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LUNG CANCER SYMPOSIUM

EGFR Inhibition for Locally Advanced and Metastatic NSCLC

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Disclosures

Honoraria: None

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Outline

- Locally Advanced NSCLC
  - LAURA study and implications
- Metastatic NSCLC
  - 1st line therapy
  - Salvage therapy

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Locally Advanced NSCLC

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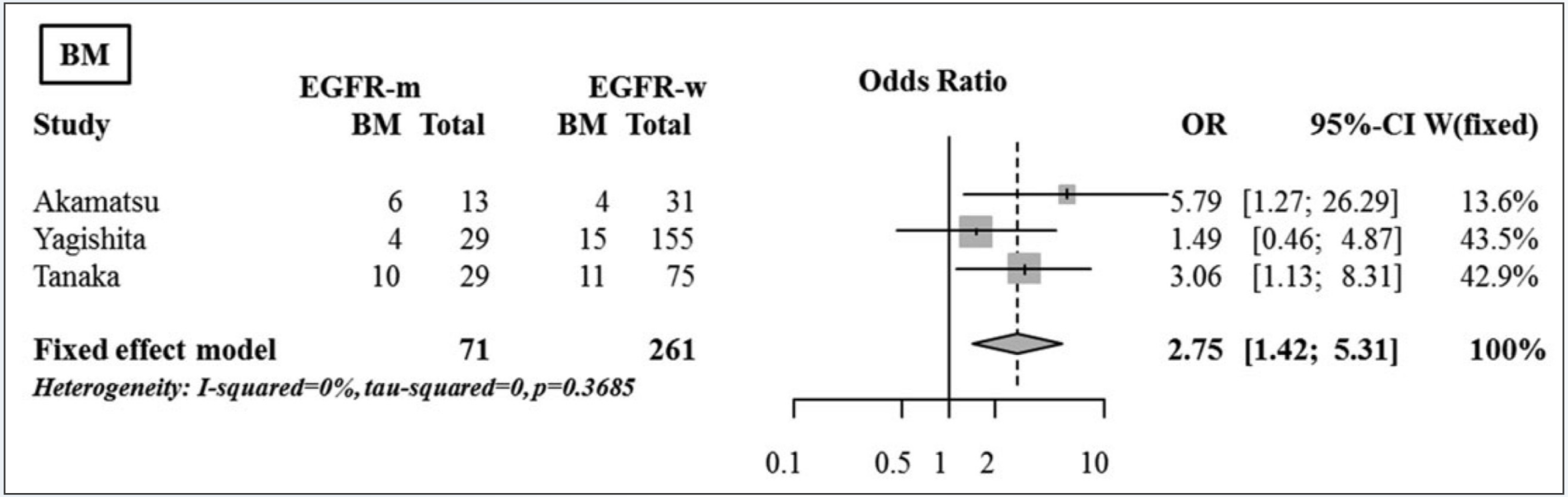
Relapse Patterns Following Chemo-RT

Higher rate of systemic relapse in EGFR mutated patients

	Akamatsu et al	Yagishita et al	Tanaka et al	Lim et al	Our Study
Failure					
EGFR wild-type	84 (26/31)	79 (129/164)	71 (53/75)	NA	79 (110/139)
EGFR mutated	77 (10/13)	74 (25/34)	83 (24/29)	NA	94 (32/34)
ALK positive					85 (11/13)
Locoregional failure					
EGFR wild-type	32 (10/31)	33 (54/164)[a]	35 (26/75)	45 (31/69)[a]	45 (63/139)
EGFR mutated	15 (2/13)	15 (5/34)[a]	14 (4/29)	12 (3/26)[a]	21 (7/34)
ALK positive					54 (7/13)
Distant failure					
EGFR wild-type	58 (18/31)	63 (102/164)[b]	40 (30/75)	39 (27/69)[b]	61 (85/139)
EGFR mutated	69 (9/13)	71 (24/34)[b]	76 (22/29)	50 (13/26)[b]	79 (27/34)
ALK positive					46 (6/13)

Nakamura et al, Clin Lung Cancer, 2019.

Incidence of Brain Metastasis Post Chemo-RT



Ochiai et al, J Rad Res, 2016

LAURA Phase 3 double-blind study design

Patients with locally advanced, unresectable stage III* EGFRm NSCLC with no progression during / following definitive CRT† treatment

Key inclusion criteria:

- ≥18 years (Japan: ≥20)
- WHO PS 0 / 1
- Confirmed locally advanced, unresectable stage III* NSCLC
- Ex19del / L858R‡
- Maximum interval between last dose of CRT and randomization: 6 weeks

Osimertinib 80 mg, once daily

Randomization
2:1
(N=216)

Stratification by:
Concurrent vs sequential CRT
Stage IIIA vs stage IIIB/IIIC
China vs non-China

Placebo, once daily

Treatment duration until BICR-assessed progression (per RECIST v1.1), toxicity, or other discontinuation criteria

Open-label osimertinib after BICR-confirmed progression offered to both treatment arms§

Tumor assessments:

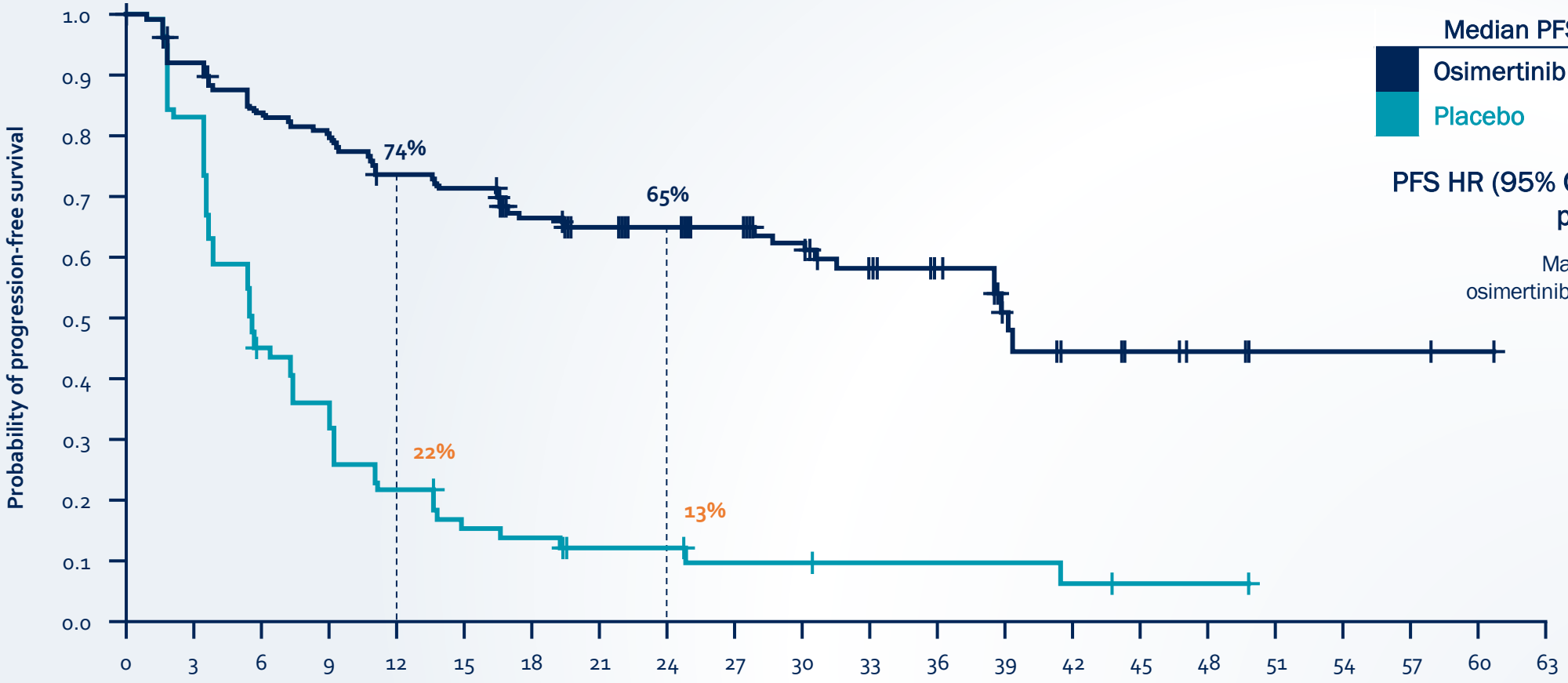
- Chest CT / MRI and brain MRI
- At baseline, every 8 weeks to Week 48, then every 12 weeks until BICR-assessed progression

