Best Approaches for First Line EGFRm NSCLC

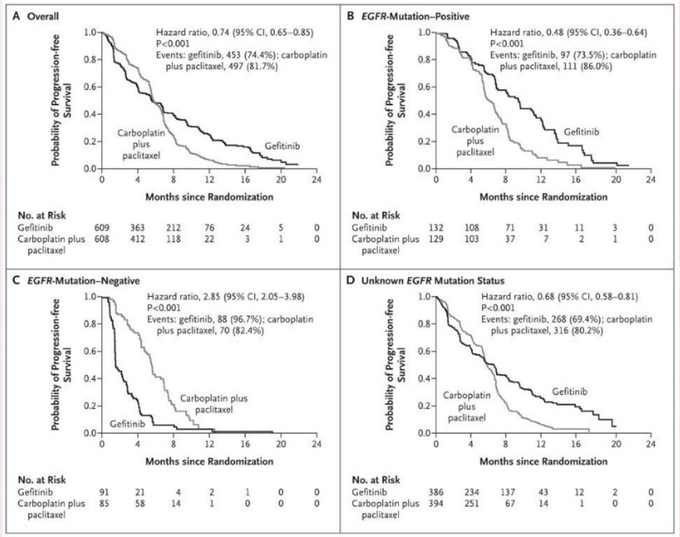
Masters in Thoracic Oncology Summit 2023

November 17, 2023

Joshua K. Sabari, MD
Assistant Professor of Medicine
Thoracic Medical Oncology
Perlmutter Cancer Center

NYU Langone Health

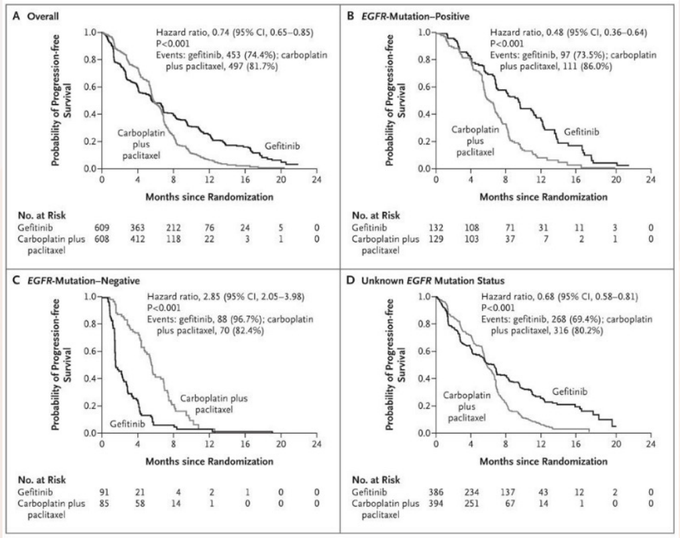
Where are we going?

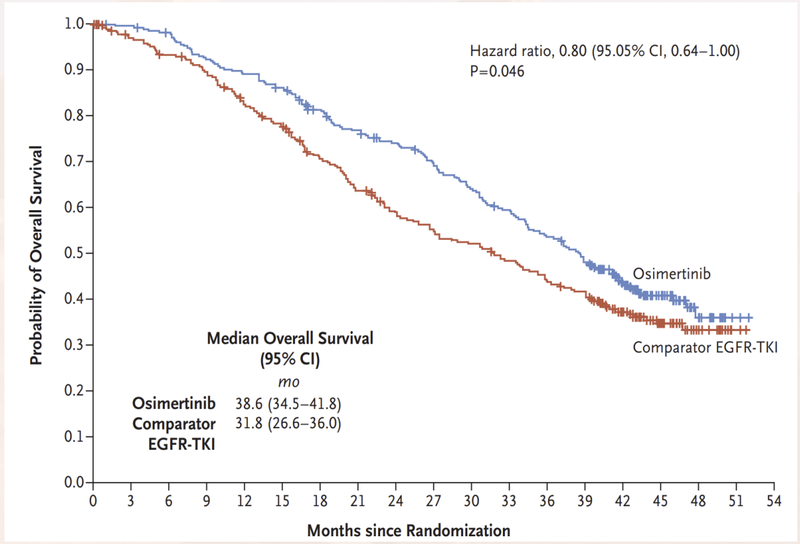


IPASS 2009

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

Where are we going?



