New treatment options for EGFR-mutant NSCLC

Prof, David Planchard, MD, PhD

Head of Thoracic Unit

Department of Cancer Medicine

Gustave Roussy – Villejuif, France

DISCLOSURE SLIDE

Consulting, advisory role or lectures: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, Roche, Janssen, Abbvie, Seagen, Gilead

Honoraria: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, Roche, Janssen, Abbvie, Seagen, Gilead

Clinical trials research as principal or co-investigator (Institutional financial interests): AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, Pfizer, Roche, Medimmun, Sanofi-Aventis, Taiho Pharma, Daiichi Sankyo, Janssen, Abbvie

Travel, Accommodations, Expenses: AstraZeneca, Roche, Novartis, Pfizer

EGFR mutations structure-based classification: different different EGFR-TKI sensitivity even within the same subgroup

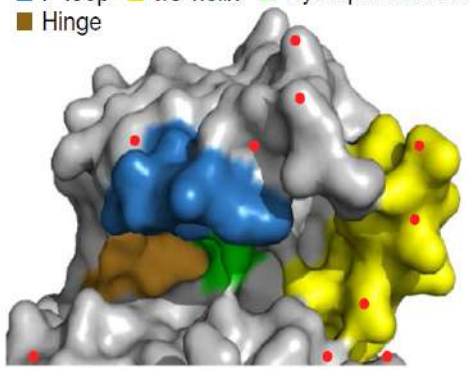
Classical-like: Distant from ATP binding pocket

Exon 20 loop insertion: Near (NL) versus far loop (FL)

1

Classical-like

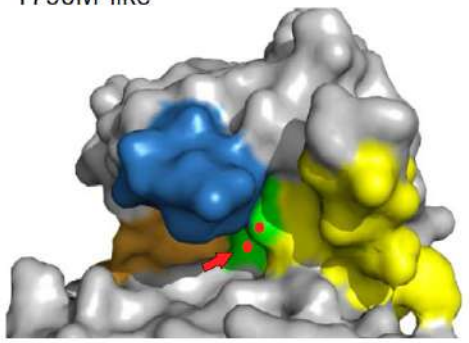
P-loop αC-helix Hydrophobic core Hinge



Description	Representative mutations	Drug selectivity
Distal to drug-binding pocket Modest to no impact on drug binding	L858R Ex19dels S720P L861Q/R S811F K754E T725M L833F/V A763insFQEA A763insLQEA	Selective Intermediate Resistant 3rd gen 2nd gen 1st gen Ex20ins-active

2

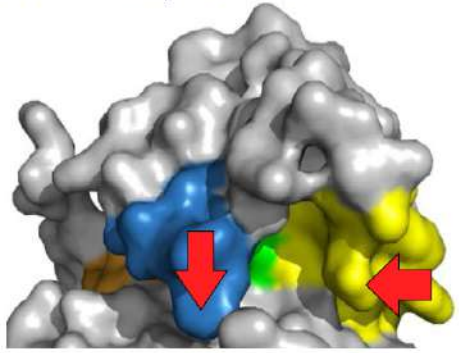
T790M-like



Description	Representative mutations	Drug selectivity
At least one mutation in hydrophobic core Increased affinity for ATP compared to classical-like mutations Two subgroups: T790M-like-3S T790M-like-3R	T790M-3S Classical/T790M G719X/T790M L747_K745del insATSPE S768I/T790M T790M-3R Ex19del/T790M/L792H L858R/T790M/L718X Classical/T790M/ C797S	T790M-3S 3rd gen PKCi ALKi 2nd gen 1st gen T790M-3R PKCi ALKi 3rd gen 2nd gen 1st gen

3

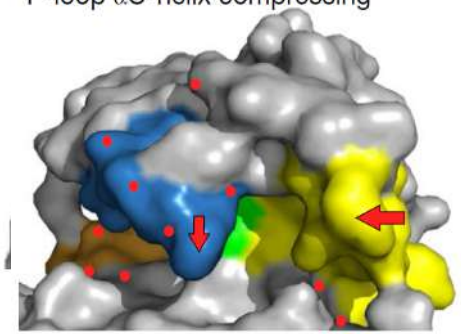
Exon 20 loop insertion



C-terminal loop of αC-helix Indirect and substantial impact on drug binding (P-loop and αC-helix) Two subgroups: Ex20ins-near loop Ex20ins- far loop	Ex20ins-NL S768dupSVD A767dupASV D770insNPG D770del insGY Ex20ins-FL H773insNPH H773dupH V774insAV V774insPR	Ex20ins-NL Ex20ins-active 2nd gen 1st gen 3rd gen Ex20ins-FL Ex20ins-active 2nd gen 1st gen 3rd gen

4

P-loop αC-helix compressing



Proximal to drug-binding pocket Direct or indirect impact on drug binding via moderate displacement of P-loop and/or αC-helix	Primary G719X S768I L747P/S V769L E709_T710 delinsD Acquired C797S L792H G724S L718X T854I	2nd gen 1st gen Ex20ins-active 3rd gen

T790M-like located in the hydrophobic core: third-gen TKI sensitive (3S) versus resistant (3R)

PACC: Located in the interior surface of the ATP binding pocket

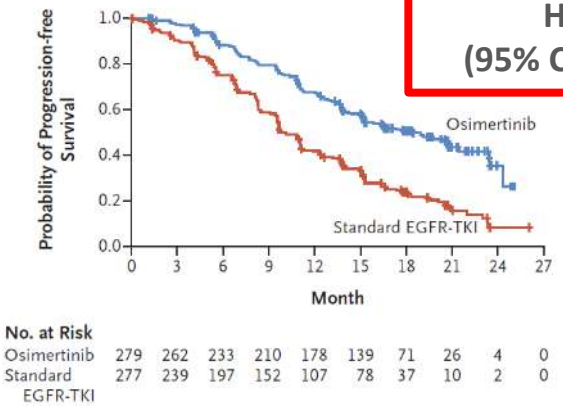
Robichaux JP et al Nature 2021

EGFR mutation, upfront treatment option

FLAURA Trial Osimertinib *vs*. Gefitinib/Erlotinib

PFS

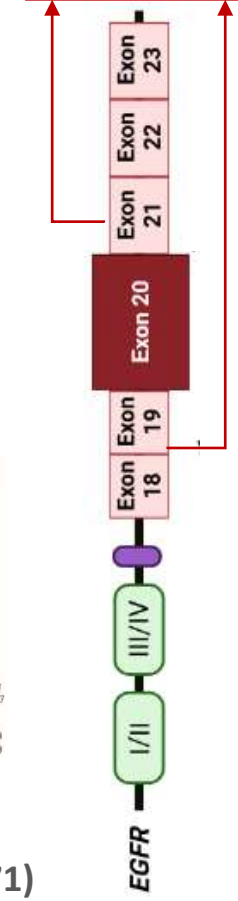
18.9 vs 10.2 mo
HR 0.46
(95% CI 0.37-0.57)



No. at Risk

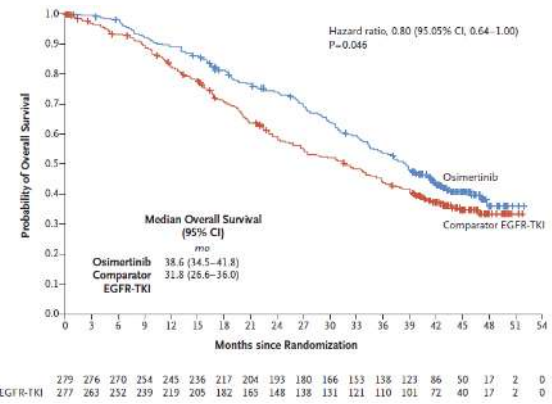
Osimertinib	279	262	233	210	178	139	71	26	4	0
Standard EGFR-TKI	277	239	197	152	107	78	37	10	2	0

80% Common *EGFR* mut
15% Western
50% Asian



OS

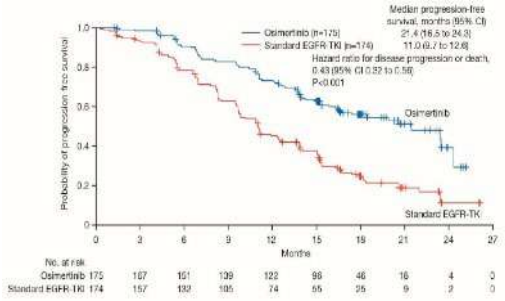
38.6 vs 31.8 mo
HR 0.80
(95% CI 0.64-1.00)



No. at Risk

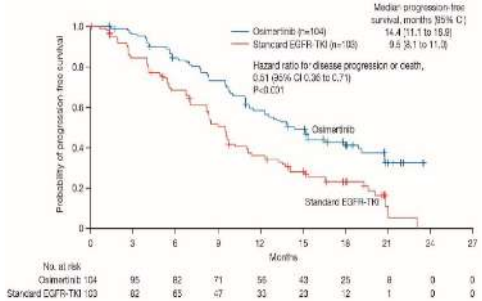
Osimertinib	279	276	270	254	245	236	217	204	193	180	166	153	138	123	86	50	17	2	0
Comparator EGFR-TKI	277	263	252	239	219	205	182	165	148	138	131	121	110	101	72	40	17	2	0

Exon 19



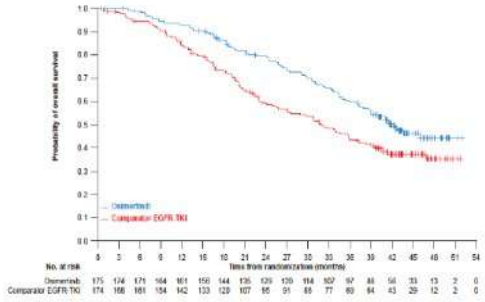
21.4 vs 11.0 mo
HR 0.43 (95% CI 0.32-0.56)

Exon 21



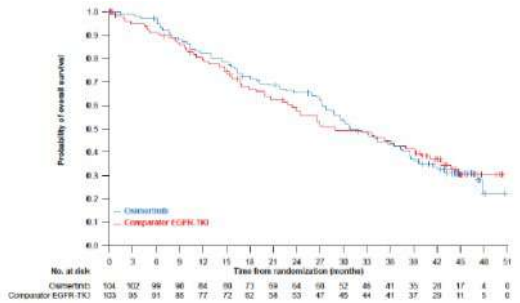
14.4 vs 9.5 mo
HR 0.51 (95% CI 0.36-0.71)

Exon 19



HR 0.68 (95% CI 0.51-0.90)

Exon 21

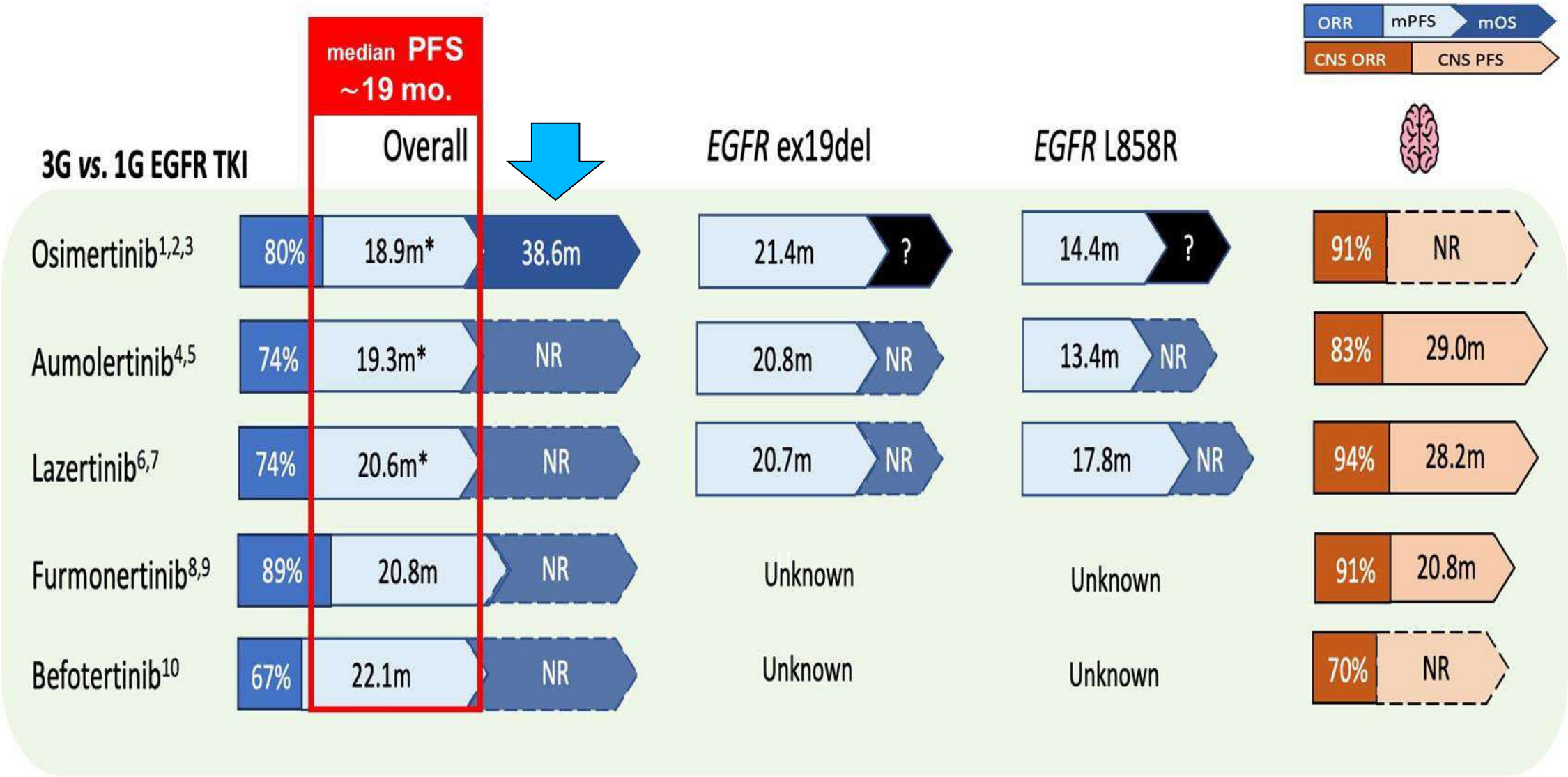


HR 1.00 (95% CI 0.71-1.40)

J.Remon slide

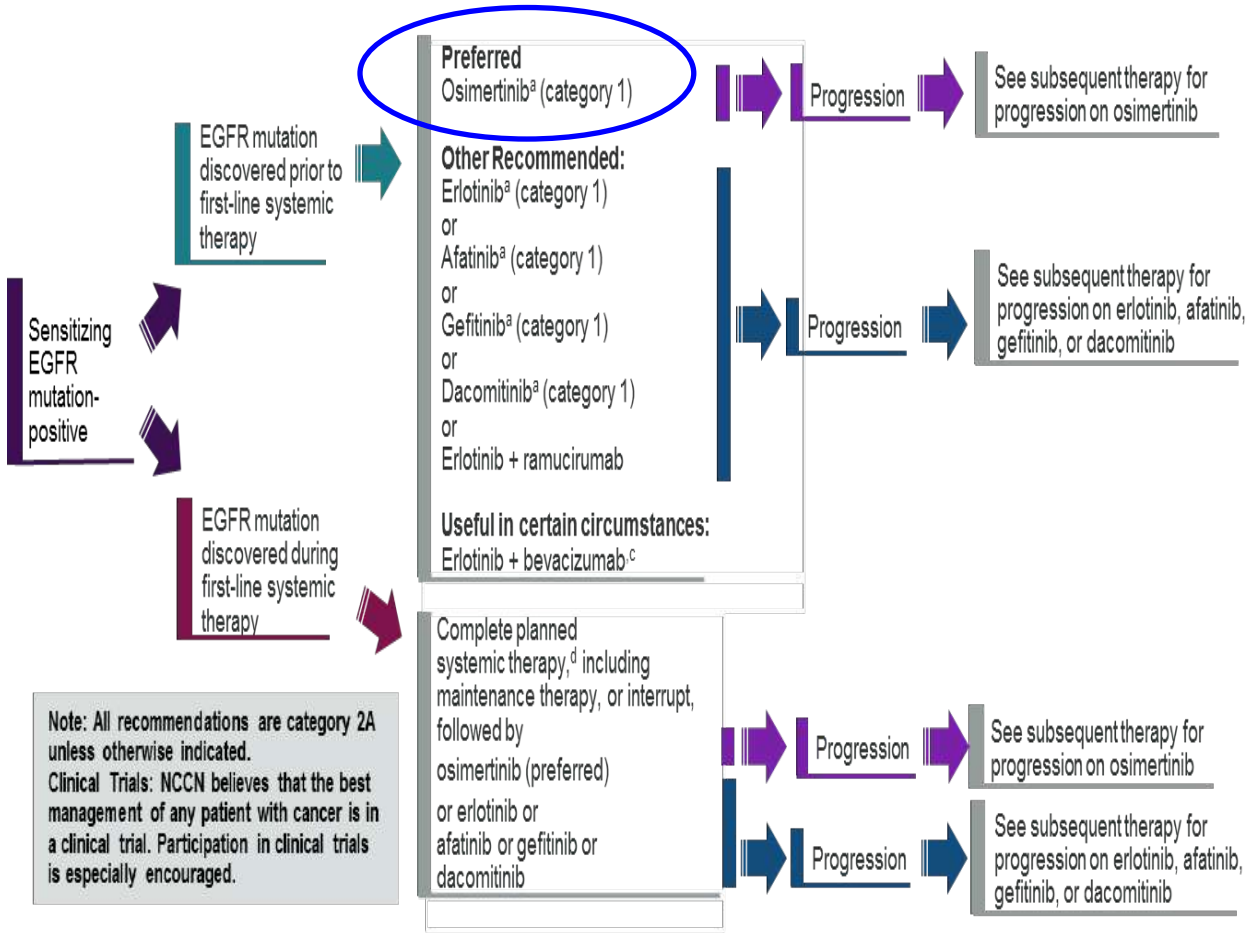
Soria NEJM 2018 * Ramalingam – NEJM 2019 * Malapelle – WCLC 2021 * Tan – JCO 2022

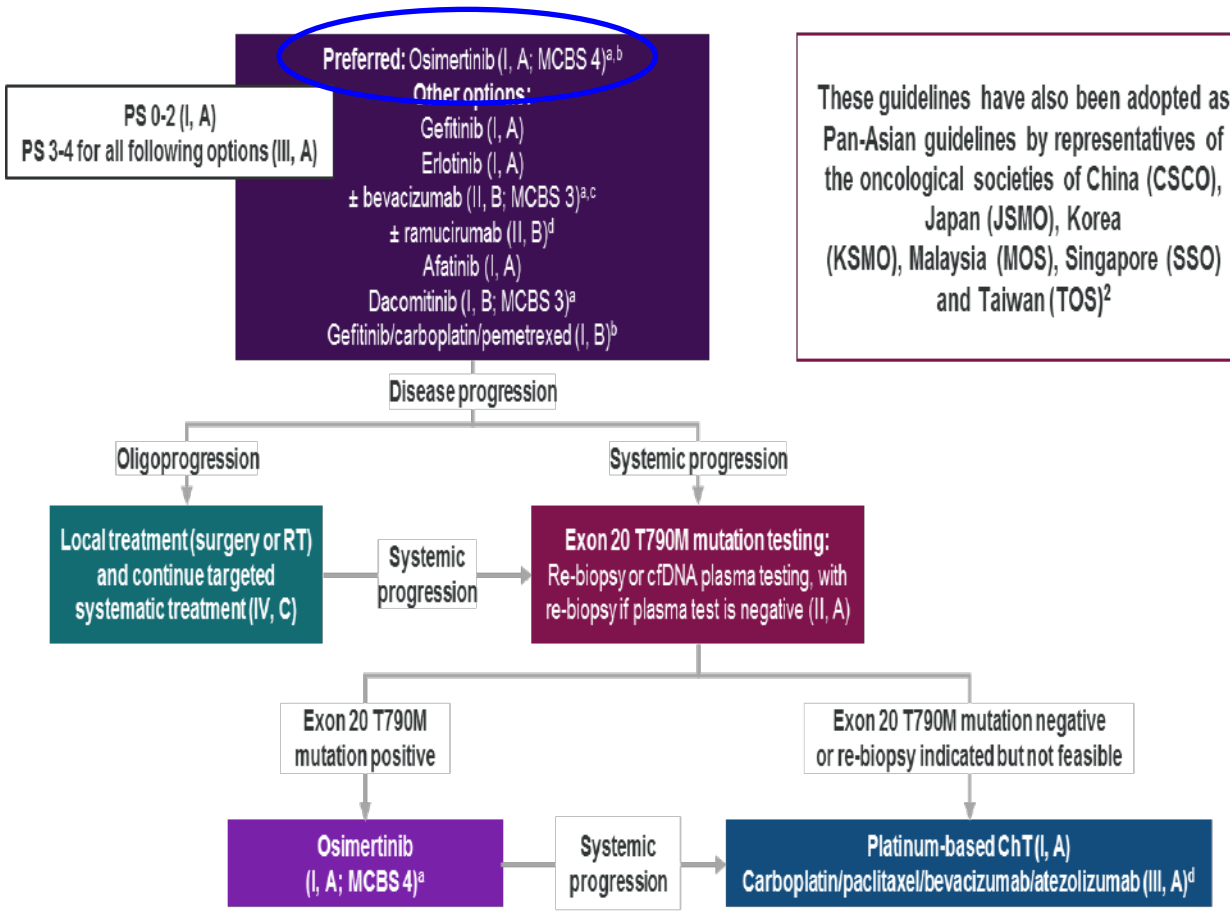
EGFR-mutant before 2024



Saw, Le, Remon – ASCO Educational Book 2024 (cross trial comparisons should undertaken with caution)

NCCN and ESMO Guidelines: Treatment recommendations for first-line therapy of metastatic EGFR mutation-positive NSCLC





These guidelines have also been adopted as Pan-Asian guidelines by representatives of the oncological societies of China (CSCO), Japan (JSMO), Korea (KSMO), Malaysia (MOS), Singapore (SSO) and Taiwan (TOS)[2]

EGFR = epidermal growth factor receptor; EGFRm = epidermal growth factor receptor mutation-positive; NCCN = National Comprehensive Cancer Network; NSCLC = non-small cell lung cancer.

[a]For performance status 0-4; [b]criteria for treatment with bevacizumab: non-squamous NSCLC, and no recent history of hemoptysis; [c]An FDA-approved biosimilar is an appropriate substitute for bevacizumab. [d]If systemic therapy regimen contains an immune checkpoint inhibitor, physicians should be aware of the long half-life of such drugs and data reporting adverse events when combining checkpoint inhibitors with osimertinib.

Adapted from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.3.2020. © 2020 National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available.

[a]ESMO-MCBS v1.1 score for new therapy/indication approved by the EMA since 1 January 2016. The score has been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee; [b]Preferred option; [c]MCBS score for the combination of bevacizumab with gefitinib or erlotinib; [d]Not EMA-approved.

1. Planchard D, et al. *Ann Oncol.* 2018;29(suppl 4):iv192–iv237 and https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer

WJOG9717L

Phase 2 study of osimertinib plus bevacizumab versus osimertinib monotherapy for untreated NSq EGFRm+ NSCLC

Background[1]

- Previous studies have demonstrated improved PFS when combining anti-VEGF therapy with 1G EGFR TKI therapy[2–4]
- This study seeks to identify if there is a PFS benefit when combining anti-VEGF therapy with osimertinib

Study design[1]

Key eligibility criteria

- Non-squamous EGFR+ NSCLC
- Clinical stage IIIB, IIIC, IV, or recurrence after surgical resection
- Previously untreated
- ECOG PS 0–1
- Age 20+ years
- No symptomatic brain metastases

Randomised 1:1

N=122

Osimertinib (80 mg, daily) + Bevacizumab (15 mg/kg, Q3W)

Osimertinib (80 mg, daily)

Primary endpoint

- PFS by BICR

Secondary endpoints

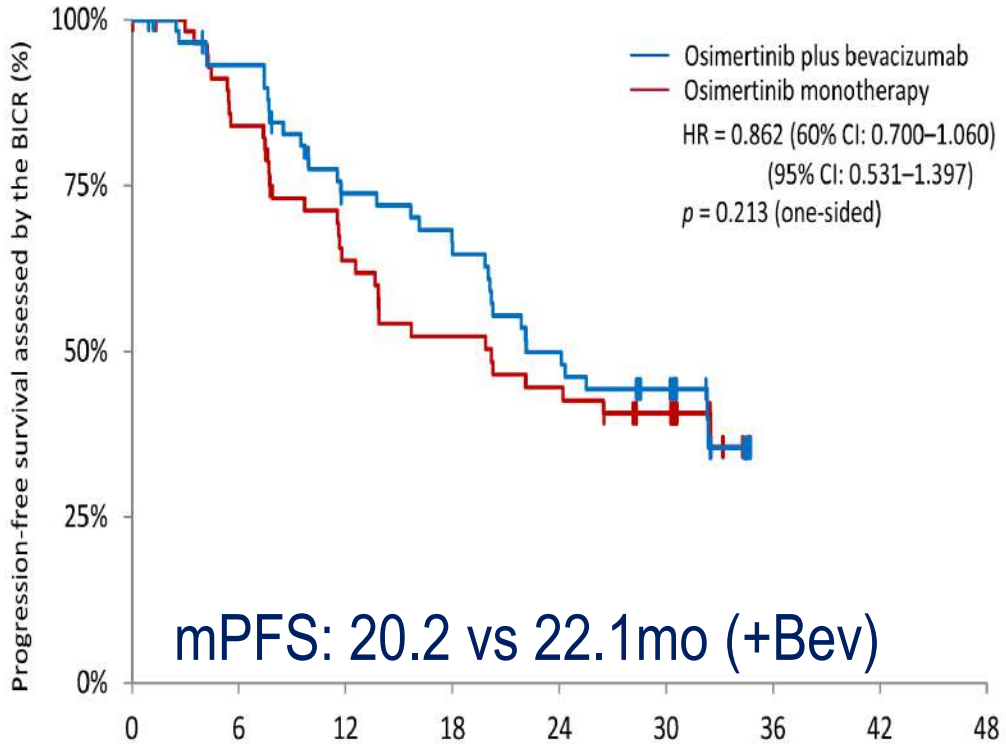
- PFS by investigators
- ORR
- OS
- AEs

1G, first generation; AE, adverse event; BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR+, EGFR-mutation-positive; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; VEGF, vascular endothelial growth factor.

1. Kenmotsu H, et al. Presented at ESMO 2021:LBA44; 2. Seto T, et al. Lancet Oncol. 2014;15:1236–44; Saito H, et al. Lancet Oncol. 2019;20:625–35; 4. Nakagawa K, et al. Lancet Oncol. 2019;20:1655–69.

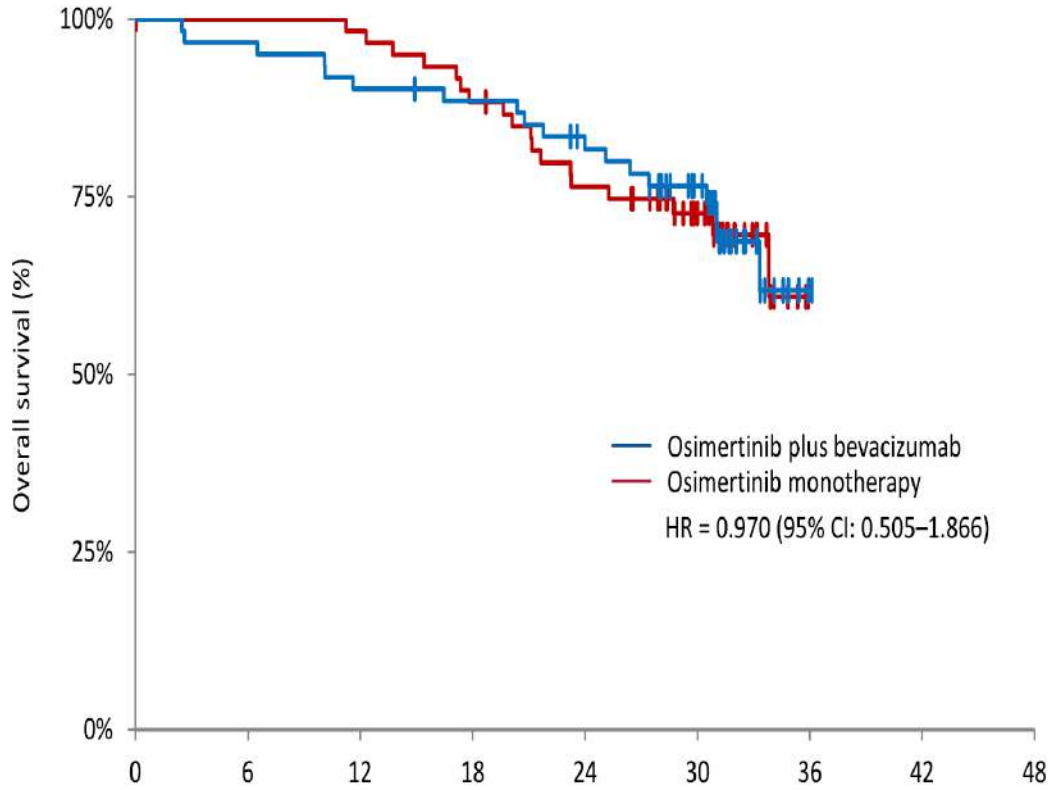
Hirotsugu Kenmotsu et al, JTO 2023

Progression-free survival



Number at risk (number censored)							
Osimertinib monotherapy	61 (0)	47 (5)	34 (7)	27 (8)	23 (8)	17 (12)	0 (28)
Osimertinib plus bevacizumab	61 (0)	54 (3)	40 (6)	36 (6)	27 (6)	20 (10)	0 (28)

Overall survival



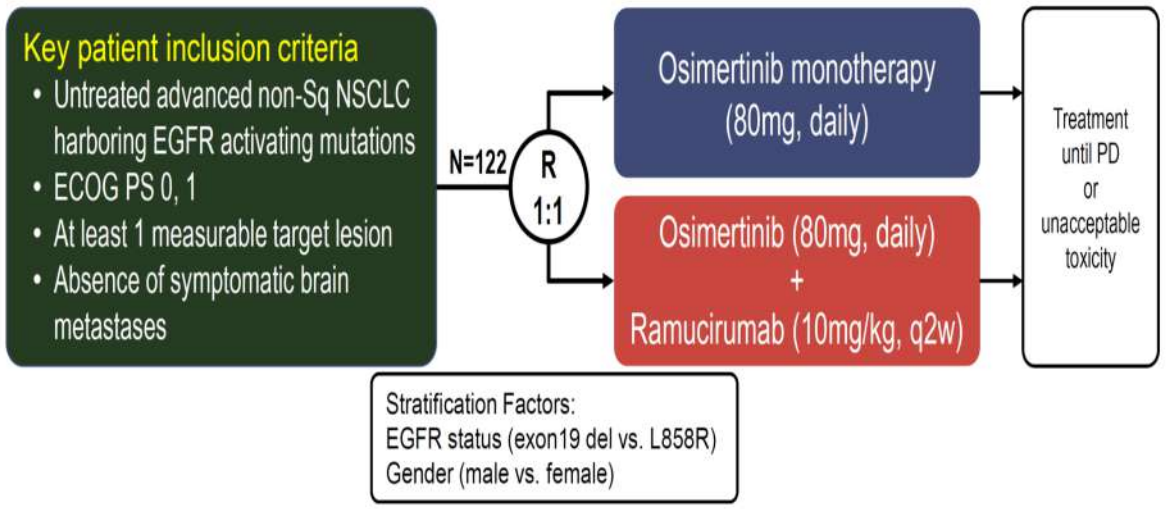
Number at risk (number censored)								
Osimertinib monotherapy	61 (0)	61 (1)	59 (1)	53 (1)	45 (2)	27 (18)	0 (43)	0 (43)
Osimertinib plus bevacizumab	61 (0)	59 (0)	55 (0)	53 (1)	47 (3)	34 (13)	1 (42)	0 (43)

ORR: 86 vs 82% (+Bev)

Hirotsugu Kenmotsu et al, JTO 2023

OSIRAM-1 (TORG1833)

OSIRAM-1 (TORG1833) : Study Design



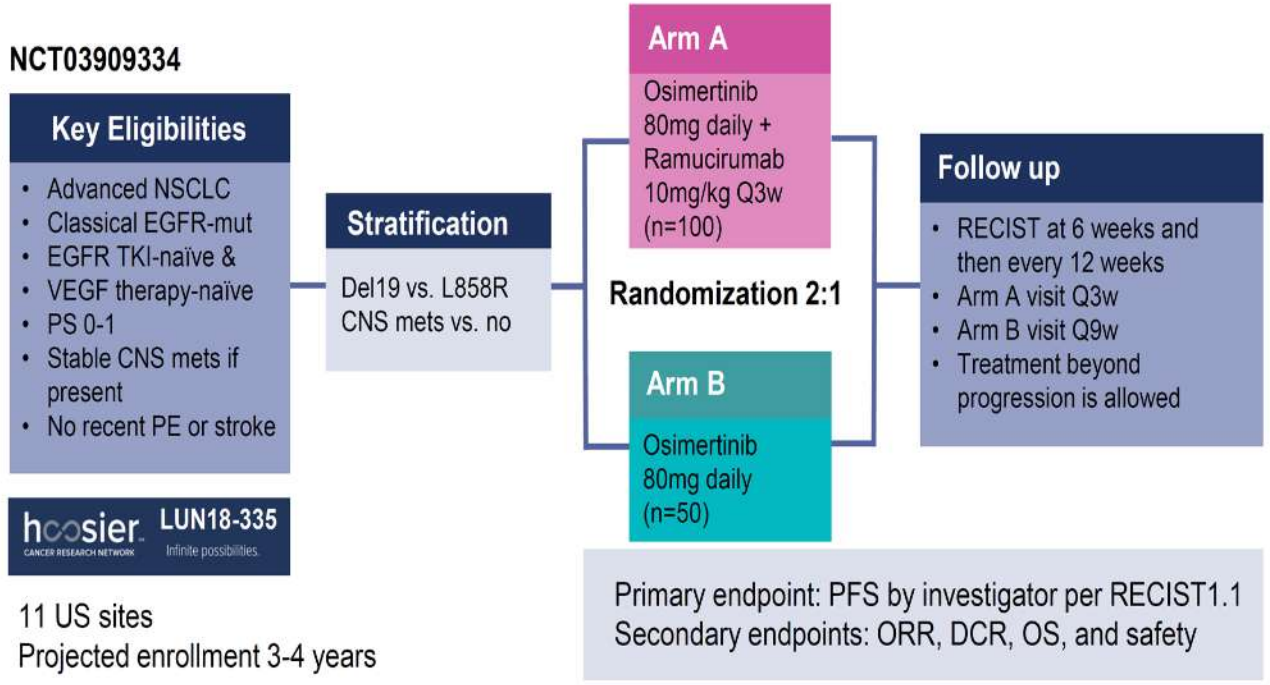
Primary Endpoint: PFS assessed by the BICRs

