EGFR and Resistant Mechanisms

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Oncology Latin American Association

Outlines

- Adjuvant- EGFR; **ADAURA trial.**
- Mechanism of resistance in early stages
- Advanced or Metastatic setting:
  - Osimertinib in front line **[FLAURA-2 trial]**
  - Lazertinib plus Amivantamab in front line **[MARIPOSA trial]**
- Mechanism of resistance to Osimertinib (metastatic setting):
  - **MARIPOSA-2 trial**
  - Resistance driven by alternative pathways

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ADJUVANT SETTING

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13th Annual WCS WINTER CANCER SYMPOSIUM
MARCH 1–3, 2024
WYNDHAM GRAND RIO MAR PUERTO RICO HOTEL | RIO GRANDE, PUERTO RICO
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Osimertinib- EGFR TKI

Adjuvant setting
Where are we now?

The ADAURA study has demonstrated a statistically significant and clinically meaningful OS benefit with adjuvant osimertinib vs placebo in patients with resected EGFRm stage IB–IIIA NSCLC

>2 million
new cases of lung cancer worldwide annually[1]

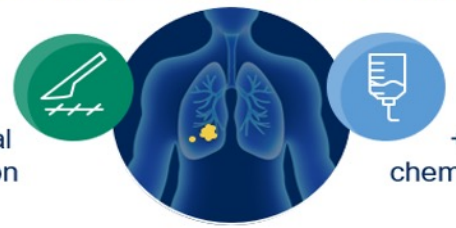
NSCLC represents **~80%** of all diagnoses[1]

Approximately **30%** of patients have resectable disease[2–4]

EGFR mutation prevalence ranges from **10–50%** in patients with NSCLC[5–9]

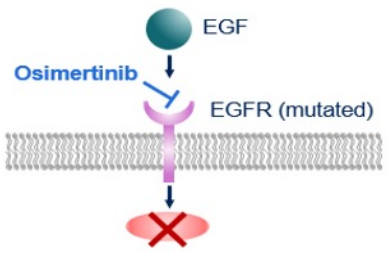
ADAURA

Surgery → Adjuvant Therapy



Osimertinib vs placebo

Adjuvant osimertinib



Osimertinib is the first EGFR-TKI to show significant OS benefit in a Phase III adjuvant study

Reinforces osimertinib as standard of care

EGFR mutation testing

Best treatments early

New era for targeted treatment in early-stage disease

1. Cancer.net 2023. Available at: https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/statistics; 2. Datta et al. Chest 2003;123:2096–2103; 3. Le Chevalier Ann Oncol 2010;21(Suppl 7):vii196–8; 4. Cagle et al. Arch Pathol Lab Med 2013;137:1191–1198; 5. Pi et al. Thorac Cancer 2018;9:814–819; 6. Hondelink et al. Eur J Cancer 2023;181:53–61; 7. Zhang et al. Oncotarget 2016;7:78985–78993; 8. Stone et al. Intern Med J 2014;44:1188–1192; 9. Kim et al. Pathology 2020;52:410–420.

ADAURA Phase III study design

Patients with completely resected stage* IB, II, IIIA NSCLC, with or without adjuvant chemotherapy†

Key inclusion criteria:
≥18 years (Japan / Taiwan: ≥20)
WHO performance status 0 / 1
Confirmed primary non-squamous NSCLC Ex19del / L858R‡
Brain imaging, if not completed pre-operatively
Complete resection with negative margins§
Maximum interval between surgery and randomization:
- 10 weeks without adjuvant chemotherapy
- 26 weeks with adjuvant chemotherapy

Stratification by:
Stage (IB vs II vs IIIA)
EGFRm (Ex19del vs L858R)
Race (Asian vs non-Asian)

Randomization 1:1 (N=682)

Osimertinib 80 mg, once daily

Placebo, once daily

Planned treatment duration: 3 years

Treatment continued until:
- Disease recurrence
- Treatment completion
- Discontinuation criterion met

Follow-up:
- Until recurrence: Week 12 and 24, then every 24 weeks to 5 years, then yearly
- After recurrence: every 24 weeks for 5 years, then yearly

Endpoints
- **Primary endpoint:** DFS by investigator assessment in stage II–IIIA patients
- **Key secondary endpoints:** DFS in the overall population (stage IB–IIIA), landmark DFS rates, OS, safety, health-related quality of life

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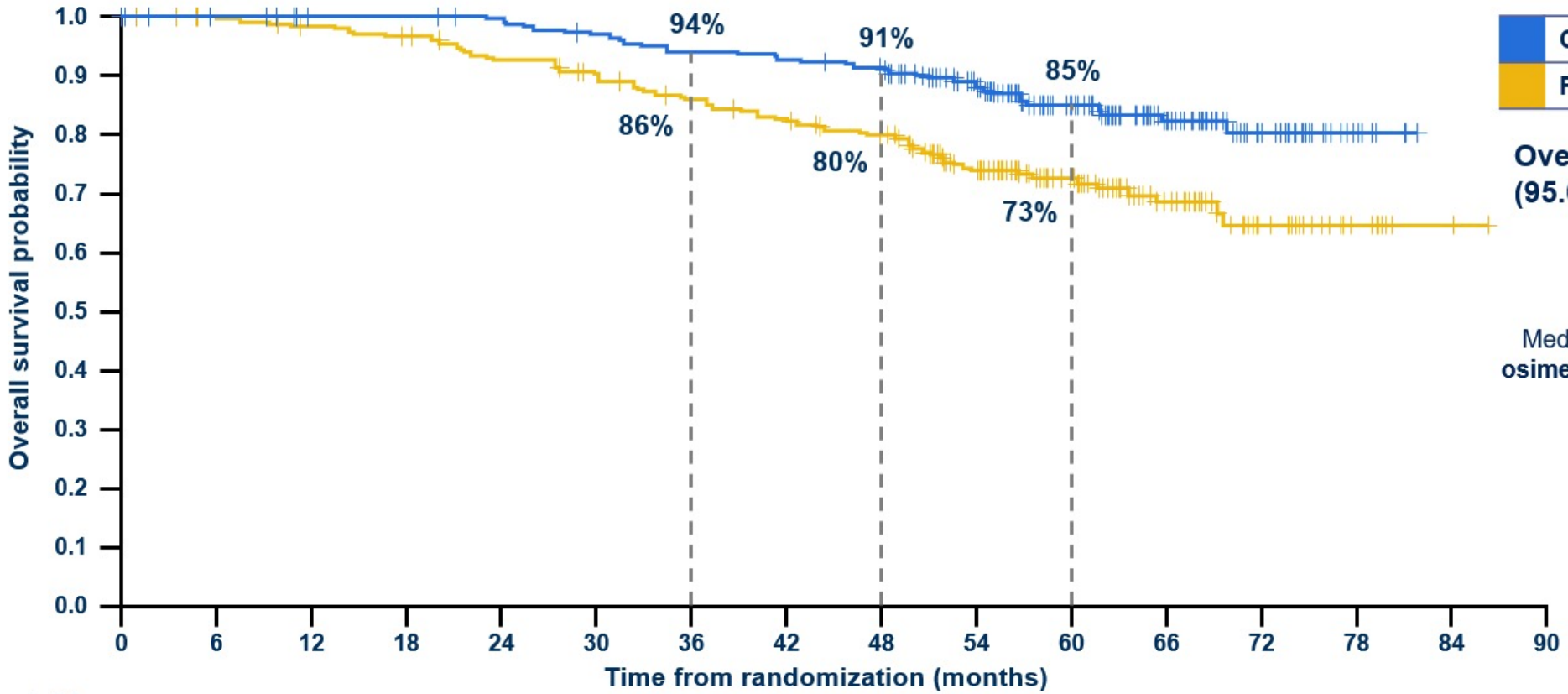
*At the time of recruitment, staging was determined by the AJCC / UICC Staging Manual 7th edition. Patients with stage IB disease were not eligible in Japan. †Pre-operative, post-operative, or planned radiotherapy was not allowed. ‡Centrally confirmed in tissue. §Patients received a CT scan after resection and within 28 days prior to treatment.

AJCC, American Joint Committee on Cancer; CT, computerized tomography; DFS, disease-free survival; EGFRm, epidermal growth factor receptor-mutated; Ex19del, exon 19 deletion; NSCLC, non-small cell lung cancer; OS, overall survival; UICC, Union for International Cancer Control; WHO, World Health Organization

Overall survival: patients with stage II / IIIA disease

- Adjuvant osimertinib demonstrated a statistically and clinically significant improvement in OS vs placebo in the primary population of stage II–IIIA disease



No. at risk																
Osimertinib	233	229	224	224	221	214	208	205	200	170	115	69	33	9	0	-
Placebo	237	232	226	221	210	202	190	182	171	138	94	53	25	8	2	0

5-year OS rate, % (95% CI)	
Osimertinib (n=233)	85 (79, 89)
Placebo (n=237)	73 (66, 78)

Overall OS HR (95.03% CI) **0.49 (0.33, 0.73); p=0.0004**

Maturity: 21%
osimertinib 15%, placebo 27%

Median follow-up for OS* (censored patients):
osimertinib 61.7 months, placebo 60.4 months


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

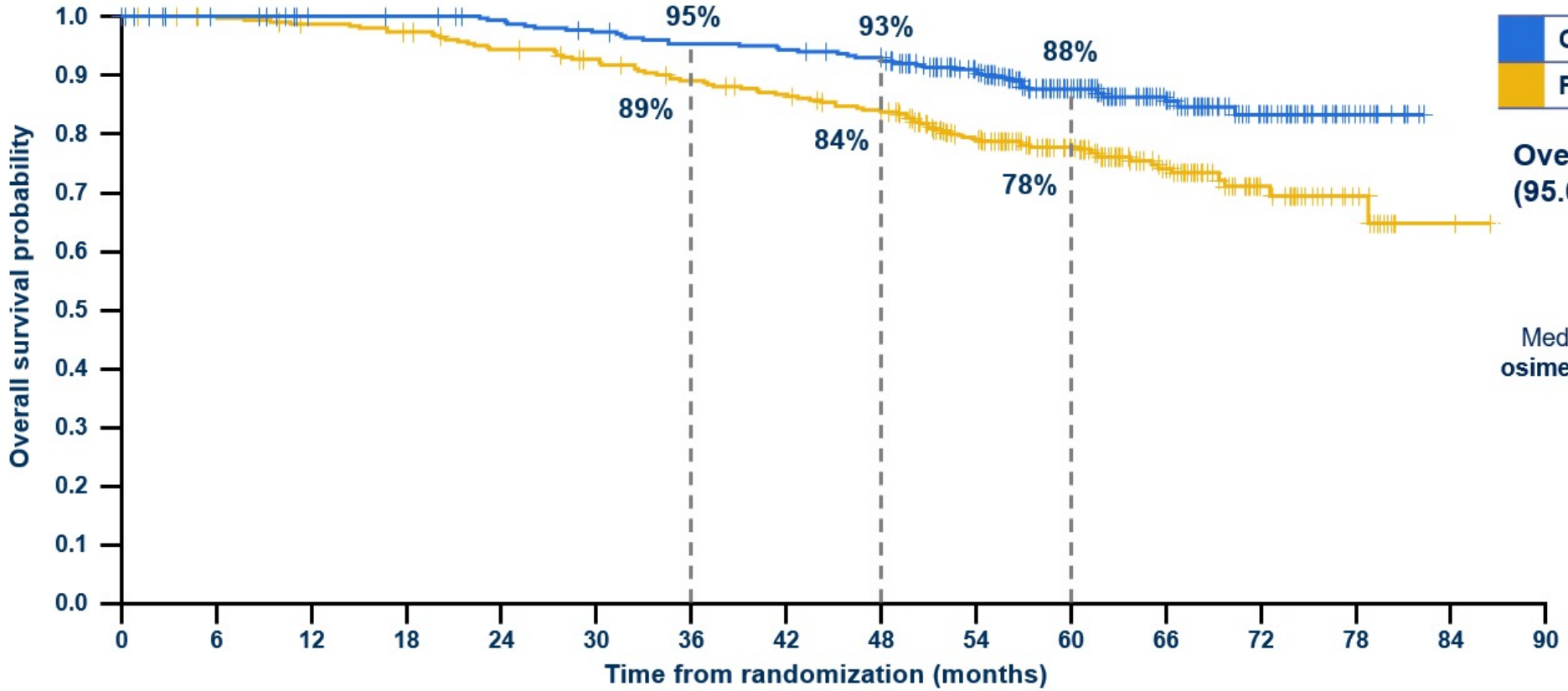
Overall Survival with Osimertinib in Resected *EGFR*-Mutated NSCLC

Masahiro Tsuboi, M.D., Roy S. Herbst, M.D., Ph.D., Thomas John, M.B., B.S., Ph.D., Terufumi Kato, M.D., Margarita Majem, M.D., Ph.D., Christian Grohé, M.D., Jie Wang, M.D., Ph.D., Jonathan W. Goldman, M.D., Shun Lu, M.D., Wu-Chou Su, M.D., Filippo de Marinis, M.D., Frances A. Shepherd, M.D., Ki Hyeong Lee, M.D., Ph.D., Nhieu Thi Le, M.D., Arunee Dechaphunkul, M.D., Dariusz Kowalski, M.D., Ph.D., Lynne Poole, M.Sc., Ana Bolanos, M.D., Yuri Rukazenkov, M.D., Ph.D., and Yi-Long Wu, M.D., for the ADAURA Investigators*

Data cut-off: January 27, 2023.
Tick marks indicate censored data. Alpha allocation of 0.0497. *Median follow-up for OS (all patients): osimertinib 59.9 months, placebo 56.2 months.
CI, confidence interval; HR, hazard ratio; OS, overall survival

Overall survival: patients with stage IB / II / IIIA disease

- Adjuvant osimertinib demonstrated a statistically and clinically significant improvement in OS vs placebo in the overall population of stage IB–IIIA disease



5-year OS rate, % (95% CI)	
Osimertinib (n=339)	88 (83, 91)
Placebo (n=343)	78 (73, 82)

Overall OS HR (95.03% CI) **0.49 (0.34, 0.70); p<0.0001**

Maturity: 18%
osimertinib 12%, placebo 24%

Median follow-up for OS* (censored patients):
osimertinib 61.5 months, placebo 61.5 months

No. at risk

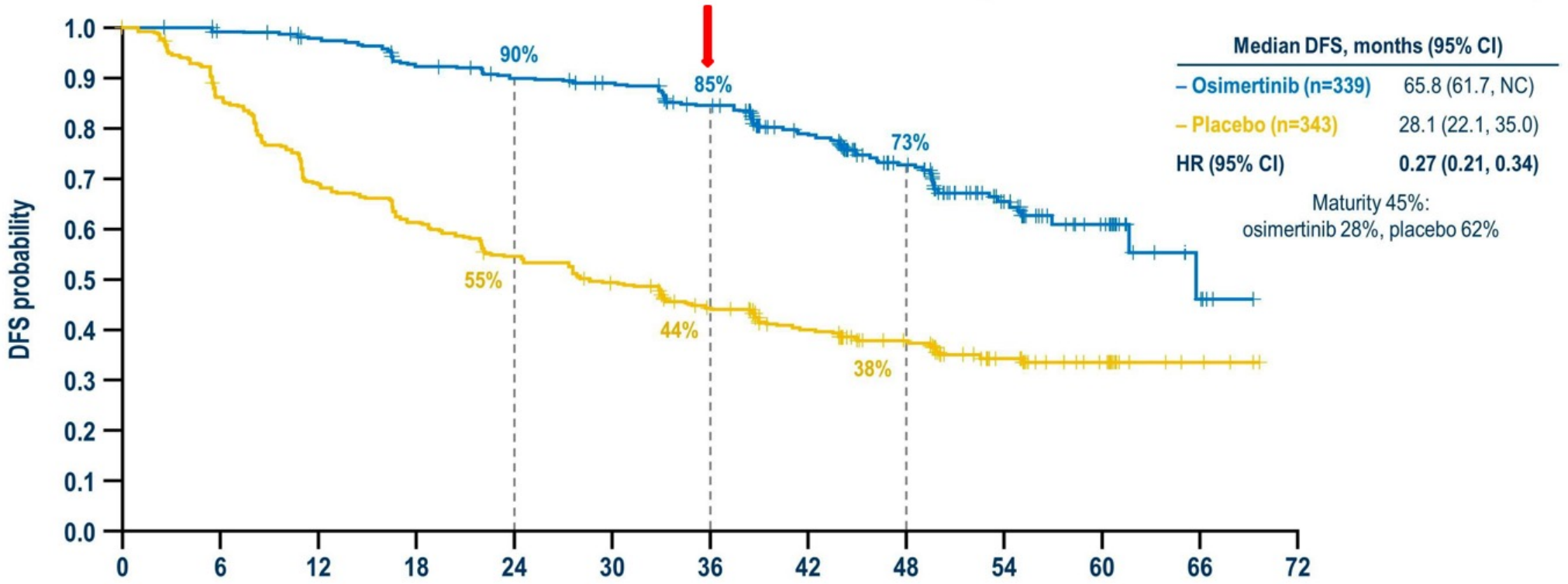
Osimertinib	339	332	325	324	319	311	304	301	294	252	176	108	50	15	0	-
Placebo	343	338	332	326	314	304	290	281	267	223	164	97	44	17	3	0

Data cut-off: January 27, 2023.
Tick marks indicate censored data. Alpha allocation of 0.0497. *Median follow-up for OS (all patients): osimertinib 60.4 months, placebo 59.4 months.