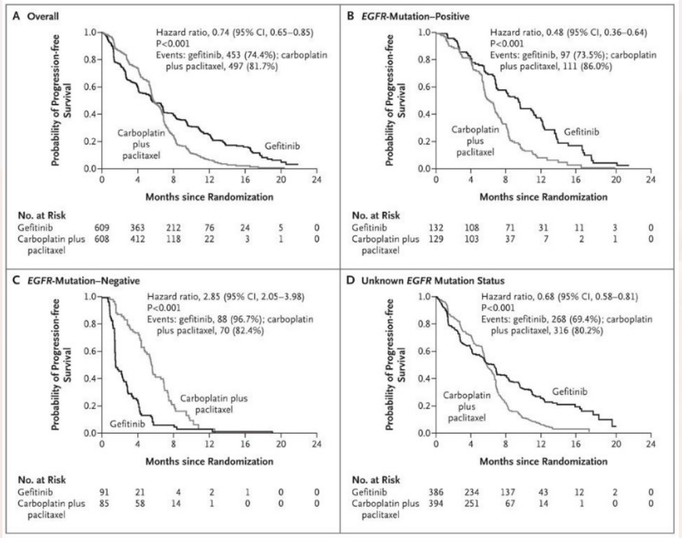


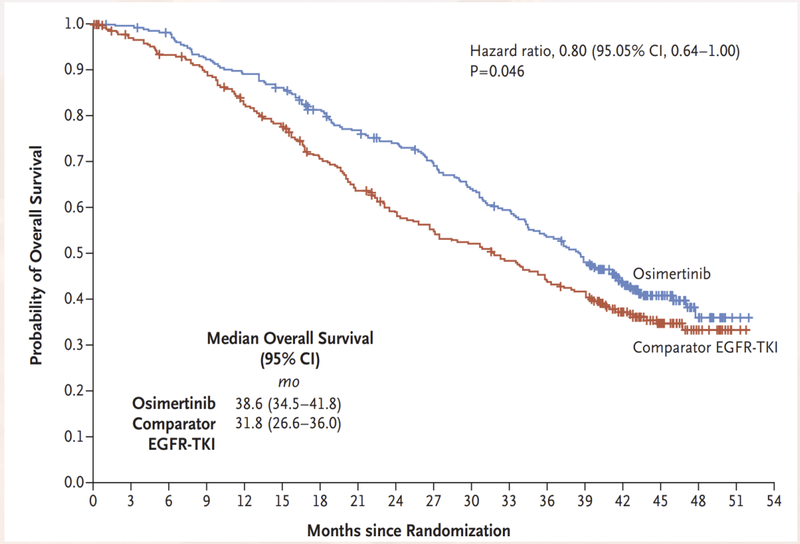
IPASS 2009

FLAURA 2018

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

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

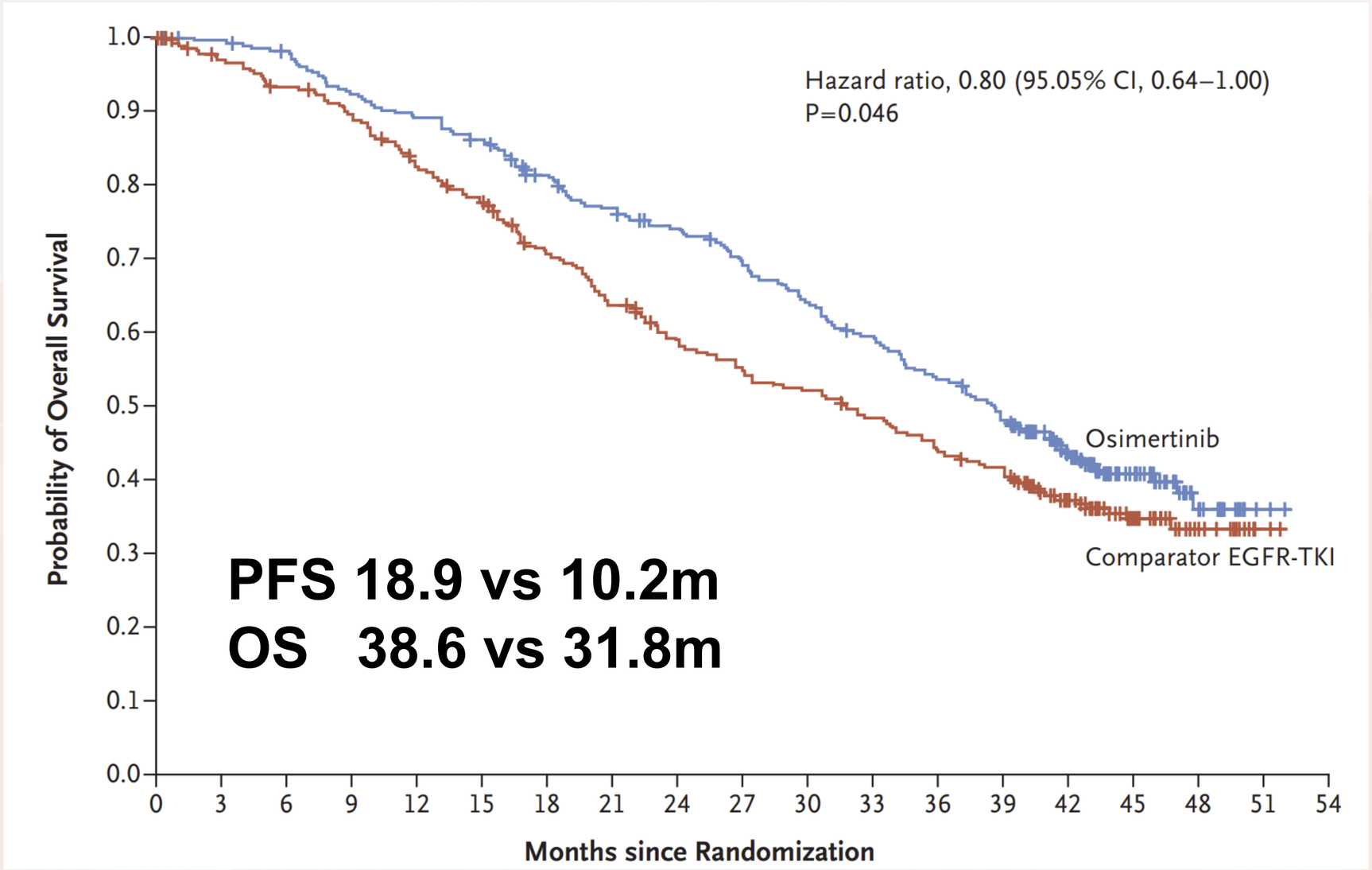
3rd Generation EGFR TKI

Study	Region	N	Drug	RR	PFS mon (HR)	OS mon (HR)	SAE %	Dose R %
FLAURA	Global	556	Osimertinib	80% vs 76%	18.9 vs 10.2 (0.46)	38.6 vs 31.8 (0.8)	8	4
AENEAS	China	429	Aumolertinib	74% vs 72%	19.2 vs 9.9 (0.46)	NA	22	3.7
FURLONG	China	358	Furmonertinib	89% vs 84%	20.8 vs 11.1 (0.44)	NA	11	3
Betta trial	China	362	Befotertinib	76% vs 78%	22.1 vs 13.8 (0.49)	NA	20.3	31.3
LASER 301	Global	393	Lazertinib	76% vs 76%	20.6 vs 9.7 (0.45)	NA	26	21

3rd Generation EGFR TKI

Study	Region	N	Drug	RR	PFS mon (HR)	OS mon (HR)	SAE %	Dose R %
FLAURA	Global	556	Osimertinib	80% vs 76%	18.9 vs 10.2 (0.46)	38.6 vs 31.8 (0.8)	8	4
AENEAS	China	429	Aumolertinib	74% vs 72%	19.2 vs 9.9 (0.46)	NA	22	3.7
FURLONG	China	358	Furmonertinib	89% vs 84%	20.8 vs 11.1 (0.44)	NA	11	3
Betta trial	China	362	Befotertinib	76% vs 78%	22.1 vs 13.8 (0.49)	NA	20.3	31.3
LASER 301	Global	393	Lazertinib	76% vs 76%	20.6 vs 9.7 (0.45)	NA	26	21

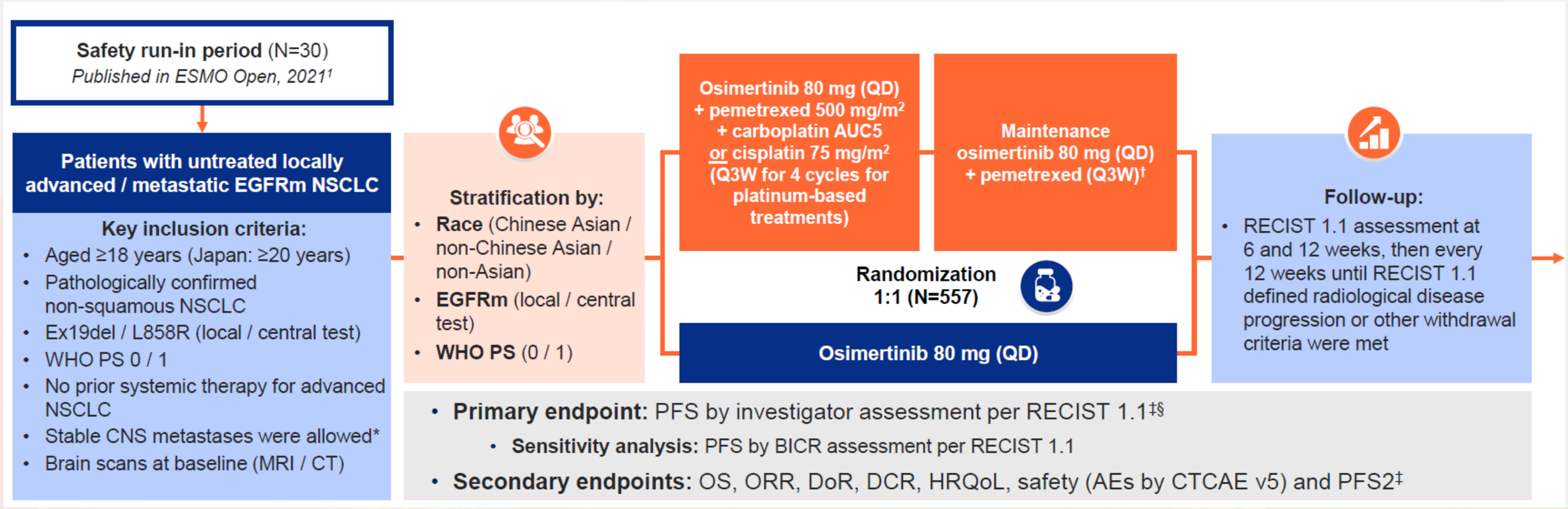
FLAURA: Osimertinib vs Gefitinib/Erlotinib



