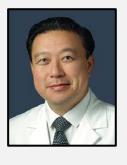
Refining the First Strike Against PeerView EGFR-Mutated Advanced NSCLC

Personalizing Frontline Treatment Decisions
Amid Increasing Complexity



Today's Faculty



Stephen V. Liu, MD
Associate Professor of Medicine
Director, Thoracic Oncology
Head, Developmental Therapeutics
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Georgetown University
Washington, District of Columbia



Zosia Piotrowska, MD, MHS Assistant Professor of Medicine Harvard Medical School Massachusetts General Hospital Boston, Massachusetts

Our Goals for Today

- Augment your knowledge of the evidence supporting the use of different first-line treatment options for EGFR-mutated advanced/metastatic NSCLC
- Equip you with skills for developing individualized first-line treatment plans with EGFR-targeted therapies or combinations for patients with EGFR-mutated advanced/metastatic NSCLC

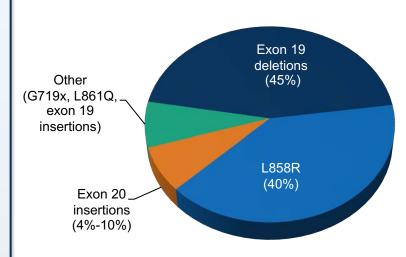
Gaps and Opportunities for Improvement: Spotlight on *EGFR*-Mutated mNSCLC

Necessary Biomarker Testing in Lung Cancer: EGFR and Beyond

Complete biomarker testing prior to therapy is needed to optimize care

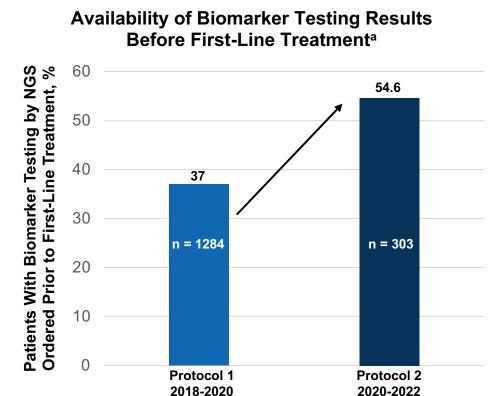
- PD-L1 tumor expression, genomic alterations (EGFR, ALK, ROS1, BRAF, NTRK, MET, RET, KRAS, ERBB2)
- Guides therapy in advanced NSCLC and now in earlier stages of disease
- Type of testing matters (NGS, DNA vs RNA)
- Interpretation of results is just as important
 - Know what you're looking for (mutation vs amplification/overexpression)
 - EGFR or biomarker "positive" is not enough → more granularity needed

Different Subtypes of EGFR Mutations





Gaps in Biomarker Testing Persist... MYLUNG Study Update¹



Patients in Advanced Cohort (N = 582) With Any Biomarker Testing Results Prior to First-Line Treatment (N = 461)		
ALK , n (%)	355 (77.0)	
<i>BRAF</i> , n (%)	335 (72.7)	
EGFR, n (%)	371 (80.5)	
KRAS, n (%)	294 (63.8)	
<i>MET</i> , n (%)	328 (71.1)	
NTRK, n (%)	253 (54.9)	
PD-L1, n (%)	388 (84.2)	
<i>RET</i> , n (%)	305 (66.2)	
ROS1, n (%)	344 (74.6)	



^a Denominator: Protocol = 3474; protocol 2, N = 555.

^{1.} Evangelist M et al. ASCO 2023. Abstract 9109.

2024 IASLC Global Survey on Biomarker Testing¹

Found improvements in the perception of testing rates vs 2018, but continued and substantial barriers in testing persist



estimate more than half of individuals with lung cancer are biomarker tested in their country, up from in the 2018

(p-value<0.0001)

LATE ranked highly important to STAGE perform comprehensive biomarker testing in respective stage **EARLY** STAGE 63% 29%



