The evolving combination treatment landscape of advanced EGFR-mutant NSCLC

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- Strategy to overcome limitation of mono EGFR-TKI resistance
  - FLAURA2
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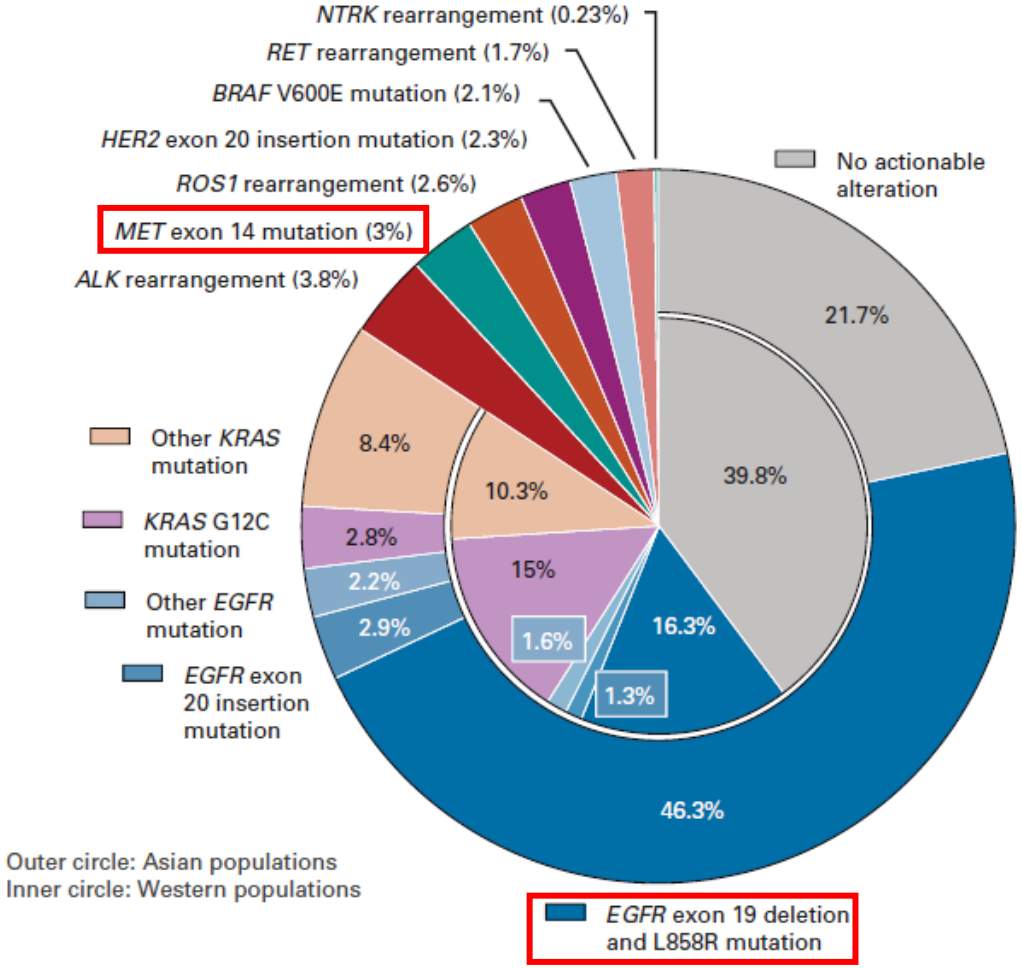
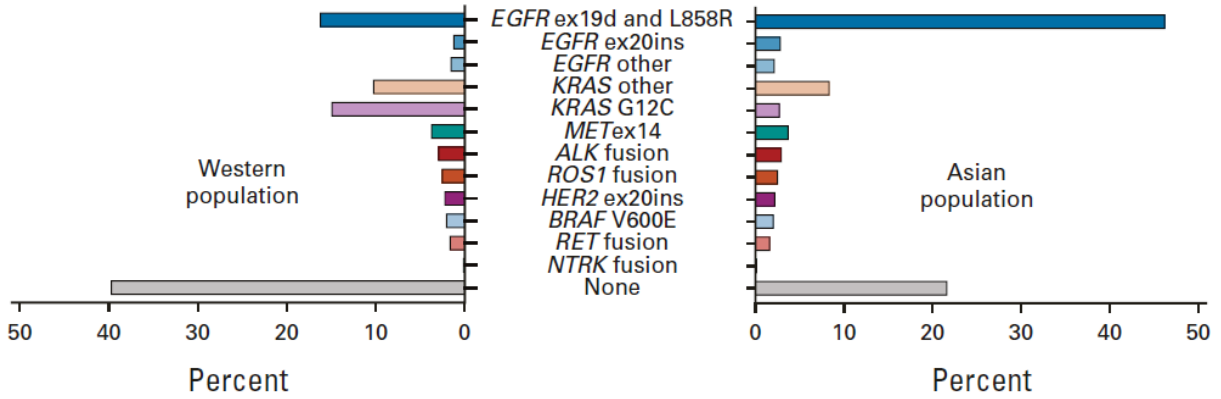
  - RELAY, RAMOSE
  - Others
- Summary

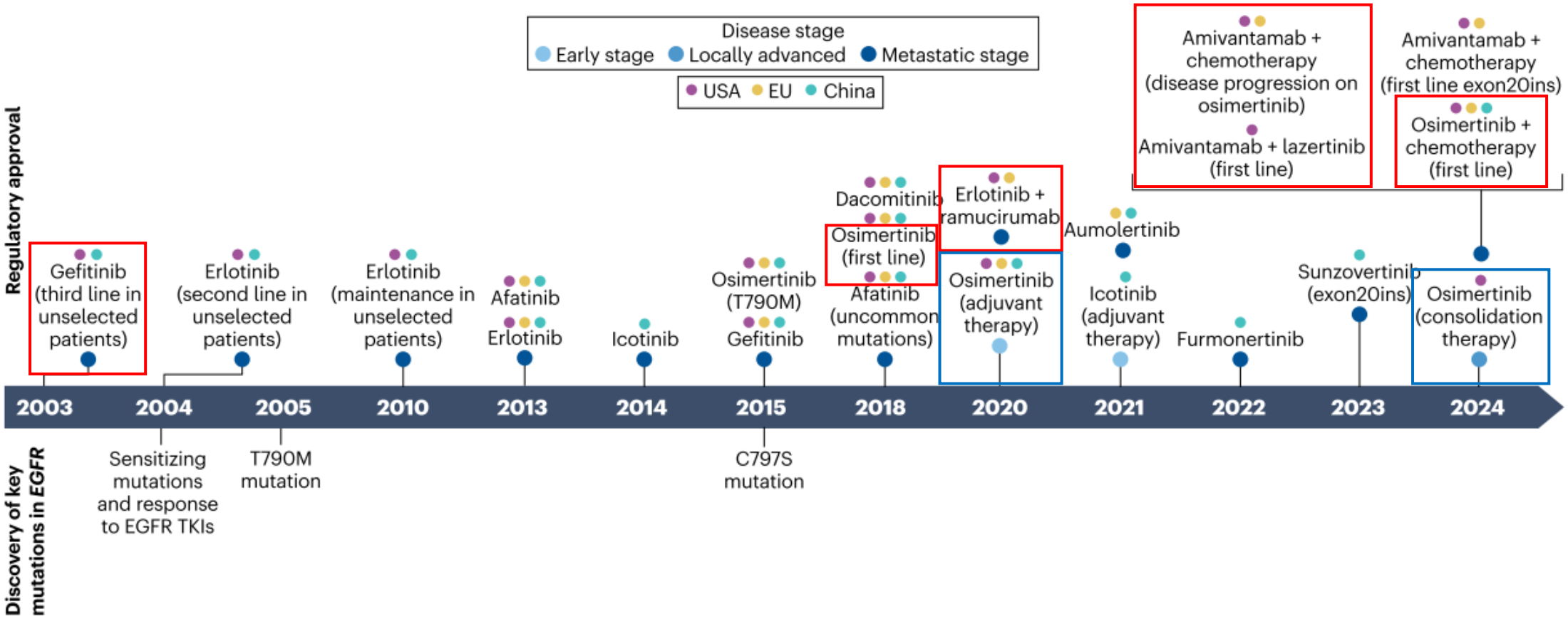
Frequency of targetable oncogenic drivers in ADCs



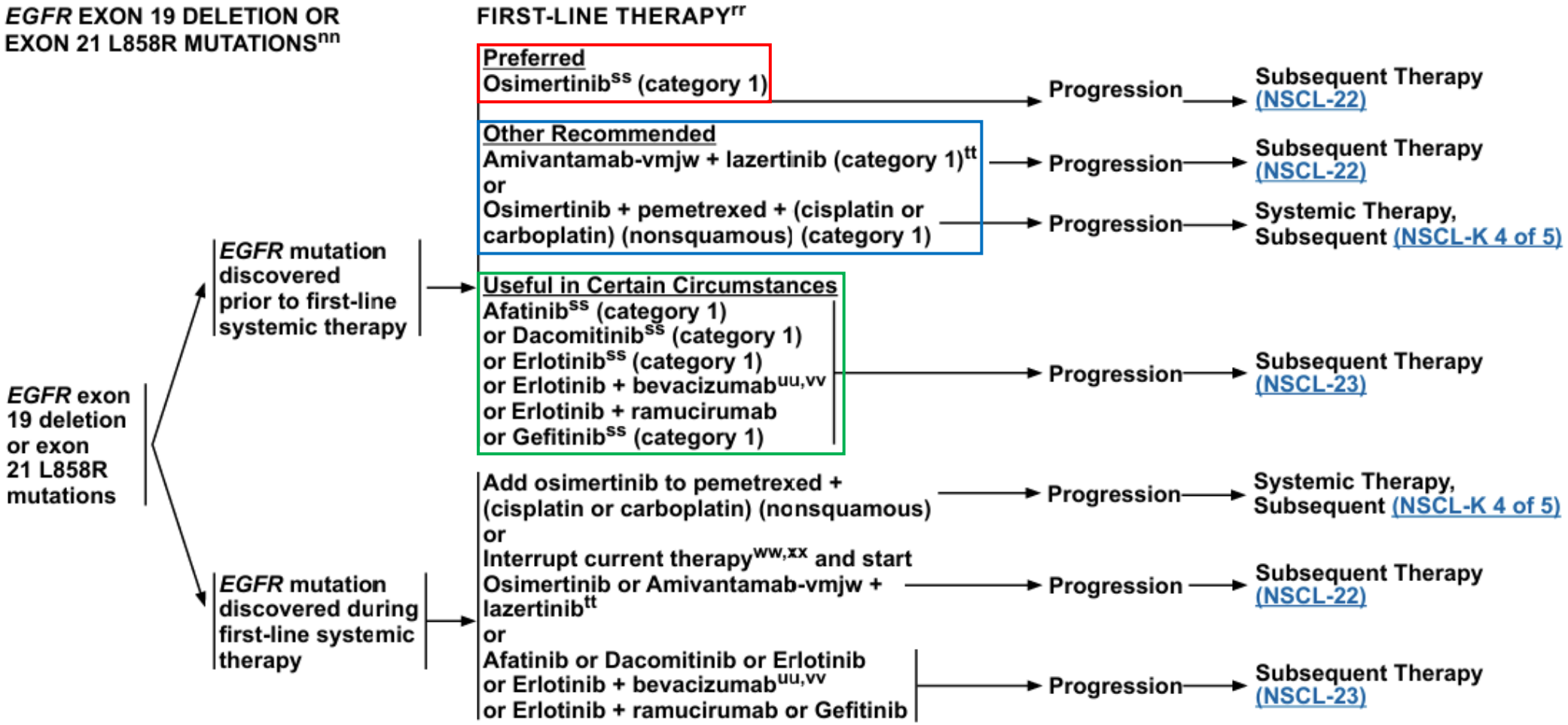


J Clin Oncol. 2022;40(6):611-625.

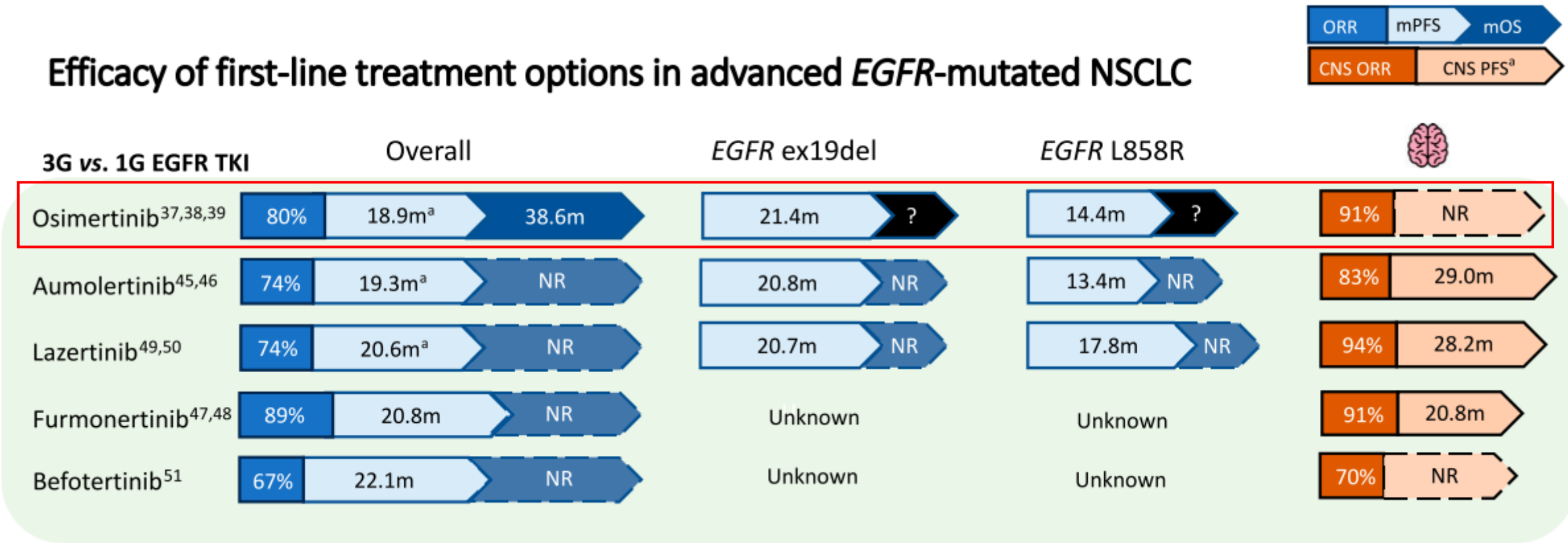
Time line of EGFR treatment



Nat Rev Clin Oncol. 2025; 22(2):95-116


EGFR EXON 19 DELETION OR EXON 21 L858R MUTATIONS[nn]
FIRST-LINE THERAPY[rr]
EGFR exon 19 deletion or exon 21 L858R mutations
EGFR mutation discovered prior to first-line systemic therapy
EGFR mutation discovered during first-line systemic therapy
Preferred
Osimertinib[ss] (category 1)
Other Recommended
Amivantamab-vmjw + lazertinib (category 1)[tt]
or
Osimertinib + pemetrexed + (cisplatin or carboplatin) (nonsquamous) (category 1)
Useful in Certain Circumstances
Afatinib[ss] (category 1)
or Dacomitinib[ss] (category 1)
or Erlotinib[ss] (category 1)
or Erlotinib + bevacizumab[uu,vv]
or Erlotinib + ramucirumab
or Gefitinib[ss] (category 1)
Add osimertinib to pemetrexed + (cisplatin or carboplatin) (nonsquamous)
or
Interrupt current therapy[ww,xx] and start Osimertinib or Amivantamab-vmjw + lazertinib[tt]
or
Afatinib or Dacomitinib or Erlotinib or Erlotinib + bevacizumab[uu,vv] or Erlotinib + ramucirumab or Gefitinib
Progression
Subsequent Therapy (NSCL-22)
Progression
Subsequent Therapy (NSCL-22)
Progression
Systemic Therapy, Subsequent (NSCL-K 4 of 5)
Progression
Subsequent Therapy (NSCL-23)
Progression
Systemic Therapy, Subsequent (NSCL-K 4 of 5)
Progression
Subsequent Therapy (NSCL-22)
Progression
Subsequent Therapy (NSCL-23)

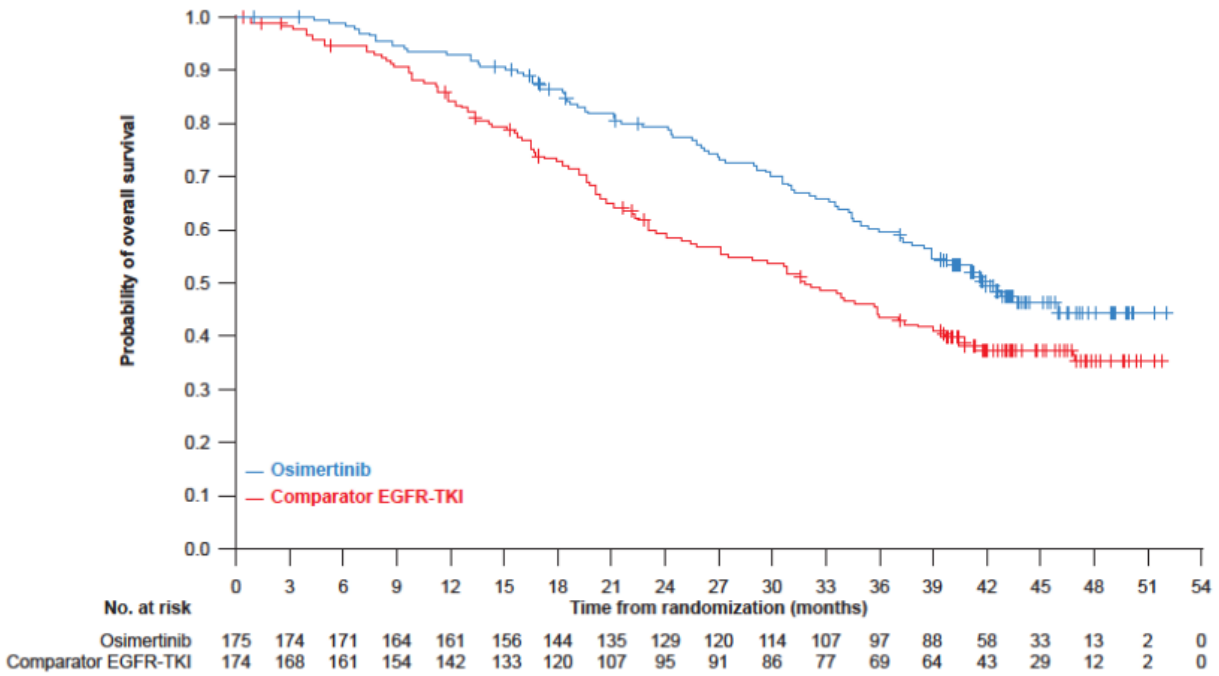
Efficacy of 3rd generation EGFR TKI monotherapy



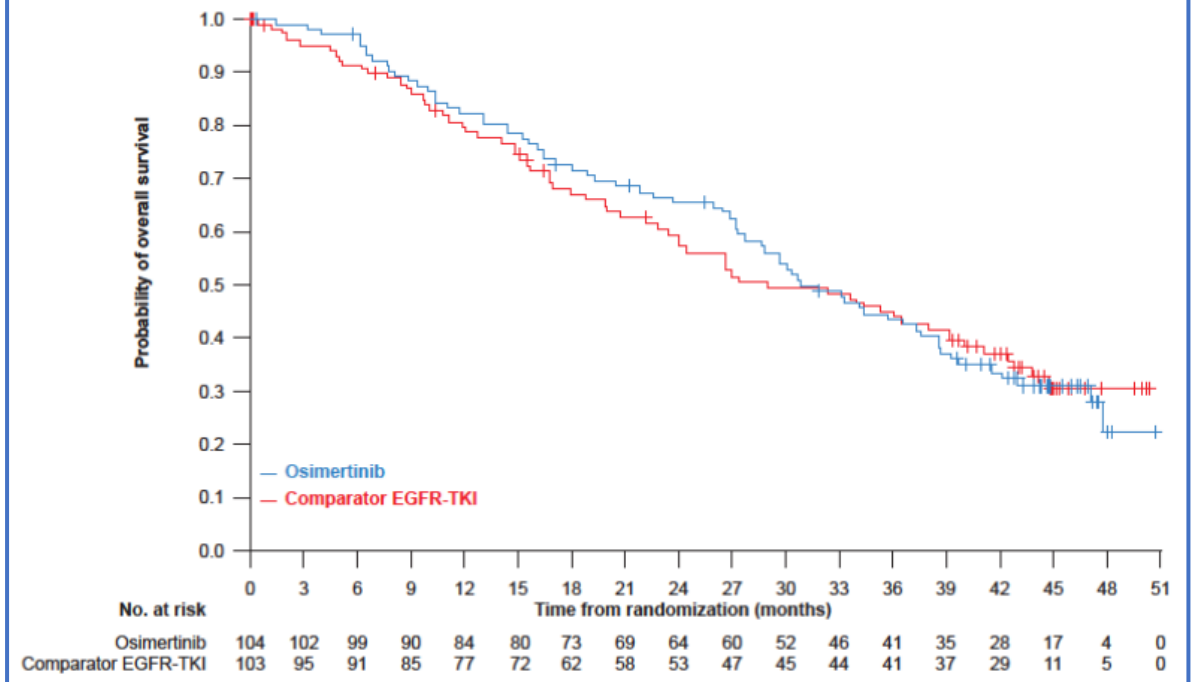
Am Soc Clin Oncol Educ Book. 2024;44(3):e432516

FLAURA: Final OS analysis by mutation type

Exon 19 deletion



L858R



- Of those patients in the EGFR-TKI comparator arm, more patients with an exon 19 deletion than L858R EGFR mutation subtype crossed over to receive osimertinib: 53 of 174 patients (30%) vs 17 of 103 patients (17%), respectively

N Engl J Med. 2020;382(1):41-50

Intrinsic resistance of EGFR (+) NSCLC

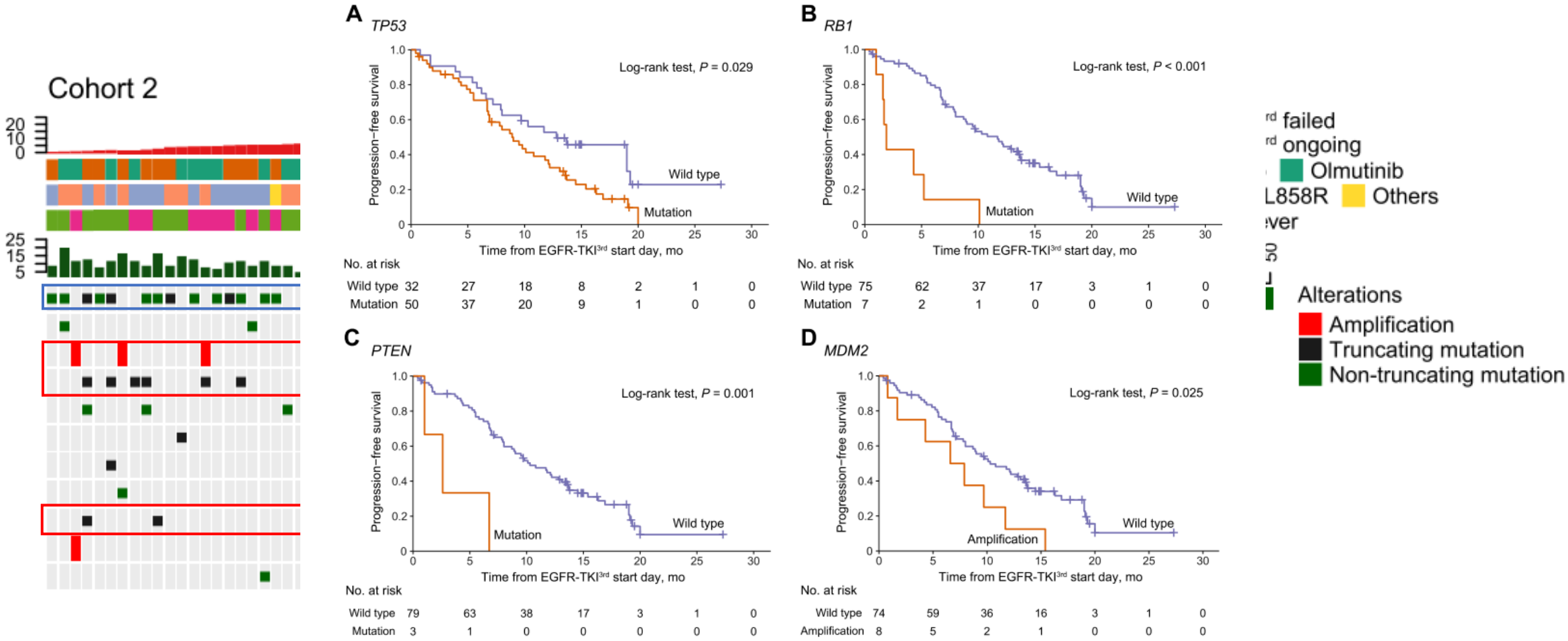
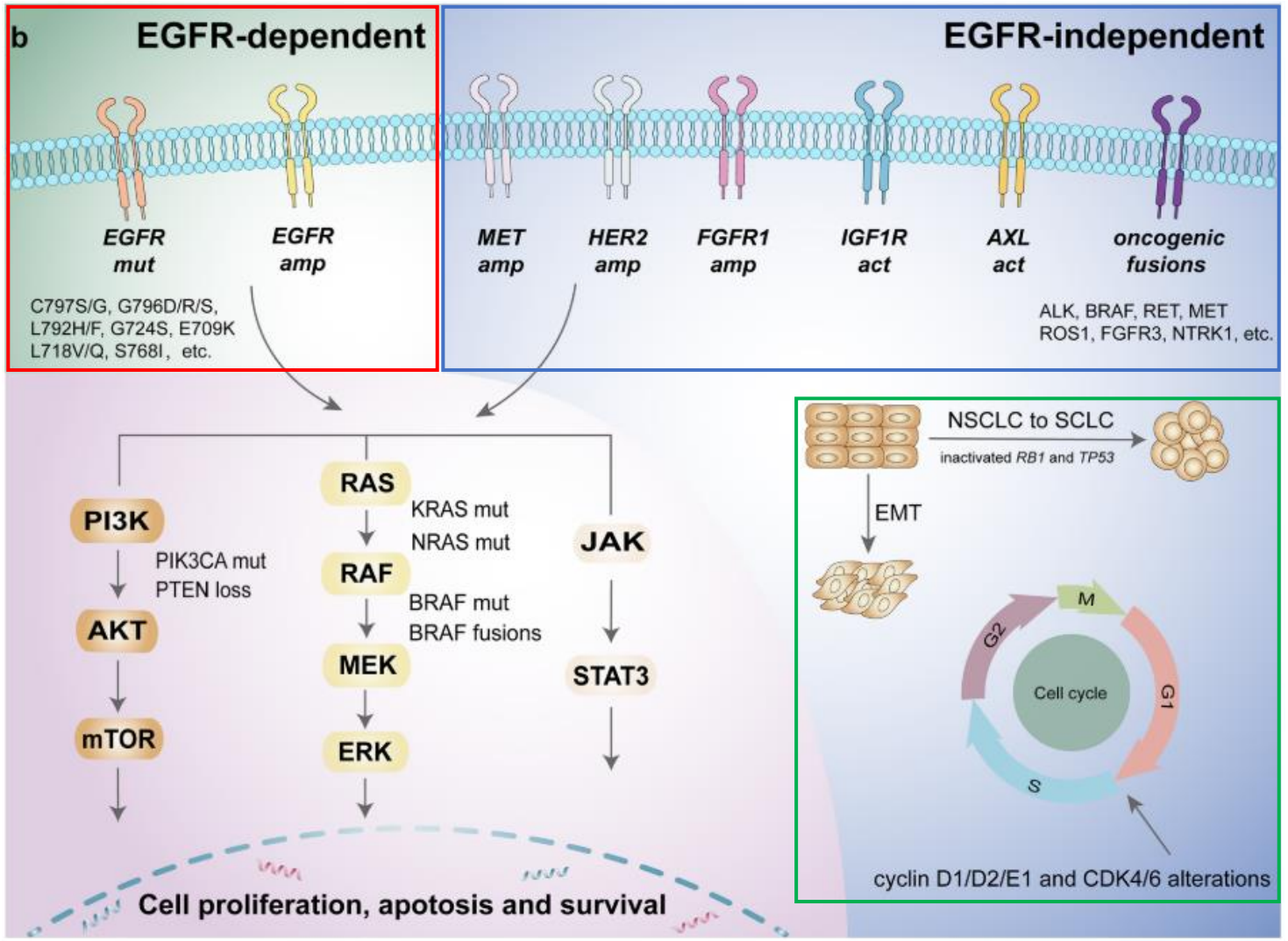


Figure 3. Kaplan–Meier curves for progression-free survival in cohort 2. Patients with or without (*A*) *TP53* mutation, (*B*) *RB1* mutation, (*C*) *PTEN* mutation, or (*D*) *MDM2* amplification. EGFR-TKI^{3rd}, third-generation EGFR tyrosine kinase inhibitor.