FLAURA Soria JC et al NEJM 2018; Ramalingan S et al NEJM 2020

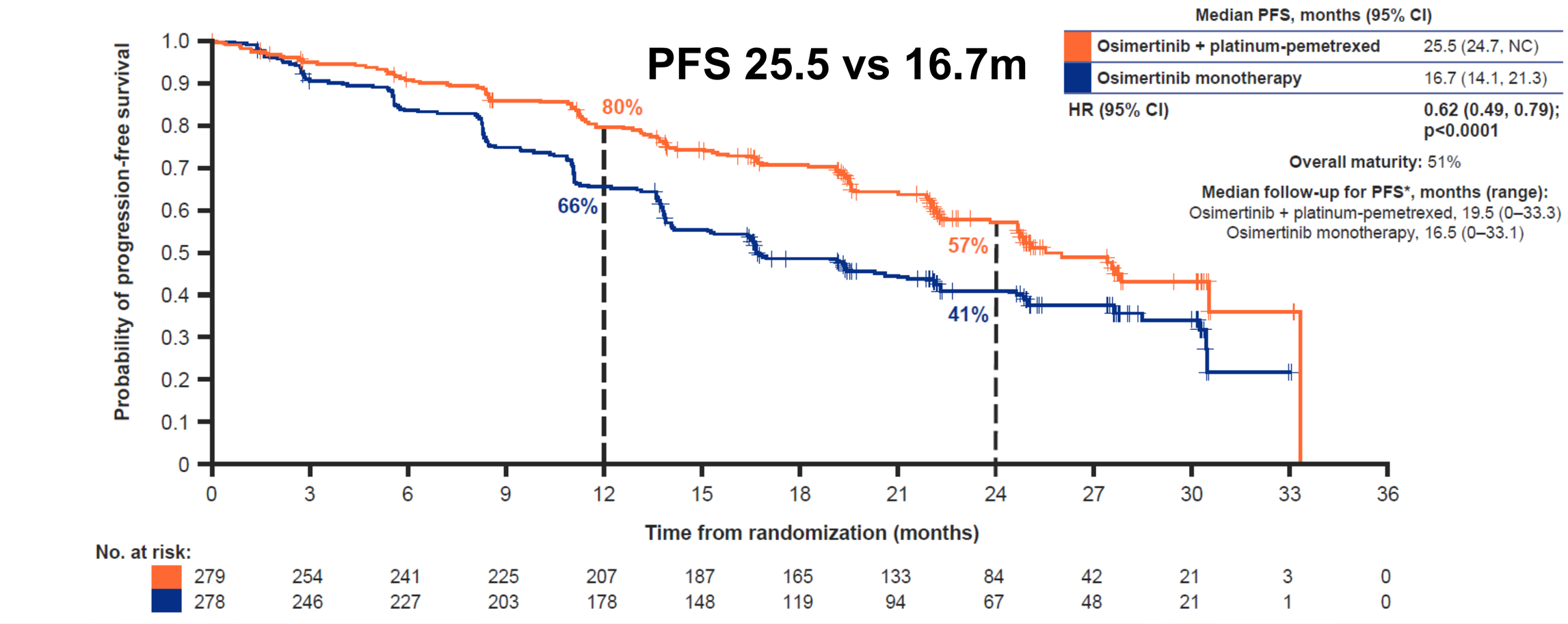
FLAURA2: 1L Osimertinib + Chemotherapy vs Osimertinib

MaTOS™
Masters in Thoracic Oncology Summit
Albuquerque, New Mexico | November 16 - 19, 2023



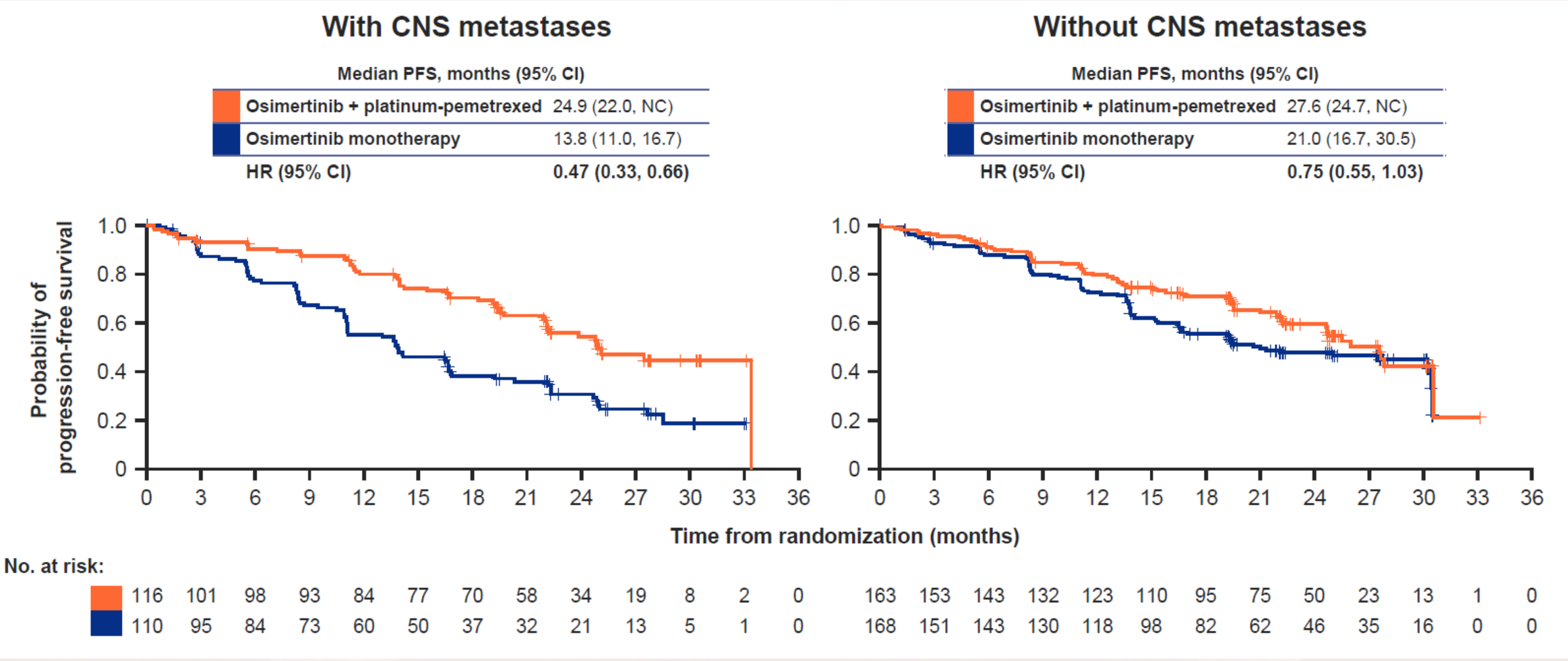
Presented by P. Janne, IASLC WCLC 2023, PL03.13

