FRONTLINE EGFR STRATEGIES: TKI + NON-CHEMOTHERAPY OPTIONS

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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
RAMOSE	**Randomized phase II** EGFR mutation NSCLC Stage IIIb/IV Primary endpoint: PFS	R	Osimertinib + Ramucirumab Osimertinib
MARIPOSA	**Randomized phase III** EGFR mutation NSCLC Stage IIIb/IV Primary endpoint: PFS	R	Lazertinib + amivantamab Lazertinib Osimertinib
NORTHSTAR	**Randomized phase II** EGFR mutation NSCLC Stage IIIb/IV Primary endpoint: PFS	Osimertinib → R	Osimertinib + XRT Osimertinib

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)

Serial brain MRIs were required for all patients[a]

2:2:1 Randomization (N=1074)

- **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

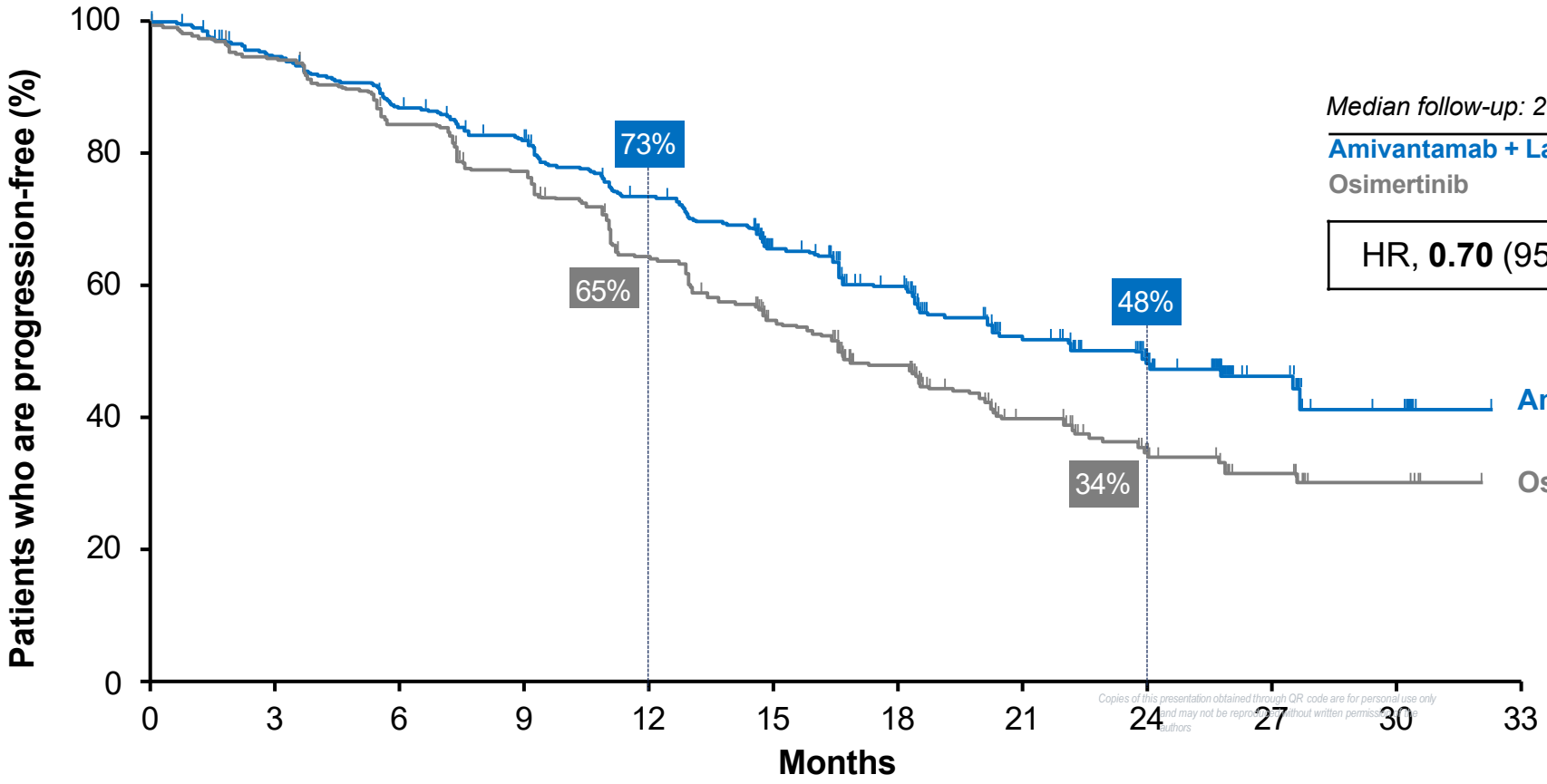
MARIPOSA (ClinicalTrials.gov Identifier: NCT04487080) enrollment period: November 2020 to May 2022; data cut-off: 11-Aug-2023.

[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.