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

Y Nakahara et al, ESMO 2023

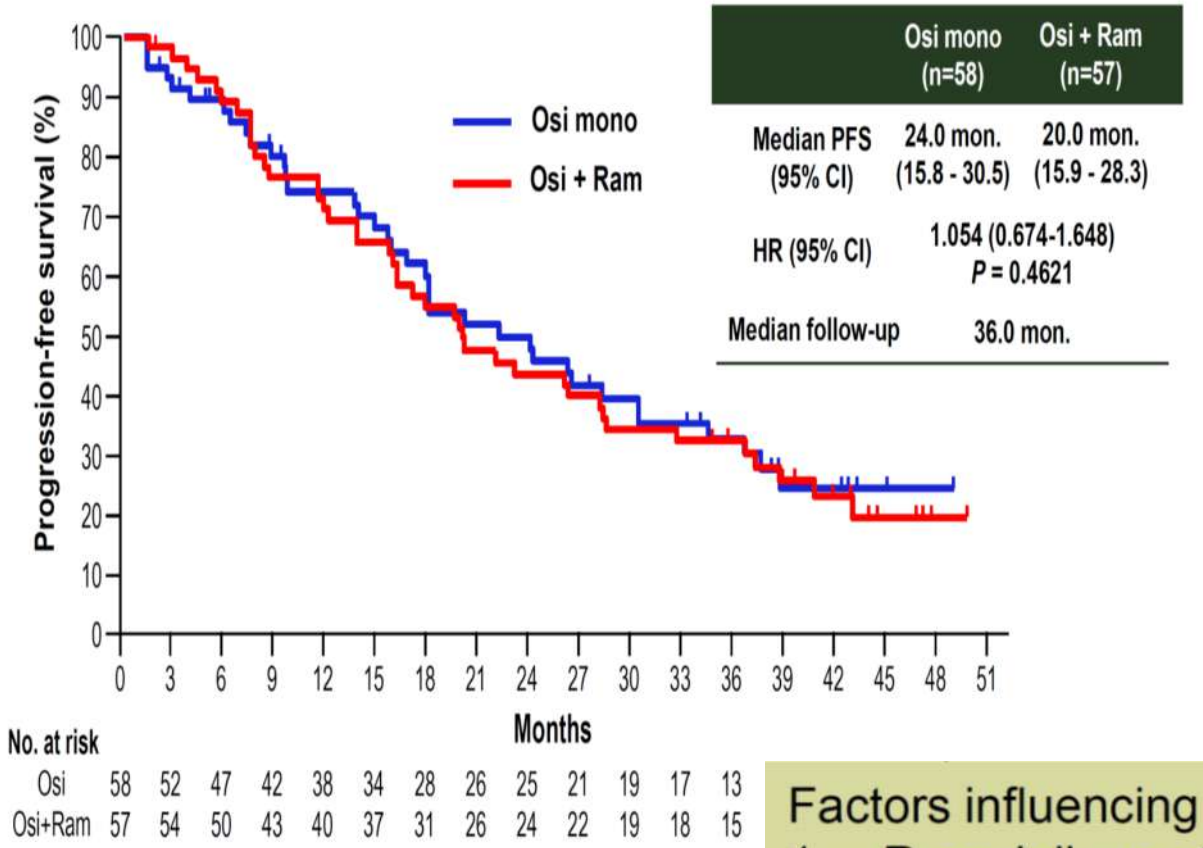
RAMOSE (LUN18-335)

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

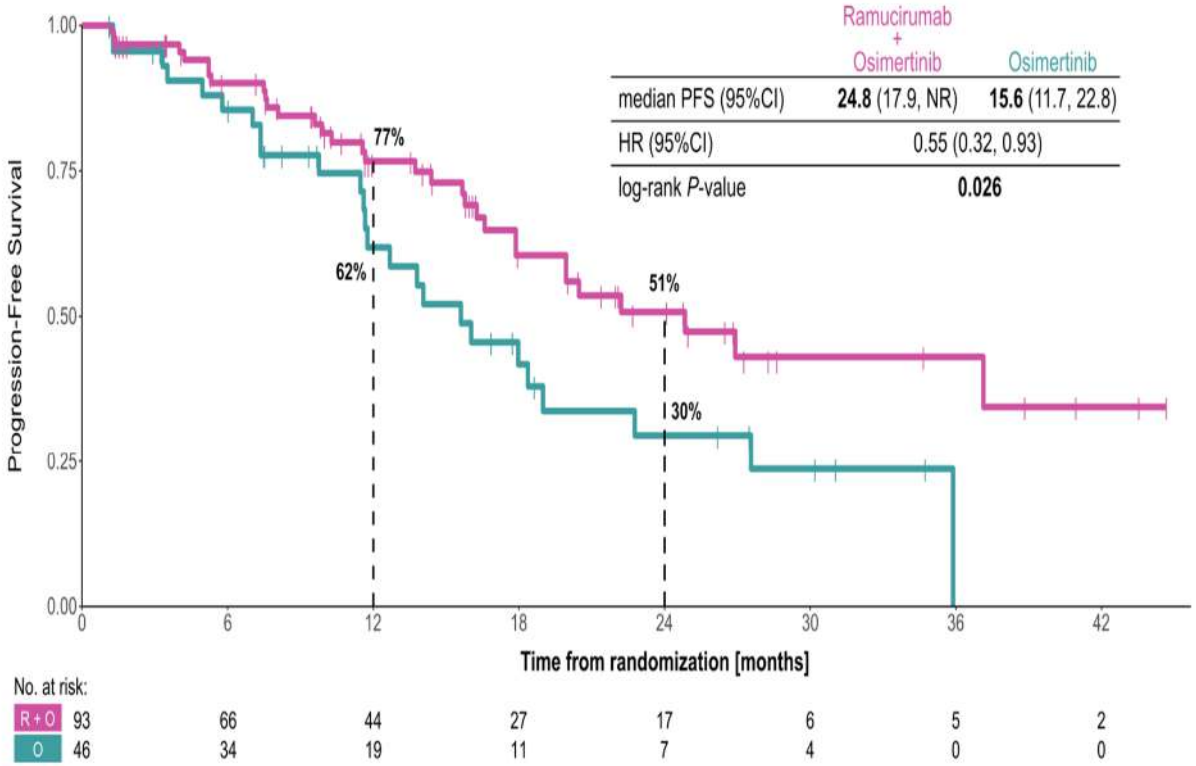


Xiuning Le et al, ESMO 2023

PFS



	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.	



	Ramucirumab + Osimertinib	Osimertinib
median PFS (95%CI)	**24.8** (17.9, NR)	**15.6** (11.7, 22.8)
HR (95%CI)	0.55 (0.32, 0.93)	
log-rank *P*-value	**0.026**	

nths
rumab treatment (Arm A): 14.2 months
ab 86.6%

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**

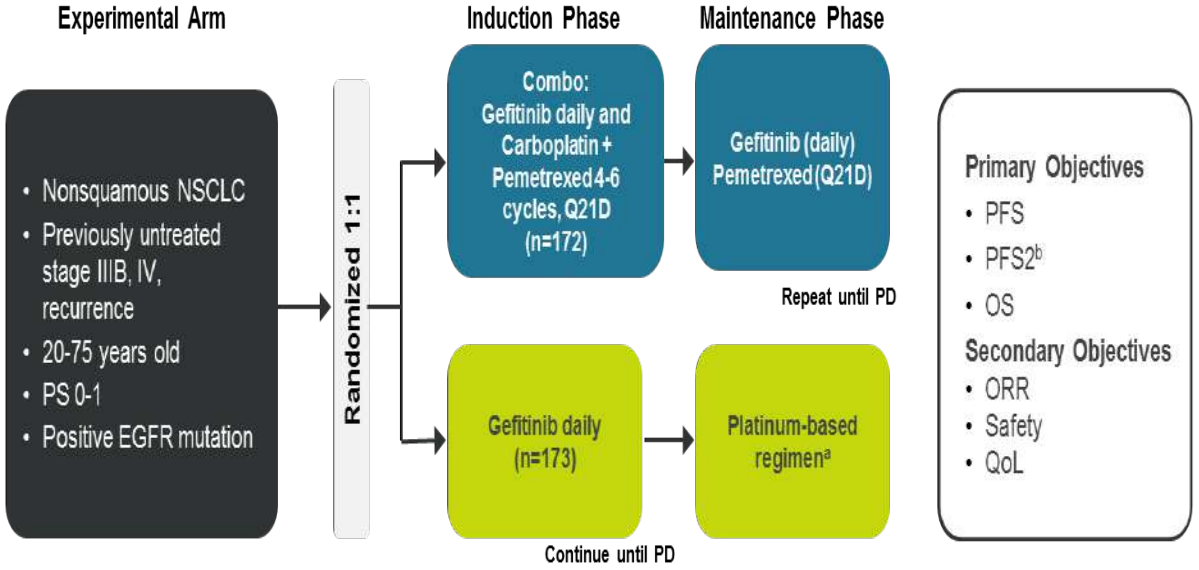
Y Nakahara et al, ESMO 2023

Xiuning Le et al, ESMO 2023

Add chemotherapy

NEJ009: Study design[1]

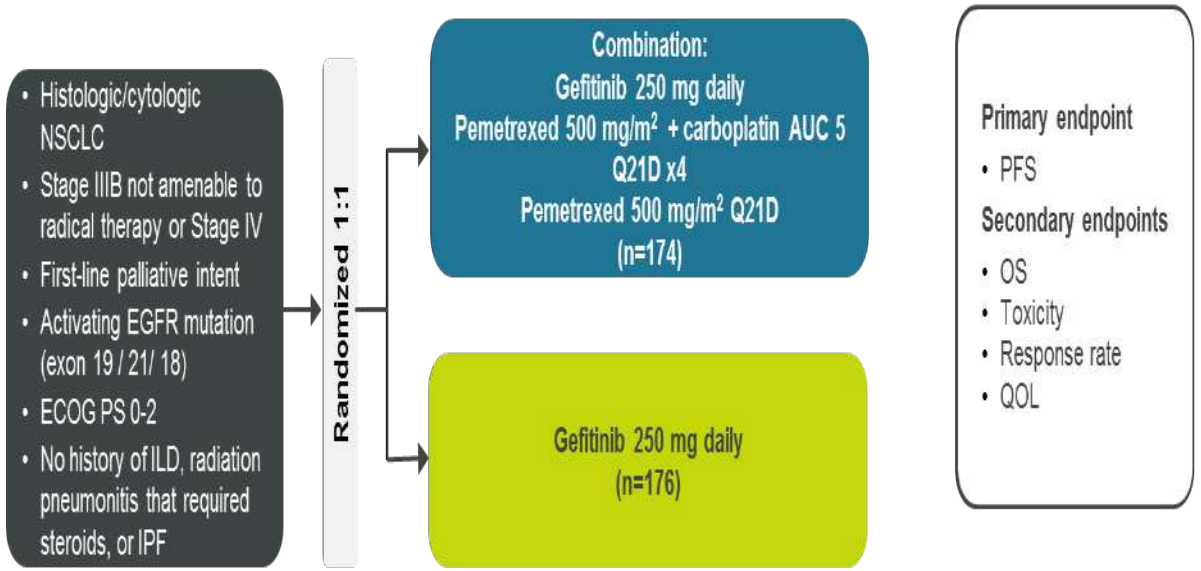
- A randomized Phase III study of gefitinib in combination with carboplatin plus pemetrexed versus gefitinib alone in untreated patients with advanced EGFR mutation-positive nonsquamous NSCLC



Stratified with gender, stage, type of EGFR mutation, and smoking history

CTRI/2016/08/007149: Study design[2]

- Phase III, randomized, open-label study of gefitinib in combination with pemetrexed-carboplatin versus gefitinib in patients with advanced, untreated EGFRm NSCLC



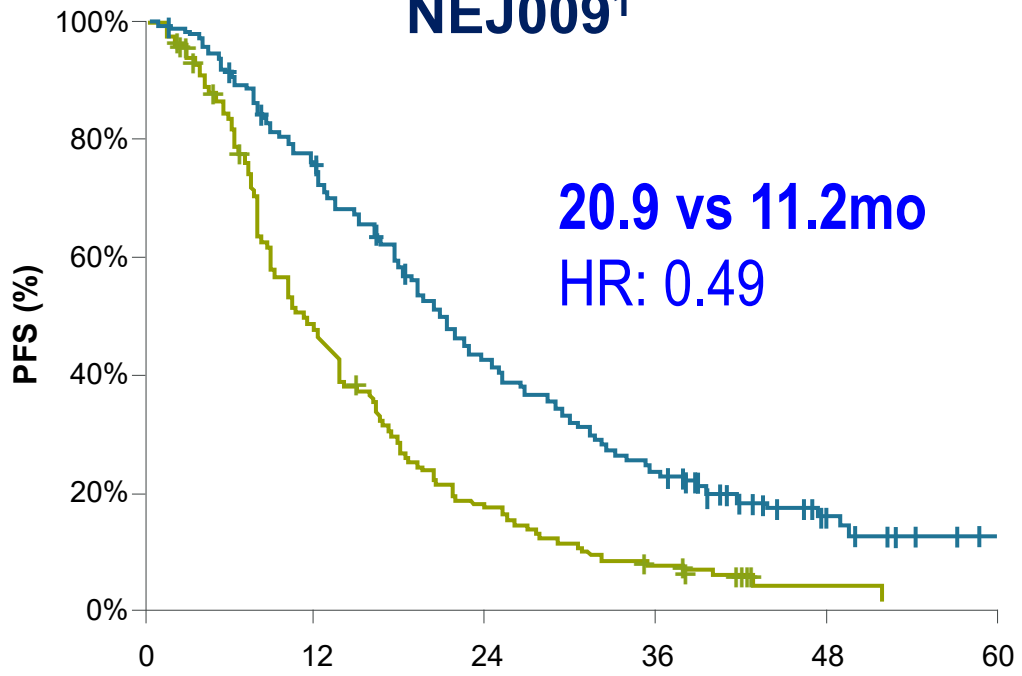
- Stratification factors:
  - ECOG PS (0/1 versus 2)
  - EGFR mutation (exon 19 versus other)
- Patients treated until PD, unacceptable toxicity, or consent withdrawal

AUC, area under the curve; ECOG PS, Eastern Cooperative Oncology Group Performance Status; *EGFR*m, epidermal growth factor receptor mutant; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, time to second objective disease progression; PS, Performance Status; Q21D, every 21 days; QoL, quality of life

1. Hosomi Y, et al. J Clin Oncol 2020;38(2):115–23; 2. Noronha V, et al. J Clin Oncol 2020;38(2):124–136

Gefitinib + chemotherapy in treatment-naïve, *EGFR*m NSCLC: PFS

NEJ009[1]

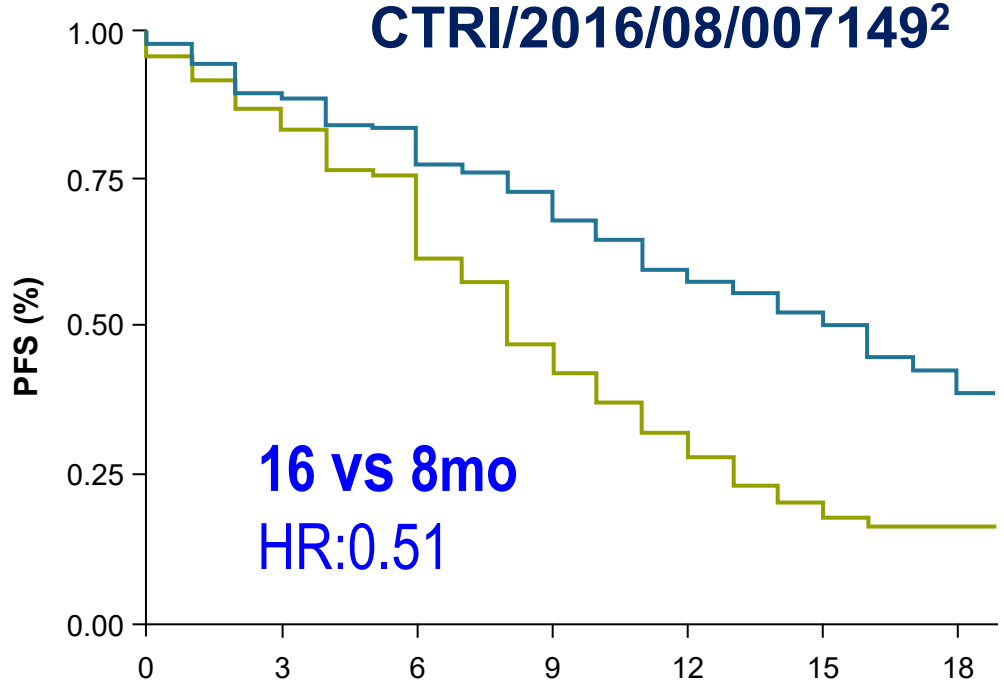


No. at risk						
Gefitinib	172	78	29	11	2	0
Gefitinib+CB+PEM	169	123	68	37	10	2

	Median PFS, months (95% CI)
Gefitinib (n=172)	11.2 (9.0-13.4)
Gefitinib + CB + PEM (n=169)	20.9 (18.0-24.0)

HR, 0.494 (95% CI, 0.391-0.625); p<0.001

CTRI/2016/08/007149[2]



No. at risk							
Gefitinib	176	152	133	77	41	21	12
Gefitinib+CB+PEM	174	155	145	118	82	61	36

	Median PFS, months (95% CI)
Gefitinib (n=176)	8 (7.0-9.0)
Gefitinib + CB + PEM (n=174)	16 (13.5-18.5)

HR, 0.51 (95% CI, 0.39-0.66); p<0.0001

The data listed are from different clinical trials. Not for cross-trial comparison.

CB = carboplatin; EGFR = epidermal growth factor receptor; EGFRm = epidermal growth factor receptor mutation-positive; HR = hazard ratio; No = number; NSCLC = non-small cell lung cancer; OS = overall survival; PEM = pemetrexed; PFS = progression-free survival; TKI = tyrosine kinase inhibitor.

1. Nakamura A et al. Presented at: ASCO Annual Meeting; June 1-5, 2018; Chicago, IL. 2. Noronha V, et al. Presented at: ASCO Annual Meeting; 31 May-4 June 2019; Chicago, IL.

FLAURA2 PHASE III STUDY

Pts 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

Osimertinib 80 mg (QD) + pemetrexed 500 mg/m² + carboplatin AUC5
or cisplatin 75 mg/m² (Q3W for 4 cycles), followed by maintenance osimertinib 80 mg (QD) + pemetrexed (Q3W)*
n=279

Randomisation 1:1 (N=557)

Osimertinib 80 mg (QD)
n=278

Primary endpoint:

- PFS by investigator assessment per RECIST 1.1†‡

Key secondary endpoints:

- OS, ORR, DoR, DCR, HRQoL, safety (AEs by CTCAE v5), PFS2†

Pts with CNS metastases which were asymptomatic (not requiring steroids) or had a stable neurological status for ≥2 weeks after completion of definitive treatment and steroids, if received, were allowed

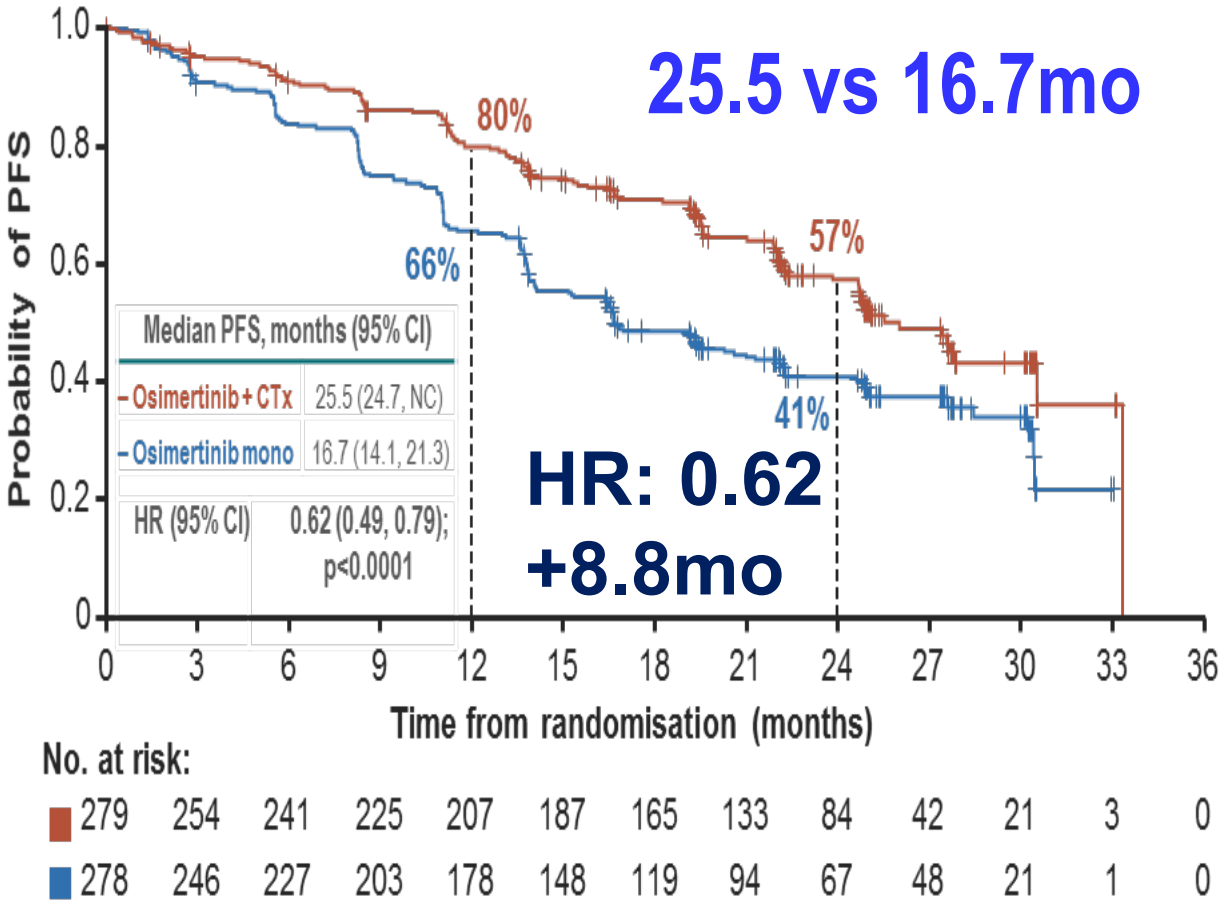
Follow-up:

- 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
- Brain imaging mandatory at baseline (all pts; 84% received MRI) and progression for all pts, and at scheduled assessments until progression for pts with baseline CNS metastases
- All CNS scans were assessed by neuroradiologist CNS BICR using modified RECIST guidance

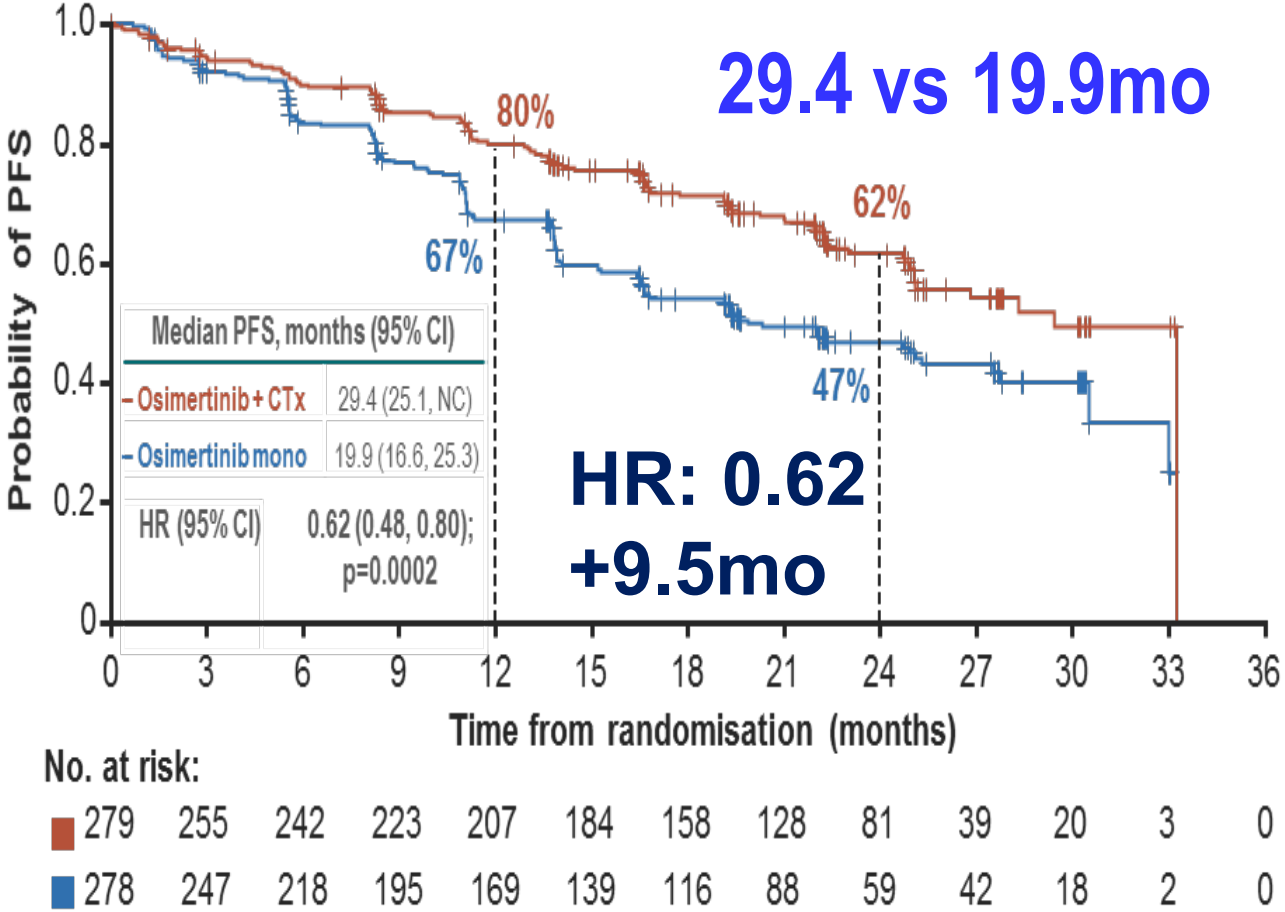
1. Jänne et al. WCLC 2023: abstract / presidential symposium PL03.13
2. D.Planchard et al, NEJM 2023

1L OSIMERTINIB WITH THE ADDITION OF CTx SIGNIFICANTLY IMPROVES PFS VS OSIMERTINIB MONOTHERAPY

PFS per investigator assessment



PFS per BICR assessment



MADRID 2023 ESMO congress

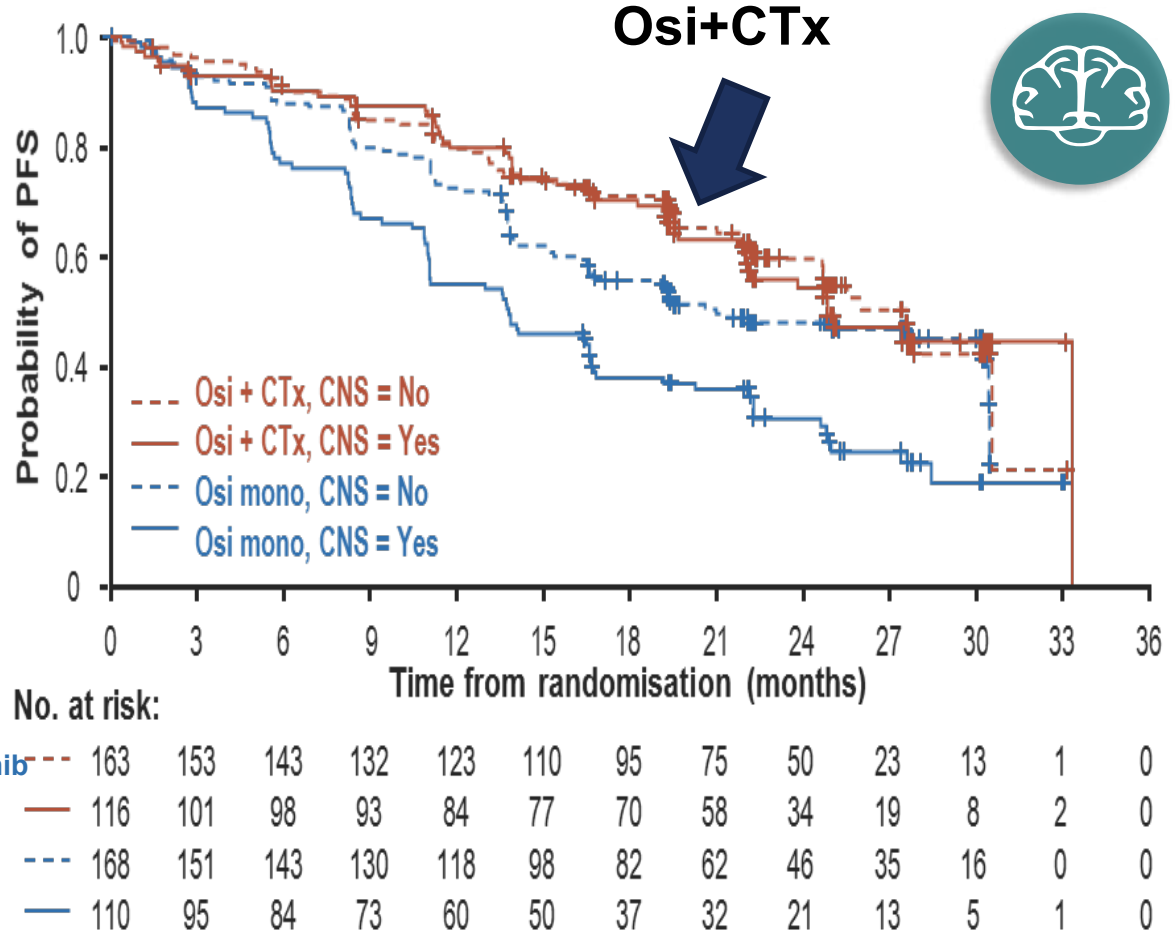
1. Jänne et al. WCLC 2023: abstract / presidential symposium PL03.13
2. D.Planchard et al, NEJM 2023

OSIMERTINIB WITH ADDITION OF CTx SHOWED CONSISTENT PFS BENEFIT ACROSS SUBGROUPS COMPARED WITH OSIMERTINIB MONOTHERAPY

PFS across subgroups*		Osi + CTx (Events / pts)	Osi mono (Events / pts)	HR (95% CI)
All pts	Stratified log-rank	120 / 279	166 / 278	**0.62** (0.49, 0.79)
	Unadjusted Cox PH	120 / 279	166 / 278	**0.62** (0.49, 0.78)
Sex	Male	51 / 106	73 / 109	**0.54** (0.37, 0.77)
	Female	69 / 173	93 / 169	**0.67** (0.49, 0.92)
Race	Chinese Asian	26 / 71	43 / 69	**0.49** (0.30, 0.81)
	Non-Chinese Asian	54 / 107	65 / 107	**0.76** (0.53, 1.09)
	Non-Asian	40 / 101	58 / 102	**0.55** (0.37, 0.83)
EGFR mutation test method	Central	52 / 121	67 / 119	**0.73** (0.51, 1.05)
	Local	68 / 158	99 / 159	**0.55** (0.40, 0.74)
Age at screening	<65 years	73 / 174	97 / 166	**0.59** (0.44, 0.80)
	≥65 years	47 / 105	69 / 112	**0.68** (0.47, 0.98)
Smoking history	Yes	43 / 91	57 / 97	**0.63** (0.42, 0.94)
	No	77 / 188	109 / 181	**0.61** (0.46, 0.82)
EGFR mutation†	Ex19del	65 / 172	94 / 169	**0.60** (0.44, 0.83)
	L858R	55 / 106	70 / 107	**0.63** (0.44, 0.90)
WHO PS	0	48 / 101	57 / 102	**0.79** (0.54, 1.16)
	1	72 / 178	109 / 176	**0.53** (0.39, 0.72)
CNS status at baseline	Yes	52 / 116	79 / 110	**0.47** (0.33, 0.66)
	No	68 / 163	87 / 168	**0.75** (0.55, 1.03)

HR: 0.47 (with BM) and 0.75 (without BM)

PFS by baseline CNS metastases status*



MADRID 2023 ESMO congress

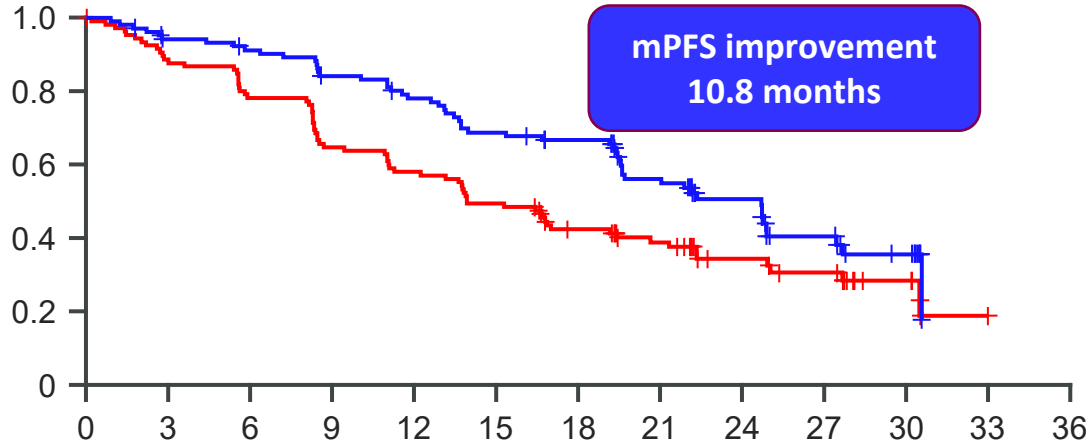
David Planchard, MD, PhD

1. Jänne et al. WCLC 2023: abstract / presidential symposium PL03.13
2. D.Planchard et al, NEJM 2023

PFS by investigator assessment in the subgroups of patients by L858R mutation / CNS metastases at baseline

