023.

FLAURA2 Trial: PFS per Investigator Assessment

	Osimertinib + Chemotherapy	Osimertinib
Median PFS (95% CI) mo	**25.5** (24.7–NC)	**16.7** (14.1–21.3)
HR (95% CI)	**0.62** (0.49–0.79)	
P value	<0.0001	



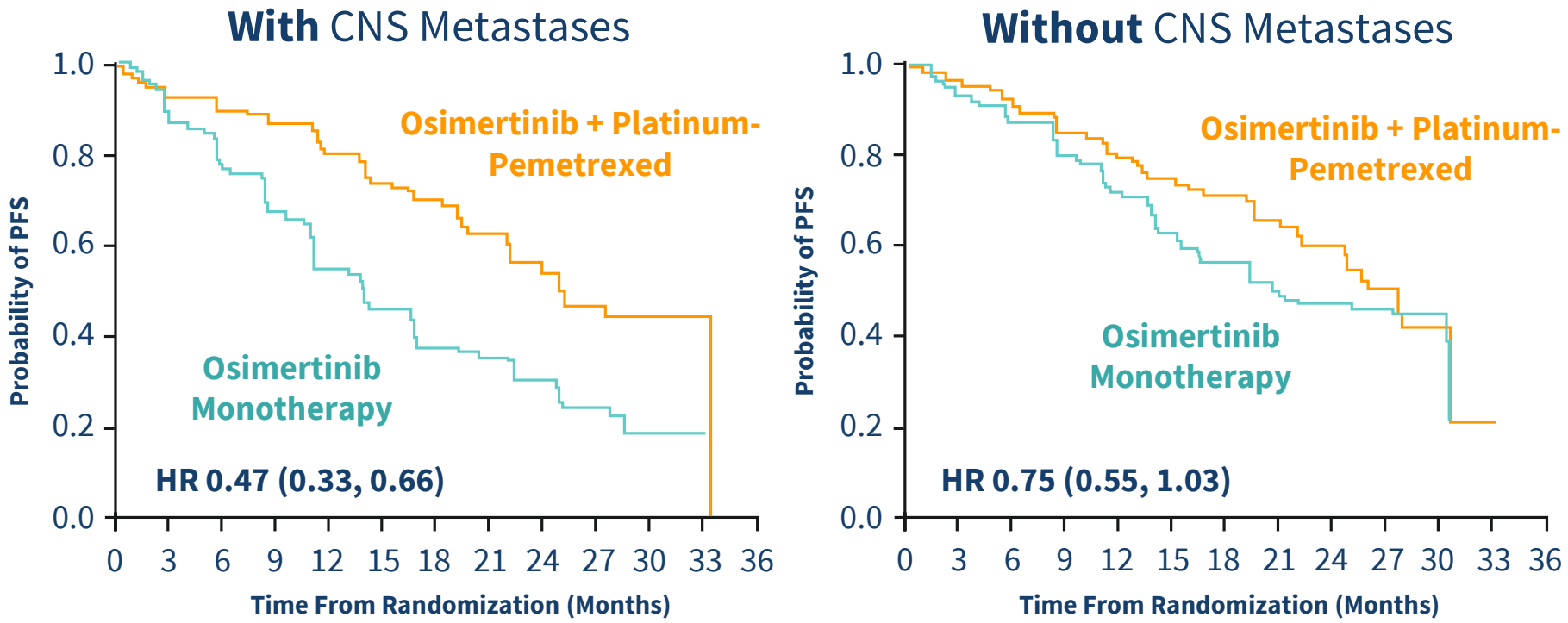
Overall Maturity: 51%
Median Follow-up for PFS*, months (range):
Osimertinib + platinum-pemetrexed, 19.5 (0–33.3)
Osimertinib monotherapy, 16.5 (0–33.1)

Subsequent Treatment in Osimertinib Arm:
Chemotherapy 40%

mPFS was improved by ~8.8 months with osimertinib + platinum-pemetrexed vs osimertinib monotherapy

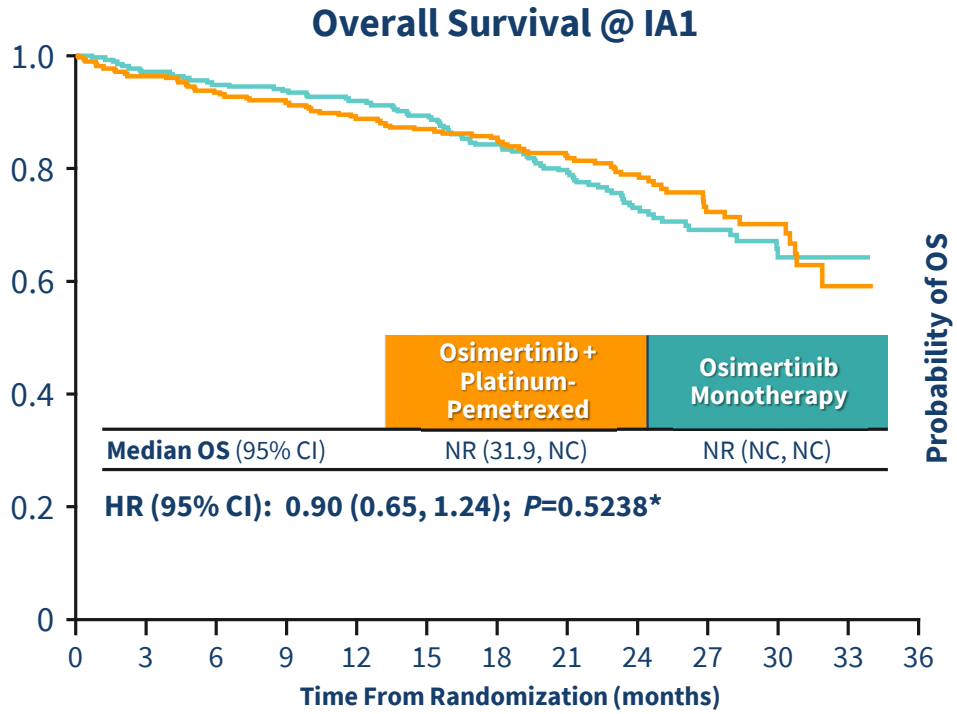
Planchard D, et al. *N Engl J Med*. 2023.

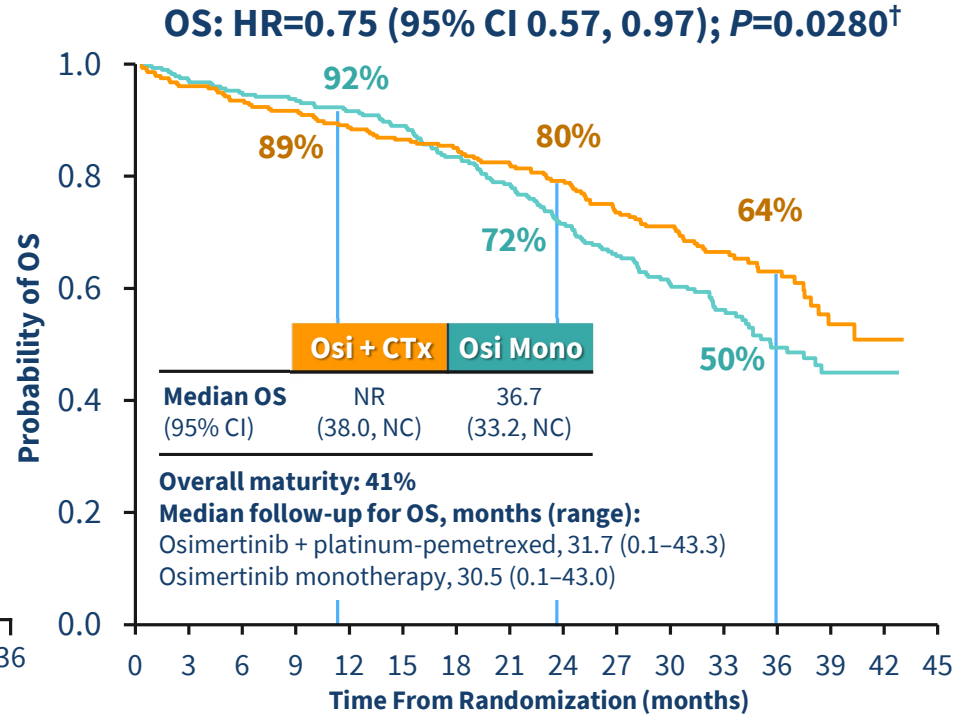
FLAURA2: PFS per Investigator by CNS Metastases



Janne P, et al. WCLC Annual Meeting 2023: Abstract PL03.13

FLAURA2: Overall Survival Updated 2nd Interim Analysis





Janne P, et al. WCLC Annual Meeting 2023: Abstract PL03.13; Gadgeel S, et al. WCLC Annual Meeting 2024: Abstract OA02.03; Valdiviezo N et al. WCLC Annual Meeting 2024: Abstract MA12.04; Yang J, et al. WCLC Annual Meeting 2024: Abstract MA12.03.

Data cut-off: 03 April 2023; Data cut-off: 08 January 2024; †A p-value of ≤0.000001 was required for statistical significance at this second interim analysis; *Subgroup analyses for OS were exploratory. †Patients with both Ex19del and L858R were included in the Ex19del group.

FLAURA2 Trial: Safety Summary

Patients with AEs, n (%)	Osimertinib + Platinum-Pemetrexed (N=276)	Osimertinib Monotherapy (N=275)
AE any cause	**276 (100)**	**268 (97)**
Any AE Grade ≥ 3	176 (64)	75 (27)
Any AE leading to death	18 (7)	8 (3)
Any serious AE	104 (38)	53 (19)
Any AE leading to discontinuation	132 (48)	17 (6)
Osimertinib / carboplatin or cisplatin / pemetrexed discontinuation	30 (11) / 46 (17) / 119 (43)	17 (6) / NA / NA
AE possibly causally related to treatment	**269 (97)**	**241 (88)**
Any AE Grade ≥ 3	146 (53)	29 (11)
Causally related to osimertinib / carboplatin or cisplatin / pemetrexed	81 (29) / 104 (38) / 130 (47)	29 (11) / NA / NA
Any AE leading to death	5 (2)	1 (< 1)
Causally related to osimertinib / carboplatin or cisplatin / pemetrexed	3 (1) / 2 (1) / 3 (1)	1 (≤ 1) / NA / NA
Any serious AE	52 (19)	15 (5)

Total duration of osimertinib exposure, median (range)

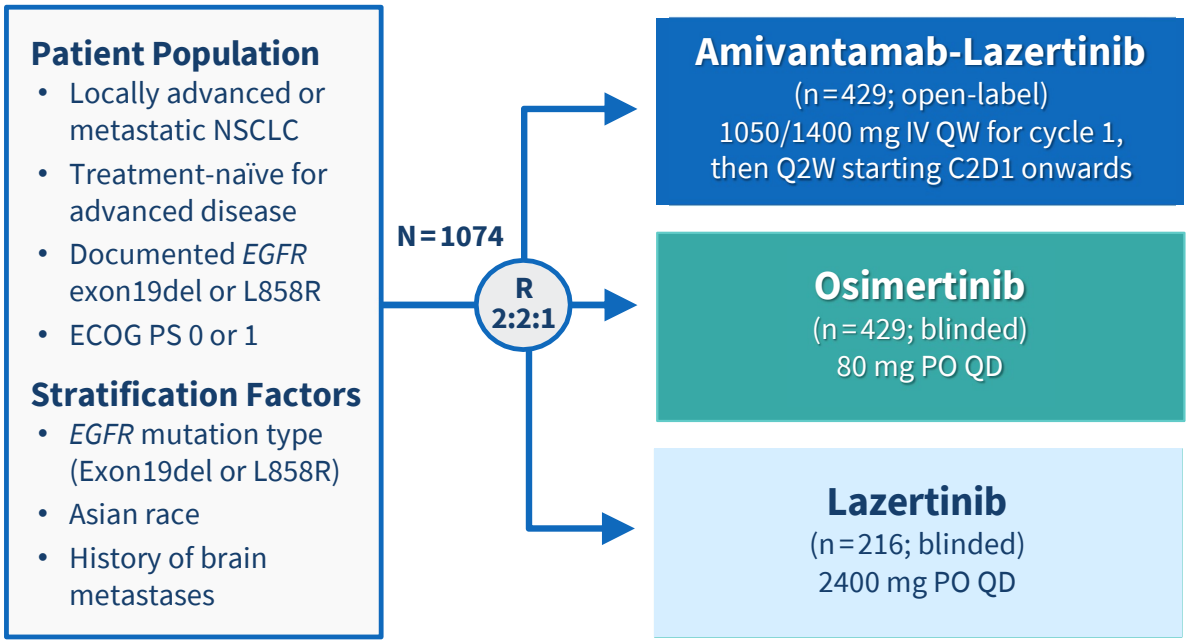
Osimertinib + Platinum-Pemetrexed: **22.3 (0.1–33.8) months**

Osimertinib Monotherapy: **19.3 (0.1–33.8) months**

In the combination arm, patients received a median of 12 cycles of pemetrexed (range 1–48) and 211 patients (76%) completed 4 cycles of platinum-based chemotherapy.

Janne P, et al. WCLC Annual Meeting 2023: Abstract PL03.13; Planchard D, et al. *N Engl J Med*. 2023.

Phase 3 MARIPOSA: Amivantamab + Lazertinib vs Osimertinib vs Lazertinib in 1L *EGFR*m NSCLC



Amivantamab-Lazertinib vs Osimertinib

Primary Endpoint

- PFS by BICR per RECIST v1.1

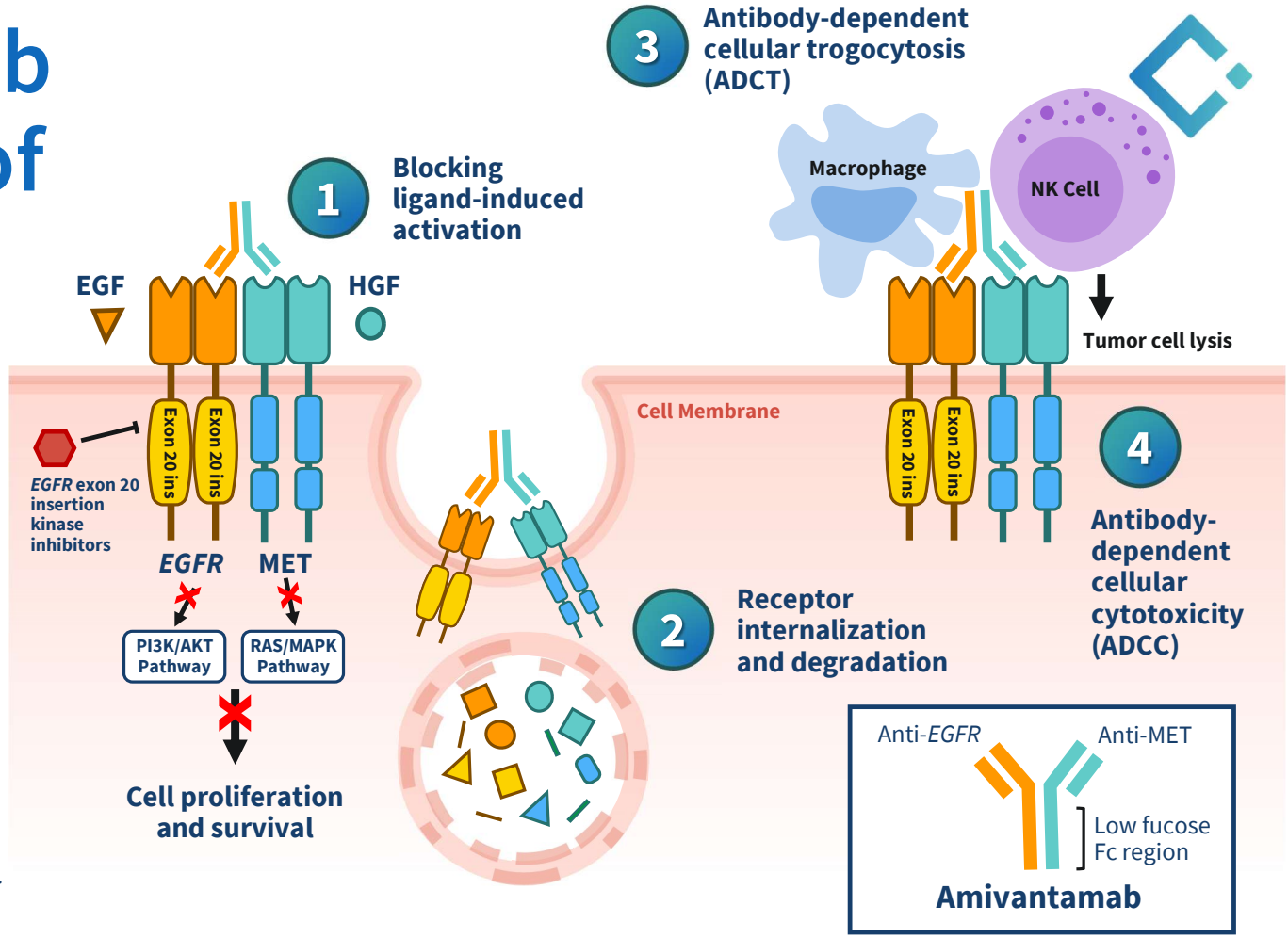
Key Secondary Endpoints

- OS
- ORR
- DoR
- PFS after first subsequent therapy
- Symptomatic PFS
- Intracranial PFS
- Safety

Cho BC, et al. *Future Oncol*. 2022.

Amivantamab Mechanism of Action

Secondary resistance is a major cause of TKI resistance (secondary *EGFR* mutations and *MET* mutations/amp).

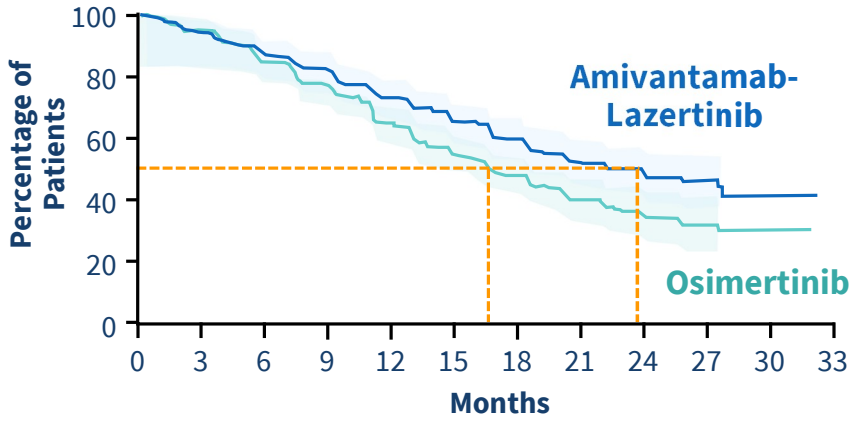


Moores SL, et al. *Cancer Res*. 2016; Haura EB, et al. ASCO Annual Meeting 2019: Abstract 9009; Vijayaraghavan S, et al. *Mol Cancer Ther*. 2020.