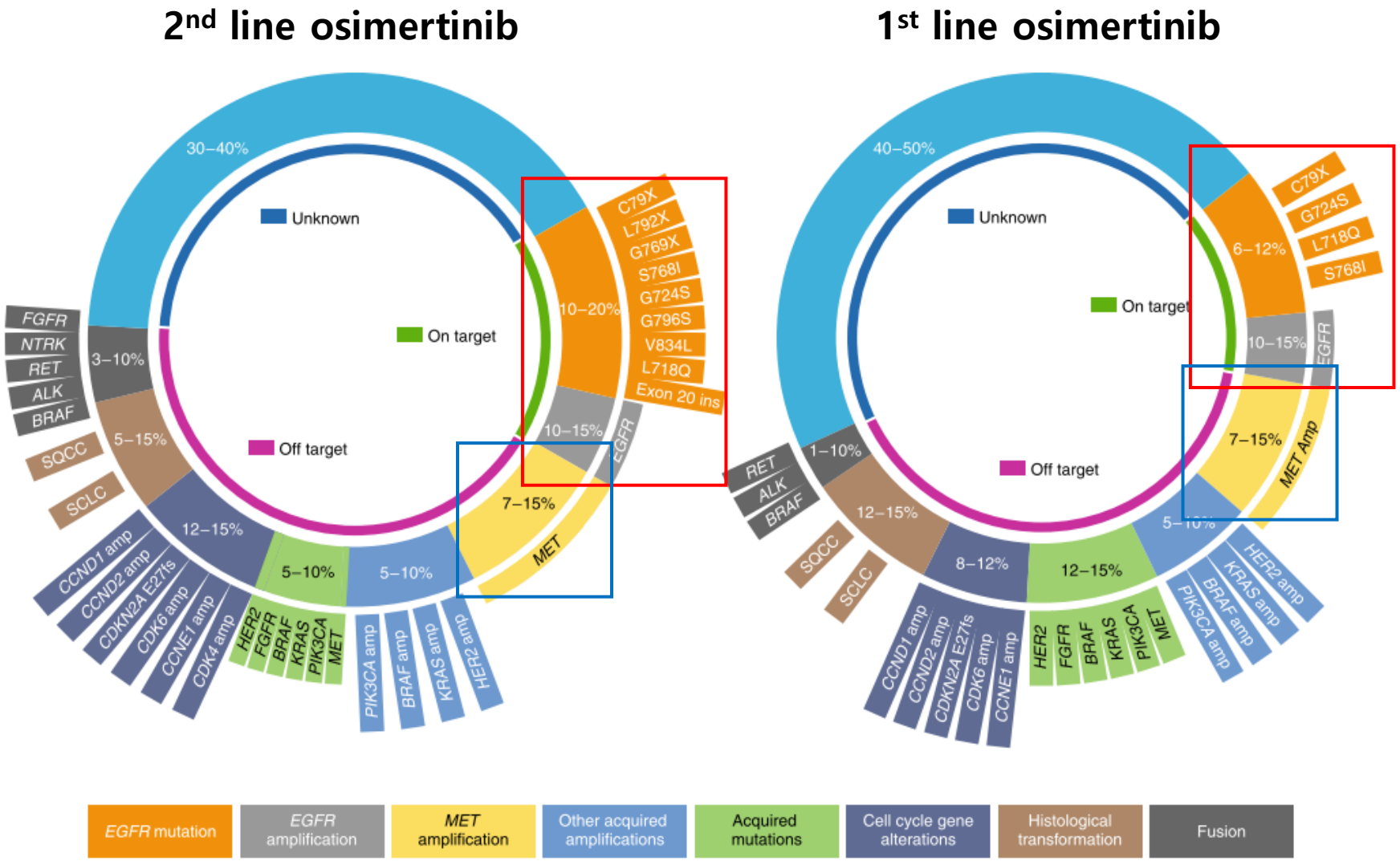
J Thorac Oncol. 2019;14(2):193-202

Mechanisms of acquired resistance to osimertinib



J Hematol Oncol. 2022;15(1):173

Mechanisms of resistance to osimertinib



Nat Cancer. 2021;2(4):377-391

Unmet need of 3rd generation EGFR-TKI

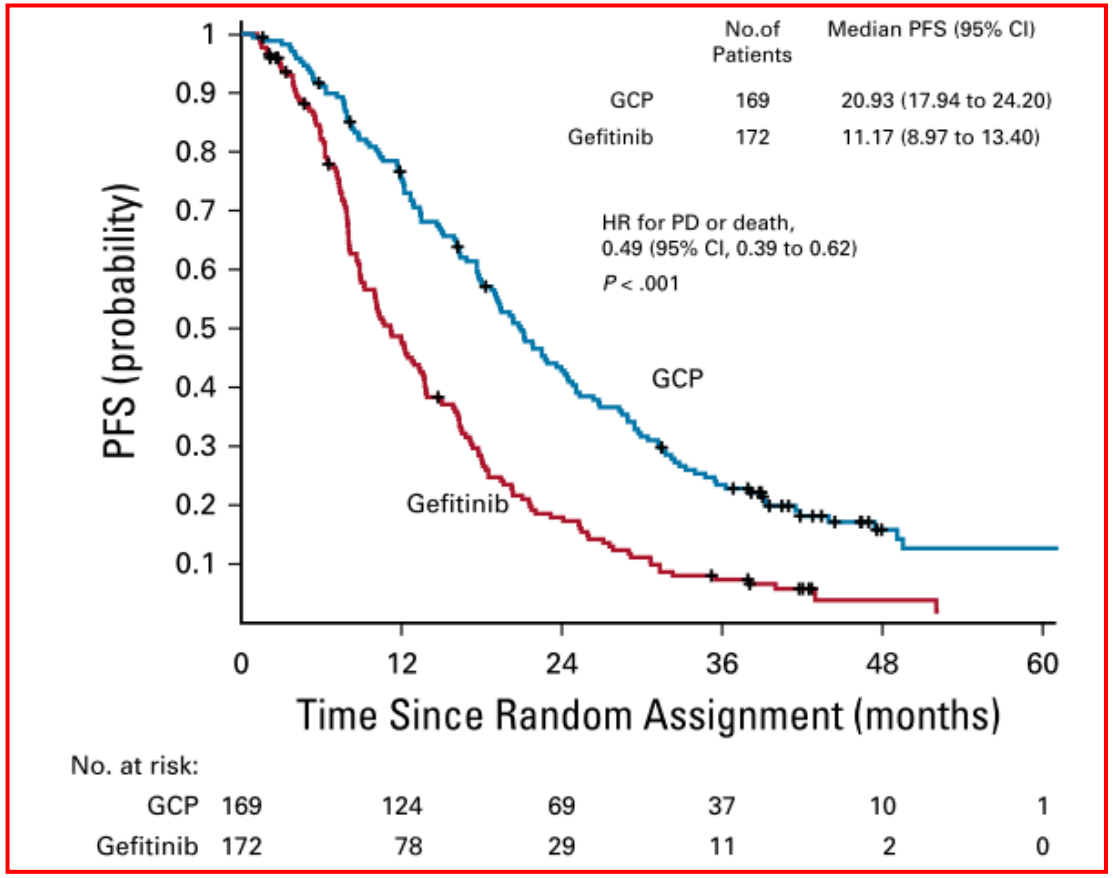
- Poor prognosis in L858R
- Intrinsic resistance (TP53, RB1, PTEN, MDM2)
- Acquired resistance (on-target, off-target)

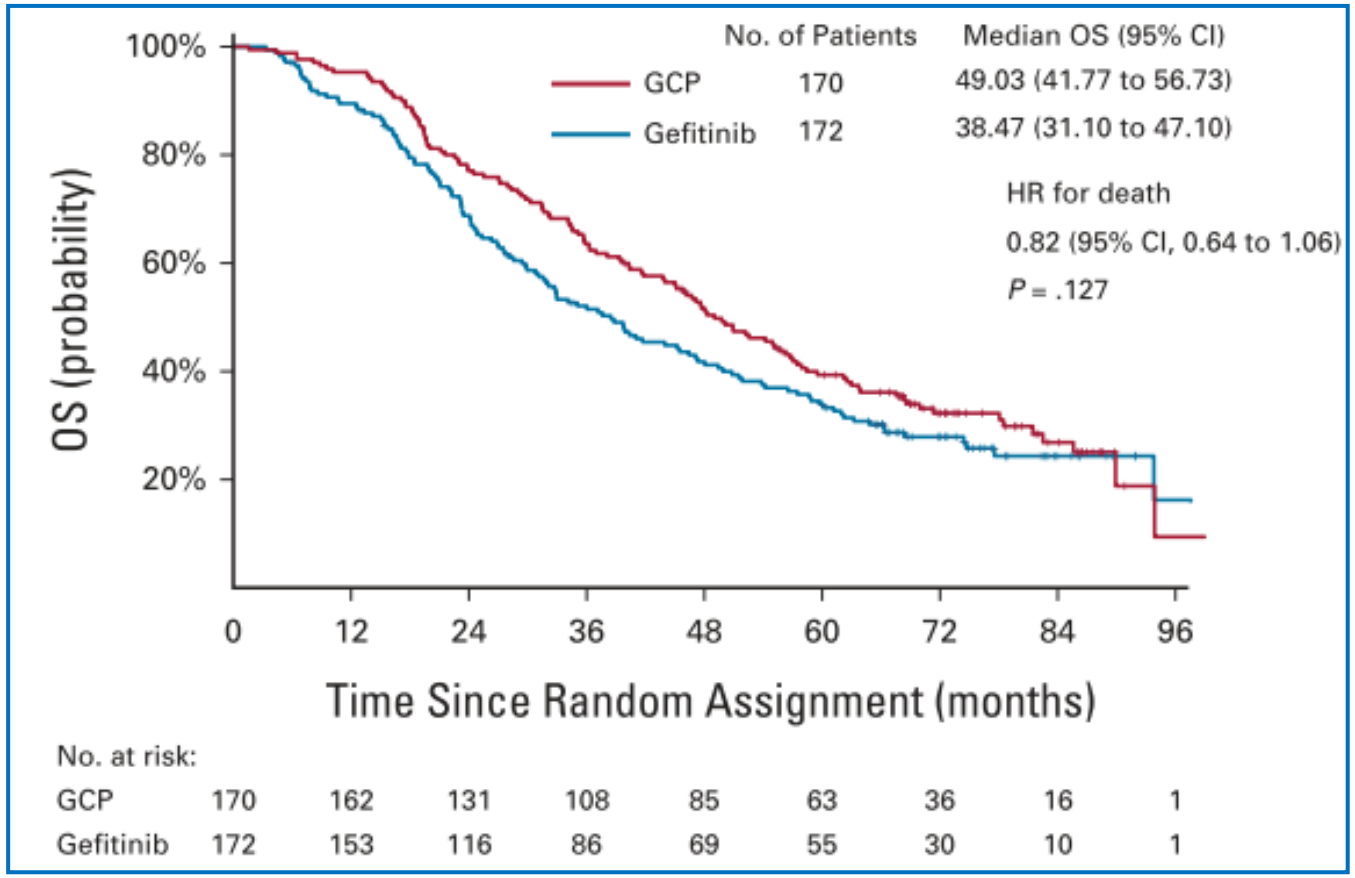
Strategy to overcome limitation of 3rd generation EGFR-TKI

- 3rd generation EGFR TKI + chemotherapy
  - FLAURA2
- 3rd generation EGFR TKI + Bi-specific antibody (EGFR, MET)
  - MARIPOSA
- EGFR TKI + anti-VEGF antibody
  - RELAY
  - RAMOSE
- Others

FLAURA2

NEJ009: Gefitinib+Chemotherapy vs Gefitinib

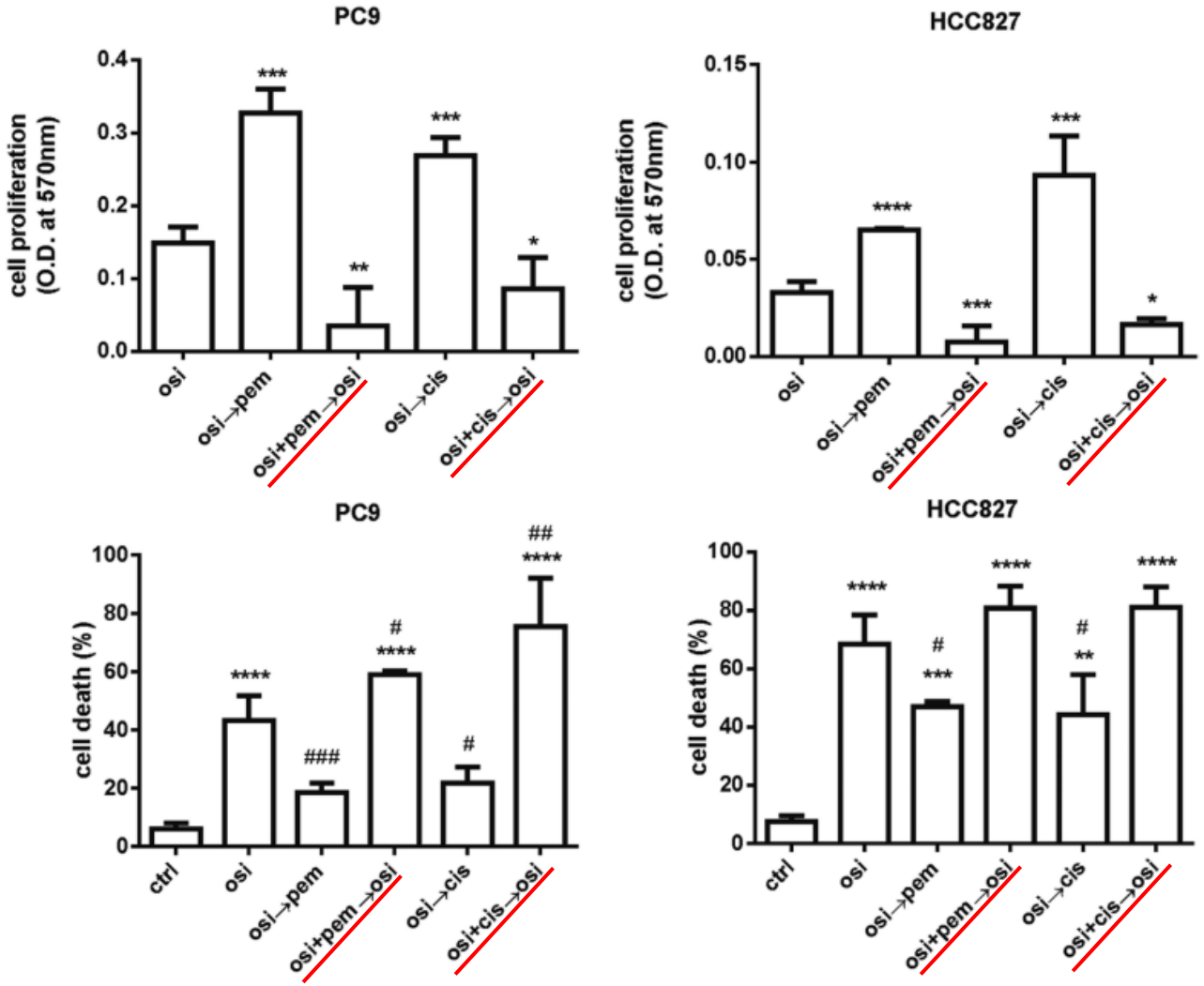




- Gefitinib + chemotherapy significantly improved PFS compared to gefitinib alone, but failed to significantly improve OS.

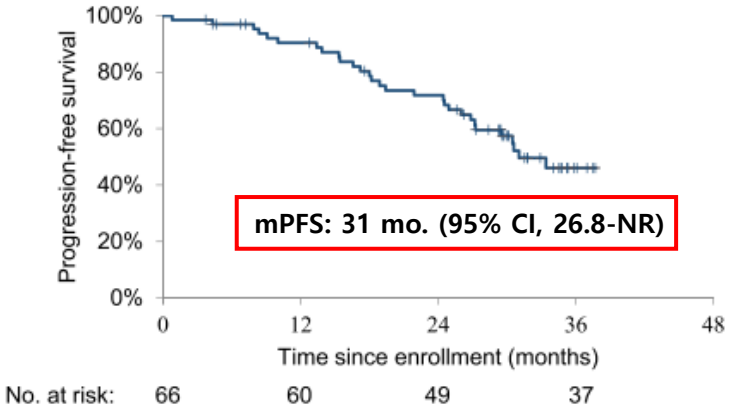
J Clin Oncol. 2020; 38(2):115-123
J Clin Oncol. 2022; 40(31):3587-3592

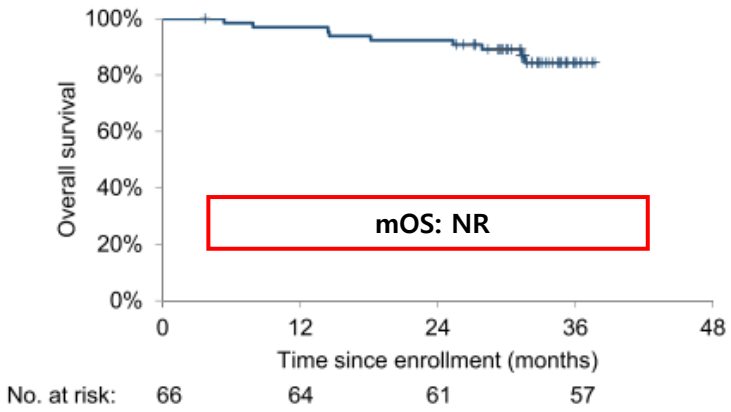
Preclinical models of FLAURA2

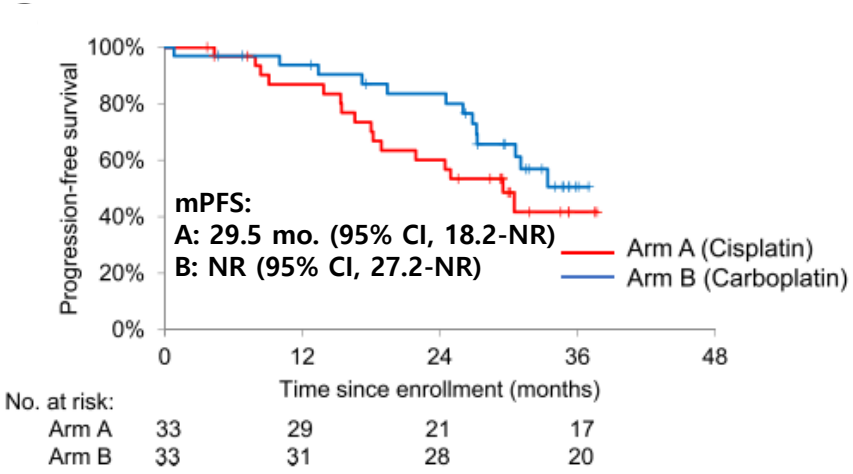


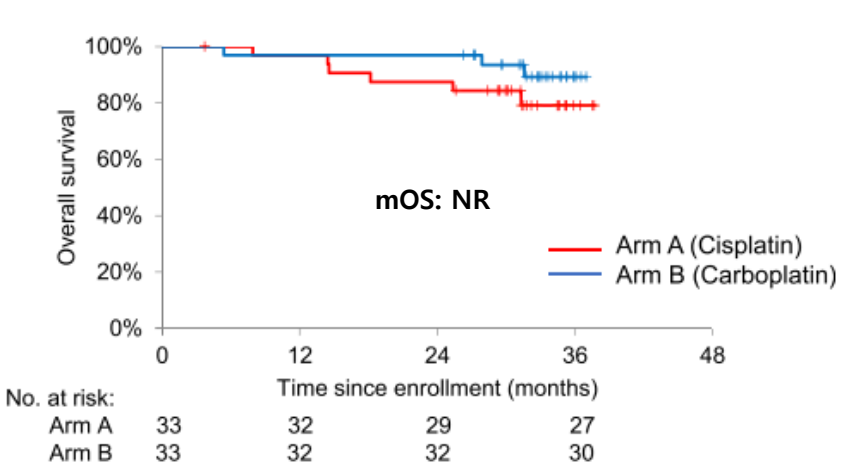
J Exp Clin Cancer Res 2019;38(1):222

OPAL study (Phase II): Osimertinib + chemotherapy



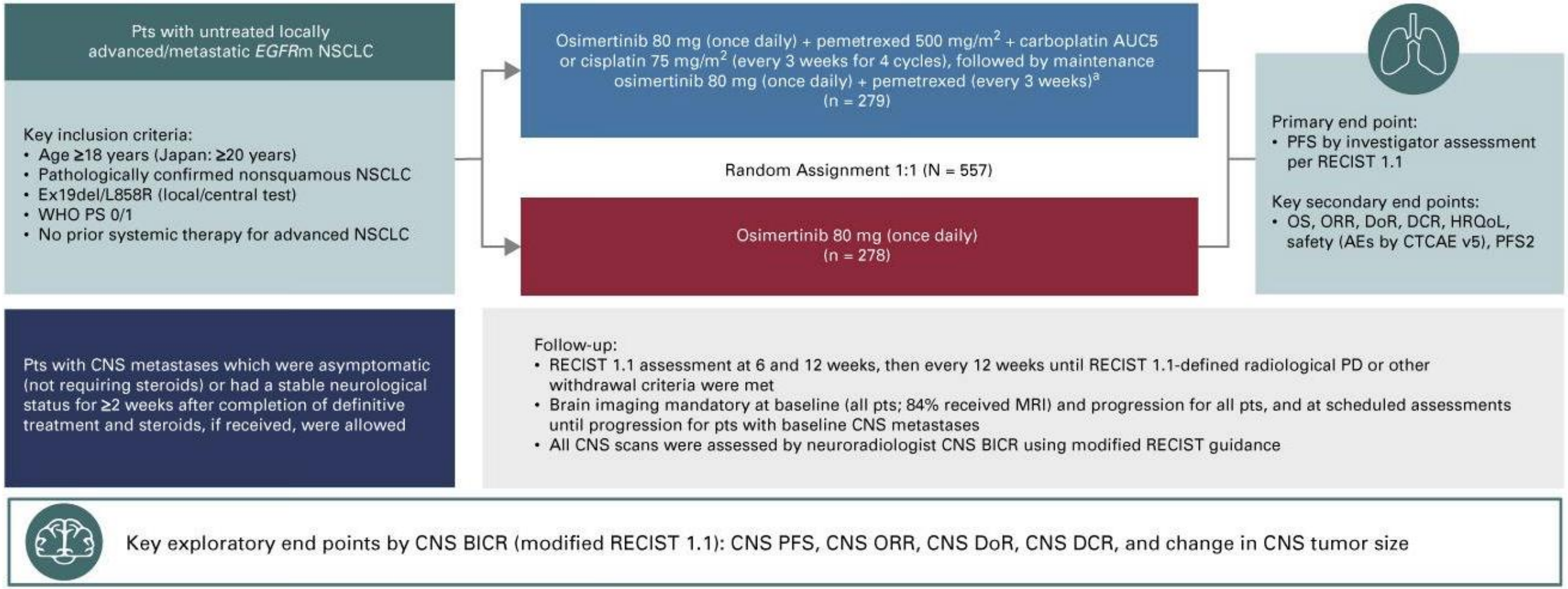






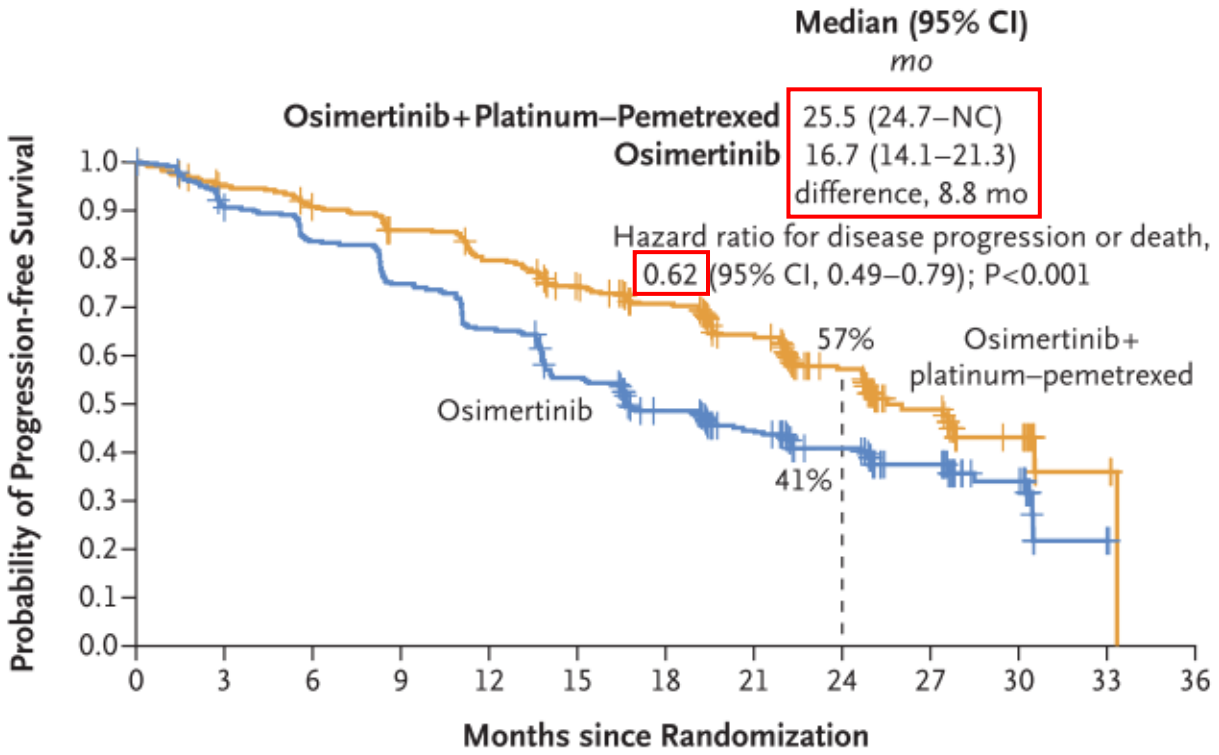
Eur J Cancer 2023;185:83-93

FLAURA2 (Phase III, RCT): design



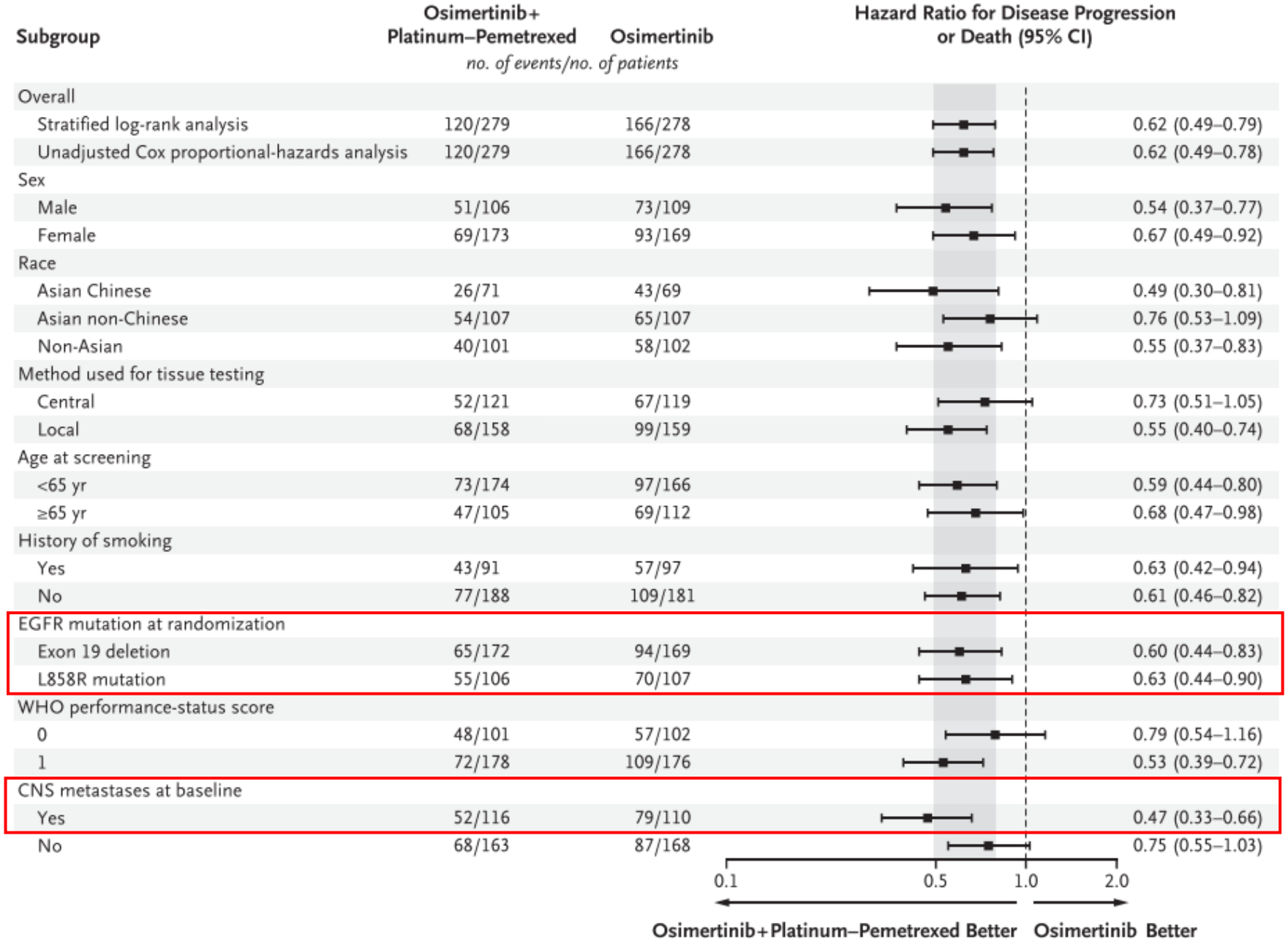
J Clin Oncol 2024;42(7):808-820.

FLAURA2: PFS per investigator assessment (IA)



No. at Risk													
Osimertinib+ platinum–pemetrexed	279	254	241	225	207	187	165	133	84	42	21	3	0
Osimertinib	278	246	227	203	178	148	119	94	67	48	21	1	0

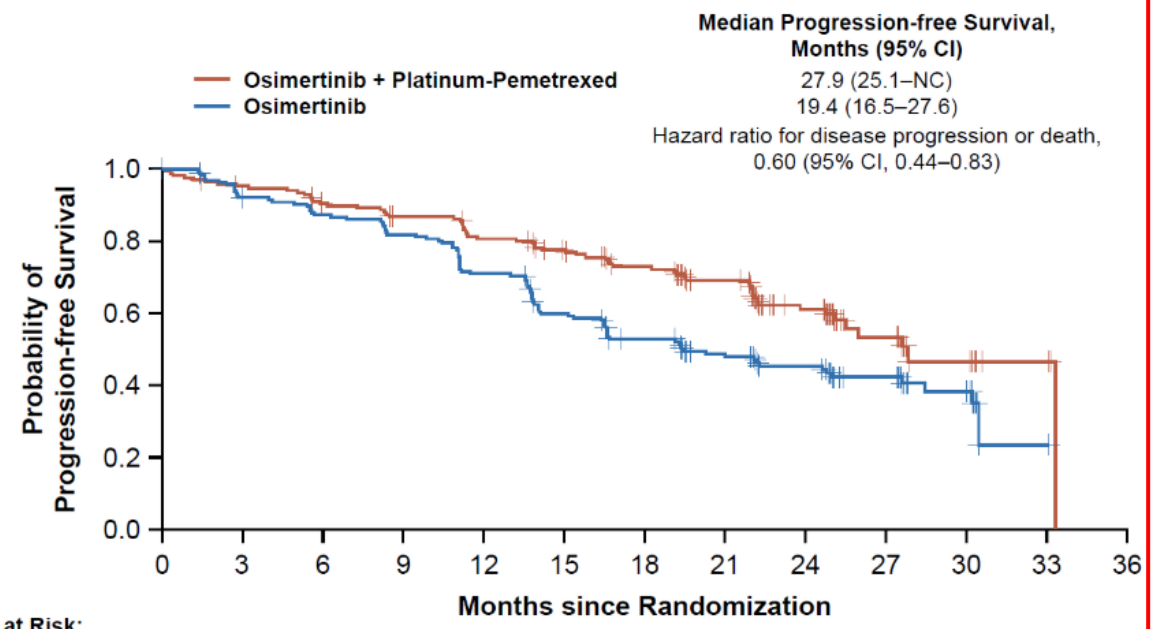
N Engl J Med 2023;389(21):1935-1948.



N Engl J Med 2023;389(21):1935-1948.

