ESMO IN FOCUS WEBINAR – LUNG CANCER

Noemi Reguart, ***Chair***
Department of Medical Oncology at Hospital Clínic de Barcelona and
University of Barcelona

ESMO WEBINAR SERIES

ESMO IN FOCUS

Programme

24 April 2025

1 min	**Welcome & Introduction** Noemi Reguart
19 min	**Systemic therapeutic strategies in localised NSCLC and limited-stage small cell lung cancer** Kersti Oselin
10 min	**Panel discussion and Q&A** All faculty
19 min	**State-of-the-art therapies for patients with locally advanced unresectable NSCLC** Ullas Batra
10 min	**Panel discussion and Q&A** All faculty
19 min	**Optimal front-line therapeutic approaches for patients with EGFRmt metastatic NSCLC** James Chih-Hsin Yang
10 min	**Panel discussion and Q&A** All faculty
2 min	**Concluding remarks** Noemi Reguart

Noemi Reguart

Chair

Department of Medical Oncology at Hospital Clínic de Barcelona and University of Barcelona's School of Medicine

Kersti Oselin

Speaker

North Estonia Medical Centre, Tallinn

Ullas Batra

Speaker

Rajiv Gandhi Cancer Institute and Research Centre

James Chih-Hsin Yang

Speaker

National Taiwan University Cancer Center Hospital

ESMO WEBINAR SERIES

ESMO IN FOCUS

SYSTEMIC THERAPEUTIC STRATEGIES IN EARLY NSCLC AND LIMITED-STAGE SMALL CELL LUNG CANCER

Kersti Oselin, MD, PhD

Senior consultant in medical oncology

Clinic of Oncology and Haematology

North Estonia Medical Centre, Estonia

ESMO WEBINAR SERIES

ESMO IN FOCUS

DECLARATION OF INTERESTS

KERSTI OSELIN

- Institutional research grant: Optellum, Pfizer, Takeda
- Advisory board: MSD, AstraZeneca, Takeda, Janssen, Amgen, Roche

EARLY STAGE (RESECTABLE) NSCLC WITHOUT AGA

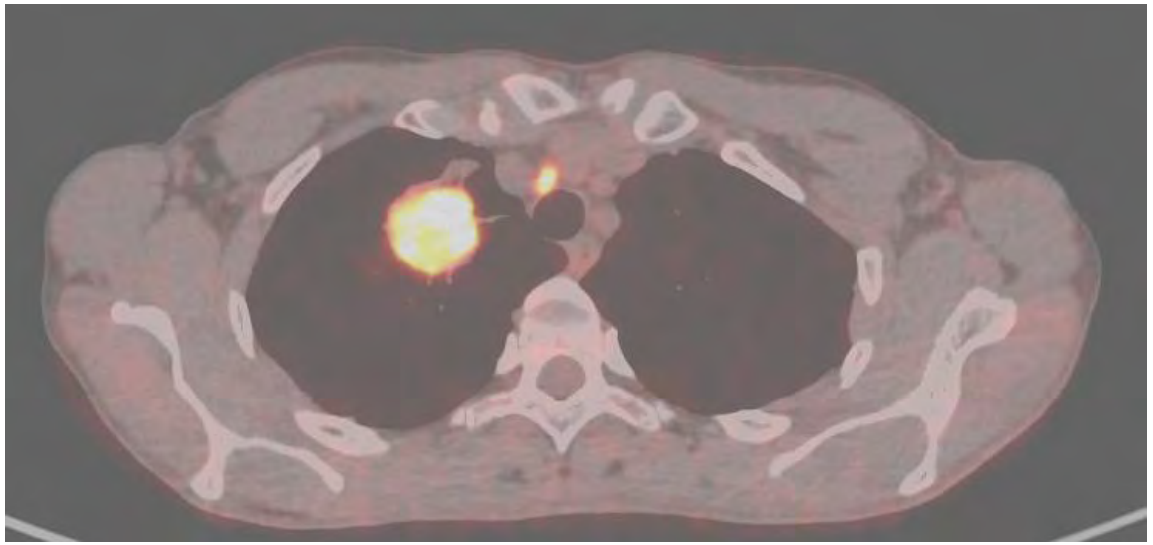
- ✓ Adjuvant IO
- ✓ Neoadjuvant IO
- ✓ Perioperative IO
- ✓ Resectability – Unresectable – PACIFIC – durvalumab after chemoradiation

K.Oselin

56 years old female

cT2a cN2b IIIB

CT guided biopsy
PD-L1 TPS 10%
adenocarcinoma, EGFR/ALK neg
(ADAURA, ALINA)



PET/CT scan

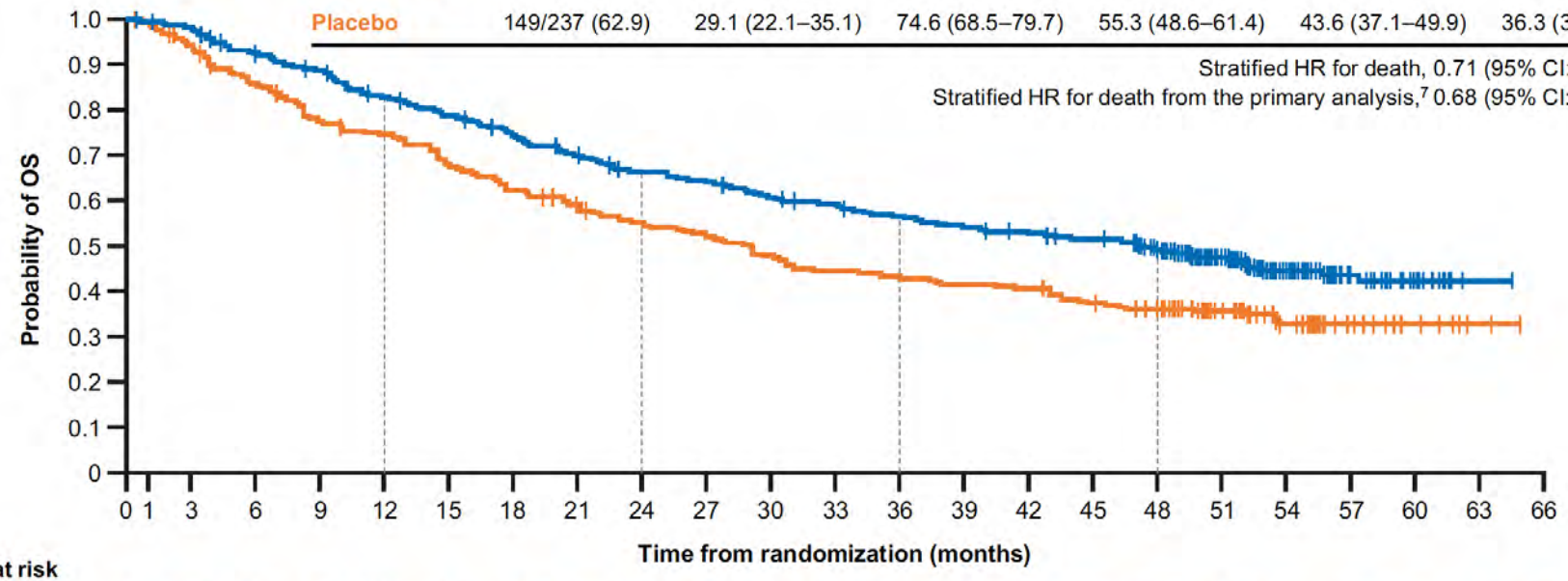
- Right lung upper lobe ca 3.3 cm (SUVmax = 16.2) lesion
- Mediastinal **2R** one 7 mm lymph node with high metabolic activity (SUVmax = 11.2)
- Mediastinal **4R** one 6 mm lymph node with moderate metabolic activity

Four-Year Survival With Durvalumab After Chemoradiotherapy in Stage III NSCLC—an Update From the PACIFIC Trial

A

	No. of events/ total no. of patients (%)	Median OS (95% CI), months	12-month OS rate (95% CI) %	24-month OS rate (95% CI) %	36-month OS rate (95% CI) %	48-month OS rate (95% CI) %
Durvalumab	247/476 (51.9)	47.5 (38.4–52.6)	83.1 (79.4–86.2)	66.3 (61.8–70.4)	56.7 (52.1–61.1)	49.6 (44.9–54.1)
Placebo	149/237 (62.9)	29.1 (22.1–35.1)	74.6 (68.5–79.7)	55.3 (48.6–61.4)	43.6 (37.1–49.9)	36.3 (30.1–42.6)

Stratified HR for death, 0.71 (95% CI: 0.57–0.88)
Stratified HR for death from the primary analysis,[7] 0.68 (95% CI: 0.53–0.87)

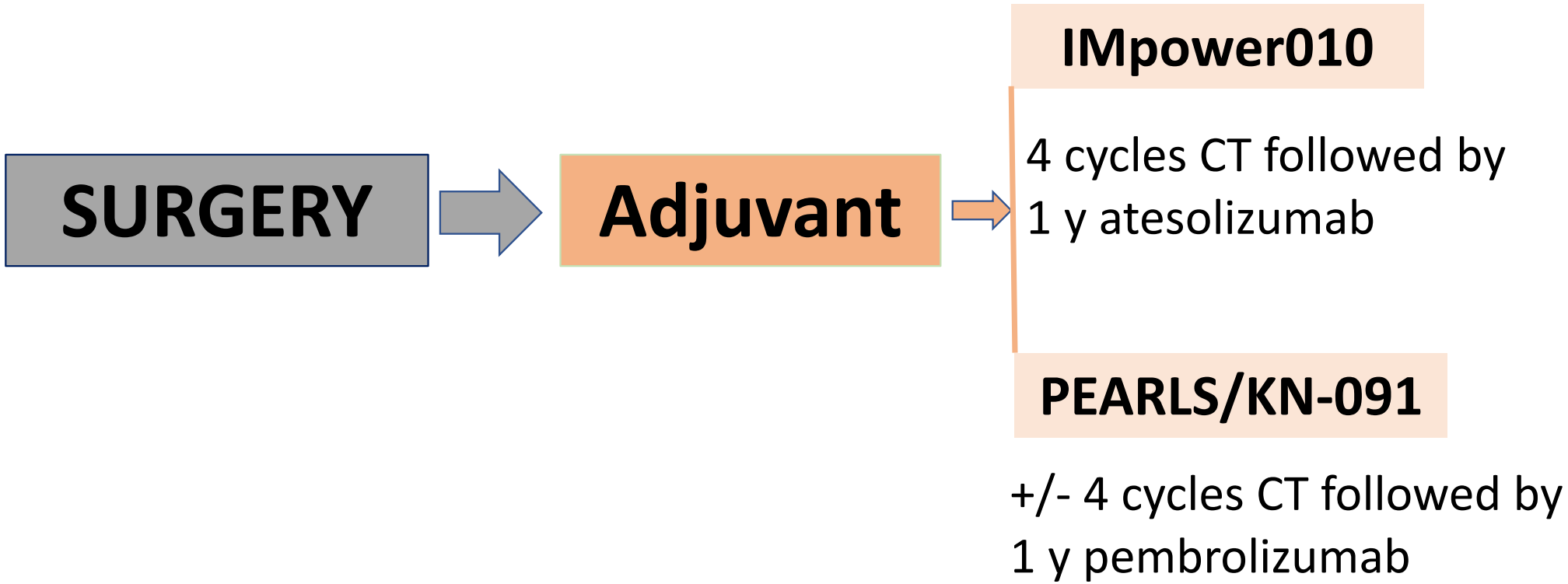


No. at risk																							
Durvalumab	476	464	431	414	385	364	343	319	299	290	274	265	252	241	235	225	195	138	75	36	15	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	75	53	29	15	7	2	0