CI, confidence interval; HR, hazard ratio; OS, overall survival

Overcoming Resistance in Earlier Stage Disease

UPDATED DFS IN THE OVERALL POPULATION (STAGE IB / II / IIIA DISEASE)



Median DFS, months (95% CI)	
– Osimertinib (n=339)	65.8 (61.7, NC)
– Placebo (n=343)	28.1 (22.1, 35.0)
HR (95% CI)	0.27 (0.21, 0.34)

Maturity 45%:
osimertinib 28%, placebo 62%

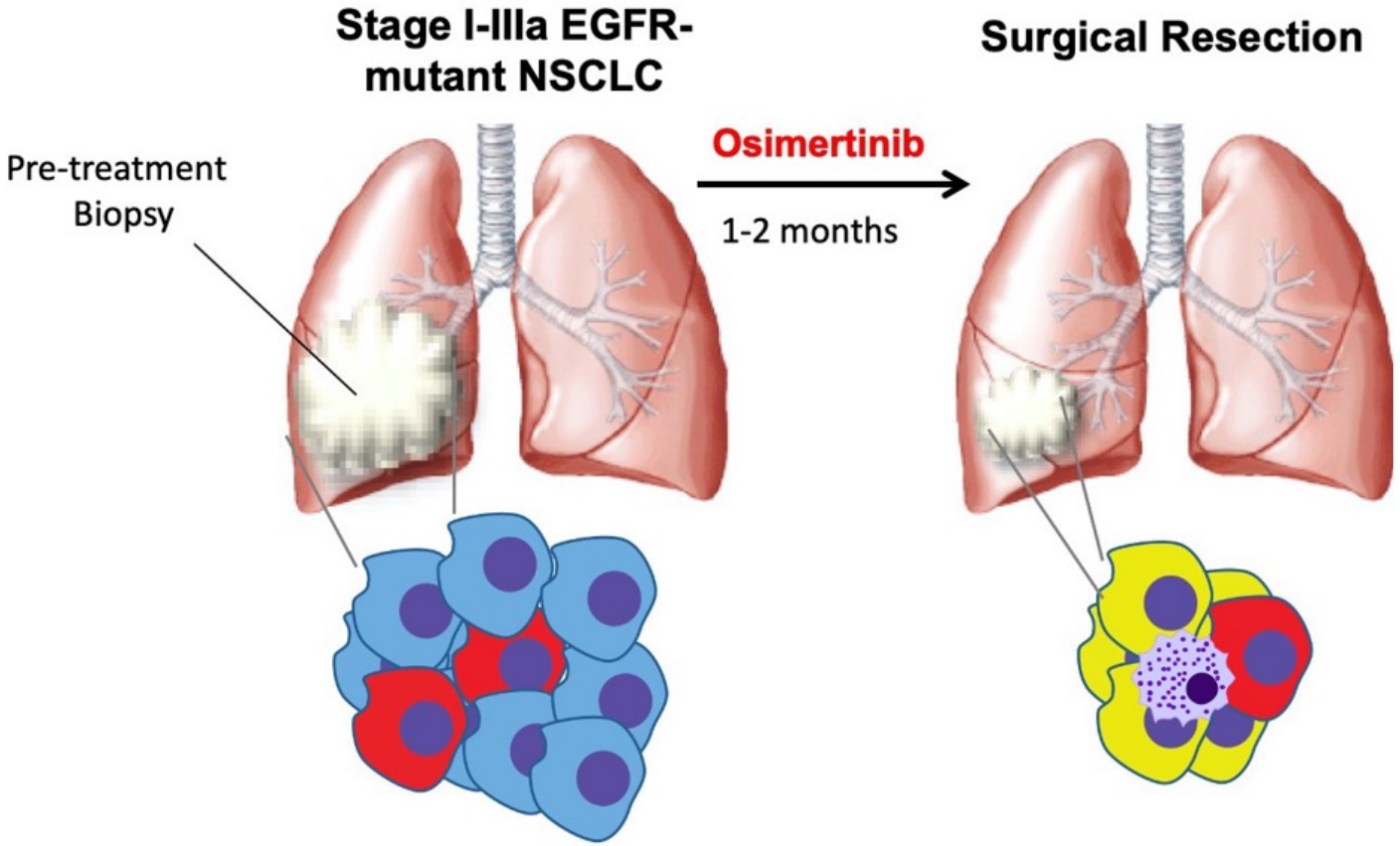
No. at risk													
Osimertinib	339	316	307	289	278	270	249	201	139	73	33	5	0
Placebo	343	288	230	205	181	162	137	115	84	48	25	4	0

Median follow-up: osimertinib 44.2 months (range 0 to 69), placebo 27.7 months (range 0 to 70); DFS by investigator assessment; Tick marks indicate censored data.

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; NC, not calculable
Data cut-off: April 11, 2022.

Tsuboi. ESMO Paris 2022

Neoadjuvant Osimertinib in Stage I-IIIA NSCLC: Interim analysis of first 13 patients



Blakely, IASLC WCLC, 2021

Primary Endpoint:
MPR: ~15%

Safety:

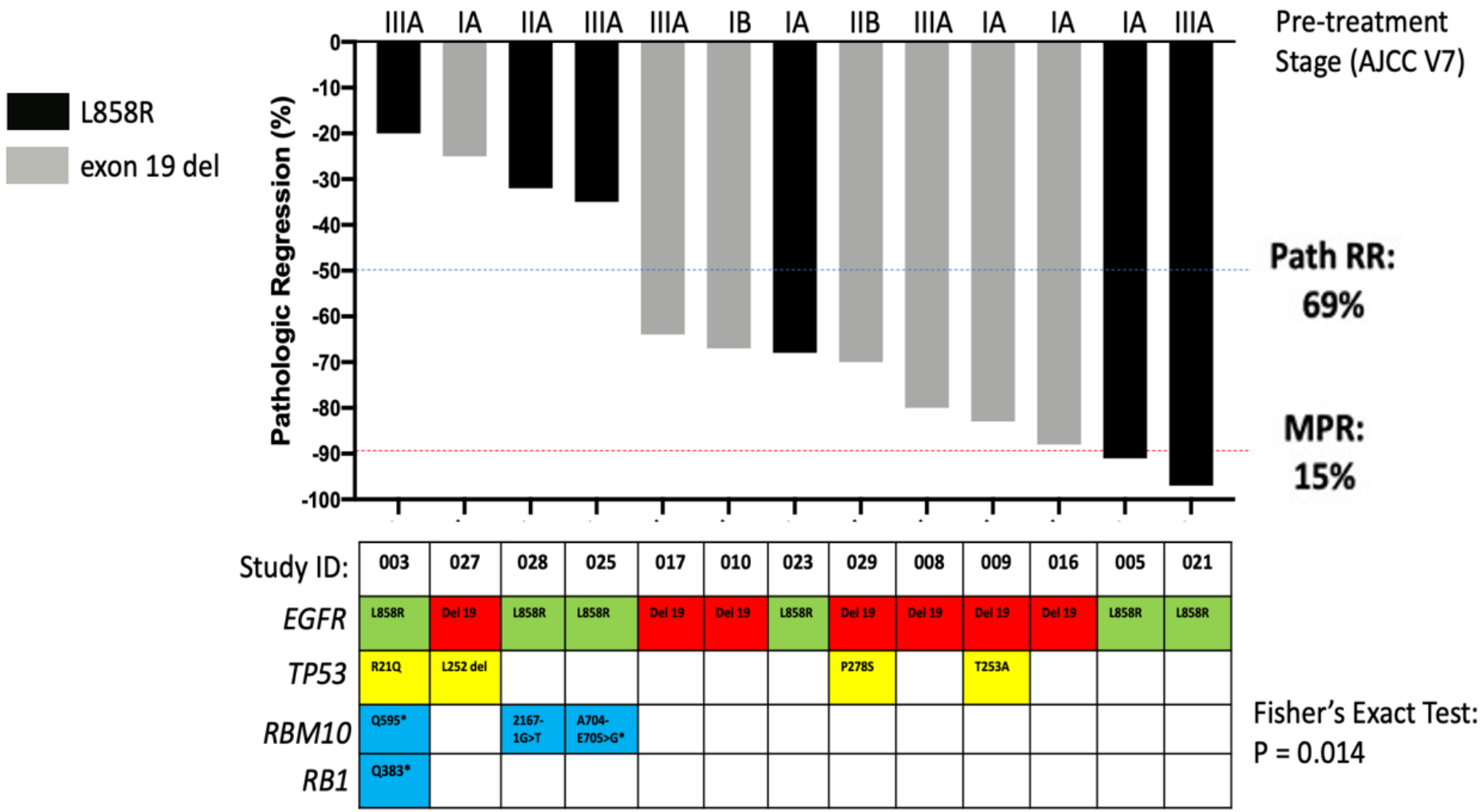
Secondary Efficacy:

80% LN downstaging (4/5)
46% ORR
0% PCR
DFS/OS: TBD

Exploratory:

RBM10 commutations
AT2 – diff
WNT/b-catenin activation
T-Cell infiltration

Co-occurring RBM10 mutations correlate with lack of pathological response



Blakely, IASLC WCLC, 2021

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ADVANCED OR METASTATIC SETTING

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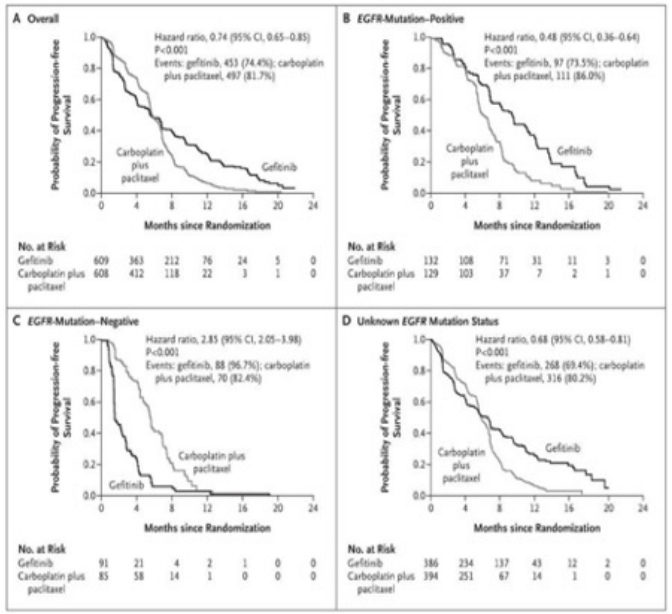
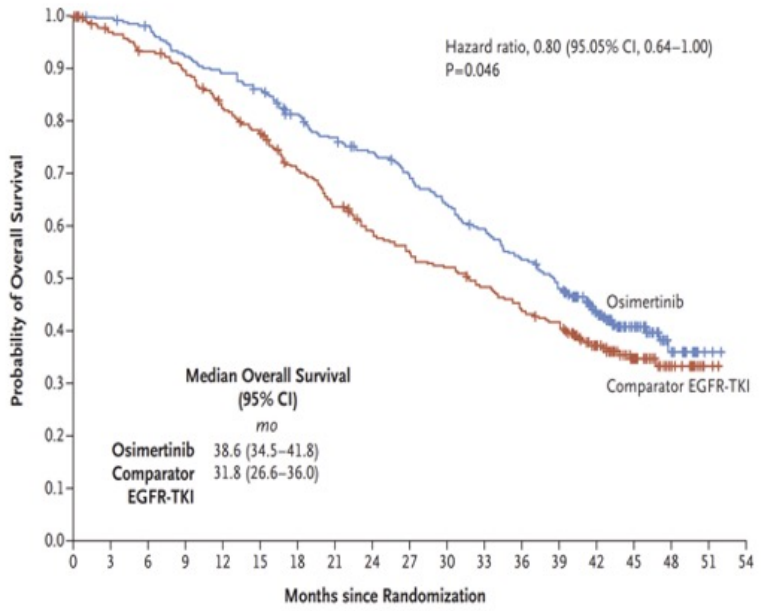
Osimertinib- EGFR TKI

Metastatic setting
Where are we going?





1L Treatment of EGFRm NSCLC November 2023

+ Chemo

FLAURA2: Osimertinib + Chemotherapy > Osimertinib

+ EGFR/MET mAb

MARIPOSA: Amivantamab + Lazertinib > Osimertinib, Lazertinib

IPASS 2009 | **FLAURA 2018** | **2023**

IPASS Mok TS et all NEJM 2009; FLAURA Soria JC et al NEJM 2018; FLAURA2 Janne P et al NEJM 2023; MARIPOSA Cho et al ESMO 2023

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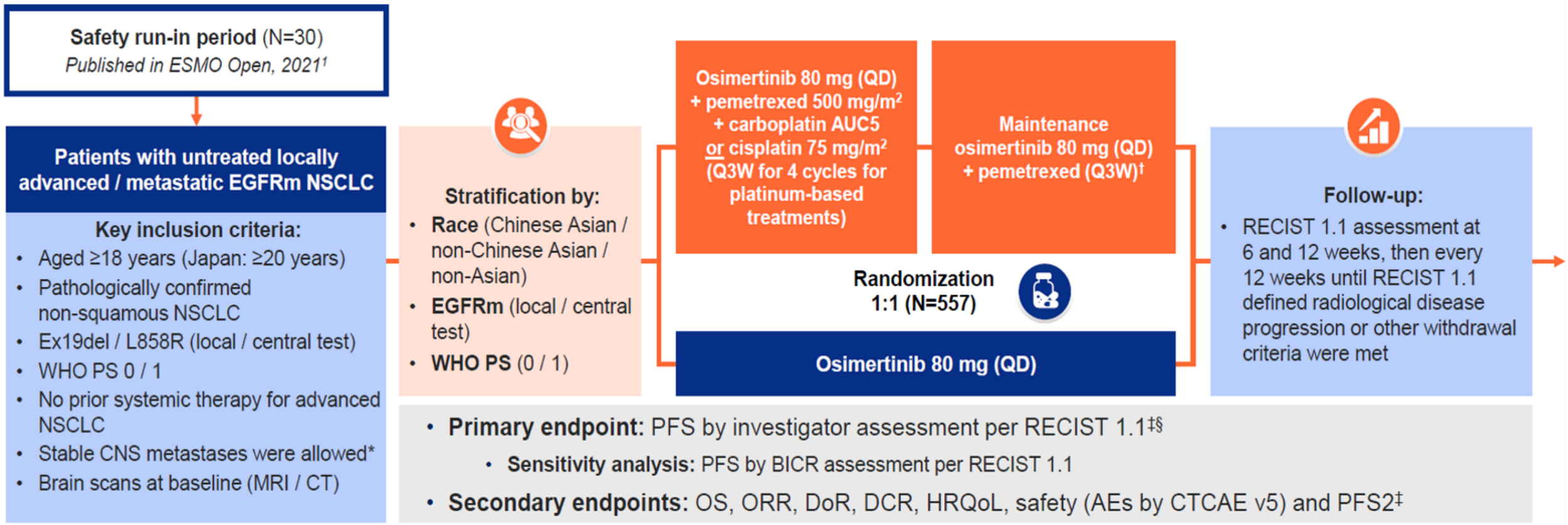
FLAURA2: 1L Osimertinib + Chemotherapy vs Osimertinib



