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EGFR-TARGETED THERAPY IN LOCALLY ADVANCED AND ADVANCED NSCLC

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DISCLOSURES

Honoraria: None

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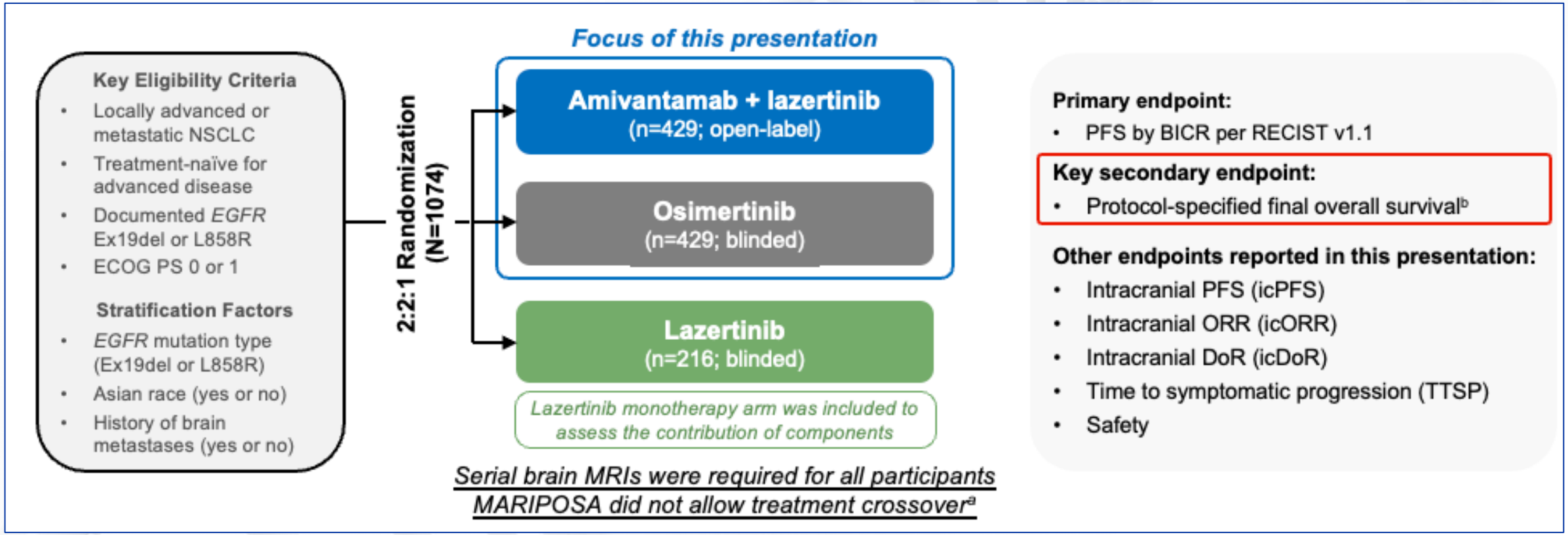
OUTLINE

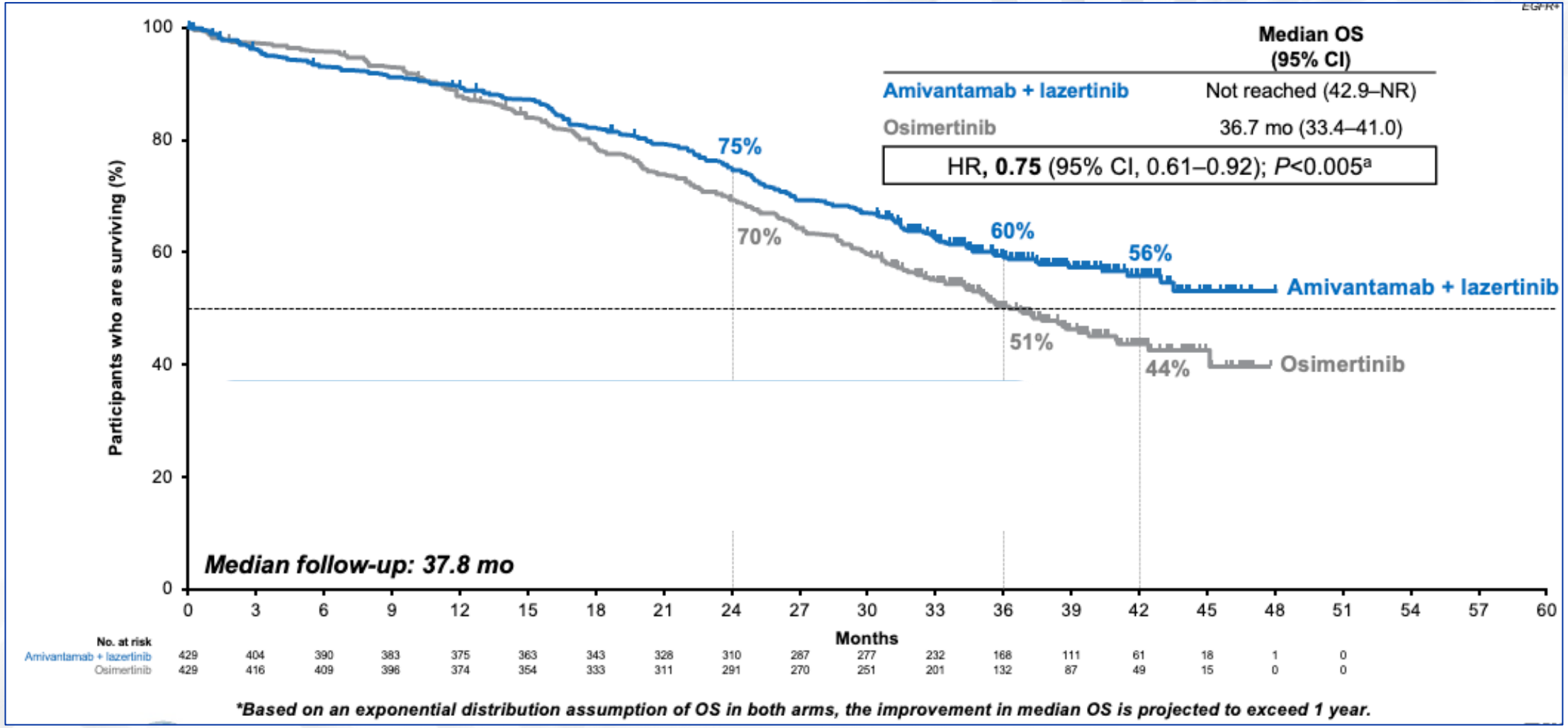
- 1st line therapy
- Management of acquired resistance
  - Continuation of TKI
  - Novel ADC
- Locally advanced NSCLC

MARIPOSA: STUDY DESIGN



Yang J et al, NEJM 2025.

