UASK 2026
Uluslararası Katılımlı
AKCİĞER SAĞLIĞI KONGRESİ
25-28 MART 2026
Sueno Deluxe Hotel, Belek/Antalya
Sizin Sesiniz, Sizin Kongreniz...
ASYOD
AKCİĞER SAĞLIĞI VE YOĞUN BAKIM DERNEĞİ

İLERİ EVRE ALK VE EGFR MUTANT mKHDAK TEDAVİSİ

İSTİNYE ÜNİVERSİTESİ

Prof. Dr. Saadettin KILIÇKAP
Tıbbi Onkoloji

liv HOSPITAL ANKARA

Exon 19 del

Exon 21 L858R

Exon 18 G719X

Exon 20 T790M

Exon 20 Aktive edici m

Exon 20 insersiyo

EGFR

EGFR - TKI

Gefitinib
Erlotinib
Afatinib
Dacomitinib
Icotinib
Osimertinib
Lazertinib
Aumolertinib
Amivantamab

TEDAVİ SEÇENEKLERİ

EGFR TKI Monoterapi

EGFR TKI + Kemoterapi

EGFR TKI + Anti VEGF

EGFR TKI + EGFR-MET Mab

Immuno / kemo / anti-VEGF

EGFR TKI vs EGFR TKI

1 ve 2. Jenerasyon

3. Jenerasyon

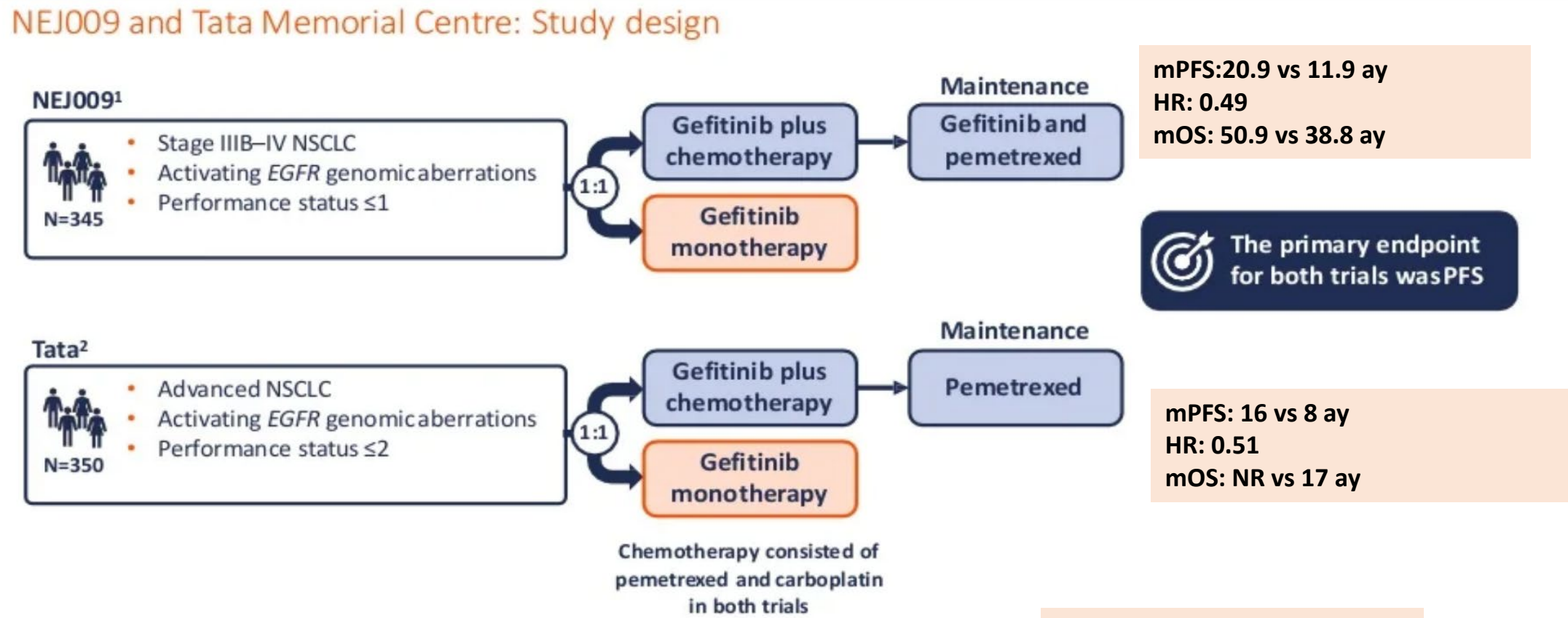
ÇALIŞMA	PFS (ay)			OS (ay)		
ARTIK TARİHSEL DEĞERİ VAR						
FLAURA	Osimertinib	Gefitinib/Erlotinib		Osimertinib	Gefitinib/Erlotinib	
	18.9	10.2	0.46 (0.37-0.57)	38.6	131.8	0.63 (0.45-0.88)
AENEAS	Aumolertinib	Gefitinib		Aumolertinib	Gefitinib	
	19.3	9.9	0.46 (0.36-0.60)	NA	NA	
LASER	Lazertinib	Gefitinib		Lazertinib	Gefitinib	
	20.6	9.7	0.45 (0.34-0.58)	NA	NA	

EGFR TKI vs EGFR TKI + Anti-VEGF

Çalışma	PFS (ay)			OS (ay)	
	Erlo-Beva	Erlotinib	HR (95%CI)	Erlo-Beva vs Erlo	HR (95%CI)
NEJ 026	16.9	13.3	0.56 (0.62-1.05)	50.7 vs 46.2	NS
	%72	%66	ORR		
	Erlo-Rami	Erlotinib	HR (95%CI)	Erlo-Rami vs Erlo	HR (95%CI)
RELAY*	19.4	12.4	0.59 (0.57-0.95)		
	%76	%75	ORR		

* Beyin metastazı olan hastalar dışlandı

EGFR TKI vs EGFR TKI + Kemoterapi



EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.
1. Hosomi Y, et al. *J Clin Oncol*. 2020;38:115–23; 2. Noronha V, et al. *J Clin Oncol*. 2020;38:124–36.

FLAURA2 Phase III study design

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)

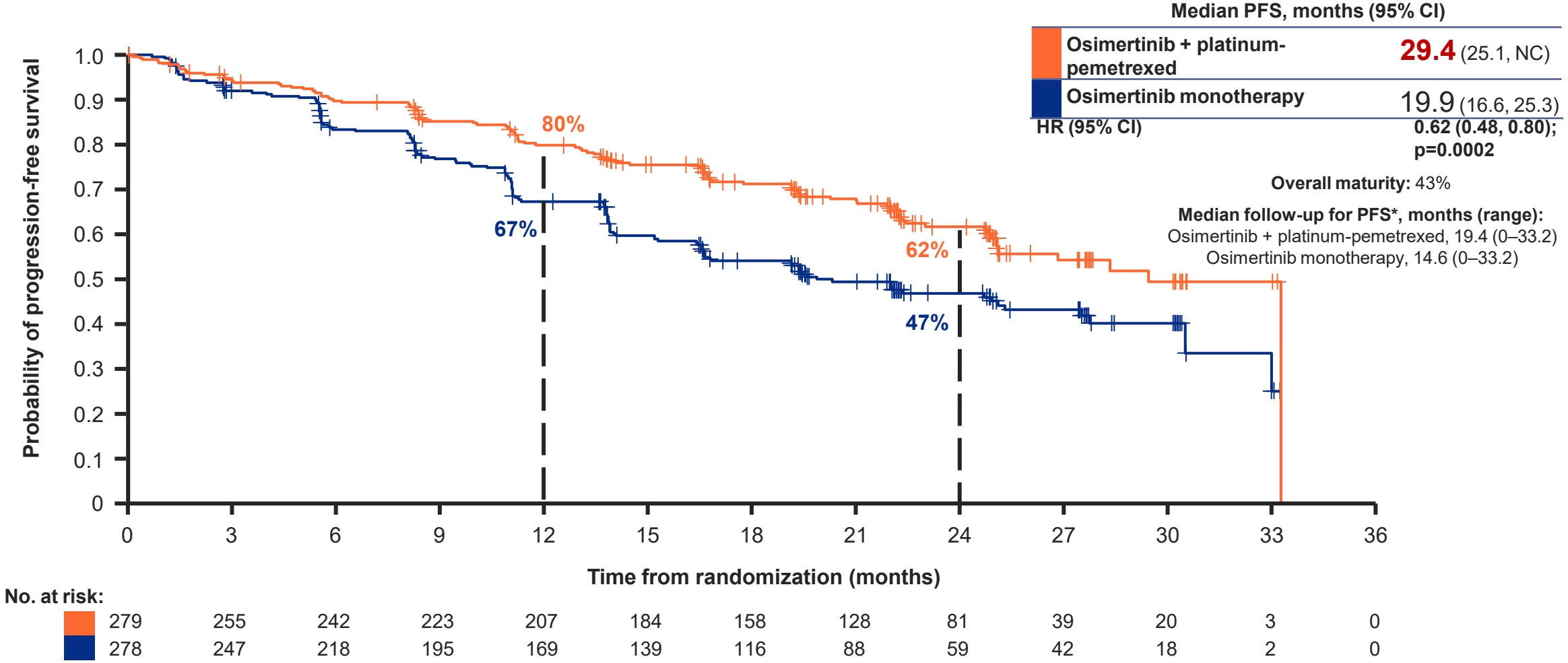
Follow-up:
- RECIST 1.1 assessment at 6 and 12 weeks, then every 12 weeks until RECIST 1.1 defined radiological disease progression or other withdrawal criteria were met

- **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‡

1. Planchard et al. ESMO Open 2021;6:100271
*Not requiring steroids for at least two weeks; †Pemetrexed maintenance continued until a discontinuation criterion was met; ‡Efficacy analyses in the full analysis set, defined as all patients randomized to study treatment regardless of the treatment actually received, and safety analyses in the safety analysis set, defined as all randomized patients who received ≥1 dose of study treatment – one patient who was randomized to osimertinib plus platinum-pemetrexed received only osimertinib and was therefore included in the osimertinib monotherapy safety analysis set; §The study provided 90% power to demonstrate a statistically significant difference in PFS assuming HR=0.68 at 5% two-sided significance level

PFS per BICR

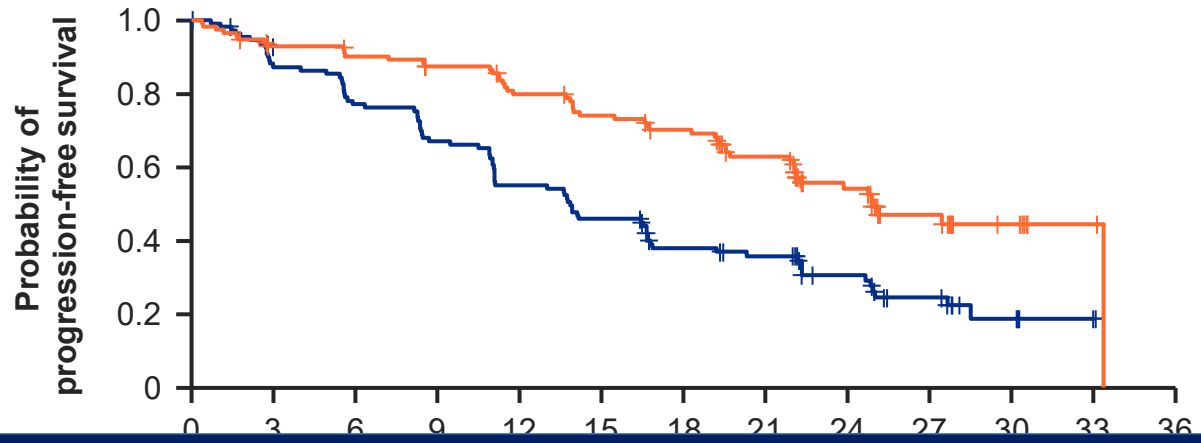
- Median PFS was improved by ~9.5 months with osimertinib plus platinum-pemetrexed vs osimertinib monotherapy



