FLAURA trial established Osimertinib as the standard 1st line therapy for metastatic EGFR-mutated NSCLC
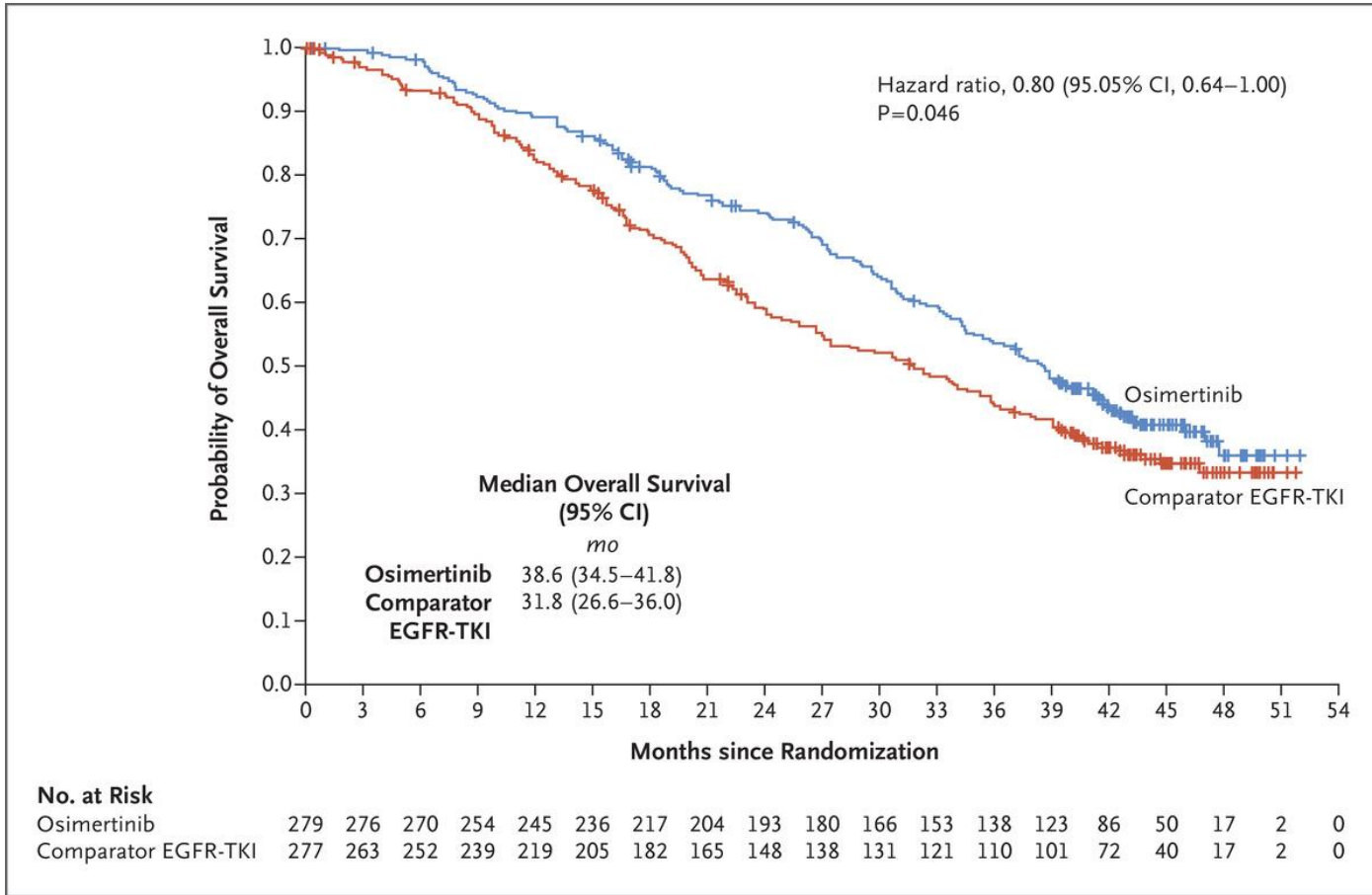
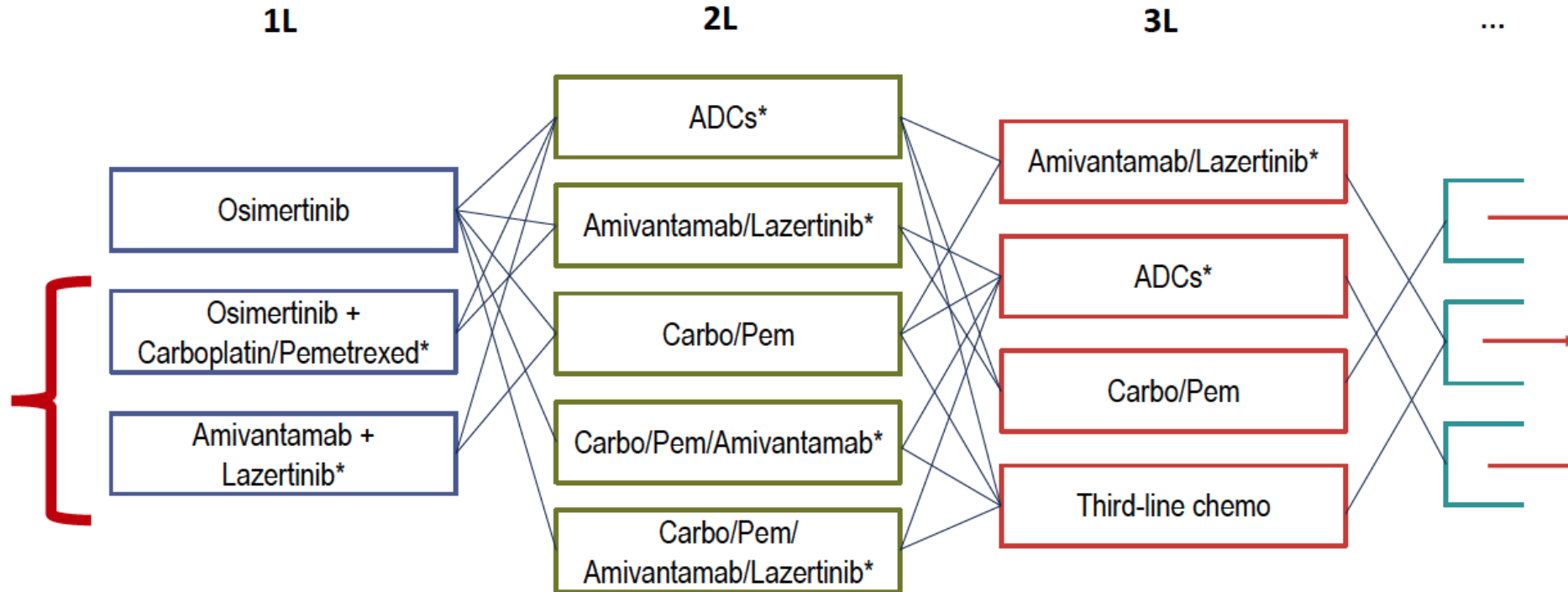**Resistance inevitably occurs**

Median PFS 18.9 months

Median OS 38.6 months

Decreased PFS benefit observed in patients with CNS metastases at baseline and in patients with EGFR p.L858R mutated tumors

SS Ramalingam et al. N Engl J Med 2020;382:41-50

How to select the optimal strategy?

1L **2L** **3L** **...**

1L:
- Osimertinib
- Osimertinib + Carboplatin/Pemetrexed*
- Amivantamab + Lazertinib*

2L:
- ADCs*
- Amivantamab/Lazertinib*
- Carbo/Pem
- Carbo/Pem/Amivantamab*
- Carbo/Pem/ Amivantamab/Lazertinib*

3L:
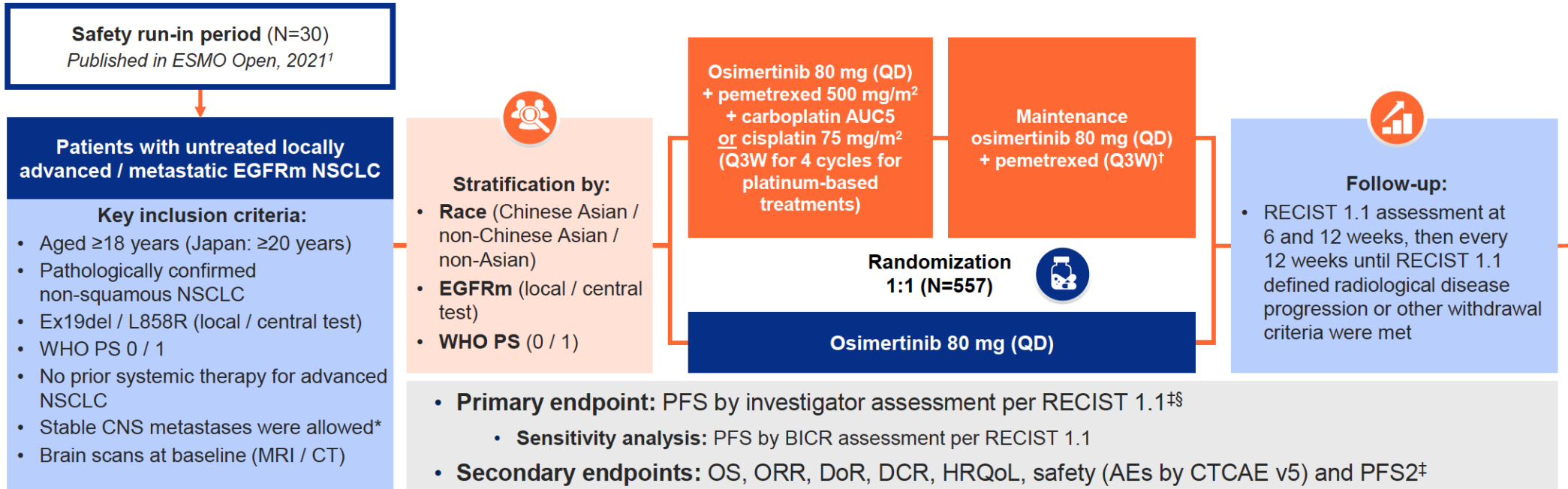- Amivantamab/Lazertinib*
- ADCs*
- Carbo/Pem
- Third-line chemo

