



DRIVING OUTCOMES IN NSCLC

Targeting EGFR and Other
Common Driver Mutations

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Faculty Disclosures

- **Faith Mutale, DNP, CRNP:** Speakers' Bureau—Astra Zeneca, Daiichi Sankyo
- **Umit Tapan, MD:**
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Learning Objectives

- Assess the clinical significance of common driver mutations in NSCLC, including *EGFR* mutations, and their role in personalized treatment selection
- Evaluate the latest clinical data and guideline-directed strategies for treatment selection and sequencing in NSCLC, including *EGFR*-mutant disease
- Apply evidence-based strategies to optimize AE management, support treatment tolerability, and improve patient outcomes in NSCLC

Program Information

- This program is provided by HMP Education, an HMP Global Company
- Supported by an educational grant from Johnson & Johnson

Polling

- Participate in polling at the beginning and end of the session to be entered to win a \$100 gift card!
- Scan this QR code to see the answer choices and submit your response



NSCLC

Cancer Burden

- ~229,410
new lung cancer cases projected in the U.S. in 2026
- ~124,990
lung cancer deaths projected in 2026
- $\approx 77\%$ of lung cancers are NSCLC
- Lung cancer remains the **2nd most commonly diagnosed cancer in both men and women in the U.S.** and the leading cause of cancer death

NSCLC: Risk Factors

Modifiable / Environmental

Tobacco exposure – cigarettes, cigars, pipes

Secondhand smoke

Radon exposure

Occupational exposures: asbestos, arsenic, chromium, nickel, beryllium

Air pollution

Occupational dusts/fumes

Nonmodifiable / Clinical

Increasing age

Personal history of lung cancer

Family history of lung cancer

Prior radiation to chest/breast

Genetic susceptibility

NSCLC: Clinical Presentation

Presentation	Symptoms	Clinical Implication
Respiratory/local	Cough, hemoptysis, dyspnea, chest pain, recurrent pneumonia	Consider thoracic imaging when persistent/unexplained
Systemic	Weight loss, fatigue, anorexia, weakness	May accompany advanced disease
Metastatic	Bone pain, headache, neurologic symptoms, hoarseness, dysphagia	Prompt diagnostic evaluation and staging
Asymptomatic	No cancer-related symptoms	Screen eligible high-risk patients with LDCT

NSCLC: LDCT

Importance of Timely Detection

- Timely Detection Through LDCT Screening
- Lung cancer can be detected before symptoms develop
- WHO SHOULD BE SCREENED?

Eligibility	Current Recommendation
Age	50–80 years
Smoking history	≥20 pack-years
Smoking status	Current smoker or former smoker
Screening test	Annual low-dose CT (LDCT)
Stop screening when	Patient has not smoked for 15 years , develops a health problem limiting curative treatment, or reaches age 81*

CT = computed tomography.

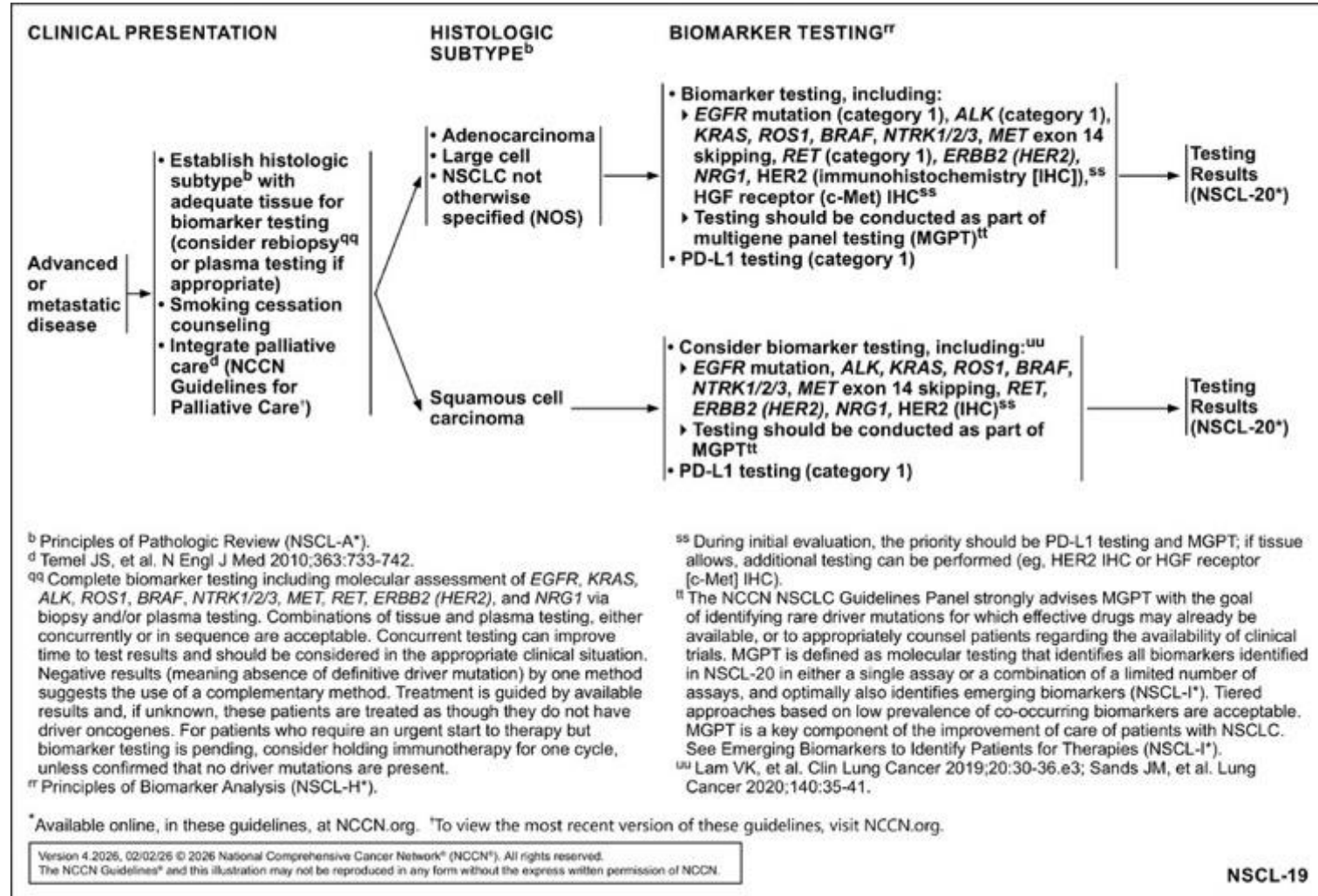
US Preventive Services Task Force. *JAMA*. 2021;325(10):962-970.

Biomarker Driven Care in NSCLC

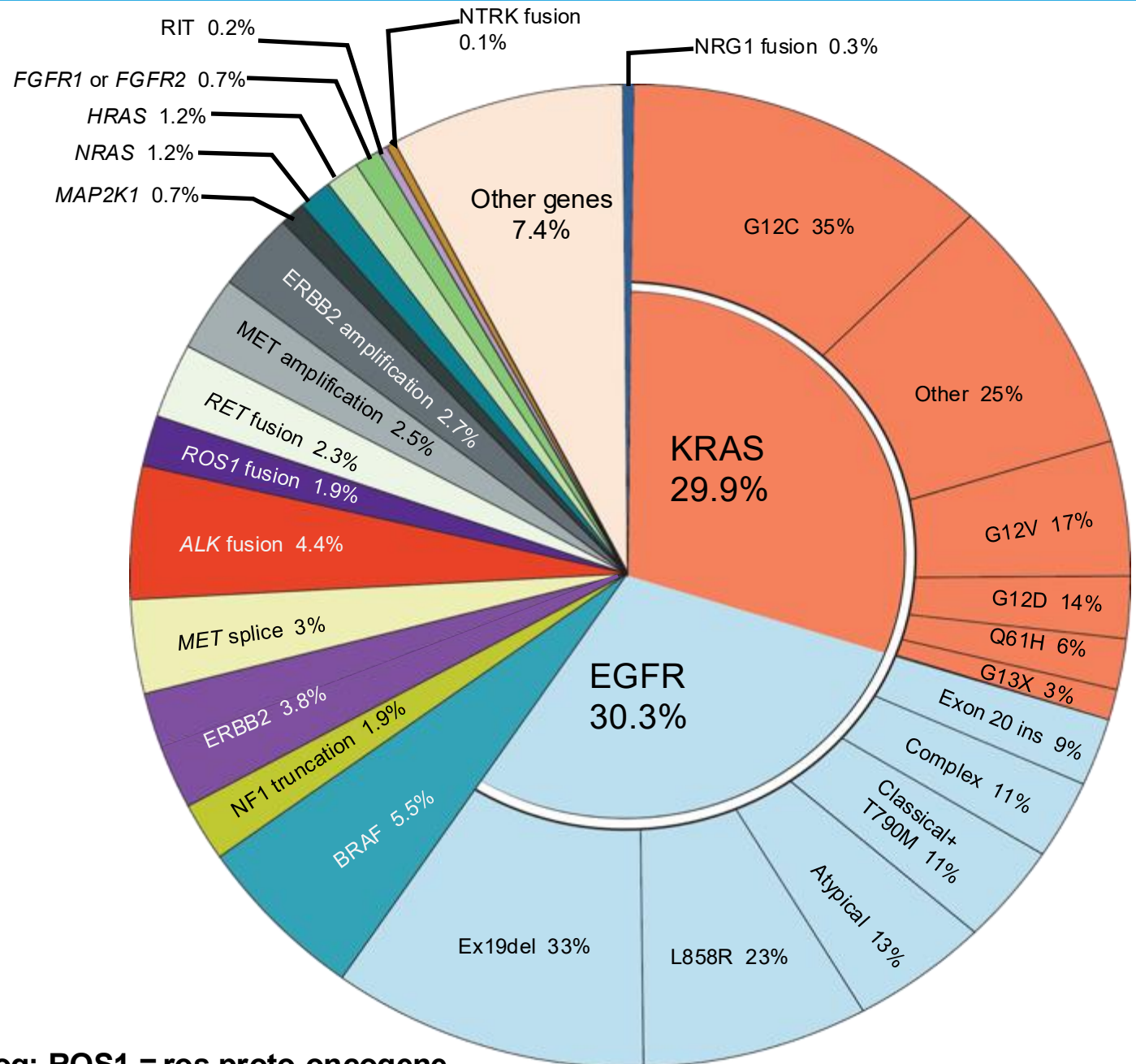


Personalized Treatment Strategies in NSCLC

From Histology to Biomarker-Guided Care



Driver Mutation Identification: The Foundation of Precision Therapy in NSCLC



KRAS = Kirsten rat sarcoma viral oncogene homolog; ROS1 = ros proto-oncogene.
 Skoulidis F, Heymach JV. *Nat Rev Cancer*. 2019;19(9):495-509. Lau ELY, et al. *Drugs*. 2026;86(7):1075-1090.

Using Biomarker Results to Guide Treatment Selection

BIOMARKER → ALTERATION → THERAPY → REASSESSMENT

1. TEST	2. IDENTIFY	3. MATCH	4. OPTIMIZE
Broad biomarker profiling	Actionable alteration	Targeted therapy	Patient-specific selection
Tissue NGS ± RNA	EGFR , ALK, ROS1, MET, RET, BRAF, KRAS, HER2, NTRK	Alteration-directed treatment	CNS activity
Plasma ctDNA when appropriate	Driver vs resistance alteration	Guideline/evidence-based	Prior therapy
PD-L1	Primary vs acquired resistance	Clinical trial when appropriate	Toxicity & comorbidities
Do not rely on PD-L1 alone when a driver alteration is present			Re-biopsy/ctDNA at progression when it may change management

CNS = central nervous system; ctDNA = circulating tumor DNA; NGS = next-generation sequencing; PD-L1 = programmed death-ligand 1.

Lau ELY, et al. *Drugs*. 2026;86(7):1075-1090.

Using Biomarker Results to Guide Treatment Selection

Biomarker profile should guide treatment & NOT phenotype alone

Biomarker	Agent(s)	Treatment Line	Clinical Pearl / Landmark Evidence
EGFR exon 19 del / L858R	Osimertinib ; osimertinib + platinum/pemetrexed, amivantamab + lazertinib	1L	CNS-active EGFR TKI; FLAURA, FLAURA2, MARIPOSA
EGFR exon 20 insertion	Amivantamab + carboplatin/pemetrexed	1L	PAPILLON: improved PFS vs chemotherapy alone; FDA-approved 1L option
ALK rearrangement	Alectinib ; lorlatinib; brigatinib	1L	Potent CNS activity; lorlatinib and alectinib provide durable intracranial disease control
ROS1 fusion	Repotrectinib ; taletrectinib	1L	Repotrectinib and taletrectinib, provides systemic and intracranial activity and better safety profile
MET exon 14 skipping	Capmatinib ; tepotinib	1L	MET-directed therapy preferred over nonspecific chemotherapy when alteration is identified
RET fusion	Selpercatinib ; pralsetinib	1L	Highly active selective RET inhibitors with CNS activity
BRAF V600E	Dabrafenib + trametinib , encorafenib + binimetinib	1L	Targeted BRAF/MEK inhibition; established biomarker-matched strategy
HER2 activating mutation	Zongertinib , Trastuzumab deruxtecan; for appropriate HER2 TKD mutations	1L (zongertinib), later line (both agents)	HER2-directed therapy is increasingly mutation-specific
KRAS G12C	Sotorasib ; adagrasib	Later line	Generally used after ≥1 prior systemic therapy; important distinction from 1L EGFR/ALK-directed therapy
NTRK fusion	Larotrectinib ; entrectinib	1L / tumor-agnostic	Rare but highly actionable; tumor-agnostic targeted treatment
No actionable driver; PD-L1 ≥50%	Pembrolizumab or other guideline-supported immunotherapy strategy	1L	PD-L1 helps guide immunotherapy selection when no actionable driver is identified
No actionable driver; PD-L1 <50%	ICI + platinum-based chemotherapy	1L	Chemoimmunotherapy commonly preferred in appropriate patients

1L = first-line; ICI = immune checkpoint inhibitor; TKI = tyrosine kinase inhibitor.

Lau ELY, et al. *Drugs*. 2026;86(7):1075-1090. Mosele F, et al. *Ann Oncol*. 2020;31(11):1491-1505. Referenced from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.6.2026. © National Comprehensive Cancer Network, Inc. 2026. All rights reserved. Accessed October 14, 2026. To view the most recent and complete version of the guideline, go online to NCCN.org.



EGFR Mutations

EGFR Mutations

- ~15% of lung adenocarcinoma
- ≈25,000–30,000 new EGFR-mutated cases/year
- Multiple subtypes
- Exon 19 deletion and Exon 21 L858R ≈80%–85% of EGFR mutations
- Higher prevalence among **never-smokers** and **Asian populations**
- ↑ **risk brain metastases** → **good CNS penetration of Osimertinib**
- Resistance to EGFR TKIs is common
- Exon 20 insertions are resistant to classical TKIs

EGFR: One Gene, Multiple Clinical Subtypes

EGFR NOT ONE BIOLOGICAL CATEGORY

EGFR alteration	Clinical significance	EGFR-TKI sensitivity	Treatment approach*
Exon 19 deletion	Common activating mutation	● Highly sensitive	Osimertinib ± combination strategy, Amivantamab + lazertinib
Exon 21 L858R	Common activating mutation	● Highly sensitive	Osimertinib ± combination strategy, Amivantamab + lazertinib
Exon 20 insertion	Distinct biology; limited activity of conventional EGFR TKIs	● Resistant to conventional EGFR TKIs	Chemotherapy + amivantamab
G719X	Uncommon activating mutation	● Sensitive , with variable activity by agent	Afatinib ; osimertinib or amivantamab + lazertinib may be considered
L861Q	Uncommon activating mutation	● Sensitive , with variable activity by agent	Afatinib; osimertinib or amivantamab + lazertinib may be considered
S768I	Uncommon activating mutation	● Sensitive , with variable activity by agent	Afatinib ; osimertinib or amivantamab + lazertinib may be considered
T790M	Acquired resistance mutation after earlier-generation EGFR TKI	● Resistant to 1st/2nd-gen TKIs ; ● sensitive to osimertinib	Osimertinib

FLAURA: Study Schema

Eligibility

- Previously untreated, locally advanced or metastatic NSCLC
- Confirmed EGFR exon 19 deletion or L858R mutation
- Stable CNS metastases allowed

1:1
Randomization
(N = 556)

Osimertinib

80 mg PO once daily
(n = 279)

Investigator's Choice EGFR-TKI

Gefitinib 250 mg PO daily
or erlotinib 150 mg PO daily
(n = 277)

Treatment until:

- Disease progression
- Unacceptable toxicity
- Withdrawal

Primary Endpoint

- Investigator-assessed progression-free survival (PFS)

Secondary Endpoints

- Overall survival (OS)
- Objective response rate (ORR)
- Duration of response (DoR)
- Safety