FLAURA2: PFS per investigator



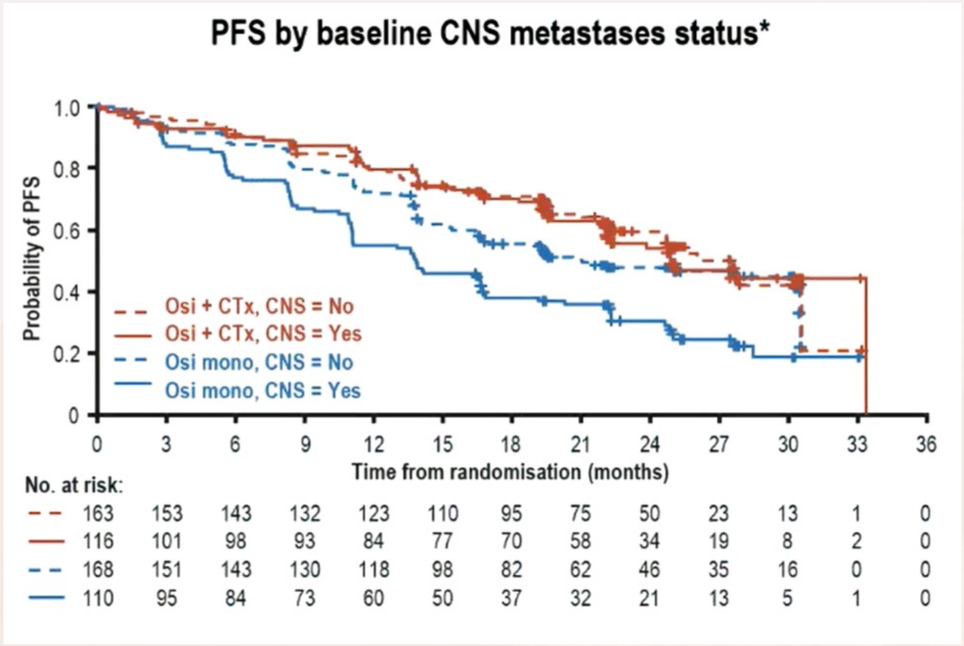
Presented by P. Janne, IASLC WCLC 2023, PL03.13

FLAURA2: PFS per investigator by CNS metastases

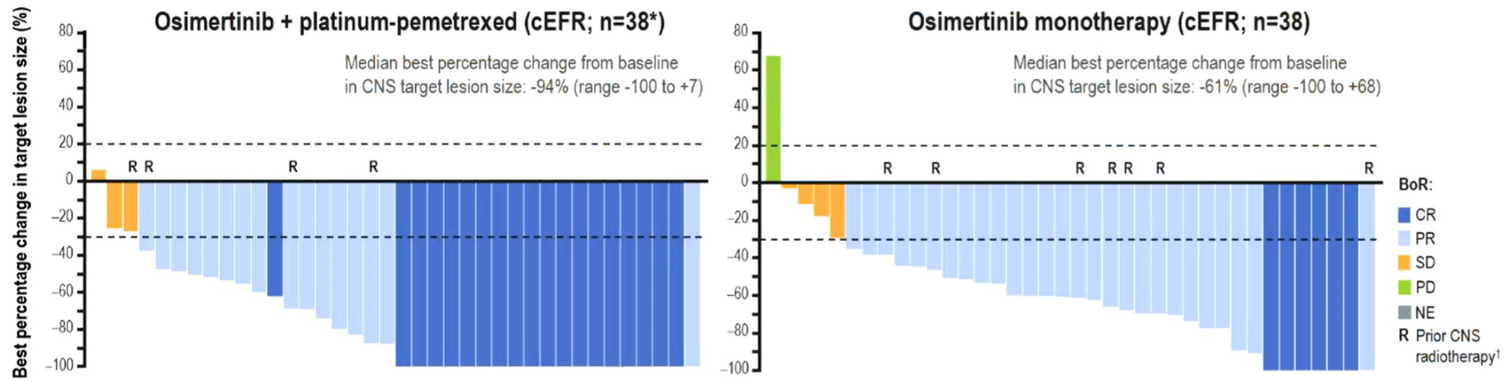


Presented by P. Janne, IASLC WCLC 2023, PL03.13

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

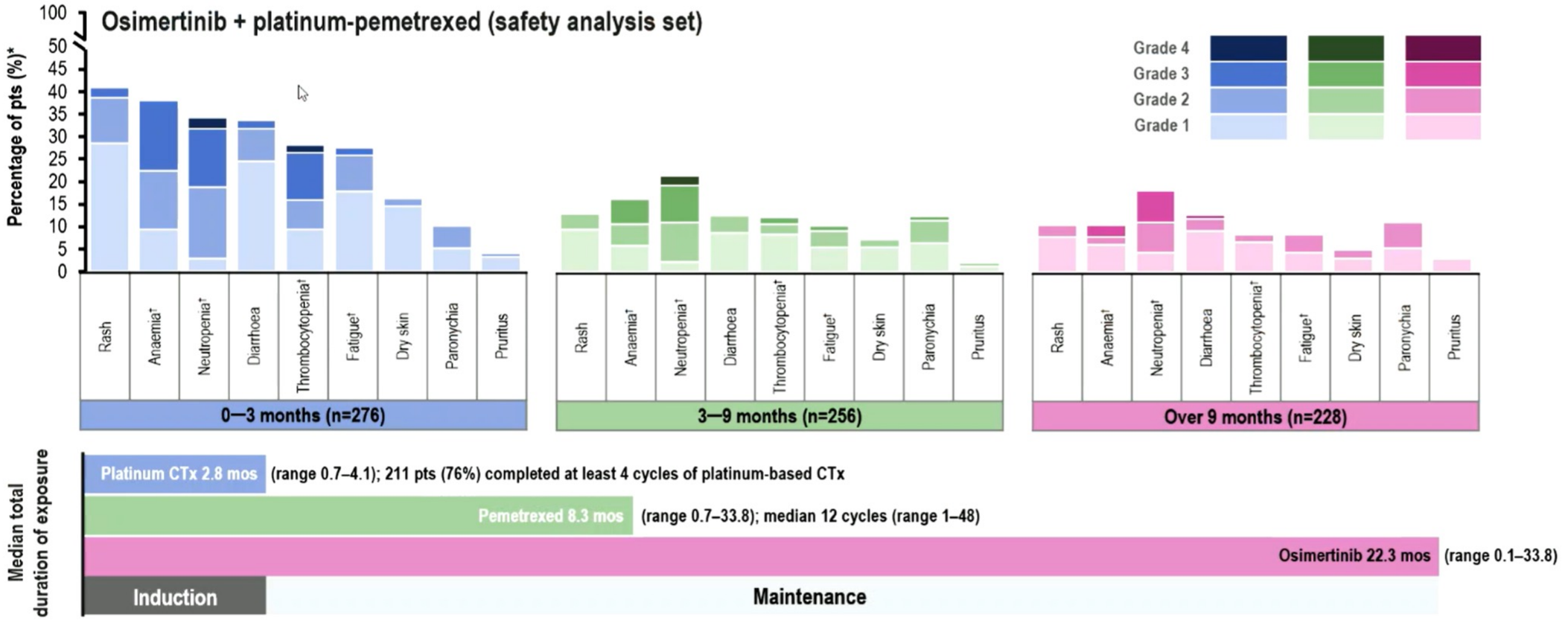
Measurable CNS lesions: CR rate 16% vs 48%

Presented Planchard et al. ESMO 2023 Abstract LBA68

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%)