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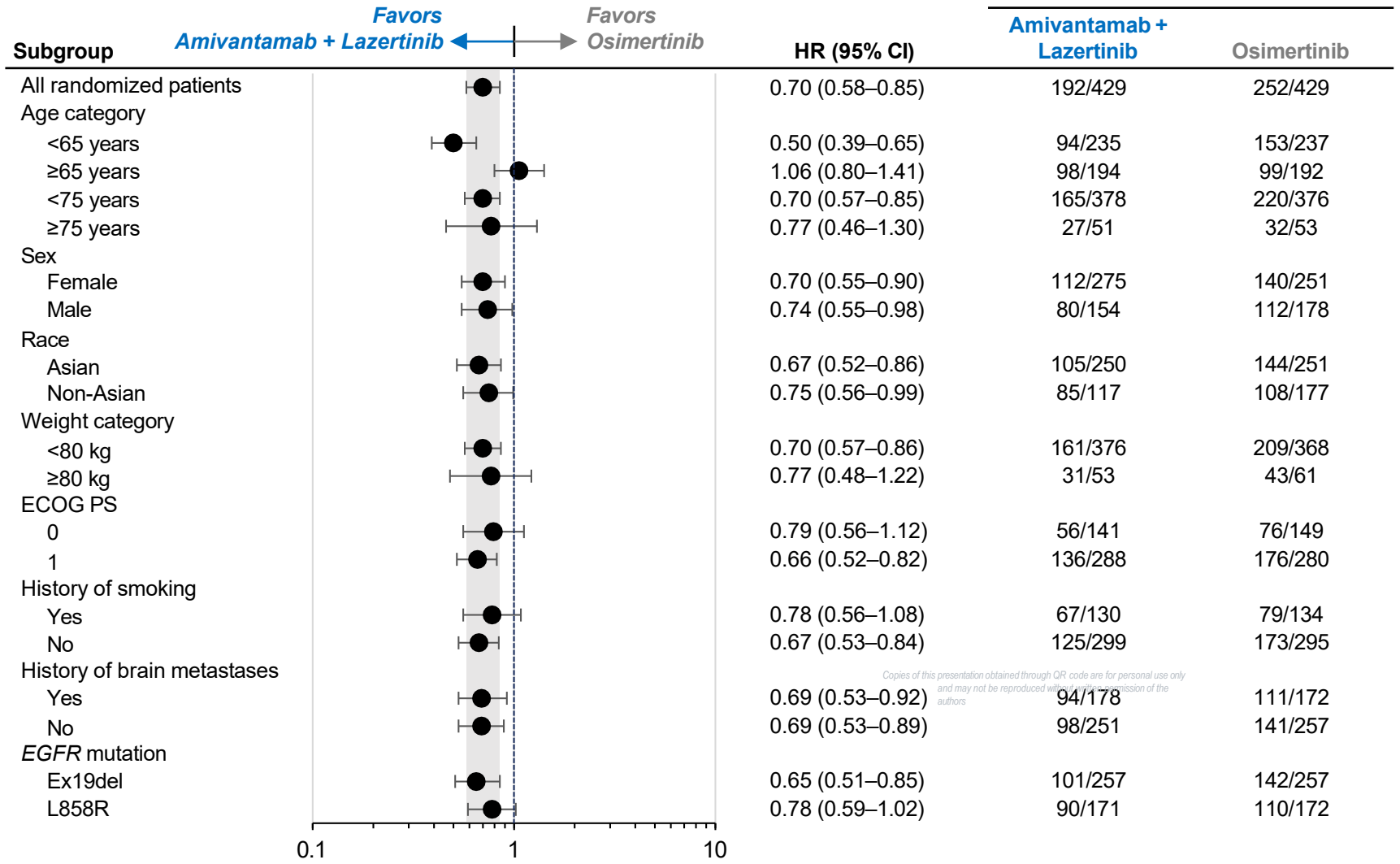
PFS Benefit Seen Across Predefined Subgroups



Subgroup	HR (95% CI)	Events/N: Amivantamab + Lazertinib	Events/N: Osimertinib
All randomized patients	0.70 (0.58–0.85)	192/429	252/429
Age category			
<65 years	0.50 (0.39–0.65)	94/235	153/237
≥65 years	1.06 (0.80–1.41)	98/194	99/192
<75 years	0.70 (0.57–0.85)	165/378	220/376
≥75 years	0.77 (0.46–1.30)	27/51	32/53
Sex			
Female	0.70 (0.55–0.90)	112/275	140/251
Male	0.74 (0.55–0.98)	80/154	112/178
Race			
Asian	0.67 (0.52–0.86)	105/250	144/251
Non-Asian	0.75 (0.56–0.99)	85/117	108/177
Weight category			
<80 kg	0.70 (0.57–0.86)	161/376	209/368
≥80 kg	0.77 (0.48–1.22)	31/53	43/61
ECOG PS			
0	0.79 (0.56–1.12)	56/141	76/149
1	0.66 (0.52–0.82)	136/288	176/280
History of smoking			
Yes	0.78 (0.56–1.08)	67/130	79/134
No	0.67 (0.53–0.84)	125/299	173/295
History of brain metastases			
Yes	0.69 (0.53–0.92)	94/178	111/172
No	0.69 (0.53–0.89)	98/251	141/257
EGFR mutation			
Ex19del	0.65 (0.51–0.85)	101/257	142/257
L858R	0.78 (0.59–1.02)	90/171	110/172

Note: Gray box indicates 95% CI of HR for all randomized patients.

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletions; HR, hazard ratio; PFS, progression-free survival.

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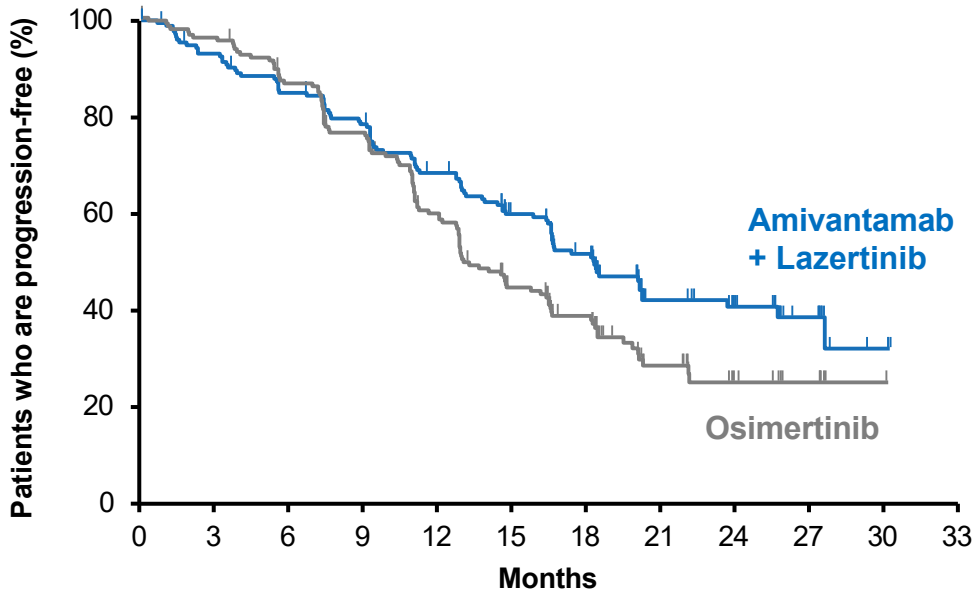
Consistent PFS (BICR) Benefit With or Without Brain Metastases