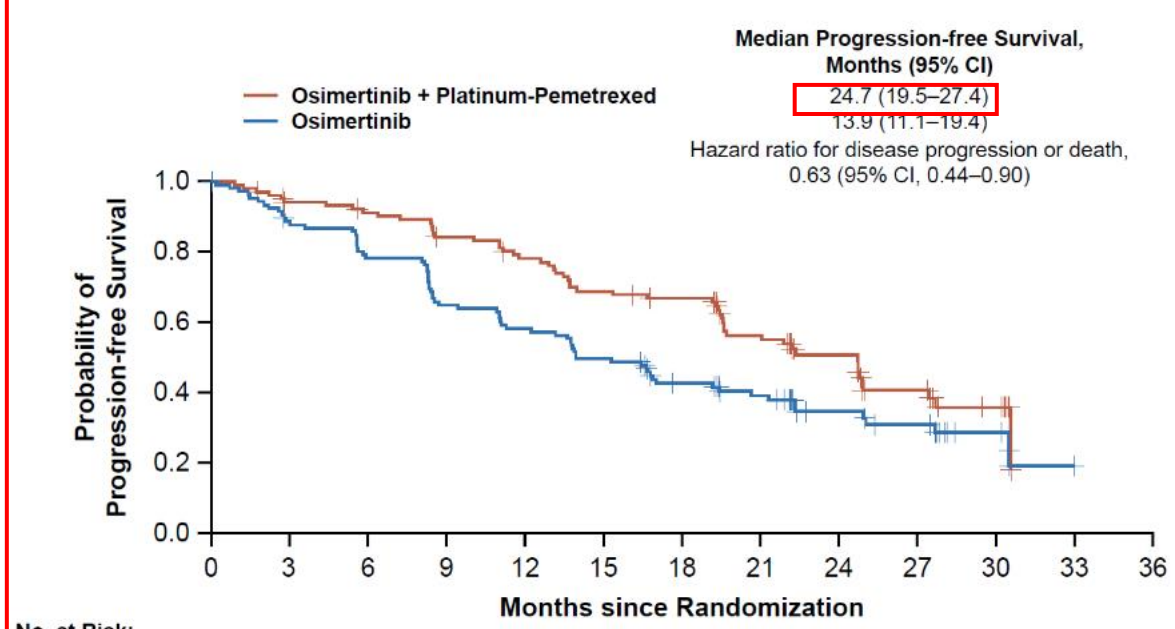
FLAURA2: PFS (IA) based on EGFR mutation type

Ex19del mutation



No. at Risk:													
Osimertinib + Platinum-Pemetrexed	172	159	150	142	131	120	103	86	53	23	9	3	0
Osimertinib	169	152	144	135	117	96	79	63	48	33	16	1	0

L858R mutation

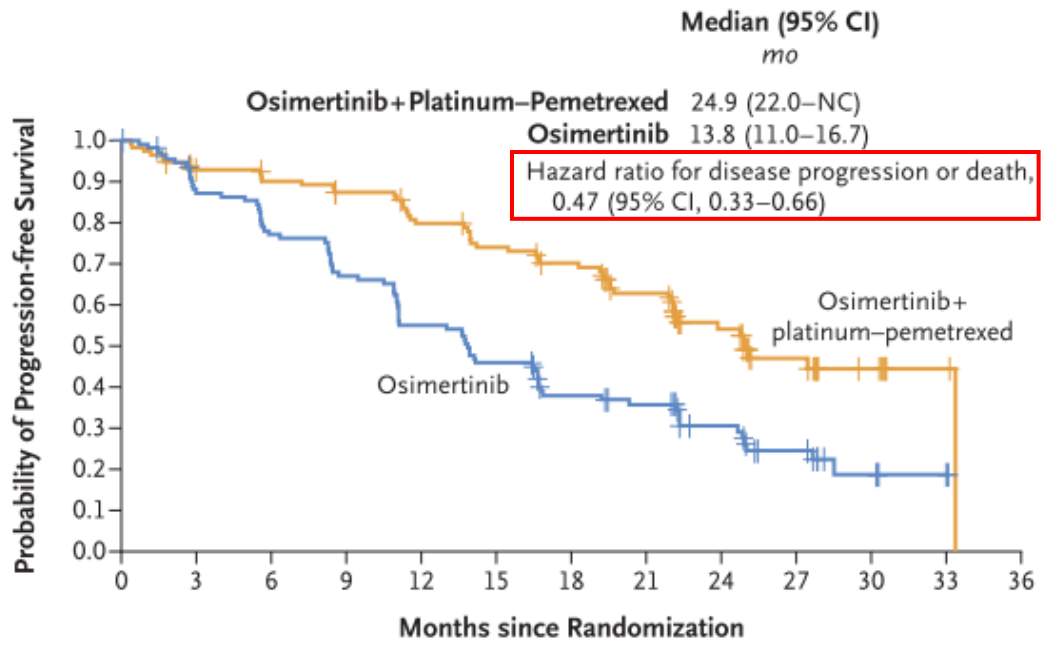


No. at Risk:													
Osimertinib + Platinum-Pemetrexed	106	95	91	83	76	67	62	47	31	19	12	0	0
Osimertinib	107	92	82	68	61	52	40	31	19	15	5	0	0

N Engl J Med 2023;389(21):1935-1948.

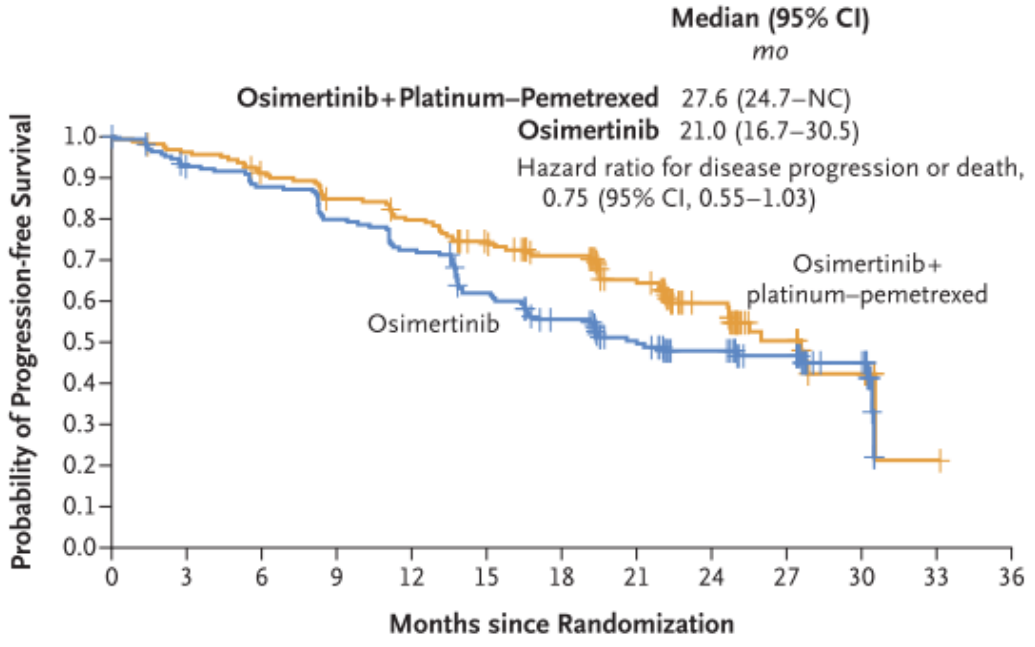
FLAURA2: PFS (IA) based on CNS metastasis

With CNS metastasis



No. at Risk													
Osimertinib+ platinum–pemetrexed	116	101	98	93	84	77	70	58	34	19	8	2	0
Osimertinib	110	95	84	73	60	50	37	32	21	13	5	1	0

Without CNS metastasis

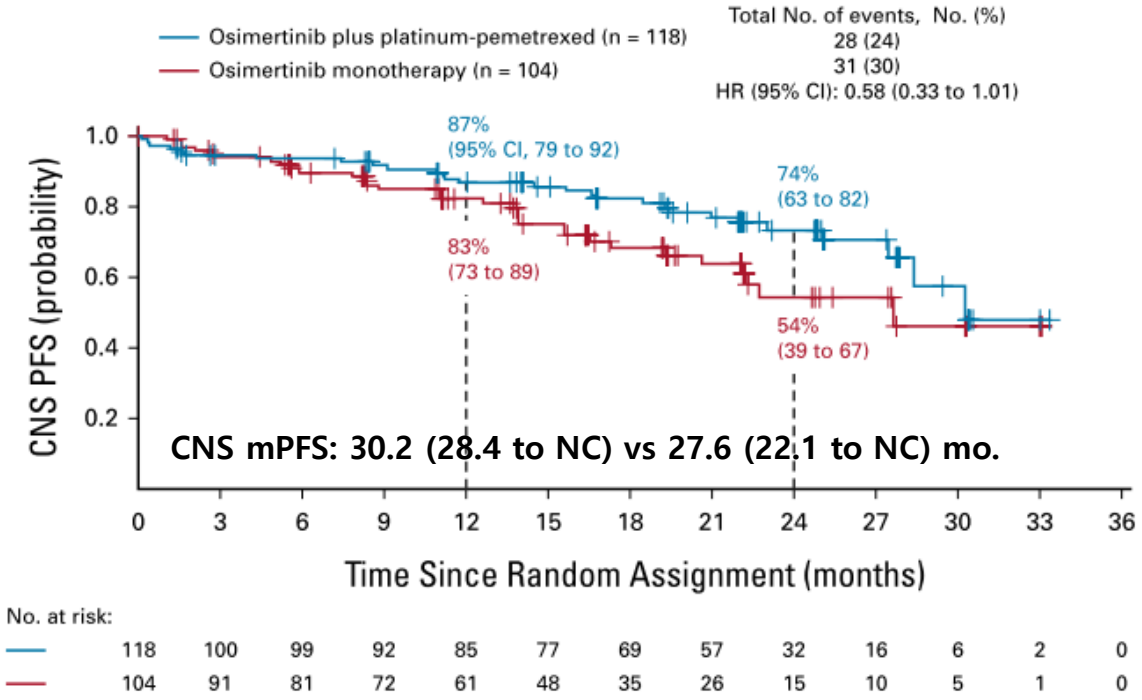


No. at Risk													
Osimertinib+ platinum–pemetrexed	163	153	143	132	123	110	95	75	50	23	13	1	0
Osimertinib	168	151	143	130	118	98	82	62	46	35	16	0	0

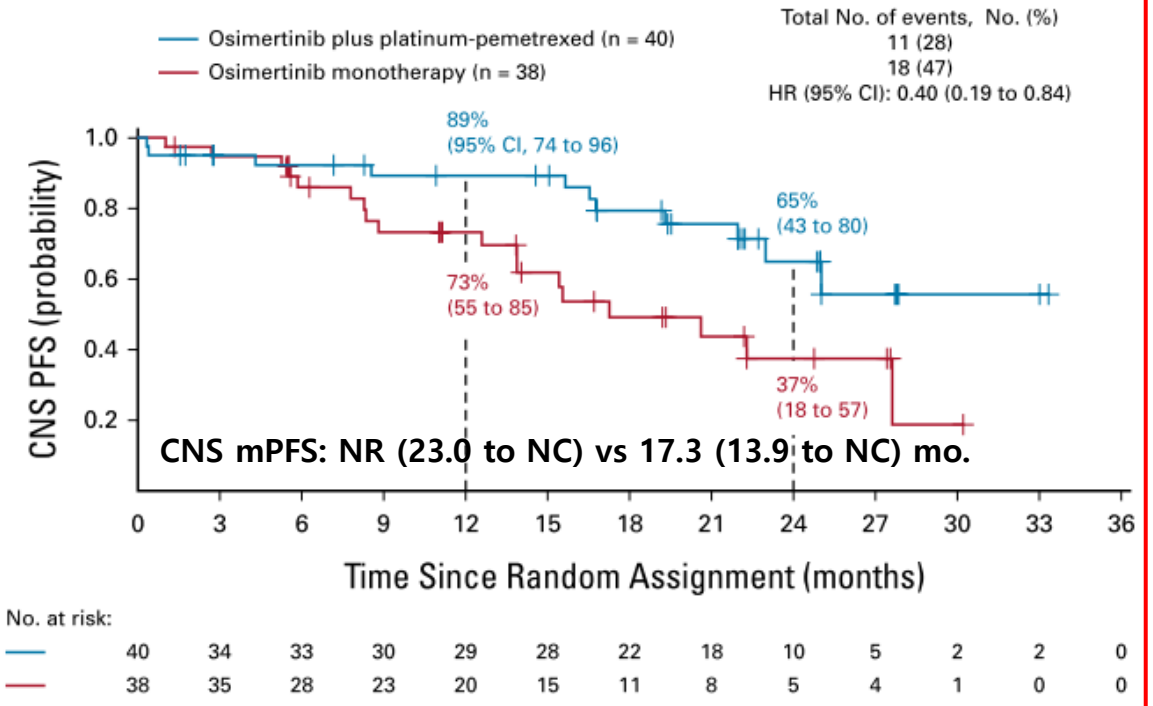
N Engl J Med 2023;389(21):1935-1948.

FLAURA2: CNS PFS per blinded independent review (BICR)

CNS full analysis set (cFAS)



CNS evaluable-for-response set (cEFR)



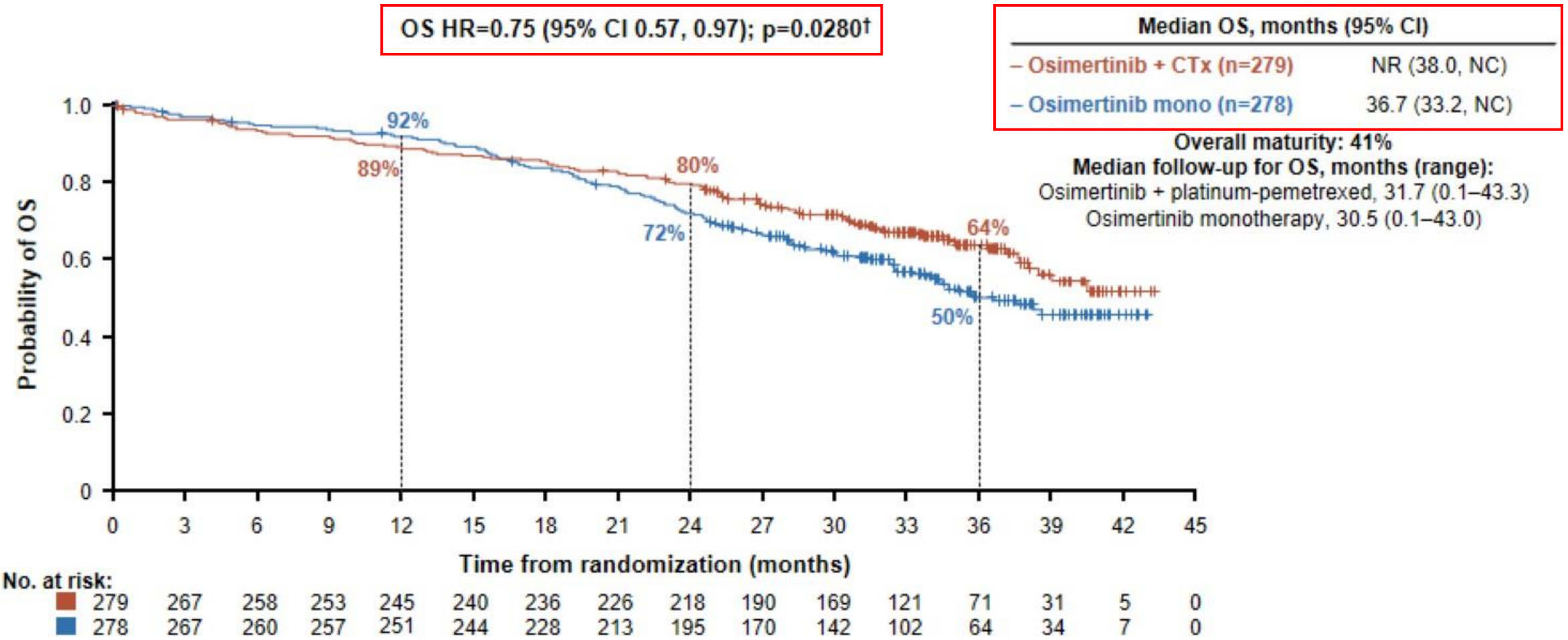
J Clin Oncol 2024;42(7):808-820.

FLAURA2: CNS response

Response	cFAS (n = 222)		cEFR (n = 78)	
	Osimertinib Plus Platinum-Pemetrexed (n = 118)	Osimertinib Monotherapy (n = 104)	Osimertinib Plus Platinum-Pemetrexed (n = 40)	Osimertinib Monotherapy (n = 38)
CNS best objective response, No. (%)[a]	86 (73)	72 (69)	35 (88)	33 (87)
CR	70 (59)	45 (43)	19 (48)	6 (16)
PR	16 (14)	27 (26)	16 (40)	27 (71)
CNS ORR, % (95% CI)	73 (64 to 81)	69 (59 to 78)	88 (73 to 96)	87 (72 to 96)
OR (95% CI)	1.19 (0.67 to 2.14)		1.06 (0.28 to 4.00)	
Nominal two-sided *P*	*P* = .5492		*P* = .9308	
CNS DCR, % (95% CI)	91 (84 to 95)	93 (87 to 97)	95 (83 to 99)	97 (86 to 100)
OR (95% CI)	0.70 (0.26 to 1.88)		0.51 (0.04 to 5.91)	
Nominal two-sided *P*	*P* = .4781		*P* = .5827	
Responders who subsequently CNS progressed or died, No. (%)	17 (20)	19 (26)	8 (23)	13 (39)
Median CNS DoR, months (95% CI)[b]	NR (23.8 to NC)	26.2 (19.4 to NC)	NR (21.6 to NC)	20.9 (12.6 to NC)
Estimated percent remaining in response, % (95% CI)[b]				
At 6 months	99 (92 to 100)	87 (75 to 93)	100 (100 to 100)	78 (57 to 90)
At 12 months	93 (85 to 97)	81 (68 to 89)	93 (75 to 98)	74 (53 to 87)
At 18 months	82 (70 to 90)	73 (58 to 83)	80 (58 to 91)	58 (36 to 76)
At 24 months	62 (40 to 77)	57 (38 to 72)	57 (27 to 78)	45 (22 to 65)

J Clin Oncol 2024;42(7):808-820.

At second interim analysis, there was a trend towards OS benefit with osimertinib plus chemotherapy versus osimertinib alone



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

Table 3. Adverse Events.*

Event	Osimertinib + Platinum–Pemetrexed (N = 276)					Osimertinib Monotherapy (N = 275)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	128 (46)	30 (11)	43 (16)	55 (20)	0	22 (8)	15 (5)	6 (2)	1 (<1)	0
Diarrhea	120 (43)	83 (30)	29 (11)	8 (3)	0	112 (41)	89 (32)	22 (8)	1 (<1)	0
Nausea	119 (43)	81 (29)	34 (12)	4 (1)	0	28 (10)	22 (8)	6 (2)	0	0
Decreased appetite	85 (31)	49 (18)	28 (10)	8 (3)	0	26 (9)	18 (7)	6 (2)	2 (1)	0
Constipation	81 (29)	60 (22)	20 (7)	1 (<1)	0	28 (10)	23 (8)	5 (2)	0	0
Rash	77 (28)	55 (20)	21 (8)	1 (<1)	0	57 (21)	46 (17)	11 (4)	0	0
Fatigue	76 (28)	45 (16)	23 (8)	8 (3)	0	26 (9)	24 (9)	1 (<1)	1 (<1)	0
Vomiting	73 (26)	50 (18)	20 (7)	3 (1)	0	17 (6)	13 (5)	4 (1)	0	0
Stomatitis	68 (25)	40 (14)	27 (10)	1 (<1)	0	50 (18)	32 (12)	17 (6)	1 (<1)	0
Neutropenia	68 (25)	4 (1)	27 (10)	30 (11)	7 (3)	9 (3)	3 (1)	4 (1)	2 (1)	0
Paronychia	65 (24)	28 (10)	35 (13)	2 (1)	0	73 (27)	37 (13)	35 (13)	1 (<1)	0
Neutrophil count decrease	62 (22)	5 (2)	26 (9)	25 (9)	6 (2)	16 (6)	6 (2)	8 (3)	2 (1)	0
Covid-19†	57 (21)	23 (8)	31 (11)	2 (1)	0	39 (14)	18 (7)	21 (8)	0	0
ALT increase	56 (20)	36 (13)	16 (6)	4 (1)	0	21 (8)	17 (6)	3 (1)	1 (<1)	0
Platelet count decrease	51 (18)	19 (7)	11 (4)	18 (7)	3 (1)	19 (7)	18 (7)	1 (<1)	0	0
Thrombocytopenia	51 (18)	19 (7)	13 (5)	16 (6)	3 (1)	12 (4)	6 (2)	3 (1)	3 (1)	0
Dry skin	50 (18)	43 (16)	7 (3)	0	0	66 (24)	62 (23)	4 (1)	0	0
AST increase	48 (17)	42 (15)	5 (2)	1 (<1)	0	13 (5)	12 (4)	0	1 (<1)	0
Blood creatinine increase	46 (17)	33 (12)	13 (5)	0	0	12 (4)	10 (4)	2 (1)	0	0
White-cell count decrease	44 (16)	7 (3)	28 (10)	8 (3)	1 (<1)	18 (7)	9 (3)	8 (3)	1 (<1)	0
Peripheral edema	42 (15)	33 (12)	9 (3)	0	0	12 (4)	9 (3)	3 (1)	0	0

N Engl J Med 2023;389(21):1935-1948.

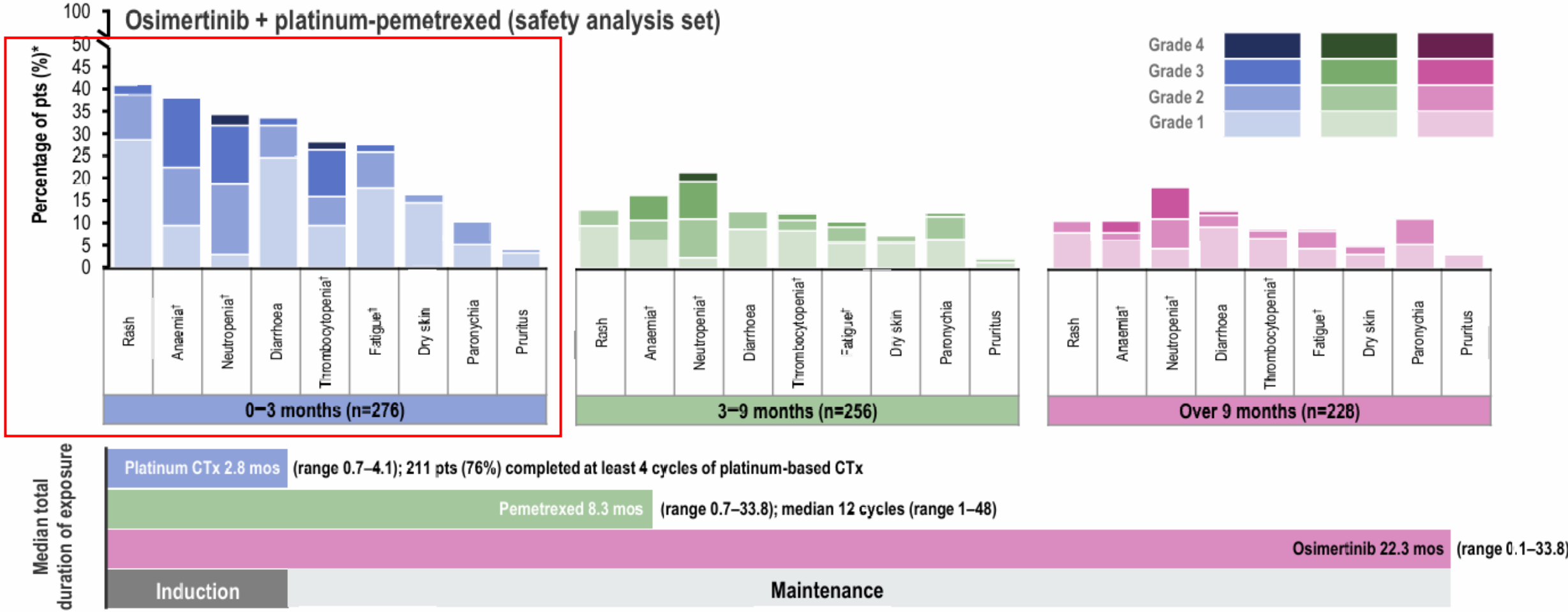
FLAURA2: Adverse event

Patients with AEs, n (%)[a]	Osimertinib + platinum-pemetrexed (n=276)	Osimertinib monotherapy (n=275)
AE any cause	**276 (100)**	**268 (97)**
Any AE Grade ≥3	176 (64)	75 (27)
Any AE leading to death	18 (7)	8 (3)
Any serious AE	104 (38)	53 (19)
Any AE leading to discontinuation	132 (48)	17 (6)
Osimertinib / carboplatin or cisplatin / pemetrexed discontinuation	30 (11) / 46 (17) / 119 (43)	17 (6) / NA / NA
Any AE possible causally related to treatment[b]	**269 (97)**	**241 (88)**
Any AE Grade ≥3	146 (53)	29 (11)
Causally related to osimertinib / carboplatin or cisplatin / pemetrexed	81 (29) / 104 (38) / 130 (47)	29 (11) / NA / NA
Any AE leading to death	5 (2)	1 (<1)
Causally related to osimertinib / carboplatin or cisplatin / pemetrexed	3 (1) / 2 (1) / 3 (1)	1 (<1) / NA / NA
Any serious AE	52 (19)	15 (5)

N Engl J Med 2023;389(21):1935-1948.

AE ONSET FREQUENCY AND SEVERITY WERE HIGHEST DURING THE INDUCTION PERIOD, AND GRADUALLY REDUCED OVER TIME

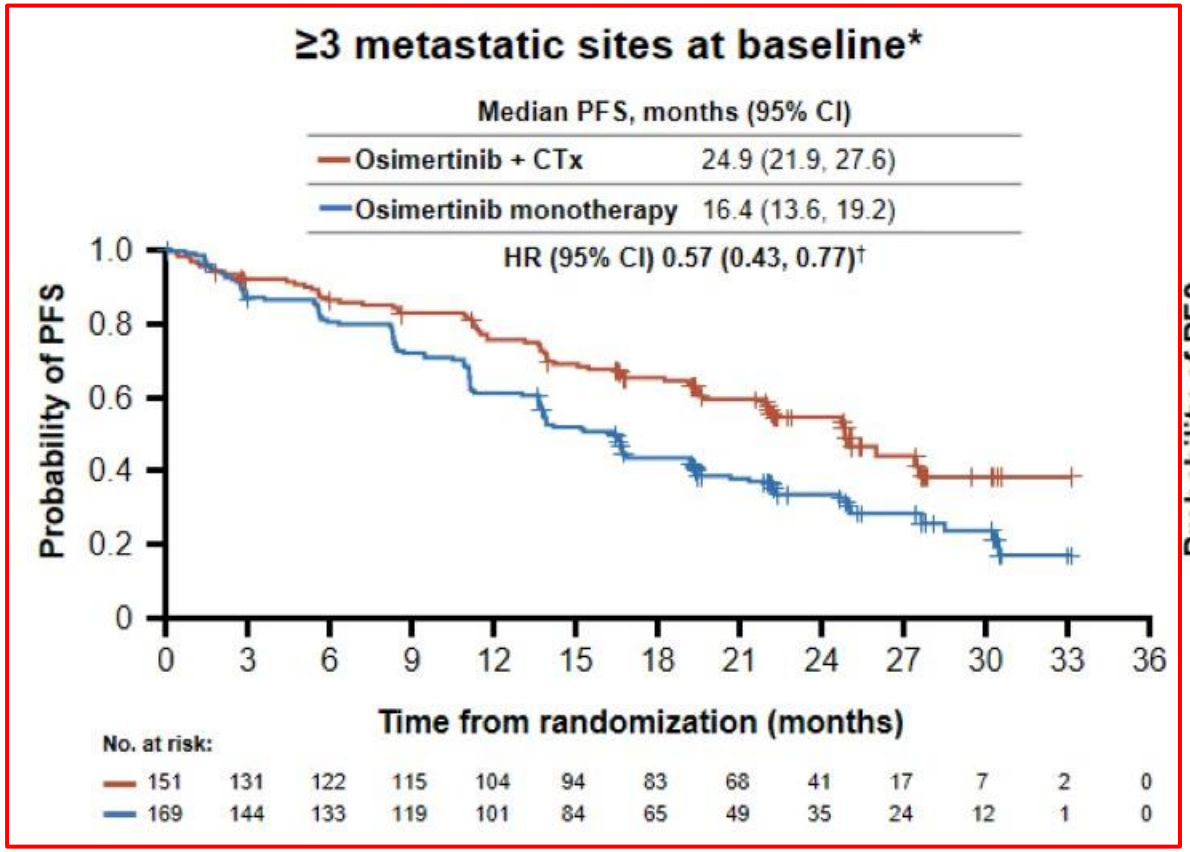
- In the osi + CTx arm, the onset of ≥Grade 3 AEs reduced by ~50% between 0–3 mos (n=135; 49%) and 3–9 mos (n=62; 24%)

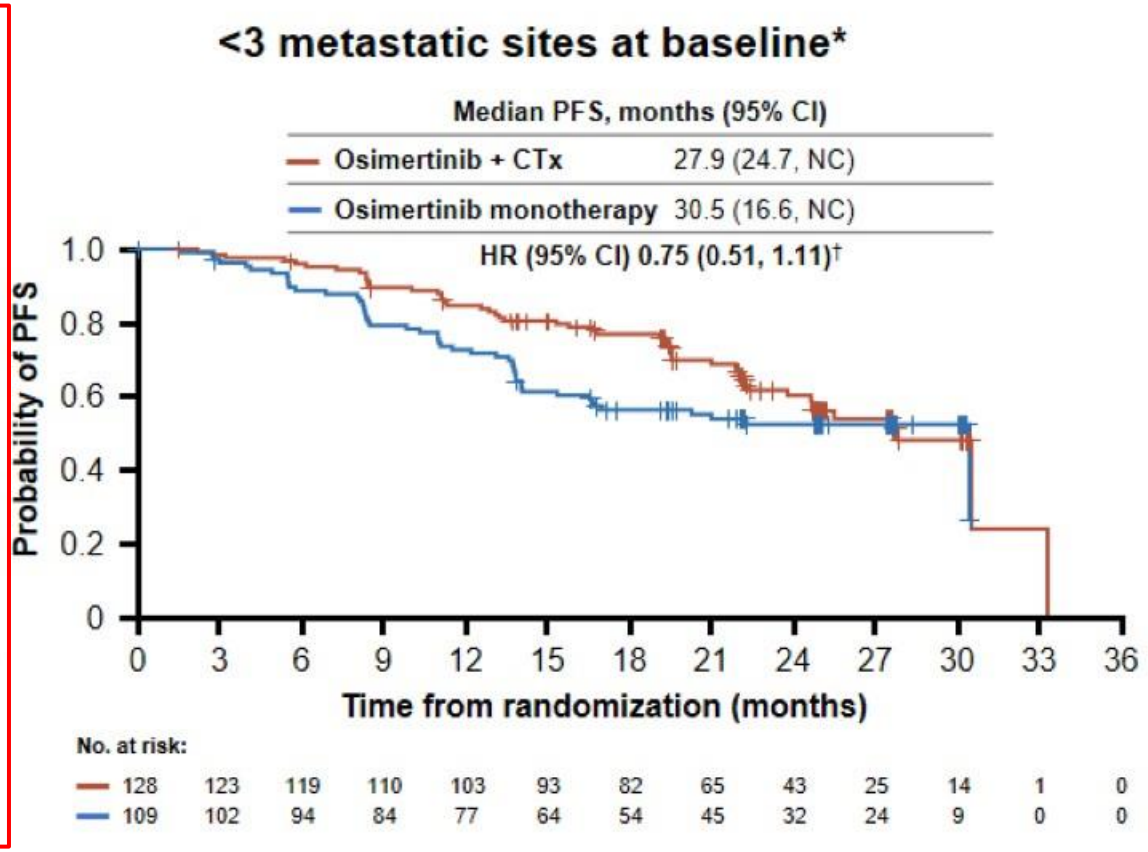


*Includes AEs with an onset date within the study months noted, for pts still on study at the start of the respective time period; †Grouped term: anaemia / haemoglobin decreased, thrombocytopenia / platelet count decreased, neutropenia / neutrophil count decreased, and asthenia / fatigue (by preferred terms); AE, adverse event; CTx, chemotherapy; mos, months; osi, osimertinib; pts, patients

Data cut-off: 03 April 2023.

