Lung Cancer with EGFR E19del and L858R mutations: Optimal 1L Therapy

Jonathan W. Riess, MD MS
Professor
Medical Director Thoracic Oncology
UC Davis Comprehensive Cancer Center

UCDAVIS COMPREHENSIVE CANCER CENTER

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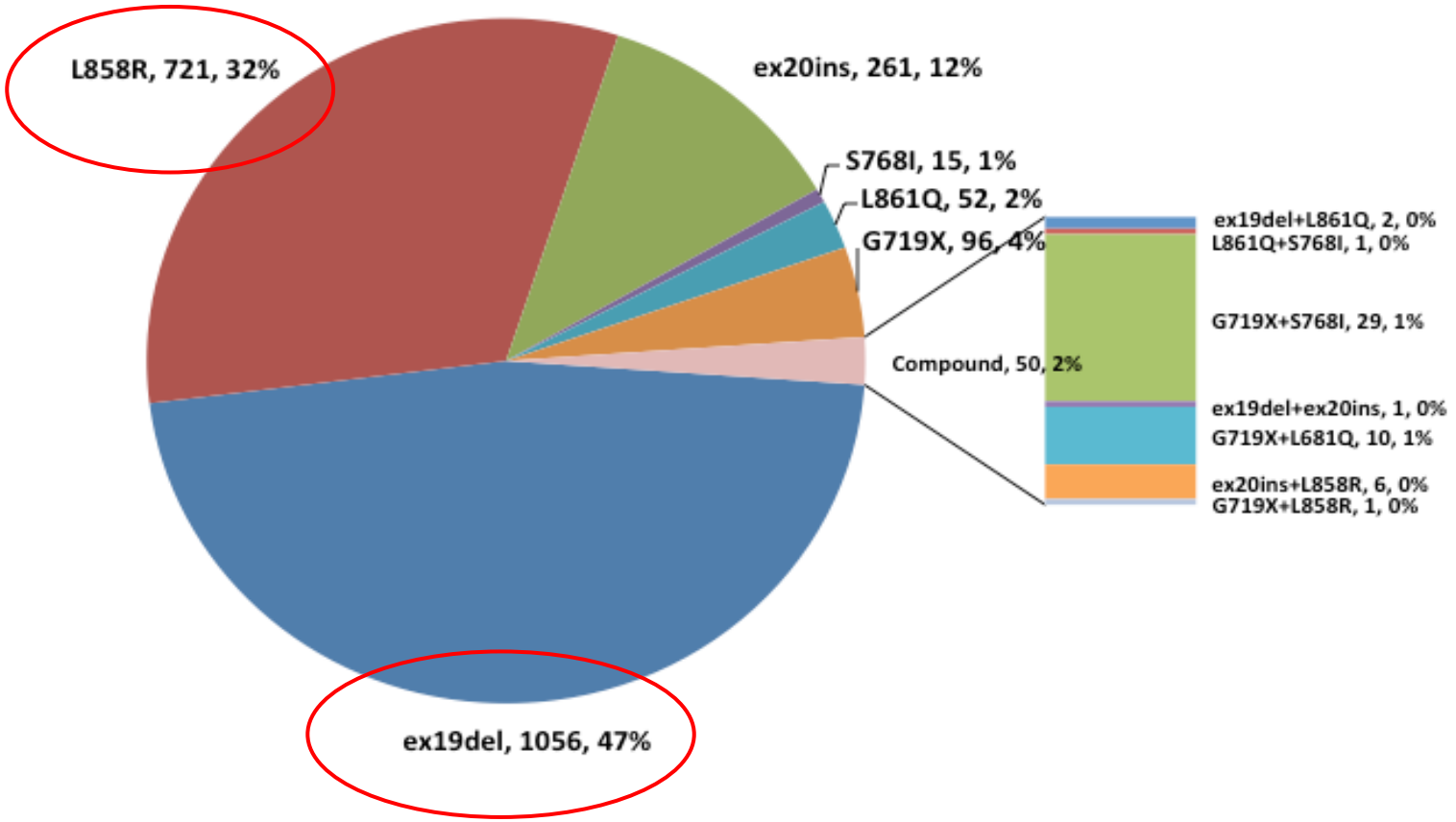
A Comprehensive Cancer Center Designated by the National Cancer Institute

Frequency and Distribution of 2,251 *EGFR* mutations in NSCLC Detected by Broad Genomic Profiling.



JW Riess et al. Journal of Thoracic Oncology 2018.

FLAURA: Osimertinib vs comparator EGFR-TKI as first-line treatment for EGFRm advanced NSCLC

Patients with locally advanced or metastatic NSCLC

Key inclusion criteria

- ≥18 years old
- WHO performance status 0/1
- Exon 19 deletion/L858R (enrollment by local or central *EGFR* testing)
- No prior systemic anticancer/ EGFR-TKI therapy
- Stable CNS metastases were allowed

Stratification by **mutation status** (exon 19 deletion/ L858R) and **race** (Asian/non-Asian)

