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

Disclosures

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration)

- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity

- This activity has been independently reviewed for balance

- This CME activity includes brand names for participant clarity purposes only. No product promotion or recommendation should be inferred

- NCCN makes no warranties of any kind whatsoever regarding their content, use, or application, and disclaims any responsibility for their application or use in any way
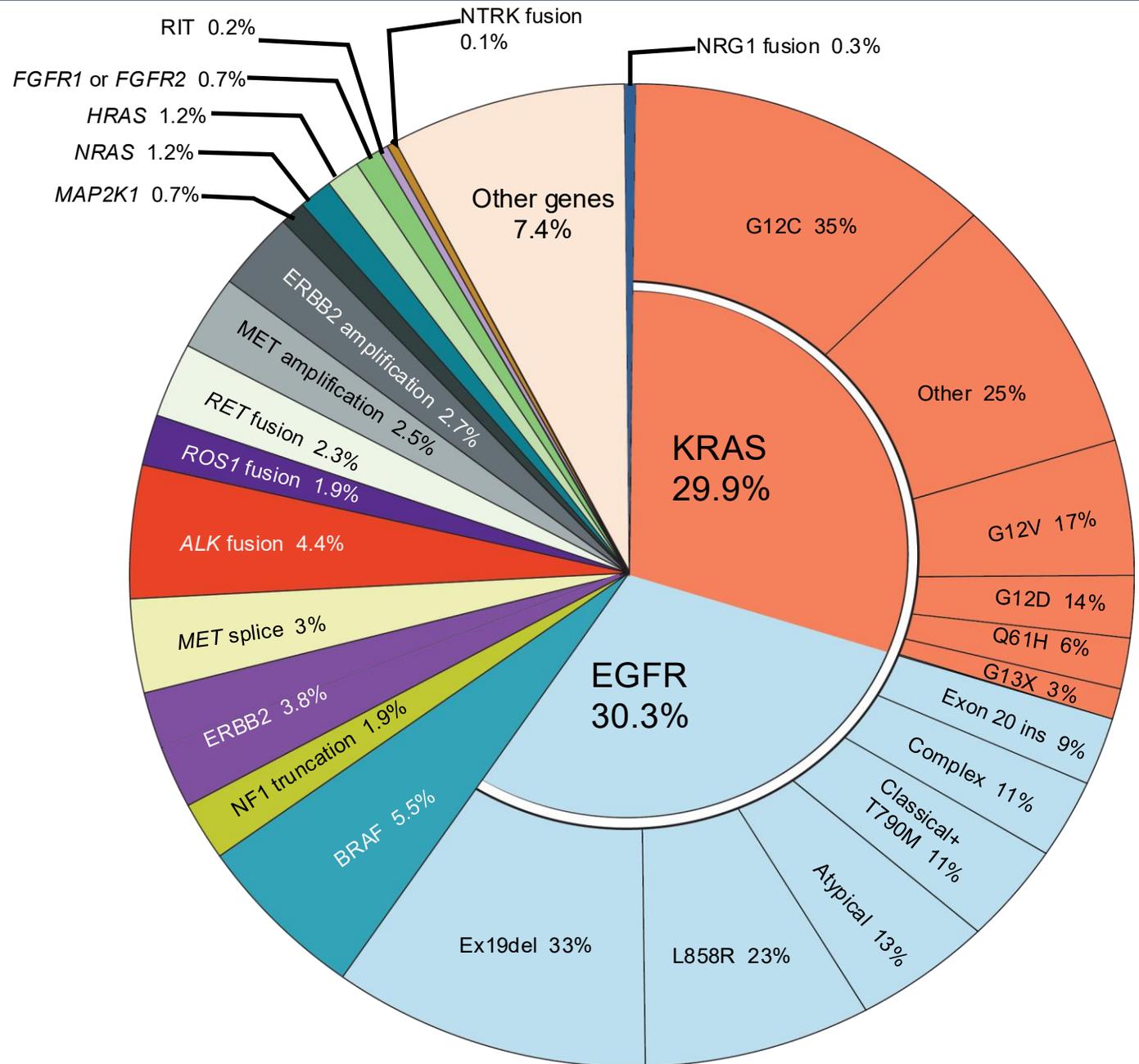
Program Information

- Provided by HMP Education, LLC, an HMP Global Company

- Supported in part by an educational grant from Johnson & Johnson.

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- <u>RESISTANCE IS INEVITABLE</u>

- 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 <u>non-squamous</u> 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

	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Osimertinib	279	18.9 (15.2–21.4)
Standard EGFR-TKI	277	10.2 (9.6–11.1)

Hazard ratio for disease progression or death, 0.46 (95% CI, 0.37–0.57)
P<0.001
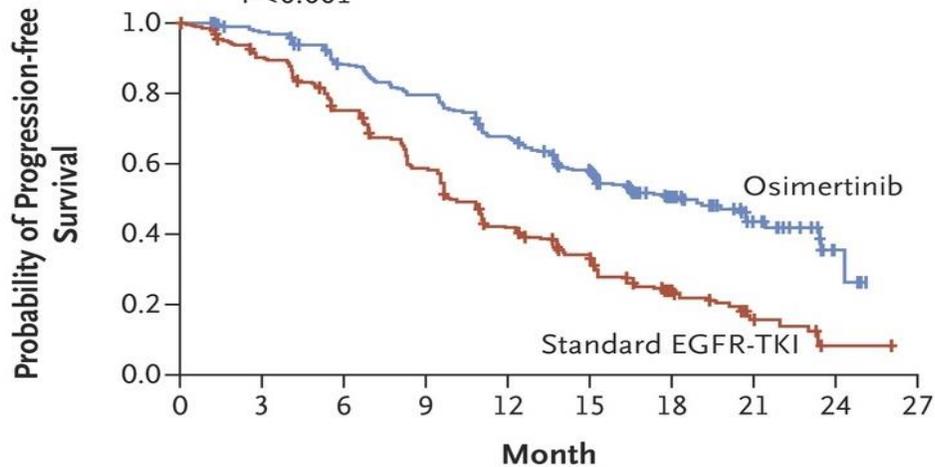
No. at Risk
Osimertinib	279	262	233	210	178	139	71	26	4	0
Standard EGFR-TKI	277	239	197	152	107	78	37	10	2	0

OS

HR, 0.80 (95% CI, 0.64-1.00)
P= .046

	Median Overall Survival (95% CI)
	mo
Osimertinib	38.6 (34.5–41.8)
Comparator EGFR-TKI	31.8 (26.6–36.0)

31% crossover rate
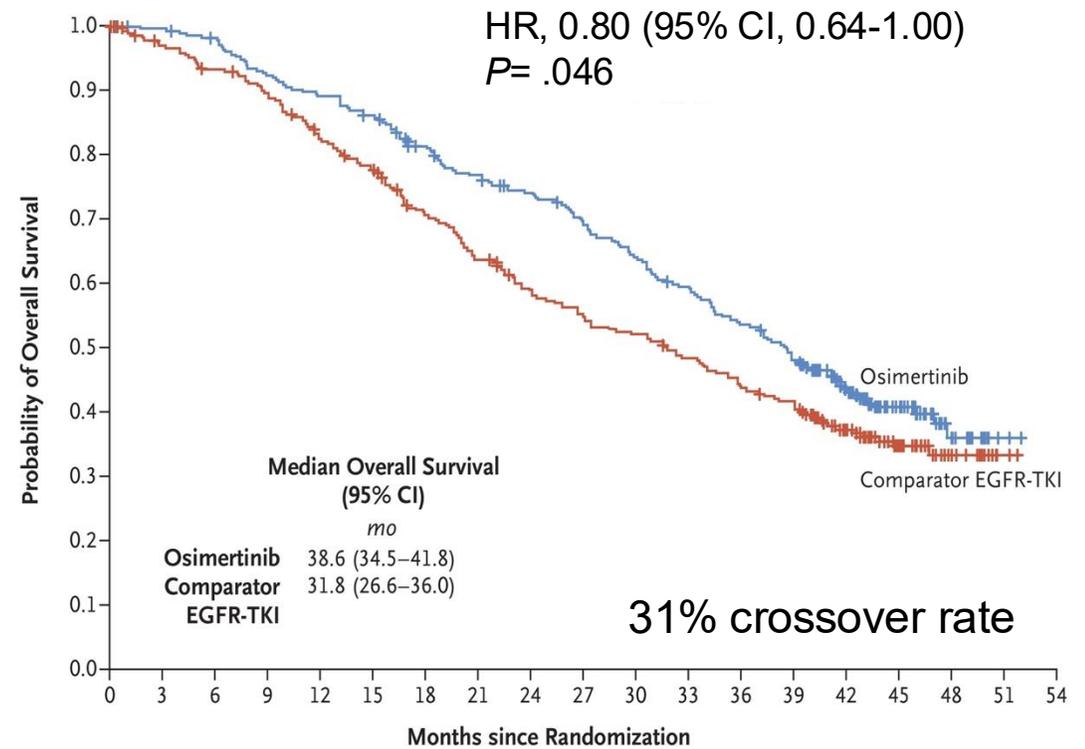
No. at Risk
Osimertinib	279	276	270	254	245	236	217	204	193	180	166	153	138	123	86	50	17	2	0
Comparator EGFR-TKI	277	263	252	239	219	205	182	165	148	138	131	121	110	101	72	40	17	2	0

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

Key eligibility
- Untreated locally advanced/metastatic *EGFR*m NSCLC
- EX 19del/L858R
- ≥18 years (Japan ≥20 years)
- Pathologically confirmed non-squamous NSCLC
- WHO PS 0/1
- No prior systemic therapy for advanced NSCLCS
- Patients with asymptomatic/stable CNS mets allowed

R 1:1

N=557

Osimertinib 80 mg QD+ chemo
(Q3W cycles, followed by maintenance osimertinib 80 mg QD + pemetrexed Q3W)
(n=279)

Osimertinib 80 mg QD (n=278)