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

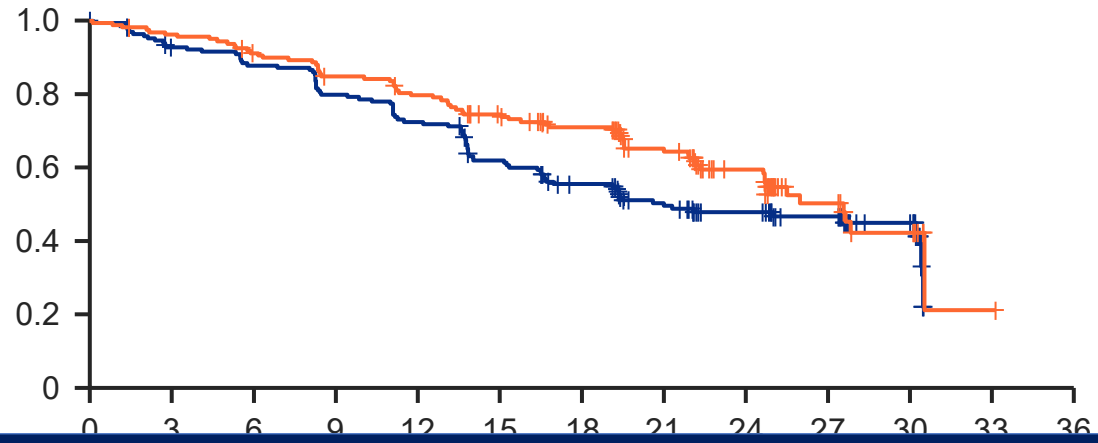
With CNS metastases

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)**



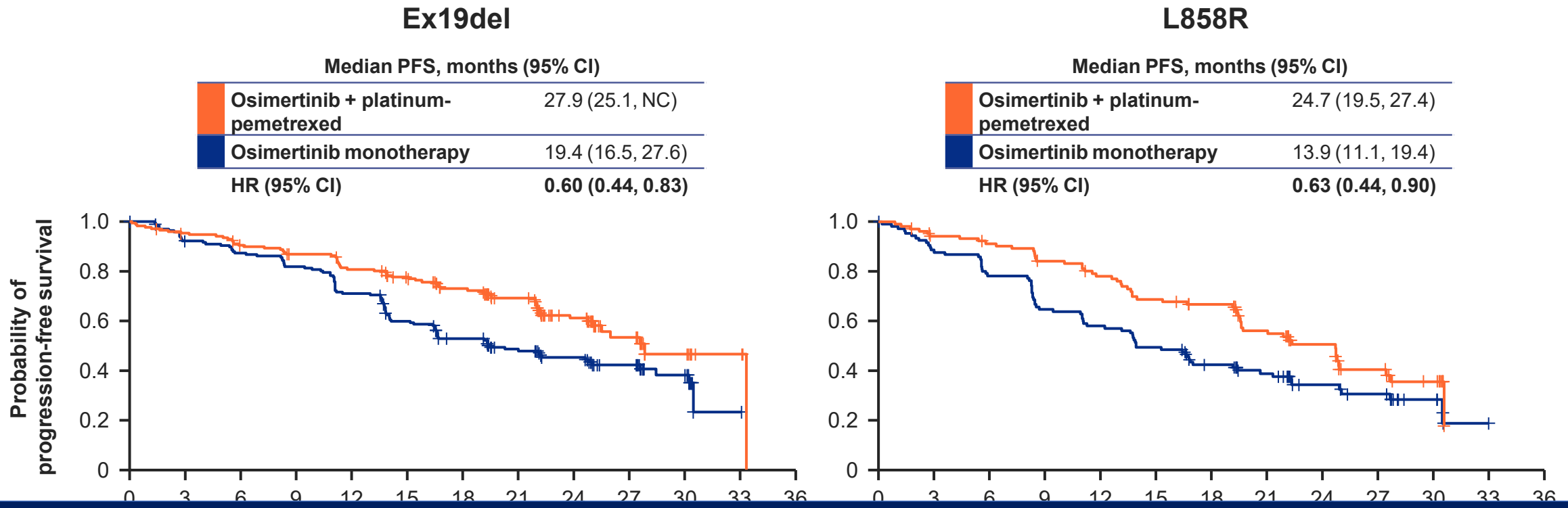
Without CNS metastases

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)**



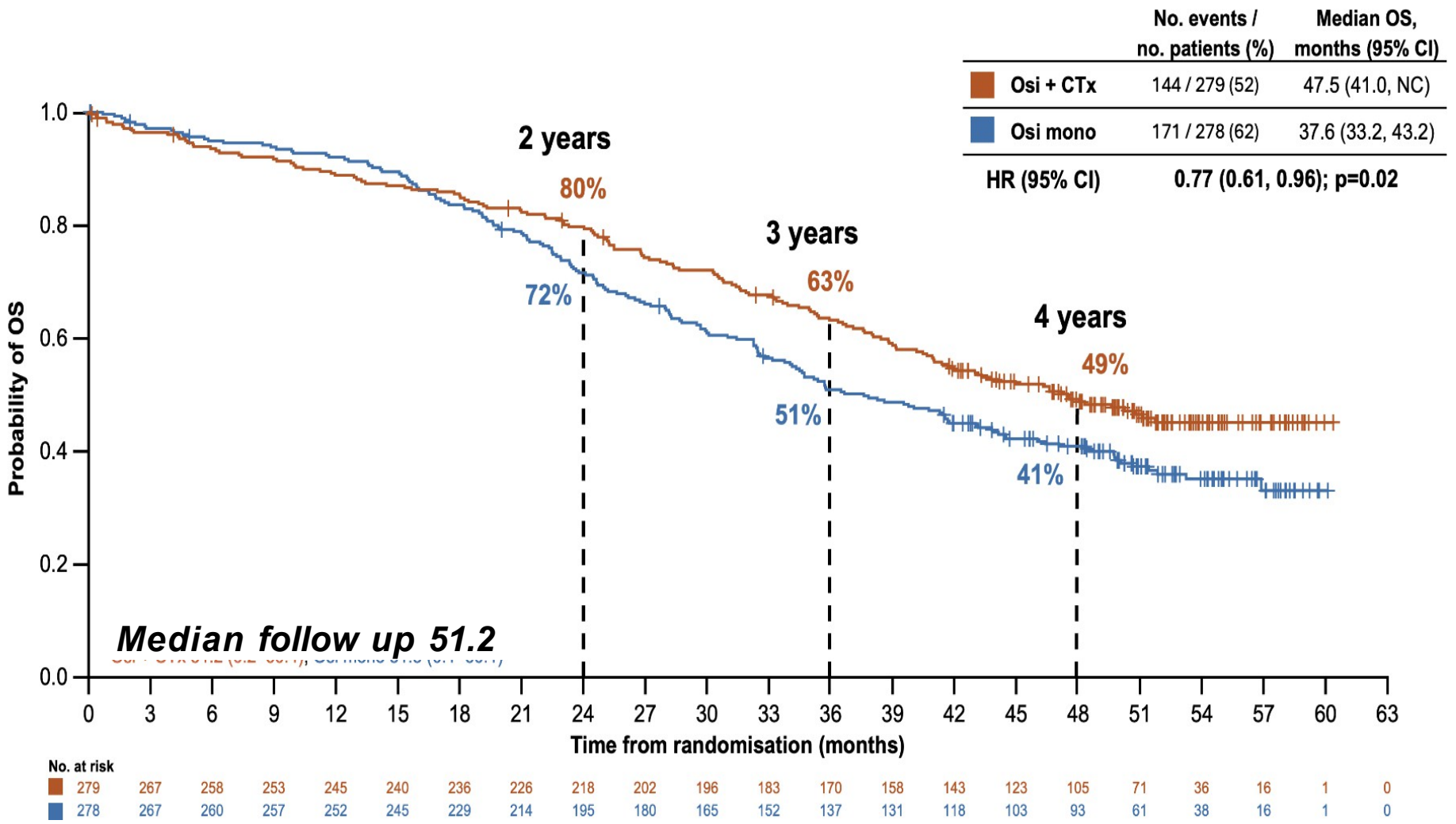
Beyin metastazı olanlarda Olmayanlara yakın bir PFS

PFS per investigator by EGFR mutation type at baseline*



Exon 21'deki PFS
Exon 19'a benzer

Overall Survival- FLAURA-2



Planchard et al. WCLC 2025

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

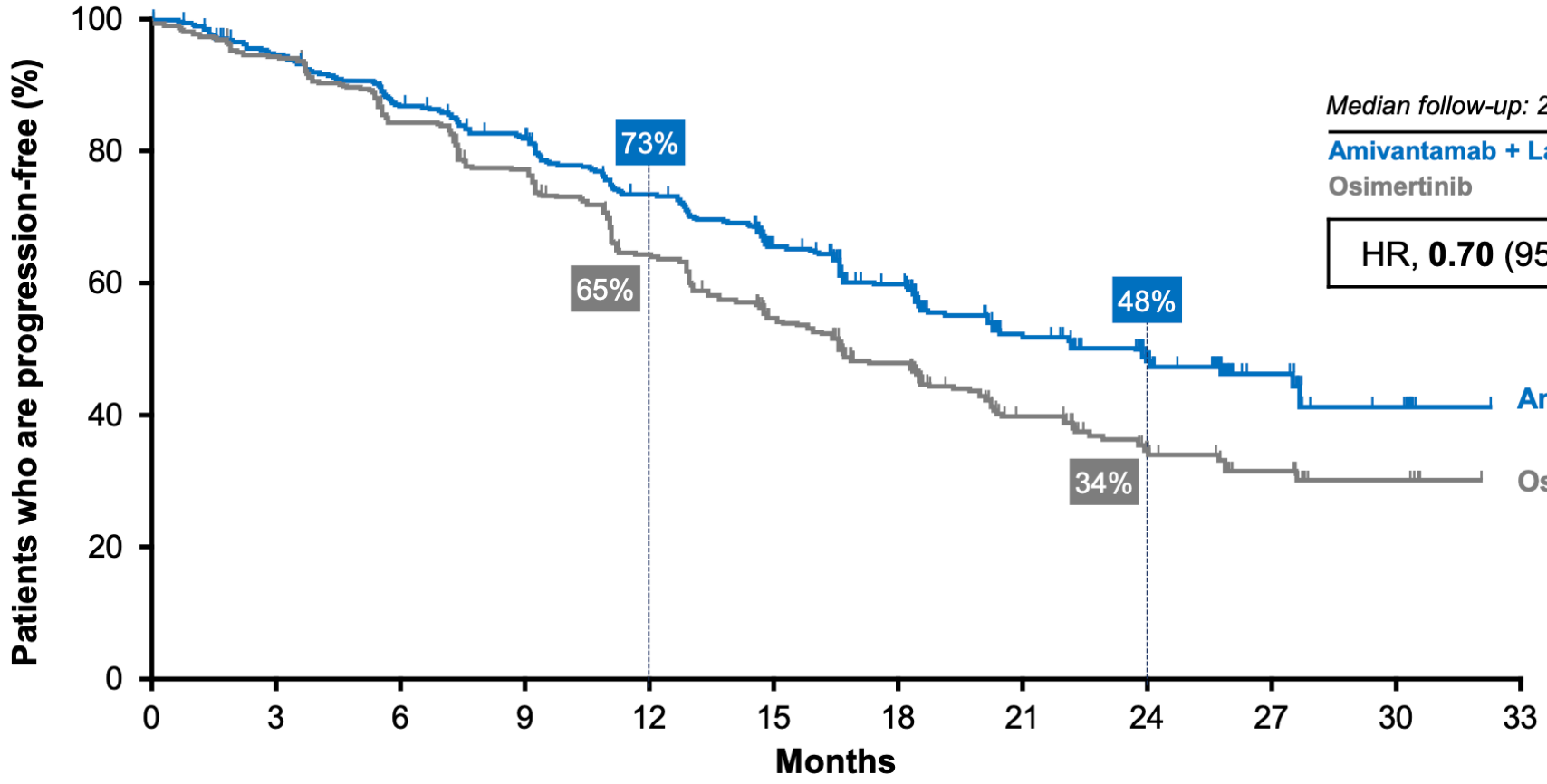
MARIPOSA (ClinicalTrials.gov Identifier: NCT04487080) enrollment period: November 2020 to May 2022; data cut-off: 11-Aug-2023.

[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; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; RECIST, Response Evaluation Criteria in Solid Tumors.

Primary Endpoint: Progression-free Survival by BICR[a]

Amivantamab + lazertinib reduced the risk of progression or death by 30% and improved median PFS by 7.1 months



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

MADRID 2023 ESMO congress

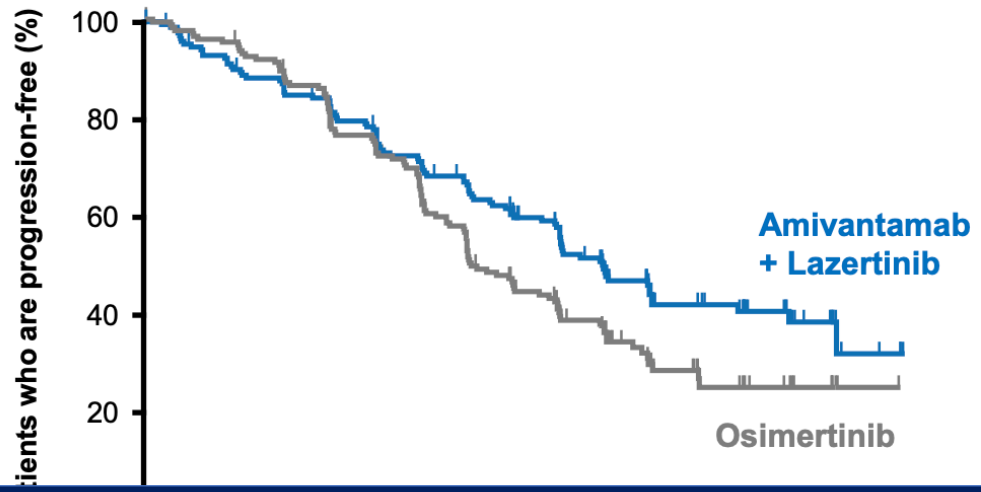
[a]At time of the prespecified final PFS analysis, there were a total of 444 PFS events in the amivantamab + lazertinib and osimertinib arms combined.

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

Consistent PFS (BICR) Benefit With or Without Brain Metastases

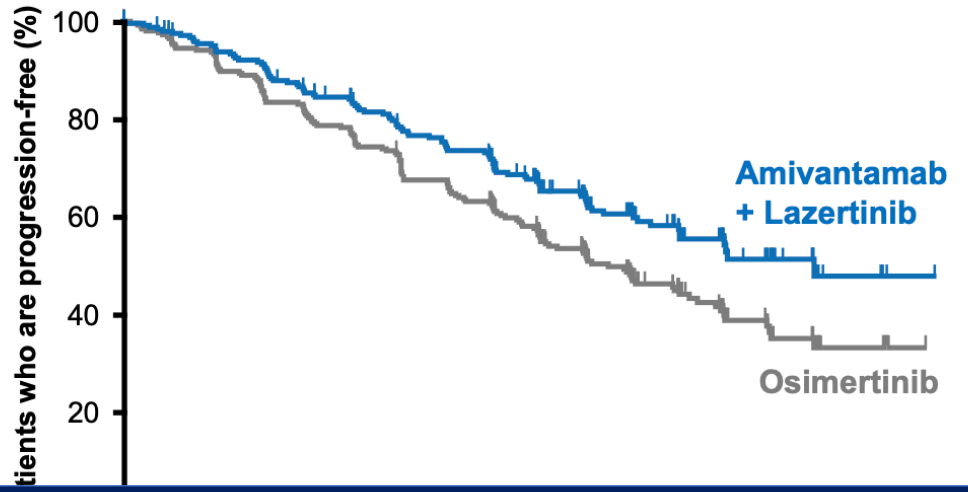
With History of Brain Metastases	Median PFS (95% CI)
Amivantamab + Lazertinib	18.3 mo (16.6–23.7)
Osimertinib	13.0 mo (12.2–16.4)

HR, **0.69** (95% CI, 0.53–0.92)



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)

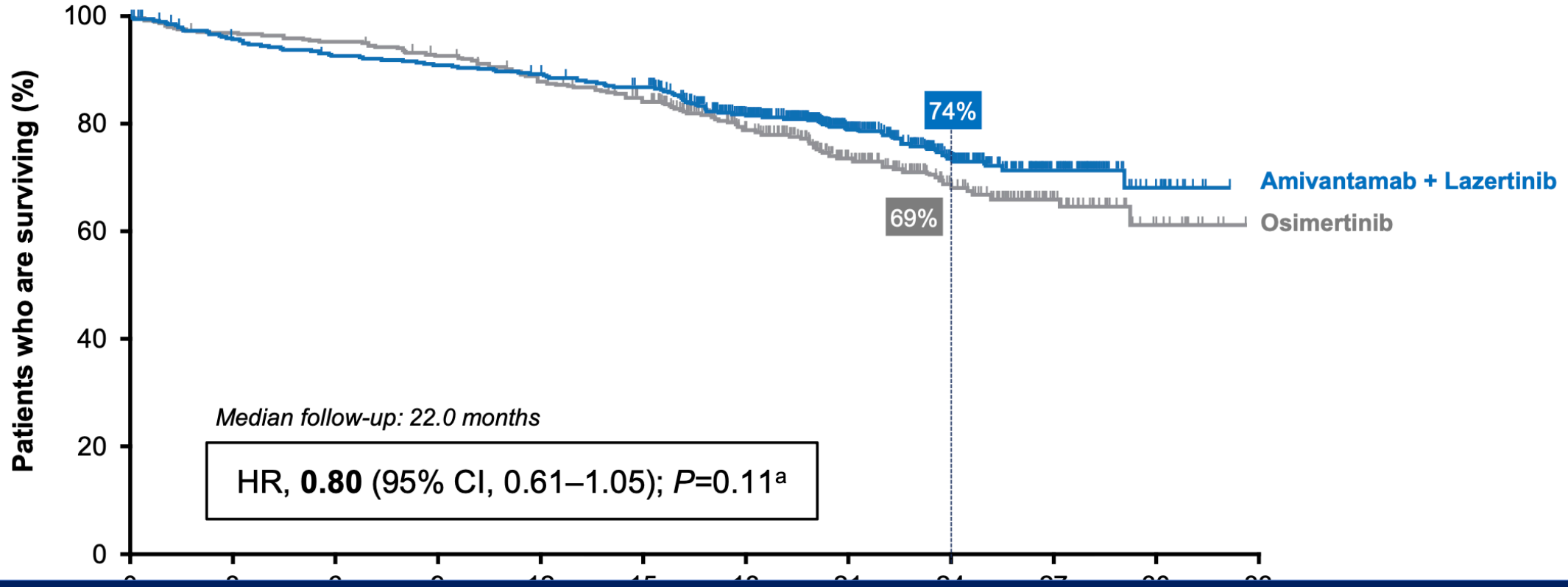
HR, **0.69** (95% CI, 0.53–0.89)



Beyin metastazı olanlarda PFS Daha düşük

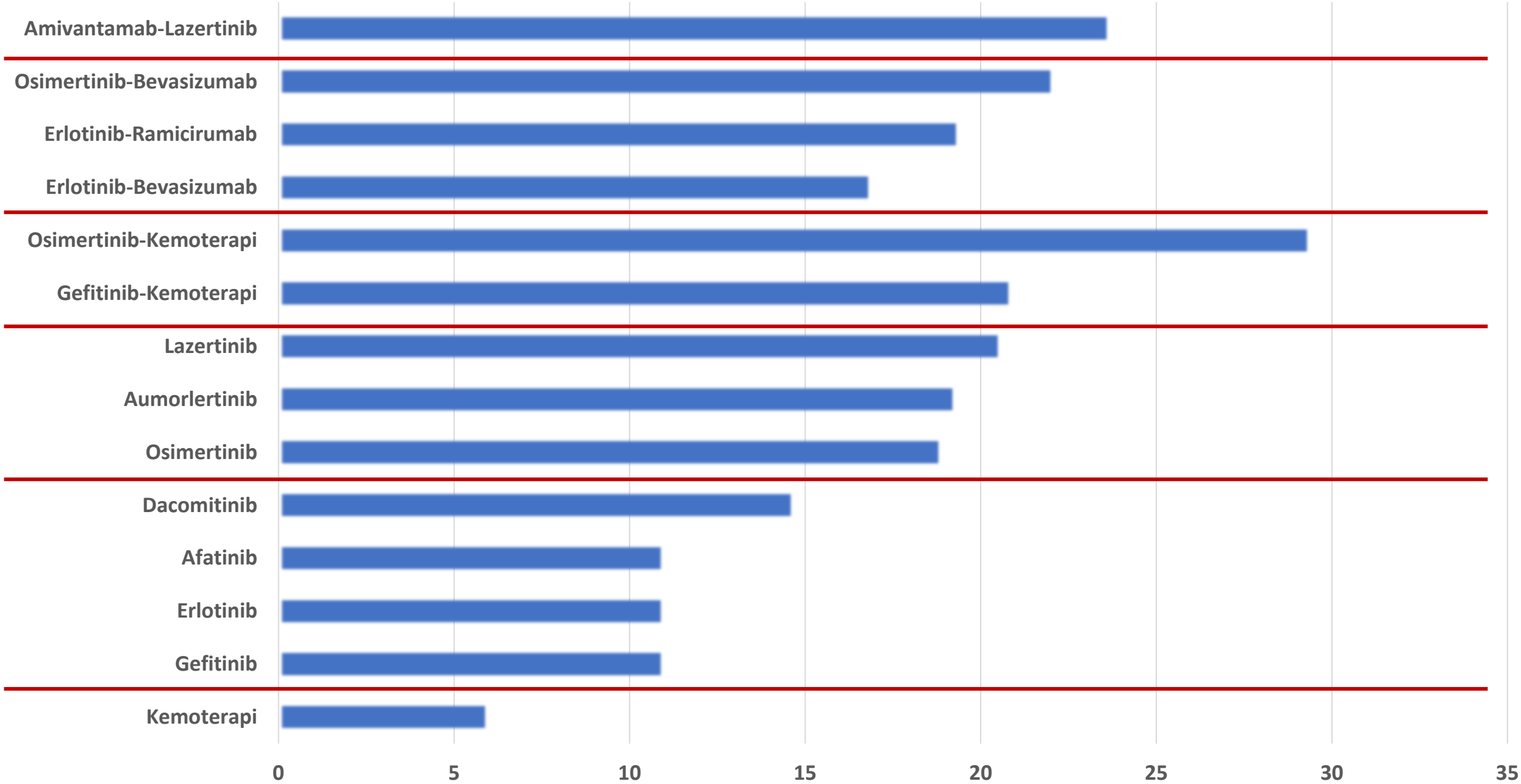
Interim Overall Survival

Early survival data show a trend favoring amivantamab + lazertinib vs osimertinib