Presented by P. Janne, IASLC WCLC 2023, PL03.13

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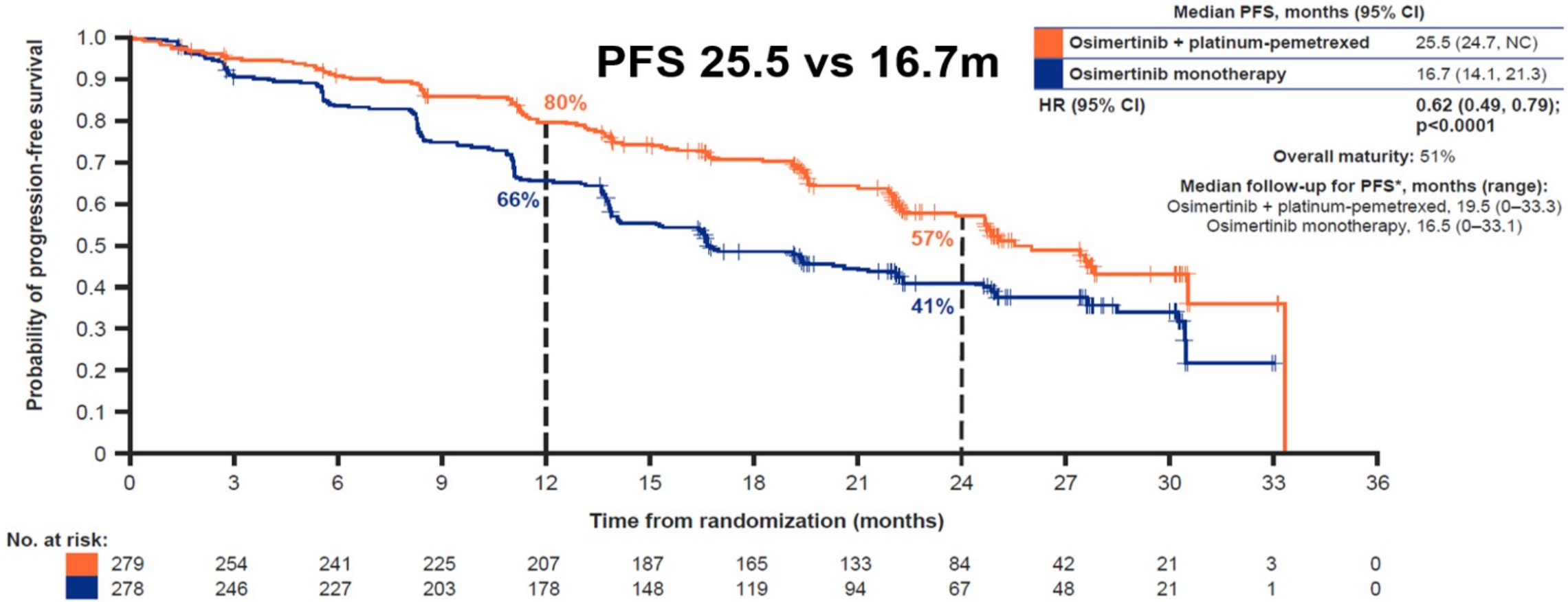
FLAURA2: PFS per investigator



Median PFS, months (95% CI)	
Osimertinib + platinum-pemetrexed	25.5 (24.7, NC)
Osimertinib monotherapy	16.7 (14.1, 21.3)
HR (95% CI)	0.62 (0.49, 0.79); p<0.0001

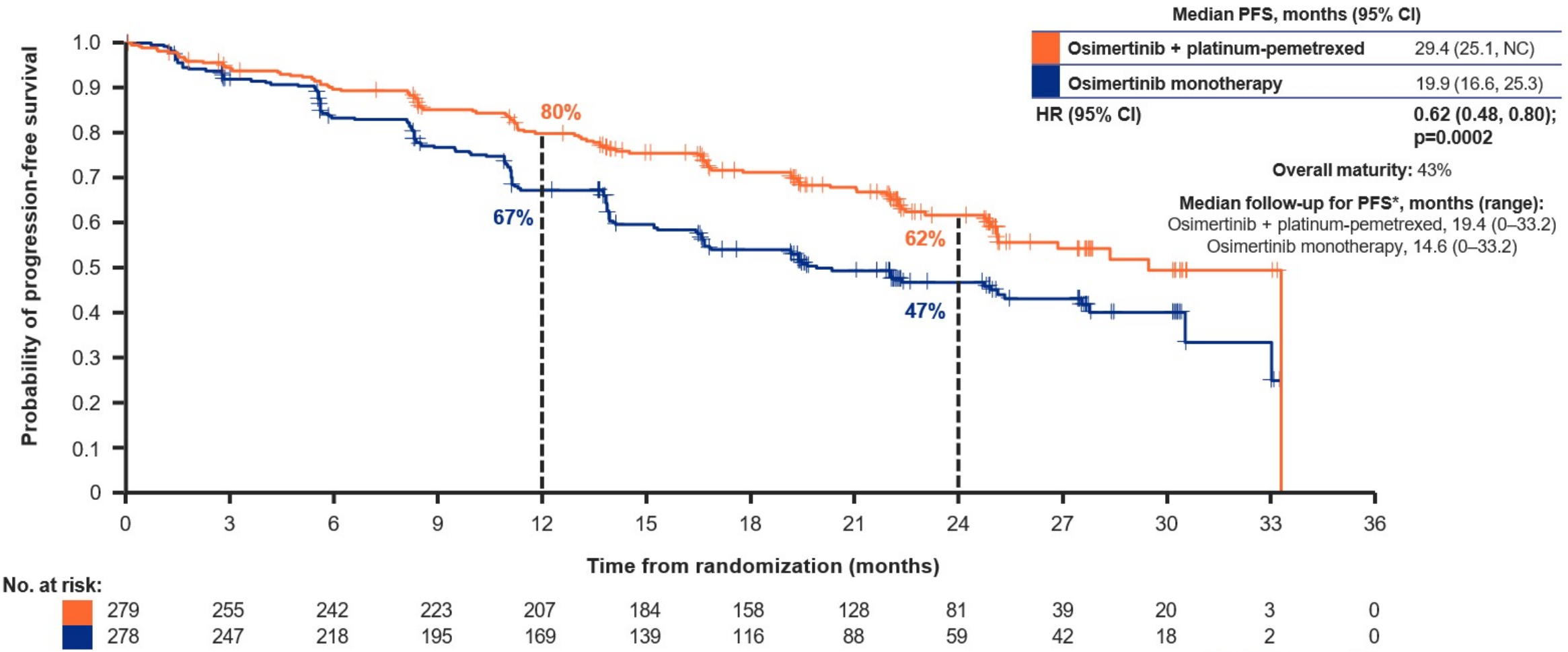
Overall maturity: 51%

Median follow-up for PFS*, months (range):
Osimertinib + platinum-pemetrexed, 19.5 (0–33.3)
Osimertinib monotherapy, 16.5 (0–33.1)

Presented by P. Janne, IASLC WCLC 2023, PL03.13

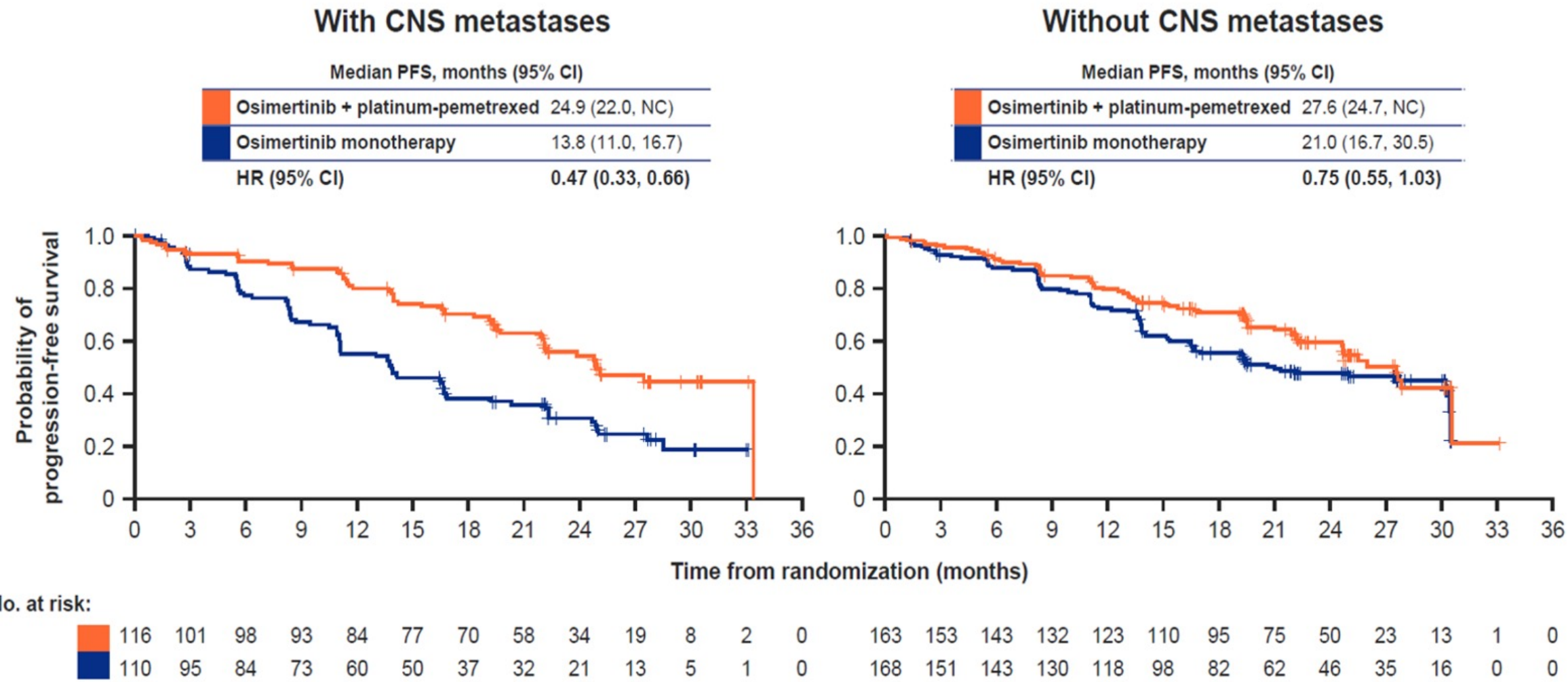
Progression-free survival per BICR

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



Data cut-off: 03 April 2023
*In all patients
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NC, not calculable; PFS, progression-free survival

FLAURA2: PFS per investigator by CNS Metastases



Presented by P. Janne, IASLC WCLC 2023, PL03.13

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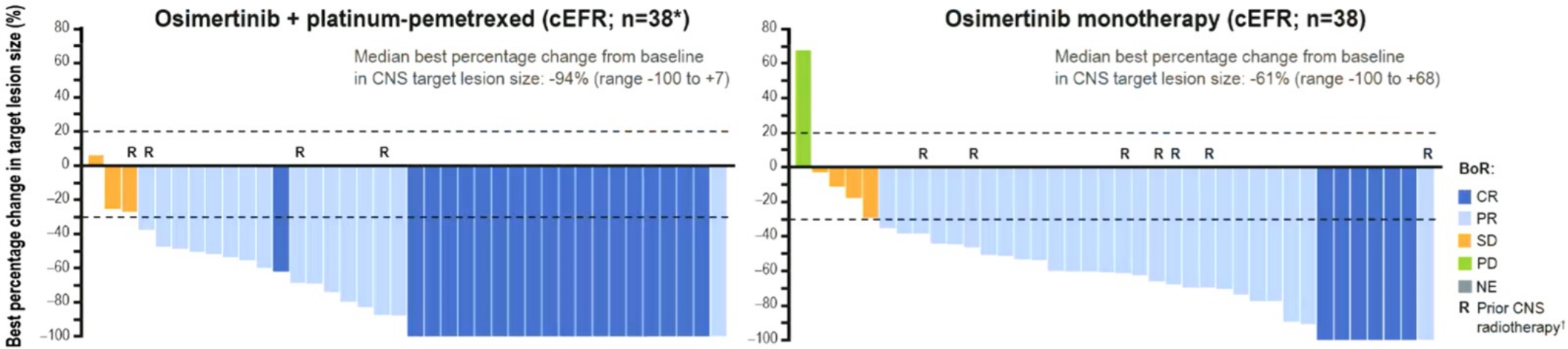
FLAURA2: Updated CNS Data ESMO 2023

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)**

*Two pts had ≥1 measurable CNS lesion at baseline by CNS BICR but died before the follow-up CNS BICR scan; †In the cEFR, 4/40 pts (10%) in the osimertinib + platinum-pemetrexed arm and 7/38 pts (18%) in the osimertinib arm had received prior CNS radiotherapy; stable neurological status for ≥2 weeks after completion of definitive treatment and steroids was required before study entry, if received; ‡Responses did not require confirmation, per RECIST guidance on randomized studies; §Kaplan–Meier estimates.

BICR, blinded independent central review; BM, brain metastases; BoR, best overall response; cEFR, CNS evaluable-for-response set; cFAS, CNS full analysis set; CI, confidence interval; CNS, central nervous system; CR, complete response; CTx, chemotherapy; DCR, disease control rate; DoR, duration of response; mono, monotherapy; NC, not calculable; NE, not evaluable; NR, not reached; ORR, objective response rate; osi, osimertinib; PD, progressive disease; PR, partial response; pts, patients; SD, stable disease

Data cut-off: 03 April 2023.

MADRID 2023 ESMO congress

Measurable CNS lesions: CR rate 16% vs 48%

Presented Planchard et al. ESMO 2023 Abstract LBA68

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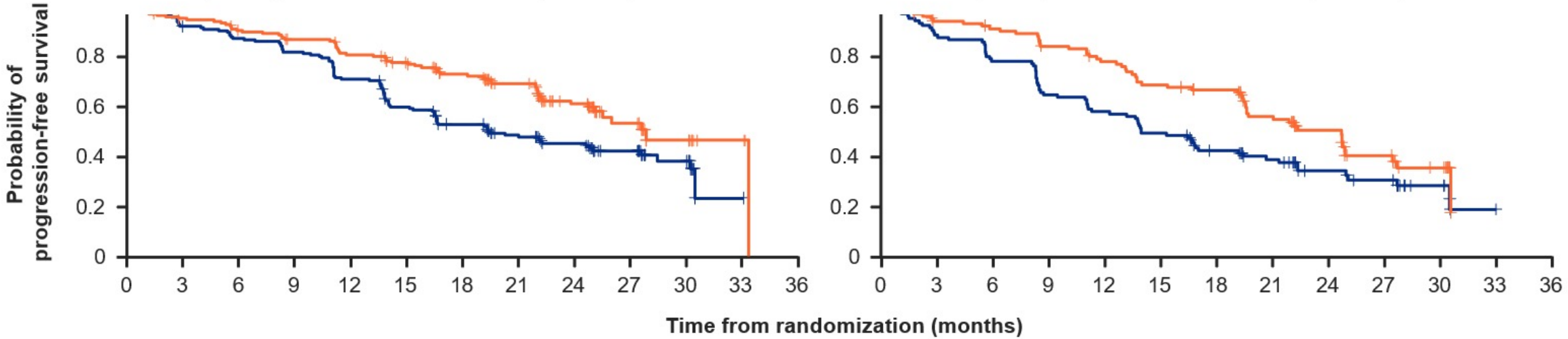
PFS per investigator by EGFR mutation type at baseline*

Ex19del

Median PFS, months (95% CI)	
Osimertinib + platinum-pemetrexed	27.9 (25.1, NC)
Osimertinib monotherapy	19.4 (16.5, 27.6)
HR (95% CI)	**0.60 (0.44, 0.83)**

L858R

Median PFS, months (95% CI)	
Osimertinib + platinum-pemetrexed	24.7 (19.5, 27.4)
Osimertinib monotherapy	13.9 (11.1, 19.4)
HR (95% CI)	**0.63 (0.44, 0.90)**



No. at risk:

Ex19del	172	159	150	142	131	120	103	86	53	23	9	3	0	L858R	106	95	91	83	76	67	62	47	31	19	12	0	0
Osimertinib monotherapy	169	152	144	135	117	96	79	63	48	33	16	1	0	Osimertinib monotherapy	107	92	82	68	61	52	40	31	19	15	5	0	0

Data cut-off: 03 April 2023

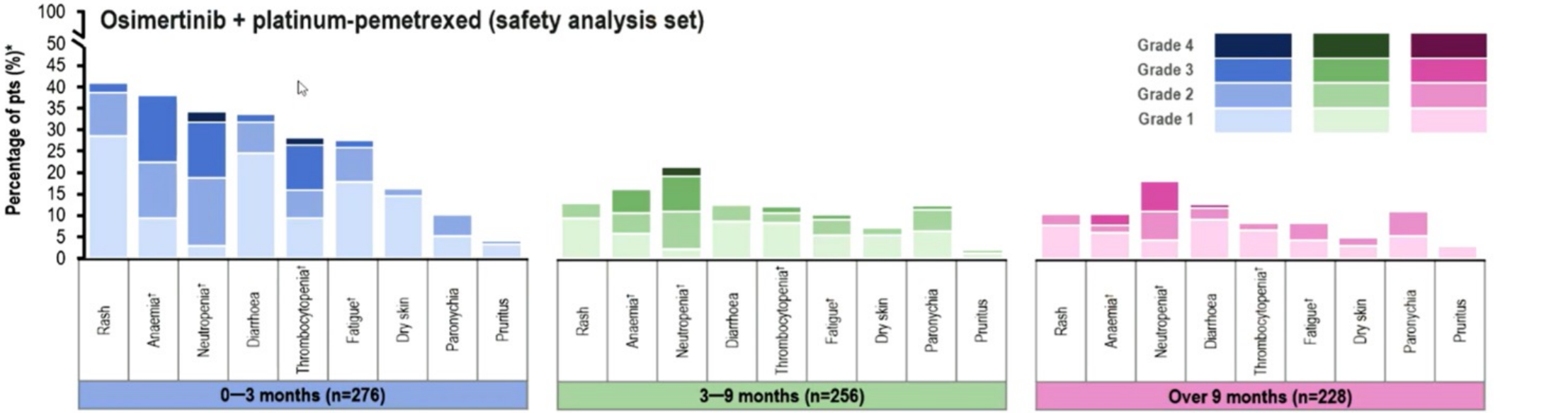
*Patients with co-occurring Ex19del and L858R mutations were included in the Ex19del group

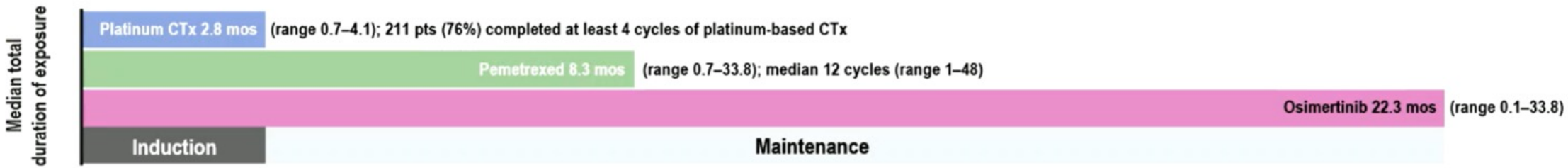
CI, confidence interval; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; HR, hazard ratio; NC, not calculable; PFS, progression-free survival

What about toxicity?