Key Results

Median PFS

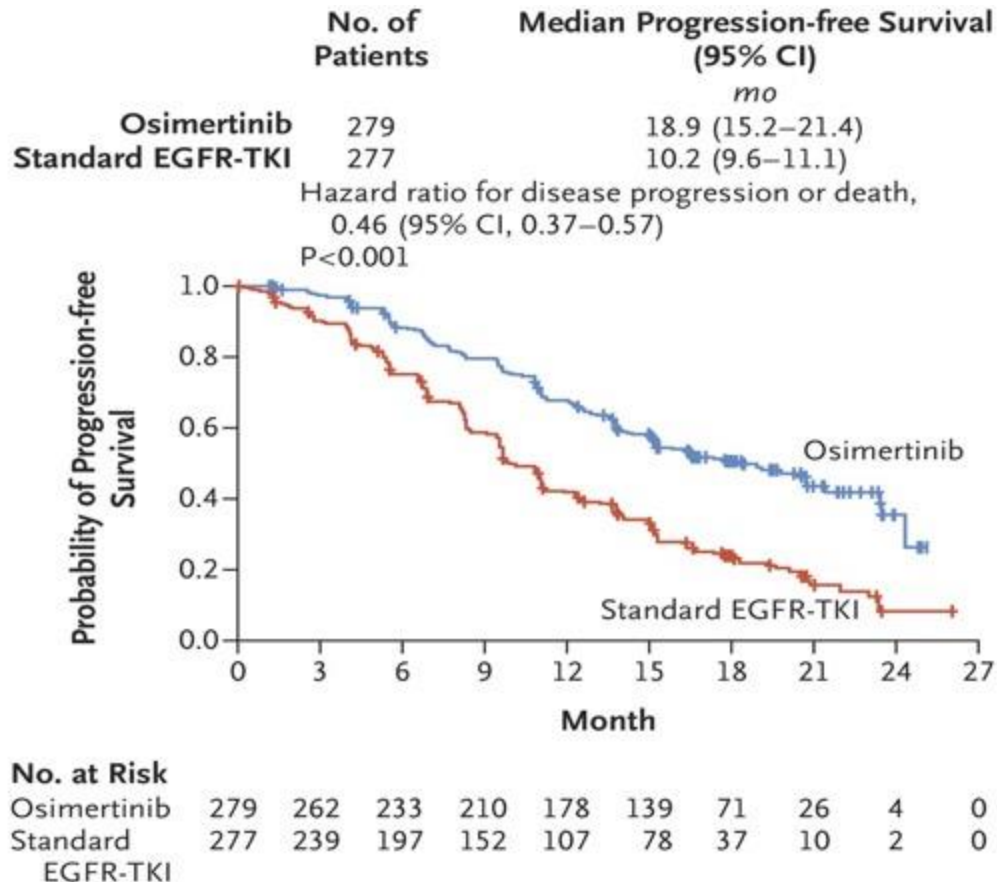
18.9 mo vs **10.2 mo**
(osimertinib) (gefitinib/erlotinib)
HR 0.46 (95% CI 0.37–0.57), $P < 0.001$

Final OS (longer follow-up)

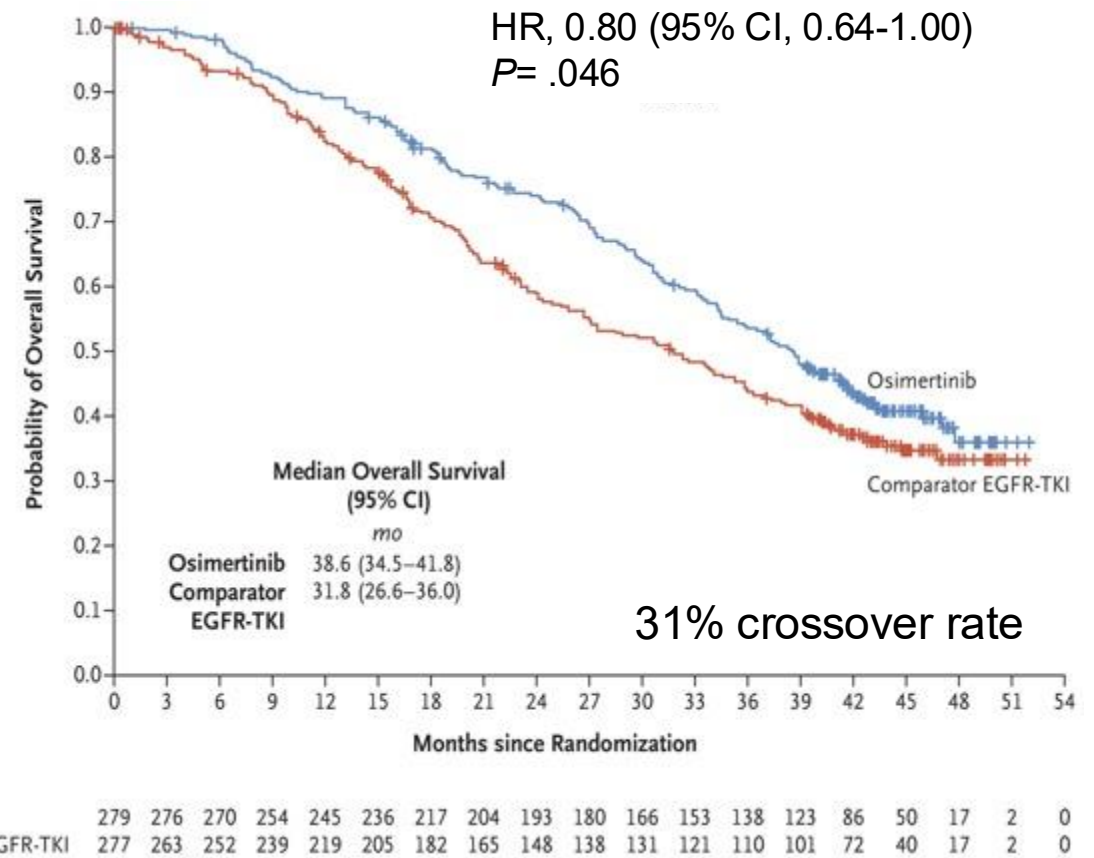
38.6 mo vs **31.8 mo**
(osimertinib) (gefitinib/erlotinib)
HR 0.80 (95% CI 0.64–1.00), $P = 0.046$

FLAURA: Osimertinib Delivers Superior PFS and OS vs First- Generation EGFR TKIs

PFS

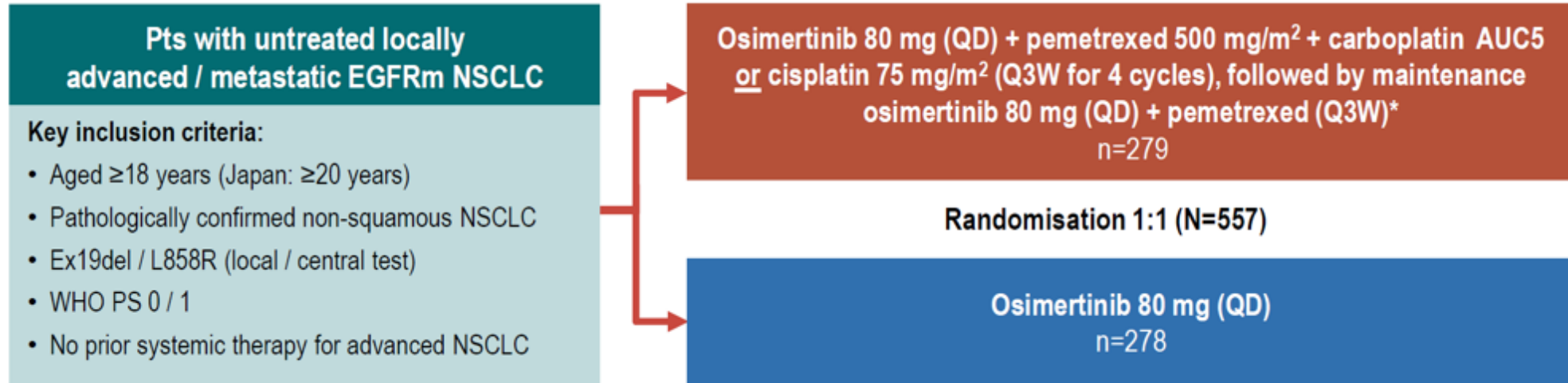


OS



FLAURA2: Osimertinib ± Platinum-Based CT as 1L Treatment

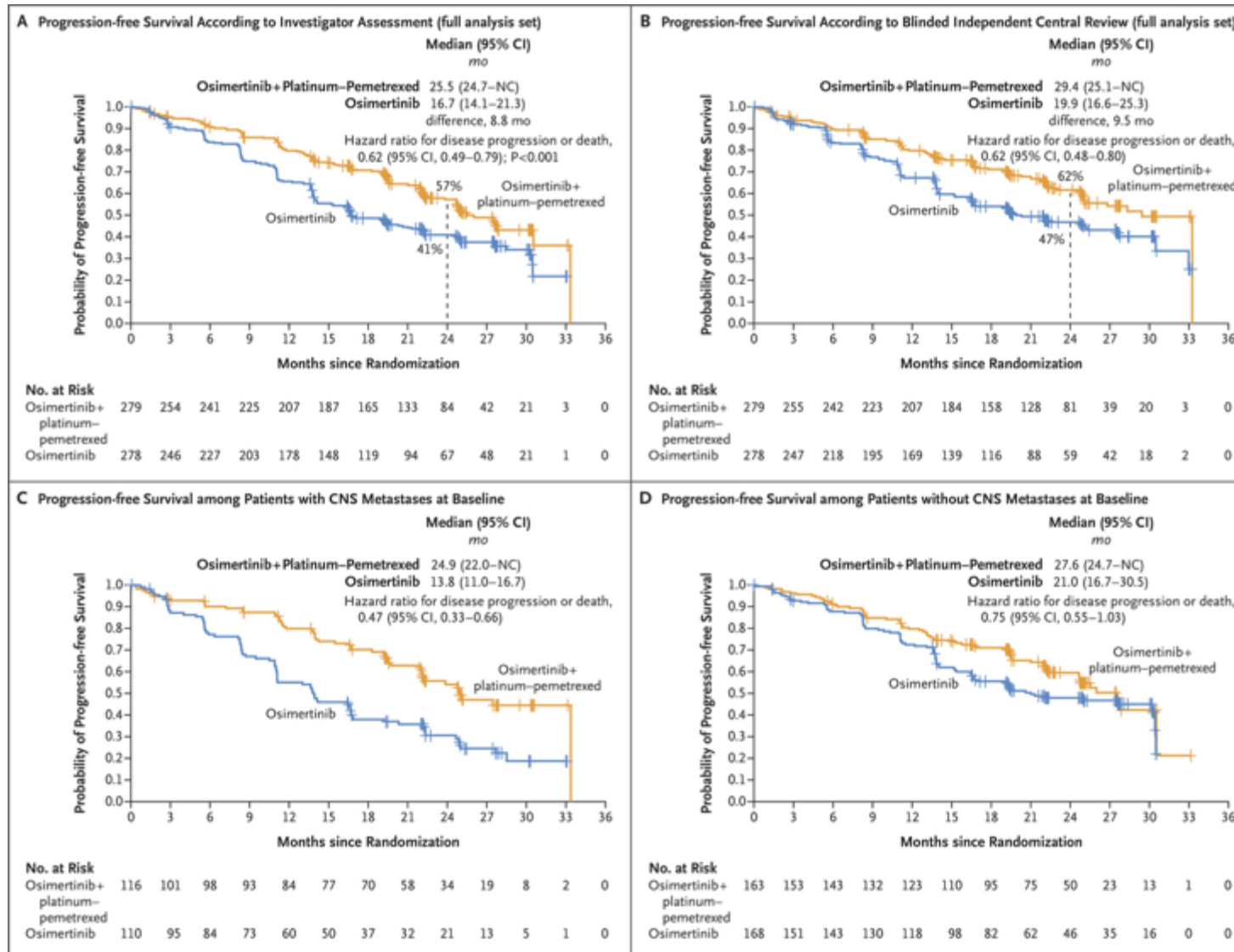
Study Design



- **Primary endpoint:** PFS by investigator assessment per RECIST 1.1^{‡§}
 - **Sensitivity analysis:** PFS by BICR assessment per RECIST 1.1
- **Secondary endpoints included:** OS, ORR, DoR, DCR, HRQoL, safety (AEs by CTCAE v5), PFS2, TFST, TSST[‡]

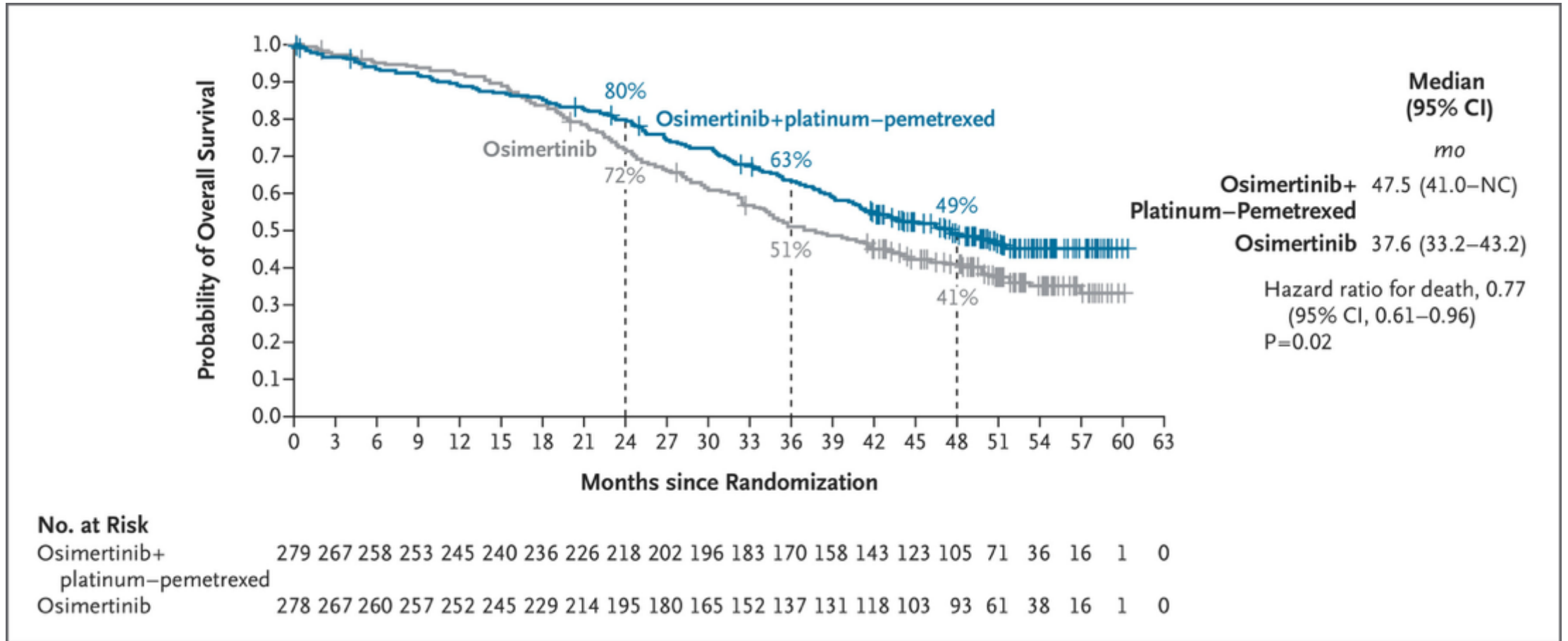
AUC = area under the curve; BICR = blinded independent central review; CTCAE = Common Terminology Criteria for Adverse Events; DCR = disease control rate; HRQoL = health-related quality of life; PFS2 = time to second disease progression; Q3W = every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; TFST = time to first subsequent therapy; TSST = time to second subsequent therapy; WHO PS = World Health Organization performance status.
Planchard D, et al. *N Engl J Med*. 2023;389(21):1935-1948.

FLAURA2: Osimertinib + Chemo Improves PFS



Feb 2024: FDA approved osimertinib + chemo treatment in patients with metastatic EGFR+ NSCLC

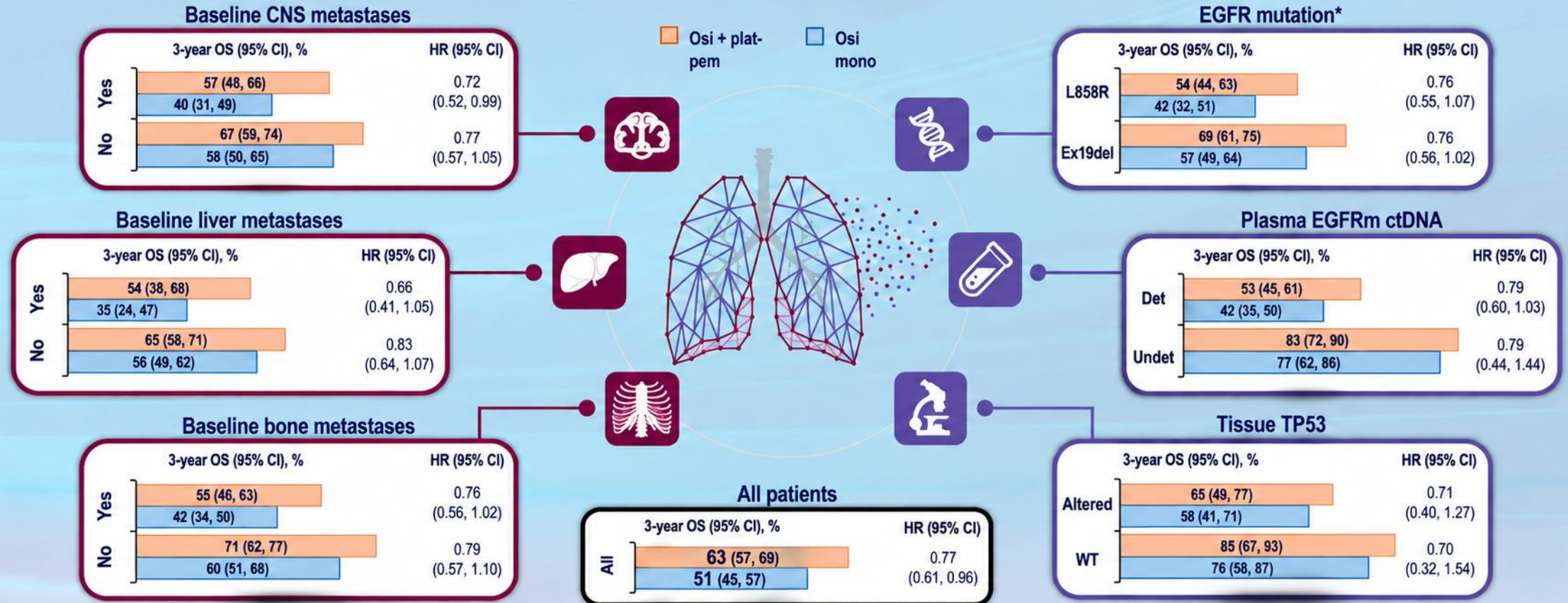
FLAURA2: Osimertinib + Chemo Improves OS