K.Oselin

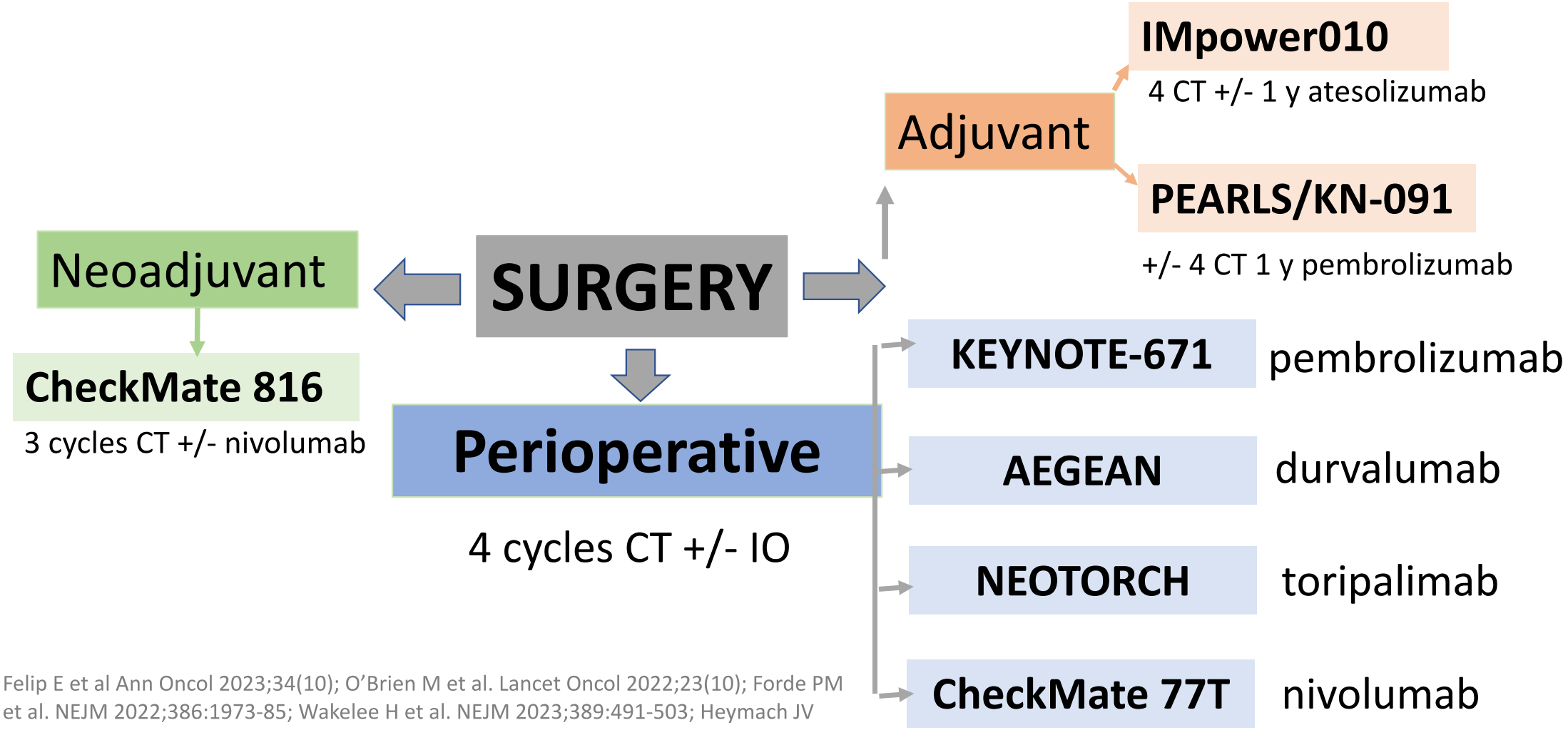
JTO 2021;16(5):860-867

Phase III randomized trials in early stage LC



1- Felip E et al. Ann Oncol 2023;34(10); 2- O'Brien M et al. Lancet Oncol 2022;23(10).

Phase III randomized trials in early stage LC



Felip E et al Ann Oncol 2023;34(10); O'Brien M et al. Lancet Oncol 2022;23(10); Forde PM et al. NEJM 2022;386:1973-85; Wakelee H et al. NEJM 2023;389:491-503; Heymach JV etal. NEJM 2023;389:1672-84; Lu S et al. JAMA 2024;331(3):201-211; Cascone T. ESMO 2023. LBA1.

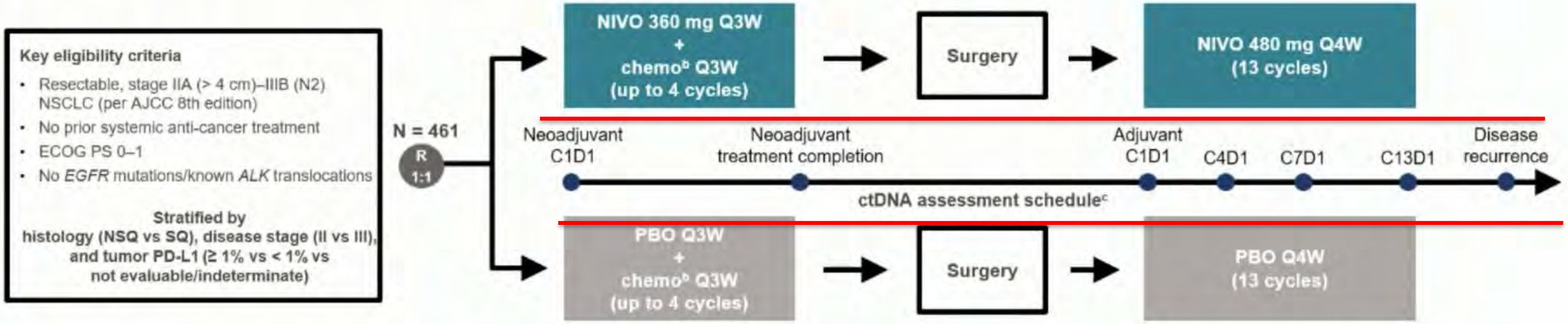
EARLY STAGE RESECTABLE NSCLC WITHOUT AGA

- ✓ CheckMate 77T – ctDNA clearance and relation with clinical outcome
- ✓ AEGEAN – ctDNA clearance and relation with clinical outcome

K.Oselin

In the phase 3 CheckMate 77T[a] study, perioperative NIVO demonstrated statistically significant and clinically meaningful EFS benefit vs PBO in patients with resectable NSCLC (HR, 0.58; 97.36% CI, 0.42–0.81; $P < 0.001$); pCR was also improved[1]

Here we report updated clinical outcomes from CheckMate 77T with a median follow-up of 33.3 months, exploratory outcomes by pCR status, and ctDNA analyses