Osimertinib + CTx showed PFS benefit in patients with ≥3 metastatic anatomical sites at baseline vs osimertinib alone





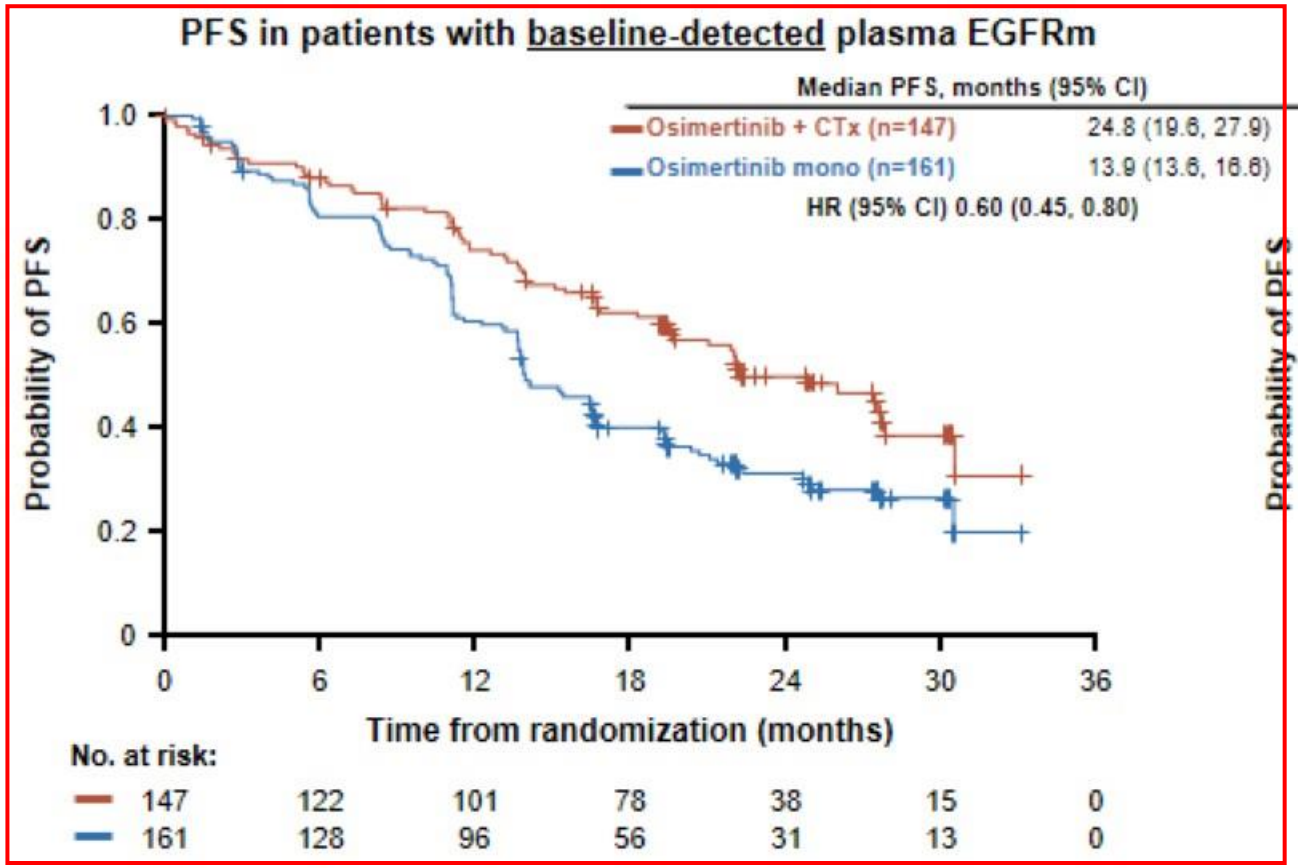
- A PFS benefit with osimertinib plus chemotherapy vs osimertinib alone was observed in patients with extra-thoracic metastases at baseline:†‡
  - Intra-thoracic: median PFS (95% CI) was 26.0 months (21.9, NC) vs NC (16.7, NC), respectively; HR 0.97 (95% CI 0.59, 1.60)
  - Extra-thoracic: median PFS (95% CI) was 25.1 months (22.2, NC) vs 16.4 months (13.6, 19.4), respectively; HR 0.54 (95% CI 0.41, 0.71)

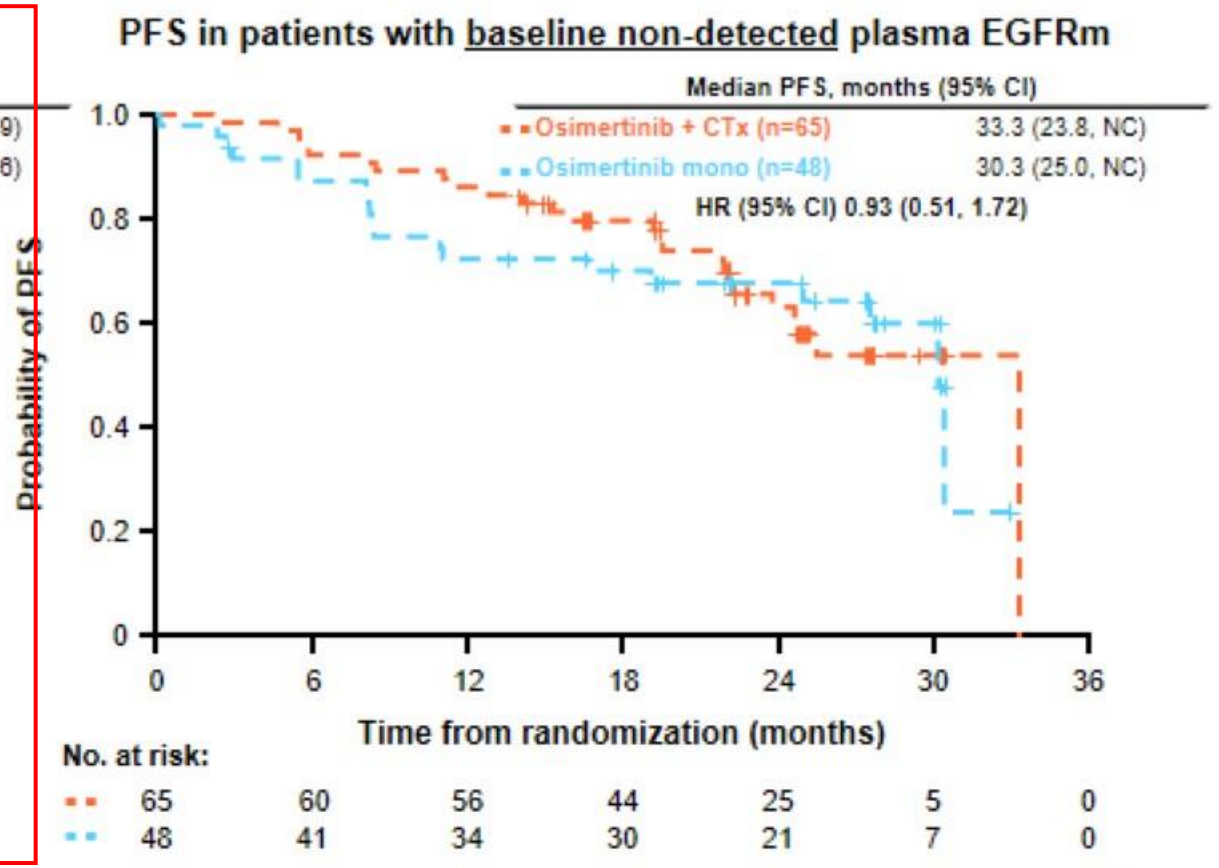
Data cut-off: April 03 2023

*Patients with baseline metastatic disease at the following sites contribute: adrenal, bone and locomotor, brain / CNS, cardiovascular, genitourinary, hepatic (including gall bladder), lung, lymph nodes, other metastatic sites, pericardial effusion, pleural effusion or skin / soft tissue. Note two patients with locally advanced indication for bone and locomotor / cardiovascular have also been included. Patients are counted only once within a site; †Subgroup analysis was performed using a Cox proportional hazards model including treatment, subgroup and a treatment-by subgroup interaction term; ‡Intra-thoracic = M1a, extra-thoracic = M1b and M1c, patients with M0 and M1 stage disease were excluded according to version 8 of the IASLC staging manual in thoracic oncology.

CI, confidence interval; CTx, chemotherapy; HR, hazard ratio; NC, not calculable; PFS, progression-free survival

PFS improved with osimertinib plus chemotherapy in patients with baseline-detected plasma EGFRm versus osimertinib alone





Baseline-detected plasma EGFRm was prognostic and may select for a higher degree of clinical benefit with osimertinib plus chemotherapy versus osimertinib alone

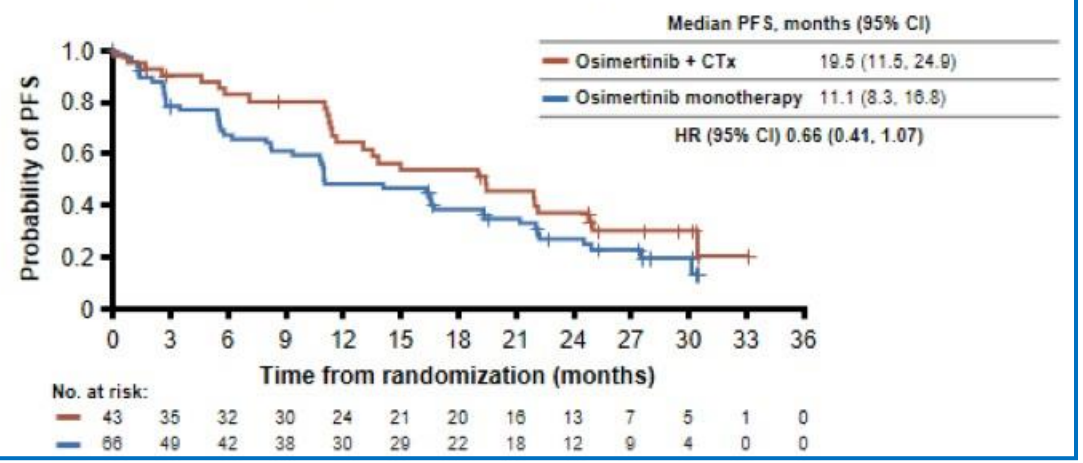
HR was calculated by an unstratified log-rank test

CI, confidence interval; CTx, chemotherapy; EGFRm, epidermal growth factor receptor mutation; HR, hazard ratio; mono, monotherapy; NC, not calculable; PFS, progression-free survival

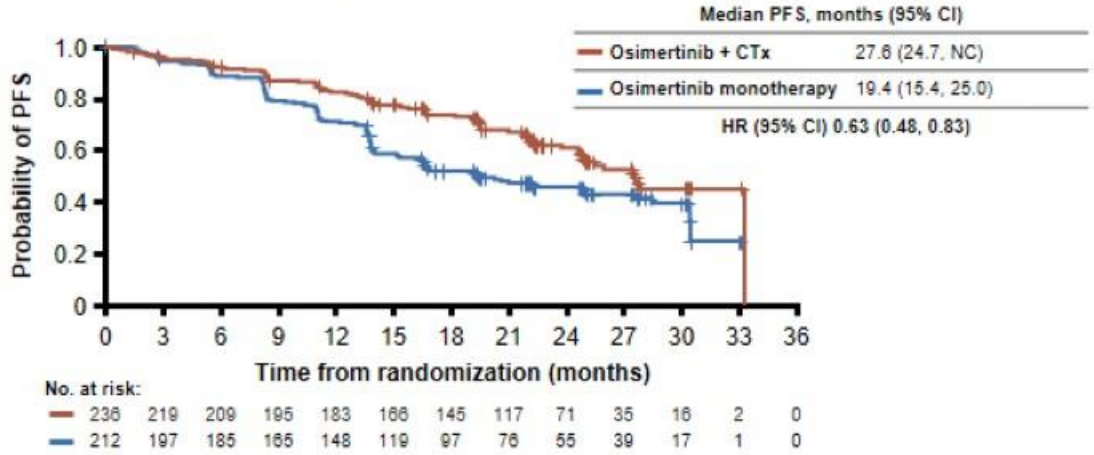
Planchard D et al. *N Engl J Med*. 2023;389(21):1935-1948.

Osimertinib + CTx showed PFS benefit in patients with and without liver or bone metastases at baseline vs osimertinib alone

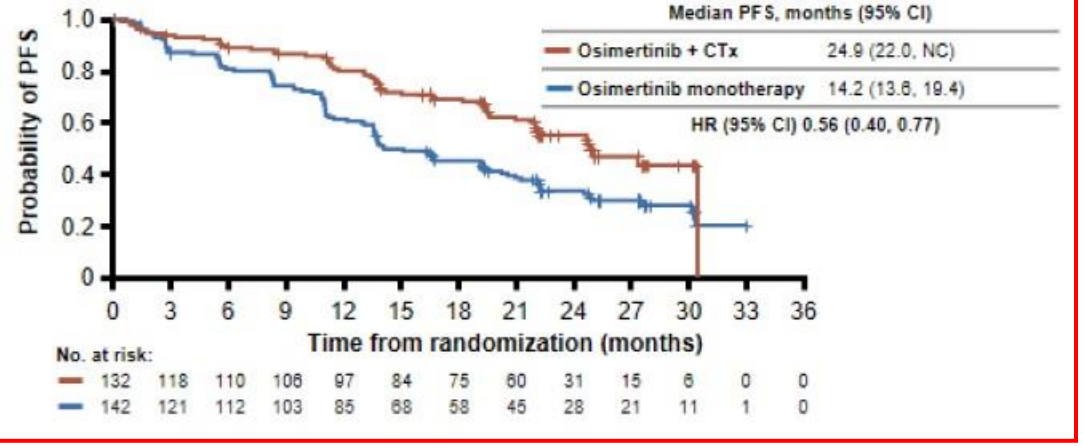
With liver metastases



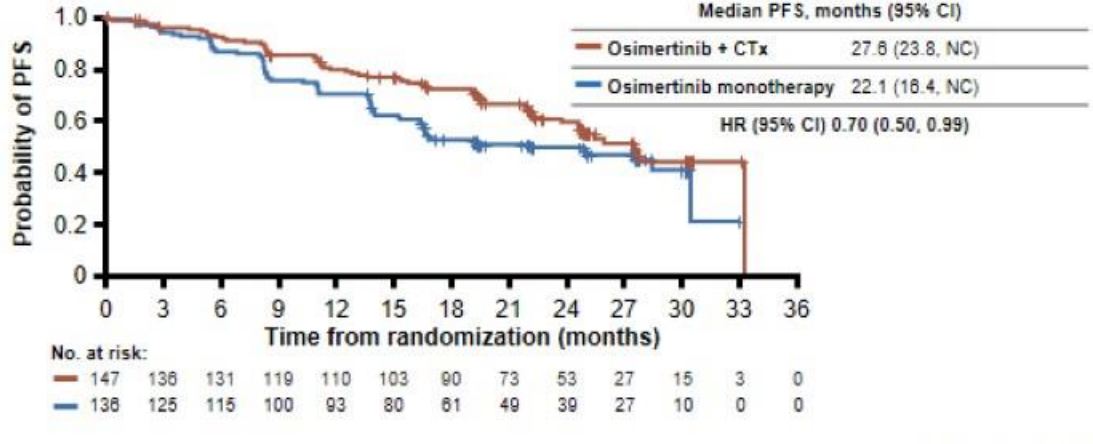
Without liver metastases



With bone metastases



Without bone metastases



Natalia Valdiviezo | Impact of tumor burden on outcomes of 1L osimertinib ± chemotherapy in patients with EGFR-mutated advanced NSCLC

Data cut-off: April 03 2023

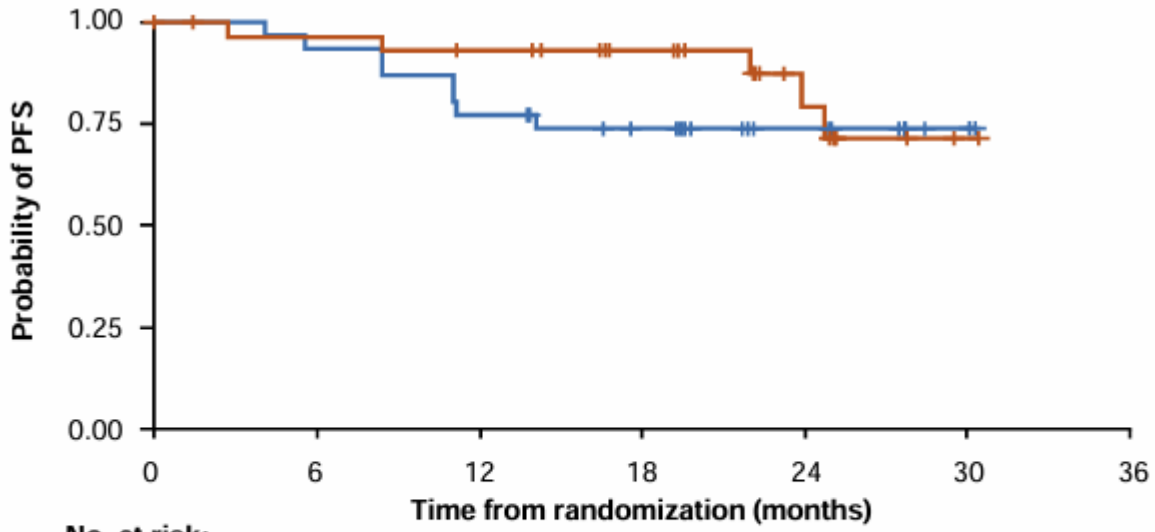
Subgroup analysis was performed using a Cox proportional hazards model including treatment, subgroup and a treatment-by subgroup interaction term.
CI, confidence interval; CTx, chemotherapy; HR, hazard ratio; NC, not calculable; PFS, progression-free survival

The PFS benefit of osimertinib + chemotherapy versus osimertinib alone appeared to be similar irrespective of baseline TP53 status

TP53 wild-type at baseline

Median PFS, months (95% CI)	
Osimertinib + chemotherapy (n=31)	NR (24.7, NC)
Osimertinib monotherapy (n=31)	NR (NC, NC)

HR (95% CI) NC*

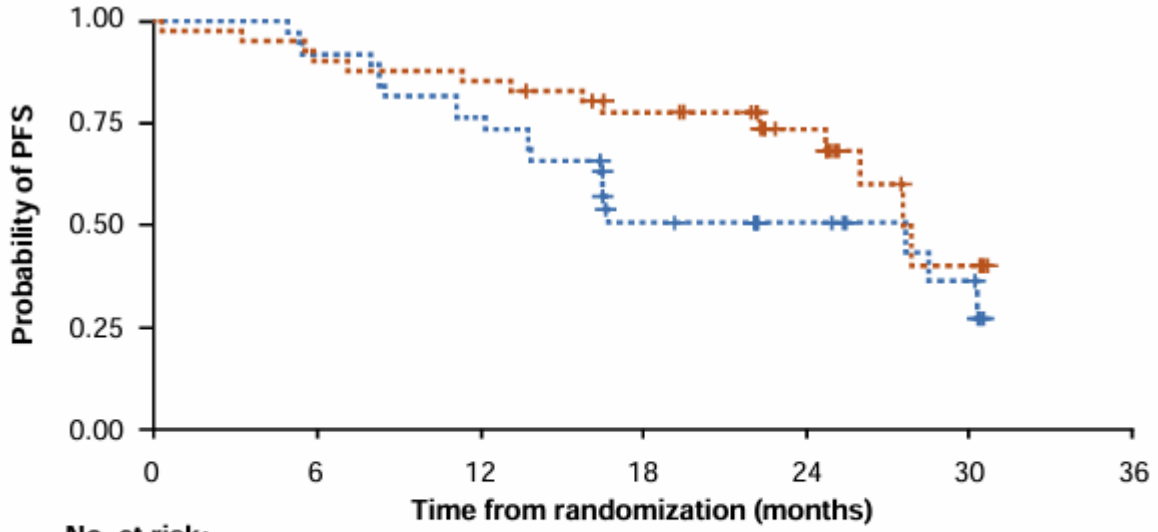


No. at risk:						
31	28	26	21	10	1	0
31	29	24	19	11	3	0

TP53 altered† at baseline

Median PFS, months (95% CI)	
Osimertinib + chemotherapy (n=41)	27.6 (24.7, NC)
Osimertinib monotherapy (n=38)	27.6 (13.9, 30.3)

HR (95% CI) 0.57 (0.29, 1.12)



No. at risk:						
41	37	35	29	14	4	0
38	35	29	15	10	5	0

James Chih-Hsin Yang | FLAURA2: Resistance, and impact of baseline TP53 alterations in patients treated with 1L osimertinib ± platinum-pemetrexed

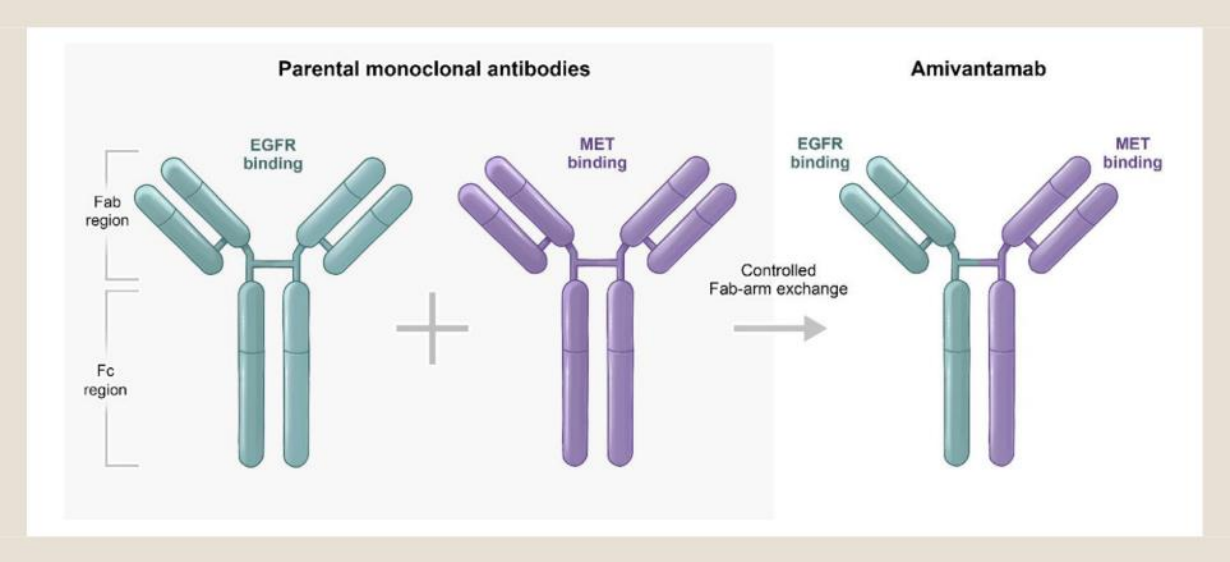
Data cut-off for clinical outcomes: Apr 03 2023. HR determined by unstratified log-rank method.
*HR not calculated where there were <20 events across both treatment arms; †TP53 alterations excluded variants with unknown oncogenic significance.
CI, confidence interval; CTx, chemotherapy; HR, hazard ratio; NC, not calculable; NR, not reached; PFS, progression-free survival;

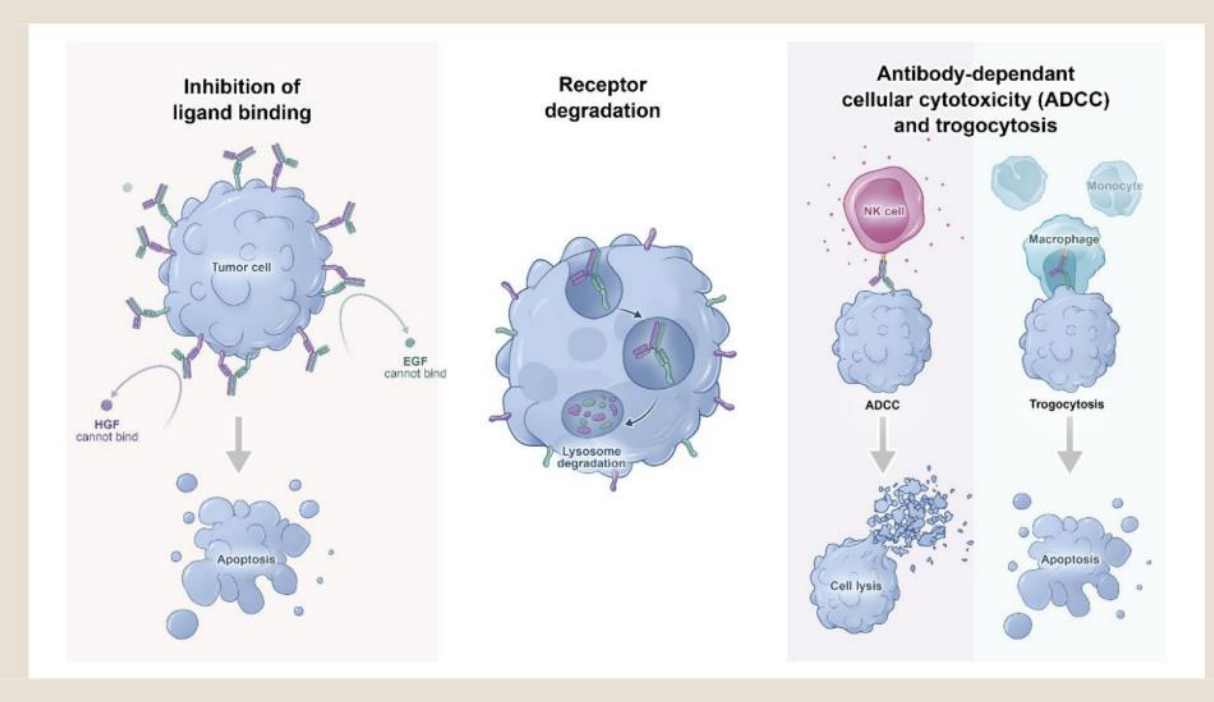
Summary (1)

- Osimertinib + chemotherapy significantly improved PFS over osimertinib in first-line therapy with EGFR-mutant advanced NSCLC.
- Osimertinib + chemotherapy showed significant PFS benefit over osimertinib in patients with CNS metastasis, and consistent irrespective of EGFR mutation type.
- Osimertinib + chemotherapy had higher rates of chemotherapy related AEs (ex: neutropenia, thrombocytopenia), majority grade 1-3.
- Osimertinib + chemotherapy also showed significant PFS benefit over osimertinib in patients with ≥3 metastatic sites, ctDNA+, bone metastasis.

MARIPOSA

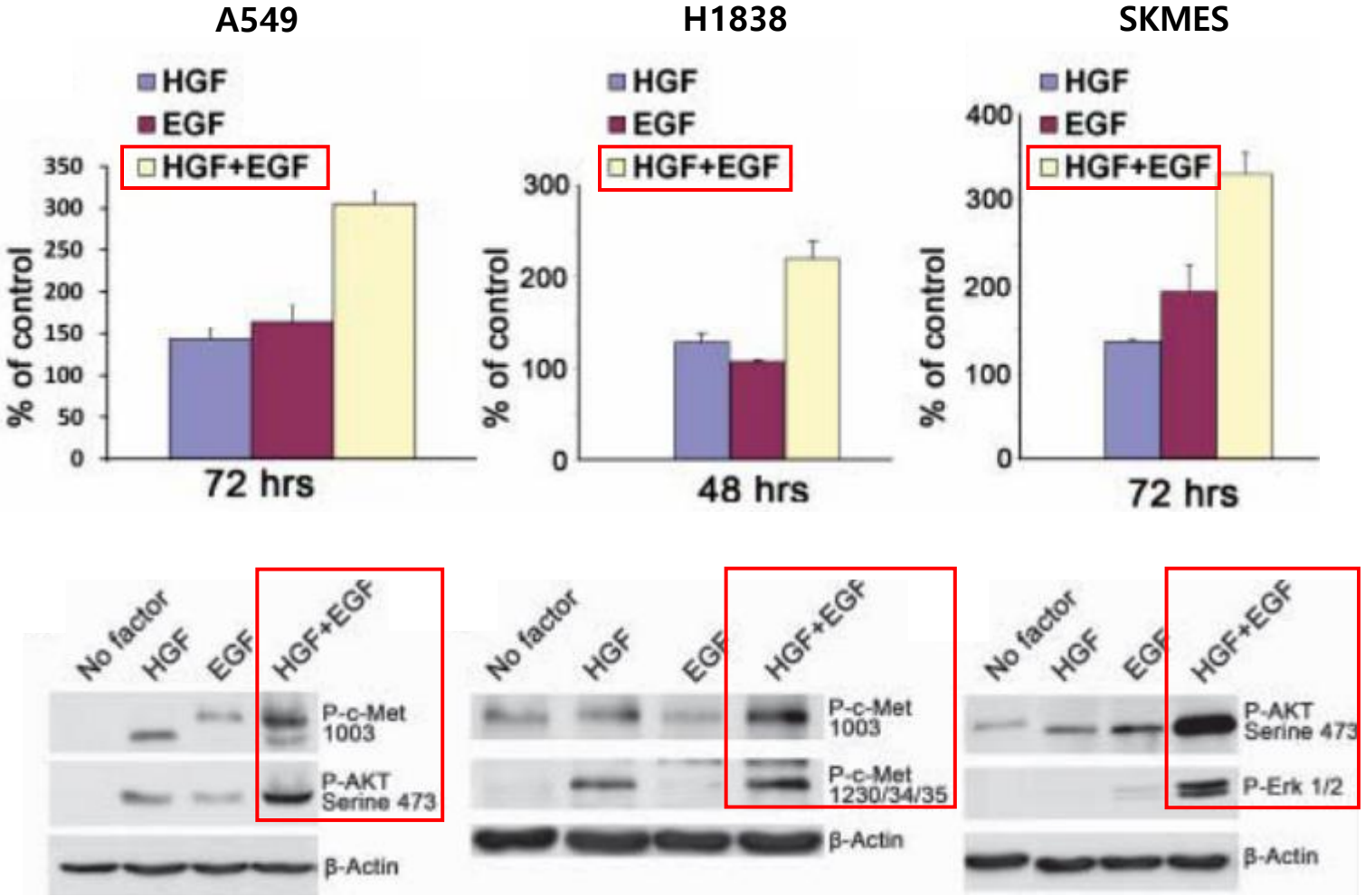
Amivantamab: EGFR-MET Bispecific antibody





Clin Lung Cancer. 2023;24(2):89-97

Crosstalk between EGFR and MET in NSCLC

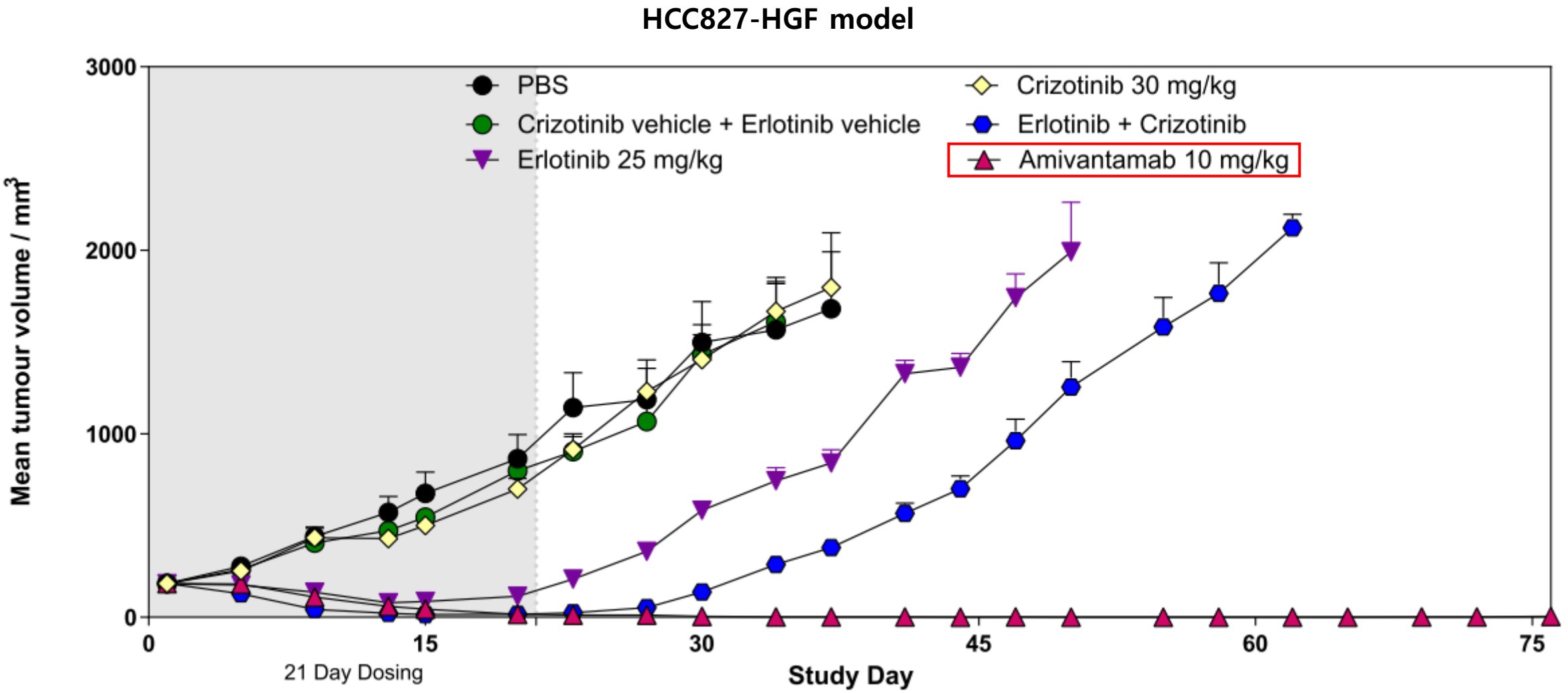


A549 and H1838 cell lines

- **HGF (hepatocyte growth factor)**
  - ➢ Ligand for c-MET
  - ➢ Combination of HGF and EGF
    - ✓ Synergistic effect on cell proliferation
    - ✓ Synergistic effect on downstream signaling intermediates

J Carinog. 2008;7:9.