Sometimes or often treat patients prior to receiving biomarker results

COST TIME SAMPLE QUALITY **ACCESS**

Key Solutions Identified



TESTING PROTOCOLS





INCREASE AWARENESS









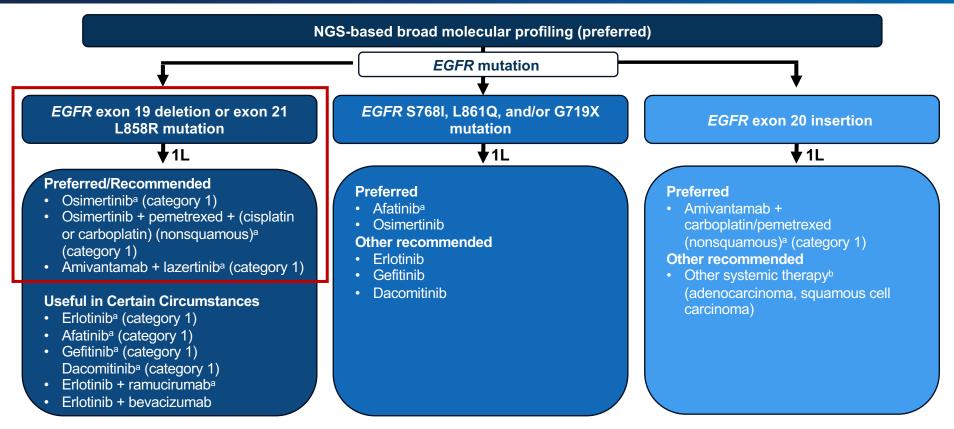
GOVERNMENT LEVEL

STRATEGIES

The Highest Ranked Barriers

AWARENESS

Increasing Complexity of First-Line EGFR-Targeted Therapy Options for *EGFR*-Mutated mNSCLC: NCCN Guidelines¹



^a FDA approved. ^b Please consult NCCN Guidelines for details on systemic therapy options.



^{1.} NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer. Version 11.2024. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.

Candid Conversations and Clinical Consults:

How to Interpret the Evidence and Make Multifactorial Clinical Decisions in First-Line Treatment of *EGFR*-Mutated Advanced NSCLC

Let's Consider Case #1

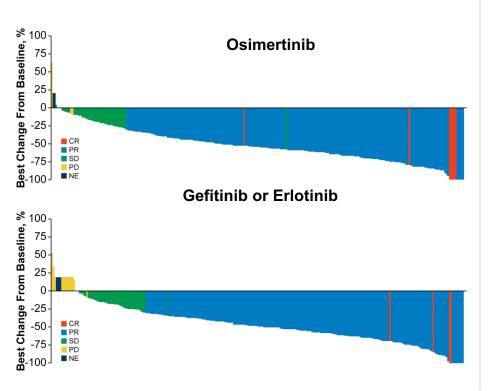


A 61-year-old woman with no history of smoking presents with cough, dyspnea, and generalized fatigue x 3 months

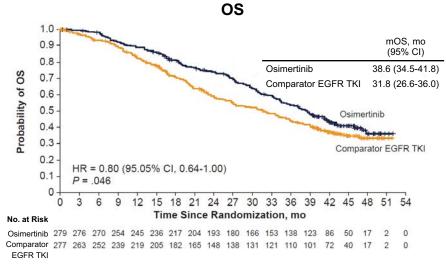
- Initial CXR: LUL opacity → PET/CT: 3-cm LLL lung nodule and enlarged mediastinal nodes + multiple FDG-avid hepatic hypodensities and extensive bone marrow uptake c/w skeletal metastasis
- MRI of the brain: 4 subcentimeter parenchymal lesions consistent with metastases and without perilesional edema
- FNA of the lung lesion shows adenocarcinoma (TTF-1+)
- Biomarker testing reveals EGFR exon 21 L858R mutation; PD-L1 TPS <1%
- Comes to your clinic to discuss first-line treatment options

FLAURA: Phase 3 Study of First-Line Osimertinib in EGFR-Mutated mNSCLC^{1,2}

Best Change From Baseline in Target Lesions

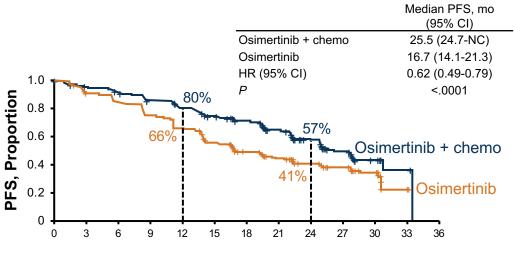


- mPFS = 18.9 mo
- Improved intracranial penetration vs 1G TKIs
- Toxicities: rash, diarrhea, paronychia (low grade),
 QTc prolongation, and ILD (rare)



FLAURA2: PFS With First-Line Osimertinib ± Chemotherapy in *EGFR*-Mutated mNSCLC¹⁻⁴

PFS per Investigator Assessment



Time Since Randomization, mo

No. at Risk Osimertinib 279 254 241 225 207 187 165 133 84

- Clinically meaningful PFS benefit observed across predefined subgroups, including patients with CNS metastases and EGFR L858R mutations
- mOS (2nd interim analysis):
 NR vs 36.7 mo, HR, 0.75 (95% CI, 0.57-0.97; P = .0280)
- Toxicities: myelosuppression, diarrhea, nausea, anorexia, rash

Data cutoff: April 3, 2023.

