AIGOM
ASSOCIAZIONE ITALIANA
GRUPPI ONCOLOGICI MULTIDISCIPLINARI

Congresso Nazionale

CARCINOMA DEL POLMONE:
QUALI NOVITÀ NEL 2024?

V EDIZIONE

28 OTTOBRE 2024

VERONA

Hotel Leon D'Oro

Responsabile Scientifico
STEFANIA GORI

Il Trattamento della malattia EGFR mutata: dalla prima linea alle successive



Diego Signorelli

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Milano

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Ospedale Niguarda Cancer Center

Regione Lombardia

Potential conflicts of interest to declare

Type of affiliation / financial interest	Name of commercial company
Advisory Board	AstraZeneca, Boehringer Ingelheim, MSD, Sanofi, Roche, Johnson&Johnson, Amgen, Daiichi
Speaker Fees	AstraZeneca, BMS, Novartis
Consultant	AstraZeneca, MSD, Sanofi, Roche
Travel Grants	Pfizer, AstraZeneca, MSD, Roche, Sanofi, BMS

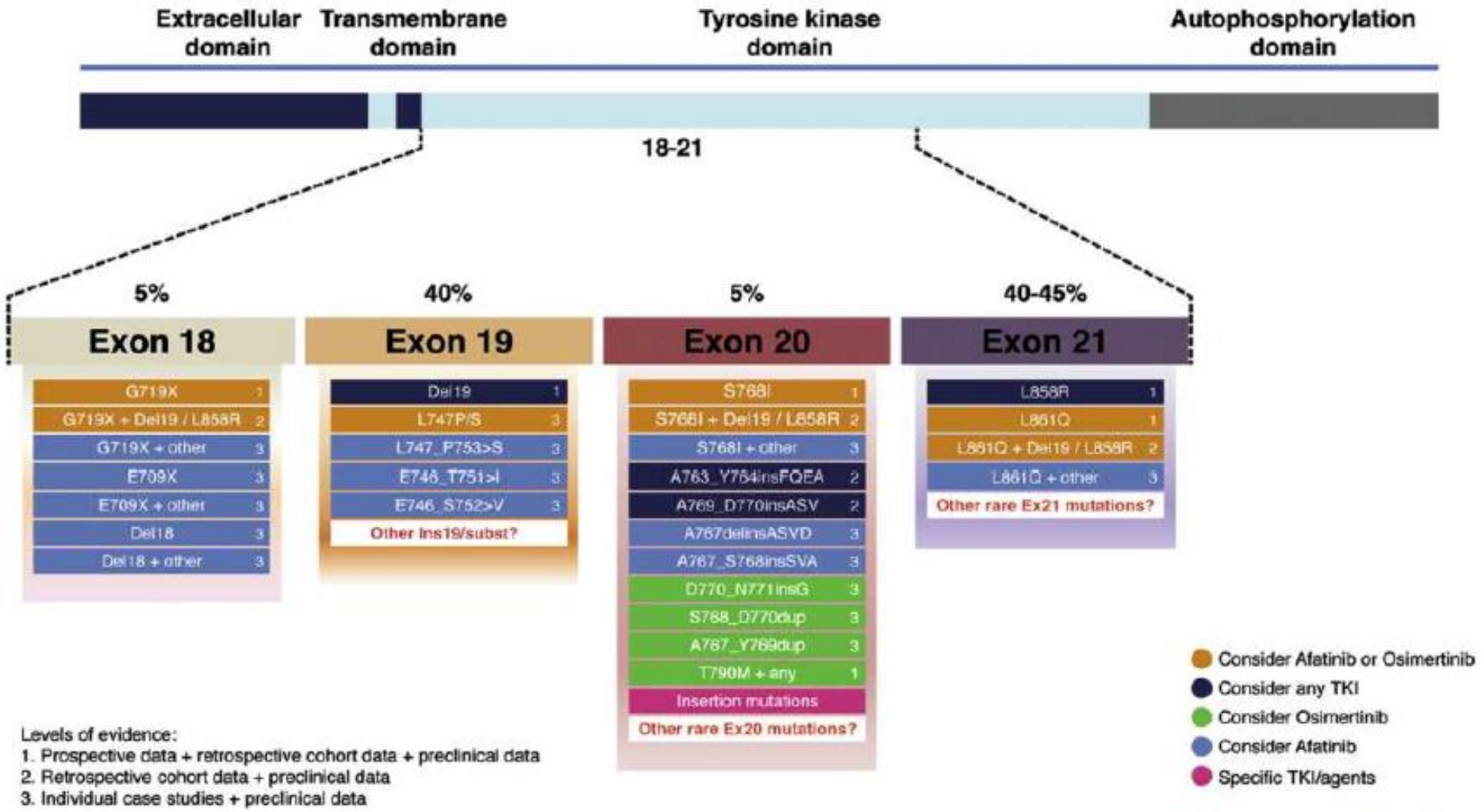
Agenda

- First line
- Subsequent lines
- Exon 20 insertions

Agenda

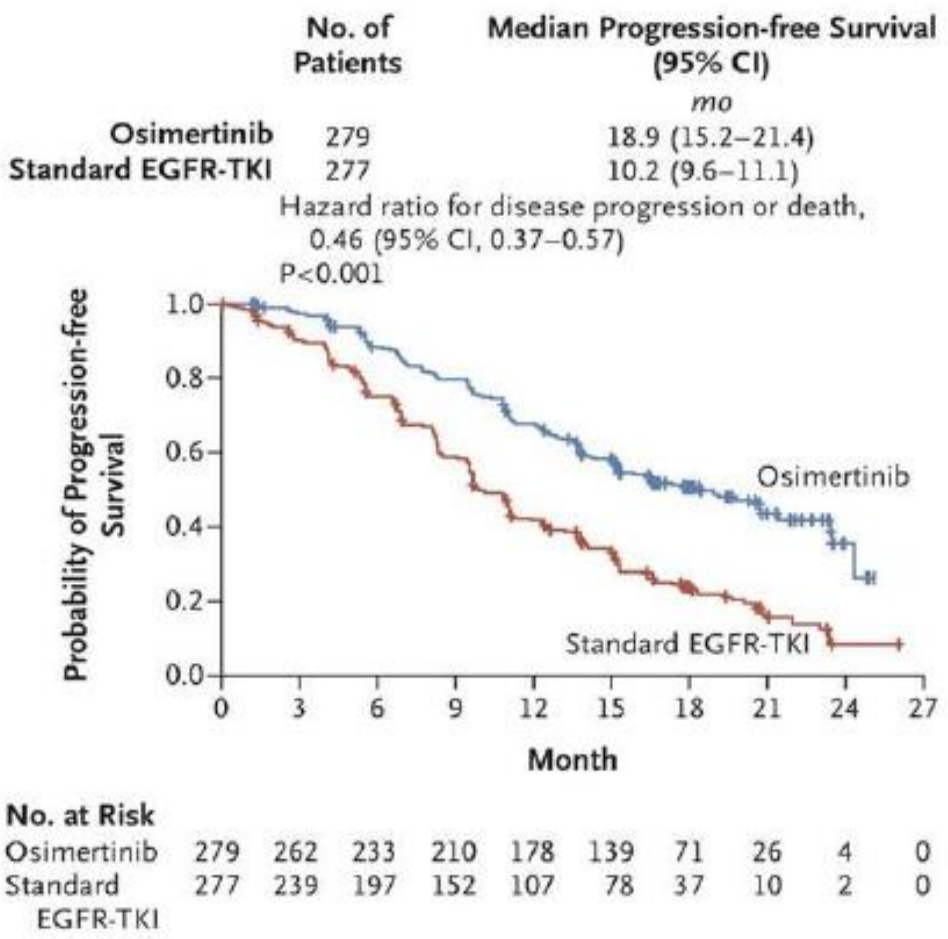
- First line
- Subsequent lines
- Exon 20 insertions

EGFR MUTATION IN LUNG CANCER

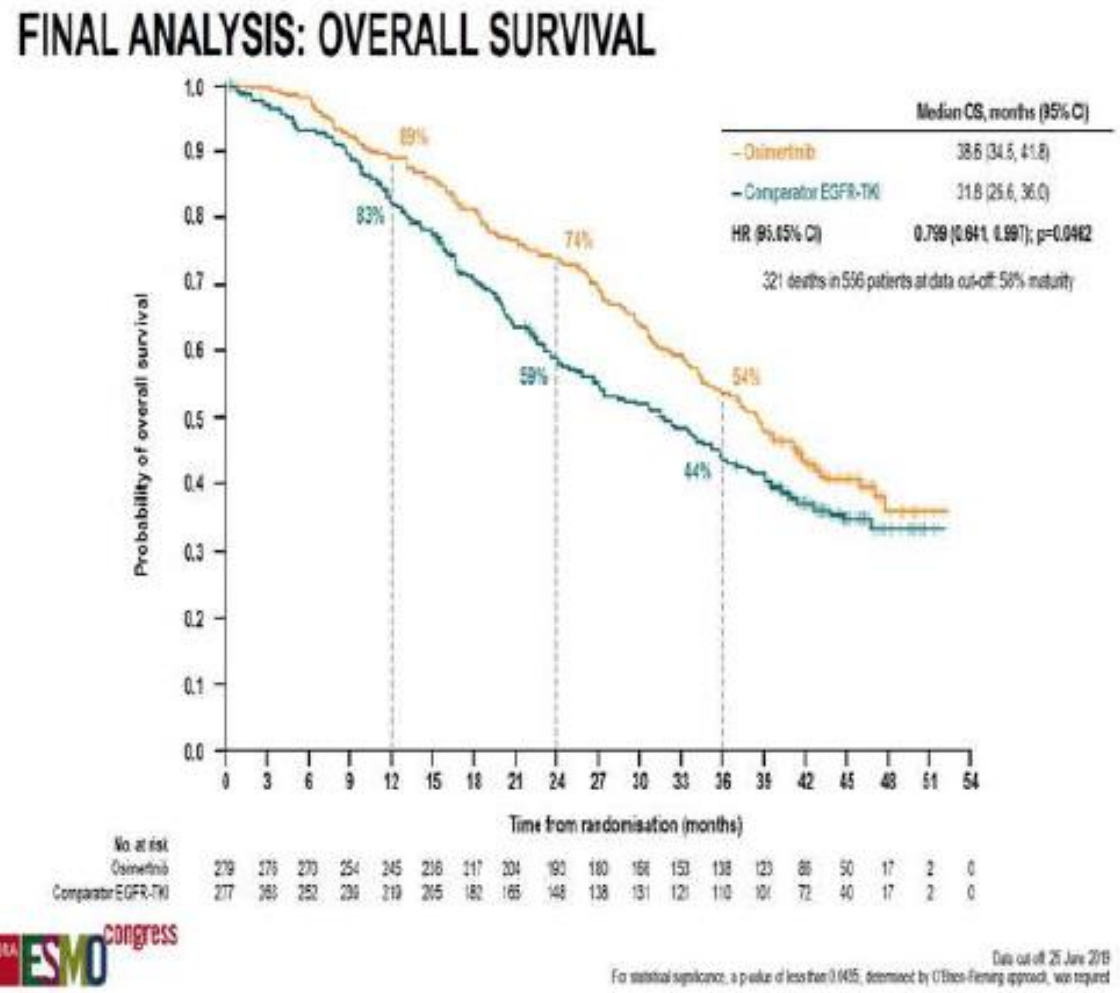


Passaro et al. J Thoracic Oncol 2020

FLAURA: OSIMERTINIB IN UNTREATED EGFR + NSCLC

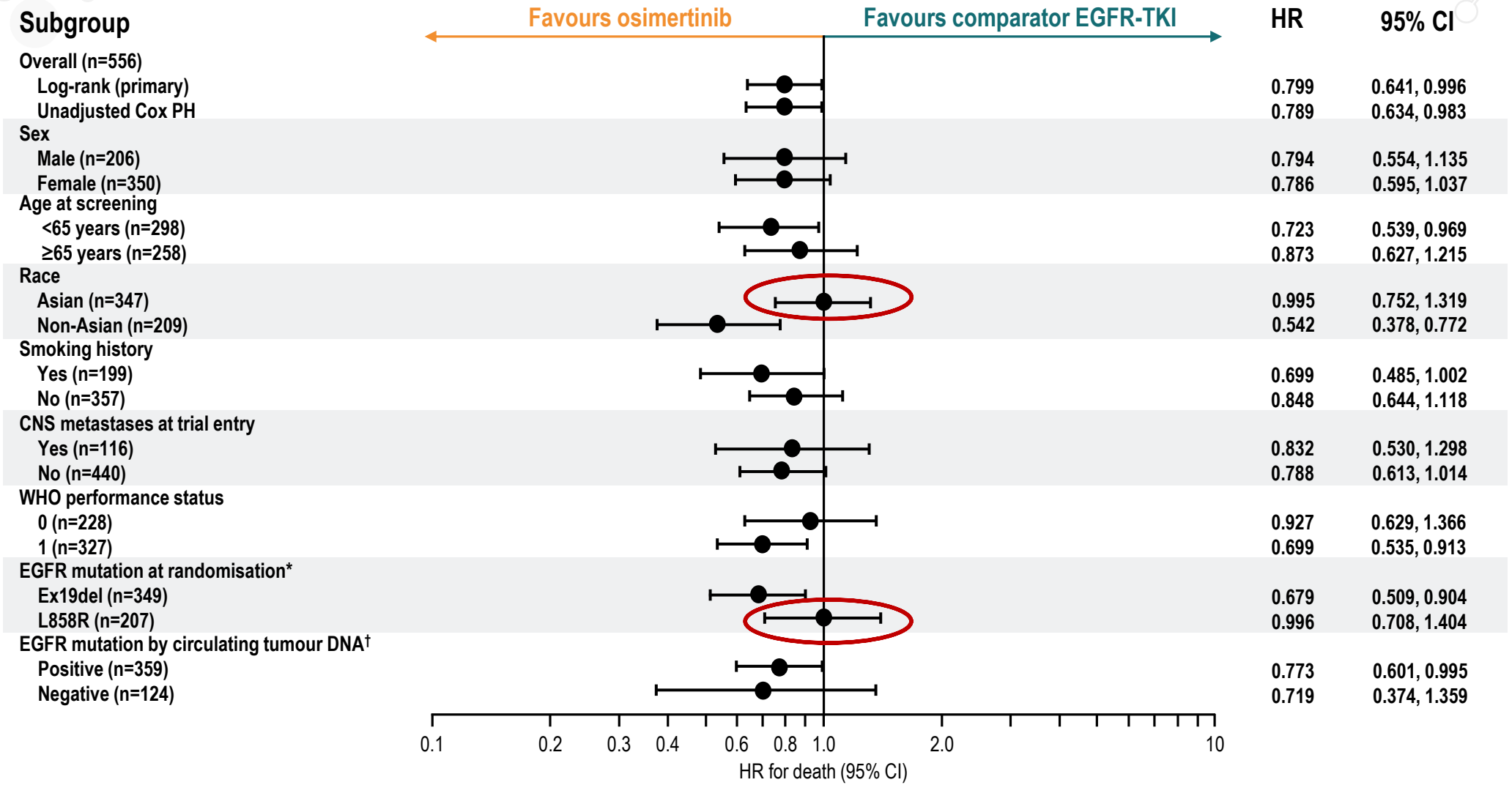


Soria et al. NEJM 2017



Ramalingam et al. ESMO 2019

Overall survival across subgroups



Data cut-off: 25 June 2019

Hazard ratio <1 implies a lower risk of death on osimertinib

*Local or central test; †Result missing for 36 patients in the osimertinib arm and 37 patients in the comparator EGFR-TKI arm

1. Ramalingam SS, et al. NEJM. 2020; 2, Ramalingam SS, et al. NEJM. appendix

Osimertinib CNS Efficacy in FLAURA study

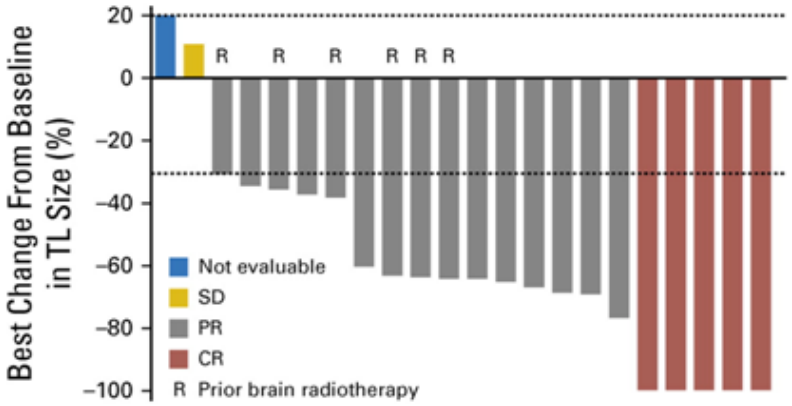
Practice Changing Data

VOLUME 36 · NUMBER 33 · NOVEMBER 20, 2018

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

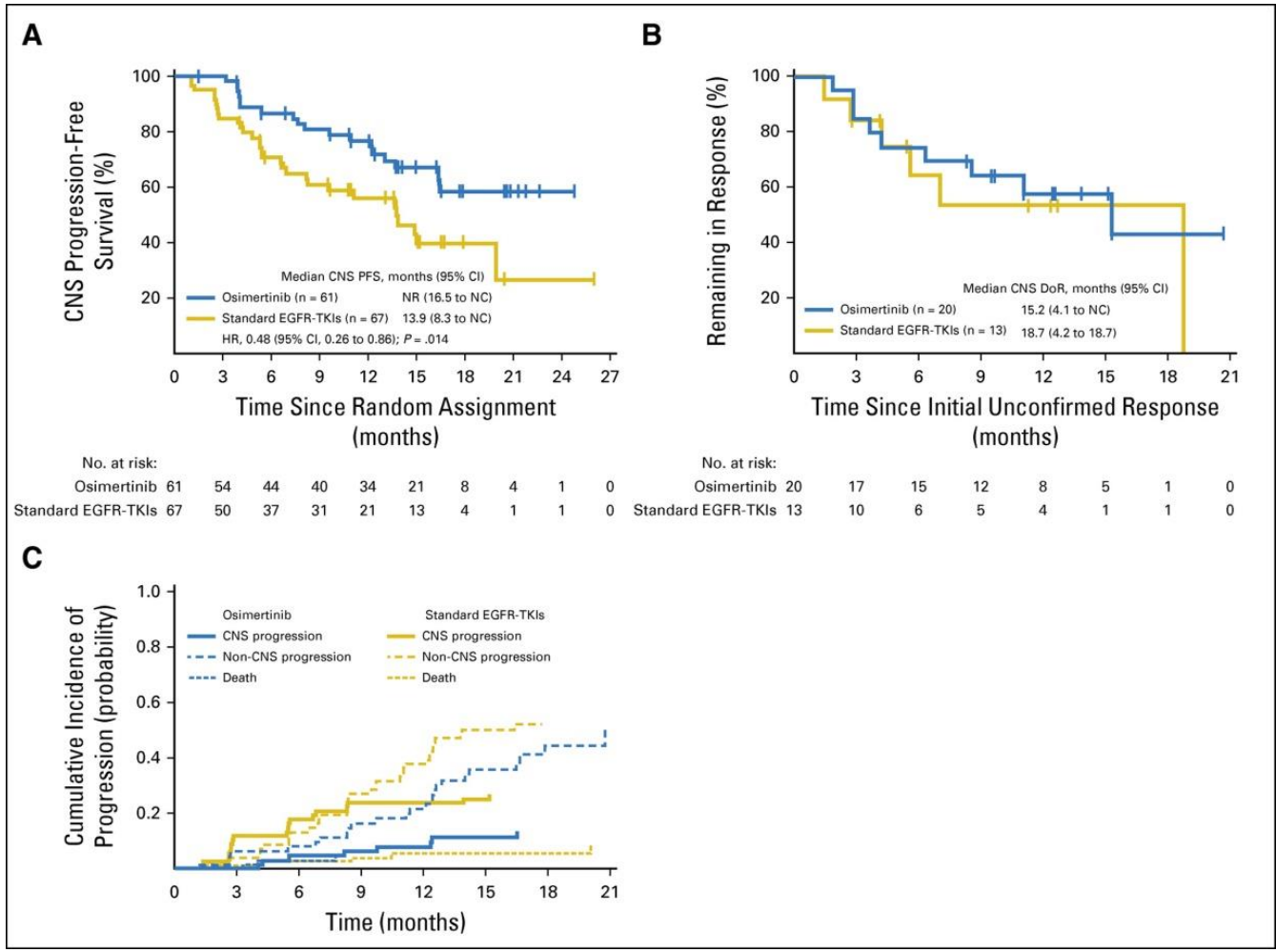
CNS Response to Osimertinib Versus Standard Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Patients With Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

Thanyanan Reungwetwattana, Kazuhiko Nakagawa, Byoung Chul Cho, Manuel Cobo, Eun Kyung Cho, Alessandro Bertolini, Sabine Bohnet, Caicun Zhou, Ki Hyeong Lee, Naoyuki Nogami, Isamu Okamoto, Natasha Leighl, Rachel Hodge, Astrid McKeown, Andrew P. Brown, Yuri Rukazenkov, Suresh S. Ramalingam, and Johan Vansteenkiste



CNS evaluable for response set (n=41)	
Osimertinib (n=22)	SoC (n=19)
91% (71, 99)	68% (43, 87)

Odds Ratio 4.6 (95%CI 0.9-34.9, p=0.066)



mPFS: NR vs 13.9 months (HR 0.48, 95%CI 0.26-0.86, p=0.014)

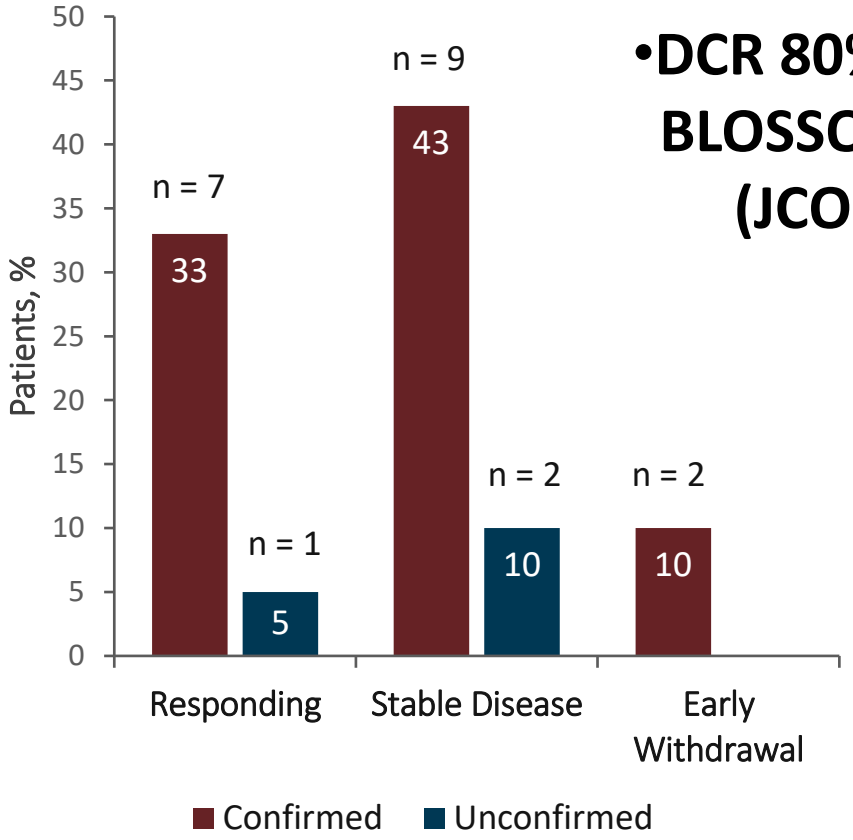
…what about lepto-meningeal diffusion?