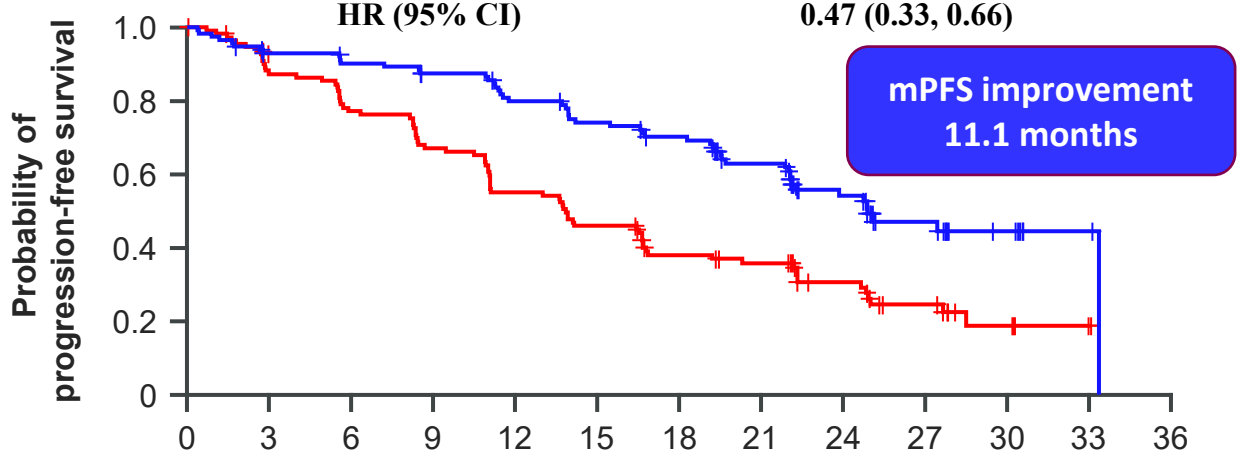
L858R*

mPFS, months (95% CI)	
Osimertinib + CTx	24.7 (19.5, 27.4)
Osimertinib monotherapy	13.9 (11.1, 19.4)
HR (95% CI)	0.63 (0.44, 0.90)



With CNS metastases†

mPFS, 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)



Time from randomisation (months)

No. at risk:

	106	95	91	83	76	67	62	47	31	19	12	0	0
	107	92	82	68	61	52	40	31	19	15	5	0	0

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

Data cut-off: 03 April 2023

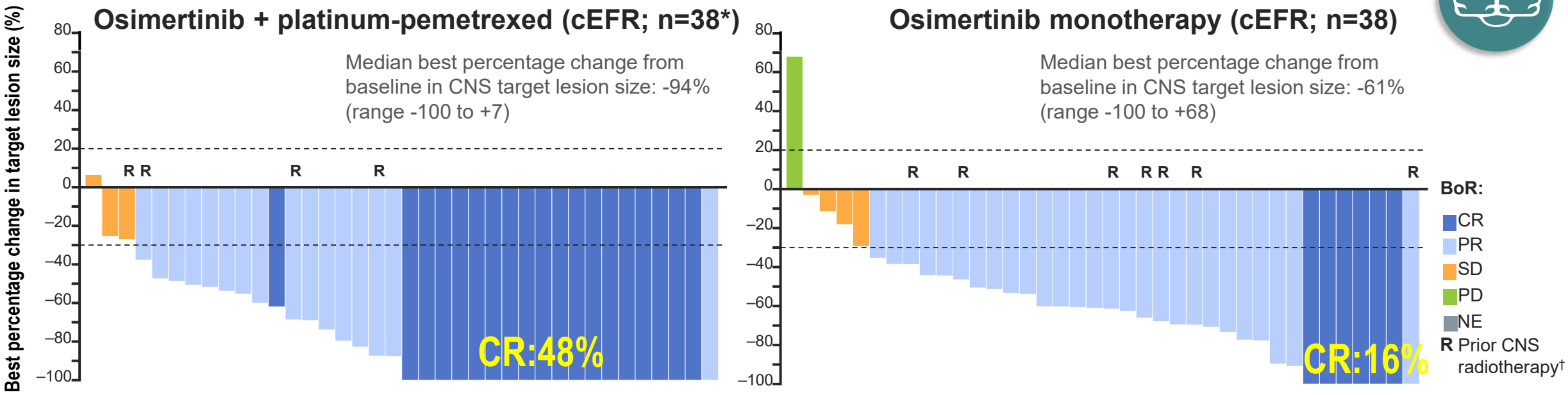
*Per investigator; patients with co-occurring Ex19del and L858R mutations were included in the Ex19del group; †CNS metastases determined by the investigator and recorded in the eCRF

CI, confidence interval; ; CNS, central nervous system; CTx, chemotherapy; eCRF, electronic case report form; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; HR, hazard ratio; (m)PFS, (median) progression-free survival; NC, not calculable

AstraZeneca data on file

Prof Pasi A. Jänne et al, WCLC 2023

OSIMERTINIB WITH THE ADDITION OF CTx DEMONSTRATED A HIGH PROPORTION OF COMPLETE RESPONSES IN THE CNS BY CNS BICR

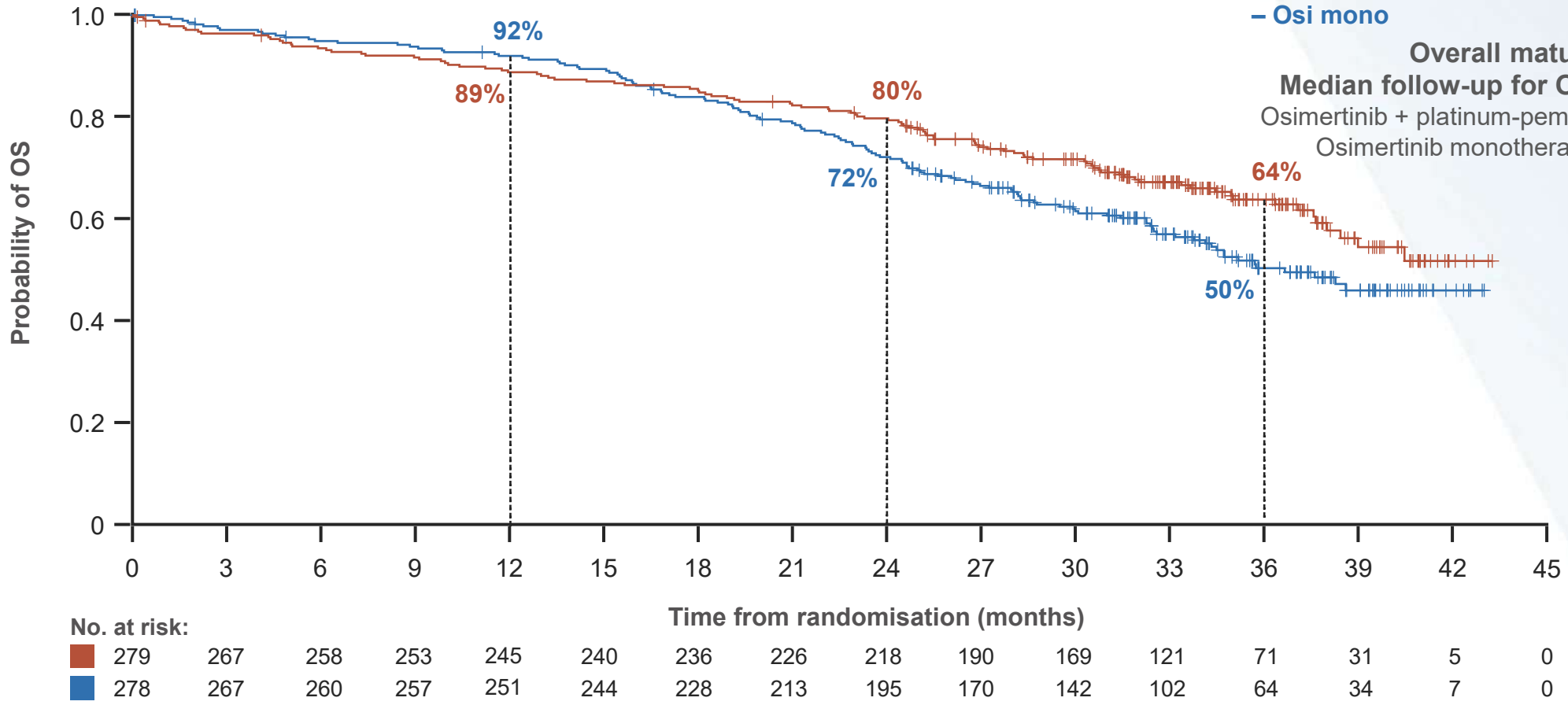


	cFAS (n=222) Measurable + non-measurable BM		cEFR (n=78) Measurable BM	
CNS response‡	**Osi + CTx (n=118)**	**Osi mono (n=104)**	**Osi + CTx (n=40)**	**Osi mono (n=38)**
CNS ORR, % (95% CI)	**73 (64 to 81)**	**69 (59 to 78)**	**88 (73 to 96)**	**87 (72 to 96)**
Complete response, n (%)	70 (59)	45 (43)	19 (48)	6 (16)
Partial response, n (%)	16 (14)	27 (26)	16 (40)	27 (71)
CNS DCR, % (95% CI)	91 (84 to 95)	93 (87 to 97)	95 (83 to 99)	97 (86 to 100)
Median DoR, months (95% CI)§	**NR (23.8, NC)**	**26.2 (19.4, NC)**	**NR (21.6, NC)**	**20.9 (12.6, NC)**

Pasi A. Jänne; David Planchard et al, JCO 2023

SECOND INTERIM OVERALL SURVIVAL ANALYSIS

OS: HR=0.75 (95% CI 0.57, 0.97); p=0.0280†



Median OS, months (95% CI)	
– Osi + CTx	NR (38.0, NC)
– Osi mono	36.7 (33.2, NC)

Overall maturity: 41%

Median follow-up for OS, months (range):

Osimertinib + platinum-pemetrexed, 31.7 (0.1–43.3)

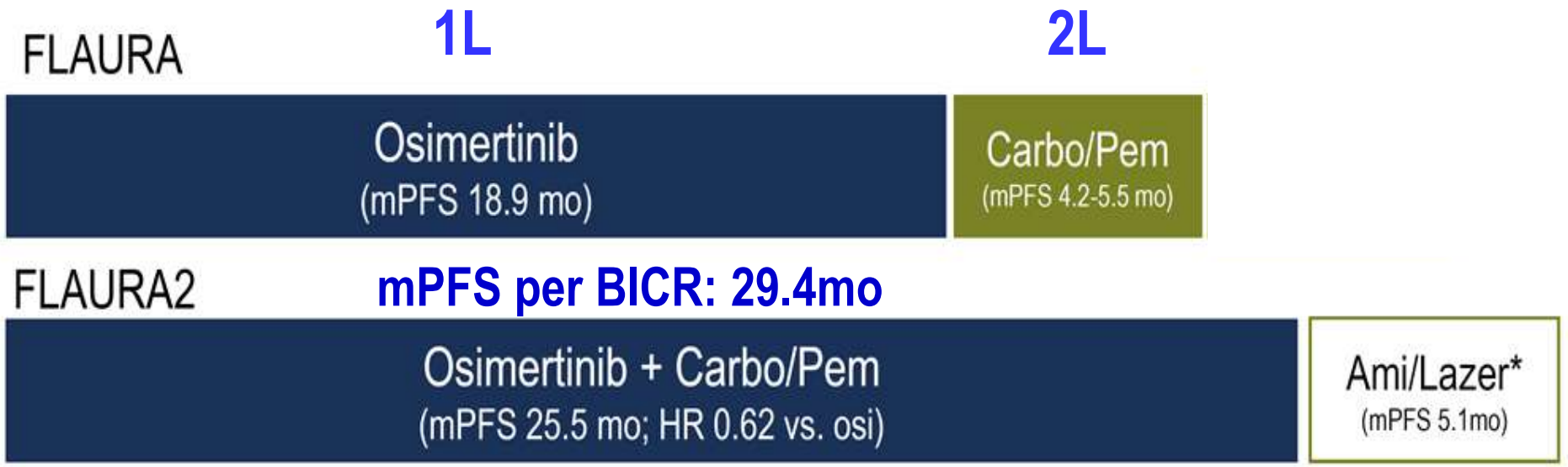
Osimertinib monotherapy, 30.5 (0.1–43.0)

†A p-value of ≤0.000001 was required for statistical significance at this second interim analysis

CI, confidence interval; CTx, chemotherapy; HR, hazard ratio; mono, monotherapy; NC, not calculable; NR, not reached; OS, overall survival; osi, osimertinib

Data cut-off: 08 January 2024

Management of EGFR-mutant NSCLC in early 2023



-All comers ?

✓ -BM ?

✓ -L858R ?

-High tumor burden ?

-ctDNA+ ?

-co-mutations ?

-Pt preference ?

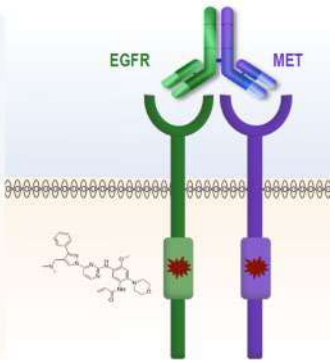
Amivantamab in Combination with Lazertinib

Amivantamab (am-e-van-tuh-mab)

- Fully human bispecific antibody that targets EGFR and MET
- Fc portion has immune cell-directing activity[1]
- Demonstrated clinical activity across diverse EGFRm NSCLC[2,3]
- Approved in the USA for EGFRm Exon20ins NSCLC post-platinum chemotherapy

Lazertinib (la-zer-tin-ib)

- Potent 3rd-gen TKI with efficacy in activating EGFR mutations, T790M, and CNS disease[4,5]
- Low rates of EGFR-related toxicity such as rash and diarrhea[5]
- Low risk for QTc prolongation,[6] no cardiotoxicity signal observed to date
- Safety profile supports combination with other anti-EGFR molecules



FLAURA J.C.Soria et al, NEJM 2018

FLAURA 2 D.Planchard et al, NEJM 2023

MARIPOSA: 1st line Amivantamb + Lazertinib

Key Eligibility Criteria

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

Stratification Factors

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

2:2:1 Randomization (N=1074)

Serial brain MRIs were required for all patients[a]

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

Osimertinib
(n=429; blinded)

Lazertinib
(n=216; blinded)

Dosing (in 28-day cycles)

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

Primary endpoint of progression-free survival (PFS)[b] by BICR per RECIST v1.1:

- Amivantamab + lazertinib vs osimertinib

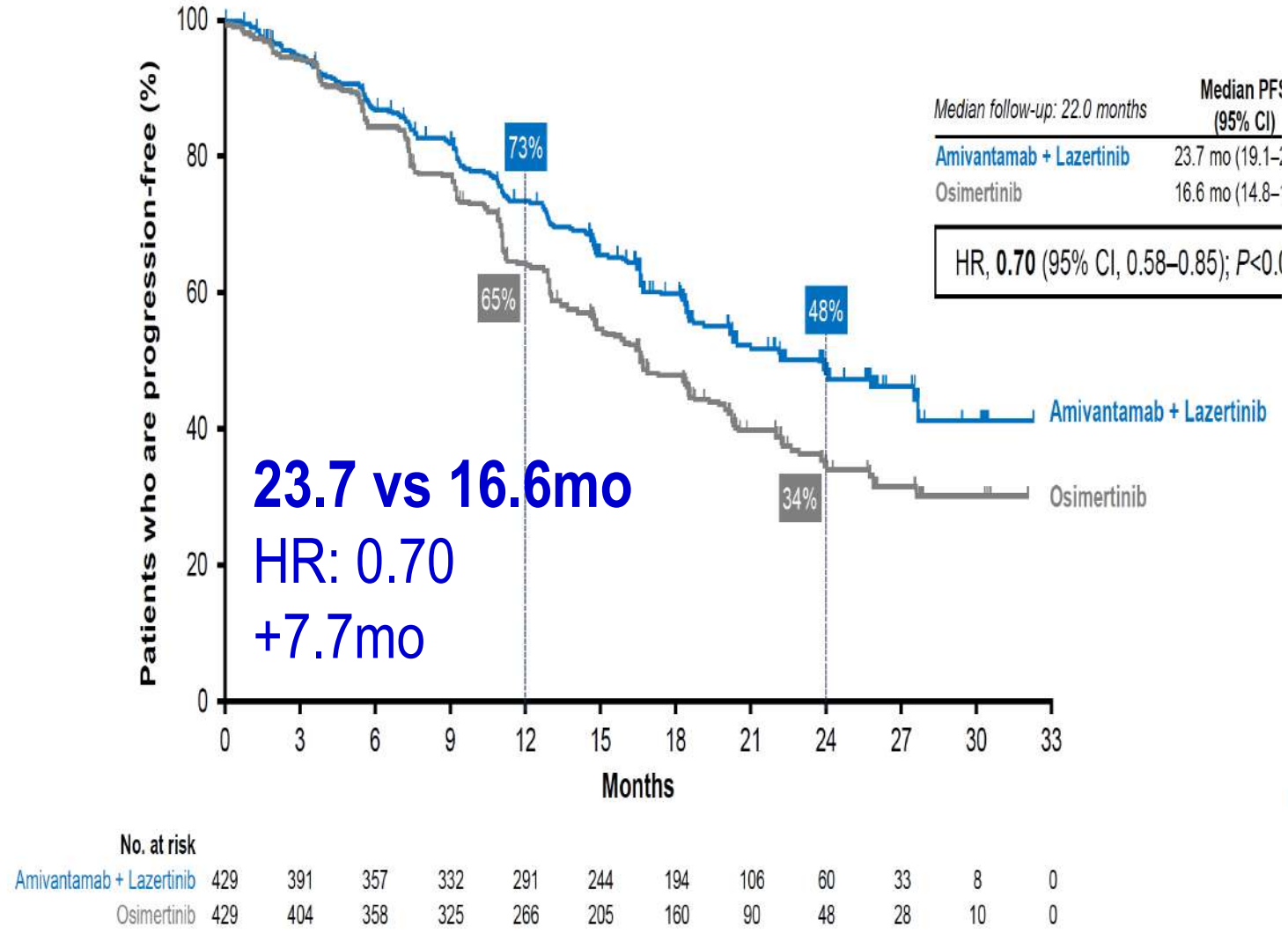
Secondary endpoints of amivantamab + lazertinib vs osimertinib:

- Overall survival (OS)[b]
- Objective response rate (ORR)
- Duration of response (DoR)
- PFS after first subsequent therapy (PFS2)
- Symptomatic PFS[c]
- Intracranial PFS[c]
- Safety

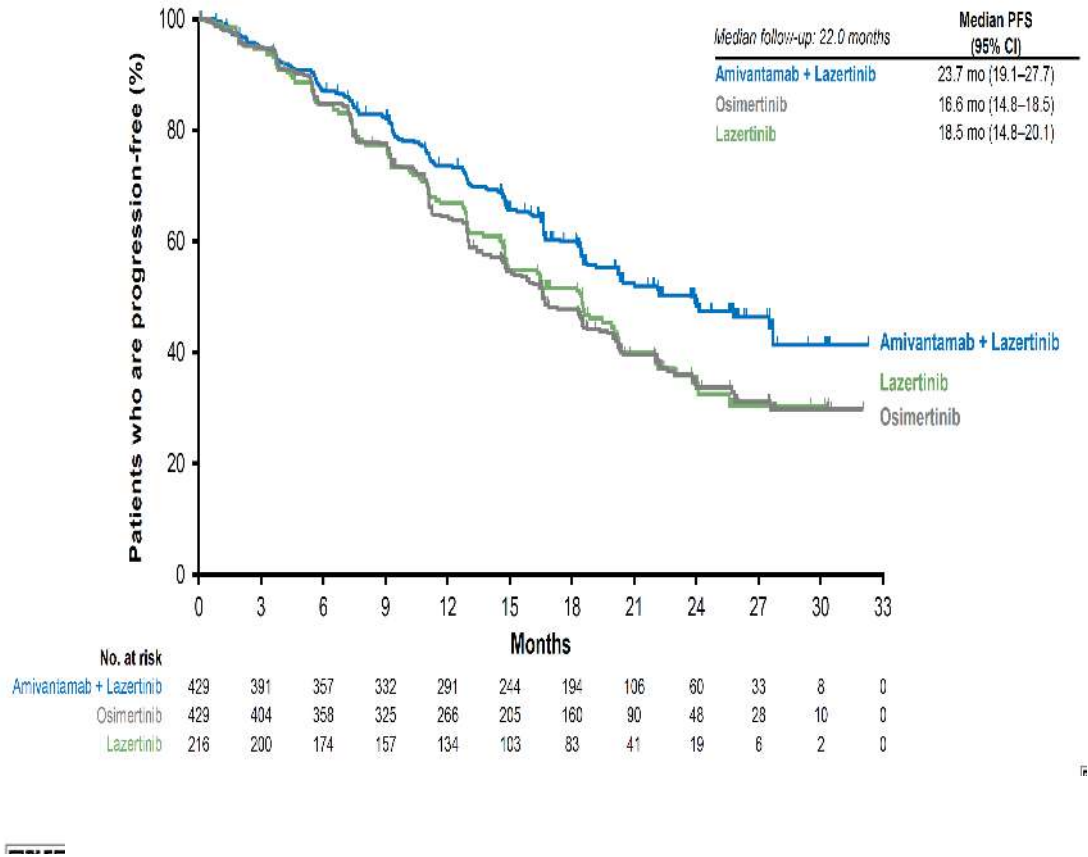
Lazertinib monotherapy arm was included to assess the contribution of components

B.C.Choy et al, ESMO 2023

PFS by BIRC (Primary Endpoint)

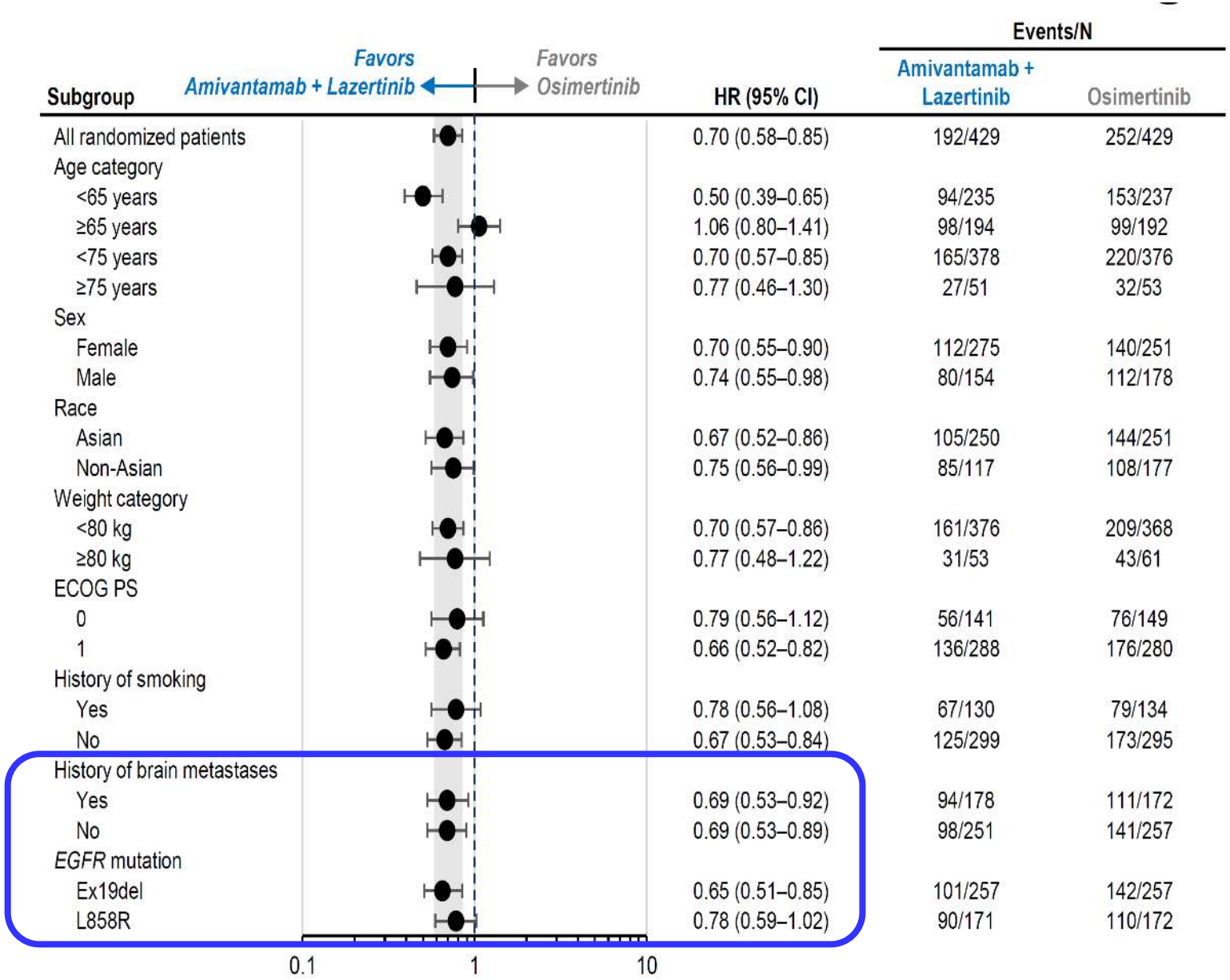


Lazertinib Monotherapy Demonstrates Meaningful Clinical Activity



B.C.Choy et al, ESMO 2023

PFS 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

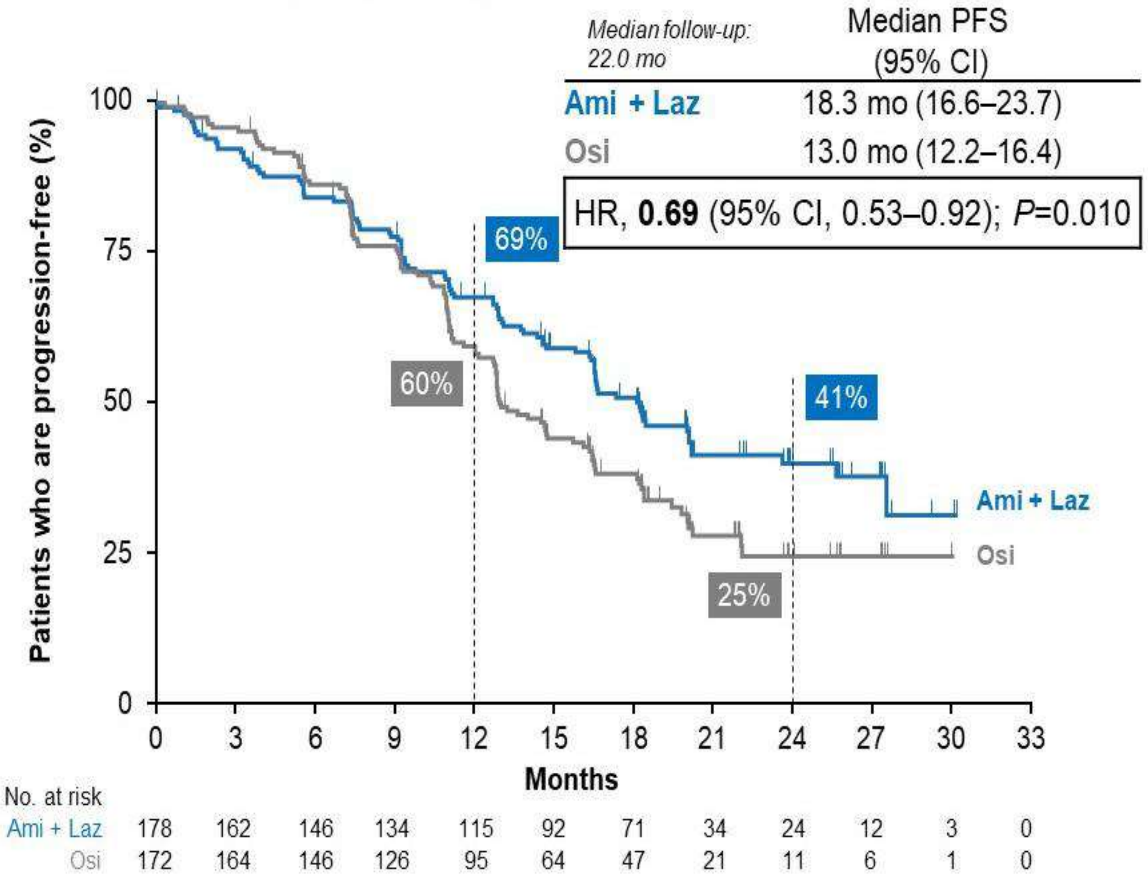
BICR-assessed response, n (%)[a]	Amivantamab + Lazertinib (n=429)	Osimertinib (n=429)
ORR		
All responders	86% (95% CI, 83–89)	85% (95% CI, 81–88)
Confirmed responders	80% (95% CI, 76–84)	76% (95% CI, 71–80)
Best response[b]		
CR	29 (7)	15 (4)
PR	334 (79)	335 (81)
SD	30 (7)	42 (10)
PD	7 (2)	11 (3)
NE/UNK	21 (5)	11 (3)
Ongoing responses	209 of 336 (62%)	151 of 314 (48%)

B.C.Choy et al, ESMO 2023

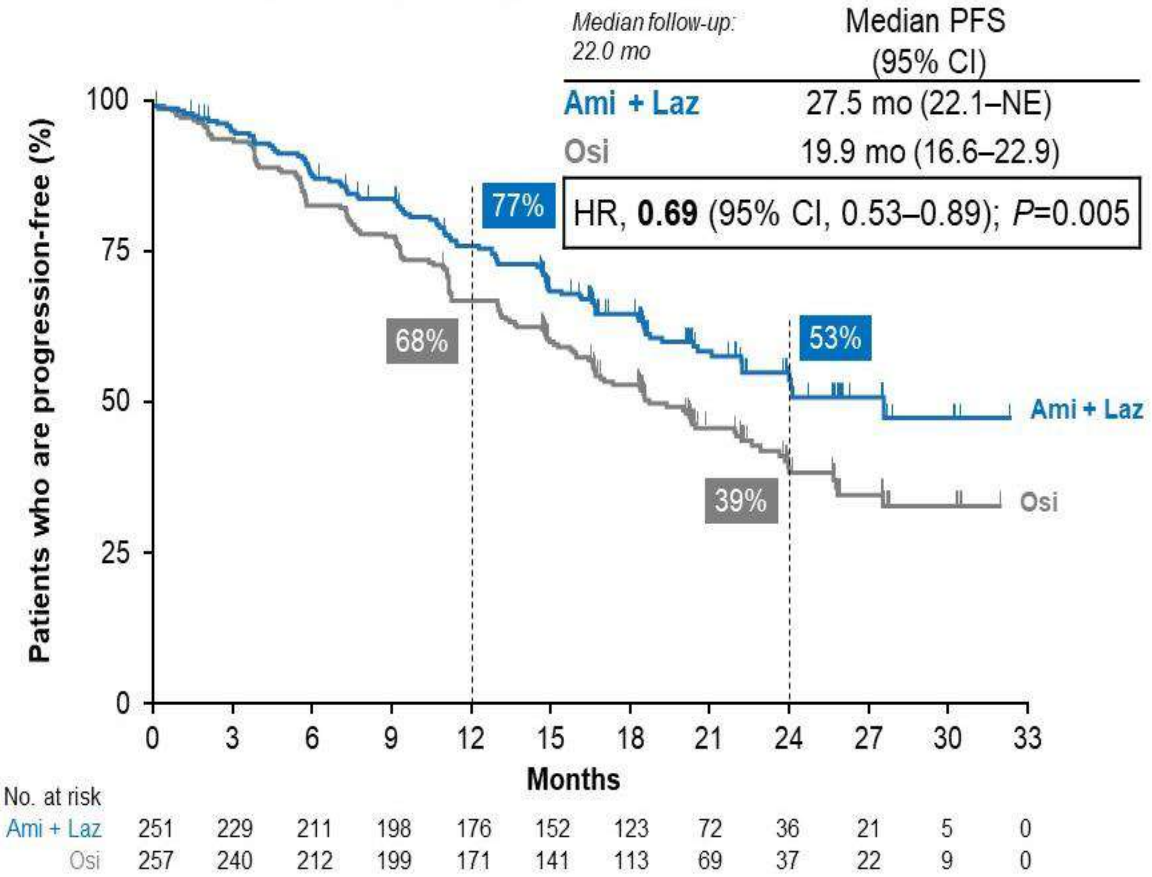
PFS by baseline brain metastases

- In the amivantamab + lazertinib arm, 41% of patients had a history of brain metastases vs 40% in the osimertinib arm
- Osimertinib showed a median PFS of 13.0 mo in patients with a history of brain metastases
- Amivantamab + lazertinib reduced the risk of progression or death by 31% in this subgroup

With History of Brain Metastases



Without History of Brain Metastases



Ami, amivantamab; Laz, lazertinib; Osi, osimertinib.

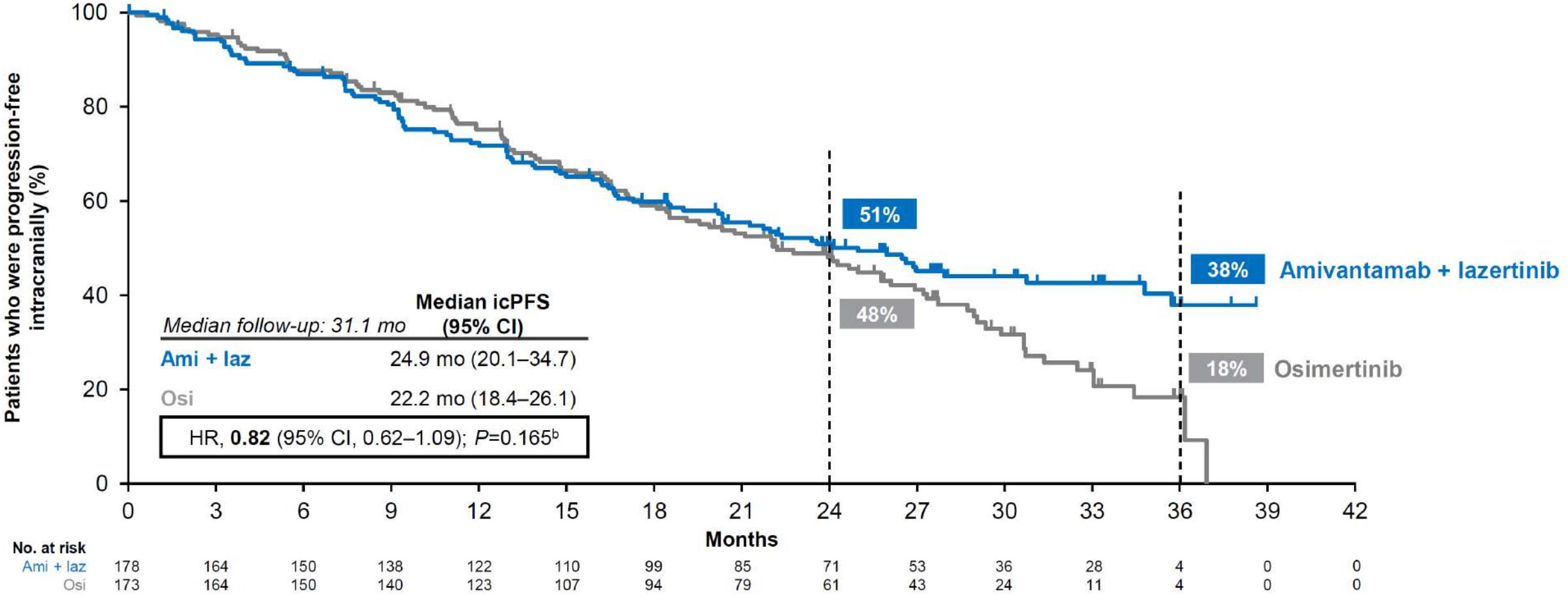
1. Cho BC, et al. Presented at the European Society for Medical Oncology (ESMO) Congress; October 20-24, 2023; Madrid, Spain. LBA14.