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

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





Presented Planchard et al. ESMO 2023 Abstract LBA68

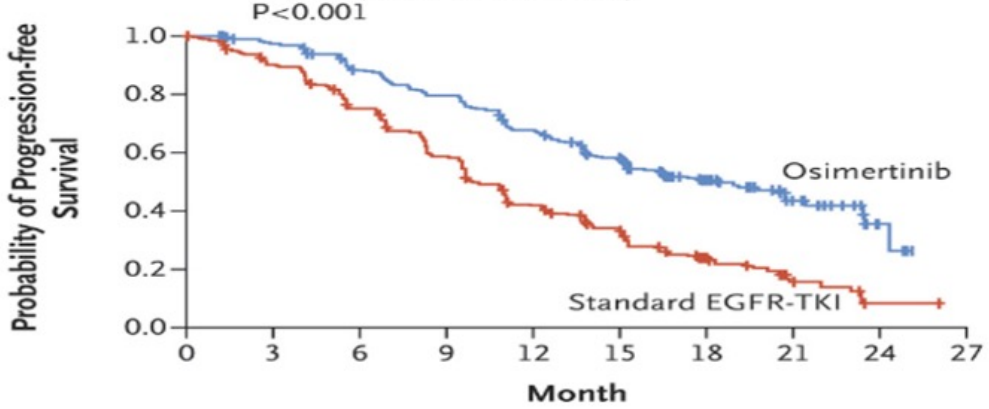
Just to Remember…..

FLAURA vs FLAURA2

A Progression-free Survival in Full Analysis Set

	No. of Patients	Median Progression-free Survival (95% CI) mo
Osimertinib	279	18.9 (15.2–21.4)
Standard EGFR-TKI	277	10.2 (9.6–11.1)

Hazard ratio for disease progression or death, 0.46 (95% CI, 0.37–0.57)
P<0.001

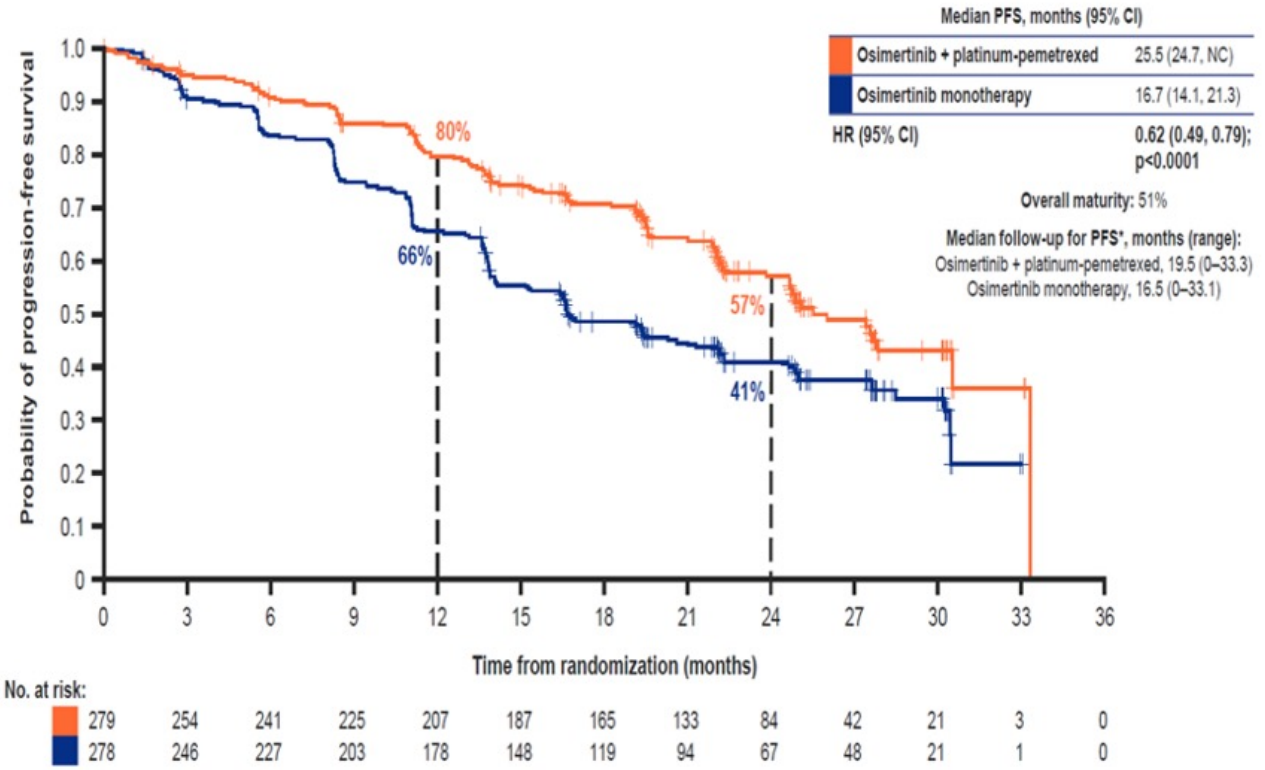


No. at Risk

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

FLAURA mPFS: 18.9 months

mOS 38.6 months



FLAURA2 mPFS: 25.5 months

mOS not mature

Edgardo Santos, MD. 2023 Updates in Cancer Therapies.

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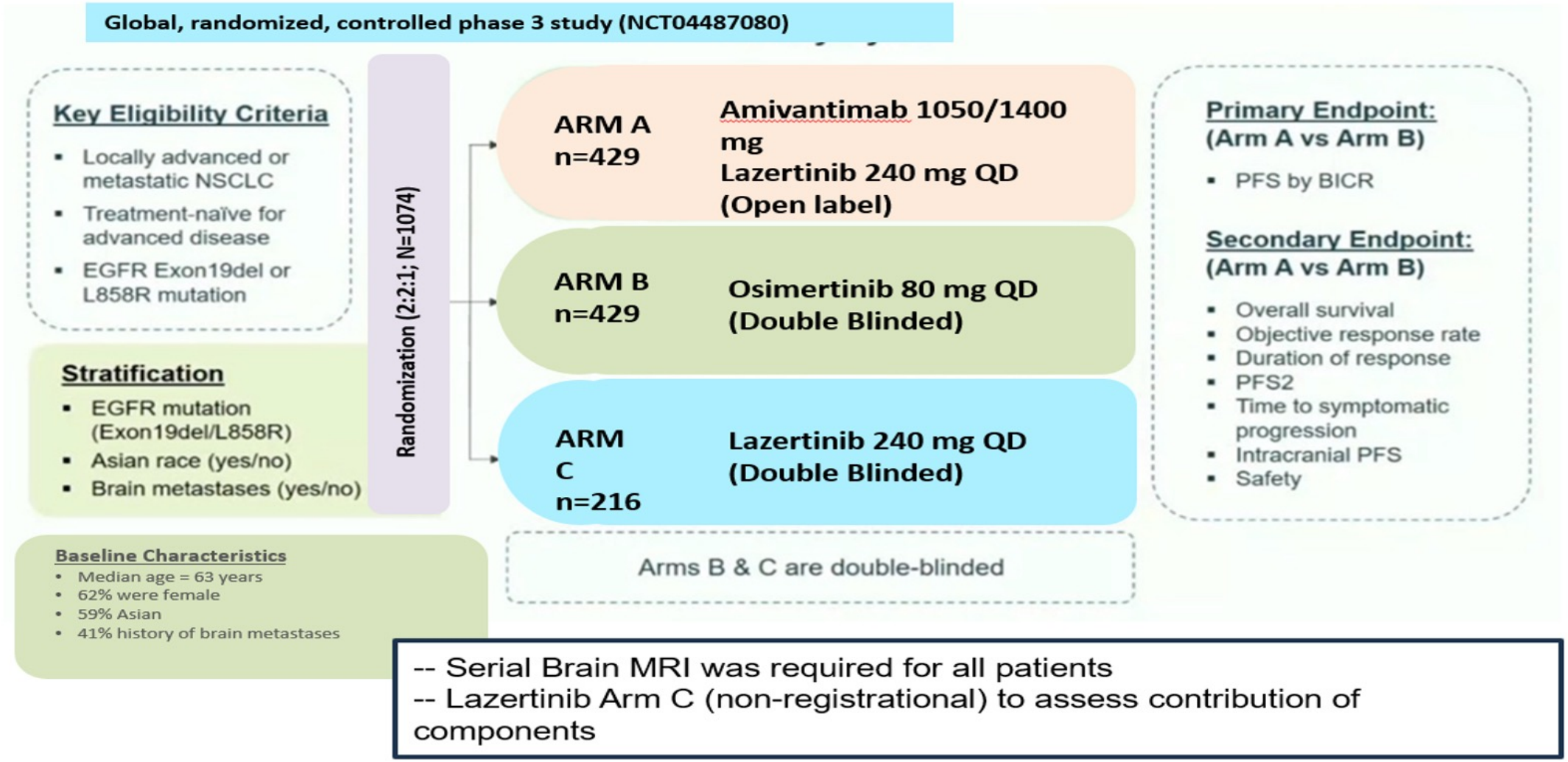
MARIPOSA: 1L Amivantamab + Lazertinib



-- Serial Brain MRI was required for all patients
-- Lazertinib Arm C (non-registrational) to assess contribution of components

Presented by B. Cho. ESMO 2023. LBA14

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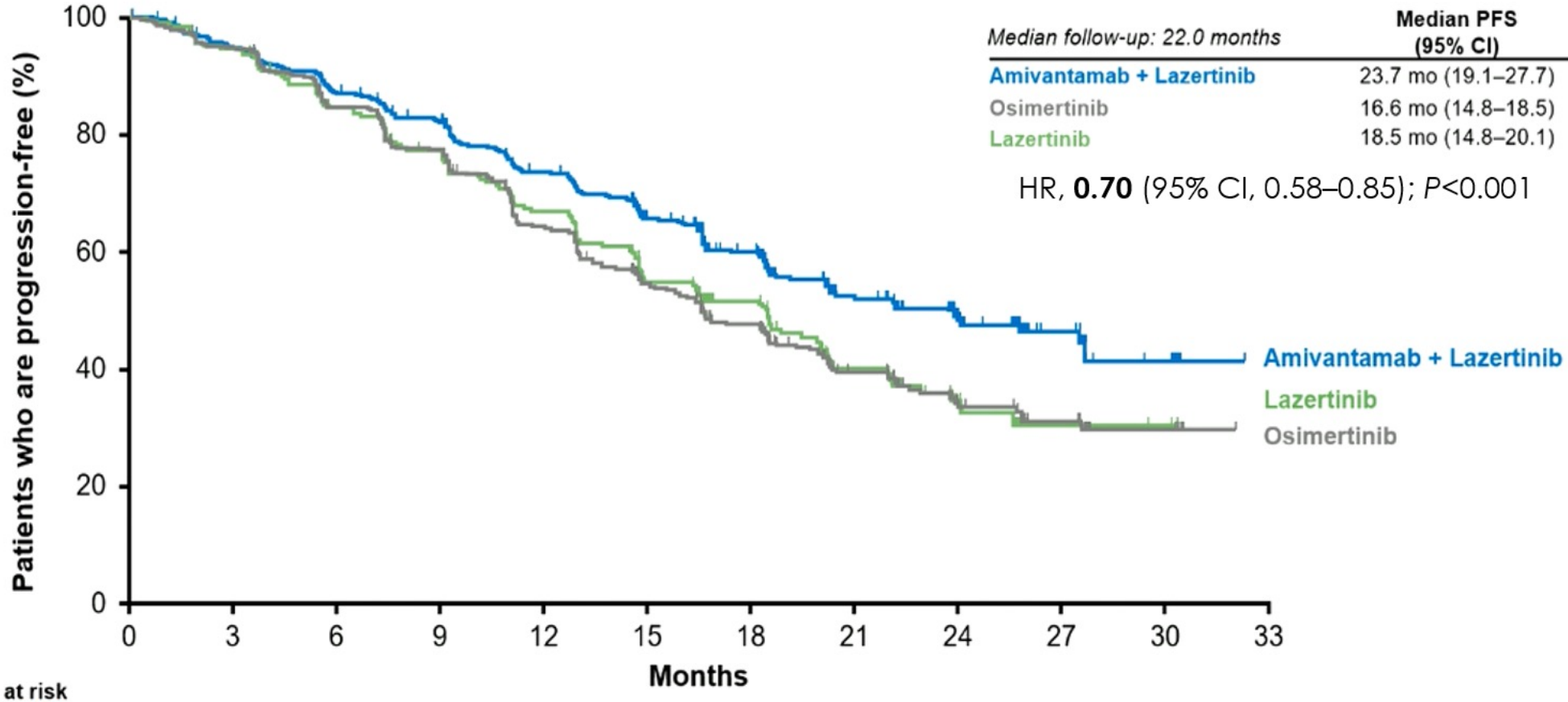
MARIPOSA: PFS by BICR

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



Median follow-up: 22.0 months	Median PFS (95% CI)
Amivantamab + Lazertinib	23.7 mo (19.1–27.7)
Osimertinib	16.6 mo (14.8–18.5)
Lazertinib	18.5 mo (14.8–20.1)

HR, **0.70** (95% CI, 0.58–0.85); *P*<0.001

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

Presented by B. Cho. ESMO 2023. LBA14

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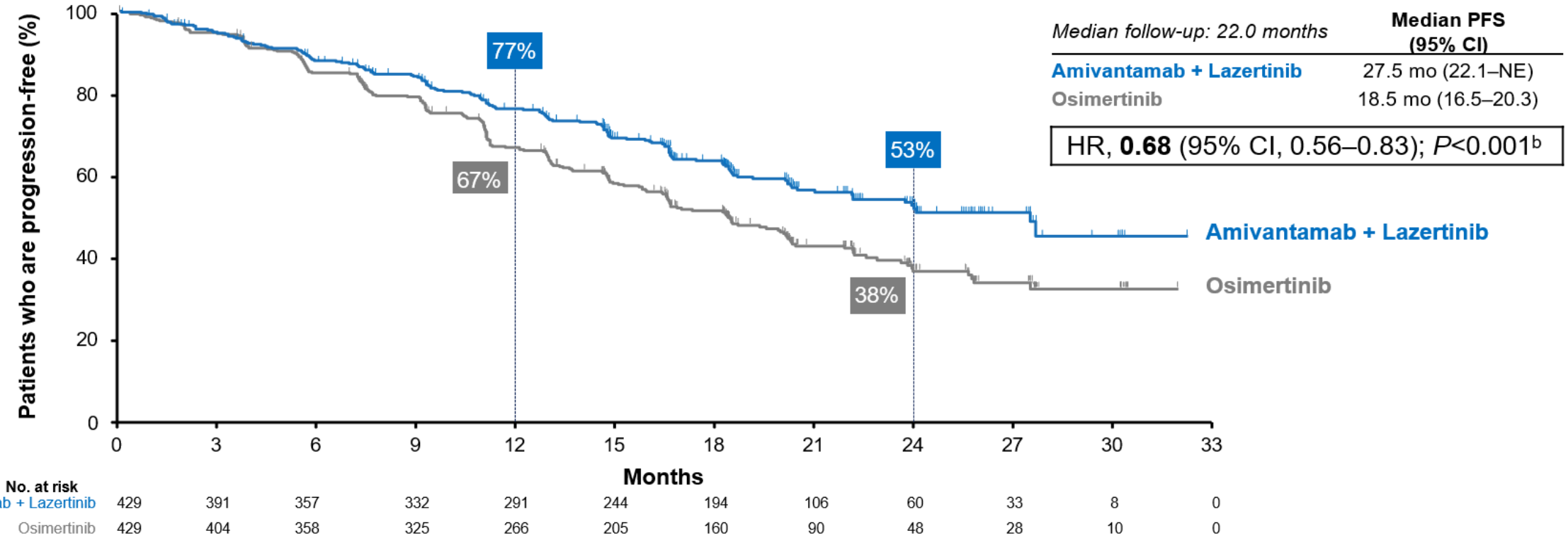
Extracranial Progression-free Survival by BICR[a]

Amivantamab + lazertinib reduced the risk of extracranial progression or death by **32%** and improved median PFS by 9 months

MARIPOSA conducted serial brain MRIs on all patients, which is not routinely done in *EGFR*-mutant NSCLC trials
Both median PFS estimates increase if CNS-only first progressions are censored but a consistent benefit is observed



[a]Extracranial PFS was defined as time from randomization to disease progression (detected by extracranial scans) or death. If first progression was solely detected by CNS, these patients were censored at the time of CNS disease progression.
[b]Nominal *P*-value; endpoint was exploratory and not part of hierarchical hypothesis testing.
BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; HR, hazard ratio; mo, months; NE, not estimable; PFS, progression-free survival.