MARIPOSA: OVERALL SURVIVAL



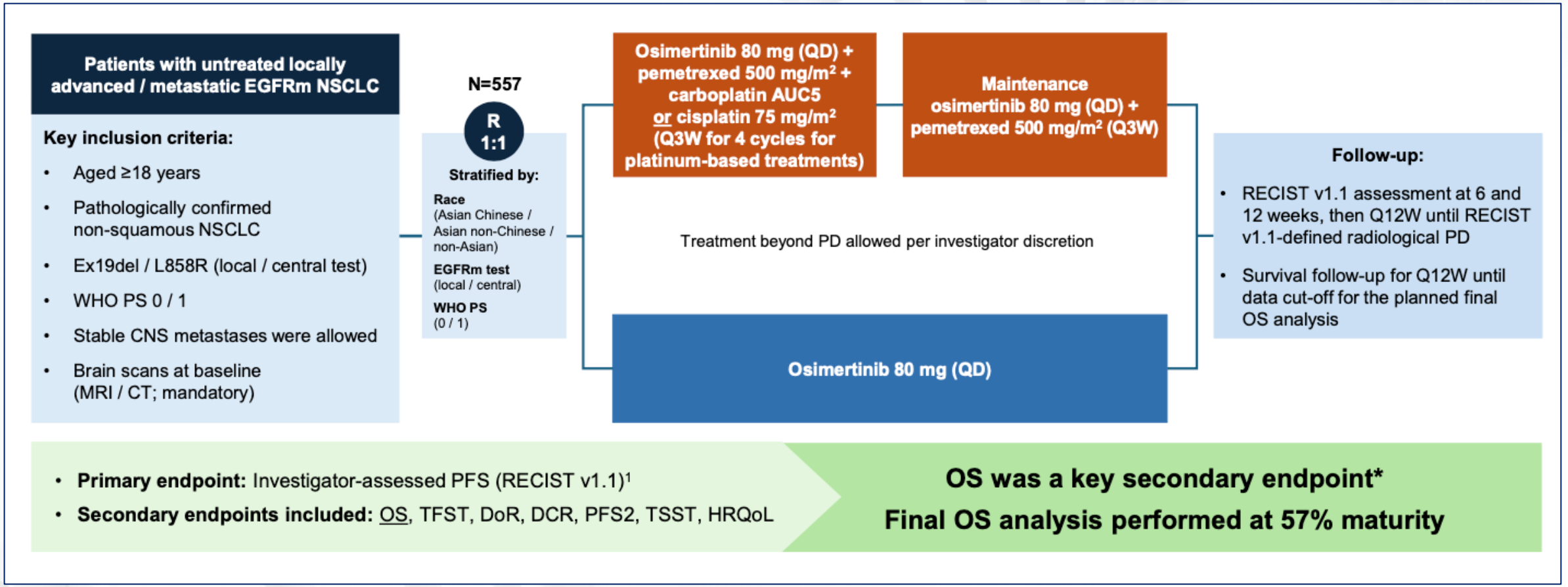
Yang J et al, NEJM 2025.

MARIPOSA: ADVERSE EVENTS

AEs by preferred term (≥20% of participants in either group)	Amivantamab + lazertinib (n=421)		Osimertinib (n=428)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Related to EGFR inhibition				
Paronychia	291 (69)	49 (12)	127 (30)	2 (<1)
Rash	271 (64)	73 (17)	136 (32)	3 (<1)
Diarrhea	133 (32)	9 (2)	200 (47)	4 (<1)
Dermatitis acneiform	127 (30)	37 (9)	55 (13)	0
Stomatitis	126 (30)	5 (1)	92 (21)	1 (<1)
Pruritus	107 (25)	2 (<1)	75 (18)	1 (<1)
Related to MET inhibition				
Hypoalbuminemia	216 (51)	26 (6)	29 (7)	0
Peripheral edema	162 (38)	8 (2)	29 (7)	1 (<1)
Other				
Infusion-related reaction	275 (65)	27 (6)	0	0
ALT increased	170 (40)	28 (7)	66 (15)	8 (2)
AST increased	139 (33)	15 (4)	68 (16)	6 (1)
Constipation	130 (31)	0	70 (16)	0
COVID-19	125 (30)	8 (2)	112 (26)	9 (2)
Anemia	114 (27)	20 (5)	112 (26)	10 (2)
Decreased appetite	114 (27)	4 (1)	84 (20)	7 (2)
Nausea	99 (24)	5 (1)	65 (15)	1 (<1)
Hypocalcemia	96 (23)	11 (3)	37 (9)	0
Asthenia	84 (20)	13 (3)	54 (13)	7 (2)
Muscle spasms	84 (20)	3 (<1)	36 (8)	0
Thrombocytopenia	74 (18)	4 (1)	92 (21)	6 (1)

Yang J et al, NEJM 2025.

FLAURA 2: OVERALL SURVIVAL RESULTS

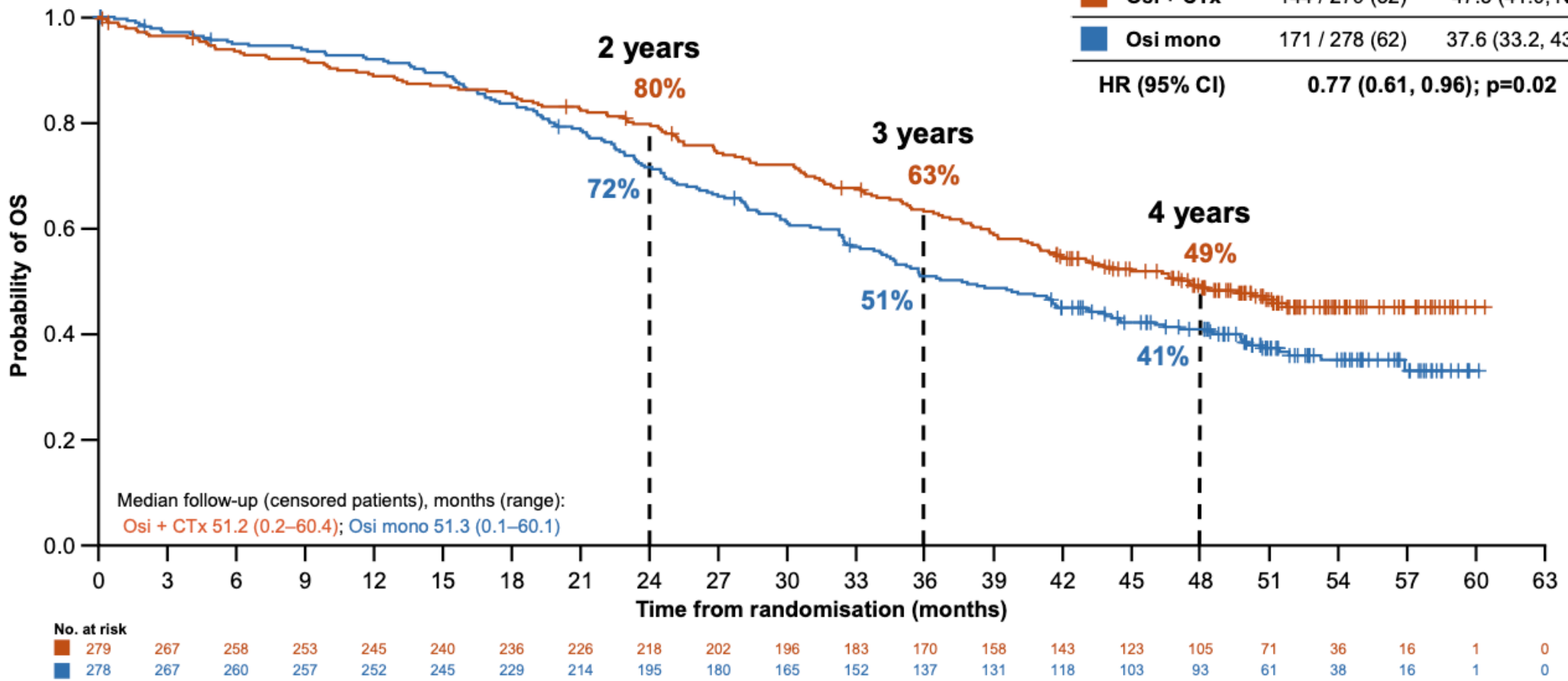


Planchard D et al, WCLC 2025.