Primary endpoint:
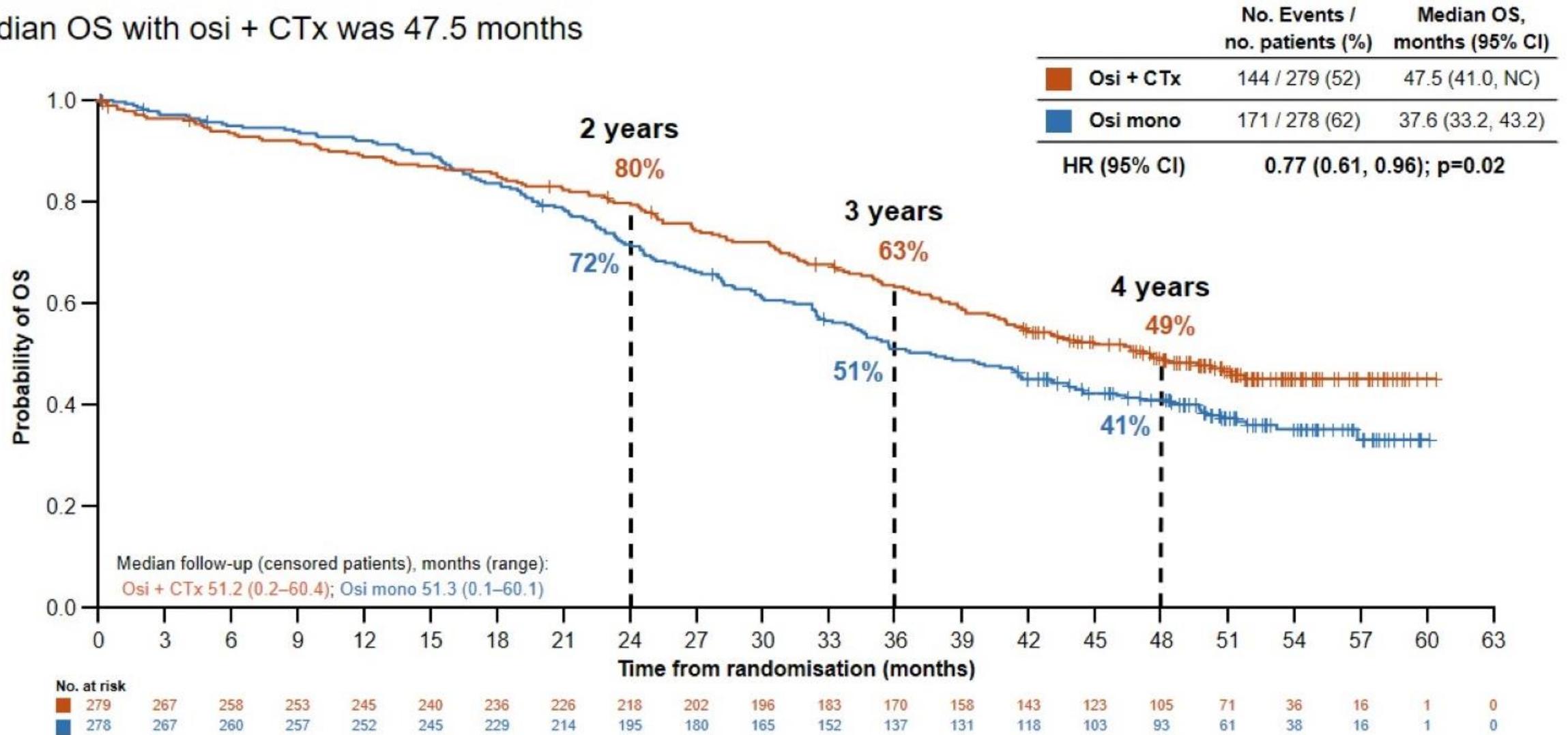- PFS by RECIST 1.1

Secondary endpoints:
- OS, ORR, DOR, DCR, HRQoL, safety, PFS2

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

	No. Events / no. patients (%)	Median OS, months (95% CI)
Osi + CTx	144 / 279 (52)	47.5 (41.0, NC)
Osi mono	171 / 278 (62)	37.6 (33.2, 43.2)
HR (95% CI)	0.77 (0.61, 0.96); p=0.02	

2 years — 80% / 72%
3 years — 63% / 51%
4 years — 49% / 41%

Median follow-up (censored patients), months (range):
Osi + CTx 51.2 (0.2–60.4); Osi mono 51.3 (0.1–60.1)

Probability of OS — Time from randomisation (months)

No. at risk

| 279 | 267 | 258 | 253 | 245 | 240 | 236 | 226 | 218 | 202 | 196 | 183 | 170 | 158 | 143 | 123 | 105 | 71 | 36 | 16 | 1 | 0 |
| 278 | 267 | 260 | 257 | 252 | 245 | 229 | 214 | 195 | 180 | 165 | 152 | 137 | 131 | 118 | 103 | 93 | 61 | 38 | 16 | 1 | 0 |

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

Most common AEs*

Patients with AE (%)

Osi + CTx
- Grade 1 / 2
- Grade 3
- Grade 4

Osi mono
- Grade 1 / 2
- Grade 3

Planchard D, et al. WCLC 2025. Abstract PL02.04.
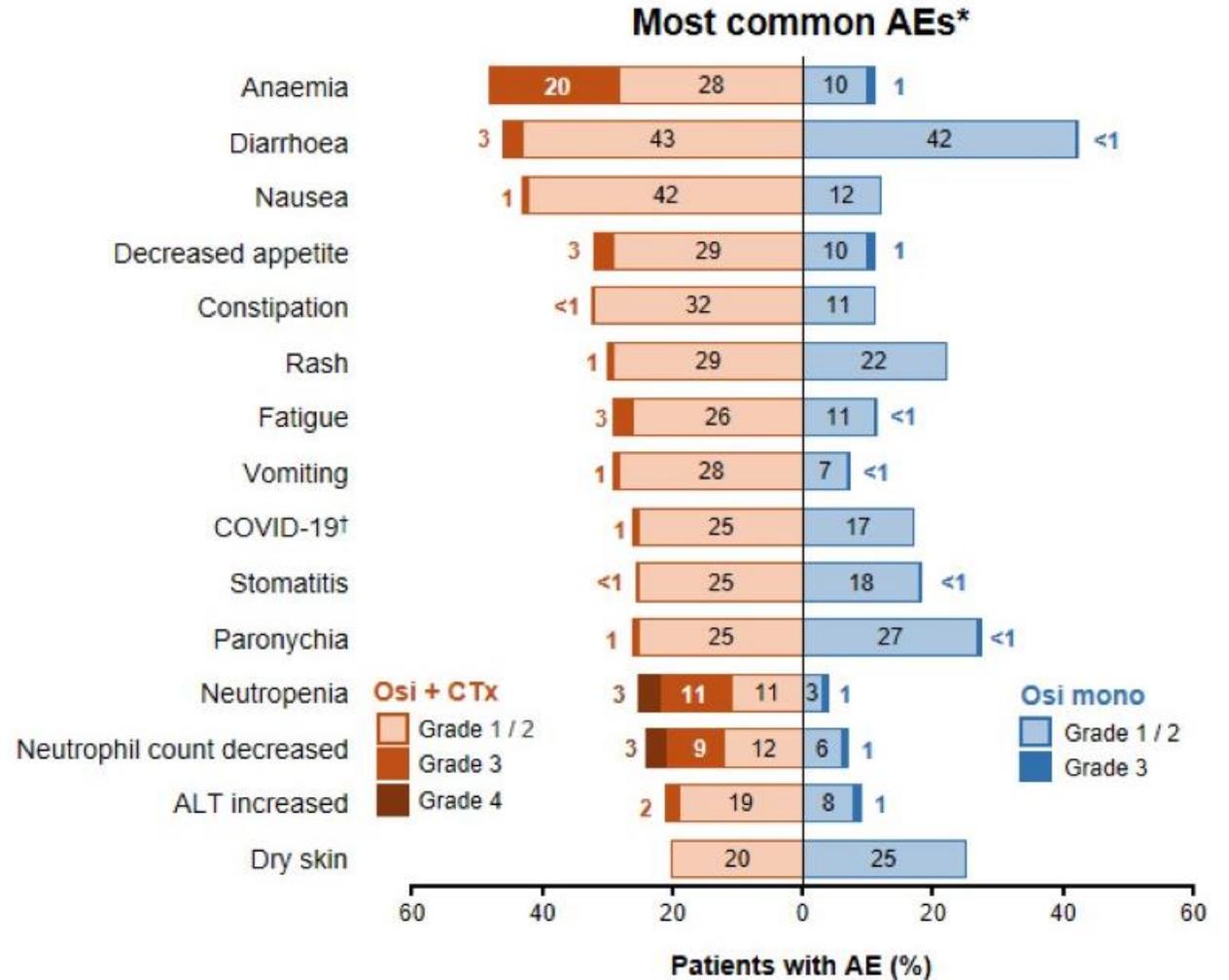
MARIPOSA (Phase 3): 1L amivantamab + lazertinib vs osimertinib among patients with *EGFR*-mutated, advanced NSCLC

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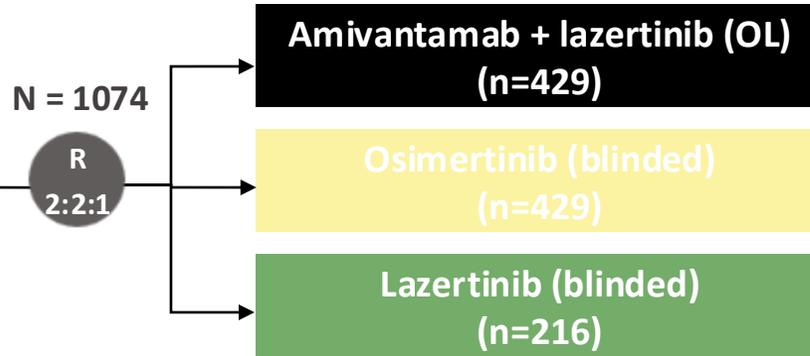
Primary endpoint of PFS[b] by BICR perRESIST v1.1:
- Amivantamab + lazertinib vs osimertinib

