Oncology Learning Network

Non-Small Cell Lung Cancer

Updates on Molecular Diagnostics, Targeted Treatment, and Adverse Event Management for Optimized Patient Outcomes

Faculty Disclosures

- **Millie Das, MD:** Advisory Board—Janssen, AstraZeneca, Gilead, Bristol Myers Squibb, Novocure, Guardant, EMD Serono, Natera, Merus, OncoHost, Jazz Pharmaceuticals, Summit, Novartis, Genentech, Boeringer Ingelheim; Consultant—AbbVie, Janssen, Gilead, Daiichi Sankyo, Bristol Myers Squibb; Research—Merck, Genentech, CellSight, Novartis, Varian; CME—Plexus, IDEOlogy Health, Springer, Medical Educator Consortium, Dedham Group, DAVA Oncology, MJH Healthcare Holdings/PER, Targeted Oncology (MJH), OncLive (MJH), ANCO, Aptitude Health, MashUp Media, Med Learning Group, Curio, Triptych Health, American Cancer Society

- **Shahnaz Singh-Kandah, NP**: Speaker Podcast: Johnson & Johnson

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Program Information

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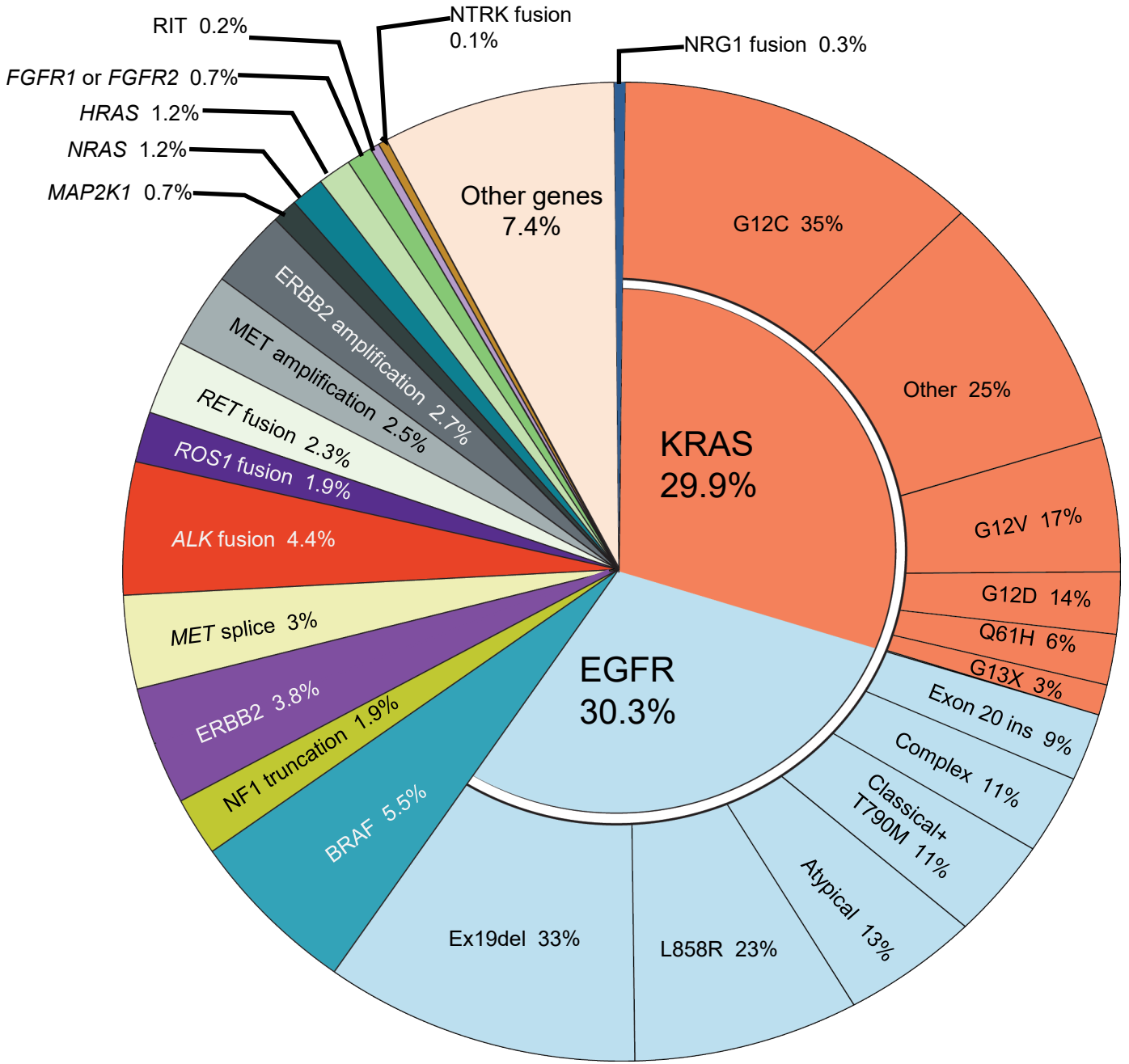
References

Learning Objectives

- Describe the clinical significance of driver mutations in NSCLC and the importance of molecular testing strategies to identify specific genetic markers for tailored treatment plans
- Apply the latest clinical data and treatment guidelines for targeted therapies, emphasizing strategies for appropriate treatment selection and sequencing, minimizing interruptions, managing potential AEs, and optimizing patient outcomes
- Employ specific actions for oncology APs regarding molecular testing, patient/caregiver education, personalized care coordination, and AE management

Biomarker Testing

Identification of driver mutations leads to treatment with targeted therapies in metastatic NSCLC



NSCLC = non–small cell lung cancer; KRAS = Kirsten rat sarcoma viral oncogene homolog; EGFR = epidermal growth factor receptor; ROS1 = ros proto-oncogene 1.

Skoulidis F, Heymach JV. *Nat Rev Cancer*. 2019;19(9):495-509.

Treatment Overview

- Targeted therapies in the metastatic setting result in robust responses and prolonged disease control for NSCLC but cannot cure- RESISTANCE IS INEVITABLE

- For patients without a targetable mutation, standard first-line treatment recommendation is chemotherapy + IO, regardless of PD-L1 status

- Immunotherapy alone can be considered for patients with PD-L1 ≥50%

PD-L1 = programmed death-ligand 1.

Treatment Considerations

Who should get molecular testing?	All patients with metastatic non-squamous NSCLC Consider in patients with metastatic SCC, especially those with never/light smoking history
Timing of Treatment	Wait for rapid molecular testing (EGFR, ALK, ROS1, PD-L1) or NGS results prior to treatment initiation

SCC = squamous cell carcinoma.

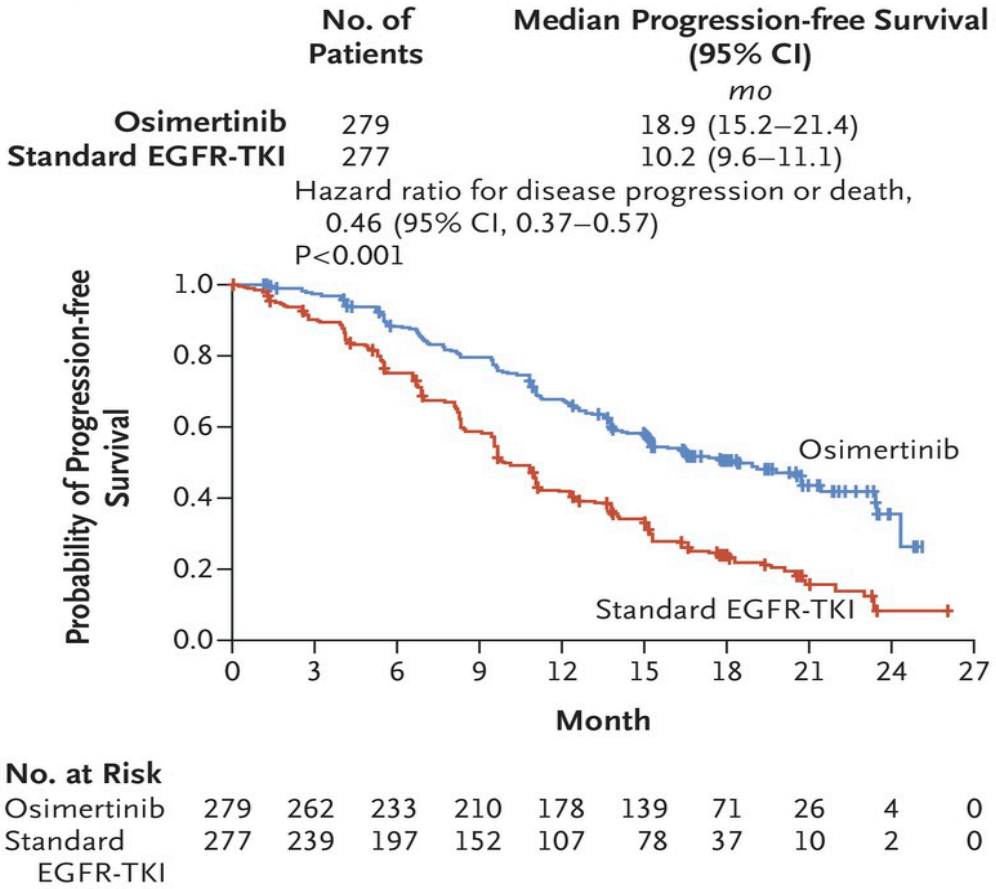
Background: EGFR Mutations

- 15%-20% of NSCLC
  - More frequently seen in Asian populations, never or light smokers
- Most common sensitizing mutations are exon 19 del and L858R
- First-line treatment with osimertinib in stage IV (FLAURA)
- Brain metastases seen commonly with good CNS penetration of osimertinib
- Resistance to EGFR TKIs is common
- Adjuvant osimertinib now FDA approved (ADAURA)
- Exon 20 insertions are generally resistant to classical TKIs with some variant exceptions

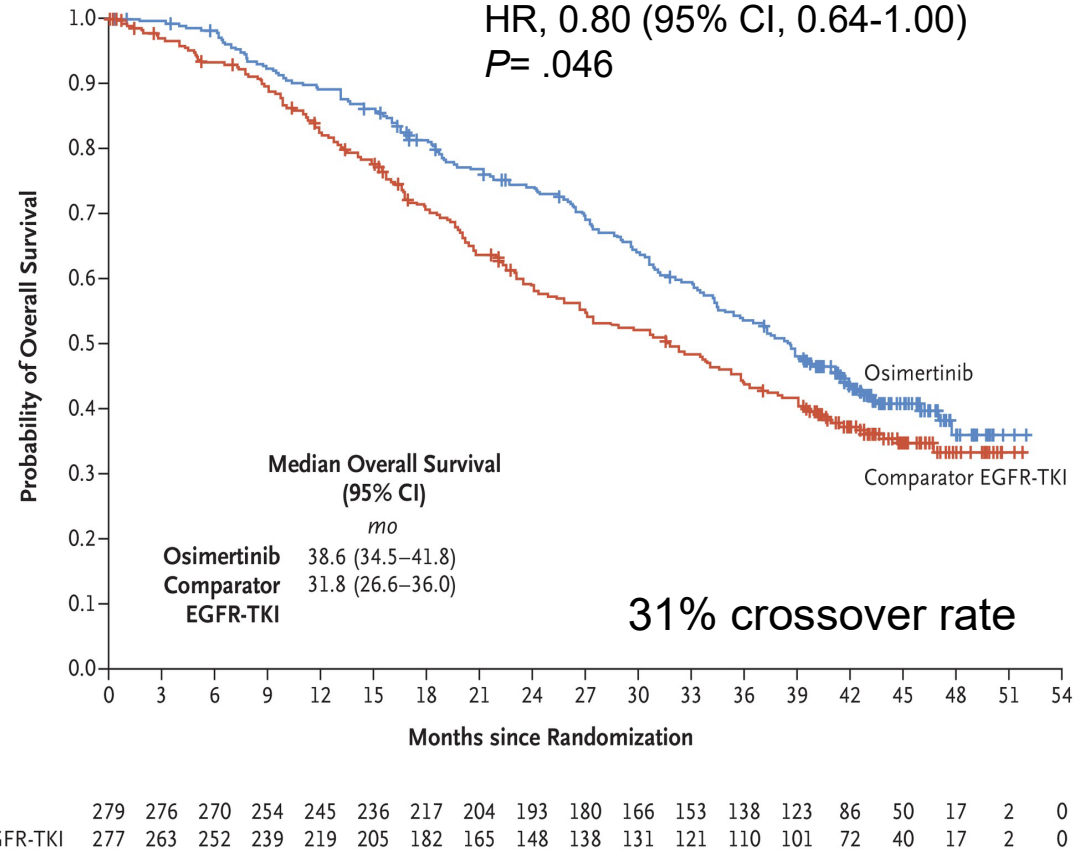
TKI = tyrosine kinase inhibitor.

FLAURA TRIAL: Osimertinib Improves PFS & OS Compared to Older Generation EGFR TKIs in Stage IV EGFR+ NSCLC

PFS



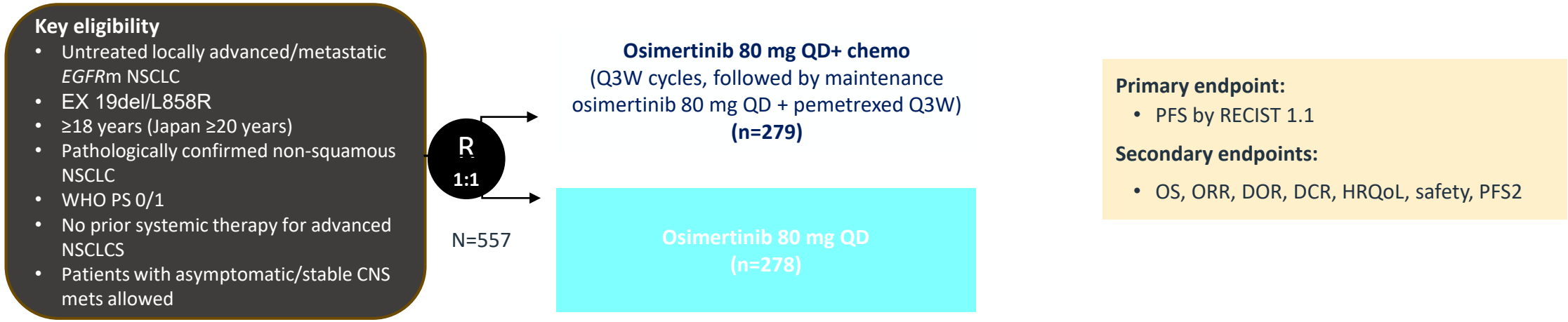
OS



PFS = progression-free survival; OS = overall survival; CI = confidence interval; HR = hazard ratio.

Soria JC, et al. *N Engl J Med*. 2018;378(2):113-125. Ramalingam S, et al. NEJM. 2020;382(1):41-50.