FLAURA2: Overall survival

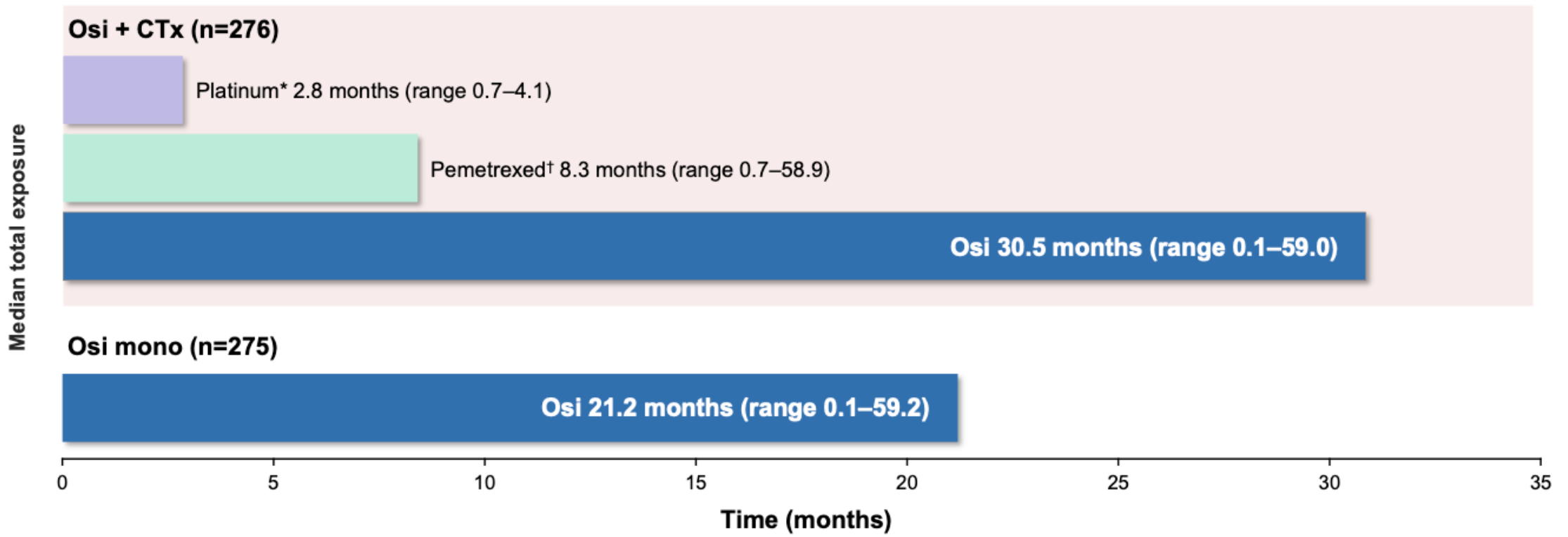
Median OS with osi + CTx was 47.5 months

	No. Events / no. patients (%)	Median OS, months (95% CI)
Osi + CTx	144 / 279 (52)	47.5 (41.0, NC)
Osi mono	171 / 278 (62)	37.6 (33.2, 43.2)
HR (95% CI)	0.77 (0.61, 0.96); p=0.02	



Planchard D et al, WCLC 2025.

FLAURA2: TREATMENT EXPOSURE



The osi + CTx arm had a long CTx-free period – median exposure to osi vs pem was 30.5 vs 8.3 months

Planchard D et al, WCLC 2025.

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SECOND LINE THERAPY

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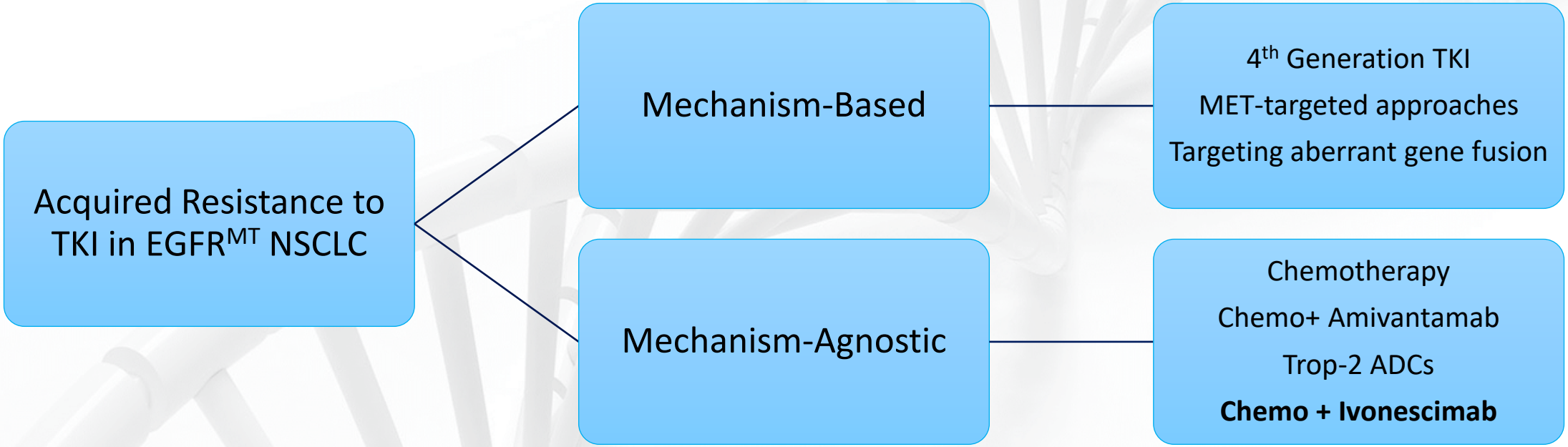
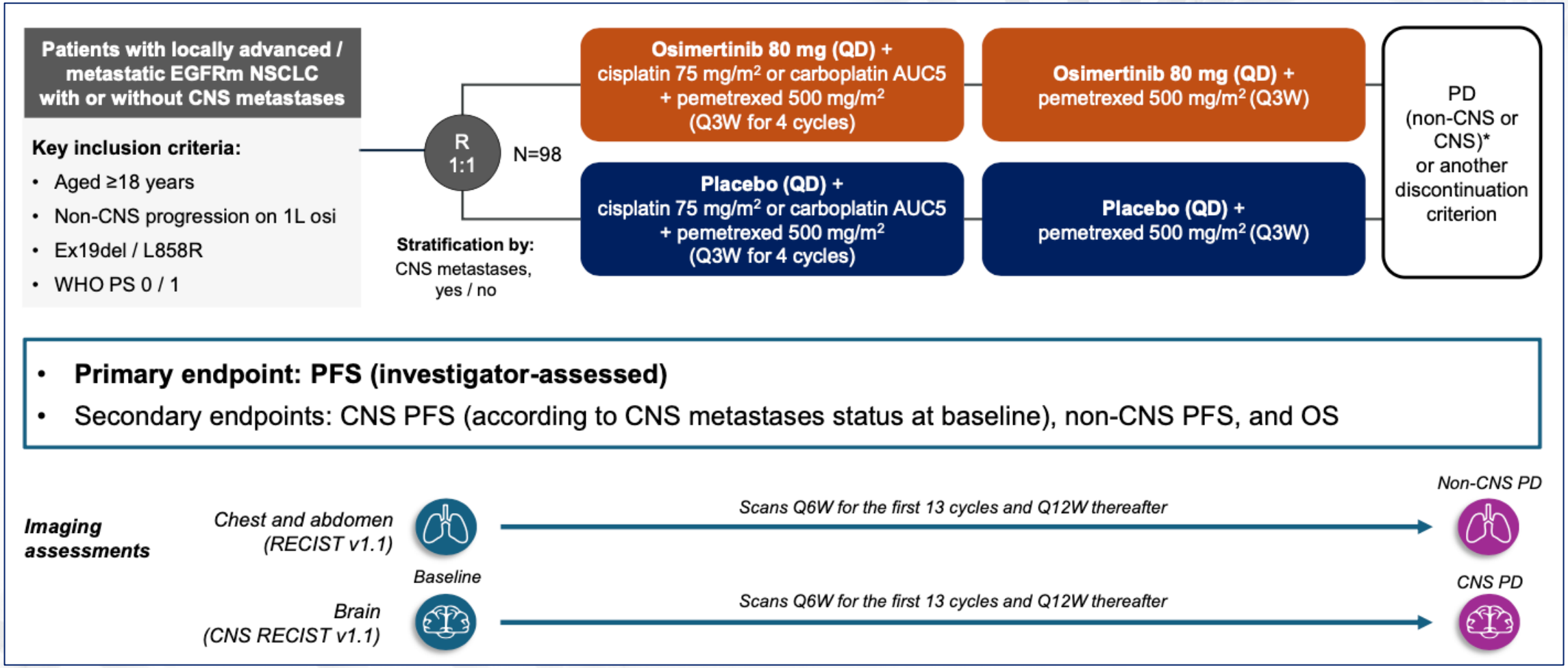
CURRENT APPROACHES FOR TREATMENT OF ACQUIRED RESISTANCE IN EGFR^{MT} NSCLC