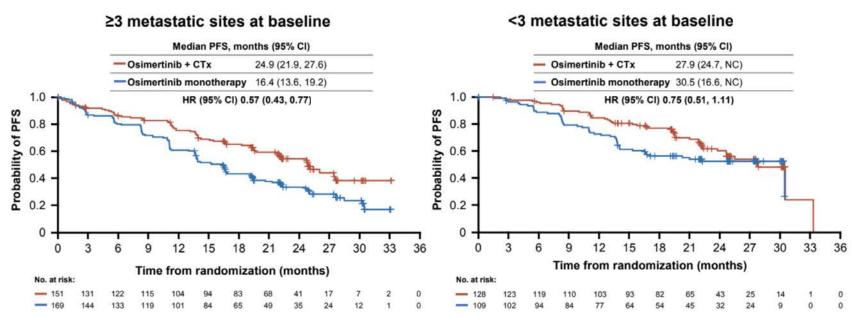


^{1.} Janne P et al. WCLC 2023. Abstract PL03.13. 2. Planchard D et al. ESMO 2023. Abstract LBA68. 3. Planchard D et al. N Engl J Med. 2023;389:1935-1948.

^{4.} Valdiviezo N et al. Ann Oncol. 2024;9:1-53.

FLAURA2: Impact of Tumor Burden on Outcomes of First-Line Osimertinib ± Chemotherapy in *EGFR*-Mutated mNSCLC¹

Osimertinib + Chemo Showed PFS Benefit in Patients With ≥3 Metastatic Anatomical Sites at Baseline vs Osimertinib Alone

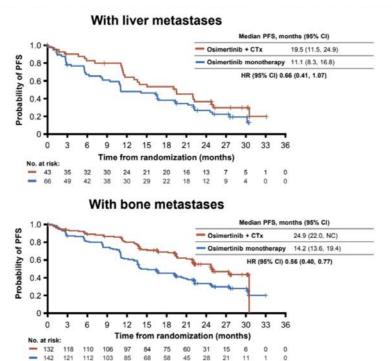


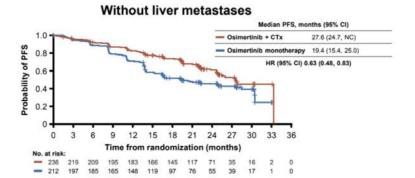
- A PFS benefit with osimertinib plus chemotherapy vs osimertinib alone was observed in patients with extra-thoracic metastases at baseline:
 - Intra-thoracic: median PFS (95% CI) was 26.0 months (21.9, NC) vs NC (16.7, NC), respectively; HR 0.97 (95% CI 0.59, 1.60)
 - Extra-thoracic: median PFS (95% CI) was 25.1 months (22.2, NC) vs 16.4 months (13.6, 19.4), respectively; HR 0.54 (95% CI 0.41, 0.71)

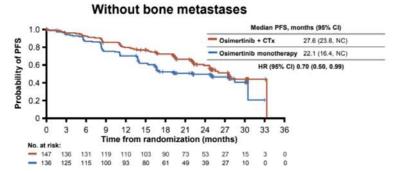


FLAURA2: Impact of Tumor Burden on Outcomes of First-Line Osimertinib ± Chemotherapy in *EGFR*-Mutated mNSCLC¹

Osimertinib + Chemo Showed PFS Benefit in Patients With or Without Liver or Bone Metastases at Baseline vs Osimertinib Alone