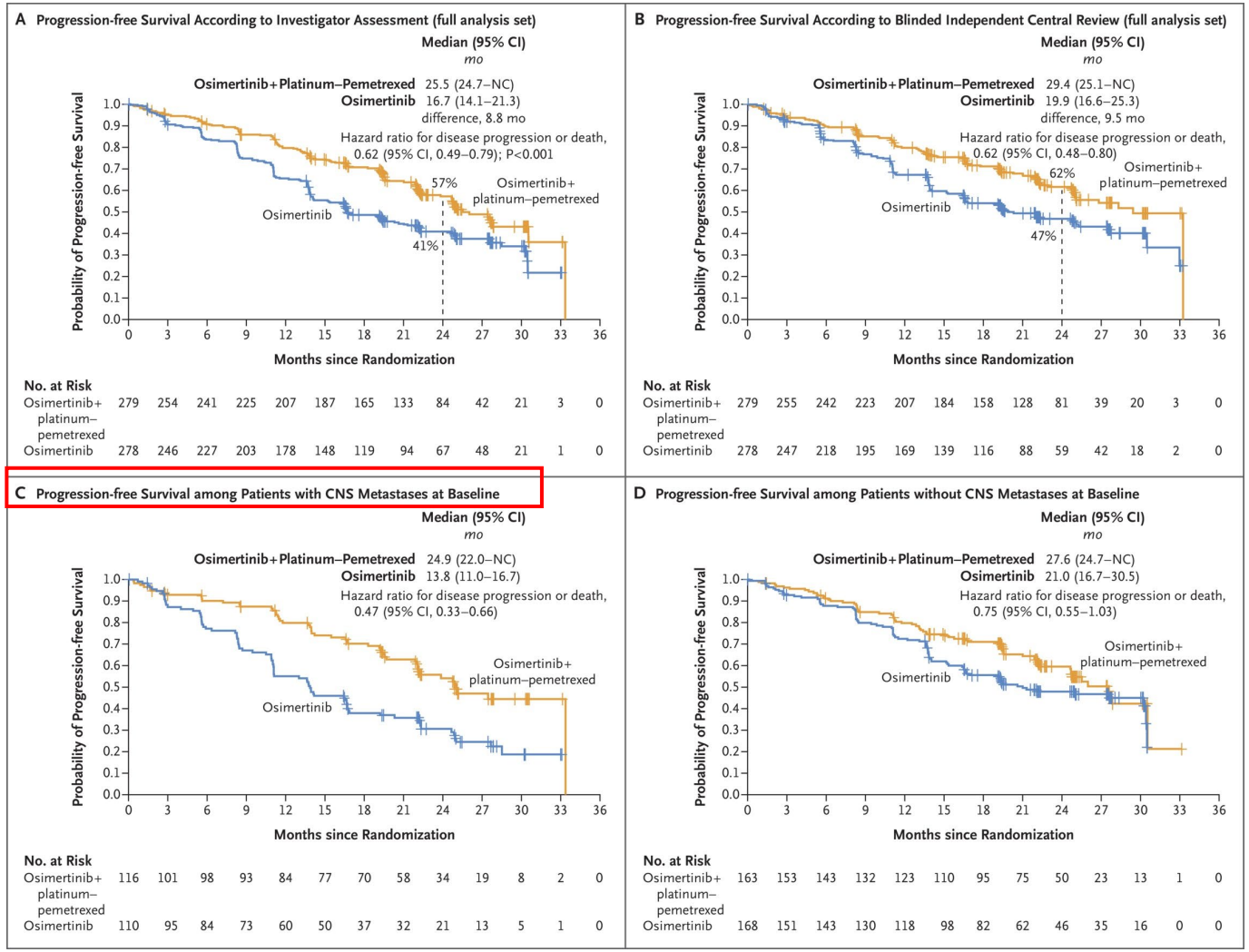
FLAURA2: Phase III Trial of Osimertinib +/- Chemo in EGFR-Mutated Advanced NSCLC



PS = performance status; CNS = central nervous system; ORR = objective response rate; DOR = duration of response; HRQoL = health-related quality of life; PFS2 = time to second progression.

ClinicalTrials.gov. NCT04035486. Accessed October 2025. https://clinicaltrials.gov/study/NCT04035486.

FLAURA2: Osimertinib + Chemo Improves PFS

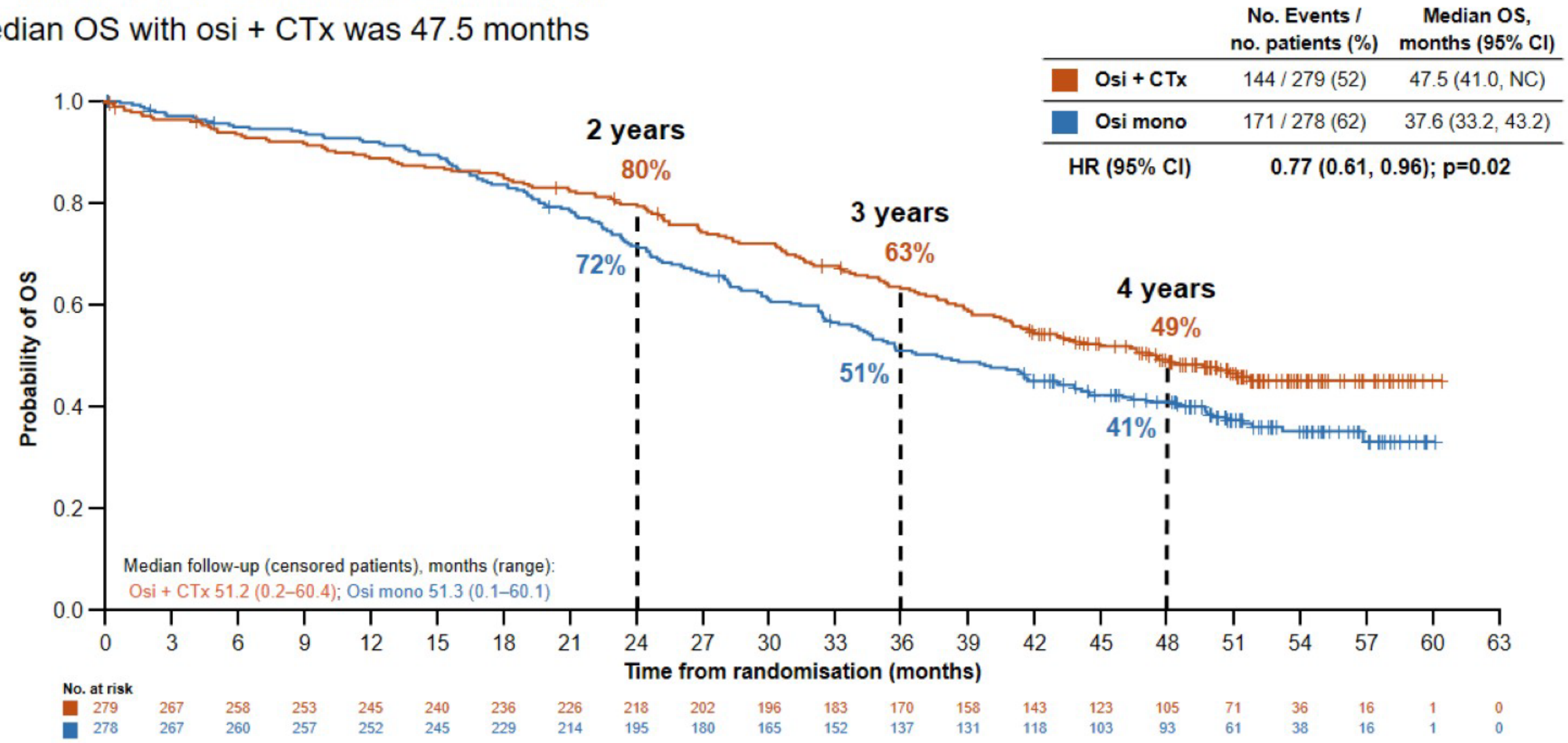


Feb 2024: FDA approved osimertinib + chemo treatment in patients with metastatic EGFR+ NSCLC

Planchard D, et al. *NEJM*. 2023;389:1935-1948.

FLAURA2: Osimertinib + Chemo Improves OS

Median OS with osi + CTx was 47.5 months



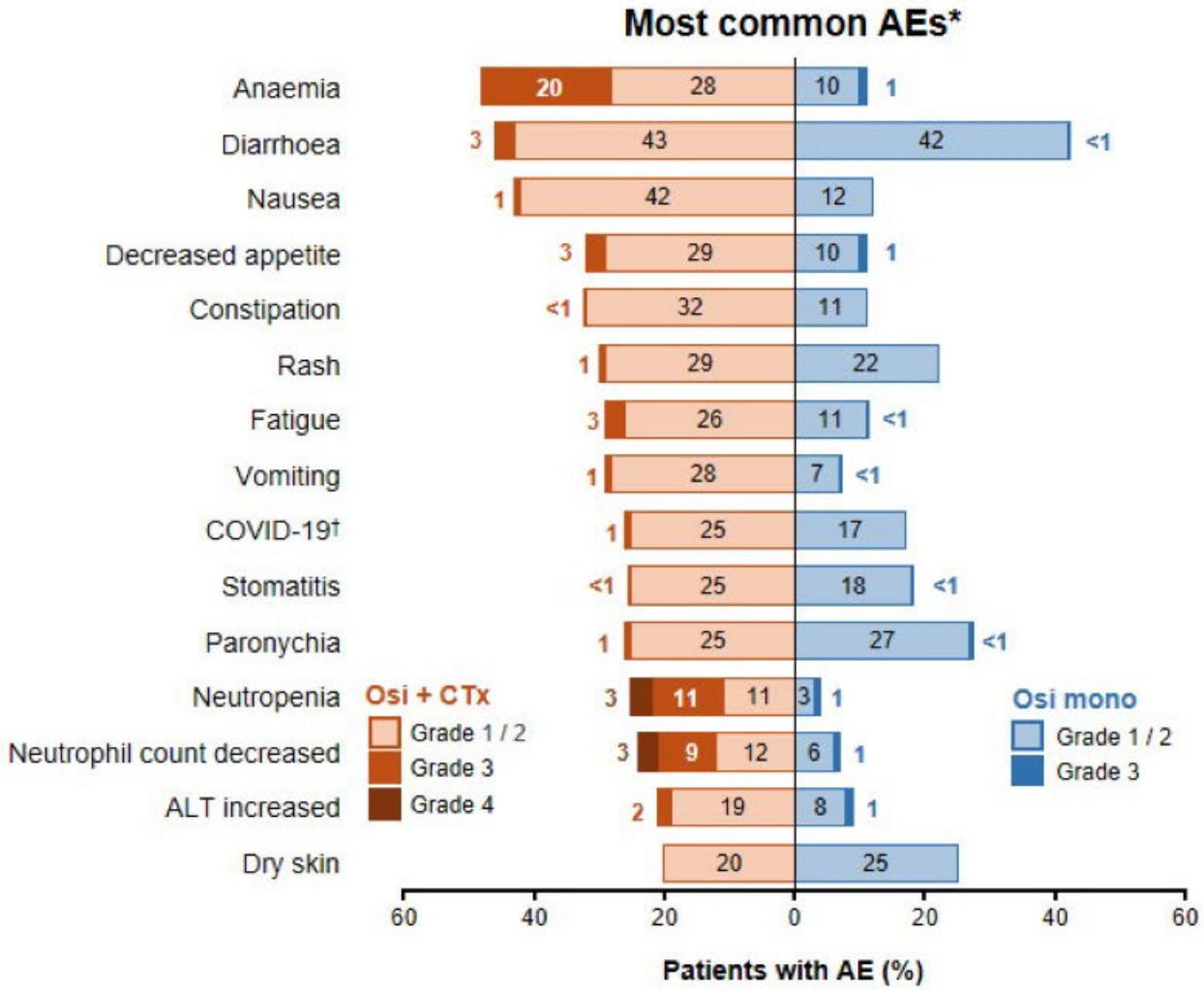
Planchard D, et al. WCLC 2025. Abstract PL02.04.

FLAURA2: Safety

Since the primary analysis[1] (>2 years additional follow-up):

- No new safety signals observed
- AEs leading to discontinuation of osi remained low
- No new treatment-related deaths observed with osi + CTx (vs 1 with osi mono)

AE summary	Osi + CTx (n=276)	Osi mono (n=275)
AE any cause, n (%)		
Any grade	276 (100)	269 (98)
Grade ≥3	193 (70)	94 (34)
Serious	126 (46)	75 (27)
Outcome of death	22 (8)	10 (4)
Considered possibly related to treatment	5 (2)	2 (1)
Leading to discontinuation of osi	34 (12)	20 (7)
Leading to discontinuation of pemetrexed	137 (50)	NA
Leading to discontinuation of platinum	46 (17)	NA



Planchard D, et al. WCLC 2025. Abstract PL02.04.

MARIPOSA (Phase 3): 1L amivantamab + lazertinib vs osimertinib among patients with *EGFR*-mutated, advanced NSCLC

Key eligibility
- Locally advanced or metastatic NSCLC
- Treatment-naïve for advanced disease
- Documented for *EGFR* Ex19del or L858R
- ECOG PS 0 or 1

N = 1074

R 2:2:1

- **Amivantamab + lazertinib (OL) (n=429)**
- **Osimertinib (blinded) (n=429)**
- **Lazertinib (blinded) (n=216)**

Primary endpoint of PFS[b] by BICR perRESIST v1.1:
- Amivantamab + lazertinib vs osimertinib

Secondary endpoints of amivantamab + lazertinib vs Osimertinib
- OS
- ORR
- DOR
- PFS2
- Symptomatic PFS
- Intercranial PFS
- Safety

Lazertinib monotherapy arm was included to assess the contribution of components

Stratification factors
- *EGFR* mutation type (Ex19del vs L868R)
- Asian race (yes vs no)
- History of brain metastases

Baseline demographics/characteristics
- Asian patients 60%
- Smokers 30%
- Brain mets 40%
- Exon 19 60%

Dosing (in 28-day cycles)
Amivantamab: 1050 mg (1400 mg if ≥80 kg) weekly for the first 4 weeks, then Q2W
Lazertinib: 240 mg daily
Osimertinib: 80 mg daily

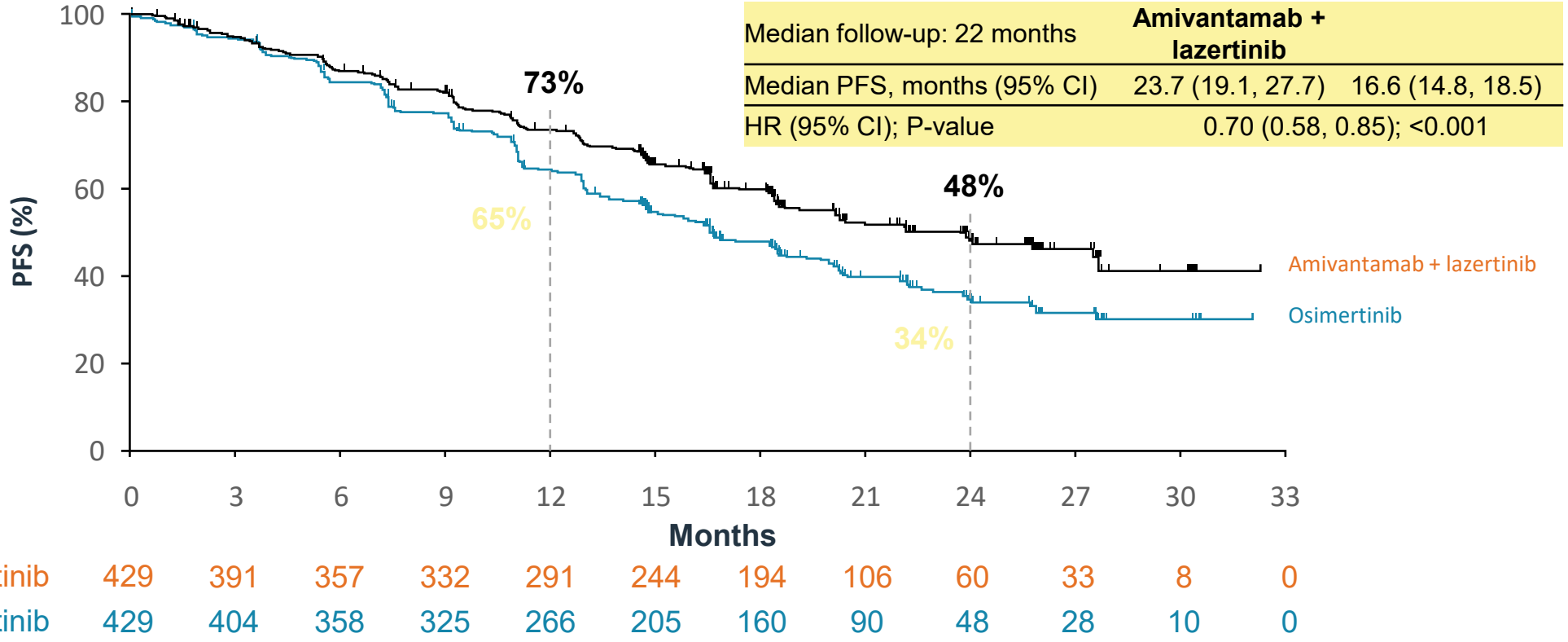
Brain scans
- Baseline brain MRI required for all patients ≤28 days prior to randomization
- Patients who could not have MRIs were allowed to have CT scans
- Brain scan frequency was every 8 weeks for the first 30 months and then every 12 weeks thereafter for patients with a history of brain metastasis and every 24 weeks for patients with no history of brain metastasis

ECOG = Eastern Cooperative Oncology Group; OL = open-label; BICR = blinded independent central review; Q2W = every 2 weeks; MRI = magnetic resonance imaging; CT = computed tomography.