•Poor prognosis (mOS 1-3 mo with WBRT and IT CT)

Gainor JF, *JTO* 2013

- BLOOM[a]

Best MRI Intracranial Response (n = 21)



Yang JC-H, ASCO 2017

•DCR 80%, CR 15% BLOSSOM Study (JCO 2024)

CR in 4 pts out of 5 with suspect of LM

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Table 4. Responses in Patients With Suspected LMs*

Treatment Arm	Highest Response		Best Objective Response	
	LMs	TL	CNS	Systemic
Osimertinib	CR	PR	PR	PR
Osimertinib	Non-CR, non-PD	No TL	SD	PR
Osimertinib	CR	No TL	CR	PR
Osimertinib	CR	No TL	SD	PR
Osimertinib	CR	CR	CR	PR
Standard EGFR-TKIs	Non-CR, non-PD	No TL	SD	PR
Standard EGFR-TKIs	Baseline only	No TL	NE	PR

Abbreviations: CR, complete response; *EGFR*, epidermal growth factor receptor; LMs, leptomeningeal metastases; NE, nonevaluable; PD, progressive disease; PR, partial response; SD, stable disease; TL, target lesion; TKI, tyrosine kinase inhibitor.
*LMs, TL and CNS responses were assessed by CNS BICR; systemic response was assessed by study BICR.

Reungwettwana T, *JCO* 2018

1. What is the optimal first-line therapy for patients with common *EGFR* mutations?

STATEMENT: First-line third-generation EGFR TKIs, such as osimertinib, is considered the preferred option for patients with a tumor with common *EGFR* mutations [I,A].

2. What is the optimal management of patients with CNS disease and/or with leptomeningeal involvement?

STATEMENT: Third-generation EGFR TKIs should be prioritized for those patients with CNS metastasis, including leptomeningeal disease, as initial therapy. The benefit of radiotherapy in addition to EGFR TKIs is not supported by prospective controlled trials data. For those with intracra-

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

ESMO expert consensus statements on the management of *EGFR* mutant non-small-cell lung cancer

A. Passaro[1*], N. Leighl[2†], F. Blackhall[3,4†], S. Popat[5,6,7†], K. Kerr[8†], M. J. Ahn[9], M. E. Arcila[10], O. Arrieta[11], D. Planchard[12], F. de Marinis[1], A. M. Dingemans[13], R. Dziadziuszko[14], C. Faivre-Finn[15], J. Feldman[16], E. Felip[17], G. Curigliano[18], R. Herbst[19], P. A. Jänne[20], T. John[21], T. Mitsudomi[22], T. Mok[23], N. Normanno[24], L. Paz-Ares[25], S. Ramalingam[26], L. Sequist[27], J. Vansteenkiste[28], I. I. Wistuba[29], J. Wolf[30], Y. L. Wu[31], S. R. Yang[7], J. C. H. Yang[32], Y. Yatabe[33], G. Pentheroudakis[34] & S. Peters[35]

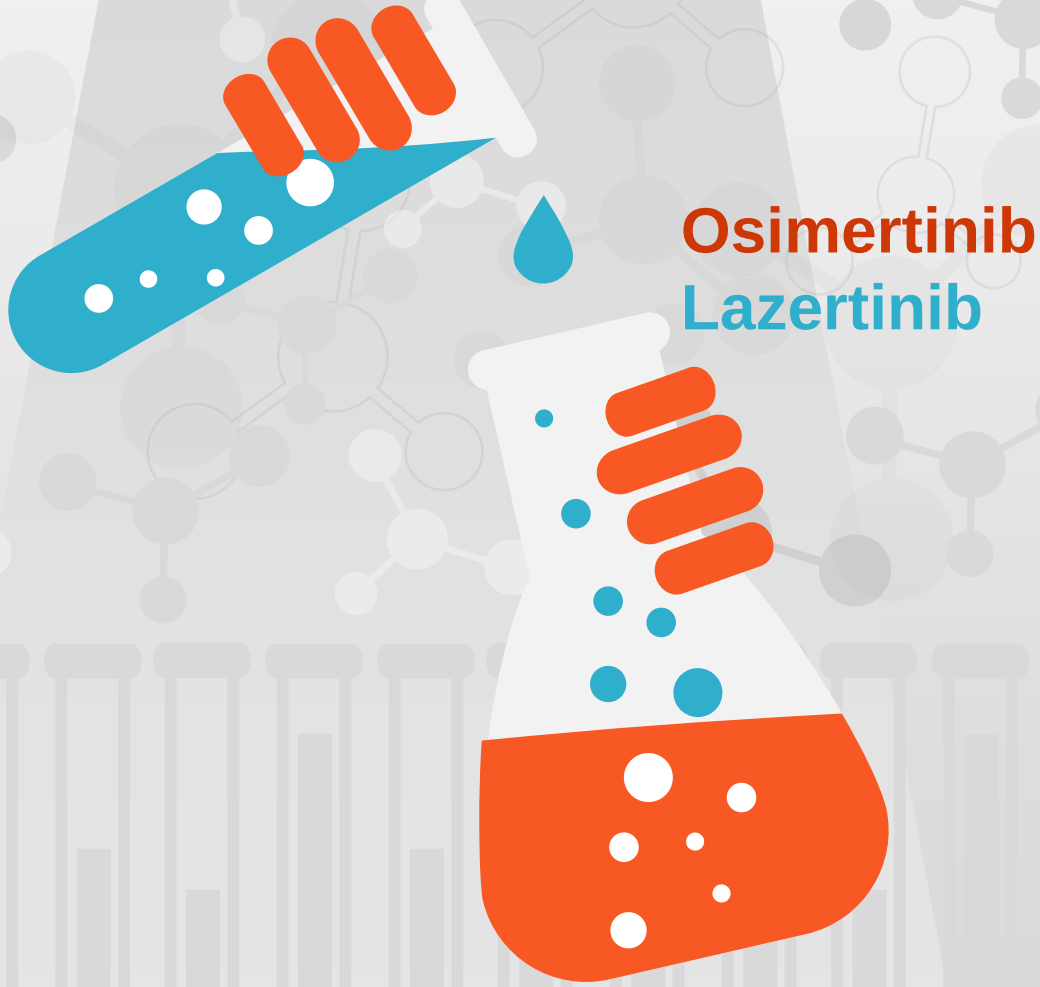
Passaro A, et al. Ann Oncol 2022;

What about combination strategies in first line EGFR+?

Third generation EGFR TKIs: Standard of Care
From 2020

BEYOND OSIMERTINIB in first line?

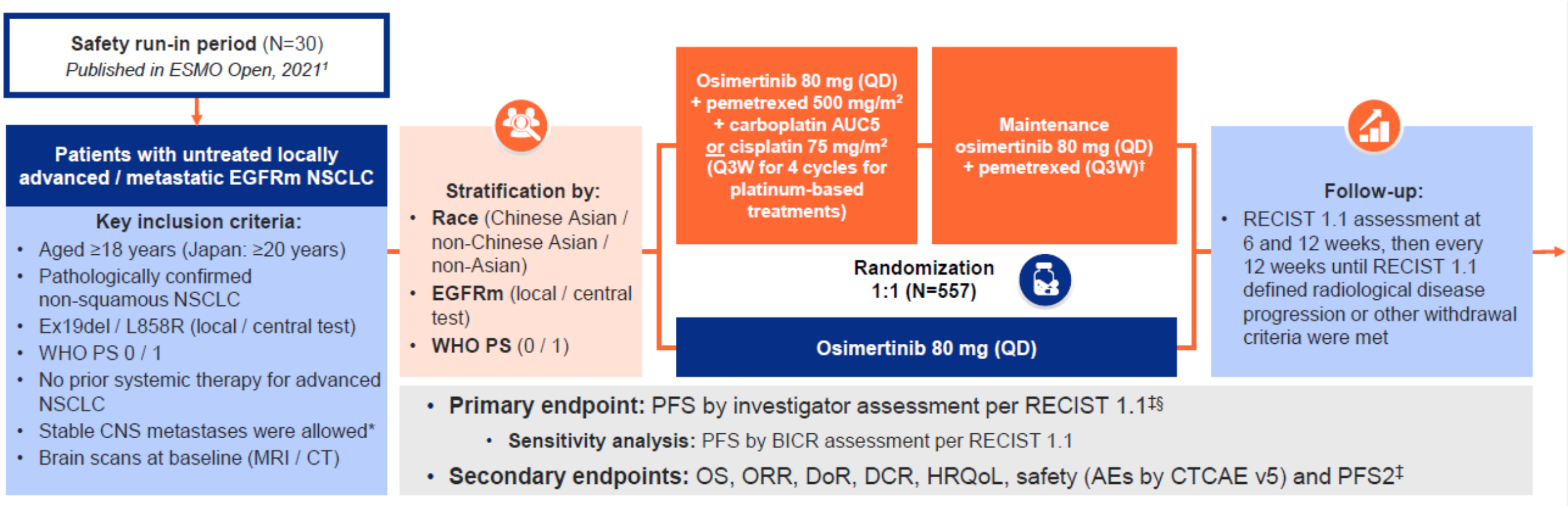
Combination Approaches



Chemotherapy+Osimertinib
FLAURA-2

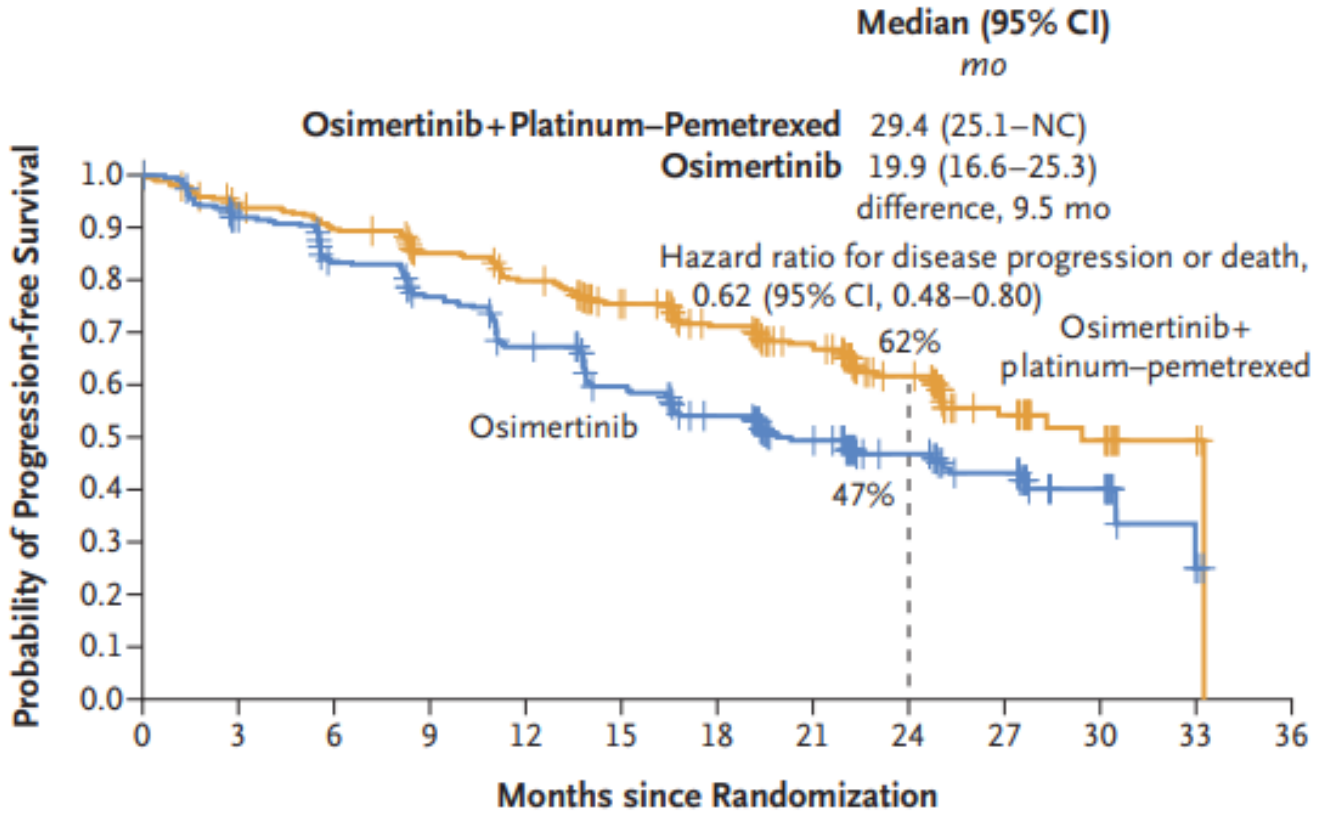
Amivantamab+Lazertinib
MARIPOSA

FLAURA 2: study design



Planchard D, NEJM 2023

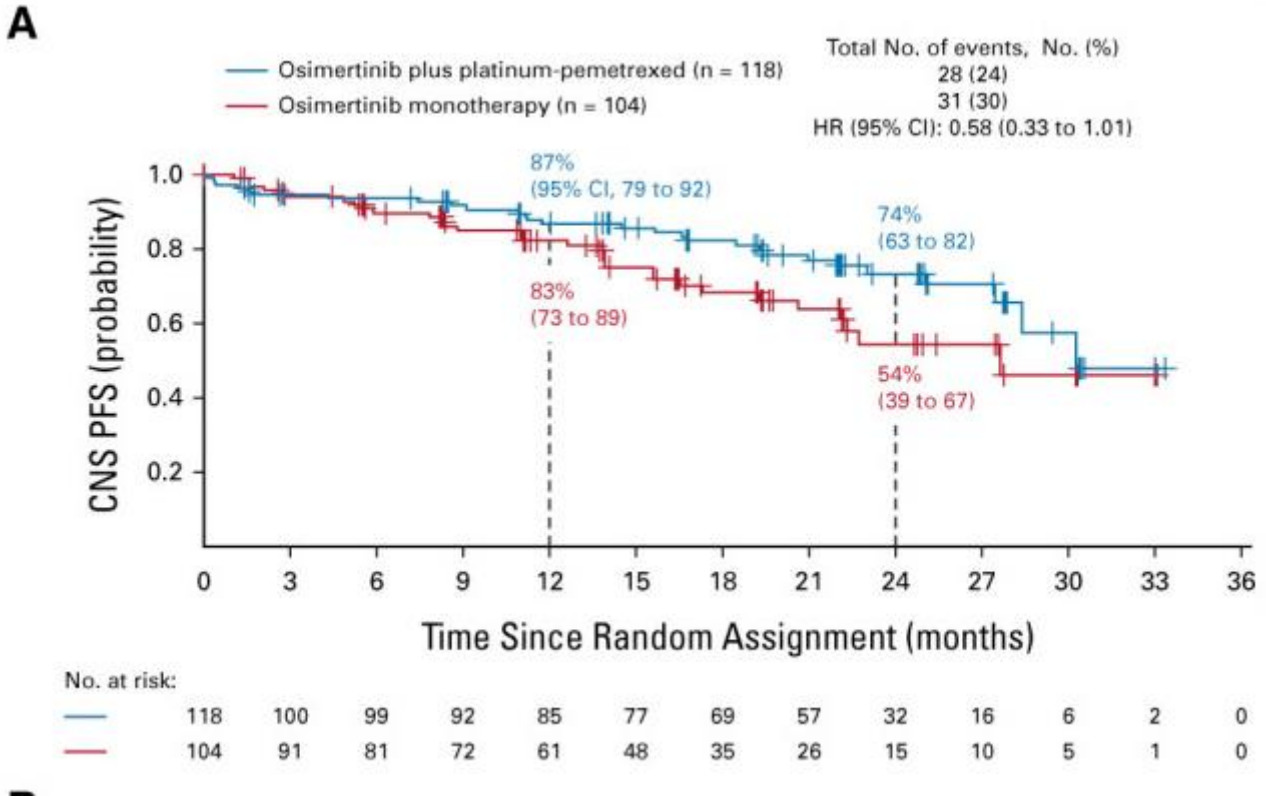
FLAURA 2: PFS according to blinded independent central review (full analysis set)

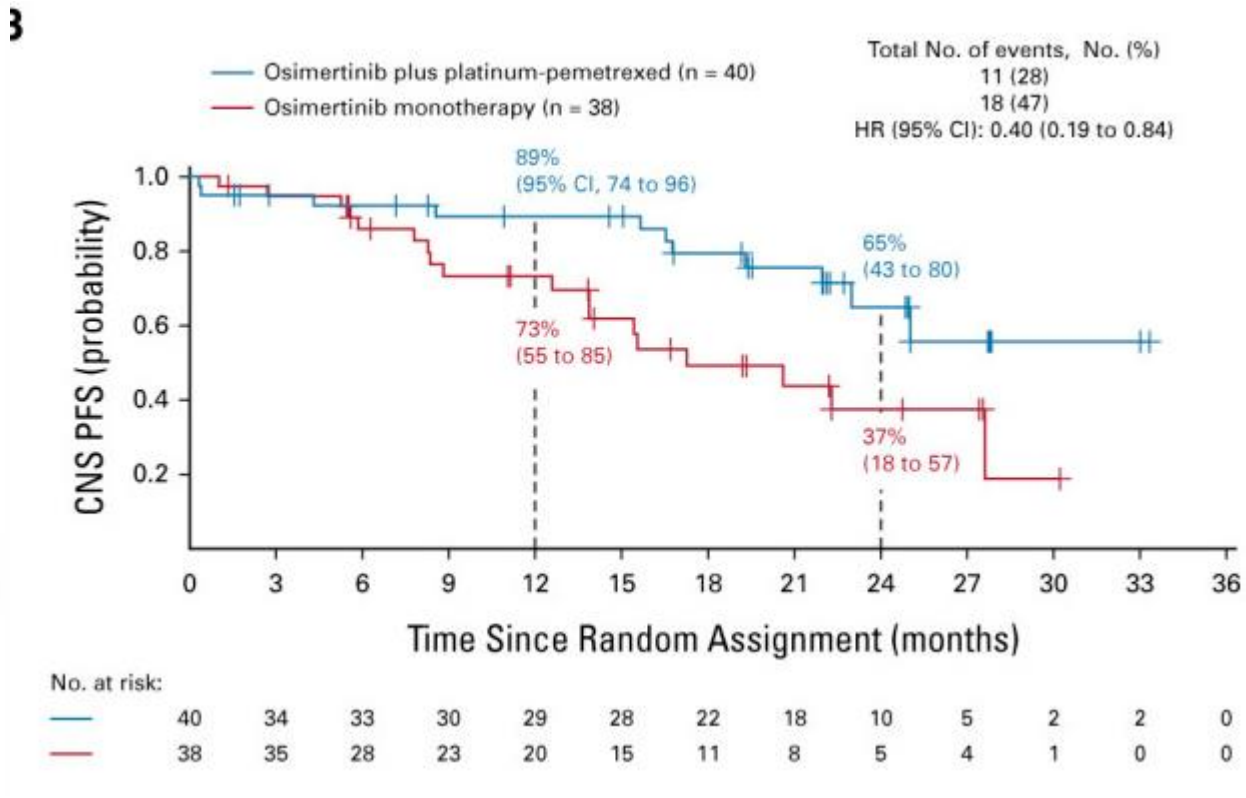


No. at Risk													
Osimertinib+ platinum–pemetrexed	279	255	242	223	207	184	158	128	81	39	20	3	0
Osimertinib	278	247	218	195	169	139	116	88	59	42	18	2	0