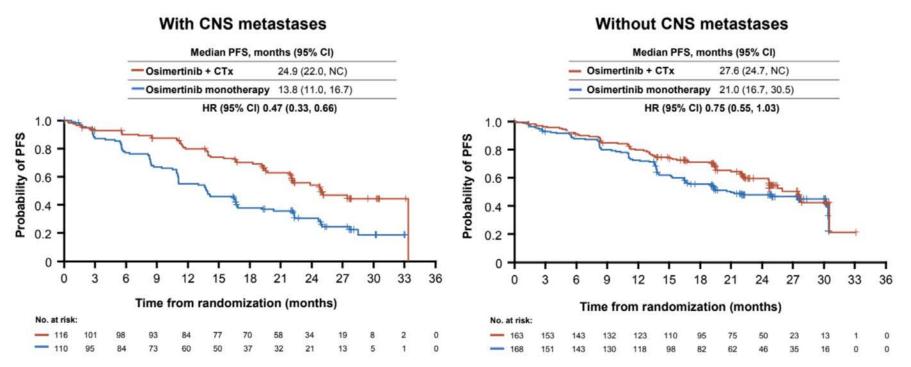






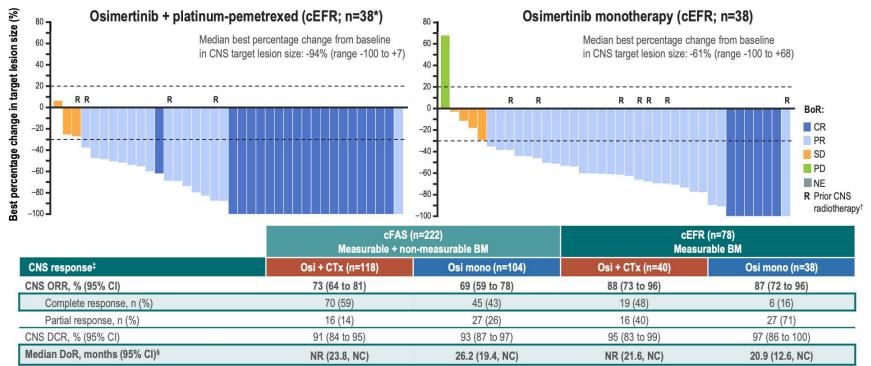
FLAURA2: Impact of Tumor Burden on Outcomes of First-Line Osimertinib ± Chemotherapy in *EGFR*-Mutated mNSCLC¹

Osimertinib + Chemo Showed PFS Benefit in Patients With or Without CNS Metastases at Baseline vs Osimertinib Alone



FLAURA2: CNS Outcomes With First-Line Osimertinib ± Chemotherapy in *EGFR*-Mutated mNSCLC¹

Osimertinib + Chemo Showed a High Proportion of CRs in the CNS by CNS BICR

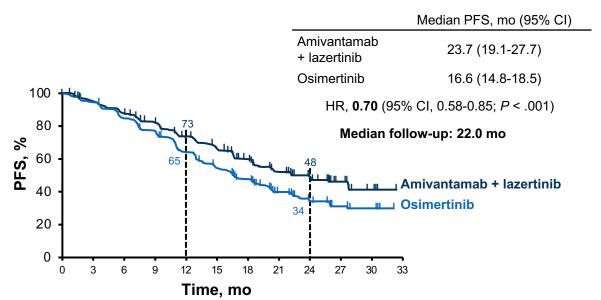


^{*}Two pts had ≥1 measurable CNS lesion at baseline by CNS BICR but died before the follow-up CNS BICR scan; † In the cEFR, 4/40 pts (10%) in the osimertinib + platinum-pemetrexed arm and 7/38 pts (18%) in the osimertinib arm had received prior CNS radiotherapy; stable neurological statustus for ≥2 weeks after completion of definitive treatment and steroids was required before study entry, if received; ‡Responses did not require confirmation, per RECIST guidance on randomized studies; §Kaplan-Meier estimates



MARIPOSA: PFS of First-Line Amivantamab + Lazertinib in *EGFR*-Mutated mNSCLC¹⁻³

Primary Endpoint: PFS by BICR^a



- mOS (interim analysis):
 HR, 0.77 (95% CI,
 0.61-0.96; P = .019);
 did not reach
 prespecified level of
 statistical significance
- Toxicities: paronychia, IRR, rash, VTE



No. at Risk

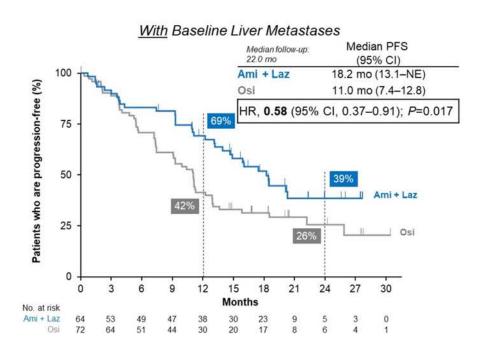
 Amivantamab + lazertinib
 429 391 357 332 291 244 194 106 60 33 8

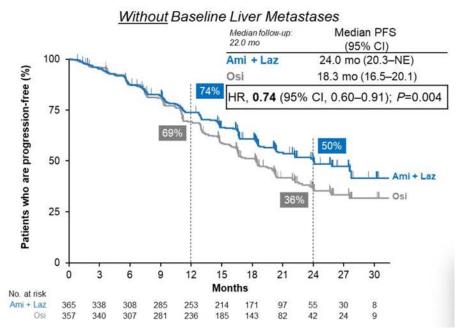
 Osimertinib
 429 404 358 325 266 205 160 90 48 28 10

a At the time of prespecified final PFS analysis, there were a total of 444 PFS events in the amivantamab + lazertinib and osimertinib arms combined.

^{1.} Cho BC et al. ESMO 2023. Abstract LBA14. 2. Cho BC et al. N Engl J Med. 2024;391:1486-1498. 3. Gadgeel S et al. WCLC 2024. Abstract OA02.03.