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

MARIPOSA: PFS with 1L amivantamab + lazertinib vs osimertinib among patients with *EGFR*-mutated, advanced NSCLC

Aug 2024: FDA approved ami + laz in patients with metastatic EGFR+ NSCLC



Median follow-up: 22 months	Amivantamab + lazertinib	
Median PFS, months (95% CI)	23.7 (19.1, 27.7)	16.6 (14.8, 18.5)
HR (95% CI); P-value	0.70 (0.58, 0.85); <0.001	

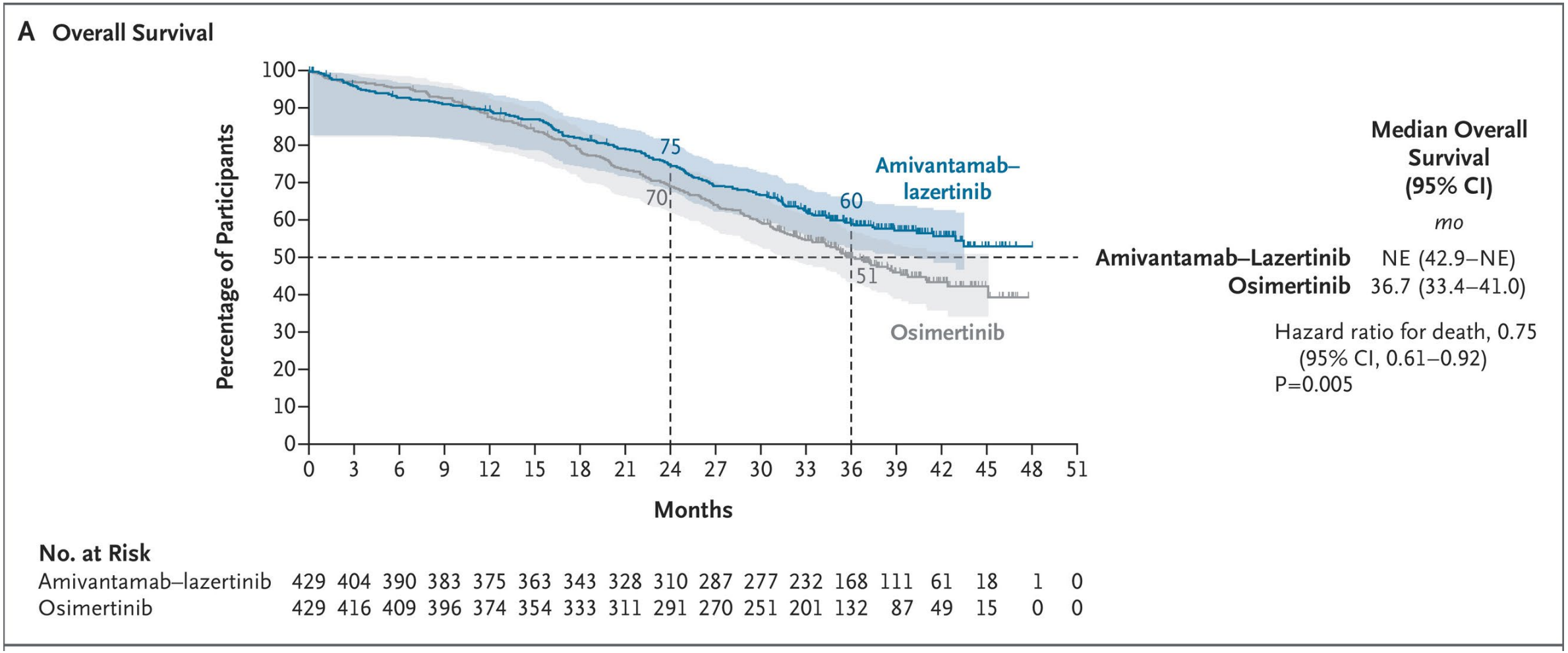
No. at risk (no. censored)												
Amivantamab + Lazertinib	429	391	357	332	291	244	194	106	60	33	8	0
Osimertinib	429	404	358	325	266	205	160	90	48	28	10	0

- 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.

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

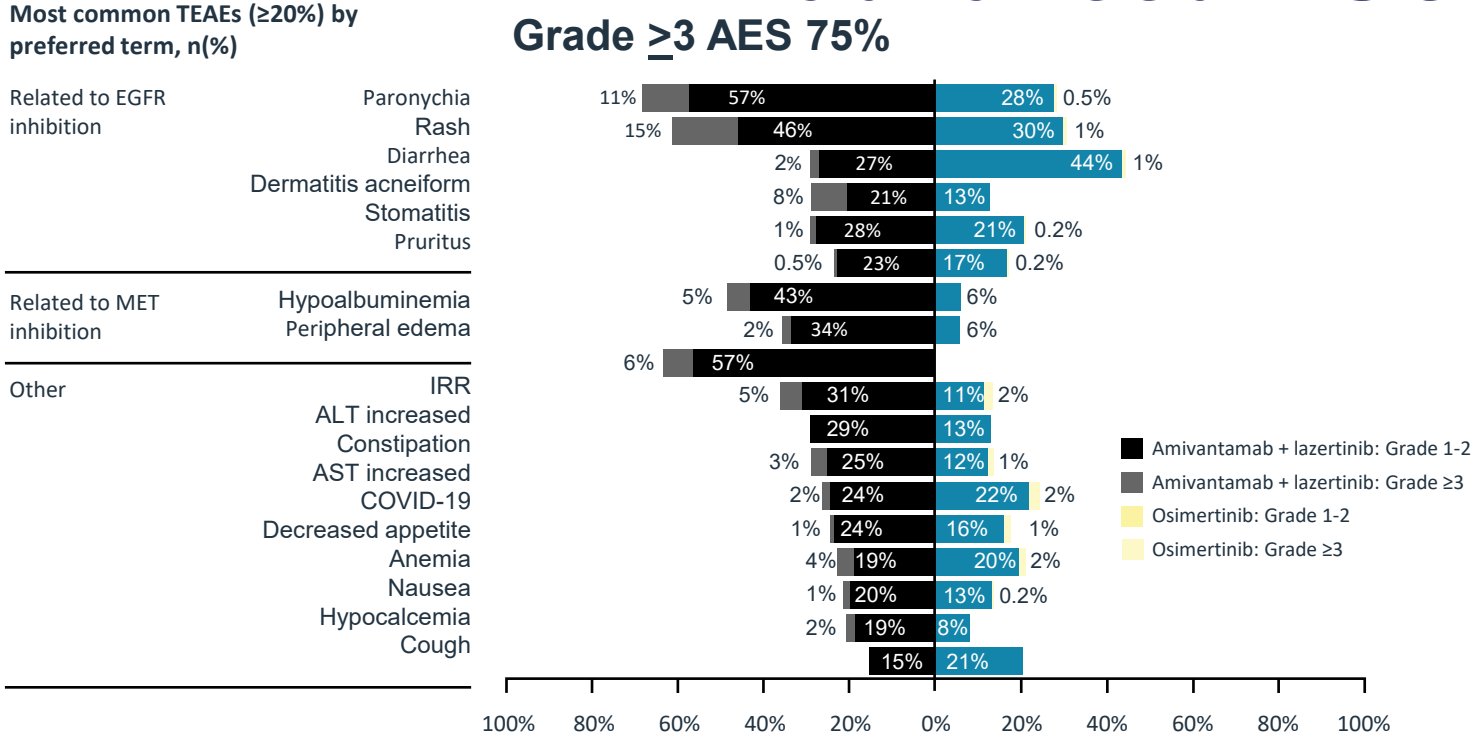
MARIPOSA: OS with 1L amivantamab + lazertinib vs osimertinib among patients with *EGFR*-mutated, advanced NSCLC



Yang JC-H, et al. *N Engl J Med*. 2025.

MARIPOSA: Safety of amivantamab + lazertinib vs osimertinib among patients with *EGFR*-mutated, advanced NSCLC

Most common TEAEs (≥20%) by preferred term, n(%)



	Amivantamab + lazertinib (n=421)	Osimertinib (n=428)
Any VTE, n (%)	157 (37)	39 (9)
Grade 1	5 (1)	0
Grade 2	105 (25)	24 (6)

VTE rates were higher for amivantamab + lazertinib

- Most common preferred terms were pulmonary embolism and deep vein thrombosis
- Most VTEs were Grade 1–2
- Incidence of Grade 4–5 VTEs was low (<1%) and comparable between arms
- Rates of discontinuations due to VTE were low and comparable between arms

At time of first VTE:

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

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

TEAE = treatment-emergent adverse event; AE = adverse event; IRR = infusion-related reaction; ALT = alanine aminotransferase; AST = aspartate aminotransferase; VTE = venous thromboembolism.

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

Key Take-Aways

- Biomarker testing prior to treatment initiation is critical
- Do not administer IO in patient with suspected driver mutation
  - Likely no benefit with increased risk of toxicity of giving TKI after IO
- Patients with stage IV EGFR+ NSCLC now have multiple frontline options
  - Osi + chemo (FLAURA2) and Ami + Laz (MARIPOSA) demonstrate PFS and OS benefit over Osi alone
  - Which EGFR+ patients should get osi alone vs FLAURA2/MARIPOSA?
    - Consider in high-risk groups, brain mets

Targeted Therapies in NSCLC

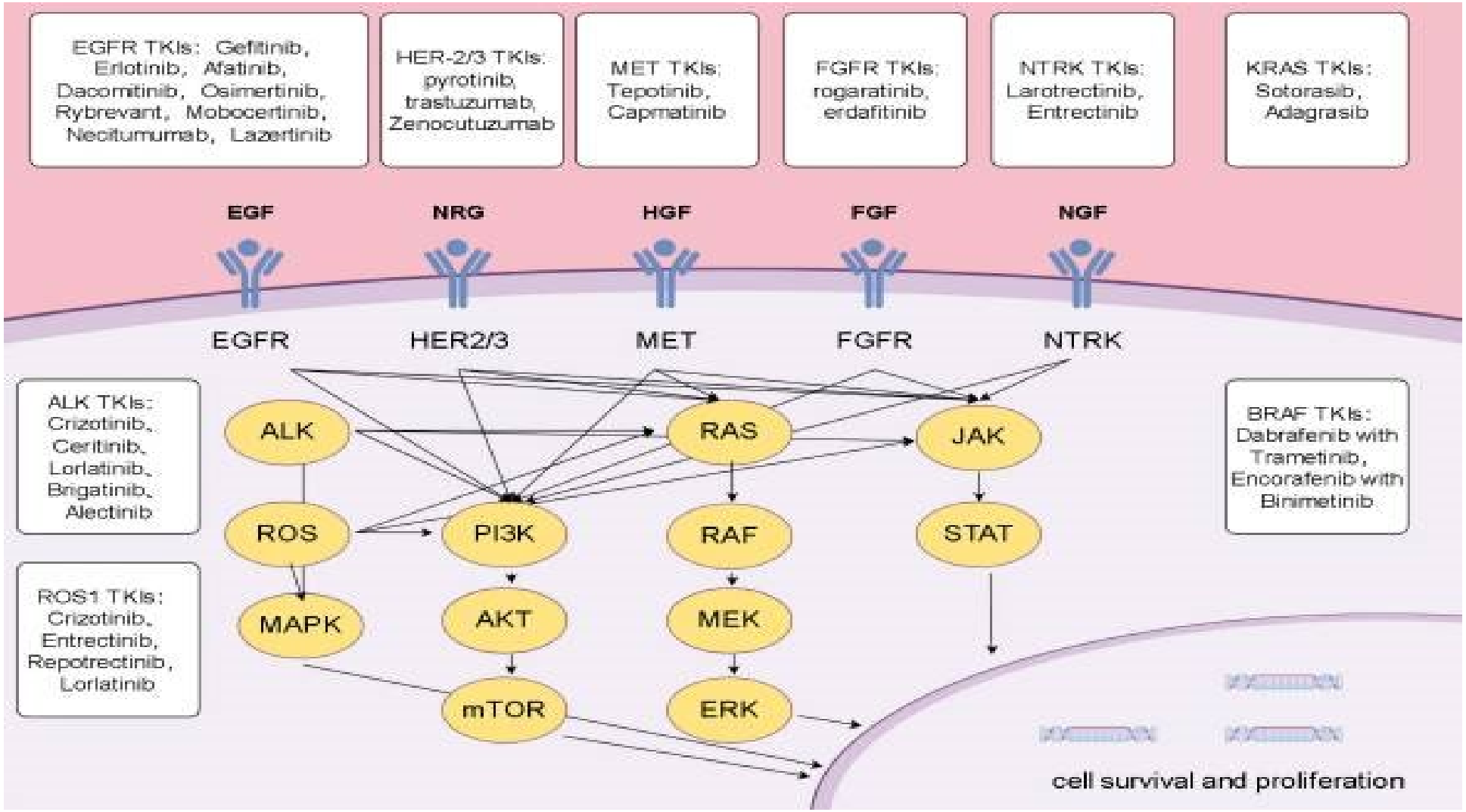
- Mechanisms of Action, Safety, and Efficacy Data
- Administration Considerations and Best Practices
- Adverse Event Management & Mitigation Strategies

Targeted Therapy Biomarkers in NSCLC

Biomarker	Prevalence	Preferred Testing Method(s)	Approved Targeted Therapy Options	Pivotal Trial(s)
EGFR	32%	NGS/PCR	Afatinib, Amivantamab, Dacomitinib, Erlotinib, Gefitinib, Osimertinib	ADAURA, FLAURA, FLAURA2, MARIPOSA
EGFR exon 20	0.1–4%	NGS (preferred); PCR-based approaches may under-detect EGFRex20in	Amivantamab	PAPILLON, CHRYSALIS
ALK	2–8%	RNA-based NGS, IHC, FISH, PCR	Alectinib, Brigatinib, Ceritinib, Crizotinib, Ensartinib, Lorlatinib	ALINA, ALEX, ALTA-1L, CROWN, eXALT
ROS1	0.9–2%	RNA-based NGS, IHC, FISH, PCR	Crizotinib, Entrectinib, Repotrectinib	PROFILE 1001, STARTRK-1/2, ALKA-372-001, TRIDENT-1
BRAF V600E	1–2%	NGS/PCR	Dabrafenib + Trametinib, Encorafenib + Binimetinib	BRF113928, PHAROS
KRAS G12C	13%	NGS/PCR	Adagrasib, Sotorasib	KRYSTAL-1, CodeBreaK 100
METex14	3–4% (adenocarcinoma); 1–2% (all NSCLC)	RNA-based NGS	Capmatinib, Tepotinib	GEOMETRY mono-1, VISION
RET fusions	1–2%	RNA-based NGS	Pralsetinib, Selpercatinib	ARROW, LIBRETTO-001
HER2	2–4% (mutation/amplification); 1–5% (overexpression)	NGS/PCR (mutations), IHC (overexpression)	Trastuzumab deruxtecan (T-DXd), Zanidatamab	DESTINY-Lung01/02, Beamion LUNG-1
NTRK fusions	<1%	RNA-based NGS	Entrectinib, Larotrectinib, Repotrectinib	STARTRK-1/2, ALKA-372-001
NRG1	0.2% (all solid tumors)	RNA-based NGS	Zenocutuzumab	eNRGy
cMet	(overexpression)	IHC	Telisotuzumab vedotin (Teliso-V)	LUMINOSITY
TROP2 (TROP2 NMR*)	-	IHC, QCS*	Datopotamab deruxtecan (Dato-DXd)	TROPION-Lung05
PD-L1	-	IHC	Atezolizumab, Cemiplimab, Durvalumab + Tremelimumab, Nivolumab + Ipilimumab, Pembrolizumab	IMpower, EMPOWER, AEGEAN, CheckMate, KEYNOTE studies

FISH = fluorescence in situ hybridization; IHC = immunohistochemistry; NGS = next-generation sequencing; PCR = polymerase chain reaction.