Endpoints

- **Primary endpoint:** PFS assessed by BICR per RECIST v1.1 (sensitivity analysis: PFS by investigator assessment)
- **Secondary endpoints included:** OS, CNS PFS, safety

Lu S et al, NEJM, 2024.

Progression-free survival by BICR



Median PFS, months (95% CI)	
Osimertinib	39.1 (31.5, NC)
Placebo	5.6 (3.7, 7.4)

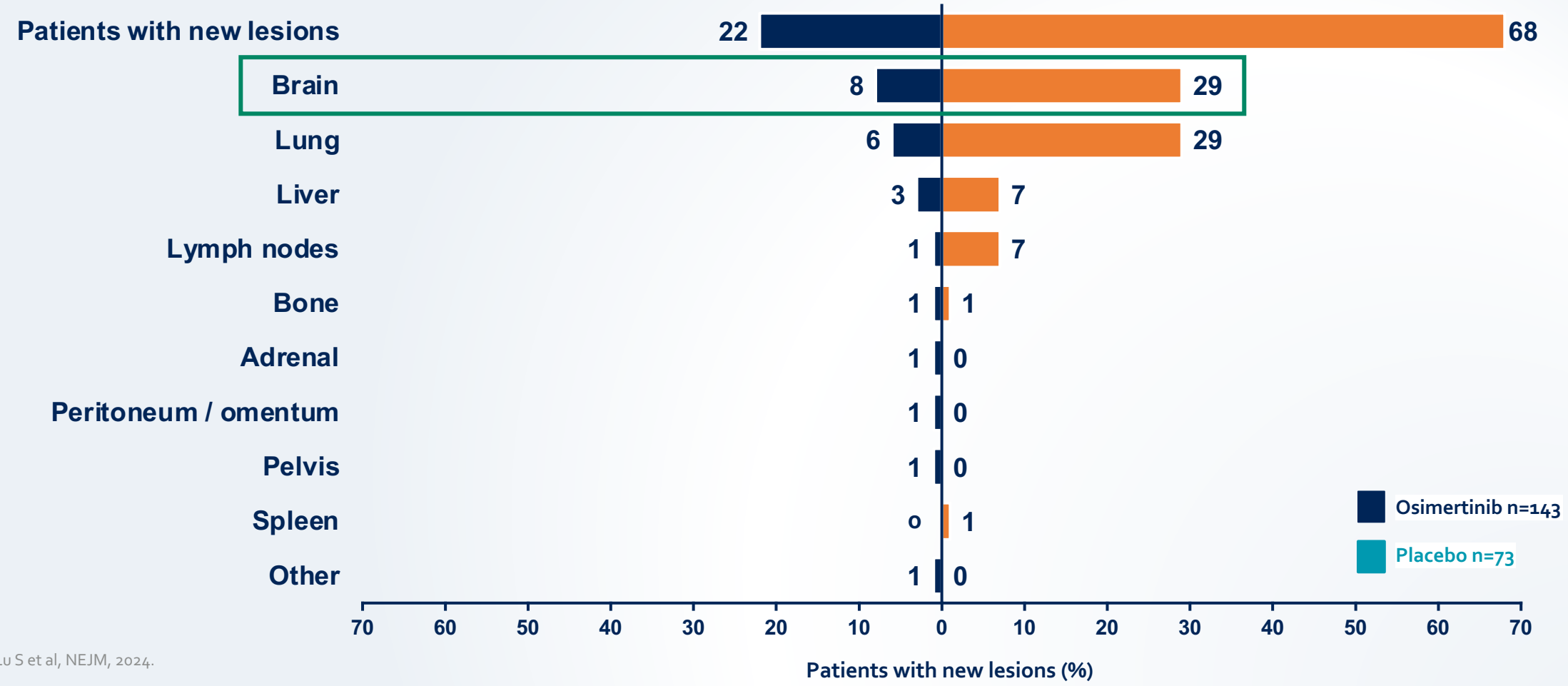
PFS HR (95% CI): 0.16 (0.10, 0.24), p<0.001

Maturity 56%:
osimertinib 40%, placebo 86%

No. at risk																					
Osimertinib	143	127	1 14	109	99	96	83	76	69	61	49	37	28	16	9	6	4	2	2	2	1	0
Placebo	73	59	31	25	15	10	9	6	6	4	4	3	3	3	2	1	1	0	0	0	0	0

Lu S et al, NEJM, 2024.