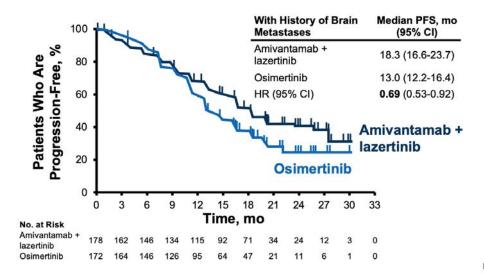
MARIPOSA: PFS by Baseline Liver Metastases With First-Line Amivantamab + Lazertinib in *EGFR*-Mutated mNSCLC¹

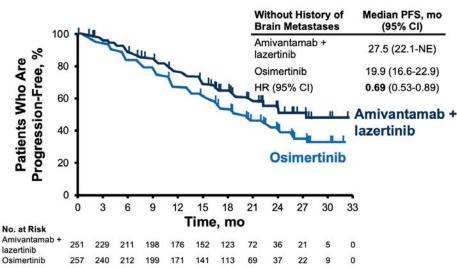






MARIPOSA: PFS Benefit With/Without CNS Metastases With First-Line Amivantamab + Lazertinib in EGFR-Mutated mNSCLC¹⁻³







PALOMA-3: SC vs IV Amivantamab (Both in Combination With Lazertinib) in Refractory *EGFR*-Mutated mNSCLC^{1,2}

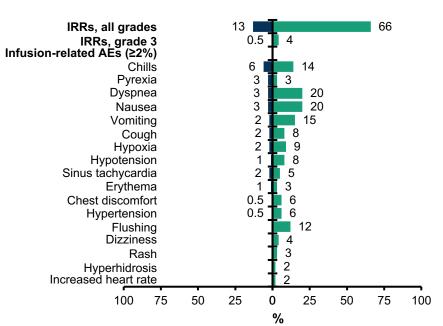
- SC amivantamab + lazertinib demonstrated PK and ORR noninferiority to IV amivantamab + lazertinib in patients with EGFR-mutated advanced NSCLC with disease progression on or after osimertinib and chemotherapy
- Compared with the IV arm, SC amivantamab also showed:
 - Numerically longer DOR (11.2 vs 8.3 mo) and PFS (6.1 vs 4.3 mo)
 - Significant improvement in OS (HR = 0.62; nominal P = .02)

	SC Amivantamab (n = 206)	IV Amivantamab (n = 212)
ORR, % (95% CI)		
All responders	30 (24-37)	33 (26-39)
	Relative risk, 0.92 (0.70-1.23); <i>P</i> = .001	
Confirmed responders	27 (21-33)	27 (21-33)
	Relative risk, 0.99 (0.72-1.36); P < .001	
Best response, n (%)		
CR	1 (0.5)	1 (0.5)
PR	61 (30)	68 (32)
SD	93 (45)	81 (38)
PD	37 (18)	42 (20)
NE	14 (7)	20 (9)
DCR, % (95% CI)	75 (69-81)	71 (64-77)
Median TTR (range), mo	1.5 (1.2-6.9)	1.5 (1.2-9.9)

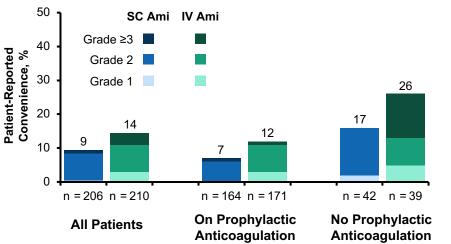
PALOMA-3: SC vs IV Amivantamab (Both in Combination With Lazertinib) in Refractory *EGFR*-Mutated mNSCLC^{1,2}

 The safety profile of SC amivantamab was consistent with IV, with fewer IRRs (13% vs 66%) and VTE (9% vs 14%)

Incidence of IRR-Related Symptoms



Rates of VTE by Treatment Arm and Prophylaxis Status



Let's Come Back to Case #1



A 61-year-old woman with no history of smoking presents with cough, dyspnea, and generalized fatigue x 3 months

- Initial CXR: LUL opacity → PET/CT: 3-cm LLL lung nodule and enlarged mediastinal nodes + multiple FDG avid hepatic hypodensities and extensive bone marrow uptake c/w skeletal metastasis
- MRI of the brain: 4 subcentimeter parenchymal lesions consistent with metastases and without perilesional edema
- FNA of the lung lesion shows adenocarcinoma (TTF-1+)
- Biomarker testing reveals EGFR exon 21 L858R mutation; PD-L1 TPS <1%
- Comes to your clinic to discuss first-line treatment options

Let's Discuss

✓ What first-line treatment would you recommend and why?

Let's Consider Case #1 Variations



A 61-year-old woman with no history of smoking presents with cough, dyspnea, and generalized fatigue x 3 months

- Initial CXR: LUL opacity → PET/CT: 3-cm LLL lung nodule and enlarged mediastinal nodes + multiple FDG avid hepatic hypodensities and extensive bone marrow uptake c/w skeletal metastasis
- MRI of the brain: 4 subcentimeter parenchymal lesions consistent with metastases and without perilesional edema
- FNA of the lung lesion shows adenocarcinoma (TTF-1+)
- Biomarker testing reveals EGFR exon 21 L858R mutation; PD-L1 TPS <1%
- Comes to your clinic to discuss first-line treatment options

Let's Discuss

What if...