MARIPOSA: PFS Amivantamab + Lazertinib vs Osimertinib

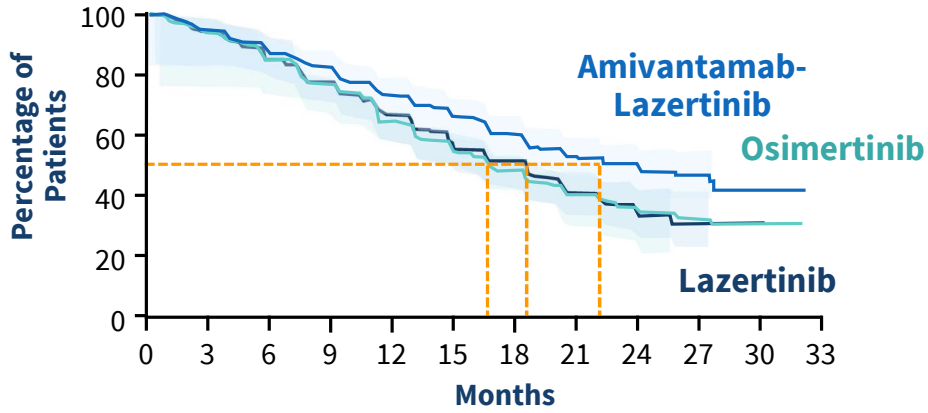
PFS in the Amivantamab-Lazertinib Group vs Osimertinib Group

	Amivantamab-Lazertinib	Osimertinib
Median PFS (95% CI) mo	**23.7** (19.1–27.7)	**16.6** (14.8–18.5)
HR (95% CI)	**0.70** (0.58–0.85)	
P-value	**< 0.001**	



PFS in the Amivantamab-Lazertinib Group vs Osimertinib and Lazertinib Monotherapy Groups

	Amivantamab-Lazertinib	Osimertinib	Lazertinib
Median PFS (95% CI) mo	**23.7** (19.1–27.7)	**16.6** (14.8–18.5)	**18.5** (14.8–20.1)
HR (95% CI) for Ami+Laz vs Laz	**0.72** (0.57–0.90)		

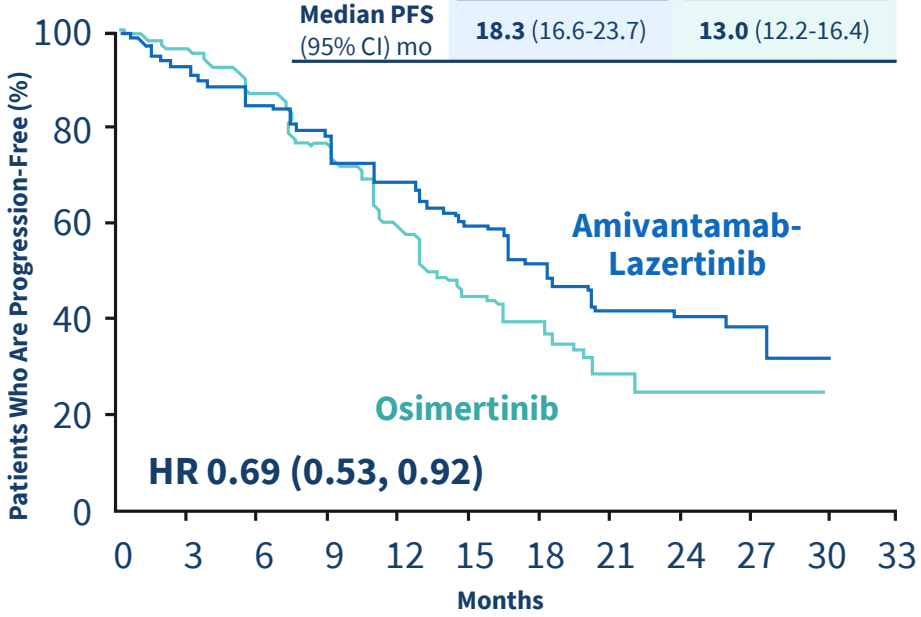


Cho BC, et al. *N Engl J Med*. 2024.

MARIPOSA: PFS by CNS Metastases

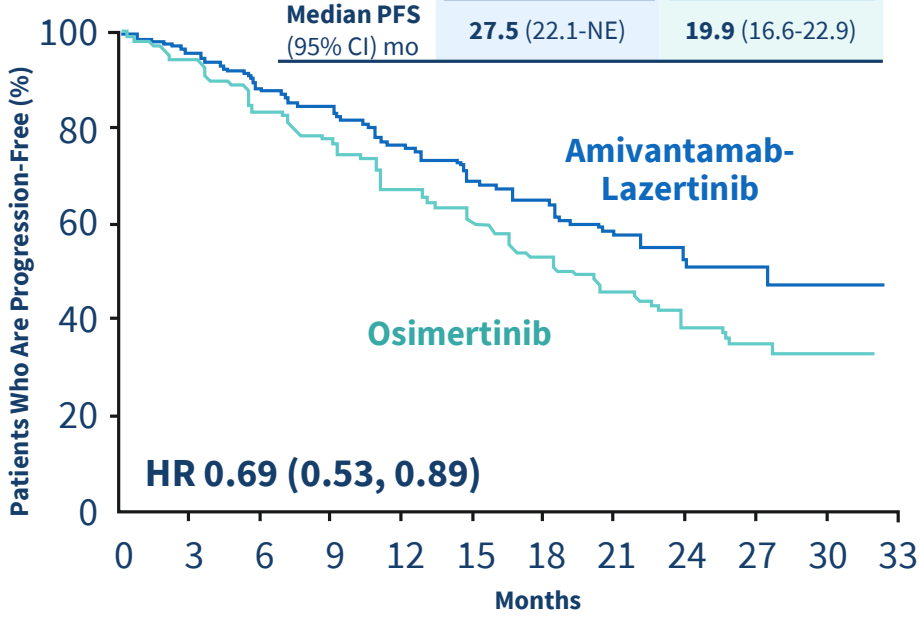
With History of Brain Metastases

	Amivantamab-Lazertinib	Osimertinib
Median PFS (95% CI) mo	**18.3** (16.6-23.7)	**13.0** (12.2-16.4)



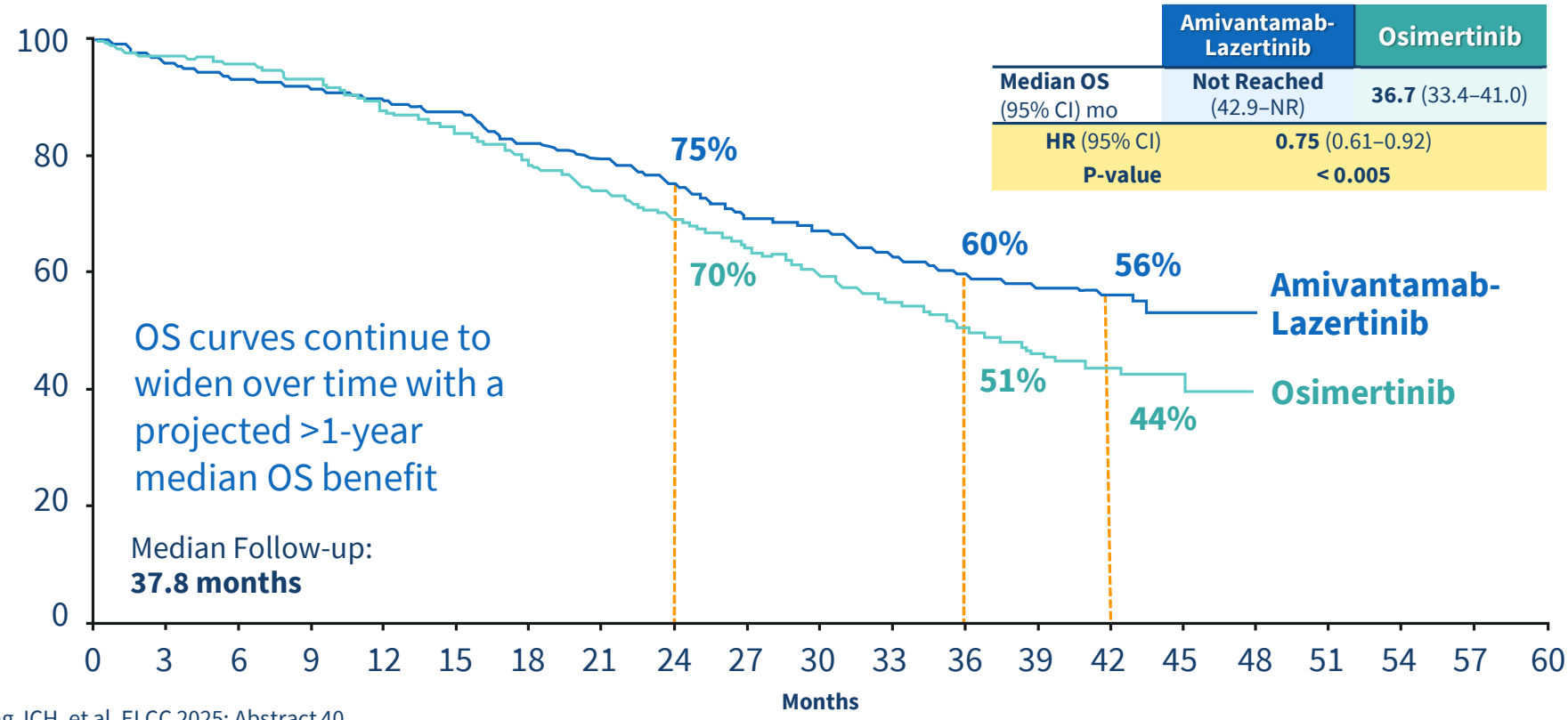
Without History of Brain Metastases

	Amivantamab-Lazertinib	Osimertinib
Median PFS (95% CI) mo	**27.5** (22.1-NE)	**19.9** (16.6-22.9)



Cho B, et al. *Ann Oncol*. 2023.

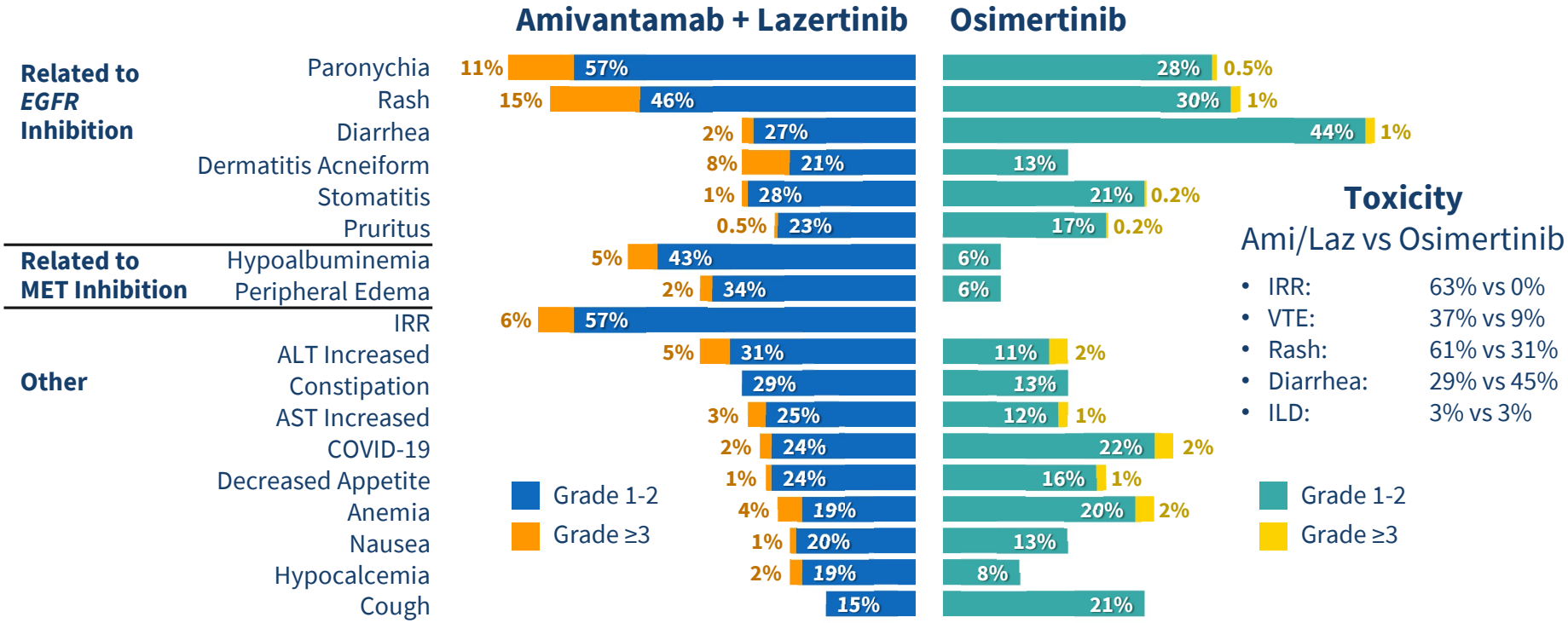
MARIPOSA: Overall Survival



	Amivantamab-Lazertinib	Osimertinib
Median OS (95% CI) mo	**Not Reached** (42.9–NR)	**36.7** (33.4–41.0)
HR (95% CI)	**0.75** (0.61–0.92)	
P-value	**< 0.005**	

Yang JCH, et al. ELCC 2025: Abstract 40.

What About Toxicity?



Toxicity

Ami/Laz vs Osimertinib

- IRR: 63% vs 0%
- VTE: 37% vs 9%
- Rash: 61% vs 31%
- Diarrhea: 29% vs 45%
- ILD: 3% vs 3%

Cho BC, et al. *Ann Oncol*. 2023.

MARIPOSA: Safety Profile With Amivantamab + Lazertinib vs Osimertinib

Event	Amivantamab-Lazertinib (n = 421)		Osimertinib (n = 428)	
	All	Grade ≥ 3	All	Grade ≥ 3
Any event, n (%)	421 (100)	316 (75)	425 (99)	183 (43)
Any serious event, n (%)	205 (49)		143 (33)	
Any event resulting in death, n (%)	—	34 (8)	—	31 (7)
Event leading to interruption of any trial agent, n (%)	350 (83)		165 (39)	
Event leading to dose reduction of any trial agent, n (%)	249 (59)		23 (5)	
Event leading to discontinuation of any trial agent, n (%)	147 (35)		58 (14)	

TRAE Discontinuation Rate:

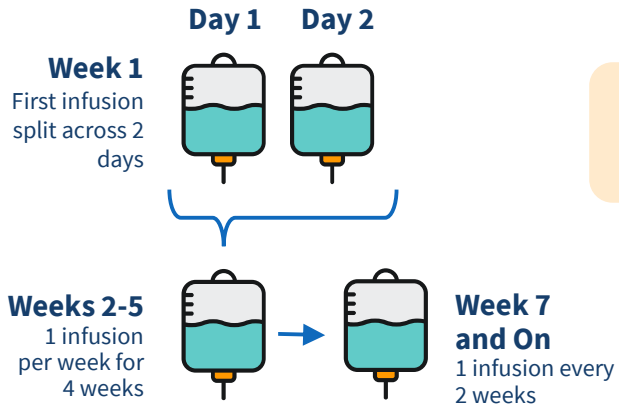
- 10% Amivantamab + Lazertinib
- 3% with Osimertinib

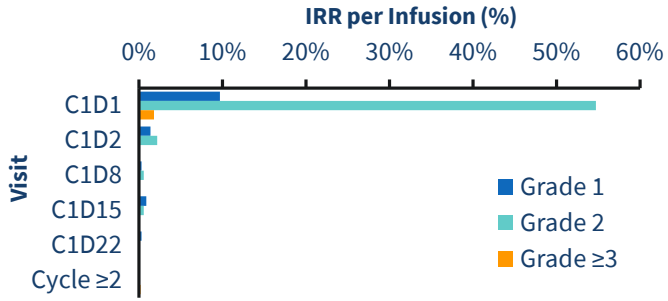
EGFR-related toxicities & pulmonary embolism higher in Amivantamab + Lazertinib arm

TRAE, treatment-related adverse event

Cho BC, et al. *N Engl J Med*. 2024.

Infusion Related Reaction





Park K, et al. *Ann Oncol*. 2021.

The initial infusion should be administered in split doses on Week 1, Day 1 and 2

Prior to initial infusion (Week 1), antihistamines, antipyretics, and glucocorticoids should be administered to reduce the risk of IRRs

For subsequent doses, antihistamines and antipyretics should be administered.

Patients should be treated in a setting with appropriate medical support to treat IRRs.

Infusions should be interrupted at the first sign of IRRs of any severity and additional medicinal products* should be administered as clinically indicated

Upon resolution of symptoms, the infusion should be resumed at 50% of the previous rate.

For recurrent Grade 3 or Grade 4 IRRs, amivantamab should be permanently discontinued.

*e.g., additional glucocorticoids, antihistamine, antipyretics and antiemetics.

SKIPPirr (WCLC2024)

Can We Prevent Infusion Related Reactions? SKIPPirr Study Design

IV **Amivantamab**
1050 mg (<80 kg)
1400 mg (≥80 kg)
Once weekly for 4 weeks; every 2 weeks thereafter
+
Oral **Lazertinib**
240 mg QD

If both Cohorts A and A2 have positive results, only one will move on to Stage 2 as determined by the SET.

Stage 1

Cohort A
Oral Dexamethasone (4 mg)

Cohort A2
Oral Dexamethasone (8 mg)

Cohort B
Oral Montelukast (10 mg)

Cohort C
SC Methotrexate (25 mg)

If IRR ≤3/6 pt, proceed to Stage 2

Stage 2

Enroll up to **10** additional patients per cohort.

If IRR ≤8/16 pt, proceed to Expansion Stage

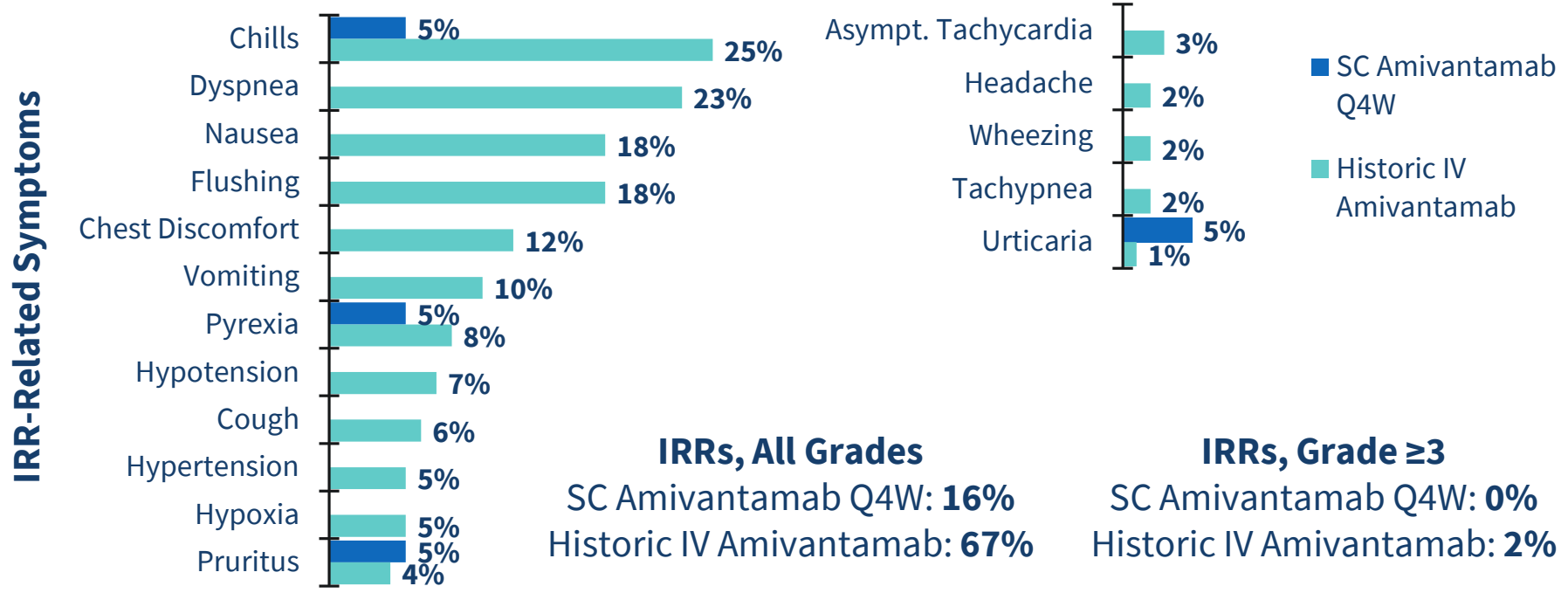
Expansion Stage

Enroll up to **24** additional patients per cohort.

Prophylaxis with 8mg oral dexamethasone resulted in reduction in IRR compared to historical data

Lopes G, et al. WCLC Annual Meeting 2024: Abstract MA12.08.