Zosia Piotrowska, MD, MHS, ESMO Annual meeting 2023 plenary discussion

Marina Chiara Garassino @marinagarassino

FLAURA2 Phase III study design

Safety run-in period (N=30)
Published in ESMO Open, 2021[1]

Patients with untreated locally advanced / metastatic EGFRm NSCLC

Key inclusion criteria:
- Aged ≥18 years (Japan: ≥20 years)
- Pathologically confirmed non-squamous NSCLC
- Ex19del / L858R (local / central test)
- WHO PS 0 / 1
- No prior systemic therapy for advanced NSCLC
- Stable CNS metastases were allowed*
- Brain scans at baseline (MRI / CT)

Stratification by:
- **Race** (Chinese Asian / non-Chinese Asian / non-Asian)
- **EGFRm** (local / central test)
- **WHO PS** (0 / 1)

Osimertinib 80 mg (QD) + pemetrexed 500 mg/m^2 + carboplatin AUC5 <u>or</u> cisplatin 75 mg/m^2 (Q3W for 4 cycles for platinum-based treatments)

Maintenance osimertinib 80 mg (QD) + pemetrexed (Q3W)†

Randomization 1:1 (N=557)

Osimertinib 80 mg (QD)

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

- **Primary endpoint:** PFS by investigator assessment per RECIST 1.1‡§
  - **Sensitivity analysis:** PFS by BICR assessment per RECIST 1.1
- **Secondary endpoints:** OS, ORR, DoR, DCR, HRQoL, safety (AEs by CTCAE v5) and PFS2‡

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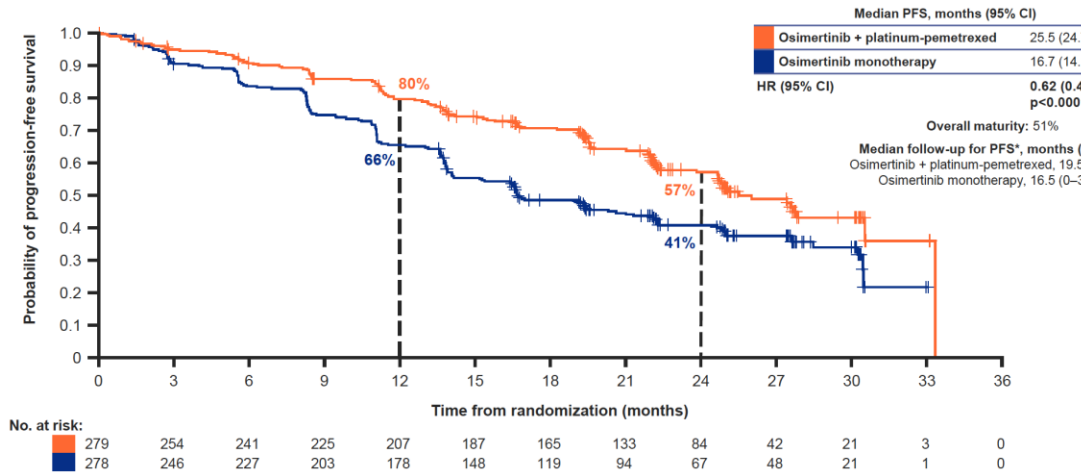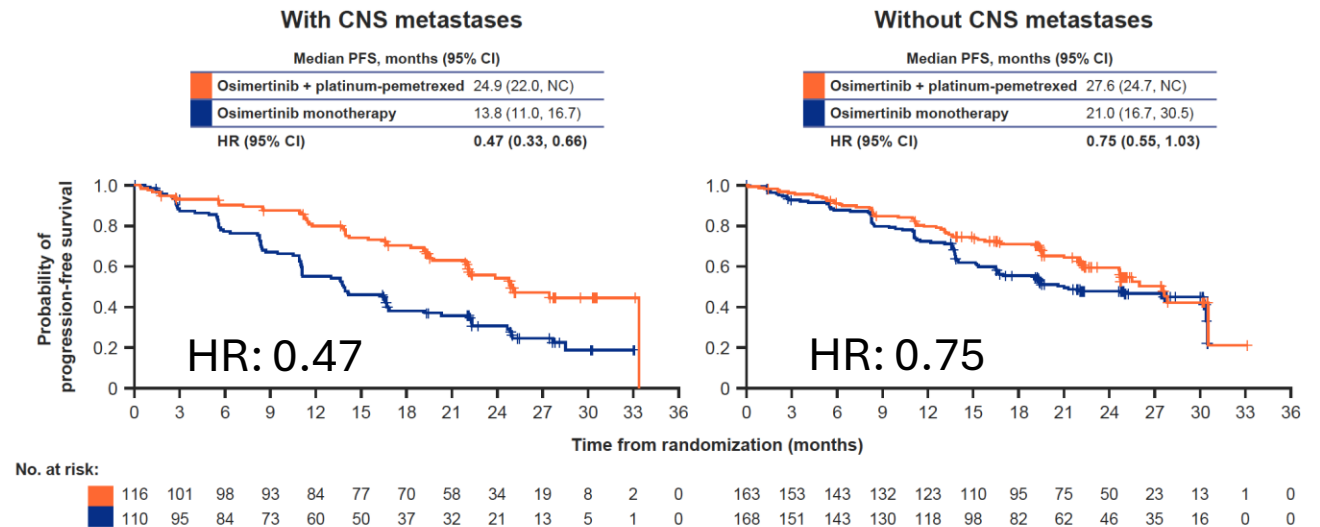## Progression-free survival per investigator

- Median PFS was improved by ~8.8 months with osimertinib plus platinum-pemetrexed vs osimertinib monotherapy

Median PFS, months (95% CI)	
Osimertinib + platinum-pemetrexed	25.5 (24.
Osimertinib monotherapy	16.7 (14.
HR (95% CI)	0.62 (0.4
	p<0.000
Overall maturity: 51%	

Median follow-up for PFS*, months (
Osimertinib + platinum-pemetrexed, 19.5
Osimertinib monotherapy, 16.5 (0–3

80%
66%
57%
41%

No. at risk:
279 254 241 225 207 187 165 133 84 42 21 3 0
278 246 227 203 178 148 119 94 67 48 21 1 0

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

With CNS metastases

Median PFS, months (95% CI)	
Osimertinib + platinum-pemetrexed	24.9 (22.0, NC)
Osimertinib monotherapy	13.8 (11.0, 16.7)
HR (95% CI)	0.47 (0.33, 0.66)

HR: 0.47

Without CNS metastases

Median PFS, months (95% CI)	
Osimertinib + platinum-pemetrexed	27.6 (24.7, NC)
Osimertinib monotherapy	21.0 (16.7, 30.5)
HR (95% CI)	0.75 (0.55, 1.03)

HR: 0.75

No. at risk:
116 101 98 93 84 77 70 58 34 19 8 2 0   163 153 143 132 123 110 95 75 50 23 13 1 0
110 95 84 73 60 50 37 32 21 13 5 1 0   168 151 143 130 118 98 82 62 46 35 16 0 0

PL.03.13 Jänne et al., WCLC 2023

FLAURA2: Resistance, and impact of baseline TP53 alterations in patients treated with first-line osimertinib with or without platinum-pemetrexed

James Chih-Hsin Yang,[1] Jacqulyne Robichaux,[2] David Planchard,[3,4] Kunihiko Kobayashi,[5] Chee Khoon Lee,[6] Shunichi Sugawara,[7] Tsung-Ying Yang,[8] Tae Min Kim,[9] Sang-We Kim,[10] Noriko Yanagitani,[11] Aleksandra Markovets,[12] Preetida J. Bhetariya,[12] Lynne Poole,[13] Yuri Rukazenkov,[14] Ryan Hartmaier,[2] Pasi A. Jänne[15]

FLAURA2: Impact of tumor burden on outcomes of first-line osimertinib ± chemotherapy in patients with EGFR-mutated advanced NSCLC

Natalia Valdiviezo,[1] Jhanelle E. Gray,[2] Pasi A. Jänne,[3] Kunihiko Kobayashi,[4] James Chih-Hsin Yang,[5] Ying Cheng,[6] Chee Khoon Lee,[7] Shunichi Sugawara,[8] Yan Yu,[9] Tae Min Kim,[10] Sarah Taggart,[11] Muna Albayaty,[12] Dana Ghiorghiu,[13] David Planchard[14,15]

Baseline characteristics and outcomes were broadly similar for the plasma analysis set and FAS