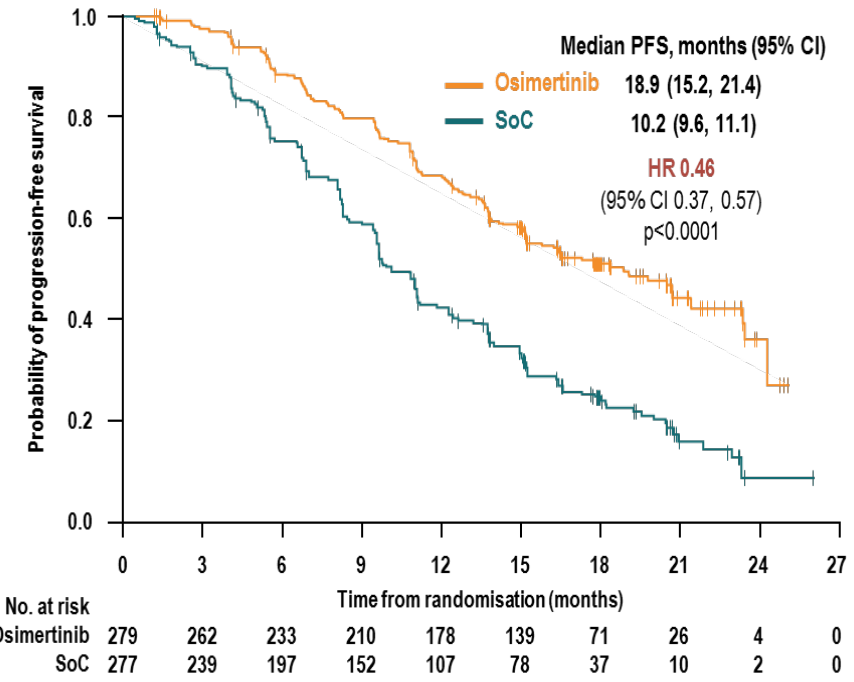
R 1:1

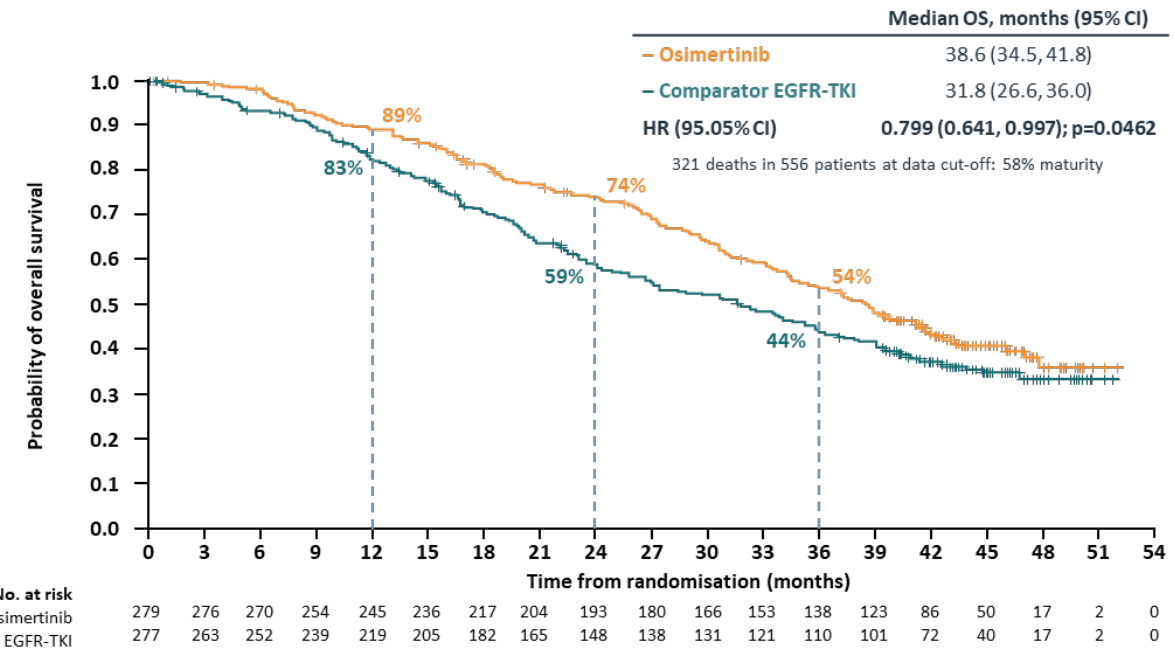
Osimertinib (80 mg po qd) (n=279)

Comparator EGFR-TKI; **Gefitinib** (250 mg po qd) or **Erlotinib** (150 mg po qd) (n=277)

RECIST v1.1 assessment every 6 weeks until objective progressive disease
Following the primary PFS analysis, progression events per RECIST 1.1 were no longer collected centrally

Crossover was allowed for patients in the **comparator** arm, who could receive open-label osimertinib upon central confirmation of progression and T790M positivity





Ramalingam SS, et al. ESMO 2019. Abstract LBA5_PR.

First-line intensification strategies

Standard-of-care for mEGFR-mut NSCLC

Osimertinib PFS 18.9 months

FLAURA2

Randomized phase III
EGFR mutation NSCLC
Stage IIIb/IV
Primary endpoint: PFS

R

- Osimertinib + carboplatin + pemetrexed x 4 cycles
- Osimertinib + pemetrexed
- Osimertinib