Sites of new lesions by BICR

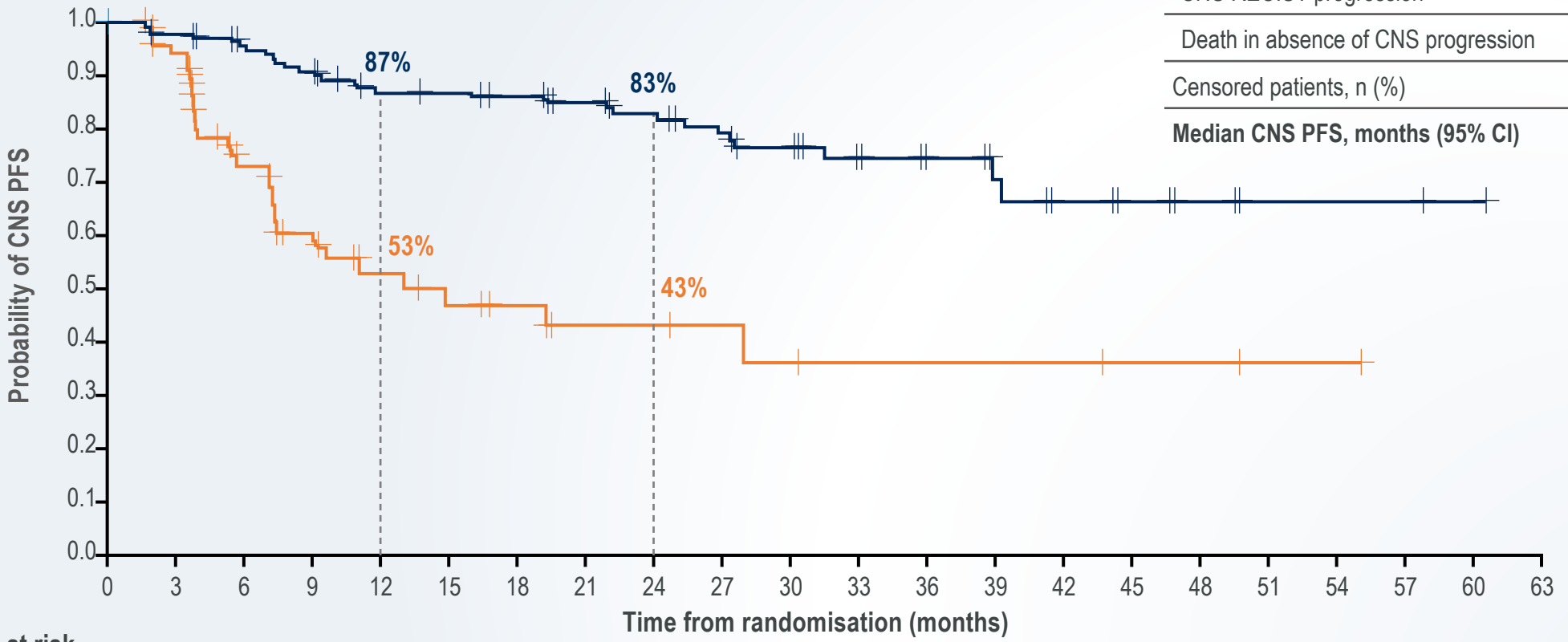


Lu S et al, NEJM, 2024.

CNS progression-free survival by neuroradiologist BICR*

- Reduced risk of CNS progression or death with osimertinib vs placebo

	Osimertinib (n=143)	Placebo (n=73)
Total CNS PFS events, n (%)†	29 (20)	30 (41)
CNS RECIST progression‡	18 (13)	26 (36)
Death in absence of CNS progression	11 (8)	4 (5)
Censored patients, n (%)	114 (80)	43 (59)
Median CNS PFS, months (95% CI)	**NR (NC, NC)**	**14.9 (7.4, NC)**



HR: 0.17 (0.09, 0.32), p<0.001 (nominal)

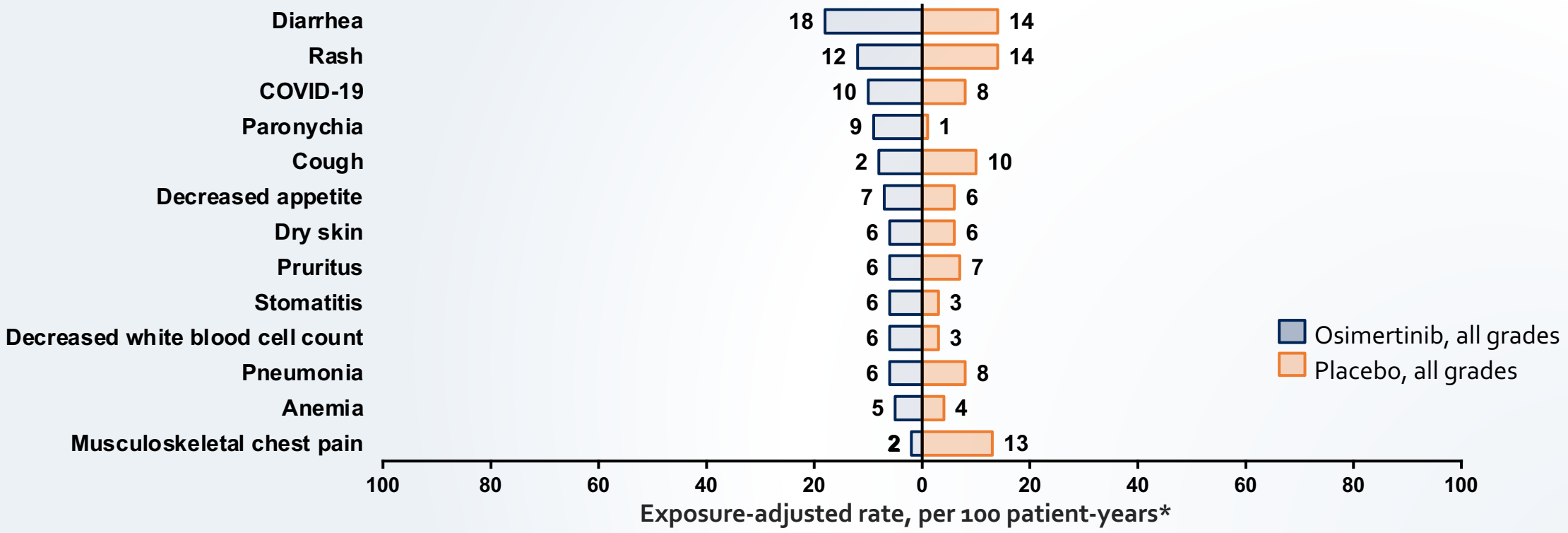
No. at risk

Osimertinib	143	130	121	115	105	104	94	84	74	63	49	37	28	17	9	6	4	2	2	2	1	0
Placebo	73	63	36	26	19	16	12	8	8	6	5	3	3	3	3	2	2	1	1	0	0	0

Exposure-adjusted analysis for most-common AEs (≥10%)

When adjusting for exposure, AEs reported at an increased rate (>3 events difference per 100 patient-years in comparison to placebo) were all previously identified osimertinib ADRs (diarrhea, paronychia, stomatitis and decreased white blood cell count)

Overall rates of exposure-adjusted Grade ≥3 AEs and SAEs (per 100 patient-years) were similar between arms: 17.7 and 19.5 (osimertinib) vs 12.6 and 15.4 (placebo), respectively



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Metastatic NSCLC

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Osimertinib + Chemo: FLAURA2

Safety run-in period (N=30)
Published in ESMO Open, 2021[1]

Patients with untreated locally advanced / metastatic EGFRm NSCLC

Key inclusion criteria:

- Aged ≥18 years (Japan: ≥20 years)
- Pathologically confirmed non-squamous NSCLC
- Ex19del / L858R (local / central test)
- WHO PS 0 / 1
- No prior systemic therapy for advanced NSCLC
- Stable CNS metastases were allowed*
- Brain scans at baseline (MRI / CT)

Stratification by:

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

Randomization 1:1 (N=557)

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

Maintenance osimertinib 80 mg (QD) + pemetrexed (Q3W)†

Osimertinib 80 mg (QD)

Follow-up:

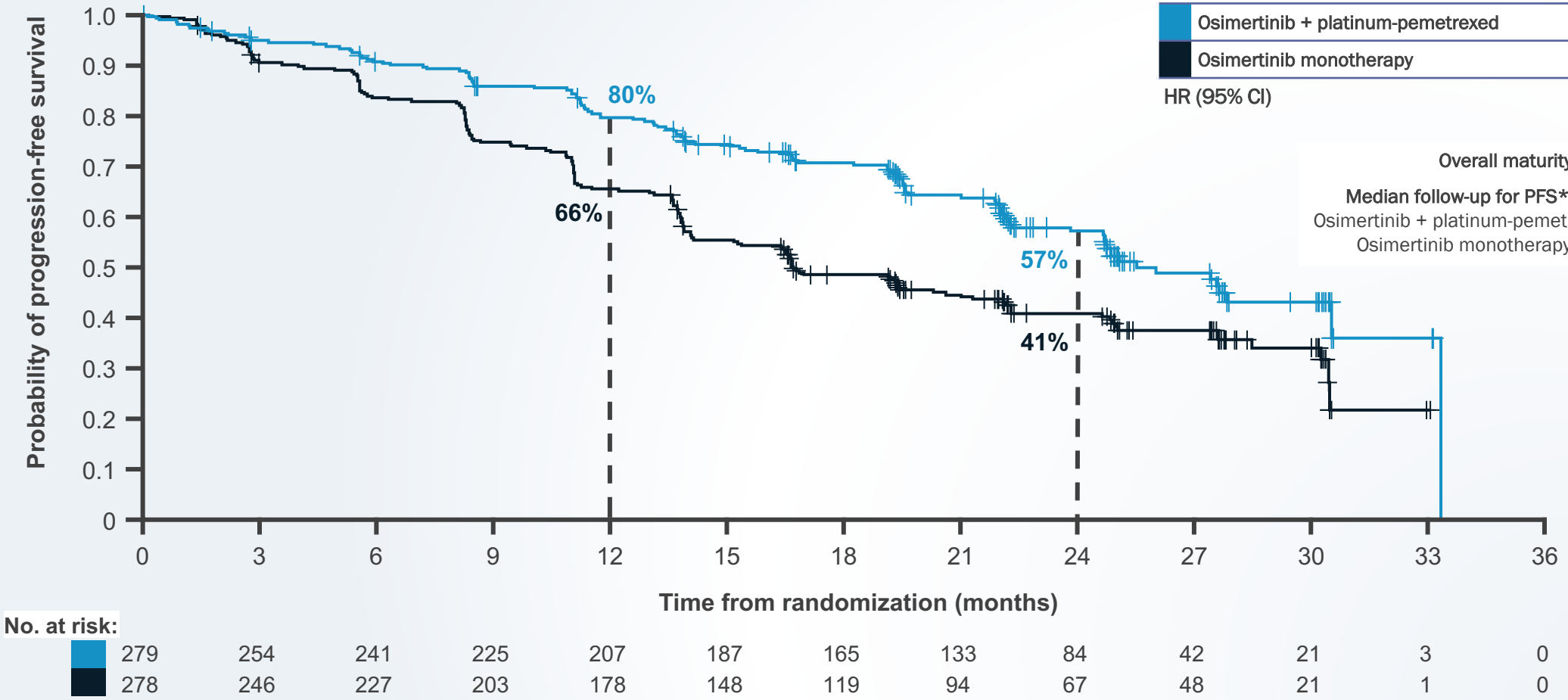
- RECIST 1.1 assessment at 6 and 12 weeks, then every 12 weeks until RECIST 1.1 defined radiological disease progression or other withdrawal criteria were met

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

Janne P et al, WCLC, 2023.

Progression-free survival per investigator

- Median PFS was improved by ~8.8 months with osimertinib plus platinum-pemetrexed vs osimertinib monotherapy



Median PFS, months (95% CI)	
Osimertinib + platinum-pemetrexed	25.5 (24.7, NC)
Osimertinib monotherapy	16.7 (14.1, 21.3)
HR (95% CI)	0.62 (0.49, 0.79); p<0.0001

Overall maturity: 51%

Median follow-up for PFS*, months (range):
Osimertinib + platinum-pemetrexed, 19.5 (0–33.3)
Osimertinib monotherapy, 16.5 (0–33.1)

Janne P et al, WCLC, 2023.

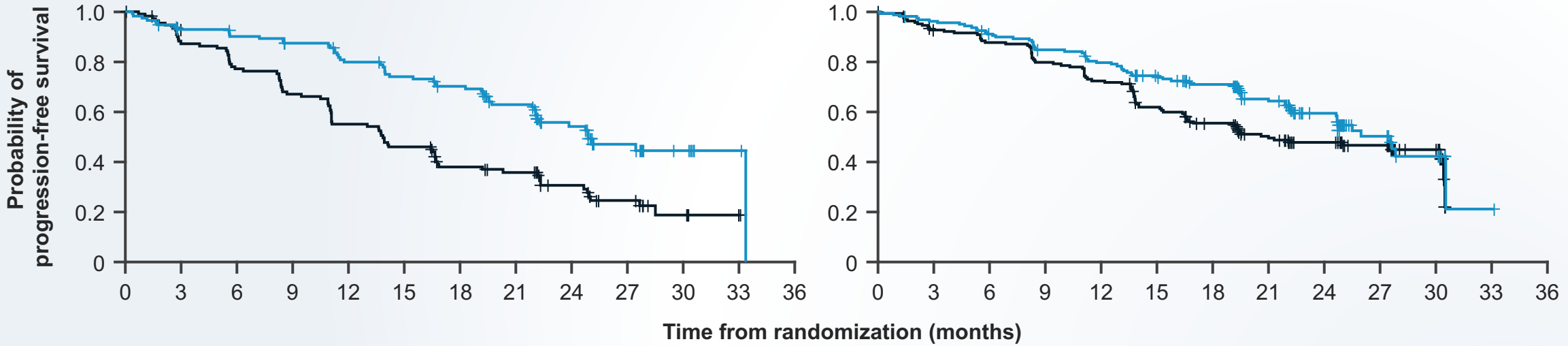
PFS per investigator in patients with / without CNS metastases at baseline*

With CNS metastases

Median PFS, months (95% CI)	
Osimertinib + platinum-pemetrexed	24.9 (22.0, NC)
Osimertinib monotherapy	13.8 (11.0, 16.7)
HR (95% CI)	0.47 (0.33, 0.66)

Without CNS metastases

Median PFS, months (95% CI)	
Osimertinib + platinum-pemetrexed	27.6 (24.7, NC)
Osimertinib monotherapy	21.0 (16.7, 30.5)
HR (95% CI)	0.75 (0.55, 1.03)