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)

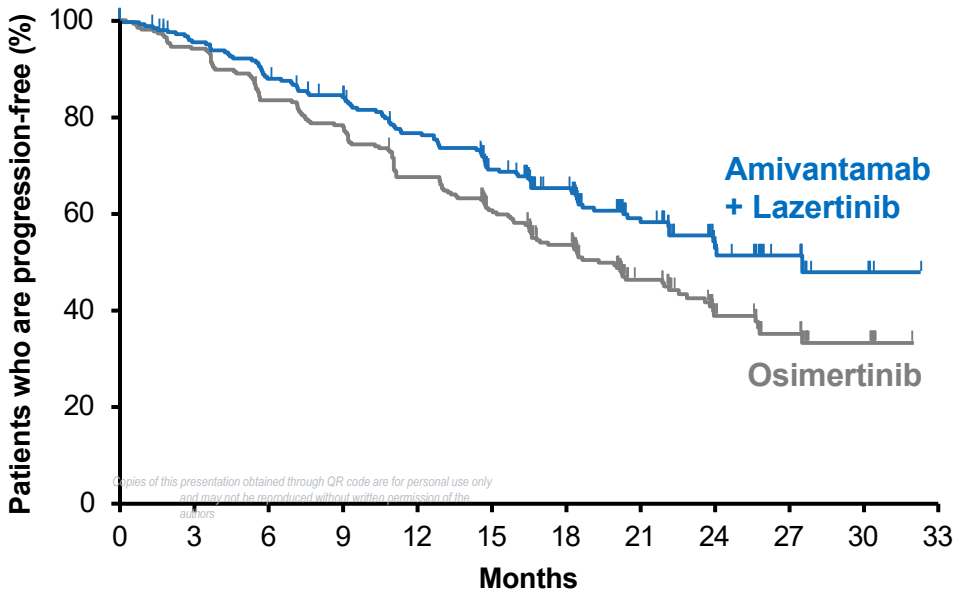
HR, **0.69** (95% CI, 0.53–0.92)



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

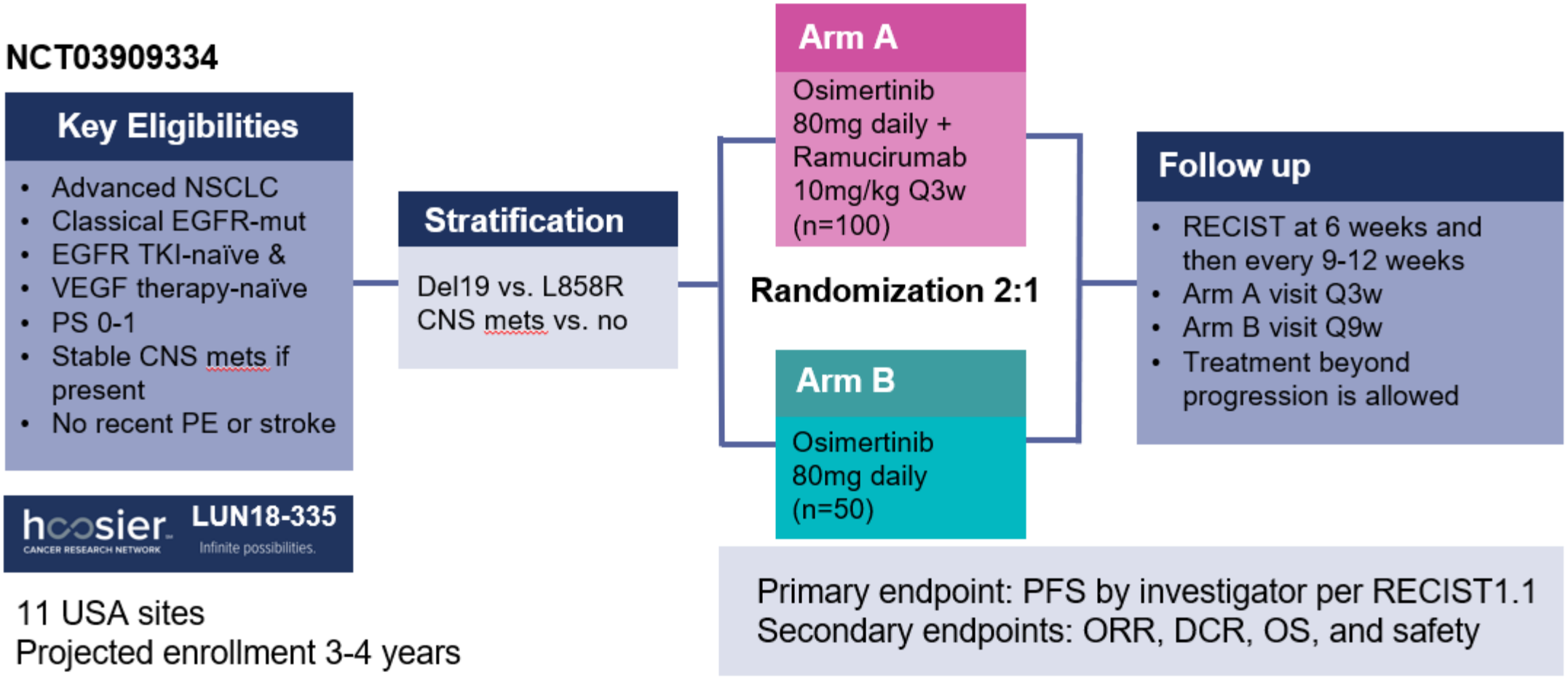
TEAE, n (%)	Amivantamab + Lazertinib (n=421)	Osimertinib (n=428)
Any AE	421 (100)	425 (99)
Grade ≥3 AEs	316 (75)	183 (43)
Serious AEs	205 (49)	143 (33)
AEs leading to death	34 (8)	31 (7)
Any AE leading to treatment:		
Interruptions of any agent	350 (83)	165 (39)
Reductions of any agent	249 (59)	23 (5)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