FLAURA-2: Baseline Prognostic Factors

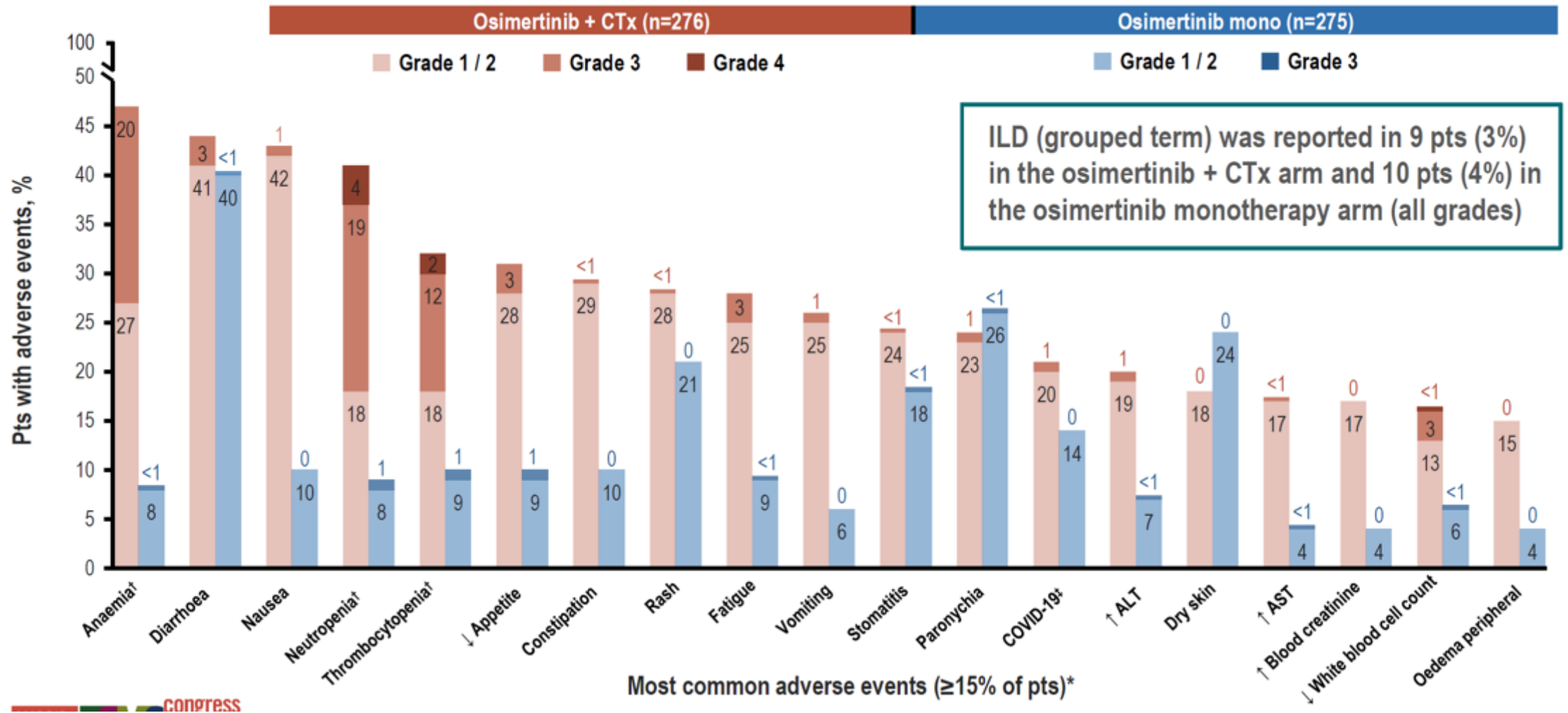
ESMO • Berlin, Germany • October 2025

FLAURA2: OS by baseline prognostic factors



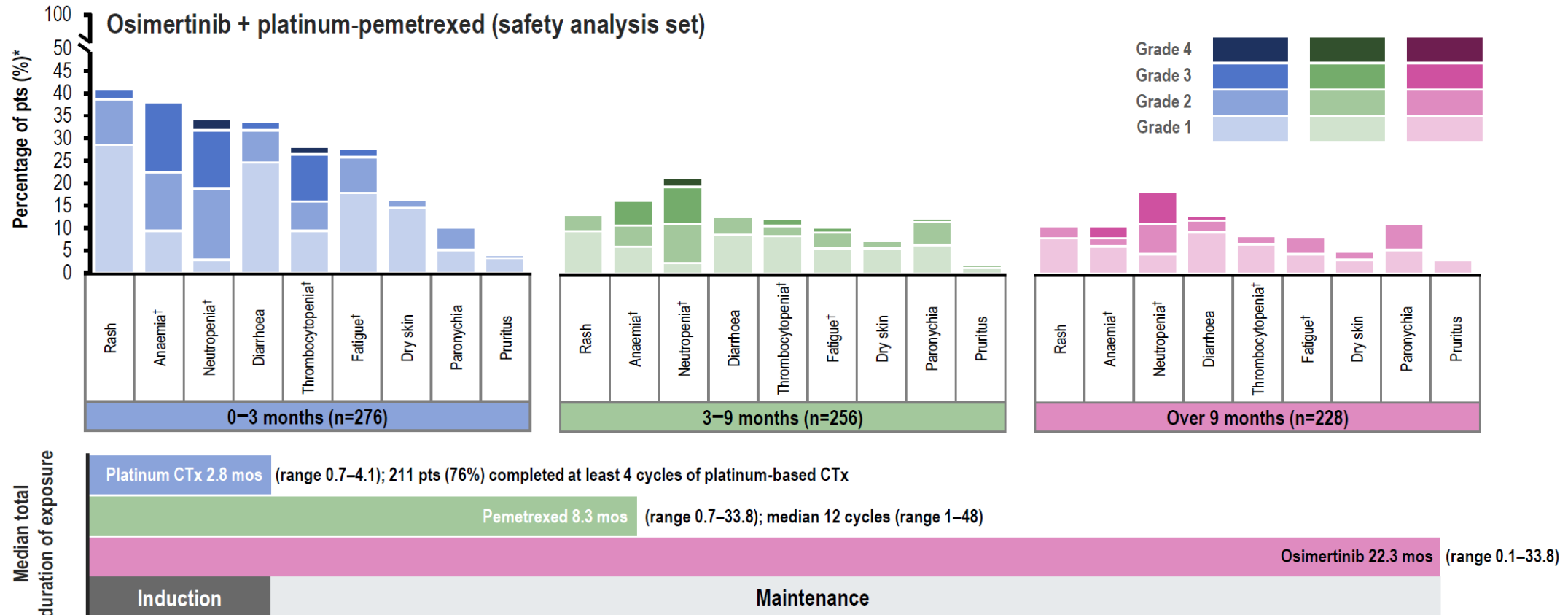
An OS benefit with osimertinib plus platinum-pemetrexed versus osimertinib monotherapy was consistently observed regardless of baseline prognostic factors

FLAURA2 Trial: Adverse Events



FLAURA2 Trial: Adverse Events

- In the osi + CTx arm, the onset of $\geq$ Grade 3 AEs reduced by ~50% between 0–3 mos (n=135; 49%) and 3–9 mos (n=62; 24%)

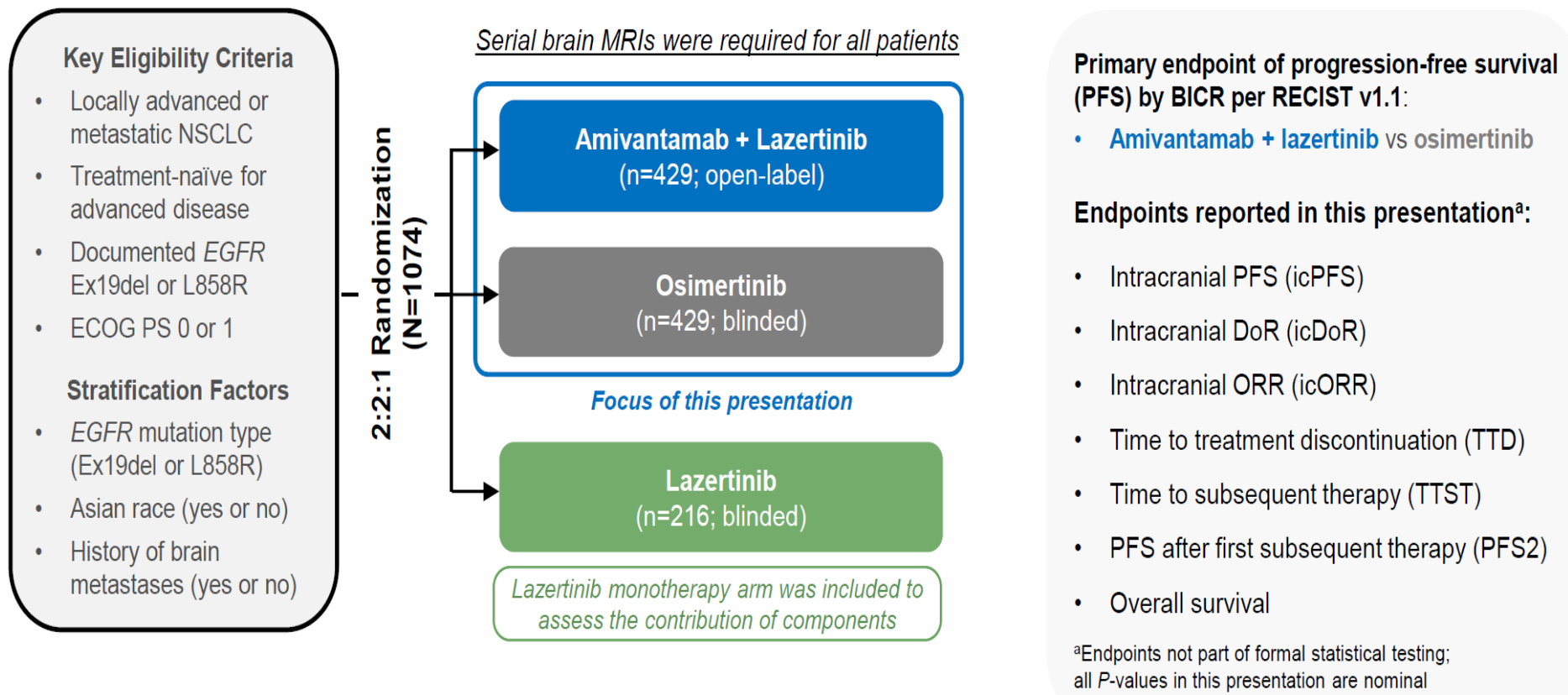




Can we Improve upon Osimertinib with Dual EGFR/MET Targeting?

MARIPOSA: 1L Amivantamab + Lazertinib vs Osimertinib

Study Design



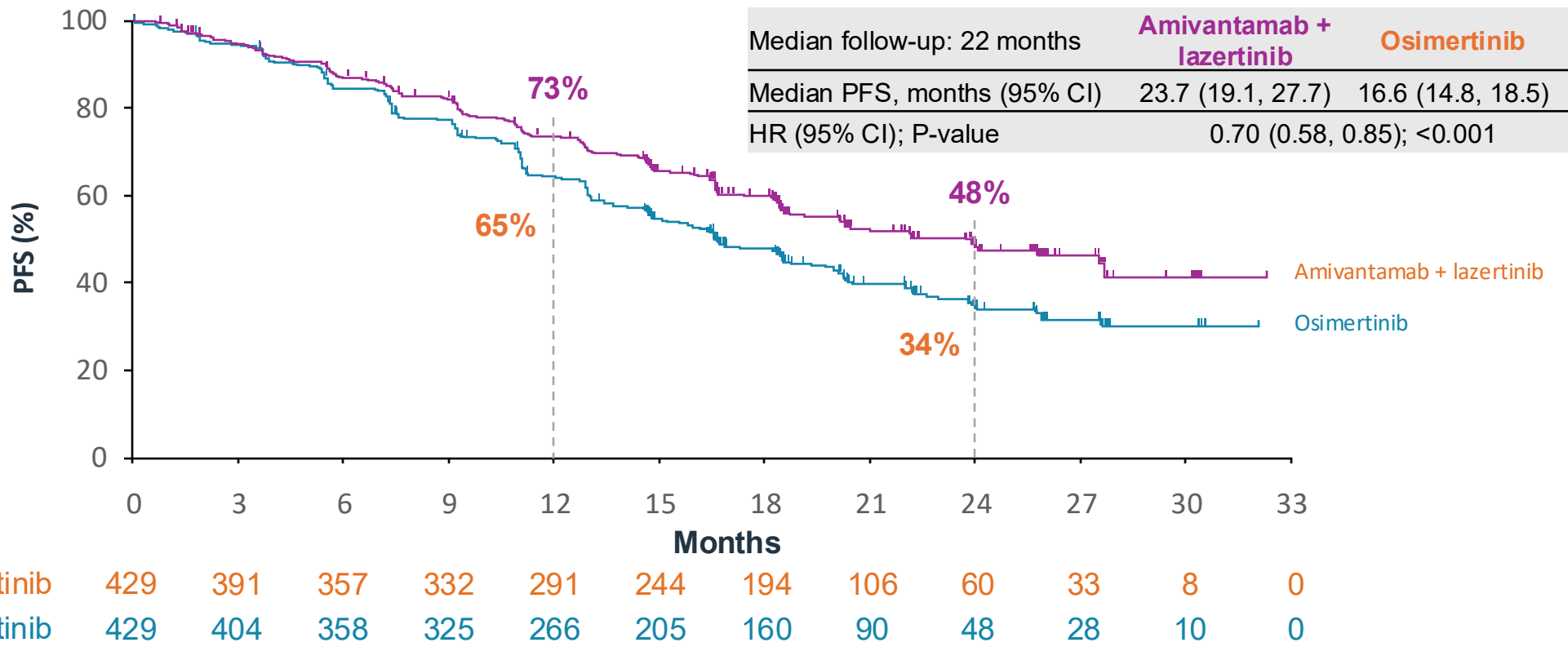
^aP-value was calculated from a log-rank test stratified by mutation type (ex19del or exon 21 L858R), race (Asian or Non-Asian), and history of brain metastases (present or absent). Hazard ratio was calculated from a stratified proportional hazards model. ^c2 patients in the osimertinib arm received amivantamab as a subsequent treatment (1 as a monotherapy and 1 in combination with lazertinib). ^dIncludes 1 patient who received herbal + doublet CT. ^eOther category included herbals, ADCs, ALK TKIs, C-MET TKIs, amivantamab, and investigational agents.

ADC = antibody-drug conjugate; ELCC = European Lung Cancer Congress; WCLC = World Conference on Lung Cancer.

Yang JC-H, et al. ELCC 2025; March 26-29, 2025; Paris, France. Abstract 40. Gadgeel S, et al. WCLC 2024; September 7-10, 2024; San Diego, CA. Abstract OA02.03.

MARIPOSA: PFS with 1L Amivantamab + Lazertinib vs Osimertinib in patients with *EGFR*-mutated, Advanced NSCLC

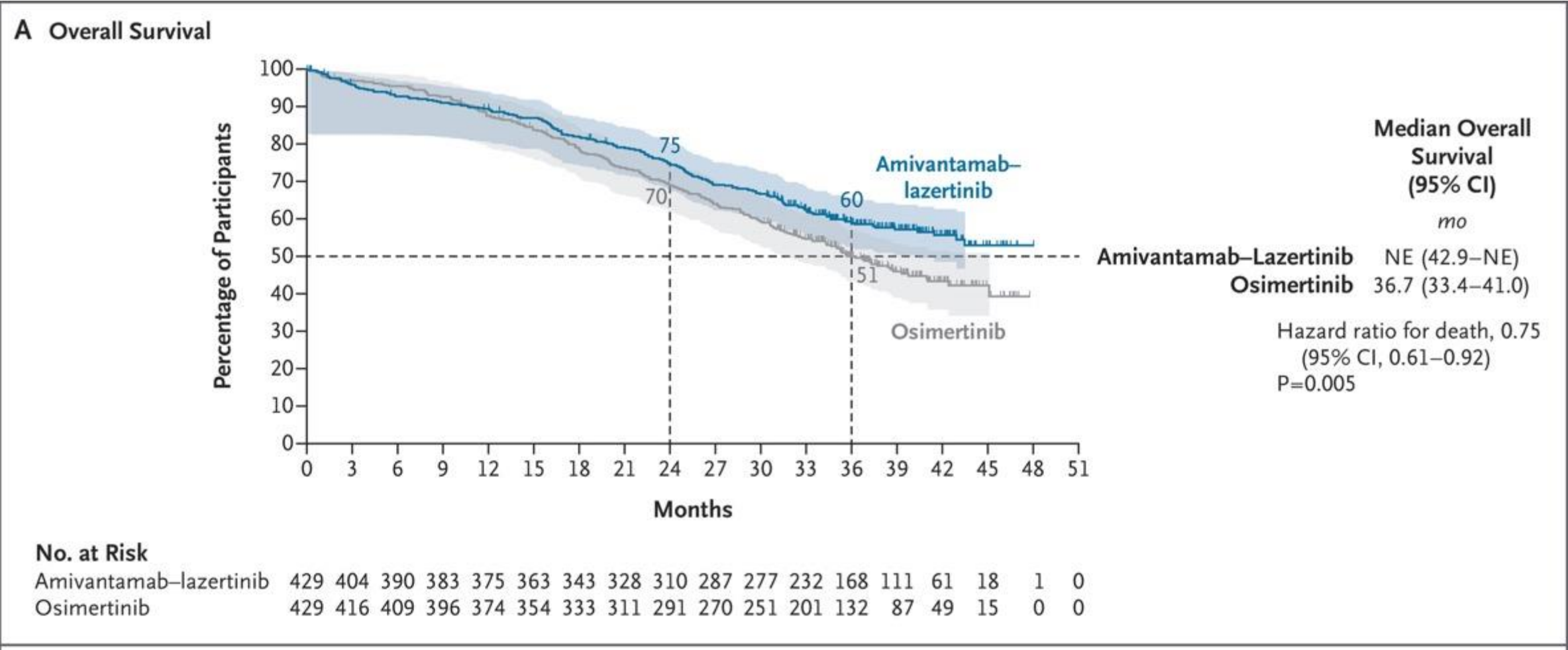
Aug 2024:
FDA approved
Ami + Laz in
patients with
metastatic
EGFR+
NSCLC



- Lazertinib comparable with osimertinib (PFS 16.6 and 18.5 months), superimposable KM curves
- PFS benefit seen across all subgroups, confirmed RR 80% vs 76% osimertinib; DOR 25.8 vs 16.8 months
- If CNS-only first progressions are censored, consistent benefit is observed (PFS 27.5 vs 18.5, HR 0.68)

KM = Kaplan–Meier; RR = response rate.
Cho BC, et al. MARIPOSA primary results. Presented at: ESMO Congress 2023; October 20-24, 2023; Madrid, Spain. Abstract LBA14.