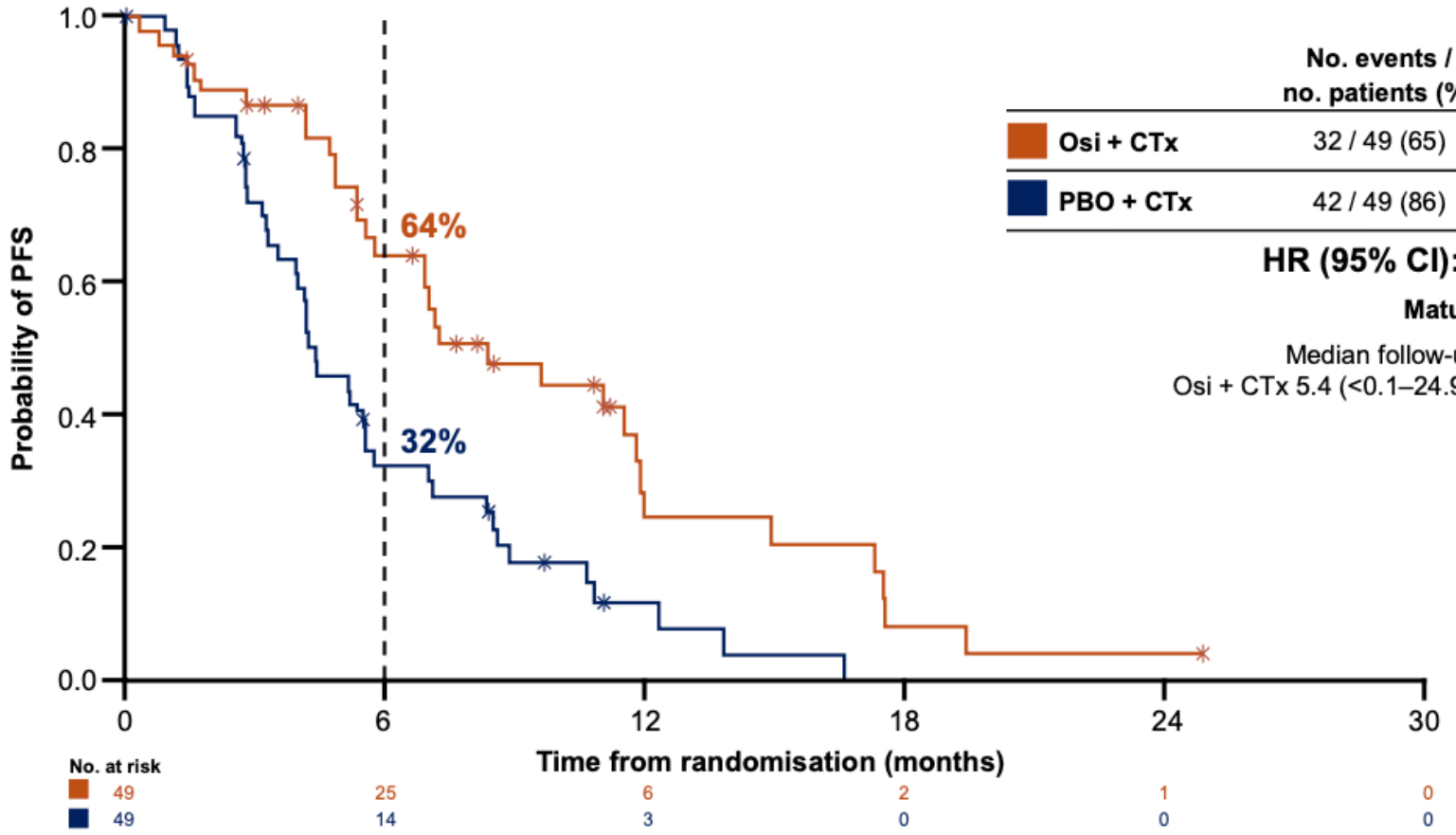
- Regardless of the strategy, median PFS is relatively modest
- Relative merits of incremental efficacy versus toxicity should be contextualized to individual patients

COMPEL STUDY: CONTINUATION OF OSIMERTINIB WITH CHEMOTHERAPY



Pasello G et al, WCLC 2025.

COMPEL: PROGRESSION-FREE SURVIVAL



	No. events / no. patients (%)	Median PFS, months (95% CI)
Osi + CTx	32 / 49 (65)	8.4 (5.7, 11.8)
PBO + CTx	42 / 49 (86)	4.4 (3.5, 5.6)

HR (95% CI): 0.43 (0.27, 0.70)

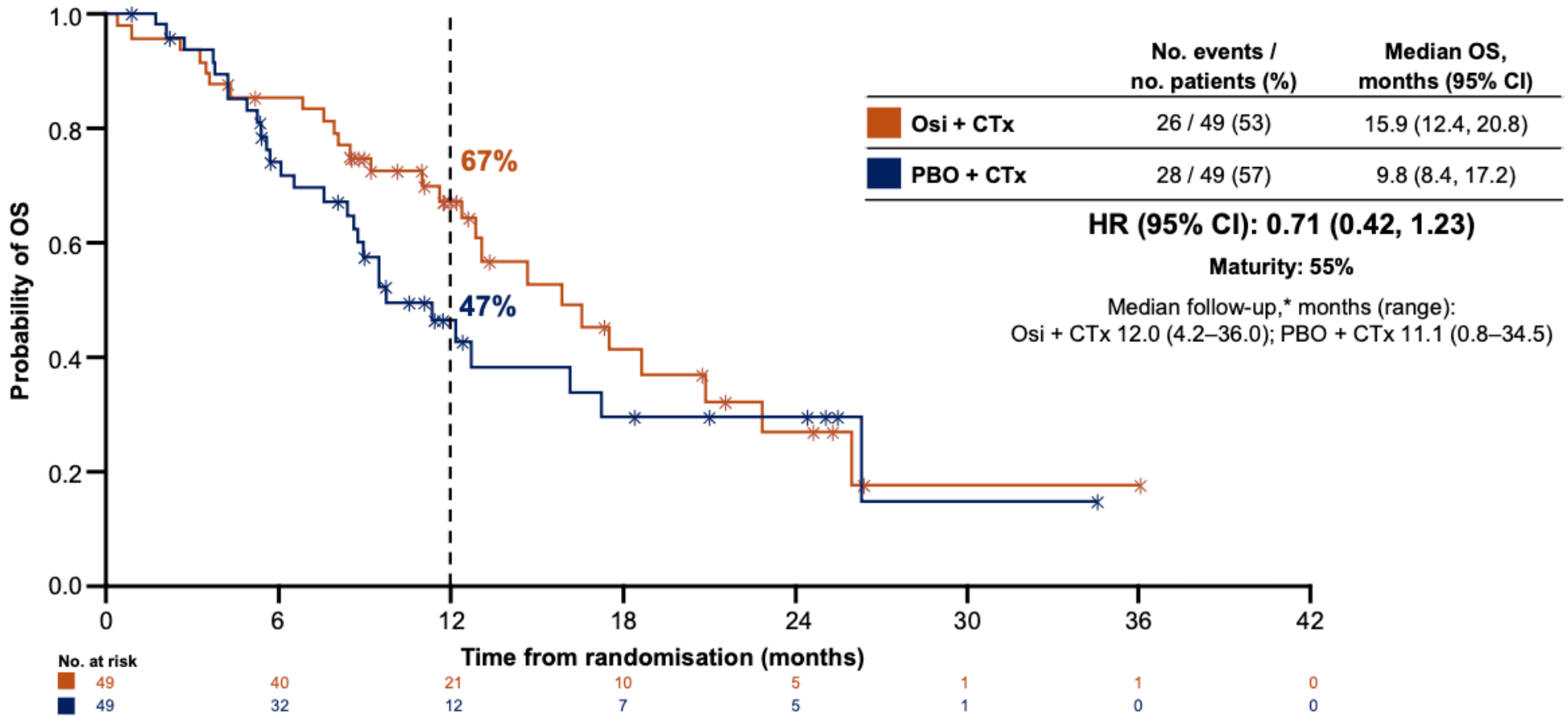
Maturity: 76%

Median follow-up,† months (range):
Osi + CTx 5.4 (<0.1–24.9); PBO + CTx 5.5 (<0.1–11.1)

Osi + CTx was associated with improved PFS versus PBO + CTx

Pasello G et al, WCLC 2025.