E.Felip et al, ASCO 2024

Intracranial PFS

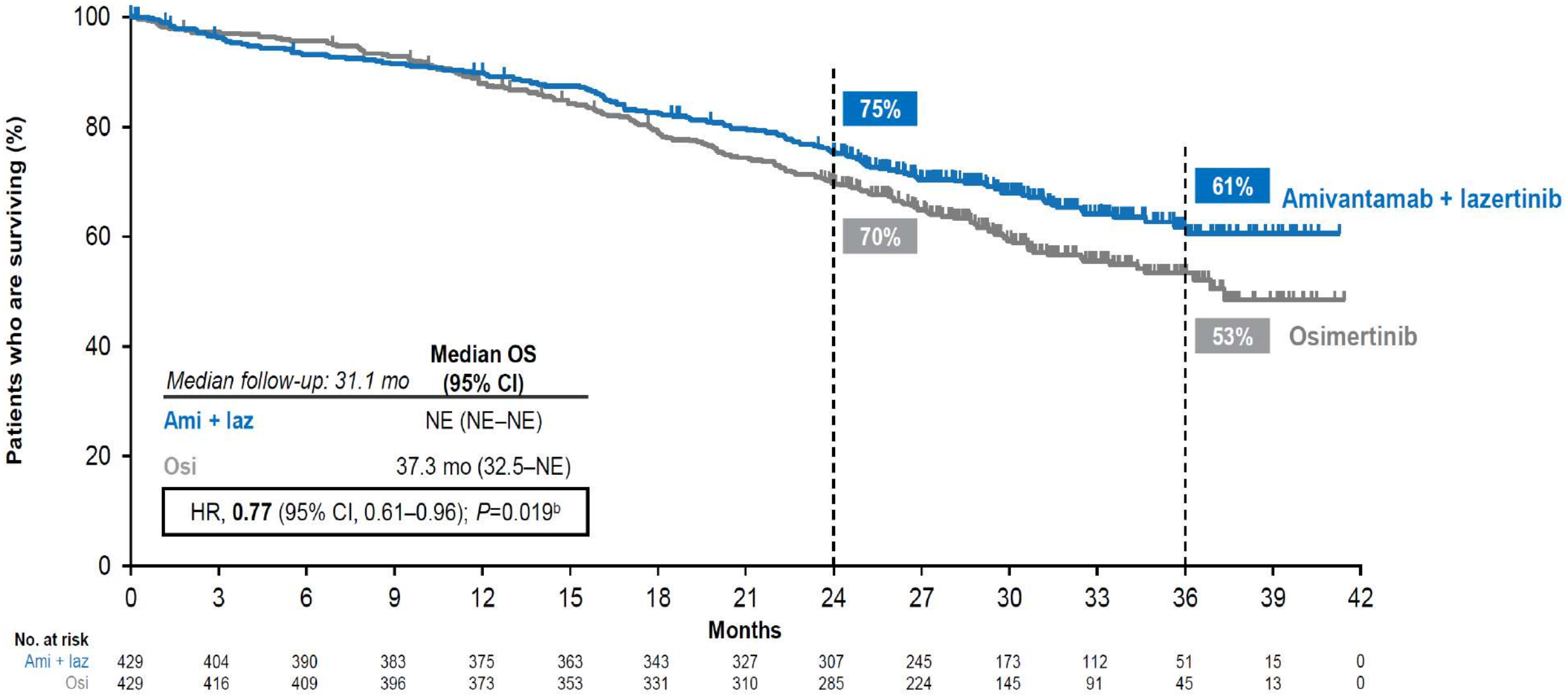
1L *EG*

MARIPOSA required serial brain imaging for all patients, which provides robust evaluation of CNS outcomes
Amivantamab + lazertinib showed a favorable trend in icPFS with sustained and durable CNS control at 3 years



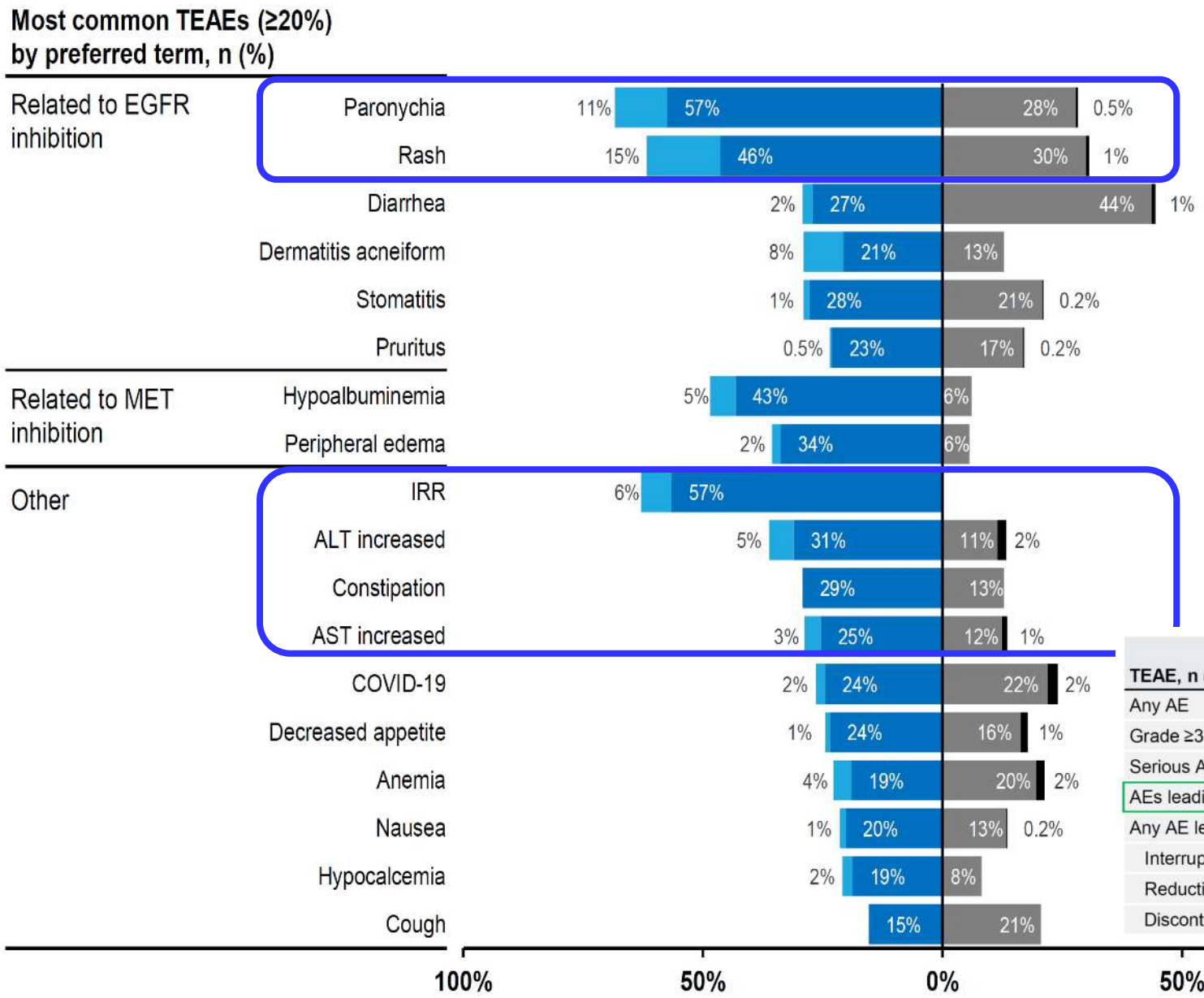
SM.Gadgeel et al, WCLC 2024

Updated Overall Survival Analysisa



SM.Gadgeel et al, WCLC 2024

Safety Profile



	Amivantamab + Lazertinib (n=421)	Osimertinib (n=428)
Any VTE, n (%)	37% 157 (37)	9% 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)

+ Prophylactic dose anticoagulations first 4 mo…

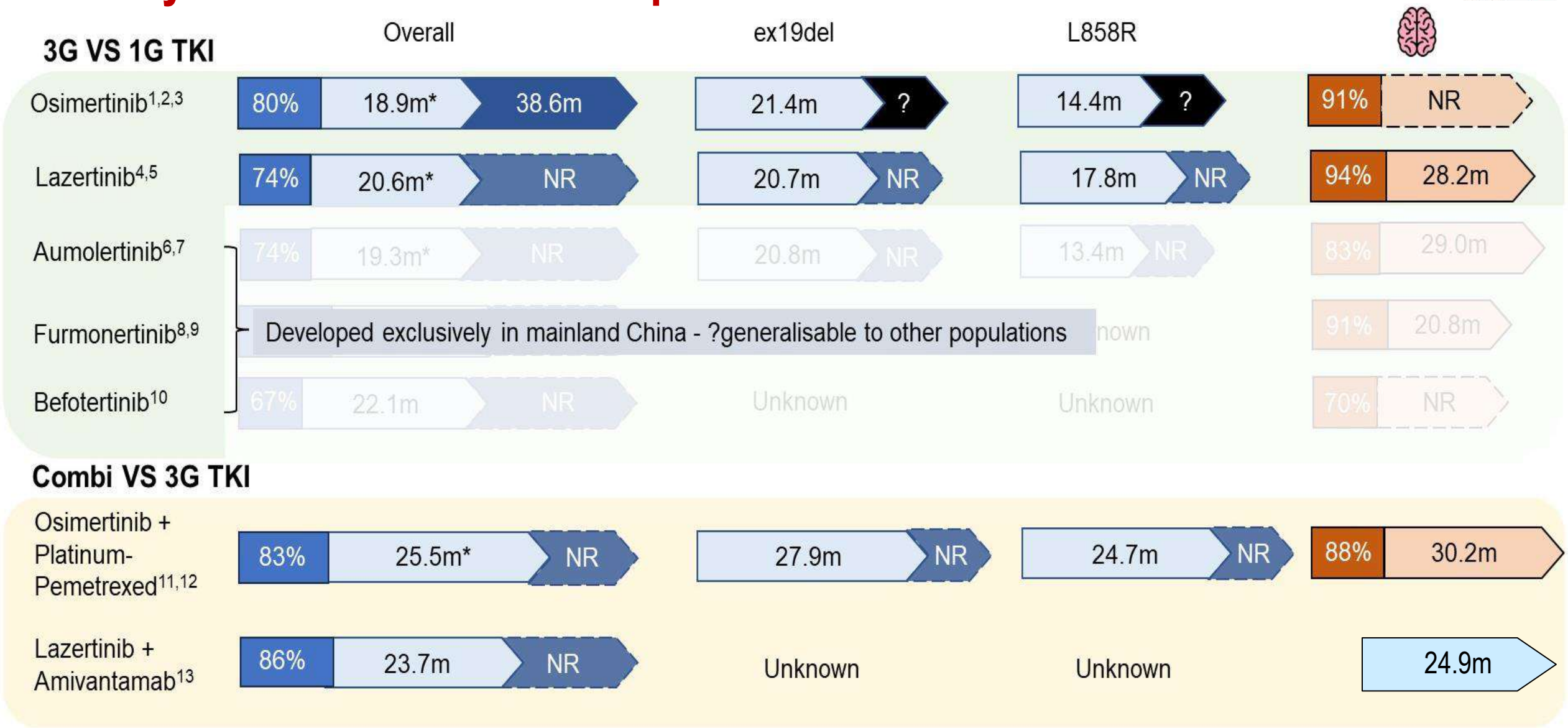
TEAE, n (%)	Amivantamab + Lazertinib (n=421)	Osimertinib (n=428)
Any AE	421 (100)	425 (99)
Grade ≥3 AEs	316 (75)	183 (43)
Serious AEs	205 (49)	143 (33)
AEs leading to death	34 (8)	31 (7)
Any AE leading to treatment:		
Interruptions of any agent	350 (83)	165 (39)
Reductions of any agent	249 (59)	23 (5)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

IRR: infusion-related reactions

VTE: venous thromboembolism

B.C.Choy et al, ESMO 2023

Efficacy of 1st line treatment options

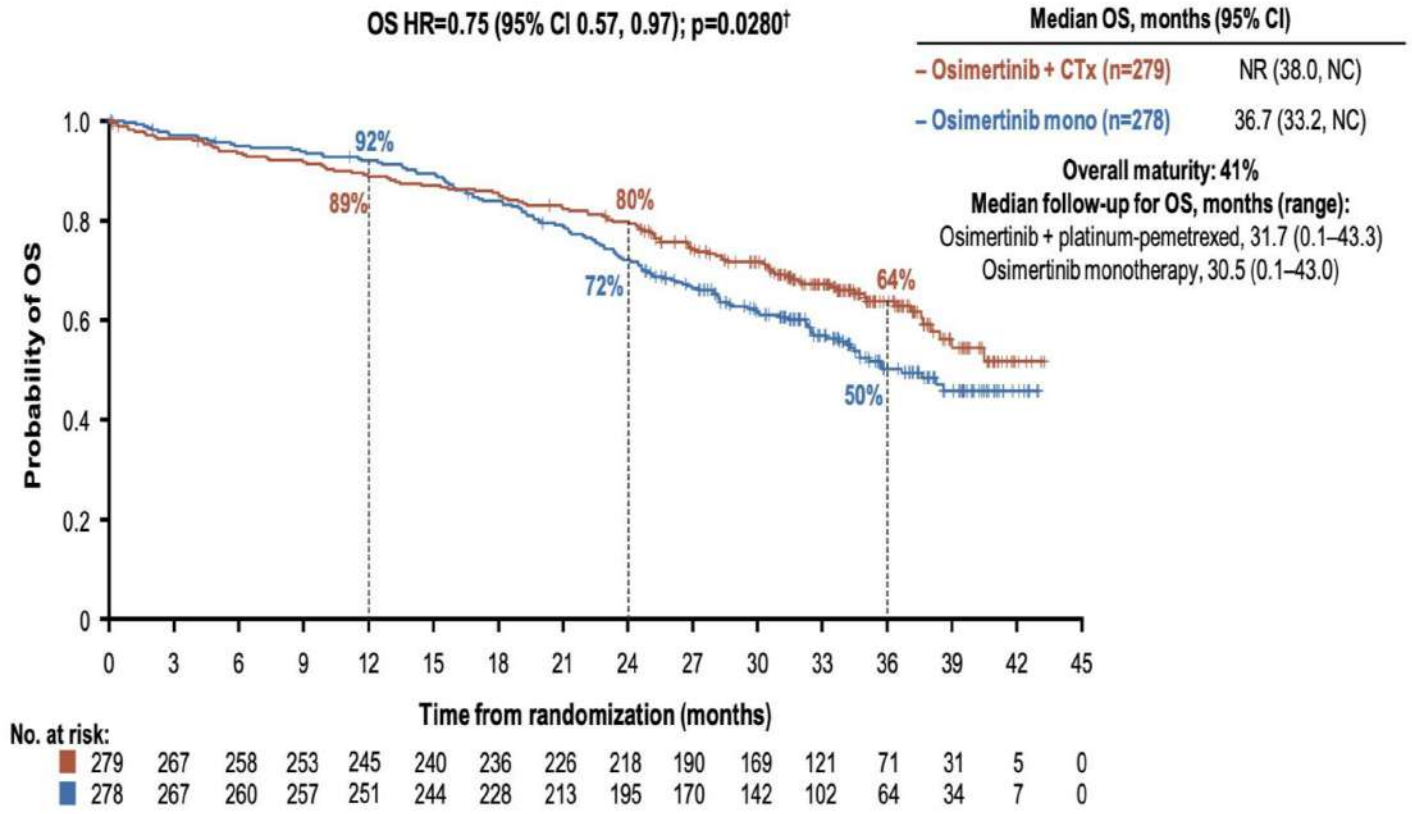


ORR = objective response rate; mPFS = median progression-free survival; mOS = median overall survival; CNS = central nervous system; NR = not reached; m = month
*Primary endpoint investigator-assessed PFS

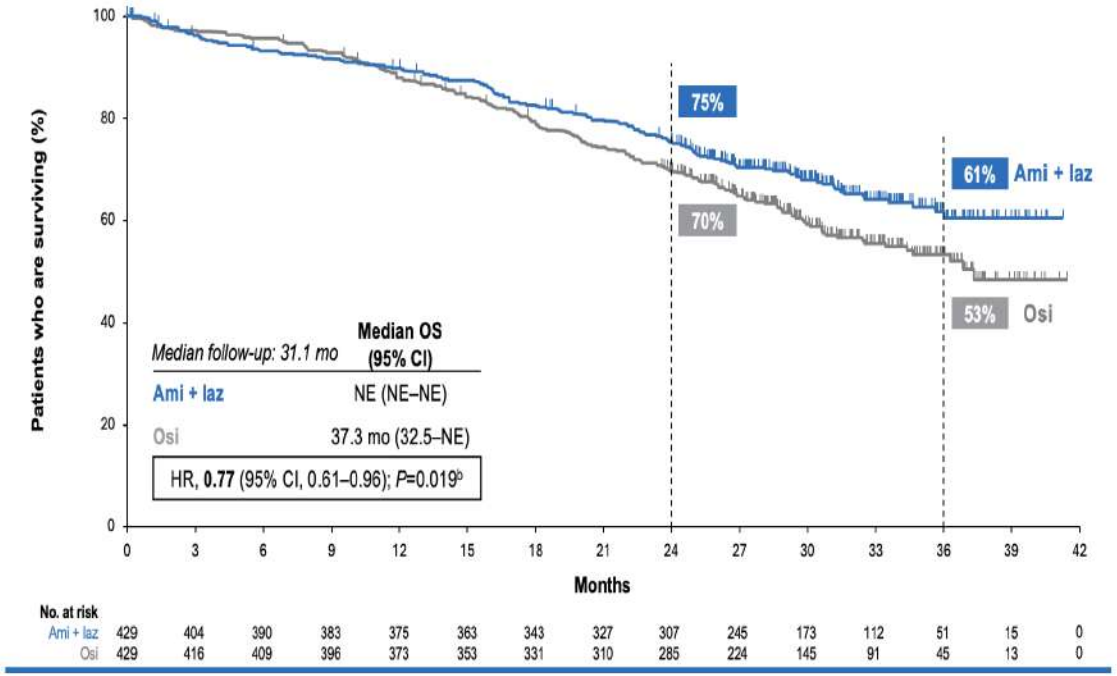
1. Soria et al, NEJM 2018; 2. Ramalingam et al, NEJM 2020; 3. Reungwetwattana et al, JCO 2018; 4. Cho et al, JCO 2023; 5. Soo et al, JTO 2023; 6.Lu et al, JCO 2022; 7. Lu et al, ASCO 2022; 8. Shi et al, Lancet Resp Med 2022; 9. Shi et al, JTO 2022; 10. Lu et al, Lancet Resp Med 2023; 11. Planchard et al, NEJM 2023; 12. Janne et al, JCO 2023; 13. Cho et al, ESMO 2023

Similar OS…

Flaura 2
HR 0.75



Mariposa
HR 0.77



BUT increased toxicities

AE of interest	Osimertinib + Pemetrexed + Platinum	Amivantamab + Lazertinib
Anaemia (≥G3)	46% (20%)	23% (4%)
Neutropenia (≥G3)	25% (14%)	Not reported
Thrombocytopenia (≥G3)	18% (7%)	Not reported
Nausea (≥G3)	43% (1%)	21% (1%)
Diarrhoea (≥G3)	43% (3%)	29% (2%)
Rash	28% (<1%)	61% (15%)
Paronychia	24% (1%)	68% (11%)
Peripheral edema	0	36% (2%)
Infusion-related reaction (≥G3)	0	63% (6%)
Venous thromboembolism (≥G3)	0	37% (11%)

Chemo-related

EGFR-inhibition

EGFR-inhibition

MET-inhibition

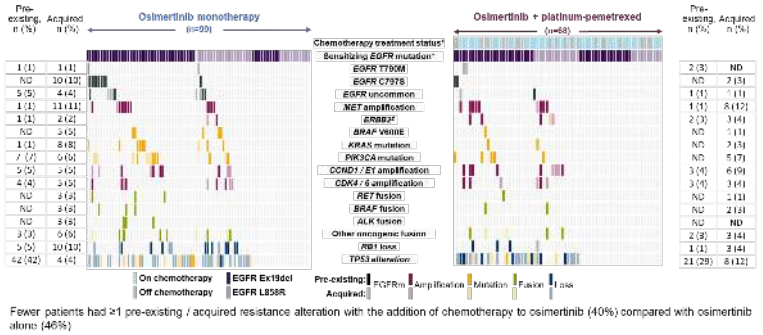
Role of SC formulation?

Anticoagulation prophylaxis for first 4m

[1]Jänne WCLC 2023; [2]Cho ESMO 2023, [3]Planchard et al, NEJM 2024

FLAURA2: Ongoing exploratory analysis

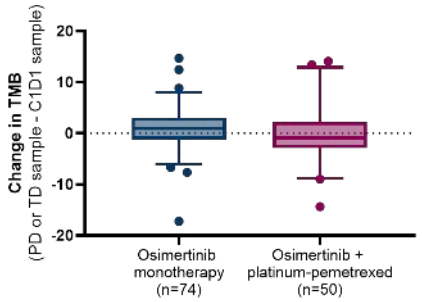
Acquired mechanisms of resistance



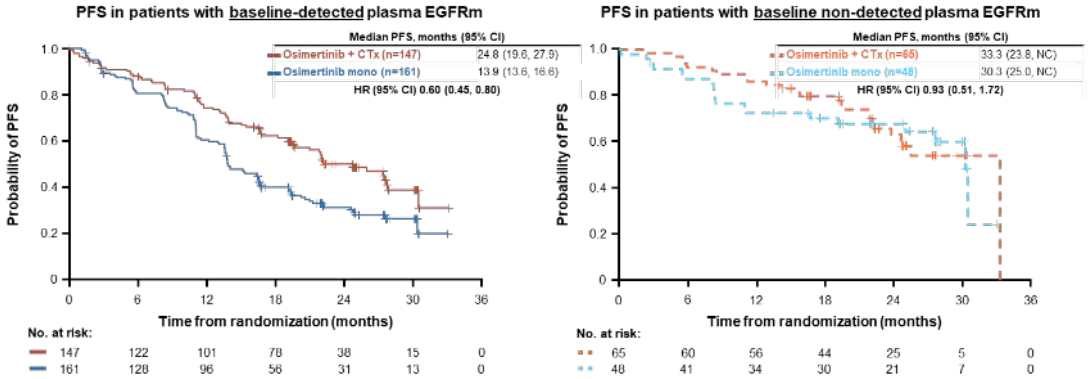
- Fewer patients had ≥1 pre-existing / acquired resistance alteration with the addition of chemotherapy to osimertinib (40%) compared with osimertinib alone (46%)

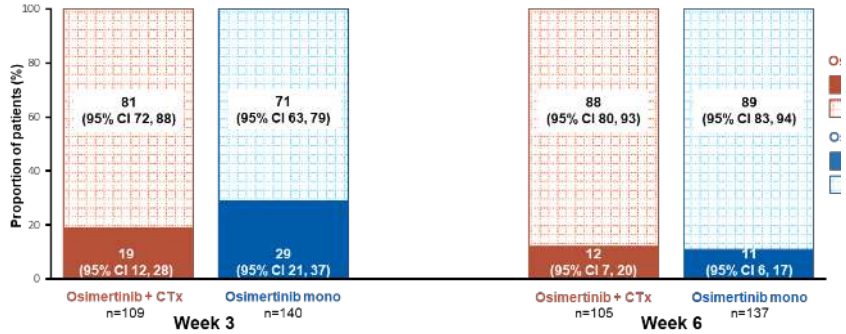
Acquired resistance mechanisms were similar between treatment arms

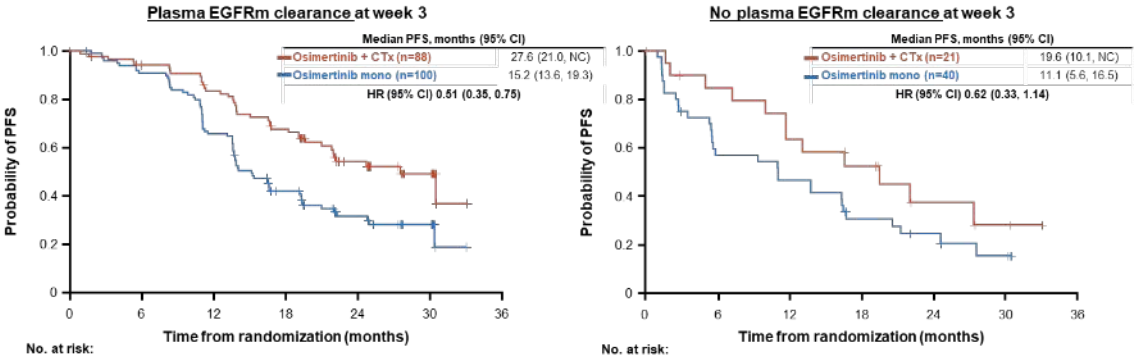
Functional groups	Acquired gene alteration, n (%)	FLAURA2 osimertinib + platinum-pemetrexed (n=68)	FLAURA2 osimertinib monotherapy (n=99)	FLAURA osimertinib monotherapy (n=109)†
EGFR mutations	C797S	2 (3)	12 (12)	7 (6)
	Other uncommon	1 (1)	4 (4)	5 (5)
RTK amplifications	MET amplification	8 (12)	11 (11)	17 (16)
	ERRB2 amplification	3 (4)	1 (1)	2 (2)
MAPK / PI3K mutations	BRAF V600E	1 (1)	5 (5)	3 (3)
	KRAS mutation	2 (3)	8 (8)	3 (3)
	PIK3CA mutation	5 (7)	6 (6)	6 (6)
	ERBB2 mutation	ND	1 (1)	ND
Cell cycle gene amplifications	CCND1 / E1 amplification	6 (9)	5 (5)	7 (6)
	CDK4 / 6 amplification	3 (4)	5 (5)	7 (6)
Fusions	RET	1 (1)	3 (3)	ND
	BRAF	2 (3)	3 (3)	ND
	ALK	ND	3 (3)	1 (1)
	Other	3 (4)	6 (6)	NR
RB1 loss (with TP53 alteration)		2 (3)	4 (4)	NR
No known acquired resistance alteration detected		46 (68)	54 (55)	NR



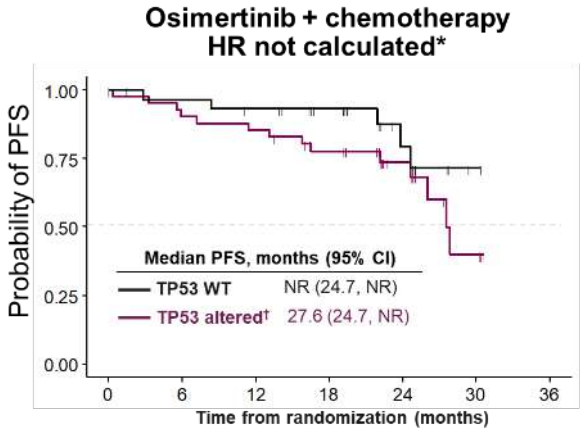
Baseline and on-treatment plasma EGFRm

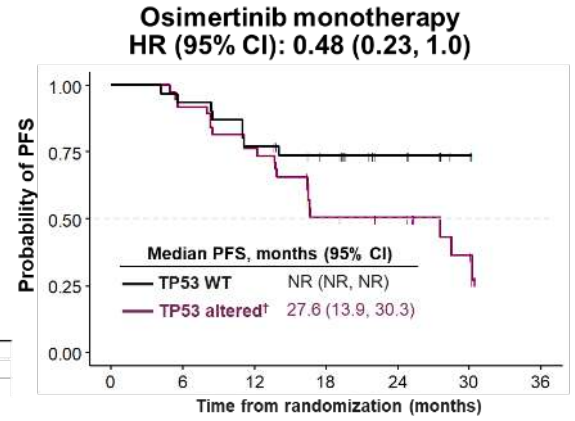






Impact of baseline TP53 alterations



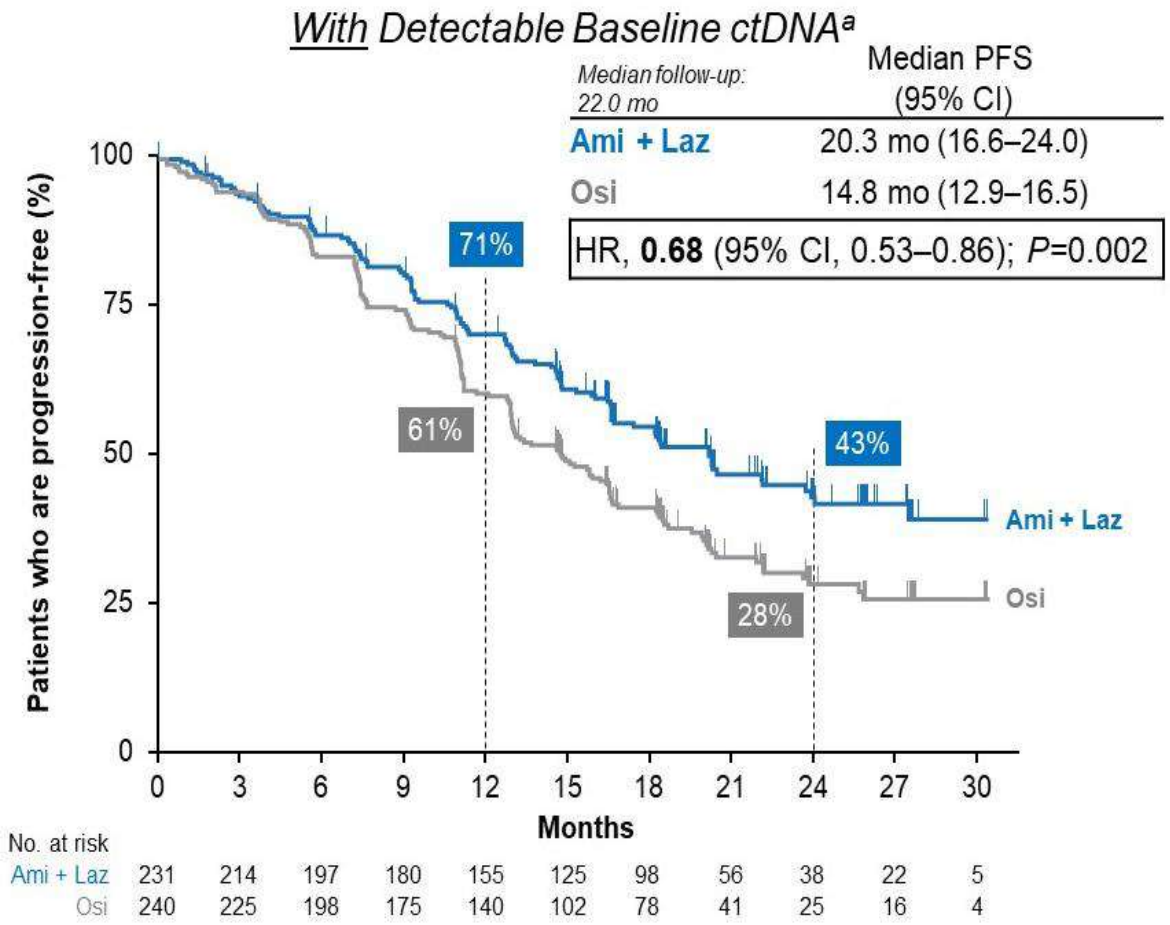


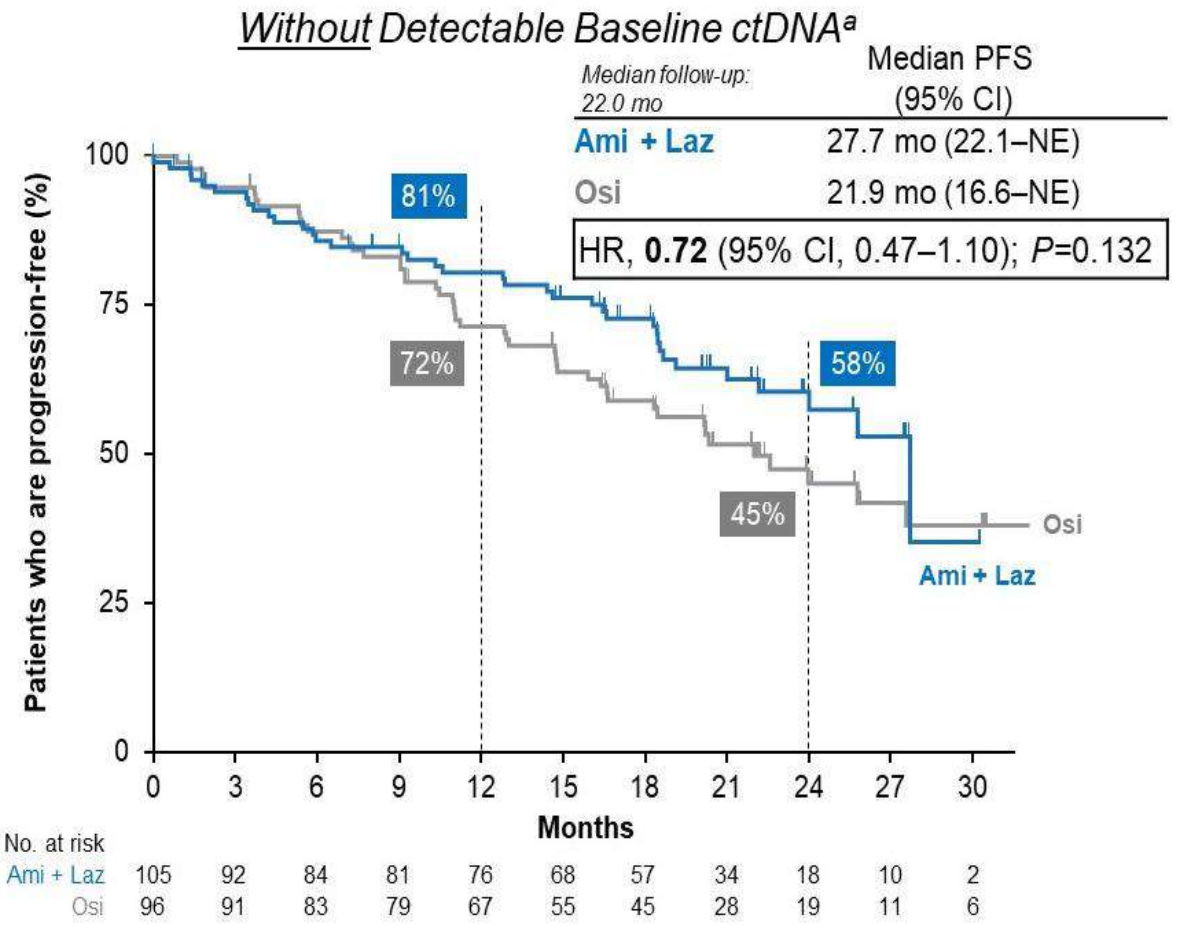
TP53 alterations appeared to be a prognostic factor for PFS across both treatment arms

ESMO Asia 2023 AACR 2024 WCLC 2024

PFS by detectable baseline EGFRm 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.