Planchard D, NEJM 2023

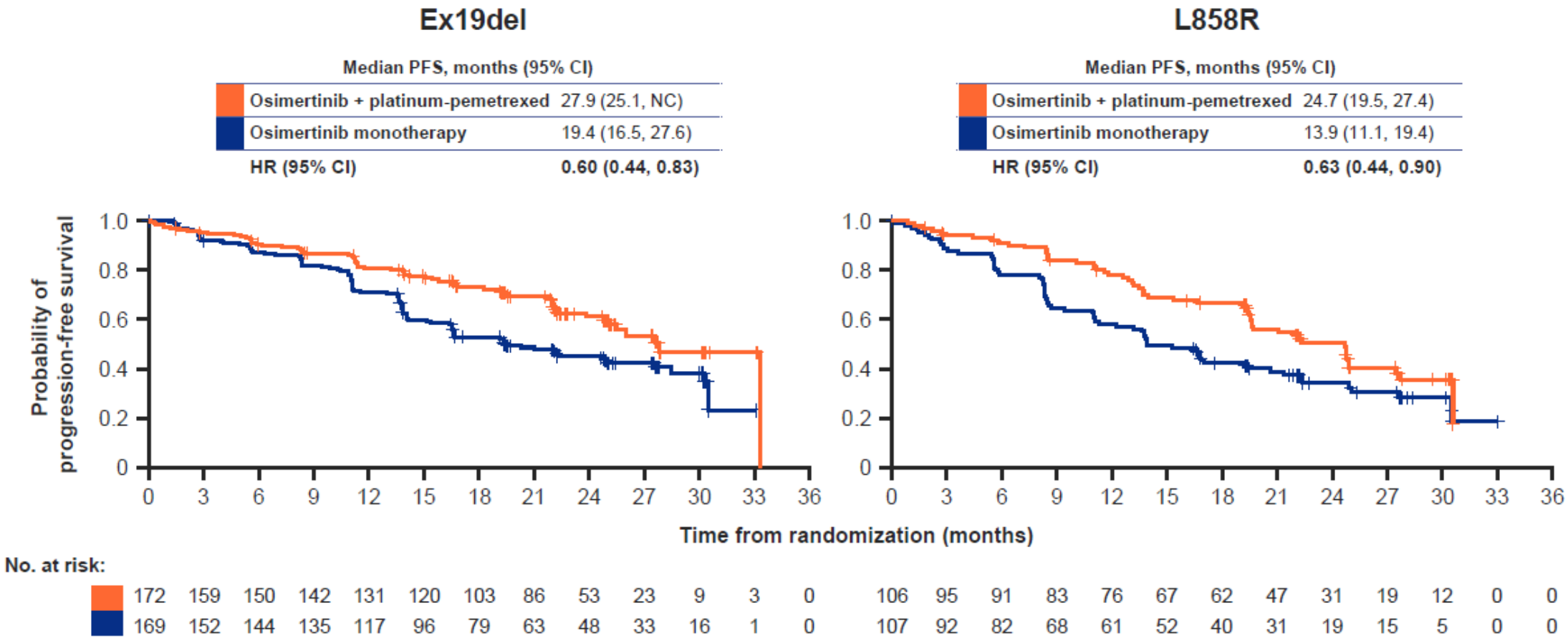
FLAURA 2
CNS Efficacy





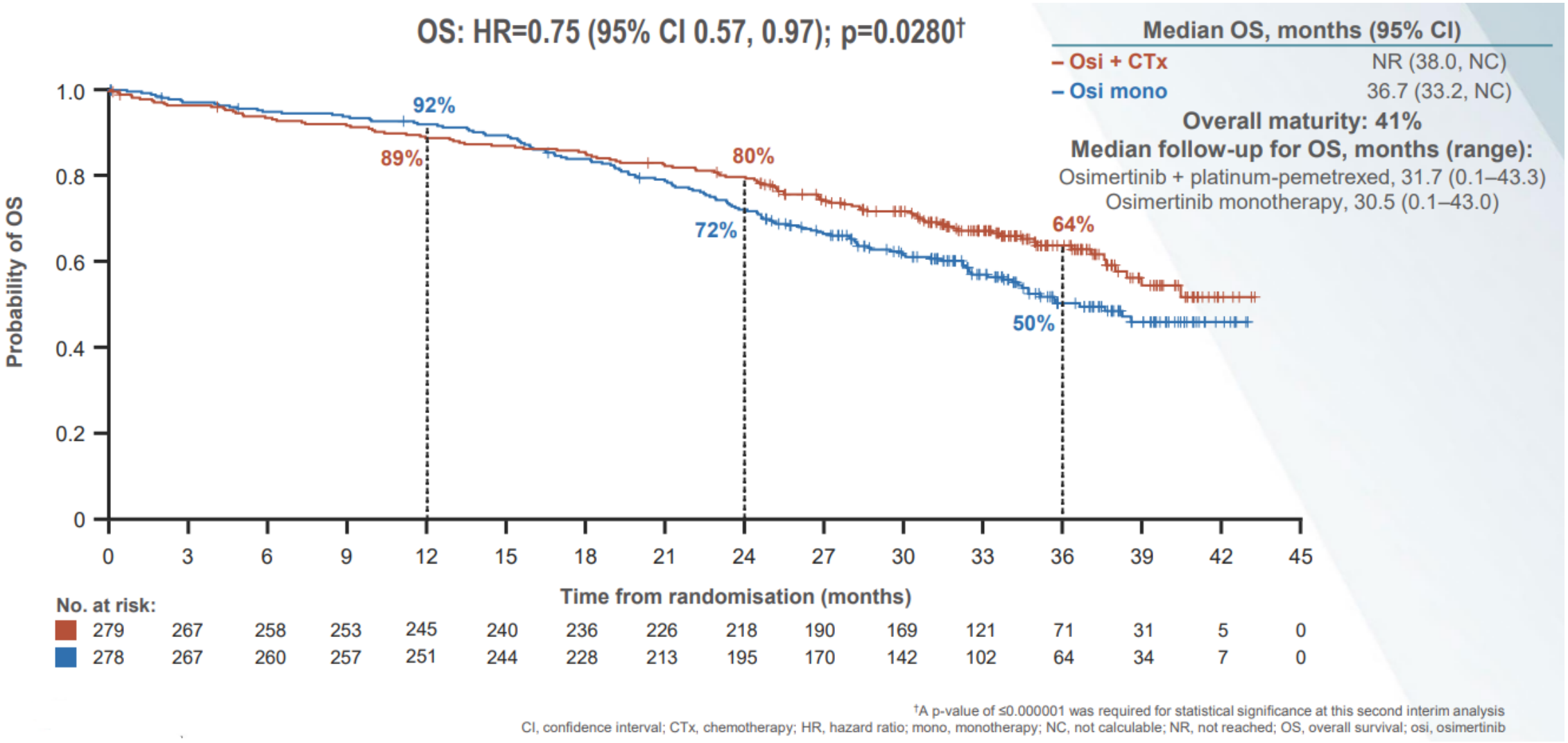
Janne PA, JCO 2024

FLAURA 2: PFS per investigator by EGFR mutation type at baseline



Janne P, WCLC 2023

FLAURA 2: second interim overall survival analysis



†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

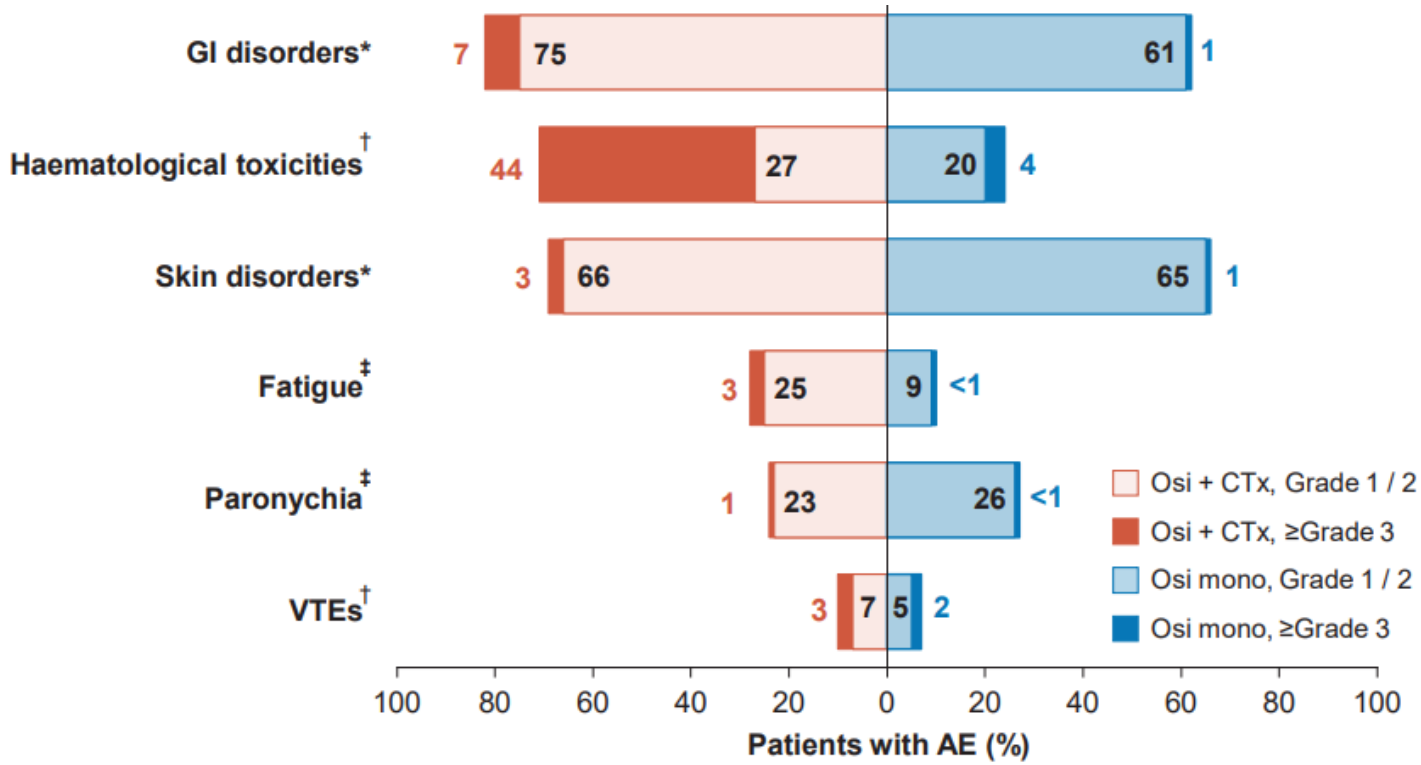
Valdiviezo N, ELCC 2024

Safety summary and selected AEs of clinical interest (safety analysis set)

Patients with AEs, n (%)	Osi + CTx (n=276)	Osi mono (n=275)†
AE any cause	276 (100)	268 (97)
Any AE Grade ≥3	176 (64)	75 (27)
Any AE leading to death	18 (7)	8 (3)
Any AE leading to discontinuation of any study drug	132 (48)	17 (6)

*Patients with multiple events in the same category were counted only once in that category. †One patient randomised to osi + platinum-pemetrexed received only osi and was therefore included in the osi mono arm of the safety analysis set.

AE, adverse event; CTx, chemotherapy; mono, monotherapy; osi, osimertinib.



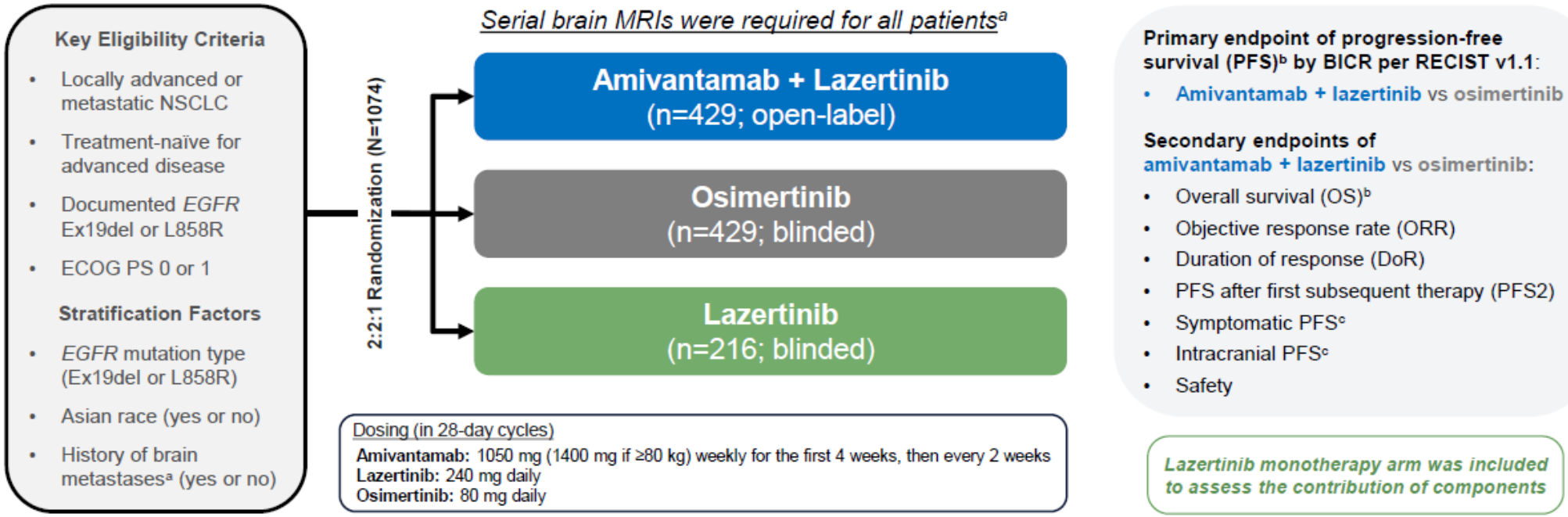
Lee CK, ELCC 2024

Acquired resistance mechanisms in plasma were broadly similar between treatment arms

Functional groups	Acquired gene alteration, n (%)	Plasma analysis set		FLAURA osimertinib monotherapy (n=109)[1]
		Osimertinib + chemotherapy (n=68)	Osimertinib monotherapy (n=99)	
EGFR mutations	C797S	2 (3)	10 (10)	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)	–
RB1 loss (with TP53 alteration)*		2 (3)	4 (4)	–
No known acquired resistance alteration detected*		46 (68)	54 (55)	–

Yang JCH, WCLC 2024

MARIPOSA: study design



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.

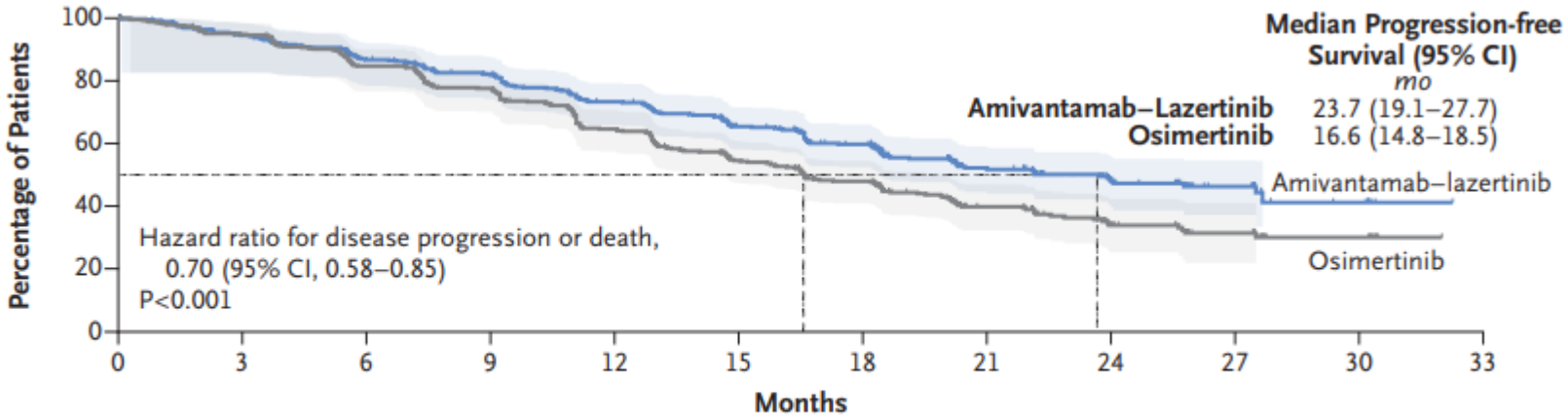
[b]Key statistical assumptions: 800 patients with 450 PFS events would provide approximately 90% power for amivantamab + lazertinib vs osimertinib to detect a HR of 0.73 using a log-rank test, with an overall two-sided alpha of 0.05 (assuming an incremental median PFS of 7 months). Statistical hypothesis testing included PFS and then OS.

[c]These secondary endpoints (symptomatic and intracranial PFS) will be presented at a future congress.

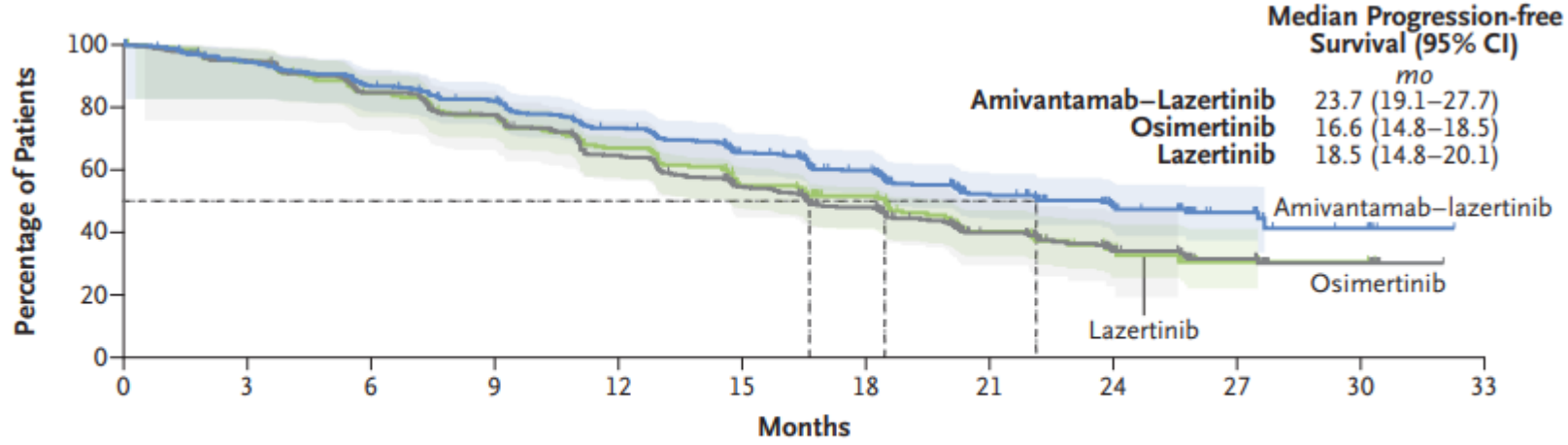
BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletion; HR, hazard ratio; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; RECIST, Response Evaluation Criteria in Solid Tumors.