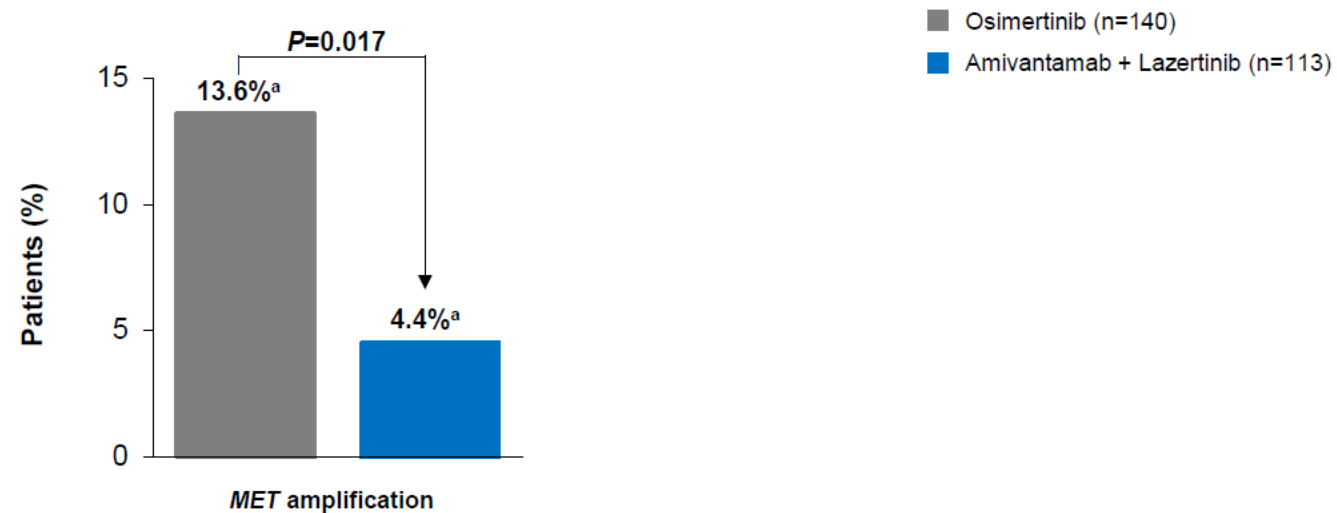
MARIPOSA: OS with 1L Amivantamab + Lazertinib vs Osimertinib in patients with *EGFR*-mutated, Advanced NSCLC



Mechanisms of Resistance to MARIPOSA

***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

Subset Analyses of MARIPOSA and FLAURA 2

	MARIPOSA	FLAURA 2
CNS metastases (+)	HR: 0.67 (CI: 0.50-0.90)	HR: 0.72 (CI: 0.52-0.99)
CNS metastases (-)	HR: 0.82 (CI: 0.62-1.08)	HR: 0.77 (CI: 0.57-1.05)
Exon 19 del	HR: 0.66 (CI: 0.50-0.86)	HR: 0.76 (CI: 0.56-1.02)
L858R	HR: 0.90 (CI: 0.67-1.21)	HR: 0.76 (CI: 0.55-1.07)
Age ≥ 65	HR: 1.11 (CI: 0.84-1.48)	HR: 0.87 (CI: 0.63-1.22)
Age < 65	HR: 0.53 (CI: 0.40-0.70)	HR: 0.71 (CI: 0.53-0.95)
TP 53 (+)	PFS HR: 0.65 (CI: 0.48-0.86)	PFS HR: 0.57 (CI: 0.29-1.12) OS HR: 0.71 (CI: 0.40-1.27)
TP 53 (-)	PFS HR: 0.75 (CI: 0.52-1.07)	OS HR: 0.71 (CI: 0.32-1.54)
Liver metastases (+)	PFS HR: 0.58 (0.37–0.91)	PFS HR: 0.66 (0.41–1.07) OS HR: 0.66 (CI: 0.41-1.05)
Liver metastases (-)	PFS HR: 0.74 (0.60–0.91)	PFS HR: 0.63 (0.48–0.83) OS HR: 0.83 (CI: 0.64-1.07)

MARIPOSA: Adverse Events of Special Interest

AESI, n (%)	Amivantamab + Lazertinib (n=421)	Osimertinib (n=428)
Any Venous Thromboembolism, n (%) [*]	157 (37)	39 (9)
• Grade 1	5 (1)	0
• Grade 2	105 (25)	24 (6)
• Grade 3	43 (10)	12 (3)
• Grade 4	2 (0.5)	1 (0.2)
• Grade 5	2 (0.5)	2 (0.5)
Any VTE Leading to Death, n (%)	2 (0.5)	2 (0.5)
Any VTE Leading to Any Discontinuation, n(%)	12 (3)	2 (0.5)
Anticoagulant Use at Time of First VTE, n (%)		
• On Anticoagulants	5 (1)	0
• Not on Anticoagulants	152 (36)	39 (9)
Median Onset to First VTE, days	84	194
Within First 4 Months, n (%)	97 of 157 (62)	13 of 39 (33)

^{*}Most common preferred terms were pulmonary embolism and deep vein thrombosis

Most VTEs were Grade 1-2

Incidence of Grade 4-5 VTEs was <1% and comparable between arms

At the Time of First VTE:

- Most patients were not on anticoagulants
- Majority in the amivantamab plus lazertinib arm occurred within the first 4 months

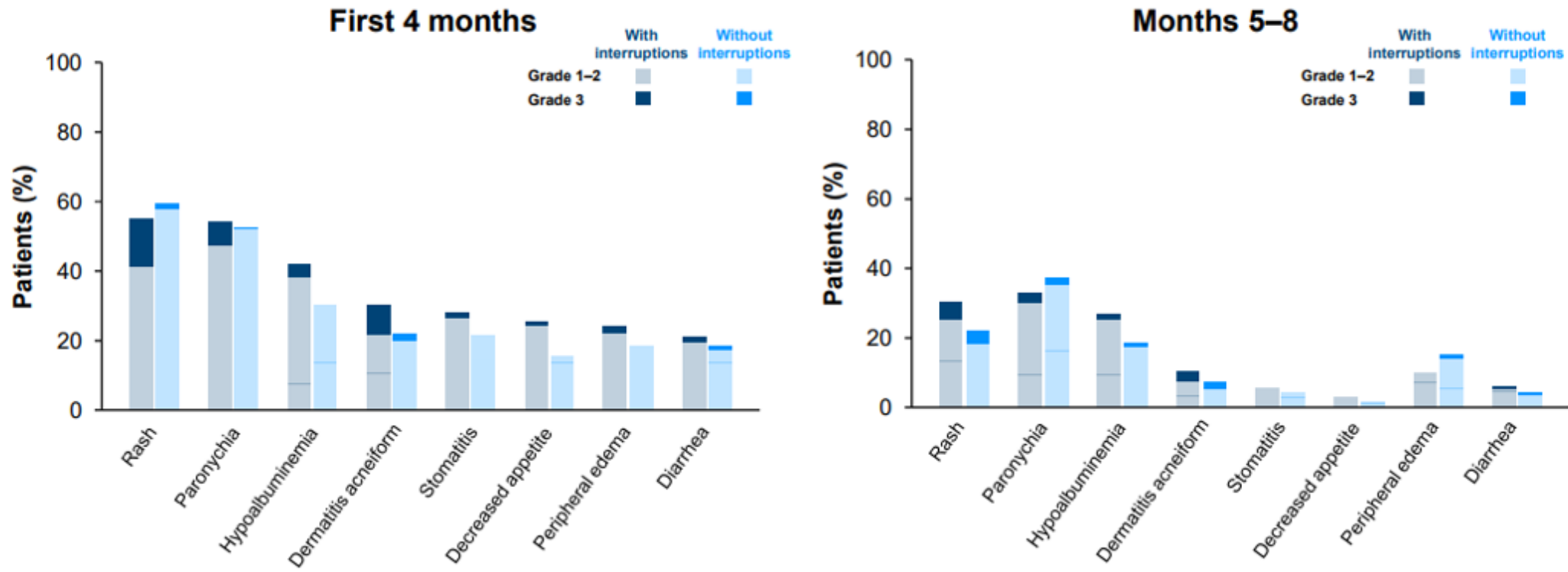
Prophylactic dose anticoagulation is now recommended for the initial 4 months of treatment in ongoing trials of amivantamab + lazertinib

AESI = adverse event of special interest; VTE = venous thromboembolism.

Cho BC, et al. MARIPOSA primary results. Presented at: ESMO Congress 2023; October 20-24, 2023; Madrid, Spain. Abstract LBA14.

MARIPOSA: Prevalence of Key AEs Over Time

- Key AEs occurred most frequently during the first 4 months and declined over the next 4 months^a
 - Notably, rash decreased by ~50%, paronychia by ~30%, and diarrhea by ~70%
- No grade 4 or 5 AEs were reported



	FLAURA	FLAURA-2	MARIPOSA
Population	aNSCLC w/ EGFR ex19del/ L858R	aNSCLC w/ EGFR ex19del/ L858R	aNSCLC w/ EGFR ex19del/L858R
Intervention	Osi alone vs Gefiti or Erloti	Osi+chemo vs Osi alone	Ami-Laz vs Osi (vs Laz)
mPFS	18.9 mo vs 10.2 mo (HR 0.46)	25.5 mo vs 16.7 mo (HR 0.62)	23.7 mo vs 16.6 mo (HR 0.7)
mOS	38.6 mo vs 31.8 mo (HR 0.80)	47.5 mo vs 37.6 mo (HR 0.77)	At 3 yrs: NE vs 36.7 mo (HR 0.75)

aNSCLC = advanced non-small cell lung cancer; mOS = median overall survival; mPFS = median PFS; NE = not estimable.
 Planchard D, et al. *NEJM*. 2023;389:1935-1948. Jänne PA, et al. *N Engl J Med*. 2026;394:27-38.

How to measure the cost of more intensive 1L therapy?

- Rates of high-grade adverse events?
- Adverse events impacting QoL or compromising continuation of treatment?
- Time toxicity – how much time will a patient spend interacting with the healthcare system
- Cost to the healthcare system – of treatment and of toxicity management

Estimated Number of Clinic Visits in the First Year of Tx
Assuming no extra encounters for AE management
Assuming no treatment discontinuations

FLAURA
~7 Visits

Daily Oral
Therapy
Moisturizer
PRN
Antidiarrheal

FLAURA2
~19 Visits

Daily Oral
Therapy
~40 min Infusions
Moisturizer
PRN
Antidiarrheal
Folic Acid
Dexamethasone
PRN Antiemetics

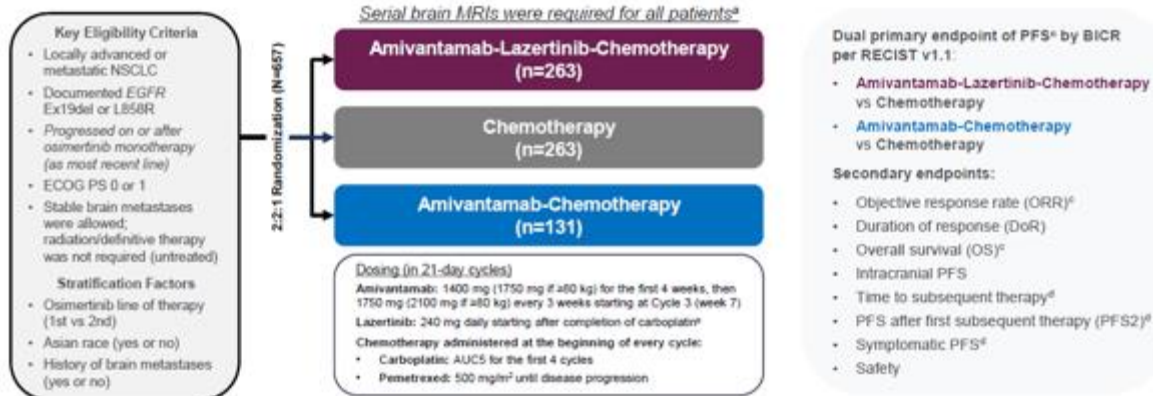
MARIPOSA
~15 Visits

Daily Oral Therapy
~4-6 hrs → 2 hrs inf. →
now S.C. is available
Moisturizer
PRN
Antidiarrheal
Oral antibiotics
Topical Steroids
Topical Rx to
Nails
Anticoagulant

PRN = as needed; QoL = quality of life; Tx = treatment.

MARIPOSA 2: Phase III Study Schema

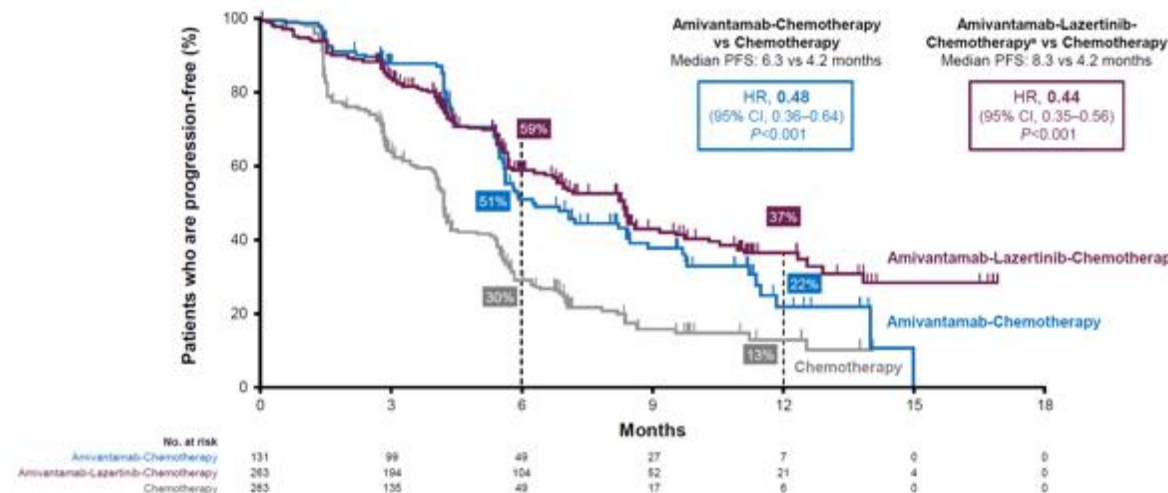
Study Design



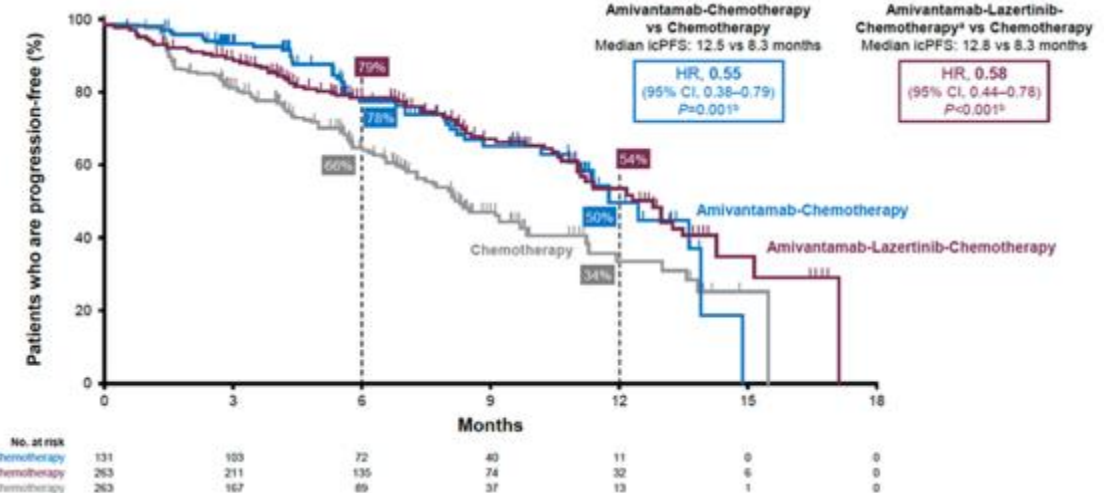
Response

BICR-assessed Response, n (%) ^b	Chemotherapy (n=263)	Amivantamab-Chemotherapy (n=131)	Amivantamab-Lazertinib-Chemotherapy (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 ^c	5.6 mo (95% CI, 4.2–9.6)	6.9 mo (95% CI, 5.5–NE)	9.4 mo (95% CI, 6.9–NE)