COMPEL: OVERALL SURVIVAL



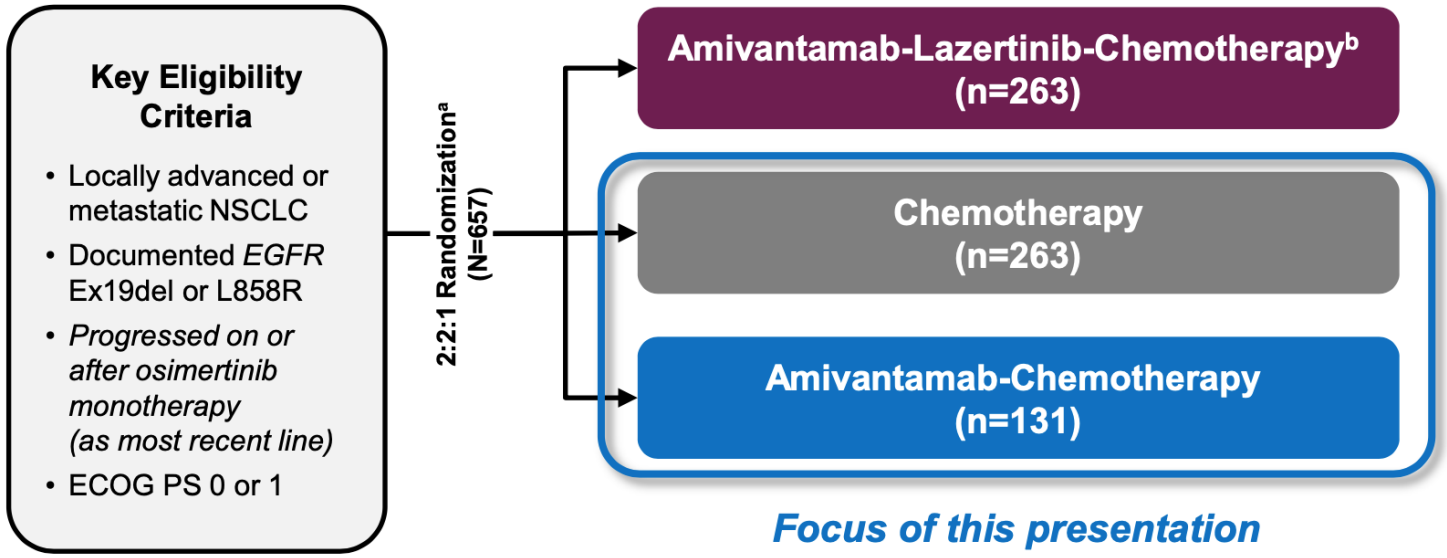
Pasello G et al, WCLC 2025.

COMPEL: INCIDENCE OF NEW LESIONS

	Osi + CTx (n=49)	PBO + CTx (n=49)
Patients with new lesions, n (%)†	18 (37)	25 (51)
Brain	5 (10)	13 (27)
Liver	6 (12)	7 (14)
Lung	6 (12)	3 (6)
Bone	2 (4)	4 (8)
Adrenal gland	1 (2)	2 (4)
Pleural effusion	1 (2)	2 (4)

Pasello G et al, WCLC 2025.

MARIPOSA-2 TRIAL



Secondary/Exploratory Efficacy Endpoints Reported:

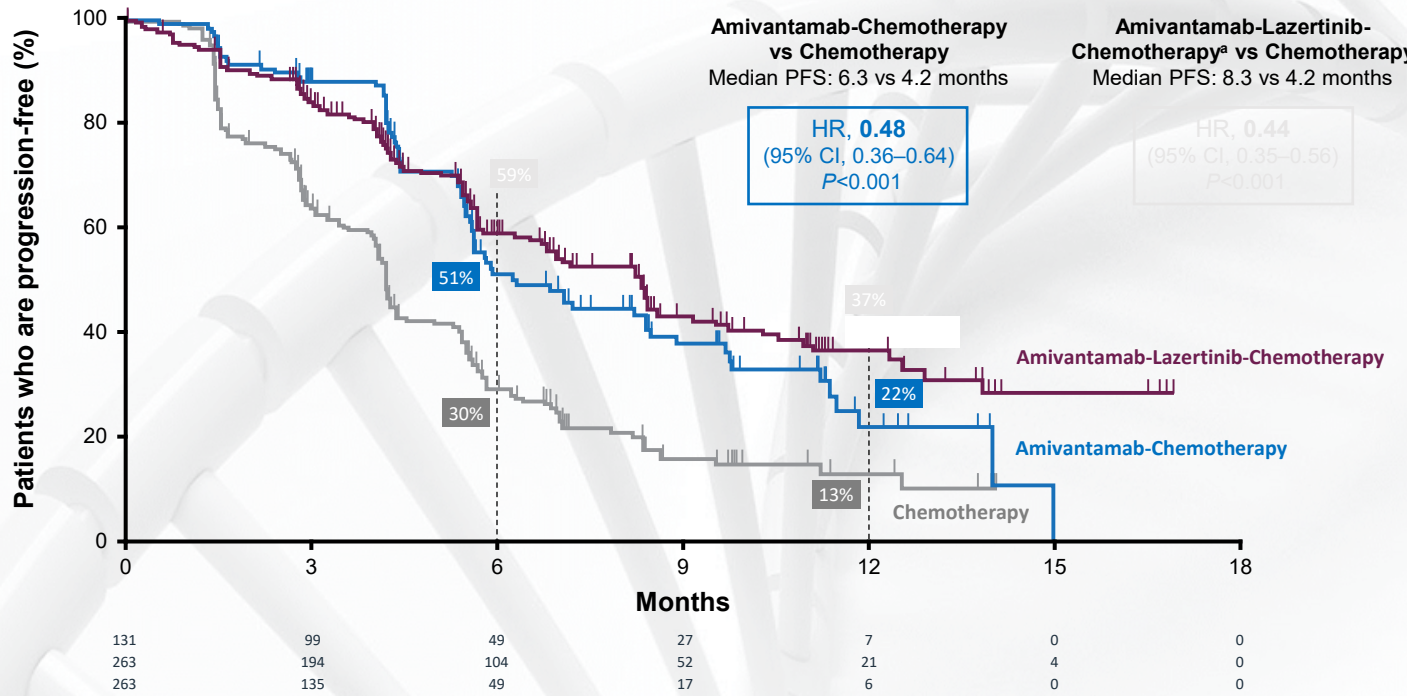
- Overall survival (OS)
- Time to symptomatic progression (TTSP)
- Time to treatment discontinuation (TTD)
- Time to subsequent therapy (TTST)
- PFS after first subsequent therapy (PFS2)