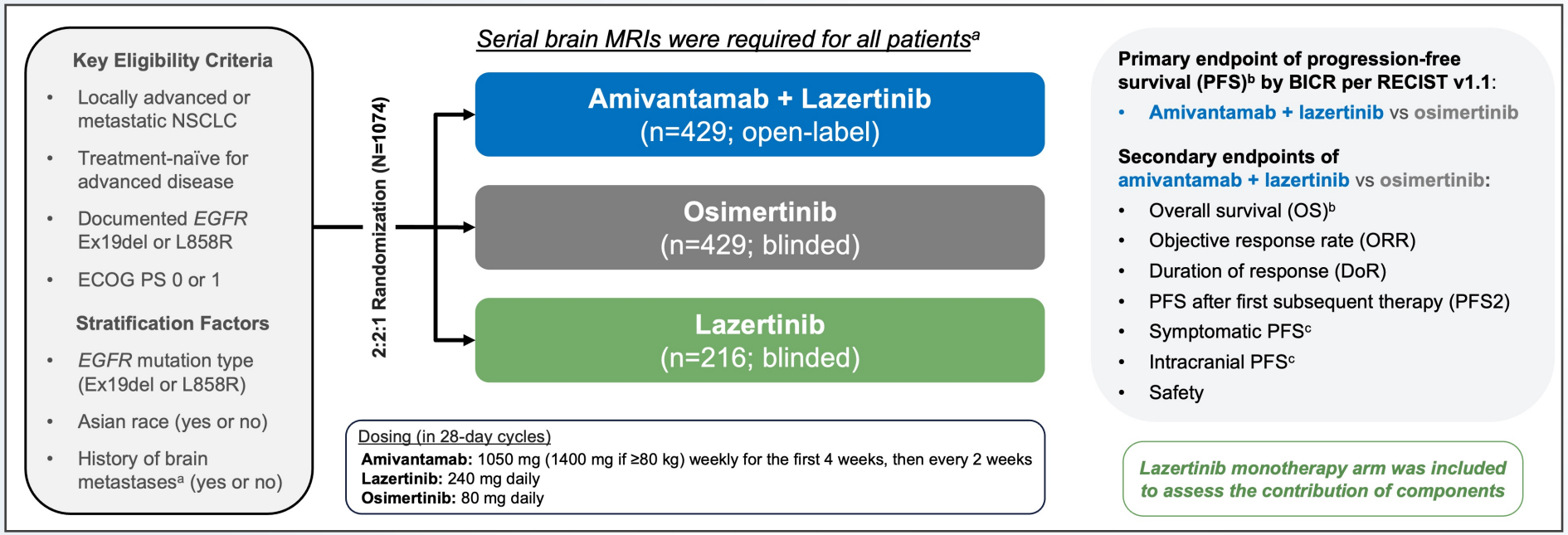
No. at risk:

116	101	98	93	84	77	70	58	34	19	8	2	0	
110	95	84	73	60	50	37	32	21	13	5	1	0	

163	153	143	132	123	110	95	75	50	23	13	1	0	
168	151	143	130	118	98	82	62	46	35	16	0	0	

Janne P et al, WCLC, 2023.

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

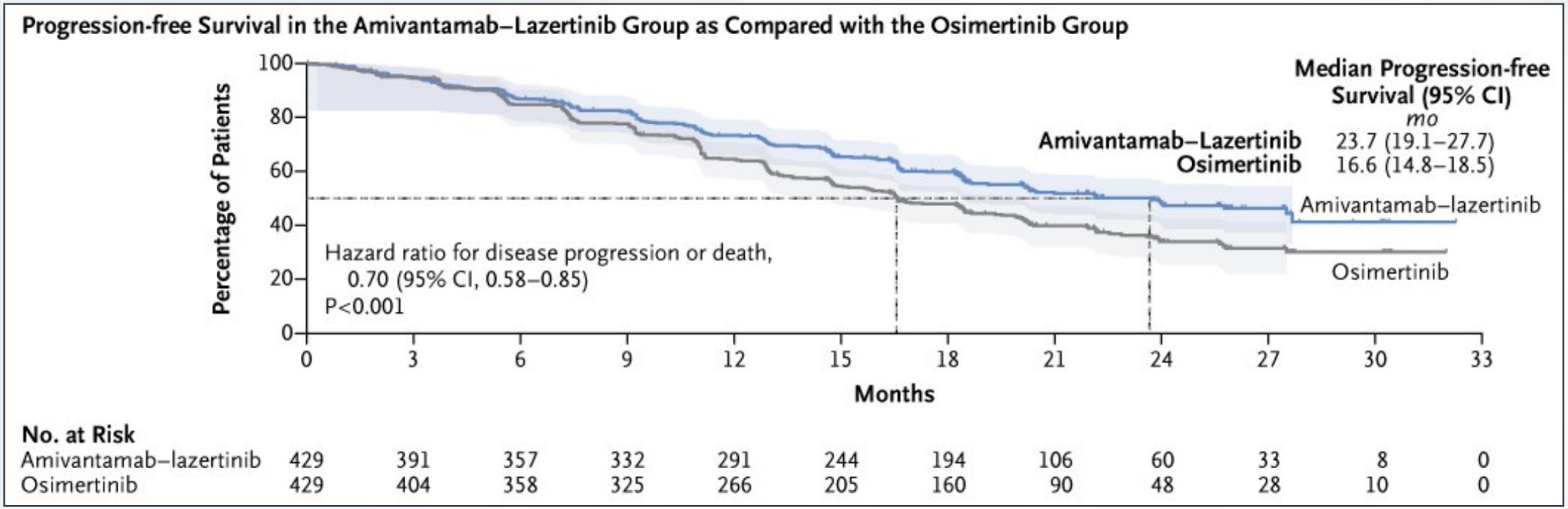


Baseline brain MRI was required for all patients and performed ≤28 days prior to randomization; patients who could not have MRIs were allowed to have CT scans. Brain scan frequency was every 8 weeks for the first 30 months and then every 12 weeks thereafter for patients with a history of brain metastasis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

- Asian patients 60%
- Smokers 30%
- Brain mets 40%
- Exon 19 60%

Cho BC, et al. ESMO 2023. Abstract LBA14.

MARIPOSA: Progression-free Survival



Cho B et al, NEJM, 2024.