OS yararı trendi var

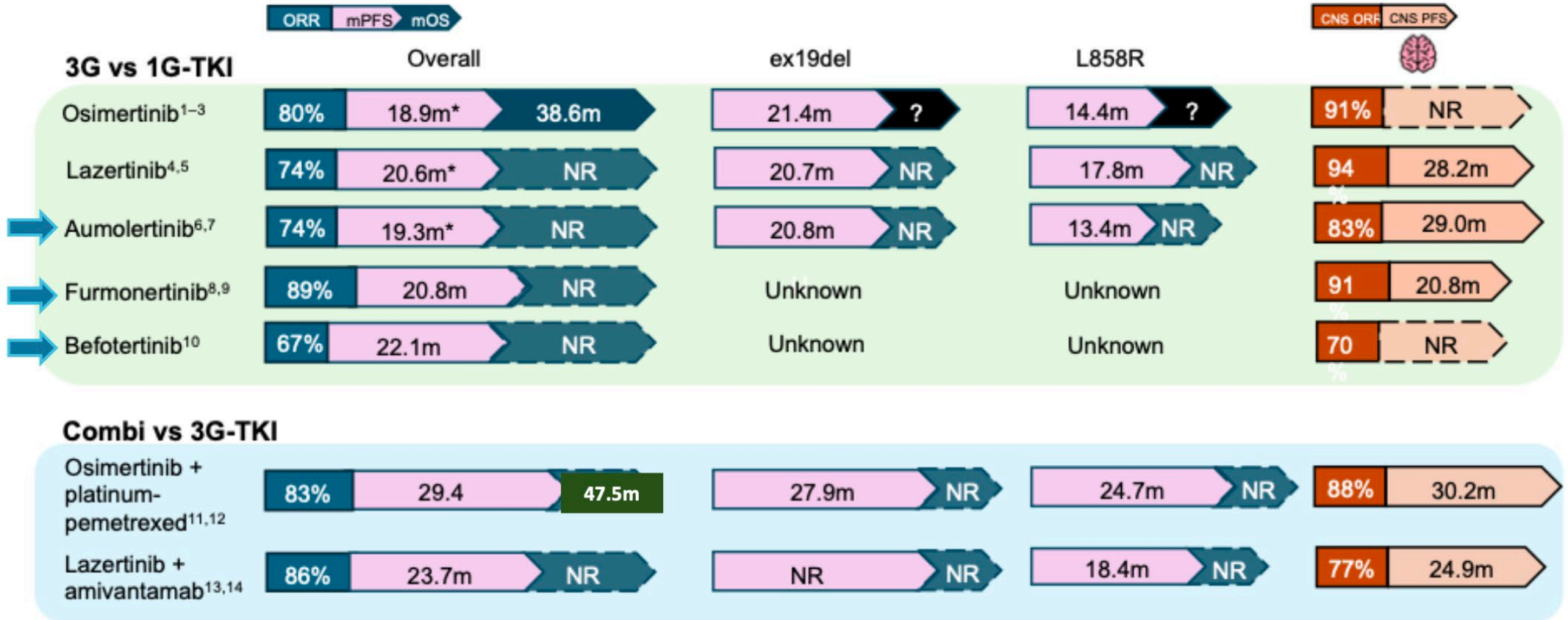
EGFR Mutant Hastalarda Faz 3 klinik çalışma sonuçları - PFS (ay)



Modified from S Saw

1L treatment options for advanced stage EGFRm NSCLC

Other 3d generation EGFR-TKI

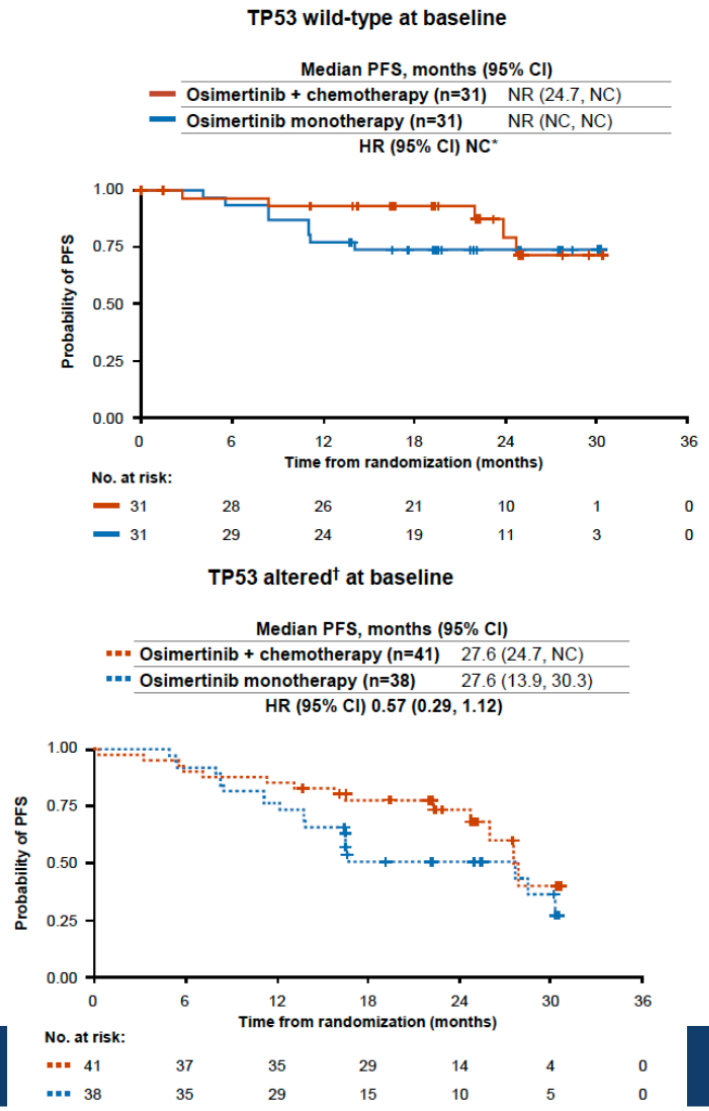


•*Primary endpoint investigator-assessed PFS
•1/3G, first/third generation; CNS, central nervous system; m, months; (m)OS, median overall survival; (m)PFS, (median) progression-free survival; NR, not reached ORR, objective response rate
•1. Soria J-C et al. N Eng J Med 2018;378:113–125; 2. Ramalingam S, et al. N Eng J Med 2020;382:41–50; 3. Reungwetwattana N, et al, J Clin Oncol 2018;26:DOI: https://doi.org/10.1200/jco.2018.78.3118; 4. Cho B, et al, J Clin Oncol 2023;41:4206–4127; 5. Soo R, et al, J Thorac Oncol 2023;18:1756–1766; 6. Lu S. et al, J Clin Oncol 2022;40:3162–3171; 7. Lu S, et al. Oral presentation at ASCO 2022 (Abstract 9096); 8. Shi et al, Lancet Resp Med 2022;10:1019-1028;
9. Shi Y et al. J Thorac Oncol 2022;17:1297–1305; 10. Lu et al, Lancet Resp Med 2023;11:905–915; 11. Planchard D, et al, N Eng J Med 2023;389:1935–1948; 12. Jänne P, et al, J Clin Oncol 2023;41:808-22; 13. Cho B, et al. N Eng J Med 2024;391:1486–1498; 14. Gadgeel S, et al. Oral presentation at WCLC 2024 (Abstract OA02.03)

Saw, Le, Remon – ASCO Educational Book 2024 (updated)

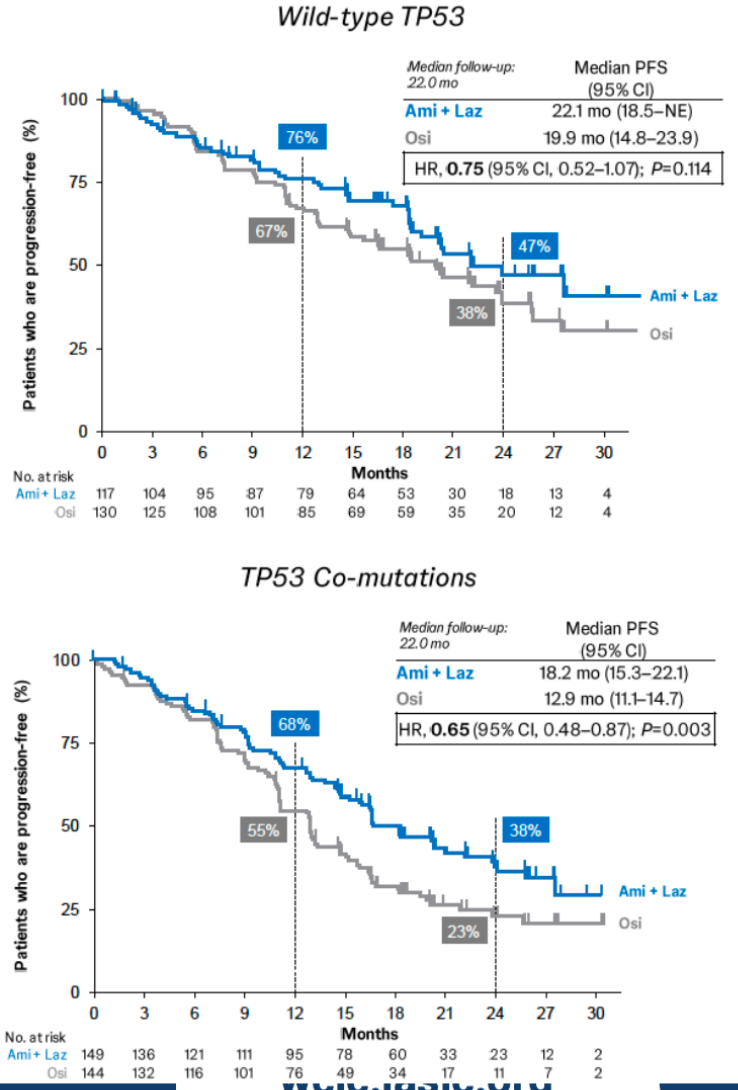
HIGH RISK PATIENTS BENEFIT MOST FROM COMBOS: TP53 CO-MUT+

FLAURA2: Osimertinib ± Chemo



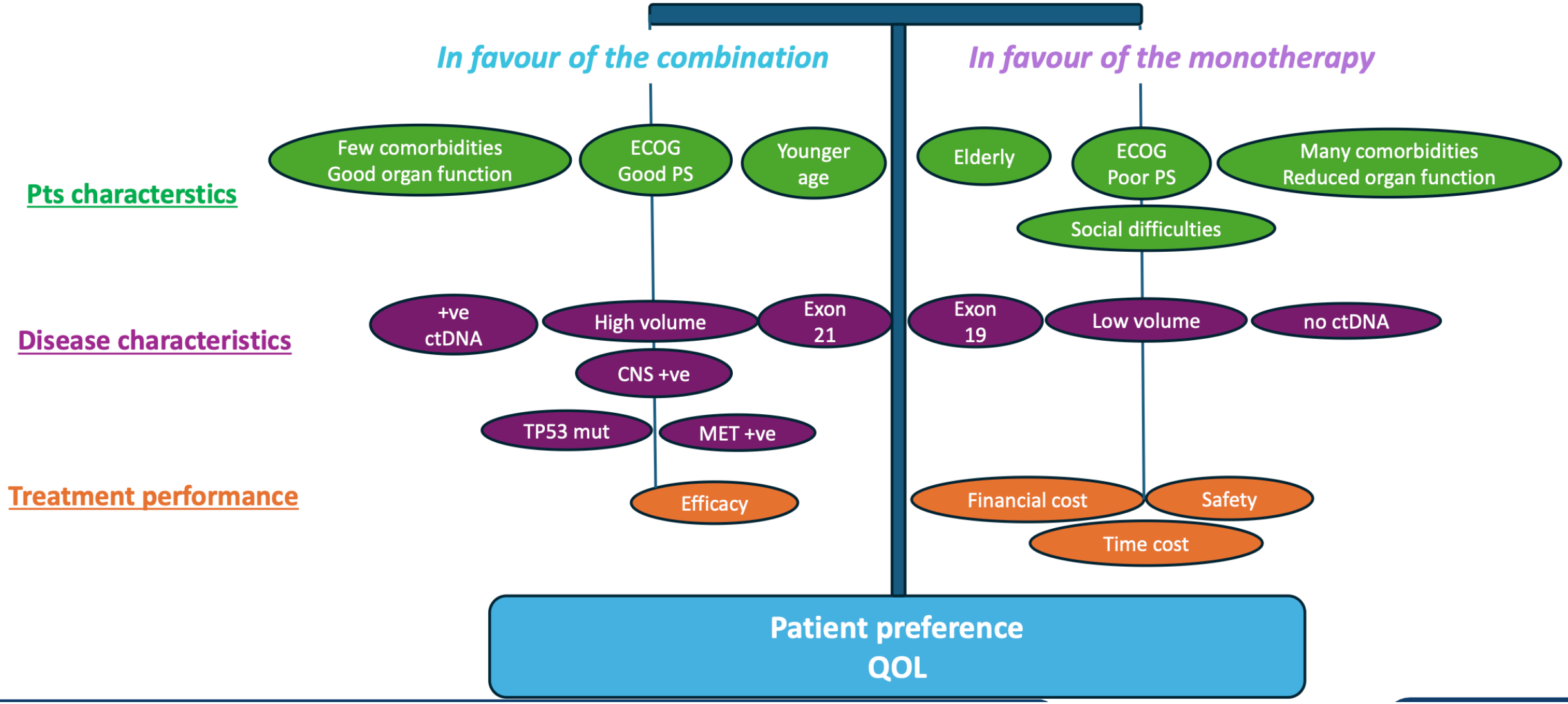
Yang JC, et al. WCLC 2024

MARIPOSA: Amivantamab + Lazertinib



Felip E, et al. ASCO 2024

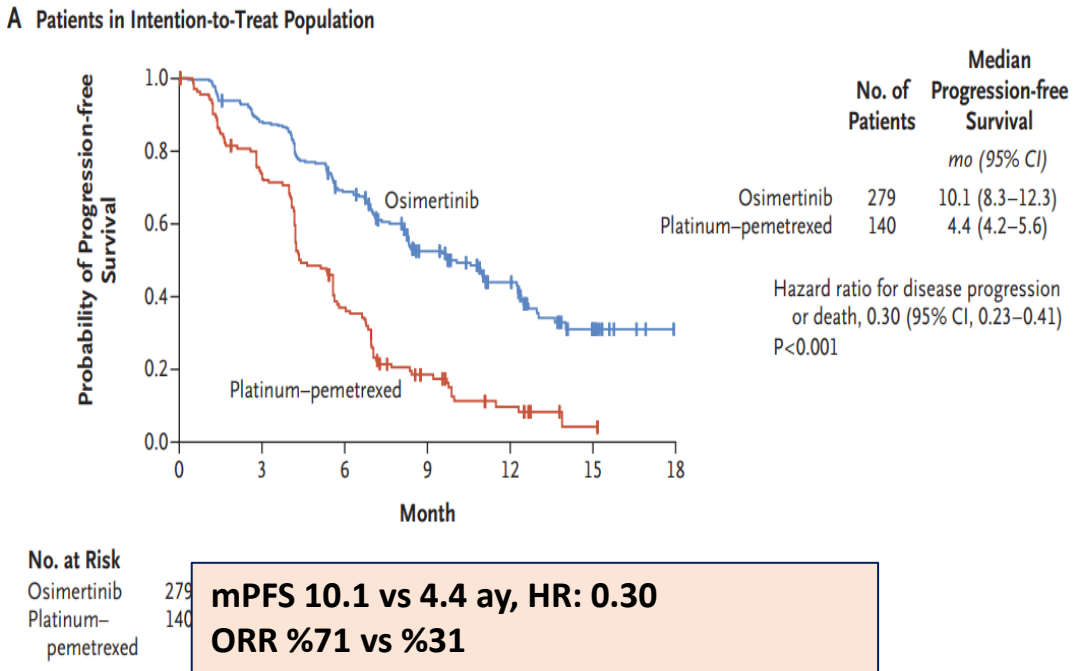
How to choose the best strategy? *While waiting for all final OS data*