Incidence of IRR and IRR Related Symptoms PALOMA (Subcutaneous)



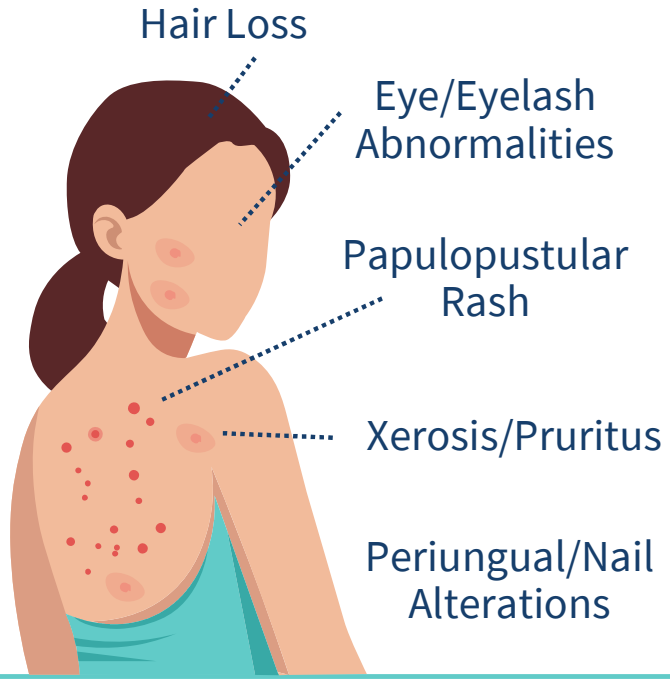
IRRs, All Grades
SC Amivantamab Q4W: **16%**
Historic IV Amivantamab: **67%**

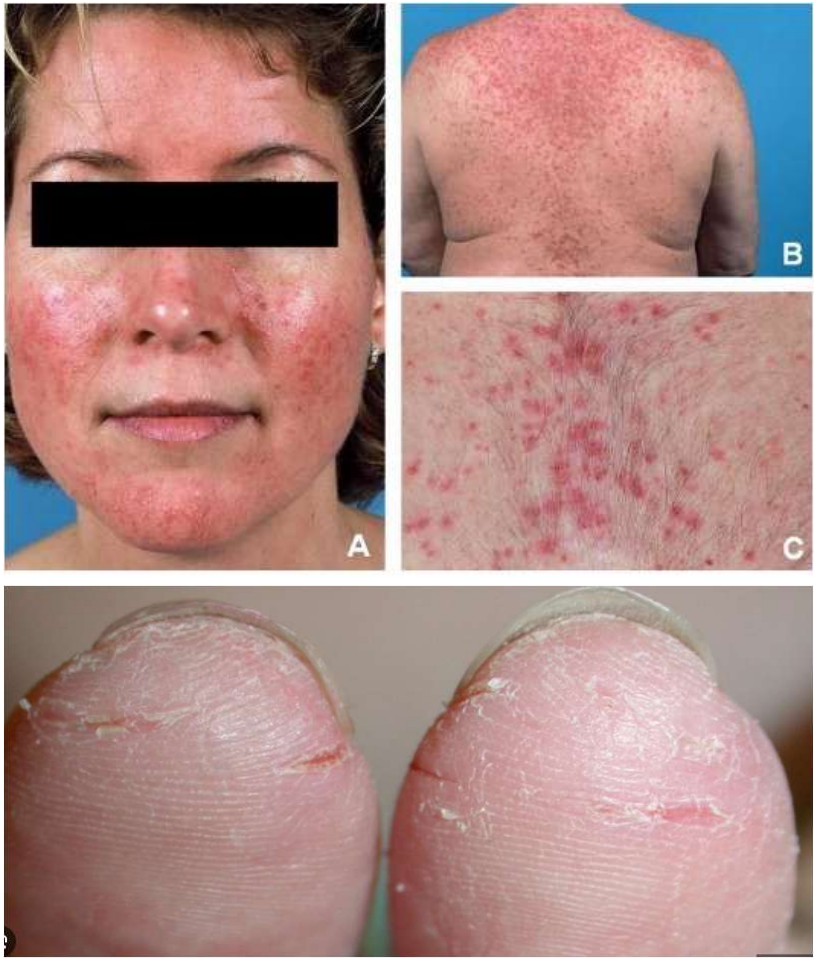
IRRs, Grade ≥3
SC Amivantamab Q4W: **0%**
Historic IV Amivantamab: **2%**

Leighl NB, et al. ELCC 2024: Abstract 6MO.

EGFR Inhibition Mediated Cutaneous Toxicities

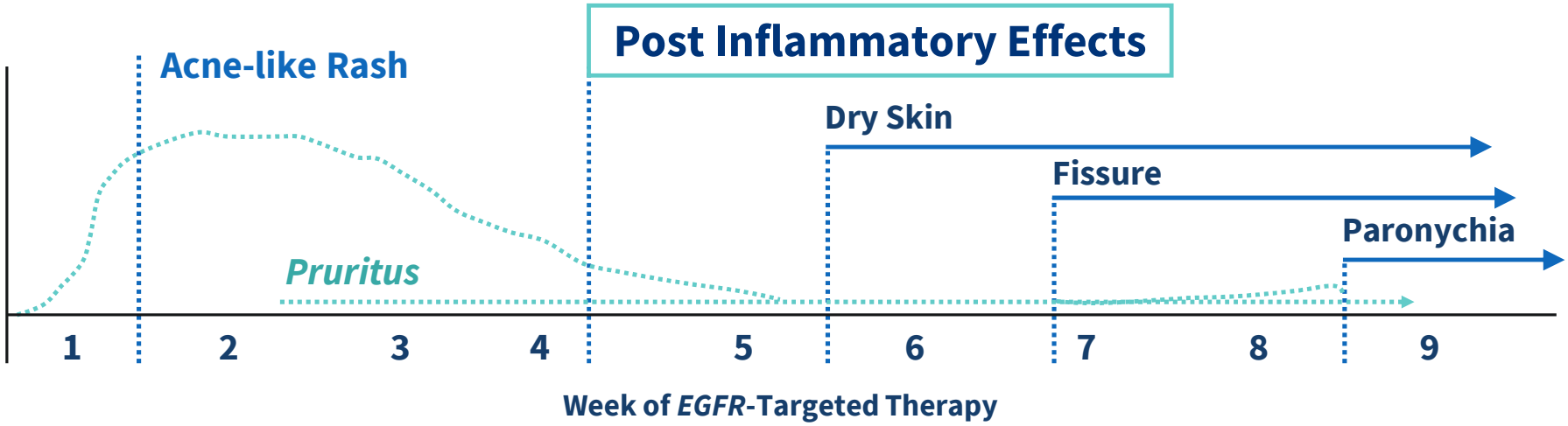
Cutaneous





Images courtesy of Dr. Sabari.

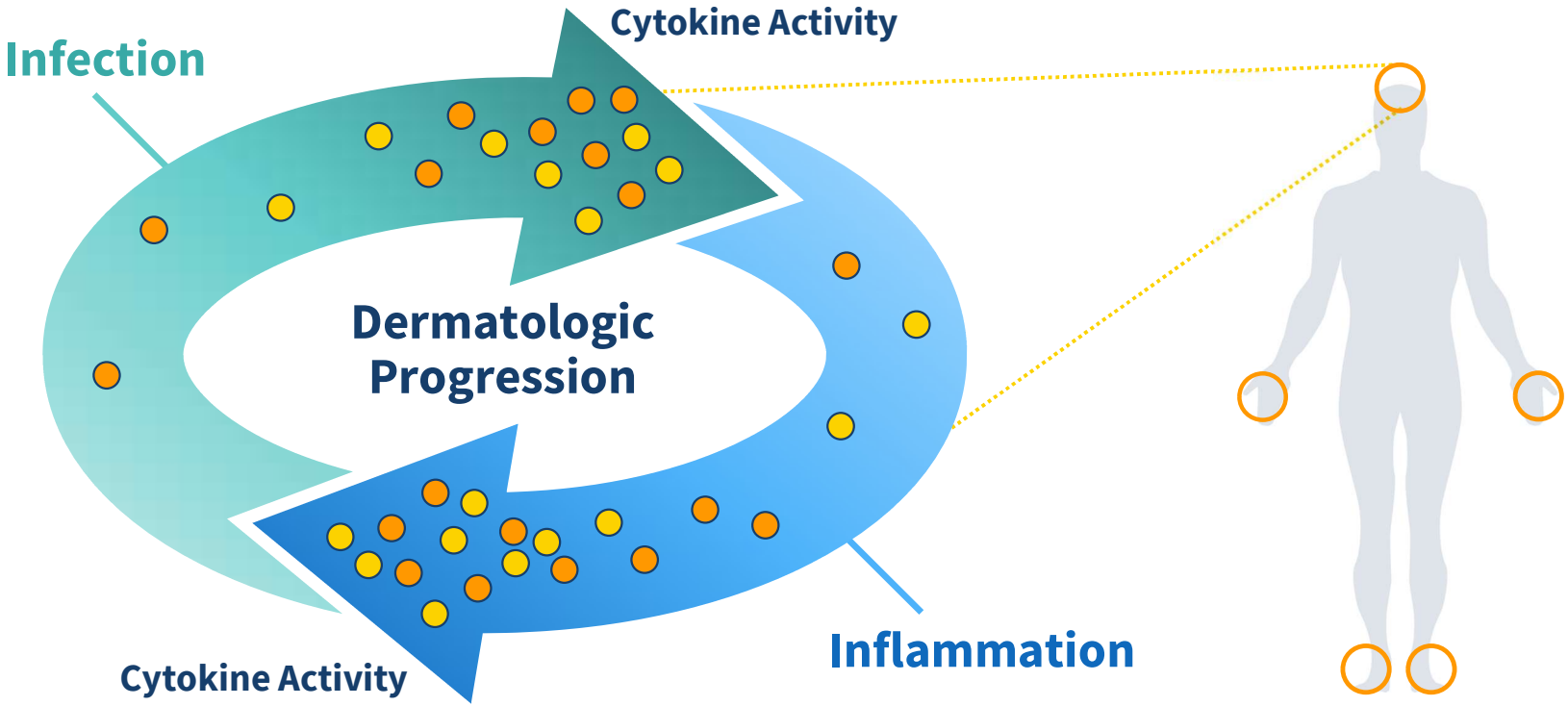
Timing of *EGFR*i Associated Dermatologic Toxicities



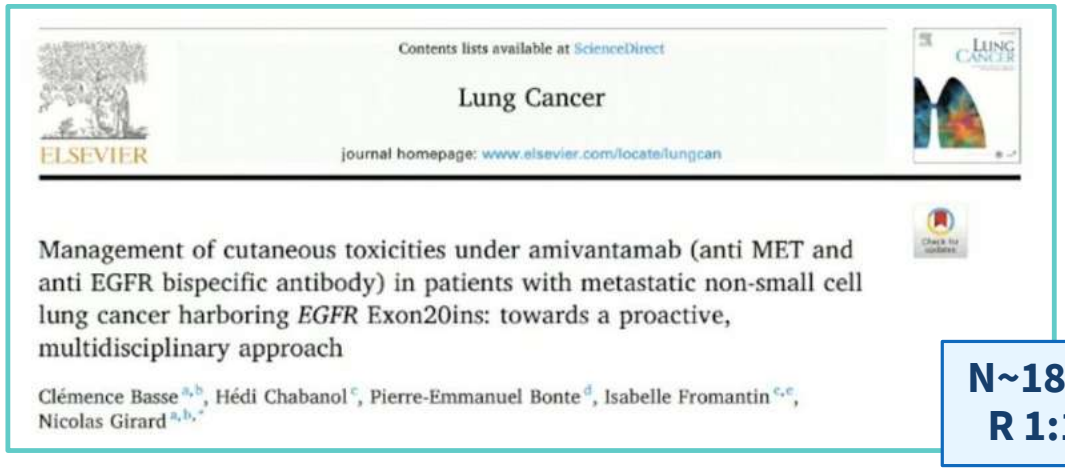
Clinical sequelae of **skin drying and cracking** emphasize the important role of **proactive management**

Van Cutsem E. *Oncologist*. 2006; Lacouture ME, et al. *J Clin Oncol*. 2010; Scope A, et al. *J Clin Oncol*. 2007.

Cycle of Dermatologic Toxicities



Cocoon Trial: First-line Ami/Laz With Enhanced Dermatologic Care



Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Management of cutaneous toxicities under amivantamab (anti MET and anti EGFR bispecific antibody) in patients with metastatic non-small cell lung cancer harboring *EGFR* Exon20ins: towards a proactive, multidisciplinary approach

Clémence Basse[a,b], Hédi Chabanol[c], Pierre-Emmanuel Bonte[d], Isabelle Fromantin[c,e], Nicolas Girard[a,b,*]

N~180, R 1:1

Enhanced Dermatologic Management Group

Arm A (n~90)

Doxycycline or **Minocycline** 100 mg PO BID for 12 weeks +
Clindamycin 1% topical lotion +
Chlorhexidine 4% topical solution +
Noncomedogenic Skin Moisturizer QD +
Amivantamab IV + **Lazertinib** 240 mg PO QD

SOC Dermatologic Management Group

Arm B (n~90)

SOC Dermatologic Management per local practice +
Amivantamab IV + **Lazertinib** 240 mg PO QD

Key Points

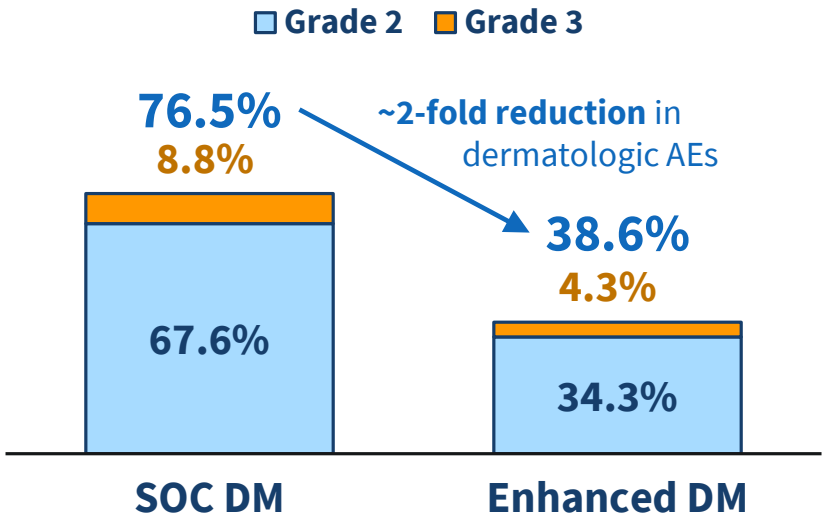
- Prophylactic tetracycline antibiotics at the start of treatment
- Early introduction of moisturizers and topical corticosteroids
- Consider treatment interruption if grade 2+
- Multidisciplinary care with dermatology

Basse C, et al. *Lung Cancer*. 2022; COCOON (ClinicalTrials.gov Identifier: NCT06120140).

Early Onset Adverse Event Can Be Significantly Reduced With Prophylactic Approaches

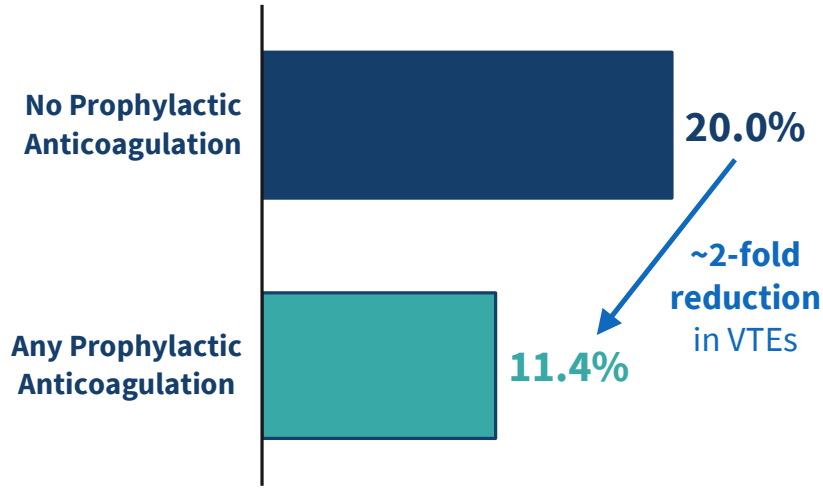
COCOON DM Regimen

Substantially Reduced Grade ≥2 Dermatologic AEs



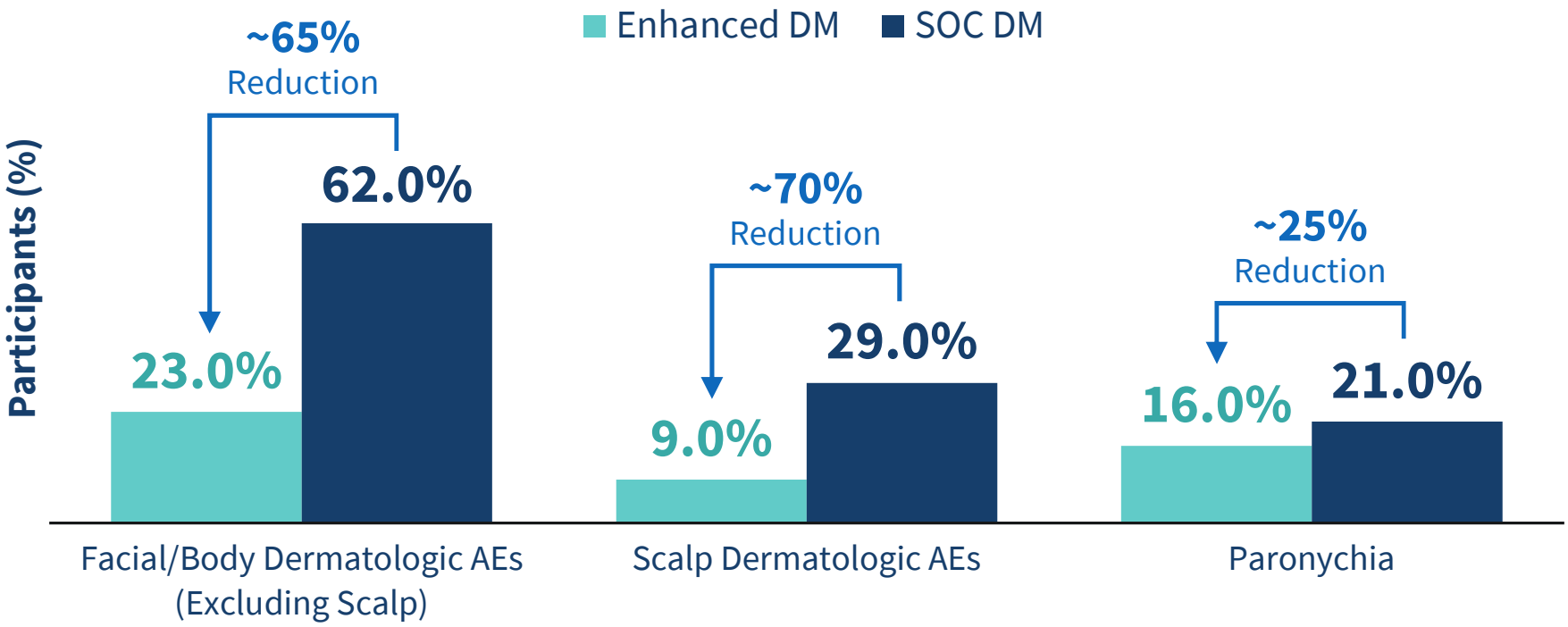
Prophylactic Anticoagulation

Substantially Reduced VTEs



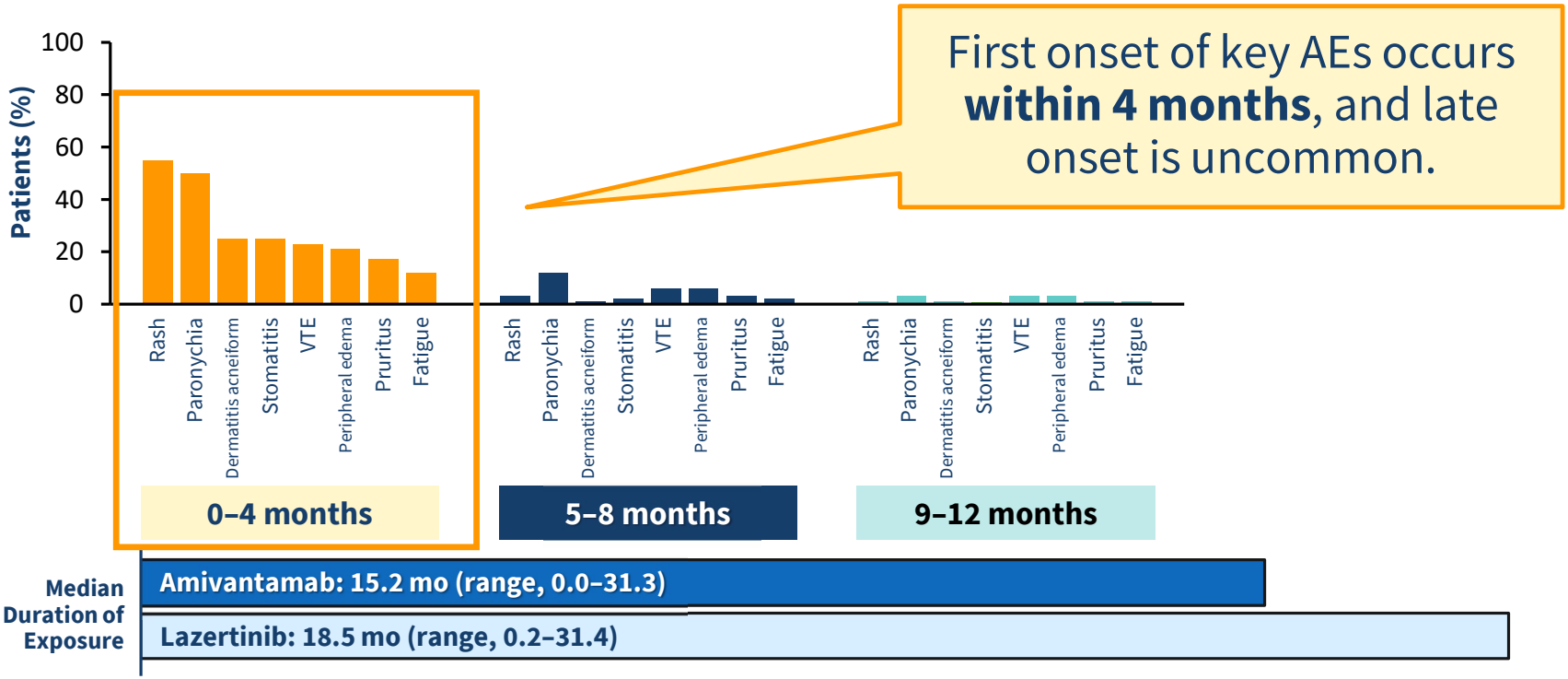
Girard N, et al. ELCC 2025: Abstract 10MO.