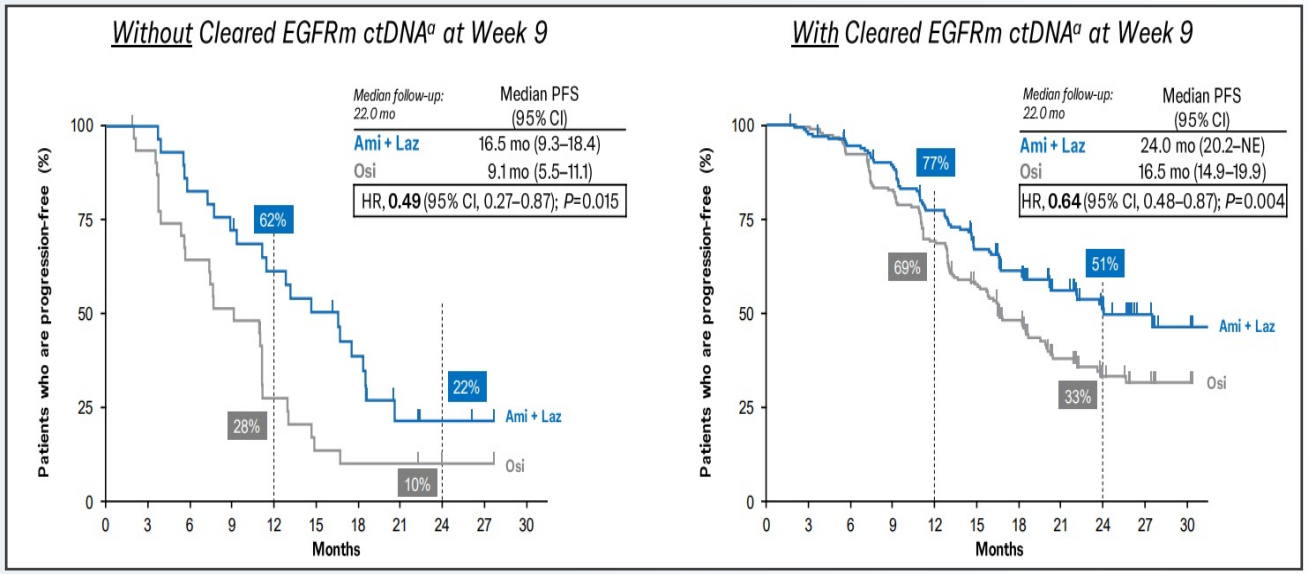
MARIPOSA: Safety Results

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

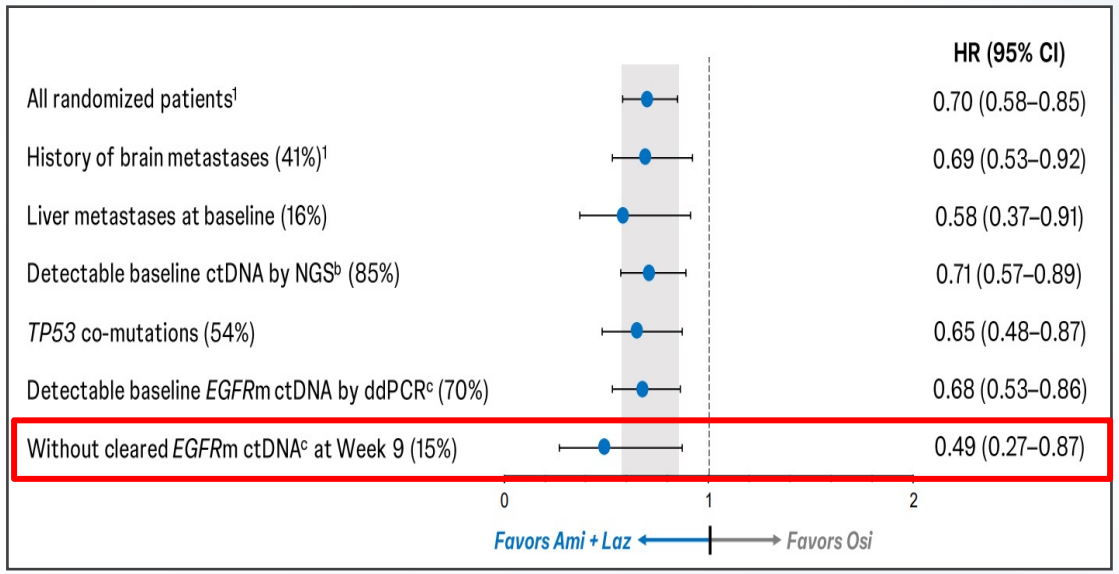
Cho B et al, NEJM, 2024.

Similar HR in patients with or without the high-risk factor

PFS without and with cleared EGFRm ctDNA at Week 9



PFS for patients with high-risk features (89% of patients had ≥1 high-risk feature at baseline)



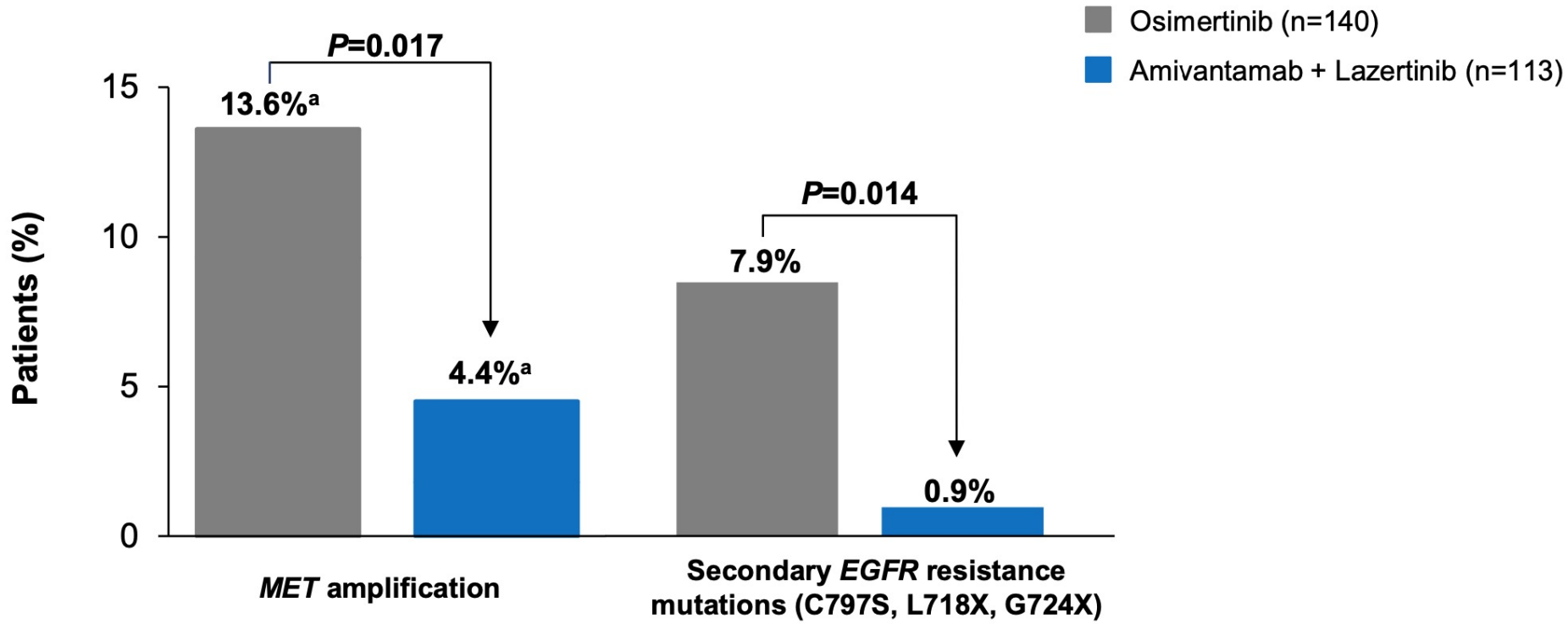
- Subgroup analysis showed similar HR in patients with or without the “high risk” factors
- Thus, these factors are prognostic but not predictive
- NOT clinically applicable for selection of patient for Ami/Laz

Felip E, et al. ASCO 2024. Abstract 8504.

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

Besse B et al, ESMO 2024.

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Salvage Therapy

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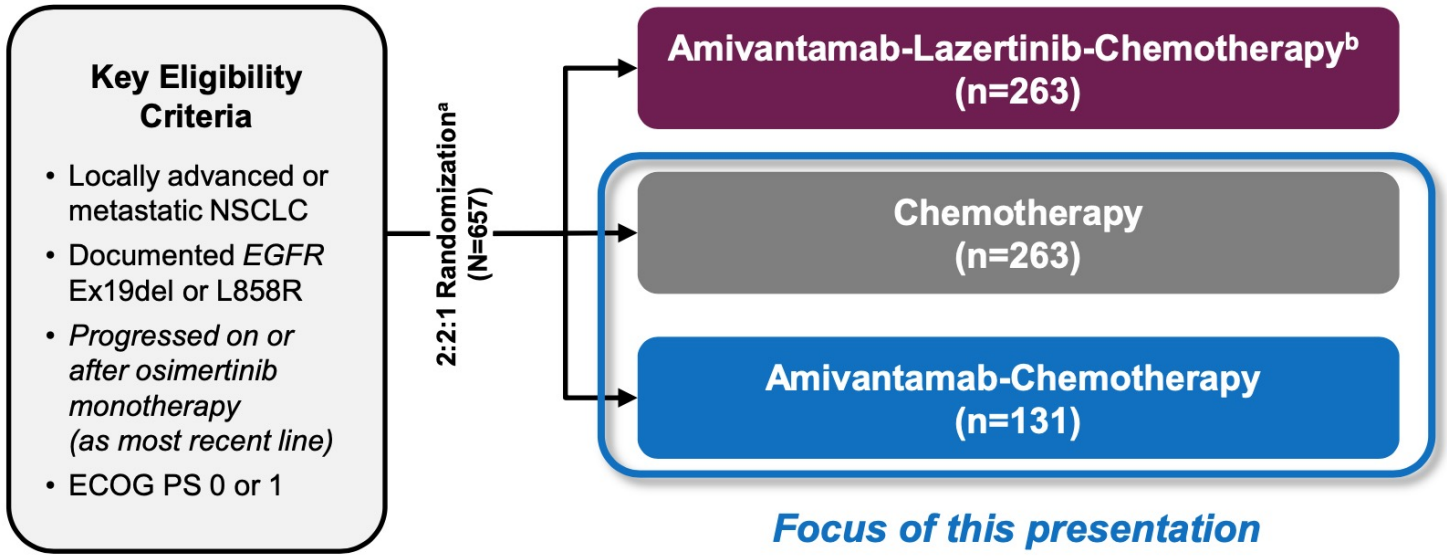
MARIPOSA-2 TRIAL