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

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
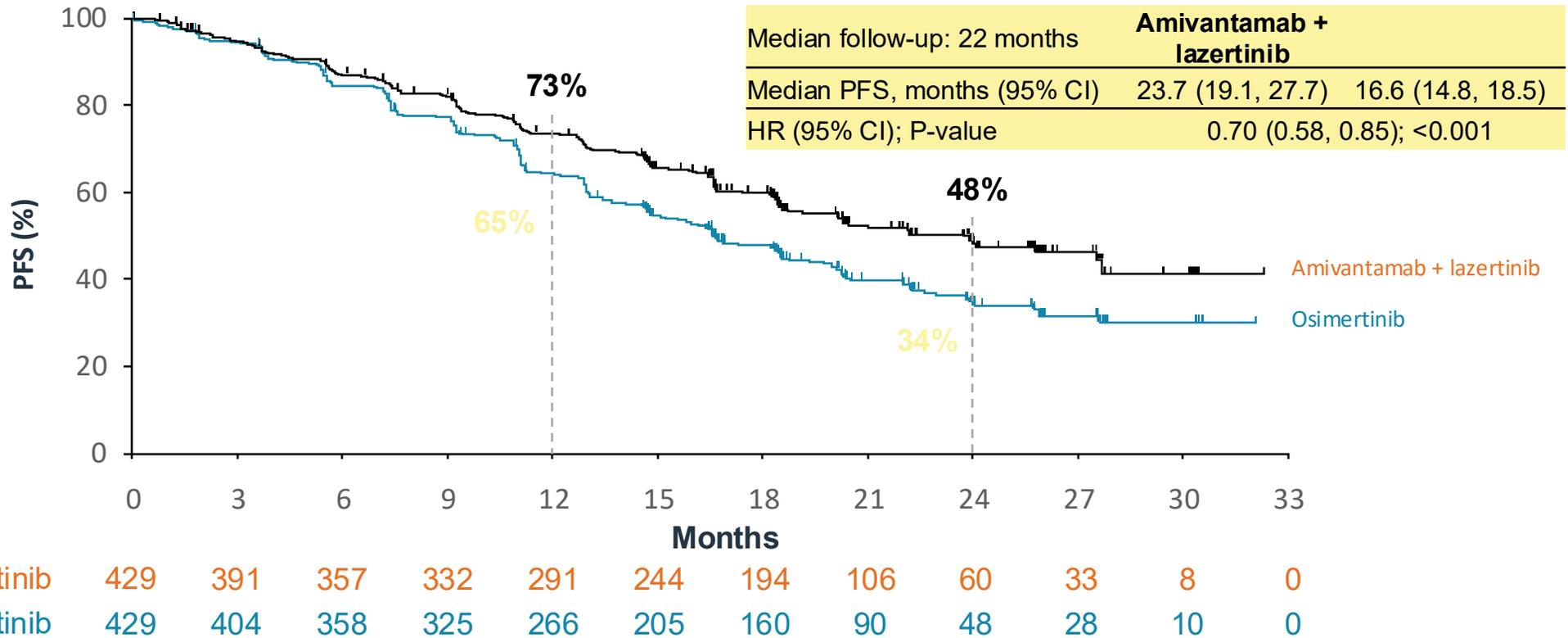**Osimertinib:** 80 mg daily
Brain scans
- Baseline brain MRI required for all patients ≤28 days prior to randomization
- Patients who could not have MRIs were allowed to have CT scans
- Brain scan frequency was every 8 weeks for the first 30 months and then every 12 weeks thereafter for patients with a history of brain metastasis and every 24 weeks for patients with no history of brain metastasis

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

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

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

Graph: PFS (%) vs Months

- 73% (dashed line at 12 months, Amivantamab + lazertinib)
- 65% (at 12 months, Osimertinib)
- 48% (dashed line at 24 months, Amivantamab + lazertinib)
- 34% (at 24 months, Osimertinib)

Curves labeled: Amivantamab + lazertinib, Osimertinib

	Amivantamab + lazertinib	
Median follow-up: 22 months		
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)

	0	3	6	9	12	15	18	21	24	27	30	33
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.
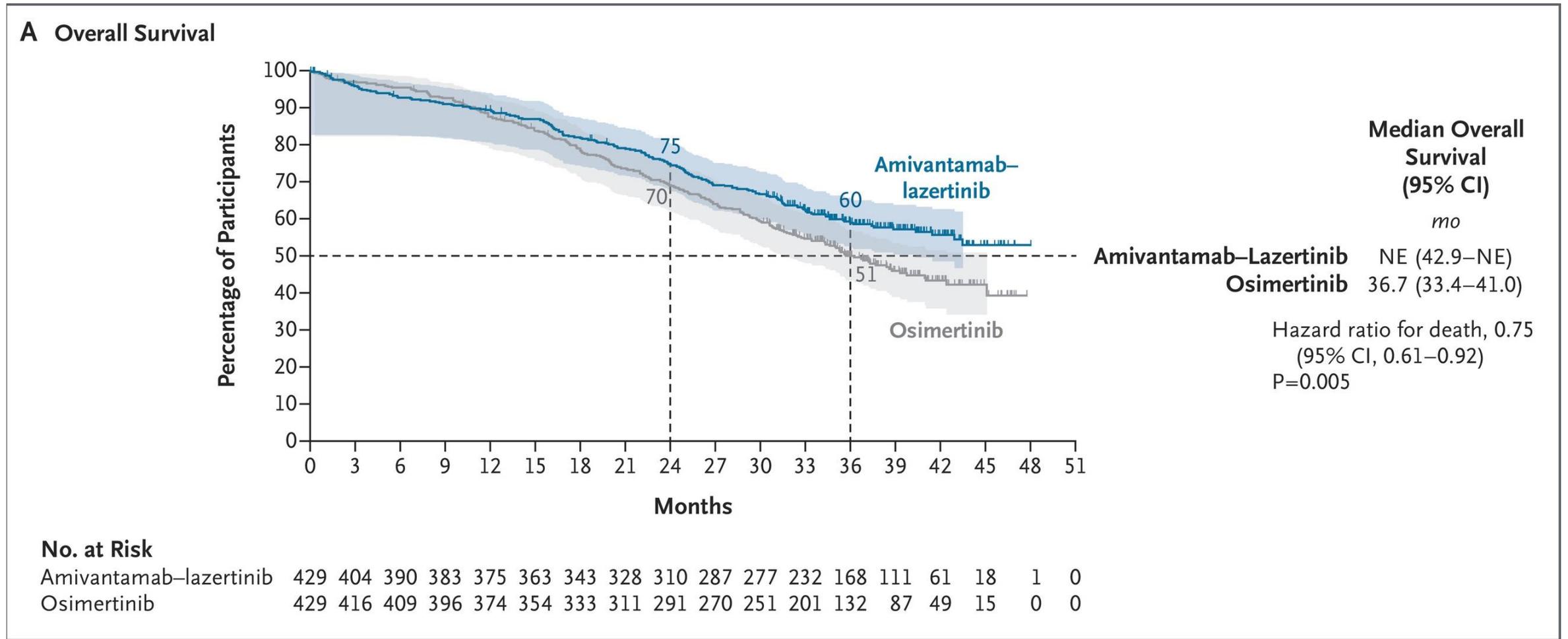
MARIPOSA: Safety of amivantamab + lazertinib vs osimertinib among patients with *EGFR*-mutated, advanced NSCLC

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

Grade >3 AES 75%

Related to EGFR inhibition	Paronychia
	Rash
	Diarrhea
	Dermatitis acneiform
	Stomatitis
	Pruritus
Related to MET inhibition	Hypoalbuminemia
	Peripheral edema
Other	IRR
	ALT increased
	Constipation
	AST increased
	COVID-19
	Decreased appetite
	Anemia
	Nausea
	Hypocalcemia
	Cough

Legend:
- ■ Amivantamab + lazertinib: Grade 1-2
- ■ Amivantamab + lazertinib: Grade ≥3
- ■ Osimertinib: Grade 1-2
- ■ Osimertinib: Grade ≥3
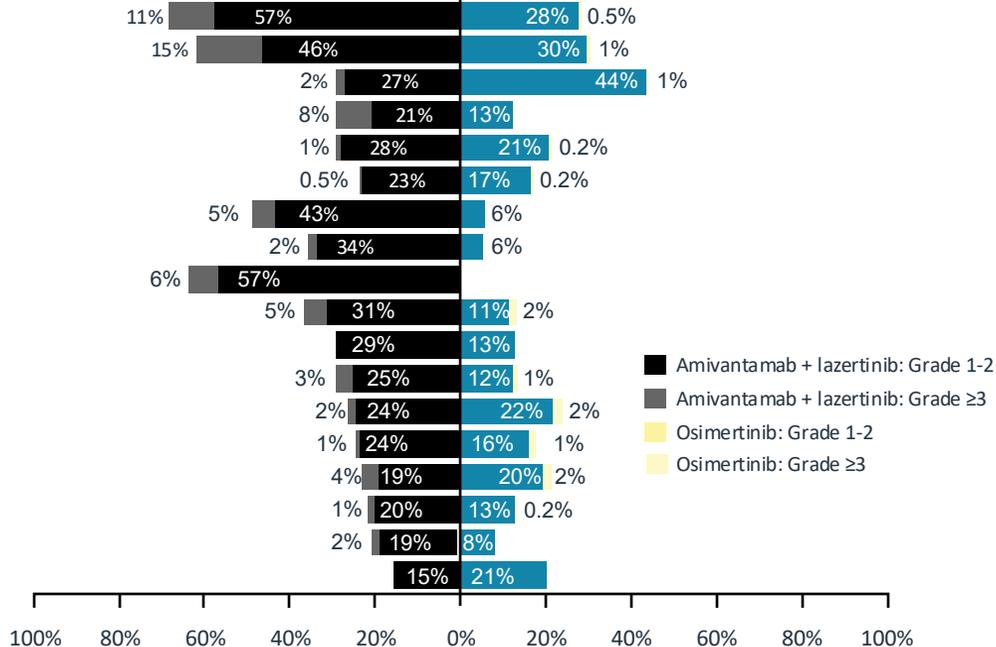
VTE rates were higher for amivantamab + lazertinib
- Most common preferred terms were pulmonary embolism and deep vein thrombosis
- Most VTEs were Grade 1–2
- Incidence of Grade 4–5 VTEs was low (<1%) and comparable between arms
- Rates of discontinuations due to VTE were low and comparable between arms

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

	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)