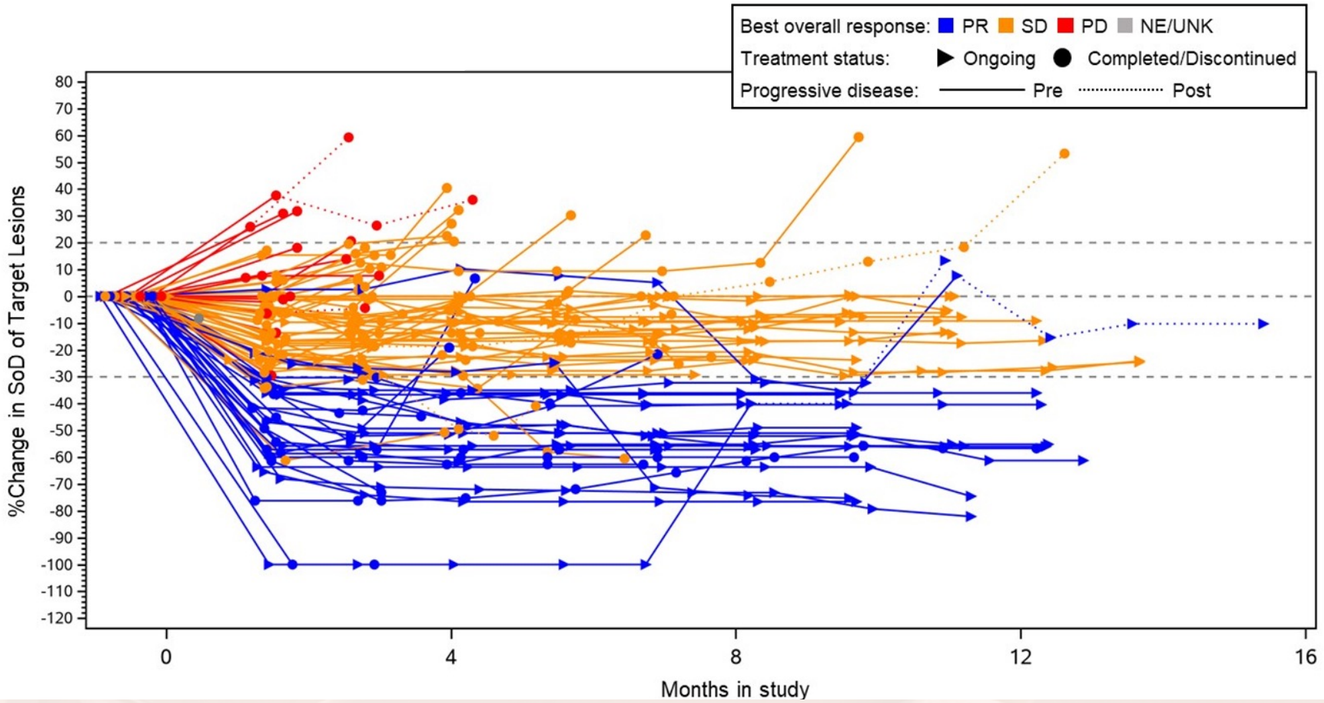
Presented Planchard et al. ESMO 2023 Abstract LBA68

FLAURA2: Unanswered Questions

- Overall Survival?
- Is benefit of addition of chemotherapy to Osimertinib worth the risk/increased toxicity?
  - Subgroups: CNS mets, EGFR L8585R, co-mutations
- Is benefit of addition of chemotherapy to Osimertinib better than other combination strategies?
  - 4th Generation EGFR TKI
  - MET targeting agents (TKI, bispecifics)
  - ADCs, e.g. patritumab deruxtecan (HER3 targeting ADC)
- Resistance mechanisms and persister cell populations
  - Helena Yu Shedder Study Ongoing

CHRYSALIS-2: 2L Amivantamab + Lazertinib post progression on Osimertinib

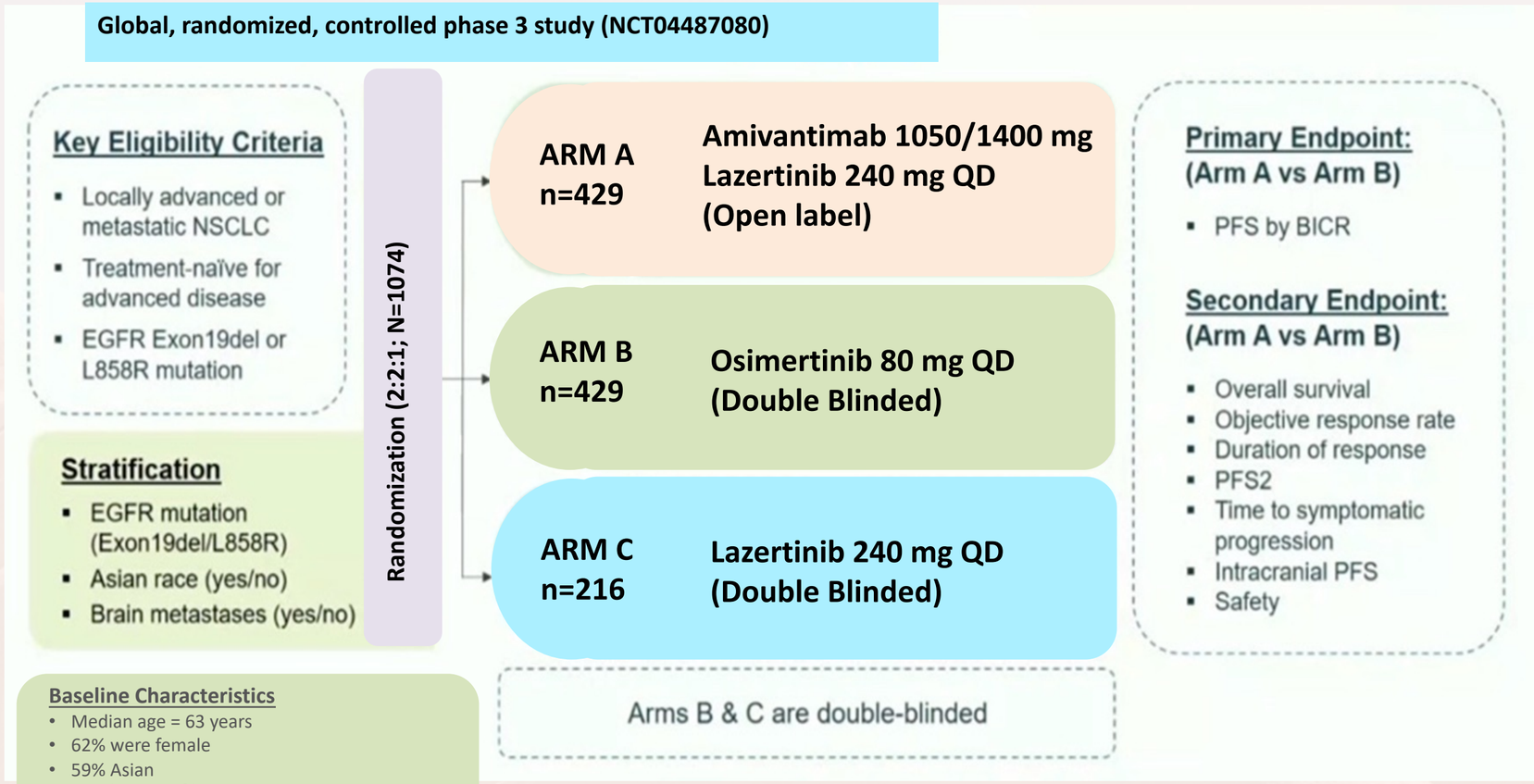
	n=101
ORR	30% (95% CI, 21–40)
Median DOR	10.8 months (95% CI, 5.5–NE)
CBR[b]	69% (95% CI, 59–78)
Median PFS	5.7 months (95% CI, 4.0–8.2)
Median OS	Not estimable