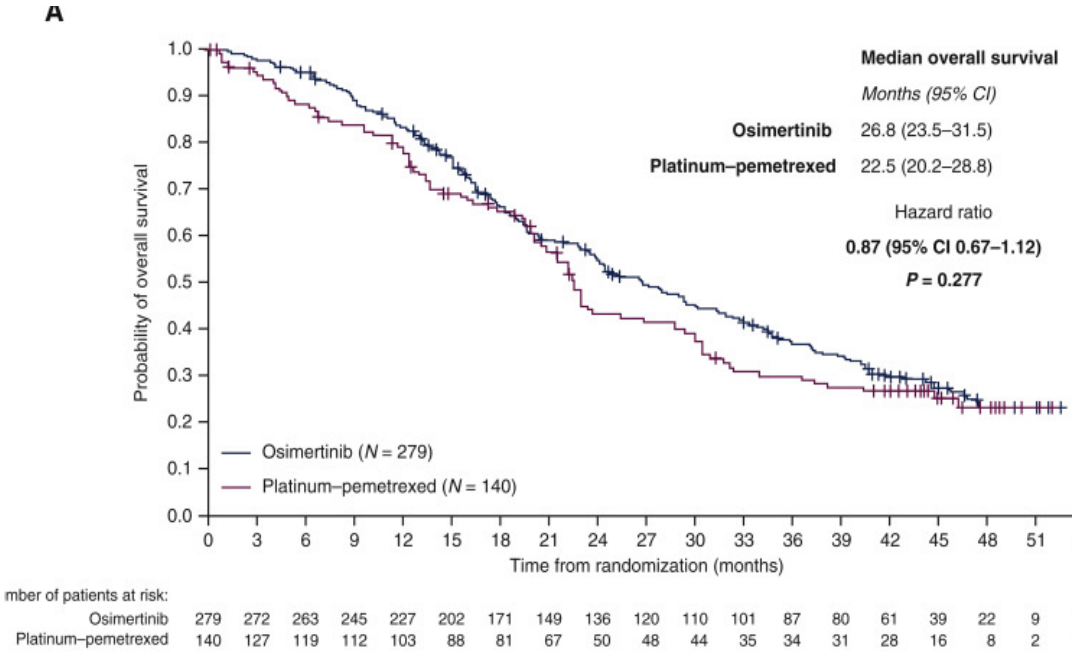
İKİNCİ BASAMAK

1L EGFR TKI SONRASI T790M MUTASYONU OSIMERTINIB

Seri EGFR TKI almış,
T790M (+) 419 hasta, 2:1
%73 çapraz geçiş



mPFS 10.1 vs 4.4 ay, HR: 0.30
ORR %71 vs %31
mOS 26.8 vs 22.5 ay, HR: 0.87
mOS 26.8 vs 15.9 ay, HR: 0.54
(Crossover etkisi düzeltilince)



N Engl J Med 2017;376:629-40
V. A. Papadimitrakopoulou et al, Ann. Oncol, 2020

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

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

Key inclusion criteria:

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

R 1:1 — N=98

Stratification by: CNS metastases, yes / no

Osimertinib 80 mg (QD) + cisplatin 75 mg/m² or carboplatin AUC5 + pemetrexed 500 mg/m² (Q3W for 4 cycles)	**Osimertinib 80 mg (QD) +** pemetrexed 500 mg/m² (Q3W)	PD (non-CNS or CNS)* or another discontinuation criterion
Placebo (QD) + cisplatin 75 mg/m² or carboplatin AUC5 + pemetrexed 500 mg/m² (Q3W for 4 cycles)	**Placebo (QD) +** pemetrexed 500 mg/m² (Q3W)	

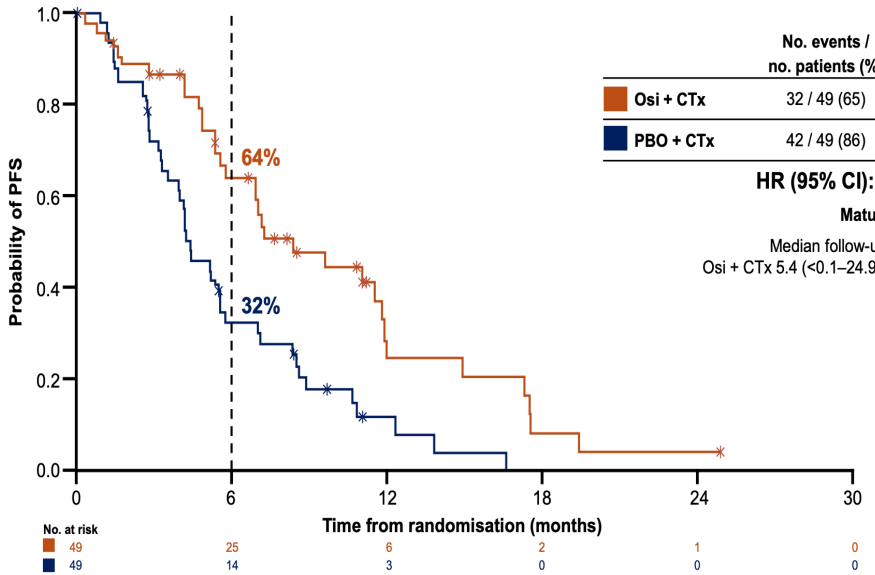
- **Primary endpoint: PFS (investigator-assessed)**
- Secondary endpoints: CNS PFS (according to CNS metastases status at baseline), non-CNS PFS, and OS

Imaging assessments

Chest and abdomen (RECIST v1.1) — *Baseline* — *Scans Q6W for the first 13 cycles and Q12W thereafter* → *Non-CNS PD*

Brain (CNS RECIST v1.1) — *Baseline* — *Scans Q6W for the first 13 cycles and Q12W thereafter* → *CNS PD*

Primary analysis: Progression-free survival (PFS)*



	No. events / no. patients (%)	Median PFS, months (95% CI)
Osi + CTx	32 / 49 (65)	8.4 (5.7, 11.8)
PBO + CTx	42 / 49 (86)	4.4 (3.5, 5.6)

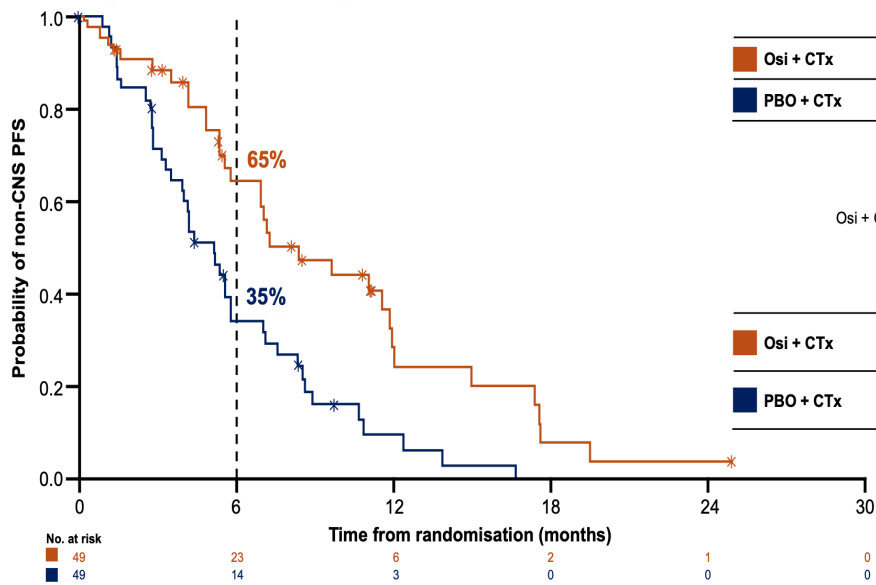
HR (95% CI): 0.43 (0.27, 0.70)

Maturity: 76%

Median follow-up,† months (range):
Osi + CTx 5.4 (<0.1–24.9); PBO + CTx 5.5 (<0.1–11.1)

Osi + CTx was associated with improved PFS versus PBO + CTx

Non-CNS (extracranial) PFS*



	No. events / no. patients (%)	Median non-CNS PFS, months (95% CI)
Osi + CTx	31 / 49 (63)	8.4 (5.7, 11.8)
PBO + CTx	41 / 49 (84)	5.2 (3.5, 5.8)

HR (95% CI): 0.43 (0.26, 0.71)

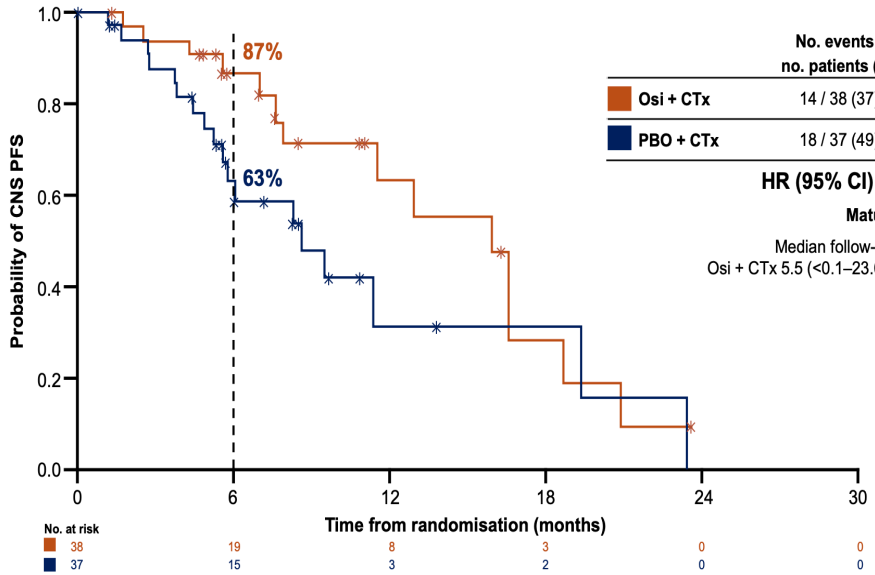
Maturity: 73%

Median follow-up,† months (range):
Osi + CTx 3.6 (<0.1–24.9); PBO + CTx 3.6 (<0.1–9.7)

	Non-CNS ORR,‡ n (%) [95% CI]	Median non-CNS DOR,‡ months (IQR)
Osi + CTx	17 (35) [22, 50]	8.2 (4.4–12.2)
PBO + CTx	14 (29) [17, 43]	4.2 (3.1–7.6)

Osi + CTx was associated with improved non-CNS PFS versus PBO + CTx

CNS PFS* in patients without baseline CNS metastases



	No. events / no. patients (%)	Median CNS PFS, months (95% CI)
Osi + CTx	14 / 38 (37)	15.9 (7.9, 18.6)
PBO + CTx	18 / 37 (49)	8.6 (5.6, 19.4)

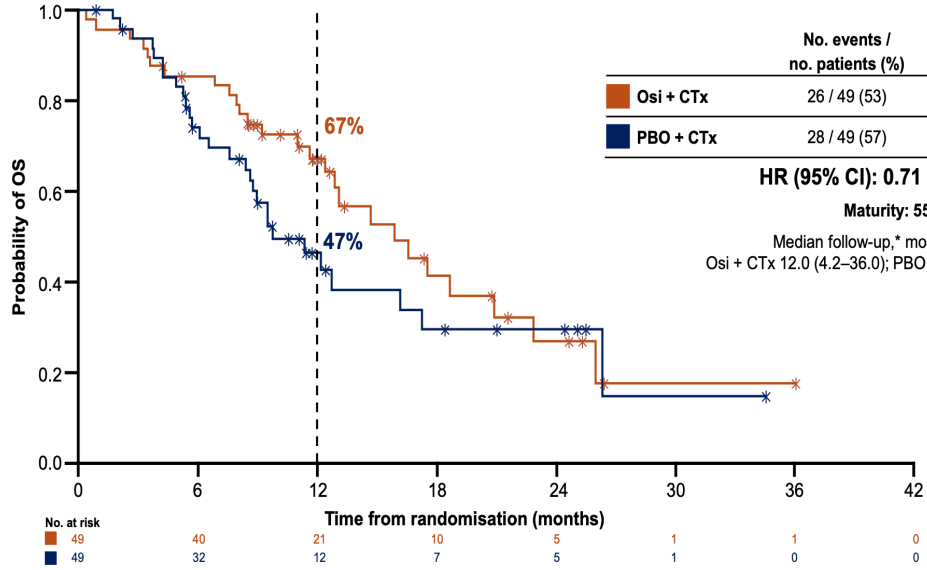
HR (95% CI): 0.56 (0.27, 1.13)

Maturity: 43%

Median follow-up,† months (range):
Osi + CTx 5.5 (<0.1–23.6); PBO + CTx 5.6 (<0.1–13.8)

CNS PFS was longer with osi + CTx versus PBO + CTx in patients without baseline CNS metastase

Overall survival (OS)



	No. events / no. patients (%)	Median OS, months (95% CI)
Osi + CTx	26 / 49 (53)	15.9 (12.4, 20.8)
PBO + CTx	28 / 49 (57)	9.8 (8.4, 17.2)

HR (95% CI): 0.71 (0.42, 1.23)

Maturity: 55%

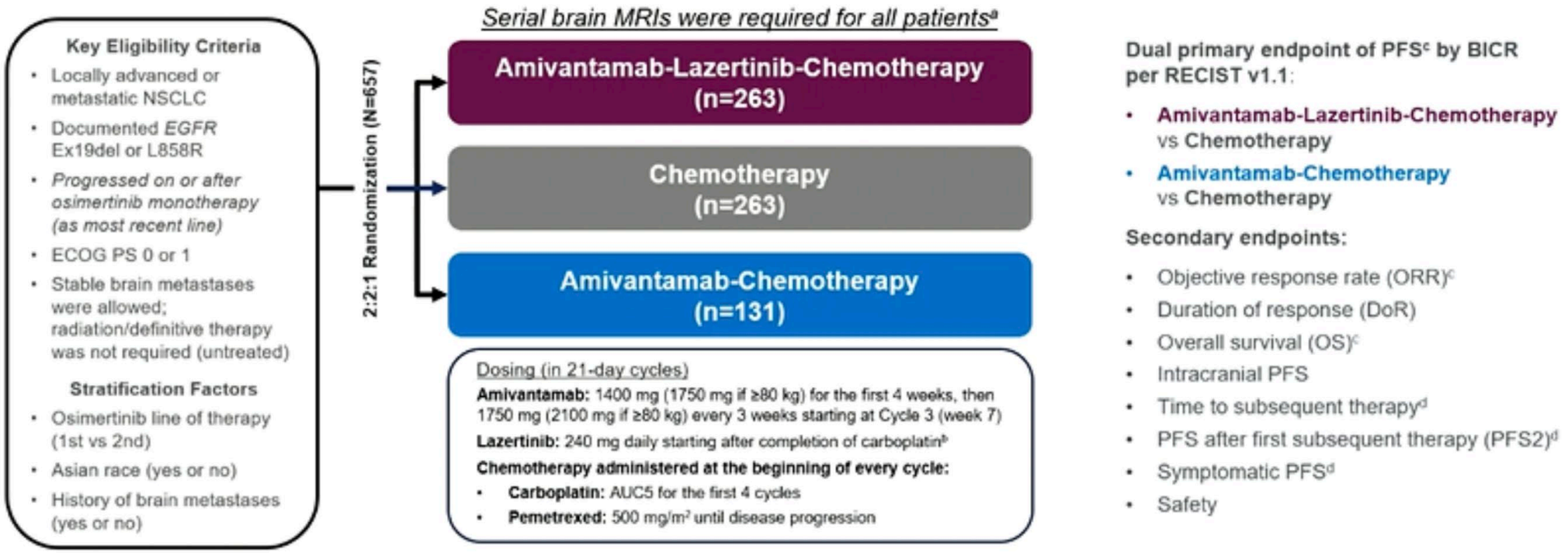
Median follow-up,* months (range):
Osi + CTx 12.0 (4.2–36.0); PBO + CTx 11.1 (0.8–34.5)

OS was longer with osi + CTx versus PBO + CTx

Amivantamab plus chemo (with or without lazertinib) vs chemo in EGFR-mutated advanced NSCLC after progression on osimertinib: MARIPOSA-2,a phase III, global, randomized, controlled trial.