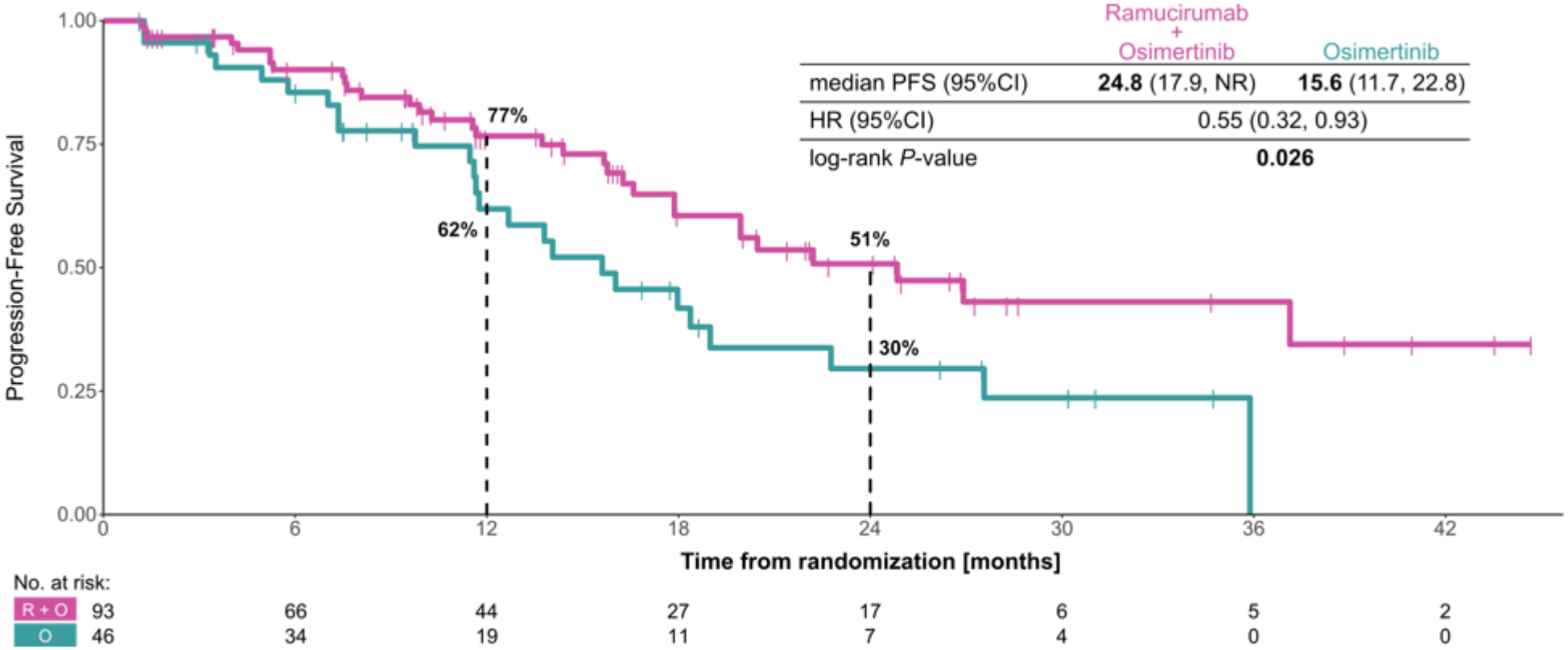
Cho B, et al., *ESMO Congress*, 2023

RAMOSE (HCRN-LUN18-335) Phase 2 Study Design



Le, X., et al., *ESMO Congress*, 2023

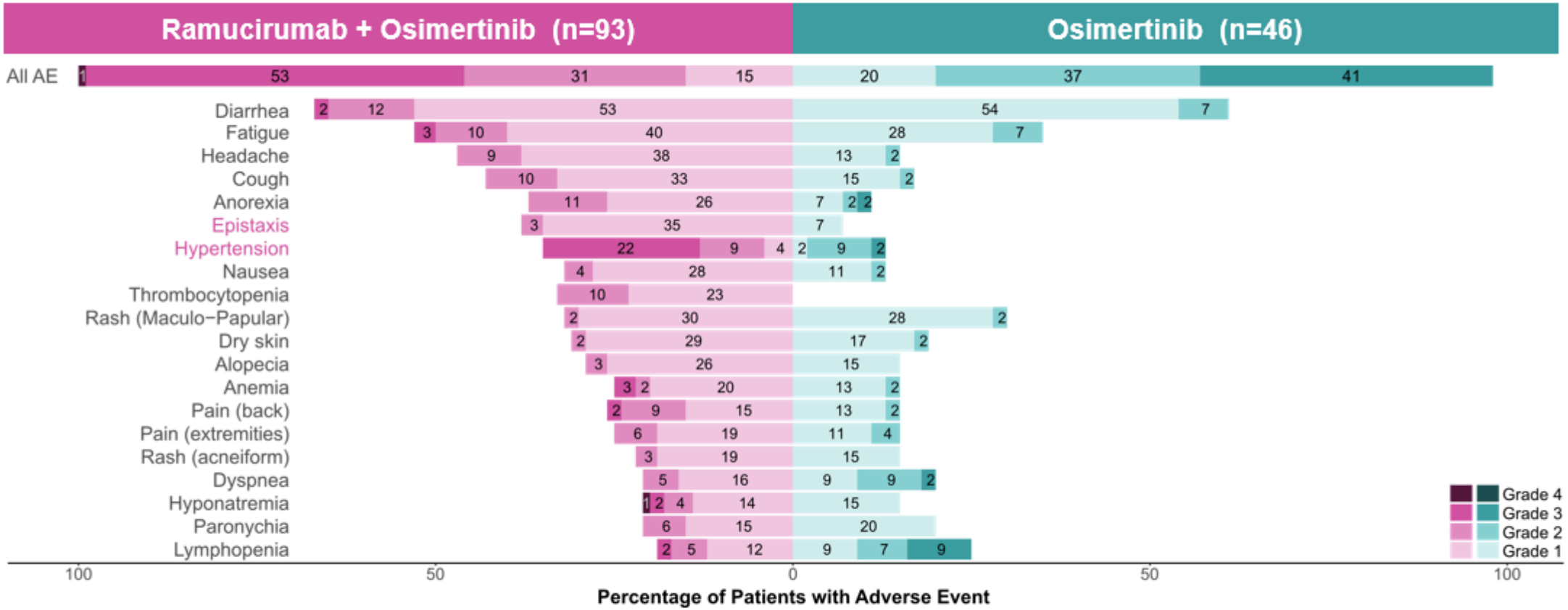
Progression-free survival by investigator (primary endpoint)