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
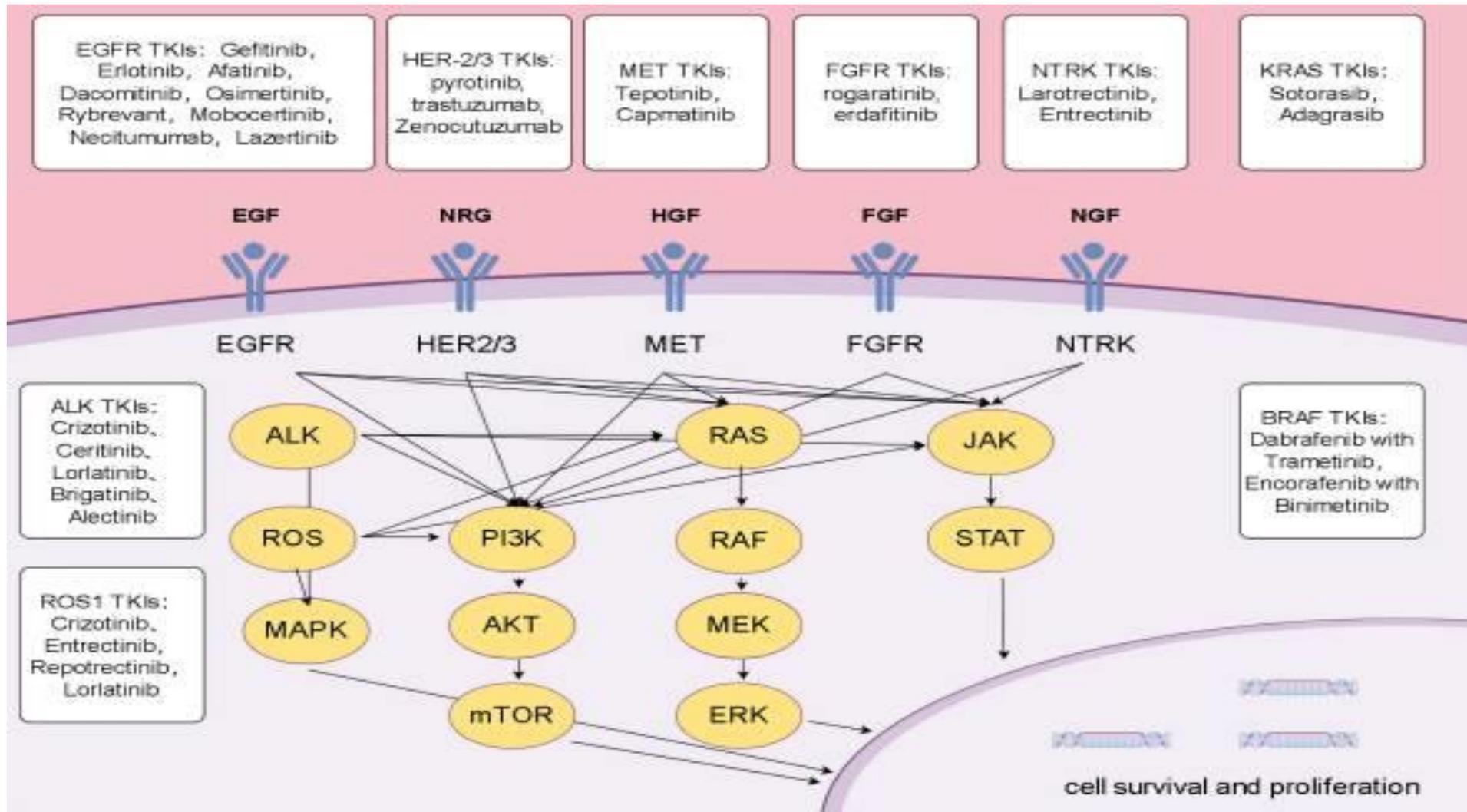
EGF = epidermal growth factor; EGFR = EGF receptor; TKI = tyrosine kinase inhibitor; NRG = neuregulin; HGF = hepatocyte growth factor; FGF = fibroblast growth factor; FGFR = FGF receptor; NGF = nerve growth factor; HER-2/3 = human epidermal growth factor receptor 2 / 3; MET = mesenchymal-epithelial transition 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
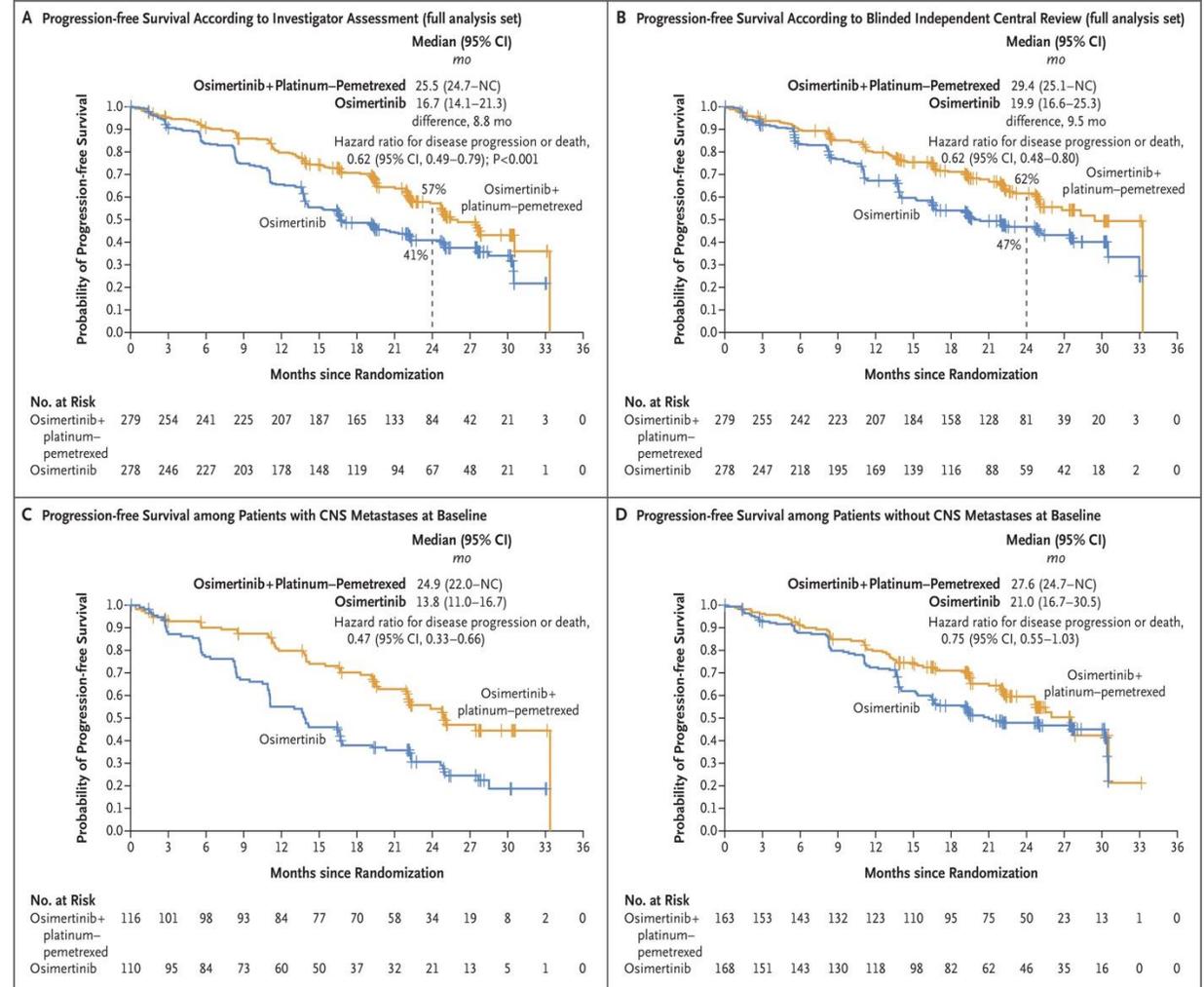
PFS = progression-free survival.
Planchard D, et al. *N Engl J Med.* 2023;389(21):1935-1948.

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)
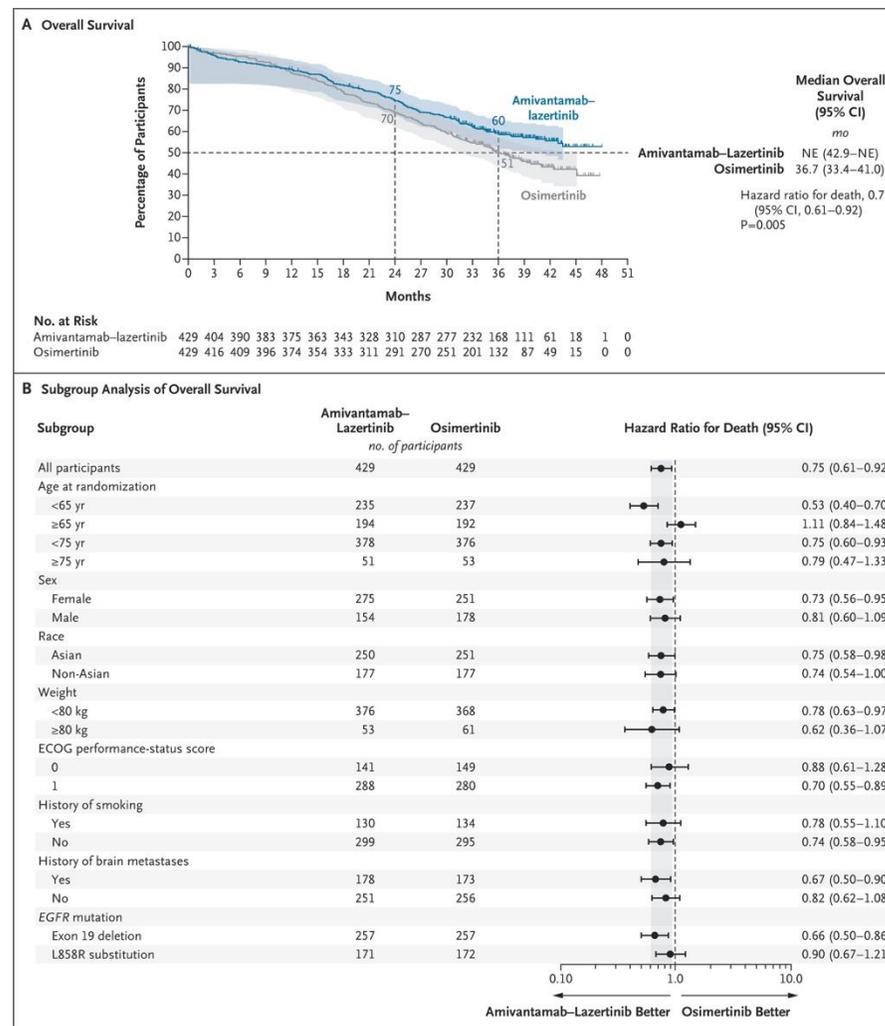
OS = overall survival.
Yang JC, et al. *N Engl J Med*. 2025.