LBA15 –Pasaro A, et al

MARIPOSA-2: Phase 3 Study Design

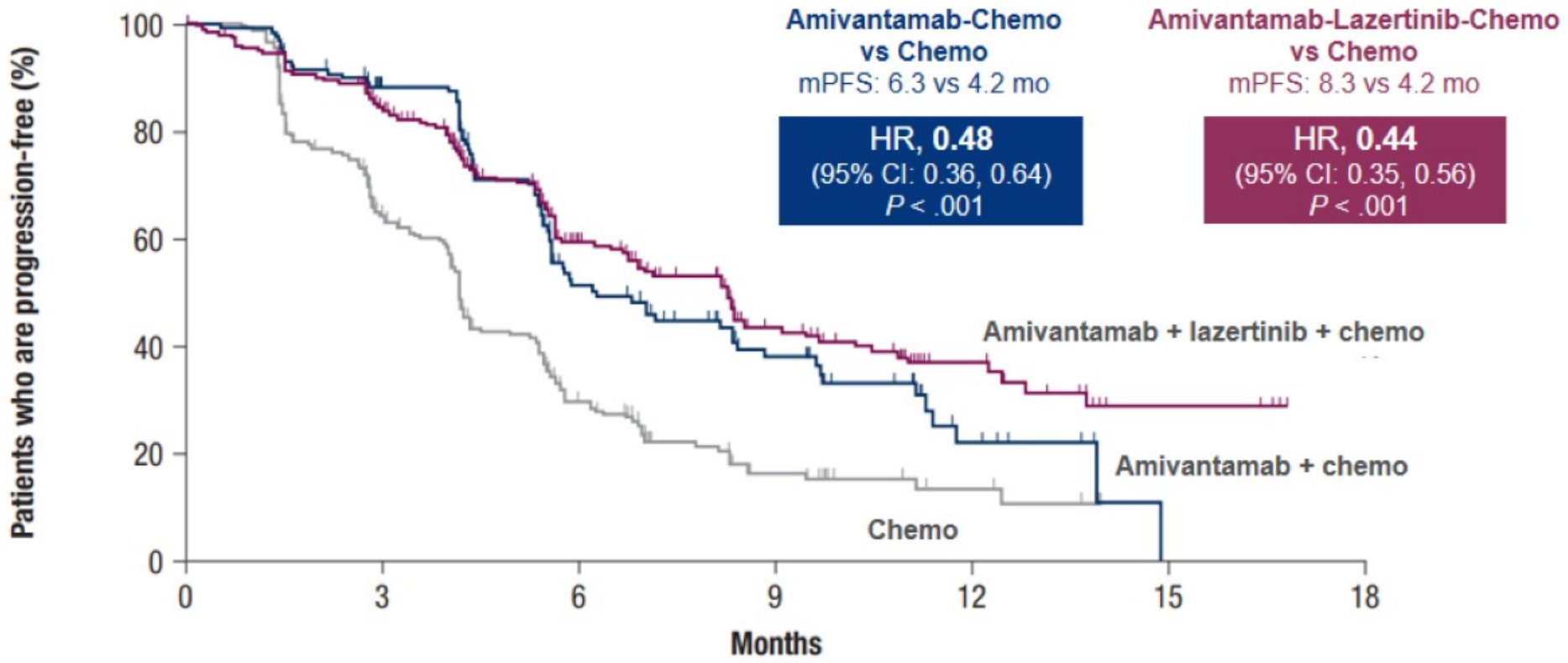


MARIPOSA-2 (ClinicalTrials.gov Identifier: NCT04988295) enrollment period: December 2021 to April 2023; data cut-off: 10 Jul 2023.

[a]Patients who could not have MRI were allowed to have CT scans.
[b]All patients randomized before 7Nov2022 initiated lazertinib on the first day of Cycle 1 (see next slide).
[c]Key statistical assumptions: 600 patients with 350 events across all 3 arms would provide approximately 83% and 93% power for amivantamab-chemotherapy and amivantamab-lazertinib-chemotherapy, respectively, vs chemotherapy to detect a HR of 0.65 using a log-rank test, with an overall two-sided alpha of 0.05 (median PFS of 8.5 months for amivantamab-containing arms vs 5.5 for chemotherapy). Statistical hypothesis testing included PFS, ORR, and then OS.
[d]These secondary endpoints (time to subsequent therapy, PFS2, and symptomatic PFS) will be presented at a future congress.

AUC, area under the curve; BICR, blinded independent central review; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletions; HR, hazard ratio; IDMC, independent data monitoring committee; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

MARIPOSA-2 Phase 3 Trial
Progression-Free Survival



No. at risk							
Amivantamab–chemotherapy	131	99	49	27	7	0	0
Amivantamab–lazertinib–chemotherapy	263	194	104	52	21	4	0
Chemotherapy	263	135	49	17	6	0	0

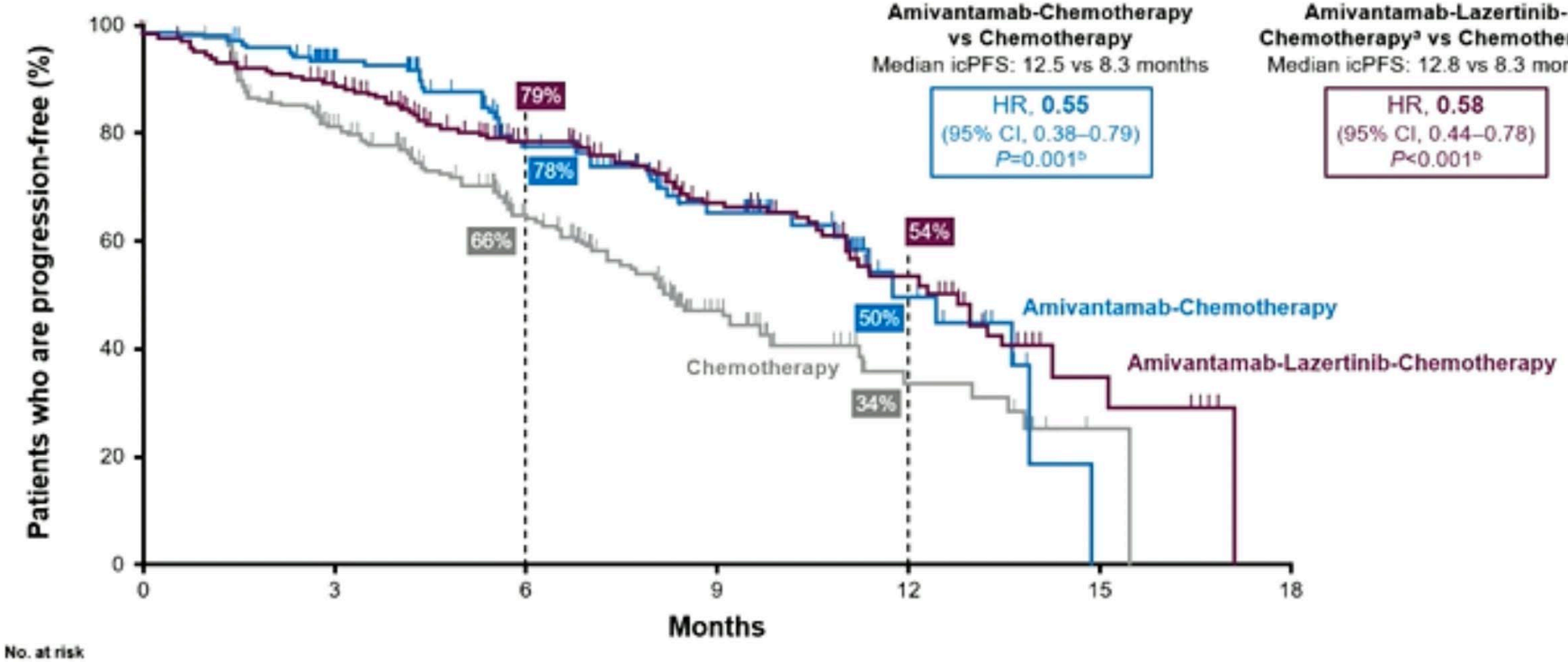
Passaro A, et al. Ann Oncol. 2024;35:77-90.

Amivantamab plus chemo (with or without lazertinib) vs chemo in EGFR-mutated advanced NSCLC after progression on osimertinib: MARIPOSA-2,a phase III, global, randomized, controlled trial.

LBA15 –Pasaro A, et al

Intracranial Progression-free Survival by BICR

Amivantamab-chemotherapy and amivantamab-lazertinib-chemotherapy reduced the risk of intracranial progression or death by 45% and 42%, respectively



No. at risk							
Amivantamab-Chemotherapy	131	103	72	40	11	0	0
Amivantamab-Lazertinib-Chemotherapy	263	211	135	74	32	6	0
Chemotherapy	263	167	89	37	13	1	0

MADRID 2023 ESMO congress

[a]Amivantamab-lazertinib-chemotherapy arm includes all patients regardless of the dosing regimen received. [b]Nominal *P* value; endpoint not part of hierarchical hypothesis testing.
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; icPFS, intracranial progression-free survival.

Phase 3 Study Design

HARMONi

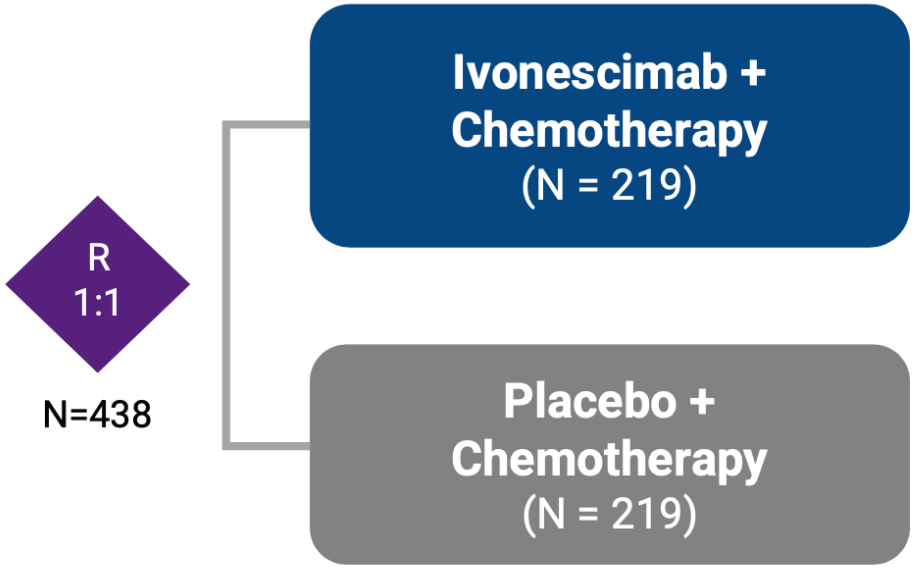
Key Eligibility Criteria

Locally advanced or metastatic NSCLC:

- EGFR sensitizing mutation+
- Progressed on 3rd gen EGFR-TKI
- ECOG 0 or 1
- Any PD-L1 expression

Stratification factor by geographic region:

- Brain metastases (yes or no)



Ivonescimab: 20 mg/kg Q3W

Chemotherapy:

- Carboplatin: AUC5 Q3W x 4 cycles (21 day/cycle)
- Pemetrexed: 500 mg/m^2 Q3W

Endpoints:

Primary

- OS, PFS by IRRC per RECIST 1.1

Secondary

- ORR by IRRC, DoR, safety and tolerability

Planned Efficacy Analyses

- PFS primary (at ~231 events) & OS interim analyses
- OS final analysis (at ~261 events)

FPI: Jan 2022 (overall)
LPI Asia: Nov 2022
LPI NA & EU (and overall): Oct 2024

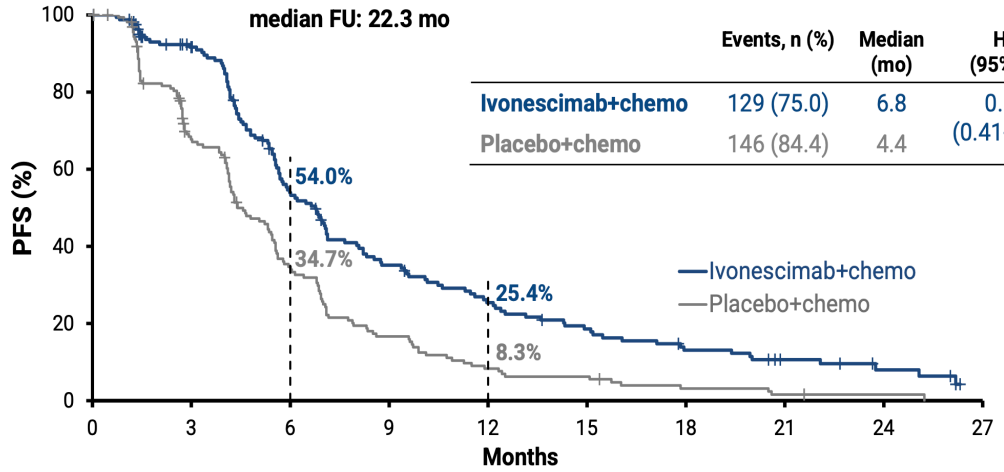
Note: Positive outcomes were reported from the single-region (Asia) study HARMONi-A, with PFS as the primary endpoint.

DoR=duration of response; ECOG=eastern cooperative oncology group; EGFR= Epidermal growth factor receptor; EU=Europe; FPI=first patient in; IRRC= independent radiology review committee; LPI=last patient in; mets=metastases; NA=North America; ORR=overall response rate; OS=overall survival; NSCLC=non-small cell lung cancer; TKI=tyrosine kinase inhibitor; PD-L1= programmed cell death ligand; PFS=progression-free survival; Q3W=every 3 weeks; RECIST=response evaluation criteria in solid tumors.

Primary Endpoint: PFS by IRRC

HARMONi

Statistically significant and clinically meaningful benefit with ivonescimab



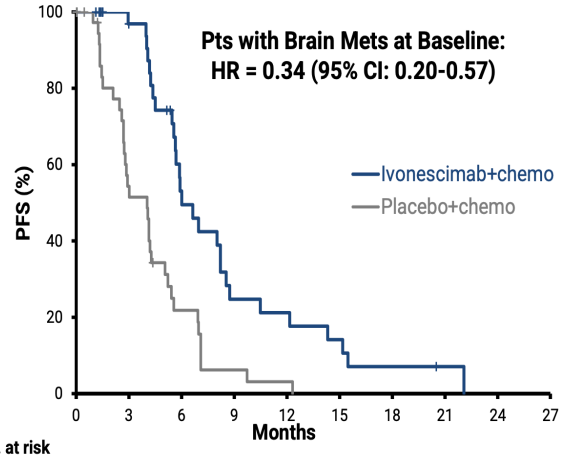
	Events, n (%)	Median (mo)	HR (95% CI)	*P* Value
Ivonescimab+chemo	129 (75.0)	6.8	0.52 (0.41-0.66)	<0.0001
Placebo+chemo	146 (84.4)	4.4		

No. at risk										
Ivonescimab+chemo	172	134	76	48	34	24	16	10	5	0
Placebo+chemo	173	100	50	24	12	9	4	2	1	0

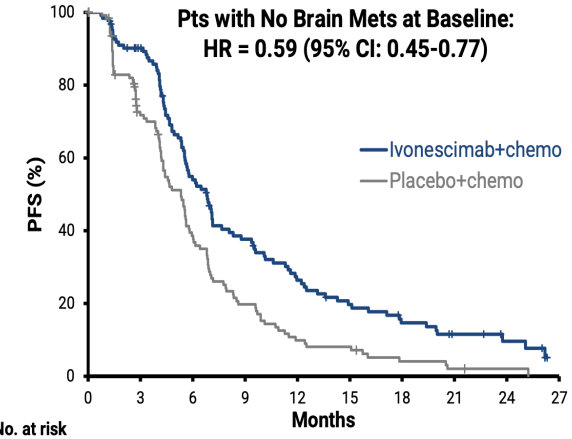
Consistent PFS benefit by investigator: HR = 0.58 (95% CI: 0.45-0.73)

PFS by Presence or Absence of Brain Mets

HARMONi



No. at risk										
Ivonescimab +chemo	41	30	15	7	6	4	2	1	0	
Placebo +chemo	42	19	7	2	1	0				

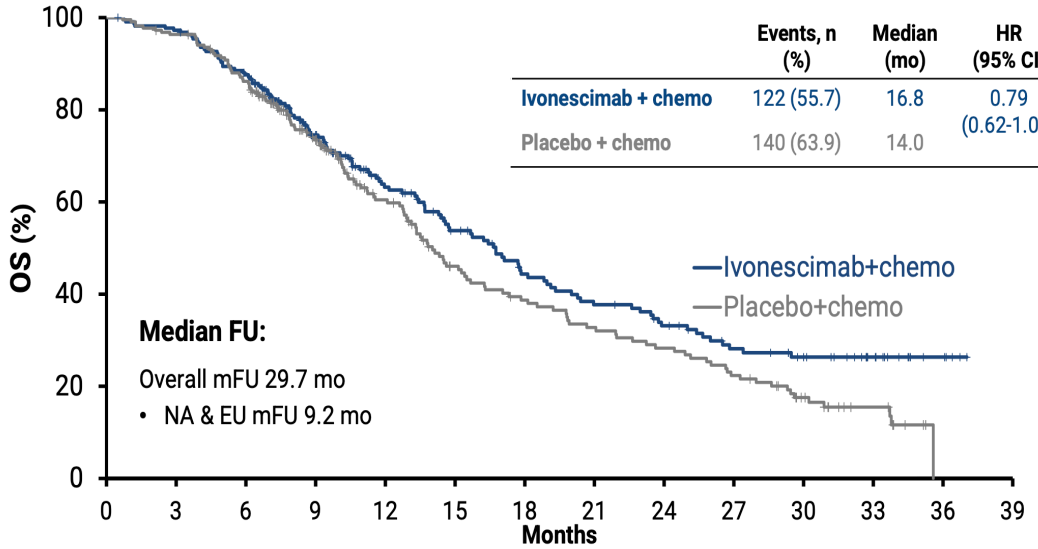


No. at risk										
Ivonescimab +chemo	131	104	61	41	28	20	14	9	5	0
Placebo +chemo	131	81	43	22	11	9	4	2	1	0