- Median follow up: 16.6 months
- Median duration of ramucirumab treatment (Arm A): 14.2 months
- Dose intensity ramucirumab 86.6%

Le, X., et al., *ESMO Congress*, 2023

Common Adverse Events

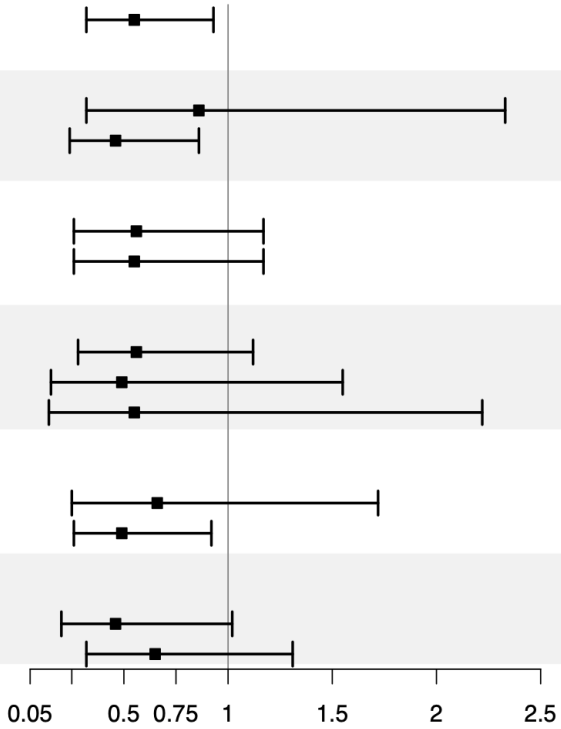


- No Grade 5 AE, one G4 AE (hyponatremia, Arm A)
- Grade 3 or higher AE, 54% in Ramu+Osi Arm A vs 41% in Osi Arm B
- Discontinuation rate 9.7% (9/93) in Ramu+Osi Arm A vs 8.7% (4/46) in Osimertinib Arm B

Le, X., et al., *ESMO Congress*, 2023

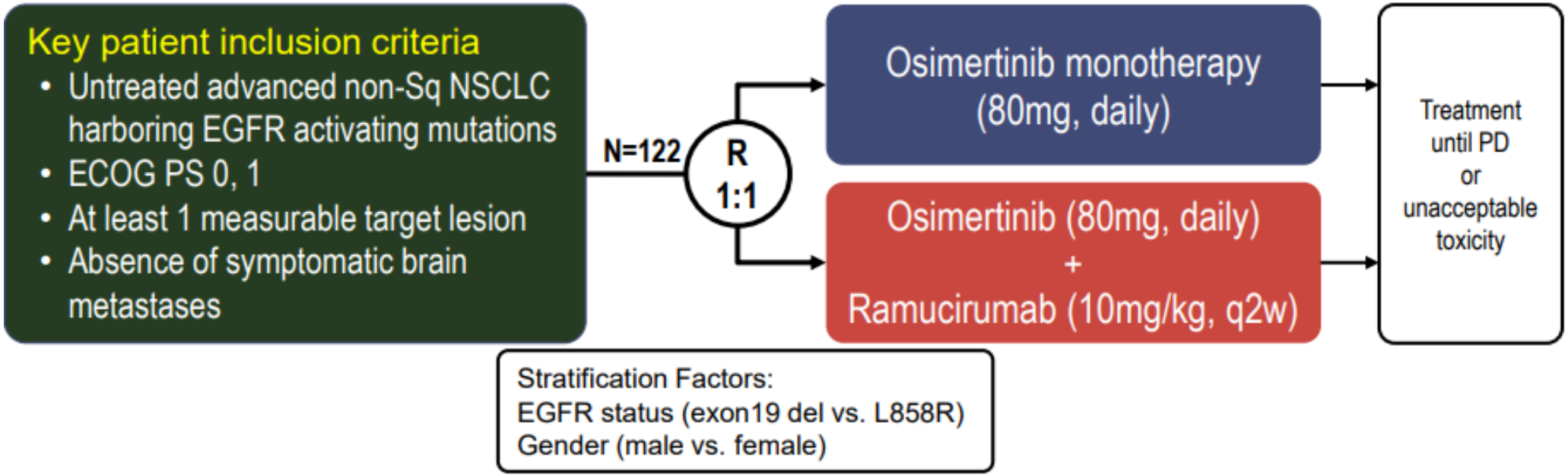
PFS benefit was consistent across pre-defined subgroups

Covariates	No. Arm A (Events)	No. Arm B (Events)	Hazards Ratio (95%CI)	P–value
All patients				
Unadjusted Cox PH	93(32)	46(25)	0.55 (0.32, 0.93)	0.026
Sex				
Male	27(9)	13(7)	0.86 (0.32, 2.33)	0.769
Female	66(23)	33(18)	0.46 (0.24, 0.86)	0.015
Age				
<65	43(18)	22(12)	0.56 (0.26, 1.17)	0.121
>=65	50(14)	24(13)	0.55 (0.26, 1.17)	0.119
Race				
White	60(21)	26(14)	0.56 (0.28, 1.12)	0.102
Asian	24(7)	10(5)	0.49 (0.15, 1.55)	0.224
Other	9(4)	10(6)	0.55 (0.14, 2.22)	0.401
EGFR type				
L858R	29(12)	14(7)	0.66 (0.25, 1.72)	0.392
Ex19del	64(20)	32(18)	0.49 (0.26, 0.92)	0.028
Brain Mets				
No	53(13)	22(11)	0.46 (0.20, 1.02)	0.057
Yes	40(19)	24(14)	0.65 (0.32, 1.31)	0.23