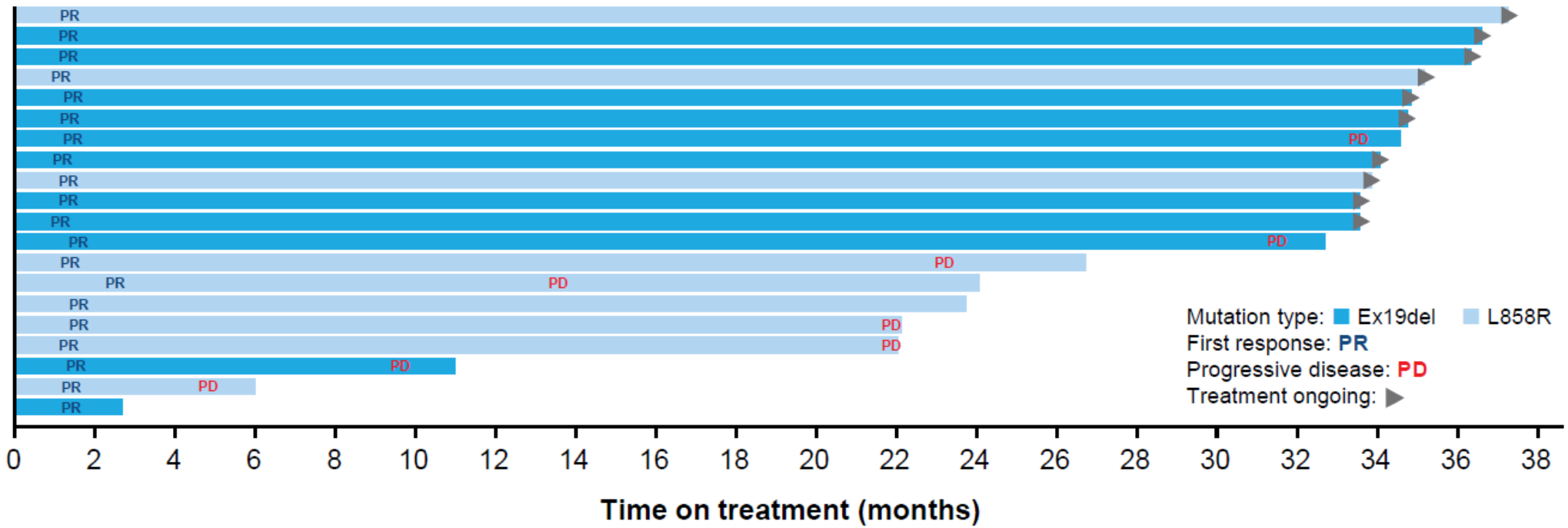
Preclinical models of amivantamab



J Biol Chem. 2021;296:100641.

Early Clinical Activity with Amivantamab + Lazertinib

Phase 1 CHRYSALIS: 20 patients with treatment-naïve, *EGFR* Ex19del/L858R advanced NSCLC

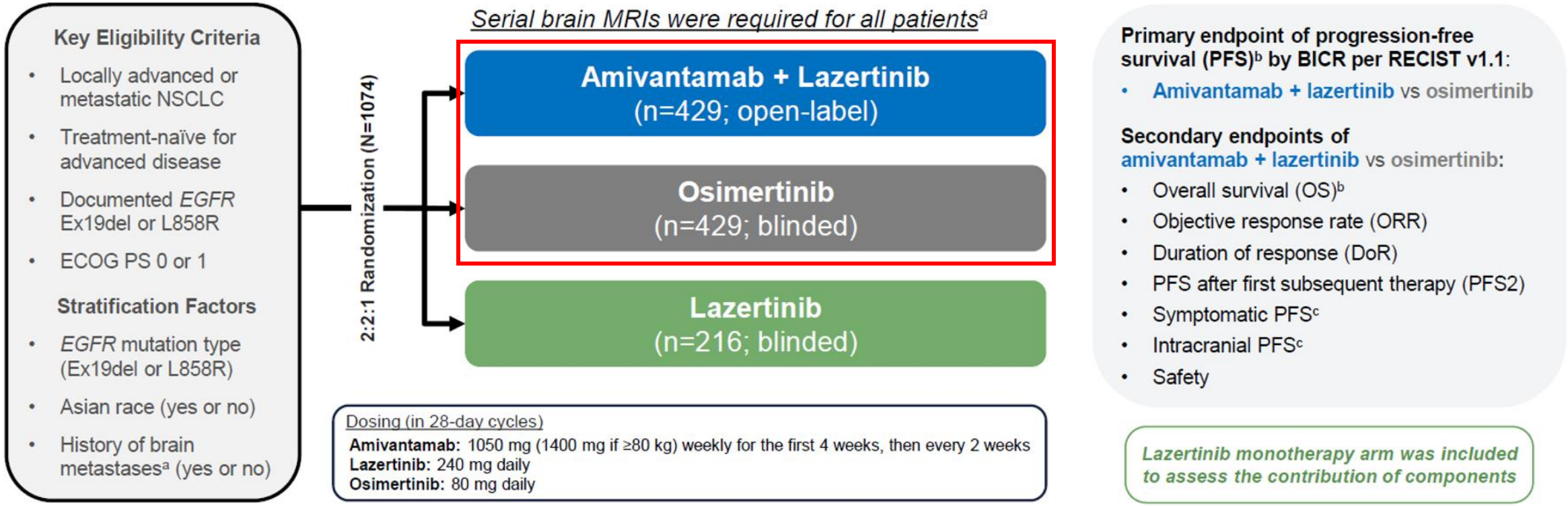


- All 20 patients responded to amivantamab + lazertinib and demonstrated durable responses[1]
- At a median follow-up of 33.6 months, 10 of 20 patients were receiving ongoing treatment[2]

EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletions; PD, progressive disease; PR, partial response; TKI, tyrosine kinase inhibitor.

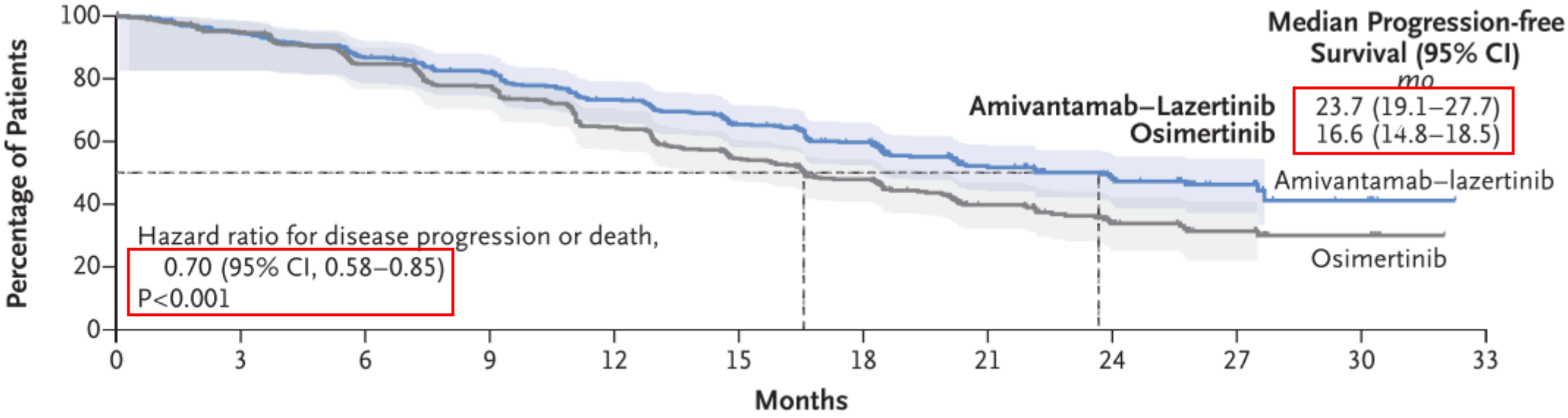
1. Cho BC, et al. *J Thorac Oncol*. 2022;17(9_suppl):S126. 2. Lee S-H, et al. *J Clin Oncol*. 2023;41(16_suppl):9134.

MARIPIOSA (Phase III, RCT): design



N Engl J Med. 2024;391(16):1486-1498.

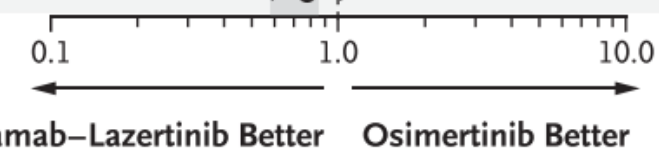
MARIPIOSA: PFS (BICR)



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

N Engl J Med. 2024;391(16):1486-1498.

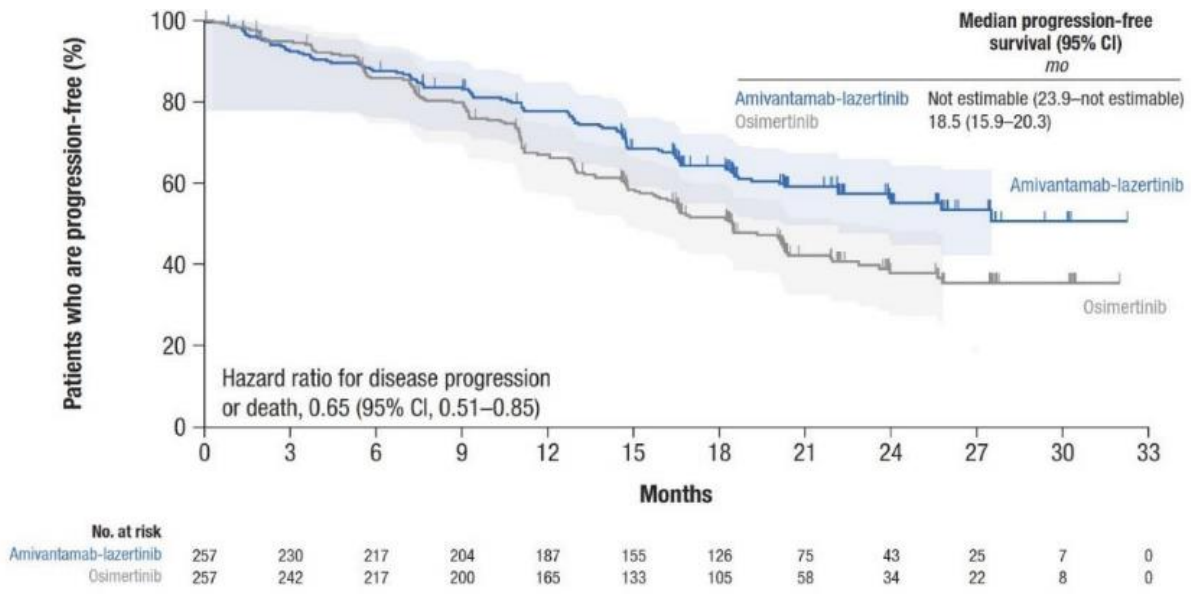
Subgroup	Amivantamab–Lazertinib	Osimertinib	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of events/total no. of patients		
All patients	192/429	252/429	0.70 (0.58–0.85)
Age			
<65 yr	94/235	153/237	0.50 (0.39–0.65)
≥65 yr	98/194	99/192	1.06 (0.80–1.41)
<75 yr	165/378	220/376	0.70 (0.57–0.85)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



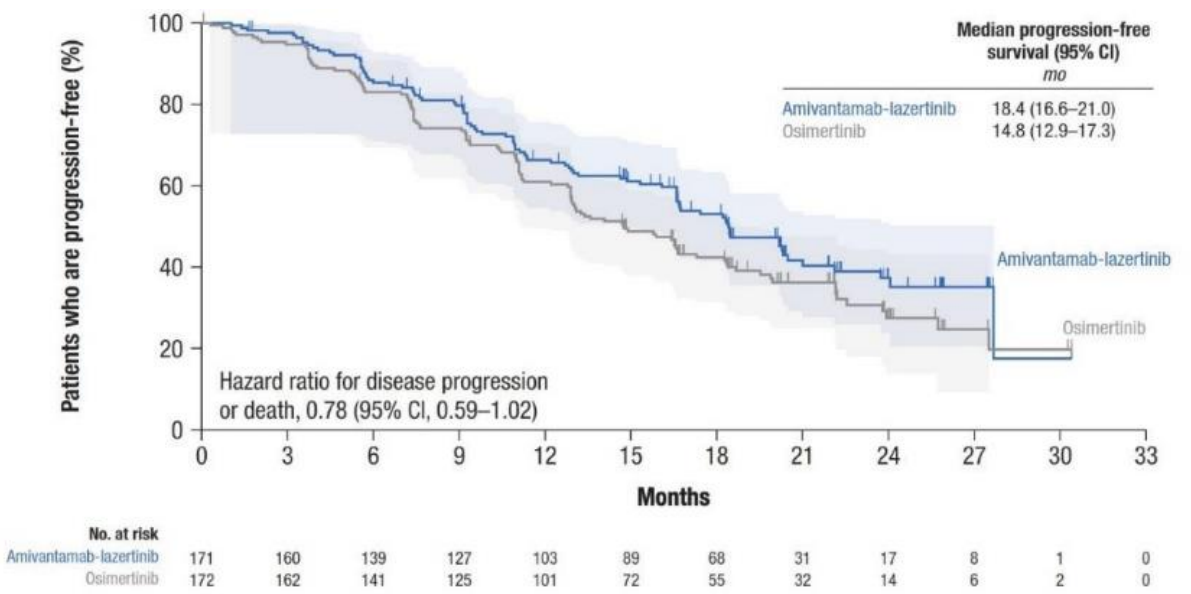
N Engl J Med. 2024;391(16):1486-1498.

MARIPIOSA: PFS (BICR) based on EGFR mutation type

Ex19del mutation



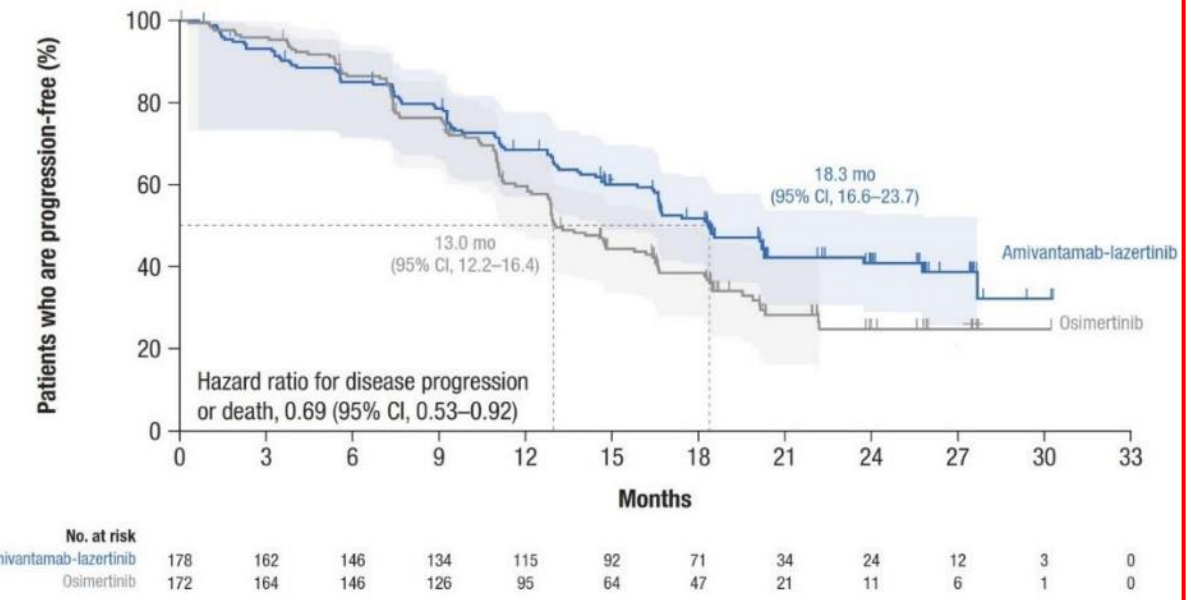
L858R mutation



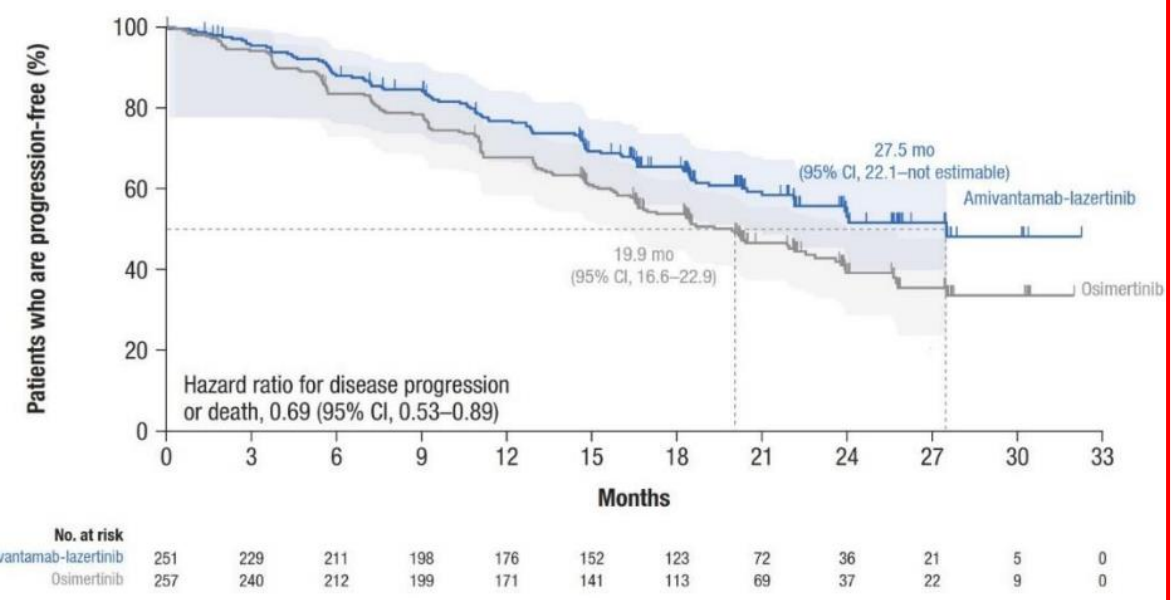
N Engl J Med. 2024;391(16):1486-1498.

MARIPIOSA: PFS (BICR) based on CNS metastasis

With CNS metastasis



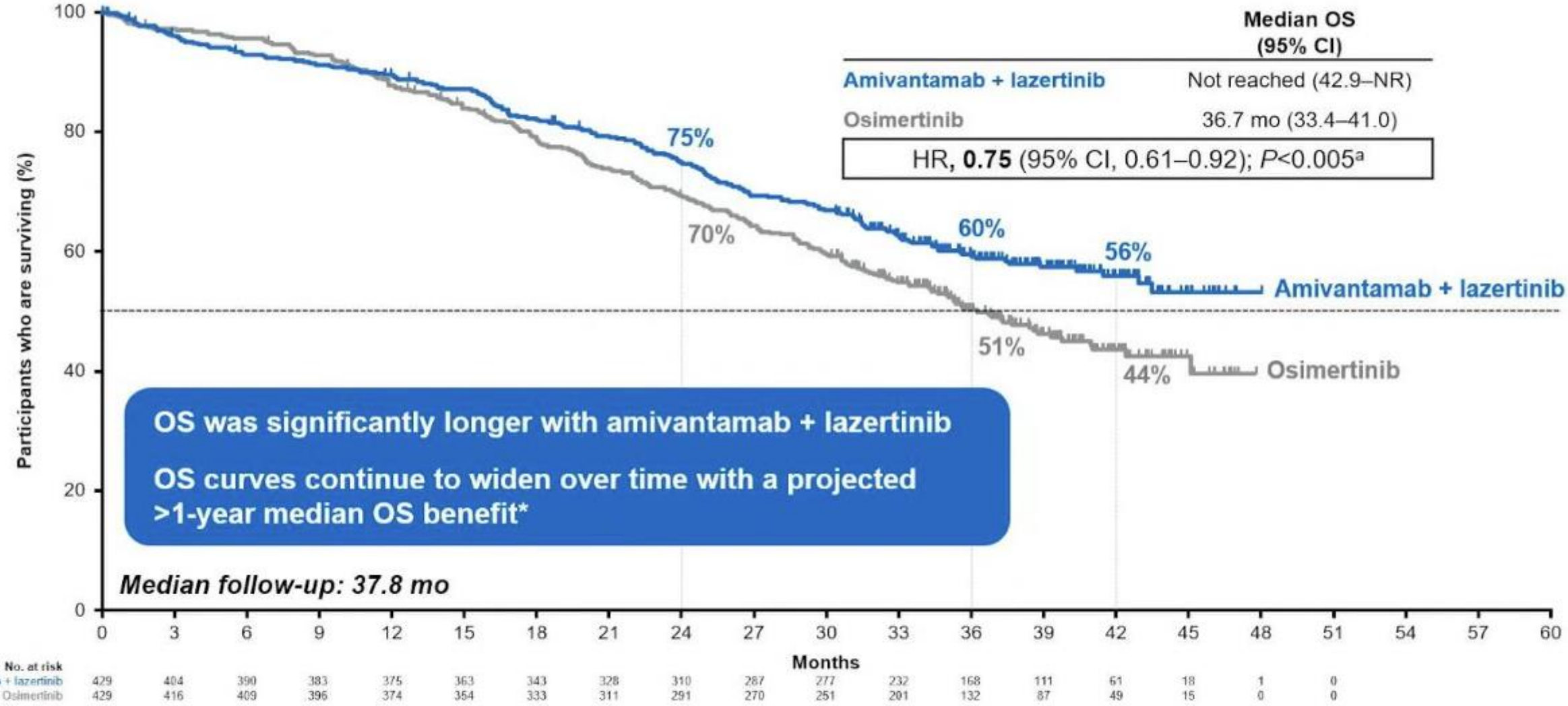
Without CNS metastasis



N Engl J Med. 2024;391(16):1486-1498.

MARIPOSA: Overall Survival

MARIPOSA
Ami + Laz in 1L
EGFR+ NSCLC



**Based on an exponential distribution assumption of OS in both arms, the improvement in median OS is projected to exceed 1 year.*

Note: Last participant was enrolled in May 2022. Clinical cutoff date was December 4, 2024. In total, 390 deaths had occurred in the amivantamab + lazertinib (173 deaths) and osimertinib (217 deaths) arms.

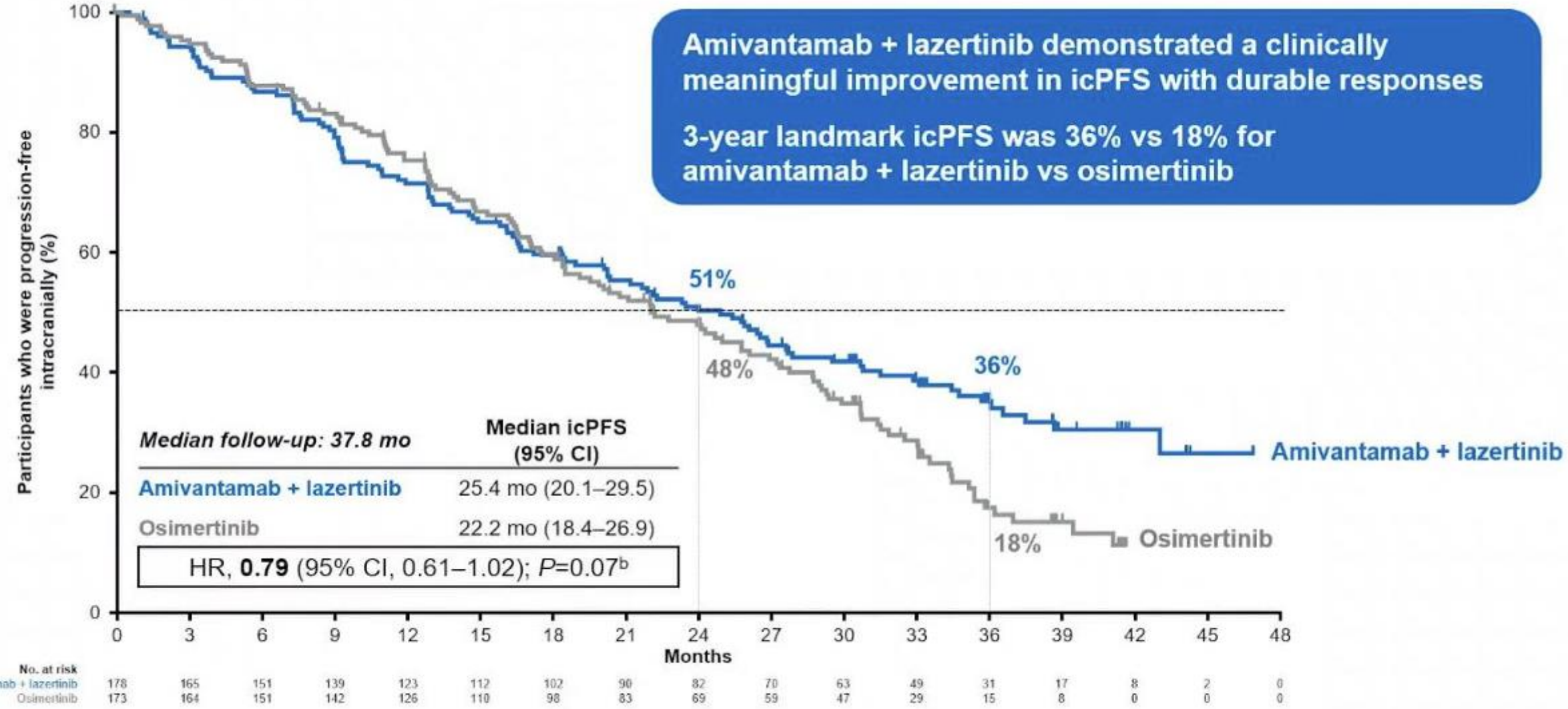
[a]*P*-value was calculated from a log-rank test stratified by mutation type (Ex19del or L858R), race (Asian or Non-Asian), and history of brain metastasis (present or absent). Hazard ratio was calculated from a stratified Cox regression model.