Primary Endpoint: Overall Survival

HARMONi

Favorable Trend Observed; NA & EU Follow-up Not Yet Mature



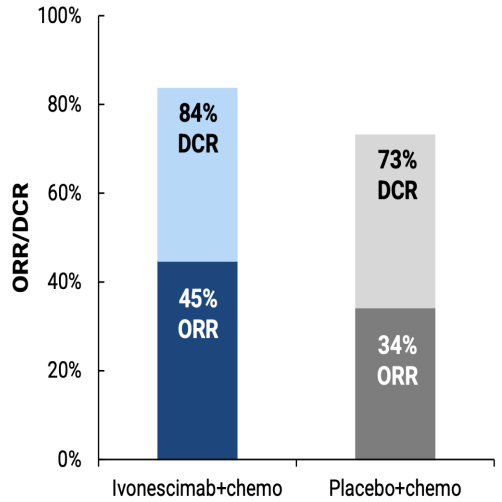
	Events, n (%)	Median (mo)	HR (95% CI)	*P* Value
Ivonescimab + chemo	122 (55.7)	16.8	0.79 (0.62-1.01)	0.0570
Placebo + chemo	140 (63.9)	14.0		

No. at risk													
Ivonescimab+chemo	219	212	189	137	98	77	60	51	43	33	26	16	5	0
Placebo+chemo	219	210	186	132	92	63	52	44	38	30	18	9	0	

Overall Response Rate and Duration of Response

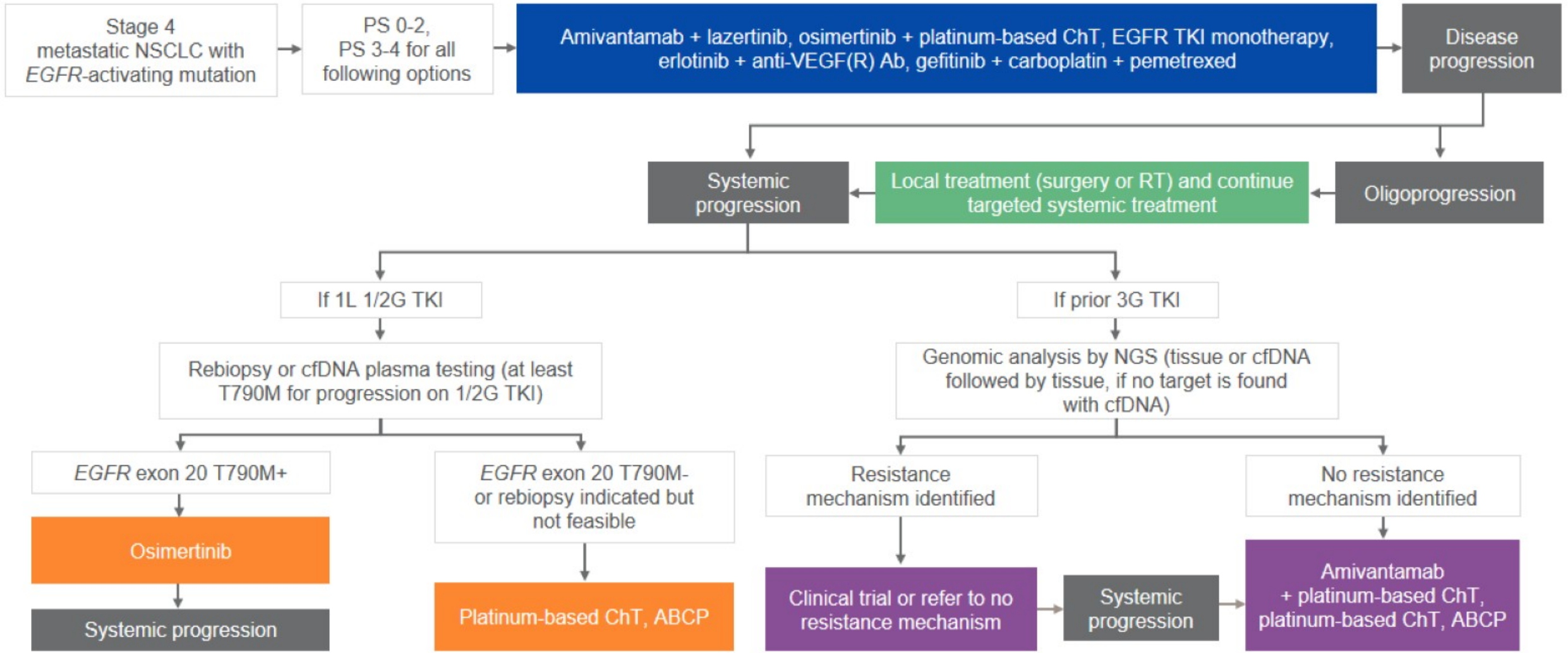
HARMONi

By IRRC



DoR (mo)	Ivonescimab + chemo	Placebo + chemo
n	98	75
Median (95% CI)	**7.6** (5.5-10.6)	**4.2** (2.9-4.7)

ESMO Living Guidelines
Advanced/Metastatic NSCLC With *EGFR* Mutation



Hendriks LE, et al. Ann Oncol. 2023;34:339-357. ESMO Living Guidelines v1.2. 2025. Accessed August 20, 2025. https://www.esmo.org/living-guidelines/esmo-oncogene-addicted-non-small-cell-lung-cancer-living-guideline

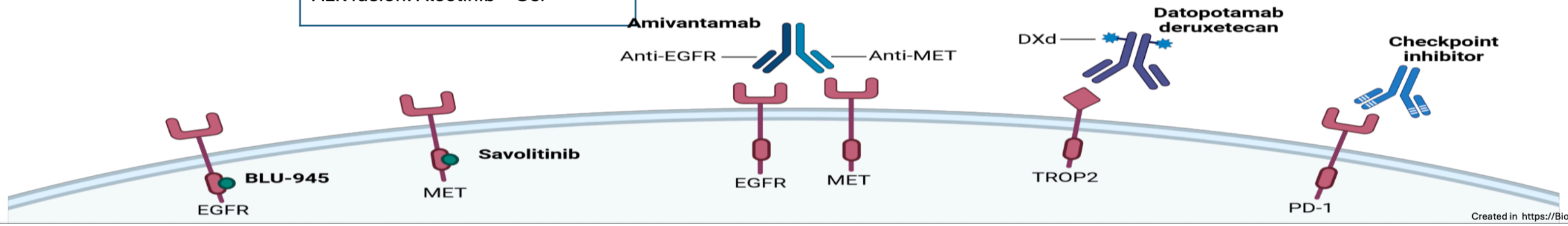
Post-Osimertinib Novel Treatment Strategies

Genotype-matched strategies

Mechanism-agnostic strategies

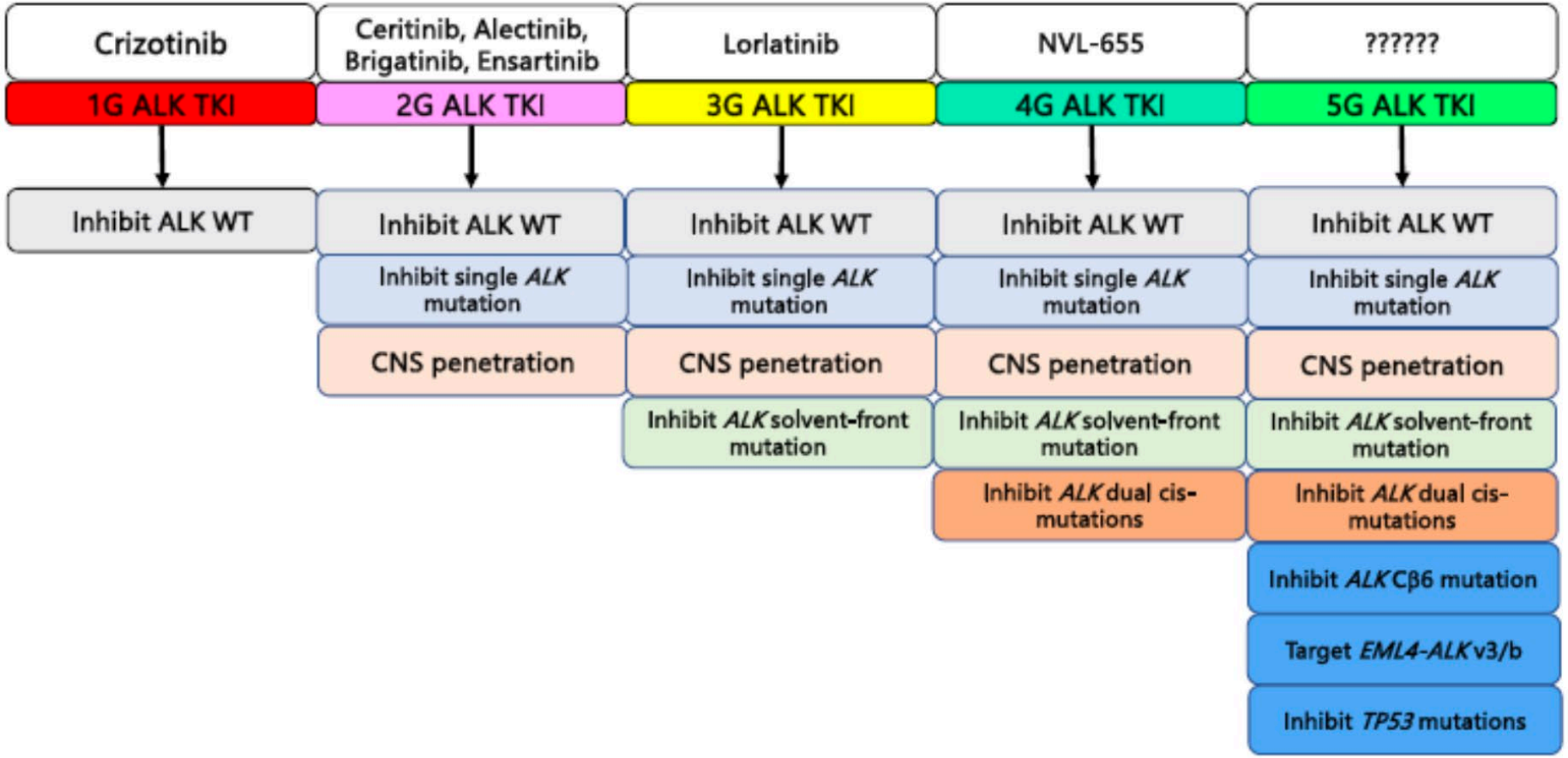
(non-genotype based)

On-target inhibition	Bypass pathway inhibition	On-target + bypass pathway inhibition	Targeting tumor-associated antigen	Targeting common escape routes
EGFR TKI/mAB	**Resistance-matched agents**	**Biespecific mAB/ADC targeting EGFR + bypass pathway**	**ADCs**	**mAB**
C797X mut: Gefitinib Gefitinib + Osi	cMET amp: Savolitinib + Osi Capmatinib + Osi Tepotinib + Osi cMET over-exp: Teliso V +/- Osi	Amivantamab (EGFR + cMET)	Datopotomab DXd (TROP2) Sacituzumab tirumotecan	Ivonescimab (PDL1 + VEGF) + Chemo
EGFR alt: Necitumumab + Osi 4G EGFR TKI	HER2 over-exp: TDM1 + Osi	Izalontamab brengitecan (EGFR + HER3)	Patritumab DXd (HER3)	Anti PD1/L1 + Antiangiogenic + Chemo
	RAS-MAPK act: Selumetinib + Osi			
	ALK fusion: Alectinib + Osi			

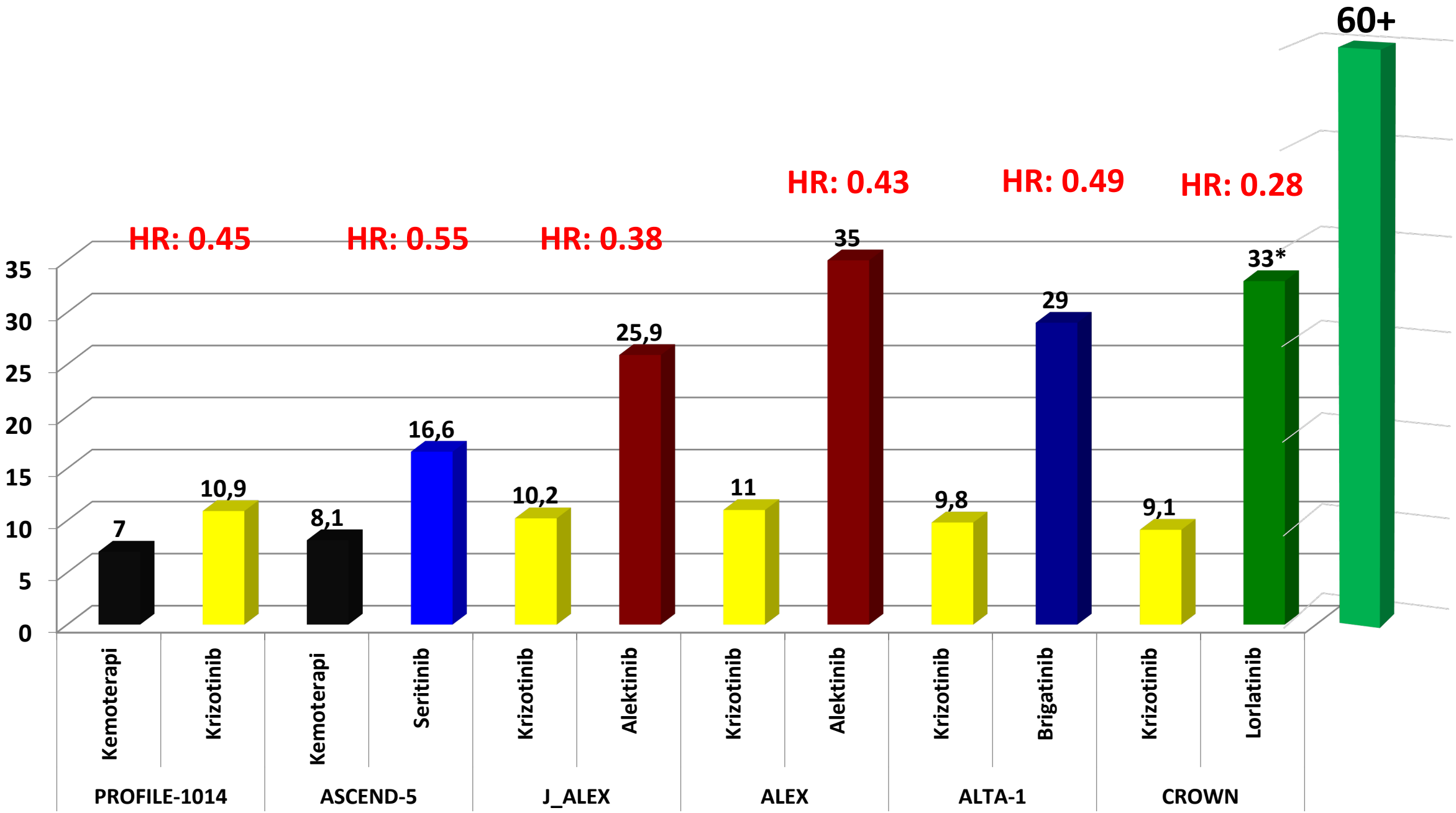


ALK+ mKHDAK

ALK-TKIs exemplify generational improvement in drug development



Lee A. & Ou, Lung Cancer: Targets and Therapies 2024


HR: 0.45
HR: 0.55
HR: 0.38
HR: 0.43
HR: 0.49
HR: 0.28
60+
35
30
25
20
15
10
5
0
7
10,9
8,1
16,6
10,2
25,9
11
35
9,8
29
9,1
33*
Kemoterapi
Krizotinib
Kemoterapi
Seritinib
Krizotinib
Alektinib
Krizotinib
Alektinib
Krizotinib
Brigatinib
Krizotinib
Lorlatinib
PROFILE-1014
ASCEND-5
J_ALEX
ALEX
ALTA-1
CROWN

2024 ASCO® ANNUAL MEETING

Lorlatinib vs Crizotinib in Treatment-Naive Patients With Advanced *ALK*+ Non-Small Cell Lung Cancer: 5-Year Progression-Free Survival and Safety From the CROWN Study