Le, X., et al., *ESMO Congress*, 2023

OSIRAM-1 (TORG1833): Study Design

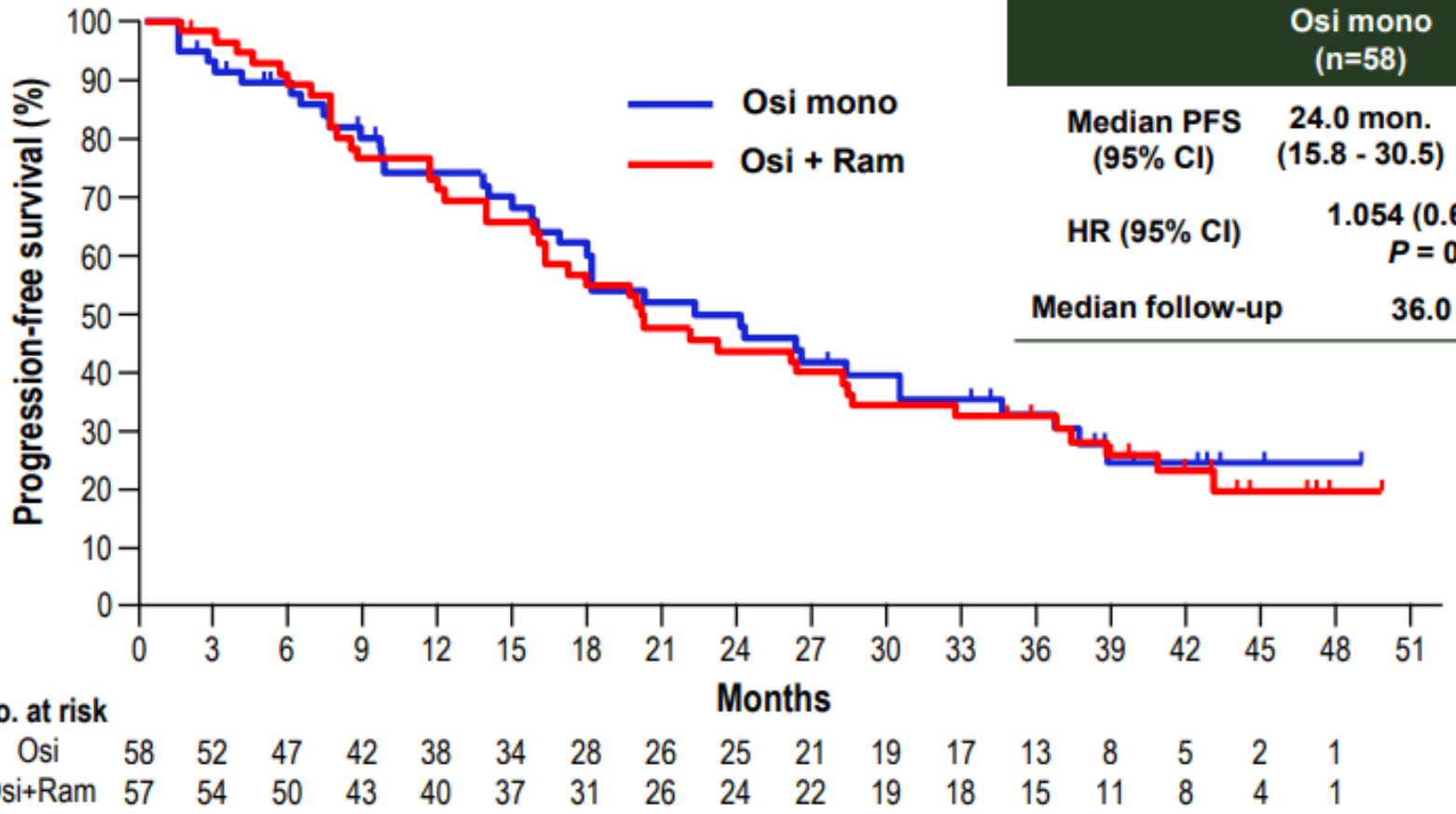


Primary Endpoint: PFS assessed by the BICRs

Secondly Endpoints: PFS assessed by investigators, ORR, DCR, OS and Safety

Nakahara, Y., et al., *ESMO Congress*, 2023

Progressin-Free Survival, assessed by BICRs (Primary Endpoint)



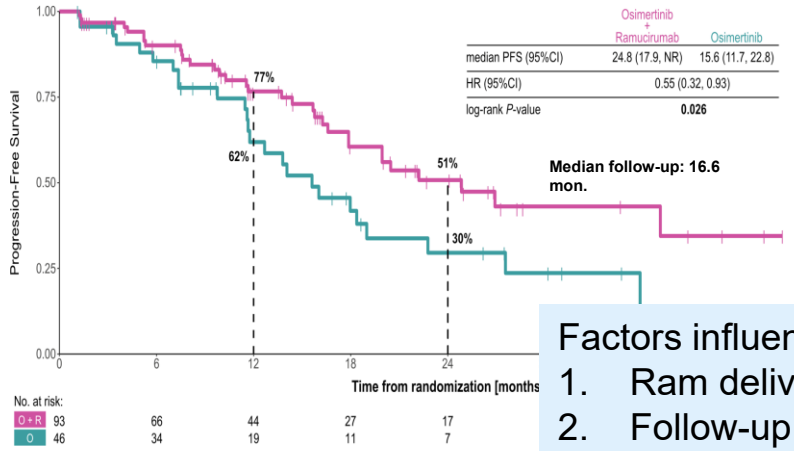
	Osi mono (n=58)	Osi + Ram (n=57)
Median PFS (95% CI)	24.0 mon. (15.8 - 30.5)	20.0 mon. (15.9 - 28.3)
HR (95% CI)	1.054 (0.674-1.648) *P* = 0.4621	
Median follow-up	36.0 mon.	