COCOON Regimen Results



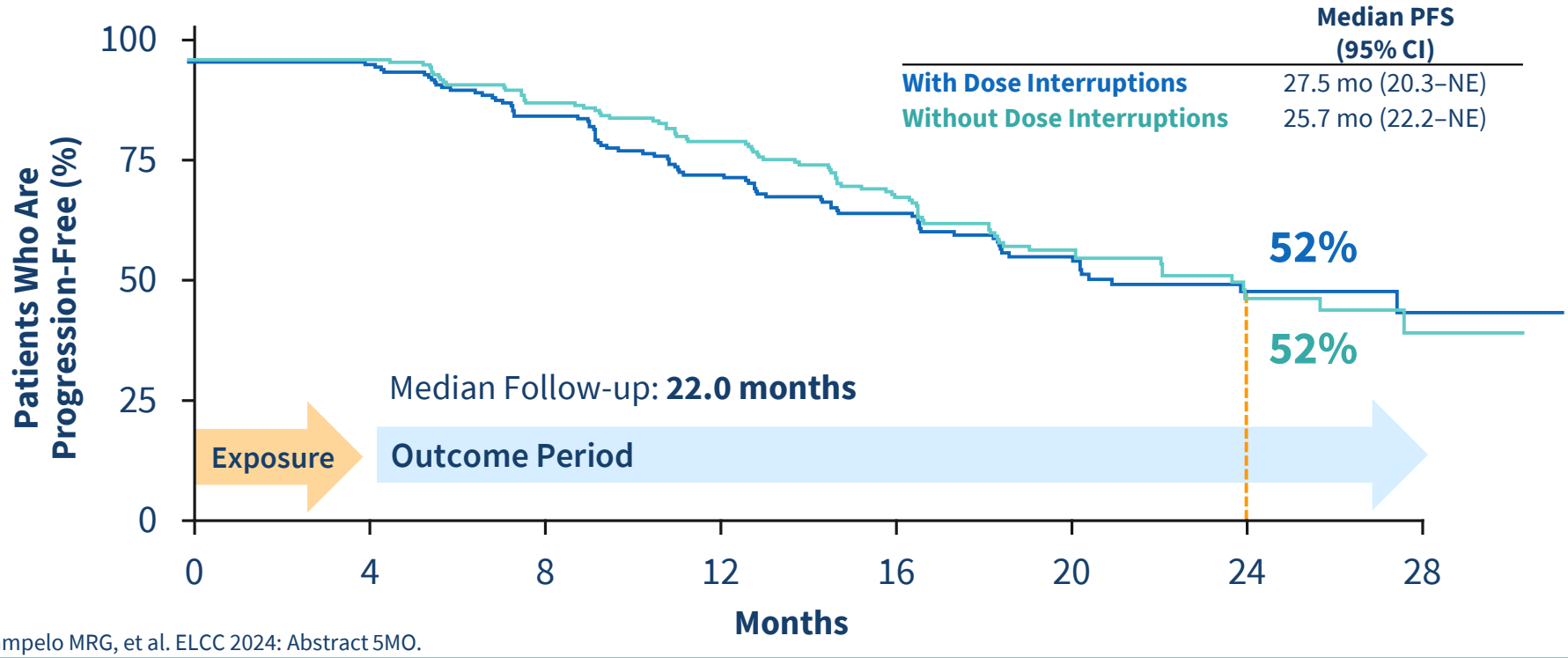
Girard N, et al. ELCC 2025: Abstract 10MO.

First Onset of Key AEs for Amivantamab + Lazertinib



Yang JCH, et al. ELCC 2025: Abstract 40.

Association of Dose Interruption With Progression-Free Survival



Campelo MRG, et al. ELCC 2024: Abstract 5MO.

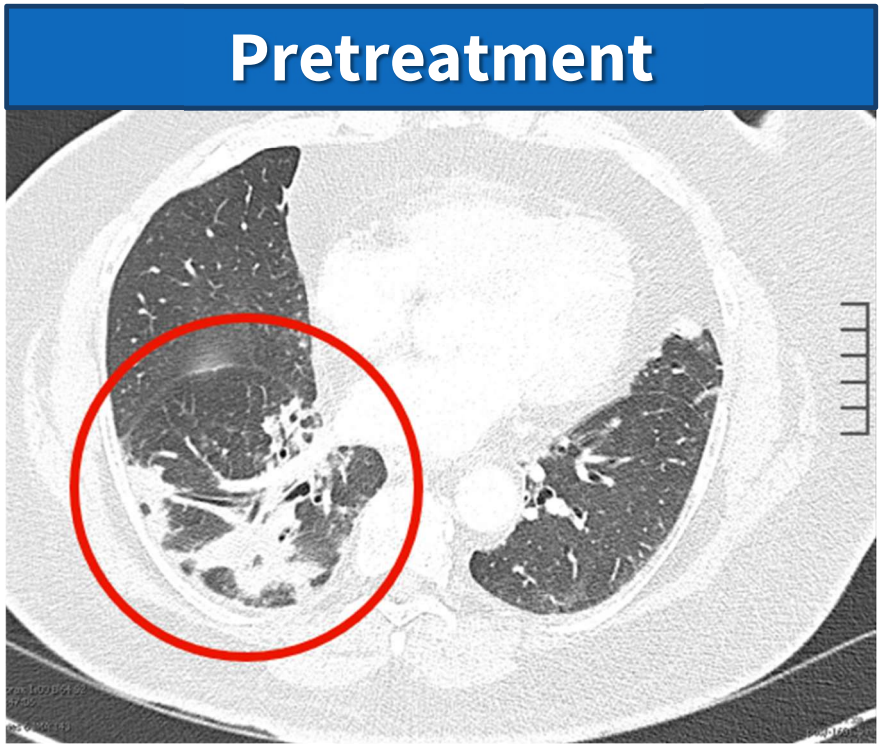
VTE Prophylactic Regimen

First 4 Months
Oral anticoagulants as per
NCCN or local guidelines

Dermatologic Prophylactic Regimen (COCOON)

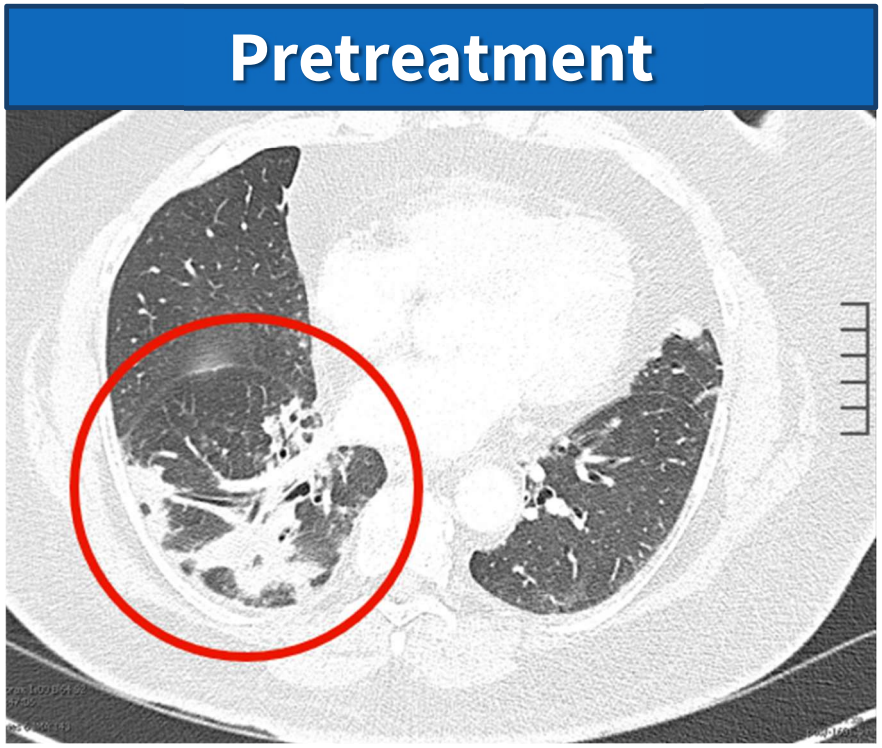
Antibiotic Prophylaxis	**Weeks 1-12** 100 mg BID Doxycycline or Minocycline	**Weeks 13+** 1% Topical Clindamycin Lotion on the scalp daily
Nail Cleaning Agent	**Weeks 1+** 4% Chlorhexidine on the fingernails and toenails daily for 12 months	
Long-Acting Skin Hydration	**Weeks 1+** Ceramide-based moisturizer at least daily for 12 months.	

Amivantamab + Lazertinib: Treatment Course



Images courtesy of Dr. Sabari.

Amivantamab + Lazertinib: Treatment Course



SKIPIRR Regimen:
- Dexamethasone 8mg BID day -2, Day -1

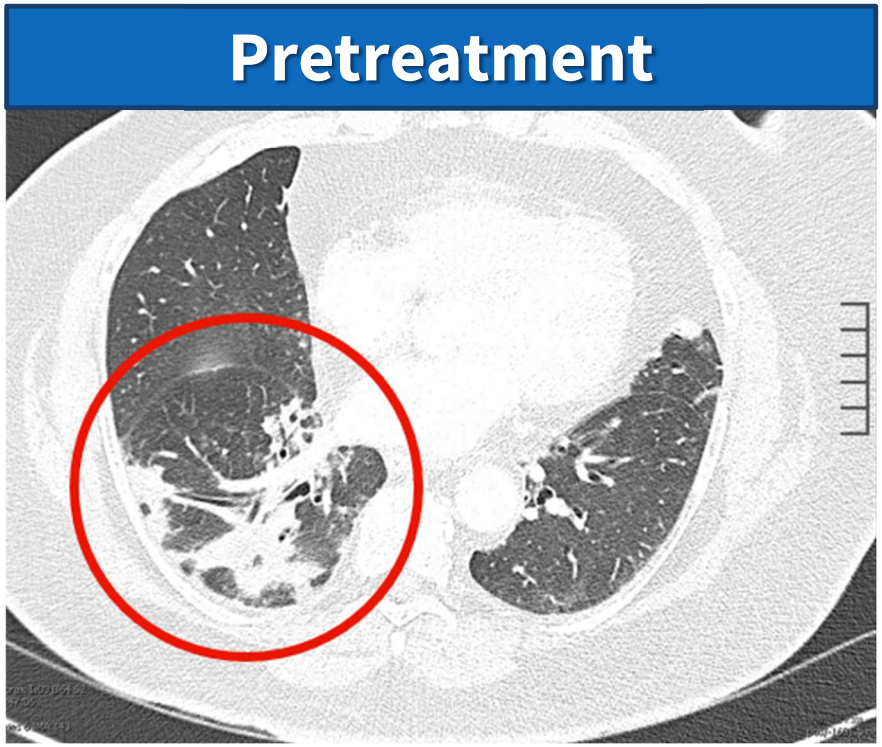
Dosing Strategy to Decrease IRR
- Amivantamab Dose split C1D1 and C1D2

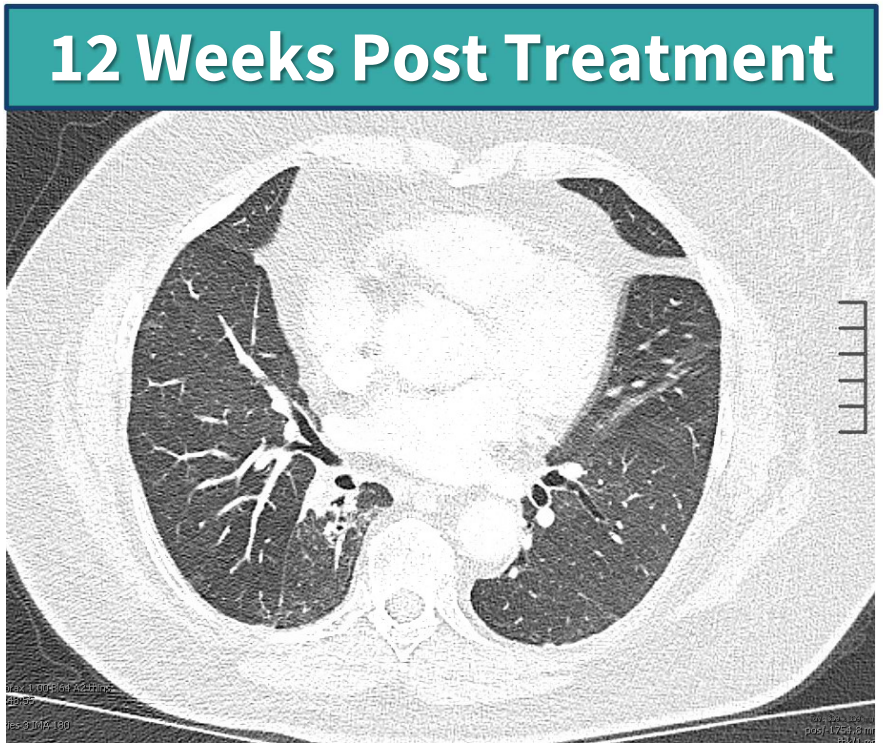
COCOON Regimen:
- Prophylactic doxycycline for week 1-12;
- Chlorhexidine nail rinse;
- Topical ceramide containing moisturizer

Decrease Risk of Thrombosis
- Prophylactic dose anticoagulation for first 4m

Images courtesy of Dr. Sabari.

Amivantamab + Lazertinib: Response to Therapy





Images courtesy of Dr. Sabari.

Clinical Updates in the Management of Advanced Metastatic *EGFR*+ NSCLC: 2L Setting, Post 3rd Generation *EGFR* TKI

CORNERSTONE MEDICAL EDUCATION

Patients With *EGFR*m NSCLC Eventually Develop *EGFR* TKI Resistance and Disease Progression

Stage IV*

*Some stage IIIb patients may be treated as stage IV patients depending on disease characteristics.

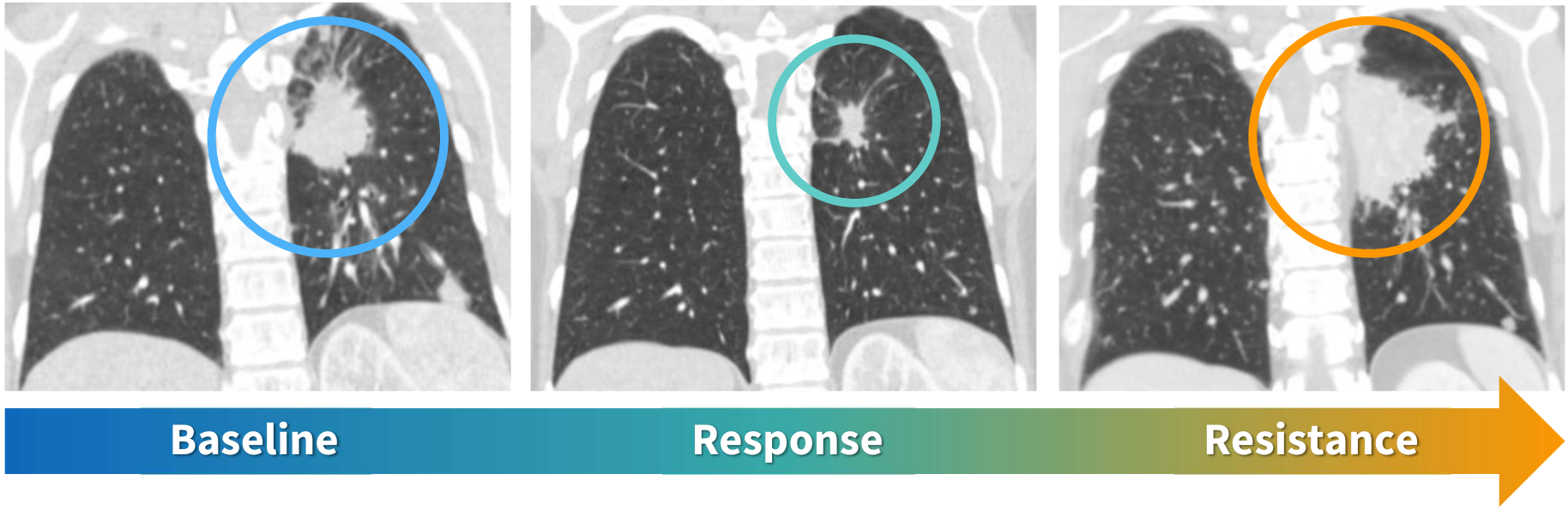
Patients With Stage IV *EGFR*m NSCLC*

	L858R and Ex19del (~79%)	Ex20ins (~12%)
1L	Historical SOC: **Osimertinib** mPFS: 18.9 months mOS: 38.6 months	Historical SOC: **Platinum Chemo** mPFS: 5.5 months mOS: 16.2 months
2L	Historical SOC: **Platinum-Based Chemotherapy** mPFS: 5.4 months mOS: 19.5 months	Historical SOC: **Docetaxel** mPFS: 3 months mOS: 12.5 months

Reiss JW, et al. *J Thorac Oncol*. 2018; Ramalingam SS, et al. *N Engl J Med.* 2020; Soria JC, et al. *Lancet Oncol.* 2015.

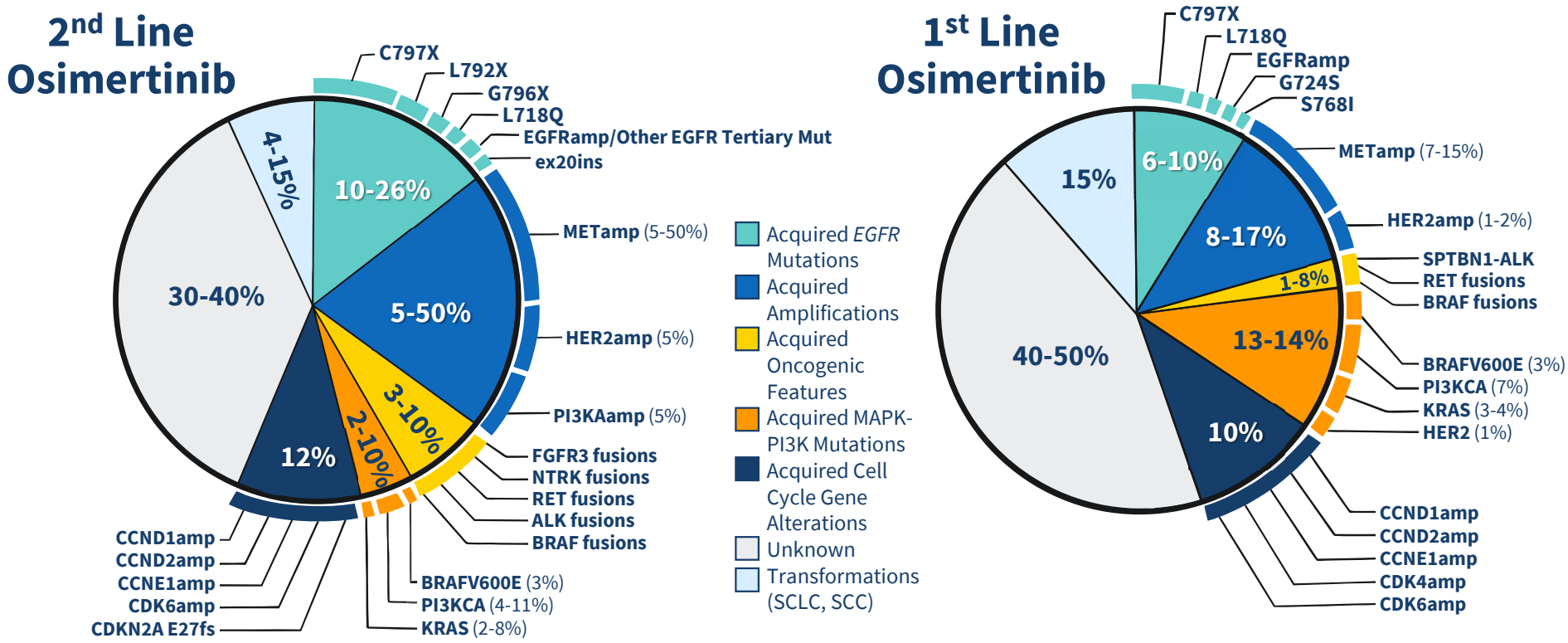
Acquired Resistance

***EGFR* Mutant NSCLC**



Images courtesy of Dr. Sabari.