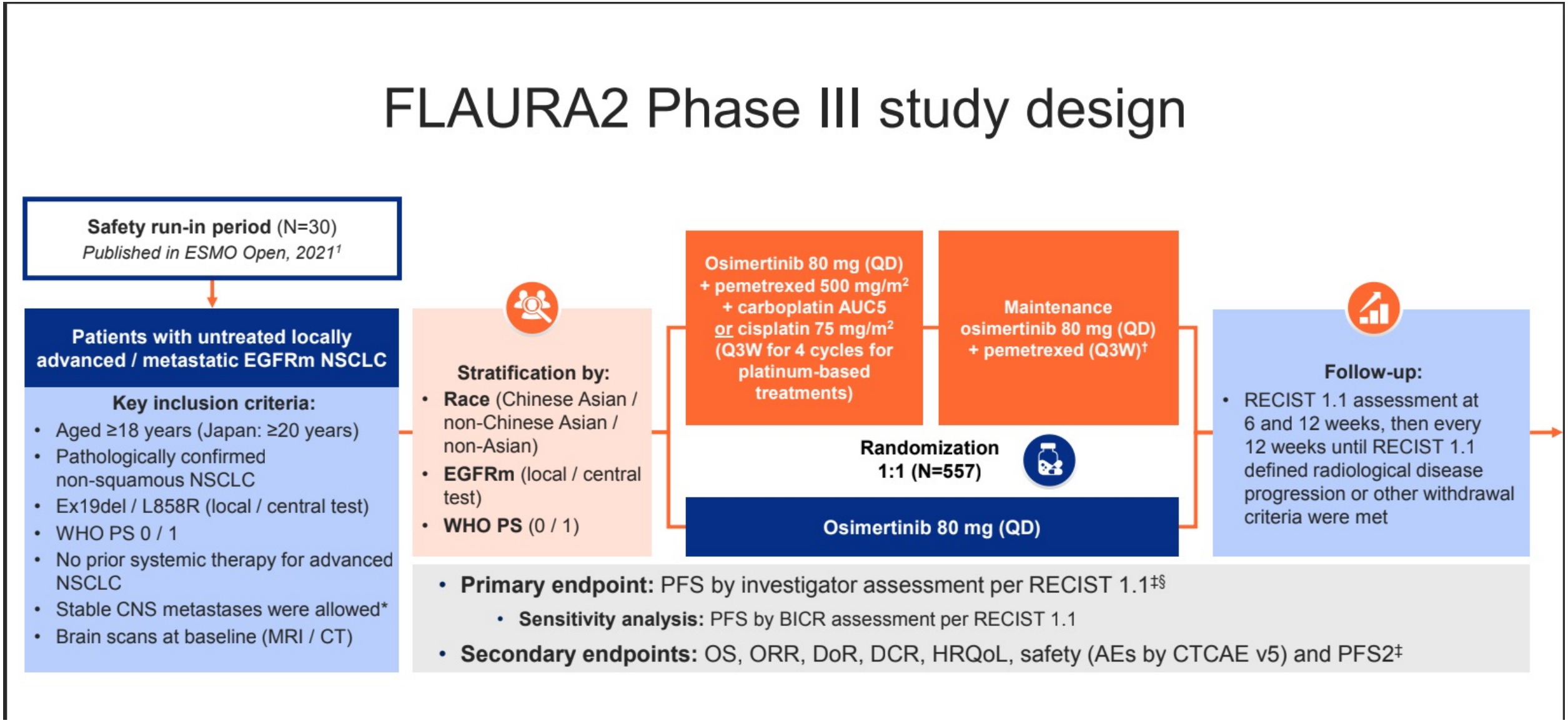
MARIPOSA

Randomized phase III
EGFR mutation NSCLC
Stage IIIb/IV
Primary endpoint: PFS

R

- Lazertinib + amivantamab
- Lazertinib
- Osimertinib

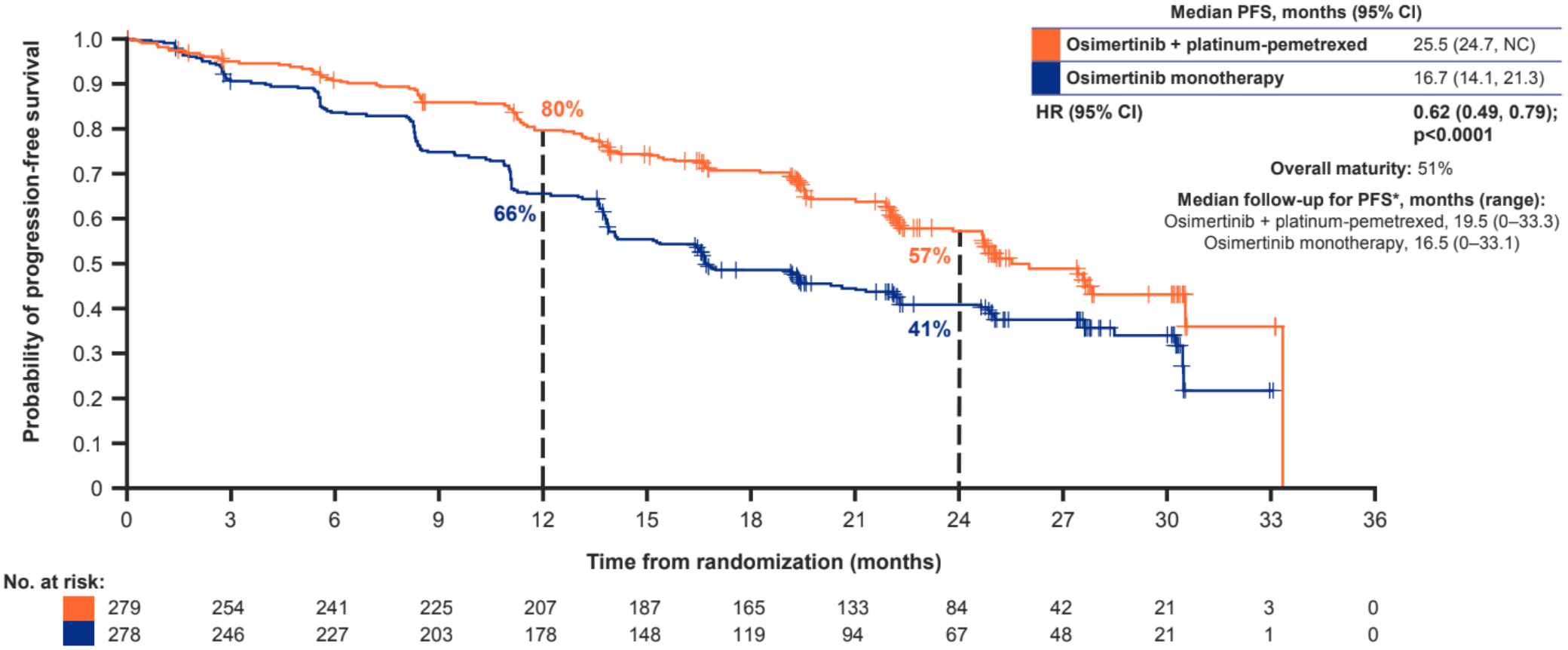
FLAURA 2: Osimertinib + Chemotherapy in the Front-Line Setting



FLAURA 2

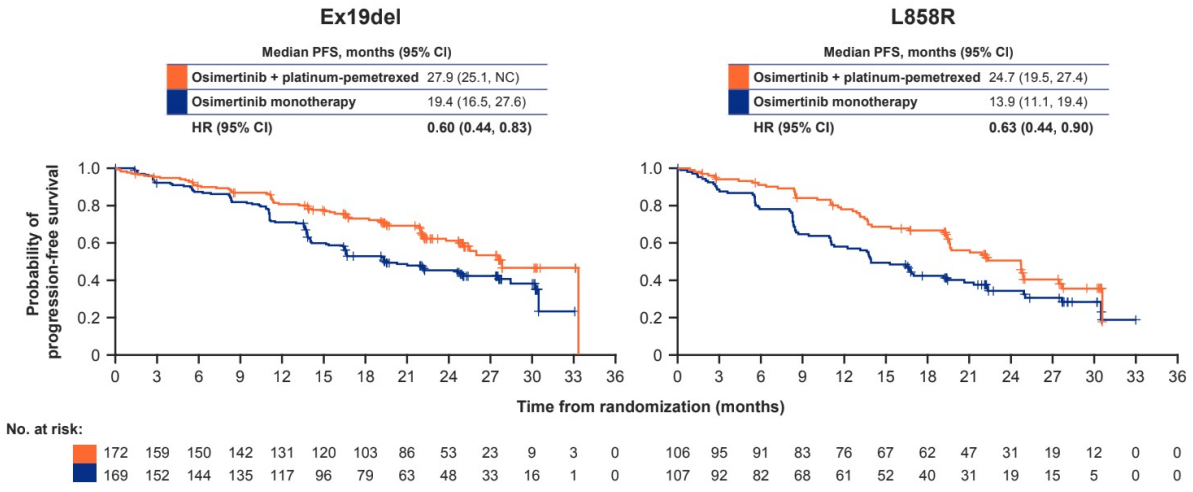
Progression-free survival per investigator

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

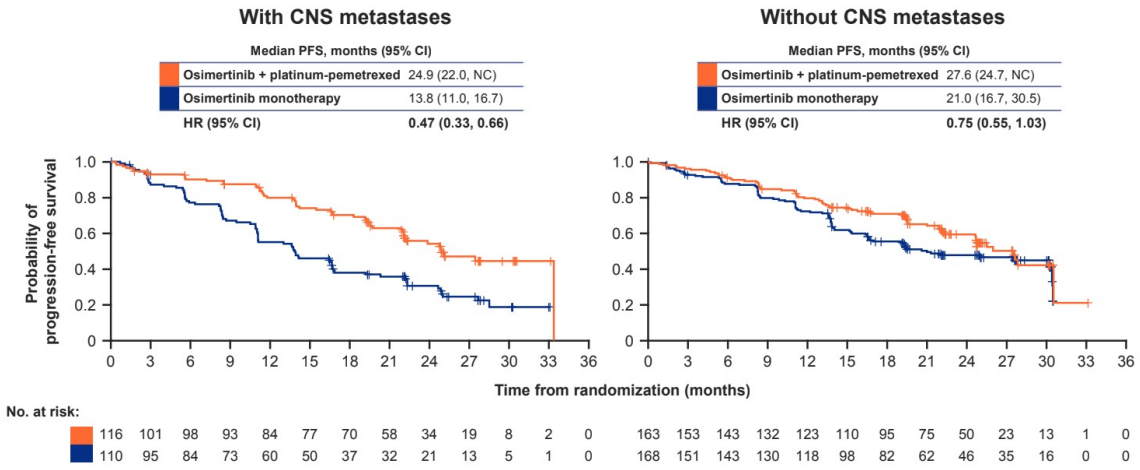


FLAURA 2: Patient Characteristics of Interest

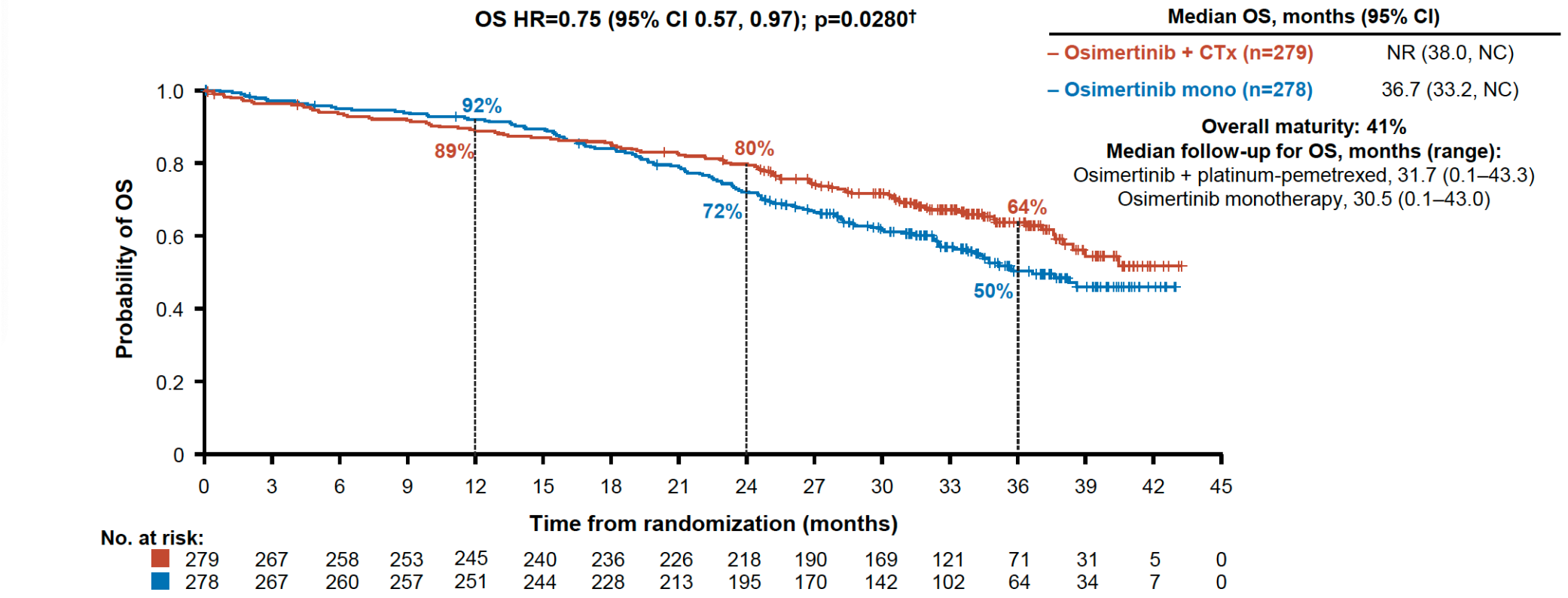
PFS per investigator by EGFR mutation type at baseline*