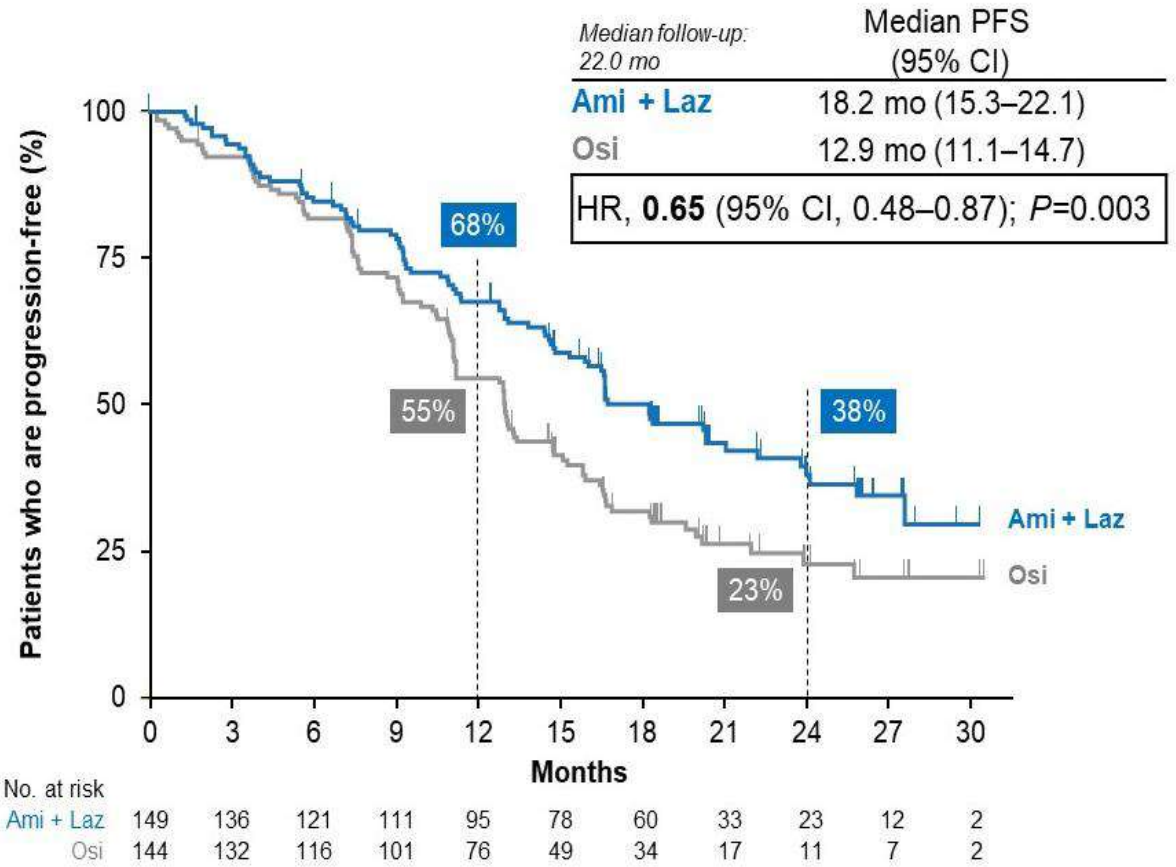
Ami, amivantamab; ctDNA, circulating tumor DNA; ddPCR, droplet digital polymerase chain reaction; Ex19del, Exon 19 deletion; Laz, lazertinib; NGS, next-generation sequencing; Osi, osimertinib.

E.Felip et al, ASCO 2024; annals of onco 2024

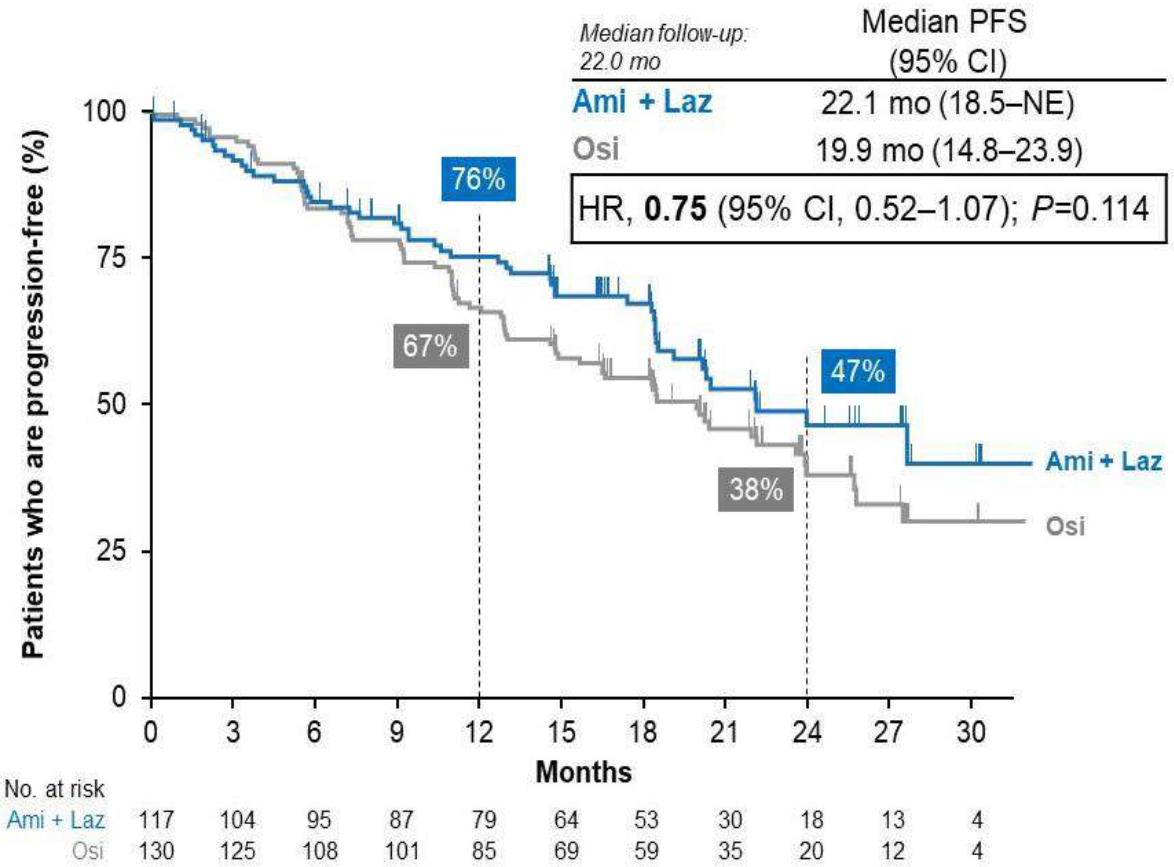
PFS by TP53 Co-mutations ands wild-type TP53

- Osimertinib showed a median PFS of 12.9 mo in patients with *TP53* co-mutations at baseline
- Amivantamab + lazertinib reduced the risk of progression or death by 35% in this subgroup

TP53 Co-mutations



Wild-type TP53

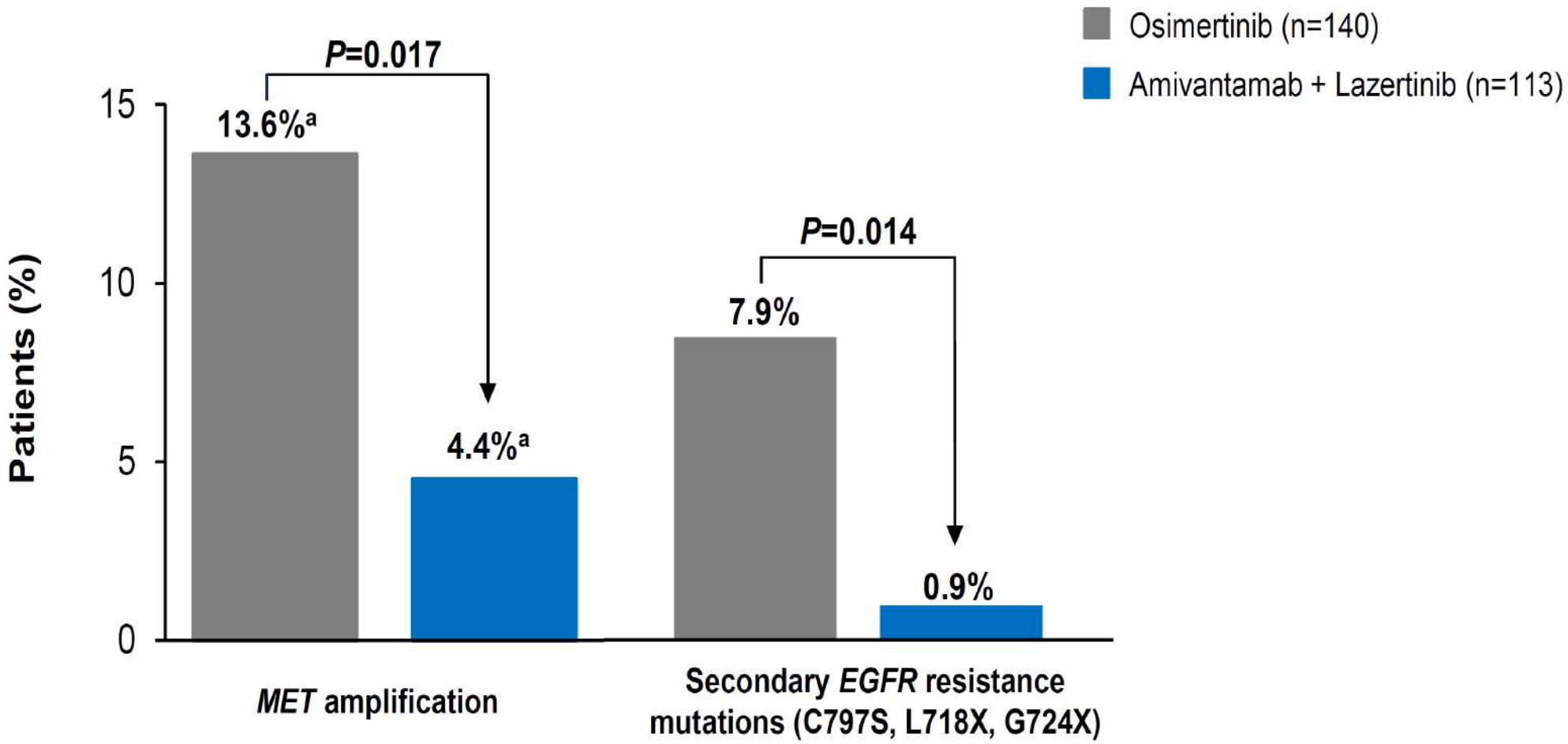


Note: Pathogenic mutations were detected with the Guardant Health G360® panel.

Ami, amivantamab; Laz, lazertinib; Osi, osimertinib.

E.Felip et al, ASCO 2024; annals of onco 2024

MET and EGFR-based resistance mechanisms

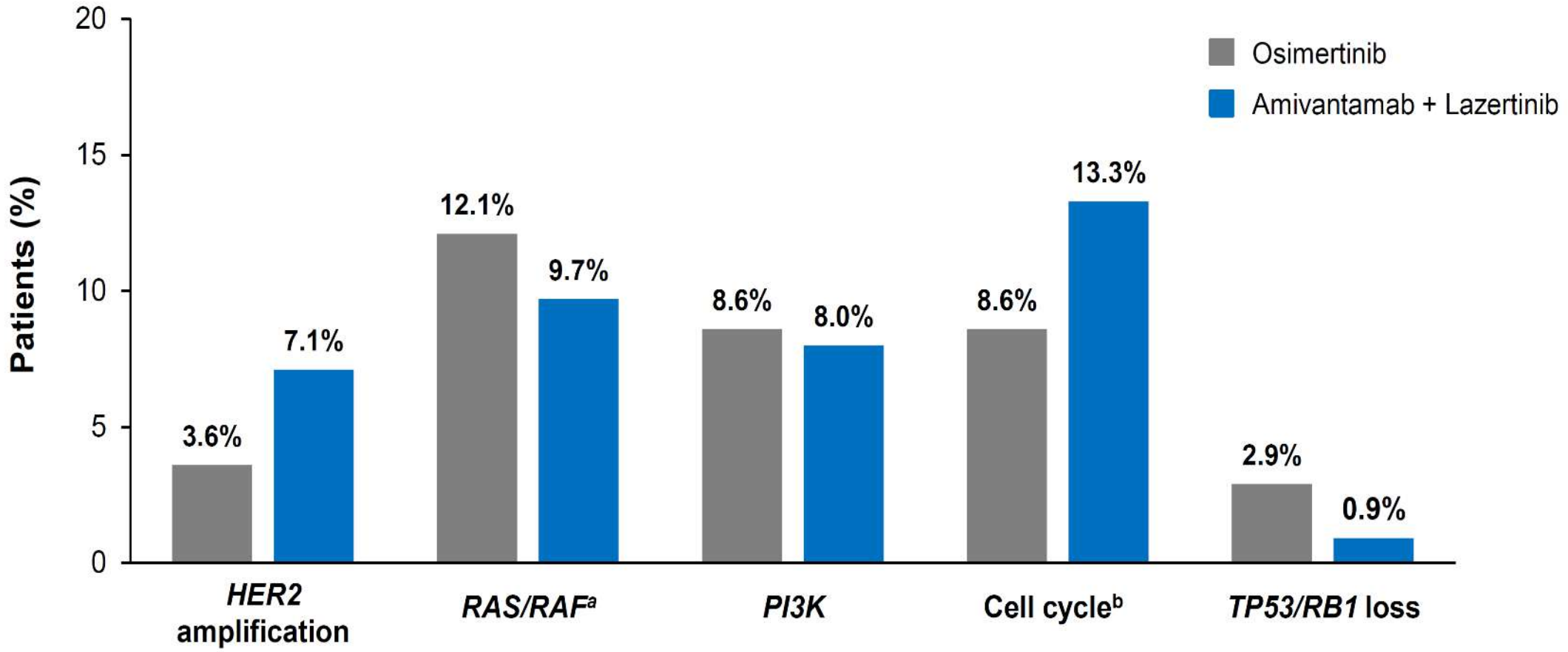


Acquired *MET* amplifications were ~3-fold lower and *EGFR* resistance mutations were ~8-fold lower for amivantamab + lazertinib versus osimertinib

B.Besse et all, ESMO 2024

MET and EGFR independent resistance mechanisms

No statistically significant differences were seen between arms for other resistance mechanisms



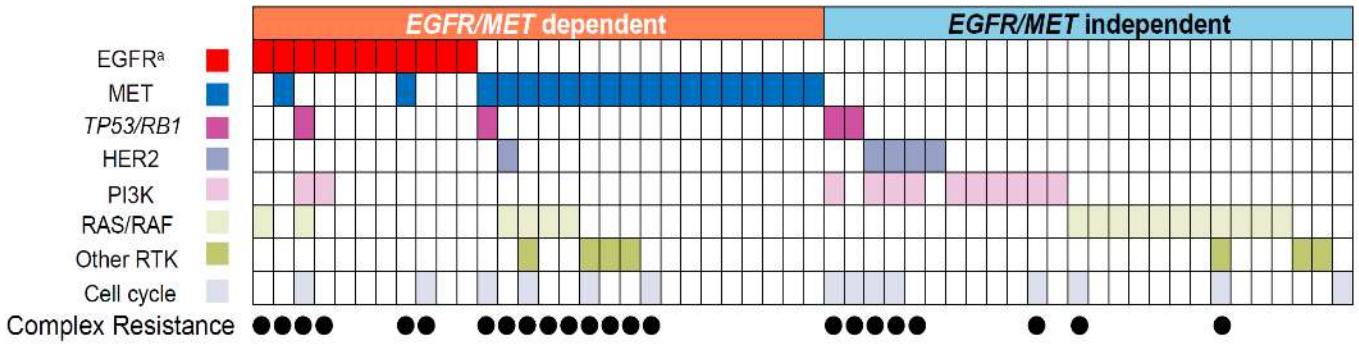
Amivantamab + lazertinib did not meaningfully increase other molecular escape pathways and had a low rate (0.9%) of *TP53/RB1* loss (associated with SCLC transformation)[1]

B.Besse et all, ESMO 2024

Frequency of complex resistance

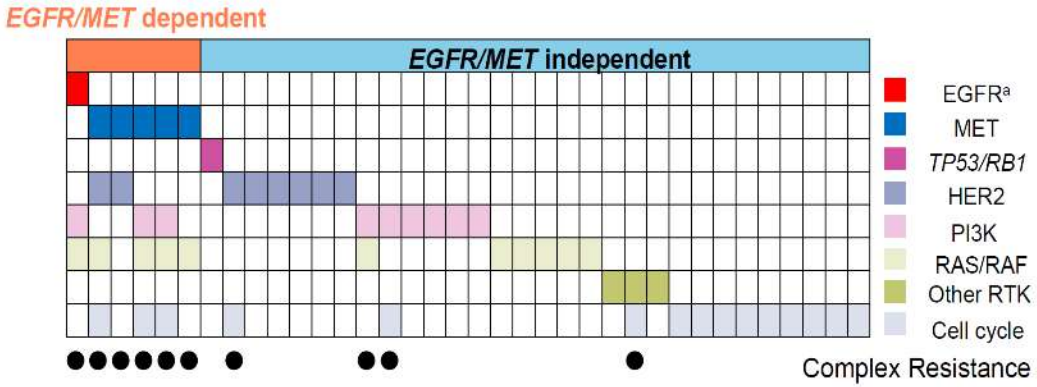
Complex resistance was defined as having 2 or more resistance pathway alterations detected by ctDNA

Osimertinib (n=54)



42.6% had alterations in ≥2 resistance pathways

Amivantamab + Lazertinib (n=36)



27.8% had alterations in ≥2 resistance pathways

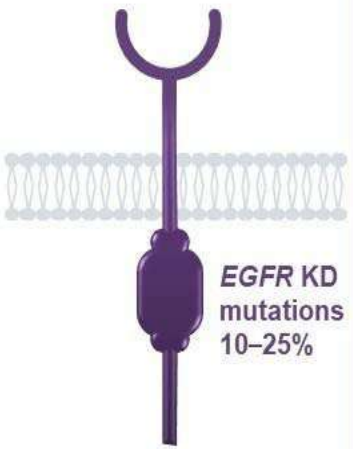
Osimertinib had a higher frequency of complex resistance than amivantamab + lazertinib (42.6% vs 27.8%)

B.Besse et all, ESMO 2024

Heterogenous mechanisms of AR on osimertinib

On-target[1–3]

EGFR

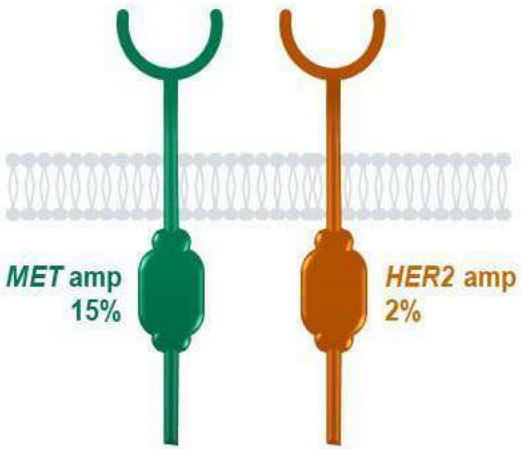


C797X
L792X
G796X
L1780
G724S
S768I
EGFR amp

~13%*

Bypass[1–3]

MET HER2



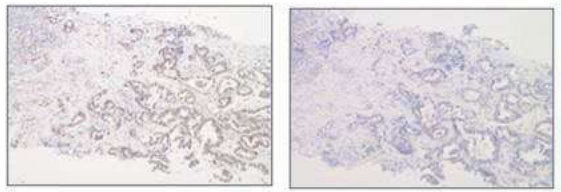
KRAS 2–8%	*PIK3CA* 4–11%	*PTEN*
BRAF 3%	*AKT*	
ERK	*MET*	

Fusions: 1–8%
ALK
BRAF
FGFR3
NTRK
RET

~26%*

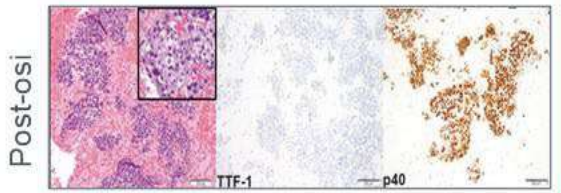
Histologic transformation[1–5]

SCLC: 5–15%



RB1/TP53 co-mutations

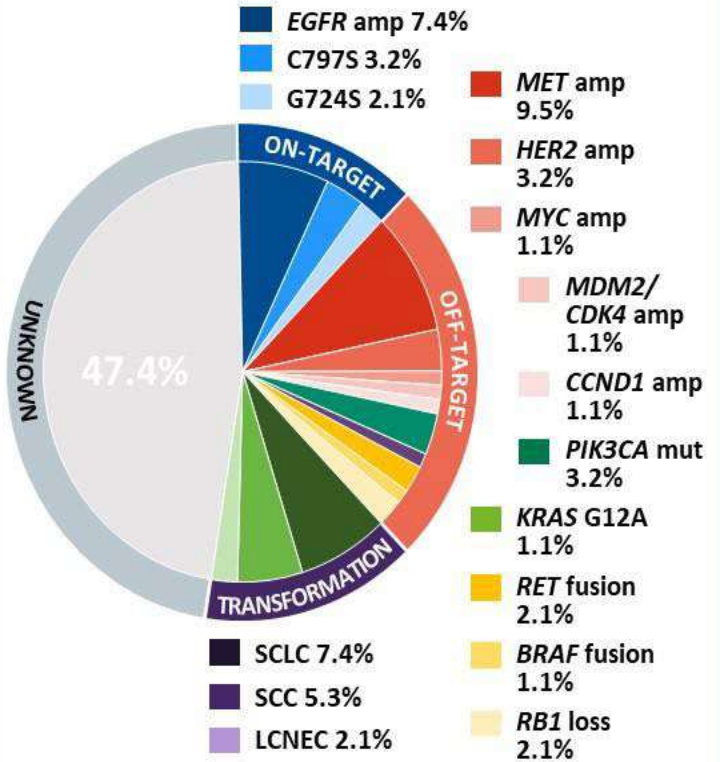
SCC: 15%



PI3K/AKT and *MYC* activation

~15%*

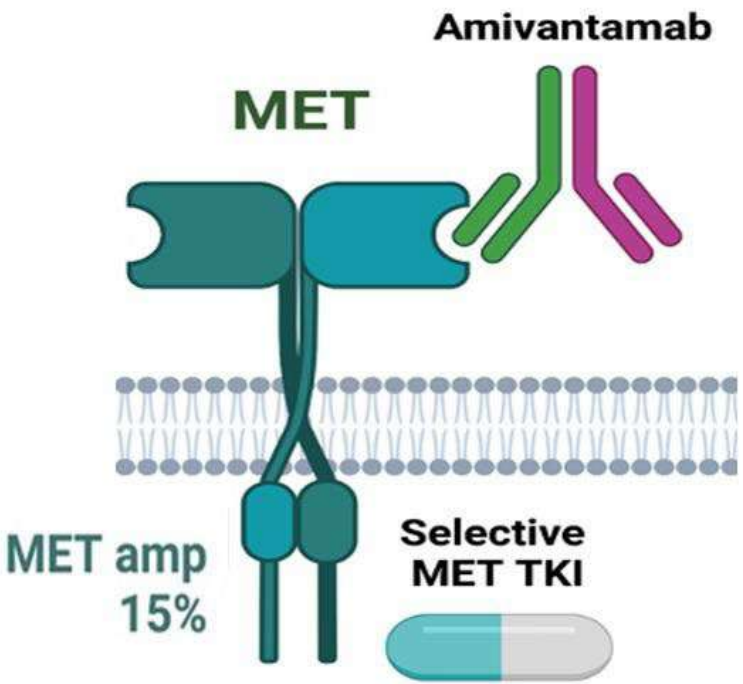
Unknown[3]



~48%*

1. Passaro - *Nature Cancer.* 2021;2:377–91; 2. Leonetti - *Br J Cancer.* 2019;121:725–37; 3. Choudhury - *J Thorac Oncol.* 2023;18:463–75; 4. Leonetti - *Front Oncol.* 2021;11:642190; 5. Schoenfeld - *Clin Cancer Res.* 2020;26:2654–63.

By-pass mechanisms: *MET* amplification



MET gene copy number (GCN) ≥5
MET/CEP7 ratio ≥2
Liquid biopsy, no clear consensus

	Trial	Drug	N	Plateau in efficacy? (%)	(mo)	(mo.)
MET TKI	TATTON	Osimertinib + Savolitinib (B1 cohort)	69	33	9.5	5.5 OS: 30.3)
	ORCHARD	Osimertinib + Savolitinib	17	41	NR	NR
	SAVANNAH	Osimertinib + Savolitinib	193	32	8.3	5.3
	INSIGHT2	Osimertinib + Tepotinib	98 Tissue 31 Lx Bx	50 52	8.5 5.6	5.6 4.6
	INSIGHT2	Tepotinib	12	8.3	NR	NR
EGFR/ MET mAb	CHRYSALIS-E	Amivantamab + Lazertinib	45	36	9.6	4.9
	CHRYSALIS-D	Amivantamab + Lazertinib	108	30	10.8	5.7
	CHRYSALIS-A (Post Osi & PBC)	Amivantamab + Lazertinib	162	33	8.4	5.1

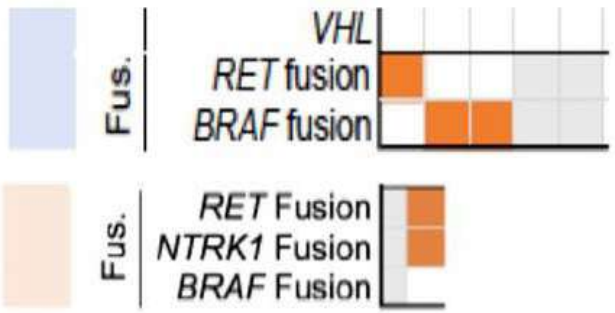
GEOMETRY-E (NCT04816214: capmatinib + osimertinib *vs.* CT). SAFFRON (NCT05261399: savolitinib + osimertinib *vs.* CT).

Hartmaier – Cancer Discov 2022 * Yu - AoO 2021 * Ahn – JTO 2022 * Kim – JTO 2023 * Mazières – AoO 2022 * Bauml – ASCO 2021 * Besse – ASCO 2023 * Shu – ASCO 2022

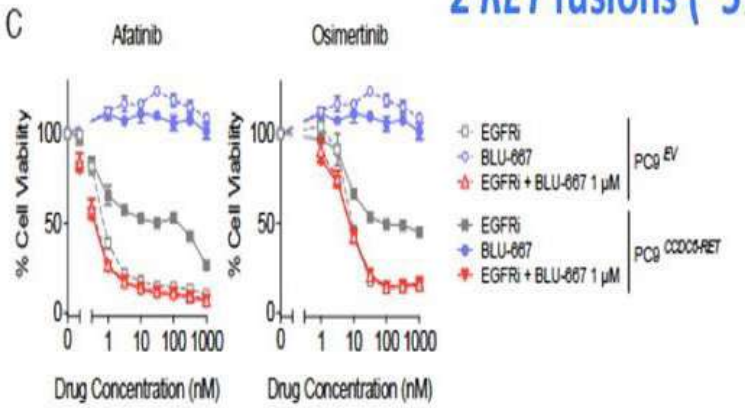
J.Remon, ASCO 2024

By pass mechanisms: *RET* fusion

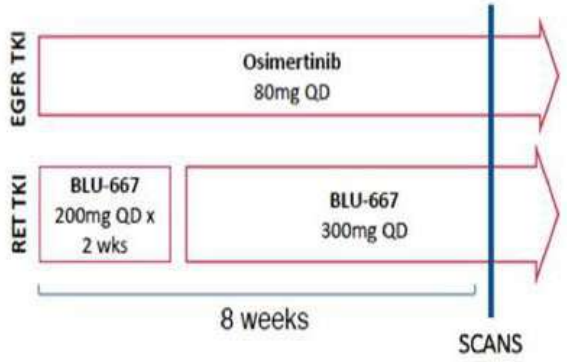
N=41 Osimertinib-resistant mechanisms tissue/blood

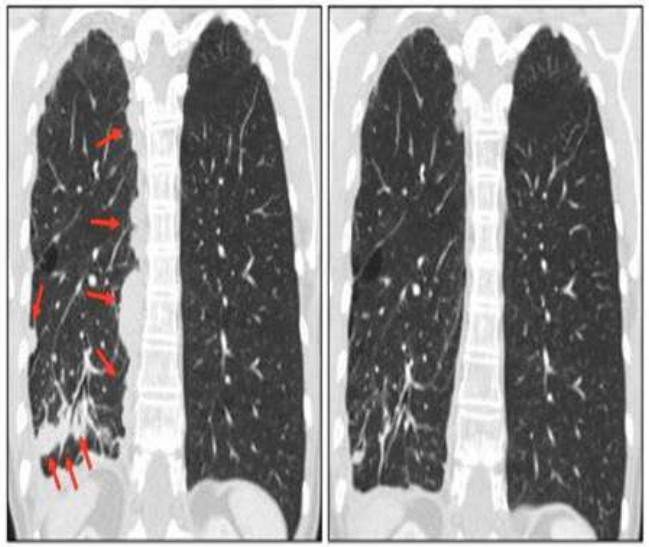


2 *RET* fusions (~5%)

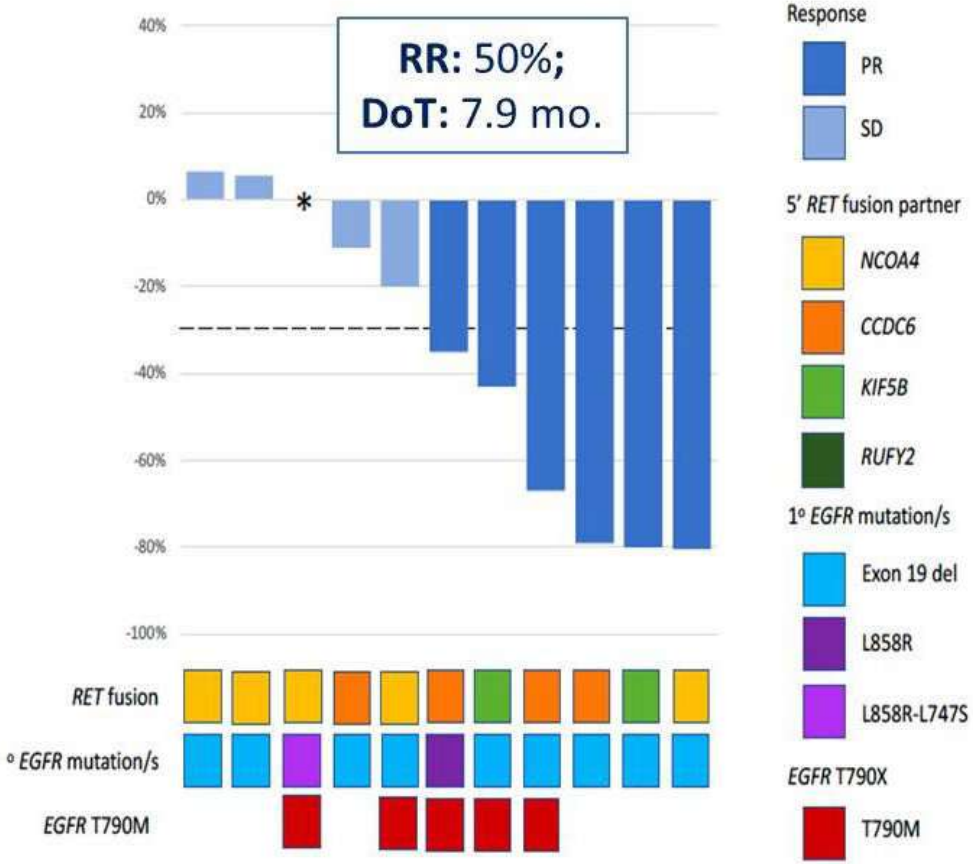


Osimertinib + BLU-667 PROTOCOL





N=14 *EGFR*-m NSCLC with *RET* as AR to osimertinib
Selpercatinib 80 mg/12h + Osimertinib 80 mg



Piotrowska – Cancer Discovery 2018 * McCoach – CCR 2018 * Rotow – CCR 2023

J.Remon, ASCO 2024

Immunotherapy at EGFR TKI PD in *EGFR*m NSCLC

Study	Treatment	N	PFS	HR; 95%IC	OS	HR, 95%IC
CheckMate 722	**Nivolumab** + PBC vs. PBC	296	**5.6 vs. 5.4**	0.75; 0.56-1.00	**19.4 vs. 15.9**	0.82; 0.61-1.10
KEYNOTE 789	**Pembrolizumab** + PBC vs PBC	480	**5.6 vs. 5.5**	0.80; 0.65-0.97	**15.9 vs. 14.7**	0.84; 0.69 -1.02
ORIENT 31	**Sintilimab** + PBC vs. PBC	318	**5.5 vs. 4.3**	0.72; 0.55-0.94	**20.5 vs. 19.2**	0.97; 0.71 -1.32
IMPOWER 150	**Atezolizumab + BVZ** + PBC vs. BVZ + PBC	58	**10.3 vs. 6.1**	0.41; 0.23-0.75	**29.4 vs. 18.1**	0.60; 0.31 -1.14
IMPOWER 151	**Atezolizumab + BVZ** + PBC vs. BVZ + PBC	163	**8.5 vs. 8.3**	0.86; 061-1.21	NR	NR
ATLAS	**Atezolizumab + BVZ** + PBC vs. PBC	215	**8.4 vs. 5.6**	0.62; 0.45-0.86	**20.6 vs. 20.3**	1.01; 0.69 -1.46
ORIENT 31	**Sintilimab + IBI305** + PBC vs. PBC	318	**7.2 vs. 4.3**	0.51; 0.39-0.67	**21.1 vs. 19.2**	0.98; 0.72 -1.34
ABC-Lung	**Atezolizumab + BVZ** + PBC vs. Atezolizumab + BVZ + Pem	95	**6.3 vs. 7.5**	NR	**15.4 vs. 15.5**	NR
HARMONi-A	**Ivonescimab** + PBC vs. PBC + Placebo	322	**7.1 vs. 4.8**	0.46; 0.34-0.62	**17.1 vs. 14.5**	0.80; 0.59-1.08

Mok – JCO 2024 * Yang – ASCO 2023 * Lu – LRM 2023 * Reck – LRM 2019 * Nogami – JTO 2021 * Zho – WCLC 2023 * Ahn – JCO 2

(PBC: platinum-based chemotherapy. BVZ: Bevacizumab. Cross trial comparison should be undertake

HARMONI-3 Trial (NCT05184712). N=470

J.Remon, ASCO 2024

HARMONi-A (Ivonescimab)

- Ivonescimab (AK112/SMT112) is an anti-PD-1/VEGF bispecific antibody displaying cooperative binding characteristics.