- In total, 167 paired plasma samples were included in this analysis

Characteristic, %*	FAS[1]		Plasma analysis set	
	Osimertinib + chemotherapy (n=279)	Osimertinib monotherapy (n=278)	Osimertinib + chemotherapy (n=68)	Osimertinib monotherapy (n=99)
Sex: male / female	38 / 62	39 / 61	31 / 69	43 / 57
Age: median (range), years[†]	61 (26–83)	62 (30–85)	60 (34–82)	63 (30–85)
Race: Asian / non-Asian	64 / 36	63 / 37	66 / 34	55 / 45
EGFR mutation at randomization:[‡] Ex19del / L858R	61 / 38	60 / 38	63 / 37	61 / 37
Metastatic	95	97	99	100
CNS metastases present at baseline	42	40	43	43
Baseline tumor size: median (range), mm[§]	57 (10–284)	57 (11–221)	65 (11–219)	69 (12–221)
Outcomes	**Osimertinib + chemotherapy vs osimertinib monotherapy**			
PFS: HR (95% CI)	0.62 (0.49, 0.79)[¶]		0.57 (0.41, 0.80)[#]	

Presented by: James Chih -Hsin Yang

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)	–

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

*Not reported in FLAURA.
1. Chmielecki J, et al. Nat Comm 2023;14:1070
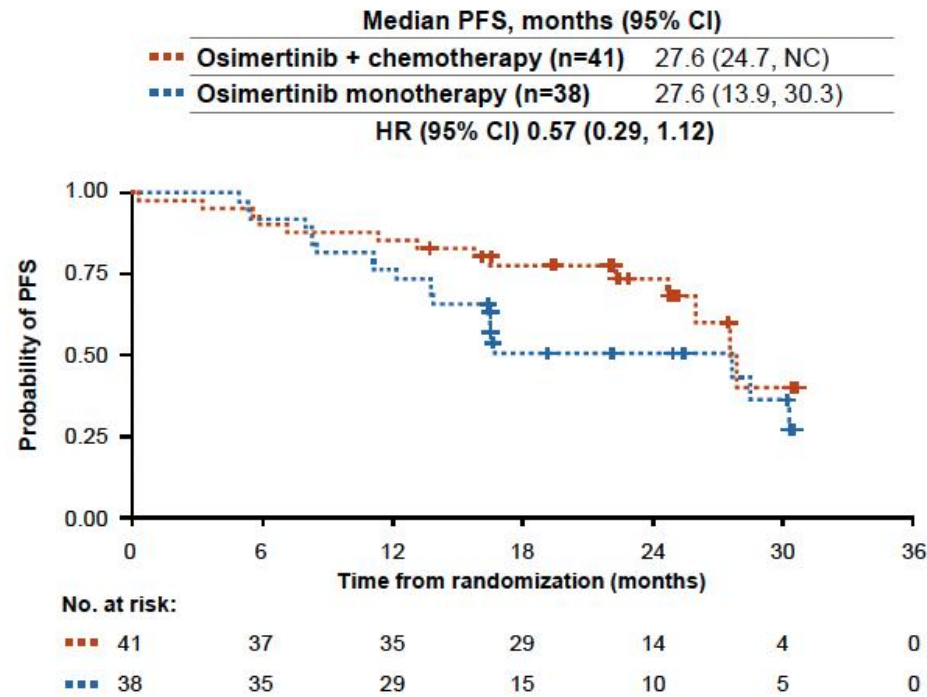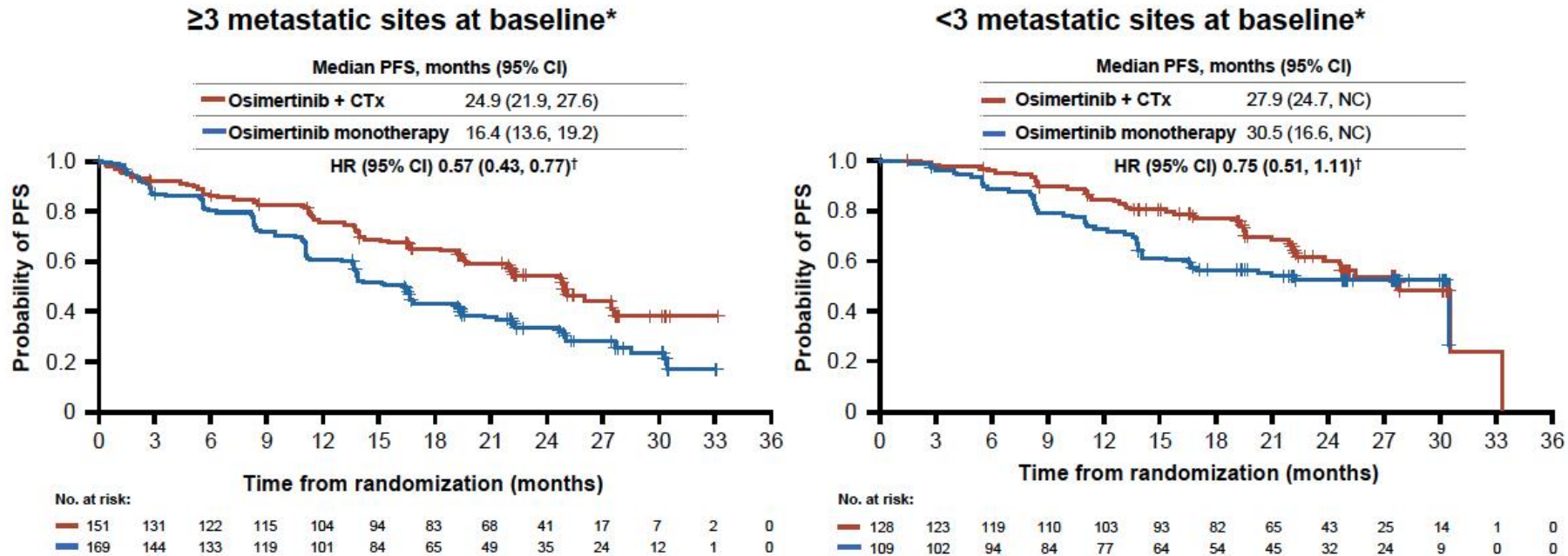EGFR, epidermal growth factor receptor; ND, not detected

Presented by: James Chih -Hsin Yang

The PFS benefit of osimertinib + chemotherapy versus osimertinib alone appeared to be similar irrespective of baseline TP53 status
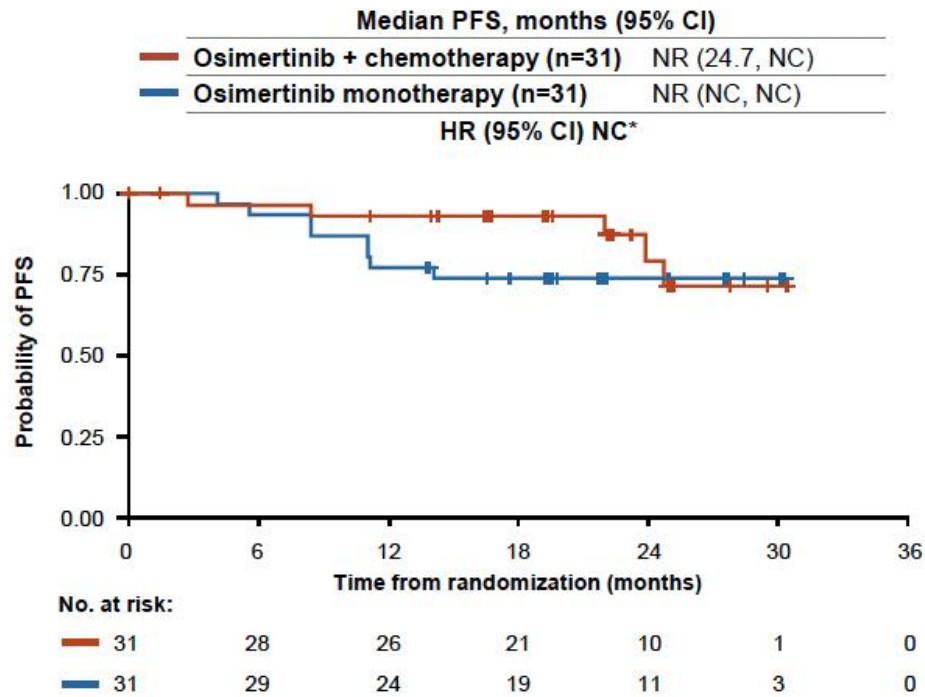
James Chih-Hsin Yang | FLAURA2: Resistance, and impact of baseline TP53 alterations in patients treated with 1L osimertinib ± platinum-pemetrexed

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

Presented by: James Chih -Hsin Yang

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

≥3 metastatic sites at baseline*

Median PFS, months (95% CI)	
Osimertinib + CTx	24.9 (21.9, 27.6)
Osimertinib monotherapy	16.4 (13.6, 19.2)
HR (95% CI) 0.57 (0.43, 0.77)[†]	

No. at risk:

151	131	122	115	104	94	83	68	41	17	7	2	0
169	144	133	119	101	84	65	49	35	24	12	1	0

<3 metastatic sites at baseline*

Median PFS, months (95% CI)	
Osimertinib + CTx	27.9 (24.7, NC)
Osimertinib monotherapy	30.5 (16.6, NC)
HR (95% CI) 0.75 (0.51, 1.11)[†]	

No. at risk:

128	123	119	110	103	93	82	65	43	25	14	1	0
109	102	94	84	77	64	54	45	32	24	9	0	0

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

Presented by: Natalia Valdivezo

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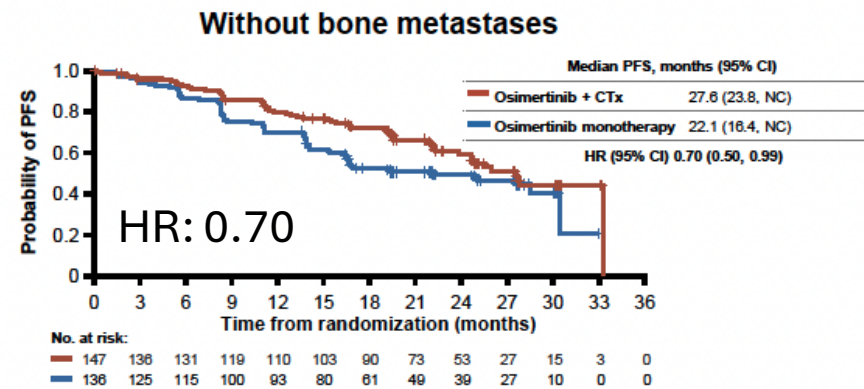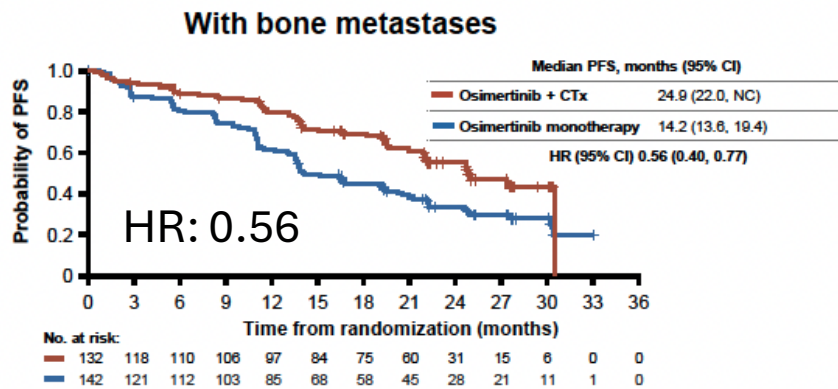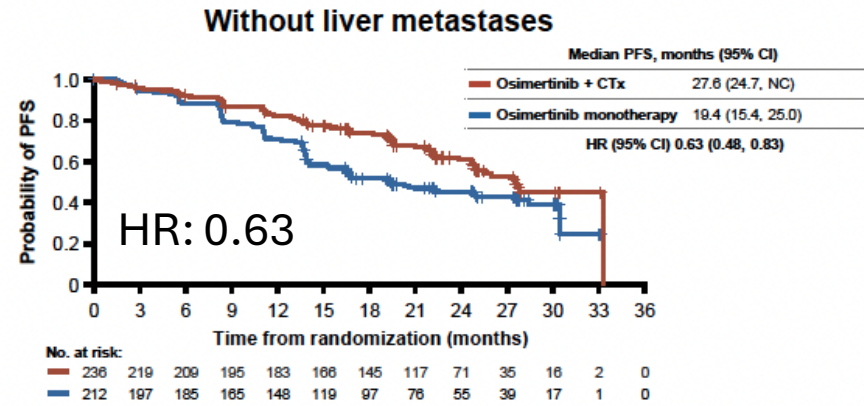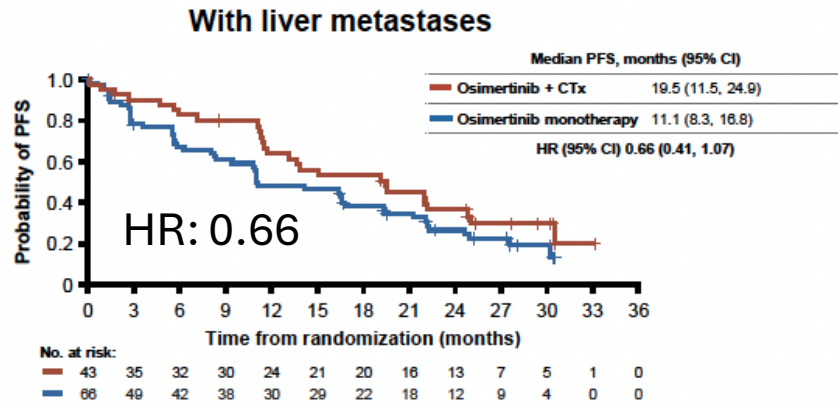
Presented by: Natalia Valdivezo

Patients with ≥ 3 metastastic sites may benefit the most from Osi + CTx

	Osimertinib PFS (months)	Osi + CTx PFS (months)	HR (95% CI)
With CNS Metastases	**13.8 (11.0 -16.7)**	**24.9 (22.0 – NC)**	**0.47 (0.33-0.66)**
Without CNS Metastases	21.0 (16.7 – 30.5)	27.6 (24.7 – NC)	0.75 (0.55-1.03)
TP53 altered	27.6 (13.9 – 30.3)	27.6 (24,7 – NC)	0.57 (0.29 – 1.12)
TP53 wild-type	NR	NR	NC
≥ 3 metastatic sites	**16.4 (13.6 – 19.2)**	**24.9 (21.9 – 27.6)**	**0.57 (0.43 – 0.77)**
< 3 metastatic sites	30.5 (16.6 – NC)	27.9 (24.7 - NC)	0.75 (0.51 – 1.11)
With Bone Metastases	**14.2 (13.6 – 19.4)**	**24.9 (22.0 – NC)**	**0.56 (0.40 – 0.77)**
Without Bone Metastases	22.1 (16.4 – NC)	27.6 (23.8 – NC)	0.70 (0.50 – 0.99)
With Liver Metastases	11.1 (8.3 – 16.8)	19.5 (11.5 – 24.9)	0.66 (0.41 – 1.07)
Without Liver Metastases	19.4 (15.4 – 25.0)	27.6 (24.7 – NC)	0.63 (0.48 – 0.83)

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Should we wait for Overall Survival data?
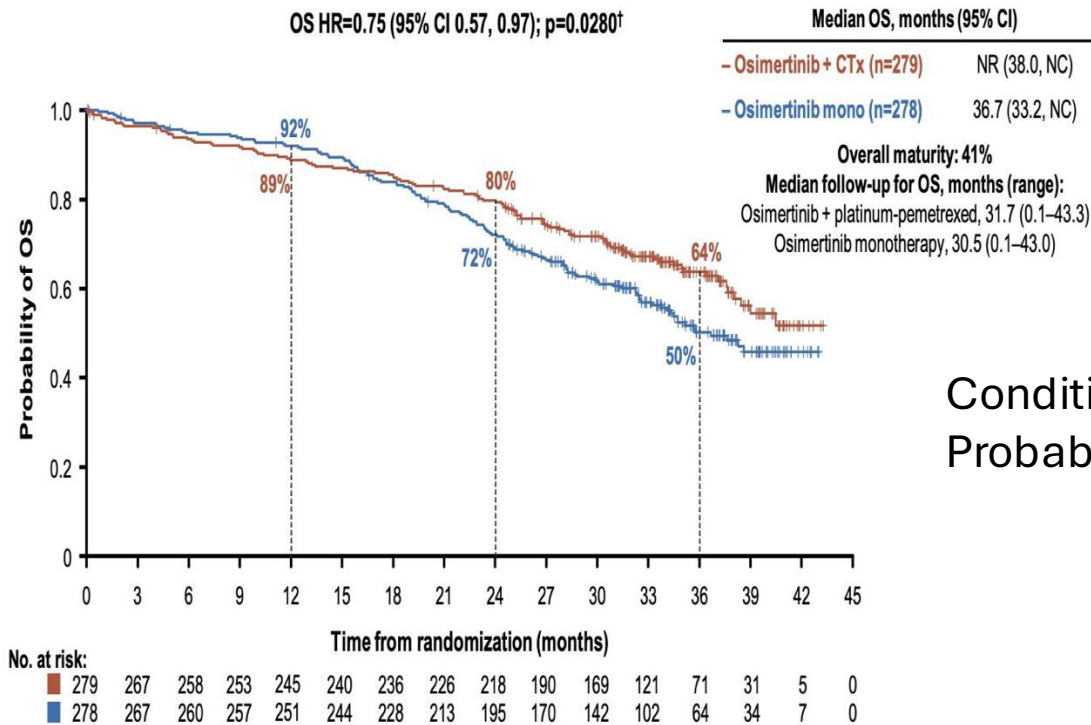
Conditional Power:
Probability of OS benefit under this trend: 92%

Presented By: Marina Chiara Garassino

Lazertinib vs Osimertinib in 1L *EGFR*-mutant Advanced NSCLC: A Randomized, Double-blind, Exploratory Analysis From MARIPOSA