Nakahara, Y., et al., *ESMO Congress*, 2023

Significant difference between ramucirumab treatment duration

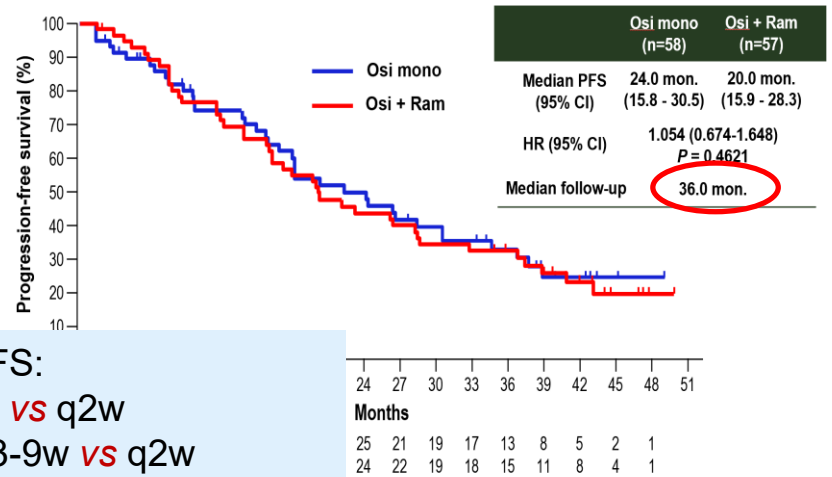
LBA71: RAMOSE

Progression-free survival by investigator (primary endpoint)



LBA70: OSIRAM-1

Progression-Free Survival, assessed by BICRs (Primary Endpoint)

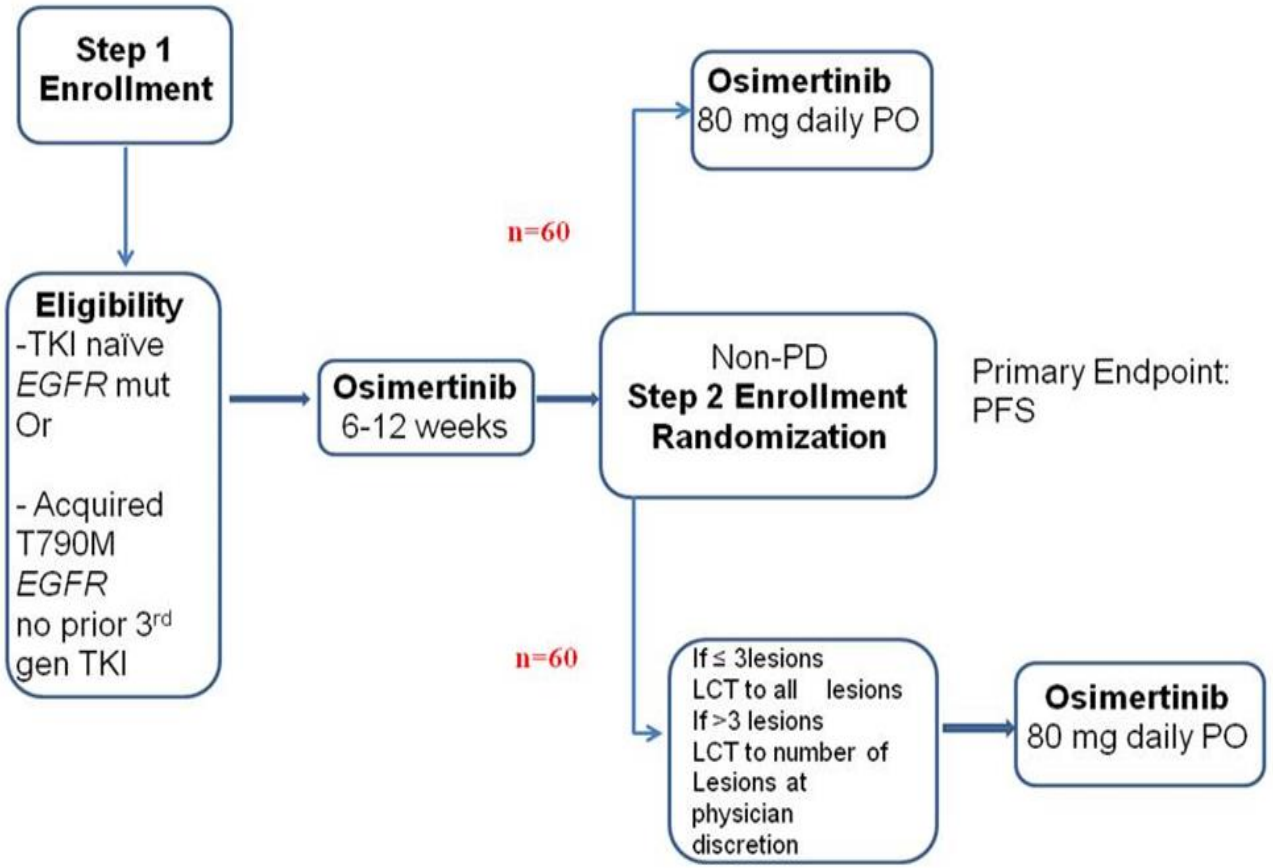


Factors influencing PFS:

1. Ram deliver: q3w *vs* q2w
2. Follow-up visit: q3-9w *vs* q2w
3. PFS by Invest. *vs* PFS by BIRC
4. Exon19: 69% *vs* 61%
5. **Exposure to Ram: 14.4 *vs* 4.7 m**