Key Eligibility Criteria

- nsq-NSCLC (Stage IIIB/C ineligible for surgery or local therapy and IV)
- EGFR sensitive mutation positive
- ECOG PS 0 or1
- Regardless PD-L1 expression

Stratification Factors:

- Exposure to 3rd EGFR-TKI before (yes vs. no)
- Brain metastases (yes vs. no)

R (1:1)

Ivonescimab
20mg/kg
+
Pemetrexed 500 mg/m²
Carboplatin AUC5
Q3W for 4 cycles

Ivonescimab
20mg/kg Q3W
+
Pemetrexed 500 mg/m² Q3W

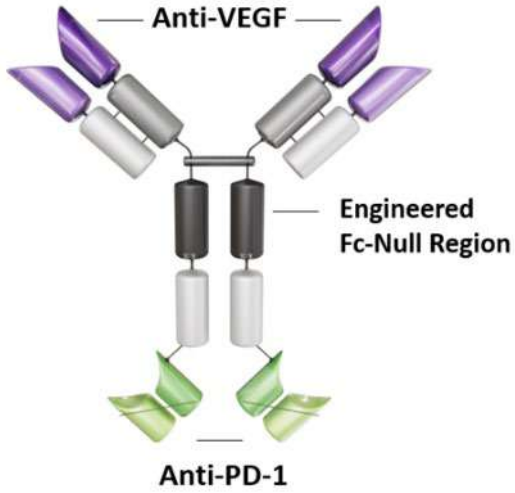
Placebo
+
Pemetrexed 500 mg/m²
Carboplatin AUC5
Q3W for 4 cycles

Placebo
Q3W
+
Pemetrexed 500 mg/m² Q3W

Treatment until:

- Intolerable toxicity
- No clinical benefit
- Initiation of new anti-tumor therapy

Up to 24 months



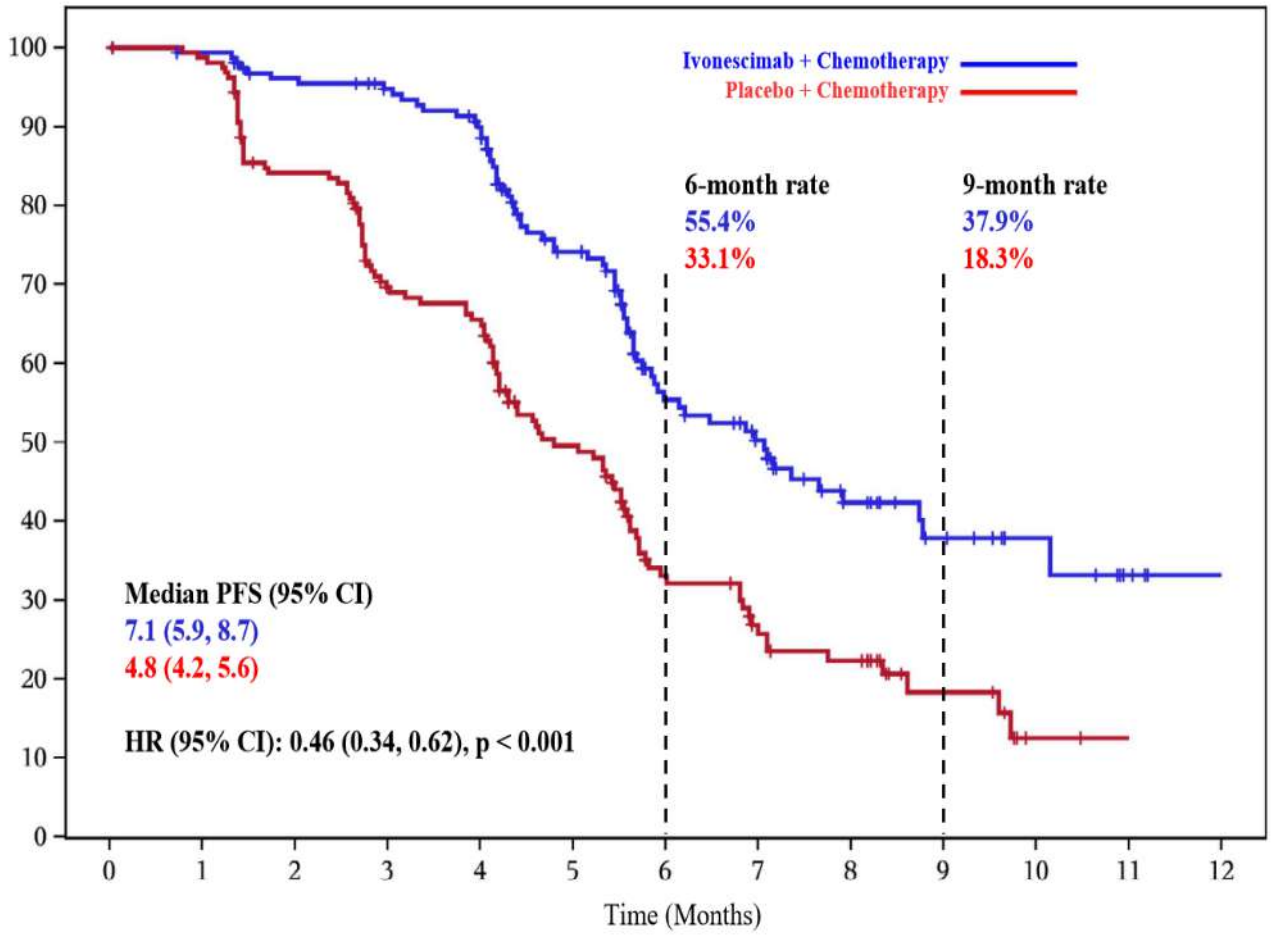
Endpoints

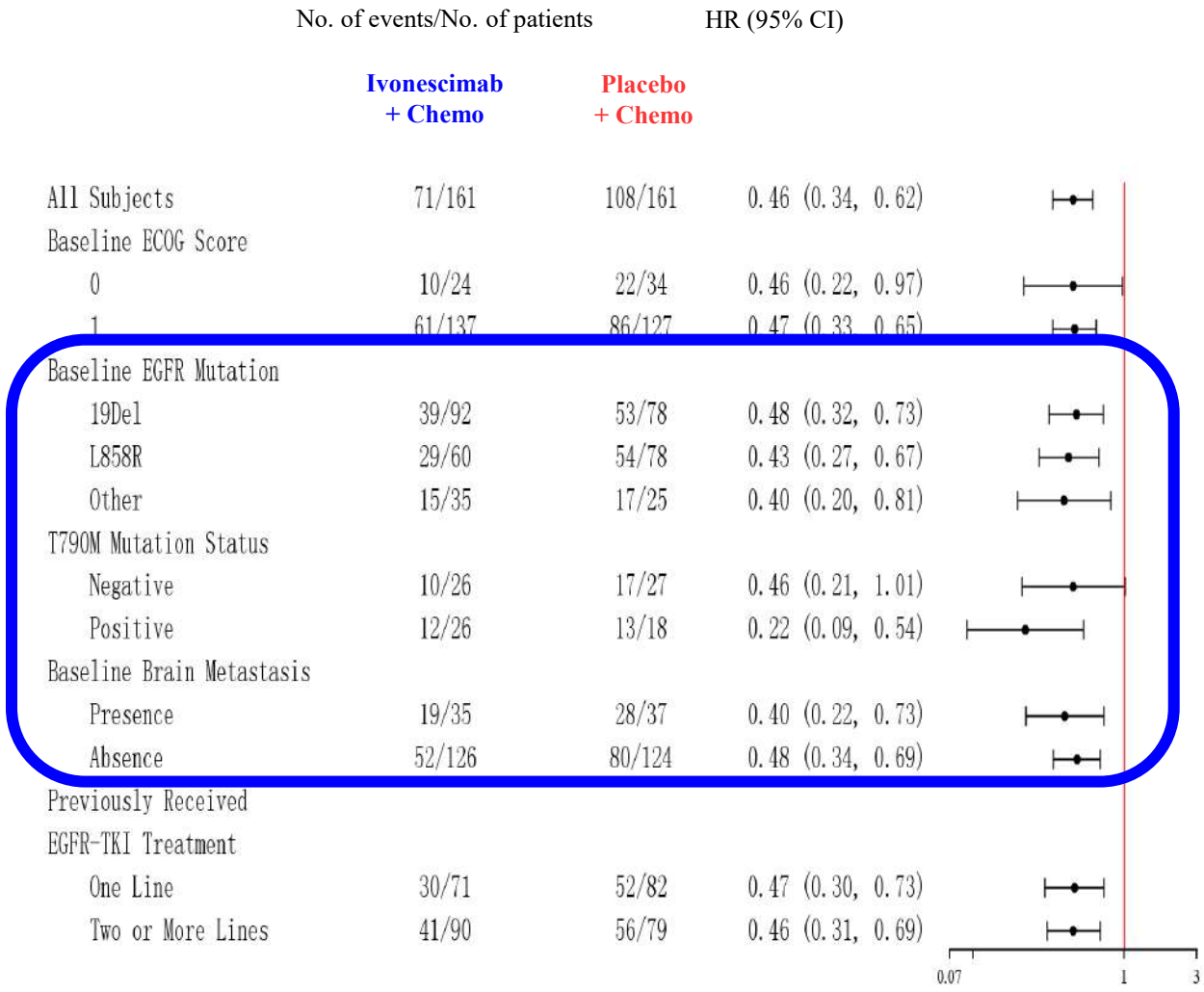
- Primary: Progression-free survival by independent radiologic review committee (IRRC)
- Secondary: Overall survival, Response rate, Duration of response, Time to response and Safety

Li Zhang et al, ASCO 2024

Study Met primary endpoint of PFS per IRRC

PFS



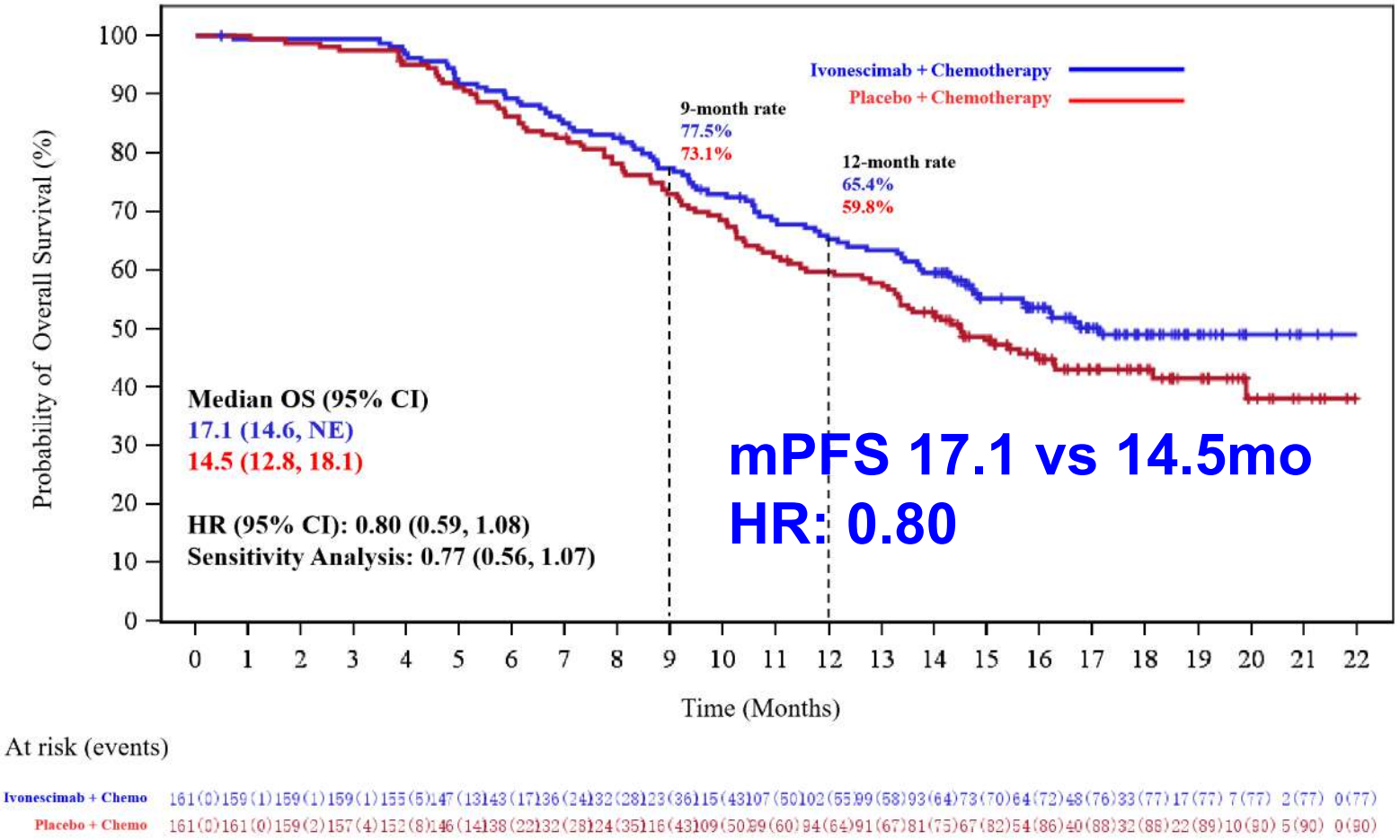


mPFS: 7.1 vs 4.8mo

HR: 0.46, p<0.001

Li Zhang et al, ASCO 2024

Overall Survival (at 52% of Data Maturity)



HR: 0.80 (0.59, 1.08) after 52% of data maturity

OS is consistent for both analysis

Data cutoff date: December 2023 (median follow-up of 17.6 months)

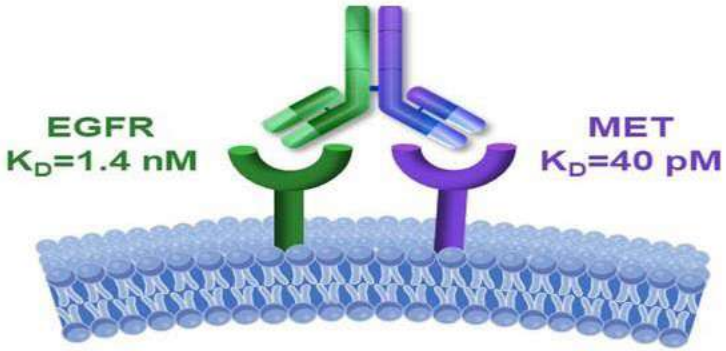
HR, hazard ratio; CI, confidence interval.

Li Zhang et al, ASCO 2024

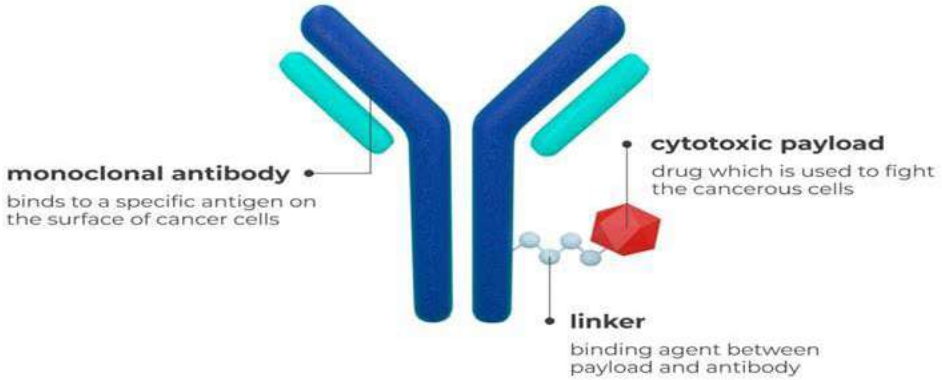
Agnostic treatment upon osimertinib disease PD

NEW AGNOSTIC HEROES

Bi-specific antibody Anti-EGFR & MET



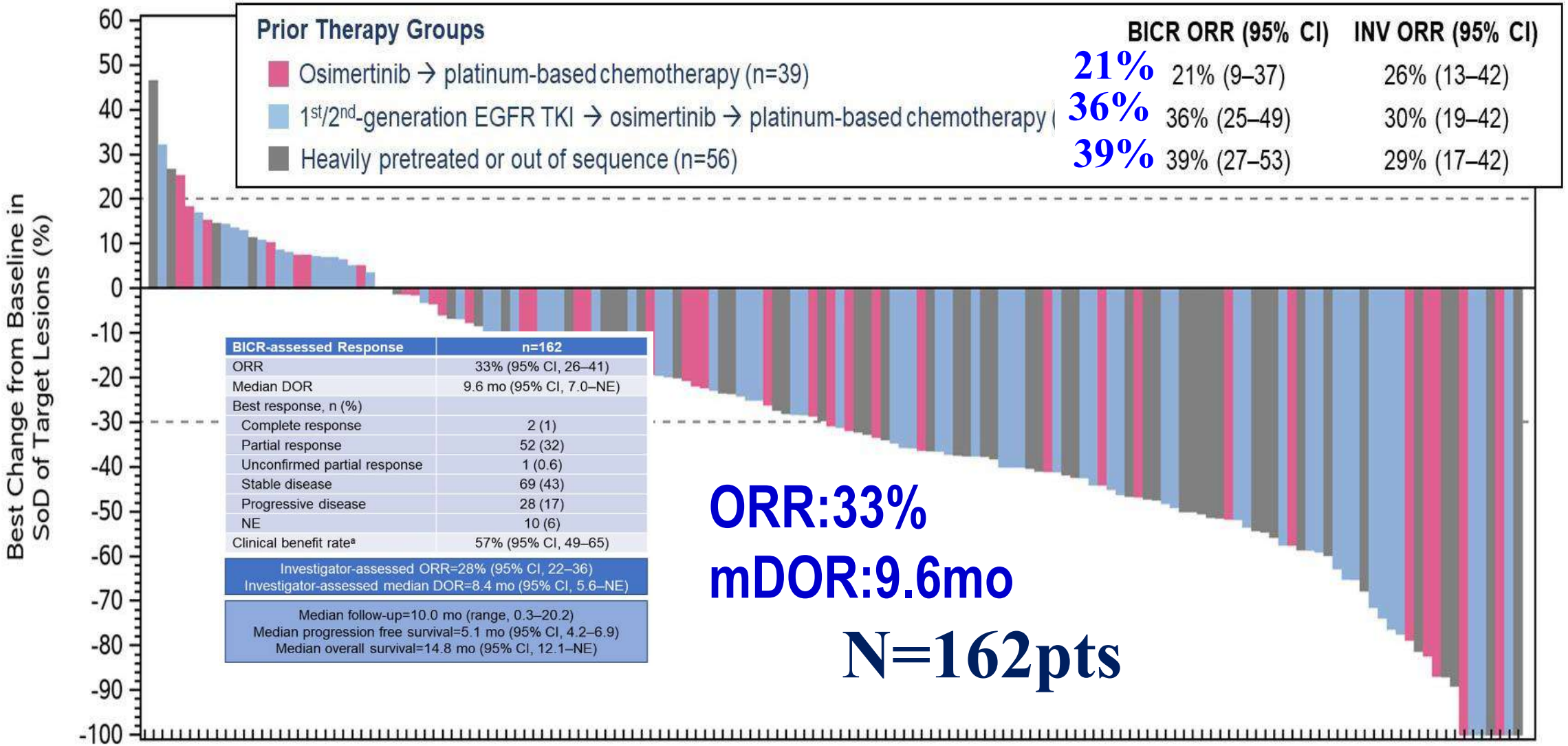
Antibody drug conjugates



J.Remon, ASCO 2024

CHRYSALIS-2 (Amivantamab+Lazertinib)

Best Antitumor Response and ORR by Prior Therapy Group



Catherine A.Shu et al, ASCO 2022

MARIPOSA-2

Key Eligibility Criteria

- Locally advanced or metastatic NSCLC
- Documented *EGFR* Ex19del or L858R
- *Progressed on or after osimertinib monotherapy (as most recent line)*
- ECOG PS 0 or 1
- Stable brain metastases were allowed; radiation/definitive therapy was not required (untreated)

Stratification Factors

- Osimertinib line of therapy (1st vs 2nd)
- Asian race (yes or no)
- History of brain metastases (yes or no)

2:2:1 Randomization (N=657)

Serial brain MRIs were required for all patients[a]

Amivantamab-Lazertinib-Chemotherapy (n=263)

Chemotherapy (n=263)

Amivantamab-Chemotherapy (n=131)

Dosing (in 21-day cycles)

Amivantamab: 1400 mg (1750 mg if ≥80 kg) for the first 4 weeks, then 1750 mg (2100 mg if ≥80 kg) every 3 weeks starting at Cycle 3 (week 7)

Lazertinib: 240 mg daily starting after completion of carboplatin[b]

Chemotherapy administered at the beginning of every cycle:

- **Carboplatin:** AUC5 for the first 4 cycles
- **Pemetrexed:** 500 mg/m^2 until disease progression

Dual primary endpoint of PFS[c] by BICR per RECIST v1.1:

- **Amivantamab-Lazertinib-Chemotherapy** vs Chemotherapy
- **Amivantamab-Chemotherapy** vs Chemotherapy

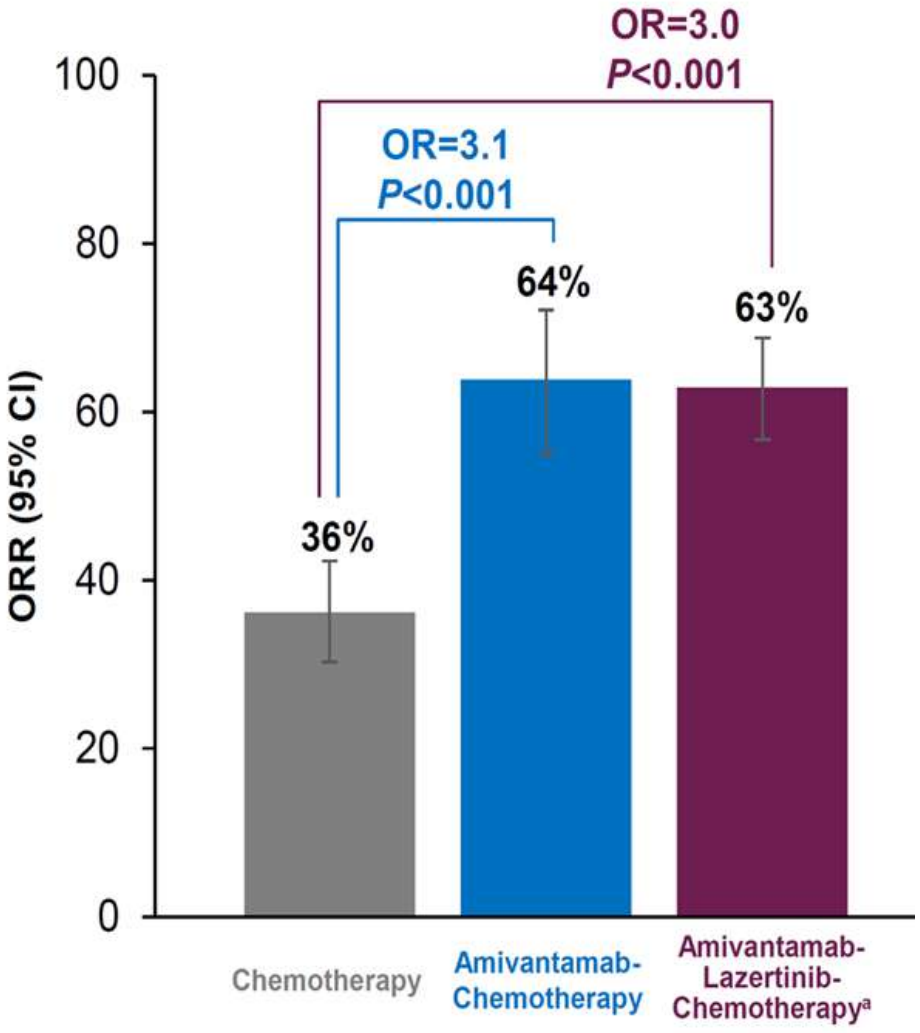
Secondary endpoints:

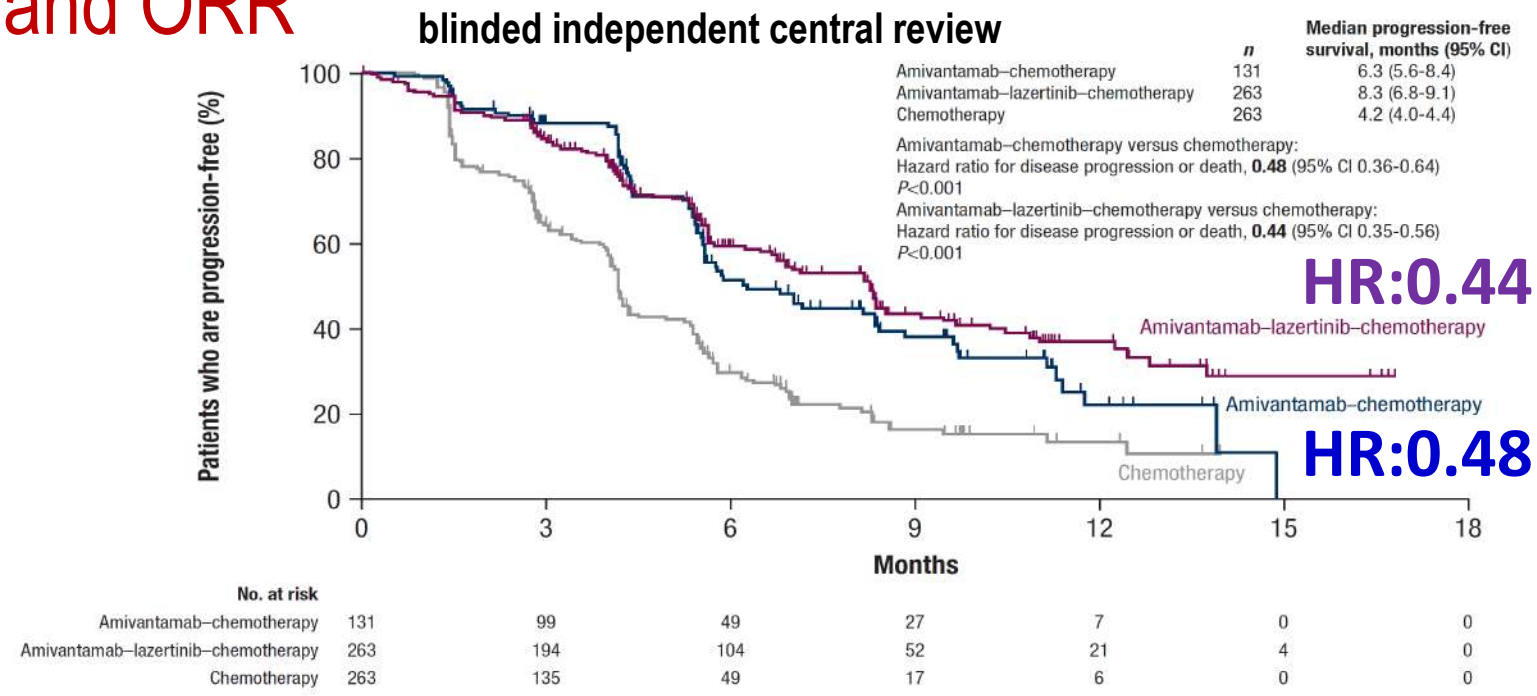
- Objective response rate (ORR)[c]
- Duration of response (DoR)
- Overall survival (OS)[c]
- Intracranial PFS
- Time to subsequent therapy[d]
- PFS after first subsequent therapy (PFS2)[d]
- Symptomatic PFS[d]
- Safety