Cho BC, ESMO 2023

MARIPOSA: primary endpoint PFS by BICR



No. at Risk												
Amivantamab–lazertinib	429	391	357	332	291	244	194	106	60	33	8	0
Osimertinib	429	404	358	325	266	205	160	90	48	28	10	0



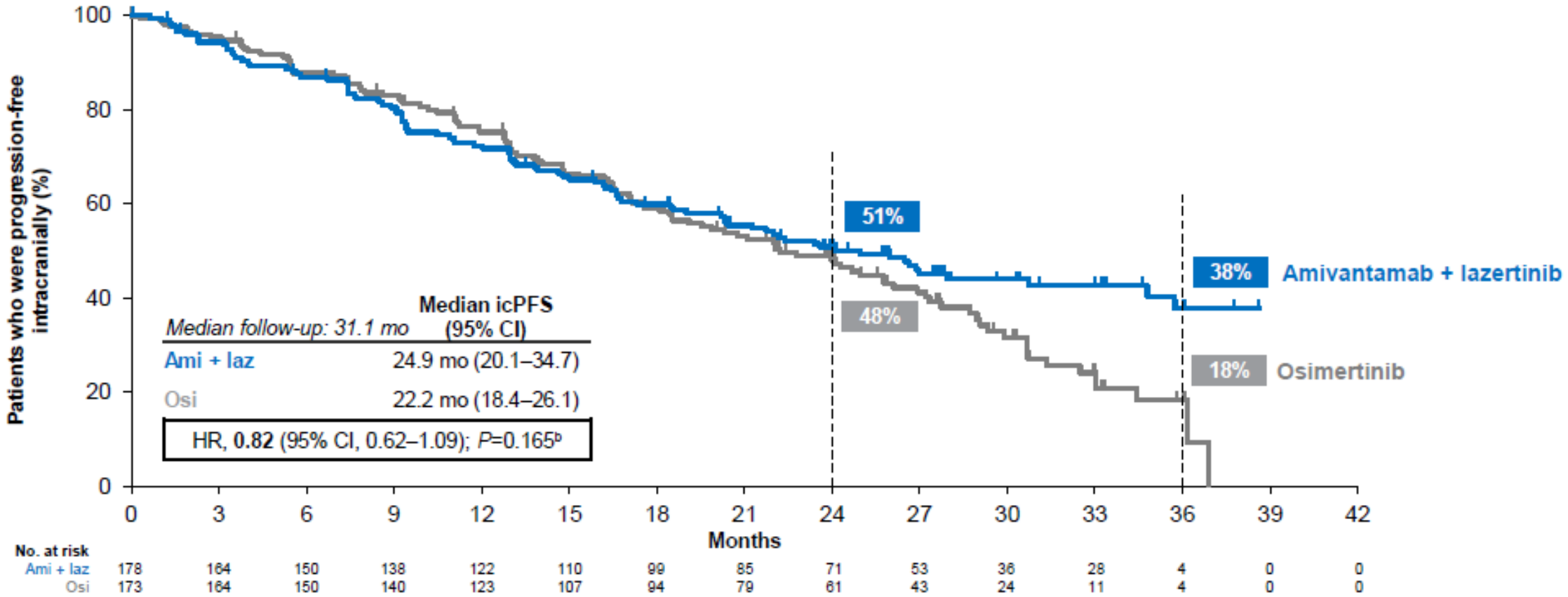
No. at Risk												
Amivantamab–lazertinib	429	391	357	332	291	244	194	106	60	33	8	0
Osimertinib	429	404	358	325	266	205	160	90	48	28	10	0
Lazertinib	216	200	174	157	134	103	83	41	19	6	2	0

Cho BC, NEJM 2024

MARIPOSA: CNS Efficacy

Intracranial PFS[a]

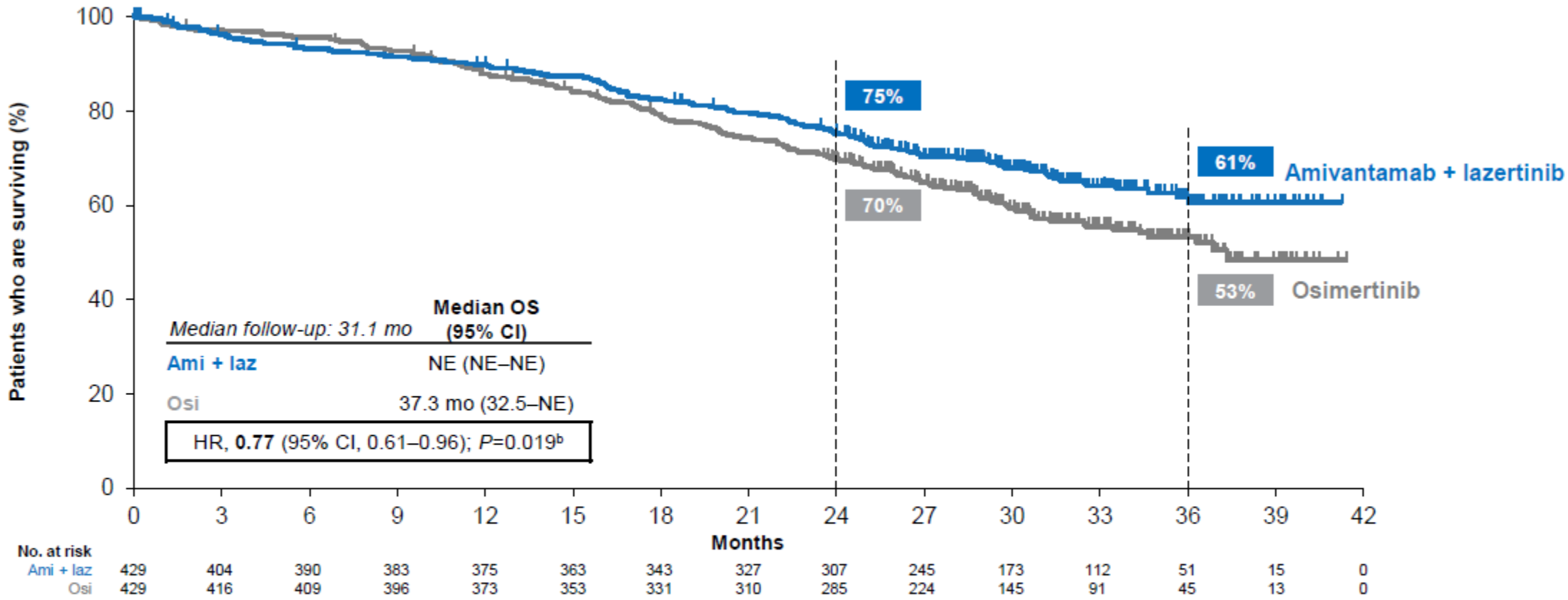
MARIPOSA required serial brain imaging for all patients, which provides robust evaluation of CNS outcomes
Amivantamab + lazertinib showed a favorable trend in icPFS with sustained and durable CNS control at 3 years



3-year landmark icPFS was double for amivantamab + lazertinib vs osimertinib (38% vs 18%)

Gadgeel S, WCLC 2024

MARIPOSA: Updated Overall Survival Analysis

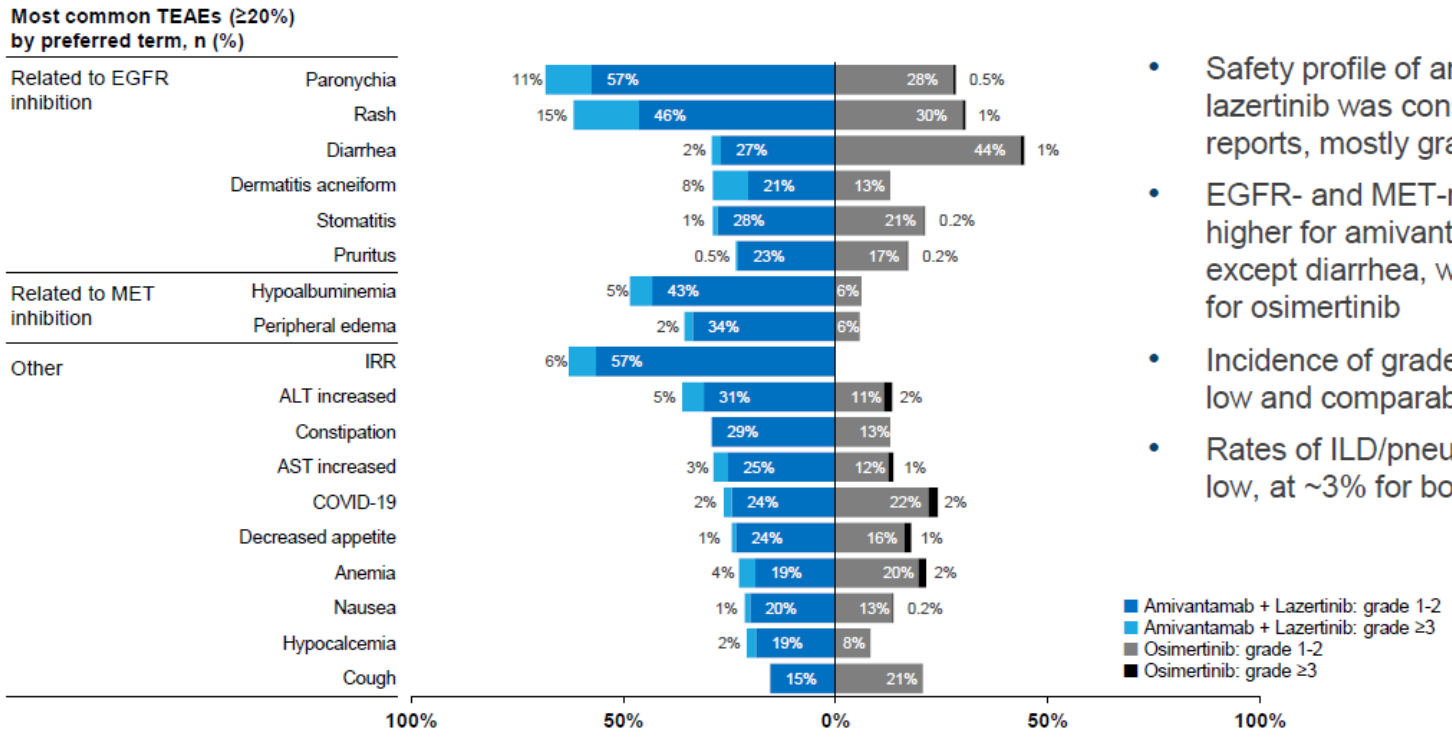


OS curves separate early and widen over time favoring amivantamab + lazertinib, with 61% of patients alive at 3 years vs 53% with osimertinib

[a]This analysis was requested by health authorities and had nominal alpha spend. A *P*-value of ≤0.00001 was required for statistical significance. [b]P-value was calculated from a log-rank test stratified by mutation type (Ex19del or Exon 21 L858R), race (Asian or Non-Asian), and history of brain metastasis (present or absent). Hazard ratio was calculated from a stratified proportional hazards model.

Gadgeel S, WCLC 2024

MARIPOSA: Safety Profile



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

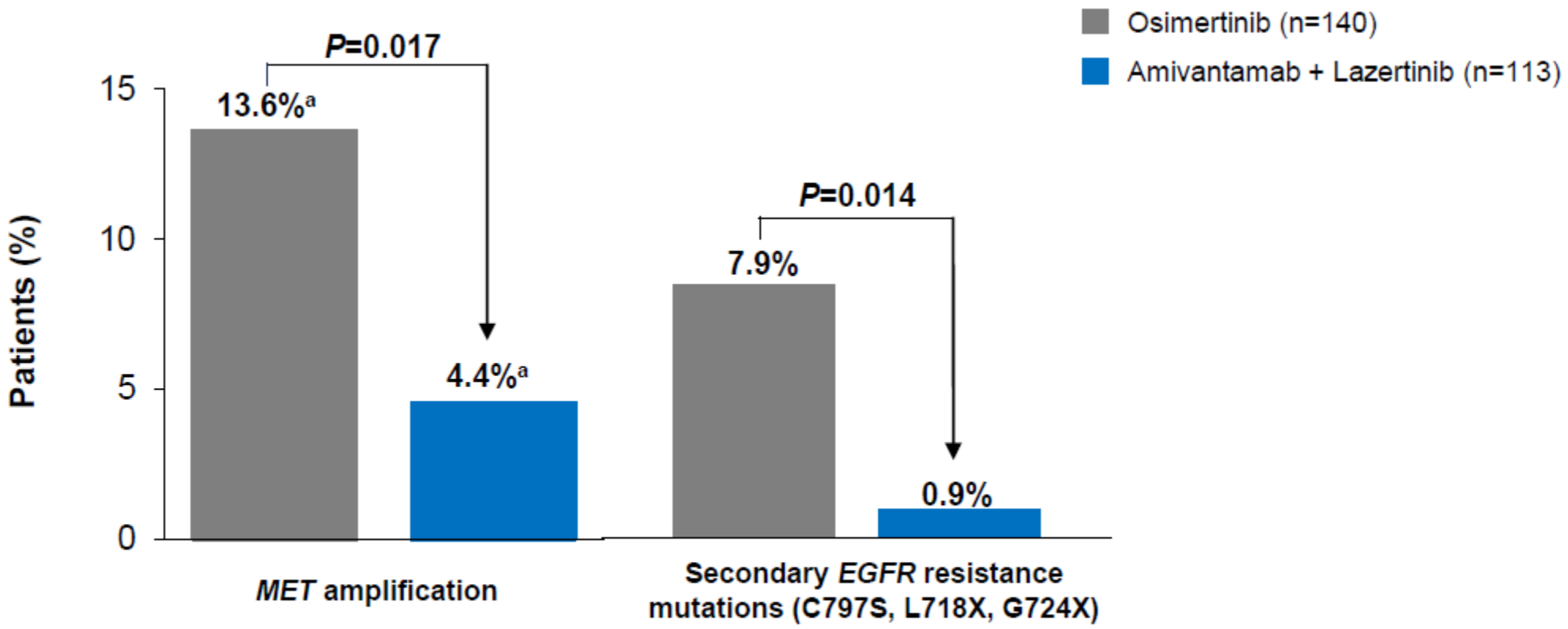
	Amivantamab + Lazertinib (n=421)	Osimertinib (n=428)
Any VTE, n (%)	157 (37)	39 (9)
Grade 1	5 (1)	0
Grade 2	105 (25)	24 (6)
Grade 3	43 (10)	12 (3)
Grade 4	2 (0.5)	1 (0.2)
Grade 5	2 (0.5)	2 (0.5)
Any VTE leading to death, n (%)	2 (0.5)	2 (0.5)
Any VTE leading to any discontinuation, n (%)	12 (3)	2 (0.5)
Anticoagulant use at time of first VTE, n (%)		
On anticoagulants	5 (1)	0
Not on anticoagulants	152 (36)	39 (9)
Median onset to first VTE	84 days	194 days
Within first 4 months, n (%)	97 of 157 (62)	13 of 39 (33)

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

Cho BC, ESMO 2023

MARIPOSA
MET and EGFR-based resistance mechanisms

Amivantamab + lazertinib significantly reduced the incidence of acquired MET amplifications and EGFR resistance mutations vs osimertinib



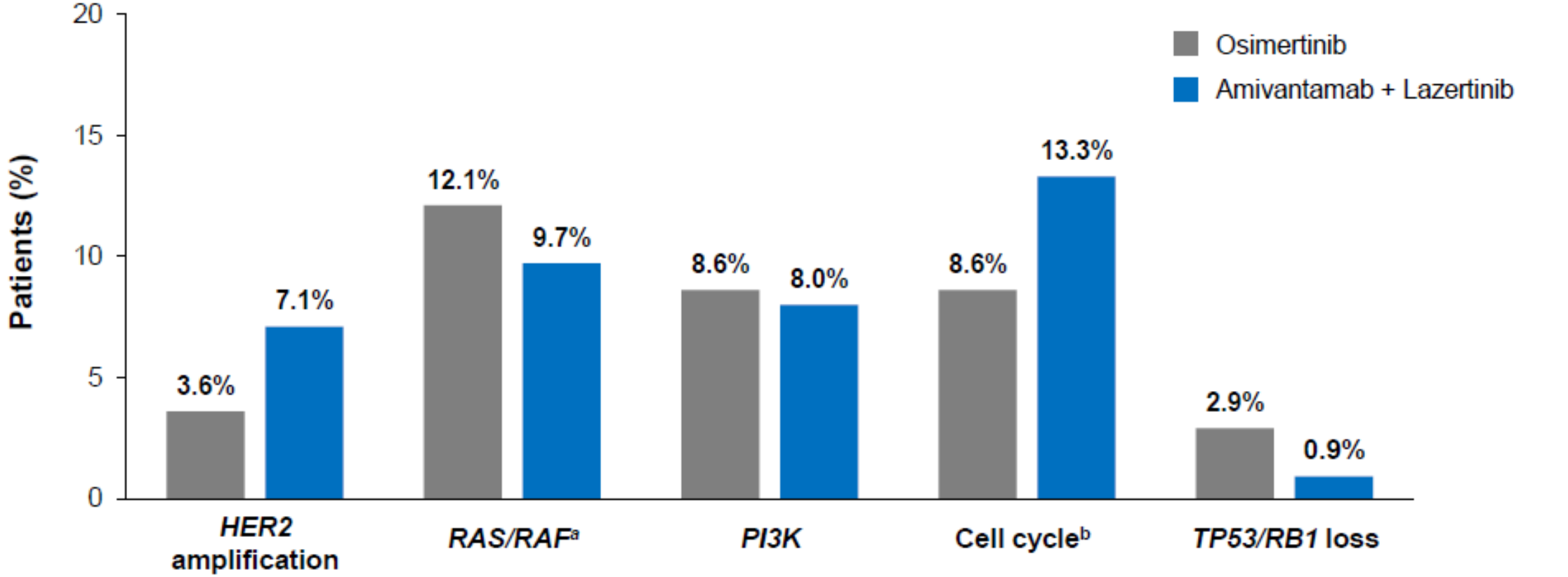
Acquired *MET* amplifications were ~3-fold lower and *EGFR* resistance mutations were ~8-fold lower for amivantamab + lazertinib versus osimertinib

Besse B, ESMO 2024

MARIPOSA
MET and EGFR independent resistance mechanisms

1L *EGFR+*

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

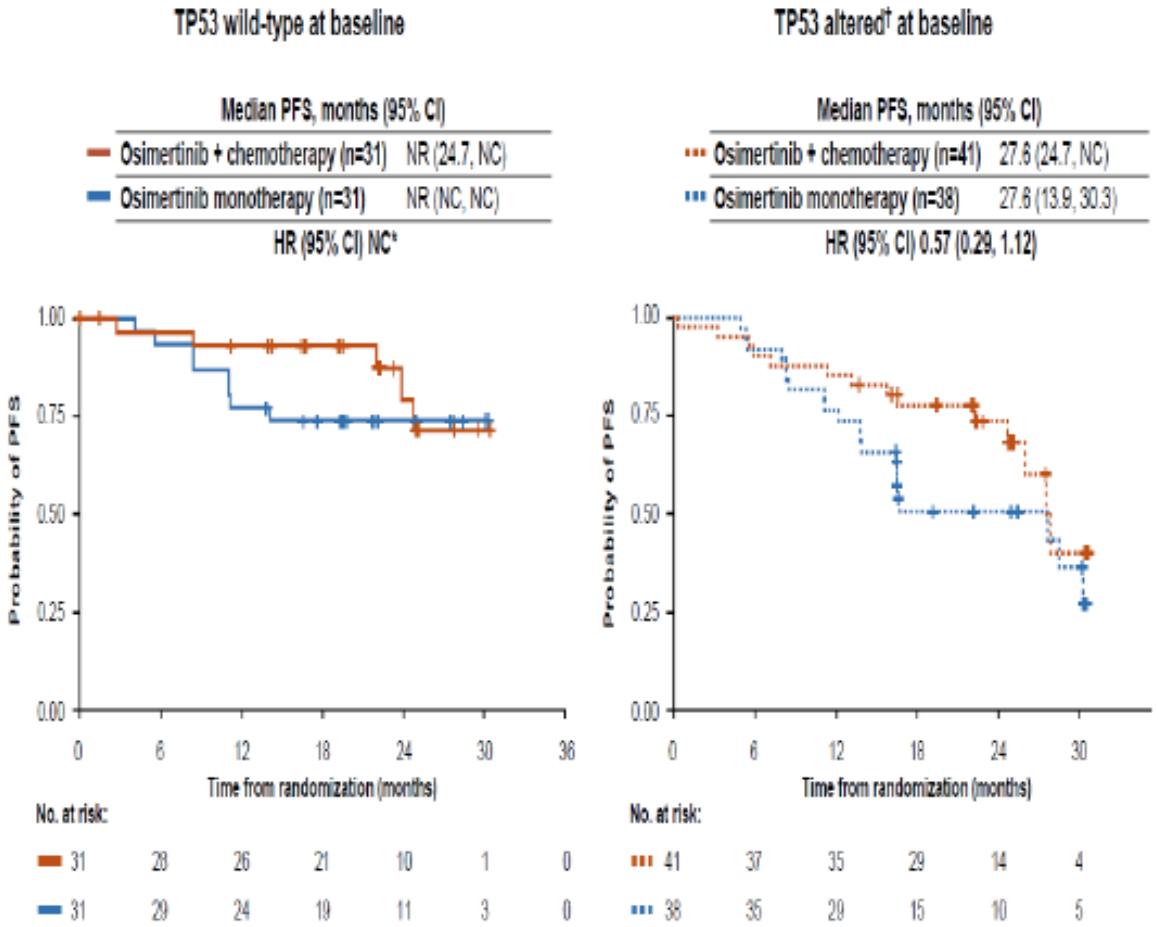


Amivantamab + lazertinib did not meaningfully increase other molecular escape pathways and had a low rate (0.9%) of *TP53/RB1* loss (associated with SCLC transformation)[1]