Therapeutic Targets

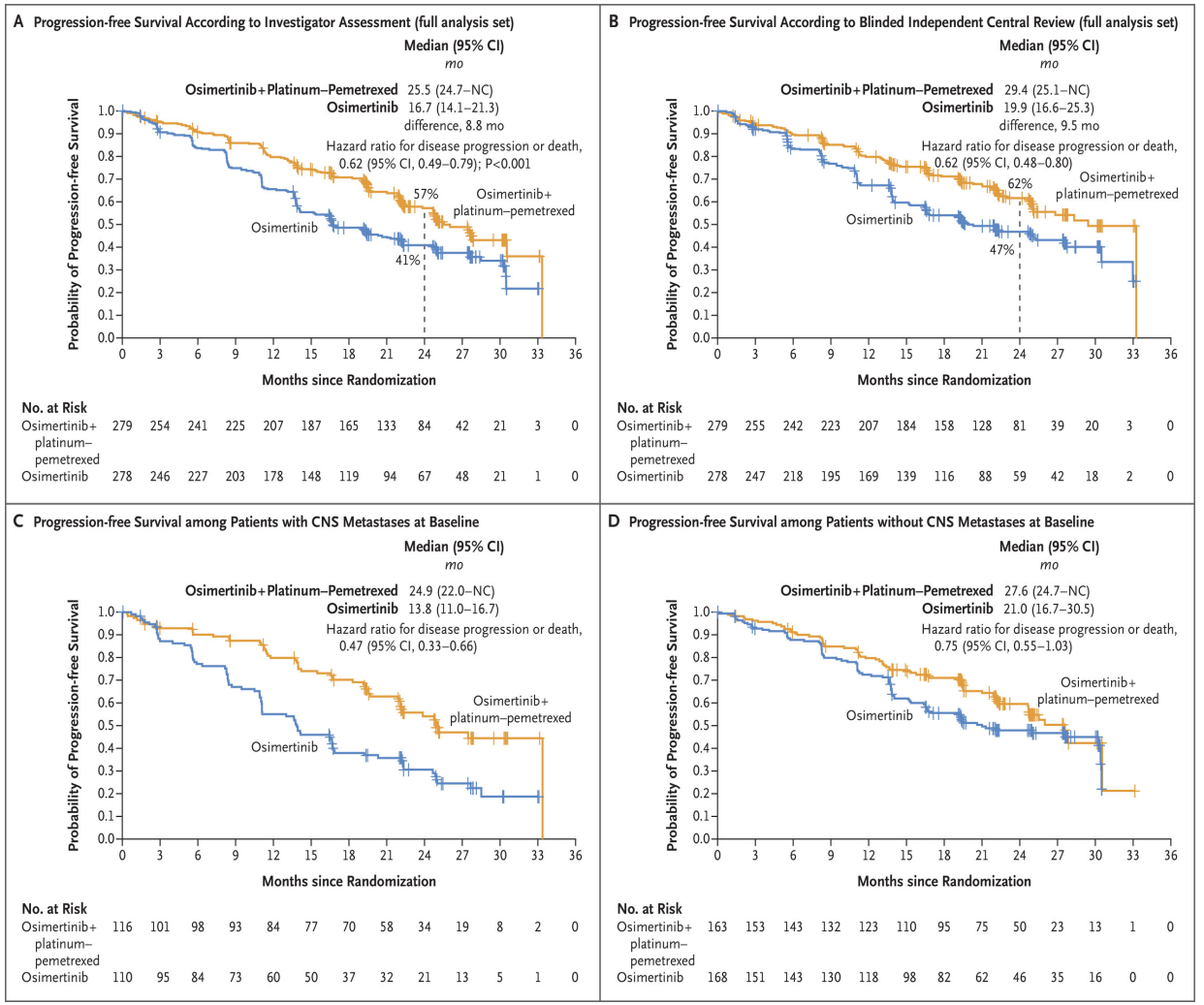


EGF = epidermal growth factor; EGFR = EGF receptor; TKI = tyrosine kinase inhibitor; NRG = neuregulin; HGF = hepatocyte growth factor; FGF = fibroblast growth factor; FGFR = FGF receptor; NGF = nerve growth factor; HER-2/3 = human epidermal growth factor receptor 2 / 3; MET = mesenchymal-epithelial transition factor; NTRK = neurotrophic tyrosine receptor kinase; ALK = anaplastic lymphoma kinase; ROS = reactive oxygen species; PI3K = phosphoinositide 3-kinase; AKT = protein kinase B; mTOR = mechanistic target of rapamycin; RAS = rat sarcoma viral oncogene homolog; RAF = rapidly accelerated fibrosarcoma; MEK = mapk/erk kinase; ERK = extracellular signal-regulated kinase; MAPK = mitogen-activated protein kinase; JAK = janus kinase; STAT = signal transducer and activator of transcription.

Yu L, et al. *Front Oncol*. 2024;14:1451230.

FLAURA 2: Osimertinib with or without Chemotherapy in EGFR-Mutated Advanced NSCLC

- Randomized, open-label phase III trial
- Osimertinib vs Osimertinib + Carboplatin/Cisplatin + Pemetrexed
- Primary Endpoint: PFS

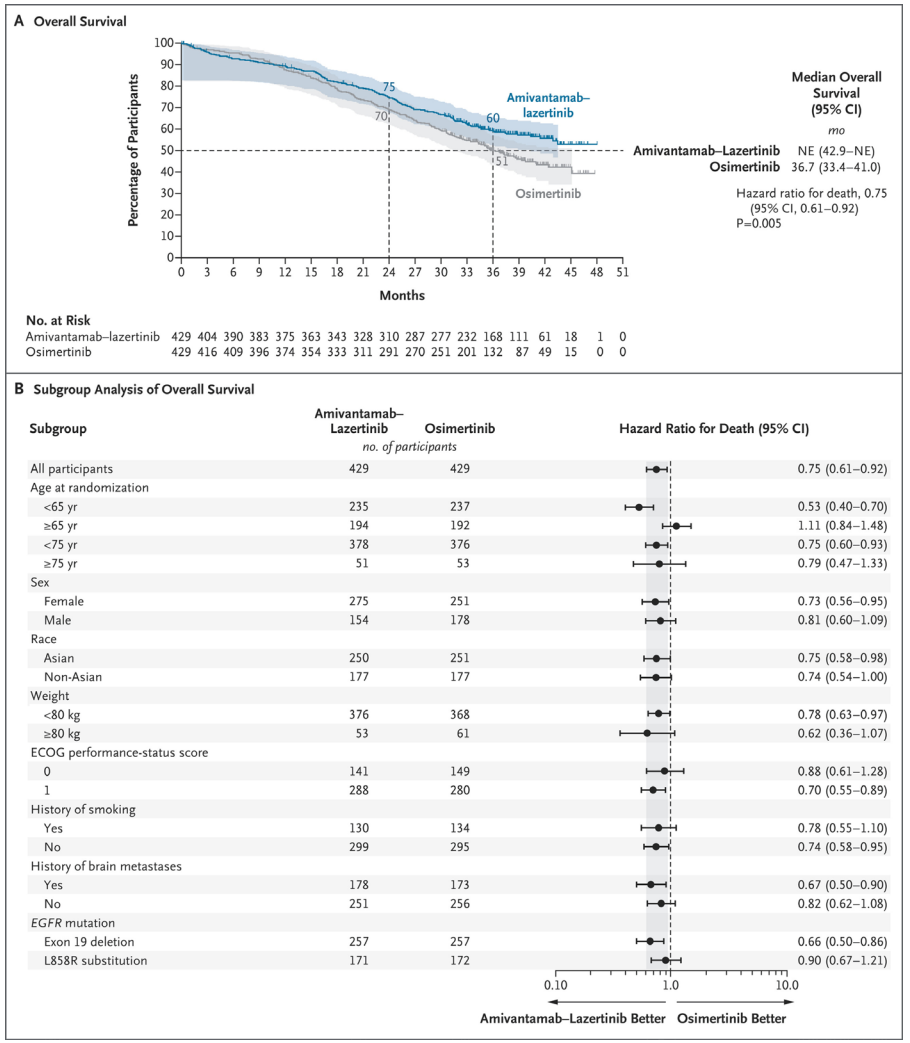


PFS = progression-free survival.

Planchard D, et al. *N Engl J Med*. 2023;389(21):1935-1948.

MARIPOSA: Overall Survival with Amivantamab-Lazertinib in EGFR-Mutated Advanced NSCLC

- Randomized phase III trial
- Amivantamab + Lazertinib (Open-Label) vs Osimertinib (Blinded) vs Lazertinib (Blinded)
- PFS– 23.7 months (Amivantamab + Lazertinib) vs 16.6 months (Osimertinib)
- OS – At 3.5 years, 56% (Amivantamab + Lazertinib) vs 44% (Osimertinib)

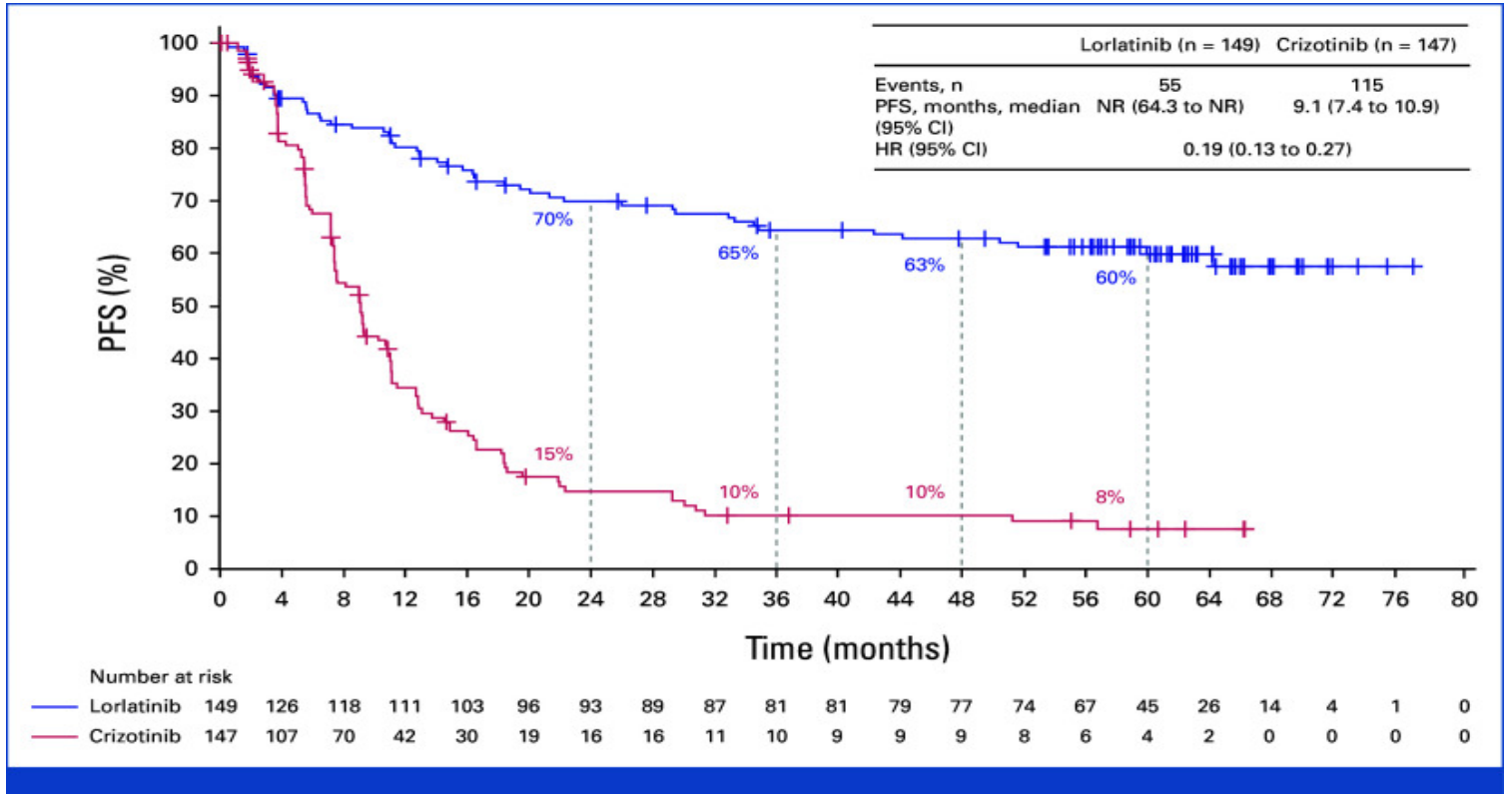


OS = overall survival.

Yang JC, et al. *N Engl J Med*. 2025.