PFS by BICR

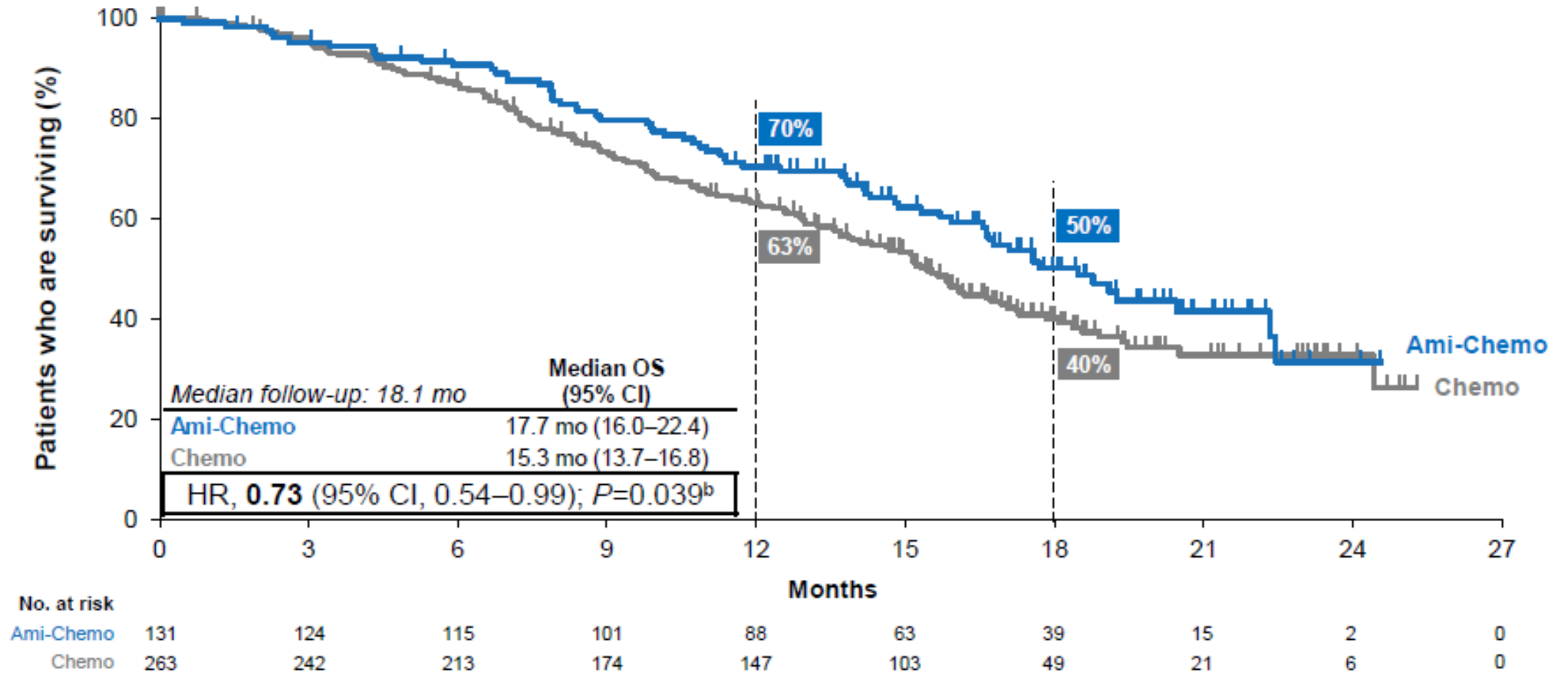


Intracranial PFS



MARIPOSA 2: 2nd Interim Overall Survival

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



MARIPOSA 2: Summary of Adverse Events

	Chemotherapy (n=243)	Amivantamab- Chemotherapy (n=130)	Amivantamab-Lazertinib- Chemotherapy ^a (n=263)
Treatment duration, median (range)	3.7 months (0–15.9)	6.3 months (0–14.7)	5.7 months (0.1–18.6)
No. of chemotherapy cycles, median (range)			
Carboplatin	4 (1–5)	4 (1–4)	4 (1–4)
Pemetrexed	6 (1–23)	9 (1–22)	7 (1–25)
TEAE, n (%)	Chemotherapy (n=243)	Amivantamab- Chemotherapy (n=130)	Amivantamab-Lazertinib- Chemotherapy ^a (n=263)
Any AEs	227 (93)	130 (100)	263 (100)
Grade ≥ 3 AEs	117 (48)	94 (72)	242 (92)
Serious AEs	49 (20)	42 (32)	137 (52)
AEs leading to death	3 (1)	3 (2)	14 (5)
Any AE leading to treatment:			
Interruptions of any agent	81 (33)	84 (65)	202 (77)
Reductions of any agent	37 (15)	53 (41)	171 (65)
Discontinuations of any agent	9 (4)	24 (18)	90 (34)
Discontinuations of all agents due to AE	10 (4)	14 (11)	38 (14)

Amivantamab-containing arms had higher rates of Grade ≥ 3 AEs and dose modifications compared with chemotherapy

- Highest reported in the amivantamab-lazertinib-chemotherapy arm

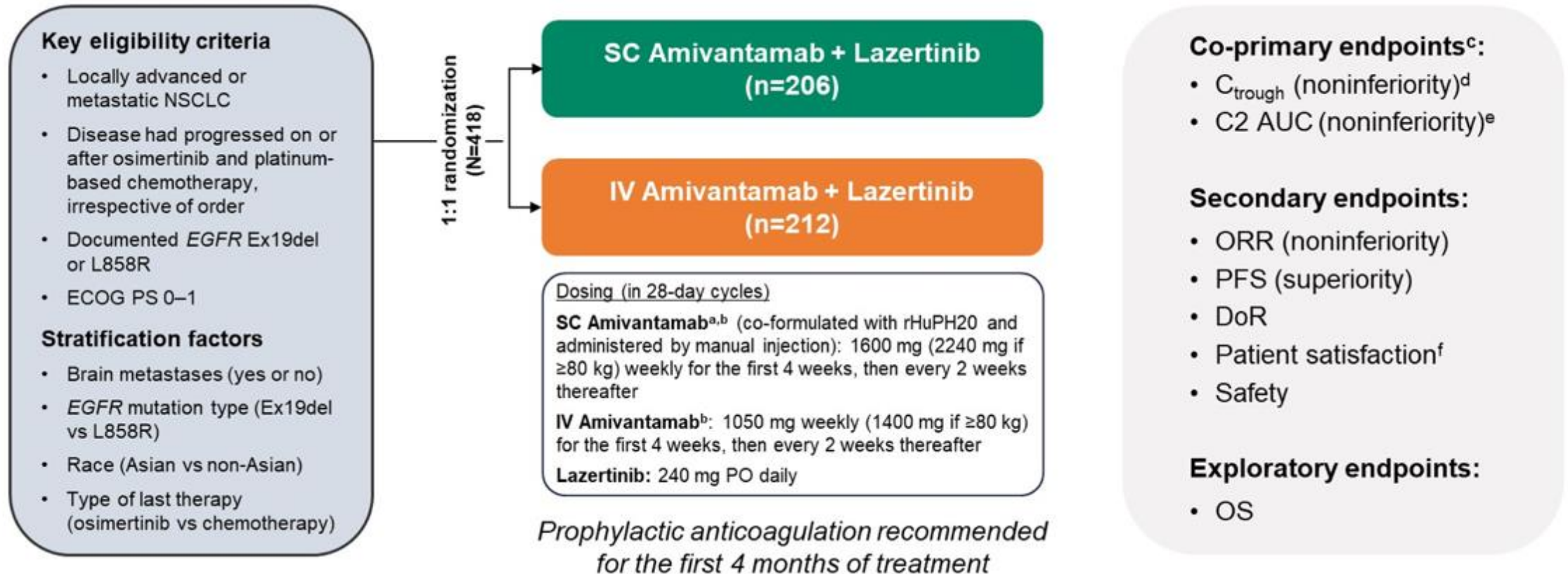
Discontinuations of all agents due to TEAEs were

- Chemotherapy: 2%
- Amivantamab-Chemotherapy: 8%
- Amivantamab-Lazertinib-Chemotherapy: 10%

TEAE = treatment-emergent adverse event.

Passaro A, et al. Presented at: ESMO Congress 2023; October 20-24, 2023; Madrid, Spain. Abstract LBA15.

PALOMA-3: Subcutaneous (SC) Amivantamab + Lazertinib in 2L Treatment of EGFR-Mutant NSCLC



2L = second-line.

Leighl NB, et al. Presented at: ASCO 2024; May 31-June 4, 2024; Chicago, IL. Abstract LBA8505.

PALOMA-3: Efficacy Outcomes

Pharmacokinetics

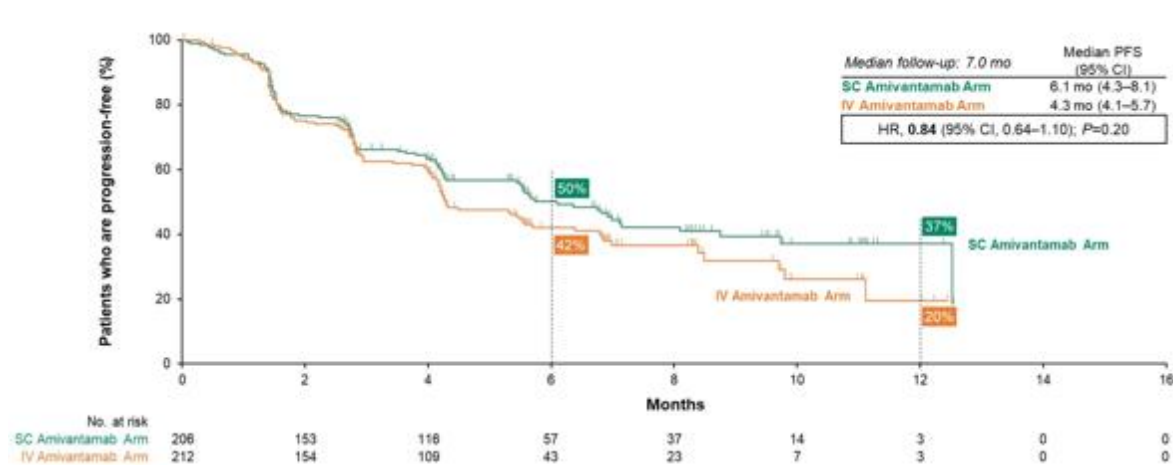
PK Parameter	Geometric Mean Ratio
C_{trough}	
C2D1, (90% CI)	1.15 (1.04–1.26)
C4D1, (90% CI)	1.43 (1.27–1.61)
C2 AUC _{D1-D15}	1.03 (0.98–1.09)

AUC_{D1-D15}, C2 area under the curve; C2D1, cycle 2 day 1; C4D1, cycle 4 day 1; C_{trough} , trough concentration

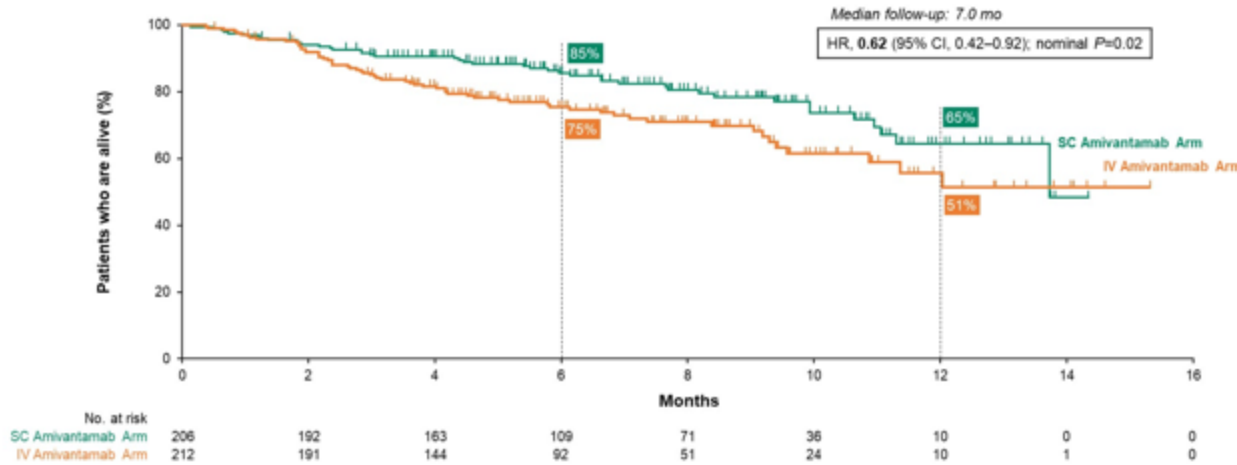
Response

	SC Amivantamab Arm (n=206)	IV Amivantamab Arm (n=212)
ORR, % (95% CI) ^a		
All responders	30 (24–37)	33 (26–39)
	Relative risk, 0.92 (95% CI, 0.70–1.23); $P=0.001$	
Confirmed responders	27 (21–33)	27 (21–33)
	Relative risk, 0.99 (95% CI, 0.72–1.36); $P<0.001$	
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)
Not evaluable	14 (7)	20 (9)
DCR, % (95% CI) ^b	75 (69–81)	71 (64–77)
Median time to response (range), mo	1.5 (1.2–6.9)	1.5 (1.2–9.9)

PFS

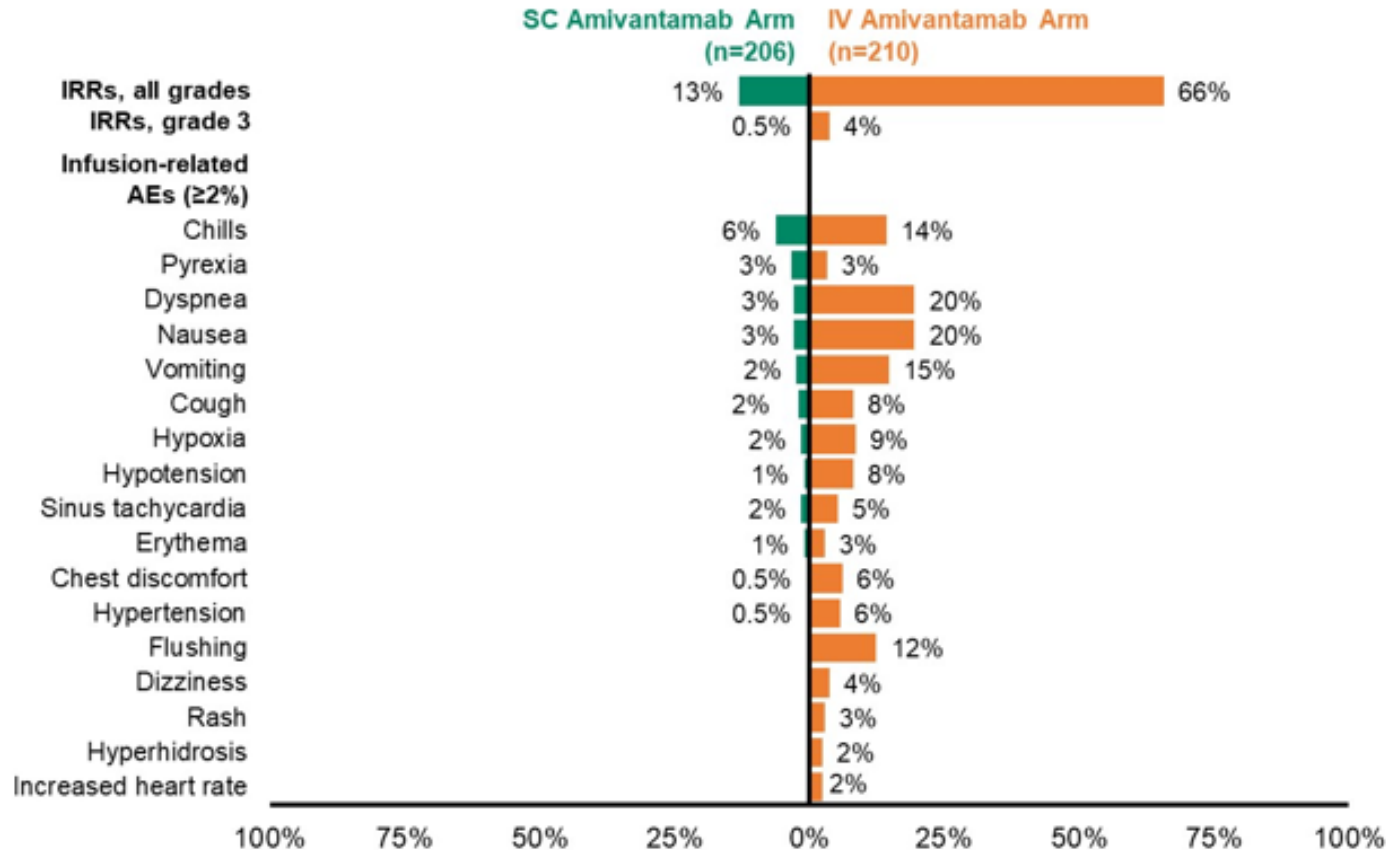


Overall Survival



C2D1 = cycle 2, day 1; C4D1 = cycle 4, day 1; C_{trough} = trough concentration; PK = pharmacokinetics.
Leighl NB, et al. Presented at: ASCO 2024; May 31-June 4, 2024; Chicago, IL. Abstract LBA8505.

PALOMA-3: Incidence of IRR-Related Symptoms



- IRRs were observed in 13% of patients in the SC arm vs 66% in the IV arm, representing a 5-fold reduction
 - There were no grade 4 or 5 IRRs
 - Most IRRs occurred during Cycle 1
- IRRs leading to hospitalization were not observed in the SC arm vs 2 events in the IV arm
- No IRR-related discontinuations occurred in the SC arm vs 4 events in the IV arm

IRR = infusion-related reaction.

Leighl NB, et al. *J Clin Oncol*. 2024;42(30):3593-3605.