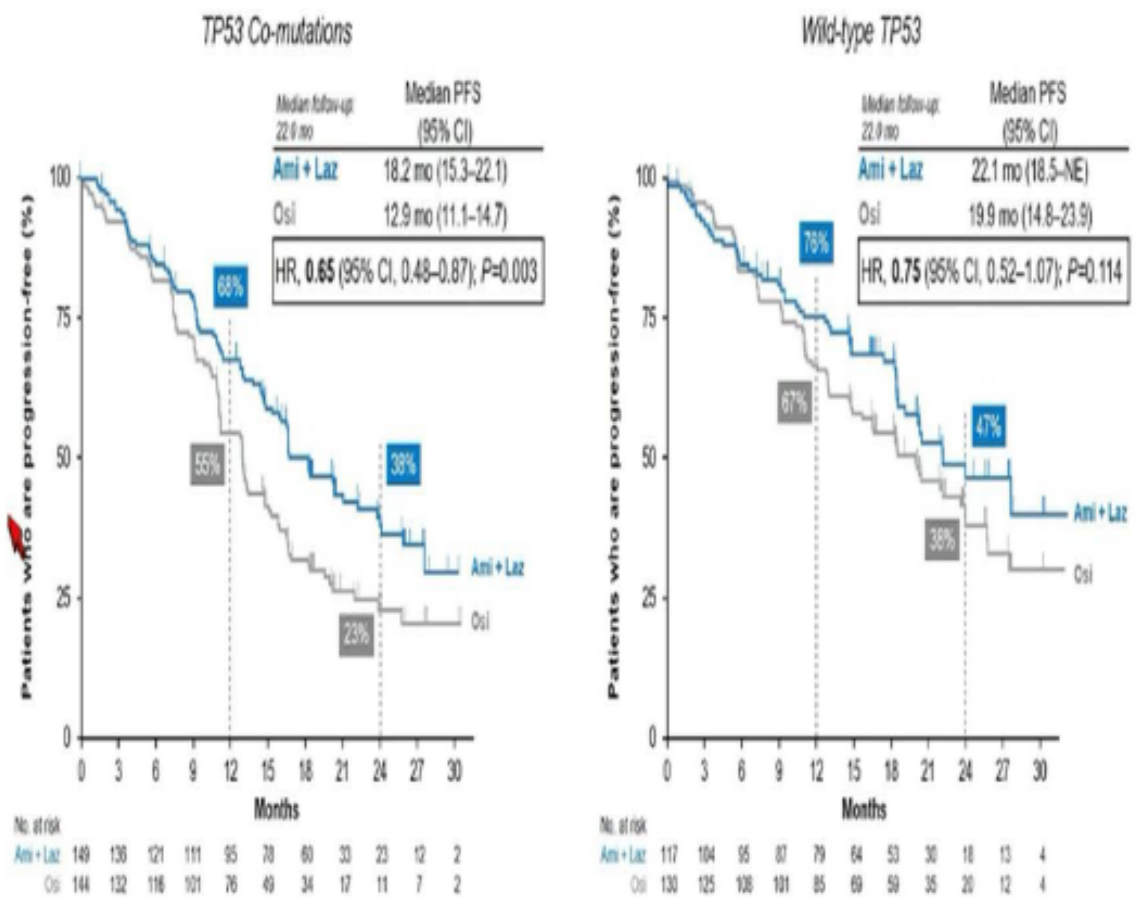
Besse B, ESMO 2024

FLAURA-2 and MARIPOSA
Efficacy in TP53 co-mutated subgroups

FLAURA 2

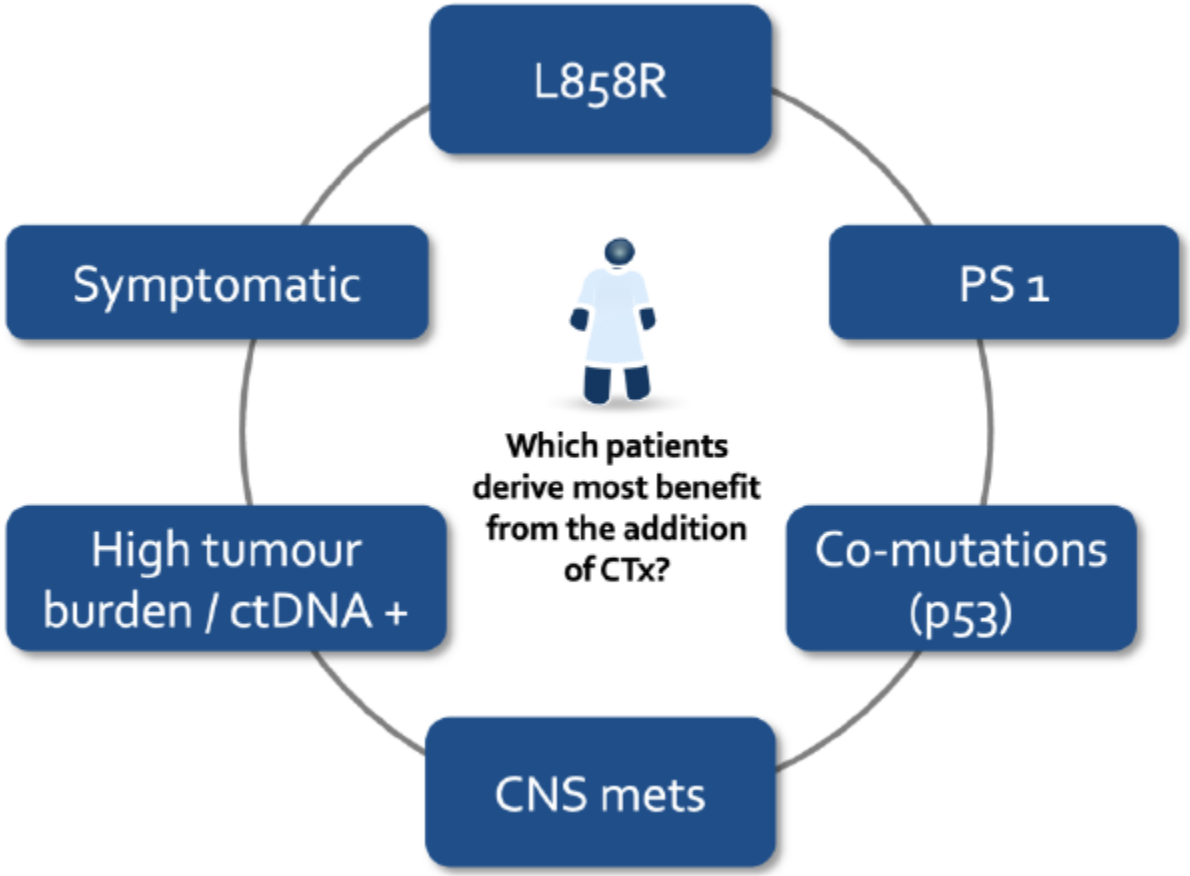


Mariposa Trial



Yang JCH, ESMO 2024; Felip E, ASCO 2024

Potential factors supporting intensification for the frontline treatment of EGFRm metastatic NSCLC?



- Is there a need to define a specific threshold for high tumour burden to facilitate patient selection?
- Are there any emerging indicators or biomarkers for patients who could benefit from treatment intensification? What about ctDNA?

Peters S, WCLC 2024

SKIPPirr Study

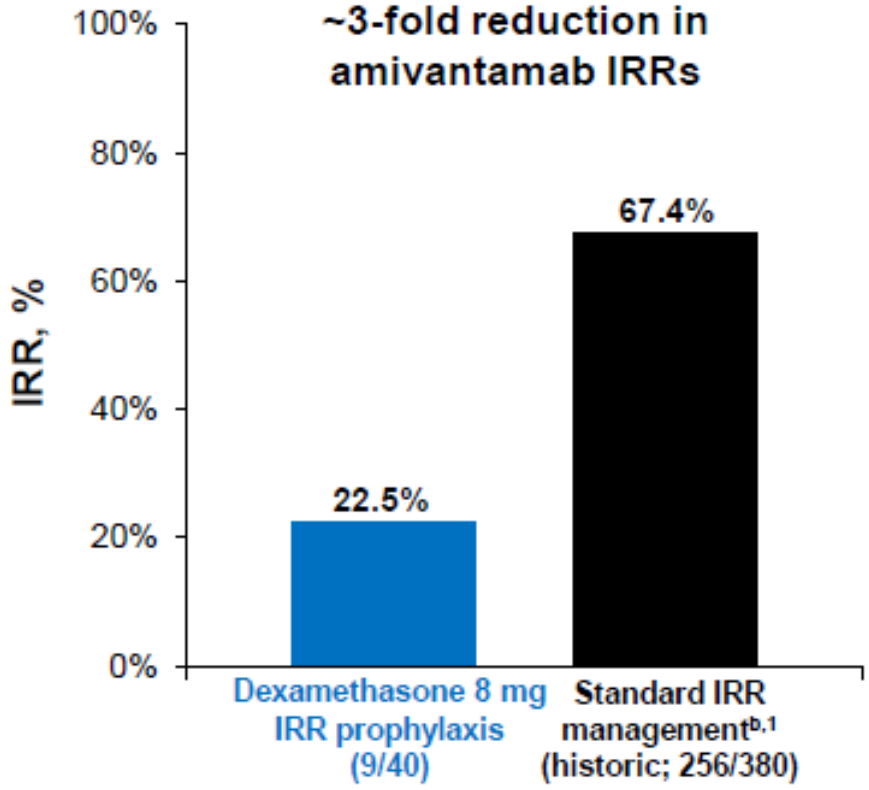
Dexamethasone 8 mg Oral Prophylaxis Reduced the Rate of IRRs[a]

Prophylaxis with dexamethasone reduced the amivantamab IRR rate to 22.5%

Prophylactic Schedule

	At home		In clinic C1D1
	2 days before	1 day before	1 hour before
AM	Dex 4 mg x2	Dex 4 mg x2	Dex 4 mg x2 + dex 10 mg IV + antihistamines + antipyretics → IV amivantamab
PM	Dex 4 mg x2	Dex 4 mg x2	

Adequate oral hydration is encouraged throughout the prophylaxis period



Lopes G, WCLC 2024

PALOMA-3: subcutaneous vs intravenous Amivantamab, both in combination with Lazertinib

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

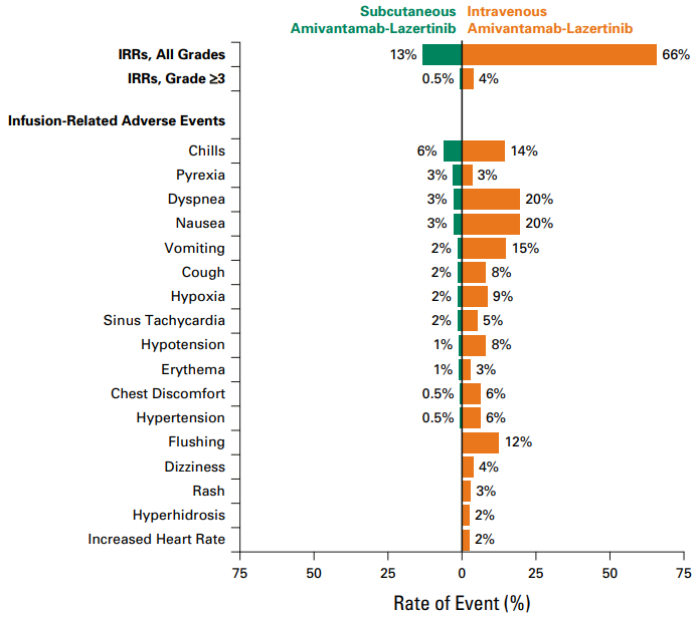
1:1 Randomization (N=418)

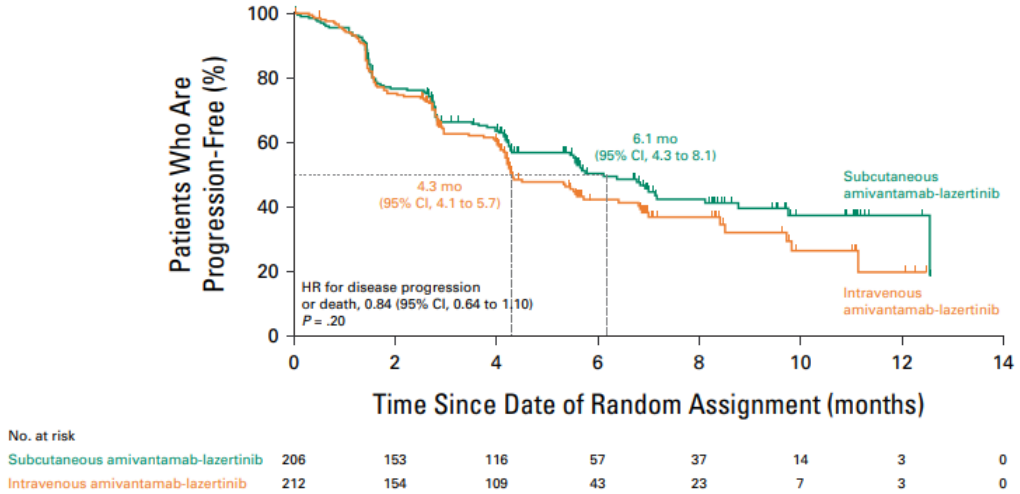
- **SC Amivantamab + Lazertinib (n=206)**
- **IV Amivantamab + Lazertinib (n=212)**

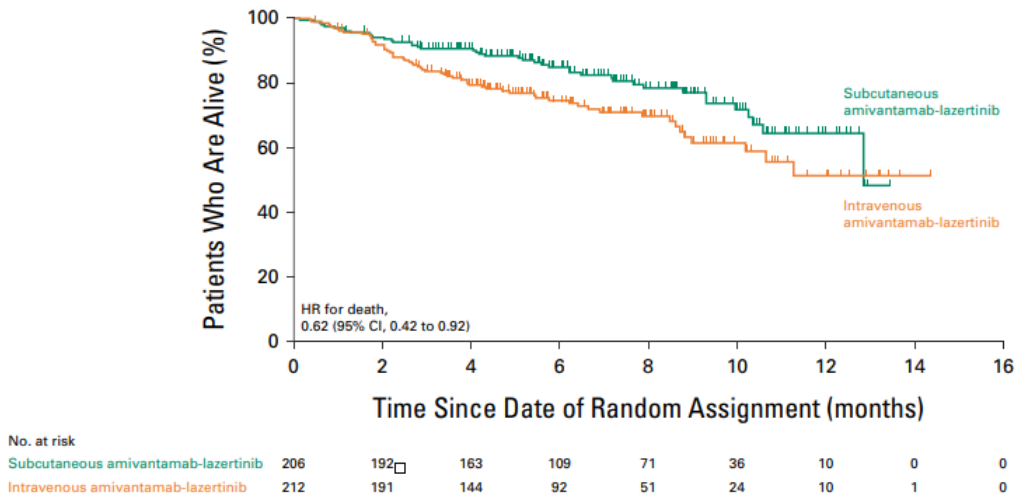
Prophylactic anticoagulation recommended for the first 4 months of treatment

Co-primary endpoints:
- C_{trough} (noninferiority)
- C2 AUC (noninferiority)

Select secondary endpoints:
- PROs by mTASQ[a]
- Healthcare resource utilization[b]
  - Chair time
  - Time in treatment room
  - Duration of treatment administration
  - Active healthcare provider time