Intracranial PFS[a]

MARIPOSA
Ami + Laz in 1L
EGFR+ NSCLC

Amivantamab + lazertinib demonstrated a clinically meaningful improvement in icPFS with durable responses

3-year landmark icPFS was 36% vs 18% for amivantamab + lazertinib vs osimertinib



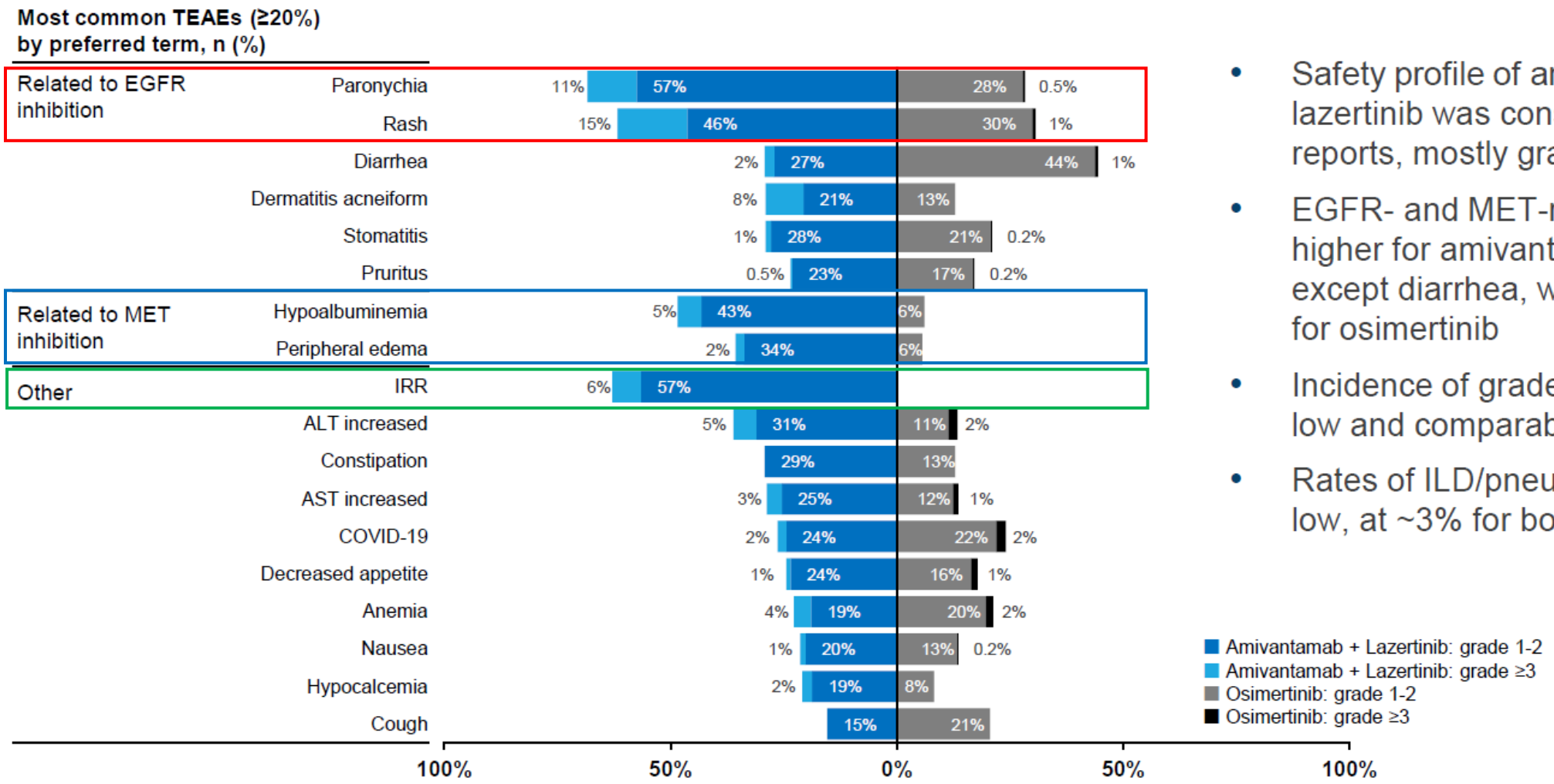
[a]Intracranial PFS was defined as time from randomization until the date of intracranial disease progression (progression of brain metastasis or occurrence of new brain lesions) or death, based on BICR using RECIST v1.1 among participants with a history of brain metastases. [b]*P*-value was calculated from a log-rank test stratified by mutation type (Ex19del or L858R) and race (Asian or Non-Asian). Hazard ratio was calculated from a stratified Cox regression model.

MARIPIOSA: Adverse event

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)	

N Engl J Med. 2024;391(16):1486-1498.

Safety Profile



- Safety profile of amivantamab + lazertinib was consistent with prior reports, mostly grades 1-2
- EGFR- and MET-related AEs were higher for amivantamab + lazertinib except diarrhea, which was higher for osimertinib
- Incidence of grade 4-5 AEs was low and comparable between arms
- Rates of ILD/pneumonitis remained low, at ~3% for both arms

MADRID 2023 ESMO congress

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EGFR, epidermal growth factor receptor; ILD, interstitial lung disease (includes pneumonitis); IRR, infusion-related reaction; TEAE, treatment-emergent AE.

Adverse Event of Special Interest: VTE[a]

	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)
Grade 3	43 (10)	12 (3)
Grade 4	2 (0.5)	1 (0.2)
Grade 5	2 (0.5)	2 (0.5)
Any VTE leading to death, n (%)	2 (0.5)	2 (0.5)
Any VTE leading to any discontinuation, n (%)	12 (3)	2 (0.5)
Anticoagulant use at time of first VTE, n (%)		
On anticoagulants	5 (1)	0
Not on anticoagulants	152 (36)	39 (9)
Median onset to first VTE	84 days	194 days
Within first 4 months, n (%)	97 of 157 (62)	13 of 39 (33)

- 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

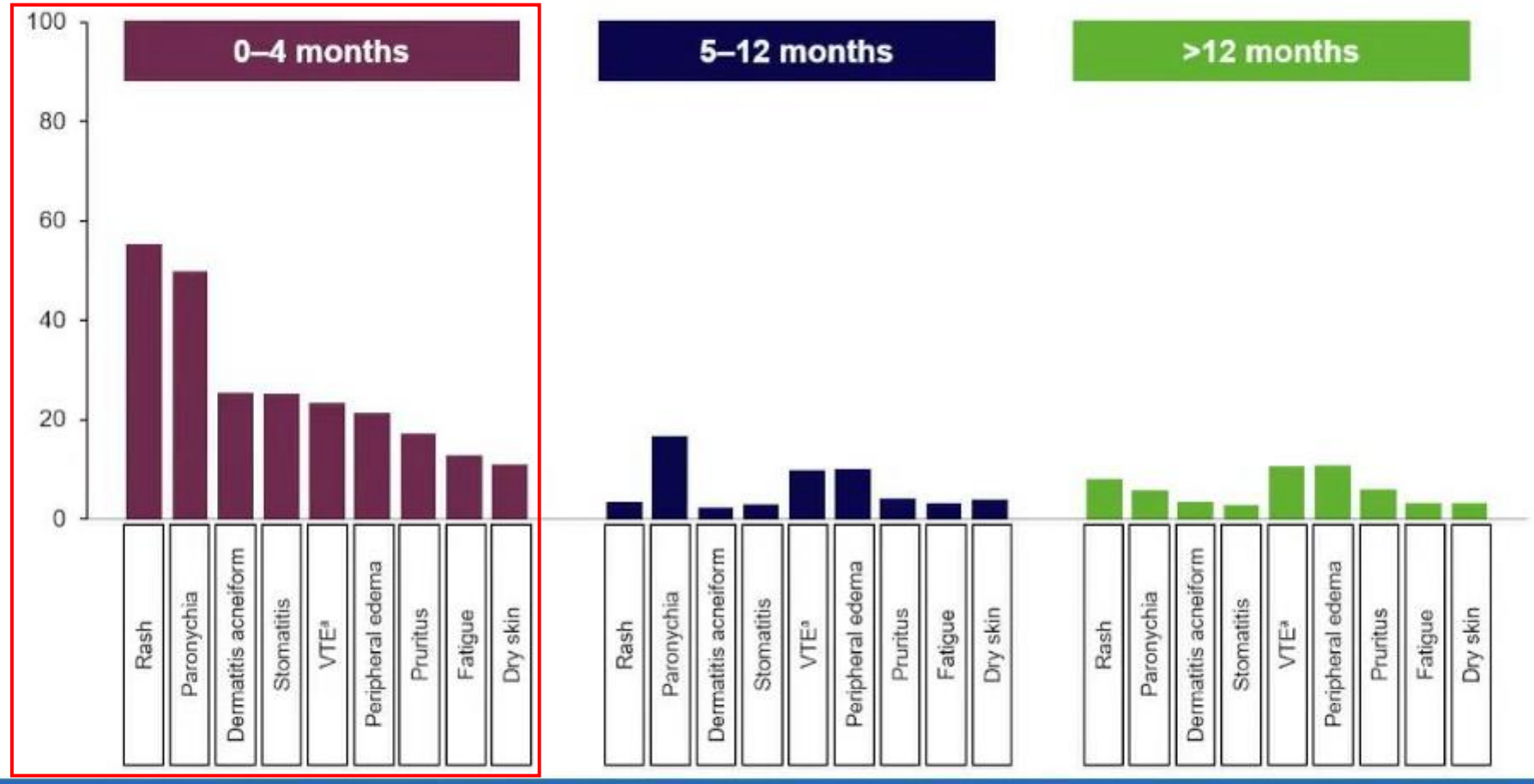
[a]Grouping includes the following preferred terms: pulmonary embolism, deep vein thrombosis, venous thrombosis limb, thrombosis, venous thrombosis, superficial vein thrombosis, thrombophlebitis, embolism, embolism venous, jugular vein thrombosis, pulmonary infarction, axillary vein thrombosis, portal vein thrombosis, post thrombotic syndrome, sigmoid sinus thrombosis, superior sagittal sinus thrombosis, vena cava thrombosis, pelvic venous thrombosis, pulmonary thrombosis, superior vena cava syndrome.

VTE, venous thromboembolism.

First Onset of Key AEs for 1L Amivantamab + Lazertinib

MARIPOSA
Ami + Laz in 1L
EGFR+ NSCLC

Median follow-up of 37.8 months

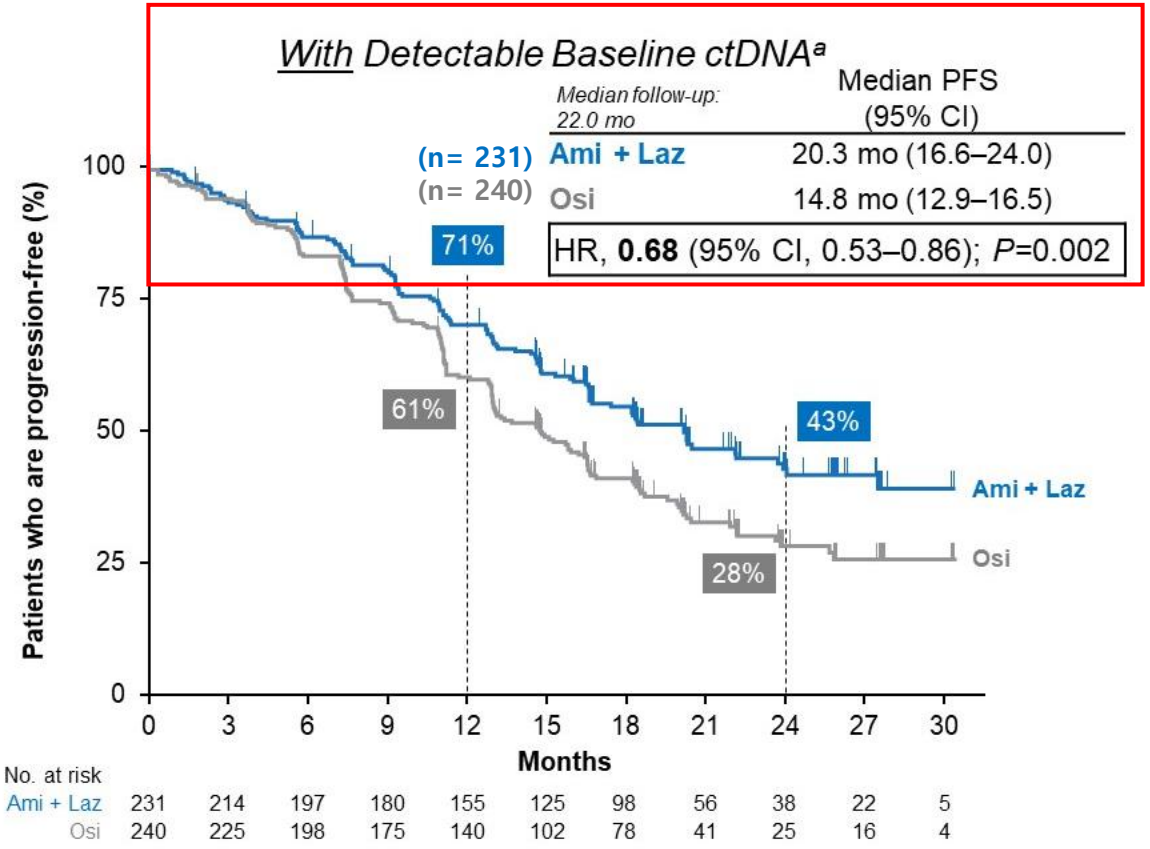


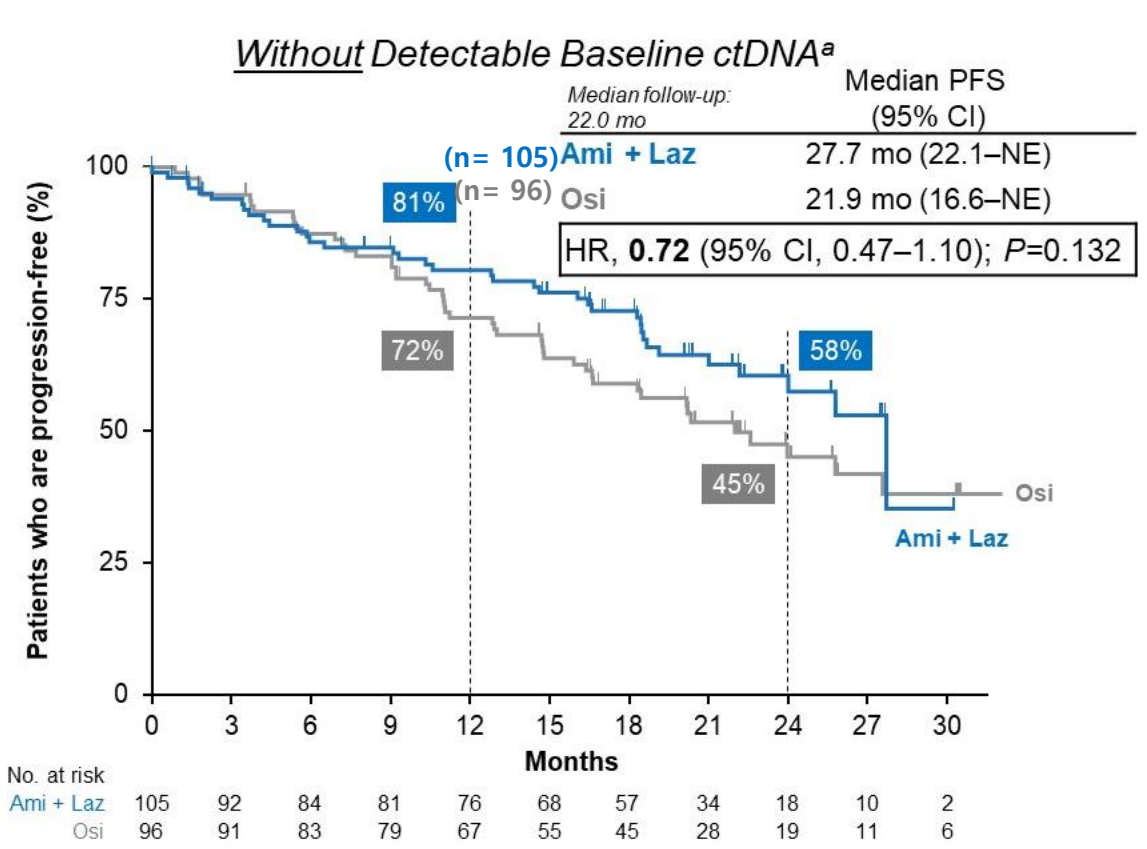
Most first onset AEs occur early (0–4 months), with longer-term follow-up showing no new safety signals and indicating that long-term treatment is feasible

[a]VTE is a grouped term, which included pulmonary embolism, deep vein thrombosis, limb venous thrombosis, venous thrombosis, thrombosis, superficial vein thrombosis, thrombophlebitis, embolism, venous embolism, jugular vein thrombosis, sigmoid sinus thrombosis, axillary vein thrombosis, pulmonary infarction, vena cava thrombosis, central venous catheterization, portal vein thrombosis, post thrombotic syndrome, pulmonary thrombosis, superior sagittal sinus thrombosis, transverse sinus thrombosis, pelvic venous thrombosis, and superior vena cava syndrome.

MARIPOSA: PFS Detectable Baseline ctDNA by ddPCR

- Osimertinib showed a median PFS of 14.8 mo in patients with detectable ctDNA[a] at baseline
- Amivantamab + lazertinib reduced the risk of progression or death by 32% in this subgroup
- Consistent results were seen in patients with detectable ctDNA using the NGS assay[b] (HR, 0.71 [95% CI, 0.57–0.89]; *P*=0.003)



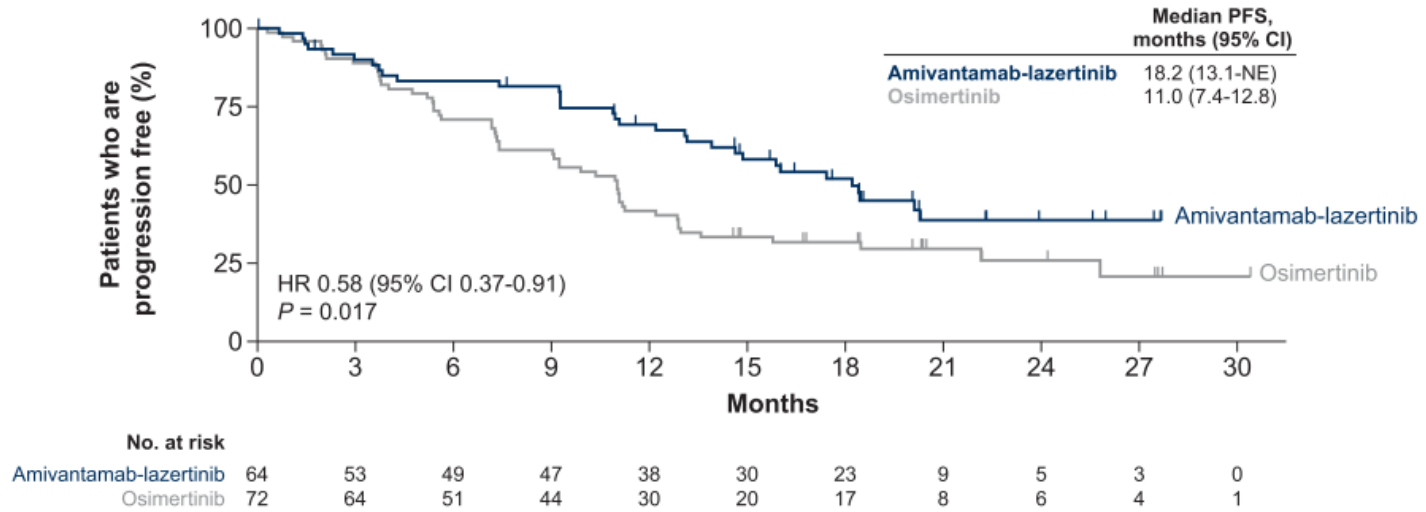


[a]Detection of Ex19del and L858R by Biodesix ddPCR. [b]Pathogenic mutations were detected with the Guardant Health G360® panel.

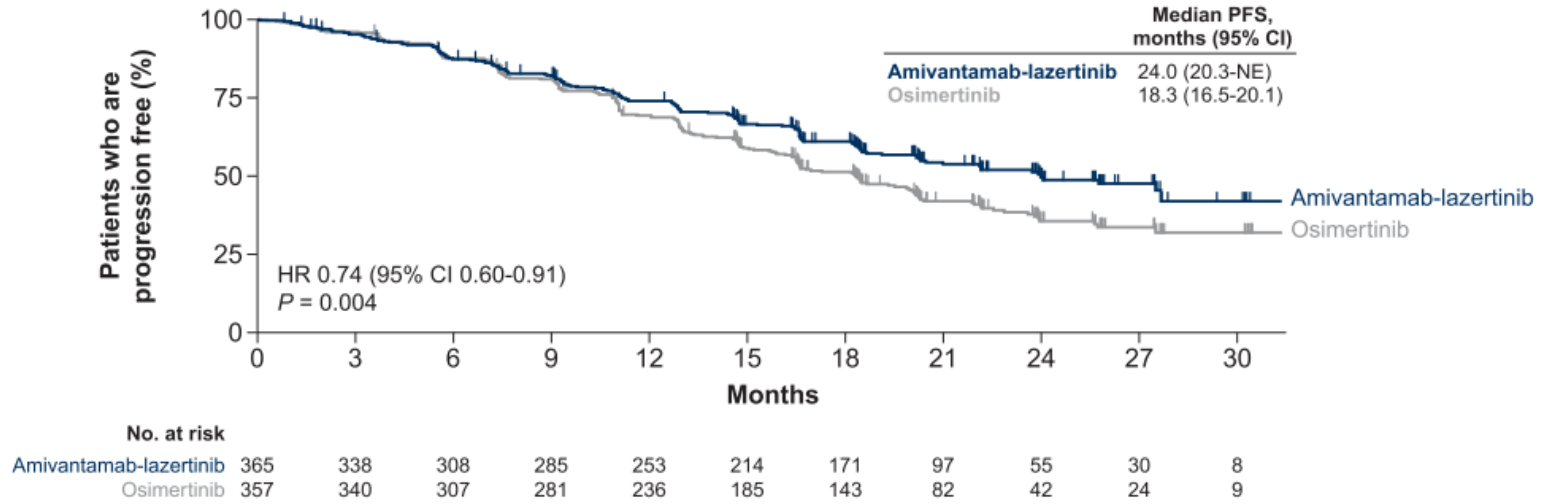
Ami, amivantamab; ctDNA, circulating tumor DNA; ddPCR, droplet digital polymerase chain reaction; Ex19del, Exon 19 deletion; Laz, lazertinib; NGS, next-generation sequencing; Osi, osimertinib.

MARIPIOSA: PFS (BICR) based on liver metastasis

With liver metastasis



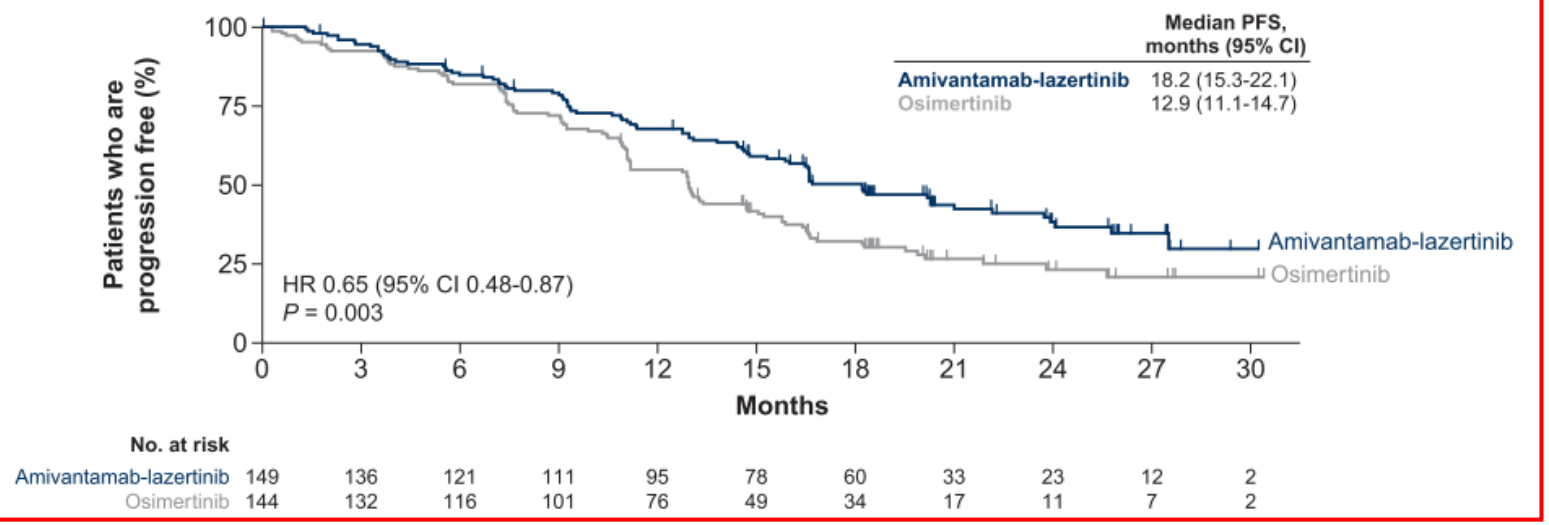
Without liver metastasis



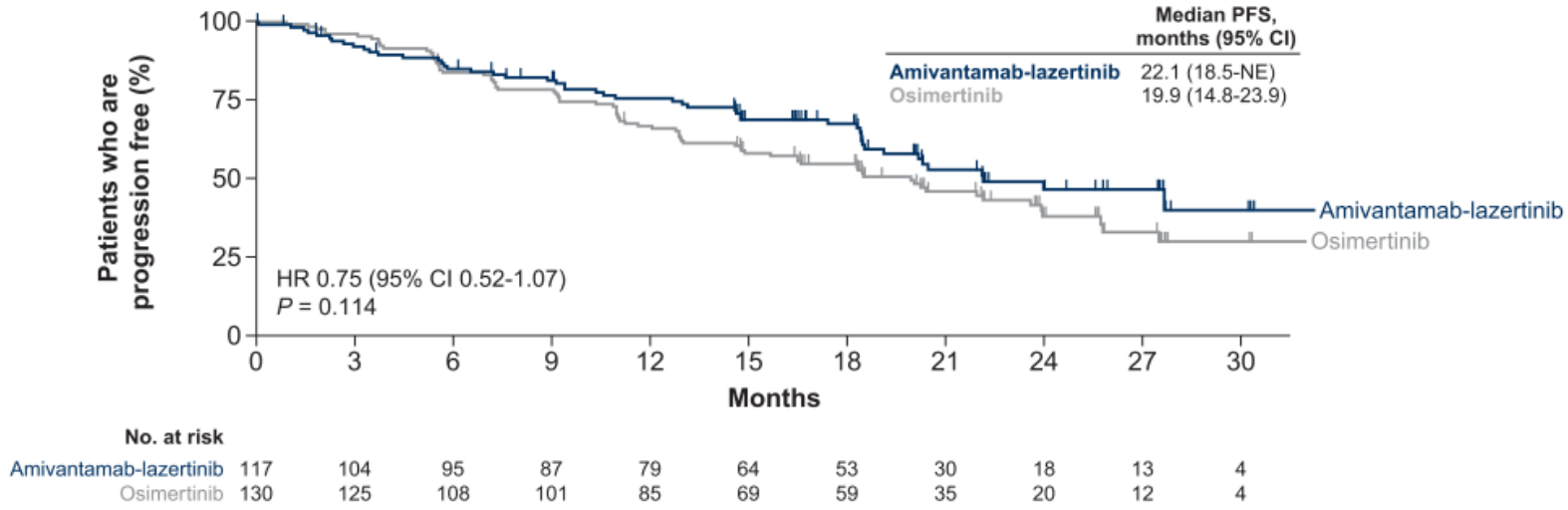
Ann Oncol. 2024;35(9):805-816.

MARIPIOSA: PFS (BICR) based on TP53 status

TP53-comutation



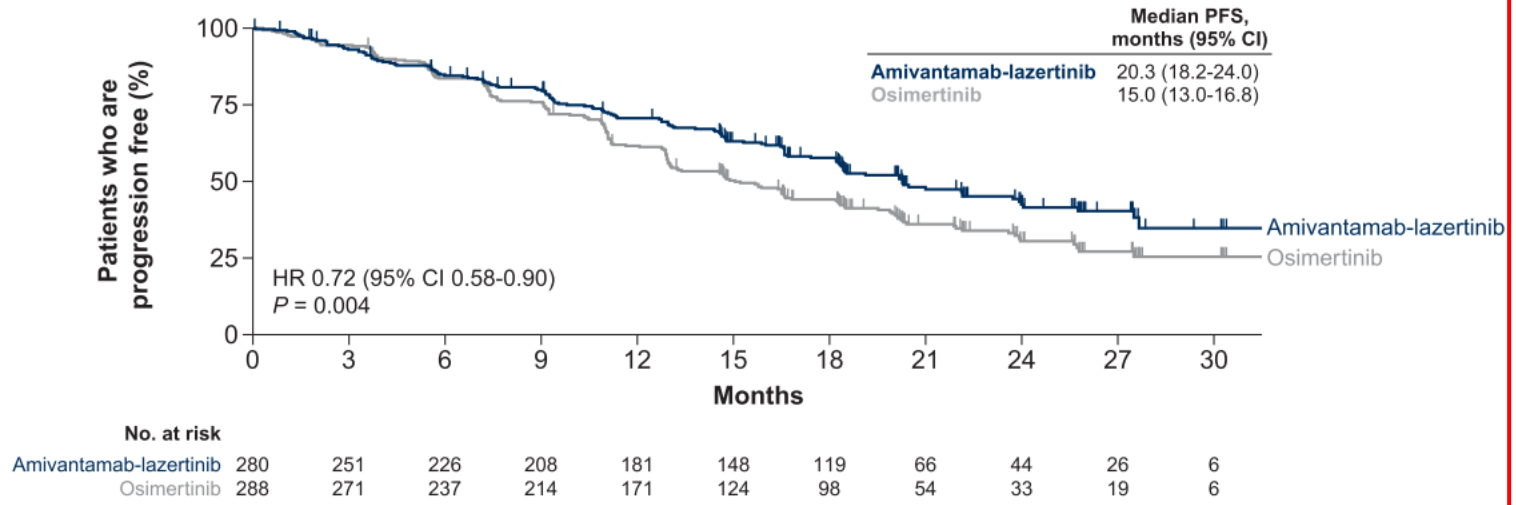
Wild type TP53



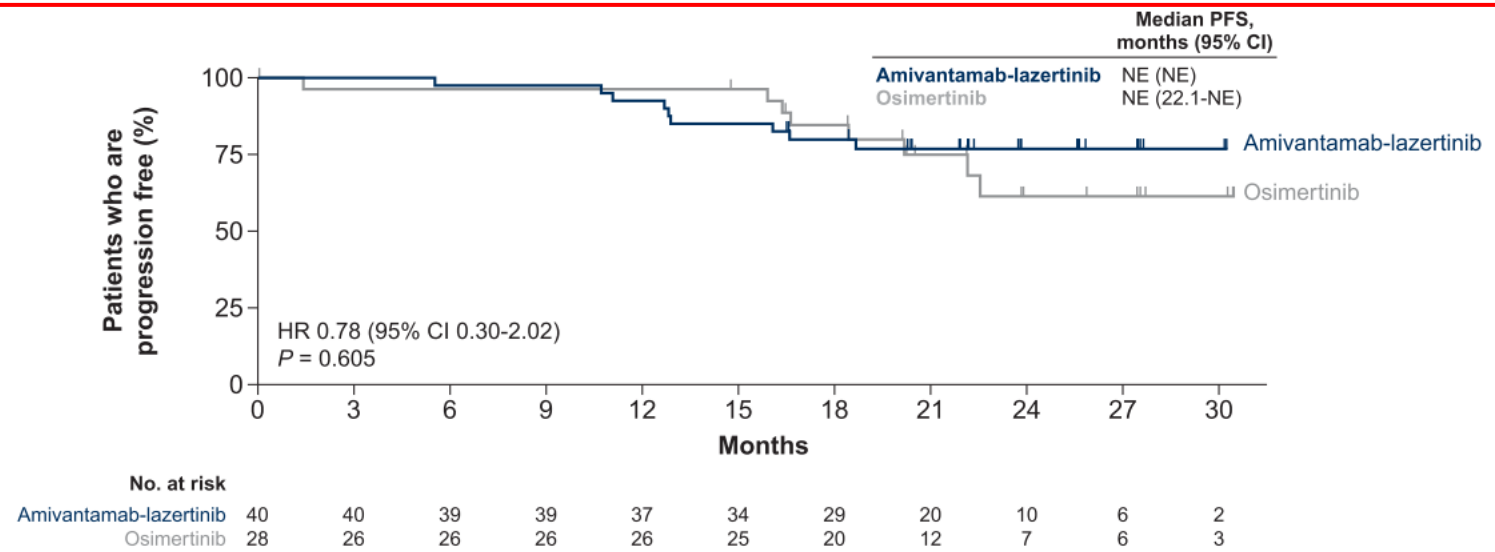
Ann Oncol. 2024;35(9):805-816.