ORR 30%
MET IHC+ 61%
MET IHC- 14%

Besse B et al ASCO 2023 Abstract 9013

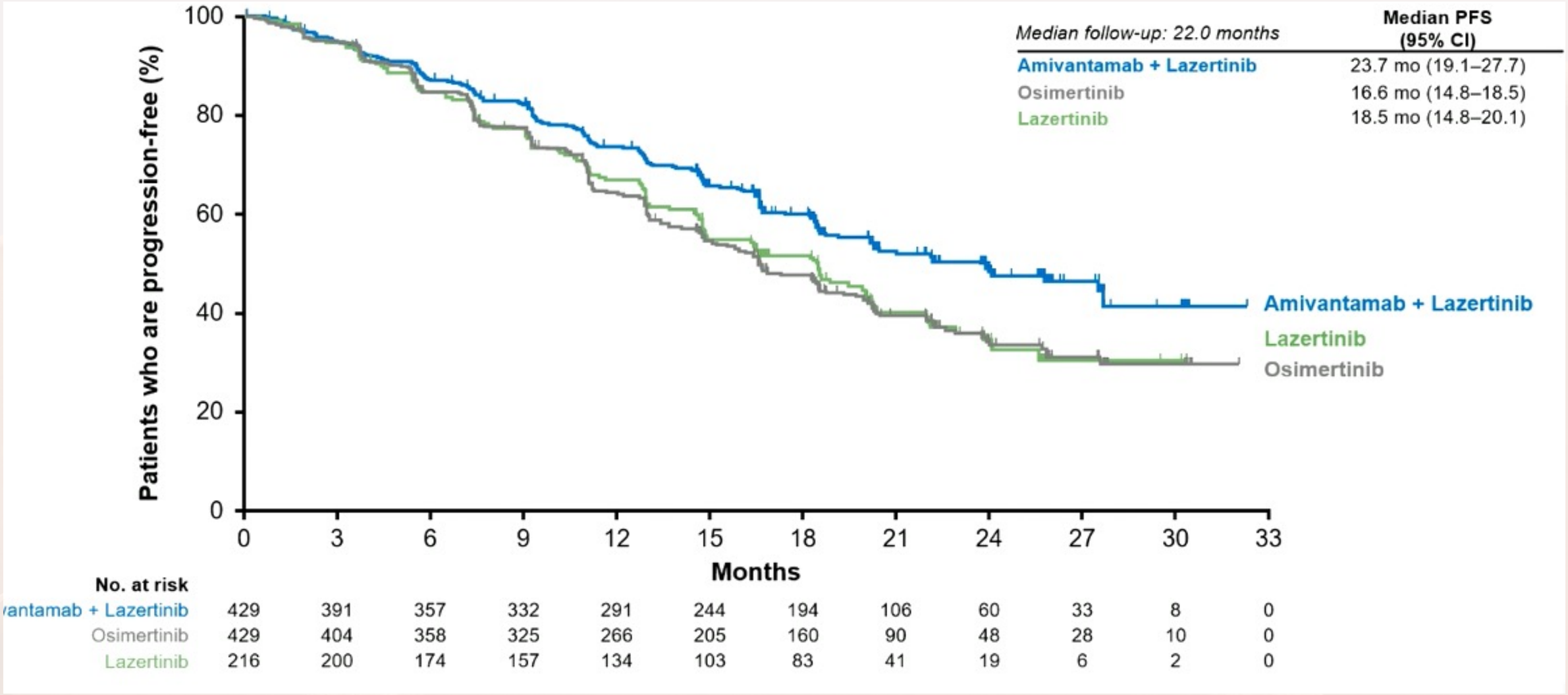
MARIPOSA: 1L Amivantamab + Lazertinib



-- 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

MARIPOSA: PFS by BICR

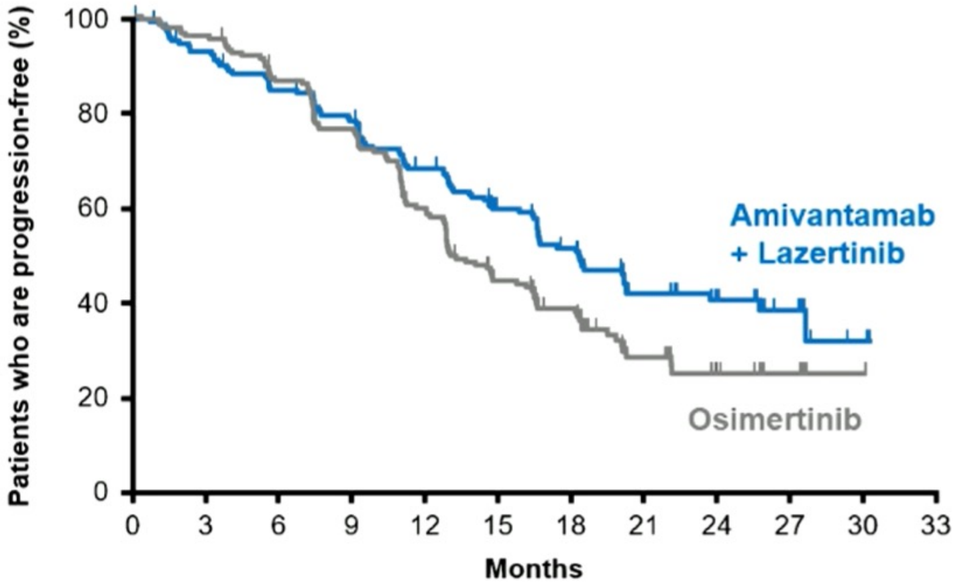


Presented by B. Cho. ESMO 2023. LBA14

MARIPOSA: PFS by CNS metastases

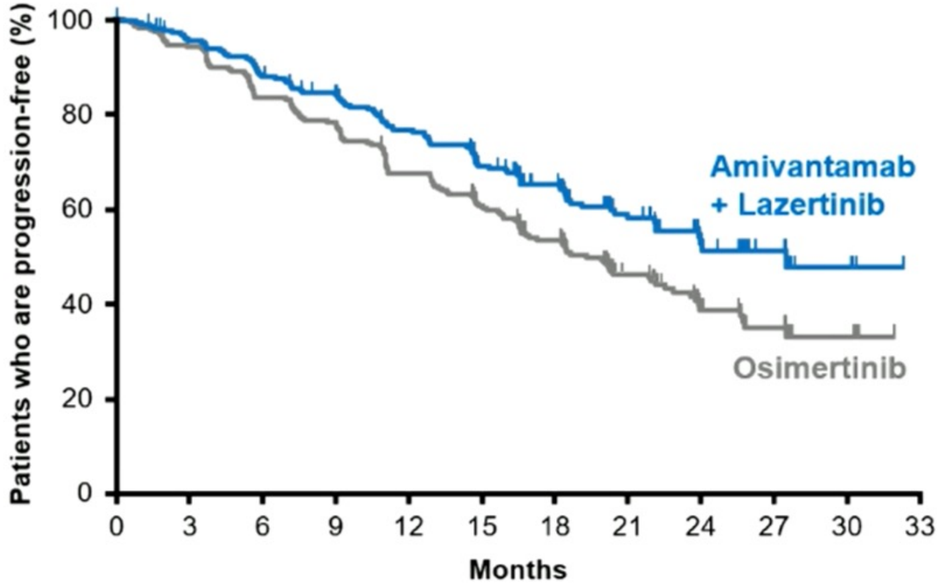
With History of Brain Metastases	Median PFS (95% CI)
Amivantamab + Lazertinib	18.3 mo (16.6–23.7)
Osimertinib	13.0 mo (12.2–16.4)

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)