Yi-Long Wu ESMO Congress 2023

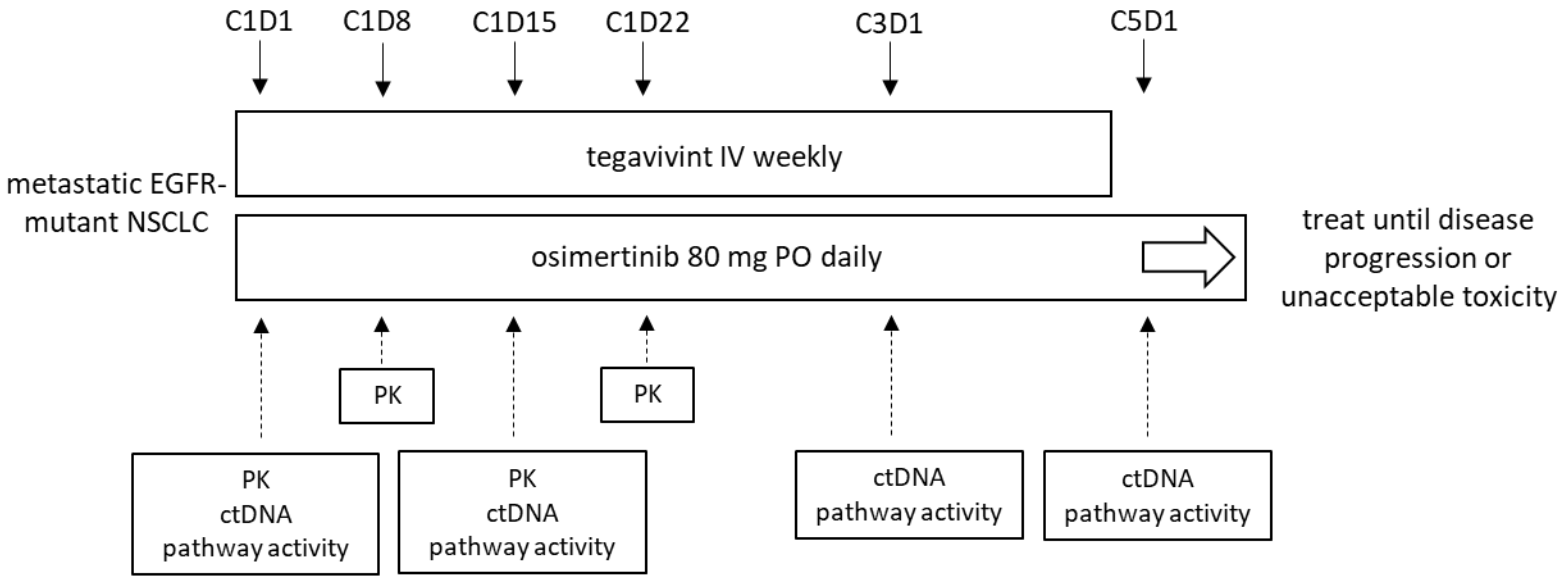
NORTHSTAR Trial– Local consolidative therapy (LCT)



Total of 120 pts randomized
Safety has been reported

PI: Y. Elamin; NCT03410043

Osimertinib and Tegavivint as First-Line Therapy for the Treatment of Metastatic EGFR-Mutant NSCLC



Primary objectives: safety and tolerability, determine RP2D of tegavivint

Secondary objectives: ORR, median PFS, duration of response, and overall survival

Exploratory objectives: β-catenin pathway activity in tumor and plasma, clearance of ctDNA

PI: Memmott, NCT04780568

Frontline therapy: which patient needs what type of intensification

- FLAURA2 = > adding chemotherapy
- RAMOSE => adding anti-VEGF
- MARIPOSA => adding anti-EGFR-MET antibody
- NORTHSTAR => adding radiation

First layer of questions for intensification

- do we improve PFS ? 

- can we preserve patients' quality of life

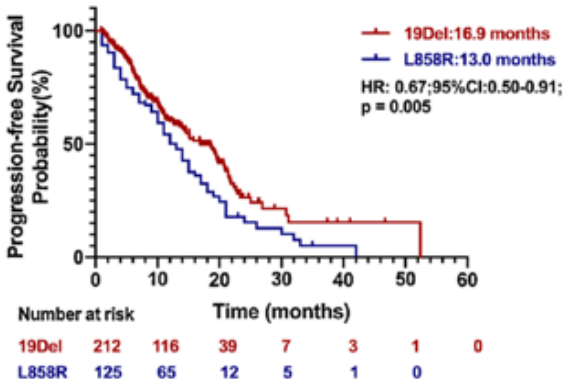
Second layer of questions:

- **Who** needs intensification? – high risk patients
  define high risk subgroups (Clinical features? Genomics features? Biomarkers?)
- **When** is the best time to intensify?
- **How** to intensify (chemo, VEGF, MET, radiation, or other novel agents)

High risk group identification

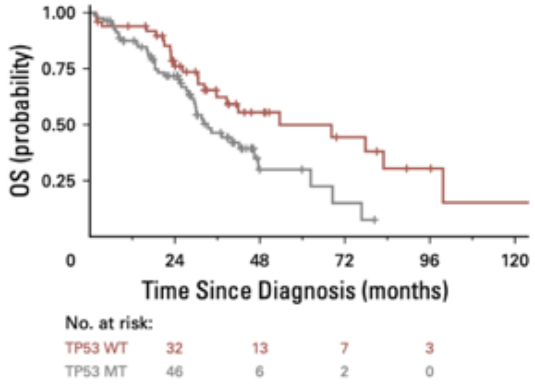
❖ Clinical features – L858R, TP53MUT, CNS/Liver met

L858R higher risk than Del19



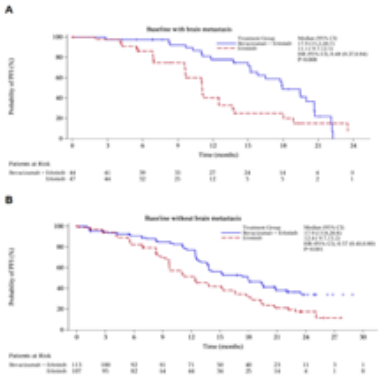
Liu and Le Lung Cancer 2020

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
- Radiomics
- Integrated modeling

❖ Molecular guided intensification

Summary

- The addition of amivantamab to lazertinib significantly improves PFS for first-line mEGFR-mut NSCLC
- The addition of ramucirumab to osimertinib significantly improves PFS for first-line mEGFR-mut NSCLC
- NORTHSTAR trial is waiting readout -- the addition of radiotherapy to osimertinib
- Other trials are ongoing to explore novel combinations

Future Directions

- Stratification to determine high-risk patients
- Early escalation or de-escalation strategies
- Molecularly-guided intensification strategies