- ✓ The patient is 85 years of age?
- ✓ The patient is 45 years of age?
- ✓ The patient lives in a remote area 6 hours away from your clinic?

Let's Consider Case #2

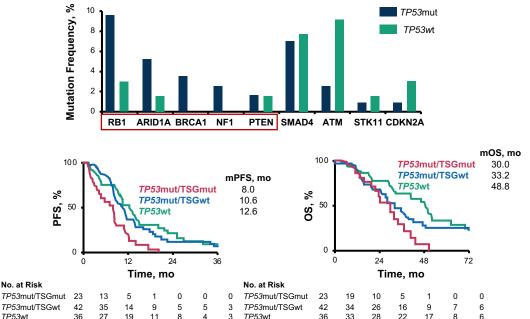


A 58-year-old man with no history of smoking noticed a nonproductive cough

- Symptoms persisted, and he went to his PCP → chest x-ray → left lung nodule detected
- CT identified a 3-cm LLL lung nodule, enlarged mediastinal nodes, and multiple lytic bone lesions c/w skeletal metastasis; no other areas of uptake
- MRI of the brain: negative
- FNA of the lung lesion shows adenocarcinoma (TTF-1+)
- Biomarker testing reveals EGFR exon 21 L858R mutation and TP53mut/TSGmut
- PD-L1 IHC: TPS 80%
- Comes to your clinic to discuss first-line treatment options

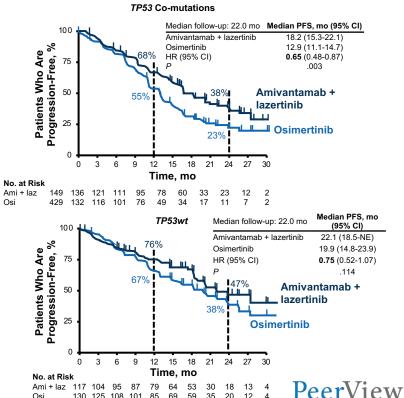
Relevance of *TP53* Status in Guiding Patient Selection for First-Line Combination Therapy in *EGFR*-Mutated mNSCLC

Can co-mutations be used as prognostic biomarkers?¹



 Co-mutations in TP53 and tumor suppressor genes are associated with worse TKI outcomes

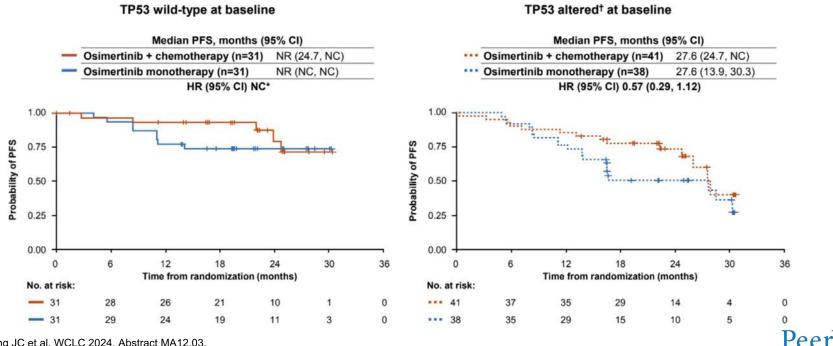
MARIPOSA: PFS by TP53 Status²



Relevance of TP53 Status in Guiding Patient Selection for First-Line Combination Therapy in EGFR-Mutated mNSCLC (Cont'd)

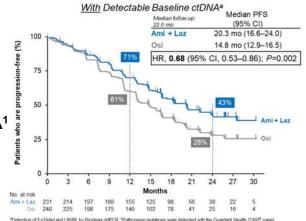
FLAURA2: Impact of Baseline TP53 Alterations on Outcomes¹

TP53 alterations may be prognostic for PFS benefit with osimertinib + platinum-pemetrexed over osimertinib monotherapy



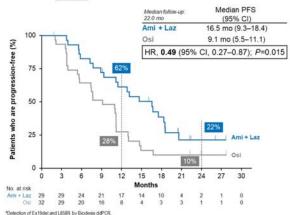
Value of Monitoring ctDNA Dynamics in EGFR-Mutated mNSCLC

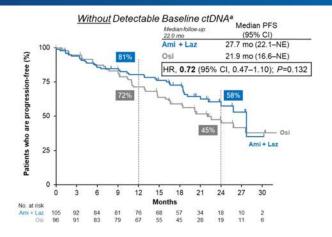
MARIPOSA: PFS by Detectable Baseline EGFRmut ctDNA1