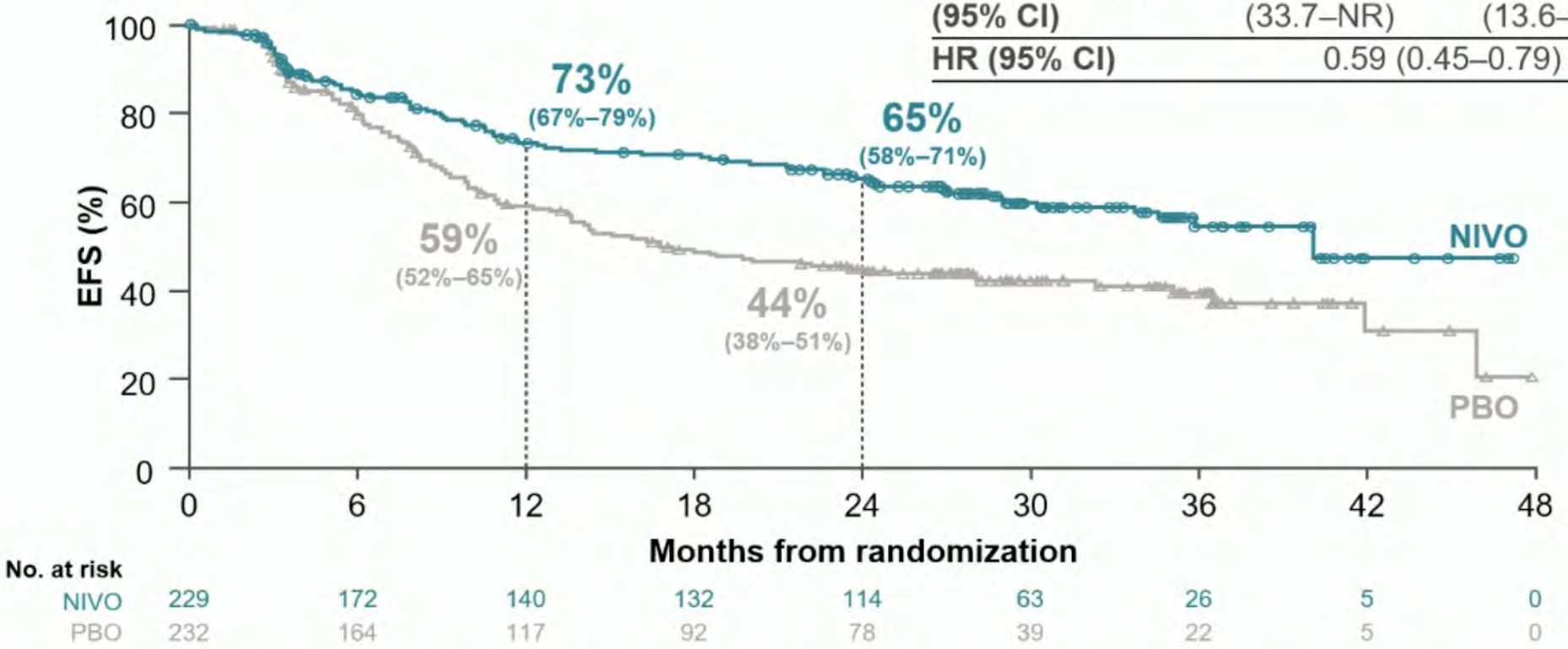


Primary endpoint
- EFS[d] by BICR

Secondary endpoints
- pCR[e] by BIPR
- MPR by BIPR
- OS
- Safety

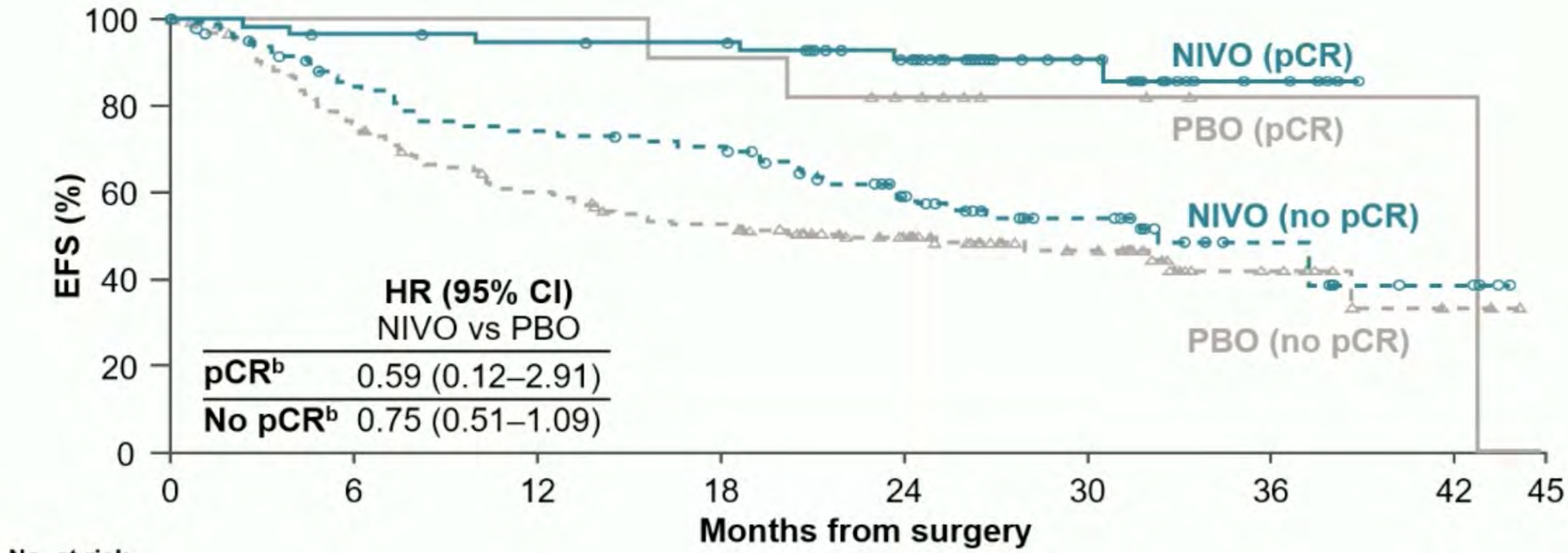
Exploratory analyses
- Outcomes by pCR status
- ctDNA clearance[f] and recurrence[g]

	NIVO (n = 229)	PBO (n = 232)
Median EFS, mo (95% CI)	40.1 (33.7–NR)	17.0 (13.6–28.1)
HR (95% CI)	0.59 (0.45–0.79)	



- Landmark EFS from definitive surgery among patients who had definitive surgery for NIVO (n = 178) vs PBO (n = 178): HR = 0.52 (95% CI, 0.37–0.73)

Median follow-up (range): 33.3 months (23.6–52.1).
95% CIs for EFS rates are designated in the parentheses.



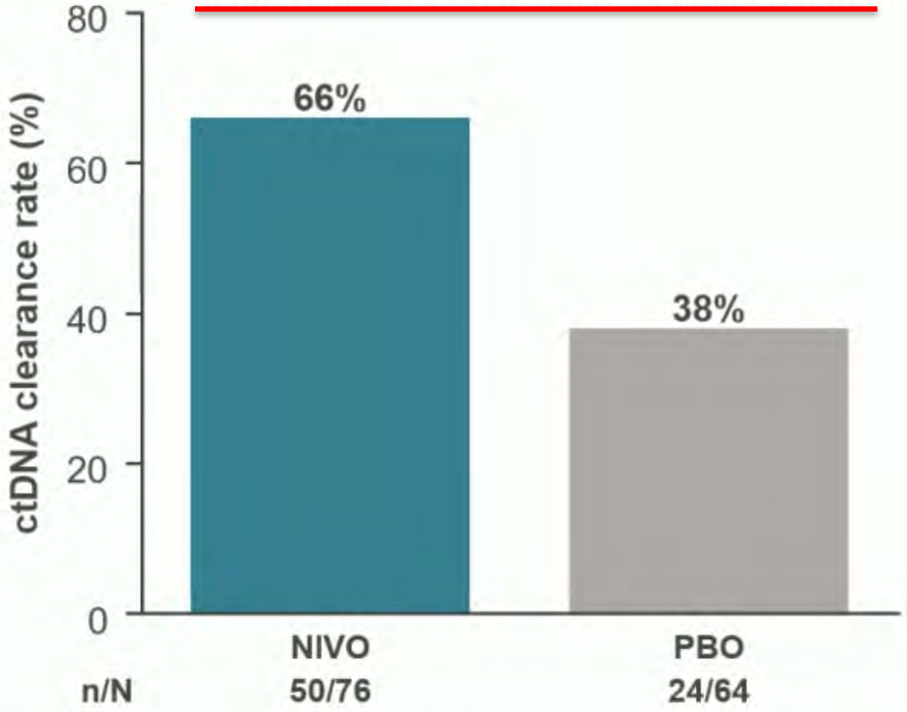
- Baseline characteristics were generally similar between patients with or without pCR and between treatment arms, except a higher proportion of patients with pCR had tumor PD-L1 ≥ 1% vs patients without pCR in the NIVO arm

Median follow-up (range): 33.3 months (23.6–52.1).

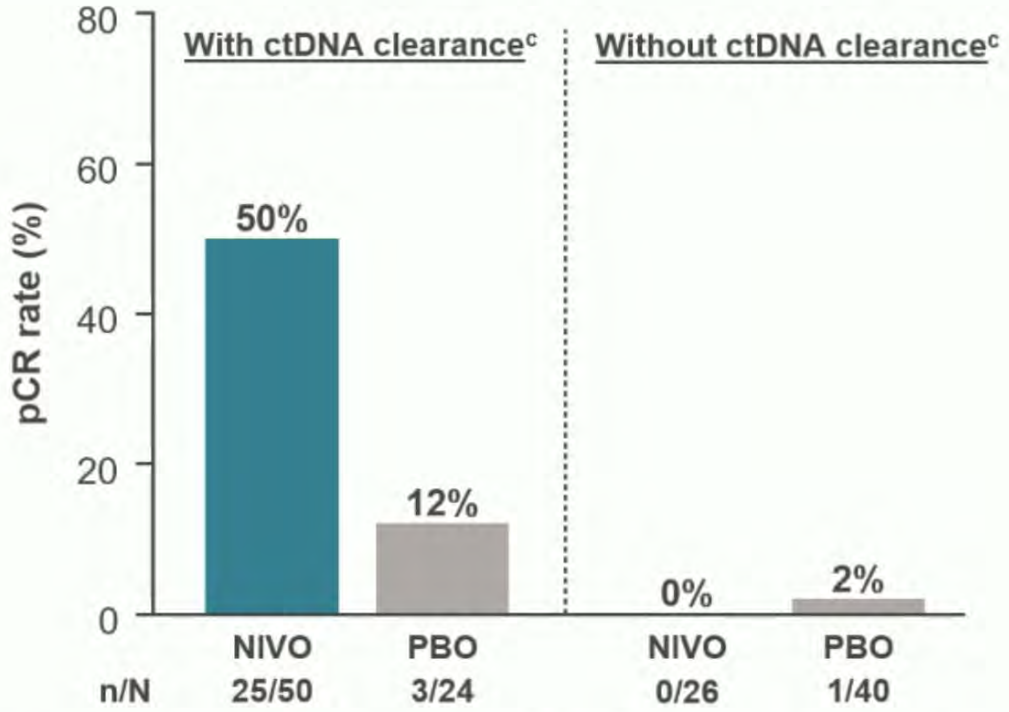
[a]Landmark timepoint was the time of definitive surgery. [b]HR (95% CI) in patients with pCR vs those without pCR: NIVO, 0.19 (0.08–0.44); PBO, 0.35 (0.11–1.10).

ctDNA clearance during the neoadjuvant period[a,b]

ctDNA clearance[c]
(neoadjuvant C1D1 to neoadjuvant completion)