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.
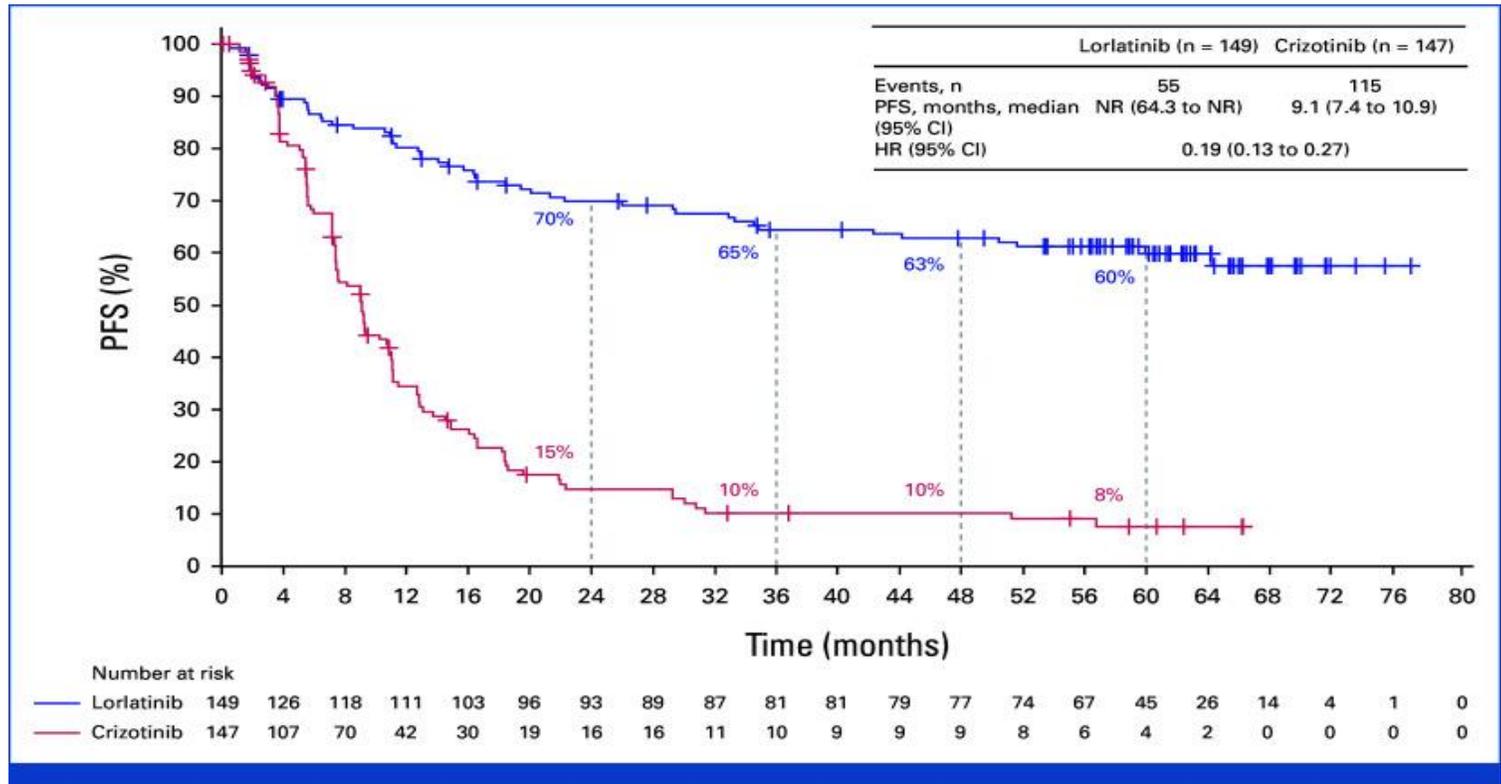
Sotorasib for Lung Cancers with KRAS p.G12C Mutation

- 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.
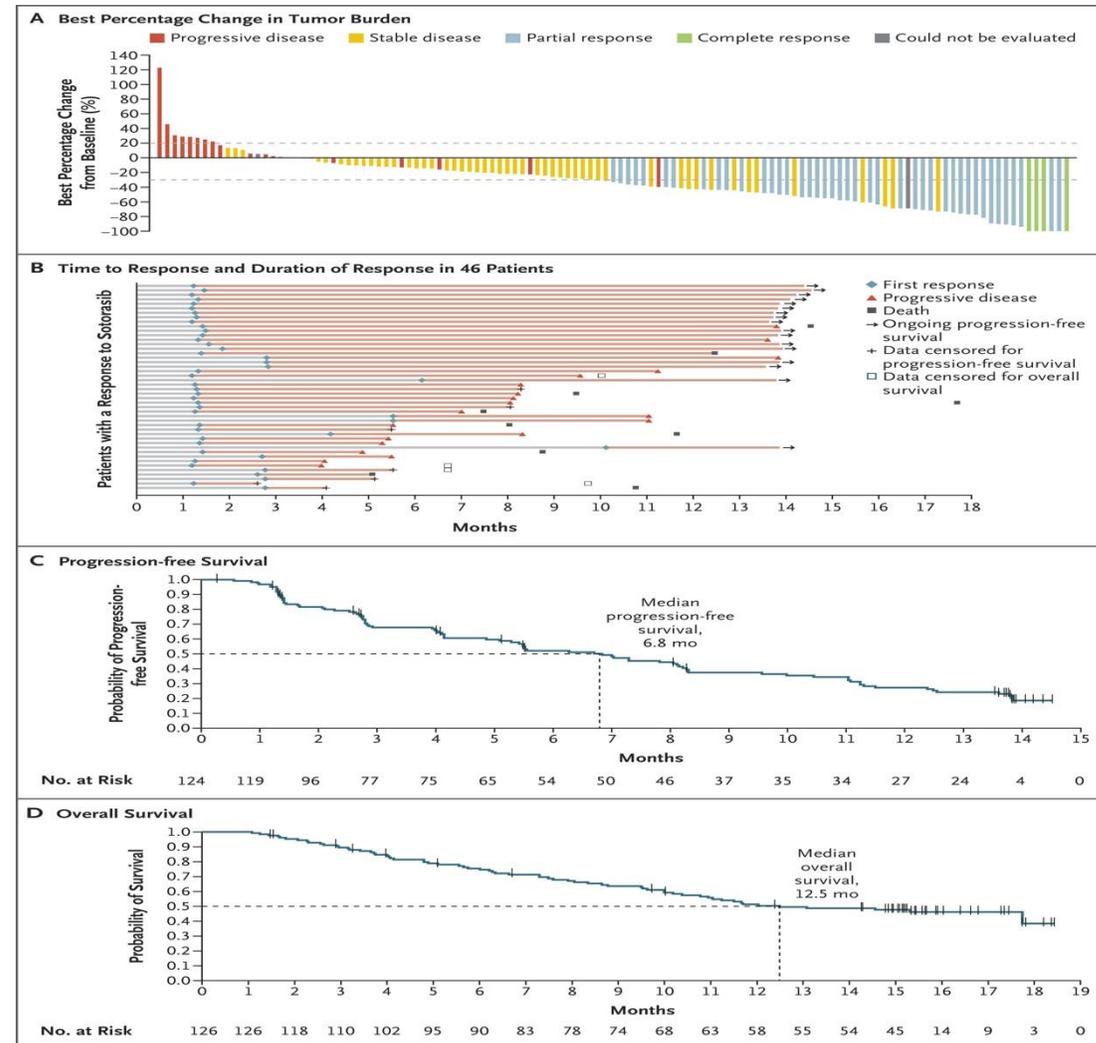
Administration Considerations and Best Practices

- 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

COCOON Study Design

Key inclusion criteria
- Frontline patients with EGFRm NSCLC
- Locally advanced or metastatic disease (Stage IIIB/C or IV)
- Asymptomatic or previously treated and stable brain metastases are allowed
- ECOG PS 0-1
- Moderate renal impairment (CrCl >45) pts are allowed

1:1 randomization[a] (N=180; US, EU, LATAM, APAC)

Arm A: Amivantamab-Lazertinib + Enhanced Dermatologic Management[b*] (n=90)

Enhanced Dermatologic Management[*]

	Week 1-12	Week 12-52
Prophylactic Antibiotics	Oral Doxycycline or Minocycline 100mg BID	Topical Clindamycin Lotion 1% on scalp daily before bedtime
Paronychia Prophylaxis	Chlorhexidine 4% apply to fingernails and toenails once daily	
Skin Moisturization	La Roche Posay Lipikar AP+M Moisturizer apply on body and face at least once daily	

Arm B: Amivantamab-Lazertinib + SoC Dermatologic Management[b] (n=90)

[a]Stratification: race (Asian vs non Asian), age (<65y vs >65y).
[*]All patients in both arms will receive venous thromboembolism prophylaxis per protocol.
APAC, Asia Pacific; BID, twice daily; CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFRm, epidermal growth factor receptor mutated; LATAM, Latin America; NSCLC, non-small cell lung cancer; pts, patients; SoC, standard of care; y, year