MARIPIOSA: PFS (BICR) based on risk (brain, ctDNA, liver)

With high risk



Without high risk



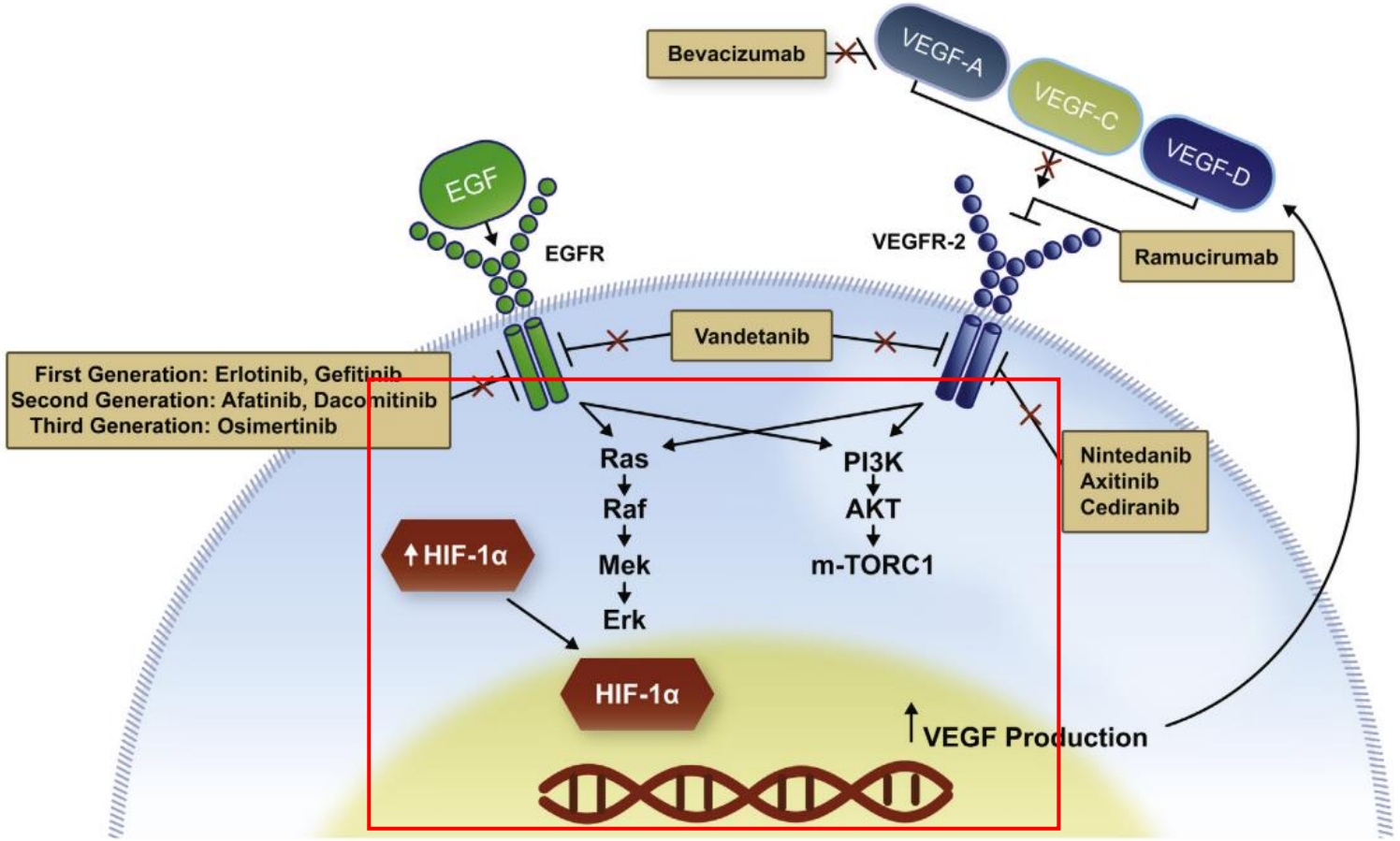
Ann Oncol. 2024;35(9):805-816.

Summary (2)

- Amivantamab + lazertinib significantly improved PFS and OS over osimertinib in first-line therapy with EGFR-mutant advanced NSCLC.
- Amivantamab + lazertinib showed significant PFS benefit over osimertinib in patients in exon 19 deletion, and consistent irrespective of CNS involvement.
- Amivantamab + lazertinib had higher rates of EGFR- and MET-related AEs and VTEs, majority grade 1-2.
- Amivantamab + lazertinib also showed significant PFS benefit over osimertinib in patients with ctDNA+, TP53-comutation, liver metastasis, and with high risk factors.

RELAY
RAMOSE

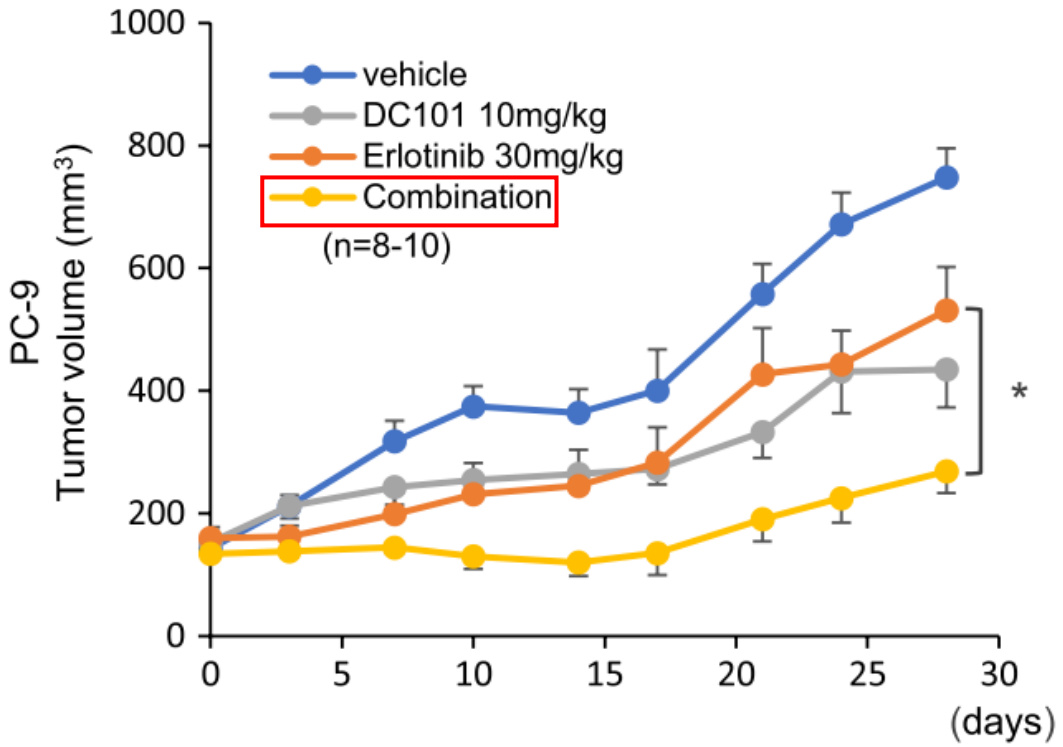
Cross-talk between EGFR AND VEGF

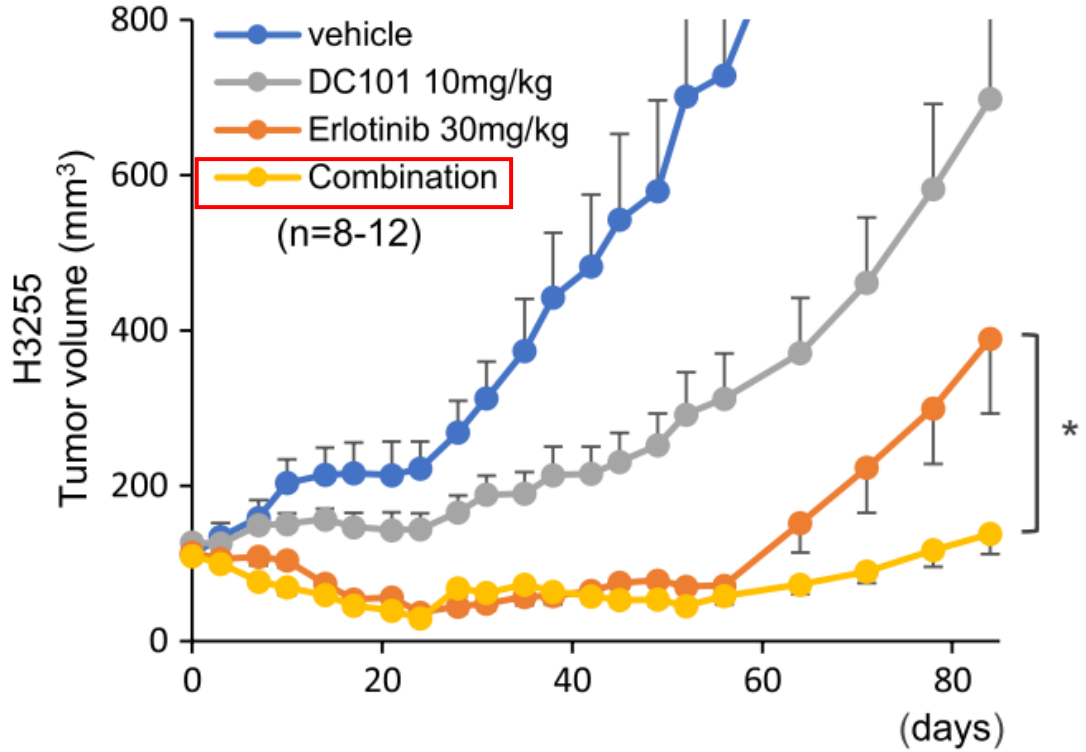


- VEGF (involved in angiogenesis) and EGF share common down-stream signaling pathways, and may function exclusively of one another during oncogenesis and resistance.

J Thorac Oncol. 2021;16(2):205-215.

Preclinical models of RELAY

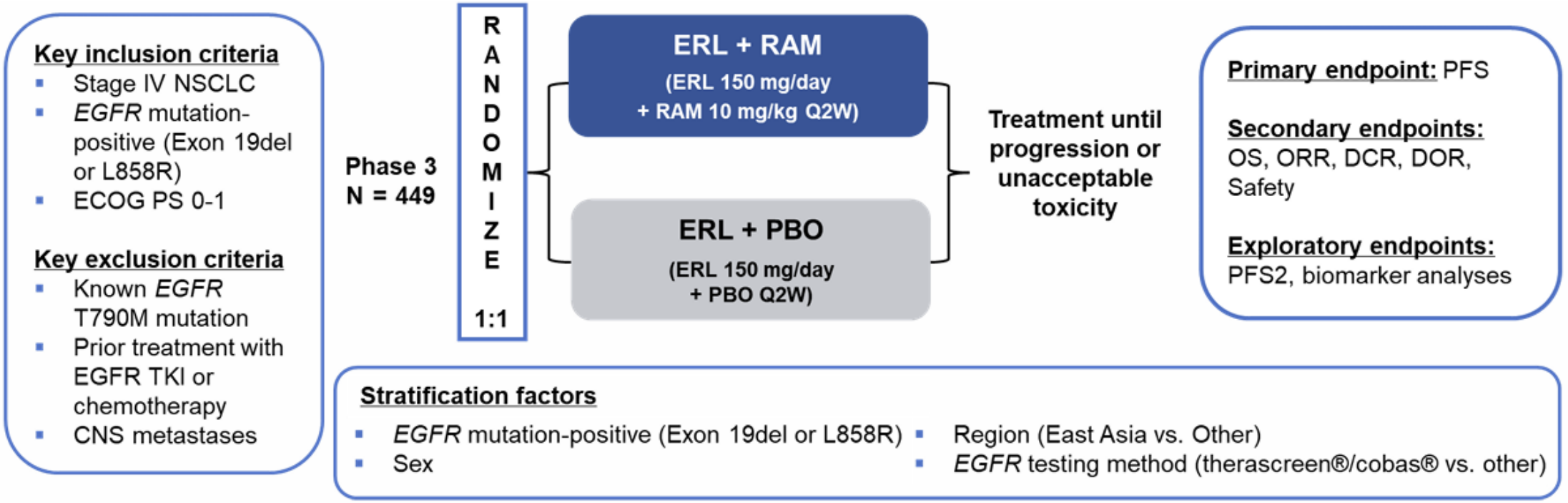




* DC101: anti-mouse VEGFR2 antibody

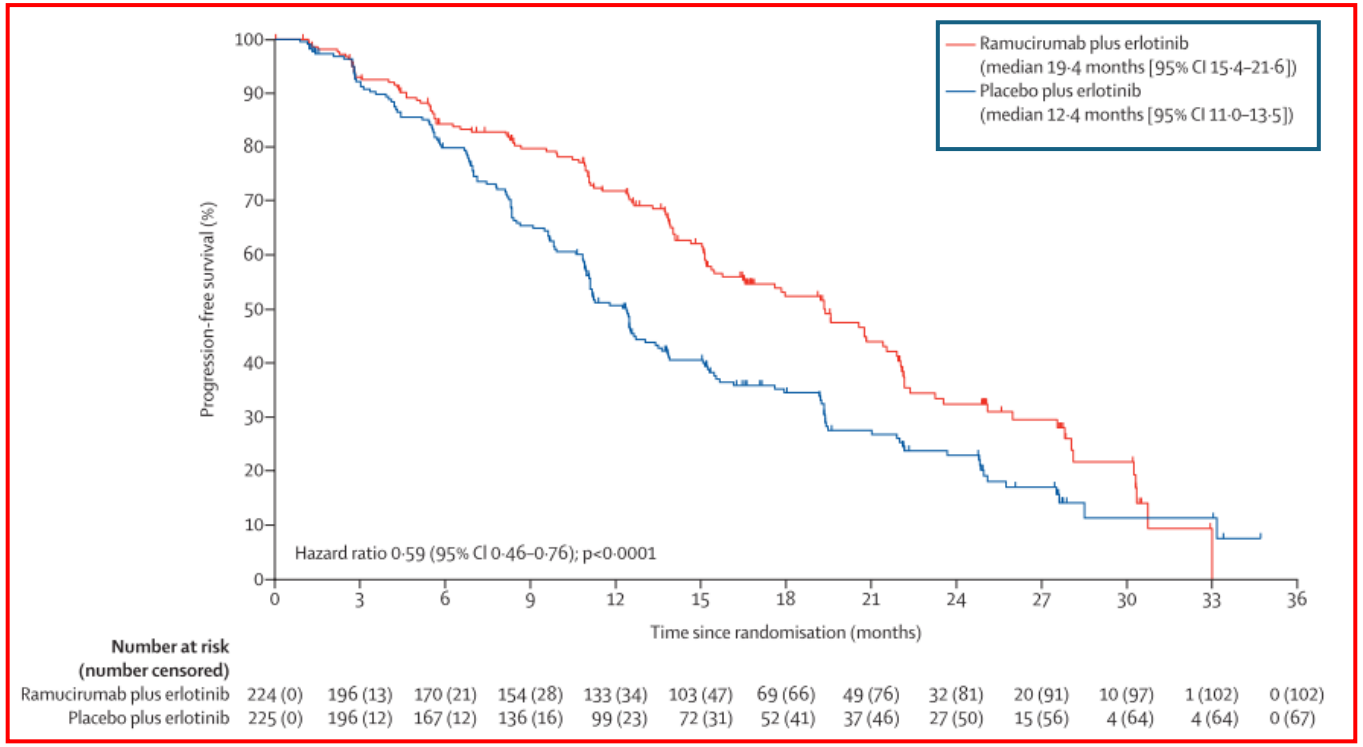
Cancer Sci. 2021;112(5):1853-1864.

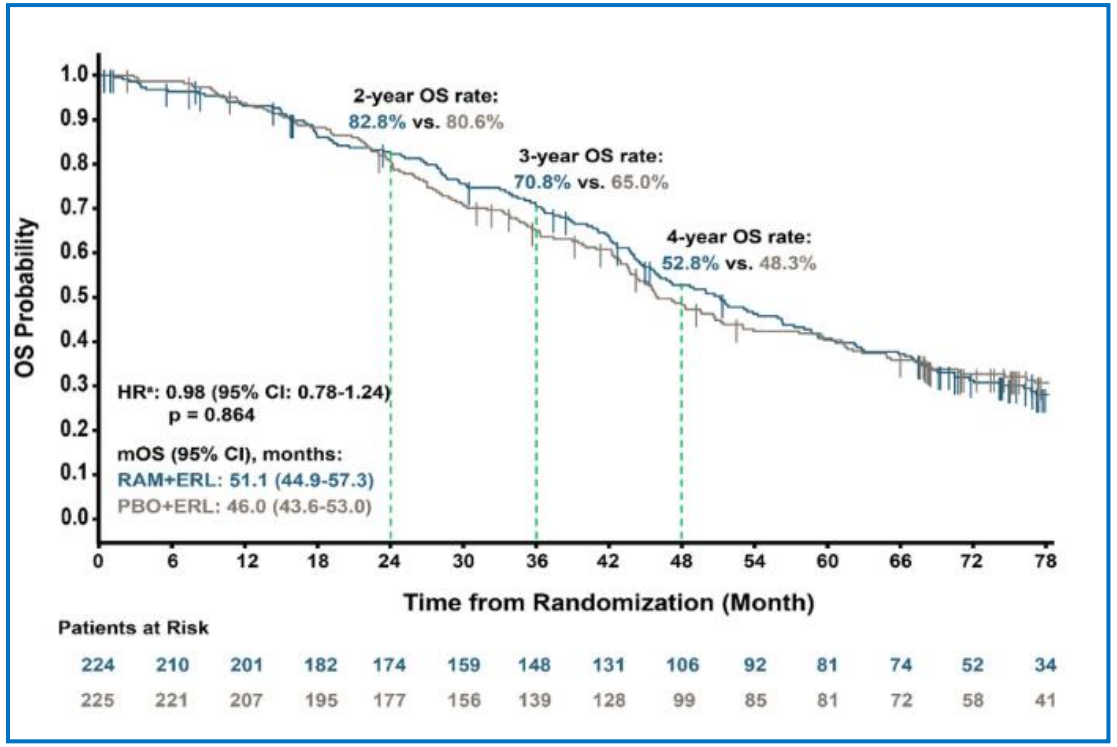
RELAY (phase III, RCT): design



Lancet Oncol. 2019;20(12):1655-1669.

RELAY: PFS, OS (IA)

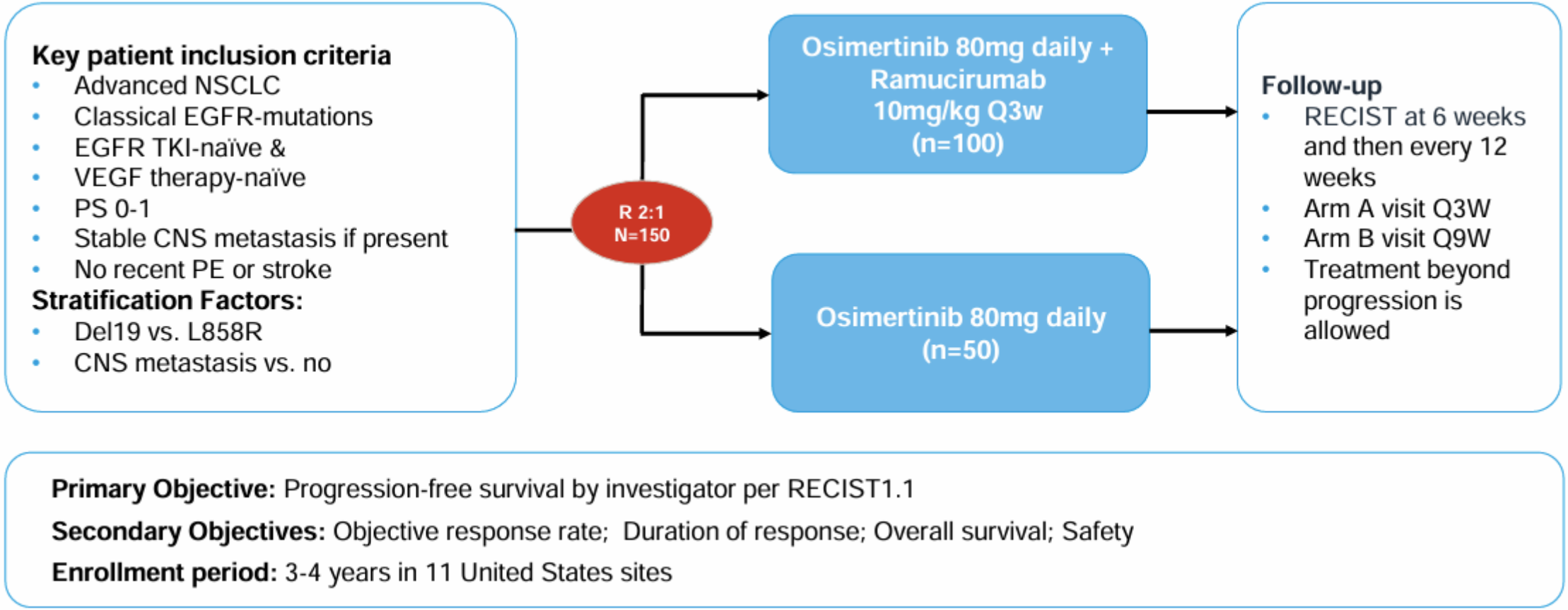




- Erlotinib + ramucirumab significantly improved PFS compared to erlotinib alone, but failed to significantly improve OS.

Lancet Oncol. 2019;20(12):1655-1669.
J Thorac Oncol. 2024;S1556-0864(24)02495-X.

RAMOSE (phase II, RCT): design



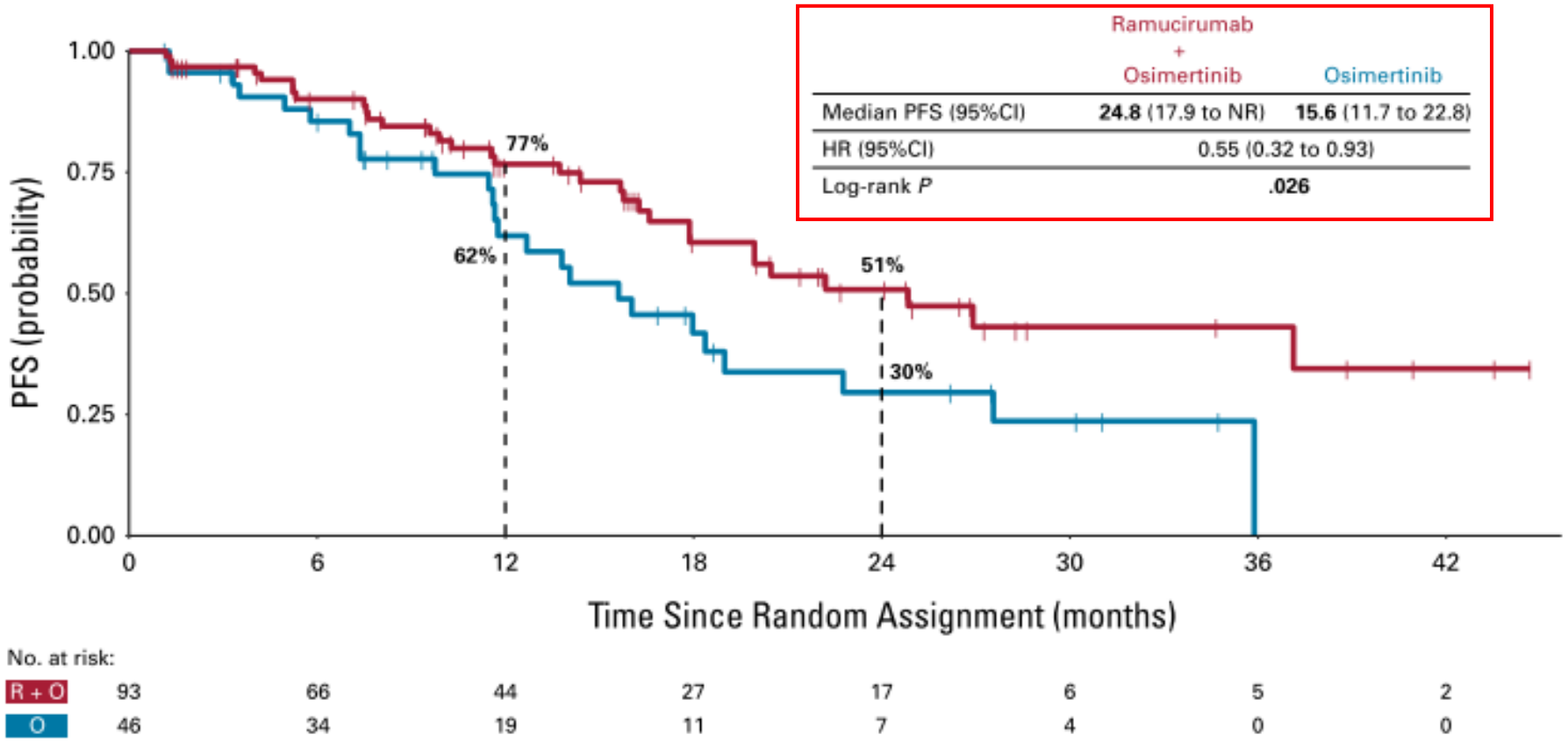
Primary Objective: Progression-free survival by investigator per RECIST1.1

Secondary Objectives: Objective response rate; Duration of response; Overall survival; Safety

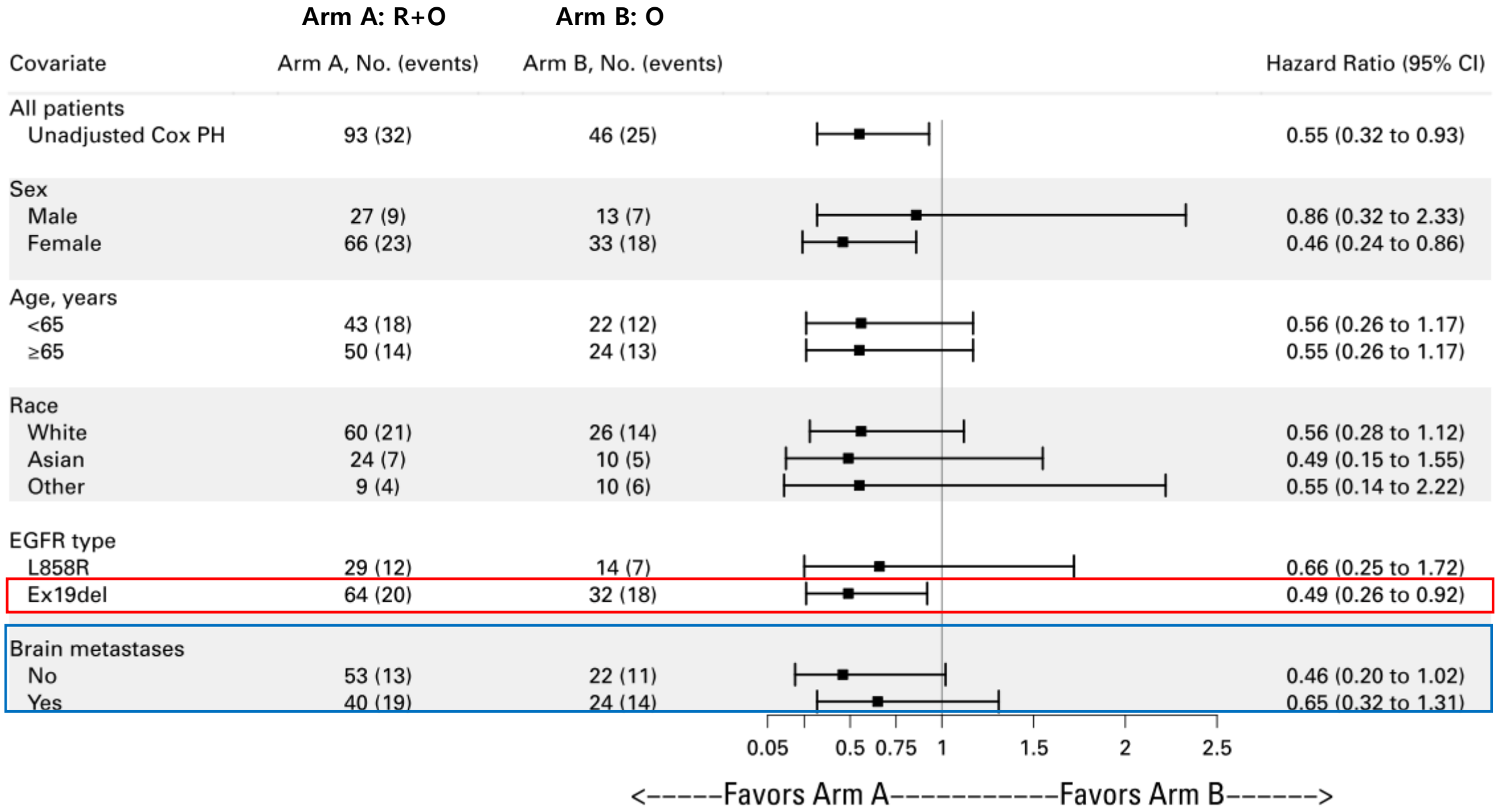
Enrollment period: 3-4 years in 11 United States sites

J Clin Oncol. 2025;43(4):403-411.

RAMOSE: PFS (IA)

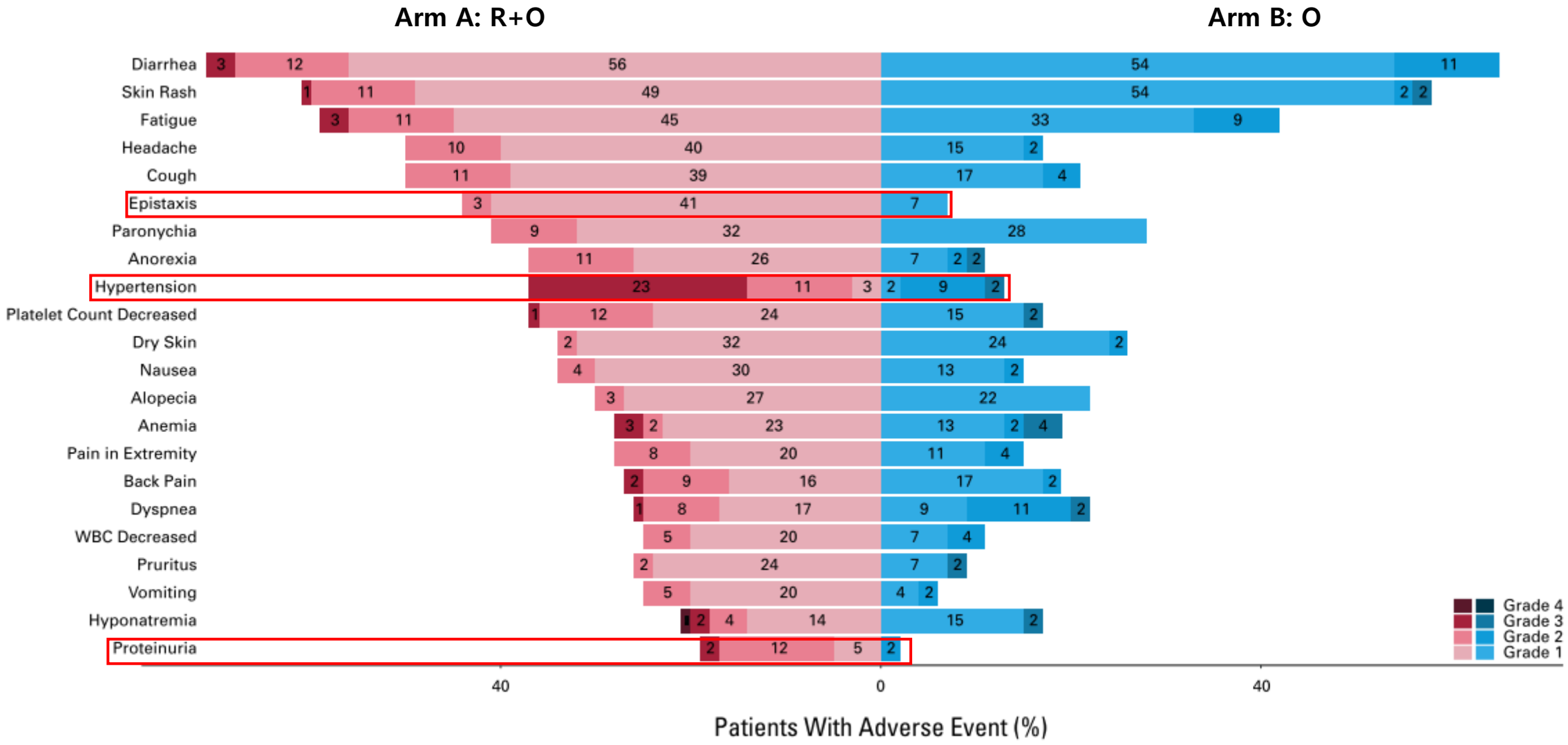


J Clin Oncol. 2025;43(4):403-411.