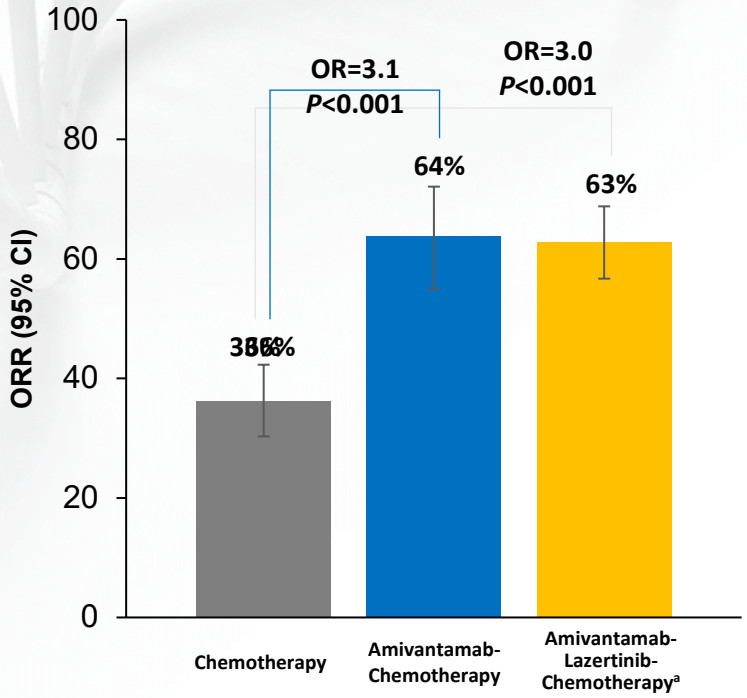
- The second interim analysis of OS was prespecified for when ~75% of the planned OS events were observed
- The significance level at the second interim analysis for OS was determined based on the O'Brien-Fleming alpha spending approach (2-sided alpha: 0.0142) as implemented by the Lan-DeMets method

Popat S et al, ESMO 2024

IMPROVEMENT IN RR AND PFS

- 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

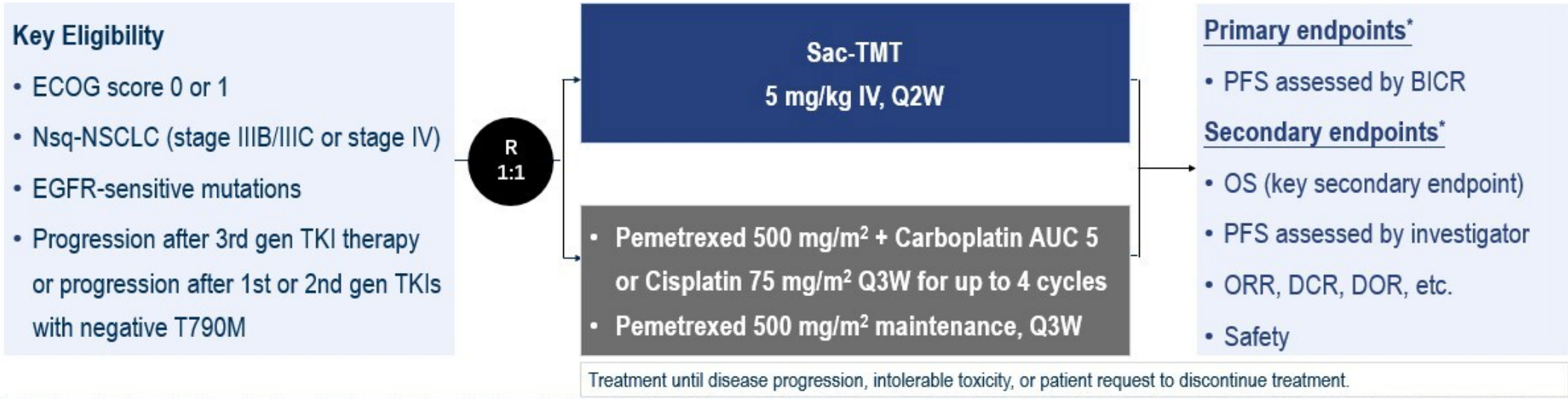




Passaro A, et al. ESMO 2023. Abstract LBA15.

OptiTROP-Lung04 Study Design

Randomized, multicenter, open-label, phase 3 trial (NCT05870319)



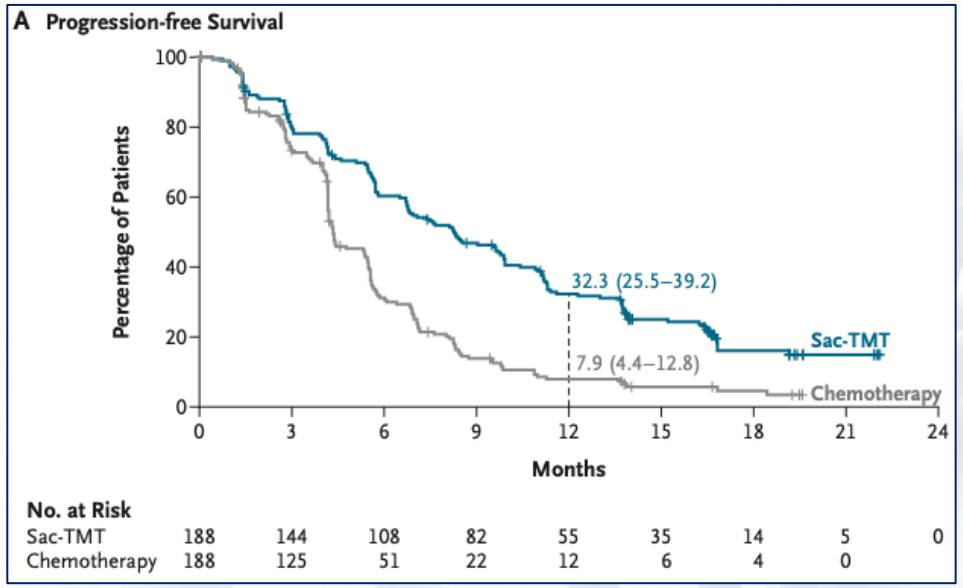
*Tumor response was assessed using RECIST version 1.1.

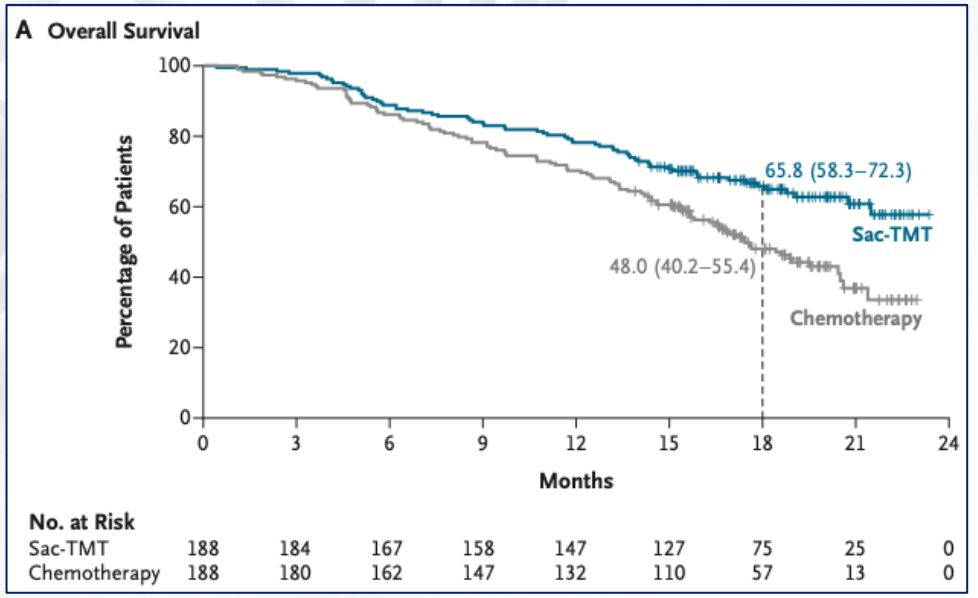
BICR, blinded independent central review; OS, overall survival; ORR, objective response rate; DOR, duration of response; DCR, disease control rate; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; IA, interim analysis; ECOG, Eastern Cooperative Oncology Group.