CROWN: Loratinib Versus Crizotinib in Patients with Advanced ALK-Positive Non-Small Cell Lung Cancer

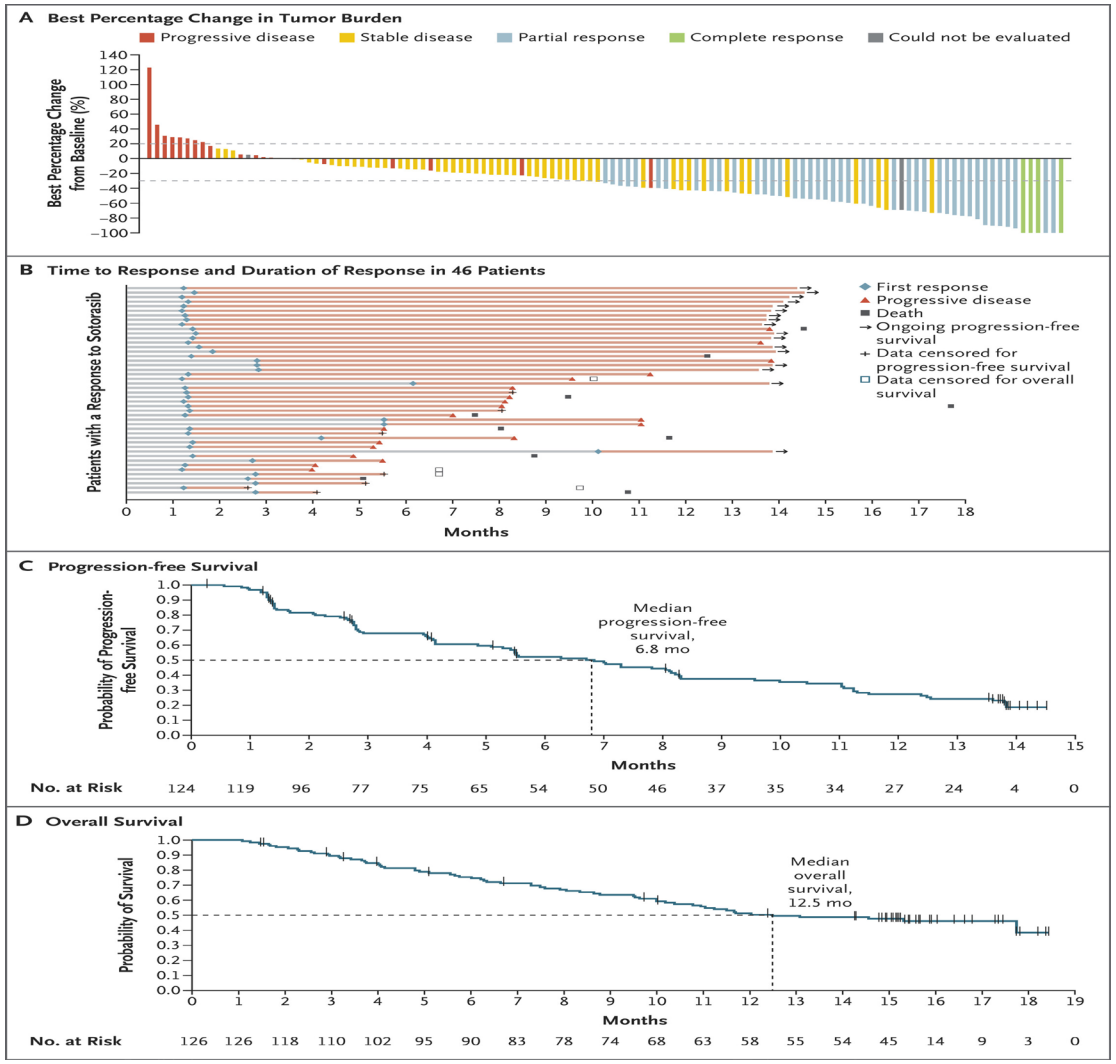
- Randomized Phase III Trial
- Loratinib vs Crizotinib
- PFS at 5 years: 60% Loratinib and 8% Crizotinib



Solomon BJ, et al. *J Clin Oncol*. 2024;42(29):3400-3409.

Sotorasib for Lung Cancers with KRAS p.G12C Mutation

- Single Group, Phase II Trial
- Sotorasib 960mg PO daily
- Primary Endpoint: Objective Response (Complete or Partial Response)
- Secondary Endpoints: Duration of Response, Disease Control, PFS, OS, and Safety



Skoulidis F, et al. *N Engl J Med*. 2021;384(25):2371-2381.

Administration Considerations and Best Practices

- Route of Administration
- Treatment Schedule
- Patient-Centered Approach
- Quality of Life

Adverse Event Management & Mitigation Strategies

PALOMA-3 Trial

Subcutaneous vs Intravenous treatment with Amivantamab

- Fewer patients in the subcutaneous group experienced IRR and venous thromboembolism
- Increased convenience

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

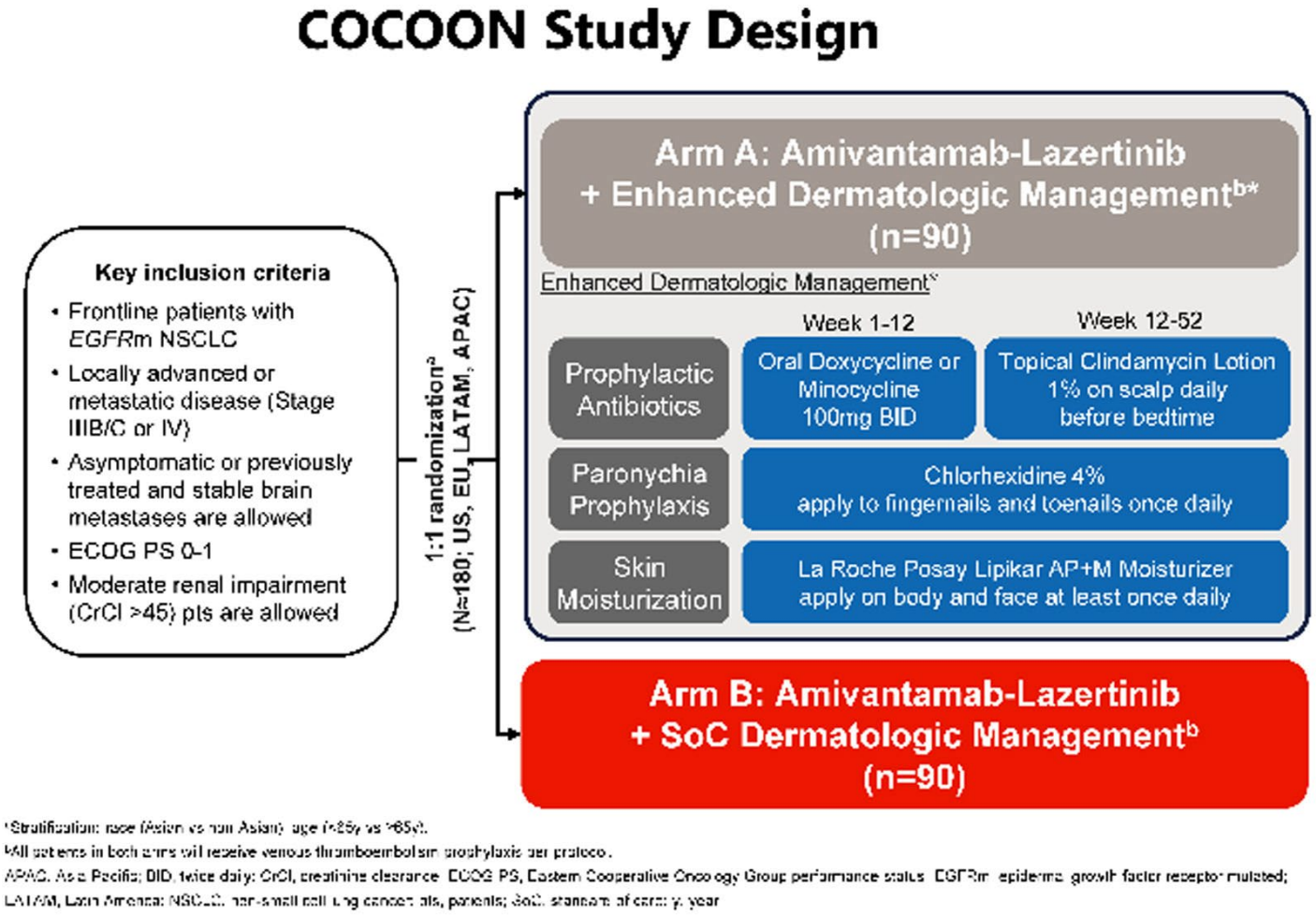
Cho BC, et al. *J Thorac Oncol*. 2025;20(10):1517-1530. Spira AI, et al. *J Thorac Oncol*. 2025;20(6):809-816.

Adverse Event Management & Mitigation Strategies

COCOON Trial

Assess prophylactic management of cutaneous toxicities

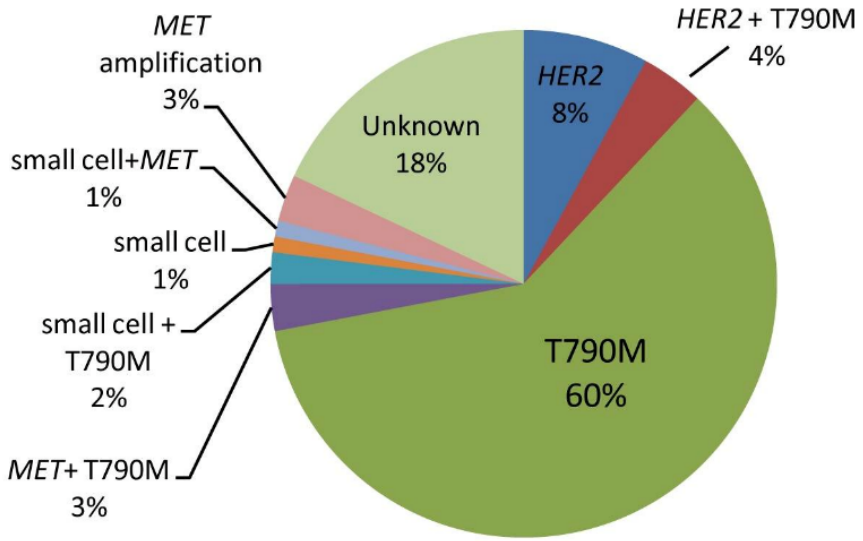
- Primary endpoint was grade 2 or higher dermatologic adverse events of interest by 12 weeks
- COCOON Dermatologic management showed a reduction in the incidence of dermatologic adverse events with amivantamab-lazertinib treatment

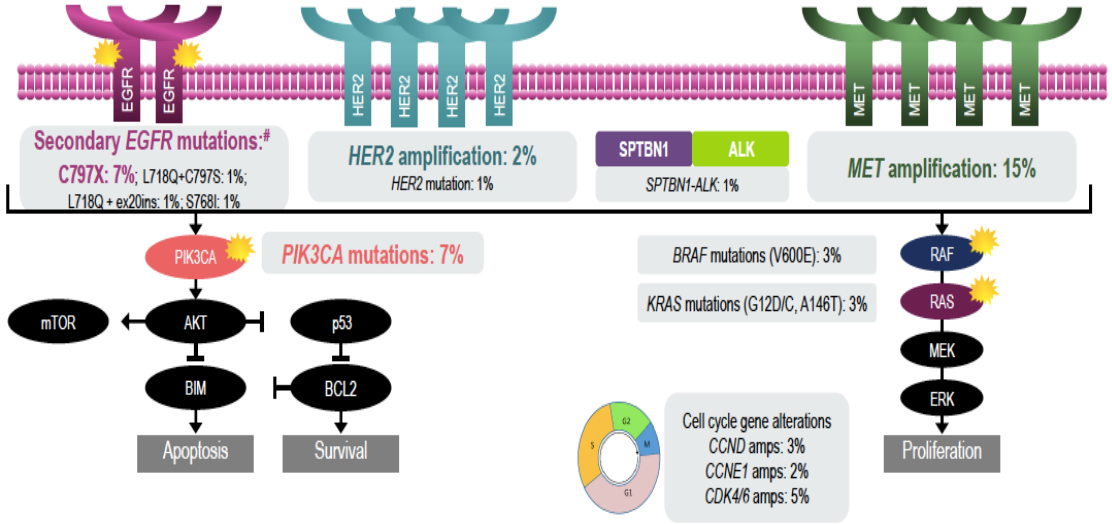


Cho BC, et al. *J Thorac Oncol*. 2025;20(10):1517-1530.

EGFR Post-Progression

Resistance to targeted therapy inevitable & resistance mechanisms more challenging with next generation drugs





Dominant mechanism of resistance for 1st generation EGFR TKIs erlotinib or gefitinib

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

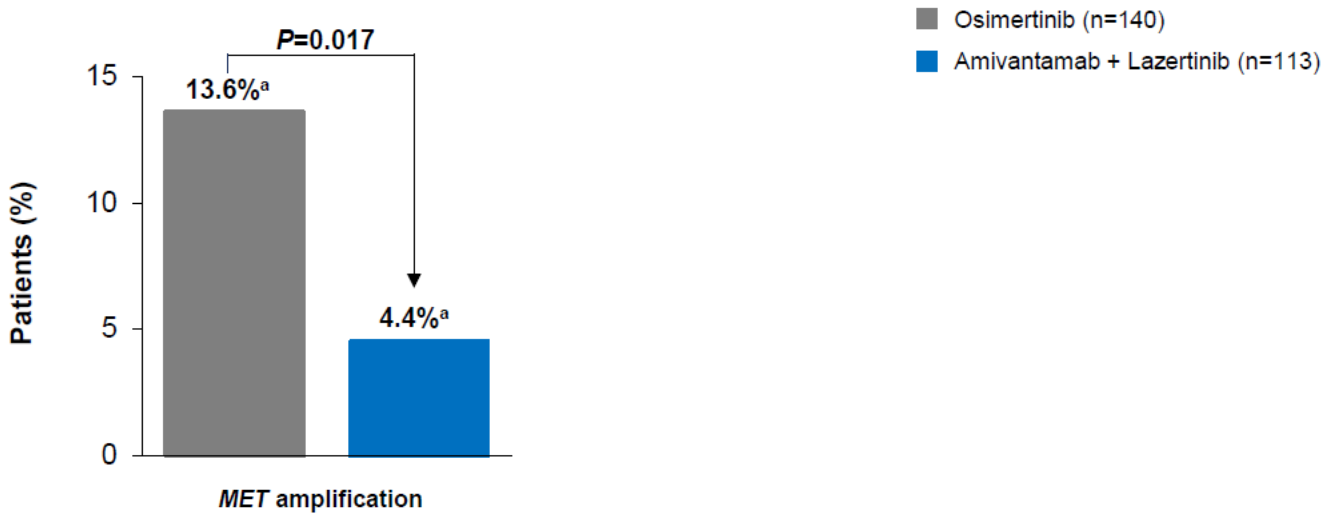
Yu H, et al. *Clin Cancer Res*. 2013;19(8):2240-2247. Ramalingam SS, et al. Presented at: ESMO Congress 2018; Munich, Germany; October 19-23, 2018.