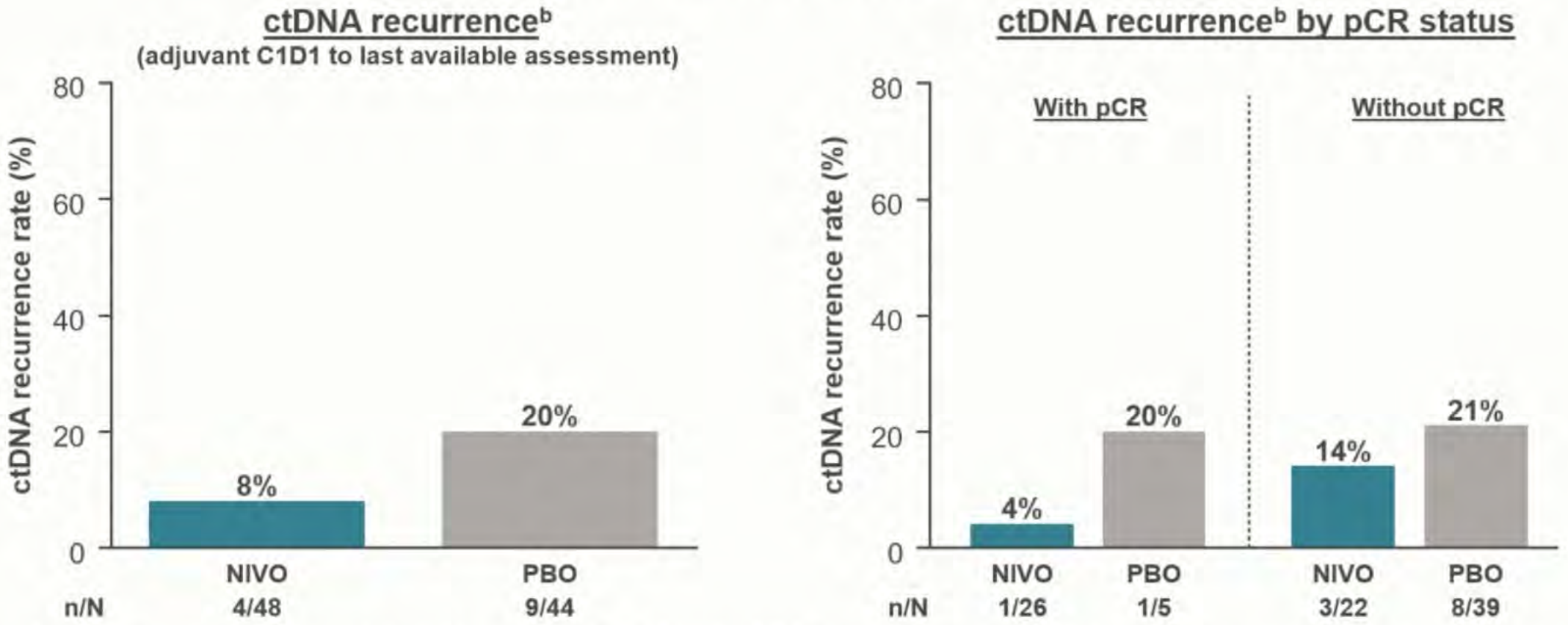


pCR by ctDNA clearance status



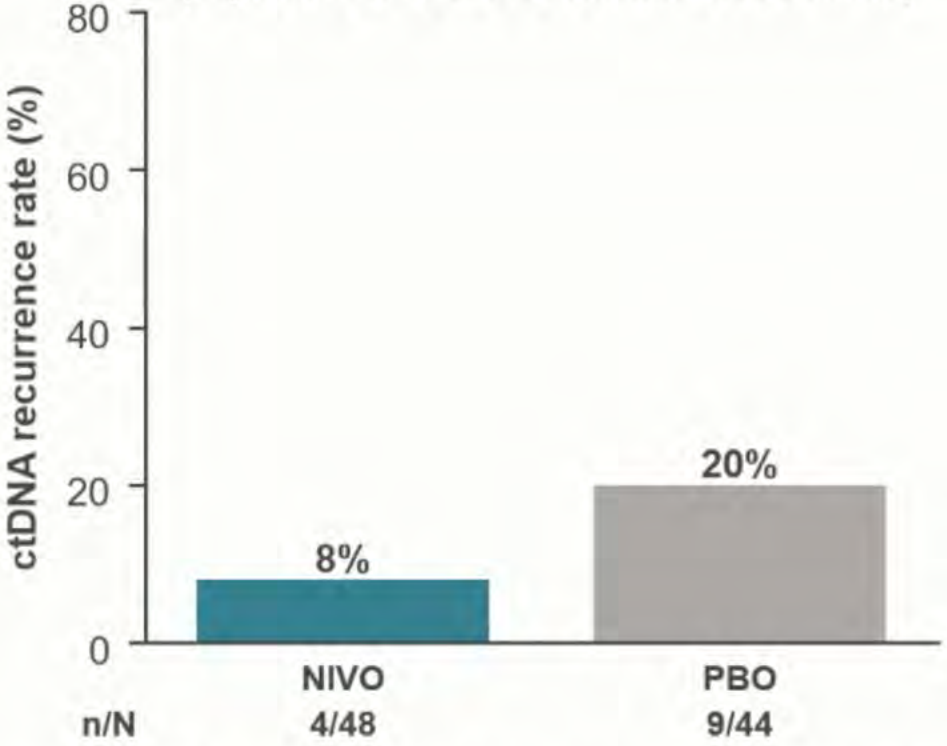
- Among patients with ctDNA clearance, the EFS HR was 0.38 (95% CI, 0.16–0.88); 2-year EFS rates were 81% (NIVO) vs 58% (PBO)
- Among patients without ctDNA clearance, the EFS HR was 0.74 (95% CI, 0.39–1.42); 2-year EFS rates were 50% (NIVO) vs 31% (PBO)

ctDNA recurrence during the post-operative period[a]

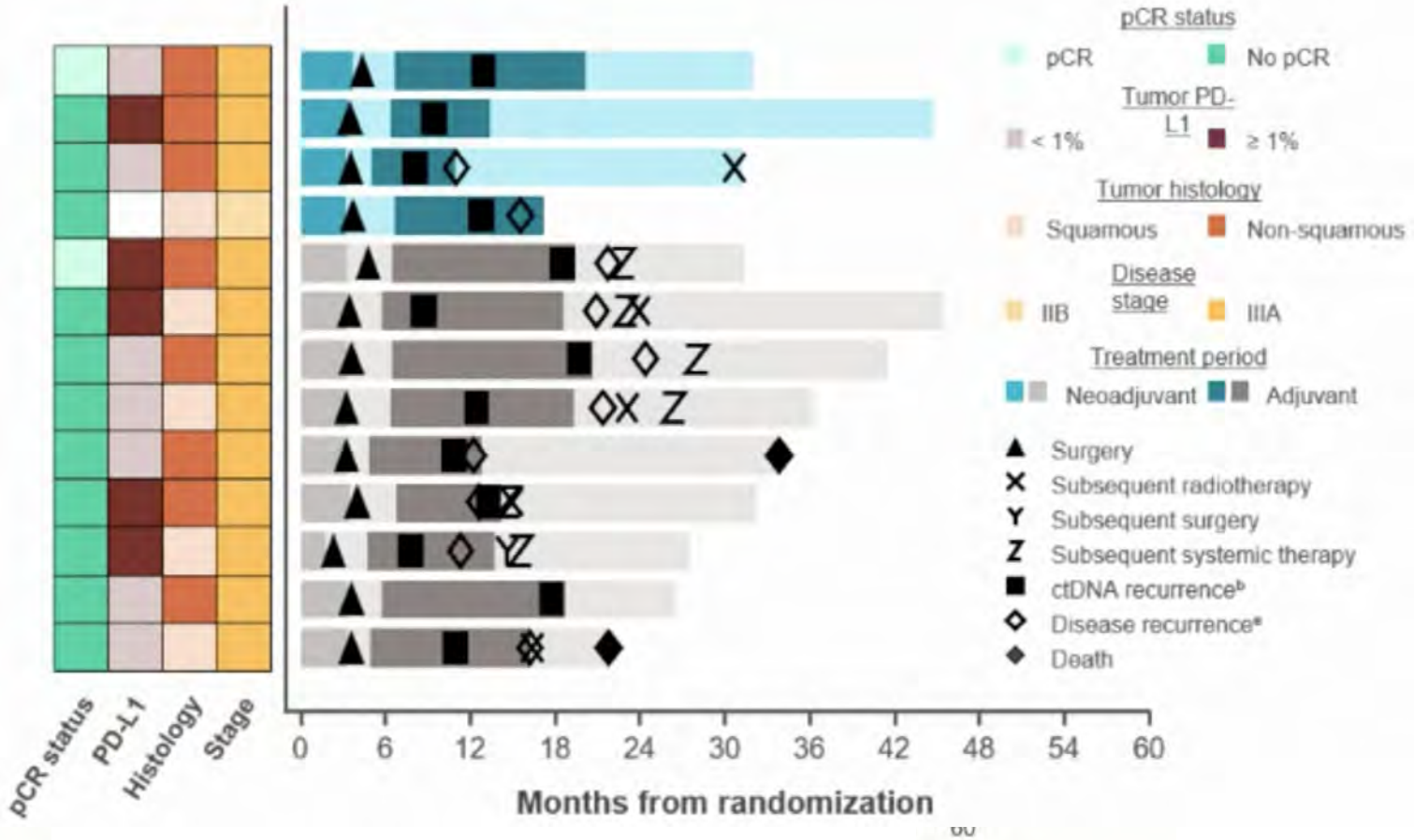


- Among 48 patients with no detectable ctDNA at C1D1 in the NIVO arm, 47 received ≥ 1 dose of adjuvant treatment[c]; all 44 patients in the PBO arm received ≥ 1 dose of adjuvant treatment

ctDNA recurrence[b]
(adjuvant C1D1 to last available assessment)



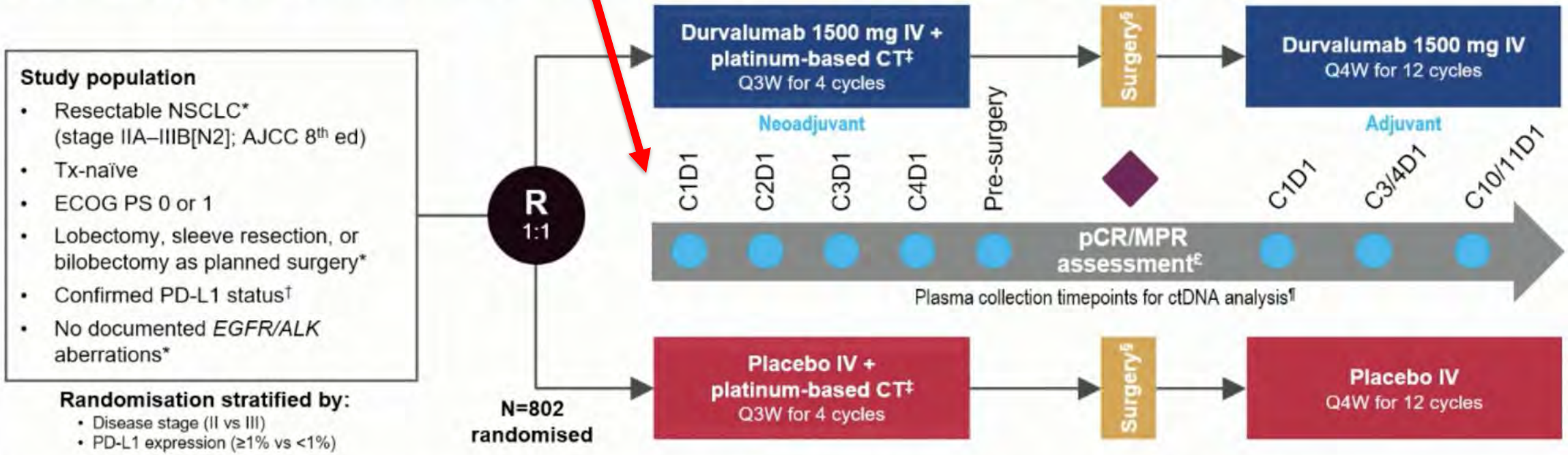
Outcomes in patients with ctDNA recurrence[d]



- Among 48 patients with no detectable ctDNA at C1D1 in the NIVO arm, 47 received ≥ 1 dose of adjuvant treatment[c]; all 44 patients in the PBO arm received ≥ 1 dose of adjuvant treatment

AEGEAN Study Design

Phase 3, global, randomised, double-blind, placebo-controlled study



- Plasma samples were collected at protocol-specified timepoints, including prior to each neoadjuvant Tx cycle, surgery, and adjuvant Tx at select cycles
- ctDNA analysis was performed using Invitae Personalized Cancer Monitoring,™ a tumour-informed MRD assay,[€1] with the exploratory analyses reported here based on data from the second EFS interim analysis
  - Patient-specific tumour-informed panels were designed to include 16-50 variants, identified by whole exome sequencing of Tx-naïve diagnostic biopsies only (rather than on-study surgical resections) to avoid selection bias