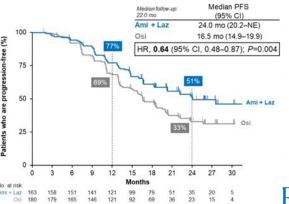
Without Cleared EGFRm ctDNA^a at Week 9

MARIPOSA: PFS Without/With Cleared EGFRmut ctDNA at Week 91





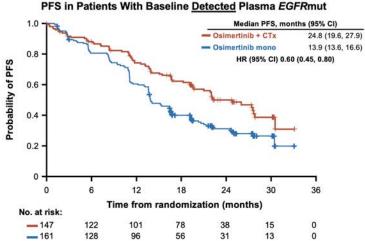




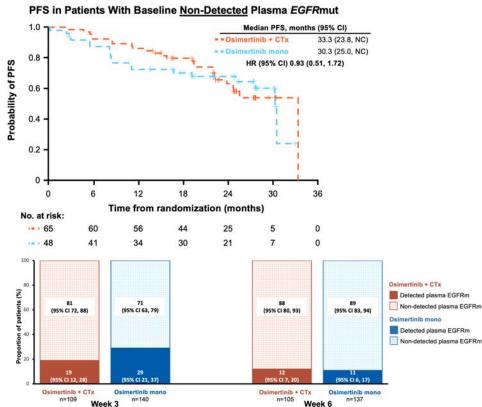
PeerView

Value of Monitoring ctDNA Dynamics in EGFR-Mutated mNSCLC (Cont'd)

• FLAURA2: baseline detected plasma *EGFR*mut was prognostic and may select for a higher degree of clinical benefit with osimertinib plus chemotherapy versus osimertinib alone¹



 FLAURA2: on-treatment plasma EGFRmut clearance was prognostic but not predictive of benefit with osimertinib plus chemotherapy versus osimertinib alone¹



Let's Come Back to Case #2



A 58-year-old man with no history of smoking noticed a nonproductive cough

- Symptoms persisted, and he went to his PCP → chest x-ray → left lung nodule detected
- CT identified a 3-cm LLL lung nodule, enlarged mediastinal nodes, and multiple lytic bone lesions c/w skeletal metastasis; no other areas of uptake
- MRI of the brain: negative
- FNA of the lung lesion shows adenocarcinoma (TTF-1+)
- Biomarker testing reveals EGFR exon 21 L858R mutation and TP53mut/TSGmut
- PD-L1 IHC: TPS 80%
- Comes to your clinic to discuss first-line treatment options

Let's Discuss

✓ What first-line treatment would you recommend and why?

Let's Consider Case #2 Variations



A 58-year-old man with no history of smoking noticed a nonproductive cough

- Symptoms persisted, and he went to his PCP → chest x-ray → left lung nodule detected
- CT identified a 3-cm LLL lung nodule, enlarged mediastinal nodes, and multiple lytic bone lesions c/w skeletal metastasis; no other areas of uptake
- MRI of the brain: negative
- FNA of the lung lesion shows adenocarcinoma (TTF-1+)
- Biomarker testing reveals EGFR exon 21 L858R mutation and TP53mut/TSGmut
- PD-L1 IHC: TPS 80%
- Comes to your clinic to discuss first-line treatment options

Let's Discuss

What if...

- ✓ ctDNA was detectable at baseline and cleared?
- ✓ ctDNA was detectable at baseline, but did not clear?

Let's Consider Case #3



A 63-year-old man with no history of smoking is incidentally found to have lung nodules on x-ray; no symptoms

- PET scan: multiple bilateral pulmonary nodules; no other areas of uptake
- MRI of the brain: negative
- FNA of the lung lesion shows adenocarcinoma (TTF-1+)
- Biomarker testing reveals EGFR exon 19 deletion
- Comes to your clinic to discuss first-line treatment options

Summary of Key Trials and Factors to Consider

FLAURA¹⁻²

- Osimertinib vs 1G TKI
- mPFS = 18.9 mo
- mOS = 38.6 mo

Toxicities: rash, diarrhea, paronychia (low grade), QTc prolongation, and ILD (rare); generally, a well tolerated treatment

Key Factors

- Improved intracranial penetration vs 1G TKIs
- Oral only administration with few clinic visits

Soria JC et al. N Engl J Med. 2018;378:113-125.
 Ramalingam SS et al. N Engl J Med. 2020;382:41-50.

FLAURA21-3

- Osimertinib/platinum-pemetrexed vs osimertinib
- mPFS = 25.5 mo (HR vs osimertinib = 0.62)
- mOS (2nd interim analysis): NR vs 36.7 mo, HR, 0.75 (95% CI, 0.57-0.97; P = .0280); did not reach prespecified level of statistical significance

Toxicities: myelosuppression, diarrhea, nausea, anorexia, and rash

Key Factors

- Requires IV administration Q21D
- Median pemetrexed exposure 8.3 mo
- More intracranial CRs and lower risk of intracranial progression with osimertinib + chemo suggests potential benefit in patients with CNS disease