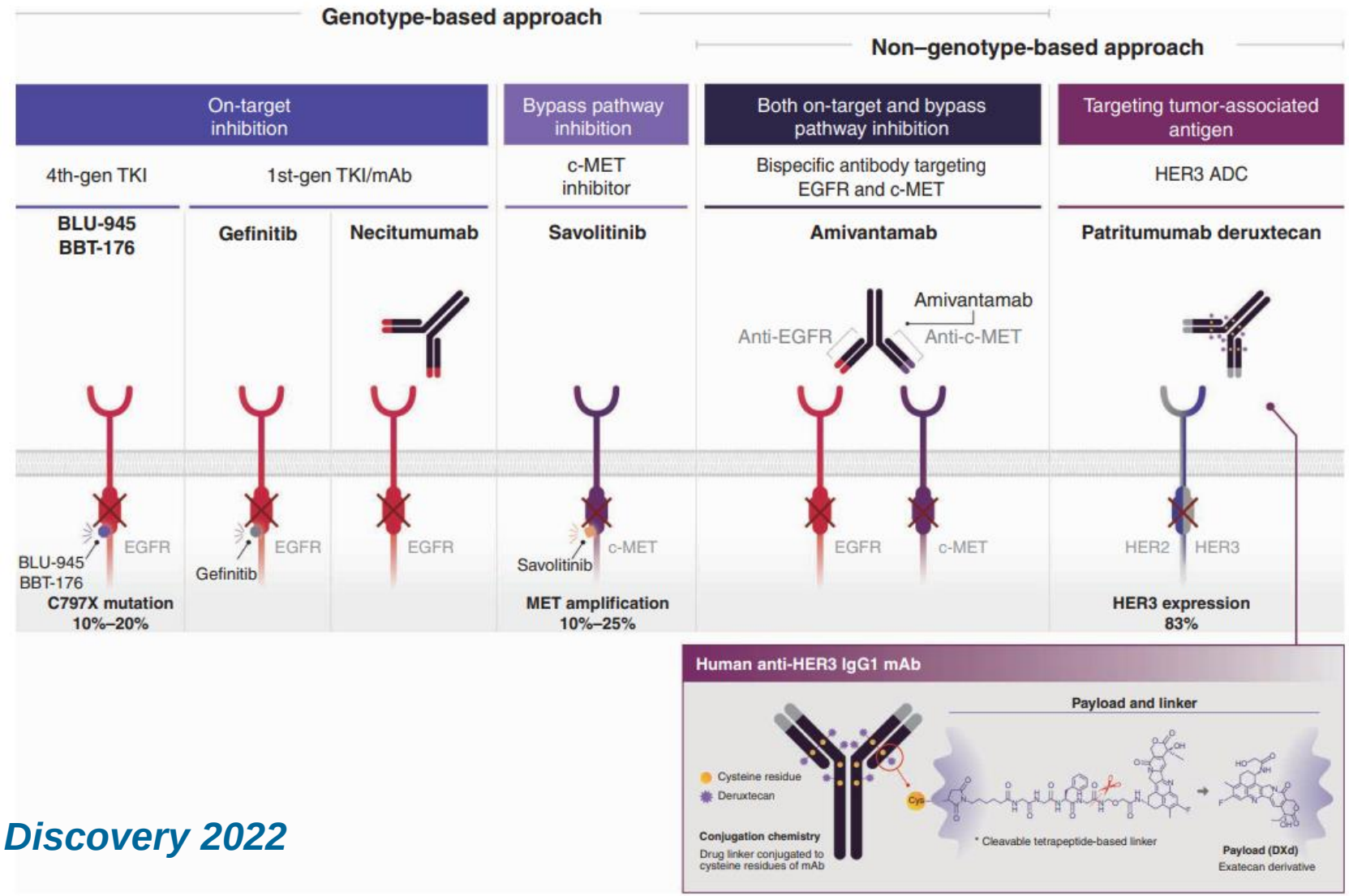


Leighl N, ASCO 2024

Agenda

- First line
- Subsequent lines
- Exon 20 insertions

Current ongoing strategies to overcome osimertinib resistance



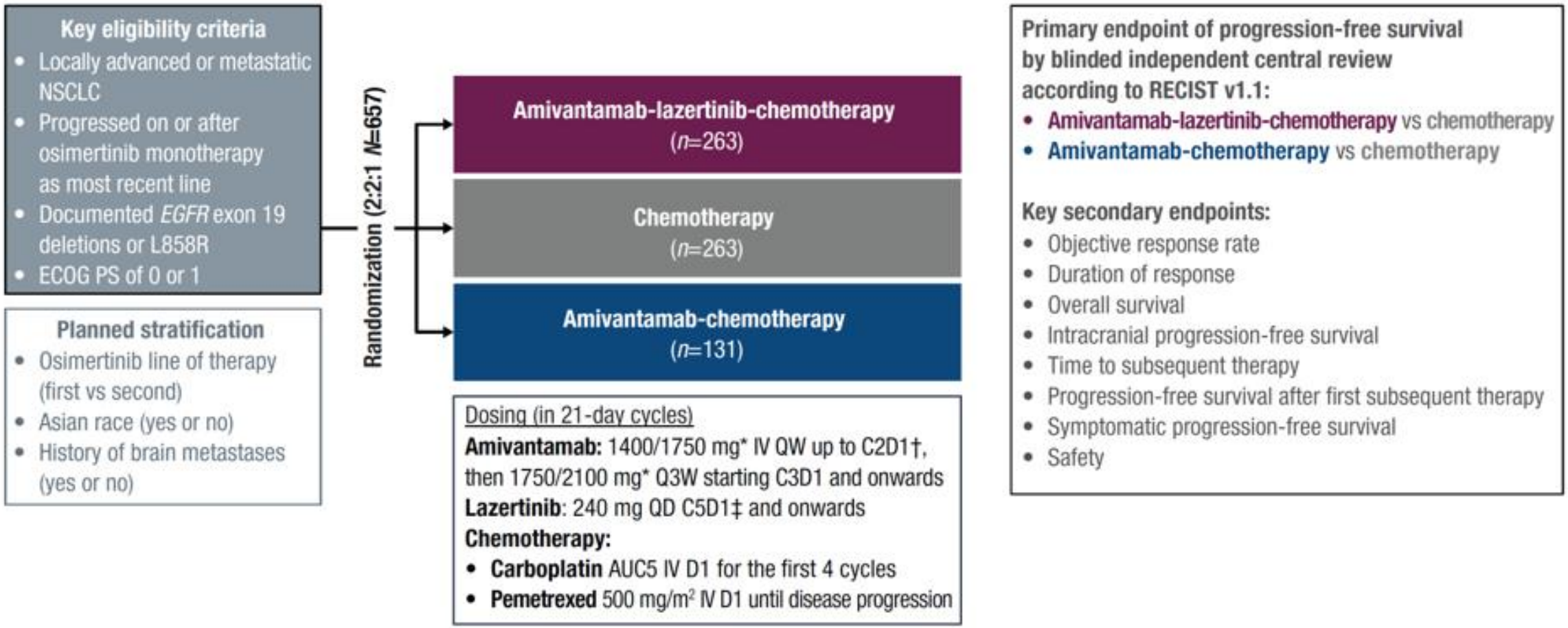
Lim SM, Cancer Discovery 2022

EGFR+MET combinations to address acquired MET alterations

Clinical Trial	Ph	Treatment	Pts (n)	Setting	MET Selection	ORR (%)	mDOR (months)	mPFS (months)	G3-4 AEs (%)
CHRYSALIS[1]	Ib	Lazertinib + **Amivantamab**	45	Post-Osi	No	36%	9.6	4.9	16%
CHRYSALIS-2[2]	Ib	Lazertinib + **Amivantamab**	162	Post-Osi and CT	No	36%	9.6	5.1	NA
CHRYSALIS-2[3]	Ib	Lazertinib + **Amivantamab** + CT	20	Post-TKI	No	50%	NE	14.0	NA
TATTON[4]	Ib	Osimertinib + **Savolitinib**	69	Post-Osi	METamp (FISH, IHC, NGS)	30%	7.9	5.4	57%
ORCHARD[5]	II	Osimertinib + **Savolitinib**	17	Post-Osi	METamp, METex14	41%	NA	NA	25%
SAVANNAH[6]	II	Osimertinib + **Savolitinib**	108	Post-Osi	MET IHC 90+ and/or MET FISH 10+	49%	9.3	7.1	45%
INSIGHT-2[7]	II	Osimertinib + **Tepotinib**	98 31	Post-Osi	METamp (FISH TBx) METamp (NGS LBx)	50.0% 54.8%	8.5 5.7	5.6 5.5	34.4%
LUMINOSITY[8]	Ib	Osimertinib + **Teliso-V**	25	Post-Osi	MET IHC	58%	NA	NA	32%

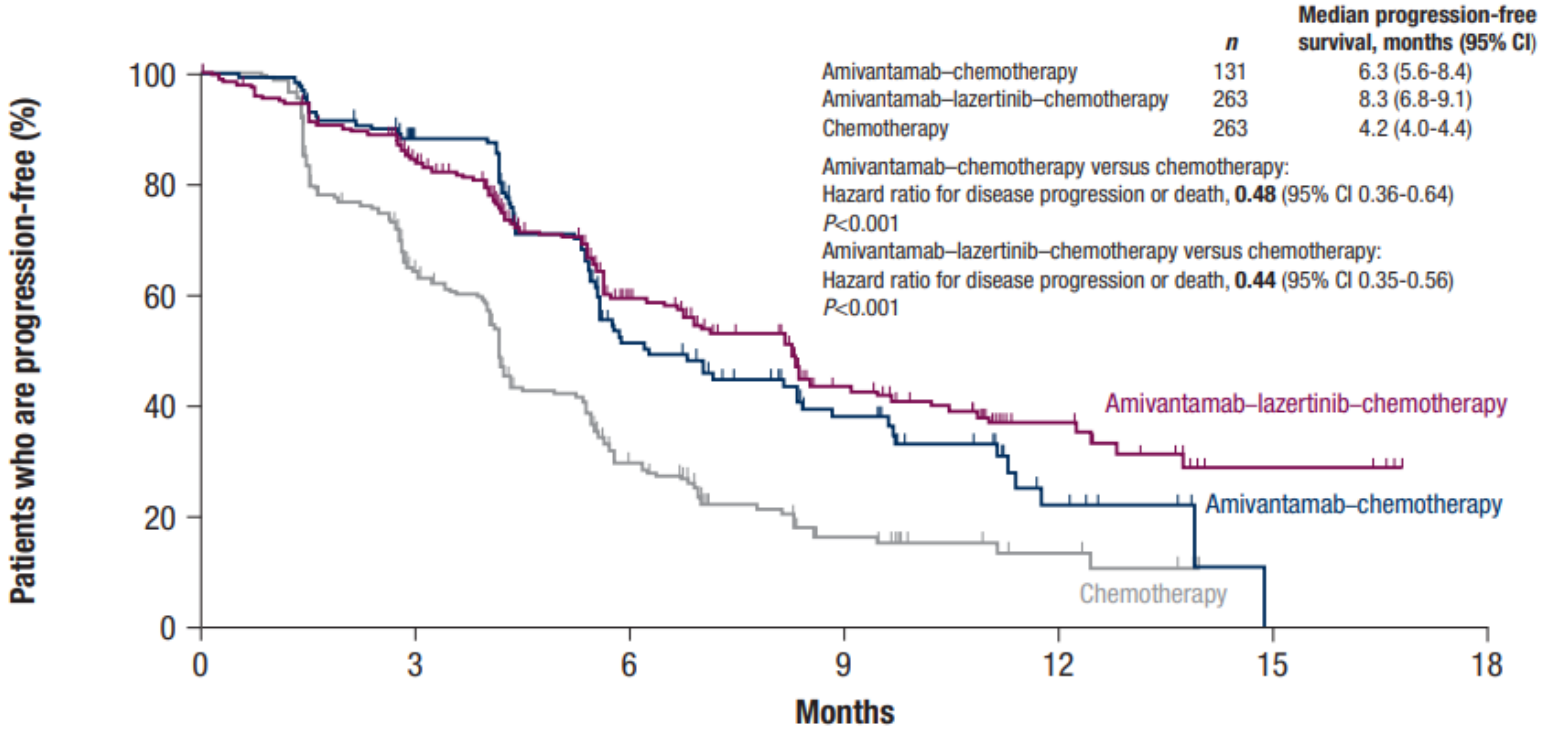
1.Baum J, J Clin Oncol 2021; 2.Shu CA, J Clin Oncol 2022; 3.Lee SH, WCLC 2023; 4.Sequist LV, Lancet 2020; 5.Yu HA, ESMO 2021; 6.Ahn MJ, WCLC 2022; 7.Kim TM, WCLC 2023; 8.Goldman JW, J Clin Oncol 2022

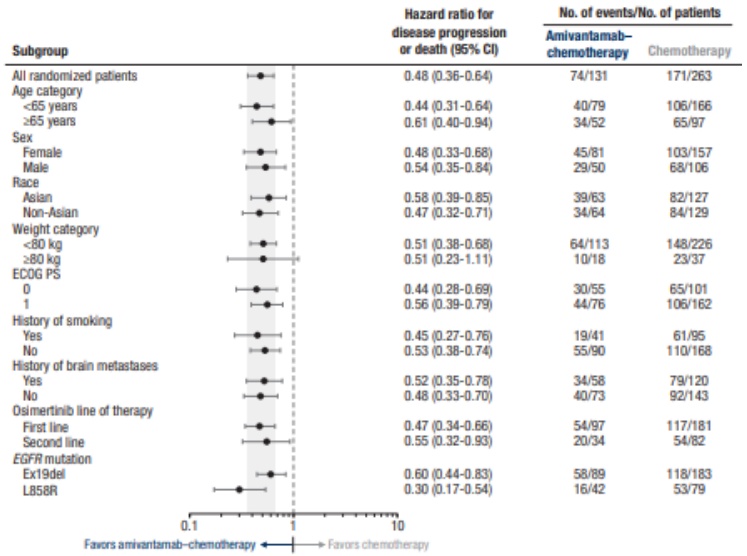
MARIPOSA 2: study design

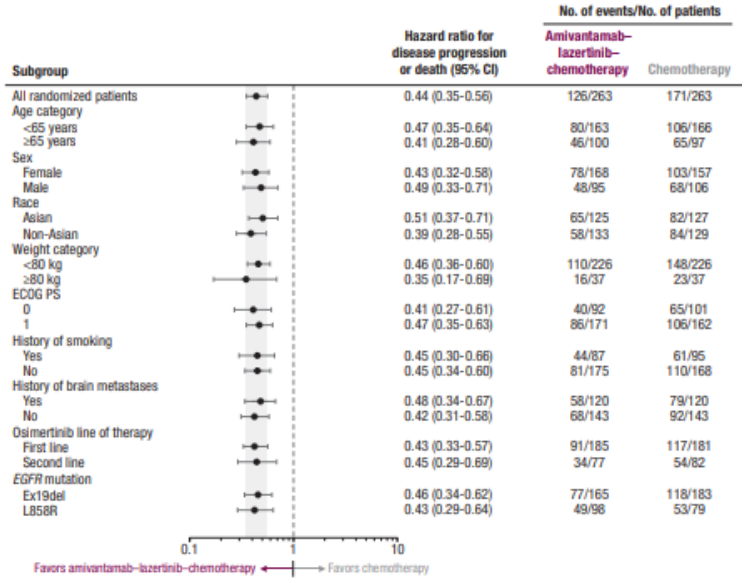


Passaro A, Ann Oncol 2023

MARIPOSA 2: PFS and adverse events





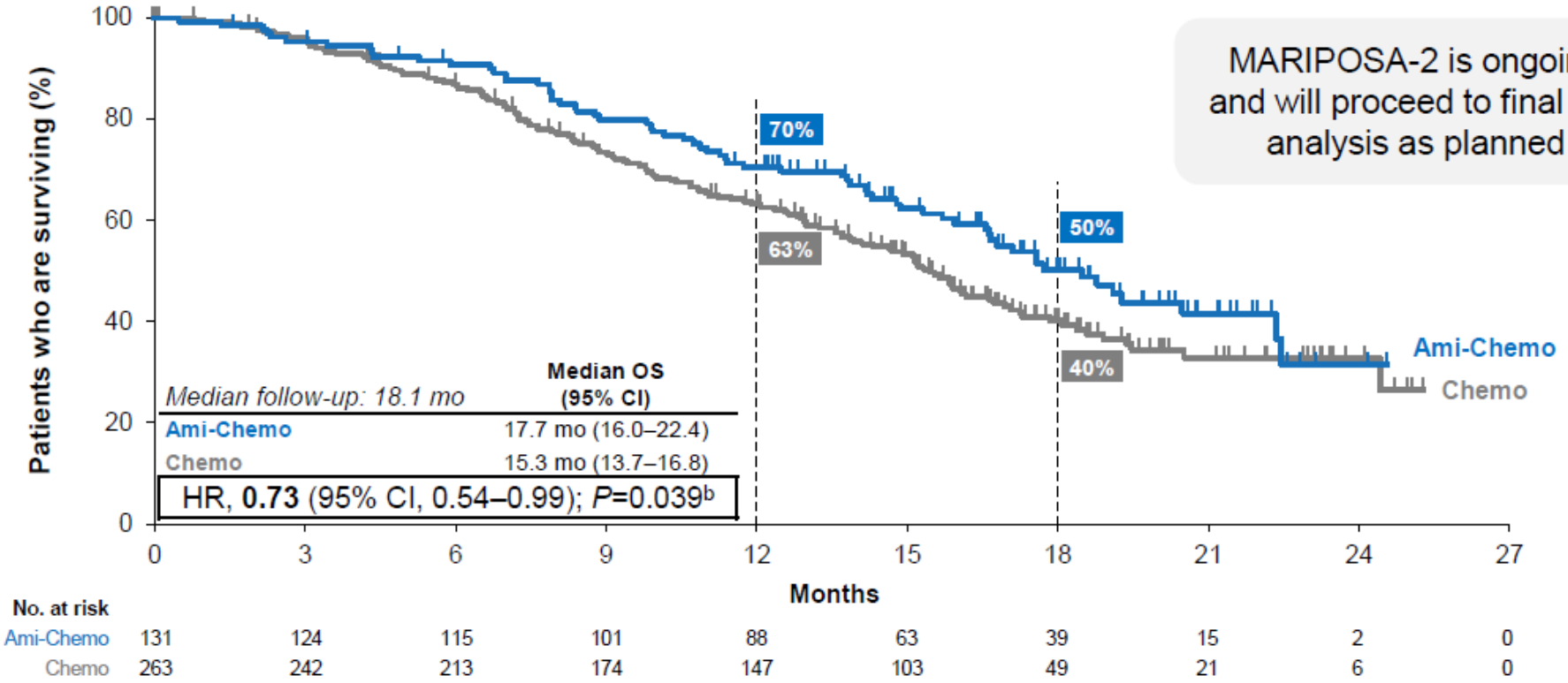


Event, *n* (%)	Chemotherapy (*n* = 243)	Amivantamab–chemotherapy (*n* = 130)	Amivantamab–lazertinib–chemotherapy (*n* = 263)
Any event	227 (93)	130 (100)	263 (100)
Grade ≥3	117 (48)	94 (72)	242 (92)
Any serious event	49 (20)	42 (32)	137 (52)
Any event resulting in death	3 (1)	3 (2)	14 (5)
Any event leading to:			
Interruptions of any study agent	81 (33)	84 (65)	202 (77)
Reductions of any study agent	37 (15)	53 (41)	171 (65)
Discontinuations of any study agent	9 (4)	24 (18)	90 (34)

Passaro A, Ann Oncol 2023

MARIPOSA 2: OS (2nd interim analysis)

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.

Popat S, ESMO 2024

HARMONi-A study: Ivonescimab + CT vs CT in EGFR mutated progressed on EGFR-TKIs

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)

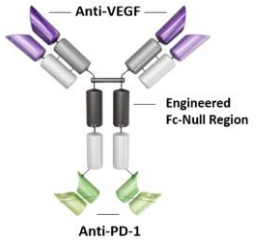
Ivonescimab 20mg/kg + Pemetrexed 500 mg/m² Carboplatin AUC5 Q3W for 4 cycles → **Ivonescimab** 20mg/kg Q3W + Pemetrexed 500 mg/m² Q3W

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



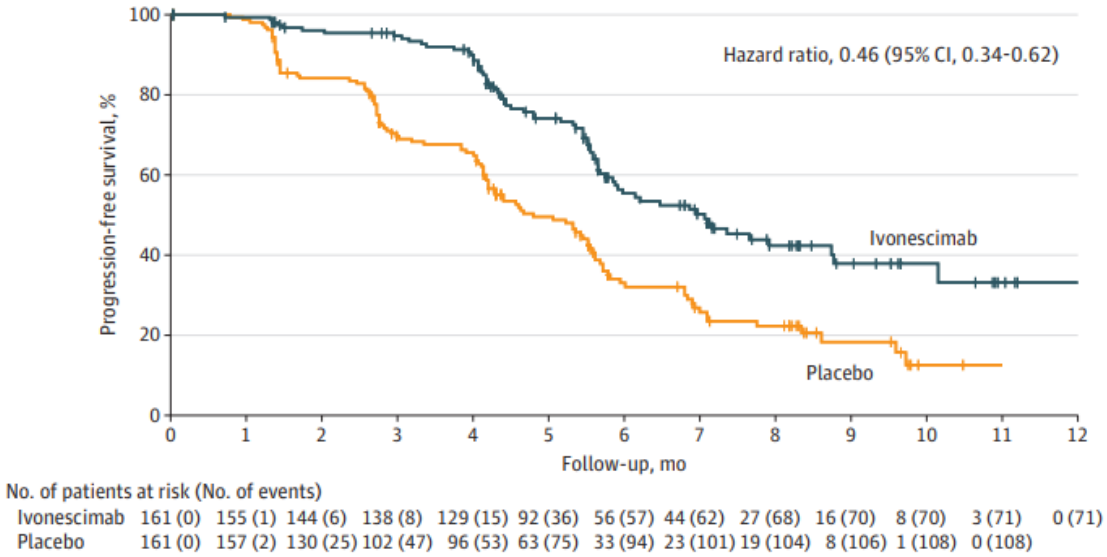
Endpoints

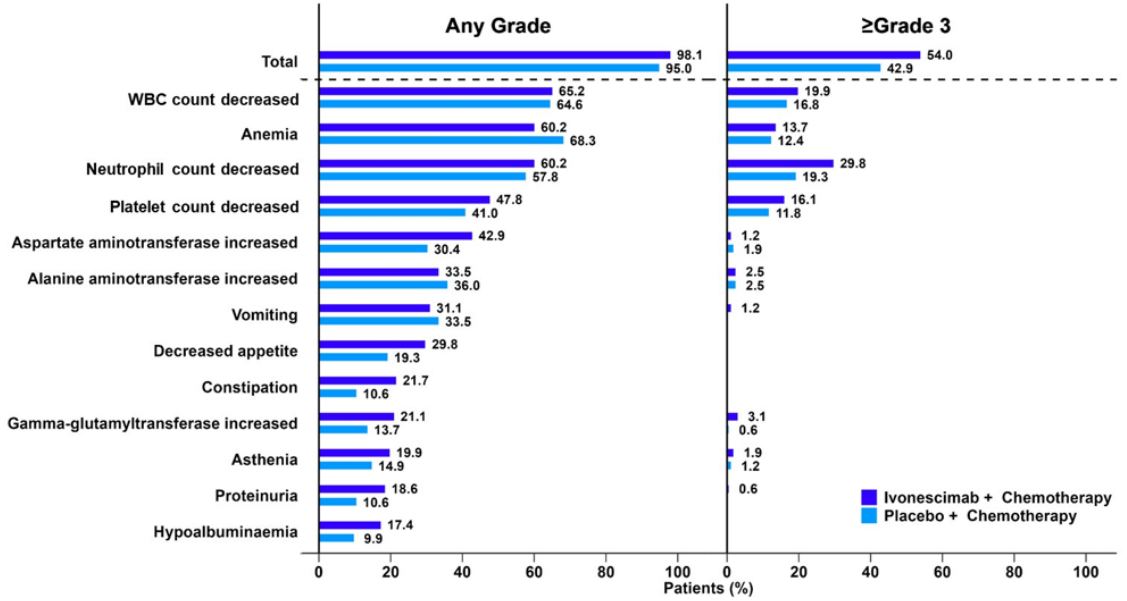
- Primary: Progression-free survival by independent radiologic review committee (IRRC)
- Secondary: Overall survival, Response rate, Duration of response, Time to response and Safety

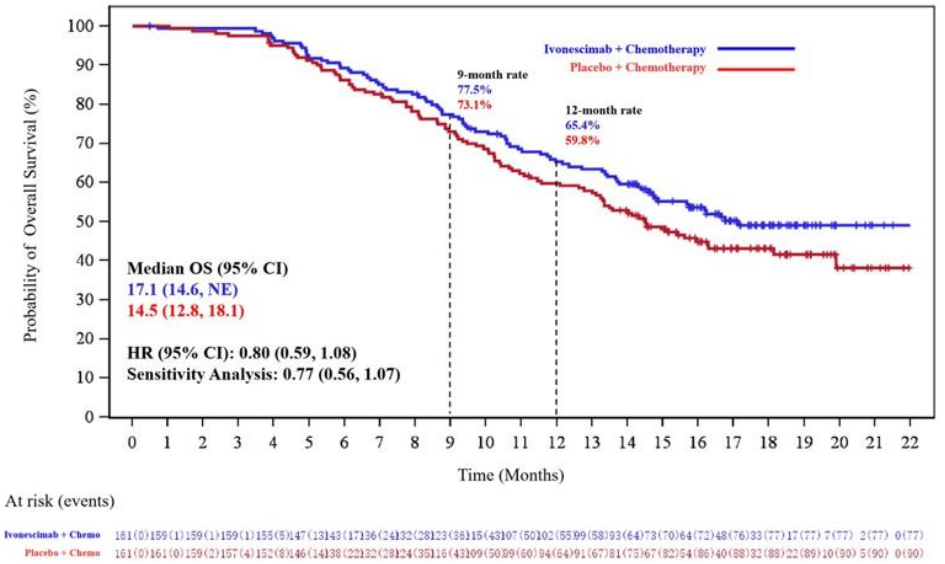
ClinicalTrials.gov, NCT05184712; NSCLC, non-small cell lung carcinoma; EGFR, epidermal growth factor receptor; ECOG, eastern copperative oncology group; TKI, tyrosine-kinase inhibitor; Q3W, every 3 weeks.