Reck M et al. ESMO 2024 LBA49 Ann Oncol 2024

Association of ctDNA Clearance* with pCR/MPR and Its Predictive Utility

- Among patients who were ctDNA-positive at baseline (neoadjuvant C1D1) in both arms (89.6%), all patients who had pCR and >93% who had MPR had ctDNA clearance at neoadjuvant C4D1†
- Absence of early ctDNA clearance may identify patients unlikely to have pCR
  - In both arms, lack of early ctDNA clearance identified patients with a low probability of having pCR (NPV: ≥89% at C2D1; 100% at C4D1)
  - Patients who had ctDNA clearance were more likely to have pCR in the D vs PBO arm (PPV: 49% vs 11% at C2D1)

Predictive Value of ctDNA Clearance at Different Timepoints for pCR‡

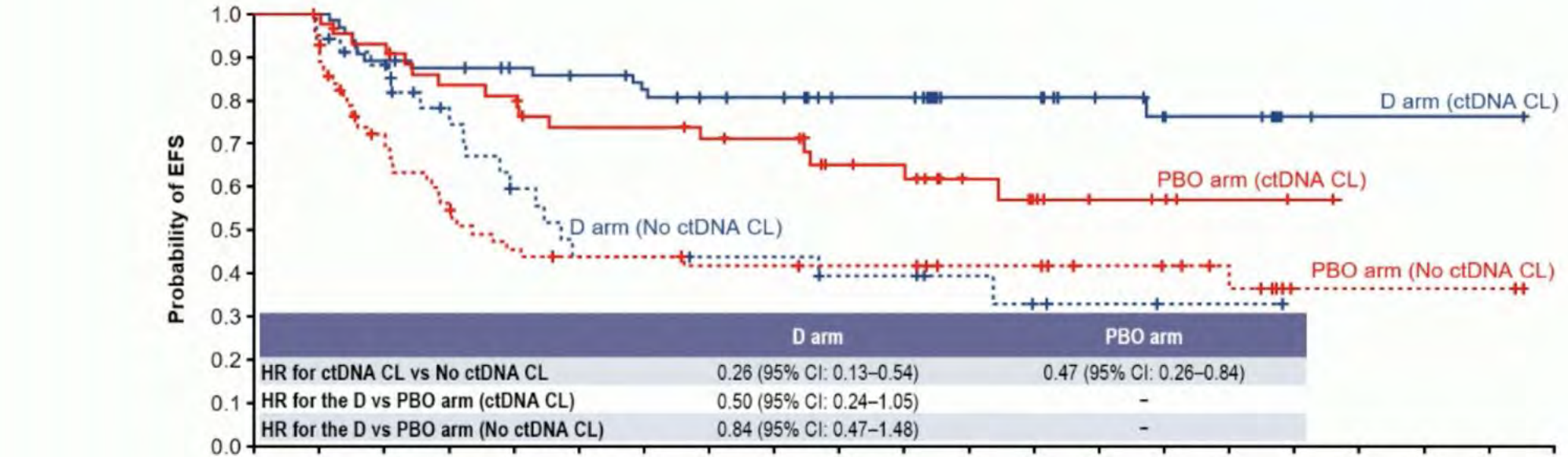
D arm	pCR	
	PPV	NPV
C2D1	49%	89%
C3D1	39%	94%
C4D1	40%	100%
Pre-surgery	40%	100%

PBO arm	pCR	
	PPV	NPV
C2D1	11%	98%
C3D1	12%	100%
C4D1	12%	100%
Pre-surgery	13%	100%

Reck M et al. ESMO 2024 LBA49 Ann Oncol 2024

Associations of ctDNA Clearance at Pre-surgery with EFS

- In both Tx arms, patients with ctDNA clearance at pre-Sx had improved EFS outcomes compared to patients without ctDNA clearance*
- Patients in the D arm had trends for longer EFS than patients in the PBO arm, regardless of ctDNA clearance status



	D arm	PBO arm
HR for ctDNA CL vs No ctDNA CL	0.26 (95% CI: 0.13–0.54)	0.47 (95% CI: 0.26–0.84)
HR for the D vs PBO arm (ctDNA CL)	0.50 (95% CI: 0.24–1.05)	-
HR for the D vs PBO arm (No ctDNA CL)	0.84 (95% CI: 0.47–1.48)	-

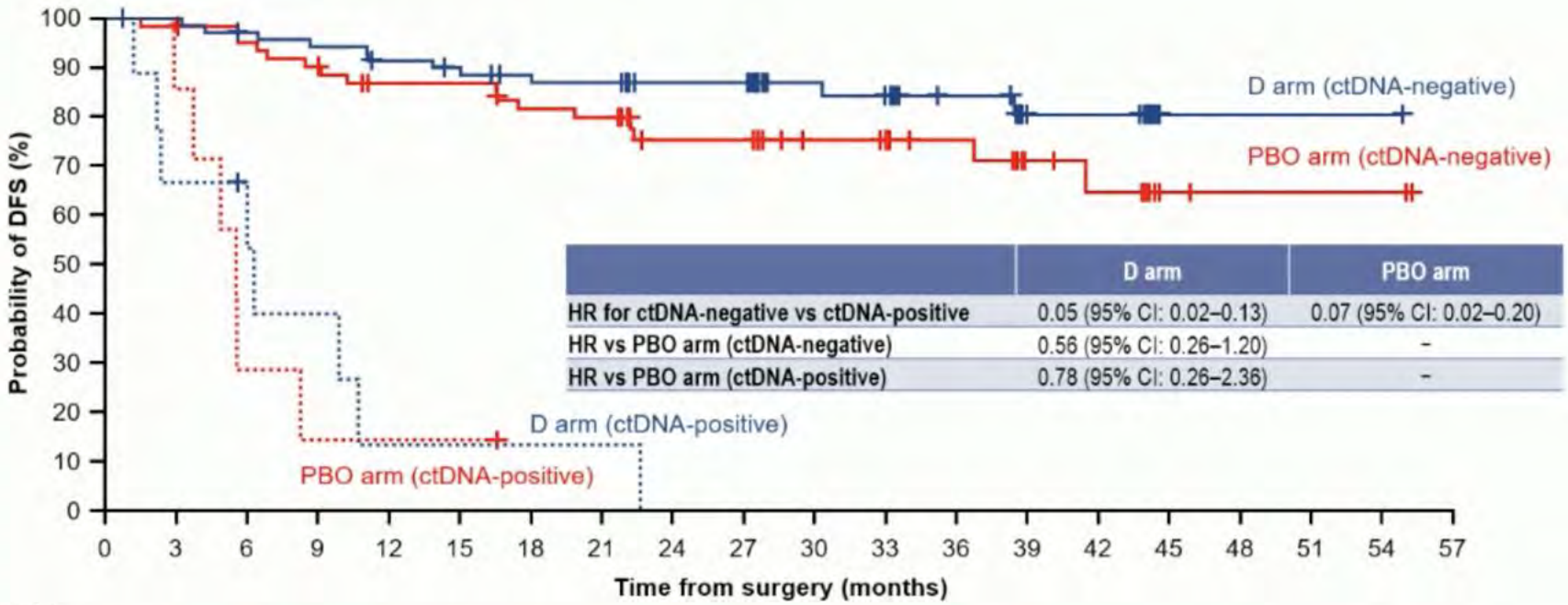
No. at risk

D arm (No ctDNA CL)	35	33	29	21	15	11	11	10	10	8	8	6	4	3	1	1	0	0	0	0	0
D arm (ctDNA CL)	65	65	57	55	52	50	47	44	43	35	35	24	24	19	14	12	2	1	1	1	0
PBO arm (No ctDNA CL)	63	60	41	31	25	23	23	21	21	17	17	14	14	11	10	7	2	2	2	2	0
PBO arm (ctDNA CL)	45	44	40	35	34	29	29	27	26	20	19	13	10	6	5	3	1	0	0	0	0

Reck M et al. ESMO 2024 LBA49 Ann Oncol 2024

Association of MRD at the Post-surgical Landmark (Adjuvant C1D1) with DFS*

- Among patients who completed Sx, patients with ctDNA detected at adjuvant C1D1 had the poorest DFS outcomes compared to ctDNA-negative patients in both Tx arms
- DFS trends favoured the D arm versus the PBO arm



	D arm	PBO arm
HR for ctDNA-negative vs ctDNA-positive	0.05 (95% CI: 0.02–0.13)	0.07 (95% CI: 0.02–0.20)
HR vs PBO arm (ctDNA-negative)	0.56 (95% CI: 0.26–1.20)	–
HR vs PBO arm (ctDNA-positive)	0.78 (95% CI: 0.26–2.36)	–

No. at risk

D arm (ctDNA-negative)	72	71	68	66	63	61	58	56	48	48	32	30	24	14	14	1	1	1	1	0
D arm (ctDNA-positive)	9	6	5	3	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0
PBO arm (ctDNA-negative)	62	61	58	55	50	50	46	45	32	32	25	24	18	12	10	3	2	2	2	0
PBO arm (ctDNA-positive)	7	6	2	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Reck M et al. ESMO 2024 LBA49 Ann Oncol 2024

CONCLUSIONS

- ctDNA clearance is a strong novel biomarker in perioperative setting
- Patients who have ctDNA clearance after completing neoadjuvant treatment, have very high likelihood to achieve pCR or MPR surgery
- Patients with ctDNA clearance have better clinical outcomes (EFS, OS)
- ctDNA positivity or recurrence after surgery is very poor prognostic factor
- True clinical value of ctDNA is currently unclear

K.Oselin

LIMITED STAGE SMALL CELL LUNG CANCER

- ✓ ADRIATIC – chemoradiation combined with IO durvalumab

/WCLC 2024, ESMO 2024, ELCC 2025/

K.Oselin

Phase 3 ADRIATIC trial

Ongoing, randomised, double-blind, placebo-controlled, multicentre, international study

- Stage I–III LS-SCLC (stage I/II inoperable)
- WHO PS 0 or 1
- Had not progressed following cCRT*
- PCI* permitted before randomisation

N=730

R†

Stratified by:
Disease stage (I/II vs III)
PCI (yes vs no)

- **Durvalumab** N=264
- **Placebo** N=266
- **Durvalumab + tremelimumab** N=200

Treatment until investigator-determined PD or intolerable toxicity, or for a **maximum of 24 months**

Dual primary endpoints:
- D vs P
  - PFS,‡ OS

Key secondary endpoints:
- D+T vs P
  - PFS,‡ OS

Other secondary endpoints:
- PFS/OS landmarks, safety

At the first interim analysis:[1]
- Consolidation durvalumab significantly improved the dual primary endpoints of OS and PFS versus placebo; generally consistent treatment benefit across predefined patient subgroups
- Treatment well tolerated; safety consistent with known safety profile of durvalumab in the post-cCRT setting
- Durvalumab + tremelimumab arm remained blinded