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



Second Interim OS Analysis

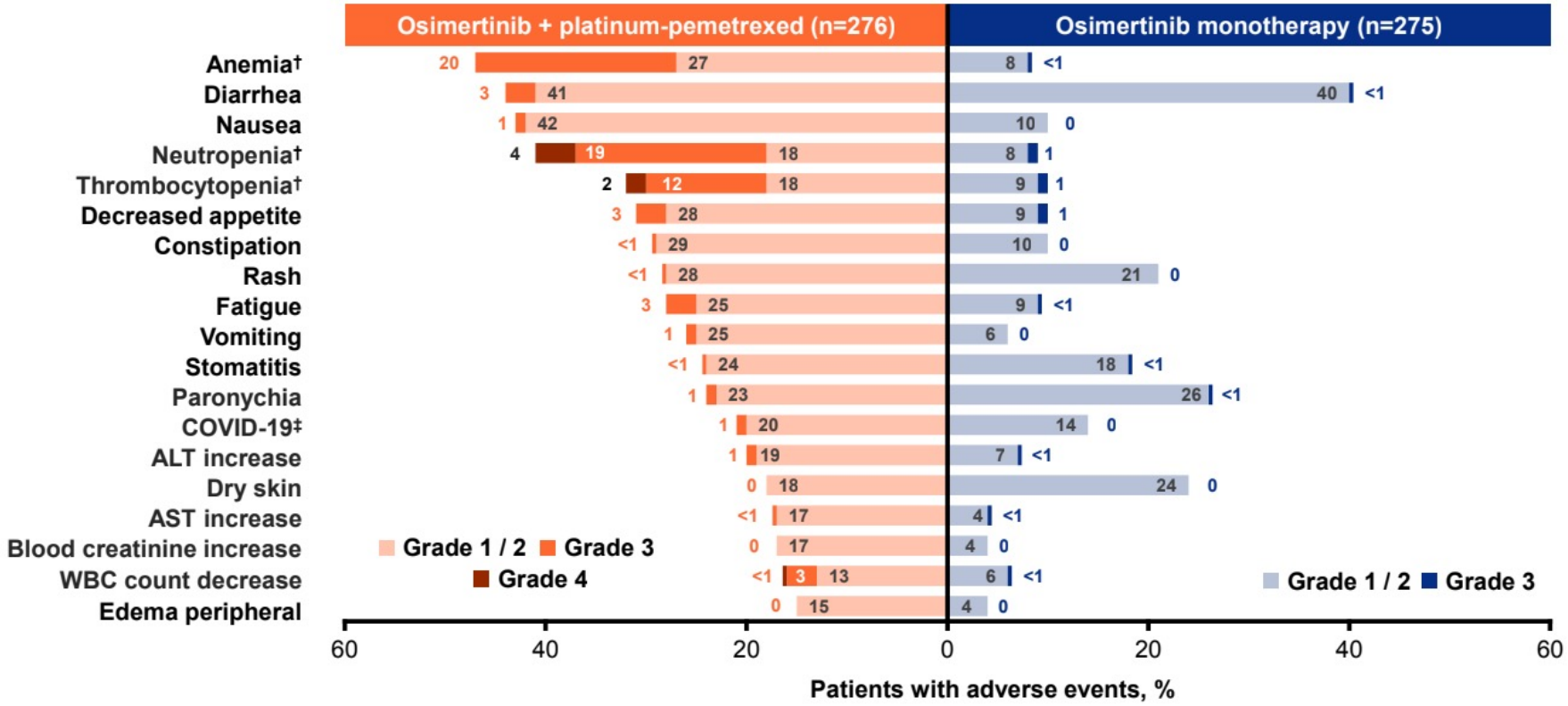


Data cut-off: 08 January 2024. HR was calculated by a stratified log-rank test. Figure from Valdiviezo N, et al. Presented at: ELCC 2024 (4O)
†A p-value of ≤0.000001 was required for statistical significance at this second interim analysis
Valdiviezo N, et al. ESMO Open 2024;9:102583
CI, confidence interval; CTx, chemotherapy; HR, hazard ratio; mono, monotherapy; NC, not calculable; NR, not reached; OS, overall survival

Valdiviezo. NA et al. ELCC 2024: Abstract 4O.

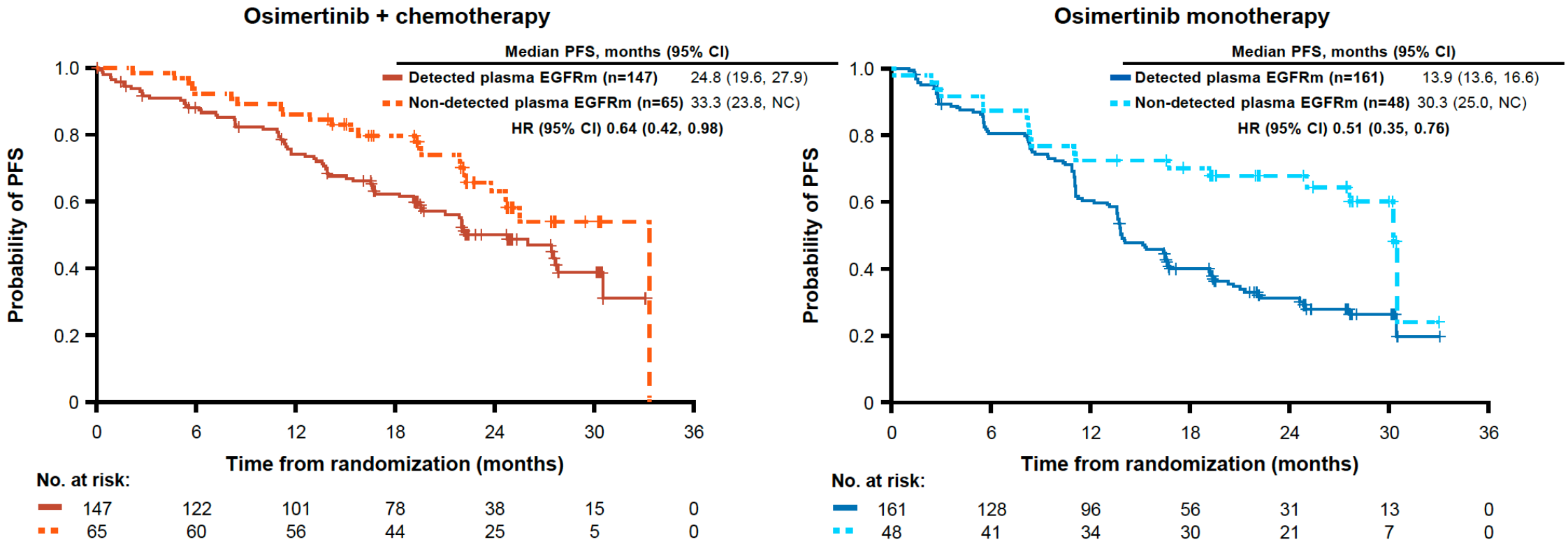
FLAURA 2

Common adverse events (≥15% of patients)*



- Of most common AEs (occurring in ≥15% of patients in either arm), all Grade 4 AEs in the osimertinib plus platinum-pemetrexed arm were hematological toxicities, known to be associated with chemotherapy; there were no common Grade 4 AEs in the monotherapy arm