Zhang L, ASCO 2024

HARMONi-A study: PFS, preliminary OS and toxicity







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

OS is consistent for both analysis

Fang W, JAMA 2024
Zhang L, ASCO 2024

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

HR, hazard ratio; CI, confidence interval.

Courtesy of F. Grossi

Patritumab Deruxtecan- HERTHENA LUNG01

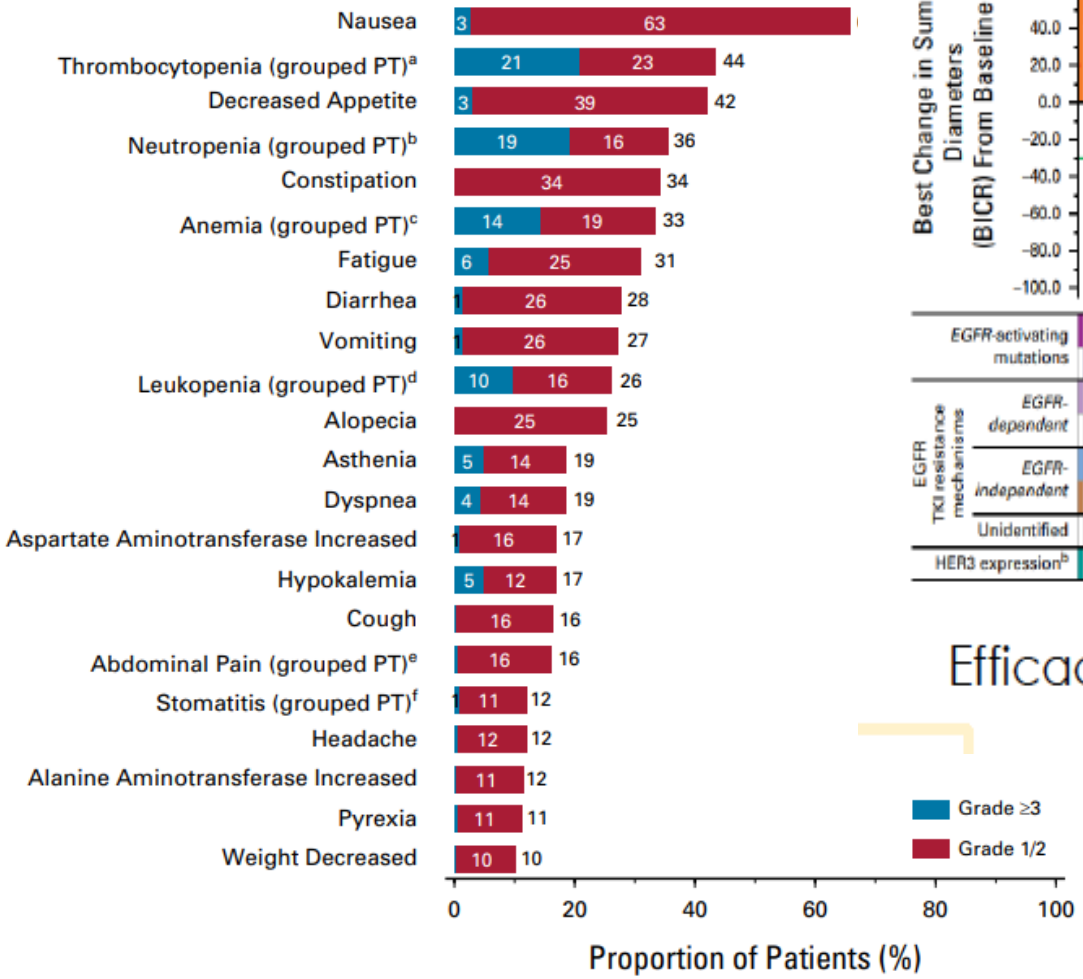
Studio di fase II, 225 pazienti già pretrattati con TKI e platinum-based CT

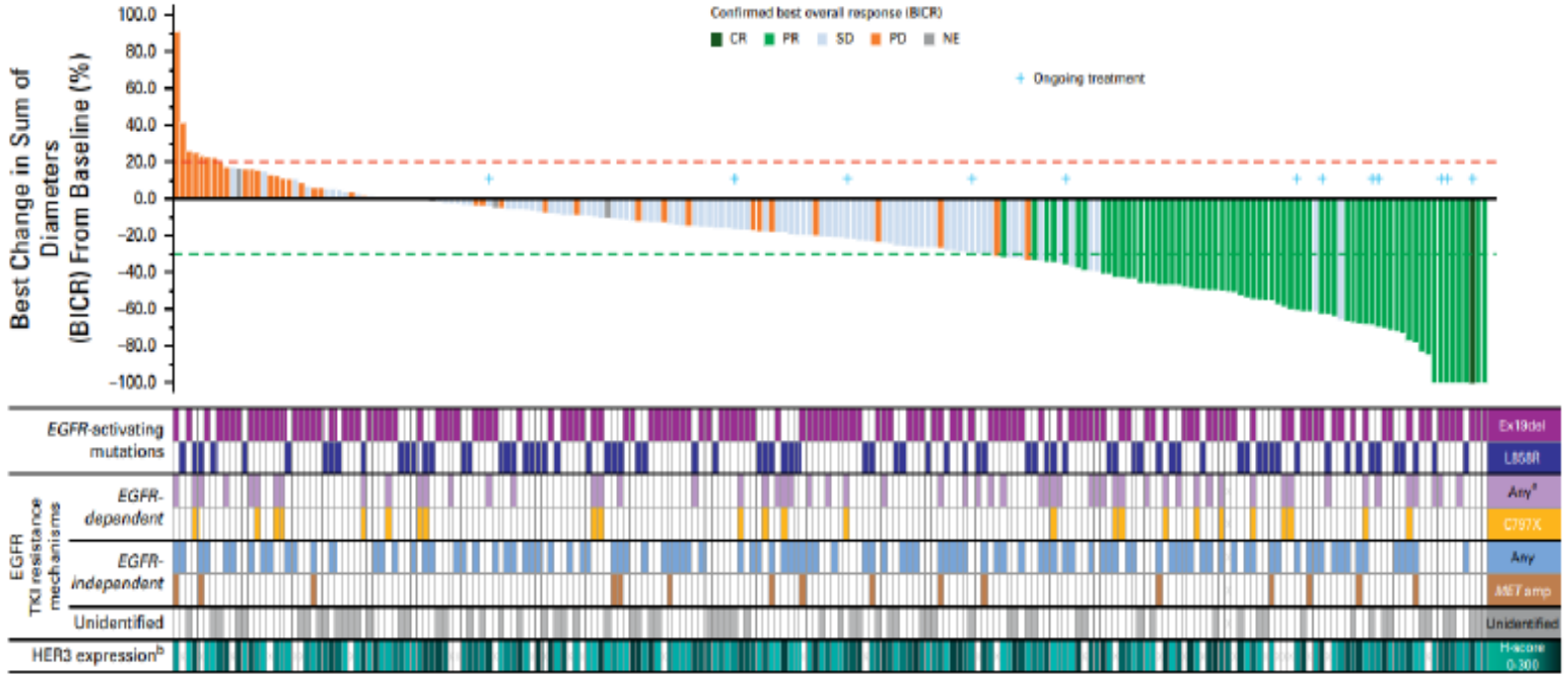
ORR 29.8%

mPFS 5.5 mesi

OS 11.9 mesi

CNS ORR 33%





Efficacy across different pretreatment tumor HER3 expression levels and diverse mechanisms of EGFR TKI resistance

Courtesy of M. Manzoni

Yu Ha et al, JCO 2023

Patritumab Deruxtecan- HERTHENA LUNG02 Press Release, 17 Sep 2024

Patritumab Deruxtecan Demonstrated Statistically Significant Improvement in Progression-Free Survival Versus Doublet Chemotherapy in Patients with Locally Advanced or Metastatic EGFR-Mutated Non-Small Cell Lung Cancer in HERTHENA-Lung02 Phase 3 Trial

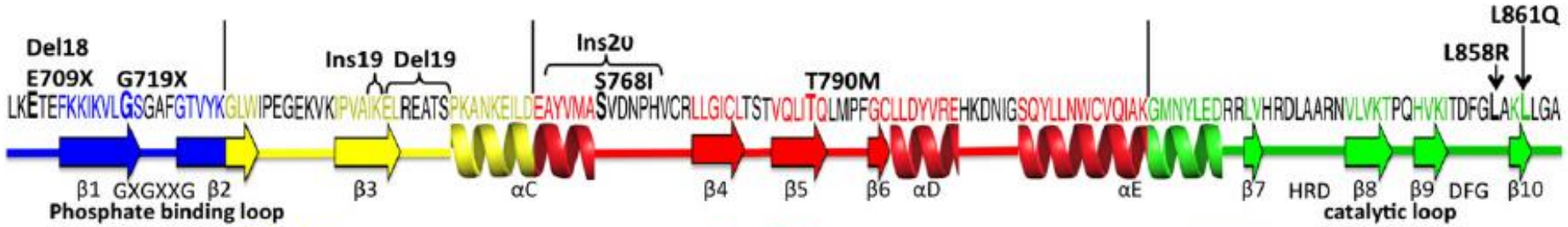
Agenda

- First line
- Subsequent lines
- Exon 20 insertions

Prevalence *EGFR* uncommon

20% of *EGFR* mut are uncommon:

- *EGFR* exon 20: - **40%** **of *EGFR* uncommon mut - 10% of *EGFR* mutation - 1.5%** of NSCLC



G719X (3.1%)	
G719A	27
G719A+S768I/L861Q/L861R	11
G719S	25
G719S+S768I/L861Q/E709A	13
G719C	12
G719C+S768I/E709K/E709H	9
others	3

E709X (0.3%)	
E709K+G719S/G719C/L858R	44
E709A+G719S/G719E	33
others	22

Del 18 (0.3%)	
delE709_T710insD	100

Del 19 (44.8%)	
delE746_A750	67
delL747_P753insS	8
delL747_T751	5
delL747_A750insP	3
delL747_S752	3
delE746_S752insV	2
delE746_P753insVS	1
delL747_T751insP	1
delE746_T751insA	1
delL747_P753	1
delS752_I759	1
others	8

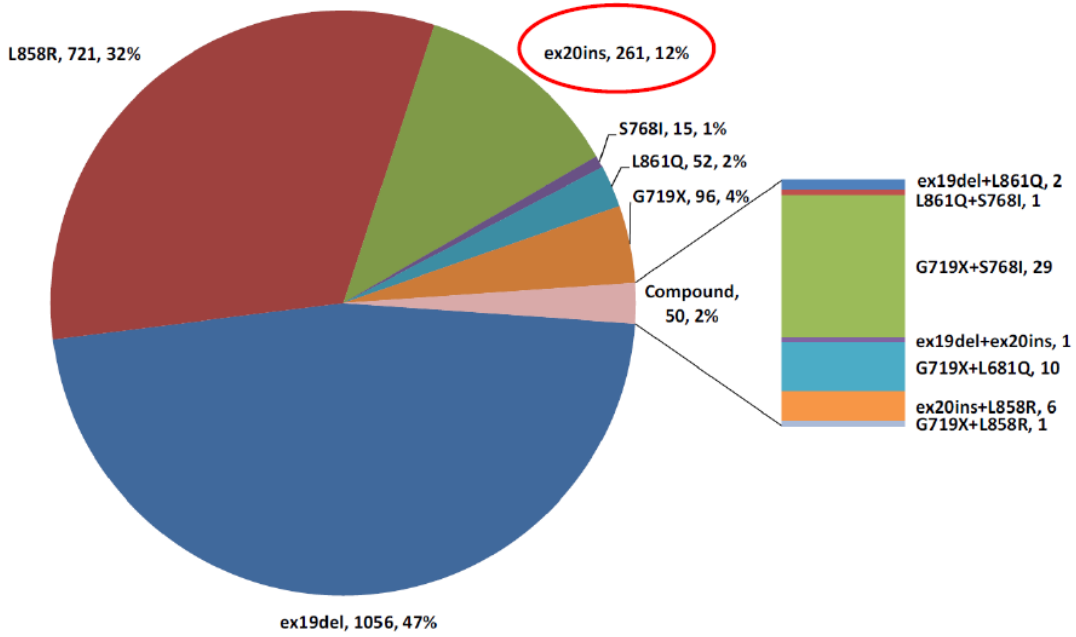
Ins 19 (0.6%)	
I744_K745insKIPVAI	58
K745_E746insIPVAIK	26
K745_E746insVPVAIK	11
K745_E746insTPVAIK	5

Ins 20 (5.8%)	
V769_D770insASV	20
D770_N771insSVD	19
H773_V774insH	8
A763_Y764insFQEA	7
H773_v774insPH	5
H773_V774insNPH	4
N771_P772insN	3
H773_V774insAH	3
D770delinsGY	2
V774_C775insHV	2
others	25

S768I (1.1%)

L858R (39.8%)

L861Q (0.9%)

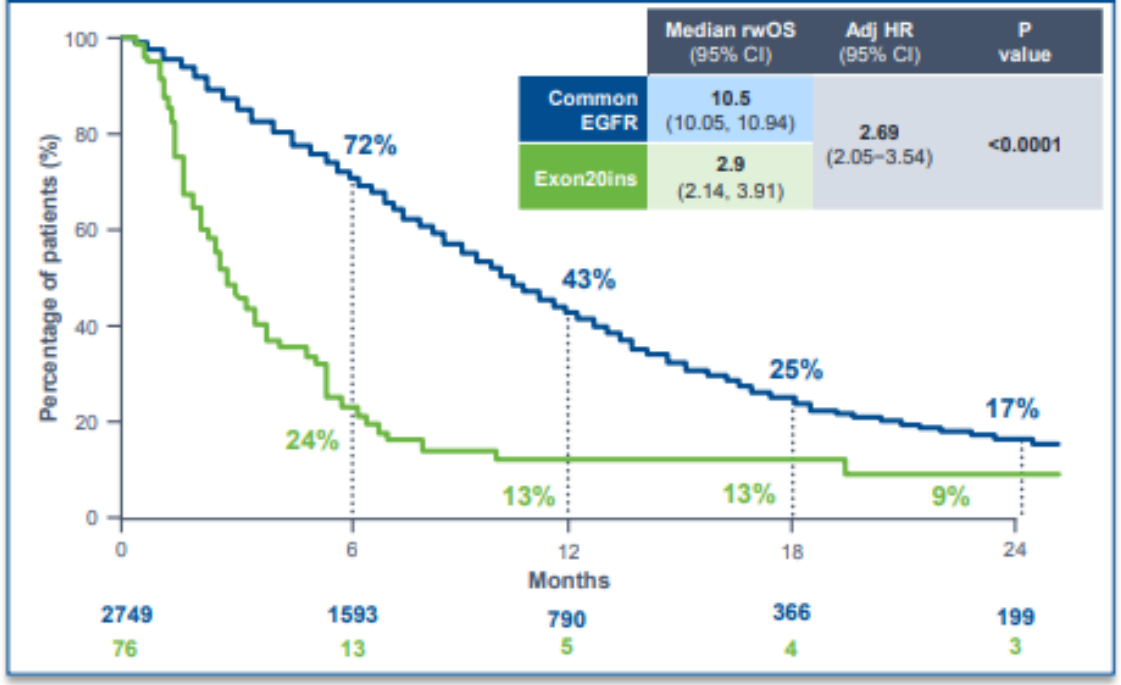


Kobayashi Cancer Science 2016, Riess JTO 2018

Differences in prognosis between sensitizing EGFR mutation and EGFR exon20ins

Prognosis for EGFR exon20ins vs common mutations: Real-world OS

Predictive value of EGFR exon20ins vs common mutations with TKI therapy: Real-world PFS*



Risk with EGFR exon20ins vs common EGFR mutations	Increase (%)
Death† (adjHR, 1.75 [95% CI, 1.45–2.13]; p<0.0001)	+75%
Progression or death (adjHR, 1.93 [95% CI, 1.61–2.31]; p<0.0001)	+93%
Shorter time to next treatment (adjHR, 1.60 [95% CI, 1.36–1.9]; p<0.0001)	+60%

Risk with EGFR exon20ins vs common EGFR mutations on TKI	Increase (%)
Progression or death† (adjHR, 2.69 [95% CI, 2.05–3.54]; p<0.0001)	+169
Death (adjHR, 2.70 [95% CI, 2.04–3.57]; p<0.0001)	+170
Shorter time to next treatment (adjHR, 2.54 [95% CI, 1.97–3.27]; p<0.0001)	+154

Adapted from Bazhenova L, et al. 2021.

Mok T, ELCC 2022

EGFR exon 20: results of clinical trials

Passiglia Cancer Treat Rev 2022

Clinical trials investigating EGFRex20ins inhibitors in EGFRex20ins mutant advanced NSCLC.