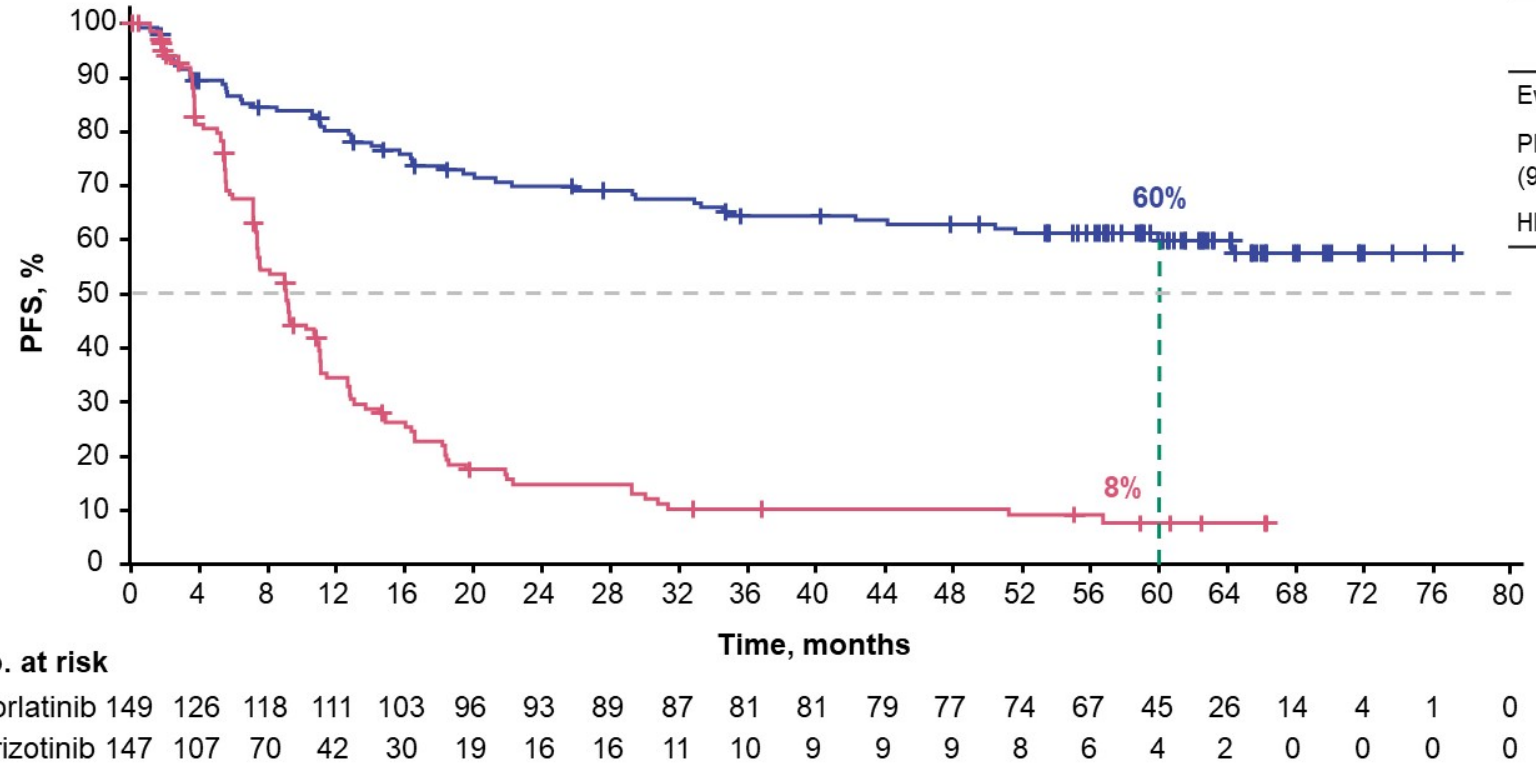
Benjamin J. Solomon,[1] Geoffrey Liu,[2] Enriqueta Felip,[3] Tony S. K. Mok,[4] Ross A. Soo,[5] Julien Mazieres,[6] Alice T. Shaw,[7] Filippo de Marinis,[8] Yasushi Goto,[9] Yi-Long Wu,[10] Dong-Wan Kim,[11] Jean-François Martini,[12] Rossella Messina,[13] Jolanda Paolini,[13] Anna Polli,[13] Despina Thomaidou,[14] Francesca Toffalorio,[13] Todd M. Bauer[15]

[1]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [2]Princess Margaret Cancer Centre, Toronto, ON, Canada; [3]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [4]State Key Laboratory of Translational Oncology, Chinese University of Hong Kong, Hong Kong; [5]National University Cancer Institute, Singapore; [6]Toulouse University Hospital, Toulouse, France; [7]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [8]European Institute of Oncology, IRCCS, Milan, Italy; [9]National Cancer Center Hospital, Tokyo, Japan; [10]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences, Guangdong, China; [11]Seoul National University College of Medicine and Seoul National University Hospital, Seoul, South Korea; [12]Pfizer, La Jolla, CA, USA; [13]Pfizer, Milan, Italy; [14]Pfizer, Athens, Greece; [15]Greco-Hainsworth Centers for Research/Tennessee Oncology, Nashville, TN, USA

Benjamin J. Solomon, MBBS, PhD
Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

PRESENTED BY: Benjamin J. Solomon (Ben.Solomon@petermac.org)

At 60.2 Months of Median Follow-Up, Median PFS by Investigator Was Still Not Reached With Lorlatinib



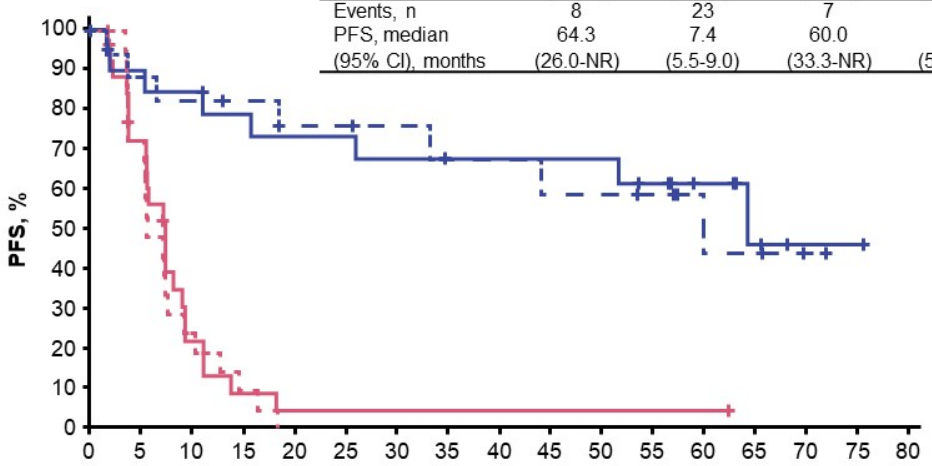
	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	55	115
PFS, median (95% CI), months	NR (64.3-NR)	9.1 (7.4-10.9)
HR (95% CI)	**0.19 (0.13-0.27)**	

HR, hazard ratio; ITT, intention to treat; NR, not reached; PFS, progression-free survival.

PRESENTED BY: Benjamin J. Solomon (Ben.Solomon@petermac.org)

Lorlatinib Treatment Benefited Patients With Poor Prognostic Biomarkers

	Variant 1		Variant 3a/b	
	Lorlatinib (n=20)	Crizotinib (n=26)	Lorlatinib (n=18)	Crizotinib (n=23)
Events, n	8	23	7	21
PFS, median (95% CI), months	64.3 (26.0-NR)	7.4 (5.5-9.0)	60.0 (33.3-NR)	5.6 (5.3-7.6)



***EML4::ALK* variant 1**

No. at risk

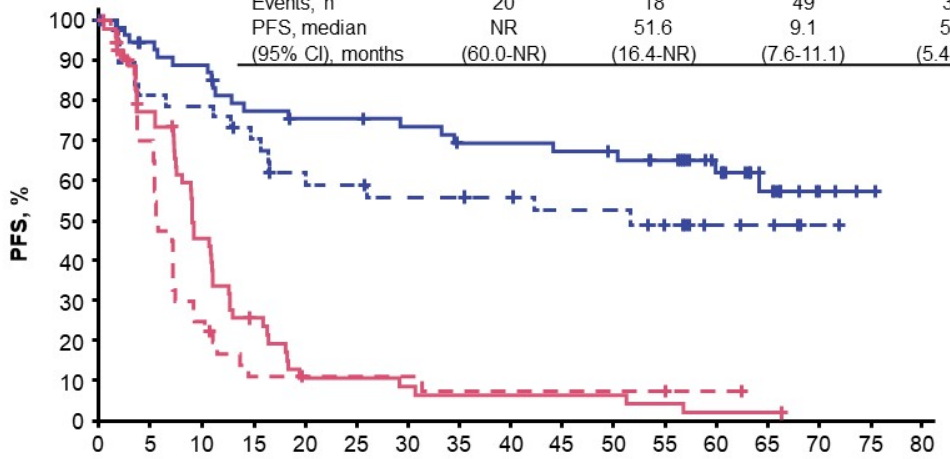
Lorlatinib	20	17	16	14	13	13	12	11	11	11	11	9	6	3	1	1	0
Crizotinib	26	18	5	2	1	1	1	1	1	1	1	1	1	0	0	0	0

***EML4::ALK* variant 3**

No. at risk

Lorlatinib	18	15	14	13	11	11	9	8	8	7	7	6	3	3	1	0	-
Crizotinib	23	15	5	2	0	0	0	0	0	0	0	0	0	0	0	0	-

	Lorlatinib		Crizotinib	
	TP53 mut (-) (n=56)	*TP53* mut (+) (n=41)	*TP53* mut (-) (n=58)	*TP53* mut (+) (n=42)
Events, n	20	18	49	36
PFS, median (95% CI), months	NR (60.0-NR)	51.6 (16.4-NR)	9.1 (7.6-11.1)	5.7 (5.4-7.2)



Lorlatinib

No. at risk

TP53 mut (-)	56	50	47	40	38	38	36	33	33	32	31	28	20	12	4	1	0
TP53 mut (+)	41	30	29	25	21	20	18	18	17	15	15	12	6	4	1	0	0

Crizotinib

No. at risk

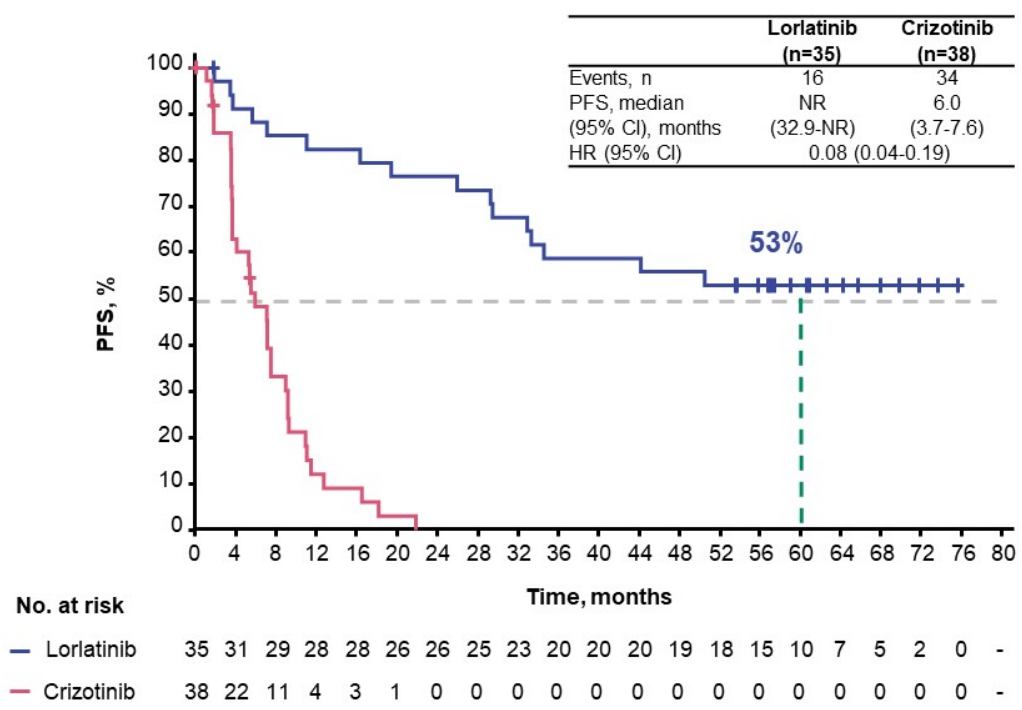
TP53 mut (-)	58	40	23	12	5	5	4	3	3	3	3	2	1	1	0	-	-
TP53 mut (+)	42	28	10	4	3	3	3	2	2	2	2	2	1	0	0	-	-

mut, mutation; NR, not reached; PFS, progression-free surviva

PRESENTED BY: Benjamin J. Solomon (Ben.Solomon@petermac.org)

Lorlatinib Showed Superior PFS Benefit Irrespective of Presence or Absence of Baseline Brain Metastases

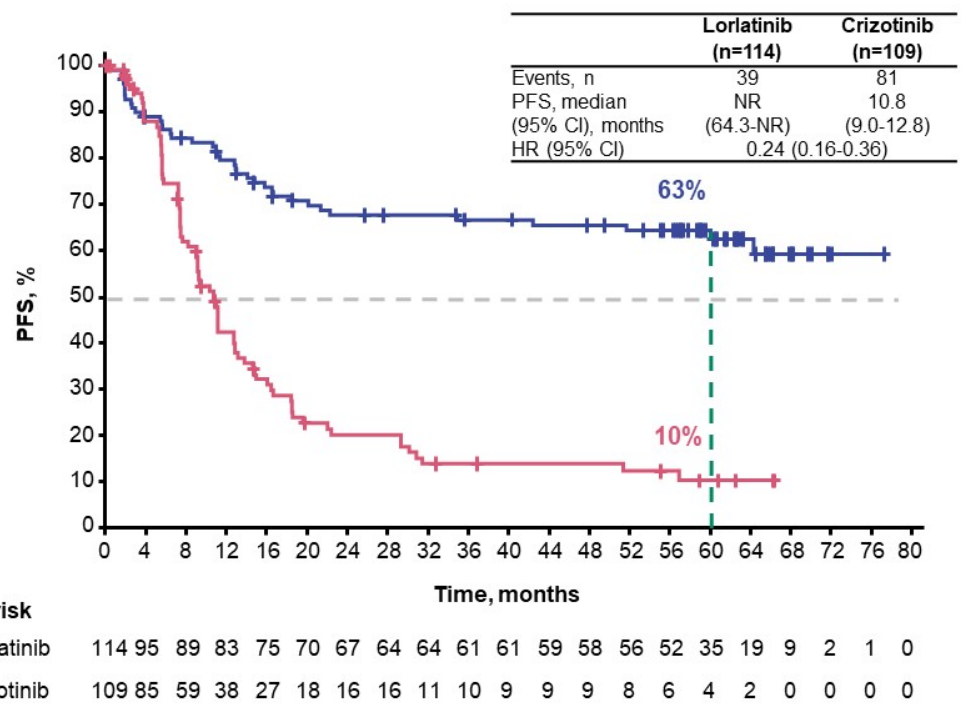
With Baseline Brain Metastases



	Lorlatinib (n=35)	Crizotinib (n=38)
Events, n	16	34
PFS, median (95% CI), months	NR (32.9-NR)	6.0 (3.7-7.6)
HR (95% CI)	0.08 (0.04-0.19)	

No. at risk																					
Lorlatinib	35	31	29	28	28	26	26	25	23	20	20	20	19	18	15	10	7	5	2	0	-
Crizotinib	38	22	11	4	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-

Without Baseline Brain Metastases



	Lorlatinib (n=114)	Crizotinib (n=109)
Events, n	39	81
PFS, median (95% CI), months	NR (64.3-NR)	10.8 (9.0-12.8)
HR (95% CI)	0.24 (0.16-0.36)	

No. at risk																					
Lorlatinib	114	95	89	83	75	70	67	64	64	61	61	59	58	56	52	35	19	9	2	1	0
Crizotinib	109	85	59	38	27	18	16	16	11	10	9	9	9	8	6	4	2	0	0	0	0

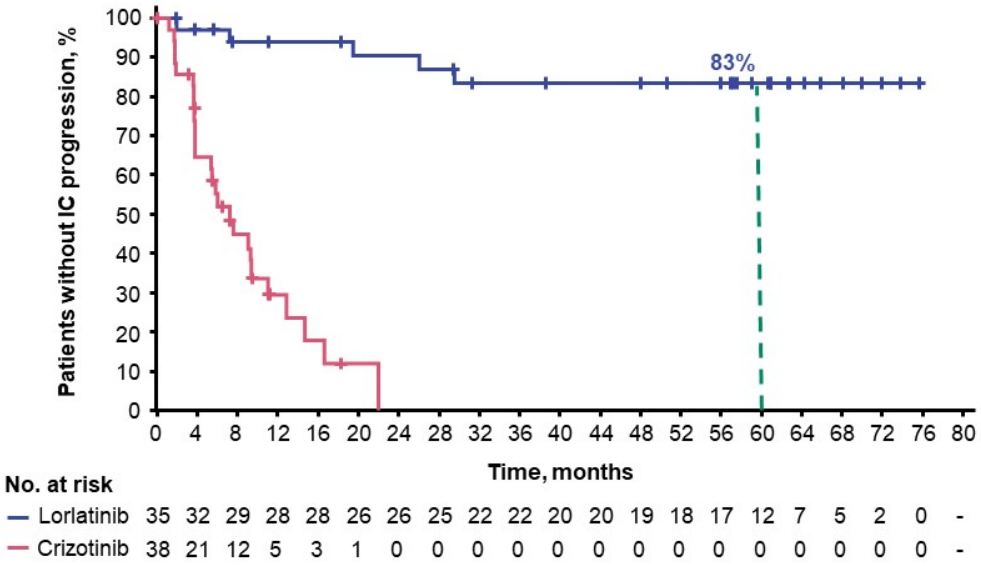
HR, hazard ratio; NR, not reached; PFS, progression-free survival.