Adverse Event Management & Mitigation Strategies

Adverse Event Management & Mitigation Strategies

PALOMA-3 Trial

Subcutaneous vs IV treatment with Amivantamab

- Fewer patients in the subcutaneous group experienced IRR and venous thromboembolism
- IV more convenient – 5 minutes

SKIPPirr Trial

Preventing Infusion-Related Reactions

- Patients received Intravenous Amivantamab + Oral Lazertinib
- Simon-two stage design with expansion stage

Cohorts

Dexamethasone 4mg PO BID

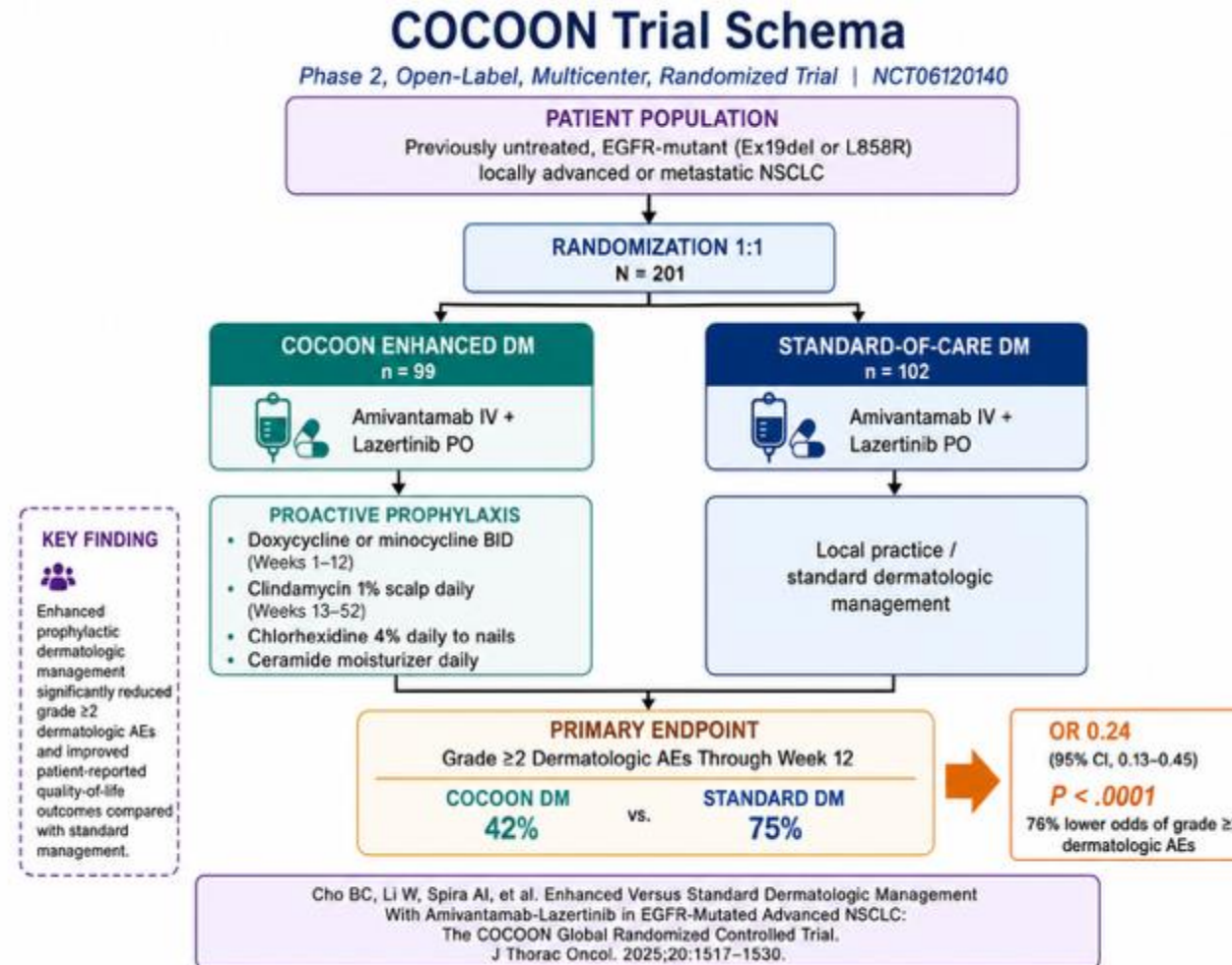
Dexamethasone 8mg PO BID

Montelukast 10mg PO Daily

Methotrexate 25mg PO Once

Adverse Event Management & Mitigation Strategies

Cocoon: Phase 2 Randomized NCT 06120140 EGFR-m NSCLC

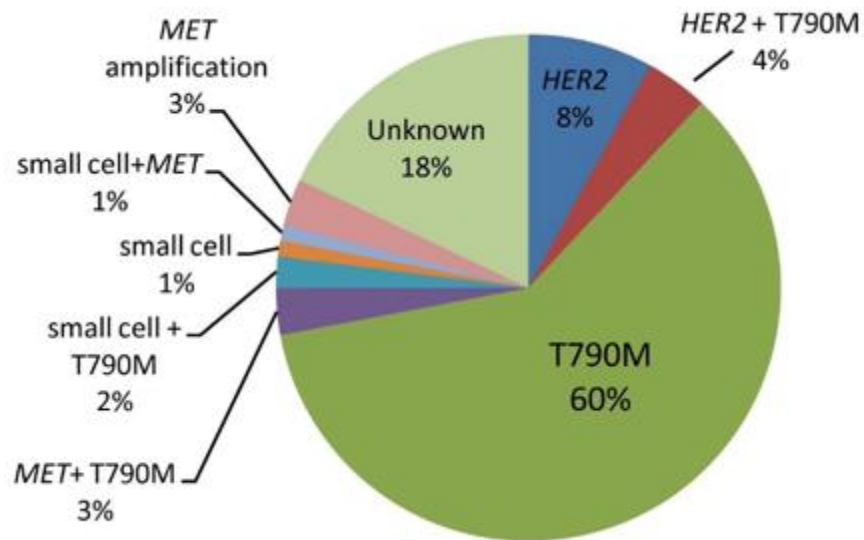


EGFR Post-TKI & Platinum-Based Chemotherapy

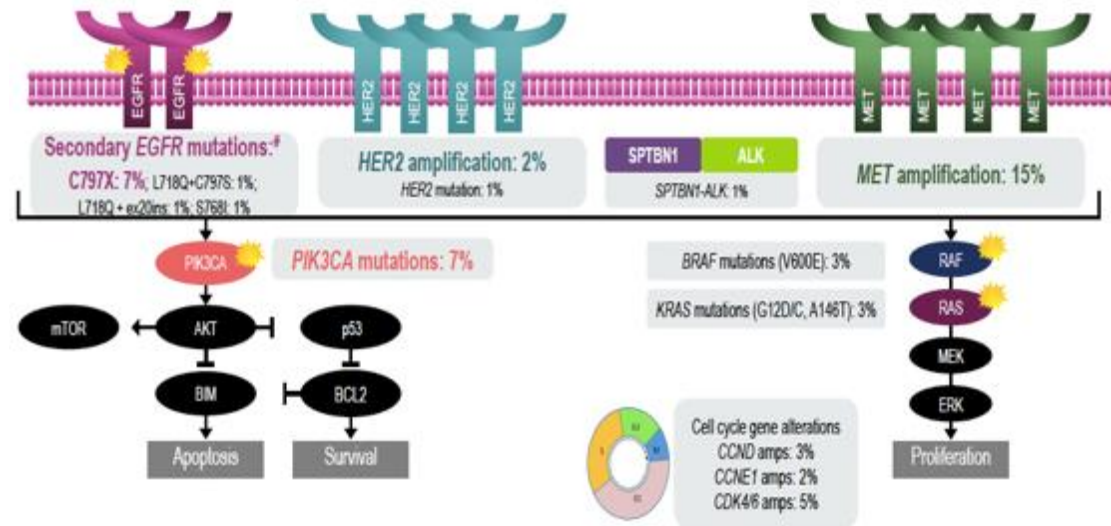
Biomarker Profiling at Progression:
Identify the Resistance Mechanism



Resistance Is Inevitable: Understanding the Mechanisms Is Critical to Treatment Selection

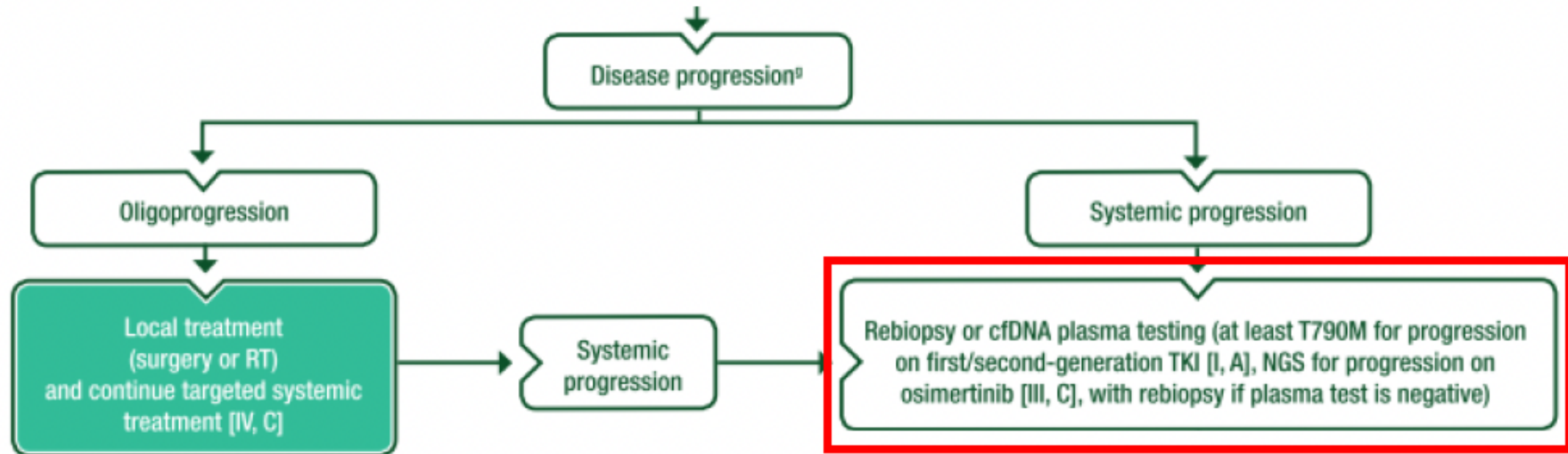


Dominant mechanism of resistance for 1st generation EGFR TKIs Erlotinib or Gefitinib



Heterogeneous & multiple simultaneous mechanisms of resistance to 3rd generation EGFR TKI Osimertinib

EGFR Post TKI & Platinum-Based Therapy : ESMO Guidelines

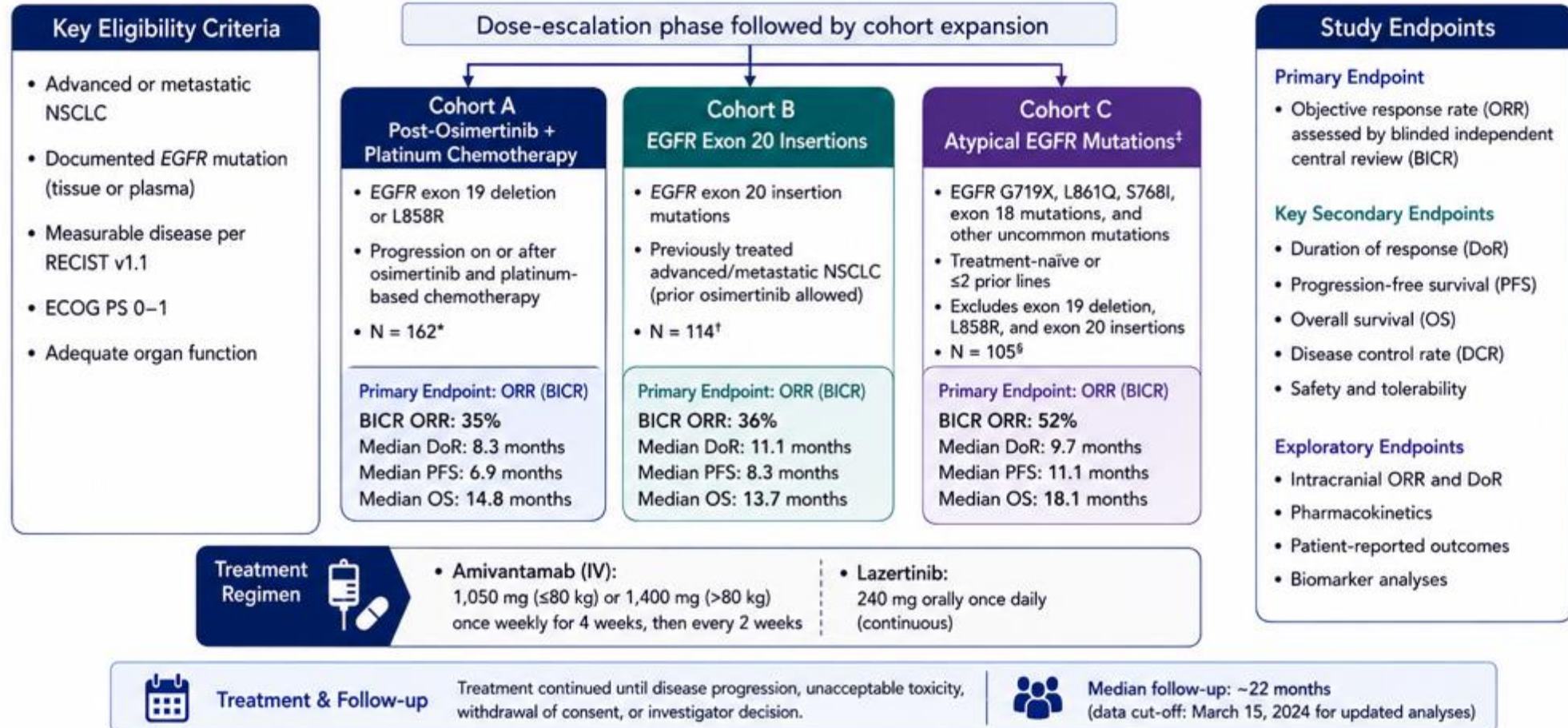


cfDNA = cell-free DNA; RT = radiation therapy.

CHRYSLIS-2 Study Schema

Amivantamab + Lazertinib in Patients With EGFR-Mutated Advanced NSCLC

Phase I/Ib, Open-Label, Multi-Cohort Study (NCT04077463)



* Updated analysis includes 162 patients.

† Includes 114 patients with *EGFR* exon 20 insertion mutations.

‡ Includes uncommon *EGFR* mutations: G719X, L861Q, S768I, exon 18 mutations, and other rare mutations.

§ Includes 105 patients in the updated analysis.

EGFR sensitizing mutations: Post Osimertinib with MET expression

Savolitinib Plus Osimertinib in *EGFR*-Mutated NSCLC After TKI: **SAVANNAH Phase 2 Study**

MET IHC3+/ $\geq 90\%$ and/or FISH10+

Key inclusion criteria in protocol version 7:

- ≥ 18 years (≥ 20 years in Japan)
- Locally advanced* or metastatic EGFRm NSCLC
- PD on first-line osimertinib
- Centrally confirmed MET overexpression (IHC3+/ $\geq 90\%$) or amplification (FISH10+)
- ECOG PS 0 / 1
- Stable CNS metastases permitted†

**Savolitinib 300 mg BID +
osimertinib 80 mg QD**

Randomization 2:1 (N=73)

Stratification by brain metastases at study entry‡
(yes vs no)

**Savolitinib 300 mg BID +
placebo**

Treatment continued until PD,
or another discontinuation
criterion was met

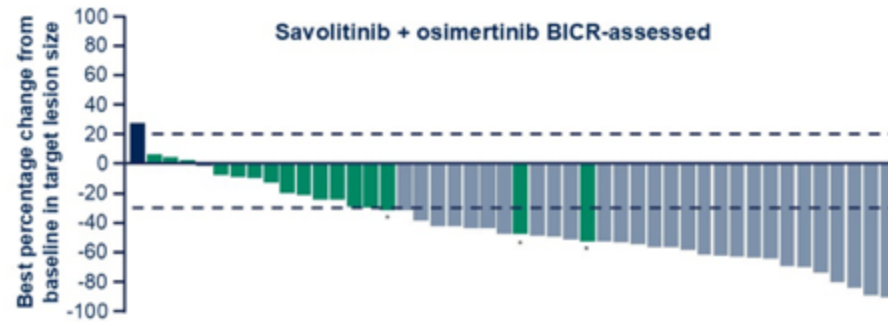
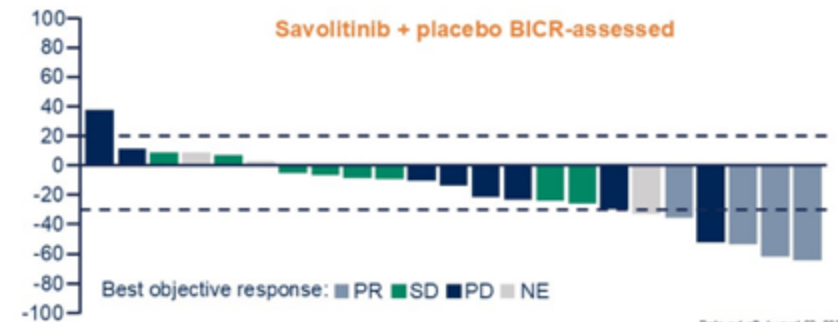
Patients could crossover to
open-label savolitinib + osimertinib
upon investigator-assessed PD

IHC3+ = immunohistochemistry score 3+; FISH10+ = fluorescence in situ hybridization with $\geq 10\%$ positive cells.