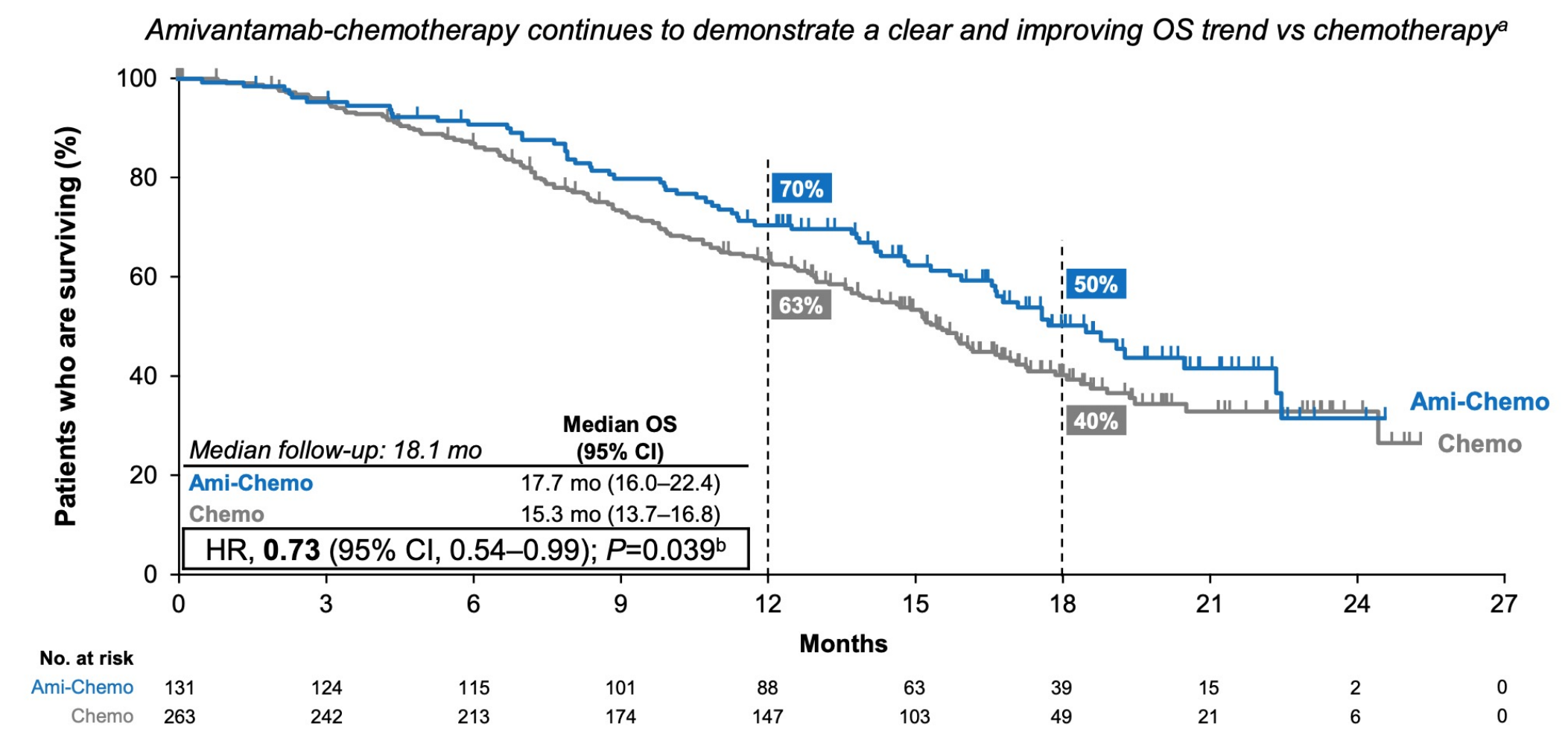
Secondary/Exploratory Efficacy Endpoints Reported:

- Overall survival (OS)
- Time to symptomatic progression (TTSP)
- Time to treatment discontinuation (TTD)
- Time to subsequent therapy (TTST)
- PFS after first subsequent therapy (PFS2)

- The second interim analysis of OS was prespecified for when ~75% of the planned OS events were observed
- The significance level at the second interim analysis for OS was determined based on the O'Brien-Fleming alpha spending approach (2-sided alpha: 0.0142) as implemented by the Lan-DeMets method