Se-Hoon Lee[1], Byoung Chul Cho[2], Hidetoshi Hayashi[3], Enriqueta Felip[4], Alexander I Spira[5], Nicolas Girard[6], Yu Jung Kim[7], Yuriy Ostapenko[8], Pongwut Danchaivijitr[9], Baogang Liu[10], Adlinda Alip[11], Ernesto Korbenfeld[12], Josiane Mourão Dias[13], Ki Hyeong Lee[14], Hailin Xiong[15], Soon Hin How[16], Ying Cheng[17], Gee-Chen Chang[18], James Chih-Hsin Yang[19], Benjamin Besse[20], Michael Thomas[21], Joshua C Curtin[22], Jiarui Zhang[22], John Xie[23], Tao Sun[23], Melissa Martinez[23], Seema Sethi[22], Roland E Knoblauch[22], Elizabeth Fennema[24], Mahesh Daksh[23], Mariah Ennis[22], Joshua M Bauml[22], Shun Lu[25]
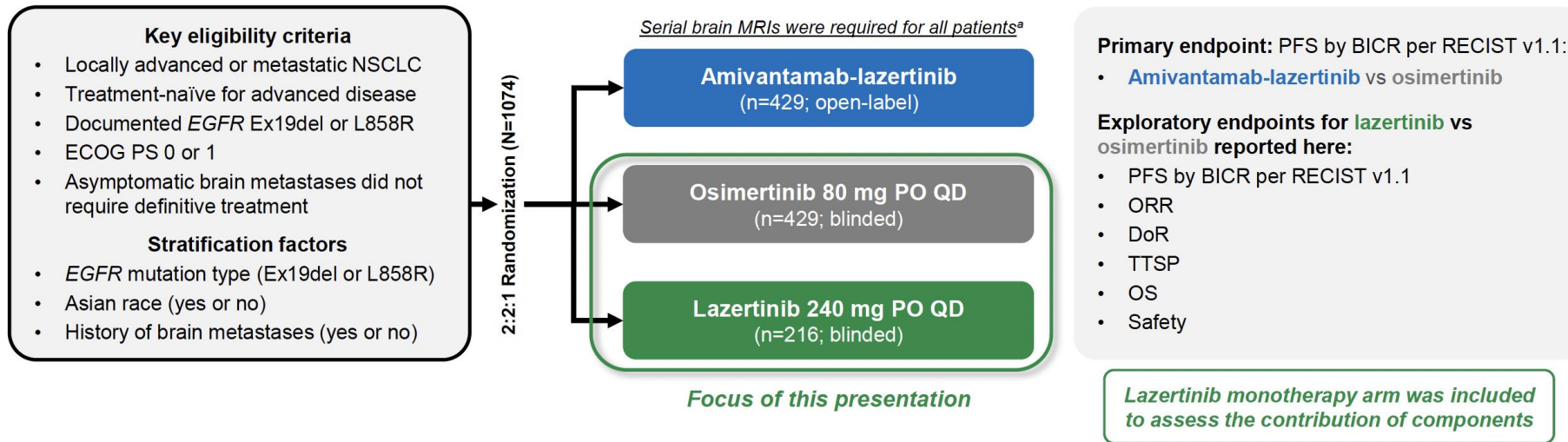
Amivantamab Plus Lazertinib vs Osimertinib in First-line *EGFR*-mutant Advanced NSCLC: Longer Follow-up of the MARIPOSA Study

Shirish M Gadgeel[1], Byoung Chul Cho[2], Shun Lu[3], Enriqueta Felip[4], Hidetoshi Hayashi[5], Alexander I Spira[6], Benjamin Besse[7], Michael Thomas[8], Scott Owen[9], Yu Jung Kim[10], Se-Hoon Lee[11], Josiane Mourão Dias[12], Yun-Gyoo Lee[13], Yanqiu Zhao[14], Yong Fang[15], Nicolas Girard[16], Zhe Liu[17], Ping Sun[18], Sulene Cunha Sousa Oliveira[19], Hong Shen[20], Luis Paz-Ares[21], Shingo Matsumoto[22], Hiroshi Tanaka[23], Azura Rozila Ahmad[24], Timur Andabekov[25], Patrapim Sunpaweravong[26], Ozgur Ozyilkan[27], James Chih-Hsin Yang[28], Maya Gottfried[29], Osvaldo Hernandez[30], Martin Kimmich[31], Diego Cortinovis[32], Diego Lucas Kaen[33], Lizbett Vanessa García Montes[34], Sanjay Popat[35], Thomas Newsom-Davis[36], John Xie[37], Tao Sun[37], Elizabeth Fennema[38], Mahesh Daksh[37], Mariah Ennis[39], Seema Sethi[39], Joshua M Bauml[39], Danny Nguyen[40]

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MARIPOSA: Phase 3 Study Design

*This is the first randomized, double-blind trial to prospectively evaluate 2 third-generation EGFR-TKI*

Key eligibility criteria
- Locally advanced or metastatic NSCLC
- Treatment-naïve for advanced disease
- Documented *EGFR* Ex19del or L858R
- ECOG PS 0 or 1
- Asymptomatic brain metastases did not require definitive treatment

Stratification factors
- *EGFR* mutation type (Ex19del or L858R)
- Asian race (yes or no)
- History of brain metastases (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 80 mg PO QD
(n=429; blinded)

Lazertinib 240 mg PO QD
(n=216; blinded)

Focus of this presentation

Primary endpoint: PFS by BICR per RECIST v1.1:
- Amivantamab-lazertinib vs osimertinib

Exploratory endpoints for lazertinib vs osimertinib reported here:
- PFS by BICR per RECIST v1.1
- ORR
- DoR
- TTSP
- OS
- Safety

Lazertinib monotherapy arm was included to assess the contribution of components

Presented by: Se-Hoon Lee

Osimertinib and Lazertinib demonstrate similar activity
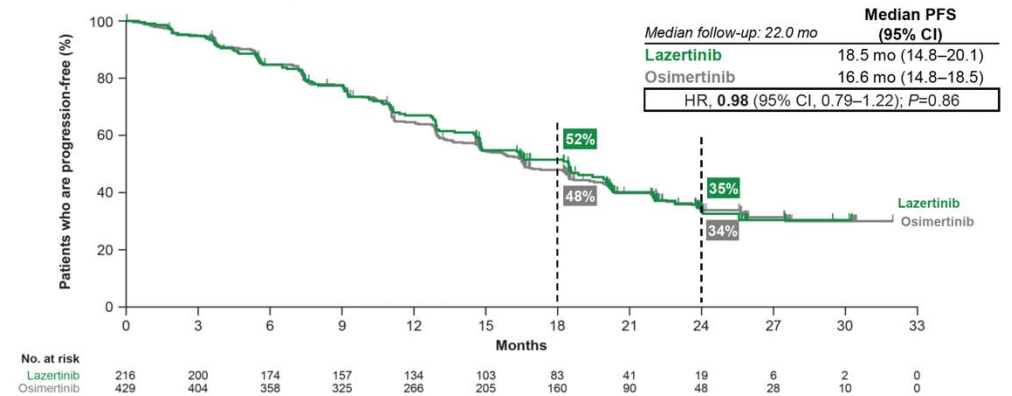

ORR and DoR by BICR

ORR and median DoR were comparable between lazertinib and osimertinib
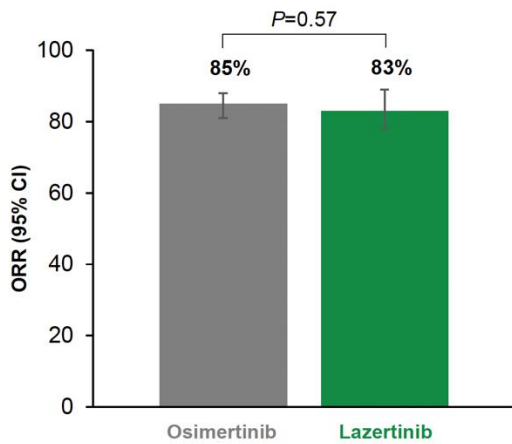
BICR-assessed response, n (%)[a]	Osimertinib (n=429)	Lazertinib (n=216)
ORR		
All responders	85% (95% CI, 81–88)	83% (95% CI, 77–88)
Confirmed responders	76% (95% CI, 71–80)	75% (95% CI, 68–80)
Best response[b]		
CR	15 (4)	9 (4)
PR	335 (81)	168 (79)
SD	42 (10)	23 (11)
PD	11 (3)	9 (4)
NE	11 (3)	5 (2)
Median DoR[c]	16.8 mo (95% CI, 14.8–18.5)	16.6 mo (95% CI, 14.8–20.2)
Ongoing responses	151 of 314 (48)	77 of 160 (48)

PFS by BICR

PFS was comparable between the lazertinib and osimertinib arms

Median follow-up: 22.0 mo

	Median PFS (95% CI)
Lazertinib	18.5 mo (14.8–20.1)
Osimertinib	16.6 mo (14.8–18.5)

HR, **0.98** (95% CI, 0.79–1.22); *P*=0.86

No. at risk

Lazertinib	216	200	174	157	134	103	83	41	19	6	2	0
Osimertinib	429	404	358	325	266	205	160	90	48	28	10	0

- PFS was comparable between lazertinib and osimertinib among prespecified subgroups including Asian race[a] and *EGFR* mutation subtype[b]

[a]HR, 1.02 (95% CI, 0.77–1.35). [b]Exon 19 deletion: HR, 1.03 (95% CI, 0.78–1.37); L858R: HR, 0.91 (95% CI, 0.65–1.28).