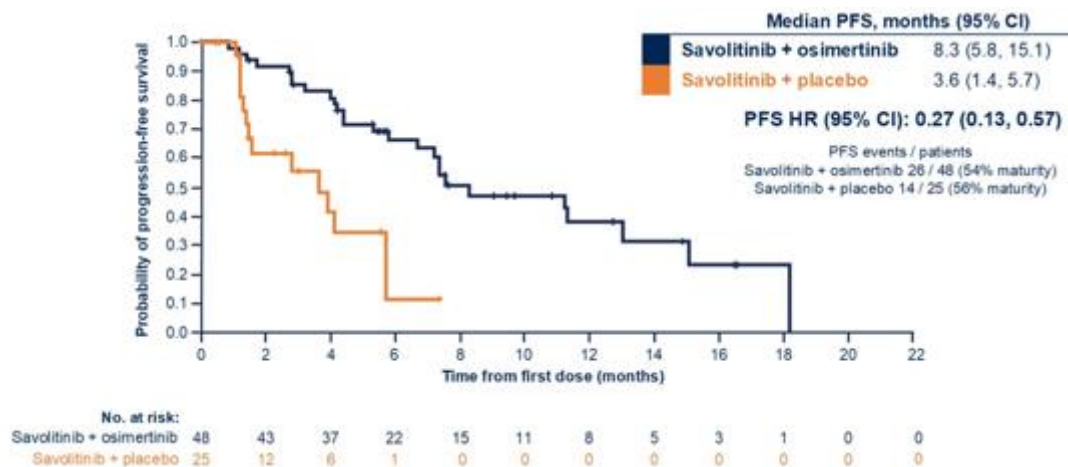
de Marinis F, et al. *Ann Oncol*. 2025;36(8):920-933. Levy B. et al. Presented at: ASCO 2025; May 30-June 3, 2025; Chicago; IL.

SAVANNAH: Results

	BICR-assessed		Investigator-assessed	
	Savolitinib + osimertinib (n=48)	Savolitinib + placebo (n=25)	Savolitinib + osimertinib (n=48)	Savolitinib + placebo (n=25)
Confirmed ORR, % (95% CI)	58 (43, 72)	16 (5, 36)	54 (39, 69)	24 (9, 45)
	(n=28)	(n=4)	(n=26)	(n=6)
Median DoR, months (95% CI)	11.8 (6.0, NC)	4.5 (2.6, NC)	8.0 (4.9, 11.7)	4.2 (2.6, NC)
Median time to onset of response, weeks (IQR)	6.0 (5.7–6.2)	6.1 (5.8–6.3)	6.1 (6.0–7.0)	6.1 (5.4–6.3)



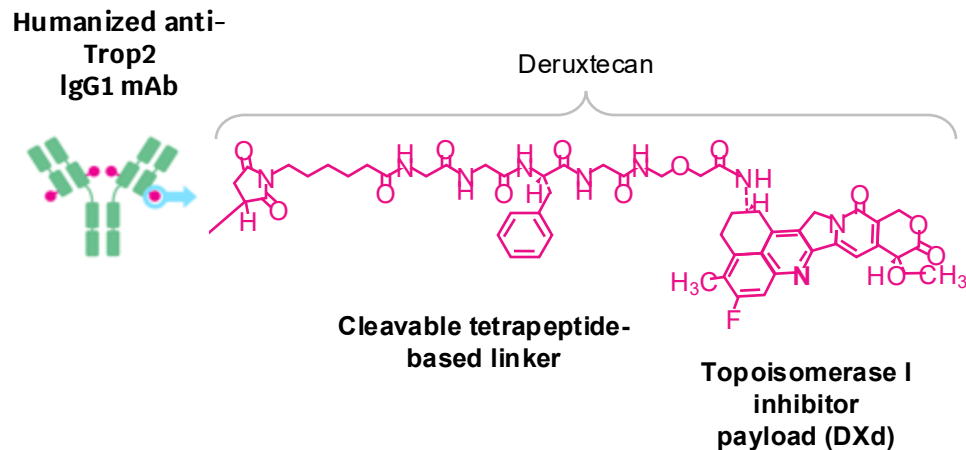
Data cut-off: August 23, 2024
*Patient had unconfirmed response



	Savolitinib + osimertinib (n=14)	Savolitinib + placebo (n=4)
CNS best objective response, n (%)		
Response	6 (43)	1 (25)
Complete response	2 (14)	0
Partial response	4 (29)	1 (25)
Non-response	8 (57)	3 (75)
Stable disease	7 (50)	1 (25)
Progressive disease	1 (7)	1 (25)
Not evaluable	0	1 (25)
CNS confirmed ORR, % (95% CI)	43 (18, 71)	25 (1, 81)
CNS median DoR, months, (95% CI)*	NR (6.0, NC)	6.9 (NC, NC)
CNS PFS events, n (%)	5 (36)	2 (50)
Median follow up for CNS PFS, months (95% CI)	5.8 (1.6, 16.6)	2.1 (0.0, 8.5)

Datopotamab deruxtecan (Dato-DXd)

June 23, 2025: FDA granted accelerated approval of datopotamab deruxtecan-dlnk for the treatment of adults with locally advanced or metastatic *EGFR*-mutated NSCLC who have previously received *EGFR*-directed therapy and platinum-based chemotherapy.



7 key attributes of Dato-DXd

- Payload mechanism of action:
Topoisomerase I inhibitor
- High potency of payload
- High drug to antibody ratio ~ 4
- Payload with short systemic half-life
- Stable linker-payload
- Tumor-selective cleavable linker
- Bystander antitumor effect

mAb = monoclonal antibody.

Steuer CE, et al. Presented at: ASCO 2022; June 3-7, 2022; Chicago, IL. Abstract 9017.

Pooled Analysis: TROPION-Lung05 and Lung01

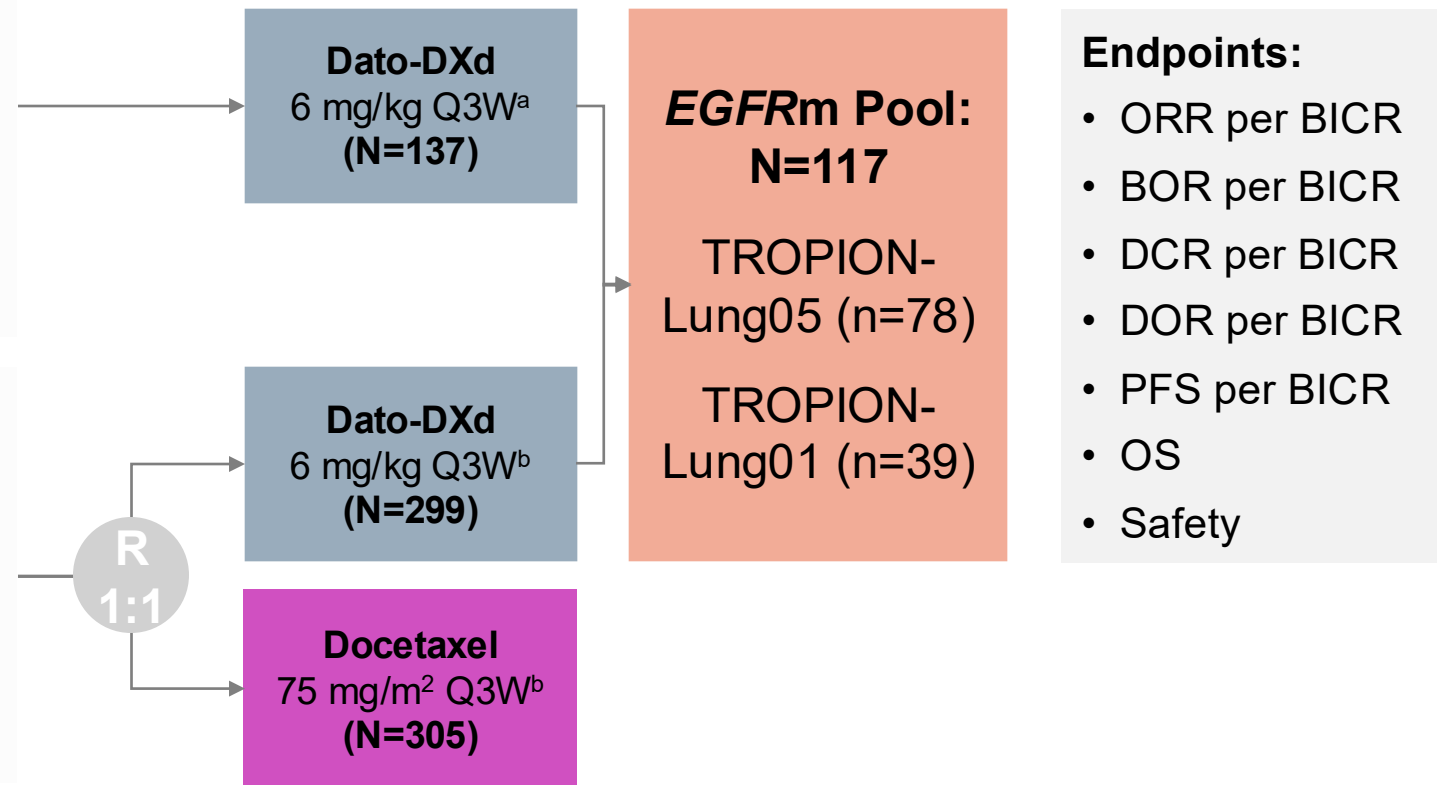
Patients with *EGFR*m NSCLC who received Dato-DXd 6 mg/kg Q3W were included in the pool

TROPION-Lung05 (Phase II study)

- Presence of ≥ 1 actionable genomic alteration (*EGFR*, *ALK*, *ROS1*, *NTRK*, *BRAF*, *MET* exon 14 skipping, or *RET*)
 - ≥ 1 line of targeted therapy
 - 1–2 prior cytotoxic agent-containing therapies including Pt-CT in the metastatic setting
 - Radiographic disease progression after most recent therapy

TROPION-Lung01 (Phase III study)

- In those with actionable genomic alterations (*EGFR*, *ALK*, *ROS1*, *NTRK*, *BRAF*, *MET* exon 14 skipping, or *RET*)
 - 1–2 prior approved targeted therapies + Pt-CT, and ≤ 1 anti-PD-(L)1 mAb
 - No prior docetaxel

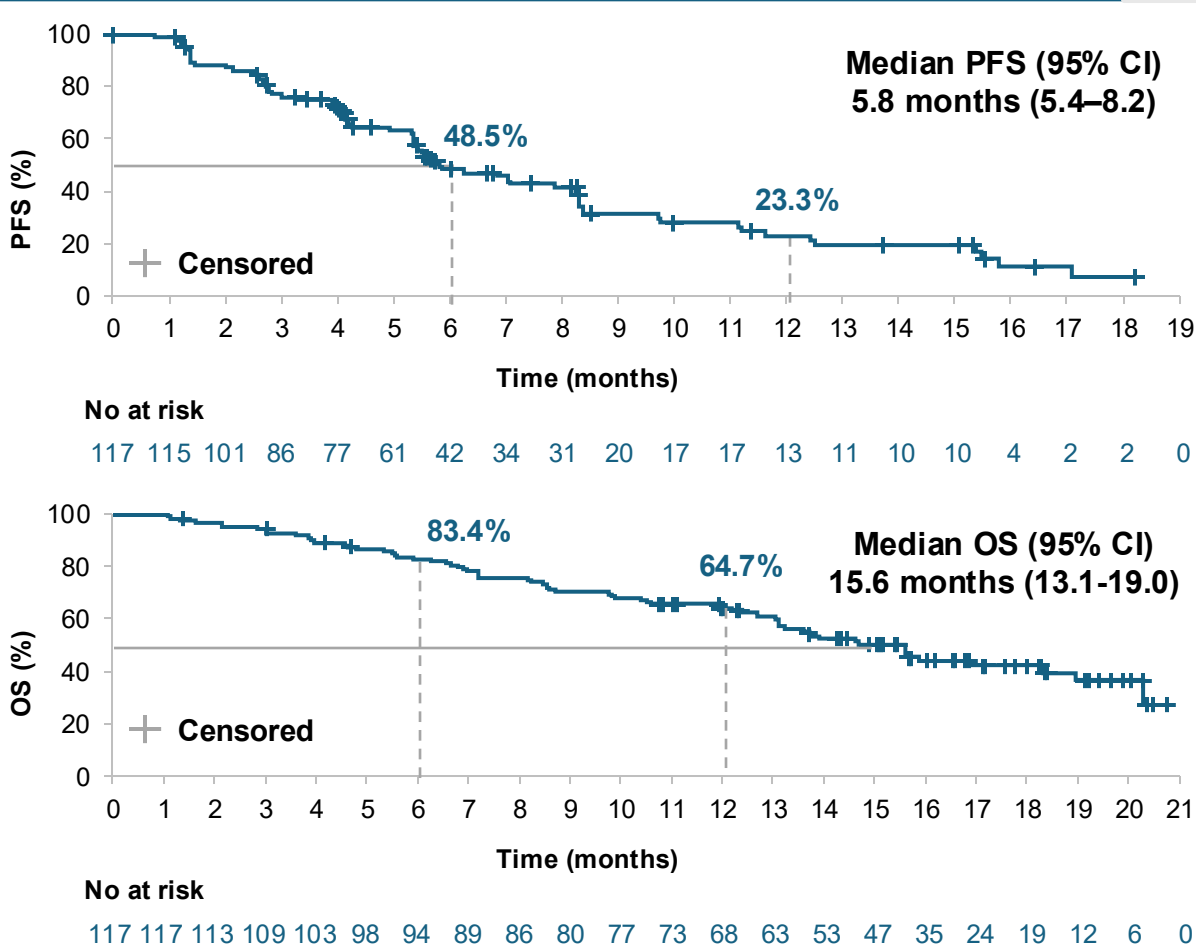


BOR = best overall response; Pt-CT = platinum-based chemotherapy.
Ahn MJ, et al. Presented at: ESMO Asia 2024; December 6-8, 2024; Singapore.

Pooled Analysis: Efficacy

Response	<i>EGFR</i> m Pool (N=117)	Prior Osimertinib (N=96)
Confirmed ORR, ^a n (%)	50 (42.7)	43 (44.8)
[95% CI]	[33.6–52.2]	[34.6–55.3]
BOR, n (%)		
CR	5 (4.3)	4 (4.2)
PR	45 (38.5)	39 (40.6)
SD	48 (41.0)	37 (38.5)
Non-CR/Non-PD	3 (2.6)	2 (2.1)
PD	12 (10.3)	10 (10.4)
NE	4 (3.4)	4 (4.2)
Median DOR, months (95% CI)	7.0 (4.2–9.8)	6.9 (4.2–9.8)
DCR, ^b n (%)	101 (86.3)	82 (85.4)
[95% CI]	[78.7–92.0]	[76.7–91.8]
Median PFS, months (95% CI)	5.8 (5.4–8.2)	5.7 (5.4–7.9)
Median OS, months (95% CI)	15.6 (13.1–19.0)	14.7 (13.0–18.3)

PFS and OS in the *EGFR*m Pool (N=117)

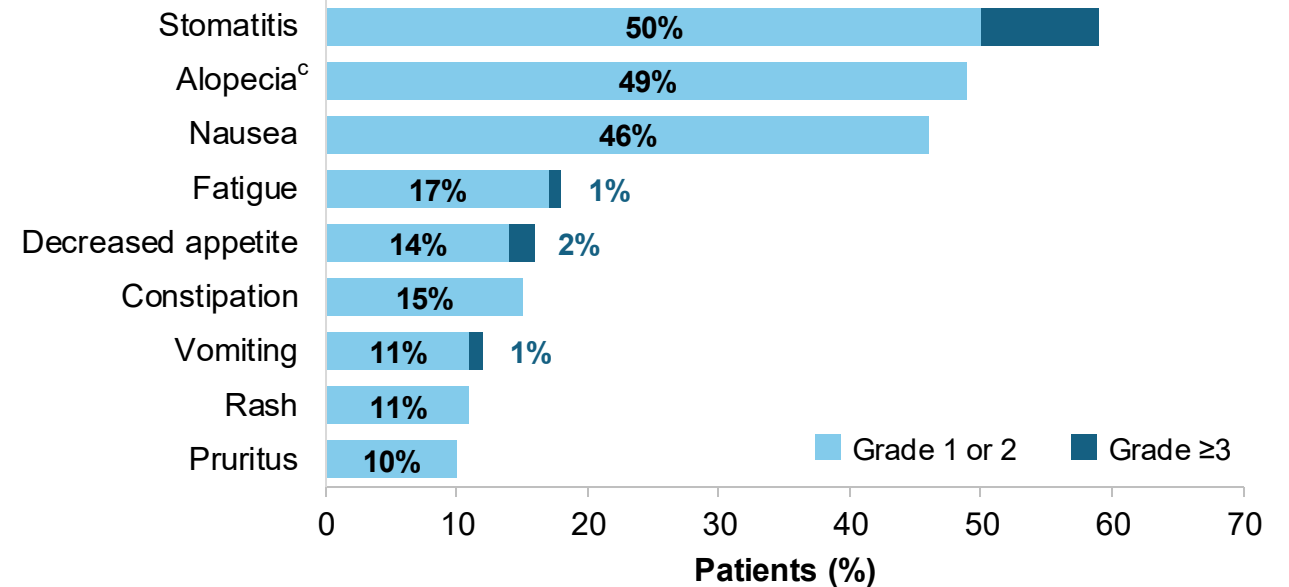


CR = complete response; NE = not evaluable; PR = partial response; SD = stable disease.
Ahn MJ, et al. Presented at: ESMO Asia 2024; December 6-8, 2024; Singapore.

Pooled Analysis: Safety

	<i>EGFRm</i> Pool (N=117)
TRAEs, n (%)	111 (95)
Grade ≥3	27 (23)
Associated with dose reduction	26 (22)
Associated with dose delay	27 (23)
Associated with treatment discontinuation	6 (5)
Associated with death	0 (0)
Serious TRAEs	9 (8)
AESIs^a, n (%)	
Stomatitis/oral mucositis	81 (69)
Grade 3 ^b	11 (9)
Ocular surface events	38 (32)
Grade 3 ^b	3 (3)
Adjudicated drug-related ILD	5 (4)
Grade 3 ^b	1 (1)

TRAEs Occurring in ≥10% of *EGFRm* Pool (N=117)



- Median Dato-DXd treatment duration: **6.1 months**

- Overall safety profile consistent with TROPION-Lung01 and 05
- No grade 4 or 5 adjudicated drug-related ILD
- Ocular surface events^a were primarily dry eye (12%), vision blurred and keratitis (each 7%)
- No TRAEs associated with death

ILD = interstitial lung disease; TRAE = treatment-related adverse event.
Ahn MJ, et al. Presented at: ESMO Asia 2024; December 6-8, 2024; Singapore.