Baseline-detected plasma EGFRm correlated with PFS in the ctDNA analysis set across both treatment arms



- Patients with baseline-detected plasma EGFRm had shorter median PFS (24.8 and 13.9 months) compared with those with baseline non-detected plasma EGFRm (33.3 and 30.3 months) in the osimertinib plus chemotherapy and osimertinib monotherapy arms, respectively

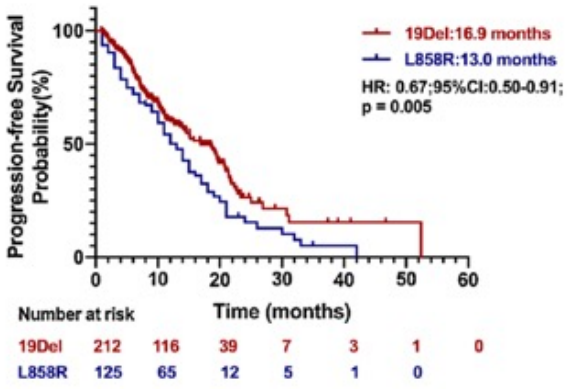
ctDNA analysis set. HR was calculated by an unstratified log-rank test
CI, confidence interval; ctDNA, circulating tumor DNA; EGFRm, epidermal growth factor receptor mutation; HR, hazard ratio; NC, not calculable; PFS, progression-free survival

P. Janne et al. AACR 2024

High risk group identification

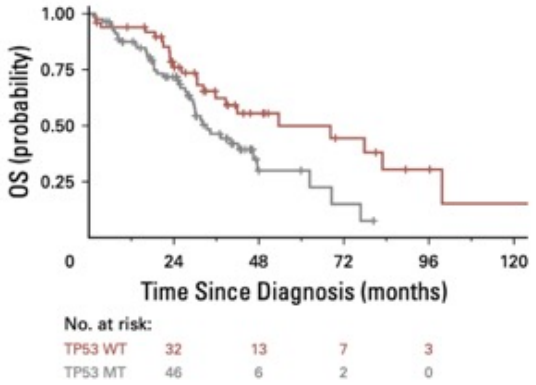
❖ **Clinical features** – L858R, TP53MUT, NRF2 genotypes, RBM10 Mut, CNS/Liver met

L858R higher risk than Del19



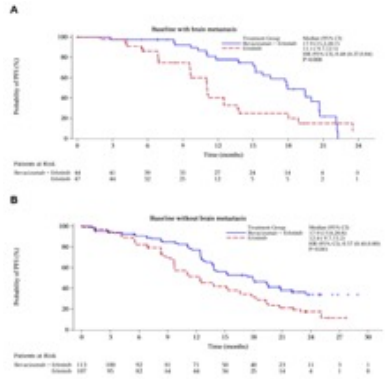
Liu and Le Lung Cancer 2020

TP53 mut higher risk than TP wt



Aggarwal et al JCO Precision Oncology 2018

CNS/liver mets higher risk than not



Zhou Q et al Cancer Cell 2021

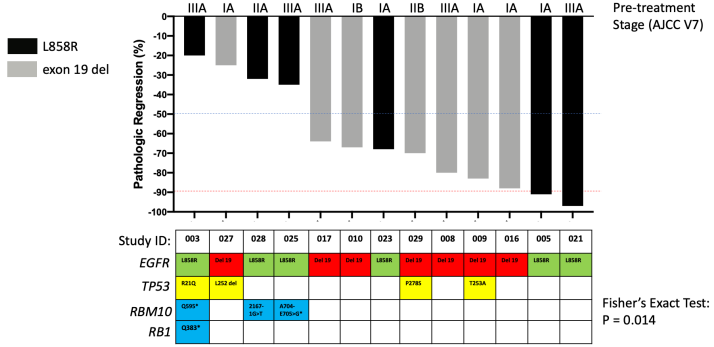
❖ **Biomarkers**

- ctDNA at baseline

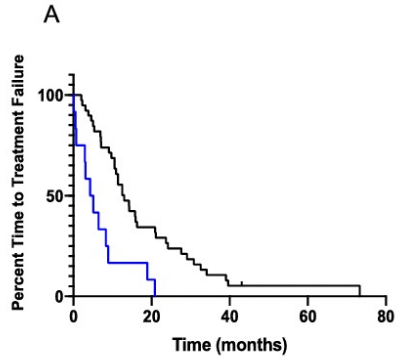
❖ **Molecular guided intensification**

- Failure to clear ctDNA

Co-occurring RBM10 mutations correlate with lack of pathological response



TTF with NRF2 Activating Genotypes In EGFR mut NSCLC (NFE2L2/KEAP1/CUL3)



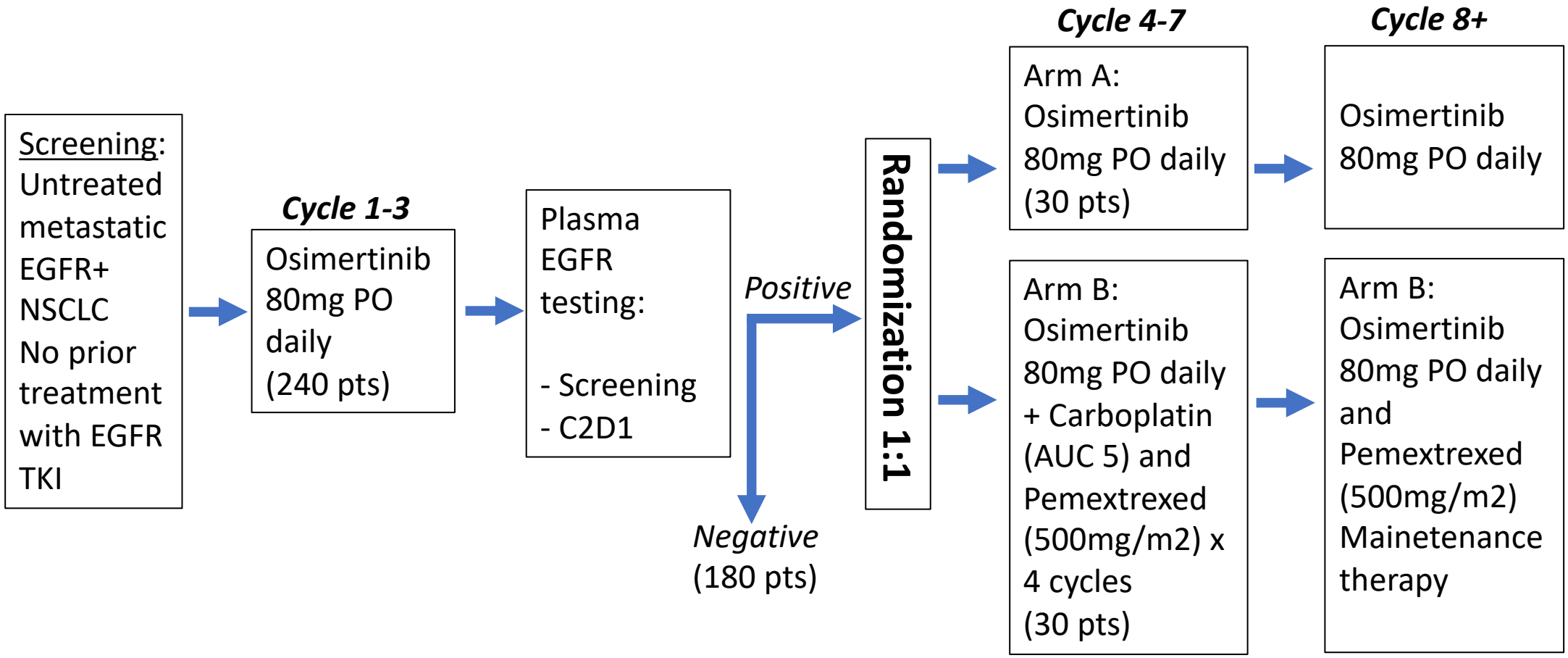
Median TTF 4.7 vs 13.0 months
HR = 2.8 (95% CI 1.1 – 7.2), *p= 0.0014*