BICR, blinded independent central review; CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; PFS, progression-free survival.
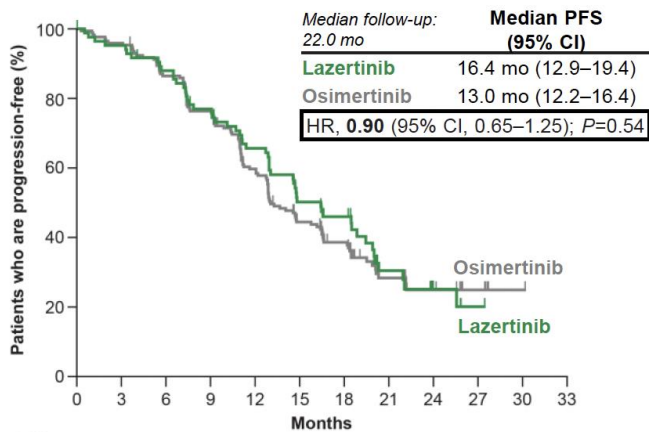
Presented by: Se-Hoon Lee

Osimertinib and Lazertinib demonstrate similar activity in high-risk subgroups
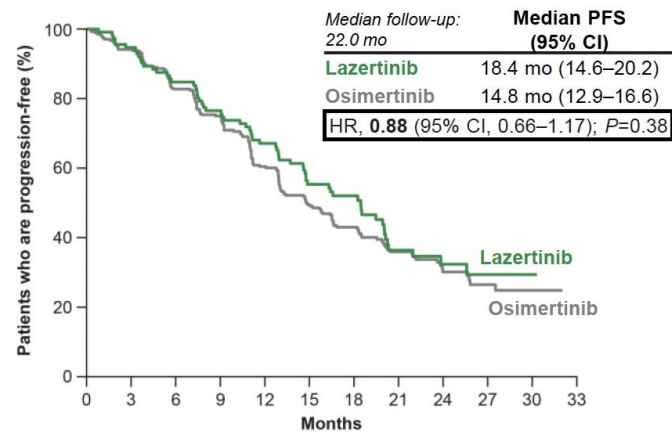
PFS by High-risk Subgroups

High-risk features, such as brain metastases, ctDNA shedding, and baseline TP53 co-mutations are common in patients with EGFR-mutated NSCLC.[1–4] PFS results in these groups were comparable across arms
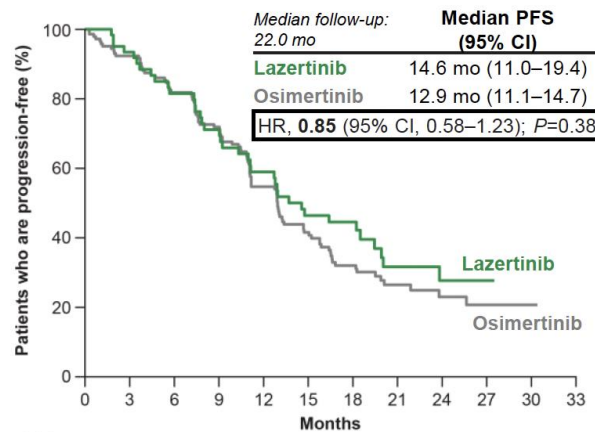

With brain metastases[a]

	Median follow-up: 22.0 mo	Median PFS (95% CI)
Lazertinib		16.4 mo (12.9–19.4)
Osimertinib		13.0 mo (12.2–16.4)

HR, **0.90** (95% CI, 0.65–1.25); *P*=0.54

No. at risk
Lazertinib 86 80 72 62 52 37 28 12 5 1 0 0
Osimertinib 172 164 146 126 95 64 47 21 11 6 1 0

With detectable ctDNA at baseline[a,b]

	Median follow-up: 22.0 mo	Median PFS (95% CI)
Lazertinib		18.4 mo (14.6–20.2)
Osimertinib		14.8 mo (12.9–16.6)

HR, **0.88** (95% CI, 0.66–1.17); *P*=0.38

No. at risk
Lazertinib 115 107 93 82 70 52 40 21 12 4 1 0
Osimertinib 274 257 224 202 161 118 93 52 31 19 6 0

With TP53 co-mutations[a,b]

	Median follow-up: 22.0 mo	Median PFS (95% CI)
Lazertinib		14.6 mo (11.0–19.4)
Osimertinib		12.9 mo (11.1–14.7)

HR, **0.85** (95% CI, 0.58–1.23); *P*=0.38

No. at risk
Lazertinib 62 57 47 41 33 25 19 9 5 2 0
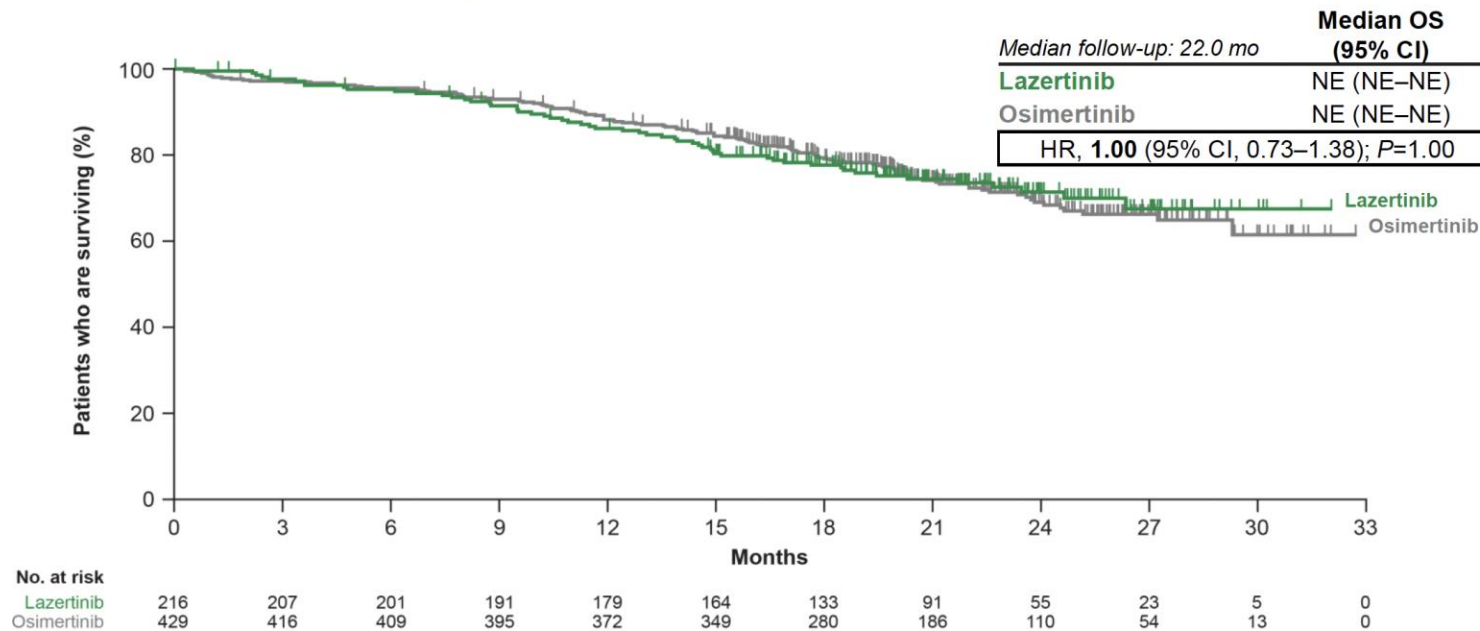Osimertinib 144 132 116 101 76 49 34 17 11 7 2

Presented by: Se-Hoon Lee

Osimertinib and Lazertinib demonstrate similar overall survival

Interim OS

Early data demonstrated comparable survival outcomes between lazertinib and osimertinib

Median follow-up: 22.0 mo	Median OS (95% CI)
Lazertinib	NE (NE–NE)
Osimertinib	NE (NE–NE)
HR, **1.00** (95% CI, 0.73–1.38); *P*=1.00	

No. at risk

	0	3	6	9	12	15	18	21	24	27	30	33
Lazertinib	216	207	201	191	179	164	133	91	55	23	5	0
Osimertinib	429	416	409	395	372	349	280	186	110	54	13	0

CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival.

Presented by: Se-Hoon Lee

Osimertinib and Lazertinib have slightly different toxicity profiles

Most common TEAEs (≥20%) by preferred term, n (%)	Osimertinib (n=428)		Lazertinib (n=213)	
Related to EGFR inhibition	Grade 1–2	Grade ≥3	Grade 1–2	Grade ≥3
Diarrhea	187 (44)	3 (1)	64 (30)	4 (2)
Rash	128 (30)	3 (1)	91 (43)	4 (2)
Paronychia	119 (28)	2 (0.5)	59 (28)	2 (1)
Stomatitis	89 (21)	1 (0.2)	37 (17)	1 (0.5)
Dermatitis acneiform	55 (13)	0	45 (21)	0
Other				
COVID-19	94 (22)	9 (2)	39 (18)	3 (1)
Cough	88 (21)	0	36 (17)	1 (0.5)
Anemia	84 (20)	7 (2)	40 (19)	3 (1)
Thrombocytopenia	79 (18)	5 (1)	19 (9)	1 (0.5)
AST increased	53 (12)	5 (1)	42 (20)	3 (1)
ALT increased	49 (11)	8 (2)	44 (21)	6 (3)
Muscle spasms	32 (7)	0	49 (23)	1 (0.5)

Percentage of patients with LVEF <LLN and >10% absolute decrease from baseline

P=0.056 — LVEF: Osimertinib 4%, Lazertinib 1%

[a]Maximum postbaseline values.
LLN, lower limit of normal; LVEF, left ventricular ejection fraction.
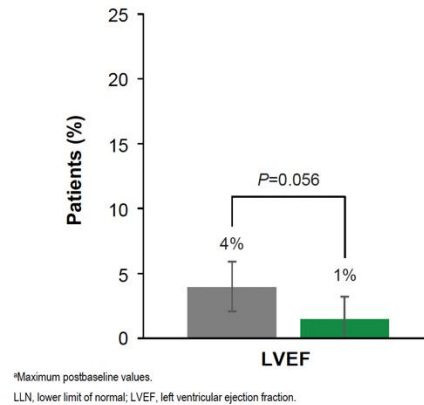
Percentage of patients with QT interval >450 and >500 msec[a]