Toxicities of Special Interest

Datopotamab Deruxtecan-dlnk (Dato-DXd)

Toxicity of Special Interest	Key Clinical Features	Proactive Management / Monitoring	When to Escalate
Stomatitis / oral mucositis	Very common; mouth ulcers, oral pain, erythema	Steroid-containing mouthwash prophylaxis ; oral hygiene; ice chips/ice water during infusion; early symptom reporting	Prompt assessment for ≥Grade 2; treatment interruption/dose modification based on severity
Ocular toxicity	Dry eye, keratitis, increased lacrimation; may include blurred vision, conjunctivitis, blepharitis	Preservative-free lubricating eye drops ≥4×/day ; avoid contact lenses; ophthalmic evaluation at baseline and periodically during treatment	Immediate ophthalmology referral for new/worsening symptoms; hold/reduce/discontinue according to severity
ILD / pneumonitis	Potentially serious or fatal; cough, dyspnea, fever, chest symptoms	Baseline pulmonary assessment; educate patient to report respiratory symptoms immediately ; monitor throughout treatment	Withhold DATROWAY® if suspected ; initiate corticosteroids as appropriate; permanently discontinue if >Grade 2 confirmed
Infusion-related reactions	Usually occur during/after infusion; hypersensitivity/IRR possible	Premedication per protocol; monitor during and after infusion; have emergency medications available	Slow/interrupt infusion for reactions; permanently discontinue for severe reactions
Embryo-fetal toxicity	Potential fetal harm	Pregnancy testing when applicable; contraception counseling	Pregnancy during therapy → immediate clinical evaluation

Proactive Management of ILD With ADCs – The 5 S Rules

1



Screen

- Careful patient selection is warranted before initiating T-DXd to optimize the monitoring strategies based on the baseline risk
- Screening continues during treatment, with regular clinical assessments to exclude signs/symptoms of ILD

2



Scan

- The fundamental diagnostic tools for ILD remain radiological scans, with preference for high-resolution CT scans of the chest
- A baseline scan is recommended, with repeat scans to be performed every 6-12 weeks

3



Synergy

- Minimizing the risk of ILD involves teamwork, which includes educating patients and all the care team, as well as multidisciplinary management once ILD is suspected

4



Suspend Treatment

- T-DXd should always be interrupted if ILD is suspected; it can only be restarted in the case of asymptomatic ILD that fully resolves

5



Steroids

- The mainstay for treating T-DXd-induced ILD remains corticosteroids, with the dose to be adapted to the toxicity grade

EGFR Post TKI & Platinum-Based Therapy: NCCN Guidelines®

- **Chemotherapy**-based options
 - Carboplatin-Pemetrexed-Amivantanab (MARIPOSA-2)
 - Carboplatin-Pemetrexed +/- Osimertinib (COMPEL)
- **MET**-targeted options
 - Amivantanab + Lazertinib (CHRYSLIS-2)
 - Savolitinib + Osimertinib (SAVANNAH)
- Antibody Drug Conjugates (**ADCs**)
 - Datopotamab-deruxtecan (TROPION-Lung01/Lung05)

EGFR Exon 20 Insertions: A Distinct Entity

- **Uncommon EGFR alteration** with distinct structural/biologic features
- Conventional EGFR TKIs have **limited activity** compared with exon 19 deletion/L858R
- Requires **mutation-specific treatment selection**
- Accurate molecular profiling is critical—**do not treat all EGFR mutations as equivalent**

PAPILLON: Practice-Changing Evidence

Platinum + Pemetrexed + Amivantamab in 1st Line Exon 20

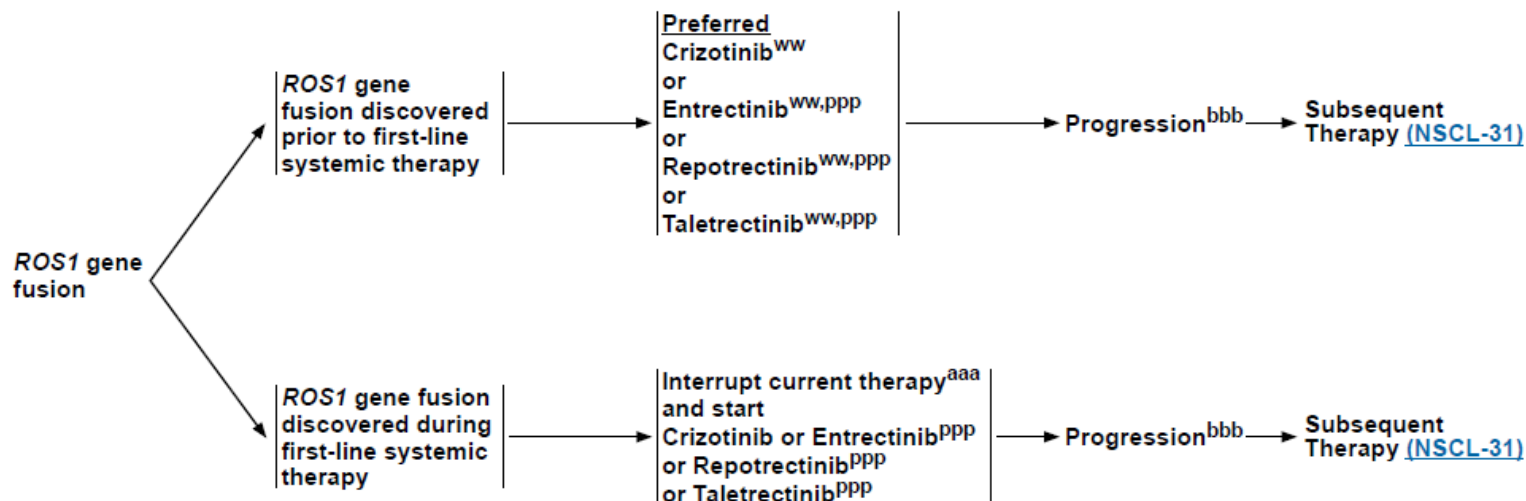
Outcome	Amivantamab + chemotherapy	Chemotherapy alone
Overall response rate	73%	47%
PFS	HR 0.40	Reference
PFS benefit	60% reduction in risk of progression/death	—

ROS1-mutated advanced NSCLC

ROS1 GENE FUSION^{rr}

FIRST-LINE THERAPY^{vv}

SUBSEQUENT THERAPY^{vv}



^{rr} [Principles of Biomarker Analysis \(NSCL-H\)](#).

^{vv} [Principles of Biomarker-Directed Therapy for Advanced or Metastatic Disease \(NSCL-J\)](#).

^{ww} For PS 0–4.

^{aaa} If there is a good response to current therapy, it is reasonable to continue therapy.

^{bbb} Beware of flare phenomenon in subset of patients who discontinue TKI. If disease flare occurs, restart TKI.

^{ppp} Entrectinib, repotrectinib, or taletrectinib may be better for patients with brain metastases.

Note: All recommendations are category 2A unless otherwise indicated.

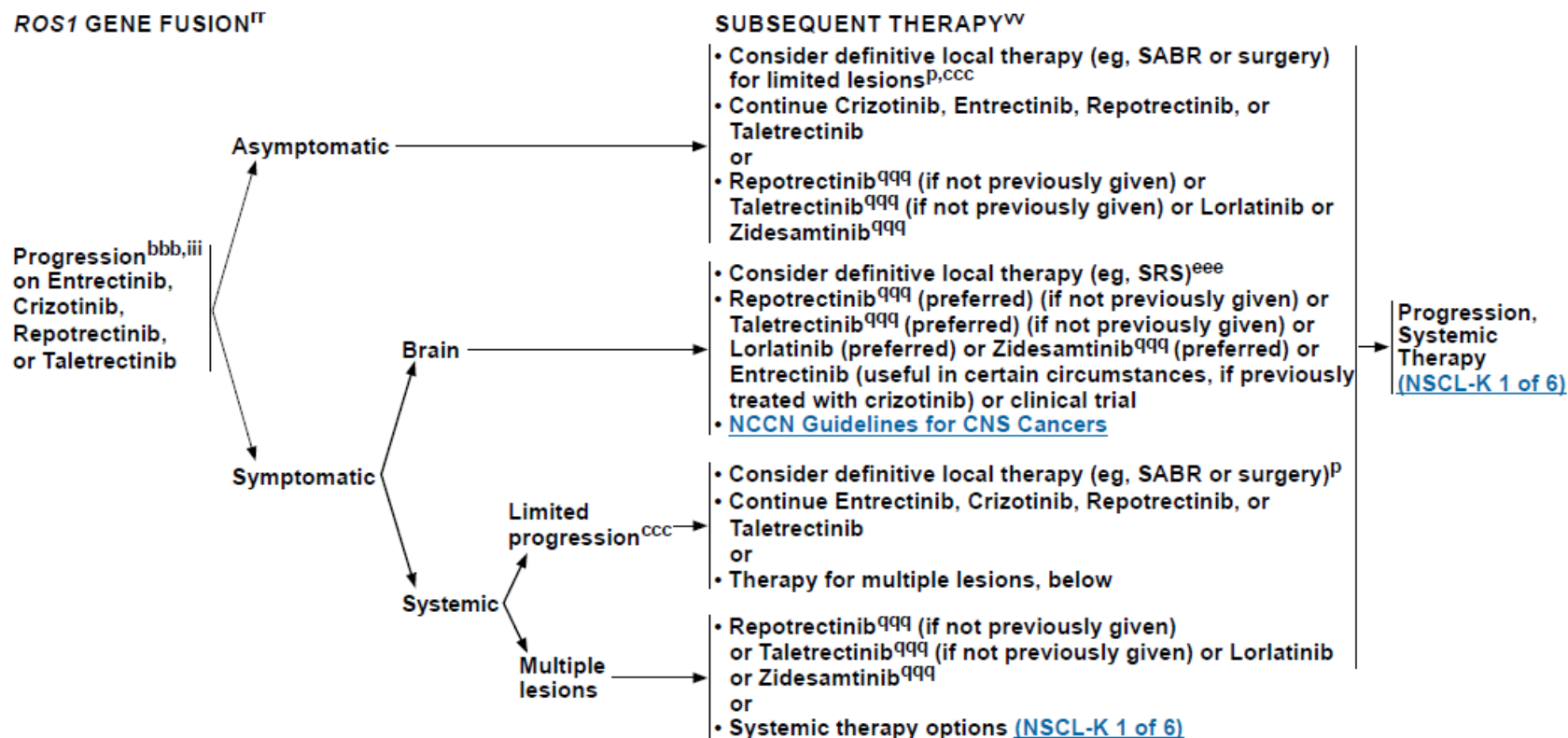
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NSCL-30

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ROS1-mutated advanced NSCLC

ROS1 GENE FUSION^{rr}



^p IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients. See [Principles of Image-Guided Thermal Ablation Therapy \(NSCL-D\)](#).

^{rr} [Principles of Biomarker Analysis \(NSCL-H\)](#).

^{vv} [Principles of Biomarker-Directed Therapy for Advanced or Metastatic Disease \(NSCL-J\)](#).

^{bbb} Beware of flare phenomenon in subset of patients who discontinue TKI. If disease flare occurs, restart TKI.

^{ccc} Clinical trials have included up to 3 to 5 progressing sites.

^{eee} Definitive local therapy of CNS disease can include asymptomatic lesions at risk for symptomatic progression based on factors including site, location, and edema.

ⁱⁱⁱ Plasma or tissue-based testing via MGPT should be considered at progression for genomic resistance mechanisms. If plasma-based testing is negative, tissue-based testing with rebiopsy material is strongly recommended. Practitioners may want to consider scheduling the biopsy concurrently with plasma testing referral.

^{qqq} Repotrectinib, taletrectinib, or zidesamitinib is an option for resistant mutations, such as *ROS1* G2032R.

Note: All recommendations are category 2A unless otherwise indicated.

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NSCL-31

SABR = stereotactic ablative radiotherapy; SRS = stereotactic radiosurgery.

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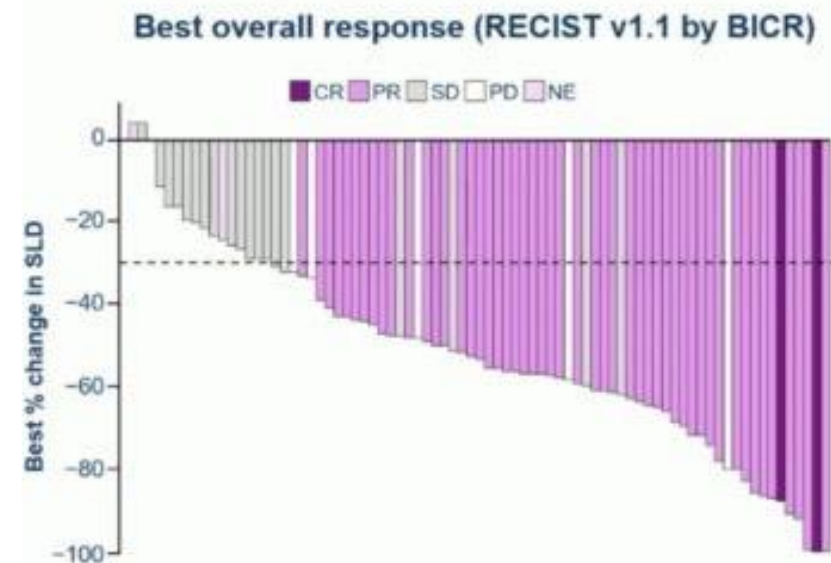
HER2-mutant NSCLC -Beamion LUNG-1-

- **Zongertinib**
 - Irreversible TKI selectively-inhibiting HER2 while sparing EGFR
- **Design:** Phase I trial
- **Population:** 75 patients with advanced HER-2 mutant NSCLC divided in multiple cohorts:
 - Cohort 1: Tumors with mutation in tyrosine kinase domain
 - Cohort 3: Tumors with non-tyrosine kinase domain
 - Cohort 5: Tumors with mutation in tyrosine kinase domain and previously treated with TDxd
- **Intervention:** Zongertinib 120mg daily or 240mg daily
- **Outcomes:**
 - **Objective response:** 67%
 - **Duration of response:** 14.1 months of those who have responded
 - **Progression-free survival:** 12.4 months in those who have responded
 - **Grade ≥ 3 adverse events:** 17% of patients, including transaminase elevations, no ILD

HER2-mutant NSCLC -SOHO-01-

- **Sevabertinib**
 - Reversible oral HER2 TKI
 - Received FDA breakthrough designation for previously treated advanced HER2-mutant NSCLC
- **Design:** Open-label Phase I/II study
 - Cohort D= naïve to HER2 exon 20 insertion therapy
 - Cohort E= previously received HER2 ADC
 - Cohort F= treatment-naïve
- **Intervention:** Sevabertinib 20mg twice daily
- **Outcomes:**
 - Objective response rate: 52% (95%CI 53-75) and in cohort F in particular 71%
 - Complete response: 2 patients
 - Progression-free survival: 8.3 mo
 - Median duration of response: 9.2 mo (6.3 – 13.5)

Objective response (ORR) by BICR



Targeted Therapies in EGFR-Mutant NSCLC and Beyond

Administration Considerations and Best Practices

- **Confirm actionable EGFR alteration & treatment indication**
- **Proactive management of predictable toxicities:** dermatologic prophylaxis, infusion-reaction precautions, VTE prophylaxis when indicated
- **Educate before first dose:** schedule, adherence, expected AEs, and when to call
- **Reinforce education and address barriers at each encounter**
- **Retest at progression**
- **Use results to guide subsequent treatment selection**

Reuss JE, et al. ASCO Living Guideline, 2026.3.1. *J Clin Oncol*. 2026;44(18):e89-e100. Drugs@FDA: FDA-Approved Drugs. Amivantamab and hyaluronidase-lpuj subcutaneous injection approval. Accessed September 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761433s000lbl.pdf. Drugs@FDA: FDA-Approved Drugs. LAZCLUZE® (lazertinib) injection Prescribing Information. Accessed September 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/219008s004lbl.pdf. Drugs@FDA: FDA-Approved Drugs. RYBREVANT® (amivantamab-vmjw) injection Prescribing Information. Accessed September 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761210s011lbl.pdf.

Key Learning Points

- Test broadly & early
- EGFR mutation, subtype matters
- First-line treatment is increasingly individualized
- CNS activity should influence treatment selection
- Proactive toxicity management is part of precision care
- Progression does not always mean “stop everything”
- Retest biology at progression
- Sequencing should preserve future options

Interdisciplinary Care & Coordination Across the Treatment Continuum

- Shared decision-making → patient & caregiver education
- Seamless communication across disciplines
- Proactive toxicity/symptom management
- Early/Proactive supportive-care integration
- Ongoing reassessment of GOC

GOC = goals of care.

Sanders JJ, et al. *J Pain Symptom Manage*. 2024;68(3):214-222.e6. Gilligan T, et al. *J Clin Oncol*. 2026;44(11):1040-1057.

Patient & Caregiver Education

Empowering Patients to Participate safely & confidently

- Understand the treatment plan
- Know what to expect
- Recognize & report early
- Empower patients with self-management skills
- Prepare caregivers
- Reinforce at every encounter

Treatment Expectations & Adherence Strategies

1. SET EXPECTATIONS

Goals & timeline

Expected benefit

Common AEs

When to call

2. ANTICIPATE BARRIERS

Transportation

Financial toxicity

Medication complexity

Caregiver needs

3. SUPPORT ADHERENCE

Teach-back

Symptom control

Navigation

Caregiver engagement

4. REASSESS

Understanding

Toxicities

Barriers

Treatment plan

Thank you!

Polling

- Participate in polling at the beginning and end of the session to be entered to win a \$100 gift card!
- Scan this QR code to see the answer choices and submit your response



Discussion and Live Q&A

Credit Claim Information

- Scan this QR code to claim credit after the session
- Participants who complete the evaluation online within 30 days of the event will receive documentation of credit