A.Passaro et al, ESMO 2023; Annals of onco 2023

Ami/Chemo and Ami/Lazer/Chemo vs Chemo

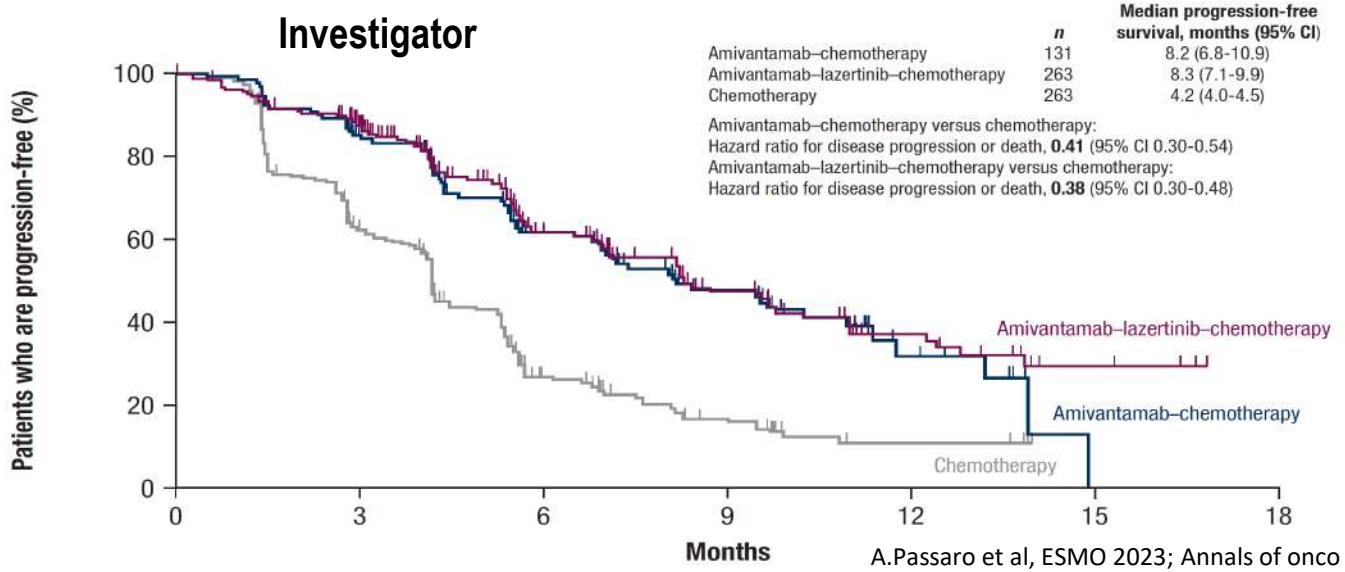
lead to improvements in PFS and ORR





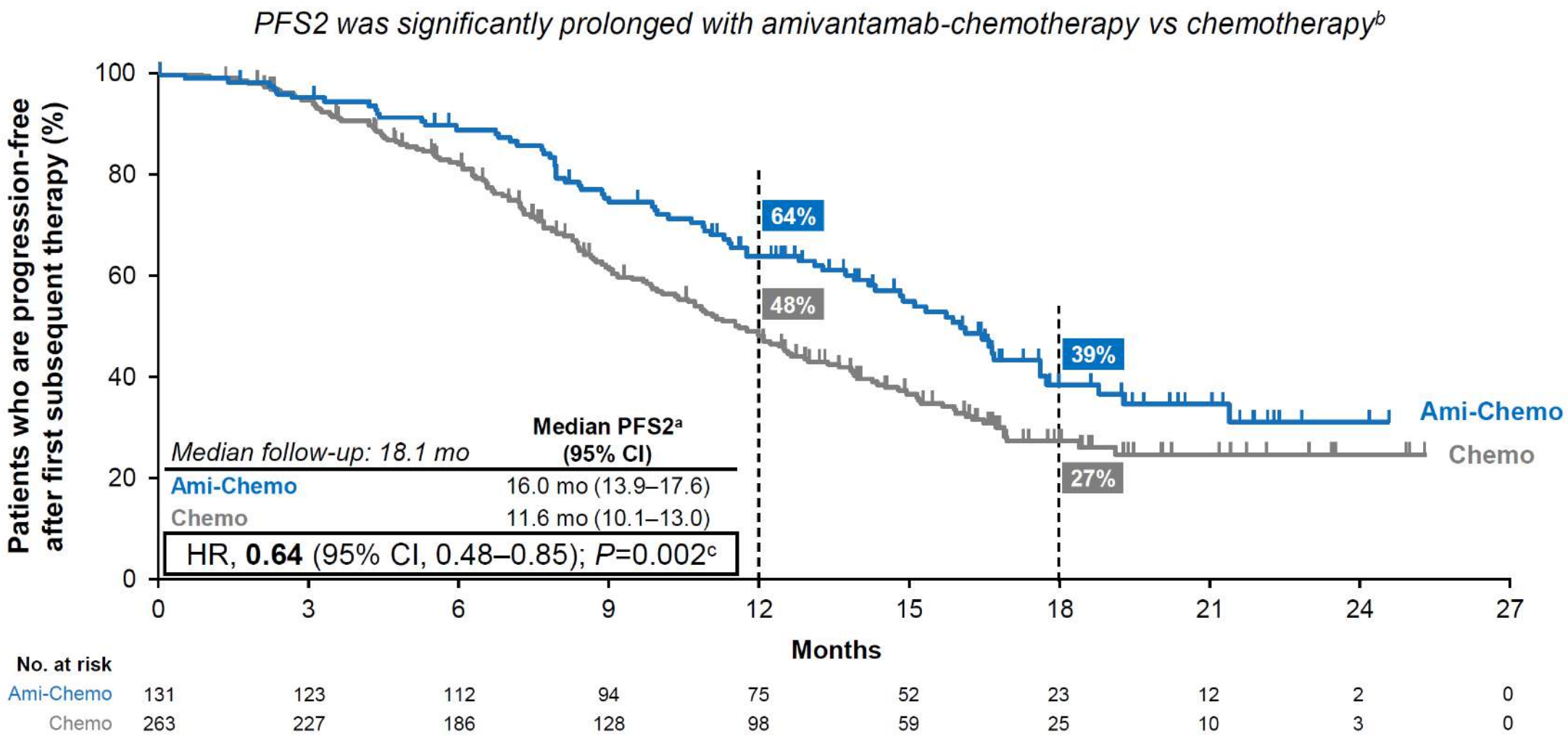
No. at risk

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



A.Passaro et al, ESMO 2023; Annals of onco 2023

PFS after first subsequent therapy

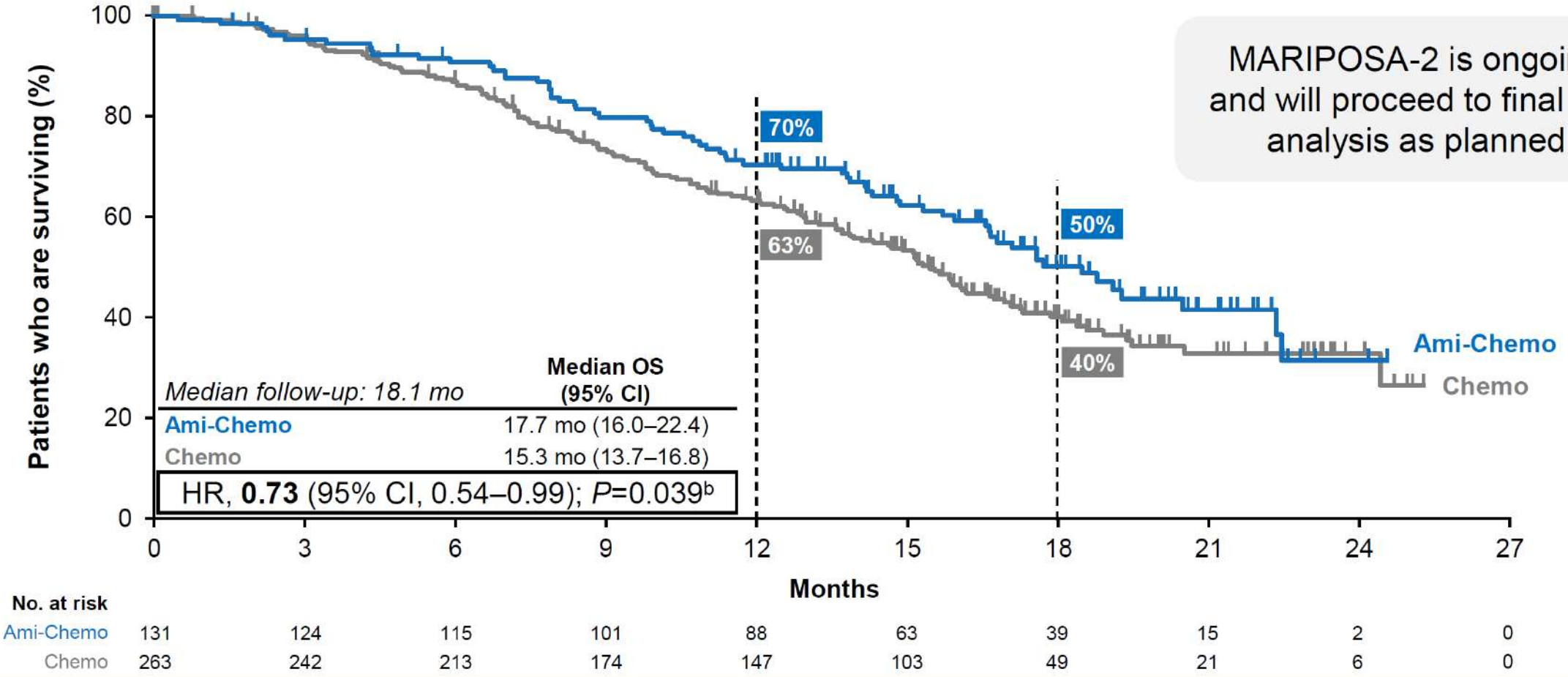


18-month landmark PFS2 was 39% for amivantamab-chemotherapy vs 27% for chemotherapy

S.Popat et al, ESMO 2024

Overall survial

Amivantamab-chemotherapy continues to demonstrate a clear and improving OS trend vs chemotherapy[a]



MARIPOSA-2 is ongoing and will proceed to final OS analysis as planned

18-month landmark for OS was 50% for amivantamab-chemotherapy vs 40% for chemotherapy

[a]OS benefit of amivantamab-chemotherapy vs chemotherapy was generally consistent among pre-defined subgroups. [b]P-value is from a log-rank test stratified by osimertinib line of therapy (first-line vs second-line), history of brain metastases (yes or no), and Asian race (yes vs no). OS was evaluated at a 2-sided alpha of 0.0142.

Ami, amivantamab; chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; OS, overall survival.

S.Popat et al, ESMO 2024

Signficant toxicities with Ami/Chemo and Ami/Lazer/Chemo

Most common TEAEs (≥25%) by preferred term, n (%)	Chemotherapy (n=243)		Amivantamab-Chemotherapy (n=130)		Amivantamab-Lazertinib-Chemotherapy[a] (n=263)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Associated with EGFR inhibition						
Paronychia	1 (0.4)	0	48 (37)	3 (2)	133 (51)	11 (4)
Rash	12 (5)	0	56 (43)	8 (6)	126 (48)	17 (6)
Stomatitis	21 (9)	0	41 (32)	1 (1)	120 (46)	24 (9)
Diarrhea	16 (7)	1 (0.4)	18 (14)	1 (1)	68 (26)	10 (4)
Associated with MET inhibition						
Hypoalbuminemia	21 (9)	1 (0.4)	29 (22)	3 (2)	104 (40)	12 (5)
Peripheral edema	15 (6)	0	42 (32)	2 (2)	85 (32)	1 (0.4)
Associated with Chemotherapy						
Neutropenia	101 (42)	52 (21)	74 (57)	59 (45)	181 (69)	144 (55)
Thrombocytopenia	72 (30)	22 (9)	57 (44)	19 (15)	158 (60)	96 (37)
Anemia	97 (40)	23 (9)	51 (39)	15 (12)	141 (54)	48 (18)
Leukopenia	68 (28)	23 (9)	37 (28)	26 (20)	106 (40)	71 (27)
Other						
Infusion-related reaction	1 (0.4)	0	76 (58)	7 (5)	148 (56)	9 (3)
Nausea	90 (37)	2 (1)	58 (45)	1 (1)	131 (50)	16 (6)
Constipation	72 (30)	0	50 (38)	1 (1)	96 (37)	3 (1)
Decreased appetite	51 (21)	3 (1)	40 (31)	0	85 (32)	7 (3)
Vomiting	42 (17)	1 (0.4)	32 (25)	1 (1)	76 (29)	10 (4)
Fatigue	47 (19)	4 (2)	36 (28)	4 (3)	69 (26)	15 (6)
Asthenia	40 (16)	5 (2)	34 (26)	1 (1)	67 (25)	14 (5)
Alanine aminotransferase increased	67 (28)	10 (4)	26 (20)	7 (5)	55 (21)	14 (5)
AESIs by grouped term, n (%)						
Rash[b]	30 (12)	0	92 (71)	13 (10)	197 (75)	40 (15)
VTE[c]	11 (5)	7 (3)	13 (10)	3 (2)	58 (22)	17 (6)
ILD	0	0	2 (2)	1 (1)	7 (3)	5 (2)
AEs leading to death	3 (1)		3 (2)		14 (5)	
Any AE leading to treatment:						
Interruptions of any agent	81 (33)		84 (65)		202 (77)	
Reductions of any agent	37 (15)		53 (41)		171 (65)	
Discontinuations of any agent	9 (4)		24 (18)		90 (34)	

40%

50%

56%

VTE: 10%

VTE: 22%

- **Ami/Lazer/Chemo led to the highest rates of toxicities, though Ami/Chemo was also challenging.**
  - 4 drugs: 92% grade ≥ 3 TEAE's
  - 3 drugs: 72% grade ≥ 3 TEAE's

Ami/Lazer/Chemo

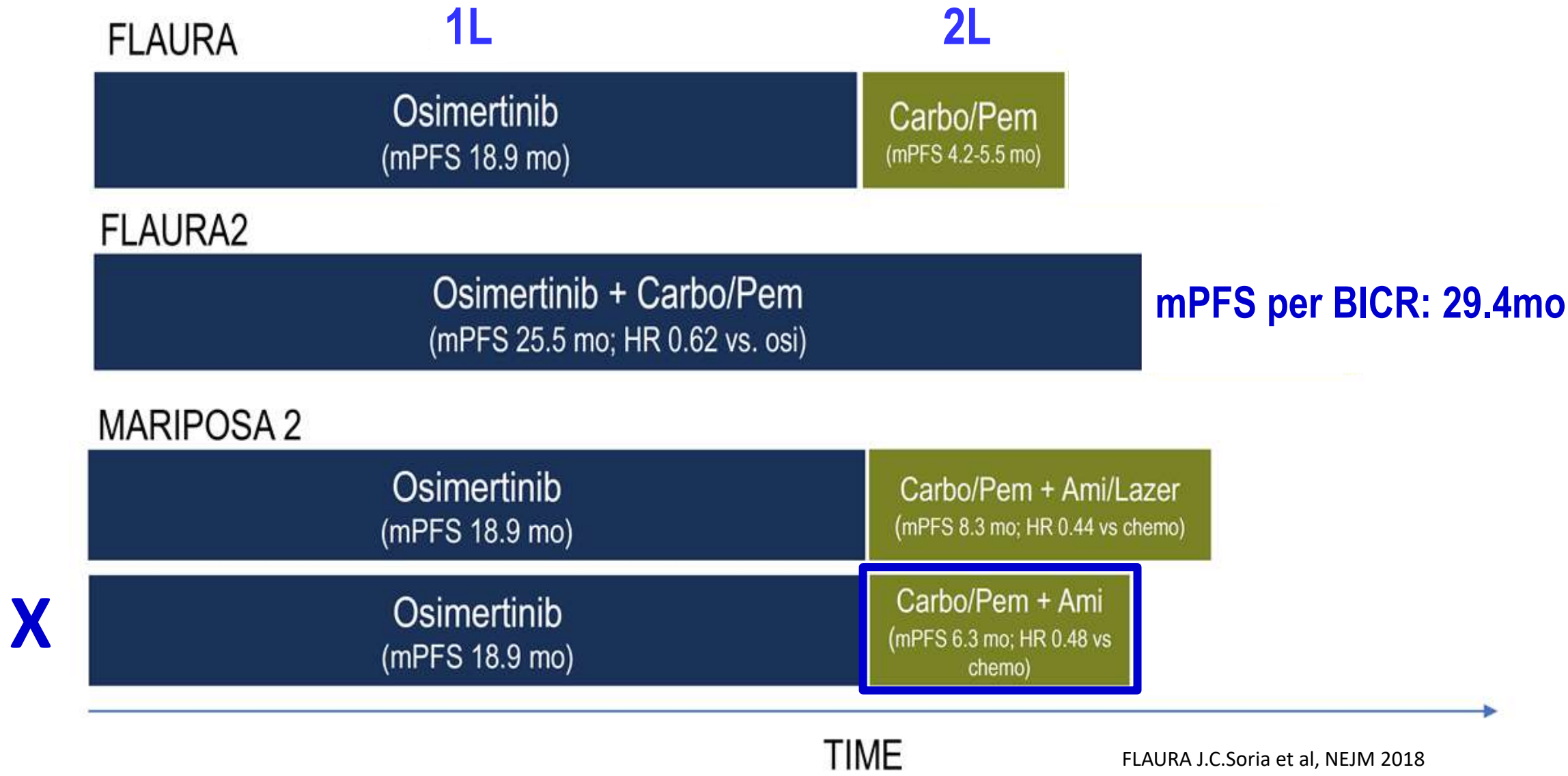
- Interruption: 77%
- Dose reduction: 65%
- Discontinuation: 34%

- Lazertinib appears to add significant toxicity to this regimen – which patients really need it?
- Will delayed initiation of Lazertinib help improve the safety profile of Ami/Lazer/Chemo?

VTE: venous thromboembolism

A.Passaro et al, ESMO 2023; Annals of onco 2023

Management of EGFR-mutant NSCLC in early 2023



FLAURA J.C.Soria et al, NEJM 2018
FLAURA 2 D.Planchard et al, NEJM 2023
MARIPOSA-2 A.Passaro et al, Annals of onco 2023

SC vs IV Amivantamab + Lazertinib (PALOMA-3)

Key eligibility criteria

- Locally advanced or metastatic NSCLC
- Disease had progressed on or after osimertinib and platinum-based chemotherapy, irrespective of order
- Documented *EGFR* Ex19del or L858R
- ECOG PS 0–1

Stratification factors

- Brain metastases (yes or no)
- *EGFR* mutation type (Ex19del vs L858R)
- Race (Asian vs non-Asian)
- Type of last therapy (osimertinib vs chemotherapy)

1:1 randomization (N=418)

SC Amivantamab + Lazertinib (n=206)

IV Amivantamab + Lazertinib (n=212)

Dosing (in 28-day cycles)

SC Amivantamab[a,b] (co-formulated with rHuPH20 and administered by manual injection): 1600 mg (2240 mg if ≥80 kg) weekly for the first 4 weeks, then every 2 weeks thereafter

IV Amivantamab[b]: 1050 mg weekly (1400 mg if ≥80 kg) for the first 4 weeks, then every 2 weeks thereafter

Lazertinib: 240 mg PO daily

Prophylactic anticoagulation recommended for the first 4 months of treatment

Co-primary endpoints[c]**:**

- C_{trough} (noninferiority)[d]
- C2 AUC (noninferiority)[e]

Secondary endpoints:

- ORR (noninferiority)
- PFS (superiority)
- DoR
- Patient satisfaction[f]
- Safety

Exploratory endpoints:

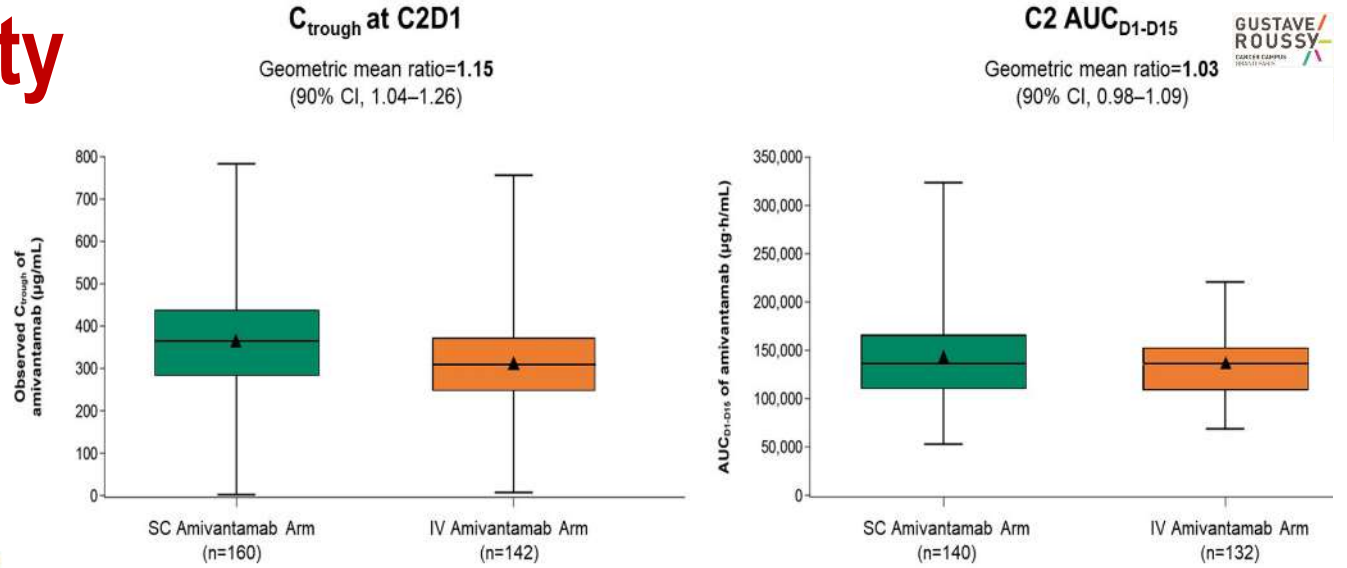
- OS

N.B.Leighl et al, ASCO 2024

PK Endpoints met noninferiority criteria

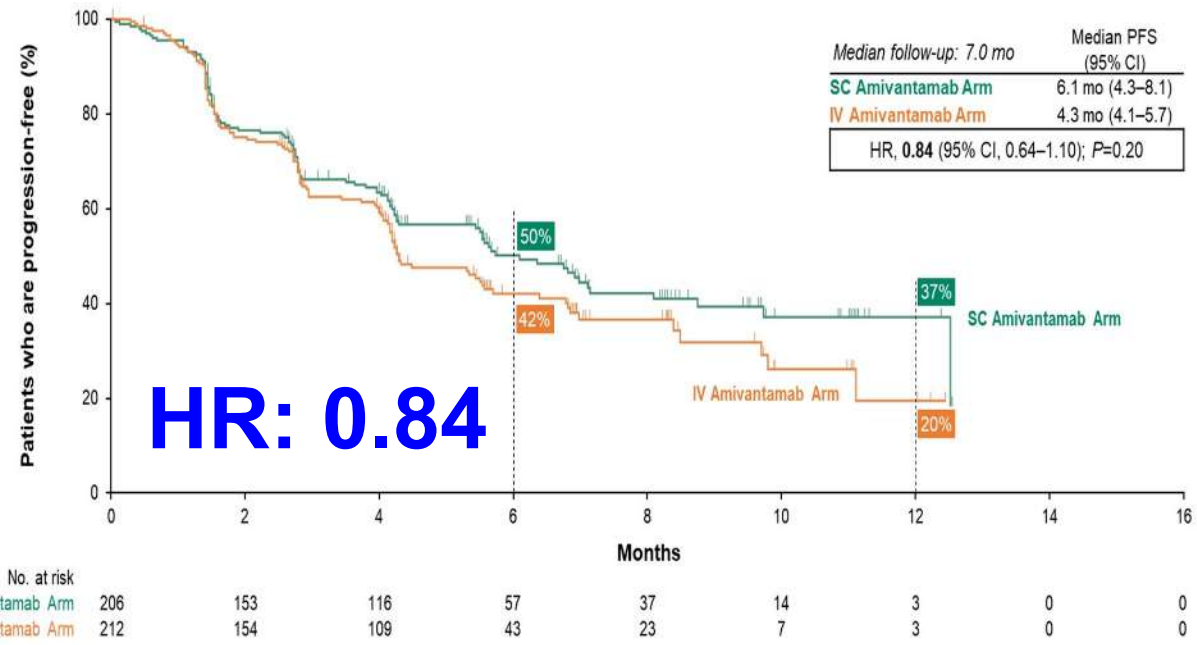
ORR and PFS

	SC Amivantamab Arm (n=206)	IV Amivantamab Arm (n=212)
ORR, % (95% CI)[a]		
All responders	**30 (24–37)**	**33 (26–39)**
	Relative risk, 0.92 (95% CI, 0.70–1.23); *P*=0.001	
Confirmed responders	**27 (21–33)**	**27 (21–33)**
	Relative risk, 0.99 (95% CI, 0.72–1.36); *P*<0.001	
Best response, n (%)		
CR	1 (0.5)	1 (0.5)
PR	61 (30)	68 (32)
SD	93 (45)	81 (38)
PD	37 (18)	42 (20)
Not evaluable	14 (7)	20 (9)
DCR, % (95% CI)[b]	**75 (69–81)**	**71 (64–77)**
Median time to response (range), mo	**1.5 (1.2–6.9)**	**1.5 (1.2–9.9)**



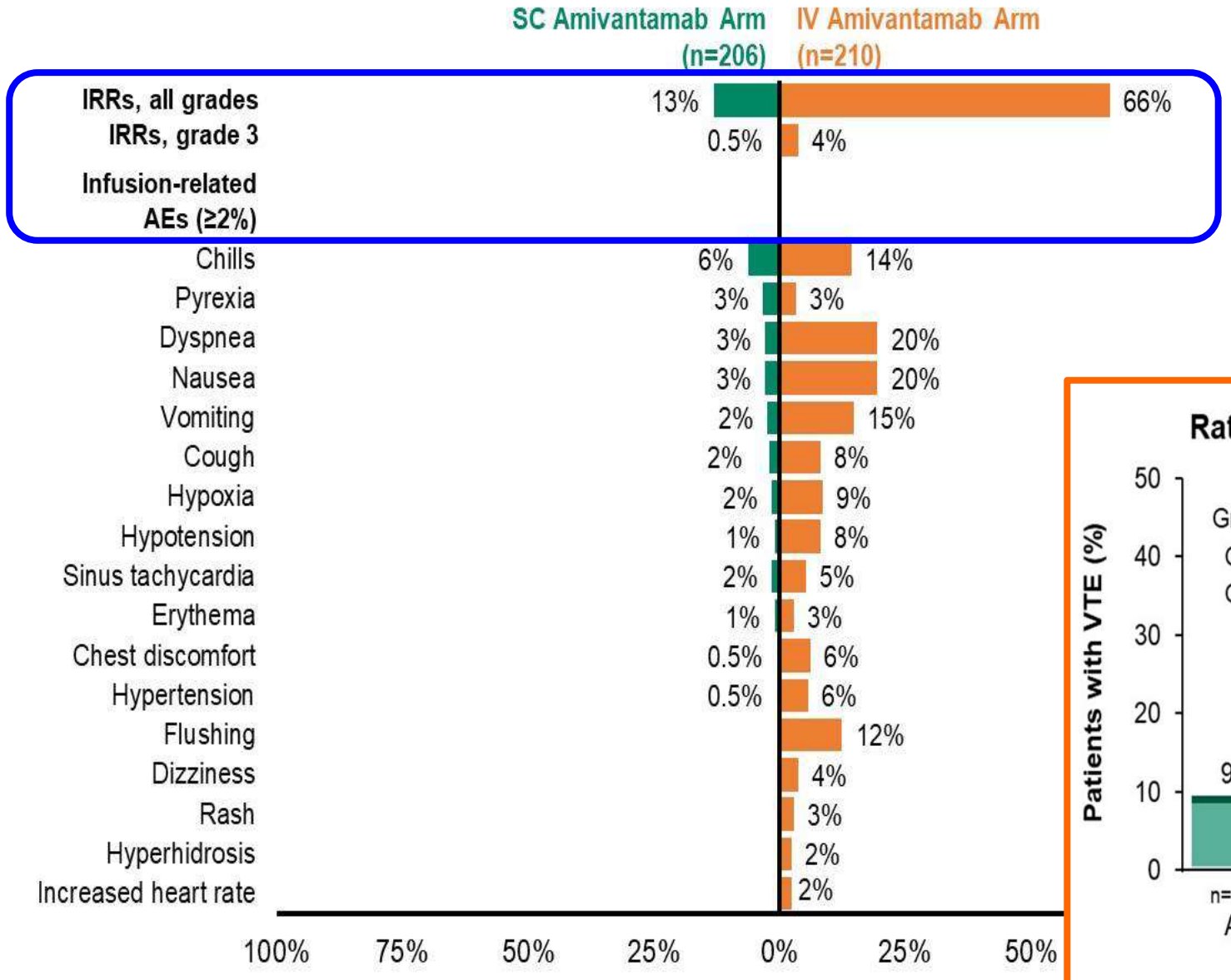
Progression-free Survival

PFS was numerically longer with SC vs IV amivantamab, with an HR of 0.84

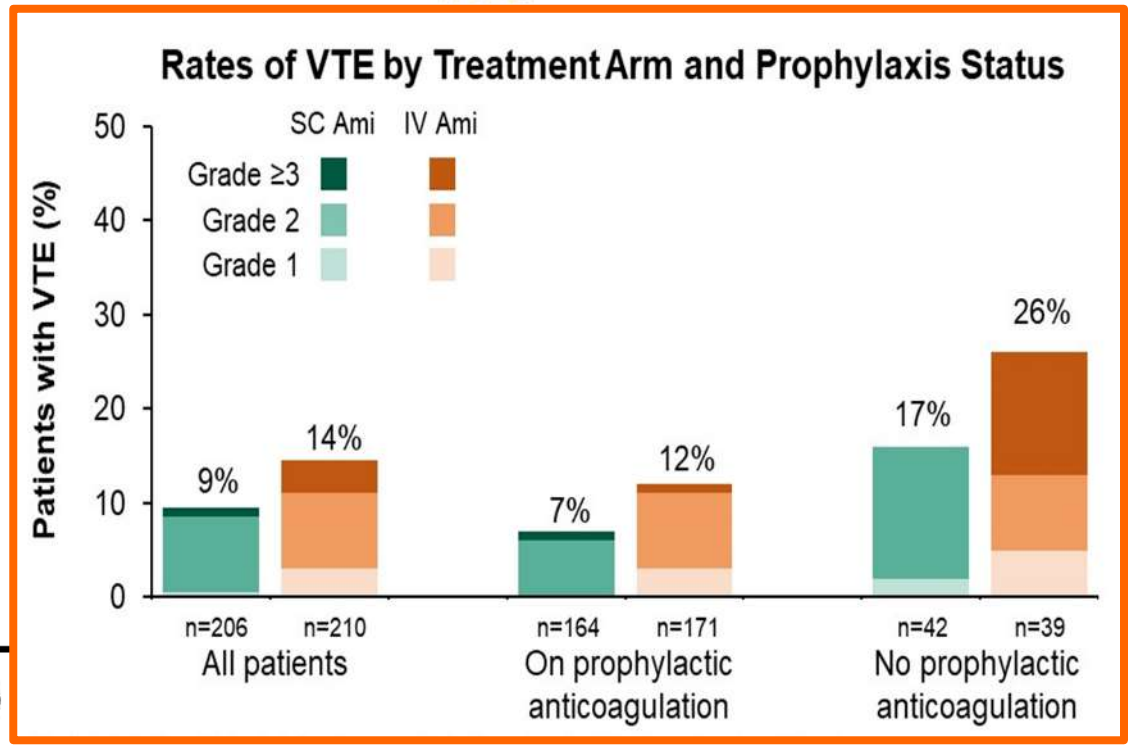


N.B.Leighl et al, ASCO 2024

Incidence of IRR-related symptoms



- IRRs were observed in 13% of patients in the SC arm vs 66% in the IV arm, representing a 5-fold reduction
  - There were no grade 4 or 5 IRRs

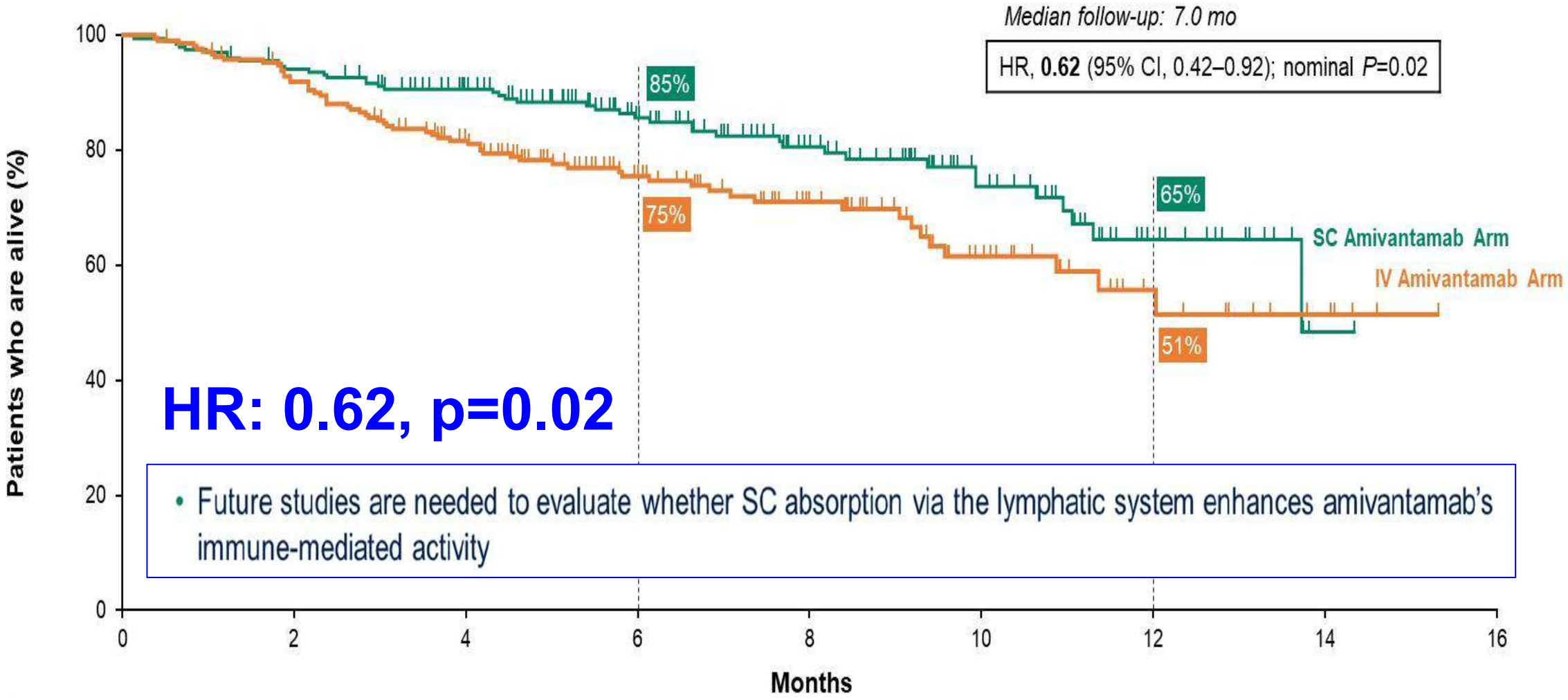


IRR: infusion-related reactions

N.B.Leighl et al, ASCO 2024

Overall Survival

There was an OS benefit associated with SC amivantamab, with an HR of 0.62 compared to the IV amivantama



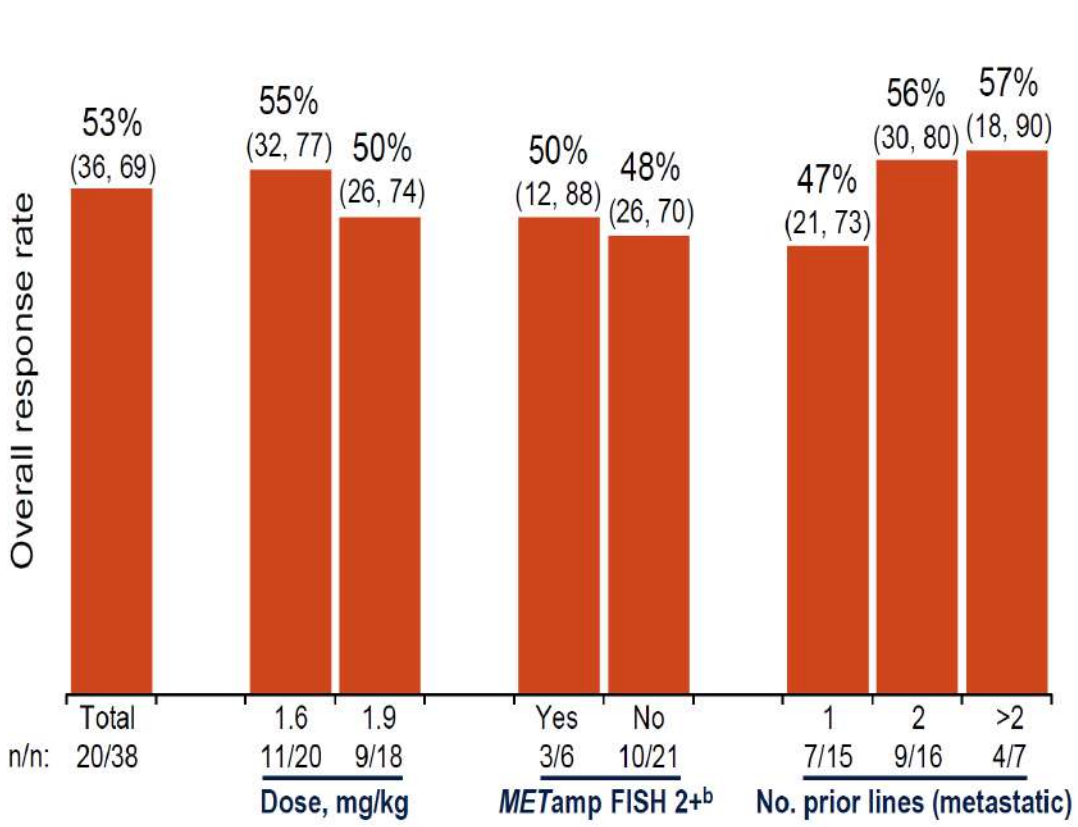
HR: 0.62, p=0.02

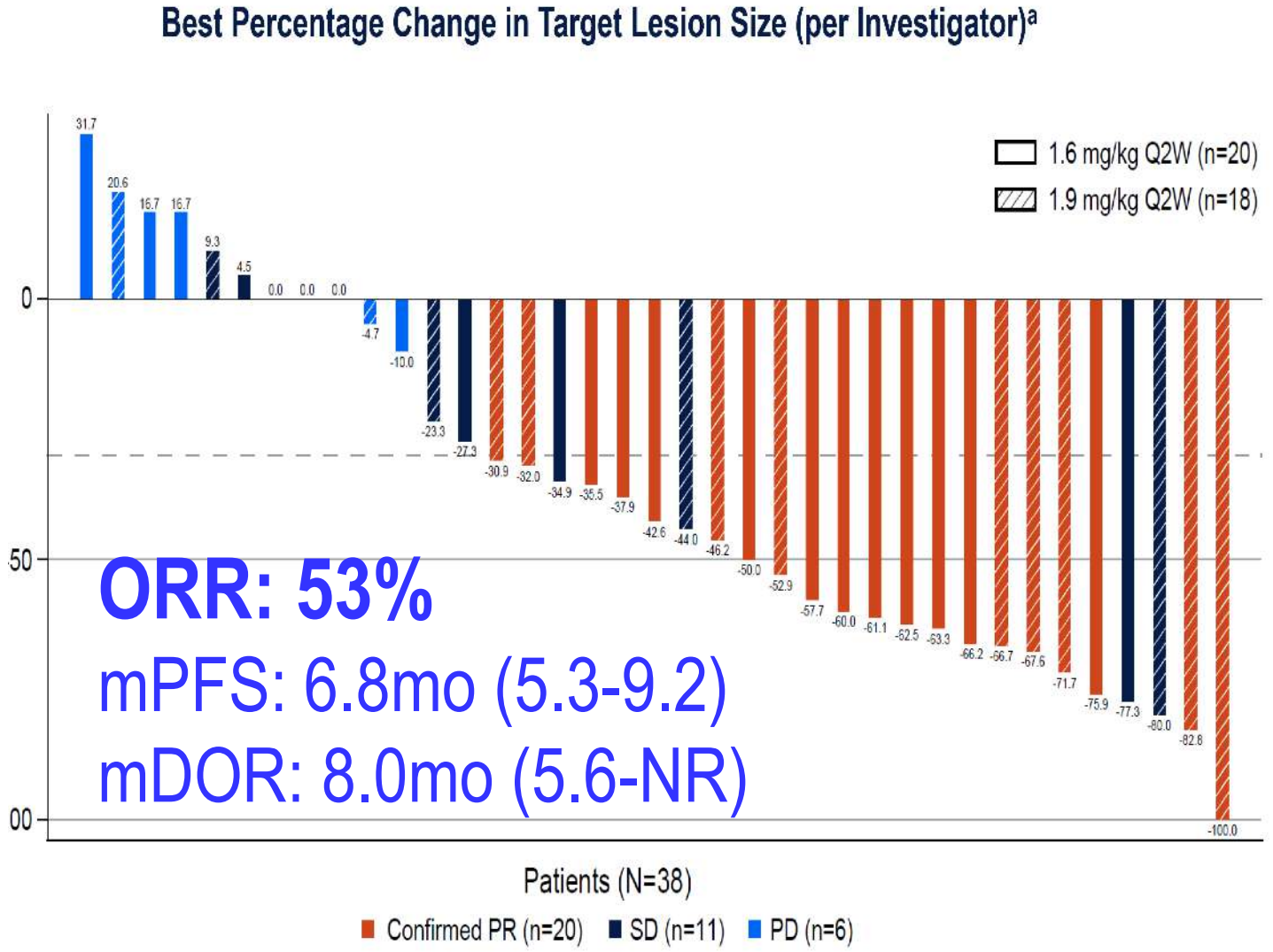
- Future studies are needed to evaluate whether SC absorption via the lymphatic system enhances amivantamab's immune-mediated activity