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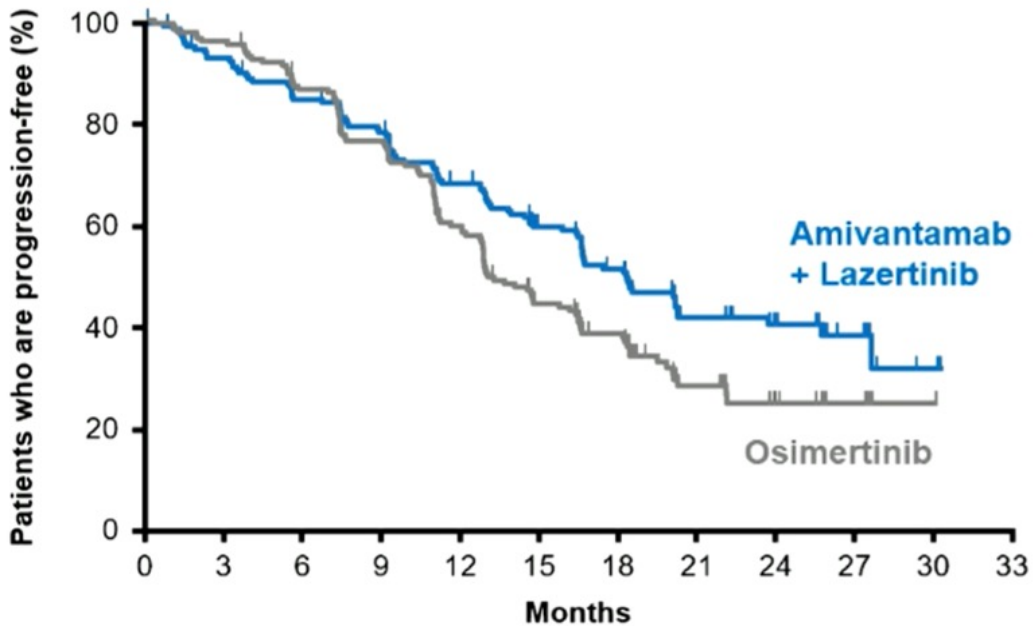
MARIPOSA: PFS by CNS Metastases

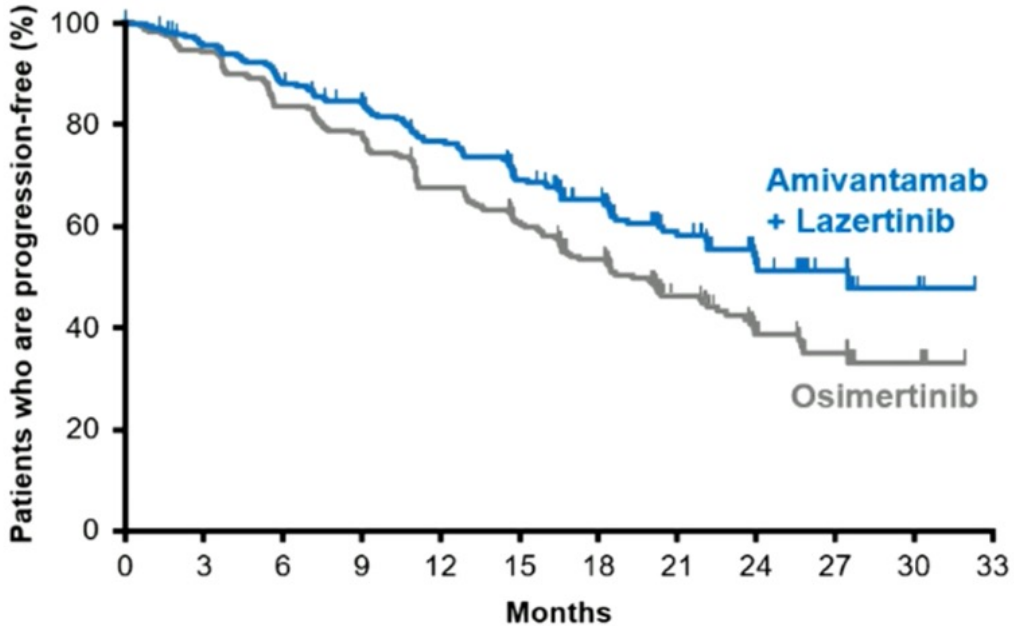
With History of Brain Metastases	Median PFS (95% CI)
Amivantamab + Lazertinib	18.3 mo (16.6–23.7)
Osimertinib	13.0 mo (12.2–16.4)

HR, **0.69** (95% CI, 0.53–0.92)



Without History of Brain Metastases	Median PFS (95% CI)
Amivantamab + Lazertinib	27.5 mo (22.1–NE)
Osimertinib	19.9 mo (16.6–22.9)

HR, **0.69** (95% CI, 0.53–0.89)

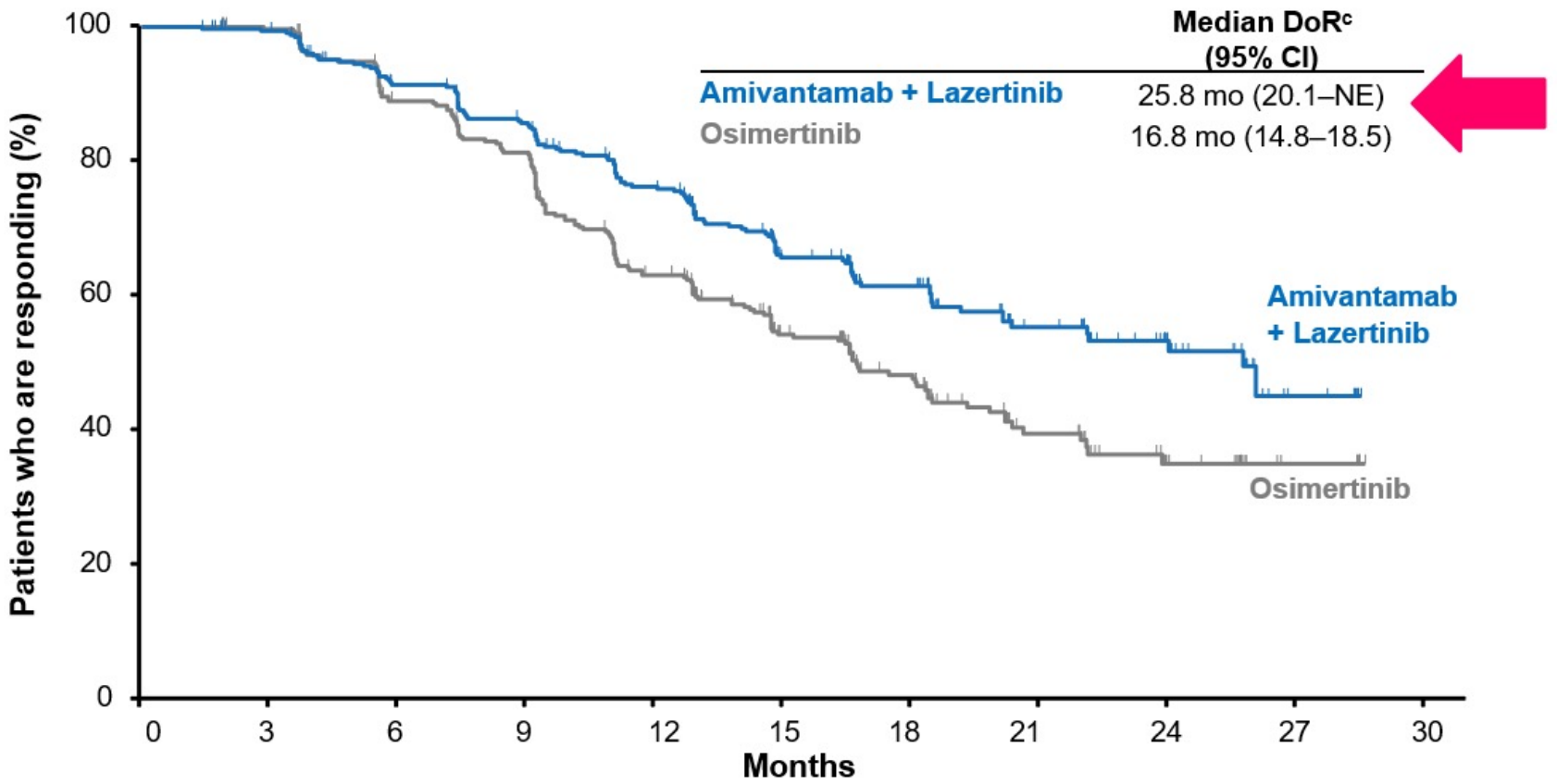


Presented by B. Cho. ESMO 2023. LBA14

ORR and DoR by BICR

- **Amivantamab + lazertinib** improved median DoR by 9 months, suggesting longer time to resistance and progression

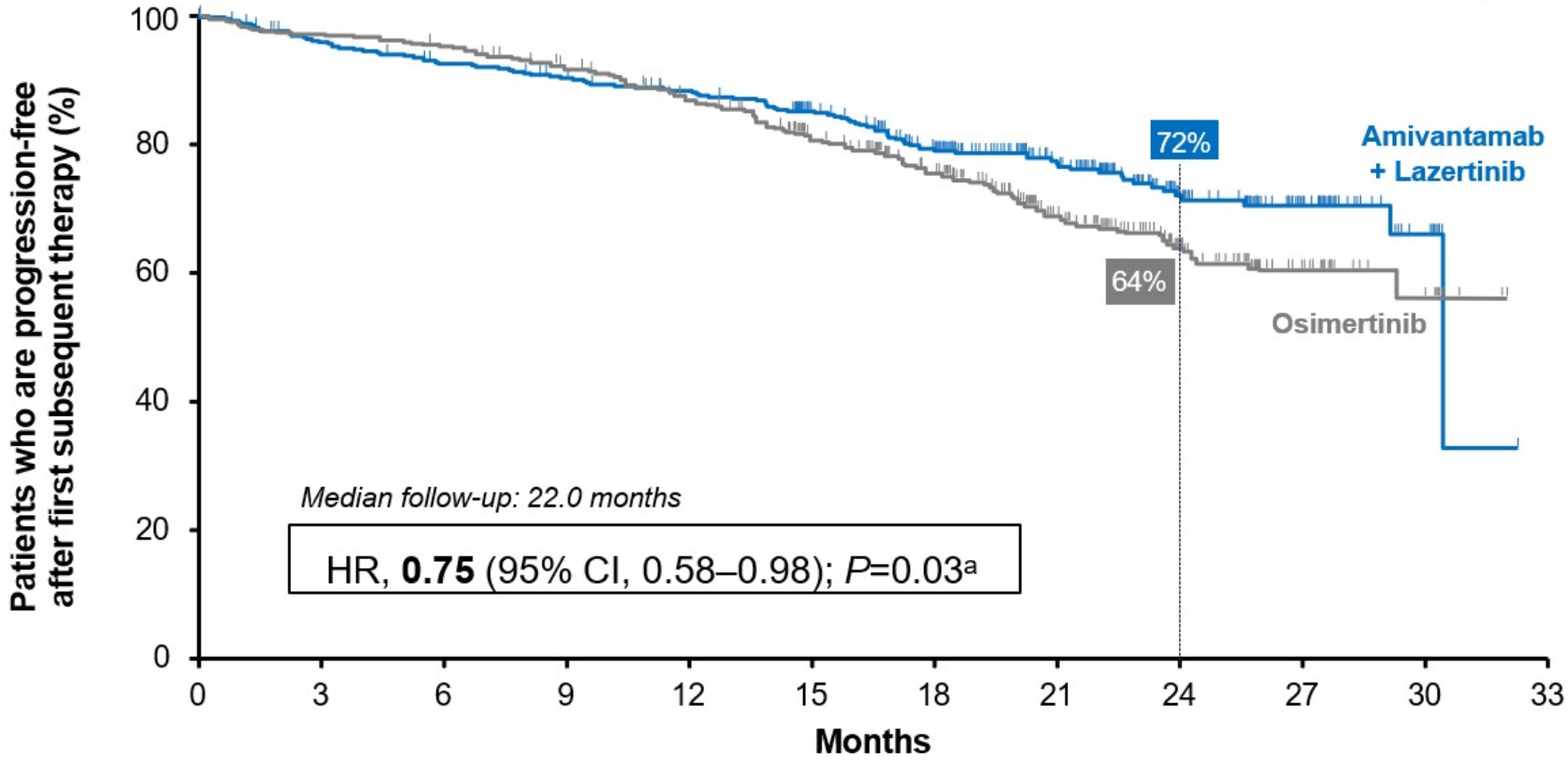
BICR-assessed response, n (%)[a]	Amivantamab + Lazertinib (n=429)	Osimertinib (n=429)
ORR		
All responders	86% (95% CI, 83–89)	85% (95% CI, 81–88)
Confirmed responders	80% (95% CI, 76–84)	76% (95% CI, 71–80)
Best response[b]		
CR	29 (7)	15 (4)
PR	334 (79)	335 (81)
SD	30 (7)	42 (10)
PD	7 (2)	11 (3)
NE/UNK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



[a]No. of patients with measurable disease at baseline by BICR was 421 for amivantamab + lazertinib and 414 for osimertinib. [b]Includes all responders. [c]Among confirmed responders. BICR, blinded independent central review; CI, confidence interval; CR, complete response; DoR, duration of response; mo, months; NE, not estimable; NE/UNK, not evaluable/unknown; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

PFS2: PFS After First Subsequent Therapy[a]

Amivantamab + lazertinib reduced the risk of 2nd disease progression or death by **25%**



Most Common First Subsequent Therapy

Amivantamab + Lazertinib 98 started subsequent therapy	
EGFR TKI monotherapy: 48 (49%)	
Chemotherapy alone: 32 (33%)	
Osimertinib 137 started subsequent therapy	
Chemotherapy alone: 53 (39%)	
EGFR TKI monotherapy: 37 (27%)	

No. at risk

Amivantamab + Lazertinib	429	400	383	370	357	325	268	175	97	47	11	0
Osimertinib	429	415	406	387	358	303	249	153	87	42	12	0

[a]Nominal *P*-value; endpoint not part of hierarchical hypothesis testing. Median estimates, at this time, are unreliable.

CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

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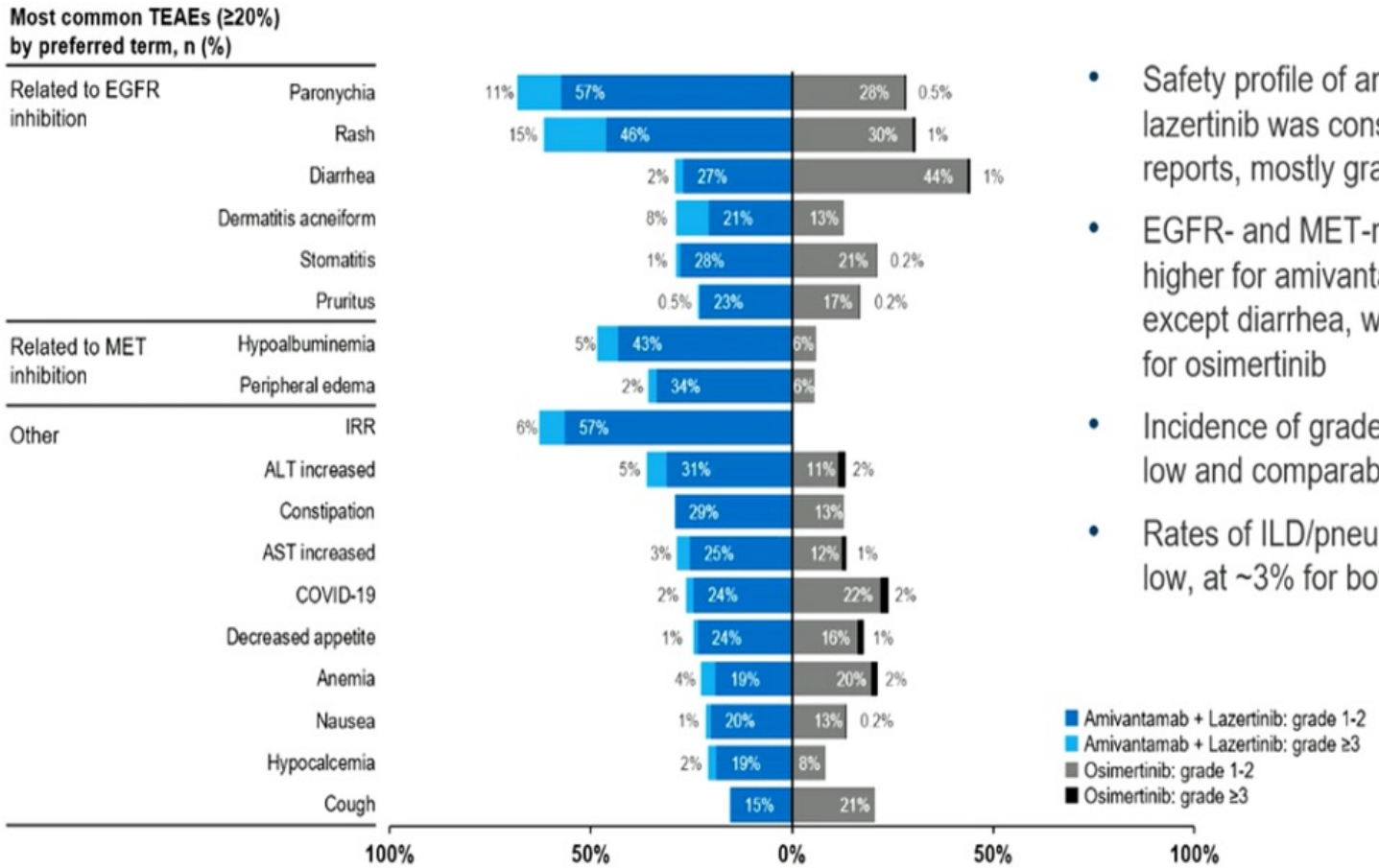
What about toxicity?



- 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

Toxicity
Ami/Laz vs Osimertinib

- IRR: 63% vs 0%
- VTE: 37% vs 9%
- Rash: 61% vs 31%
- Diarrhea: 29% vs 45%
- ILD: 3% vs 3%

Presented by B. Cho. ESMO 2023. LBA14

Adverse Event of Special Interest: VTE[a]

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

- VTE rates were higher for amivantamab + lazertinib
  - Most common preferred terms were pulmonary embolism and deep vein thrombosis
  - Most VTEs were grade 1-2
  - Incidence of grade 4-5 VTEs was low (<1%) and comparable between arms
- Rates of discontinuations due to VTE were low and comparable between arms
- At time of first VTE:
  - Most patients were not on anticoagulants
  - Majority in the amivantamab + lazertinib arm occurred within the first 4 months
- Prophylactic dose anticoagulation is now recommended for the first 4 months of treatment in ongoing trials of amivantamab + lazertinib

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

VTE, venous thromboembolism.

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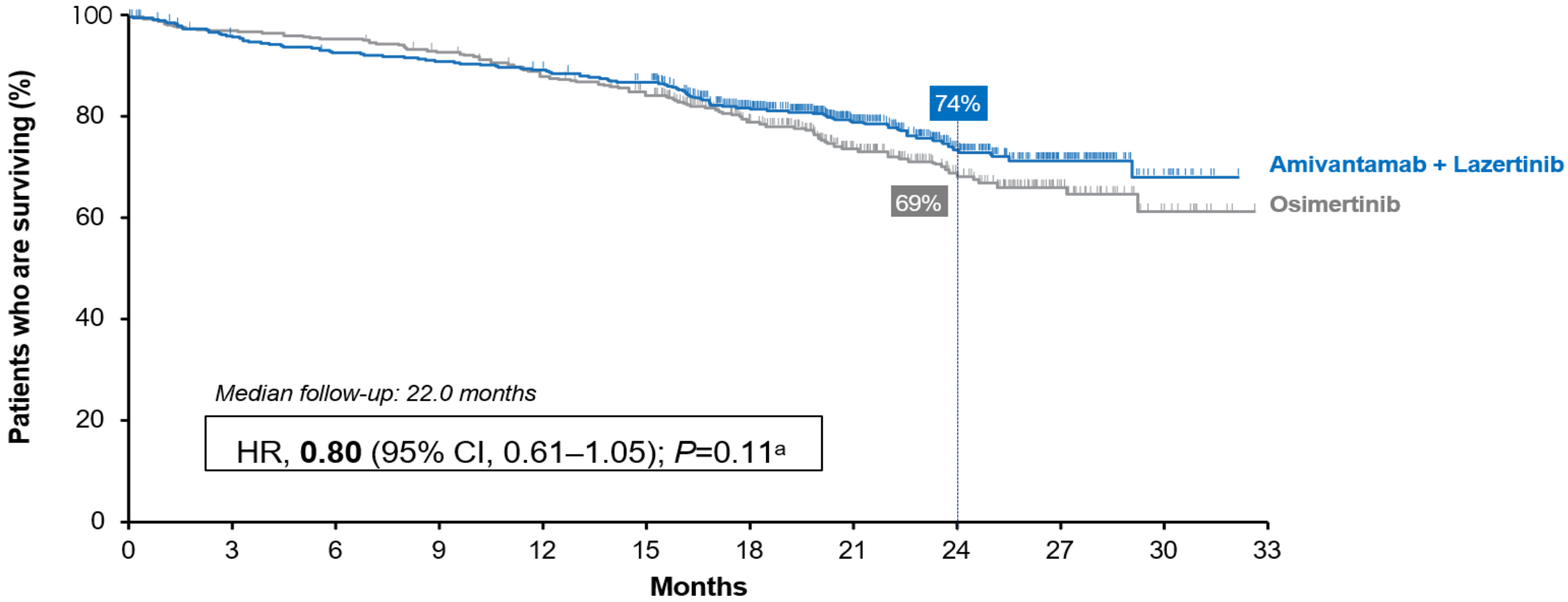
Interim Overall Survival

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



No. at risk												
Amivantamab + Lazertinib	429	403	389	382	374	360	293	201	122	58	14	0
Osimertinib	429	416	409	395	372	349	280	186	110	54	13	0

[a]There were a total of 214 deaths in the amivantamab + lazertinib and osimertinib arms at time of the prespecified interim OS analysis, which represents 25% of all randomized patients and 55% of the ~390 projected deaths for the final OS analysis. Medians at this time are not estimable.

CI, confidence interval; HR, hazard ratio; OS, overall survival.

MECHANISMS OF RESISTANCE IN ADVANCED OR METASTATIC SETTING

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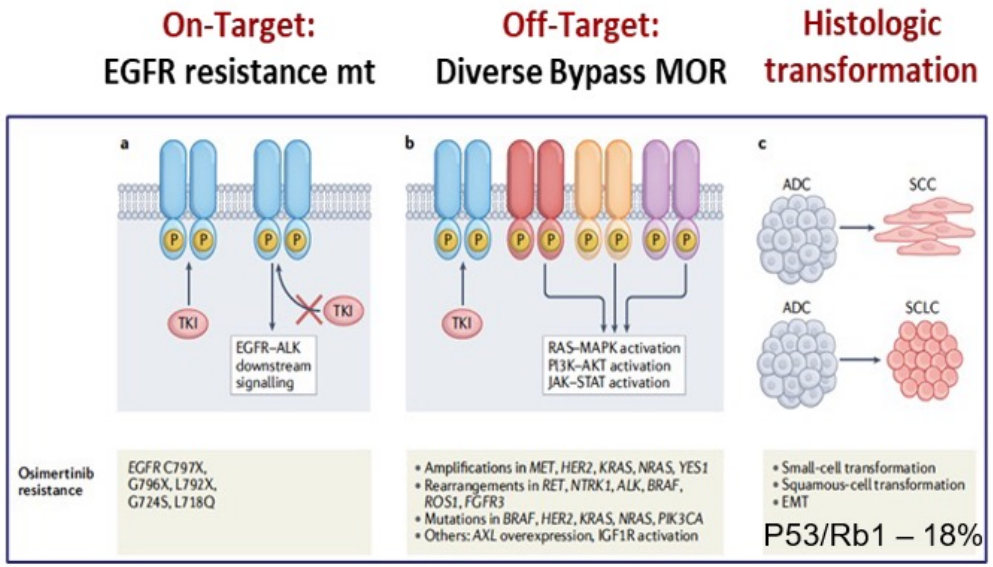
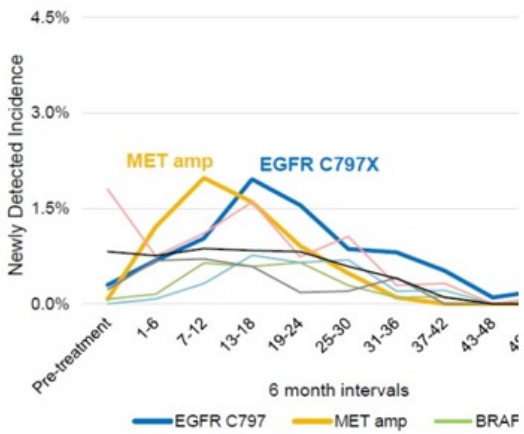
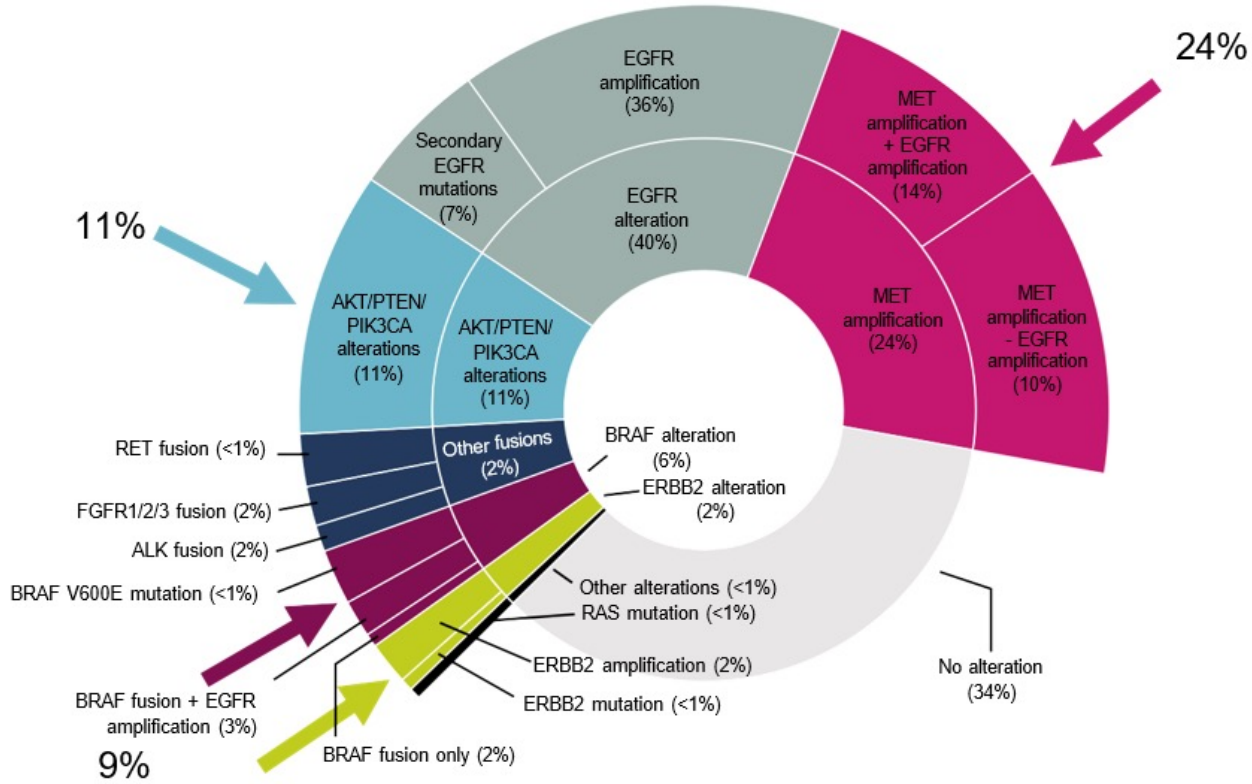
Broad Mechanisms of Resistance to EGFR-TKI and Temporal Occurrence



Cooper AS, et al, Nat Rev Clin Oncol 2022



Genomics from Orchard: N-174 tissue samples/concurrent Plasma ctDNA



- Pre-Existing Commutations Mediating Resistance (Impact for locally advanced/early-stage treatment)
- Resistance to Immunotherapy

S. Ramalingam. WCLC 2022

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MARIPOSA-2: Phase 3 Study Design

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. 2023 ESMO Congress, Madrid, Spain; LBA15

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Demographic and Baseline Disease Characteristics

Characteristic, n (%)	Chemotherapy (n=263)	Amivantamab-Chemotherapy (n=131)	Amivantamab-Lazertinib-Chemotherapy (n=263)
Median age, years (range)	62 (31–85)	62 (36–84)	61 (23–83)
Female	157 (60)	81 (62)	168 (64)
Race			
Asian	127 (48)	63 (48)	125 (48)
White	123 (47)	60 (46)	129 (49)
Other[a]	13 (5)	8 (6)	9 (3)
ECOG PS 1	162 (62)	76 (58)	171 (65)
History of smoking	95 (36)	41 (31)	87 (33)
History of brain metastases	120 (46)	58 (44)	120 (46)
No prior brain radiation	61 of 120 (51)	24 of 58 (41)	56 of 120 (47)
Osimertinib line of therapy[b]			
First	181 (69)	97 (74)	185 (70)
Second	82 (31)	34 (26)	77 (29)
EGFR mutation type			
Ex19del	183 (70)	89 (68)	165 (63)
L858R	79 (30)	42 (32)	98 (37)

Note: percentages may not sum to 100 due to rounding.

[a]Other includes American Indian or Alaska Native, Black or African American, multiple, and unknown.
[b]One patient in the amivantamab-lazertinib-chemotherapy arm received osimertinib later than second-line and is not included in the table.

ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletions.