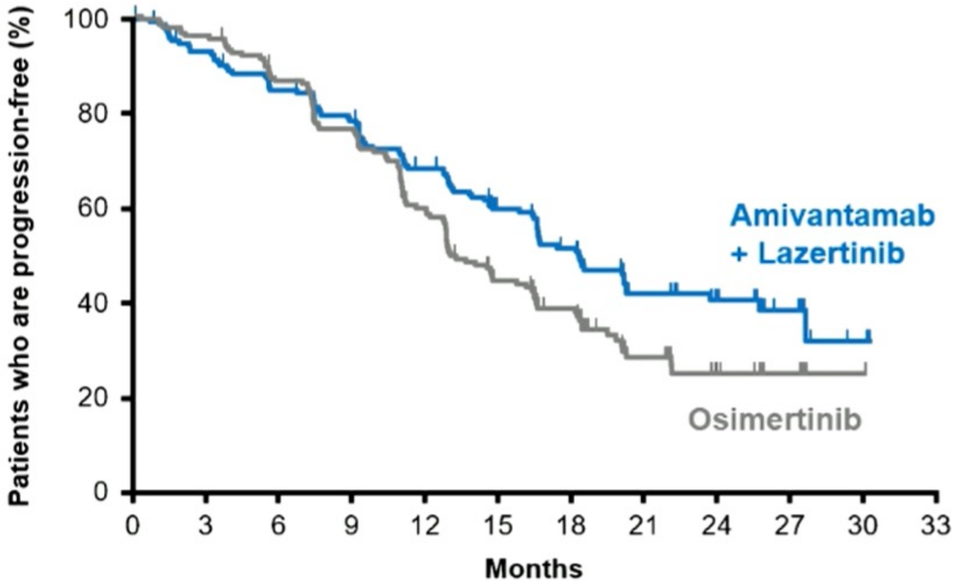


Presented by B. Cho. ESMO 2023. LBA14

MARIPOSA: PFS by CNS metastases

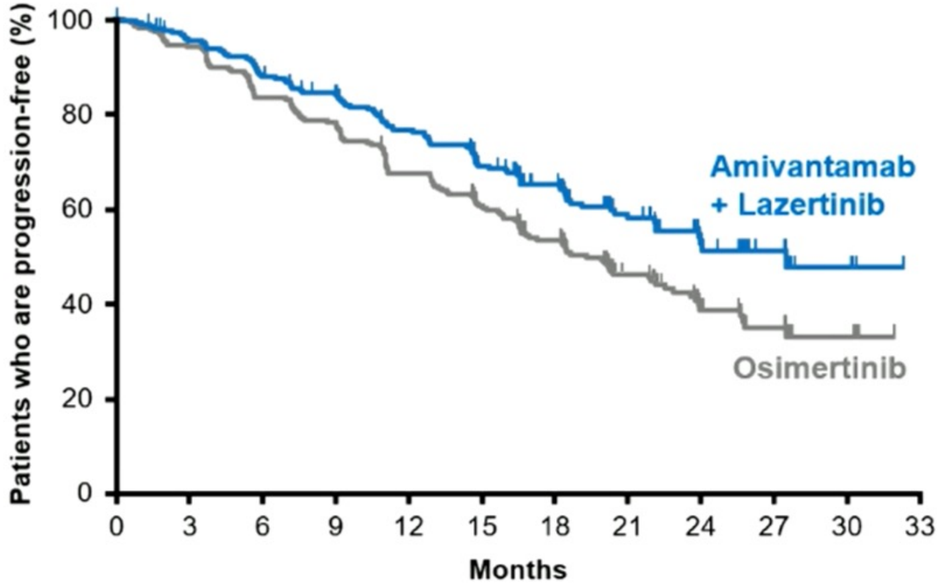
With History of Brain Metastases	Median PFS (95% CI)
Amivantamab + Lazertinib	18.3 mo (16.6–23.7)
Osimertinib	13.0 mo (12.2–16.4)

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)

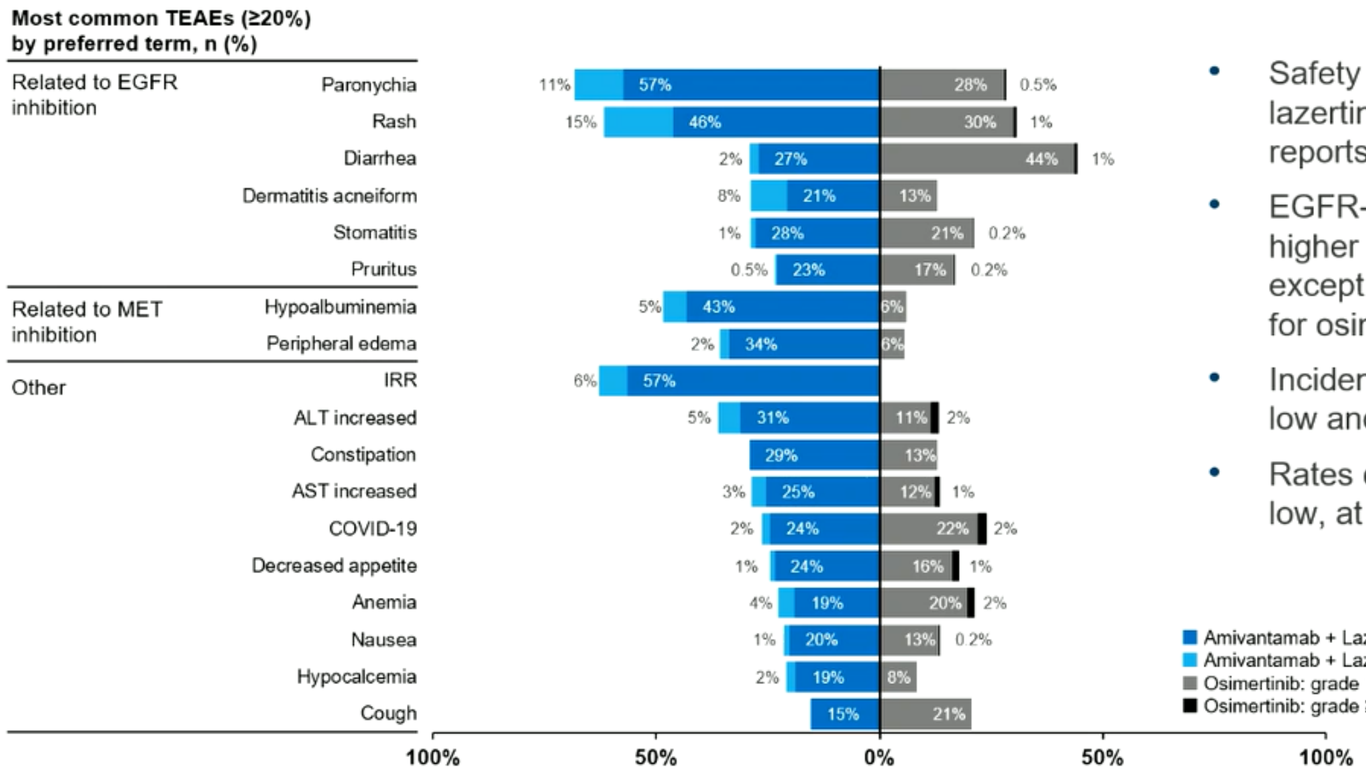
HR, **0.69** (95% CI, 0.53–0.89)



Presented by B. Cho. ESMO 2023. LBA14

What about toxicity?