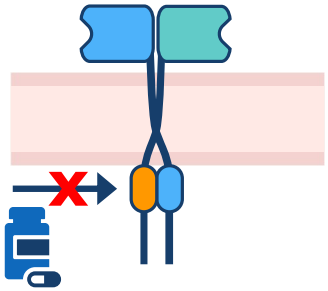
Resistance Mechanisms to *EGFR* TKI



Westover D, et al. *Ann Oncol*. 2018; Leonetti A, et al. *Br J Cancer*. 2019.

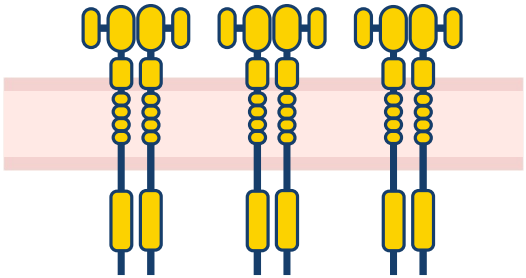
Mechanisms of Resistance to TKI

Mutations in the Drug Target



Impact Drug Binding

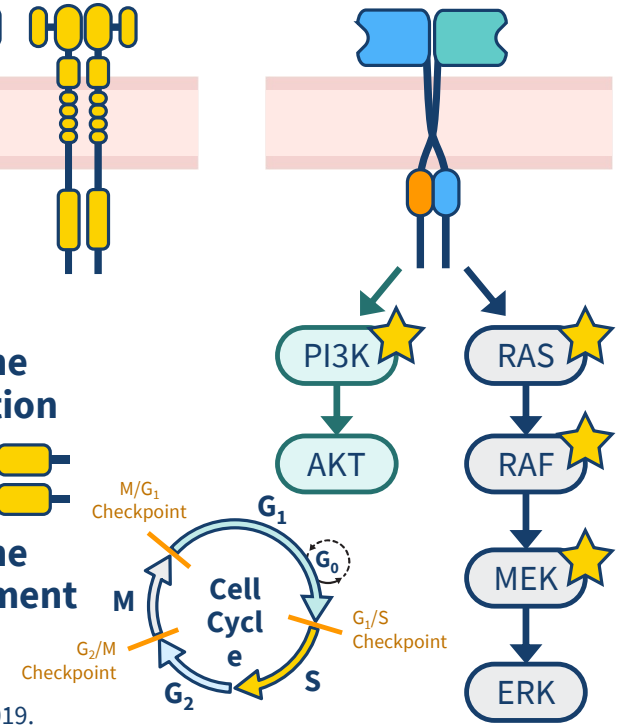
Bypass Signaling



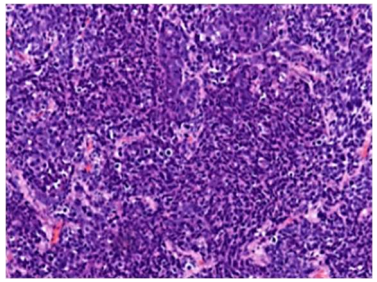
Oncogene Amplification

Oncogene Rearrangement

Mutations in Downstream Effectors



State Transformation

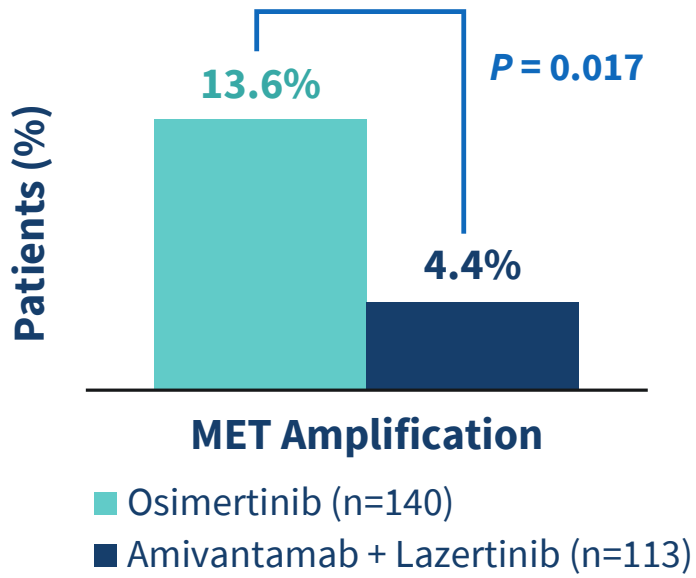


Small Cell Lung Cancer
Squamous Cell Lung Cancer

Westover D, et al. *Ann Oncol*. 2018; Leonetti A, et al. *Br J Cancer*. 2019.

MET and *EGFR*-based Resistance Mechanisms

- Amivantamab + lazertinib significantly reduced the incidence of acquired *MET* amplifications and *EGFR* resistance mutations vs osimertinib.



Acquired *MET* amplifications were ~3-fold lower and *EGFR* resistance mutations were ~8-fold lower for amivantamab + lazertinib versus osimertinib.

Besse B, et al. ESMO 2024 Annual Congress: Abstract LBA55.

MET and *EGFR*-based Resistance Mechanisms

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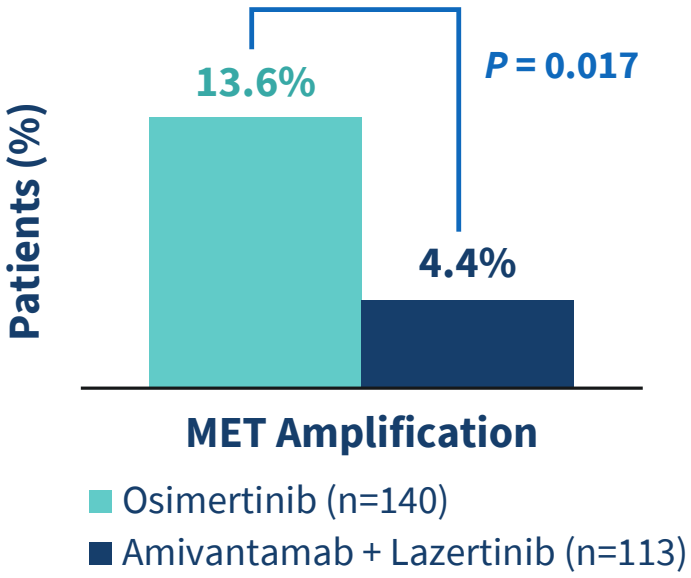

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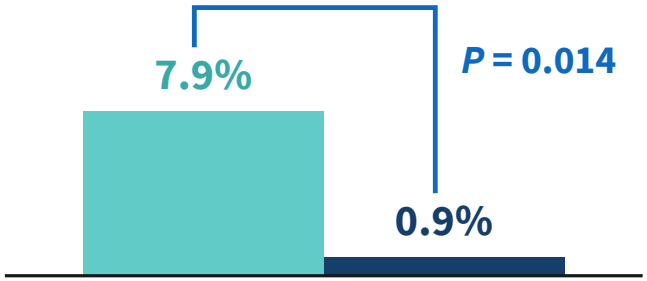
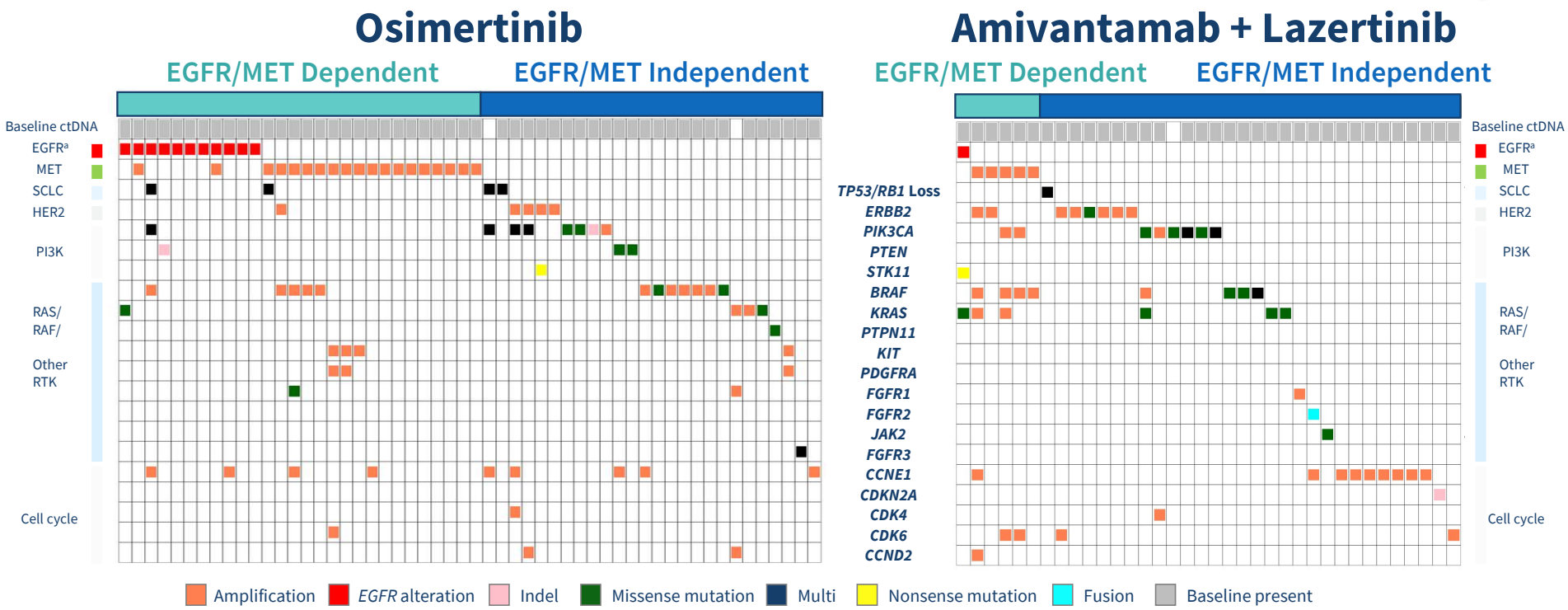


Besse B, et al. ESMO 2024 Annual Congress: Abstract LBA55.

Acquired Resistance Mutational Landscape

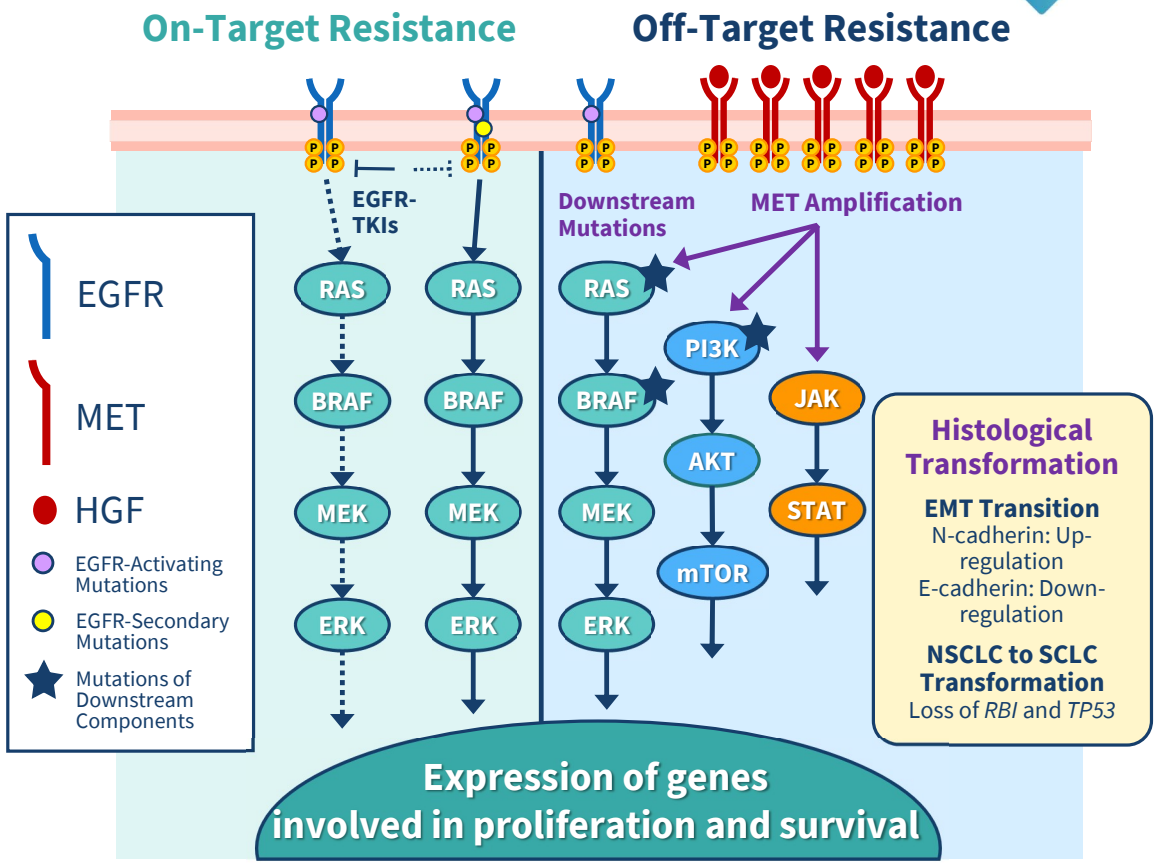


Osimertinib had a more heterogeneous mutational landscape than amivantamab + lazertinib.

Besse B, et al. ESMO 2024 Annual Congress: Abstract LBA55.

Overcoming Resistance – Combination Strategies

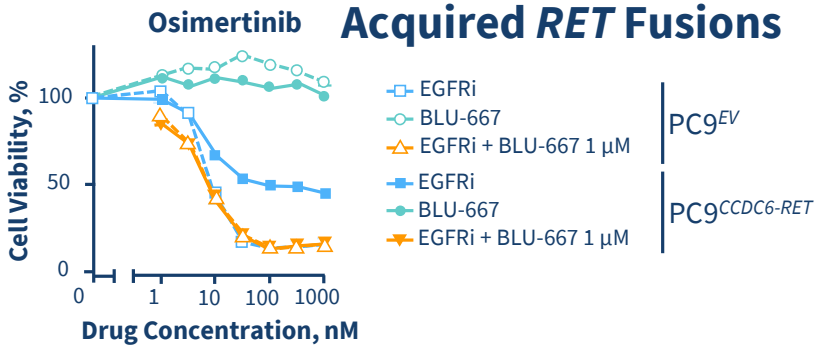
- Selective (On target resistance)
  - *EGFR* T790M, C797S, G724S
    - Acquired vs de novo
  - 3rd and 4th generation *EGFR* TKI
- Non-selective (Off target resistance)
  - *MET / BRAF / RET / ALK / HER2 / PI3K*
  - EMT State transformation
  - **Novel MOA**
    - Bispecifics
    - T-cell Engagers
    - Antibody drug conjugates
    - Conventional chemotherapy combinations

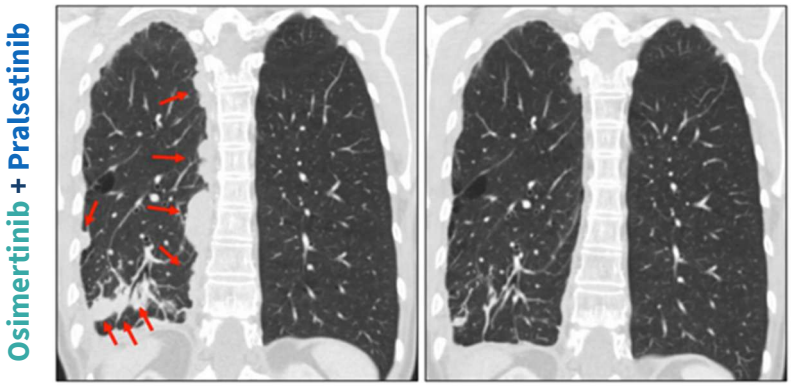


Chhouri H, et al. *Cancer*. 2023.

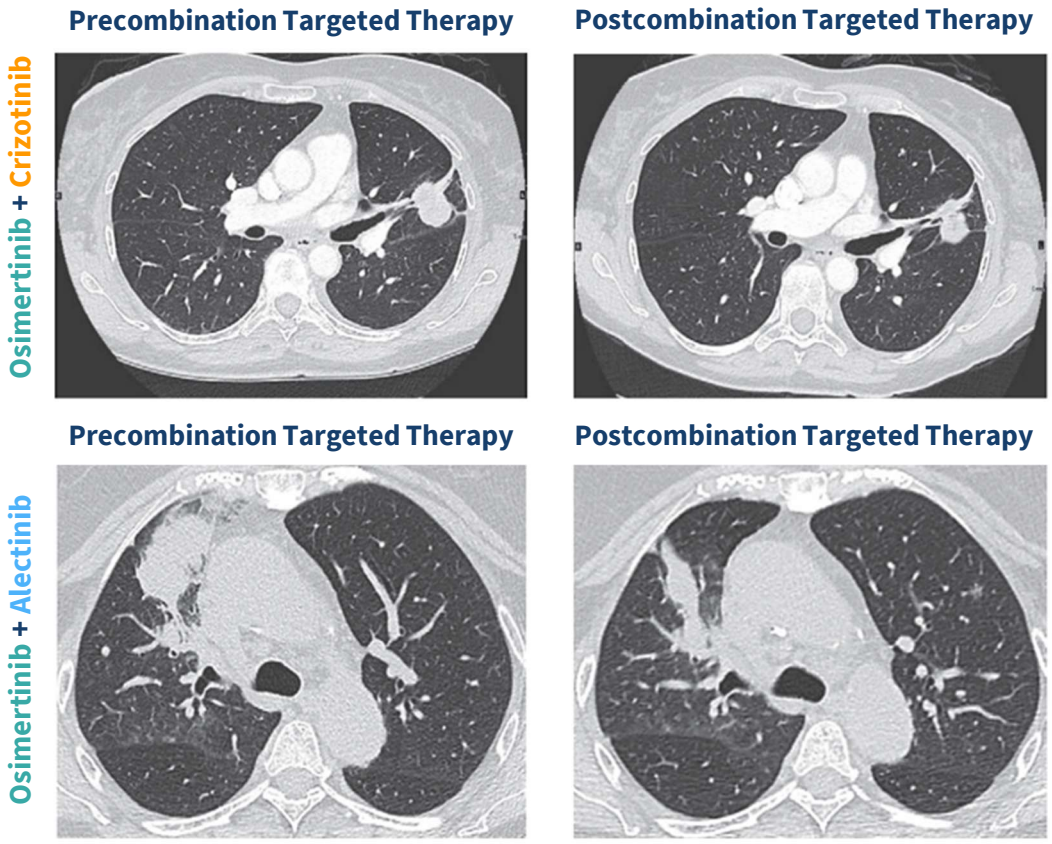
Targeting Acquired *RET*, *ALK*, and Other Fusions

Acquired *RET* Fusions





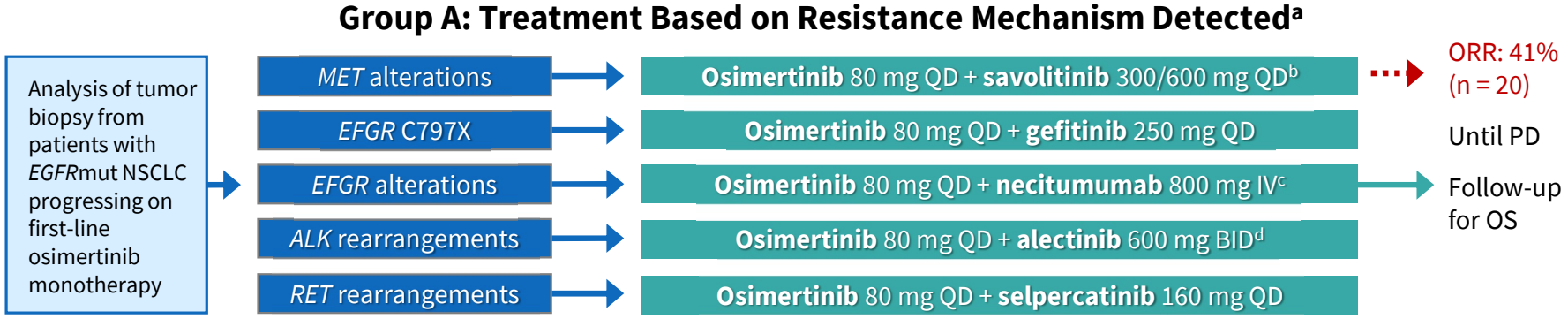
Acquired *ALK* Fusions



Piotrowska Z, et al. *Cancer Discov*. 2018; Offin M, et al. *JCO Precis Oncol*. 2018.