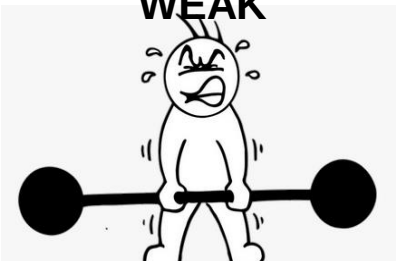
	Amivantamab	Mobocertinib	Sunvozertinib	CLN-081	Poziotinib	Osimertinib **160 mg/die**
N. of patients	81	114	52	39	115	25
ORR	40 % (BICR)	28 % (BICR)	40 %	41 %	15 %	28 %
DOR	11.1 m	15.5 m	5.9 m	NR	7.4 m	5.3 m
mPFS	8.3 m	7.3 m	NR	12 m	4.2 m	6.8 m
Major Toxicities	86 % Rash (0 % G3 +) 66 % Infusion reaction (3 % G3 +)	91 % Diarrhea (21 % G3 +) 45 % Rash (0 % G3 +)	50 % Diarrhea (5 % G3 +) 40 % Rash (0 % G3 +)	74 % Rash (0 % G3 +) 27 % Diarrhea (0 G3 +) 25 % Paronychia (0 % G3 +)	79 % Diarrhea (25 % G 3 +) 60 % Rash (28 % G3 +) 52 % Stomatitis (9 % G3 +)	72 % Diarrhea (2 % G3 +) 40 % Fatigue (0 % G3 +) 40 % Rash (0 % G3 +)
Dose Reduction	13 %	25 %	16 %	13 %	68 %	21
Drug discontinuation	10 %	17 %	6 %	3 %	10 %	8 %
Study Reference	Park et al. JCO 2021	Zhou et al. JAMA Oncol 2021	Janne et al. ASCO 2022	Yu et al. ASCO 2022	Le et al. ASCO 2020	Zwierenga et al. Lung Cancer 2022

AMIVANTAMAB

- **ORR 40%**
- **PFS 8 m**
- **<10% G3 AEs**
- **-PAPILLON phase 3 trial** (vs chemo) positive

MOBOCERTINIB EXCLAIM-2 1-line FAILURE

WEAK



SUNVOZERTINIB

- **ORR 60% (update)**
- **PFS NR**
- **<10% G3 AEs**
- **WU-KONG 28 phase 3 trial** ongoing (vs chemo)

ZIPALERTINIB

- **ORR 40%**
- **PFS 12 m**
- **0% G3 AEs**
- **REZILIENT phase 3 trial** ongoing (**ZIPA+ chemo** vs chemo)

POZIOTINIB ZENITH-20 (pretreat)

TOXIC

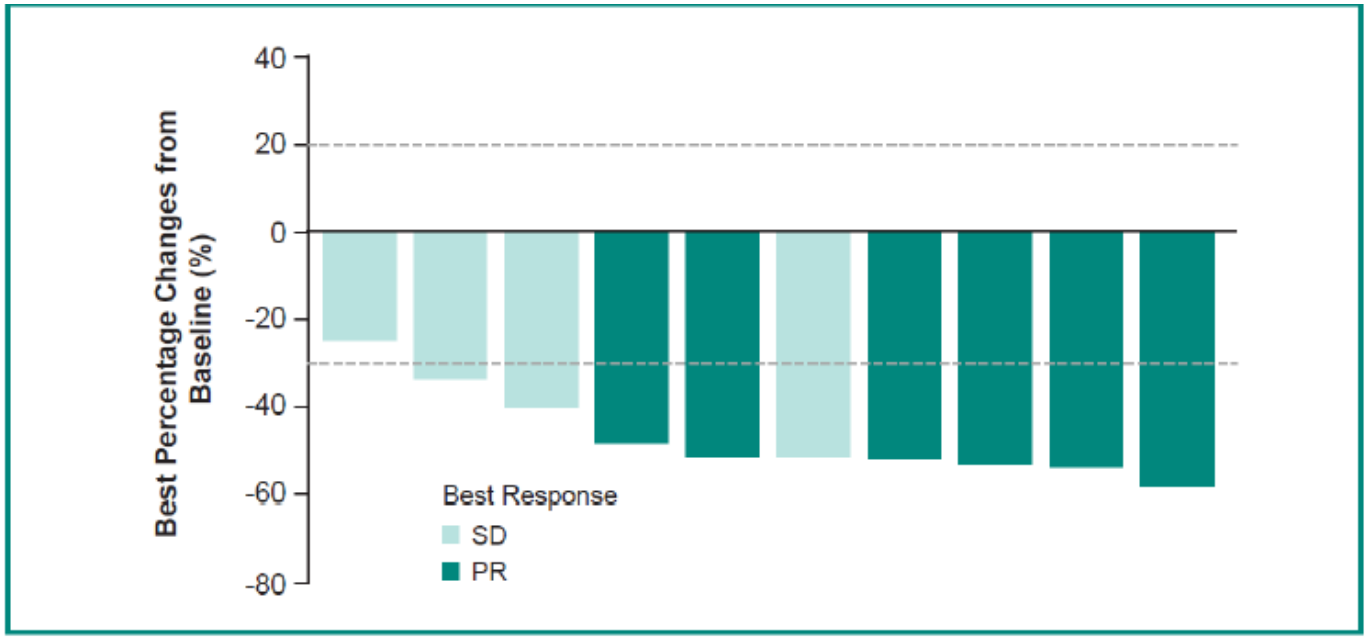
OSIMERTINIB (160 mg) 1-line POSITION-20

WEAK

FURMONERTINIB

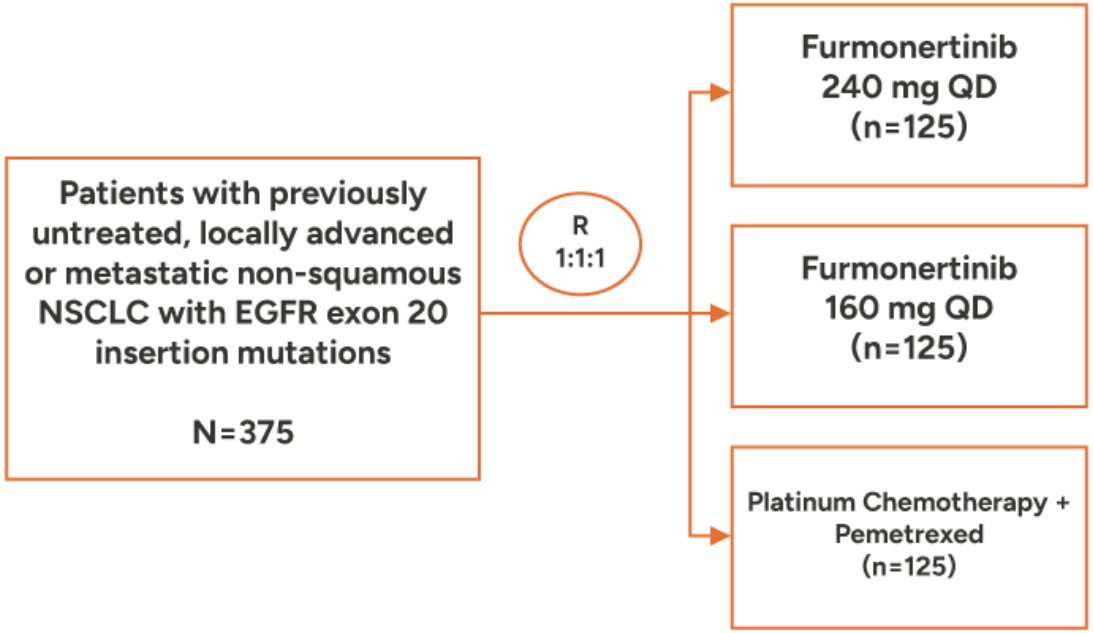
FAVOR

phase I trial **ORR: 52% (10 pts)**, **G3 AEs= 0%**



FURVENT

phase III trial



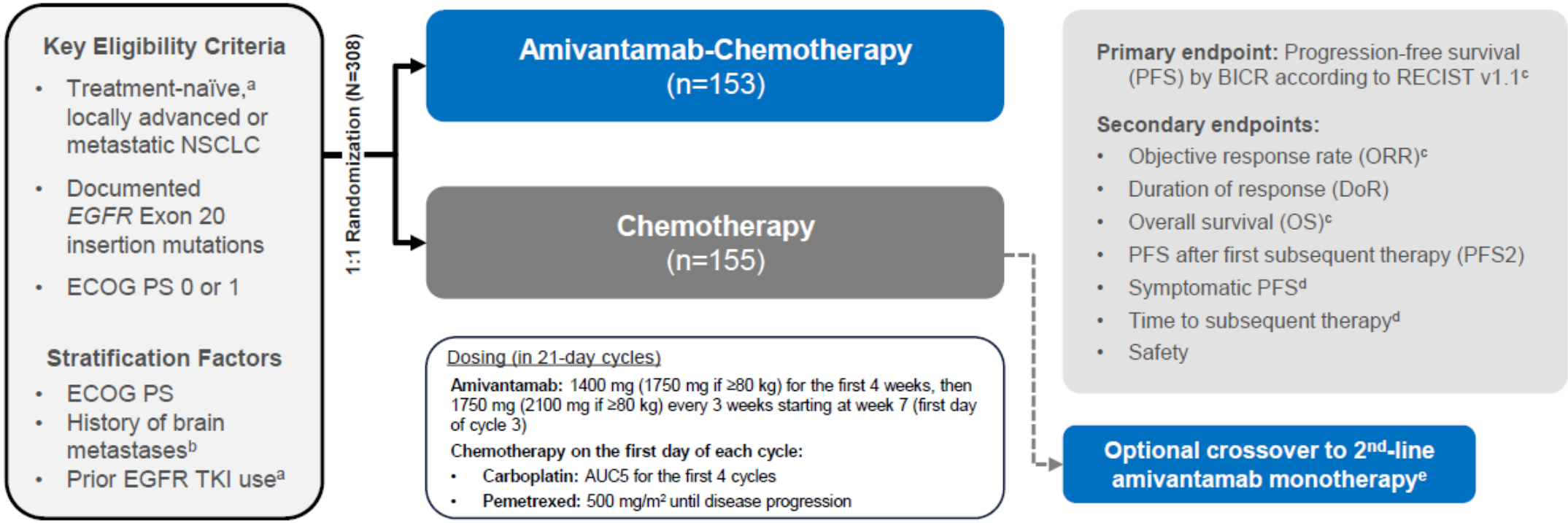
FAVOR update

ORR: 69% (**79 pts treatment naive** with Furmo 240 mg)

median **PFS**: **10.7 months**, **activity in CNS**

Han et al, WCLC 2023

Papillon: study design



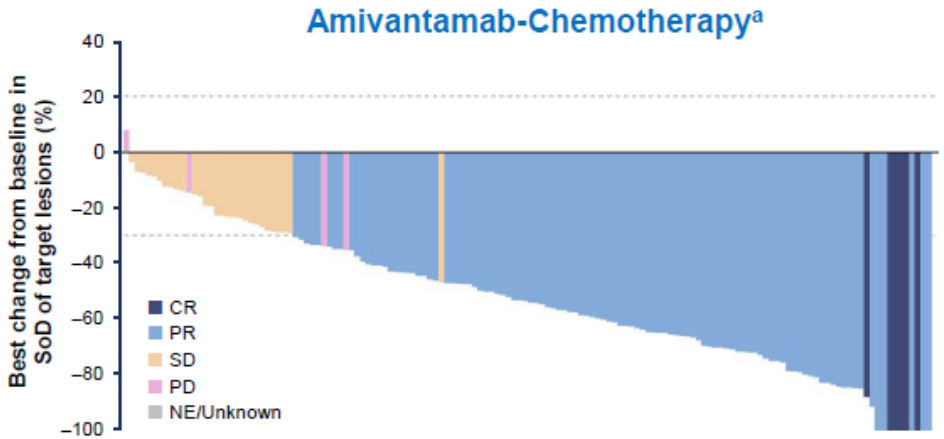
PAPILLON (ClinicalTrials.gov Identifier: NCT04538664) enrollment period: December 2020 to November 2022; data cut-off: 3-May-2023.

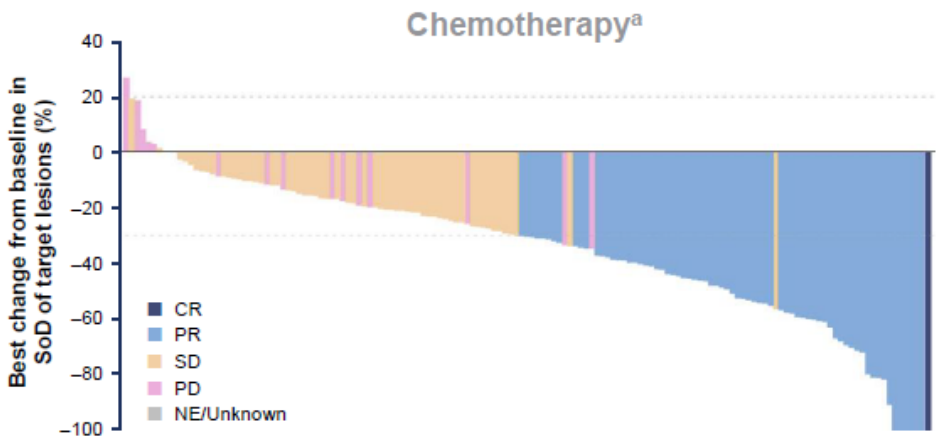
[a]Removed as stratification factor since only 4 patients had prior EGFR TKI use (brief monotherapy with common EGFR TKIs was allowed if lack of response was documented).
[b]Patients with brain metastases were eligible if they received definitive treatment and were asymptomatic, clinically stable, and off corticosteroid treatment for ≥2 weeks prior to randomization.
[c]Key statistical assumption: 300 patients with 200 events needed for 90% power to detect an HR of 0.625 (estimated PFS of 8 vs 5 months). PFS, ORR, and then OS were included in hierarchical testing.
[d]These secondary endpoints (time to subsequent therapy and symptomatic progression-free survival) will be presented at a future congress.
[e]Crossover was only allowed after BICR confirmation of disease progression; amivantamab monotherapy on Q3W dosing per main study.

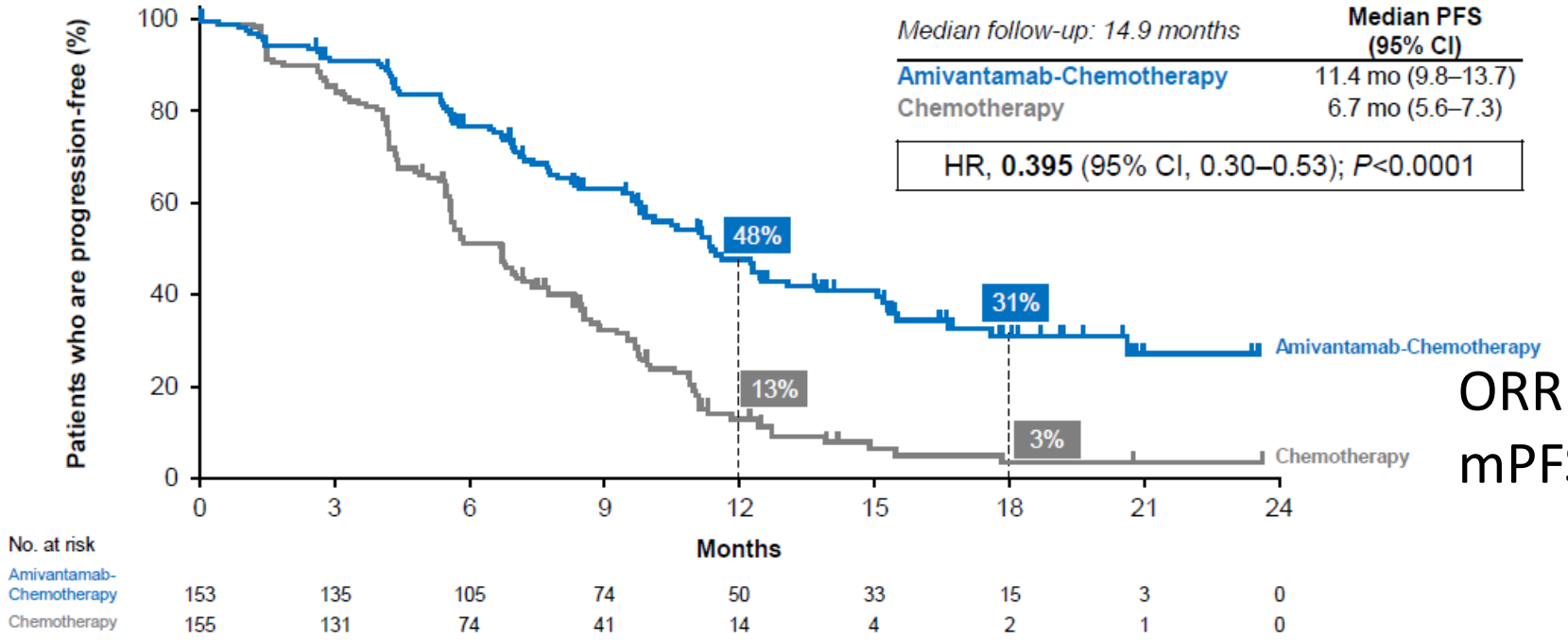
AUC, area under the curve; BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non-small cell lung cancer; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor.

Girard N, ESMO 2023

PAPILLON: Amivantamab + chemo vs chemo in EGFR ex 20







Median follow-up: 14.9 months	**Median PFS (95% CI)**
Amivantamab-Chemotherapy	11.4 mo (9.8–13.7)
Chemotherapy	6.7 mo (5.6–7.3)

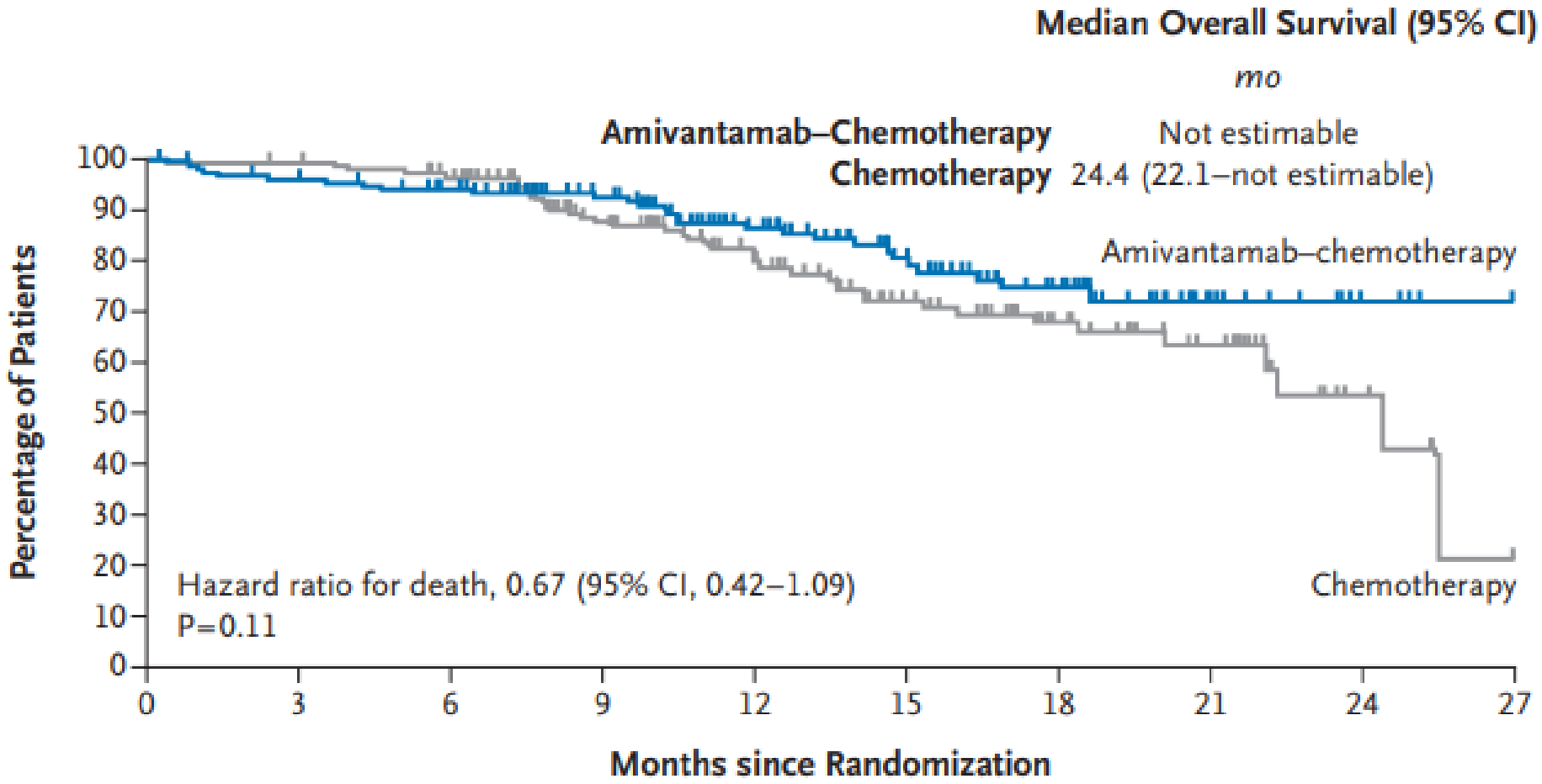
HR, **0.395** (95% CI, 0.30–0.53); *P*<0.0001

ORR (BICR) **73% vs 47%**

mPFS: **11.4 vs 6.7 months**

Zhou C, NEJM 2024

Papillon: interim OS



No. at Risk

Amivantamab–chemotherapy	153	144	133	115	88	60	38	15	5	0
Chemotherapy	155	153	144	110	85	57	37	24	6	0

Zhou C, NEJM 2024

PAPILLON: Amivantamab + chemo vs chemo in EGFR ex 20

	Amivantamab-Chemotherapy (n=151)	Chemotherapy (n=155)
Median treatment duration, months (range)	9.7 (0.1–26.9)	6.7 (0–25.3)
No. of chemotherapy cycles, median (range)		
Carboplatin	4 (1–4)	4 (1–5)
Pemetrexed	13 (1–34)	10 (1–37)

Treatment-emergent AEs, n (%)	Amivantamab-Chemotherapy (n=151)	Chemotherapy (n=155)
Any AEs	151 (100)	152 (98)
Grade ≥3 AEs	114 (75)	83 (54)
Serious AEs	56 (37)	48 (31)
AEs leading to death	7 (5)	4 (3)
Any AE leading to treatment:		
Interruptions of any agent	104 (69)	56 (36)
Related interruptions of amivantamab	63 (42)	–
Reductions of any agent	73 (48)	35 (23)
Related reductions of amivantamab	54 (36)	–
Discontinuations of any agent	36 (24)	16 (10)
Related discontinuations of amivantamab	10 (7)	–
Discontinuations of all study agents due to AEs	12 (8)	12 (8)

75% AE G≥3
35% reduction of ami
40% interruption of ami
7% discontinuation of ami

Rash
All grade: 54%
G≥3: 11%

Infusion related reactions

All grade :42%
G≥3: 1%

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Take home messages

- **Ami+Laze, CT+Osi or Osi alone will be the three options in first line in the next future (patient selection?)**

- **New potential strategy in second-line:**
  - CT+AMI new SOC?
  - What will be the role of Ivonescimab and Patritumab Deruxtecan?

- **CT+amivantamab new SOC in EGFR ins 20 first line**


THANK YOU
Any questions?