1

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
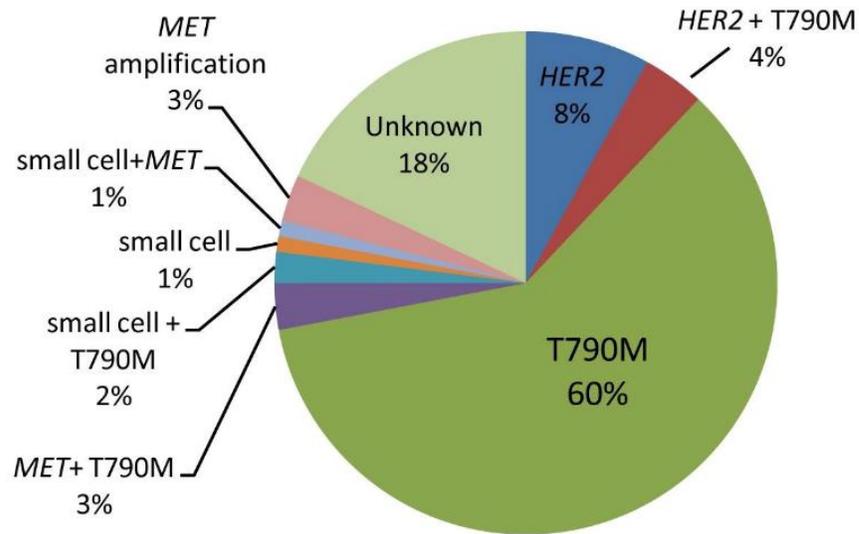
Dominant mechanism of resistance for 1st generation EGFR TKIs erlotinib or gefitinib
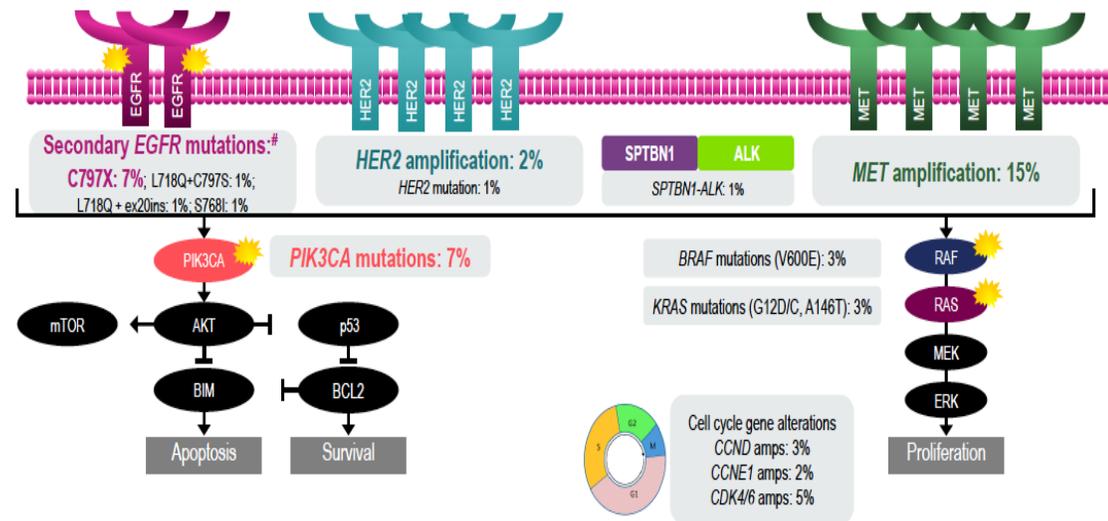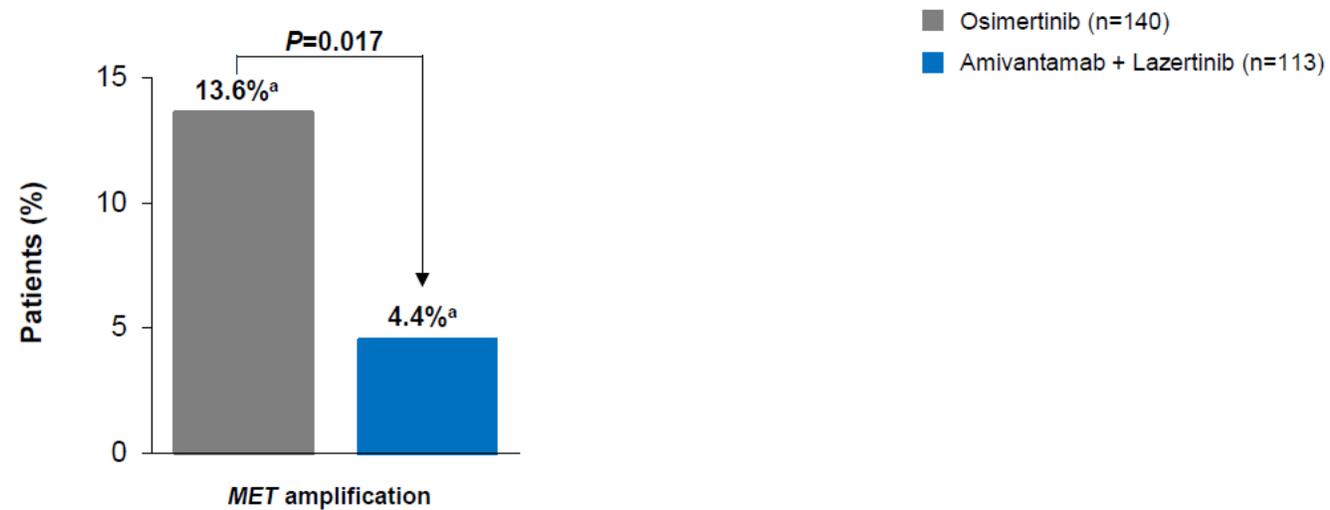
Heterogeneous & multiple simultaneous mechanisms of resistance to 3rd generation EGFR TKI osimertinib

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

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

EGFR EXON 19 DELETION OR EXON 21 L858R MUTATIONS

SUBSEQUENT THERAPY

Progression on osimertinib or amivantamab-vmjw + lazertinib

Asymptomatic
- Consider definitive local therapy (eg, SABR or surgery) for limited lesions
- Continue osimertinib or amivantamab-vmjw + lazertinib

Symptomatic

Brain
- Consider definitive local therapy (eg, SRS)
- Continue osimertinib or amivantamab-vmjw + lazertinib
- *NCCN Guidelines for CNS Cancers*

Progression, see therapy for multiple lesions below

Systemic

Limited progression
- Consider definitive local therapy (eg, SABR or surgery)
- Continue osimertinib or amivantamab-vmjw + lazertinib or
- Therapy for multiple lesions, below

Multiple lesions

Amivantamab-vmjw (if not previously given) + carboplatin + pemetrexed (nonsquamous) (category 1) (preferred) or
Systemic therapy
Adenocarcinoma (*NSCL-K 1 of 5*) or Squamous Cell Carcinoma (*NSCL-K 2 of 5*)

Progression

Systemic Therapy, Subsequent (NSCL-K 4 of 5)

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

Key Eligibility Criteria

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

Stratification Factors

- Osimertinib line of therapy (1st vs 2nd)
- Asian race (yes or no)
- History of brain metastases (yes or no)

2:2:1 Randomization (N=657)

Serial brain MRIs were required for all patients[a]

Amivantamab-Lazertinib-Chemotherapy (n=263)

Chemotherapy (n=263)

Amivantamab-Chemotherapy (n=131)

Dosing (in 21-day cycles)

Amivantamab: 1400 mg (1750 mg if ≥80 kg) for the first 4 weeks, then 1750 mg (2100 mg if ≥80 kg) every 3 weeks starting at Cycle 3 (week 7)

Lazertinib: 240 mg daily starting after completion of carboplatin[b]

Chemotherapy administered at the beginning of every cycle:

- **Carboplatin:** AUC5 for the first 4 cycles
- **Pemetrexed:** 500 mg/m^2 until disease progression

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

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); $P=0.002$	

COMPEL Study

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

Patients with locally advanced / metastatic EGFRm NSCLC with or without CNS metastases

Key inclusion criteria:
- Aged ≥18 years
- Non-CNS progression on 1L osi
- Ex19del / L858R
- WHO PS 0 / 1

R 1:1 N=98

Stratification by: CNS metastases, yes / no

Osimertinib 80 mg (QD) + cisplatin 75 mg/m² or carboplatin AUC5 + pemetrexed 500 mg/m² (Q3W for 4 cycles)

Osimertinib 80 mg (QD) + pemetrexed 500 mg/m² (Q3W)

Placebo (QD) + cisplatin 75 mg/m² or carboplatin AUC5 + pemetrexed 500 mg/m² (Q3W for 4 cycles)

Placebo (QD) + pemetrexed 500 mg/m² (Q3W)

PD (non-CNS or CNS)* or another discontinuation criterion

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

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)

No. at risk

49	25	6	2	1	0
49	14	3	0	0	0
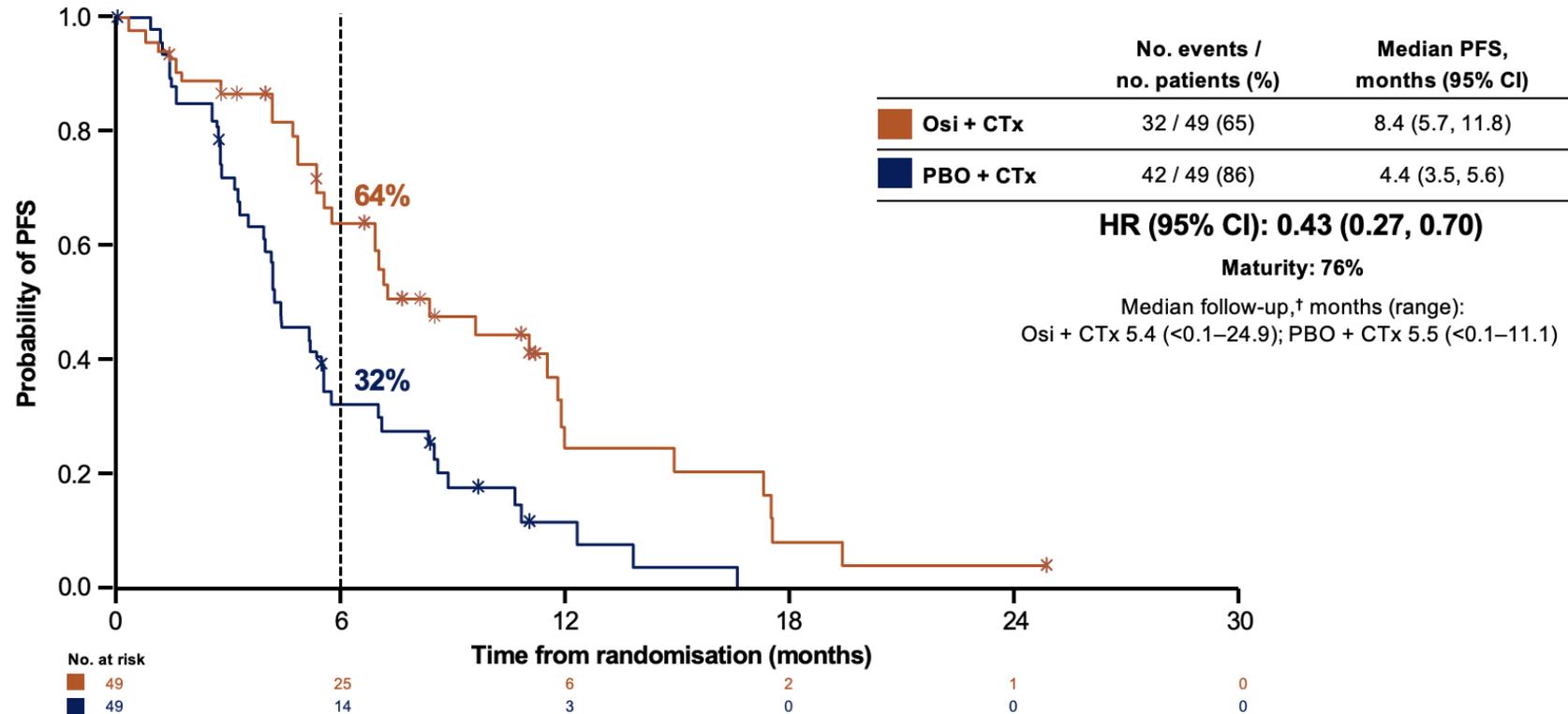
Osi + CTx was associated with improved PFS versus PBO + CTx