J Clin Oncol. 2025;43(4):403-411.

RAMOSE: Adverse event



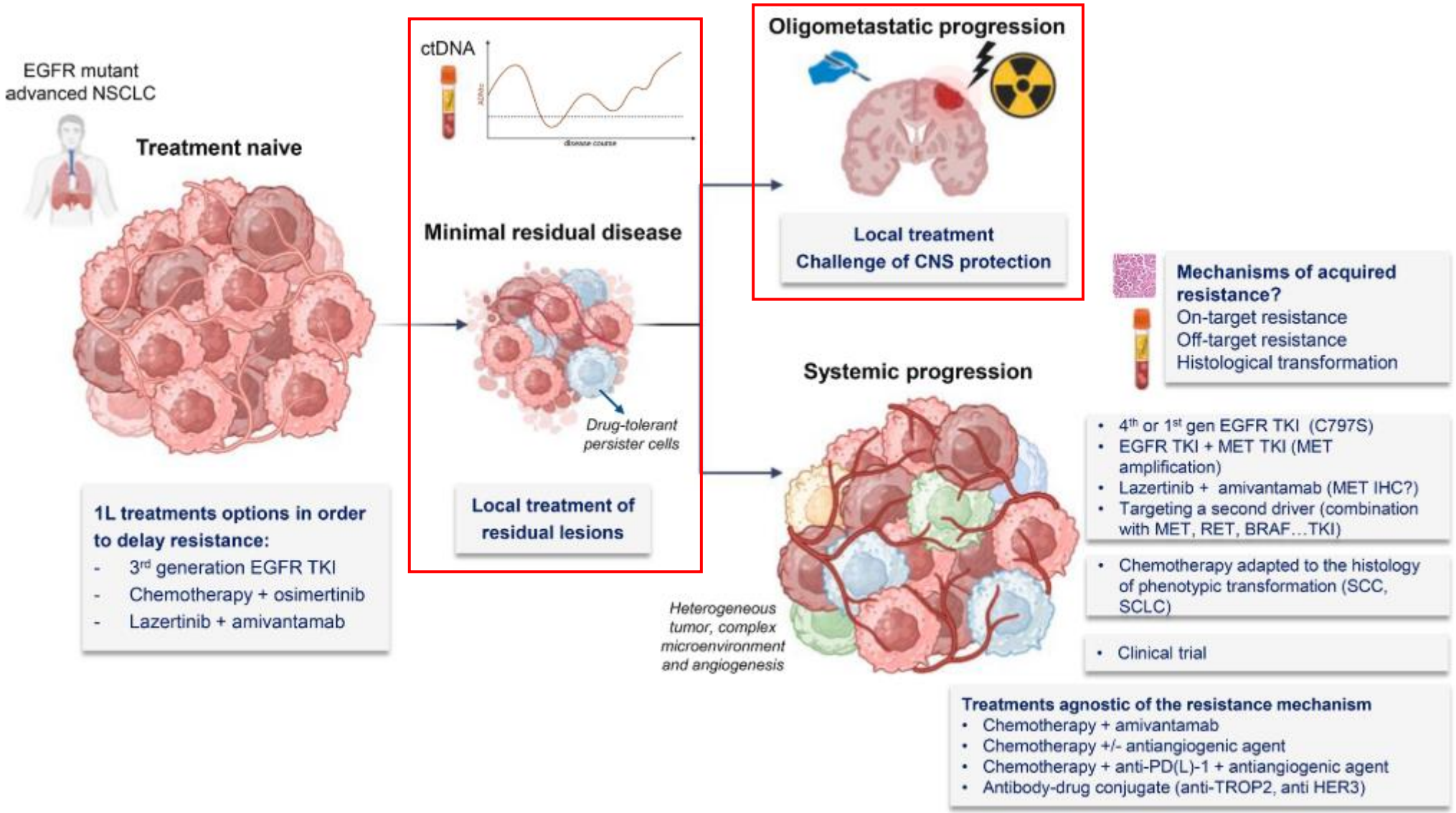
J Clin Oncol. 2025;43(4):403-411.

Summary (3)

- Ramucirumab + erlotinib significantly improved PFS over erlotinib in first-line therapy with EGFR-mutant advanced NSCLC, but not OS.
- Ramucirumab + osimertinib significantly improved PFS over osimertinib in first-line therapy with EGFR-mutant advanced NSCLC.
- Ramucirumab + osimertinib showed significant PFS benefit over osimertinib in patients with exon 19 deletion, independent of CNS metastasis status.
- Ramucirumab + osimertinib had higher rates of anti-VEGF related AEs, including hemorrhage, hypertension, and proteinuria.

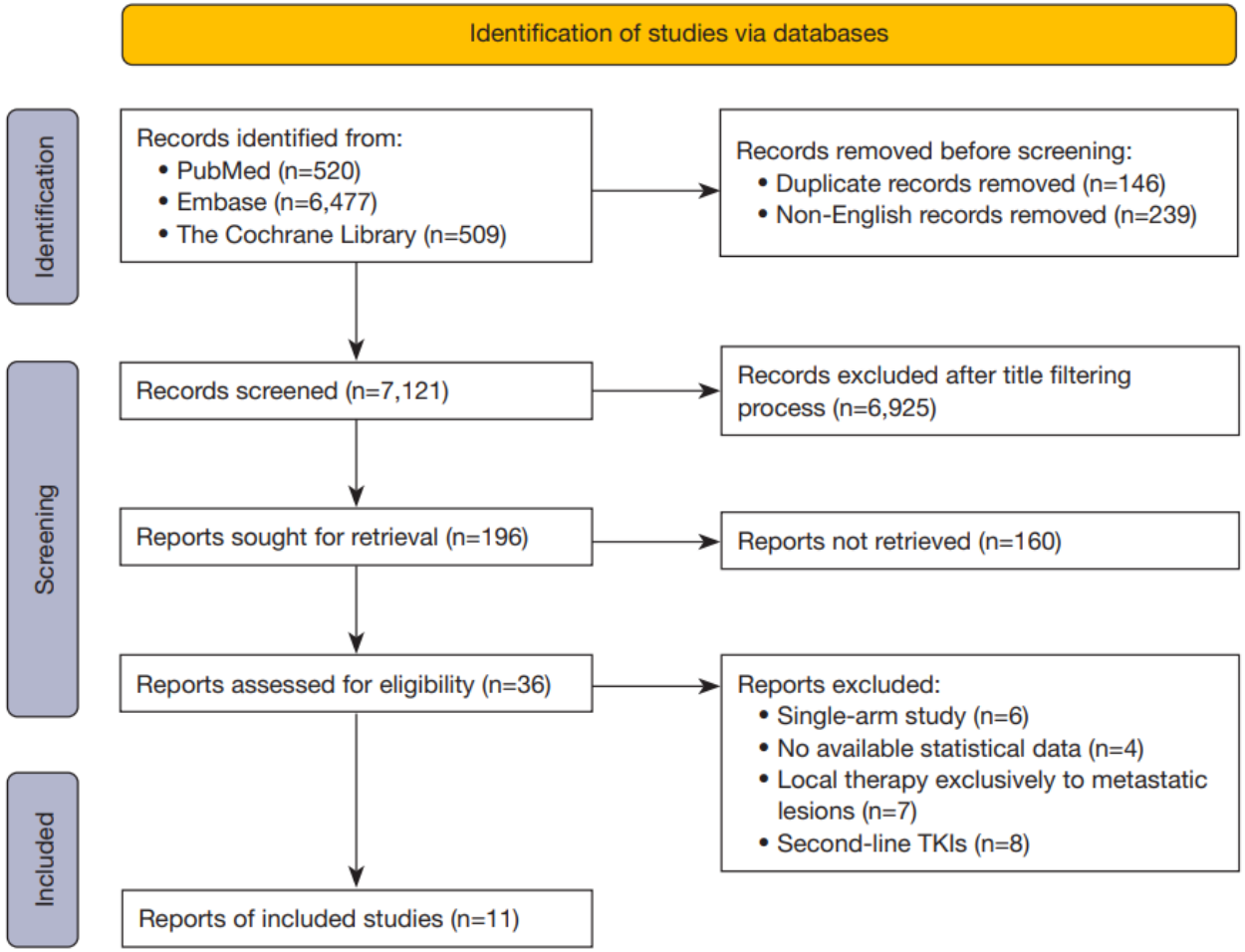
	FLAURA	FLAURA2	MARIPOSA	RAMOSE
Regimen	Osi	Osi + CTx	Ami + Laz	Osi + Ram
PFS (months, HR)	**18.9 mo.**	**25.5** vs 16.7mo. 0.62 (0.49-0.79)	**23.7** vs 16.6 mo. 0.70 (0.58-0.85)	**24.8** vs 15.6 mo. 0.55 (0.32-0.93)
OS (months, HR)	**38.6 mo.**	NR vs 36.7 mo. 0.75 (0.57-0.97)	NE vs 36.7 mo. 0.75 (0.61-0.92)	NR
Subgroup (PFS)				
Ex19 del		**0.60 (0.44-0.83)**	**0.65 (0.51-0.85)**	**0.49 (0.26-0.92)**
L858R		0.63 (0.44-0.90)	0.78 (0.59-1.02)	0.66 (0.25-1.72)
CNS met+		**0.47 (0.33-0.60)**	**0.69 (0.53-0.92)**	0.65 (0.32-1.31)
ctDNA+		0.60 (0.45-0.80)	0.68 (0.53-0.86)	
TP53+		0.57 (0.29-1.12)	0.65 (0.48-0.87)	
Liver met+		0.66 (0.41-1.07)	0.58 (0.37-0.91)	
≥ 3 meta sites		0.57 (0.43-0.77)		
Bone met+		0.56 (0.40-0.77)		
Adverse event		CTx related (ex: cytopenia)	EGFR, MET, IRR, VTE	VEGF related

Other ways to overcome resistance



Lung Cancer. 2024;194:107895.

Additional local therapy in EGFR+ advanced NSCLC

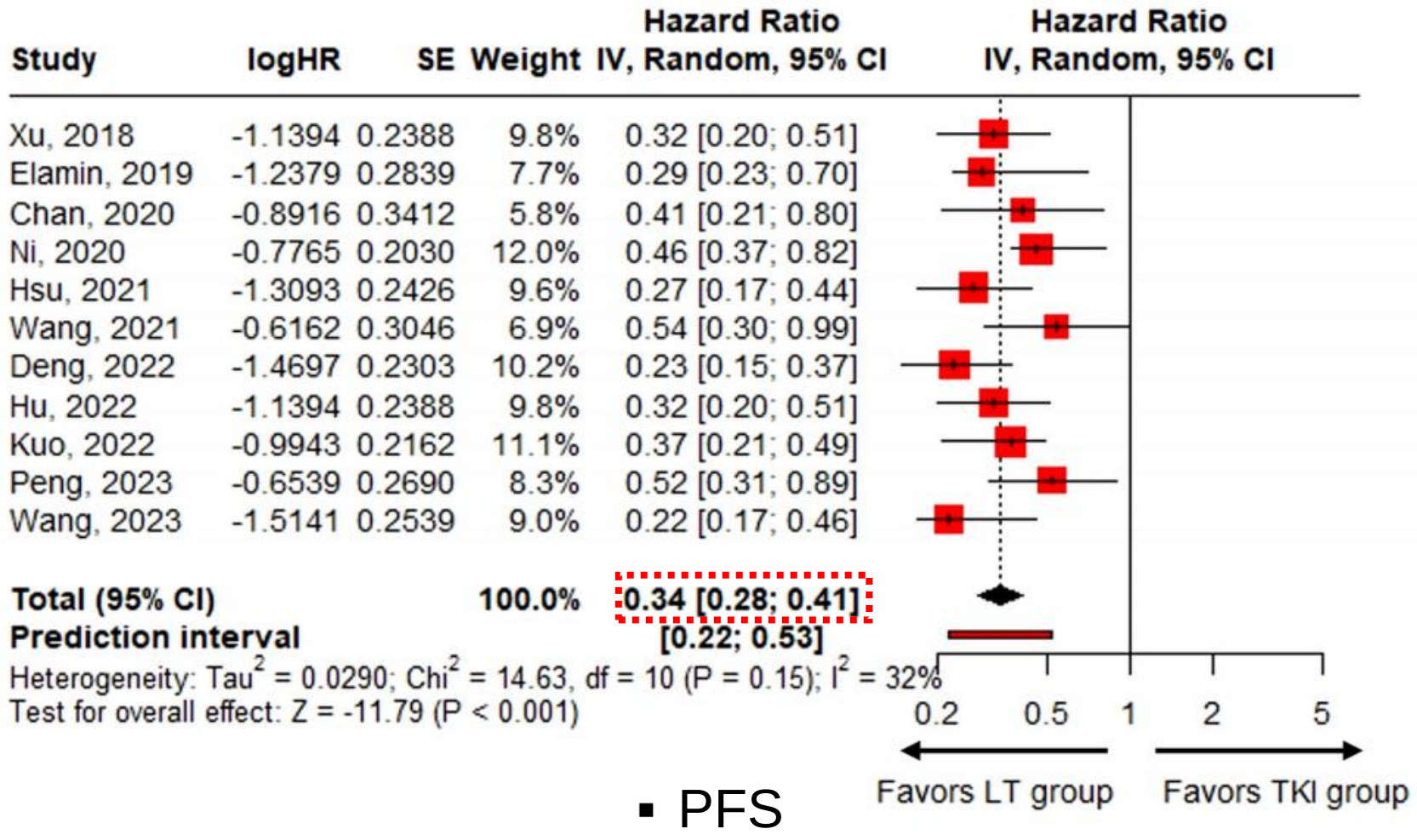


EGFR-TKI + Local therapy before PD *VS.* **EGFR-TKI alone**

- Local therapy
  - Radiotherapy or
  - Surgery or
  - Bronchoscopic ablation

Transl Lung Cancer Res. 2024;13(3):491-502

Additional local therapy in EGFR+ advanced NSCLC



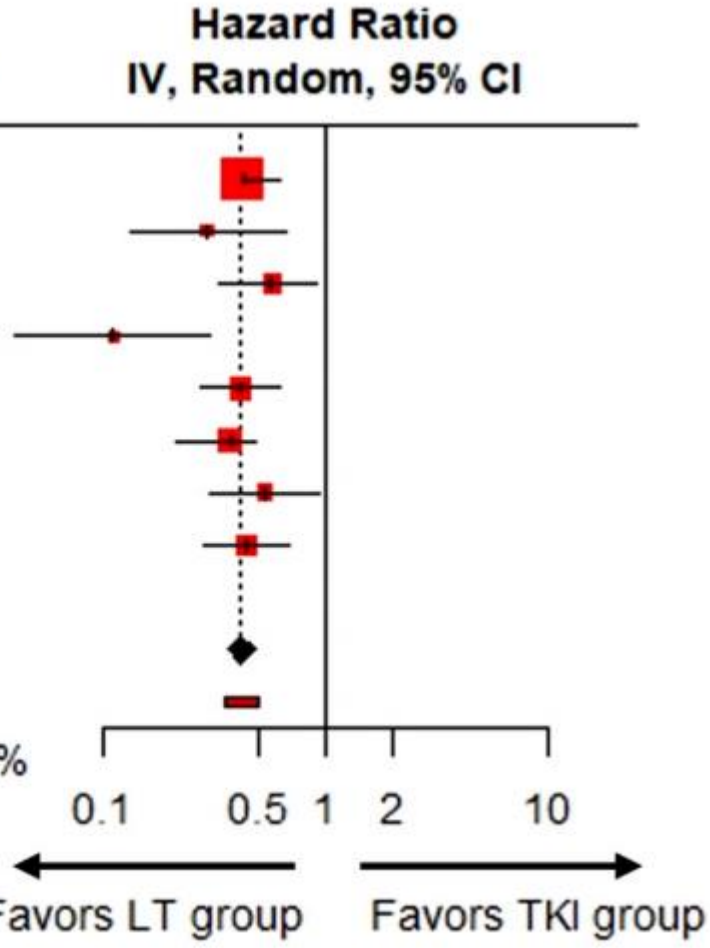
- PFS

Transl Lung Cancer Res. 2024;13(3):491-502

Additional local therapy in EGFR+ advanced NSCLC

Study	logHR	SE	Weight	Hazard Ratio IV, Random, 95% CI
Xu, 2018	-0.8675	0.0994	50.7%	0.42 [0.42; 0.62]
Elamin, 2019	-1.2379	0.4145	2.9%	0.29 [0.13; 0.66]
Ni, 2020	-0.5621	0.2588	7.5%	0.57 [0.33; 0.91]
Hsu, 2021	-2.2073	0.5140	1.9%	0.11 [0.04; 0.30]
Hu, 2022	-0.8916	0.2162	10.7%	0.41 [0.27; 0.63]
Kuo, 2022	-0.9943	0.2162	10.7%	0.37 [0.21; 0.49]
Peng, 2023	-0.6349	0.2941	5.8%	0.53 [0.30; 0.95]
Wang, 2023	-0.8210	0.2264	9.8%	0.44 [0.28; 0.68]
Total (95% CI)			**100.0%**	**0.42 [0.36; 0.48]**
Prediction interval				**[0.35; 0.49]**

Heterogeneity: $Tau^2 < 0.0001$; $Chi^2 = 9.98$, df = 7 (P = 0.19); $I^2 = 30\%$
Test for overall effect: Z = -12.42 (P < 0.001)



- OS

Transl Lung Cancer Res. 2024;13(3):491-502

Other clinical studies on combination therapy

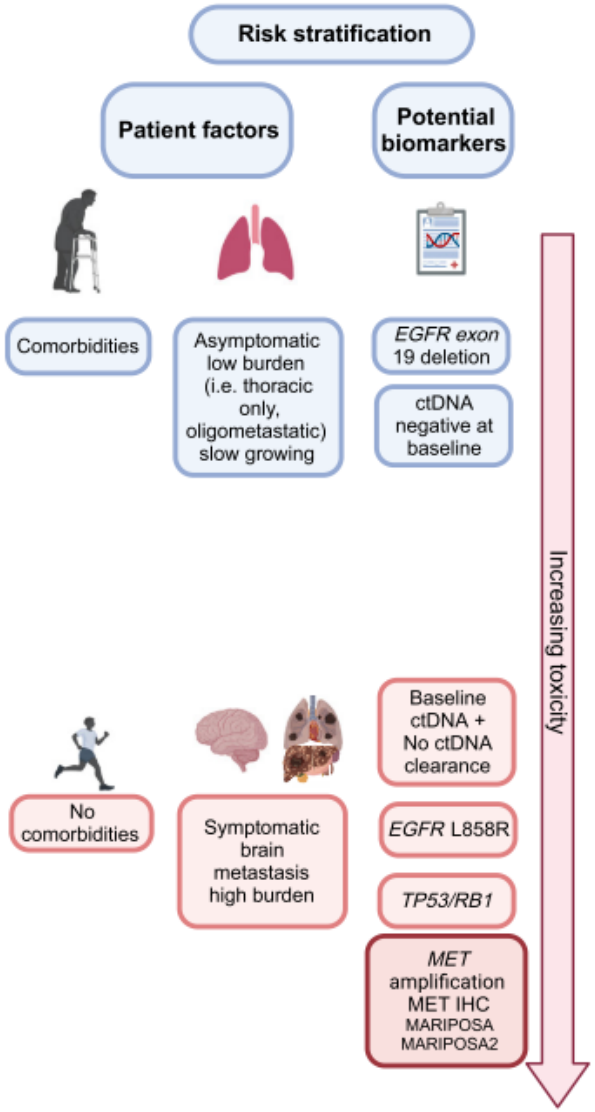
- **MET**
  - INSIGHT-2: Osimertinib + tepotinib
  - SAVANNAH: Osimertinib + savolitinib

- **Amivantamab**
  - AMAZE-lung: Amivantamab (IV) + lazertinib + bevacizumab
  - PALOMA3: Amivantamab (SC) + lazertinib

- **Immunotherapy**
  - HARMONI-A: Ivonescimab (anti-PD1 & anti-VEGF) + chemotherapy
  - ATTLAS or IMPOWER 151: Atezolizumab + bevacizumab + chemotherapy
  - KEYNOTE 789: Pembrolizumab + chemotherapy
  - CHECKMATE 722: Nivolumab + chemotherapy

- **ADC**
  - TROPION-Lung14, 15: Osimertinib + datopotamab deruxtecan (TROP2 ADC)
  - NCT04676477: Osimertinib + patritumab deruxtecan (HER-3)

Risk adaptive approach



IASLC 2025 Targeted Therapies of Lung Cancer Meeting — FEBRUARY 19-22, 2025 | HUNTINGTON BEACH, CA

FIRST-LINE FLAURA
- Osimertinib

SECOND-LINE
- Amivantamab + Platinum Doublet
- Platinum Doublet +/- Osimertinib
- HER3-DXd or Dato-DXd?
- Ivonescimab + Platinum Doublet?

THIRD-LINE
- Docetaxel
- ADC Therapy?
- Amivantamab Lazertinib?

And +/- resistance-matched therapies

FIRST-LINE FLAURA2
- Osimertinib + Platinum Doublet

SECOND-LINE
- Docetaxel
- HER3-DXd or Dato-DXd?
- Amivantamab Combinations?

THIRD-LINE
- Single Agent Chemo
- Docetaxel

And +/- resistance-matched therapies

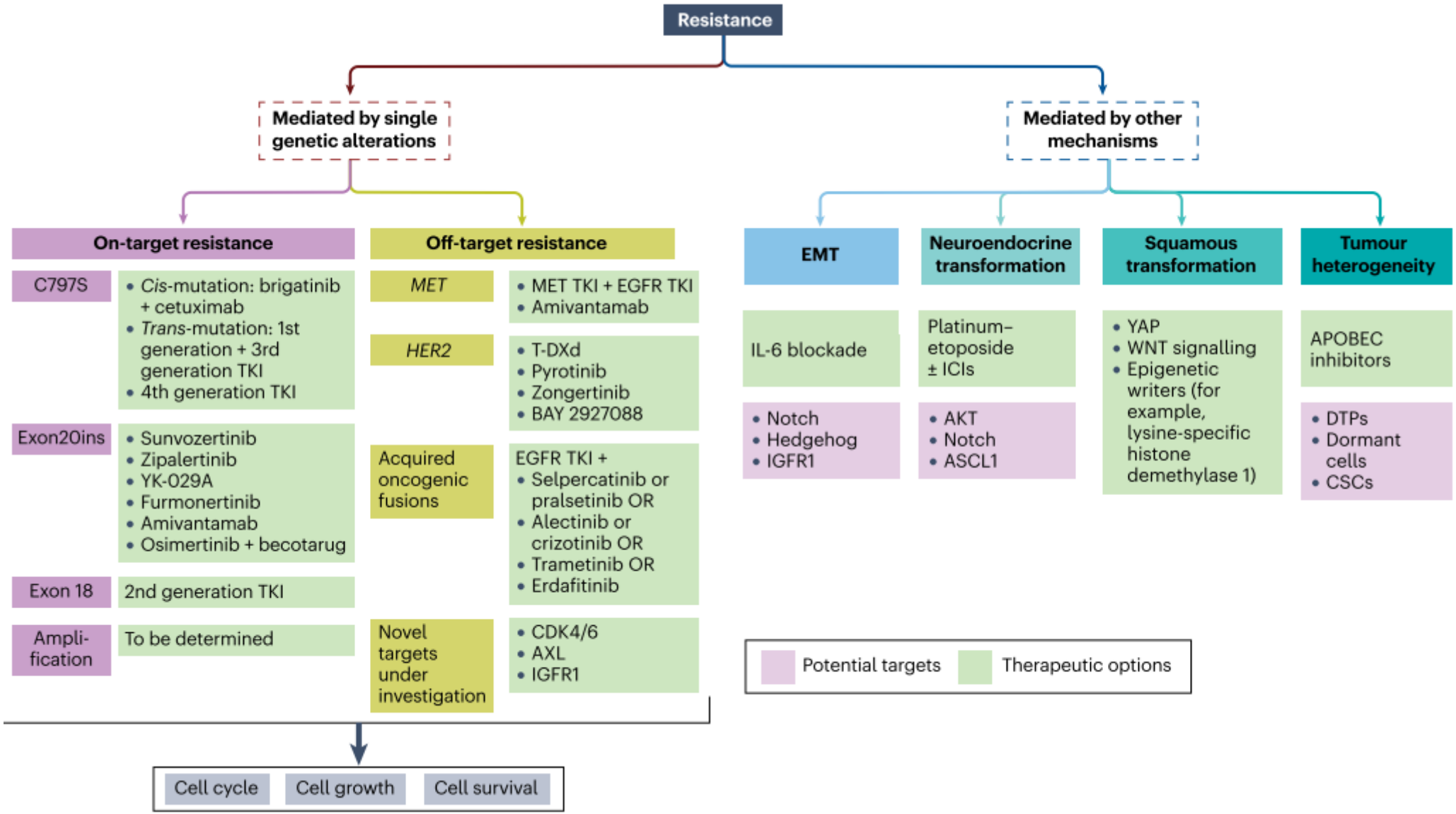
FIRST-LINE MARIPOSA
- Amivantamab + Lazertinib

SECOND-LINE
- Platinum Doublet +/- EGFR TKI
- HER3-DXd or Dato-DXd?
- Ivonescimab + Platinum Doublet?

THIRD-LINE
- Docetaxel
- ADC Therapy?
- Platinum Doublet

And +/- resistance-matched therapies

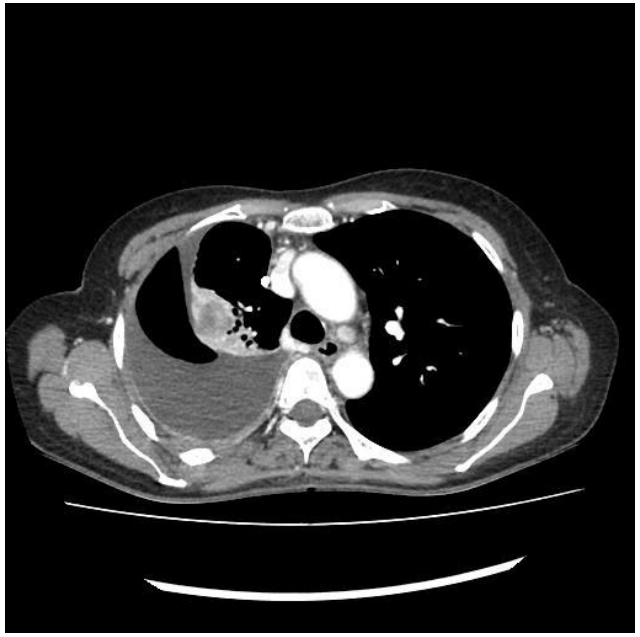
Ann Oncol. 2024;35(1):4-6.



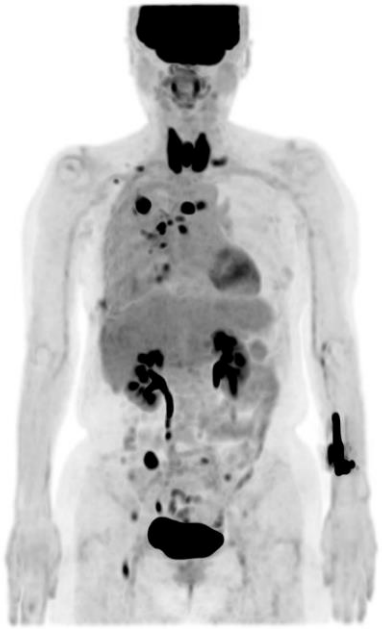
Nat Rev Clin Oncol. 2025; 22(2):95-116

Case

- 56/F, never smoker, ECOG 0
- h/o breast cancer (2005)
- NSCLC, Adenocarcinoma, RUL, cT1cN3M1c1, IVB (M/bone, pleura)
- EGFR (+, L858R), ALK (-), ROS1 (-), KRAS G12C (-)



<2024.10 chest CT>



<2024.10 PET>

Case

- 2024.11.13: 1-1 Osimertinib/pemetrexed/cisplatin 100% (ANC: 3180, Hg 10.6, Plt 285k)
  - ECOG 저하, 2024.11.25 Hg 9.9, Plt 148k
- 2024.12.04: 1-2 Osimertinib/pemetrexed/cisplatin 80% (ANC: 1830, Hg 9.1, Plt 188k)
  - 2024.12.11: ANC 970, 2024.12.16: Plt 124k
- 2024.12.31: 1-3 Osimertinib/pemetrexed/cisplatin 70% (ANC: 1520, Hg 9.3, Plt 195k)
- 2025.02.04: 1-4 Osimertinib/pemetrexed/cisplatin 70% (ANC: 1870, Hg 9.8, Plt 202k)
- 2025.02.25: 1-5 Osimertinib/pemetrexed 70% (ANC: 3180, Hg 10.6, Plt 285k)

- 2024.11.12 ~: XGEVA q 4 weeks
- Adverse event: cytopenia (Gr 1-2), fatigue (Gr 1)

Case

- Best overall response: PR

<2024.12 chest CT>

<2025.02 chest CT>

<2025.04 PET>

Overall summary

- Combination therapies generally show greater efficacy over osimertinib monotherapy, especially with L858R or high risk disease (CNS meta+, ctDNA+, TP53+, liver meta+, bone meta+).
- However, there is a concern for toxicity issue in combination therapies and lack of biomarkers to guide such therapy.
- Osimertinib monotherapy could be considered in patients with comorbidities, exon 19 del or low risk disease (exon 19 del, CNS meta-, ctDNA-, TP53-, liver meta-)
- Local therapy combined with EGFR TKI may improve outcomes in patients with minimal residual disease or oligometastasis.

Future perspectives

- Identification of novel biomarkers to guide and expand target therapies
- Biomarker driven combination therapy targeting resistance mechanisms
- Sequential treatment strategies for long-term disease control
- Innovative combinations with ADCs or immunotherapy
- Development of next generation EGFR TKI