Aredo et al. ASCO 2023. Hellyer et al. CLC 2019.

Guide for Treatment Intensification: Who are the bad actors?

- ctDNA positive at baseline
- Co-mutations p53, RBM10, NRF2 genotypes
- CNS metastases, Liver metastases
- Tumor volume/disease burden?

Shedders Trial



PI: Helena Yu, MD

MARIPOSA Phase 3 study design

Key Eligibility Criteria

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

Stratification Factors

- *EGFR* mutation type (Ex19del or L858R)
- Asian race (yes or no)
- History of brain metastases[a] (yes or no)

2:2:1 Randomization (N=1074)

Serial brain MRIs were required for all patients[a]

Amivantamab + Lazertinib
(n=429; open-label)

Osimertinib
(n=429; blinded)

Lazertinib
(n=216; blinded)

Dosing (in 28-day cycles)
Amivantamab: 1050 mg (1400 mg if ≥80 kg) weekly for the first 4 weeks, then every 2 weeks
Lazertinib: 240 mg daily
Osimertinib: 80 mg daily

Primary endpoint of progression-free survival (PFS)[b] by BICR per RECIST v1.1:
- **Amivantamab + lazertinib** vs **osimertinib**

Secondary endpoints of amivantamab + lazertinib vs osimertinib:
- Overall survival (OS)[b]
- Objective response rate (ORR)
- Duration of response (DoR)
- PFS after first subsequent therapy (PFS2)
- Symptomatic PFS[c]
- Intracranial PFS[c]
- Safety

Lazertinib monotherapy arm was included to assess the contribution of components

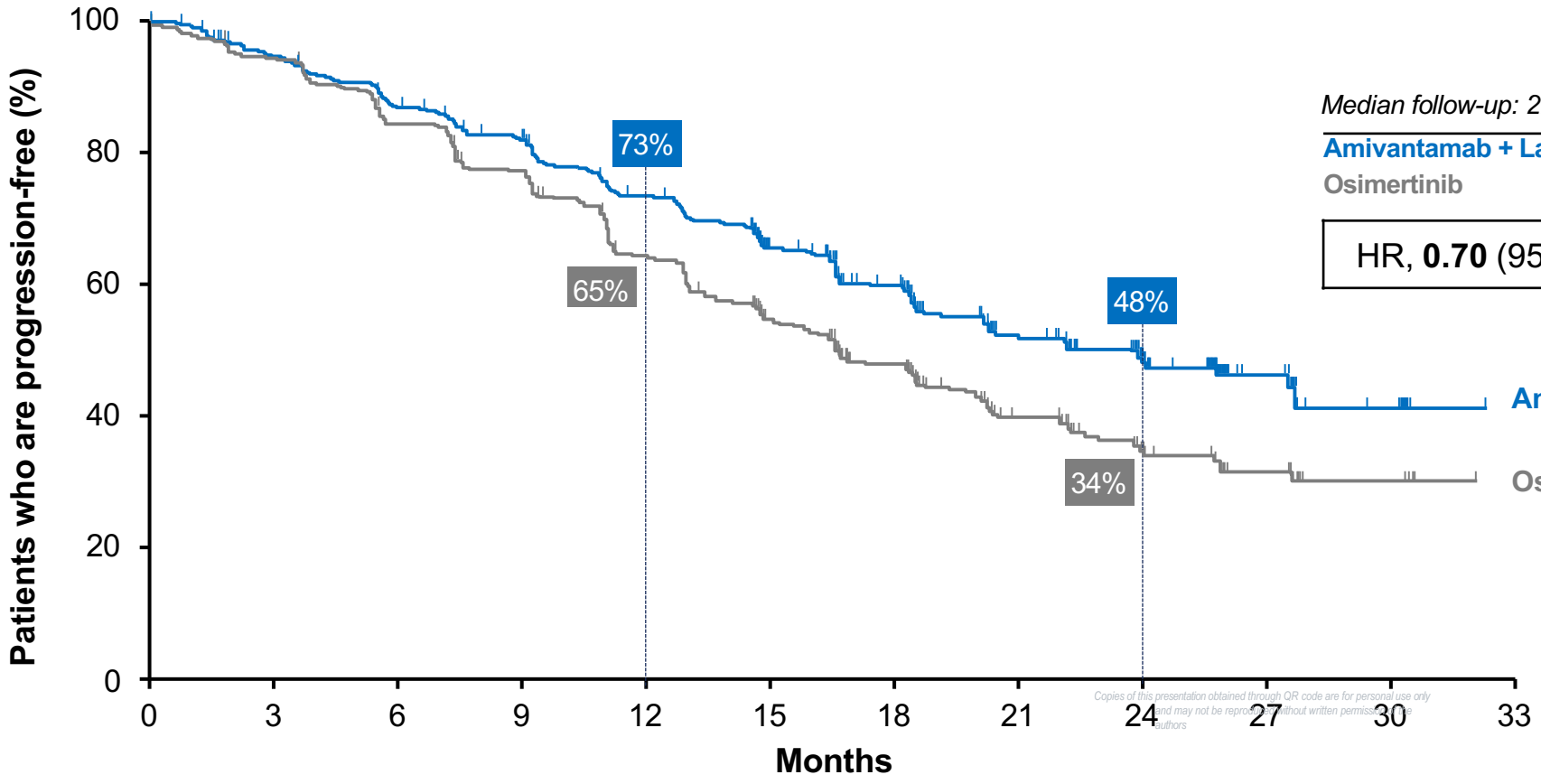
MARIPOSA (ClinicalTrials.gov Identifier: NCT04487080) enrollment period: November 2020 to May 2022; data cut-off: 11-Aug-2023.

[a]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. Extracranial tumor assessments were conducted every 8 weeks for the first 30 months and then every 12 weeks until disease progression is confirmed by BICR.
[b]Key statistical assumptions: 800 patients with 450 PFS events would provide approximately 90% power for amivantamab + lazertinib vs osimertinib to detect a HR of 0.73 using a log-rank test, with an overall two-sided alpha of 0.05 (assuming an incremental median PFS of 7 months). Statistical hypothesis testing included PFS and then OS.
[c]These secondary endpoints (symptomatic and intracranial PFS) will be presented at a future congress.

BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletion; HR, hazard ratio;

Cho B, et al., *ESMO Congress*, 2023

Progression-free survival between Ami-lazertinib vs. osimertinib



Median follow-up: 22.0 months	**Median PFS (95% CI)**
Amivantamab + Lazertinib	23.7 mo (19.1–27.7)
Osimertinib	16.6 mo (14.8–18.5)

HR, **0.70** (95% CI, 0.58–0.85); *P*<0.001

No. at risk												
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

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

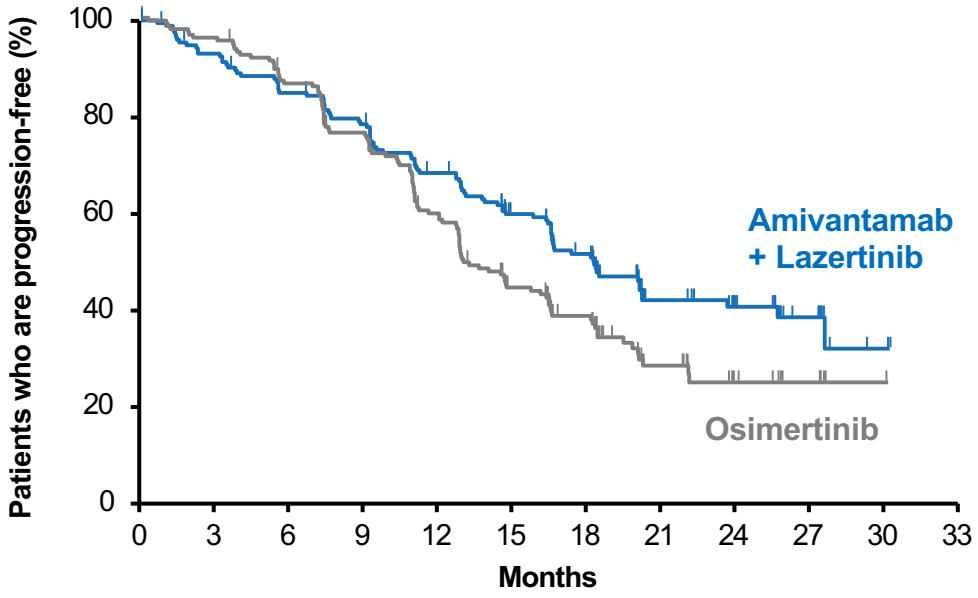
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival.

Cho B, et al., *ESMO Congress*, 2023

Consistent PFS (BICR) Benefit With or Without Brain Metastases

With History of Brain Metastases	Median PFS (95% CI)
Amivantamab + Lazertinib	18.3 mo (16.6–23.7)
Osimertinib	13.0 mo (12.2–16.4)

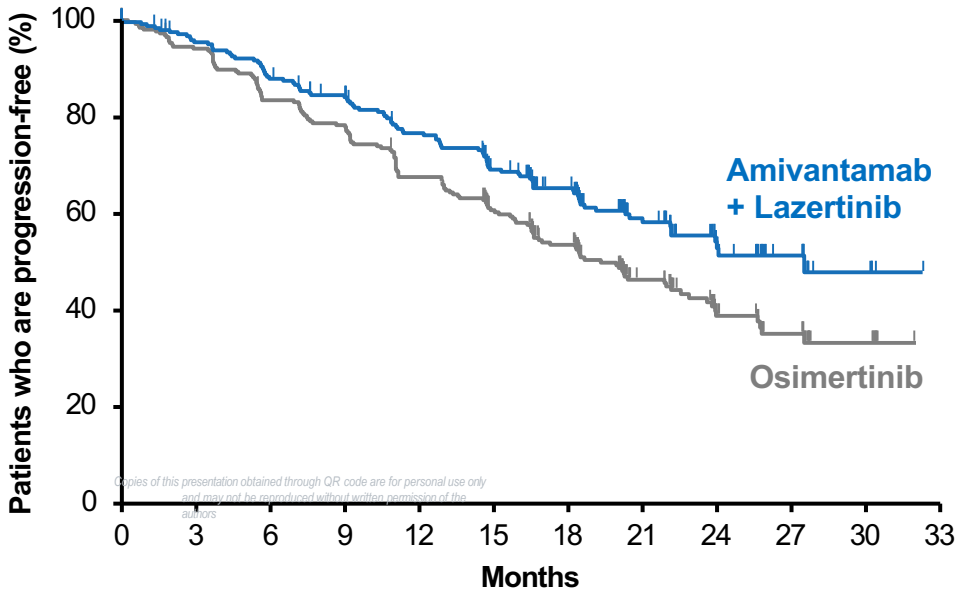
HR, **0.69** (95% CI, 0.53–0.92)



No. at risk												
Amivantamab + Lazertinib	178	162	146	134	115	92	71	34	24	12	3	0
Osimertinib	172	164	146	126	95	64	47	21	11	6	1	0

Without History of Brain Metastases	Median PFS (95% CI)
Amivantamab + Lazertinib	27.5 mo (22.1–NE)
Osimertinib	19.9 mo (16.6–22.9)

HR, **0.69** (95% CI, 0.53–0.89)



No. at risk												
Amivantamab + Lazertinib	251	229	211	198	176	152	123	72	36	21	5	0
Osimertinib	257	240	212	199	171	141	113	69	37	22	9	0

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; mo, months; NE, not estimable; PFS, progression-free survival.

Cho B, et al., *ESMO Congress*, 2023

Safety summary

- Median treatment duration was 18.5 mo for amivantamab + lazertinib and 18.0 mo for osimertinib

TEAE, n (%)	Amivantamab + Lazertinib (n=421)	Osimertinib (n=428)
Any AE	421 (100)	425 (99)
Grade ≥3 AEs	316 (75)	183 (43)
Serious AEs	205 (49)	143 (33)
AEs leading to death	34 (8)	31 (7)
Any AE leading to treatment:		
Interruptions of any agent	350 (83)	165 (39)
Reductions of any agent	249 (59)	23 (5)
Discontinuations of any agent	147 (35)	58 (14)

Treatment-related AEs leading to discontinuations of all agents occurred in 10% of patients treated with amivantamab + lazertinib and 3% with osimertinib

AE, adverse event; mo, months; TEAE, treatment-emergent AE.

Cho B, et al., *ESMO Congress*, 2023

MARIPOSA: Secondary Analysis with biomarkers of high-risk disease

	Ami+laz, osi (n)	Ami+laz vs osi, mPFS (mo)	HR (95% CI); *P* value
Detectable baseline ctDNA by NGS	266, 274	20.3 vs 14.8	0.71 (0.57–0.89); 0.003
***TP53* co-mutation**	149, 144	18.2 vs 12.9	0.65 (0.48–0.86); 0.003
***TP53* wild-type**	117, 130	22.1 vs 19.9	0.75 (0.52–1.07); 0.11
Detectable baseline ctDNA by ddPCR	231, 240	20.3 vs 14.8	0.68 (0.53–0.86); 0.002
Cleared at C3D1	163, 180	24.0 vs 16.5	0.64 (0.48–0.87); 0.004
Not cleared at C3D1	29, 32	16.5 vs 9.1	0.48 (0.27–0.86); 0.014
Liver metastases at baseline			
Present	64, 72	18.2 vs 11.0	0.58 (0.37–0.91); 0.017
Absent	365, 357	24.0 vs 18.3	0.74 (0.60–0.91); 0.004