PRESENTED BY: Benjamin J. Solomon (Ben.Solomon@petermac.org)

Time to IC Progression Was Longer With Lorlatinib in Presence or Absence of Baseline Brain Metastases

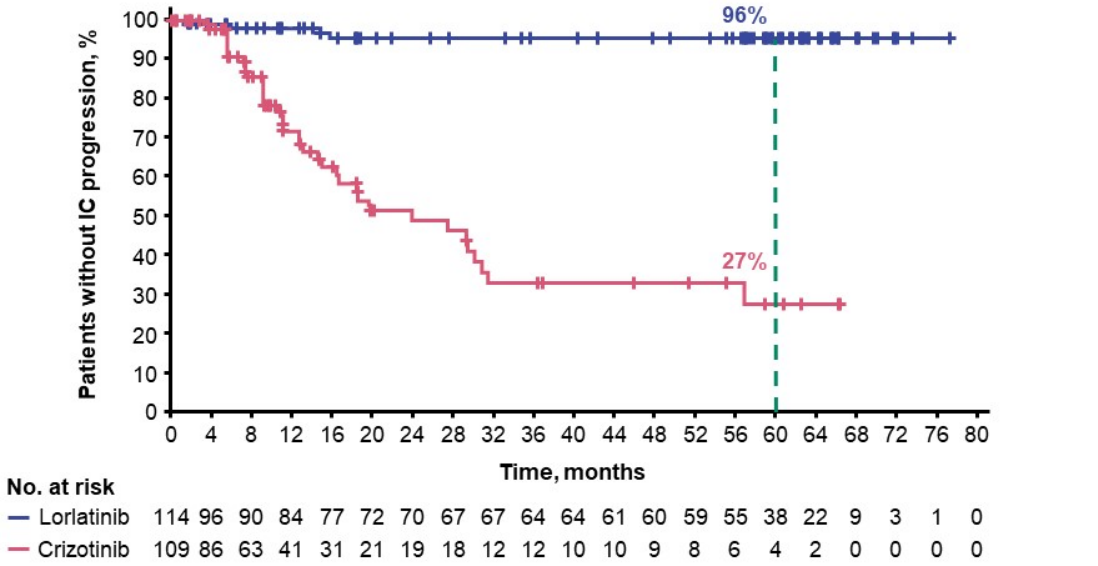
With Baseline Brain Metastases

	Lorlatinib (n=35)	Crizotinib (n=38)
Events, n	5	26
Time to IC progression, median (95% CI), months	NR (NR-NR)	7.2 (3.7-11.0)
HR (95% CI)	0.03 (0.01-0.13)	



Without Baseline Brain Metastases

	Lorlatinib (n=114)	Crizotinib (n=109)
Events, n	4	39
Time to IC progression, median (95% CI), months	NR (NR-NR)	23.9 (16.4-30.8)
HR (95% CI)	0.05 (0.02-0.13)	



HR, hazard ratio; IC, intracranial; NR, not reached.

PRESENTED BY: Benjamin J. Solomon (Ben.Solomon@petermac.org)

Emerging New *ALK* Mutations Were Not Detected in ctDNA Collected at the End of Lorlatinib Treatment

n (%)	Lorlatinib (n=31)	Crizotinib (n=89)
Resistance mechanisms		
New single ALK mutation	0	8 (9)
ALK compound mutation	0	2 (2)
Bypass mechanism	9 (29)	10 (11)
MAPK pathway aberration	3 (10)	1 (1)
PI3K/MTOR/PTEN pathway aberration	2 (6)	0
RTK pathway aberration	4 (13)	5 (6)
Cell cycle pathway aberration	2 (6)	5 (6)
Other gene aberration	11 (35)	19 (21)
Unknown	13 (42)	56 (63)

ctDNA from plasma collected at screening was analyzed with a validated, commercially available, 74-gene ctDNA next-generation sequencing assay (Guardant360 panel version 2.11; bioinformatics pipeline version 3.5.3; Guardant Health, Inc., Redwood City, CA).
ctDNA, circulating tumor DNA.

PRESENTED BY: Benjamin J. Solomon (Ben.Solomon@petermac.org)

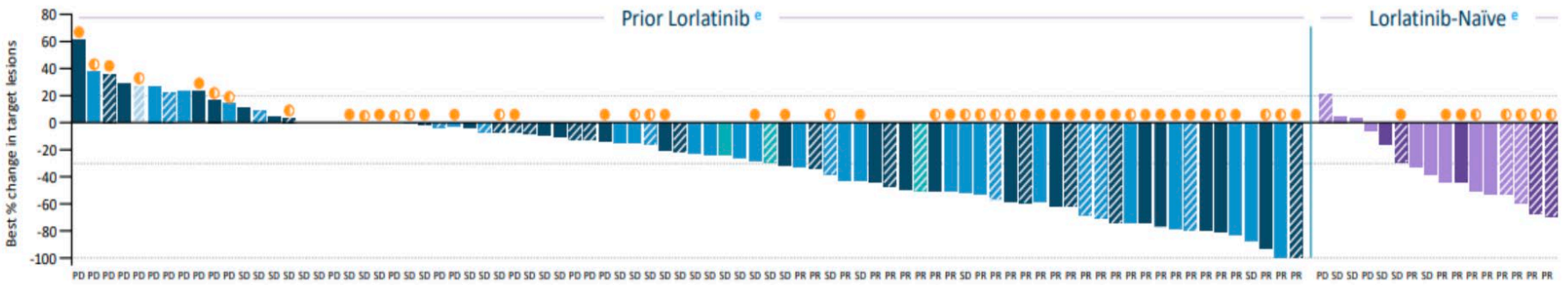
NVL-655 achieves better outcomes in pts with any ALK resistance mutation

ALK-selective, brain penetrant, TRK-sparing TKI

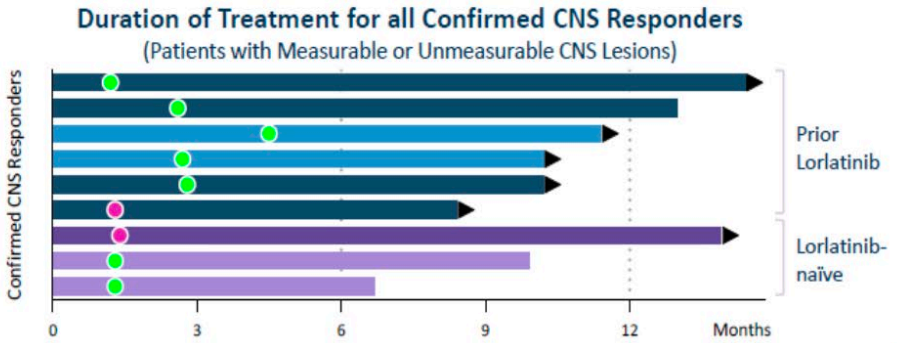
ALKove-01

Treatment History	All Treated (N = 133)	RP2D (N=52)
Prior treatments		
1 ALK TKI	18 (14%)	6 (12%)
2 ALK TKIs	54 (41%)	20 (39%)
≥3 ALK TKIs	61 (46%)	26 (50%)
Chemotherapy	74 (56%)	30 (58%)
ALK TKIs received [d]		
1G (crizotinib)	57 (43%)	24 (46%)
2G	127 (96%)	49 (94%)
alectinib	120 (90%)	46 (89%)
brigatinib	29 (22%)	12 (23%)
ceritinib	17 (13%)	8 (15%)
3G (lorlatinib)	**111 (84%)**	**44 (85%)**
Any 2G or lorlatinib	133 (100%)	52 (100%)
≥2 ALK TKIs, including 2G and lorlatinib	105 (79%)	41 (79%)
≥3 ALK TKIs, including 2G and lorlatinib	**58 (44%)**	**24 (46%)**

RECIST 1.1 ORR, % (n/N) *All patients ± chemotherapy*	NSCLC Response-Evaluable (Any Prior ALK TKI, range 1 – 5)			Prior Lorlatinib (≥2 ALK TKIs)			Lorlatinib-naive (≥1 2G ± 1G)	
	All	Any ALK mutation [a]	G1202R [b]	All	Any ALK mutation	Compound ALK mutation [c]	All	Any ALK mutation
All Doses	**38%** (39/103)	**52%** (30/58)	**69%** (22/32) [d]	**35%** (30/85)	**47%** (23/49)	**54%** (15/28)	**53%** (9/17)	**88%** (7/8)
RP2D	**38%** (15/39)	**55%** (12/22)	**71%** (10/14)	**35%** (11/31)	**50%** (8/16)	**64%** (7/11)	**57%** (4/7)	**80%** (4/5)



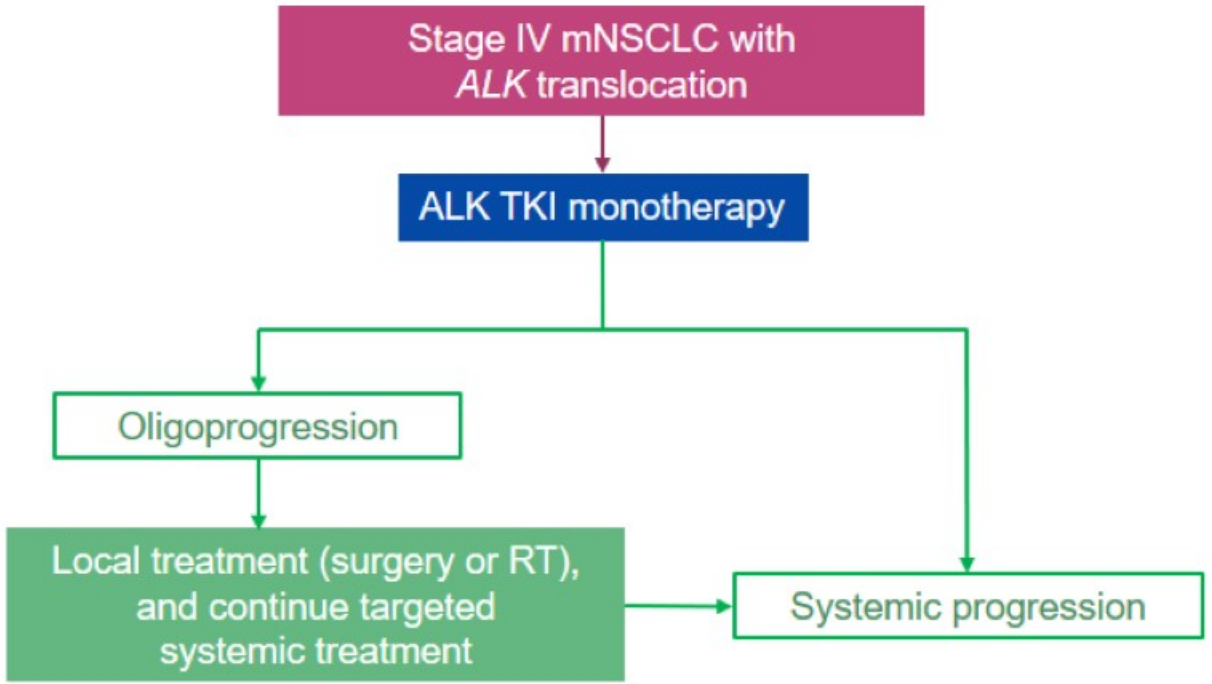
CNS ORR, % (n/N)	
Prior Lorlatinib	Lorlatinib-naive
15% (2/13) **31%** (4/13) including 2 CNS uPR	**50%** (1/2)



Drillon A, Presented at ESMO 2024

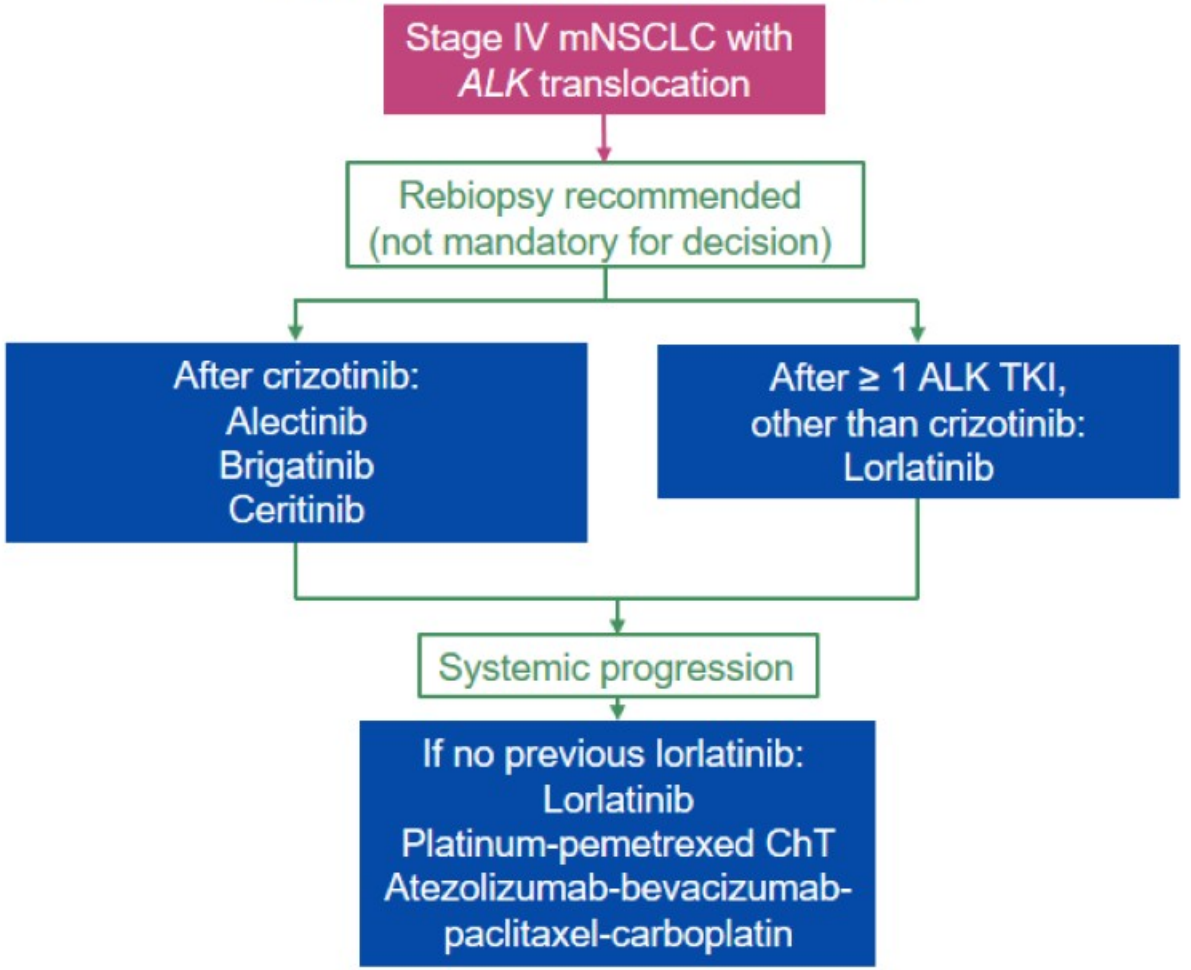
ESMO Living Guidelines
Advanced/Metastatic NSCLC With *ALK* Translocation

Before Systemic Progression



Preferred options: Alectinib, brigatinib, or lorlatinib
Other options: Crizotinib or ceritinib

After Systemic Progression



ALK, anaplastic lymphoma kinase; ChT, chemotherapy; ESMO, European Society for Medical Oncology; mNSCLC, metastatic non-small cell lung cancer; RT, radiation therapy; TKI, tyrosine kinase inhibitor.

Hendriks LE, et al. Ann Oncol. 2023;34:339-357; ESMO Living Guidelines v1.2. 2025. Accessed August 20, 2025. https://www.esmo.org/living-guidelines/esmo-oncogene-addicted-non-small-cell-lung-cancer-living-guideline