ORCHARD: Biomarker-Directed Study in Advanced *EGFR*mut NSCLC Progressing on 1L Osimertinib

- Open-label, multicenter, multidrug, biomarker-directed phase 2 platform trial



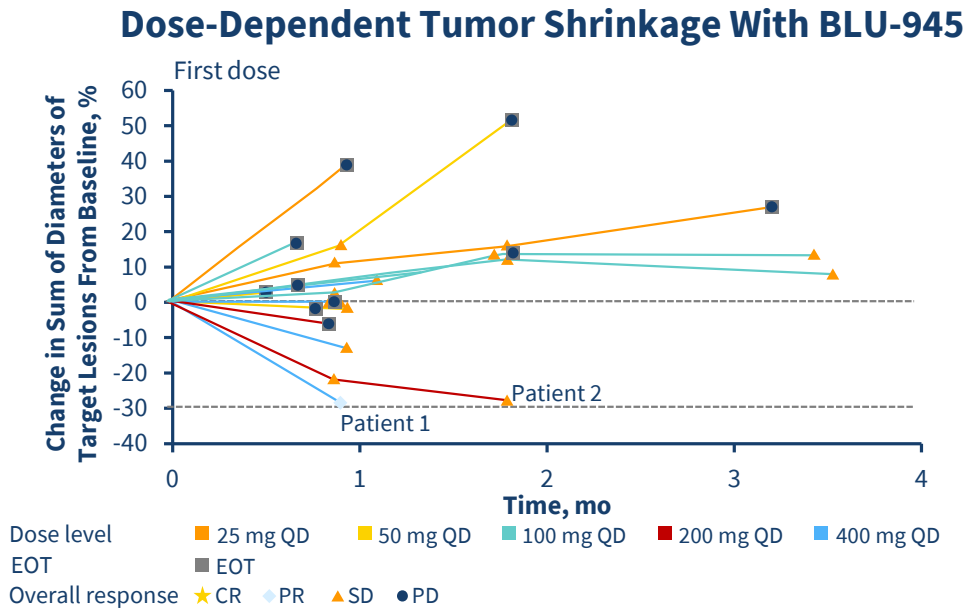
- **Group B:** Nonmatched arm for patients without a detectable resistance mechanism will sequentially be assigned to durvalumab + chemotherapy > osimertinib + necitumumab > others
- **Group C:** Observational arm for patients whose optimal treatment falls outside of group A or B (e.g., transformation to SCLC)
- Patients with failed baseline NGS results go directly to follow-up

[a]Future arms may be added. [b]Savolitinib dose 300 mg QD for all new patients. [c]Day 1 and 8 of 3 week cycle. [d]300 mg BID in Japan.

Cho BC, et al. *J Thorac Oncol*. 2021; Yu H, et al. *Clin Lung Cancer*. 2021; Yu H, et al. ESMO 2021 Annual Congress: Abstract 1239P.

Targeting *EGFR* C797S

- Limited data for 1st-gen *EGFR* TKIs
- "4th-gen" *EGFR* TKIs with activity against C797S are now entering the clinic
- Other novel agents, including amivantamab and patritumab deruxtecan, may have activity



	1G	3G	4G		Potential Combinations	
***EGFR* Mutational Coverage[a]**	**Gefitinib**	**Osimertinib**	**BLU-701**	**BLU-945**	**BLU-701 + Osimertinib**	**BLU-701 + BLU-945**
L858R (LR)						
ex19del						
LR or ex19del/T790M						
LR or ex19del/C797S						
LR or ex19del/T790M/C797S						

IC_{50} ≤10 nM
10 nM < IC_{50} ≤50 nM
IC_{50} >50 nM

Conti C, et al. AACR Annual Meeting 2021: Abstract 1262; Shum E, et al. AACR Annual Meeting 2022: Abstract CT184.

Biomarker Agnostic Approaches

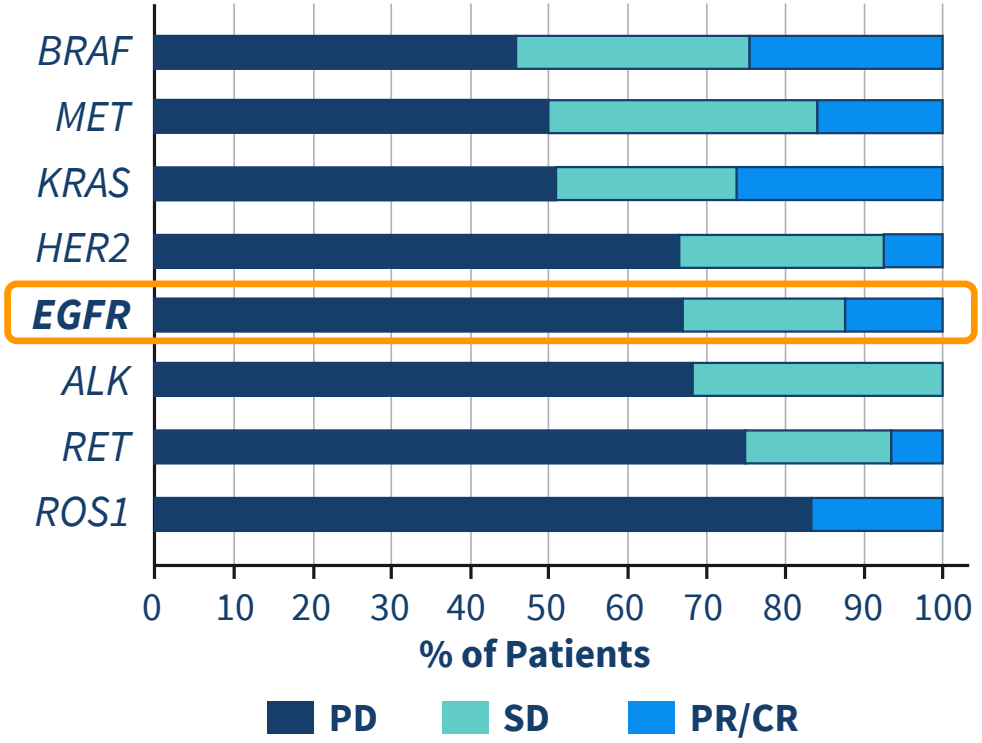
mAb

ADC

Utility of PD1/PD-L1 inhibitors in *EGFR*m NSCLC

- **Phase III IMPOWER150:** Carboplatin, Paclitaxel, Bevacizumab and Atezolizumab; Subset Analysis of ***EGFR/ALK*-mutated NSCLC**
- **Phase III ORIENT-31:** Sintilimab plus chemotherapy for patients with ***EGFR*-mutated non-squamous NSCLC** with **disease progression after *EGFR* tyrosine-kinase inhibitor therapy**
- **Phase III CHECKMATE722:** Nivolumab + Pemetrexed/Platinum Chemotherapy in **TKI-Resistant, *EGFR*-Mutated, Metastatic NSCLC**
- **Phase III KEYNOTE-789:** Pembrolizumab + Pemetrexed/Platinum Chemotherapy in **TKI-Resistant, *EGFR*-Mutated, Metastatic NSCLC**

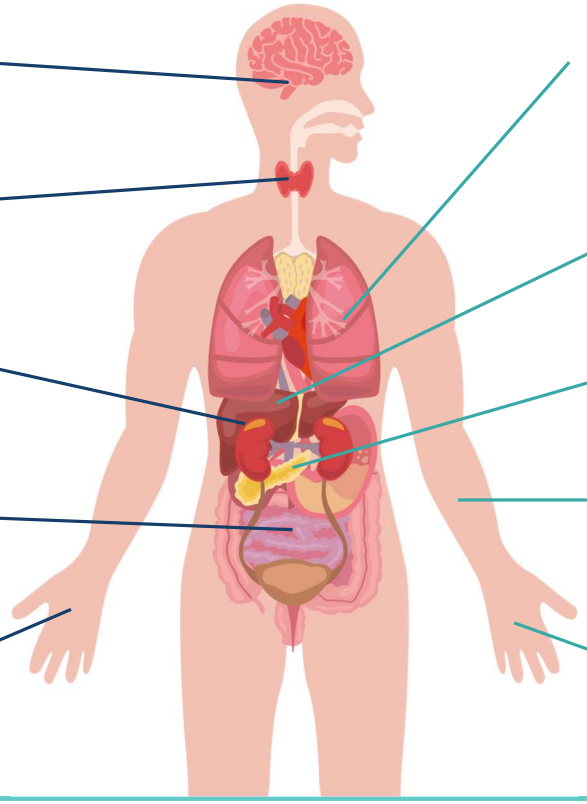
Use of Immunotherapy in Driver Mutation + NSCLC



	Event/*N*	Median PFS (95% CI)
KRAS	208/271	**3.2** (2.7, 4.5)
EGFR	117/125	**2.1** (1.8, 2.7)
BRAF	34/43	**3.1** (1.8, 4.6)
HER2	23/29	**2.5** (1.8, 3.5)
MET	26/36	**3.4** (1.7, 6.2)
ALK	21/23	**2.5** (1.5, 3.7)
ROS1	-	-
RET	15/16	**2.1** (1.3, 4.7)

Mazieres J, et al. *Ann Oncol*. 2019.

Immune Related Adverse Events



Hypophysitis

Thyroiditis

Adrenal Insufficiency

Enterocolitis

Dermatitis

Pneumonitis

Hepatitis

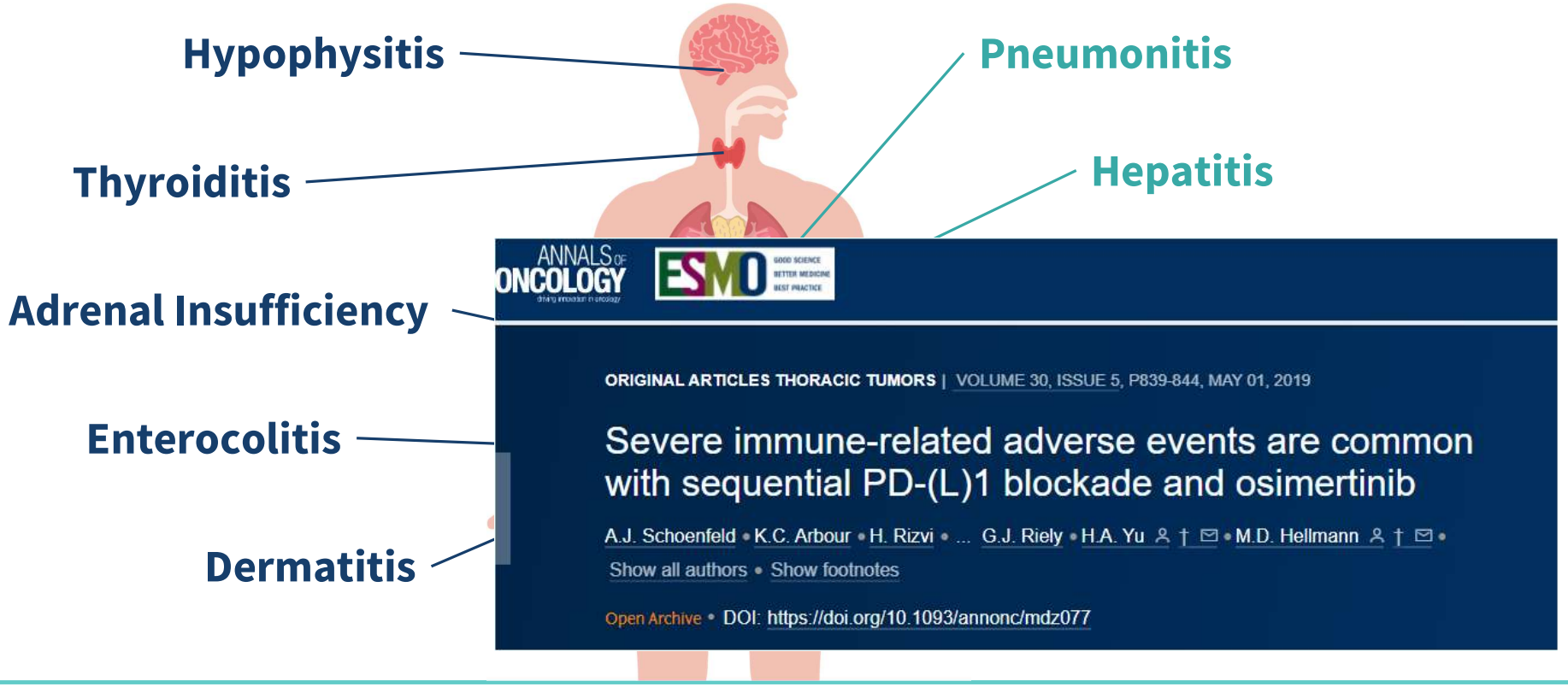
Pancreatitis

Motor and Sensory Neuropathies

Arthritis

Due to adverse effects, there needs to be a washout period between agents.

Immune Related Adverse Events



Phase III MARIPOSA 2: Study Design

Key Eligibility Criteria

- Locally advanced or metastatic NSCLC
- Documented EGFR Ex19del or L858R
- Progressed on or after osimertinib monotherapy, as most recent line of therapy
- ECOG PS 0 or 1
- Stable brain metastases were allowed:
  - Radiation or definitive therapy was not required (untreated)

Stratification Factors

- Osimertinib line of therapy (first vs second)
- Asian race (yes or no)
- History of brain metastases (yes or no)

2:2:1 Randomization (N=657)

- **Amivantamab-Lazertinib-Chemotherapy** (n=263)
- **Chemotherapy** (n=263)
- **Amivantamab-Chemotherapy** (n=131)

Dual Primary Endpoint of PFS[c] by BICR per RECIST v1.1

Amivantamab-Lazertinib-Chemotherapy vs Chemotherapy

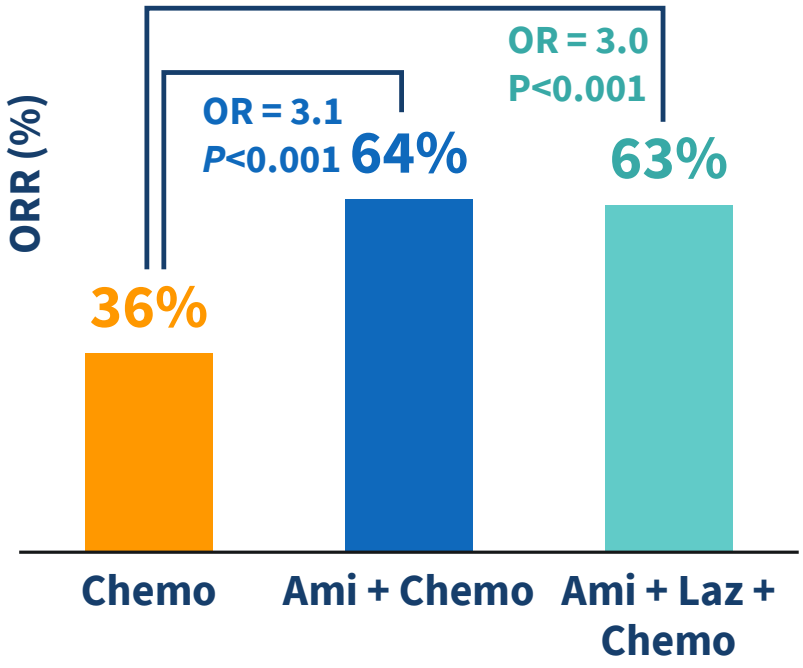
Amivantamab-Chemotherapy vs Chemotherapy

Secondary Endpoints

- Objective Response Rate (ORR)[c]
- Duration of Response (DoR)
- Overall Survival (OS)[c]
- Intracranial PFS
- Time to Subsequent Therapy[d]
- PFS After First Subsequent Therapy (PFS2)[d]
- Symptomatic PFS[d]
- Safety

Passaro A, et al. *Ann Oncol*. 2024.

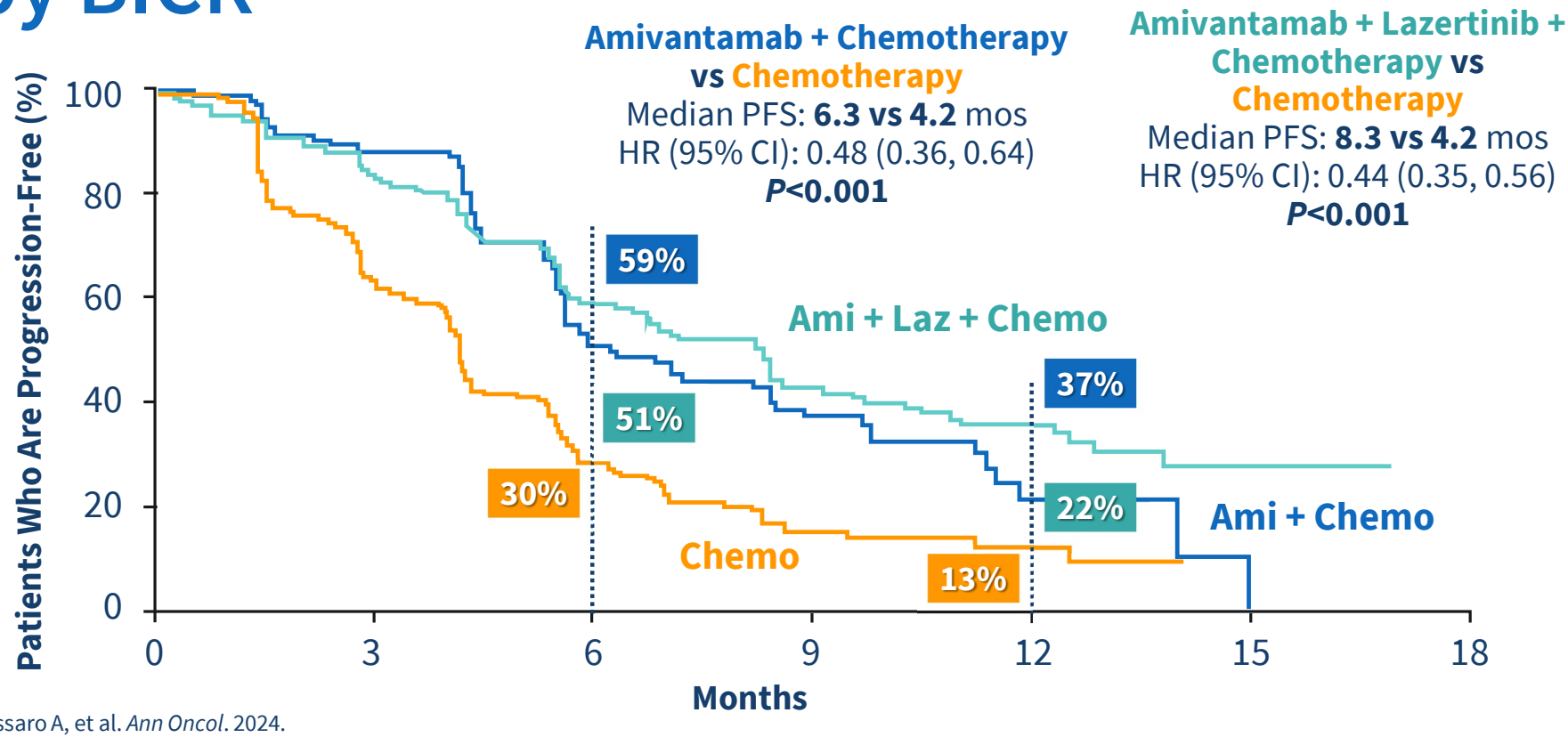
MARIPOSA 2: Objective Response Rate and Duration of Response by BICR



BICR-Assessed Response, n(%)	Chemo (n=263)	Ami + Chemo (n=131)	Ami + Laz + Chemo (n=263)
Best Response			
CR	1 (0.4)	2 (2)	6 (2)
PR	93 (36)	81 (62)	157 (61)
SD	82 (32)	30 (23)	61 (24)
PD	52 (20)	10 (8)	14 (5)
NE/UNK	32 (12)	7 (5)	21 (8)
Median DOR (95% CI)	**5.6 mo** (4.2, 9.6)	**6.9 mo** (5.5, NE)	**9.4 mo** (6.9, NE)

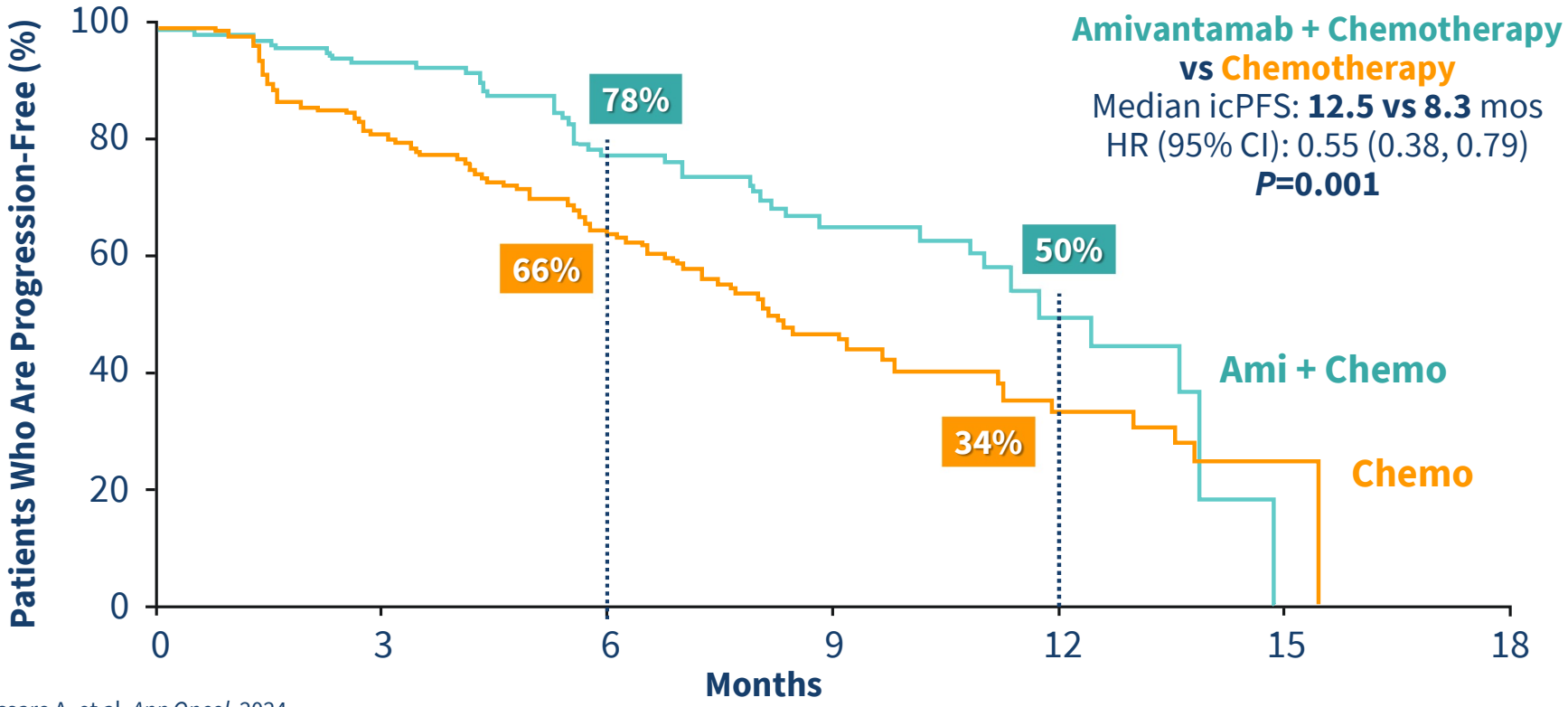
Passaro A, et al. *Ann Oncol*. 2024.