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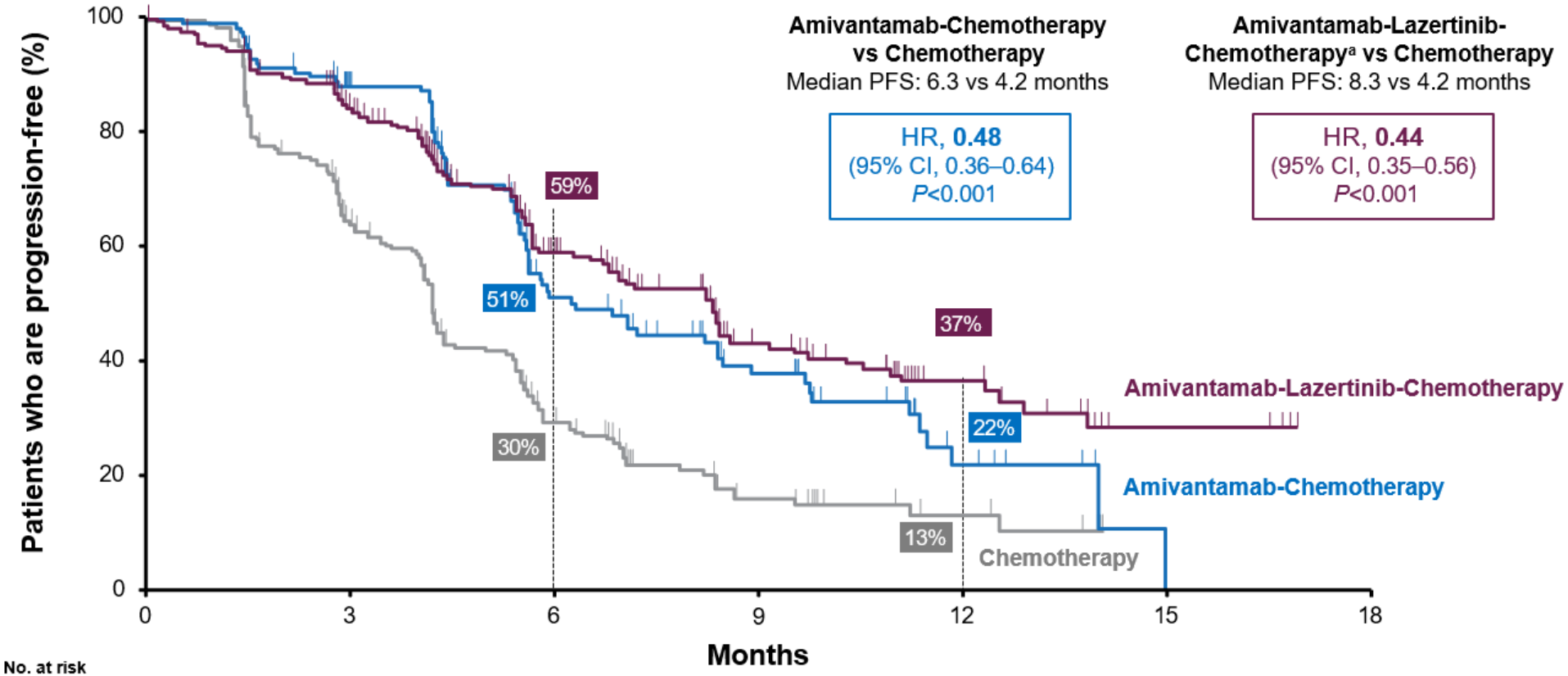
Primary Endpoint: Progression-free Survival by BICR

At a median follow-up of 8.7 months, **amivantamab-chemotherapy** and **amivantamab-lazertinib-chemotherapy** reduced the risk of progression or death by **52%** and **56%**, respectively



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

Consistent PFS benefit by investigator: HR, 0.41 (8.2 vs 4.2 mo; *P*<0.001[b]) & HR, 0.38 (8.3 vs 4.2 mo; *P*<0.001[b])

[a]Amivantamab-lazertinib-chemotherapy arm includes all patients regardless of the dosing regimen received. [b]Nominal *P*-value; endpoint not part of hierarchical hypothesis testing.

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

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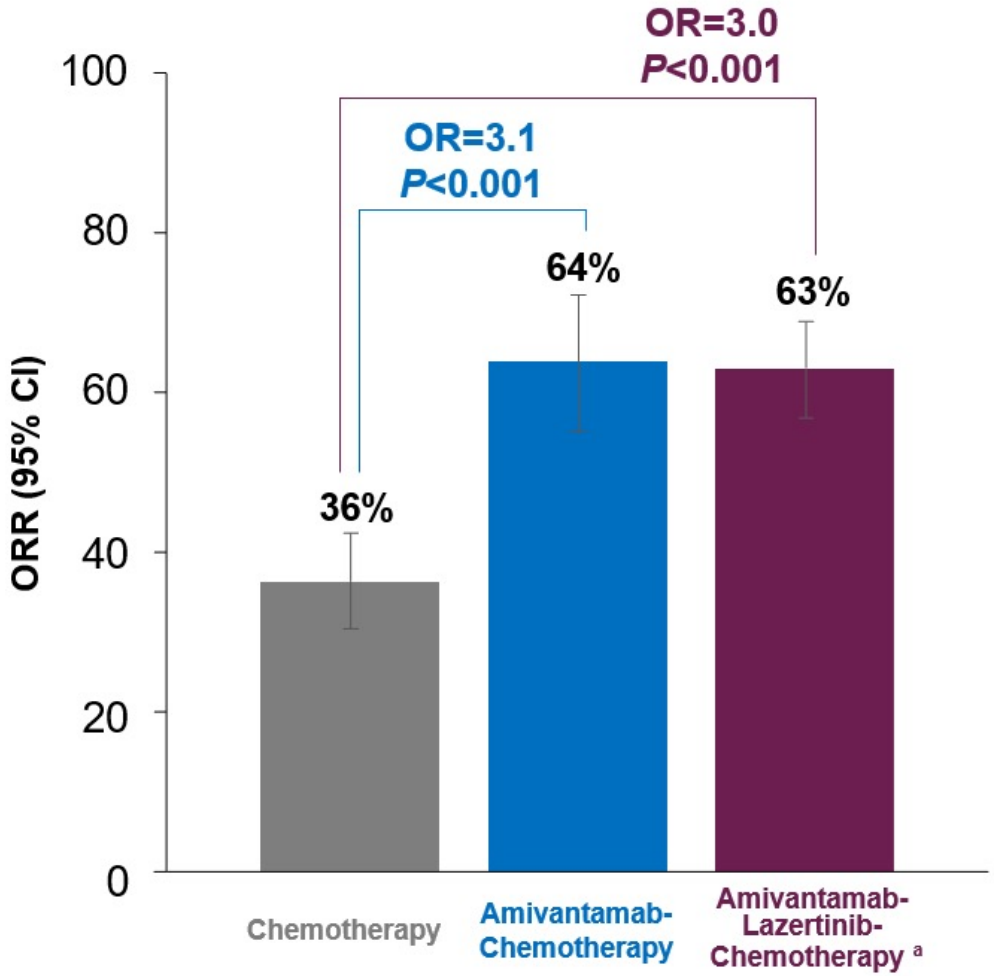
ORR and DoR by BICR



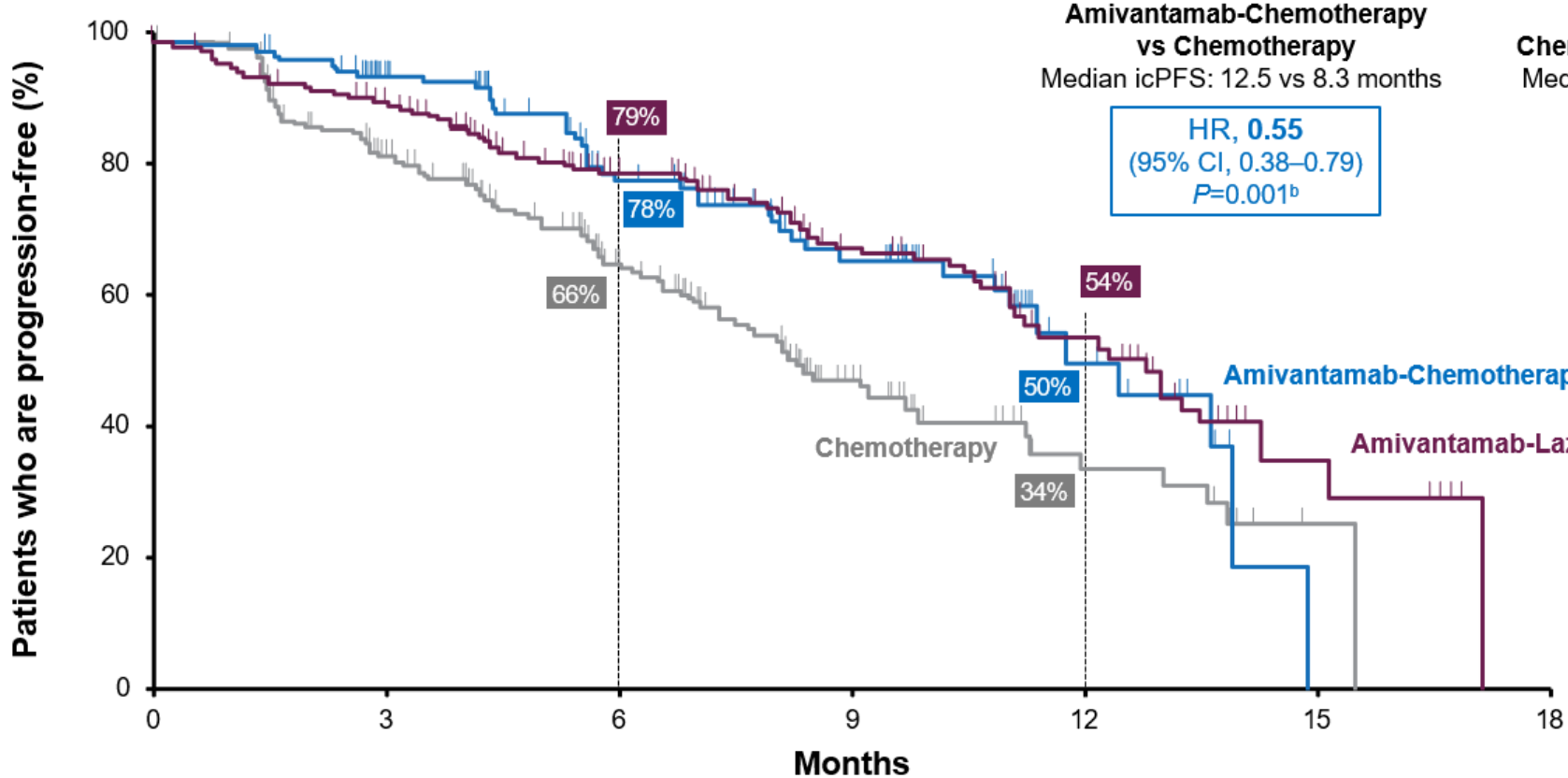
BICR-assessed Response, n (%)[b]	Chemotherapy (n=263)	Amivantamab-Chemotherapy (n=131)	Amivantamab-Lazertinib-Chemotherapy (n=263)
Best Response			
CR	1 (0.4)	2 (2)	6 (2)
PR	93 (36)	81 (62)	157 (61)
SD	82 (32)	30 (23)	61 (24)
PD	52 (20)	10 (8)	14 (5)
NE/UNK	32 (12)	7 (5)	21 (8)
Median DoR[c]	5.6 mo (95% CI, 4.2–9.6)	6.9 mo (95% CI, 5.5–NE)	9.4 mo (95% CI, 6.9–NE)

[a]Amivantamab-lazertinib-chemotherapy arm includes all patients regardless of the dosing regimen received. [b]No. of patients with measurable disease at baseline by BICR was 260 for chemotherapy, 130 for amivantamab-chemotherapy, and 259 for amivantamab-lazertinib-chemotherapy. [c]Among confirmed responders.

BICR, blinded independent central review; CI, confidence interval; CR, complete response; DoR, duration of response; mo, months; NE, not estimable; NE/UNK, not evaluable/unknown; OR: odds ratio; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Intracranial Progression-free Survival by BICR

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



Amivantamab-Chemotherapy vs Chemotherapy
Median icPFS: 12.5 vs 8.3 months
HR, **0.55** (95% CI, 0.38–0.79) *P*=0.001[b]

Amivantamab-Lazertinib-Chemotherapy[a] vs Chemotherapy
Median icPFS: 12.8 vs 8.3 months
HR, **0.58** (95% CI, 0.44–0.78) *P*<0.001[b]

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

[a]Amivantamab-lazertinib-chemotherapy arm includes all patients regardless of the dosing regimen received. [b]Nominal *P*-value; endpoint not part of hierarchical hypothesis testing.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; icPFS, intracranial progression-free survival.

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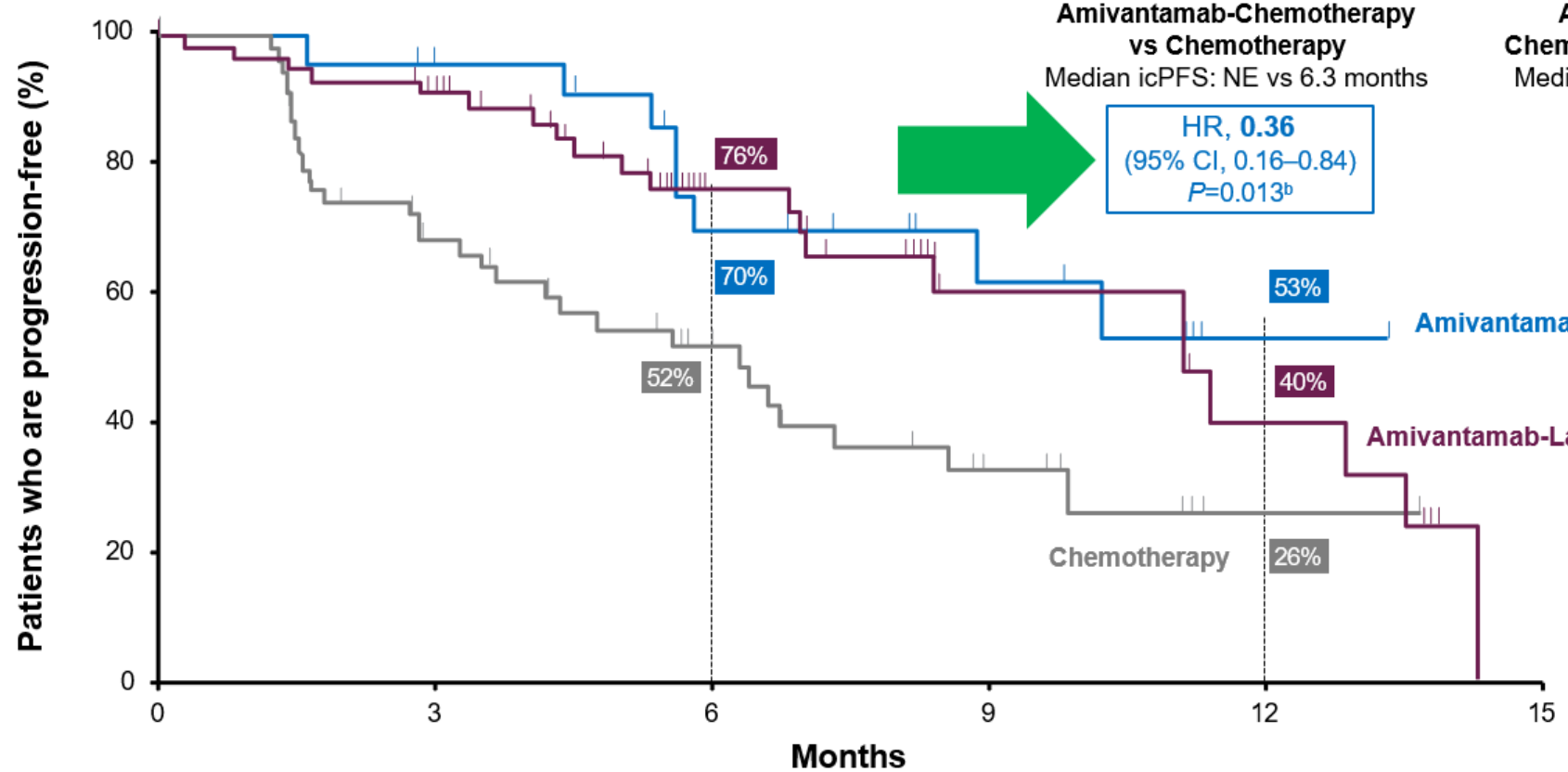
Intracranial Progression-free Survival by BICR Among Patients With a History of Brain Metastases and No Prior Brain Radiotherapy



Amivantamab-Chemotherapy vs Chemotherapy
Median icPFS: NE vs 6.3 months
HR, **0.36**
(95% CI, 0.16–0.84)
P=0.013[b]

Amivantamab-Lazertinib-Chemotherapy[a] vs Chemotherapy
Median icPFS: 11.1 vs 6.3 months
HR, **0.44**
(95% CI, 0.25–0.79)
P=0.005[b]

No. at risk						
Amivantamab-Chemotherapy	24	20	13	8	1	0
Amivantamab-Lazertinib-Chemotherapy	56	42	22	10	5	0
Chemotherapy	61	32	17	7	1	0

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

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Safety Profile

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)

[a]Amivantamab-lazertinib-chemotherapy arm includes all patients regardless of the dosing regimen received. [b]Grouping includes the following preferred terms: rash, dermatitis acneiform, rash maculo-papular, erythema, acne, rash pruritic, rash erythematous, rash macular, drug eruption, folliculitis, dermatitis, skin lesion, rash pustular, papule, rash follicular, exfoliative rash, pustule, rash papular, skin exfoliation. [c]Grouping includes the following preferred terms: pulmonary embolism, deep vein thrombosis, embolism, renal vein thrombosis, venous thrombosis limb, venous thrombosis, embolism venous, jugular vein thrombosis, superficial vein thrombosis, thrombophlebitis, thrombosis. [d]Identified by the standardized MedDRA query for "Haemorrhage Terms (Excl Laboratory Terms)".