Mechanisms of Resistance to MARIPOSA

MET and *EGFR*-based Resistance Mechanisms

MARIPOSA
Ami + Laz in 1L *EGFR*+ NSCLC

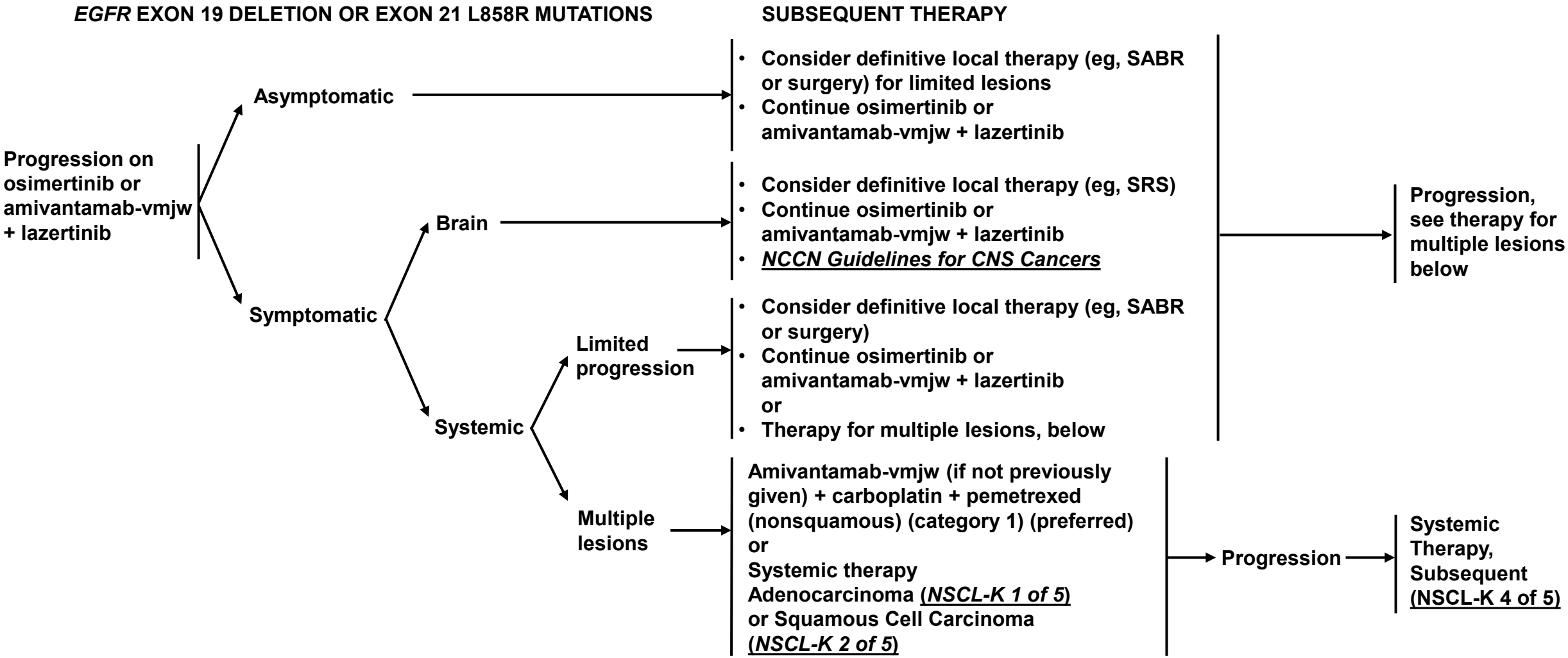
Amivantamab + lazertinib significantly reduced the incidence of acquired MET amplifications and EGFR resistance mutations vs osimertinib



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

Passaro A. Presented at: ESMO Congress 2024; September 13-17, 2024; Barcelona, Spain. Passaro A, et al. *Ann Oncol*. 2024;35(1):77-90.

NCCN Guidelines: EGFR Post Progression



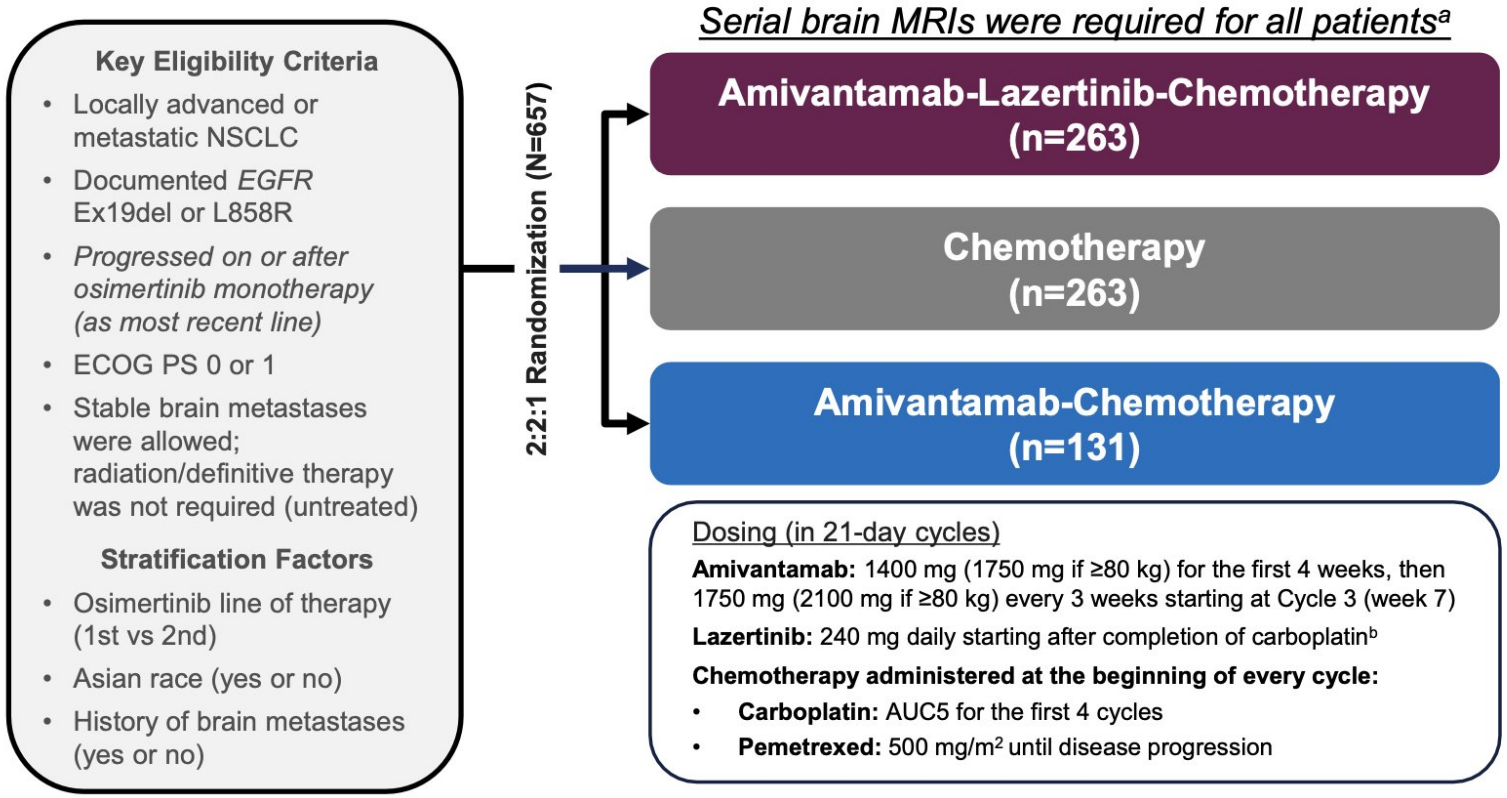
SABR = stereotactic ablative body radiotherapy; SRS = stereotactic radiosurgery.

Treatment Options Post Progression

- Chemotherapy-based options
  - Carboplatin-pemetrexed-amivantanab (MARIPOSA-2)
  - Carboplatin-pemetrexed +/- Osimertinib (COMPEL)
- MET-targeted options
  - Amivantanab + Lazertinib (CHRYSALIS-2)
  - Savolitinib + Osimertinib (SAVANNAH)
- ADCs
  - Datopotamab-deruxtecan (TROPION-Lung01/Lung05)- newly FDA approved

ADC = antibody–drug conjugate.

MARIPOSA-2



Dual primary endpoint of PFS[c] by BICR per RECIST v1.1:

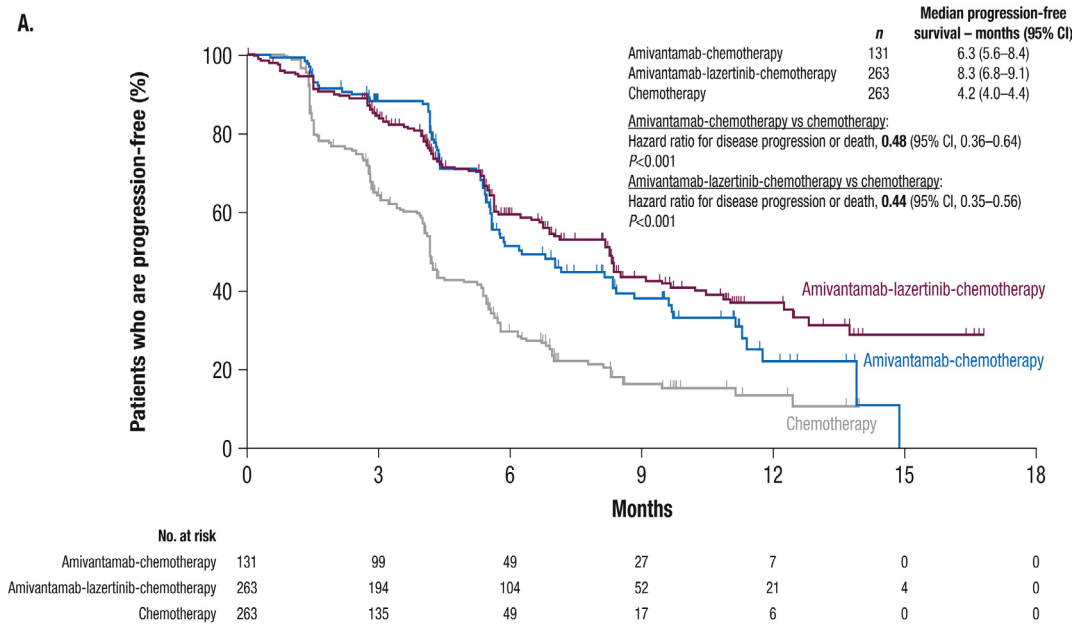
- **Amivantamab-Lazertinib-Chemotherapy** vs **Chemotherapy**
- **Amivantamab-Chemotherapy** vs **Chemotherapy**

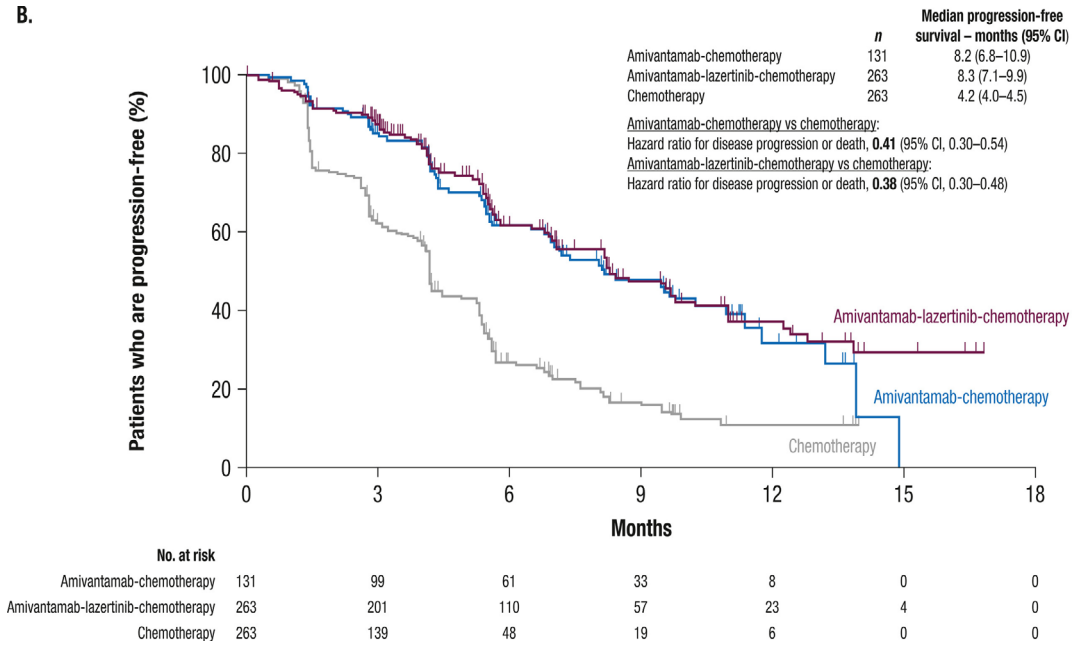
Secondary endpoints:

- 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;35(1):77-90.

MARIPOSA-2 Results





Passaro A, et al. *Ann Oncol*. 2024;35(1):77-90.

MARIPOSA-2: 2nd Interim OS

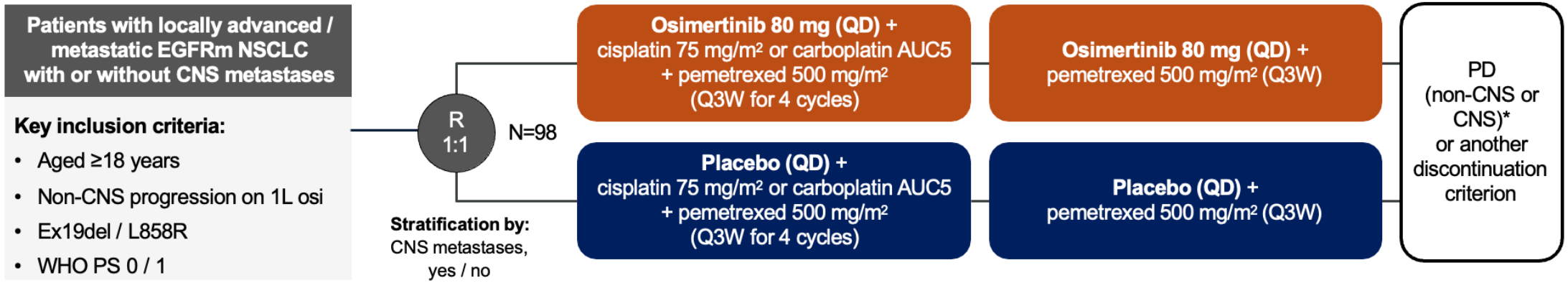
Table: LBA54 Efficacy outcomes

Endpoint	Ami-chemo (n = 131)	Chemo (n = 263)
Median follow-up, mo	18.6	17.8
OS events, n (%)	65 (50)	143 (54)
Median OS, mo (95% CI)	17.7 (16.0–22.4)	15.3 (13.7–16.8)
HR for OS (95% CI)	0.73 (0.54–0.99); *P*=0.039	
18-mo OS rate, % (95% CI)	50 (40–59)	40 (33–46)
Median TTD, mo (95% CI)	10.4 (7.9–11.6)	4.5 (4.2–5.0)
HR for TTD (95% CI)	0.42 (0.33–0.53); *P*<0.0001	
Median TTST, mo (95% CI)	12.2 (10.7–14.3)	6.6 (6.1–7.4)
HR for TTST (95% CI)	0.51 (0.39–0.65); *P*<0.0001	
Median PFS2, mo (95% CI)	16.0 (13.9–17.6)	11.6 (10.1–13.0)
HR for PFS2 (95% CI)	0.64 (0.48–0.85); *P*=0.002	

Popat S, et al. Abstract LBA54. Presented at: ESMO 2024; September 13-17, 2024; Barcelona, Spain.