MARIPOSA 2: Progression-Free Survival by BICR



Passaro A, et al. *Ann Oncol*. 2024.

MARIPOSA 2: Intracranial PFS

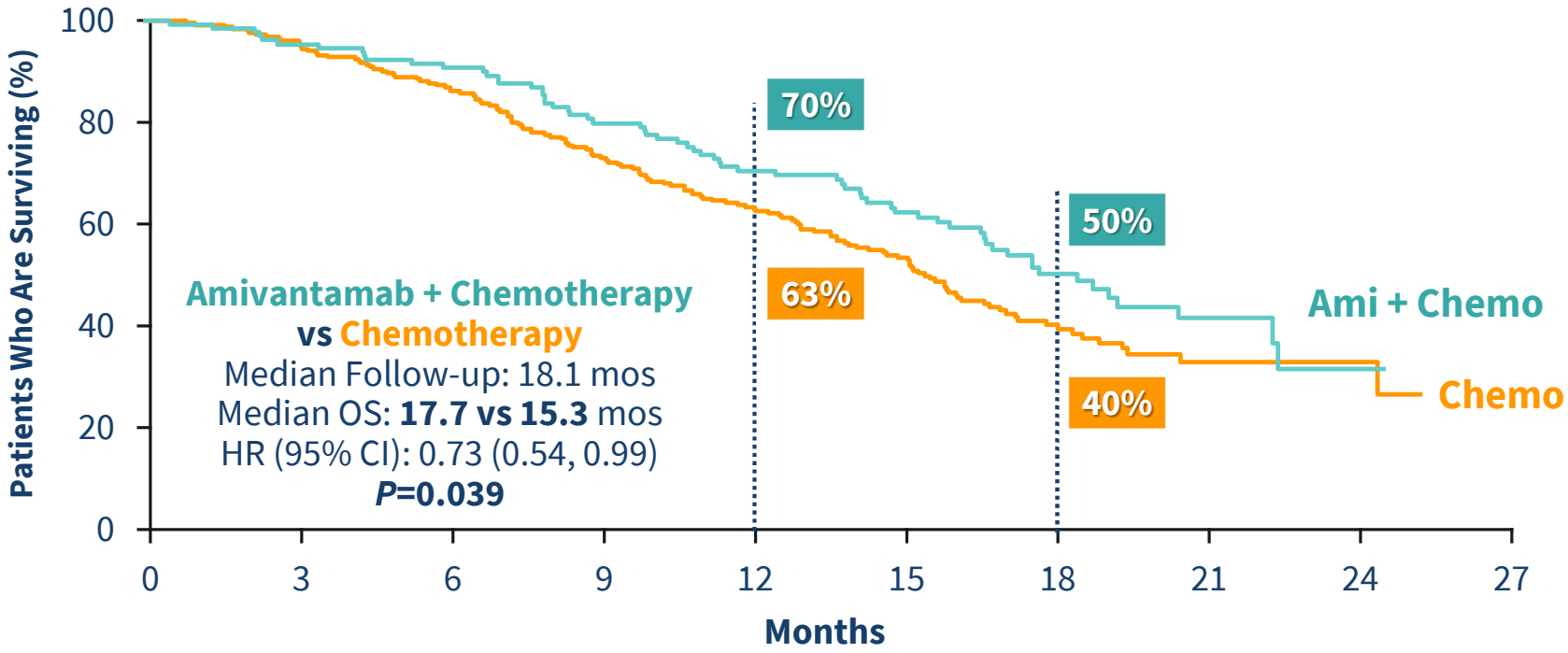


Amivantamab + Chemotherapy
vs Chemotherapy
Median icPFS: **12.5 vs 8.3** mos
HR (95% CI): 0.55 (0.38, 0.79)
***P*=0.001**

Passaro A, et al. *Ann Oncol*. 2024.

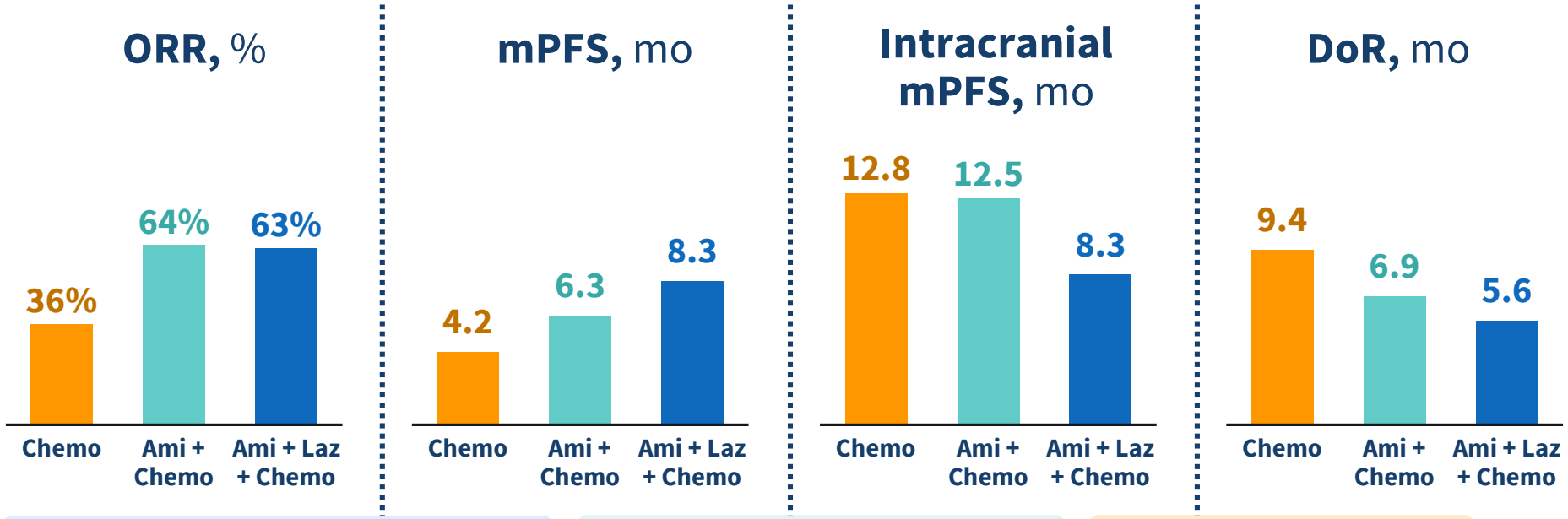
MARIPOSA 2: Overall Survival

Amivantamab-chemotherapy continues to demonstrate a clear and improving OS trend vs chemotherapy.



Popat S, et al. ESMO 2024 Annual Congress: Abstract LBA54.

MARIPOSA-2: Trial Summary



Ami + Laz + Chemo Most common TEAEs: Neutropenia, thrombocytopenia, IRR, anemia, paronychia, nausea, rash, stomatitis

Ami + Chemo Most common TEAEs: Neutropenia, thrombocytopenia, IRR, nausea, rash

Chemo Most common TEAEs: Neutropenia, anemia

Passaro A, et al. *Ann Oncol*. 2024.

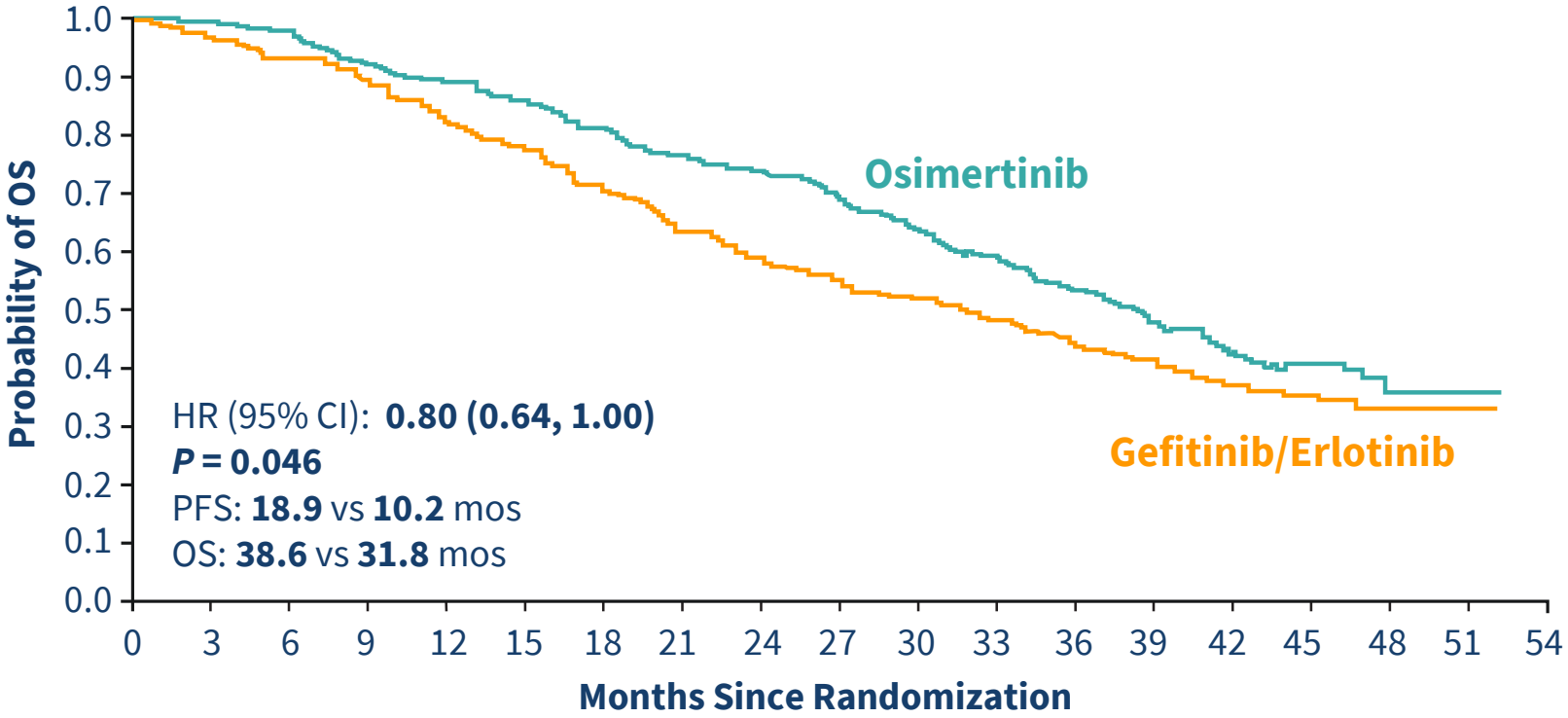
Clinical Case #2

- **CC:** 52-year-old man with cough and shortness of breath x3 months
- **HPI:** Presented to PCP who obtained a CXR which revealed a right upper lobe opacity
  - **PMHx:** former 5 pack year smoking history
  - **PMHx:** Hypertension

Clinical Case #2

- **CC:** 52-year-old man with cough and shortness of breath x3 months
- Diagnosed with **stage IV lung adenocarcinoma** right upper lobe
- **Metastatic to brain**, sub-centimeter lesions without vasogenic edema
- EGFR exon 21 (**L858R**) identified by tissue NGS
- Initiated on **1L Osimertinib 80mg PO daily** with clinical and radiographic response…

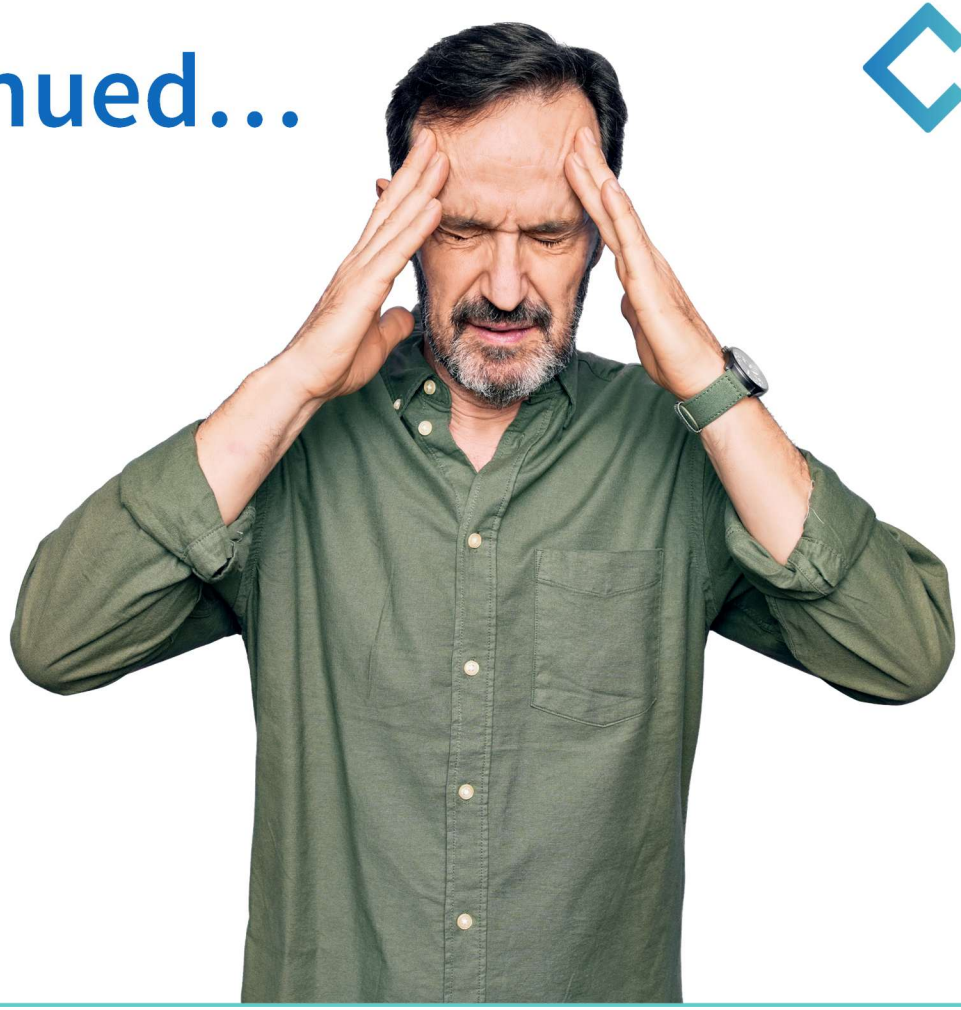
FLAURA: Osimertinib vs Gefitinib/Erlotinib



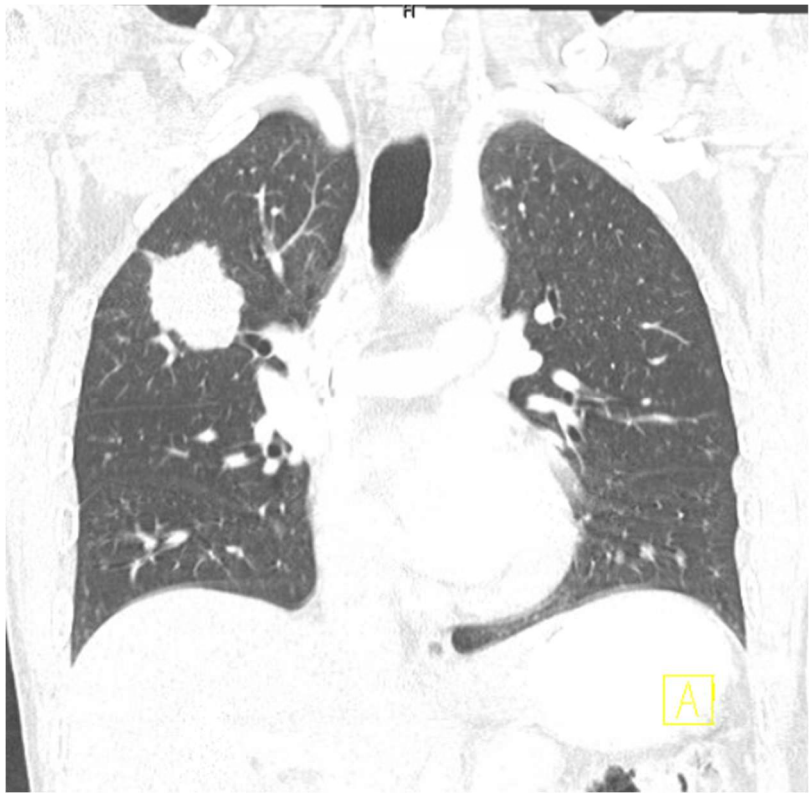
Soria JC, et al. *N Engl J Med*. 2018; Ramalingam S, et al. *N Engl J Med*. 2020.

Clinical Case Continued…

- After 11 months on therapy, he developed **worsening cough** and **headaches**.