MARIPOSA1-3

- Lazertinib + amivantamab vs osimertinib
- mPFS = 23.7 months (HR vs osimertinib = 0.70)
- mOS (interim analysis): HR, 0.77 (95% CI, 0.61-0.96, P = .019); did not reach prespecified level of statistical significance

Toxicities: paronychia, IRRa, rash, and VTE

Key Factors

- IV administration with frequent initial visits^a
- Significant dermatologic toxicities (rash, scalp irritation, and paronychia)
- Benefit observed across high risk subgroups
 - Detectable baseline ctDNA, HR = 0.68
 - TP53 co-mutations, HR = 0.65
 - Brain metastases, HR = 0.69

<sup>a IRR less frequent with subcutaneous formulation.
1. Cho BC et al. N Engl J Med. 2024.
2. Felip E et al. ASCO 2024.
Abstract 8504.
3. Gadqeel S et al. WCLC 2024.
Abstract OA02.03.</sup>

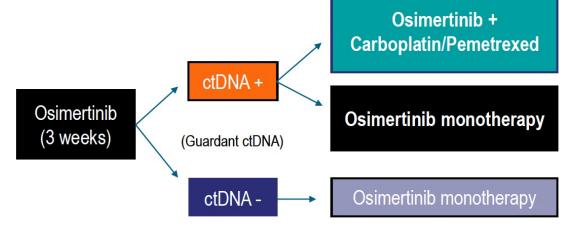


Planchard D et al. ESMO 2023. Abstract LBA68.
 Planchard D et al. N Engl J Med. 2023;389:1935-1948.
 Valdiviezo N et al. Ann Oncol. 2024;9:1-53.

Novel Approaches Under Investigation in Clinical Trials

Regimen	Trial Name	Clinicaltrials.gov#
Osimertinib + amivantamab	OSTARA	NCT05801029
Osimertinib +/- bevacizumab	EA5182	NCT04181060
Osimertinib +/- datopotamab deruxtecan	TROPION-Lung14	NCT06350097
Osimertinib + patritumab deruxtecan		NCT04676477

Risk-adaptive trial design: eg, EGFR Shedders Trial NCT04410796; PI: H. Yu





Let's Come Back to Case #3



A 63-year-old man with no history of smoking is incidentally found to have lung nodules on x-ray; no symptoms

- PET scan: multiple bilateral pulmonary nodules; no other areas of uptake
- MRI of the brain: negative
- FNA of the lung lesion shows adenocarcinoma (TTF-1+)
- Biomarker testing reveals *EGFR* exon 19 deletion
- Comes to your clinic to discuss first-line treatment options

Let's Discuss

✓ What first-line treatment would you recommend and why?

Let's Consider Case #3 Variations



A 63-year-old man with no history of smoking is incidentally found to have lung nodules on x-ray; no symptoms

- PET scan: multiple bilateral pulmonary nodules; no other areas of uptake
- MRI of the brain: negative
- FNA of the lung lesion shows adenocarcinoma (TTF-1+)
- Biomarker testing reveals EGFR exon 19 deletion
- Comes to your clinic to discuss first-line treatment options

Let's Discuss

What if...

- ✓ The tumor had an EGFR exon 21 L858R mutation instead?
- ✓ The tumor had an EGFR exon 19 deletion, but MRI of the brain had shown a solitary brain metastasis?
- ✓ The tumor had an EGFR exon
 19 deletion and also a TP53
 co-mutation?

Visit us at PeerView.com/LakeTahoe24

- Complete and submit your post-test and evaluation for credit
- Download the slides and Practice Aids
- Watch the replay of this event in the next 24 hours and the online activity in the coming weeks

Thank you for joining us!

Join the conversation on X @PeerView

Abbreviations

1L: first line

Ami: amivantamab

ASCO: American Society of Clinical Oncology

BICR: blinded independent central review

C2D1: cycle 2, day 1

CR: complete response

ctDNA: circulating tumor DNA

CXR: chest x-ray

DCR: disease control rate DOR: duration of response

ESMO: European Society for Medical Oncology

FDG: F-18-Fluorodeoxyglucose

FNA: fine needle aspiration IHC: immunohistochemistry

ILD: interstitial lung disease

IRR: incidence rate ratio

LLL: lower left lobe

LUL: left upper lobe

mNSCLC: metastatic non-small cell lung cancer

mOS: median overall survival

mPFS: median progression-free survival

NC: no change

NCCN: National Comprehensive Cancer Network

NE: not evaluable

NGS: next-generation sequencing

NR: not reached

ORR: objective response rate

PD-L1: programmed death-ligand 1

PD: progressive disease

PK: pharmacokinetics

PR: partial response

Q21D: every 21 days

SC: subcutaneous

SD: stable disease

TAT: turnaround time

TM: transmembrane

TPS: tumor proportion score

TTF-1: thyroid transcription factor 1

TTR: time to response

WCLC: World Conference on Lung Cancer