COMPEL Study

COMPEL: Global, randomised, phase III double-blind study



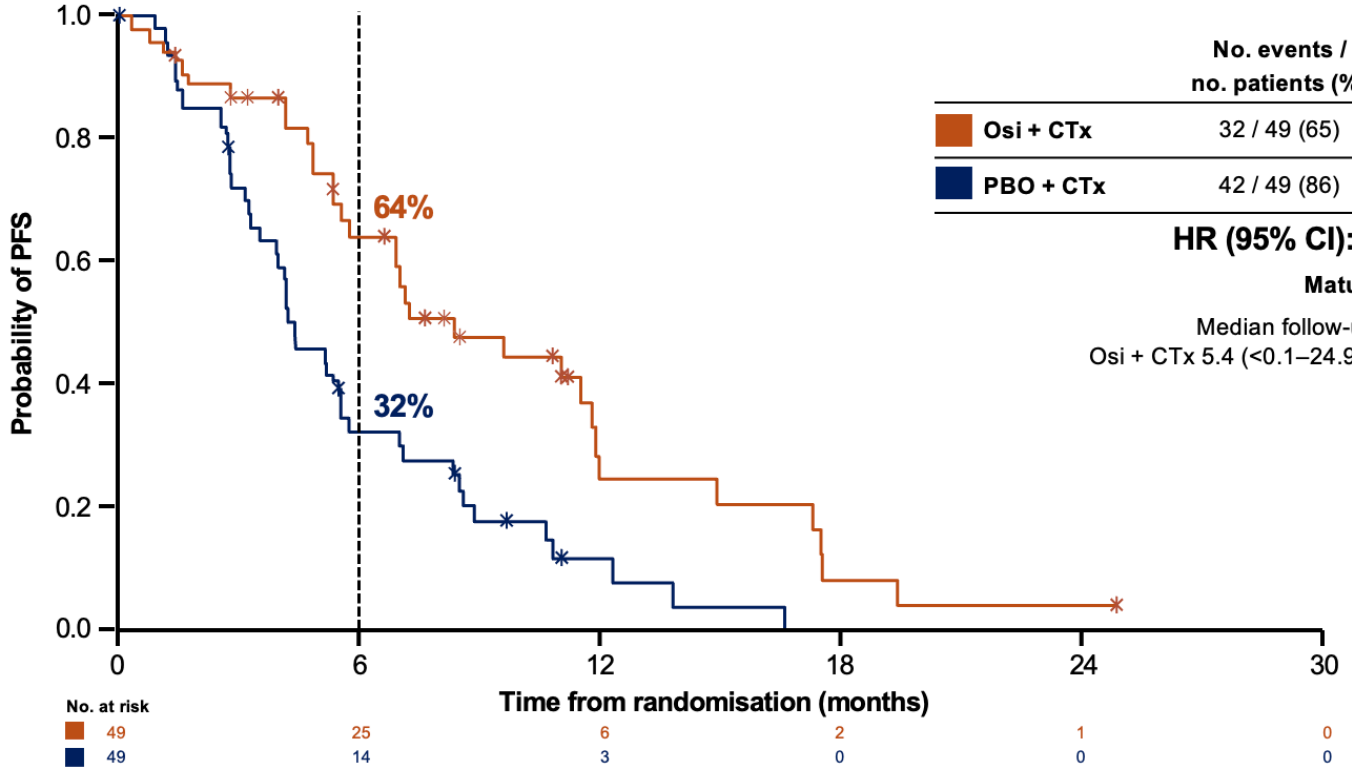
- **Primary endpoint: PFS (investigator-assessed)**
- Secondary endpoints: CNS PFS (according to CNS metastases status at baseline), non-CNS PFS, and OS

PD = progressive disease.

Pasello G, et al. Abstract 1174. Presented at: 2025 International Association for the Study of Lung Cancer 2025 World Conference on Lung Cancer; September 6-9, 2025; Barcelona, Spain.

COMPEL: Results

Primary analysis: Progression-free survival (PFS)*



	No. events / no. patients (%)	Median PFS, months (95% CI)
Osi + CTx	32 / 49 (65)	8.4 (5.7, 11.8)
PBO + CTx	42 / 49 (86)	4.4 (3.5, 5.6)

HR (95% CI): 0.43 (0.27, 0.70)

Maturity: 76%

Median follow-up,† months (range):
Osi + CTx 5.4 (<0.1–24.9); PBO + CTx 5.5 (<0.1–11.1)

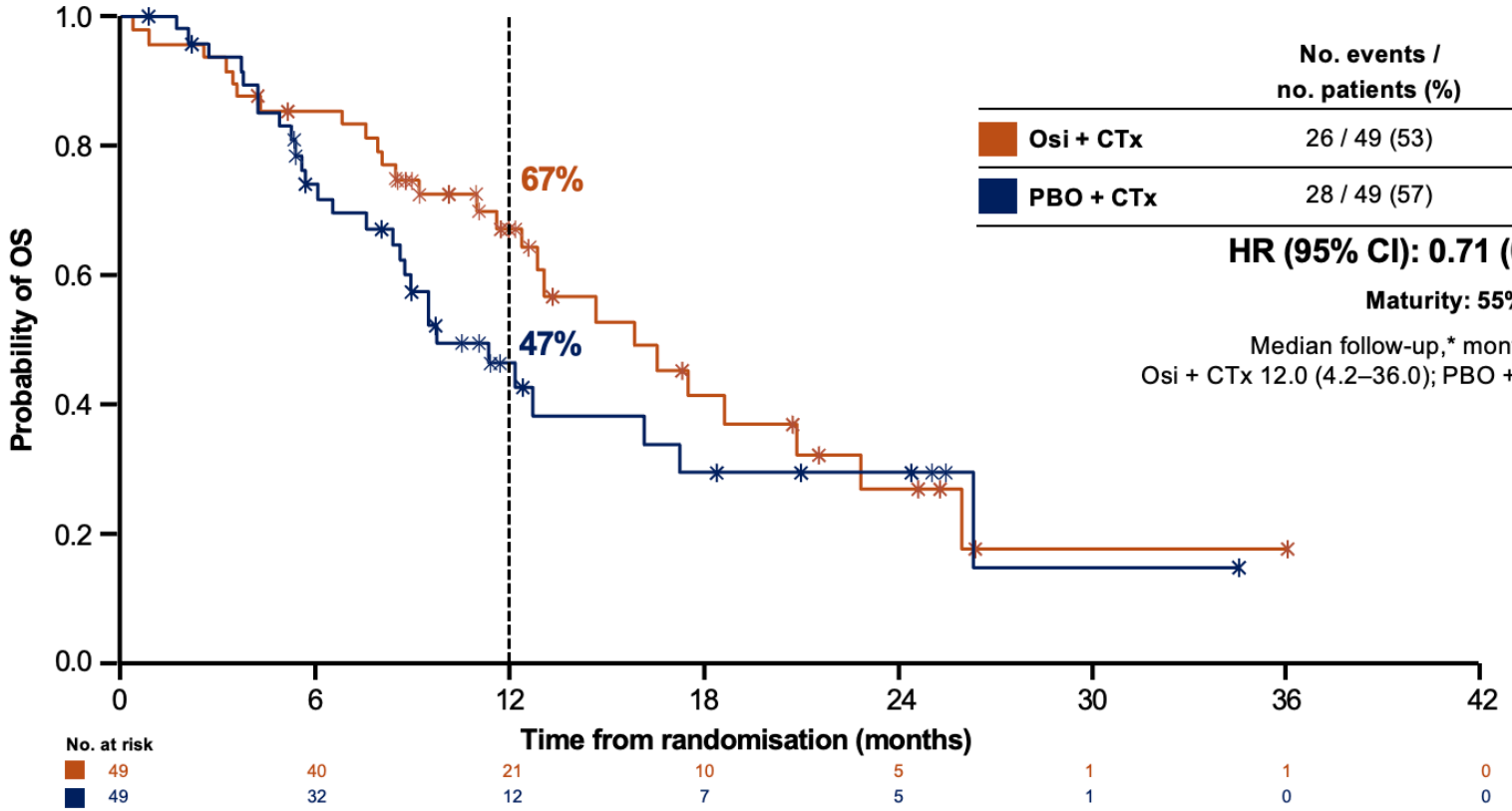
Osi + CTx was associated with improved PFS versus PBO + CTx

CTx = chemotherapy; PBO = placebo.

Pasello G, et al. Abstract 1174. Presented at: 2025 International Association for the Study of Lung Cancer 2025 World Conference on Lung Cancer; September 6-9, 2025; Barcelona, Spain.

COMPEL: Results

Overall survival (OS)



	No. events / no. patients (%)	Median OS, months (95% CI)
Osi + CTx	26 / 49 (53)	15.9 (12.4, 20.8)
PBO + CTx	28 / 49 (57)	9.8 (8.4, 17.2)

HR (95% CI): 0.71 (0.42, 1.23)

Maturity: 55%

Median follow-up,* months (range):
Osi + CTx 12.0 (4.2–36.0); PBO + CTx 11.1 (0.8–34.5)

OS was longer with osi + CTx versus PBO + CTx

Pasello G, et al. Abstract 1174. Presented at: 2025 International Association for the Study of Lung Cancer 2025 World Conference on Lung Cancer; September 6-9, 2025; Barcelona, Spain.

CHRYSALIS-2

Amivantamab and lazertinib in patients with *EGFR*-mutant non-small cell lung cancer (NSCLC) after progression on osimertinib and platinum-based chemotherapy: results from CHRYSALIS-2 Cohort A

Journal of Thoracic Oncology

Background

Population: Patients with NSCLC and *EGFR* **Exon 19 deletions** or **Exon 21 L858R** mutations whose disease **progressed on or after osimertinib and platinum-based chemotherapy**

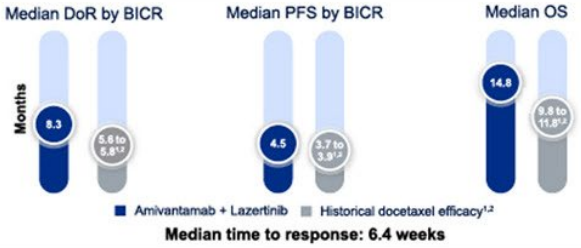
Poor clinical outcomes on SoC treatment (docetaxel)[1,2]

Study Population

CHRYSALIS-2 Cohort A (n=162): Treatment with amivantamab + lazertinib

Median age: **61.5** years	Race: **62%** Asian
Sex: **65%** female	Median: **3** prior lines of therapy

Results



Median time to response: 6.4 weeks

Antitumor response was consistent across prespecified subpopulations, with relatively similar ORRs by BICR regardless of prior therapy subgroup

Safety

	Overall	Grade ≥3
Rash (grouped term*)	81%	10%
IRR	68%	9%
Paronychia	52%	5%
Hypoalbuminemia	47%	10%
VTE (grouped term†) no prophylactic anticoagulation	19%	2%

Safety profile of amivantamab + lazertinib was **consistent with previous reports**, with many of the frequently reported AEs associated with inhibition of EGFR or MET and **mostly grade 1-2.** **11 (7%) patients discontinued amivantamab + lazertinib due to treatment-related AEs**

CONCLUSION: In the CHRYSALIS-2 (NCT04077463) study, amivantamab + lazertinib in a post–EGFR TKI and platinum-based chemotherapy setting demonstrated clinically significant and durable antitumor activity with a safety profile consistent with prior studies

IASLC

*Includes dermatitis, dermatitis acneiform, acne, erythema, folliculitis, rash, rash maculo-papular, rash pustular, rash erythematous, rash macular, rash papular, rash pruritic, skin exfoliation, skin lesion, pustule, and papule. †Includes pulmonary embolism and deep vein thrombosis.

AE, adverse event; BICR, blinded independent central review; DoR, duration of response; EGFR, epidermal growth factor receptor; INV, investigator; IRR, infusion-related reaction; MET, mesenchymal epithelial transition; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SoC, standard-of-care; TKI, tyrosine kinase inhibitor; VTE, venous thromboembolism.

1. Paz-Ares LG, Juan-Vidal O, Mountzios GS, et al. Sacituzumab govitecan versus docetaxel for previously treated advanced or metastatic non–small cell lung cancer: the randomized, open-label phase III EVOKE-01 study. *J Clin Oncol*. 2024;42(24):2860-2872. doi:10.1200/JCO.24.00733.
2. Ahn MJ, Tanaka K, Paz-Ares L, et al. Datopotamab deruxtecan versus docetaxel for previously treated advanced or metastatic non–small cell lung cancer: the randomized, open-label phase III TROPION-Lung01 study. *J Clin Oncol*. 2024; doi:10.1200/JCO-24-01544.

Besse et al. *J Thorac Onc* (2025)

SoC = standard of care.

Besse B, et al. *J Thorac Oncol*. 2025;20(5):651-664.

EGFR sensitizing mutations: Post Osimertinib with MET expression

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

MET IHC3+/≥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+/≥90%) or amplification (FISH10+)
- ECOG PS 0 / 1
- Stable CNS metastases permitted†

Treatment continued until PD, or another discontinuation criterion was met

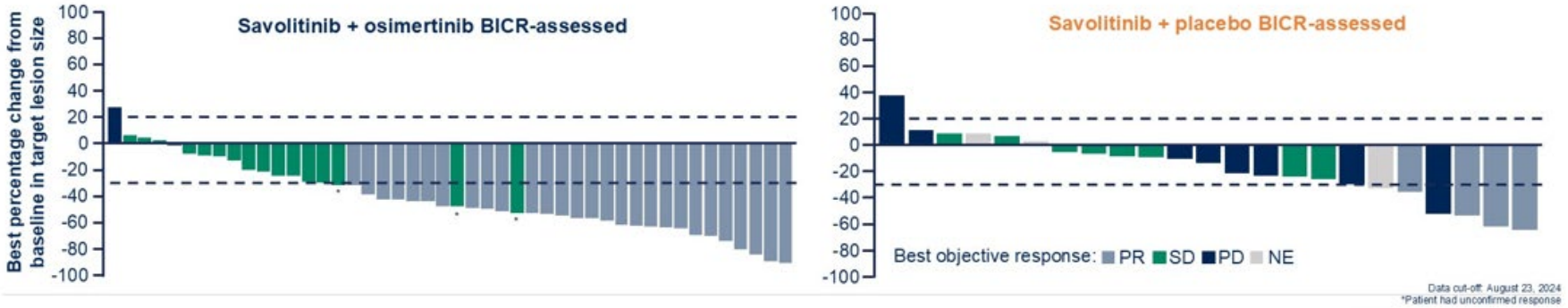
Patients could crossover to open-label savolitinib + osimertinib upon investigator-assessed PD

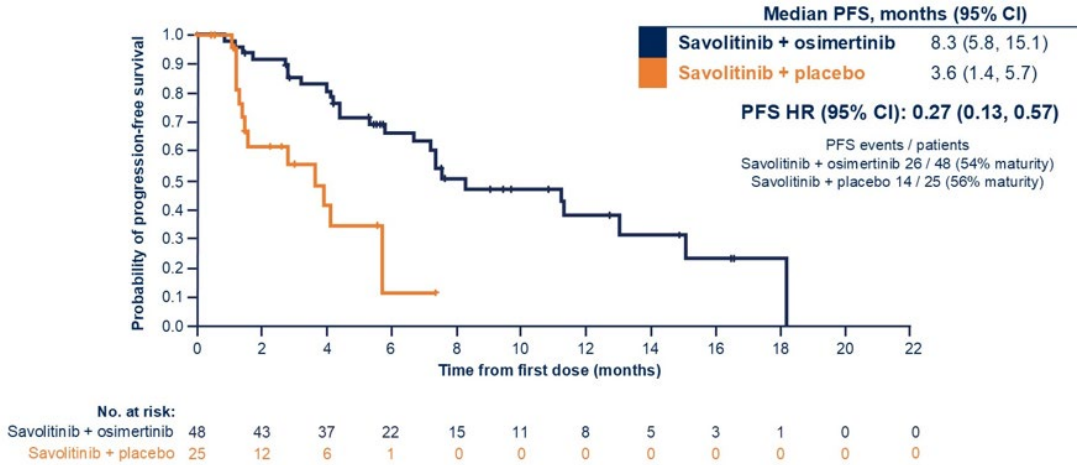
IHC3+ = immunohistochemistry score 3+; FISH10+ = fluorescence in situ hybridization with ≥10% positive cells.