AE, adverse event; AESI, AE of special interest; EGFR, epidermal growth factor receptor; ILD, interstitial lung disease (includes pneumonitis); TEAE, treatment-emergent AE; VTE, venous thromboembolism.

- Amivantamab-containing arms had higher rates of EGFR- and MET-related AEs
- Neutropenia and thrombocytopenia:
  - Mostly occurred during cycle 1
  - Low rates of febrile neutropenia (2%, 2%, and 8%)
  - Low rates of grade 3-4 bleeding[d] (0%, 1%, and 3%)
- VTE highest in amivantamab-lazertinib-chemotherapy arm
  - No grade 5 events
  - Rates of discontinuation due to VTE were low (0%, 1%, and 0.4%)
- Incidence of ILD was low in all arms (<3%)

HER-3: Patritumab deruxtecan in EGFR-mutated NSCLC with PD on Prior EGFR-TKI

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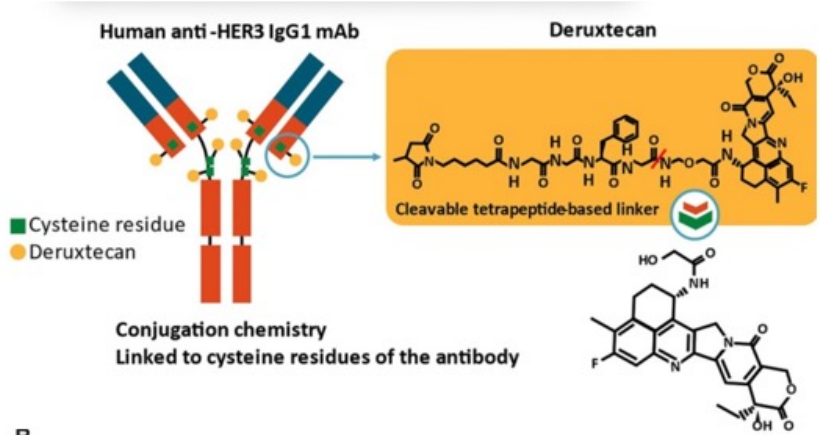

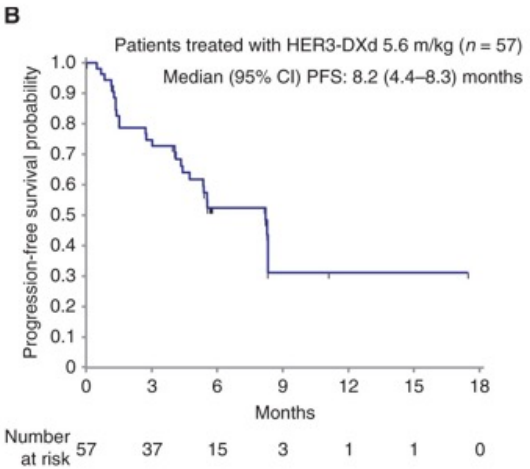

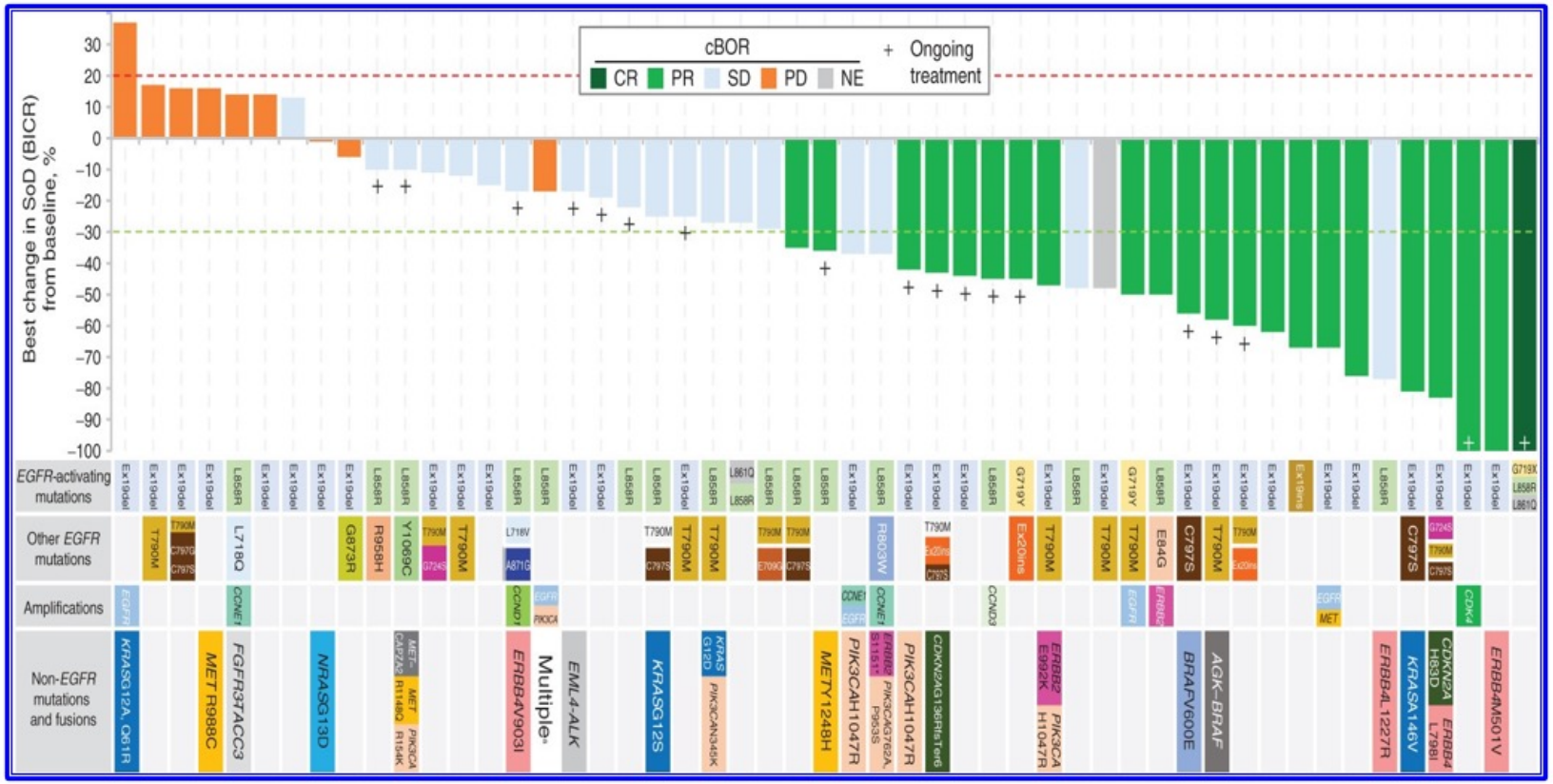

P. Janne et al. Cancer Discovery 2022.

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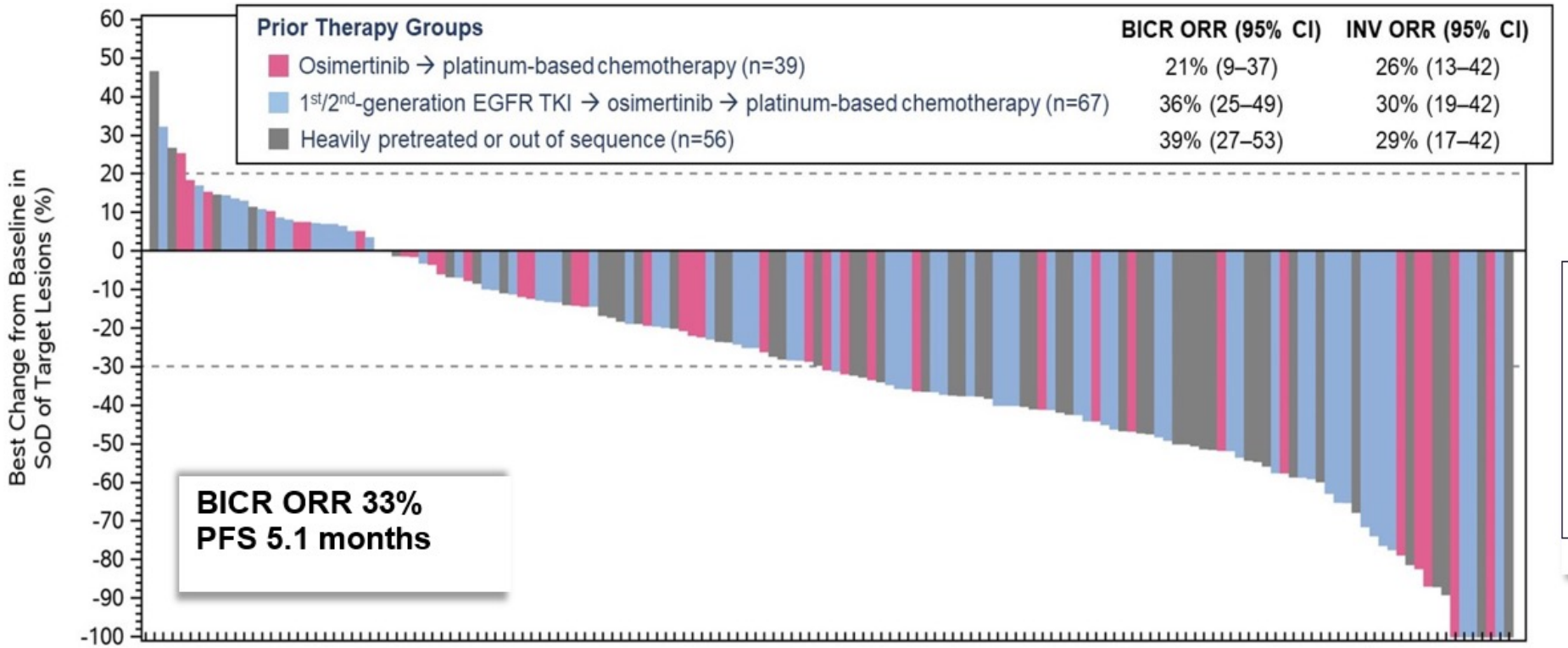
Amivantamab + Lazertinib

EGFR/MET Bispecific + 3rd Gen EGFR TKI

CHRYSALIS-2



In CHRYSALIS-1, MET/EGFR IHC score correlated with response (n=20)

ORR 90% if
IHC+ ORR 10%
if IHC-

Shu et al. ASCO 2022. #9006.; Bauml et al ASCO 2021 #9006.

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Summary/Therapies Post-Osimertinib with "MET" As A Target

Outcomes	Amivantanab + Lazertinib N = 45	Amivantanab + Lazertinb PD Chemo N = 162	Osimertinib + Savolitinib N = 69	Teliso-V + Osimertinib N = 25
Trial	CHRYSALIS	CHRYSALIS-2	TATTON (B1)	
Target	EGFR/MET	EGFR/MET	EGFR/MET	MET Expression
ORR	36%	33%	30%	58%
mDOR (months)	9.6 (95% CI: 5.3-NR)	9.6 (95% CI: 7.0-NR)	7.9 (95% CI: 6.9-11.2)	Not reported
mPFS (months)	4.9 (95% CI: 3.7-9.5)	5.1 (95% CI: 4.2-6.9)	5.4 (95% CI: 4.1-8.0)	Not reported
Grade ≥ 3 TRAE	16%	38%	57%	32%

L Sequist et al. Lancet Oncology 2020
BC Cho et al. Presented at ASCO 2021
CA Shu et al. Presented at ASCO 2022
JW Goldman et al. Presented at ASCO 2022
ES Santos. Presented at PeerView Prog June 2023

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Other Bypass Tracts That Are Potentially Actionable

ALK Fusions

Osimertinib + Alectinib
6 months DoR Reports Case

BRAF Fusions

Osimertinib + Trametinib
Response, D/c at 5 mo (Tox) Case Report

BRAF V600E

Osimertinib + Dabrafenib/Trametinib
7-8 months DoR

Osimertinib + Vemurafenib
7+ months DoR Reports Case

Jebbink et al. MA02.07. WCLC 2021; Schrock JTO 2018; Offin et al JCP Precis Oncol. 2018; Ribero et al, npj precision oncology 2021; Huang et al JTO 2019; Sun et al Thorac Cancer 2022; Dagogo-Jack et al. JTO. 2019
J. Rotow et al. WCLC 2021
Z. Piotrowska et al. Cancer Discovery 2018.

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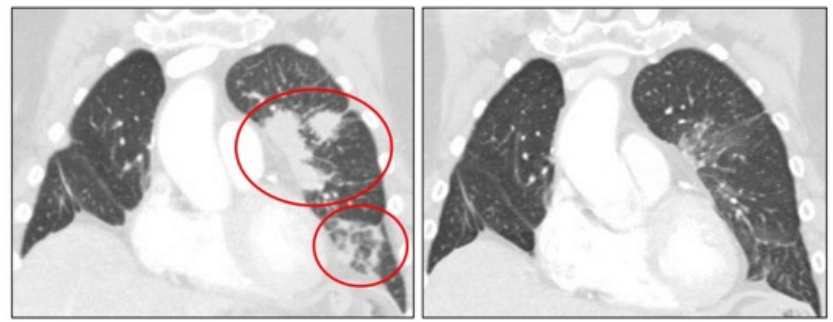
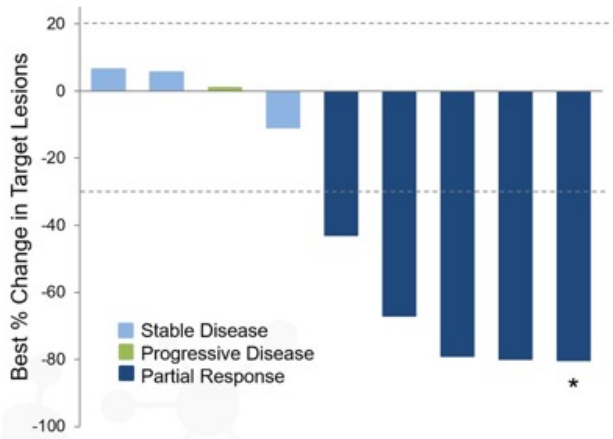
Osimertinib + RET TKI in Acquired Resistance Mediated by RET Fusion

Pralsetinib

B



Selpercatinib



Best Response (n=10)	
Objective Response n (%)	**5 (50%)**
Partial Response*	5 (50%)
Stable Disease	3 (30%)
Progressive Disease	2 (20%)
Disease Control Rate n (%)	**8 (80%)**
Median Depth of Response (%)	**-43%**

*One partial response unconfirmed

One patient with clinical progression without radiographic evaluation not shown

Conclusions

- ADAURA established a new standard of care for patients whose tumors harbor EGFR exon 19 or L858R mutations in the adjuvant setting (pathological stage IB-IIIA).
- FLAURA 2 and MARIPOSA results are challenging Osimertinib as sole 1st line monotherapy (FLAURA) for patients with EGFRex19del or L858R mutations in the metastatic setting.
- For patients with CNS disease and L858R, Osimertinib plus chemotherapy followed by maintenance Osimertinib/Pemetrexed represents a better option than Osimertinib alone (FLAURA 2).
- MARIPOSA study also showed that Ami/Chemo combination has CNS protectant effect.
- Amivantamab-chemotherapy and Amivantamab/Lazertinib/chemotherapy improved PFS in patients progressing on Osimertinib (MARIPOSA-2).
- Until today, there is no standard regimen for patients progressing on Osimertinib. Mechanism of resistance are variable (EGFR-dependent, EGFR-independent [bypass track] and histologic transformation).
- What could be an approved regimen for Osi resistance in 2024? Patritumab (anti-Her3)? or Ami/Chemo (MARIPOSA-2)? or Ami/Lazertinib (CHRYSALIS)? or selection by driven bypass track (MET, ALK, RET, etc)? or other ADC (e.g., TROP2)?

THANK YOU

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