Felip E. et al ASCO 2024 #8504

2024 ASCO® ANNUAL MEETING

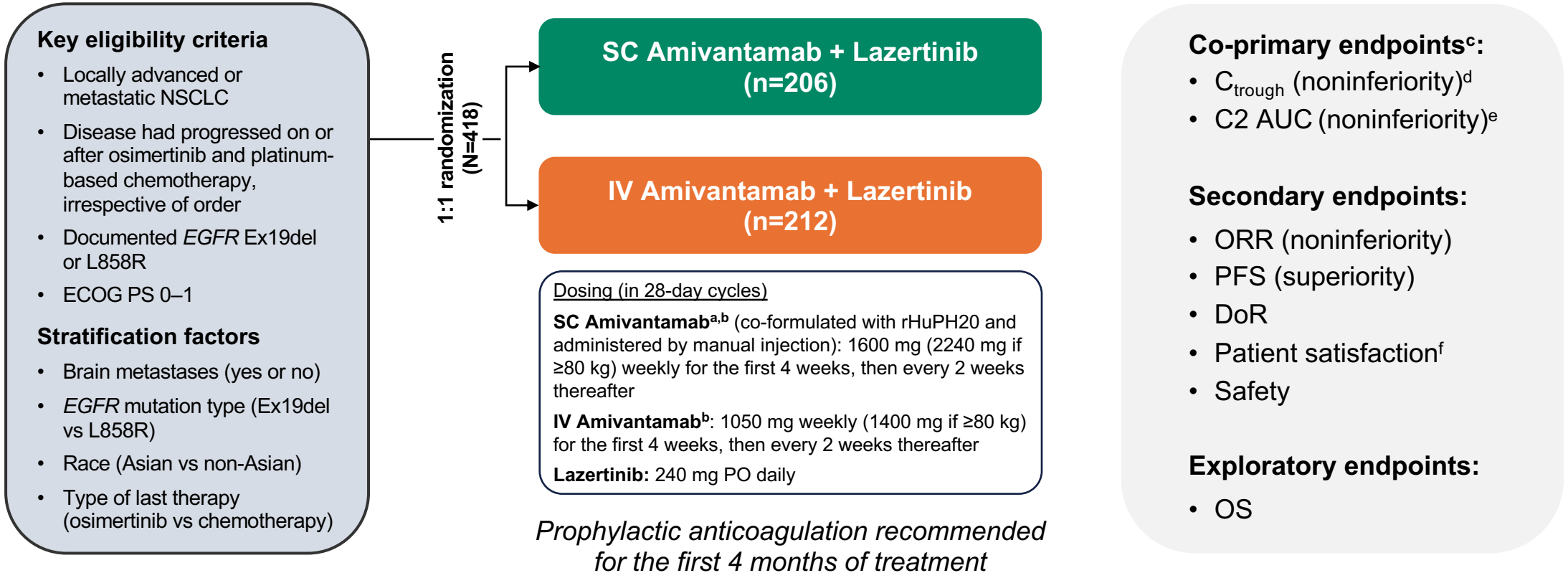
Subcutaneous amivantamab vs intravenous amivantamab, both in combination with lazertinib, in refractory *EGFR*-mutated, advanced non-small cell lung cancer

Primary results, including overall survival, from the global, phase 3, randomized controlled PALOMA-3 trial

Natasha B Leighl,[1] Hiroaki Akamatsu,[2] Sun Min Lim,[3] Ying Cheng,[4] Anna R Minchom,[5] Melina E Marmarelis,[6] Rachel E Sanborn,[7] James Chih-Hsin Yang,[8] Baogang Liu,[9] Thomas John,[10] Bartomeu Massutí,[11] Alexander I Spira,[12] John Xie,[13] Debopriya Ghosh,[13] Ali Alhadab,[14] Remy B Verheijen,[15] Mohamed Gamil,[16] Joshua M Bauml,[16] Mahadi Baig,[13] Antonio Passaro[17]

[1]Princess Margaret Cancer Centre, Toronto, ON, Canada; [2]Internal Medicine III, Wakayama Medical University, Wakayama, Japan; [3]Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea; [4]Jilin Cancer Hospital, Changchun, China; [5]Drug Development Unit, The Royal Marsden Hospital and The Institute of Cancer Research, Sutton, UK; [6]Division of Hematology and Oncology, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [7]Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR, USA; [8]Department of Medical Oncology, National Taiwan University Cancer Center, Taipei, Taiwan; [9]Harbin Medical University Cancer Hospital, Harbin, China; [10]Peter MacCallum Cancer Centre, The University of Melbourne, Melbourne, Australia; [11]Alicante University Dr. Balmis Hospital, ISABIAL, Alicante, Spain; [12]Virginia Cancer Specialists, Fairfax, VA, USA; [13]Janssen Research & Development, Raritan, NJ, USA; [14]Janssen Research & Development, San Diego, CA, USA; [15]Janssen Research & Development, Leiden, The Netherlands; [16]Janssen Research & Development, Spring House, PA, USA; [17]European Institute of Oncology IRCCS, Milano, Italy.

PALOMA-3: Phase 3 Study Design



PALOMA-3 (ClinicalTrials.gov Identifier: NCT05388669) enrollment period: August 2022 to October 2023; data cutoff: 03-Jan-2024.

[a]SC amivantamab was co-formulated with rHuPH20 at a concentration of 160 mg/mL. [b]C1 for IV: Days 1 to 2 (Day 2 applies to IV split dose only [350 mg on Day 1 and the remainder on Day 2]), 8, 15, and 22; C1 for SC: Days 1, 8 , 15, and 22; after C1 for all: Days 1 and 15 (28-day cycles). [c]For calculating primary and key secondary outcomes, we estimated that a sample size of 400 patients would provide >95% power for a 1-sided alpha of 0.05 allocated to each of the co-primary endpoints and 80% power with a 1-sided alpha of 0.025 allocated to ORR. A hierarchical testing approach at a 2-sided alpha of 0.05 was used for the co-primary endpoints (noninferiority), followed by ORR (noninferiority) and PFS (superiority), with a combined 2-sided alpha of 0.05. [d]Two definitions of the same endpoint were used as per regional health authority guidance. [e]Measured between C2D1 and C2D15. [f]Assessed by modified TASQ.

AUC, area under the concentration-time curve; C, Cycle; C_{trough}, observed serum concentration of amivantamab at steady state; D, Day; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletion; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; rHuPH20, hyaluronidase; SC, subcutaneous; TASQ, Therapy Administration Satisfaction Questionnaire.

Trial	Treatment	PFS (Months)	OS	Adverse Events of Interest
FLAURA	Osimertinib vs. gefitinib/erlotinib	18.9 vs. 10.2, P<0.001	38.6 vs. 30.8 months, p=0.046	
FLAURA2	Carbo/Pem/Osi vs. Osi	25.5 vs. 16.8, P<0.001	HR=0.75 (p=0.028)	Chemo side effects
MARIPOSA	lazertinib/amivantamab vs. osi vs lazertinib	23.7 vs. 17, p<0.001 (lazertinib 18.5)	Immature HR, 0.80 (95% CI, 0.61 1.05); P =0.11	infusion reaction, VTE (37% vs. 9%), rash

Soria et al NEJM 2018, Ramalingam et al NEJM 2020, Janne et al. WCLC 2023, AACR 2024, Cho et al. ESMO 2023

Key Takeaways

- Treatment Intensification with Chemotherapy+Osimertinib or Amivantamab+Lazertinib improves PFS
- No free lunch. Toxicity limitations that are distinct. Need for IV administration
- SC Amivantamab may alter the risk-benefit calculation for expanded treatment intensification.
- Await more mature OS data
- Need to identify patients by clinical and molecular characteristics where treatment intensification will be most helpful (or not)


YOU MUST CHOOSE...
BUT CHOOSE WISELY