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)

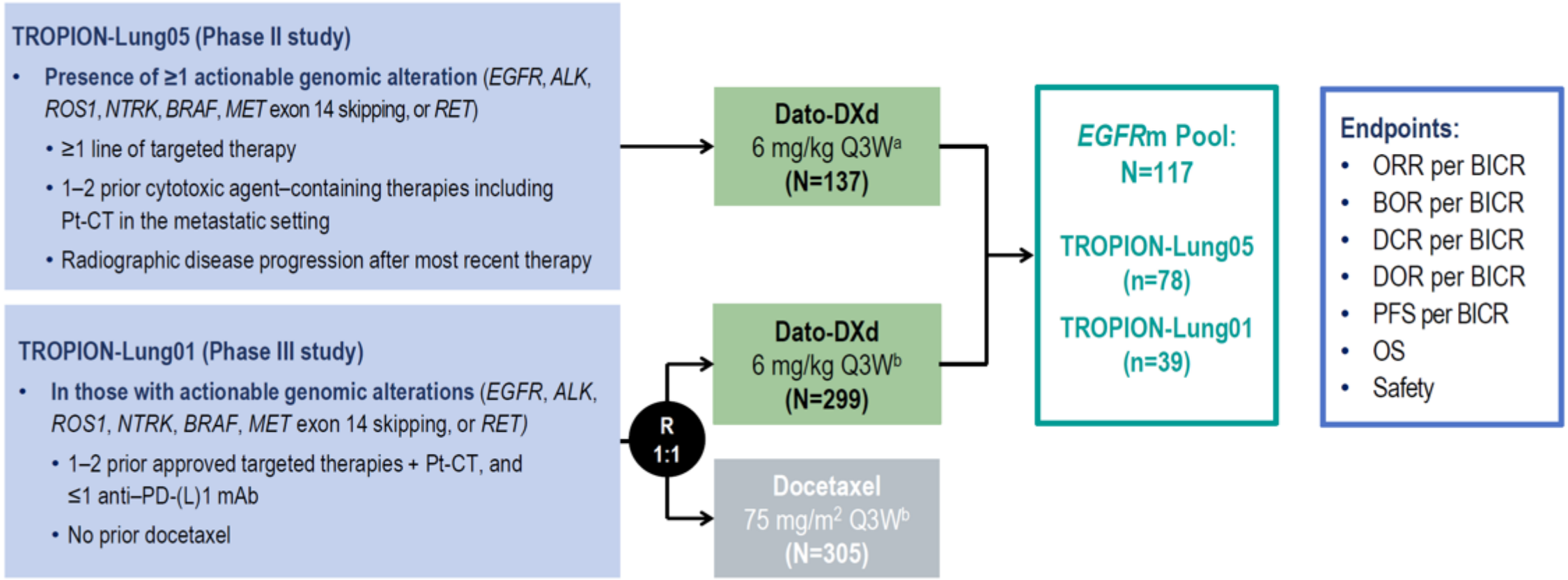




	Savolitinib + osimertinib (n=14)	Savolitinib + placebo (n=4)
CNS best objective response, n (%)		
Response	**6 (43)**	**1 (25)**
Complete response	2 (14)	0
Partial response	4 (29)	1 (25)
Non-response	**8 (57)**	**3 (75)**
Stable disease	7 (50)	1 (25)
Progressive disease	1 (7)	1 (25)
Not evaluable	0	1 (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)

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.

TROPION-LUNG1/LUNG5 Pooled Analysis



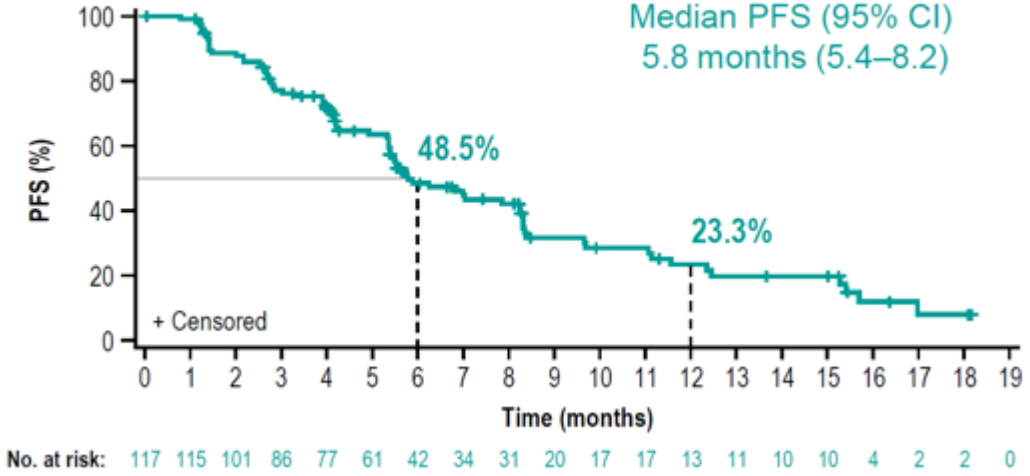
Myung-Ju Ahn, et al. Presented at: ESMO Asia 2024; December 6-8, 2024; Singapore.

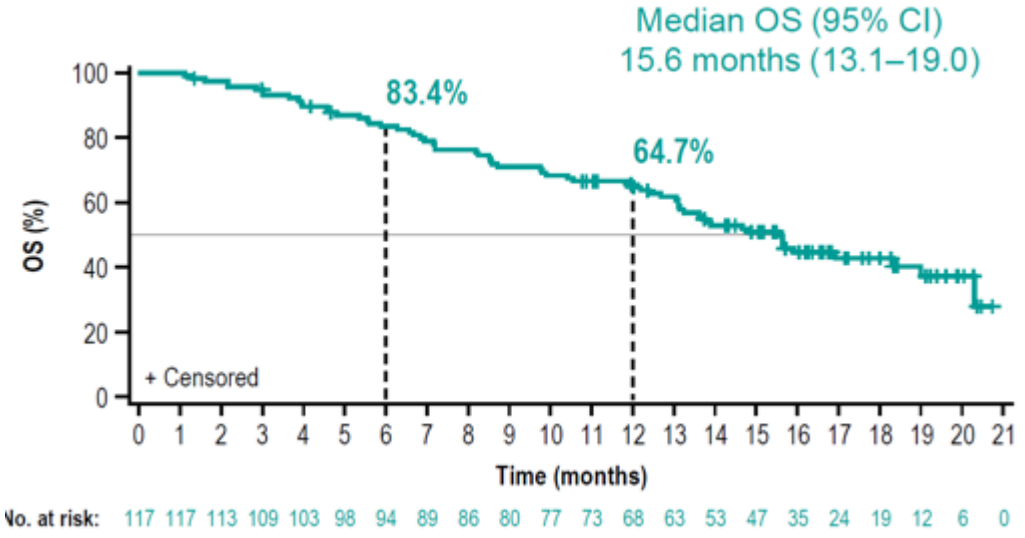
TROPION-LUNG1/LUNG5: Results

Response	*EGFR*m Pool (N=117)	Prior Osimertinib (N=96)
Confirmed ORR,[a] n (%) [95% CI]	50 (**42.7**) [33.6–52.2]	43 (**44.8**) [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 (%) [95% CI]	101 (**86.3**) [78.7–92.0]	82 (**85.4**) [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)

June 2025: FDA accelerated approval of Dato-DXd for EGFR+ NSCLC after prior EGFR directed therapy and platinum-based chemotherapy

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





Myung-Ju Ahn, et al. Presented at: ESMO Asia 2024; December 6-8, 2024; Singapore.

Key Take-Aways

- Resistance to targeted therapy is inevitable
- Consider repeat biopsy at time of disease progression to evaluate for histologic transformation and resistance pathways
- 2nd line options vary depending upon what was administered 1st line
- Dato-DXd is newly FDA approved for EGFR+ patients who have already received EGFR-directed therapy and platinum-based chemotherapy
- Recent and ongoing data of treatment strategies post-osi

Key Take-Aways: EGFR+ Post-progression Treatment Recommendations

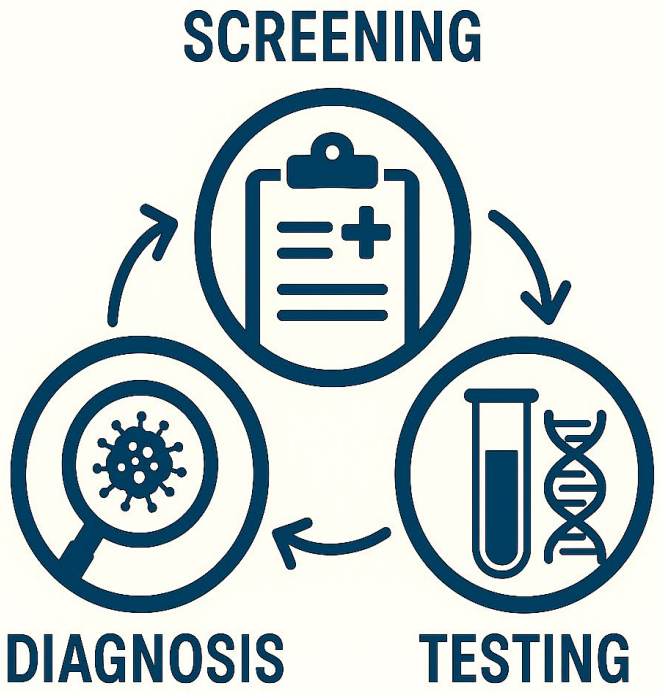
- Osimertinib monotherapy (FLAURA)
  - Amivantanab + chemotherapy
- Osimertinib + chemotherapy (FLAURA2)
  - Dato-DXd or Amivantanab + Lazertinib
- Amivantanab + Lazertinib (MARIPOSA)
  - Chemo + osi

Understanding the Role of APs in NSCLC Care

-Screening, Diagnosis, and Biomarker Testing
-Interdisciplinary Care and Coordination
-Managing Treatment-Related AEs
-Patient and Caregiver Education

AP = advanced practitioner; AE = adverse event.

Screening, Diagnosis, and Biomarker Testing



Screening

- Collecting a thorough history to recognize high-risk individuals
- Low dose CT

Diagnosis

- Coordinate initial biopsy and screening imaging

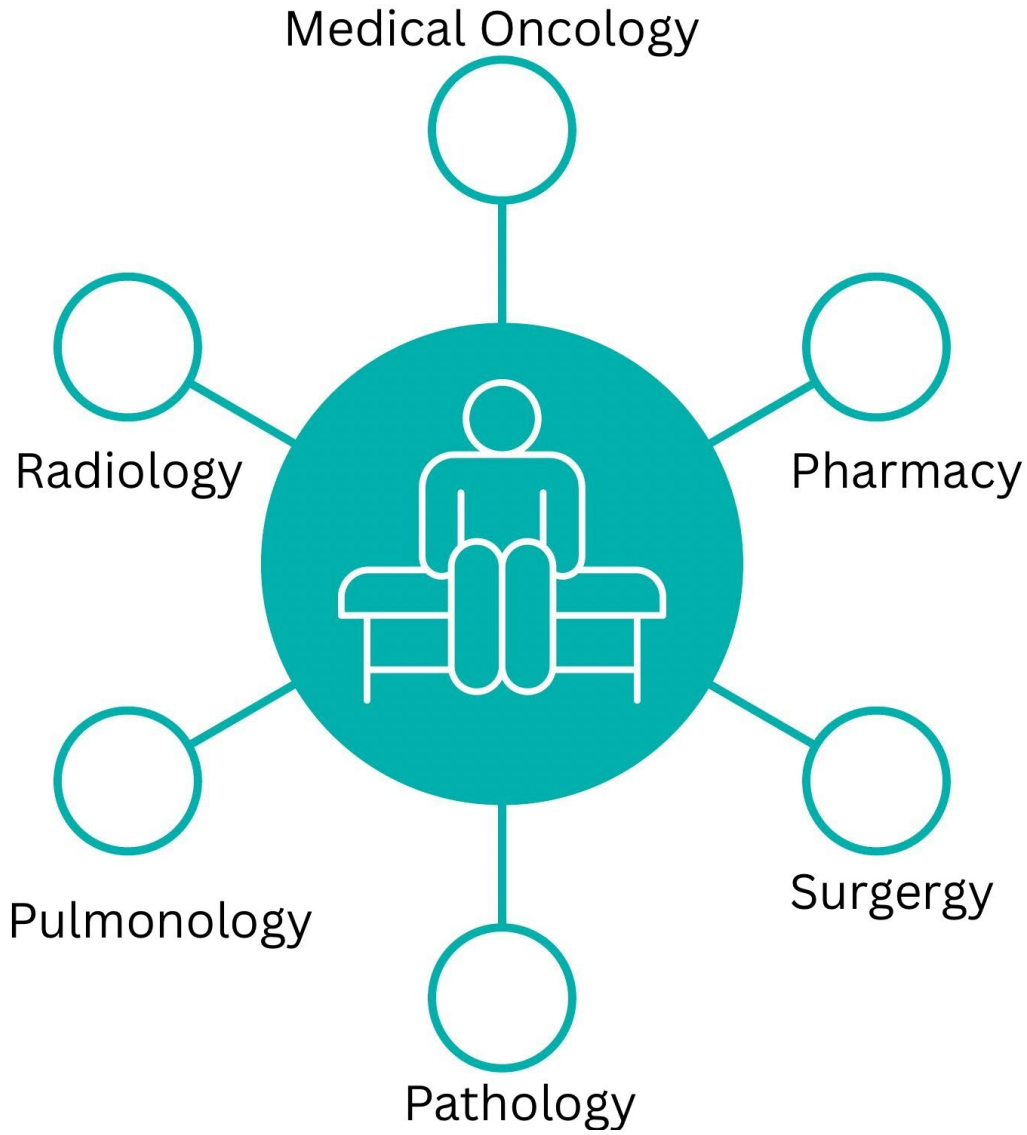
Biomarker Testing

- Ordering and Interpreting Tests

CT = computed tomography.

Interdisciplinary Care and Coordination

- Bridge Between Disciplines
- Navigation
- Identifying gaps in care coordination



Managing Treatment-Related AEs

Education

- Detailed baseline assessment

Identification

- Educating patients on the onset time of adverse events

Managing

- Providing patients with supportive medication prior to starting treatment

Patient and Caregiver Education

Treatment Expectations & Adherence Strategies

- Set realistic goals for the intent of treatment
- Treatment plan timeline
- Monitoring
- Include caregivers

Patient and Caregiver Education

Lifestyle Modifications

- Adhering to Best Practices
- Quality of Life
- Coping Strategies
- Financial Burden

Key Take-Aways

- Importance of Molecular and Biomarker Testing
- Targeted therapies have transformed NSCLC Care
- Multidisciplinary Collaboration
- Patient-Centered Education Improves Outcomes

Thank You