Limited to patients of age < 75 yrs

Fang W et al, NEJM, 2025.

OPTITROP-LUNG04 TRIAL





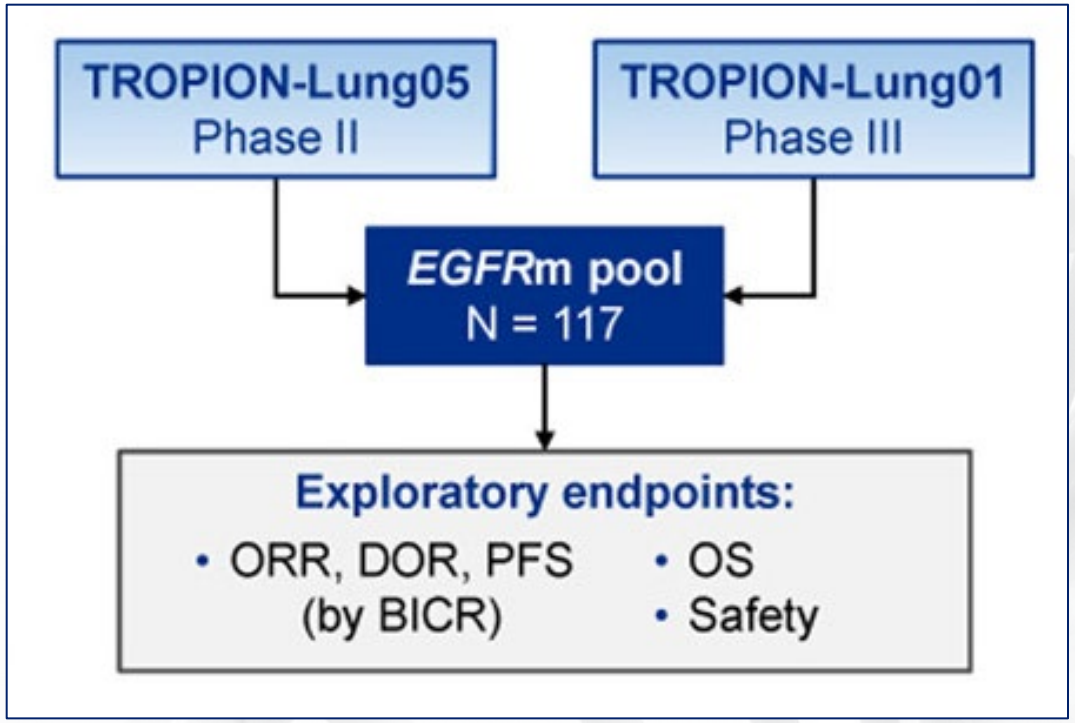
HR: 0.49; 8.3m vs. 4.3m

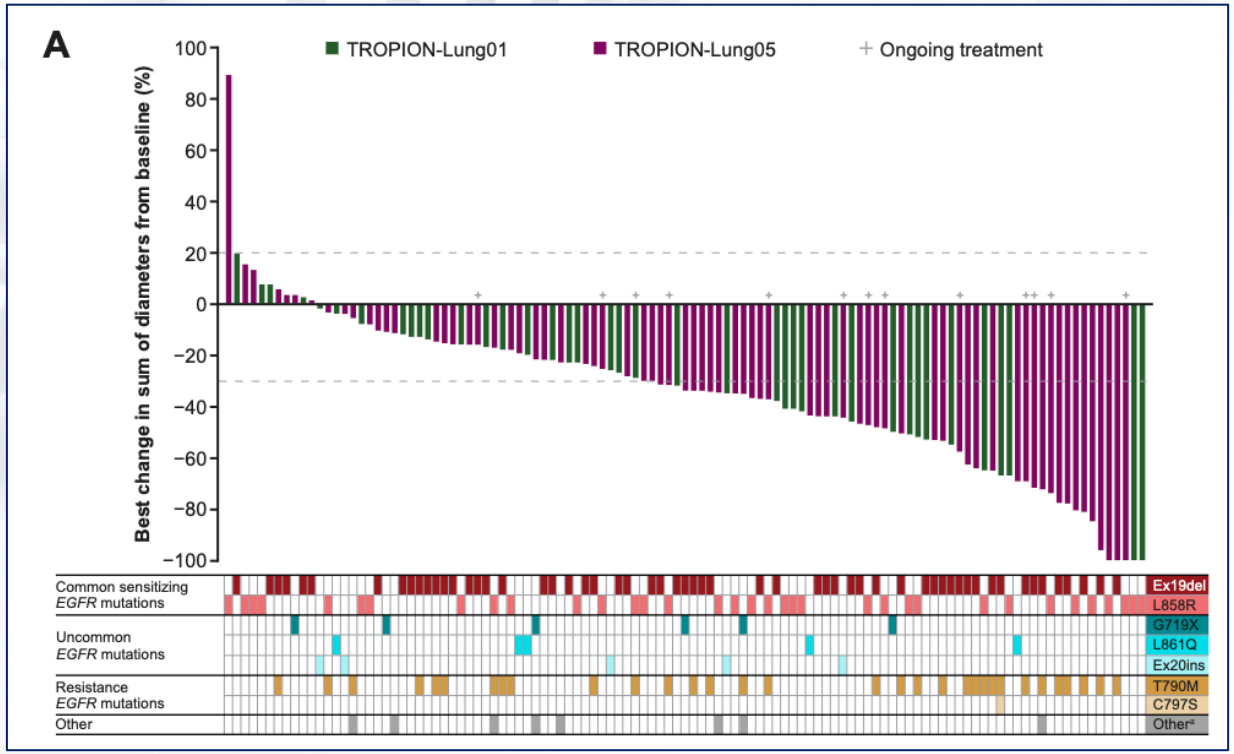
HR: 0.6; NE vs 17.4m

Salient AE with Sac-TMT:
Stomatitis; 64% (Gr 1 22%, Gr 2 37% & Gr 3 5%)

Fang W et al, NEJM, 2025.

DATOPOTAMAB IN EGFR^{MT} NSCLC





RR: 43% mPFS: 5.8m; mOS: 15.6m

AE: Stomatitis 69% (Gr 1 36%; Gr 2 24%; Gr 3 9%)

Ahn M et al, JTO 2025.

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LOCALLY ADVANCED NSCLC

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LAURA: UPDATED OVERALL SURVIVAL RESULTS

LAURA STUDY DESIGN[1]

Patients with locally advanced, unresectable stage III* EGFRm NSCLC, with no progression during / following definitive CRT†

R 2:1

N=216

Osimertinib 80 mg, once daily

Placebo, once daily

Endpoints

- **Primary endpoint:** PFS assessed by BICR per RECIST v1.1 (sensitivity analysis: PFS by investigator assessment)
- **Key secondary endpoints:** OS, CNS PFS
- **Secondary post-progression endpoints:** TFST, PFS2, TSST

Key inclusion criteria:

- ≥18 years (Japan: ≥20 years)
- WHO performance status 0 / 1
- Confirmed locally advanced, unresectable stage III* NSCLC
- Ex19del / L858R‡
- Maximum interval between last dose of CRT and randomisation: 6 weeks

Treatment continued until BICR-assessed progression (per RECIST 1.1), toxicity, or other discontinuation criteria met