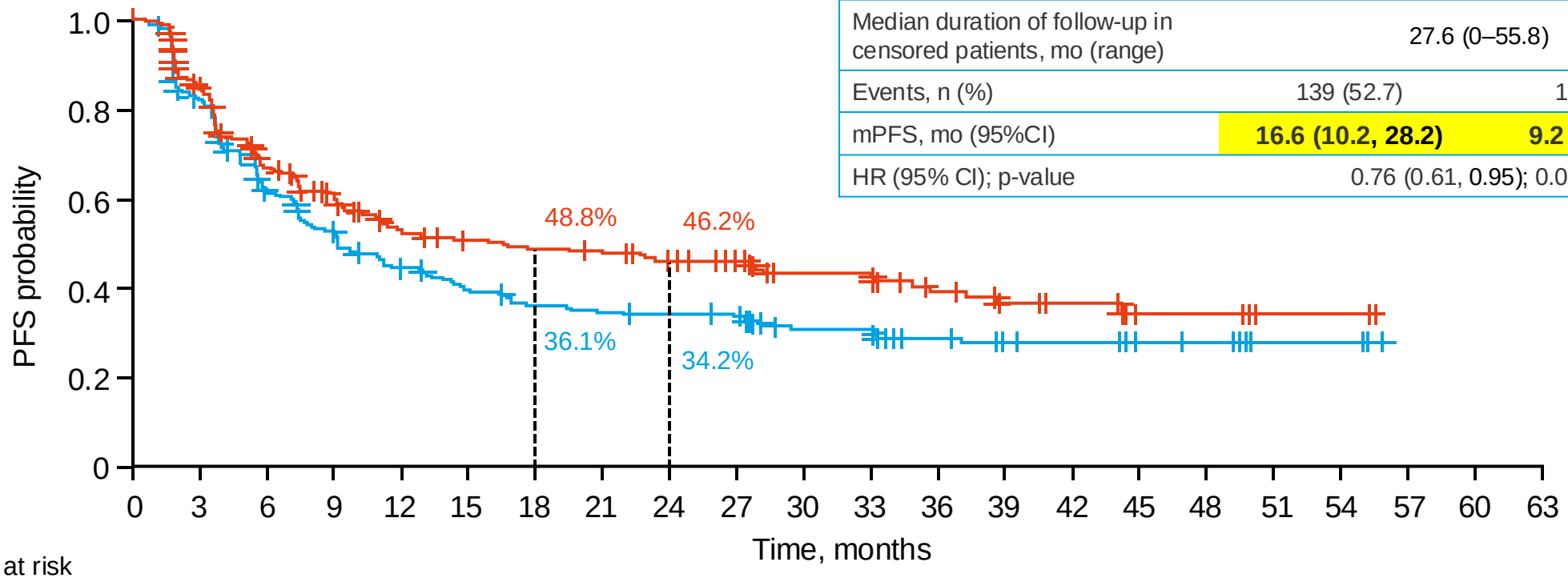
Senan S, et al. Ann Oncol 2024;35(suppl):Abstr LBA81

LBA5: ADRIATIC: durvalumab (D) as consolidation treatment (tx) for patients (pts) with limited-stage small-cell lung cancer (LS-SCLC) – Spigel DR, et al

- **Key results (cont.)**

PFS (dual primary endpoint)

	Durvalumab (n=264)	Placebo (n=266)
Median duration of follow-up in censored patients, mo (range)	27.6 (0–55.8)	
Events, n (%)	139 (52.7)	169 (63.5)
mPFS, mo (95%CI)	**16.6 (10.2, 28.2)**	**9.2 (7.4, 12.9)**
HR (95% CI); p-value	0.76 (0.61, 0.95); 0.0161	



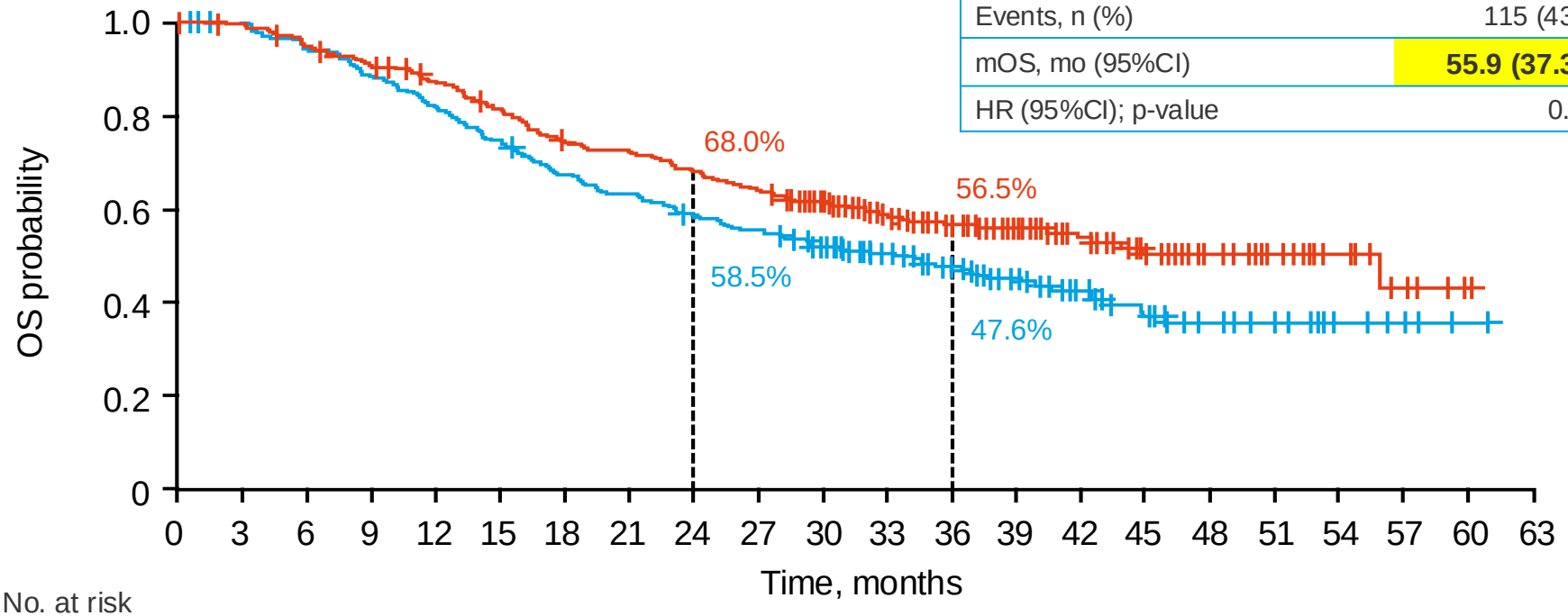
Spigel DR, et al. J Clin Oncol 2024;42(suppl):Abstr LBA5

LBA5: ADRIATIC: durvalumab (D) as consolidation treatment (tx) for patients (pts) with limited-stage small-cell lung cancer (LS-SCLC) – Spigel DR, et al

- **Key results**

OS (dual primary endpoint)

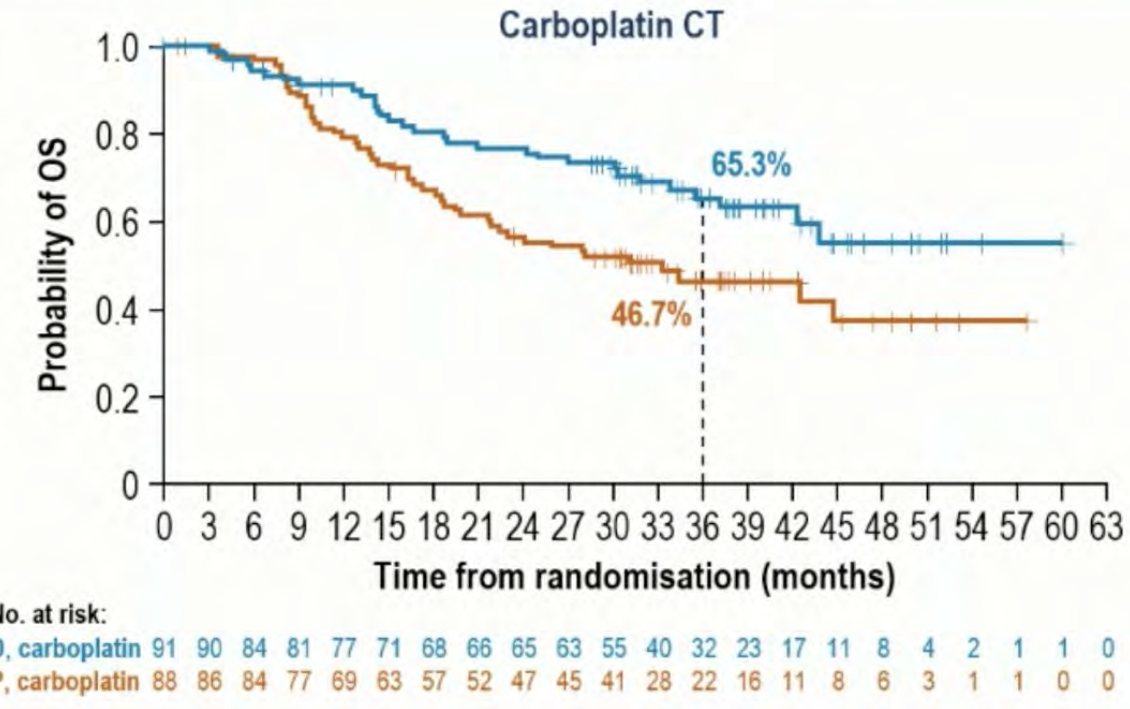
	Durvalumab (n=264)	Placebo (n=266)
Median duration of follow-up in censored patients, mo (range)	37.2 (0.1–60.9)	
Events, n (%)	115 (43.6)	146 (54.9)
mOS, mo (95%CI)	**55.9 (37.3, NE)**	**33.4 (25.5, 39.9)**
HR (95%CI); p-value	0.73 (0.57, 0.93); 0.0104	