- Osimertinib
- Lazertinib

P=0.005 — >450 msec: Osimertinib 17%, Lazertinib 9%; >500 msec: Osimertinib 0.7%, Lazertinib 0%
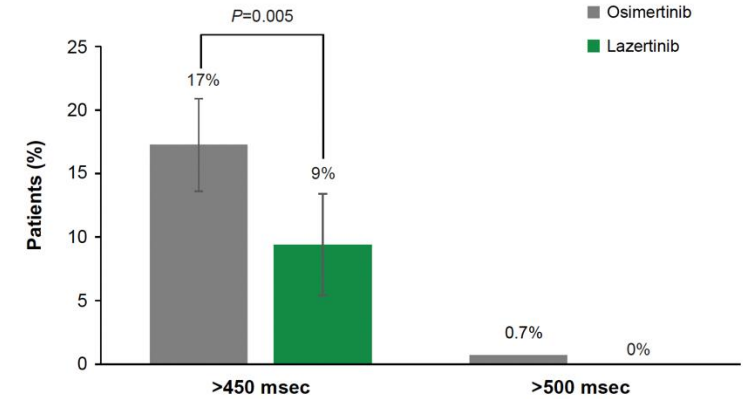
- Osimertinib had higher rates of diarrhea (**44%** vs **32%**), thrombocytopenia (**20%** vs **9%**), and neutropenia (**13%** vs **3%**) versus lazertinib

- Lazertinib had higher rates of rash (**45%** vs **31%**), muscle spasms (**23%** vs **7%**), and paresthesia (**15%** vs **6%**) versus osimertinib
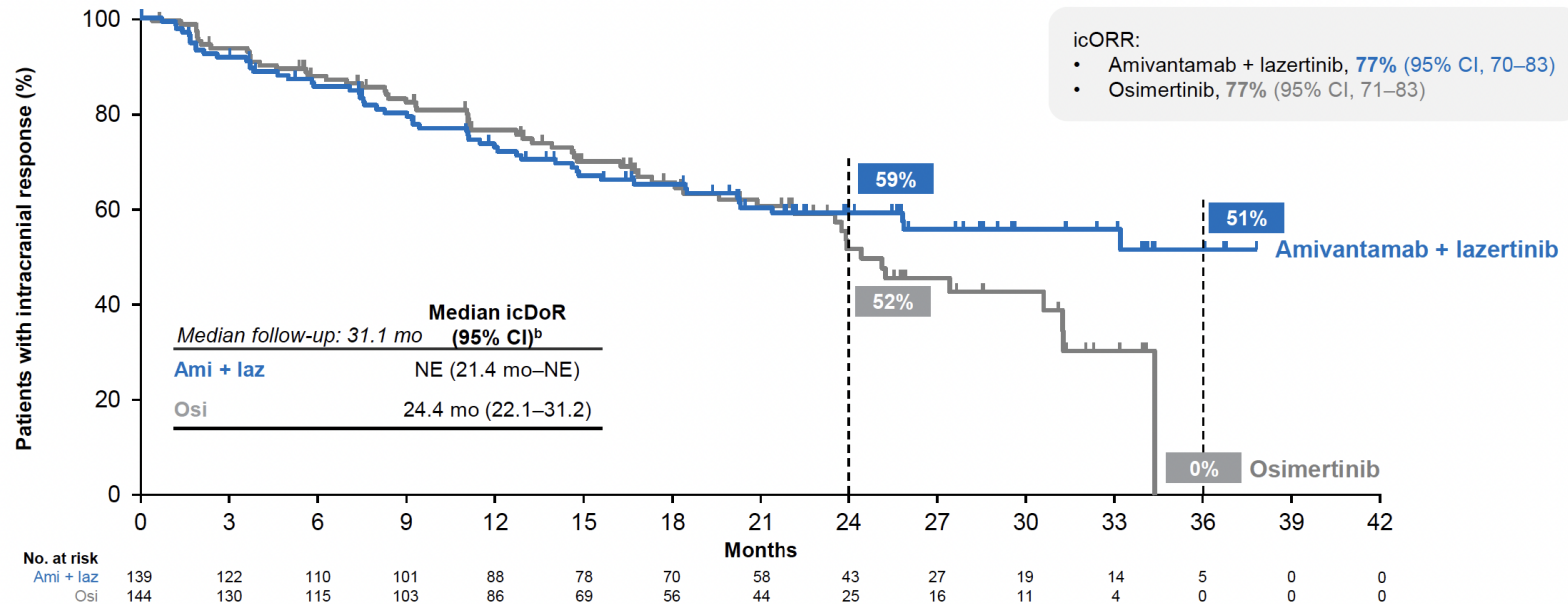
Presented by: Se-Hoon Lee

Amivantamab + Lazertinib demonstrated improved PFS compared to osimertinib in treatment naïve advanced EGFR-mutated NSCLC
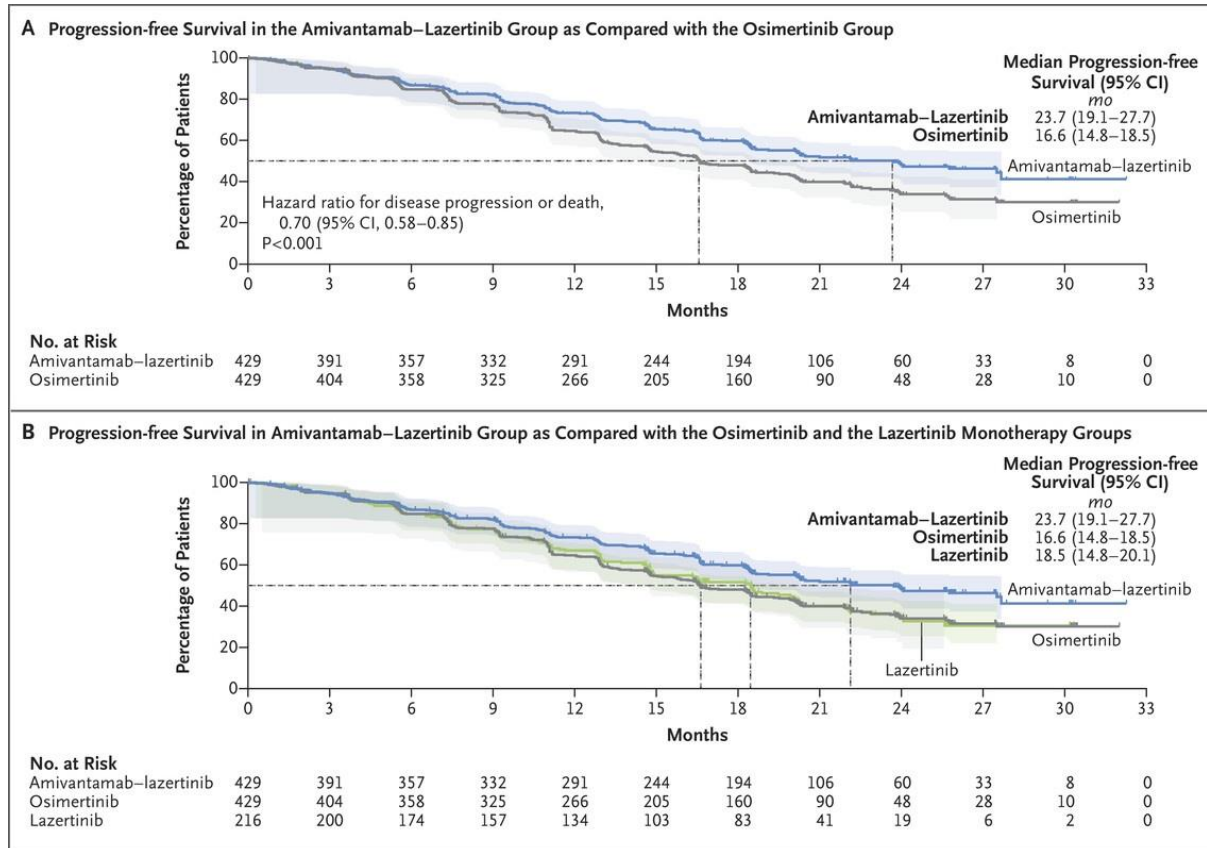
N Engl J Med. 2024 Jun 26. doi: 10.1056/NEJMoa2403614. Epub ahead of print. PMID: 38924756.