N.B.Leighl et al, ASCO 2024

Encouraging efficacy of TelisoV + Osimertinib, in pts with EGFRmut, c-MET+

Telisotuzumab vedotin + Osimertinib: Phase 1





ORR: 53%

mPFS: 6.8mo (5.3-9.2)

mDOR: 8.0mo (5.6-NR)

H. Horinouchi et al, ESMO Asia 2023

Study of BL-B01D1-101

Dose Escalation

Key Inclusion Criteria:

- Locally advanced or metastatic NSCLC or other solid tumors
- ECOG PS 0-1
- Measurable disease per RECIST v1.1
- Failed standard therapy or without feasible treatment

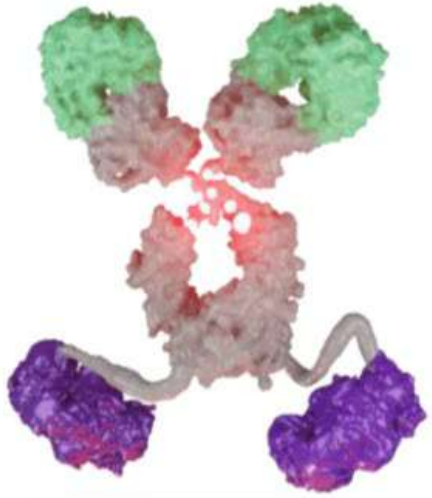
QW 4-week cycle
0.27, 1.5, 3.0 mg/kg

D1D8 Q3W
2.5, 3.0, 3.5 mg/kg

D1 Q3W
4.5, 5.0, 6.0 mg/kg

Dose Expansion

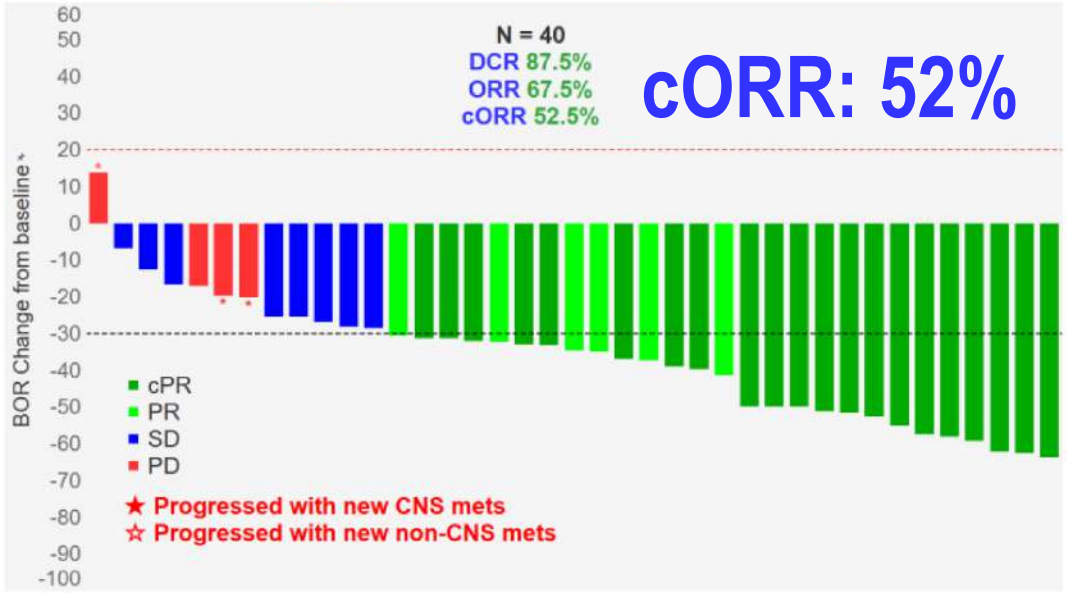
NSCLC (EGFRmt and EGFRwt)	**D1D8 Q3W + D1 Q3W**
NPC previously treated	D1D8 Q3W + D1 Q3W
SCLC previously treated	D1D8 Q3W + D1 Q3W
HNSCC previously treated	D1D8 Q3W + D1 Q3W

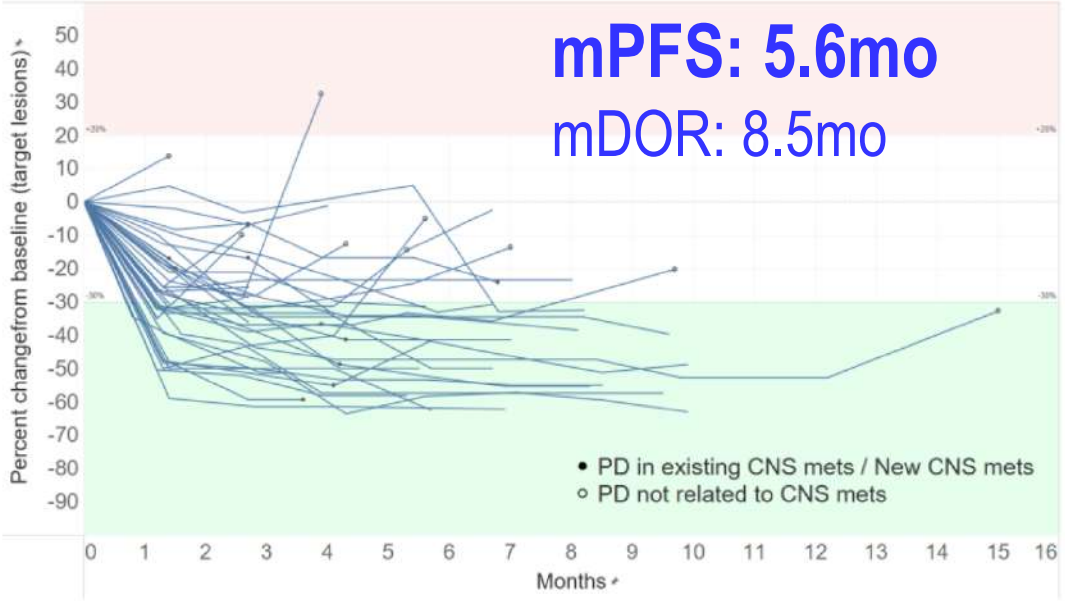


- BL-B01D1 is a first-in-class (FIC) ADC consisting of an EGFRxHER3 bispecific antibody bounded to a novel topoisomerase I inhibitor payload via a cleavable linker.
- Here, we update its safety, tolerability in patients with solid tumor and preliminary efficacy in NSCLC patient cohort in a first-in-human (FIH) trial (BL-B01D1-101).

Li Zhang et al, ESMO 2023 – Yuxiang MA et al, lancet onco 2024

Efficacy in NSCLC EGFRmut





	NSCLC EGFRmt	NSCLC EGFRmt with treated/no CNS mets (target dose)[1]
Enrolled	N = 40	N = 13
Prior systemic chemo line		
0	25% (10/40)	8% (1/13)
1	50% (20/40)	46% (6/13)
2+	25% (10/40)	46% (6/13)
DCR (95%CI), %	87.5 (73.2, 95.8)	92.3 (64.0, 99.8)
ORR (95%CI), %	67.5 (50.9, 81.4)	69.2 (38.6, 90.9)
cORR (95%CI), %	52.5 (36.1, 68.5)	61.5 (31.6, 86.1)
mDOR (95%CI), mo	8.5 (2.8, NR)	12.3 (2.7, NR)
mPFS (95%CI), mo	5.6 (3.9, 9.7)	15.0 (4.3, NR)

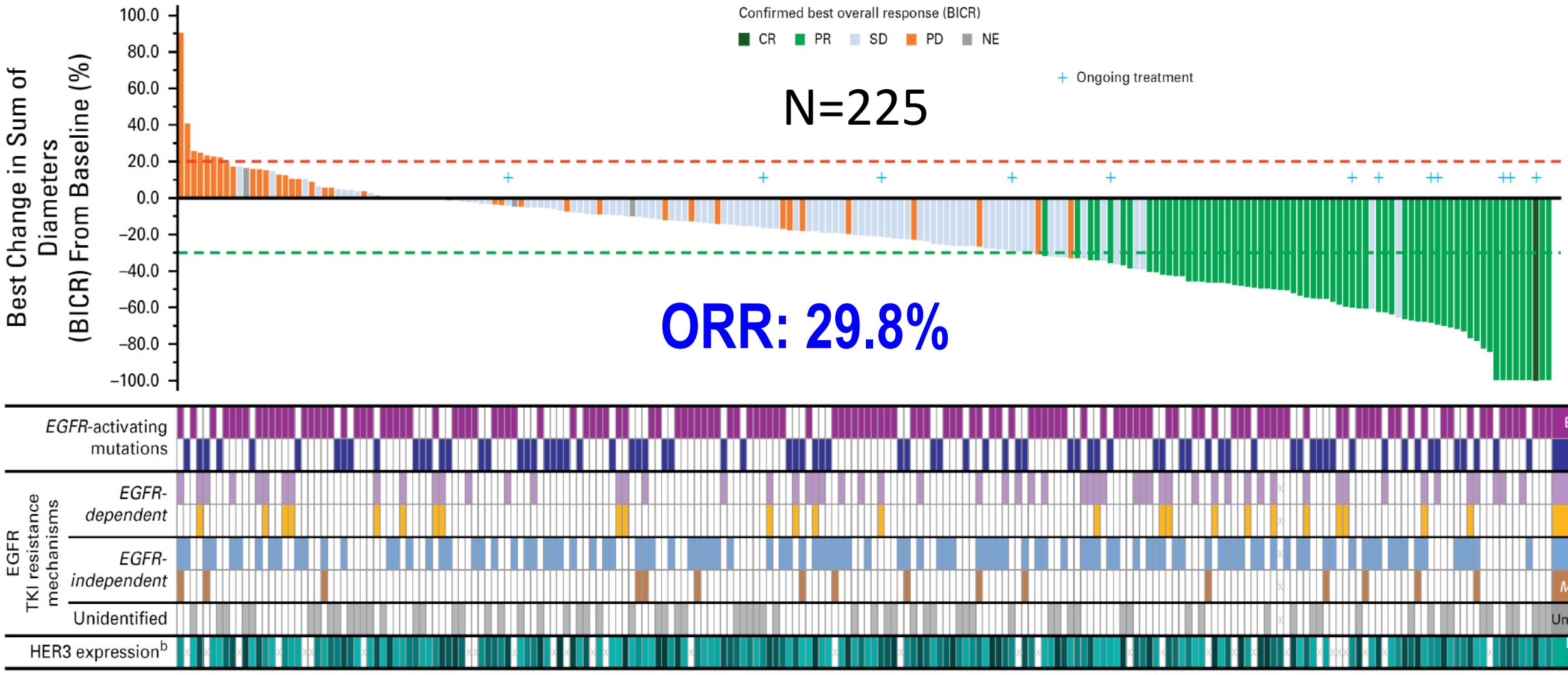
[1] 2.5mg/kg D1D8Q3W and 4.5mg/kg D1Q3W

Li Zhang et al, ESMO 2023 – Yuxiang MA et al, lancet onco 2024

Patritumab Deruxtecan (HERTHENA-Lung01 study)

phase II HERTHENA-Lung01 in pts with EGFR–mutated NSCLC after progression on EGFR TKI therapy and platinum-based chemotherapy

Tumor reduction across diverse mechanisms of EGFR TKI resistance

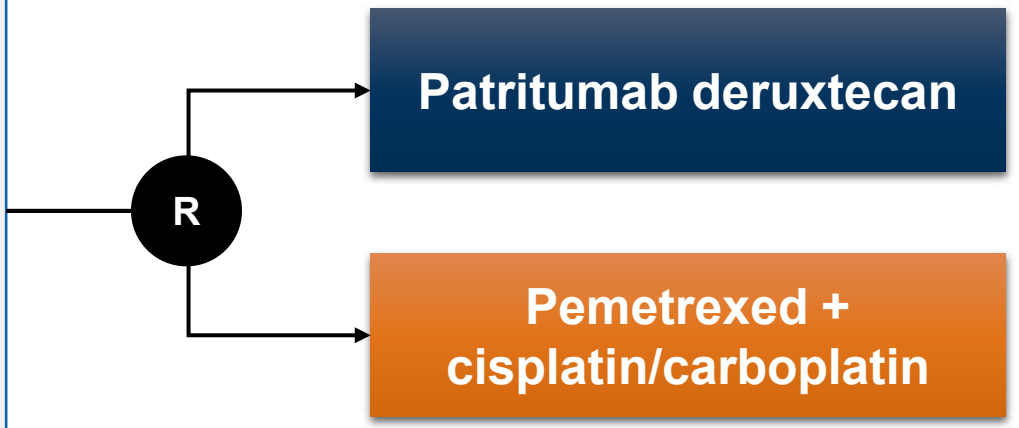


Helena A. Yu et al, JCO 2023

Patritumab Deruxtecan is Being Evaluated vs Chemotherapy in Advanced *EGFR*m NSCLC After TKI Failure in the Phase 3 HERTHENA-Lung02 trial

- Locally advanced/metastatic non-squamous NSCLC not amenable to curative surgery or radiation
- ***EGFR* exon 19 deletion or L858R**
- **1-2 prior lines of EGFR TKI** treatment, including third-generation TKI, in locally advanced/metastatic setting
- No other prior systemic therapies in the locally advanced/metastatic setting
- Progression during or after treatment with third-generation EGFR TKI for locally advanced/metastatic disease
- ≥1 measurable lesion
- ECOG PS 0-1

(N = ~560)



September 2024. Patritumab deruxtecan demonstrated statistically significant improvement in PFS vs doublet chemotherapy

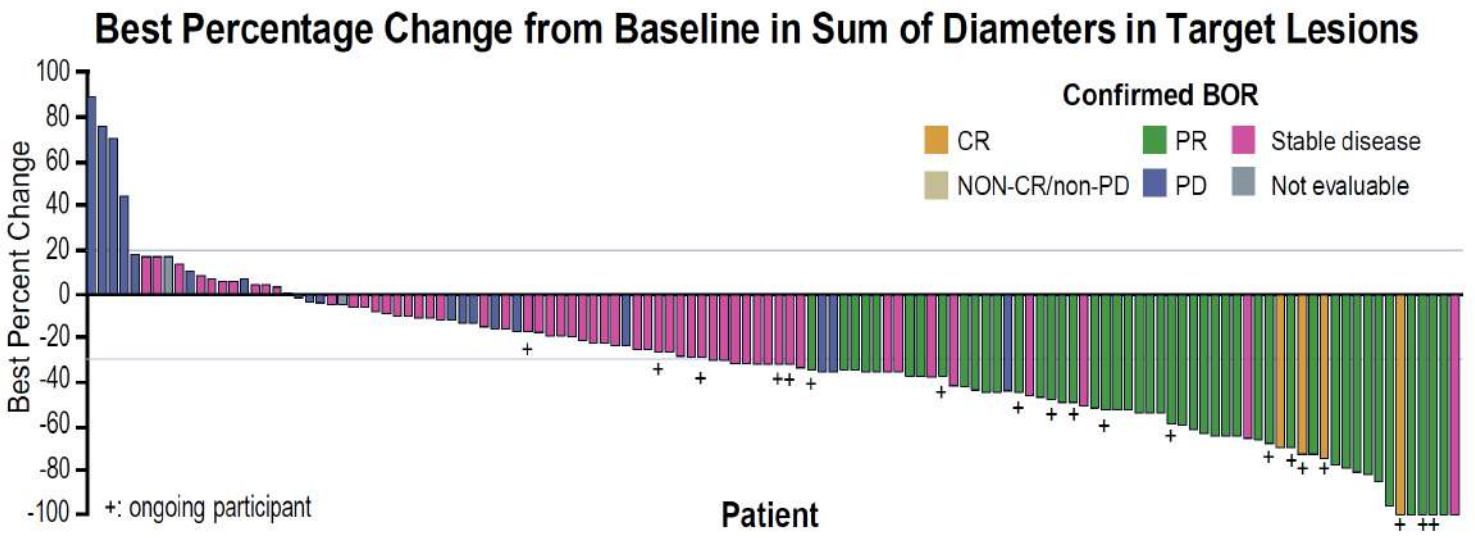
- **Primary endpoint:** PFS (BICR RECIST v1.1)
- **Secondary endpoints:** OS, PFS (INV), PFS (LSCP), ORR, DOR, CBR, DCR, TTR QOL, safety

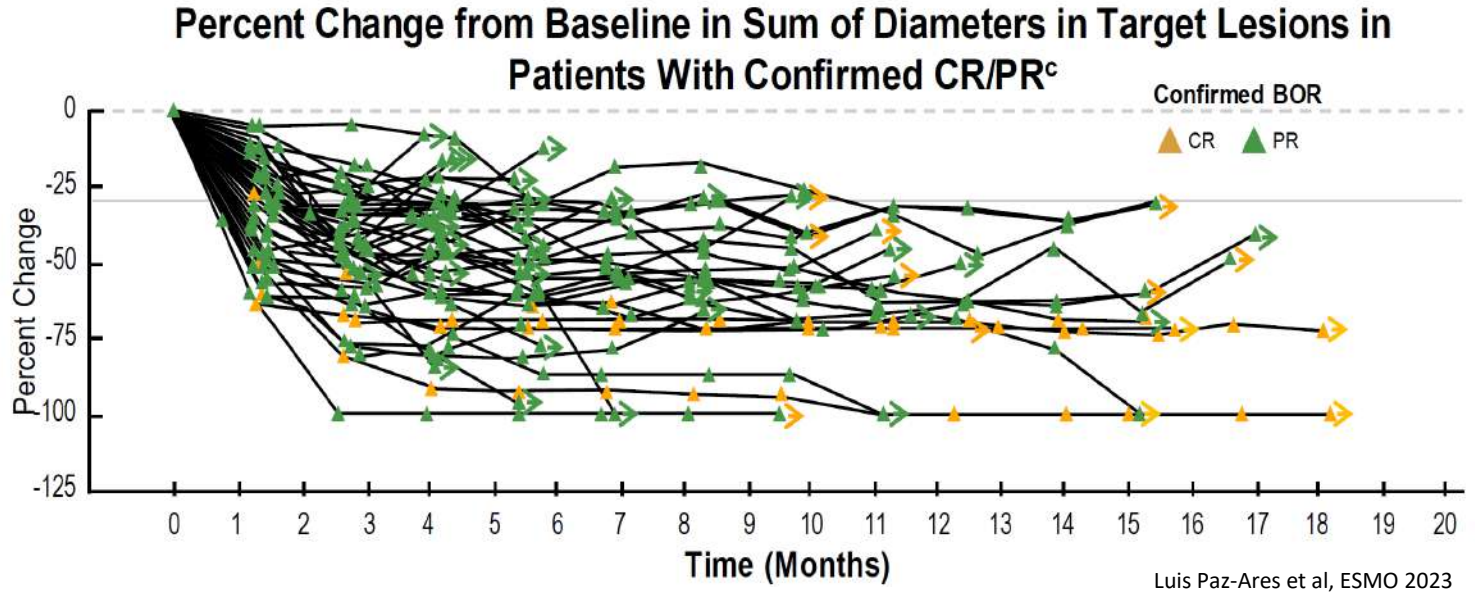
1. https:/clinicaltrials.gov/study/NCT05338970.

Tropion-Lung 05 (Dato-DXd)

Response per BICR	All treated (N=137)	Patients with *EGFR* mutations (N=78)	Patients with *ALK* rearrangement (N=34)
ORR confirmed, n (%) [95% CI][a]	49 (35.8) [27.8,44.4]	**43.6%** 34 (43.6) [32.4,55.3]	**23.5%** 8 (23.5) [10.7,41.2]
Median DOR, months[b] [95% CI]	7.0 [4.2,9.8]	7.0 [4.2,10.2]	7.0 [2.8,8.4]
DCR confirmed, n (%) [95% CI][a]	108 (78.8) [71.0,85.3]	64 (82.1) [71.7,89.8]	25 (73.5) [55.6,87.1]
Median PFS, months[b] [95% CI]	5.4 [4.7,7.0]	**5.8mo** 5.8 [5.4,8.3]	**4.3mo** 4.3 [2.6,6.9]

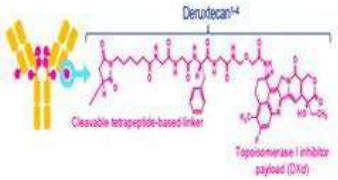
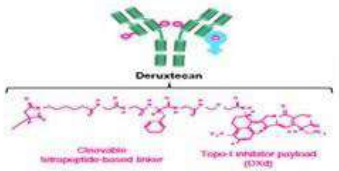
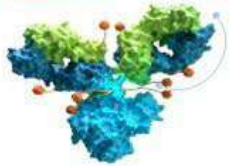
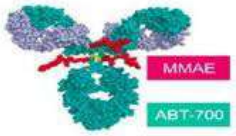
BOR: In the overall population (N=137), 4 (3%) patients achieved a CR and 45 (33%) patients achieved a PR





Luis Paz-Ares et al, ESMO 2023

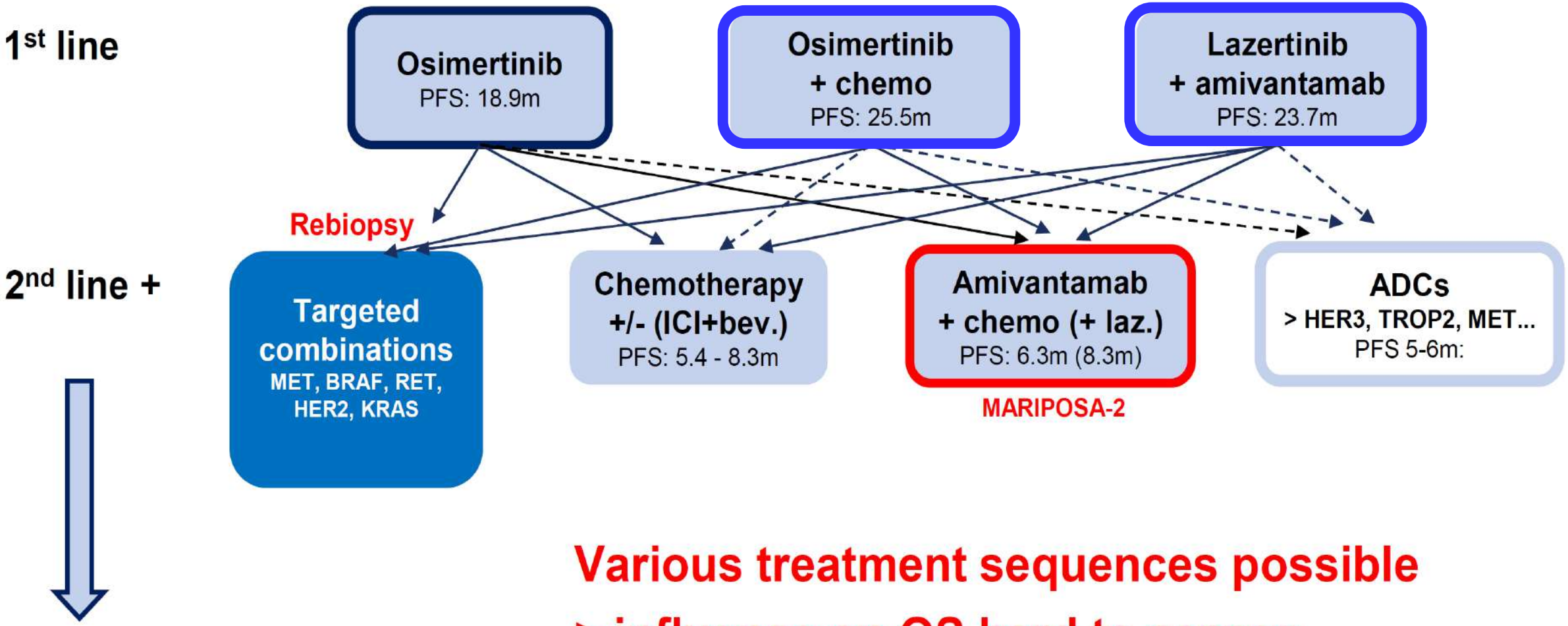
ADC in EGFR mut – upon TKI progression

ADC agent	Clinical Trial	Response Rate (%)	PFS (mo.)	OS (mo.)
 Patritumab deruxtecan ADC Anti HER3 topoisomerase I inhibitor	U31402-A-U102. Ph I N=78 Post Osimertinib + PBC. Ph i	41	6.4	16.2
	HERTHENA-Lung 01. N=209 Post Osimertinib + PBC. Ph II	30	5.5	11.2
 Datopotamab deruxtecan ADC antiTROP2 topoisomerase I inhibitor	TROPION-Lung 05. N=78 Post-TKI + PBC	44	5.8	
 SKB264 / MK2870 ADC antiTROP2 belotecan-derivate Topo I	SKB264 /MK2870. N=22 Post-TKI + PBC	60	11.5	22.7
 BL-B01D1 Bispecific ADC EGFR/HER3 topoisomerase I inhibitor	BL-B01D1. N=40 Most Post Osimertinib + PBC	53	5.6	
 Telisotuzumab Vedotin ADC anti MET microtubule inhibitor (MMAE)	TELISO-V + Osim. N=38. Post osimertinib & *MET*+	50	7.4	

Yu – AoO 2024 * Yu –JCO 2023 * Paz-Ares – ESMO 2023 * Fang – AACR 2024 * Zhang - ASCO 2023 * Zhang – ESMO 2023 * Horinouchi – ESMO Asia 2023

J.Remon, ASCO 2024

MARIPOSA-2 in the context of different trtt options



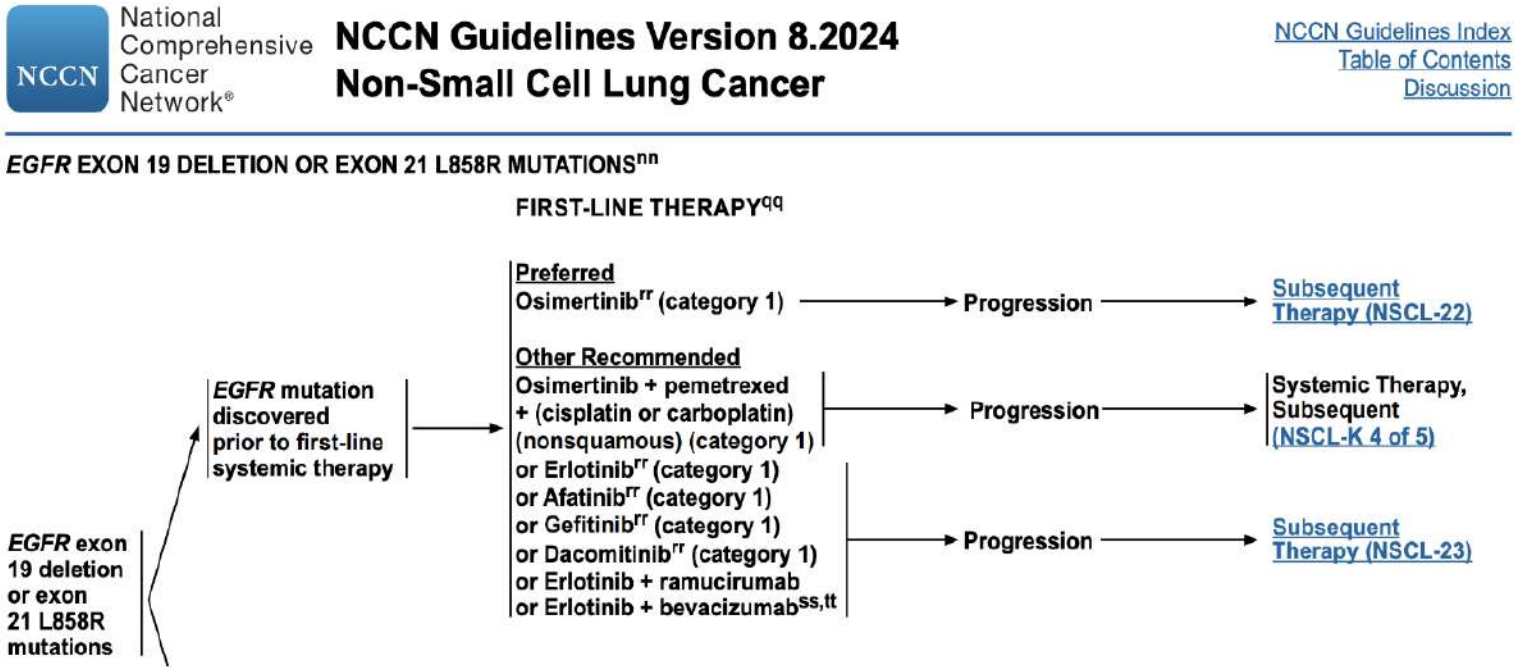
Various treatment sequences possible

> influence on OS hard to assess

J.Wolf , ESMO 2024

US Availability

Regimen	FDA Approved?	National guidelines?
Osimertinib monotherapy	Yes (April 2018)	Yes
Osimertinib + Platinum-Pemetrexed	Yes (February 2024)	Yes
Lazertinib + Amivantamab	Yes (August 2024)	No



Key considerations in choosing treatment approach

- Side effect profile
- Intensity of monitoring
- Later line options

Treatment

Patient

- **Patient preference**
- ECOG
- Co-morbidities

Shared decision-making with patient

Accessibility

- Reimbursement policies
- Chair time
- Drug availability

Tumour

- Sites of metastases
- EGFR subtype
- Co-mutations
- ctDNA positivity

Not 'one-size-fits-all'

Stephanie Saw, ASCO 2024

History of EGFR TKI

for first-line treatment of advanced EGFR-mutated NSCLC

MARIPOSA showed superiority of amivantamab + lazertinib over osimertinib[12] — **3G combi > 3G**

FLAURA2 showed superiority of osimertinib plus chemotherapy over osimertinib[11]

2 Phase 3 RCTs showed superiority of Gefitinib plus chemotherapy over Gefitinib[9,10] — **1G + chemo > 1G**

FLAURA showed superiority of Osimertinib (3rd generation TKI) over 1st generation TKI[4] — **3G > 1G**

ARCHER 1050 showed superiority of Dacomitinib (2nd generation TKI) over Gefitinib[3] — **2G > 1G**

3G + anti-VEGF vs 3G:
Bevacizumab + osimertinib[13] ✗
Ramucirumab + osimertinib[14] ✓

LUX-Lung -3 and -6 showed superiority of Afatinib (2nd generation TKI) over chemotherapy[2] — **2G > Chemo**

Other 3G > 1G:
Aumolertinib[5], Furmonertinib[6], Lazertinib[7], Befotertinib[8]

IPASS trial showed superiority of Gefitinib (1st generation TKI) over standard chemotherapy[1] — **1G > Chemo**

2009 2015 2017 2018 2020 2023

[1]Mok et al, NEJM 2009; [2]Yang et al, The Lancet Oncol 2015; [3]Wu et al, The Lancet Oncol 2017; [4]Soria et al, NEJM 2018; [5] Lu et al, JCO 2022; [6] Shi et al, Lancet Resp Med 2022; [7] Cho et al, JCO 2023; [8] Lu et al, Lancet Resp Med 2023; [9]Noronha et al, JCO 2020; [10]Nakamura et al, JCO 2018; [11]Planchard et al, NEJM 2023; [12]Cho et al, ESMO 2023; [13]Kenmotsu et al, JTO 2022; [14]Le et al, ESMO 2023

Stephanie Saw, ASCO 2024

THANK YOU !

Benjamin BESSE
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Mihaela ALDEA
Maxime FRELAUT
Cécile LE PECHOUX
Angéla BOTTICELLA
Antonin LEVY

@dplanchard