Open-label osimertinib after progression was offered to both treatment arms§

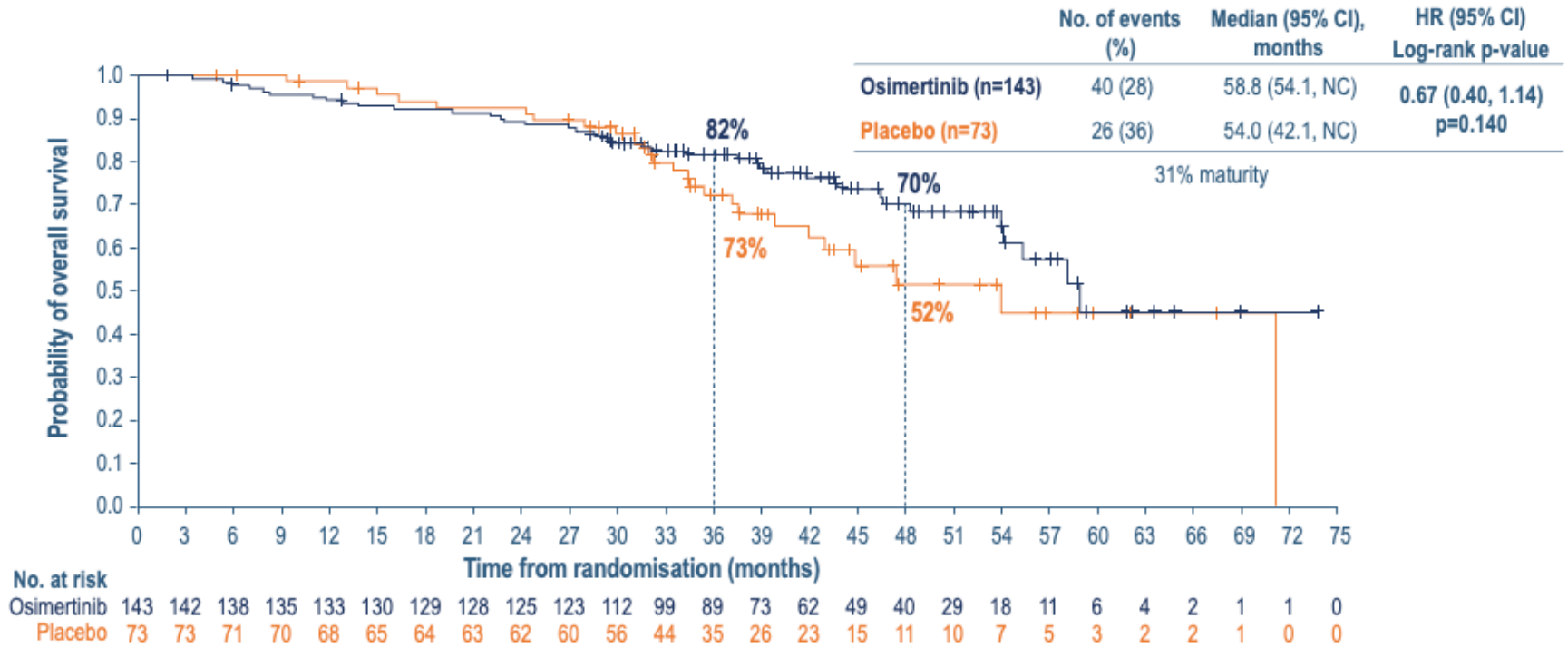
Tumour assessments:

- Chest CT / MRI and brain MRI
  - At baseline, every 8 weeks to Week 48, then every 12 weeks until progression
  - After progression, PFS2 and OS were assessed by the investigator every 12 weeks and defined by local practice

Ramalingam S et al, ELCC 2025.

Updated DCO

IMPROVED TREND TOWARDS OS BENEFIT SEEN WITH OSIMERTINIB AT UPDATED ANALYSIS



- 55/69 (80%) patients who discontinued study treatment in the placebo group received subsequent treatment with a 3rd-gen EGFR-TKI*

Ramalingam S et al, ELCC 2025.

The Personalis NeXT Personal® assay, an ultra-sensitive, tumour-informed MRD assay, was used for testing plasma samples from LAURA

Scan and plasma schedule

Exploratory analysis: Determine potential of tumour-informed plasma-based MRD testing to correlate with patient outcomes and aid early clinical decision making during osimertinib treatment

Personalis NeXT Personal® assay workflow

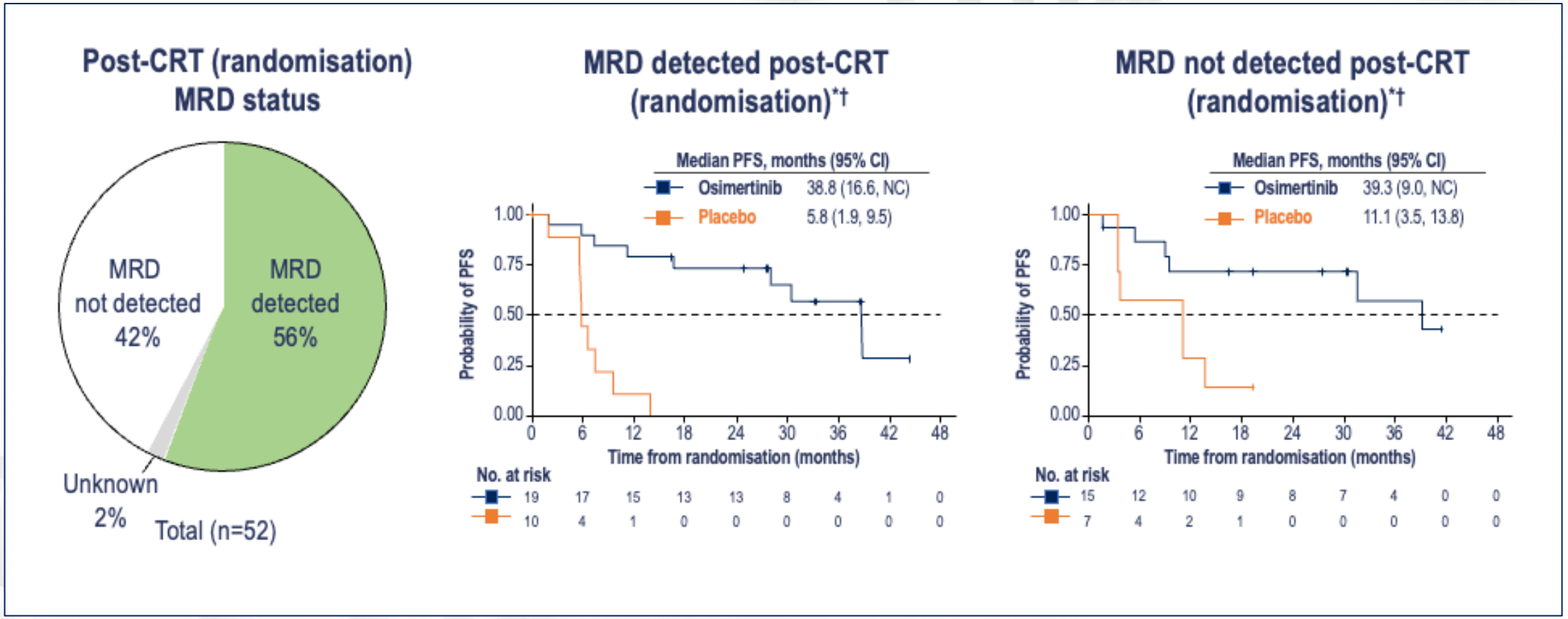
Definitions

MRD clearance: 10-fold ctDNA decrease from post-CRT (randomisation) levels or undetected MRD for 2 consecutive timepoints by Week 12

Molecular progression / MRD event: 100% increase in ctDNA at a single time point or detected MRD above the LLOQ

Arriola L et al, ESMO 2025.

LAURA: RESULTS BY MRD STATUS



Arriola L et al, ESMO 2025.

CONCLUSIONS

- Combination therapy improves outcome in 1st line treatment of EGFR mt NSCLC
  - Individualize based on brain metastasis, patient preference and co-mutation status
- Trop2-directed ADCs are an option for patients with acquired resistance
- No role of immune checkpoint inhibitors