Popat S et al, ESMO 2024

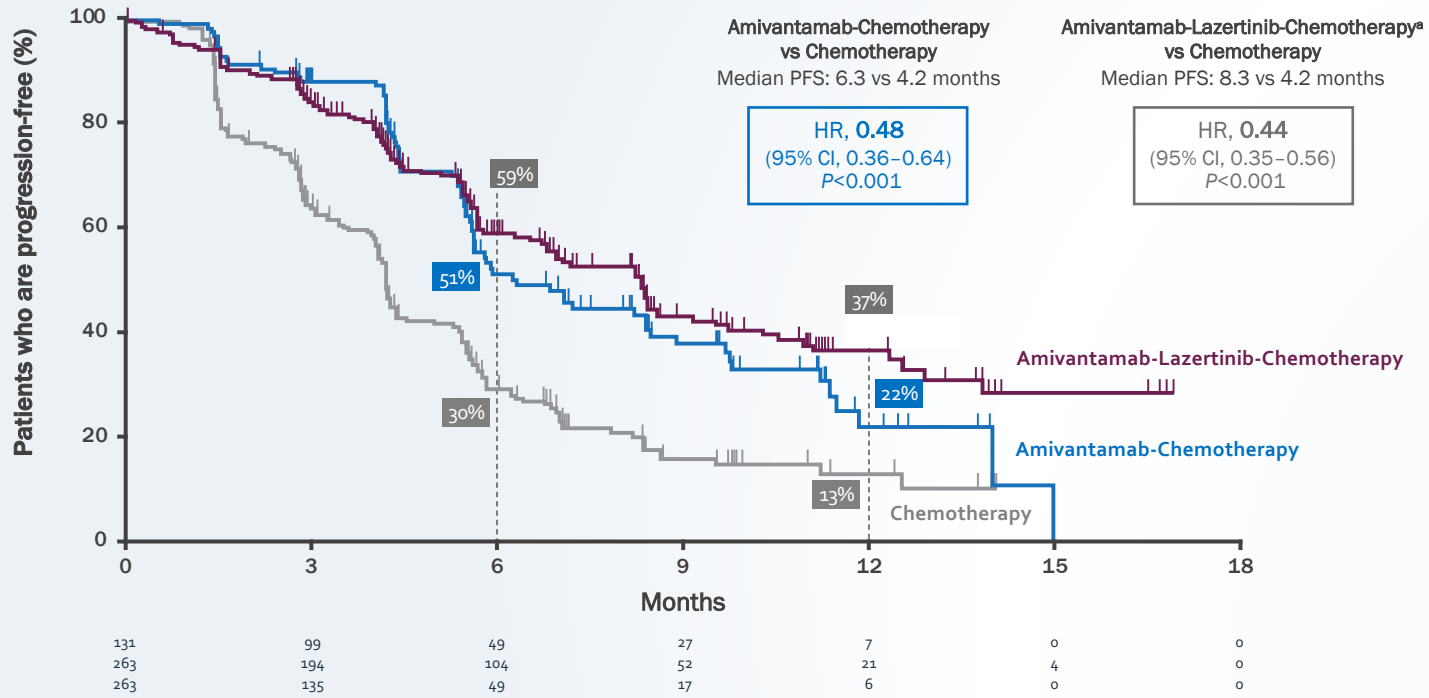
MARIPOSA 2: OVERALL SURVIVAL

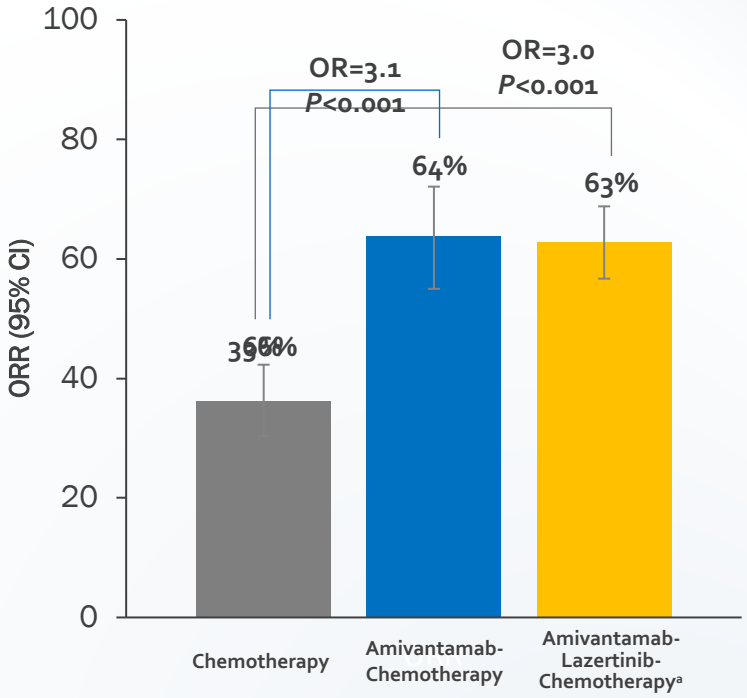


Popat S et al, ESMO 2024

Improvement in RR and PFS

- At a median follow-up of 8.7 months, amivantamab-chemotherapy and amivantamab-lazertinib-chemotherapy reduced the risk of progression or death by 52% and 56%, respectively

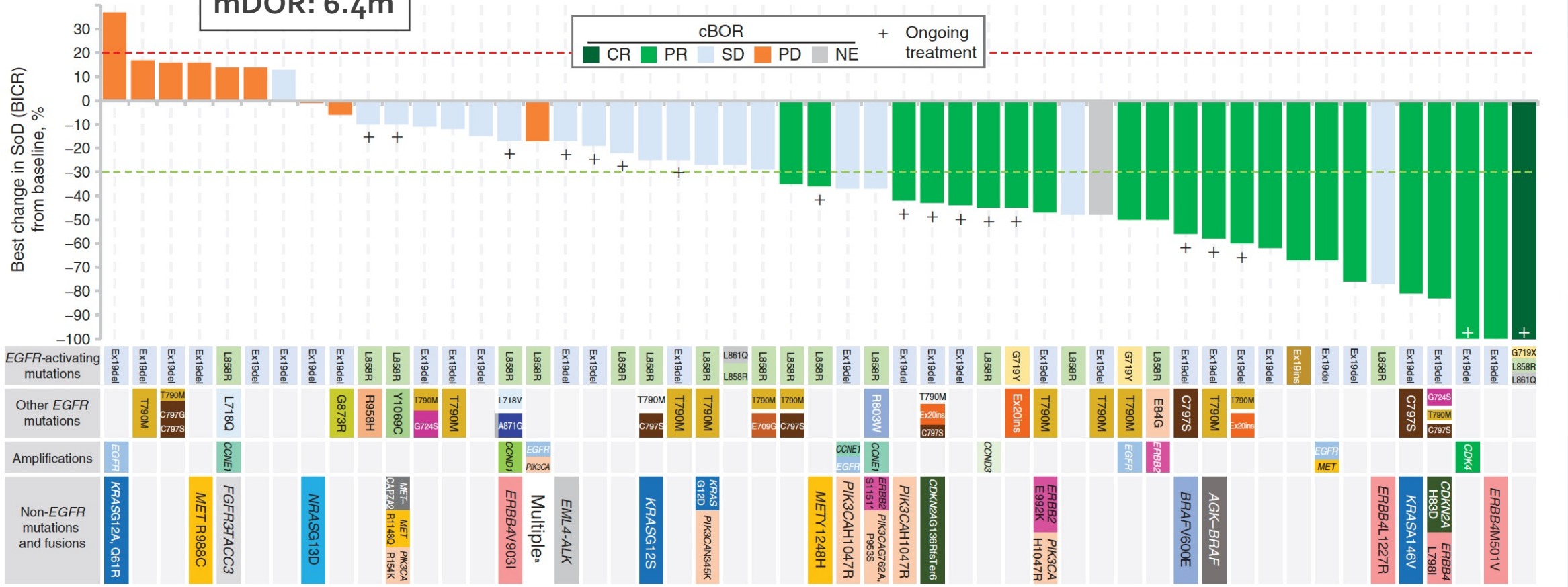




Passaro A, et al. ESMO 2023. Abstract LBA15.

Patritumab deruxtecan: efficacy in EGFR MT NSCLC

RR 30%
mDOR: 6.4m



Janne P et al, Cancer Discovery, 2022.

FDA approval delayed due to 3rd party manufacturing issues

Media > News releases > News release

Patritumab Deruxtecan Demonstrated Statistically Significant Improvement in Progression-Free Survival Versus Doublet Chemotherapy in Patients with Locally Advanced or Metastatic EGFR-Mutated Non-Small Cell Lung Cancer in HERTHENA-Lung02 Phase 3 Trial

Sept 24, 2024.

Conclusions

- EGFR mutation testing should be done for stage III NSCLC
- Osimertinib is approved following ChemoRT
- Multiple options for 1st line therapy
    - Individualized based on patient preferences and characteristics
- Salvage therapy options are increasing