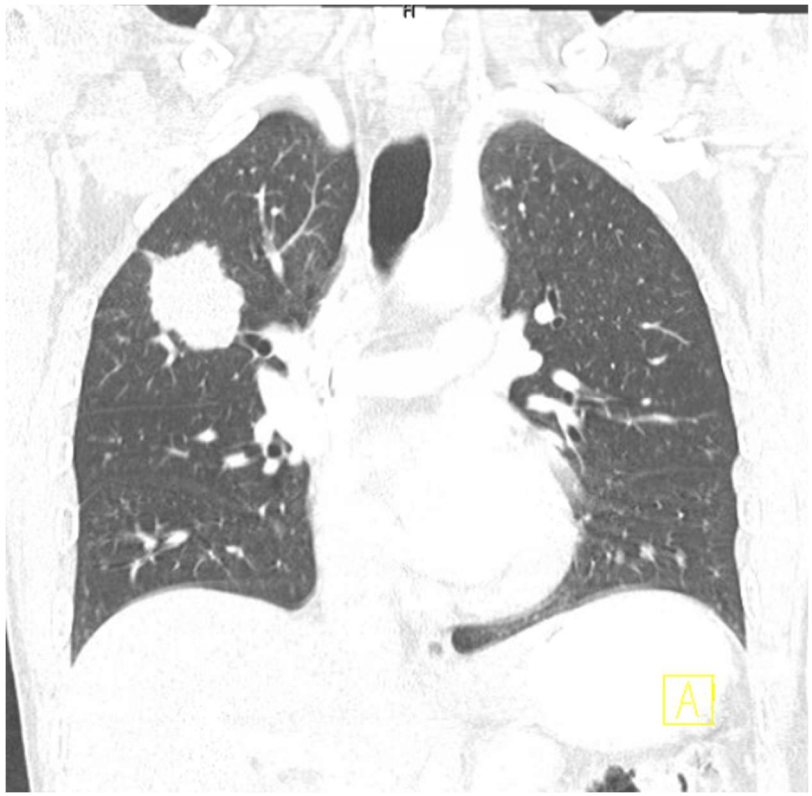


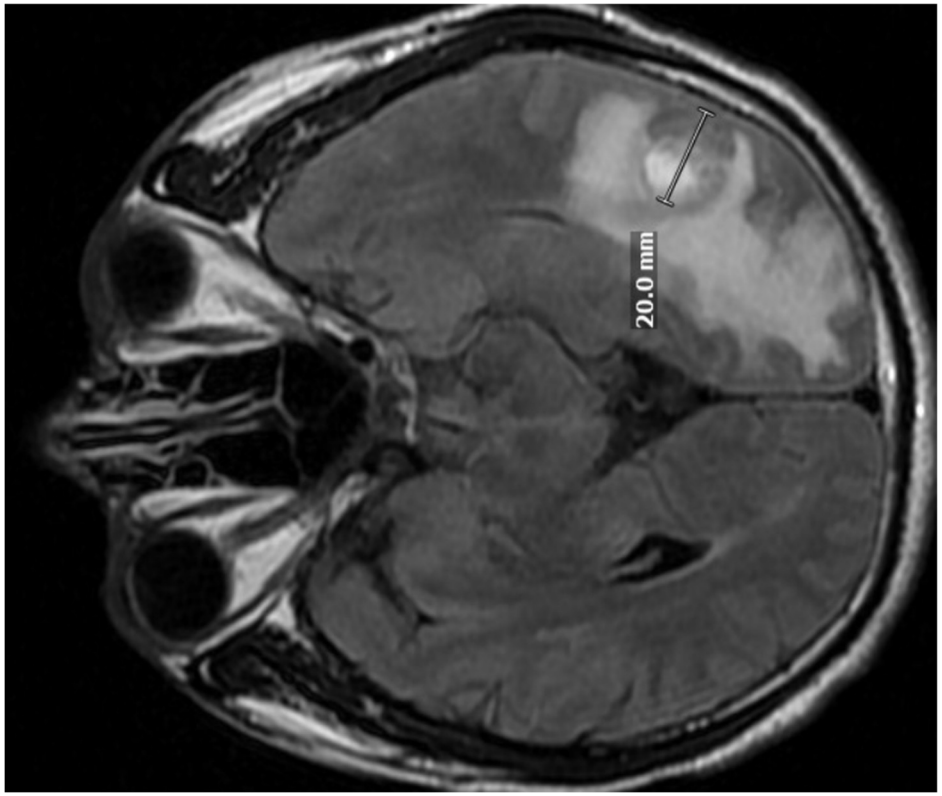
Clinical Case Continued…



Images courtesy of Dr. Sabari.

Clinical Case Continued…





Images courtesy of Dr. Sabari.

Assessing for Resistance Mechanisms

Companion Diagnostic (CDx) Associated Findings

GENOMIC FINDINGS DETECTED	FDA-APPROVED THERAPEUTIC OPTIONS
EGFR L858R	Gilotrif® (Afatinib) Iressa® (Gefitinib) Tagrisso® (Osimertinib) Tarceva® (Erlotinib) Vizimpro® (Dacomitinib)

OTHER SHORT VARIANTS AND SELECT REARRANGEMENTS AND COPY NUMBER ALTERATIONS IDENTIFIED

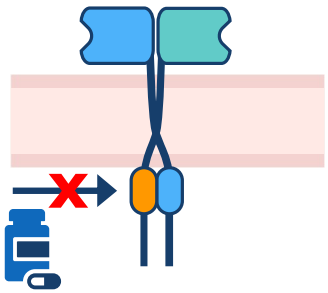
Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product.
See *professional services* section for information on the alterations listed in this section as well as any additional detected copy number alterations, gene rearrangements, or biomarkers.

OTHER BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

CHEK2 E308fs*12 #
CTNNB1 S33F
EGFR C797S

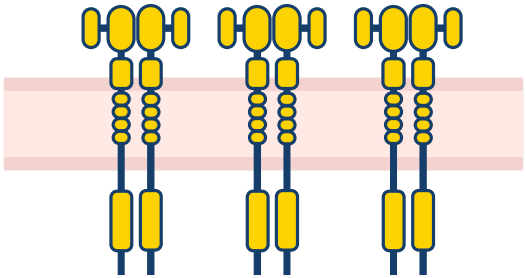
Mechanisms of Resistance to TKI

Mutations in the Drug Target



Impact Drug Binding

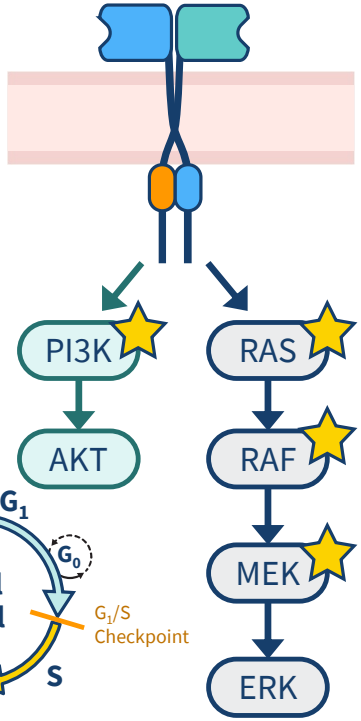
Bypass Signaling



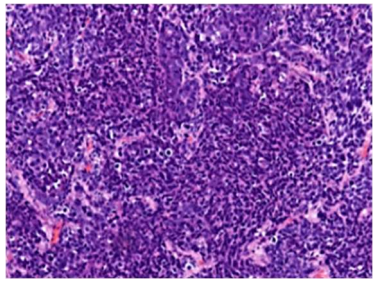
Oncogene Amplification

Oncogene Rearrangement

Mutations in Downstream Effectors



State Transformation



Small Cell Lung Cancer
Squamous Cell Lung Cancer

Westover D, et al. *Ann Oncol*. 2018; Leonetti A, et al. *Br J Cancer*. 2019.

1st Line MARIPOSA Study Design

Paired blood samples were collected at baseline and EOT for analysis of detectable ctDNA by NGS

Key Eligibility Criteria

- Locally advanced or metastatic NSCLC
- Treatment naïve for advanced disease
- Documented *EGFR* Ex19del or L858R
- ECOG PS 0 or 1
- Asymptomatic brain metastases did not require definitive treatment

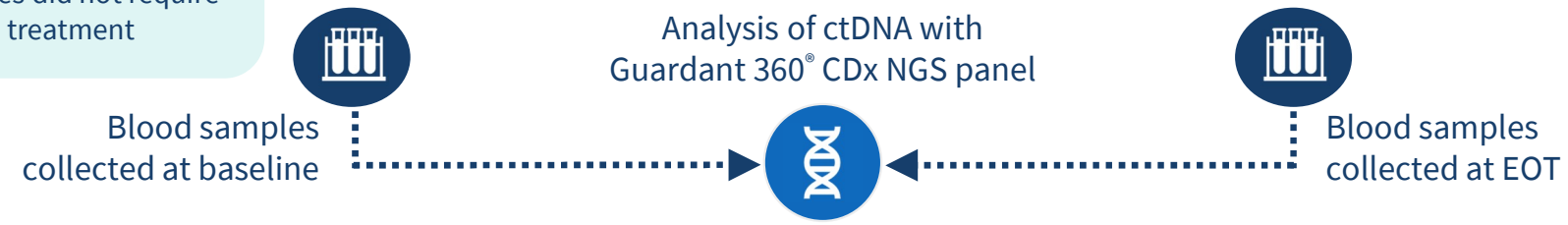
Focus of this presentation

2:2:1 Randomization (N=1074)

- **Amivantamab + Lazertinib** (n=429; open label)
- **Osimertinib** (n=429; blinded)
- **Lazertinib** (n=216; blinded)[d]

Follow-up

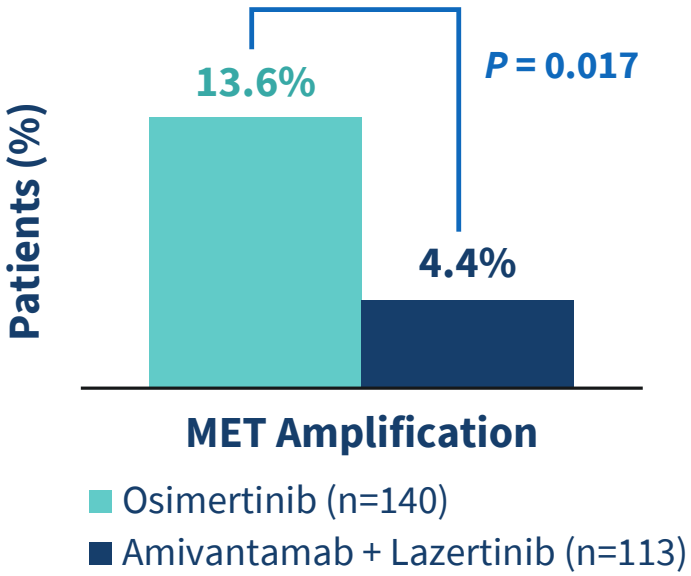
RECIST v1.1 assessments every 8 weeks (±1 week) for the first 30 months, then every 12 weeks (±1 week) until disease progression is confirmed by BICR.



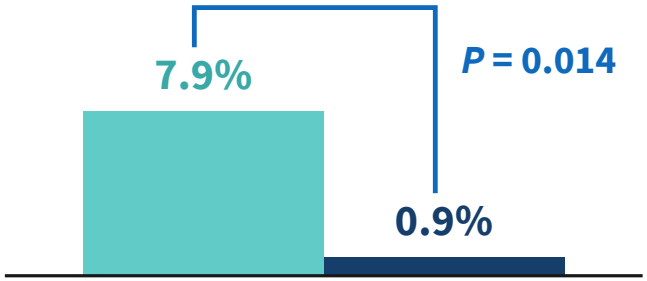
MARIPOSA (ClinicalTrials.gov Identifier: NCT04487080) enrollment period: November 2020 to May 2022.

MET and *EGFR*-based Resistance Mechanisms

- Amivantamab + lazertinib significantly reduced the incidence of acquired *MET* amplifications and *EGFR* resistance mutations vs osimertinib.



Acquired *MET* amplifications were ~3-fold lower and *EGFR* resistance mutations were ~8-fold lower for amivantamab + lazertinib versus osimertinib.



Besse B, et al. ESMO 2024 Annual Congress: Abstract LBA55.

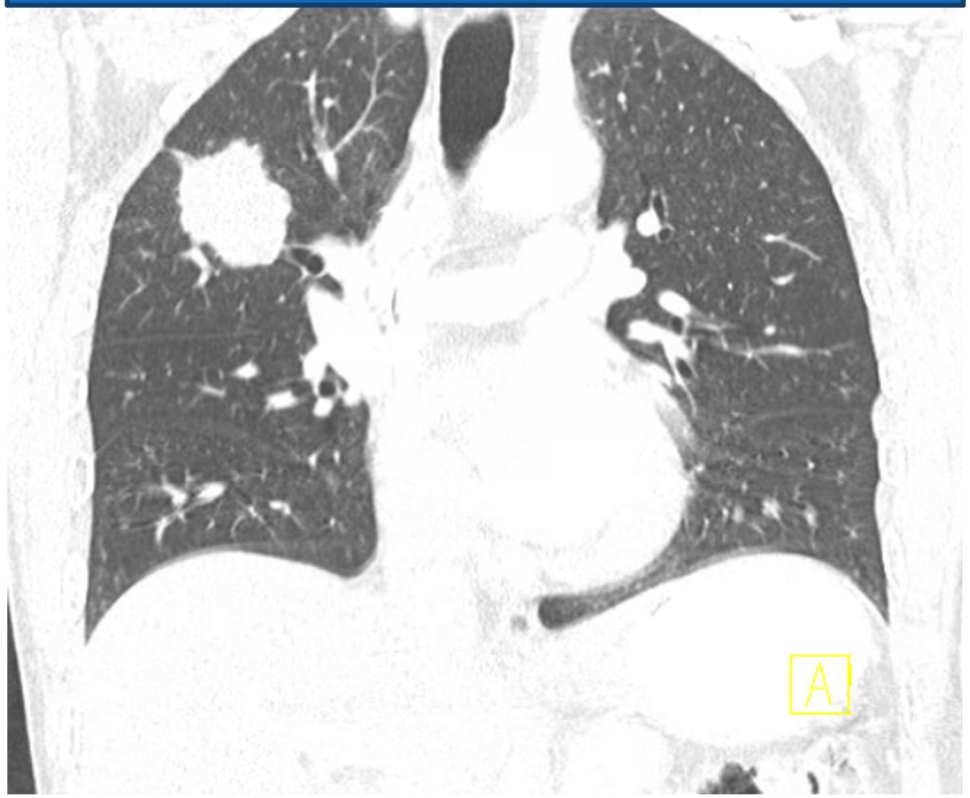
What treatment would you use in the 2nd line setting?

What treatment would you use in the 2nd line setting?

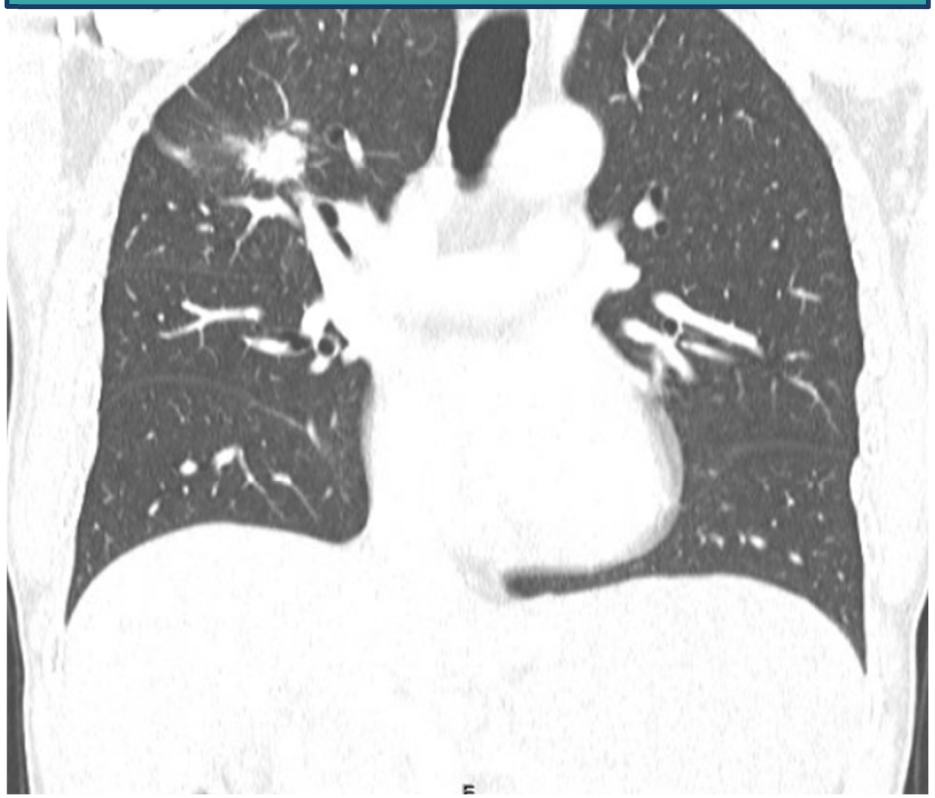
Initiated 2L therapy with **Amivantamab + Chemotherapy** (MARIPOSA2)

Expert recommendation.

Prior to Initiation of Therapy



6 Months Post Amivantamab + Chemotherapy



Images courtesy of Dr. Sabari.

Interprofessional Team Overview in Thoracic Oncology Care

Goal: deliver coordinated, patient-centered care across the cancer care continuum

Team Members & Roles

Physicians: Medical Oncologist, Radiation Oncologists, Thoracic Surgeons, Pulmonologists

- Diagnose & stage lung cancers, determine and oversee treatment plans, and coordinate complex medical decisions

Advanced Practice Providers: Nurse Practitioners, Physician Assistants

- Perform patient assessments, manage symptoms, provide follow-up care, and support treatment delivery in collaboration with physicians

Clinical Pharmacy Specialists

- Optimize pharmacologic treatment plans, manage chemotherapy and targeted therapies, educate patients on medication use and side effects, and answer drug information questions

Nursing and Social Work in Patient-Centered Care

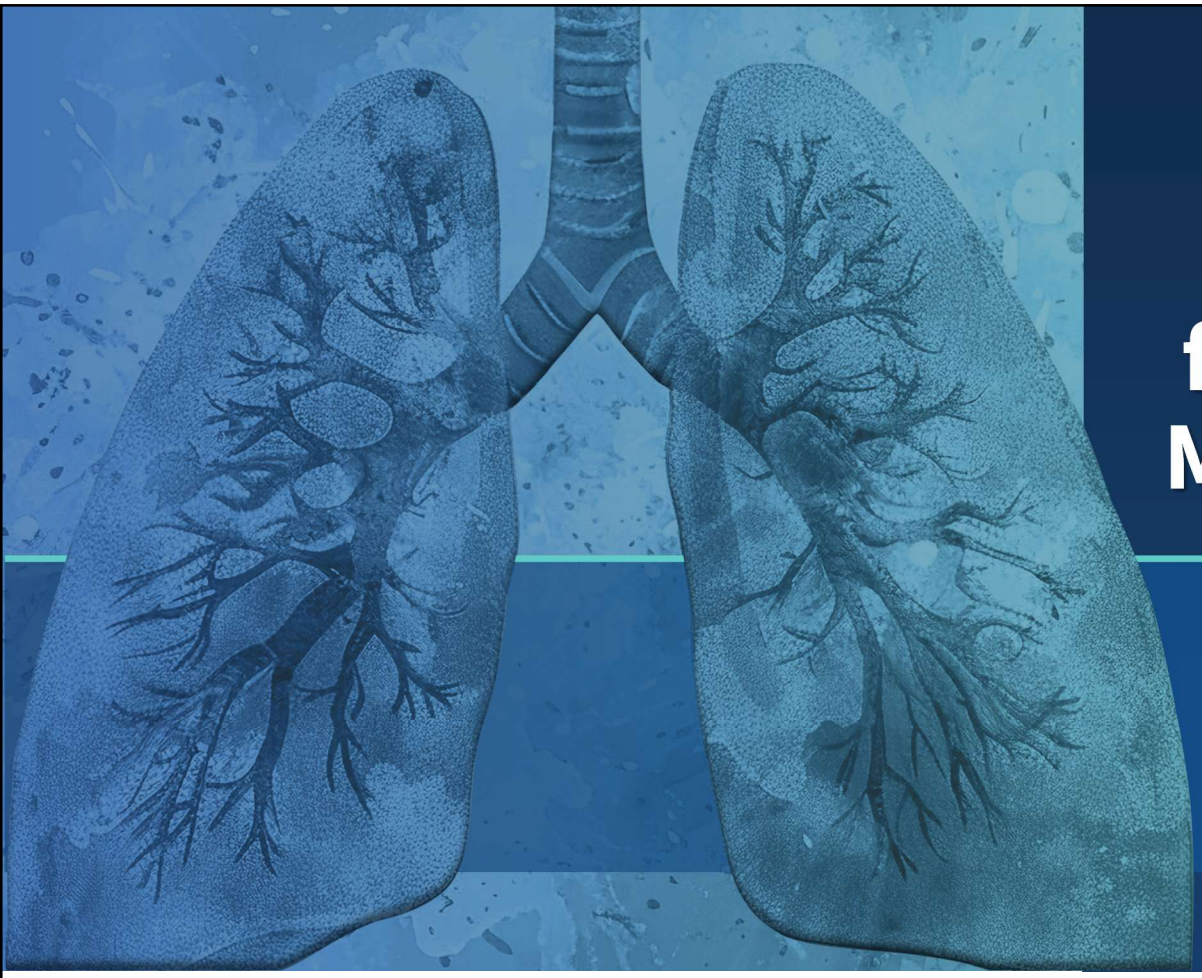
- **Nurses**
  - Provide day-to-day care coordination, triage symptoms, administer treatments, and serve as key points of patient contact
  - Educate patients and families about care plans, procedures, and symptom management

- **Social Workers**
  - Address psychosocial needs, coordinate resources (transportation, financial support, counseling), and support advanced care planning
  - Facilitate communication between patients, families, and the care team

- **Collaborative Impact**
  - Promotes continuity of care and provides outcomes by addressing medical, emotional, and logistical aspects of cancer care
  - Enables holistic, timely, and personalized treatment approaches

Key Takeaways

- 1L Setting:
  - Explosion of exciting therapeutics
    - Osimertinib monotherapy
    - Osimertinib + Chemo
    - Amivantamab + Lazertinib (MARIPOSA)
- 2L Setting:
  - 4th generation EGFR TKIs in clinical trials
  - Combination approaches
  - Bispecific antibodies
    - Amivantamab + Chemo
  - ADCs (TROP2)



The Expanding Armamentarium for EGFR-Mutated Metastatic NSCLC:

Case-Driven Strategies for the Community-Based Clinician

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