Safety Profile



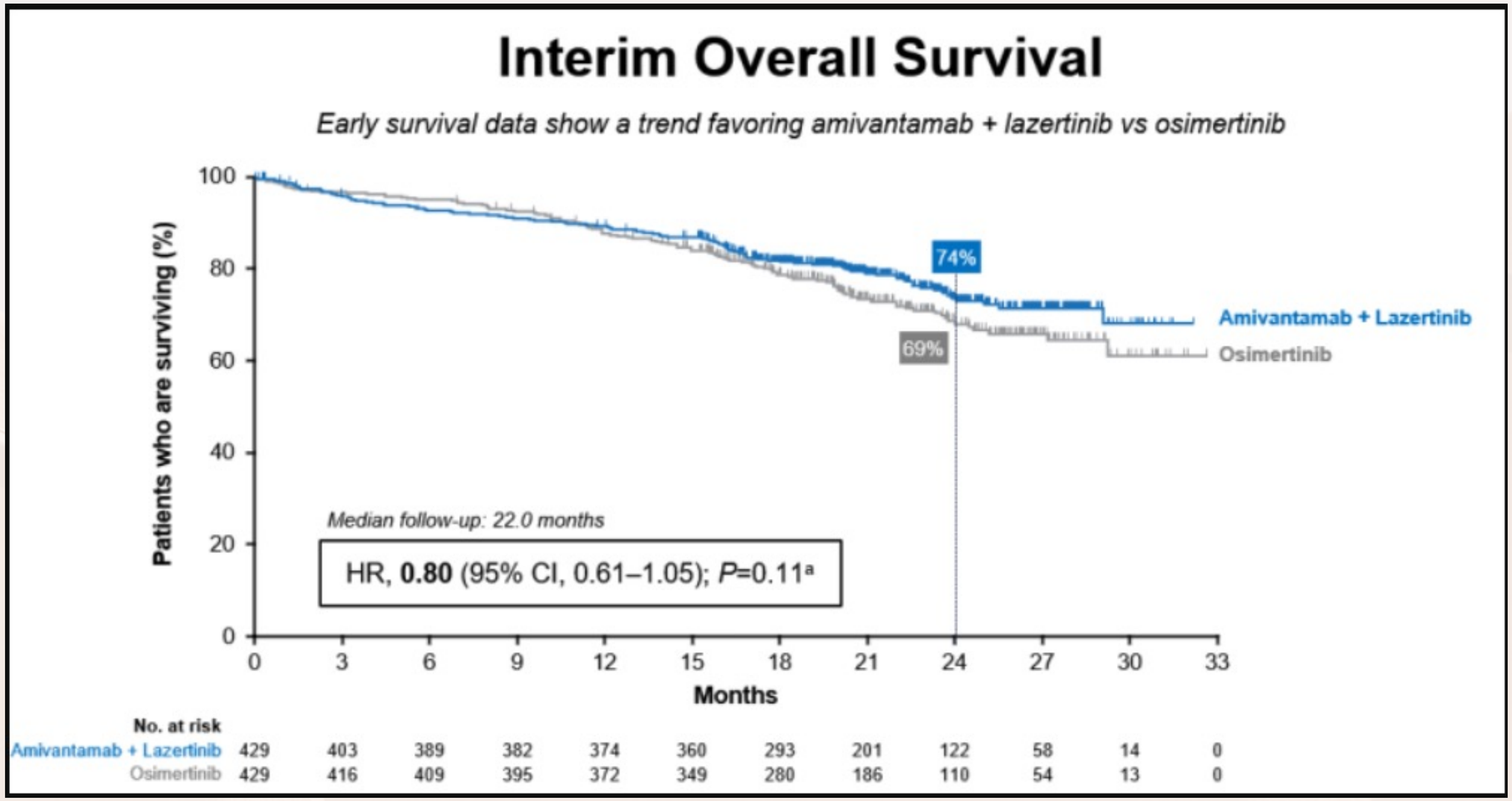
- Safety profile of amivantamab + lazertinib was consistent with prior reports, mostly grades 1-2
- EGFR- and MET-related AEs were higher for amivantamab + lazertinib except diarrhea, which was higher for osimertinib
- Incidence of grade 4-5 AEs was low and comparable between arms
- Rates of ILD/pneumonitis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

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

MARIPOSA: Overall Survival



Presented by B. Cho. ESMO 2023. LBA14

MARIPOSA: Unanswered Questions

- Overall Survival?
- Is benefit of addition of Amivantamab to Lazertinib worth the risk/increased toxicity?
  - Subgroups: CNS mets benefited in both groups, L858R, co-mutations
  - Toxicity: IRR; VTE, Rash
- Is benefit of addition of Amivantamab to Lazertinib better than other combination strategies?
  - 3rd generation EGFR TKI + Chemotherapy
  - MET targeting agents (TKI)
  - ADCs, e.g. patritumab deruxtecan (HER3 targeting ADC)
  - MARIPOSA2
- Resistance mechanisms
  - MET expression de novo vs post 3G TKI

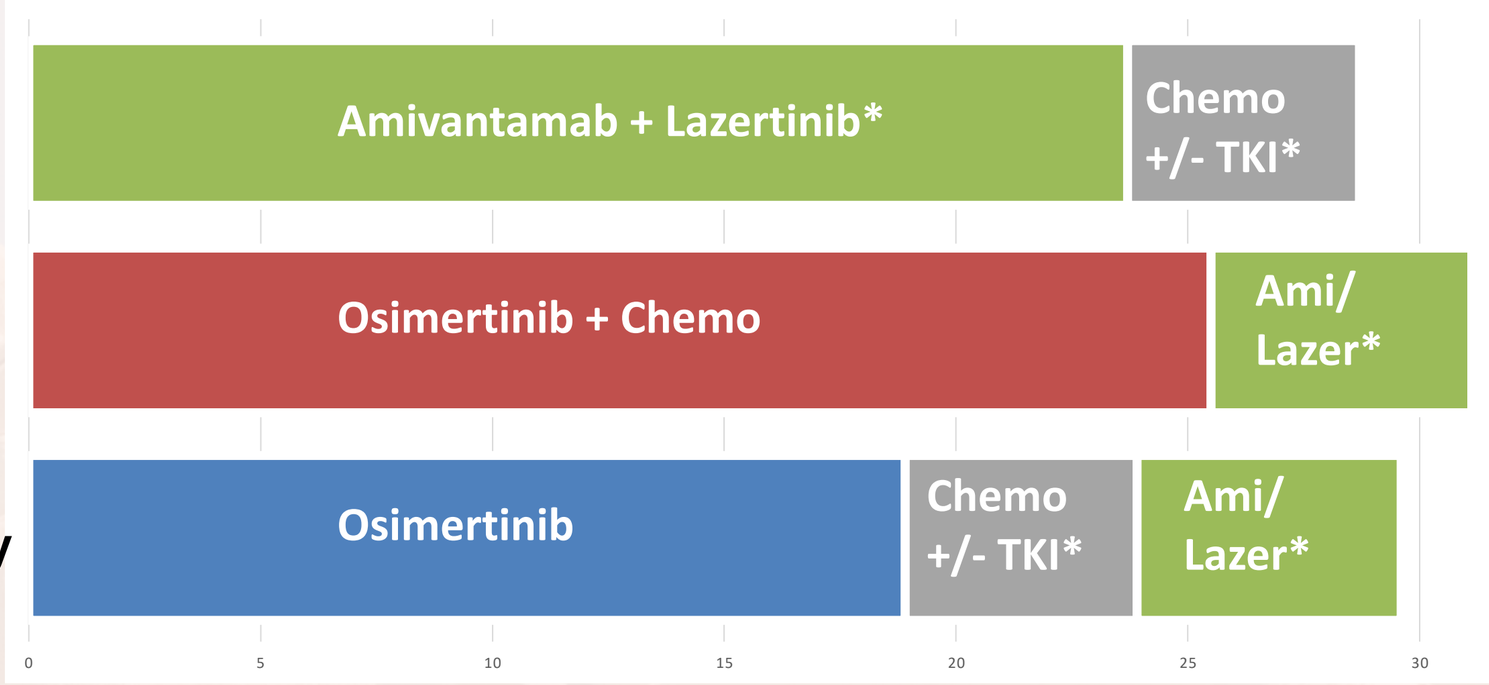
Sequencing Therapy 1L EGFRm NSCLC

MaTOS™
Masters in Thoracic Oncology Summit
Albuquerque, New Mexico | November 16 - 19, 2023

1L TKI + MET/EGFR Bispecific

1L TKI + Platinum Doublet

1L TKI Monotherapy



Q2W Infusions
Rash/IRR/VTE

Q3W Infusions
Nausea/fatigue/cytopenias

Estimated ~30 months total PFS

**Regimen no FDA-Approved*
Slide courtesy of Julia Rotow MD, DFCI
Adapted from Piotrowska et al, ESMO 2023