Intracranial DoR[a]

icORR:
- Amivantamab + lazertinib, **77%** (95% CI, 70–83)
- Osimertinib, **77%** (95% CI, 71–83)

Median follow-up: 31.1 mo	Median icDoR (95% CI)[b]
Ami + laz	NE (21.4 mo–NE)
Osi	24.4 mo (22.1–31.2)

59%   51%   Amivantamab + lazertinib

52%   0%   Osimertinib

No. at risk
	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Ami + laz	139	122	110	101	88	78	70	58	43	27	19	14	5	0	0
Osi	144	130	115	103	86	69	56	44	25	16	11	4	0	0	0

icORR was 77% for both arms; however, amivantamab + lazertinib demonstrated greater durability of response, with improved icDoR vs osimertinib

[a]Intracranial DoR was defined as the time from the date of first documented intracranial response (CR or PR) until the date of documented intracranial progression or death, whichever occurred first, among patients with a history of brain metastases at screening who have intracranial CR or PR based on BICR using RECIST v1.1 . 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, 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. [b]95% CIs were estimated with Kaplan-Meier method.
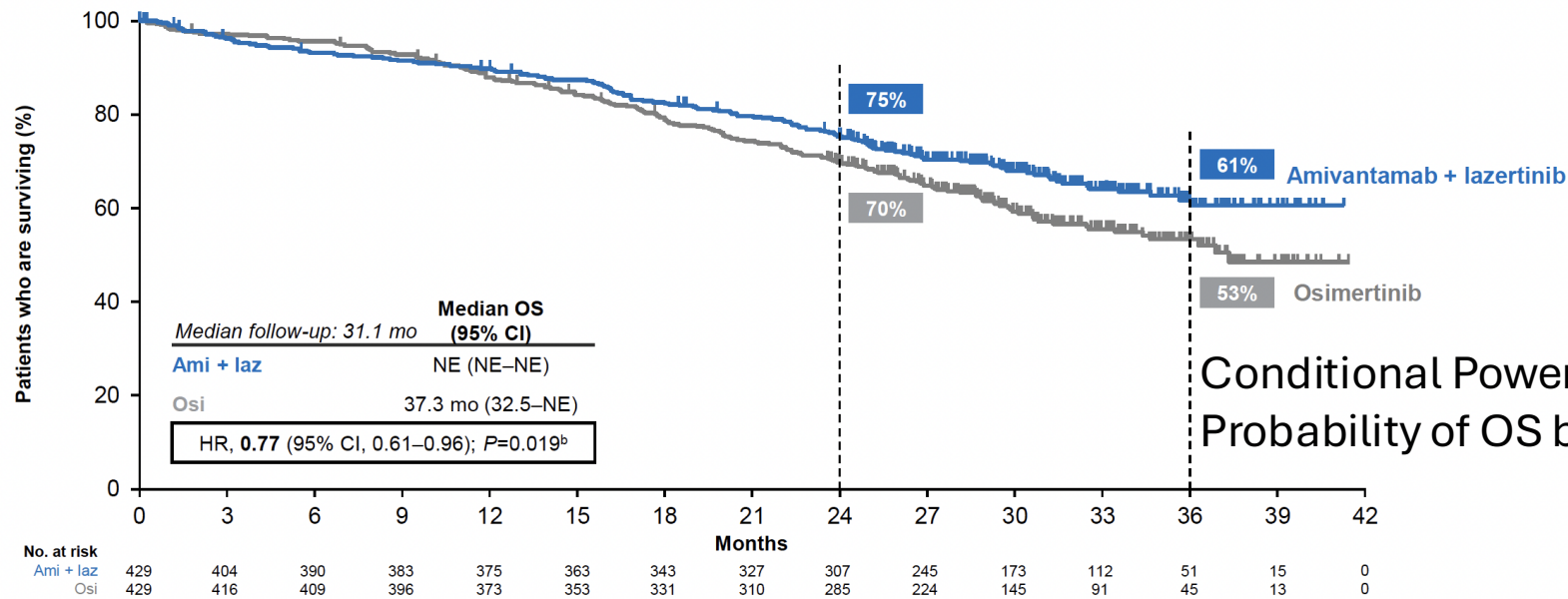
Presented by: Shirish Gadgeel

Efficacy comparison of 1st line treatment options

	FLAURA2			MARIPOSA		
	Osimertinib	**Osimertinib + Chemo**	**FLAURA2 HR (95% CI)**	**Osimertinib**	**Amivantamab + Lazertinib**	**Mariposa HR (95% CI)**
PFS	16.7 (14.1-21.3)	25.5 (24.7-NC)	0.62 (0.49-0.79)	16.6 (14.8-18.5)	23.7 (19.1-27.7)	0.70 (0.58-0.85)
OS	36.7 (33.2 –NC)	NR (38.0-NC)	0.75 (0.57-0.97)	37.3 (32.5-NE)	NE	0.77 (0.61-0.98)
Alive at 3 yrs	50%	64%		53%	61%	

Subgroup Analysis

	Mariposa HR* (95% CI)	FLAURA2 HR* (95% CI)
With CNS Mets	0.82 (0.62-1.09)	0.47 (0.33-0.66)
Without CNS Mets		0.75 (0.55-1.03)
Exon 19	0.65 (0.51-0.85)	0.60 (0.44-0.83)
L858R	0.78 (0.59-1.02)	0.63 (0.44-0.90)
ctDNA +	0.68 (0.53-0.86)	0.60 (0.45-0.80)
ctCNA -	0.72 (0.47-1.10)	0.95 (0.51-1.72)
TP53 altered	0.65 (0.48-0.87)	0.57 (0.29-1.12)
TP53 wild-type	0.75 (0.52-1.07)	NC
With Liver Mets	0.58 (0.37-0.91)	0.66 (0.41-1.07)
Without Liver Mets	0.74 (0.60-0.91)	0.63 (0.48-0.83

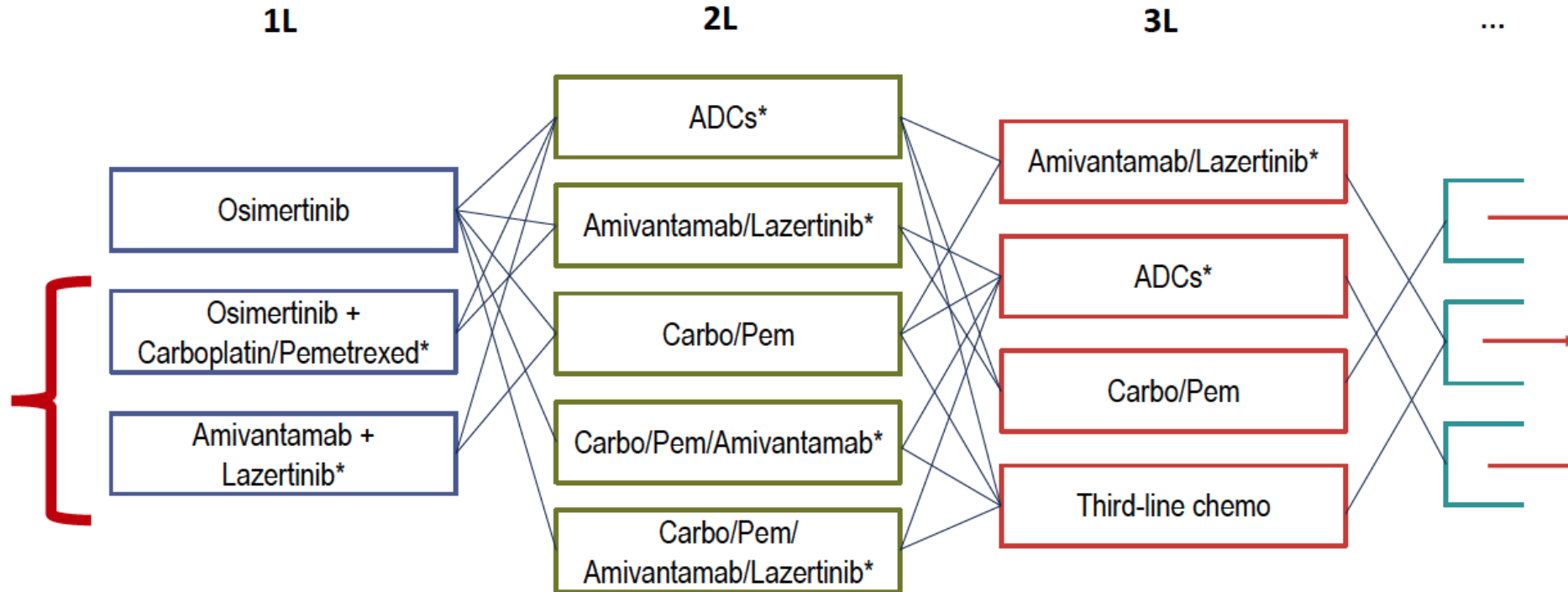**Adapted from: Marina Garassino**   * Compared to osimertinib

Toxicity comparison of 1st line treatment options

AE (%)	Osimertinib		Osimertinib + Chemo		Amivantamab + Lazertinib	
	Any	≥ grade 3	Any	≥ grade 3	Any	≥ grade 3
Any		27		64		75
Infusion reaction	0	0			63	6
Anemia	8	< 1	46	20	23	4
Diarrhea	41	<1	43	3	29	2
Nausea	10	0	43	1	21	1
Fatigue	9	<1	28	3	17	1
Neutropenia	3	1	25	11	NR	NR
Thrombocytopenia	4	1	18	1	66	16
Stomatitis	18	<1	25	<1	29	1
Paronychia	27	<1	24	1	68	11
Rash	21	0	28	<1	62	15
Peripheral Edema	4	0	15	0	36	2
Pneumonitis		0		<1		2
Any VTE	9	4	NR	4	37	11
Cardiac disorder		2		4		1
Muscle spasms	7	0	NR	NR	17	<1

How to select the optimal strategy?

Zosia Piotrowska, MD, MHS, ESMO Annual meeting 2023 plenary discussion

Marina Chiara Garassino @marinagarassino

Summary and Conclusions

1. Osimertinib and lazertinib demonstrated similar efficacy, but slightly different toxicity as 1st line treatment for advanced EGFR-mutated NSCLC.

2. Osimertinib + chemotherapy and amivantamab + lazertinib showed improved PFS and trend towards OS compared to osimertinib monotherapy.

3. Patients with brain metastases at diagnosis may benefit the most from osimertinib + chemotherapy.

4. No clear subgroup benefited more from amivantamab + lazertinib compared to osimertinib + chemotherapy in cross-trial comparison.

5. Patients with no detectable ctDNA prior to treatment demonstrated the least benefit from 1st line combination therapies.

6. Differing toxicity profiles should be taken into account in treatment decisions.