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)

67%

47%

No. at risk

49	40	21	10	5	1	1	0
49	32	12	7	5	1	0	0
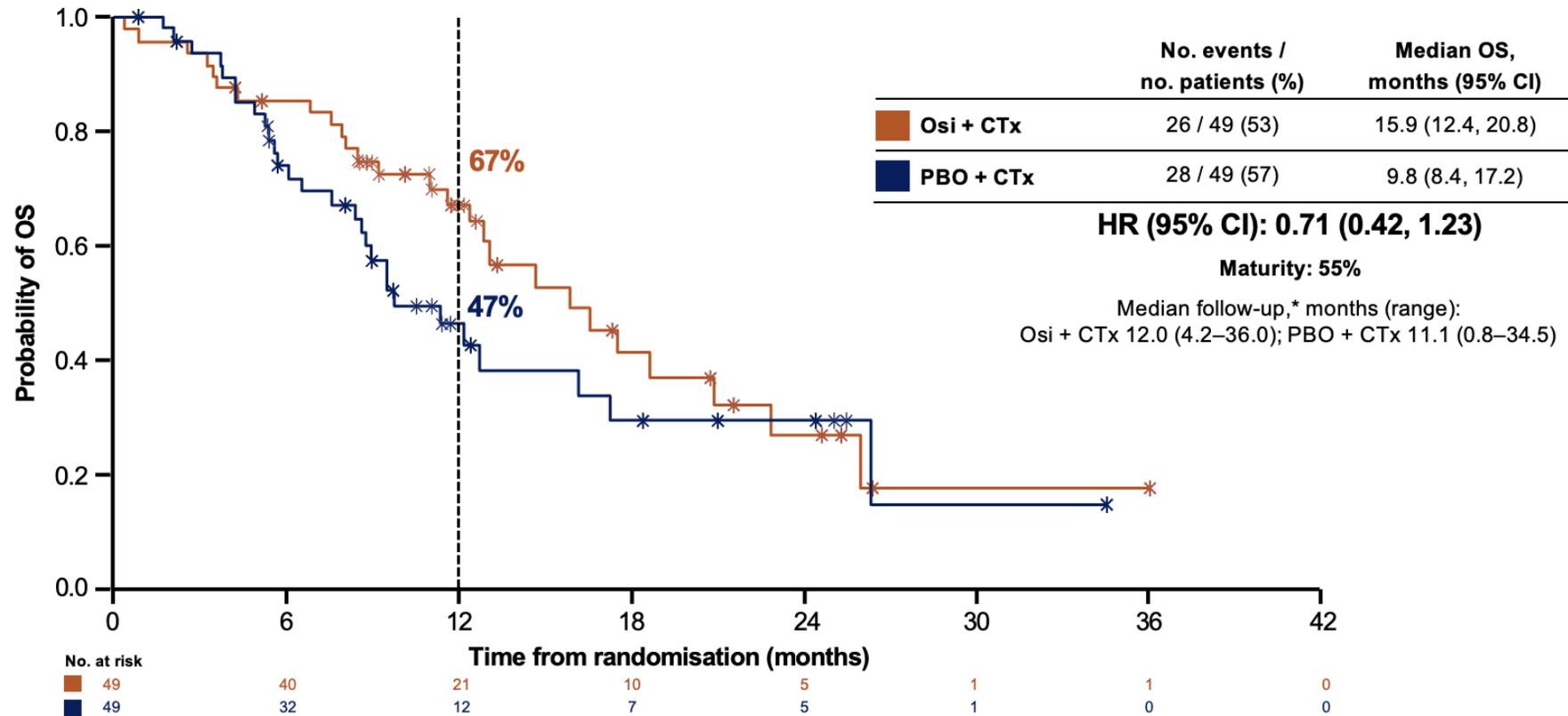
OS was longer with osi + CTx versus PBO + CTx

CHRYSALIS-2

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[†]

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

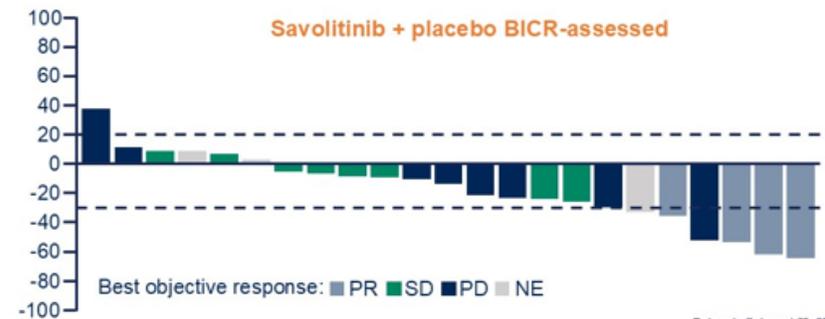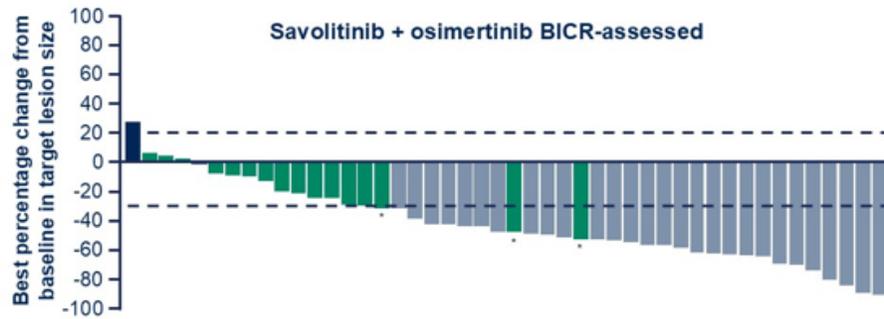Treatment continued until PD, or another discontinuation criterion was met

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

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 BICR-assessed

Savolitinib + placebo BICR-assessed

Best objective response: PR SD PD NE

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

Median PFS, months (95% CI)
Savolitinib + osimertinib   8.3 (5.8, 15.1)
Savolitinib + placebo   3.6 (1.4, 5.7)

PFS HR (95% CI): 0.27 (0.13, 0.57)

PFS events / patients
Savolitinib + osimertinib 26 / 48 (54% maturity)
Savolitinib + placebo 14 / 25 (56% maturity)
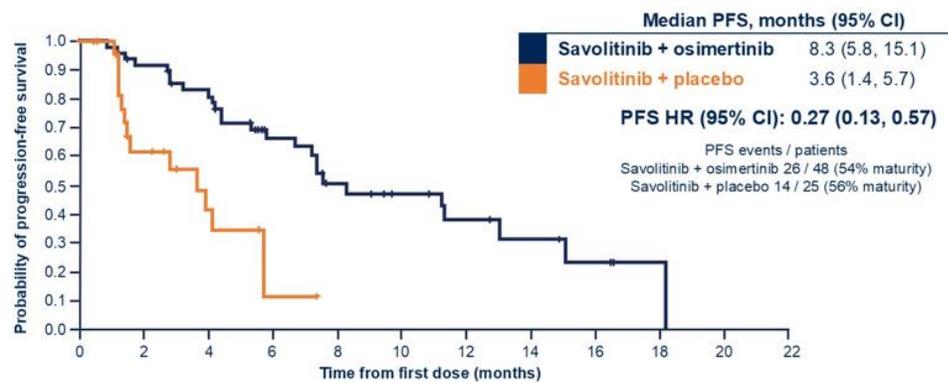
No. at risk:
Savolitinib + osimertinib 48 43 37 22 15 11 8 5 3 1 0 0
Savolitinib + placebo 25 12 6 1 0 0 0 0 0 0 0 0

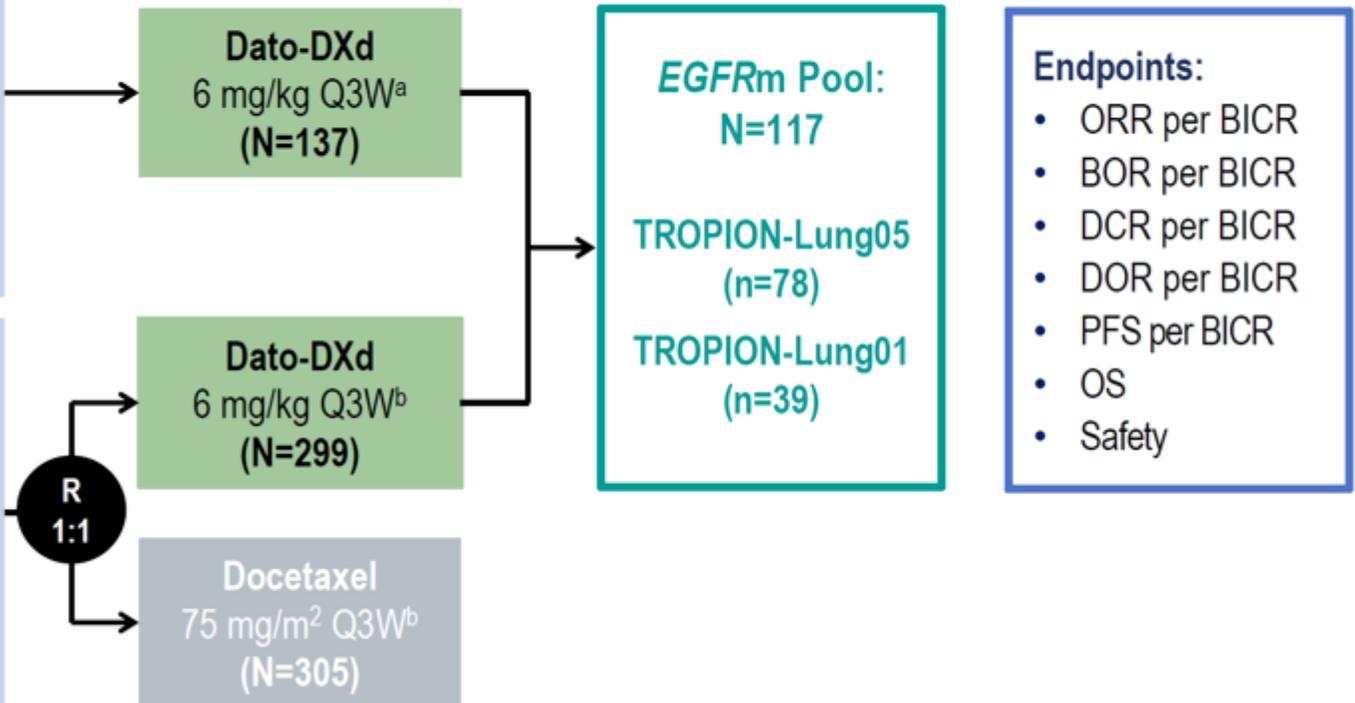|	Savolitinib + osimertinib (n=14)	Savolitinib + placebo (n=4)
CNS best objective response, n (%)		
Response	6 (43)	1 (25)
Complete response	2 (14)	0
Partial response	4 (29)	1 (25)
Non-response	8 (57)	3 (75)
Stable disease	7 (50)	1 (25)
Progressive disease	1 (7)	1 (25)
Not evaluable	0	1 (25)
CNS confirmed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

TROPION-LUNG1/LUNG5 Pooled Analysis

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

Dato-DXd
6 mg/kg Q3W[a]
(N=137)

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

**R 1:1**

Dato-DXd
6 mg/kg Q3W[b]
(N=299)

Docetaxel
75 mg/m^2 Q3W[b]
(N=305)

*EGFR*m Pool:
N=117

TROPION-Lung05
(n=78)

TROPION-Lung01
(n=39)

Endpoints:
- ORR per BICR
- BOR per BICR
- DCR per BICR
- DOR per BICR
- PFS per BICR
- OS
- Safety

TROPION-LUNG1/LUNG5: Results

Response	EGFRm 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)

Median PFS (95% CI) 5.8 months (5.4–8.2)

48.5%

23.3%

+ Censored
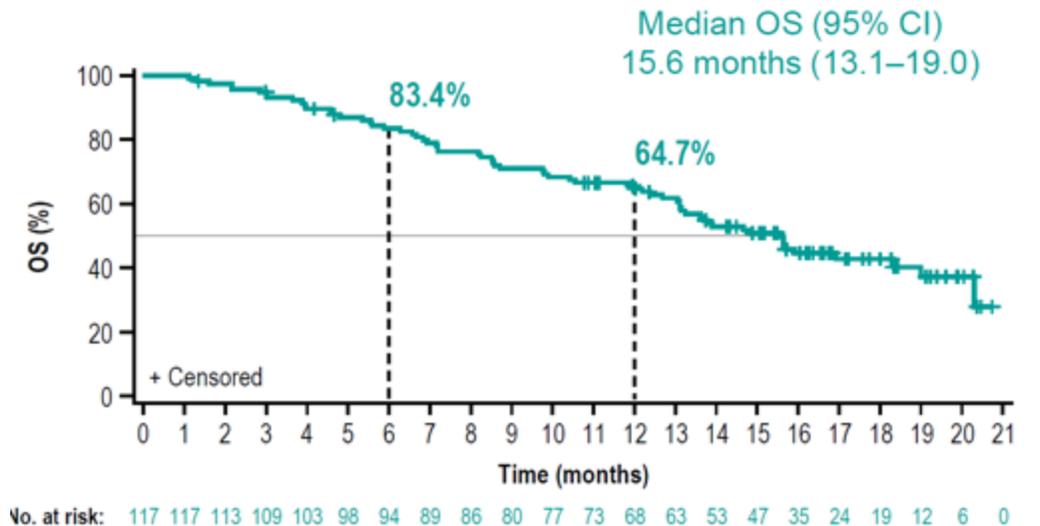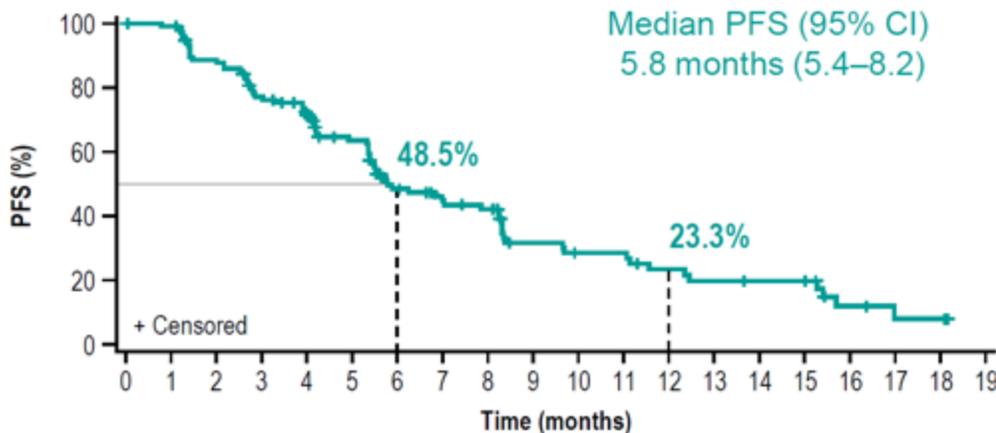
No. at risk: 117 115 101 86 77 61 42 34 31 20 17 17 13 11 10 10 4 2 2 0

Median OS (95% CI) 15.6 months (13.1–19.0)

83.4%

64.7%

+ Censored

No. at risk: 117 117 113 109 103 98 94 89 86 80 77 73 68 63 53 47 35 24 19 12 6 0

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
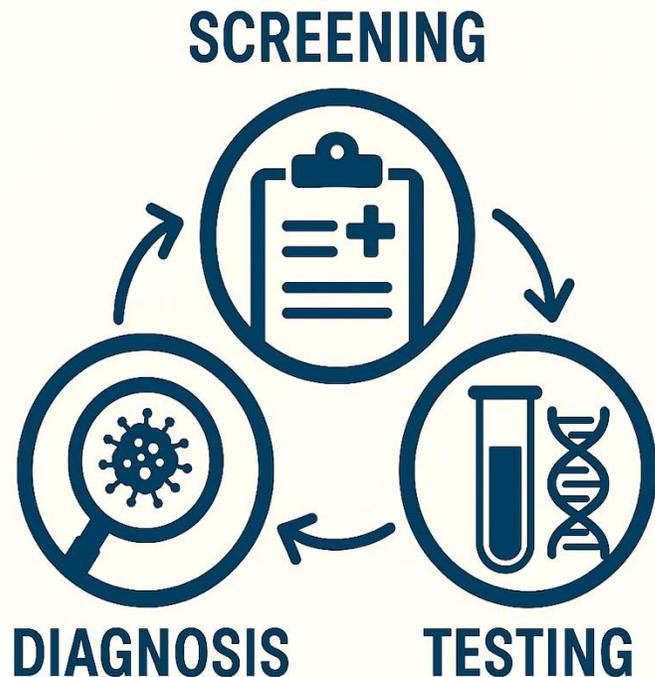
Screening

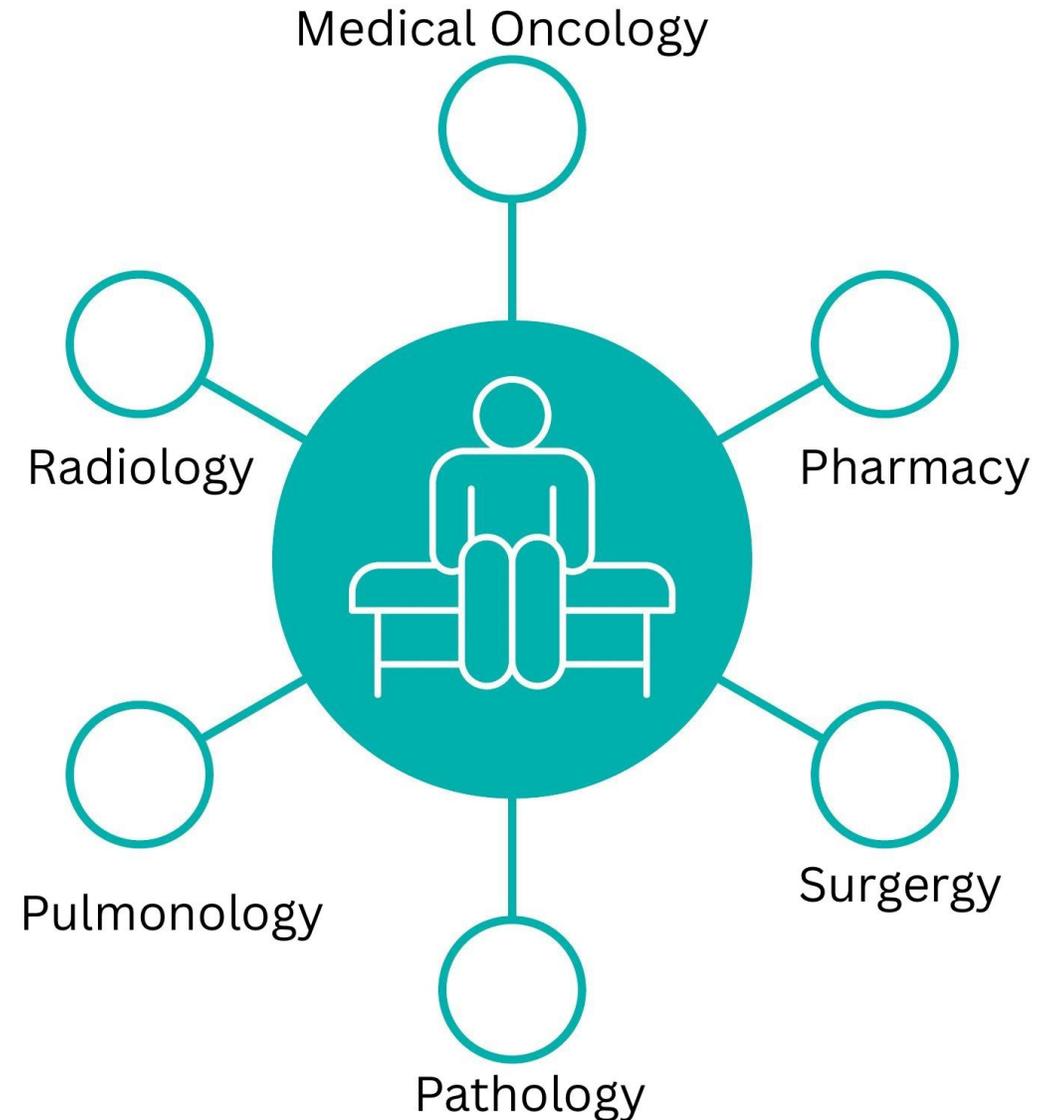- Collecting a thorough history to recognize high-risk individuals
- Low dose CT

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

<u>Education</u>

• Detailed baseline assessment

<u>Identification</u>

• Educating patients on the onset time of adverse events

<u>Managing</u>

• 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