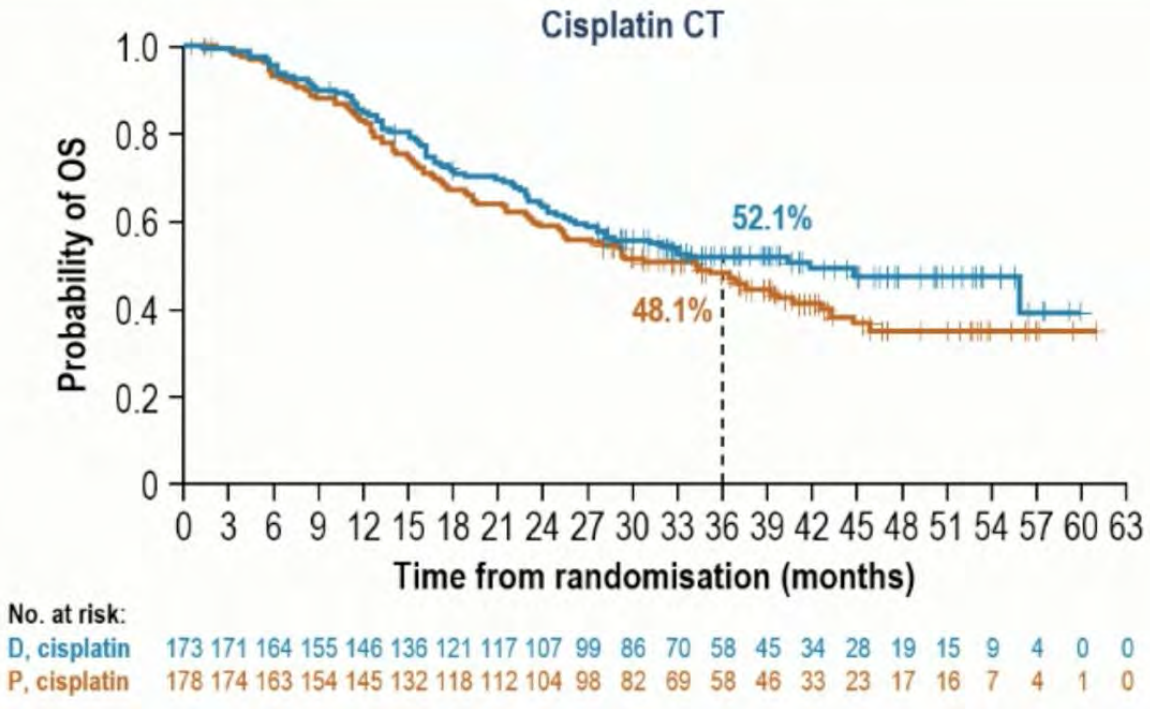


Spigel DR, et al. J Clin Oncol 2024;42(suppl):Abstr LBA5

Carboplatin and cisplatin CT subgroups – OS

	Carboplatin CT		Cisplatin CT		ITT	
	D (n = 91)	P (n = 88)	D (n = 173)	P (n = 178)	D (n = 264)	P (n = 266)
Median OS (95% CI), months	NR (42.5–NE)	33.4 (21.7–NE)	41.9 (27.7–NE)	34.3 (25.4–40.7)	55.9 (37.3–NE)	33.4 (25.5–39.9)
3-year OS, %	65.3	46.7	52.1	48.1	56.5	47.6
HR (95% CI)	0.56 (0.35–0.89)*		0.82 (0.61–1.10)*		0.73 (0.57–0.93)†	
Multivariable HR (95% CI)	0.55 (0.35–0.87)‡		0.81 (0.60–1.08)‡		–	

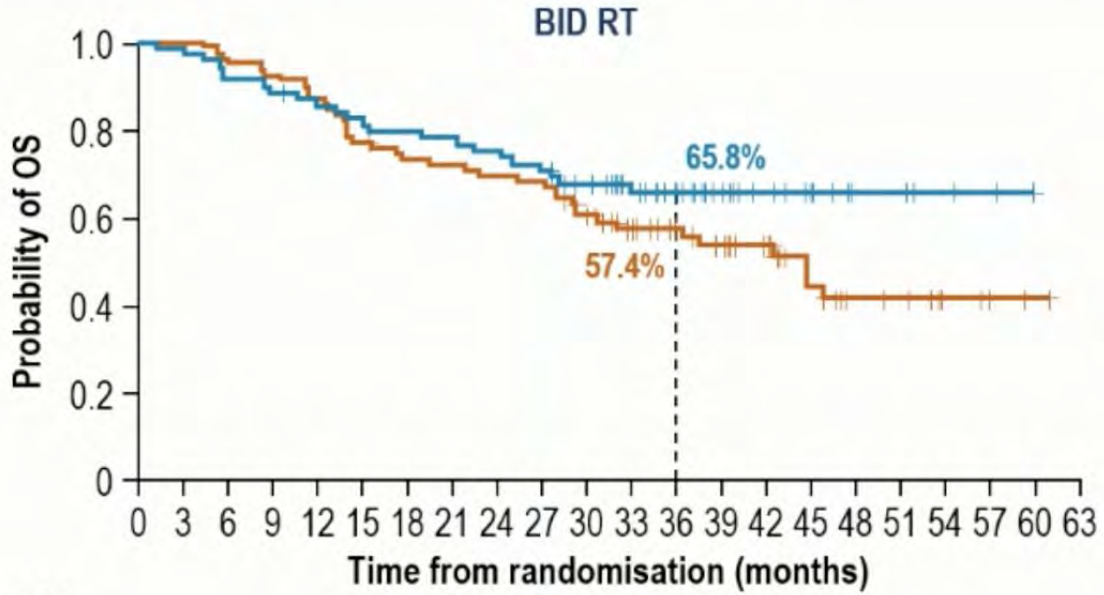




Senan S, et al. Ann Oncol 2024;35(suppl):Abstr LBA81

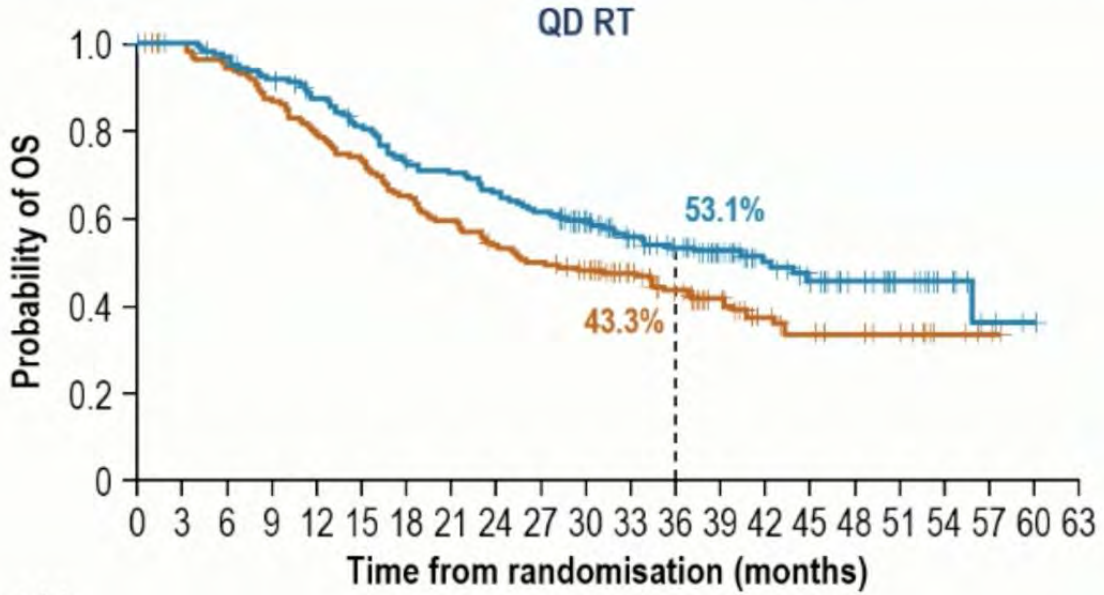
BID and QD RT subgroups – OS

	BID RT		QD RT		ITT	
	D (n = 69)	P (n = 79)	D (n = 195)	P (n = 187)	D (n = 264)	P (n = 266)
Median OS (95% CI), months	NR (NE–NE)	44.8 (29.4–NE)	41.9 (32.0–NE)	26.1 (21.7–36.8)	55.9 (37.3–NE)	33.4 (25.5–39.9)
3-year OS, %	65.8	57.4	53.1	43.3	56.5	47.6
HR (95% CI)	0.68 (0.40–1.14)*		0.72 (0.55–0.96)*		0.73 (0.57–0.93)†	
Multivariable HR (95% CI)	0.71 (0.42–1.18)‡		0.73 (0.55–0.96)‡		–	



No. at risk:

D, BID	69	68	63	61	59	56	54	53	51	48	42	35	27	18	13	10	5	5	3	2	0	0
P, BID	79	79	76	73	69	61	57	56	54	53	45	37	32	27	22	14	9	8	4	3	1	0



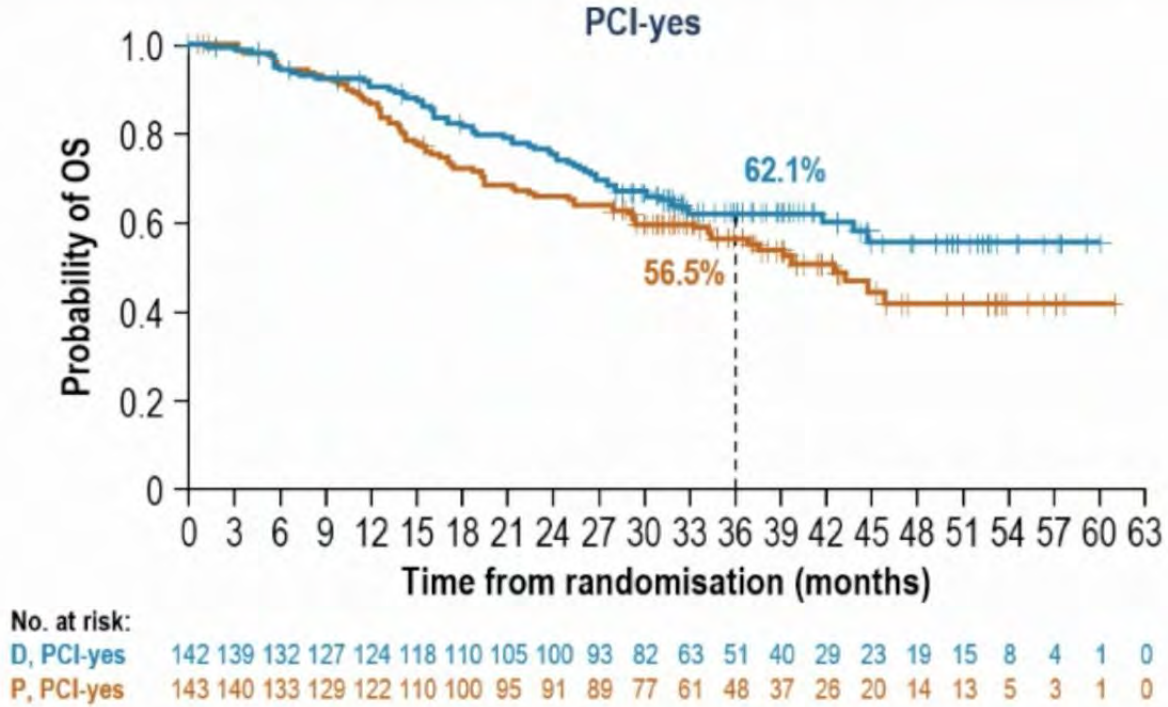
No. at risk:

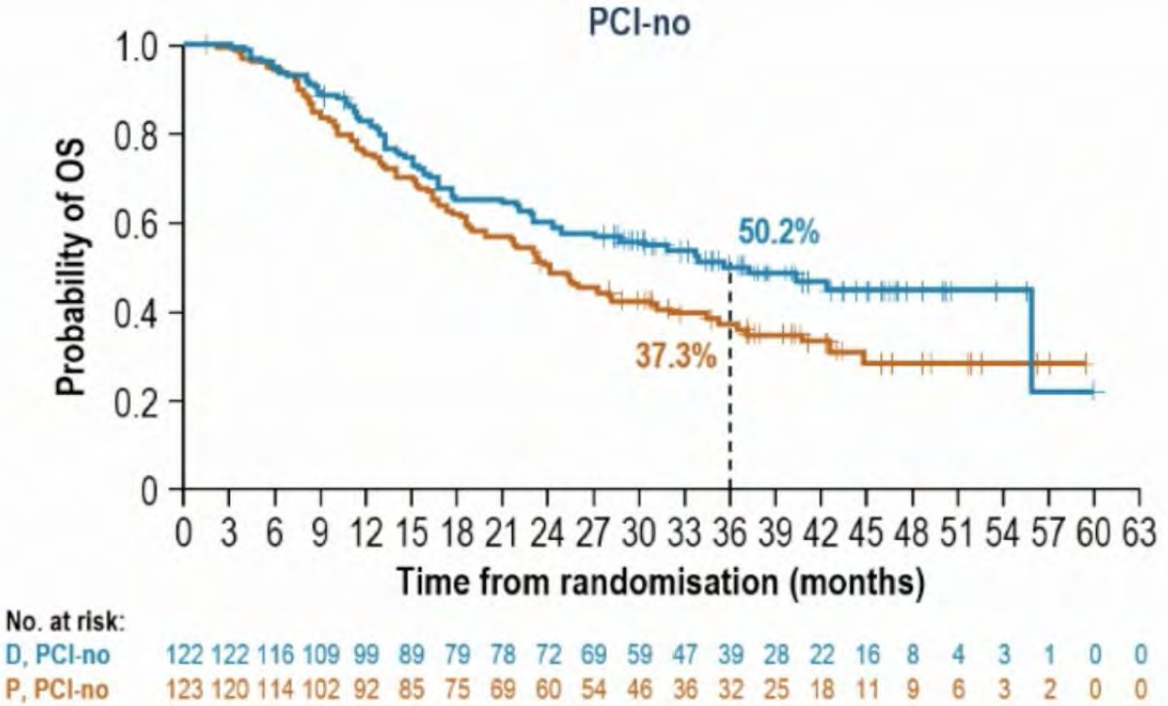
D, QD	195	193	185	175	164	151	135	130	121	114	99	75	63	50	38	29	22	14	8	3	1	0
P, QD	187	181	171	158	145	134	118	108	97	90	78	60	48	35	22	17	14	11	4	2	0	0

Senan S, et al. Ann Oncol 2024;35(suppl):Abstr LBA81

PCI-yes and PCI-no subgroups – OS

	PCI-yes		PCI-no		ITT	
	D (n = 142)	P (n = 143)	D (n = 122)	P (n = 123)	D (n = 264)	P (n = 266)
Median OS (95% CI), months	NR (43.9–NE)	42.5 (33.4–NE)	37.3 (24.3–NE)	24.1 (18.8–31.1)	55.9 (37.3–NE)	33.4 (25.5–39.9)
3-year OS, %	62.1	56.5	50.2	37.3	56.5	47.6
HR (95% CI)	0.75 (0.52–1.07)*		0.71 (0.51–0.99)*		0.73 (0.57–0.93)†	
Multivariable HR (95% CI)	0.72 (0.50–1.03)‡		0.73 (0.52–1.02)‡		–	





Senan S, et al. Ann Oncol 2024;35(suppl):Abstr LBA81

First progression by location (BICR)

Intrathoracic progression: Any lesion within the lungs and mediastinum

Extrathoracic progression: Any lesions outside the lungs, including the chest wall/diaphragm

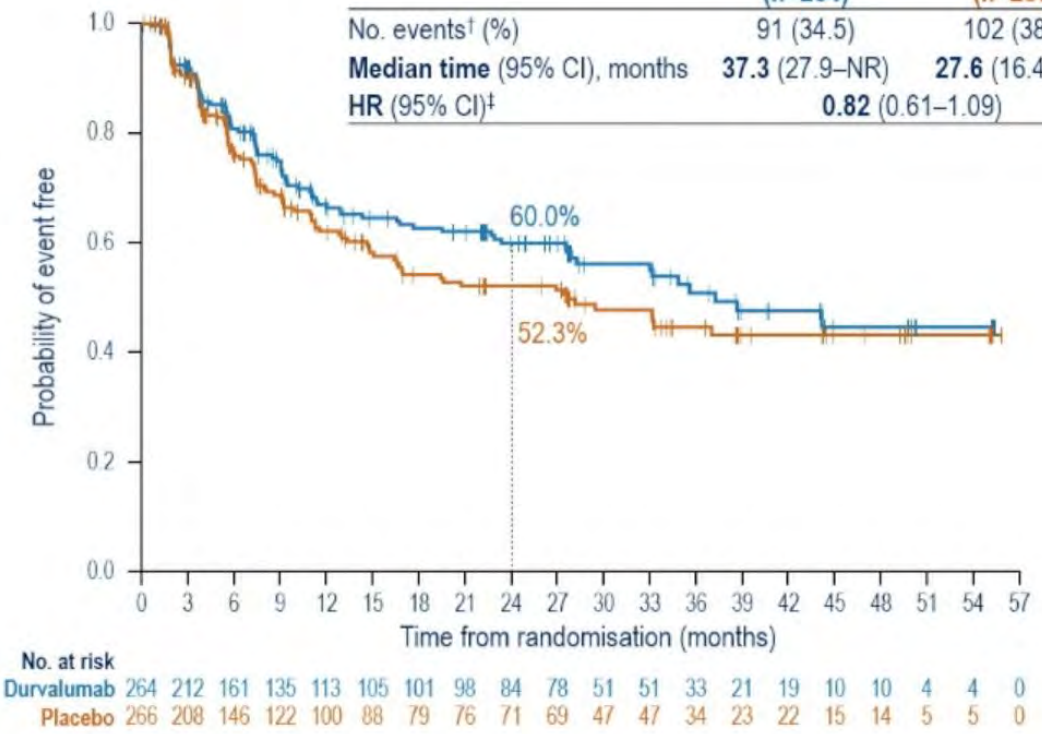
	Durvalumab (n=264)	Placebo (n=266)
First RECIST progression or death, n (%)	139 (52.7)	169 (63.5)
RECIST progression, n (%)	126 (47.7)	158 (59.4)
Intrathoracic only	74 (28.0)	79 (29.7)
Extrathoracic only	48 (18.2)	67 (25.2)
Simultaneous intrathoracic and extrathoracic	4 (1.5)	12 (4.5)
Death in absence of progression, n (%)	13 (4.9)	11 (4.1)

Senan S, et al. ELCC 2025 MO297

Time to first progression or death by location

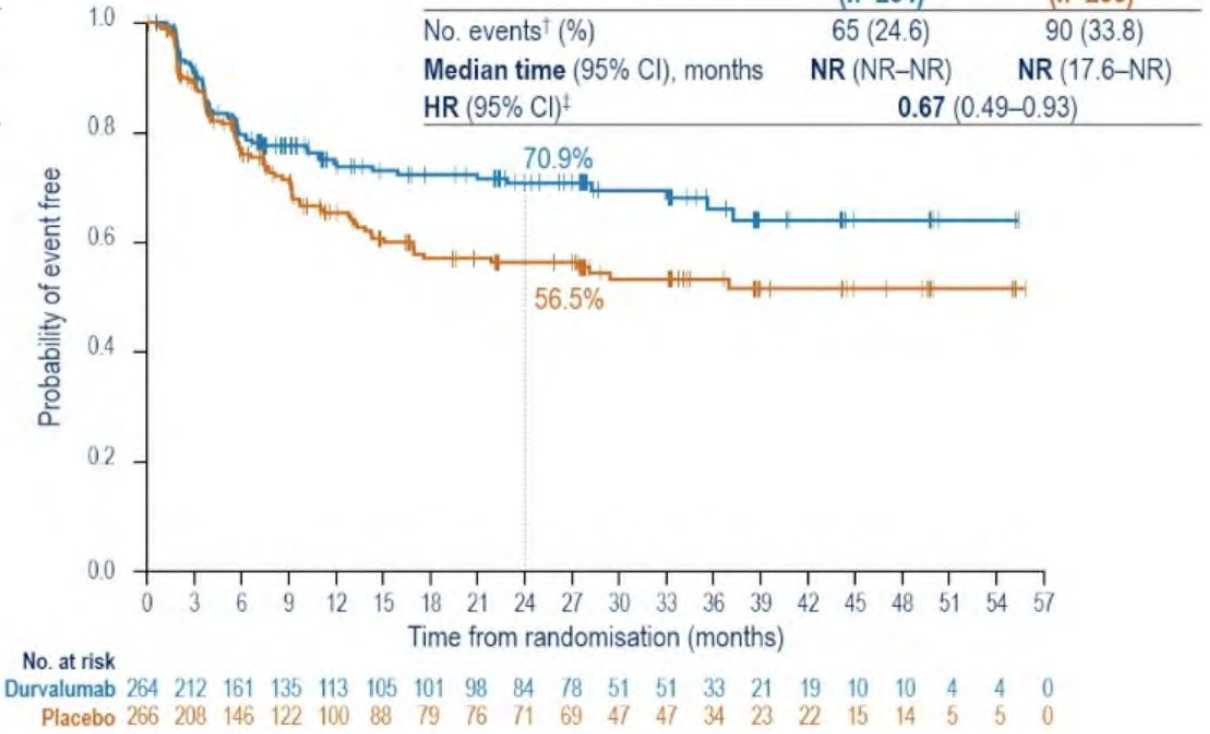
Time to intrathoracic progression* or death

	Durvalumab (n=264)	Placebo (n=266)
No. events† (%)	91 (34.5)	102 (38.3)
Median time (95% CI), months	**37.3** (27.9–NR)	**27.6** (16.4–NR)
HR (95% CI)‡	**0.82** (0.61–1.09)	



Time to extrathoracic progression* or death

	Durvalumab (n=264)	Placebo (n=266)
No. events† (%)	65 (24.6)	90 (33.8)
Median time (95% CI), months	**NR** (NR–NR)	**NR** (17.6–NR)
HR (95% CI)‡	**0.67** (0.49–0.93)	



Senan S, et al. ELCC 2025 MO297

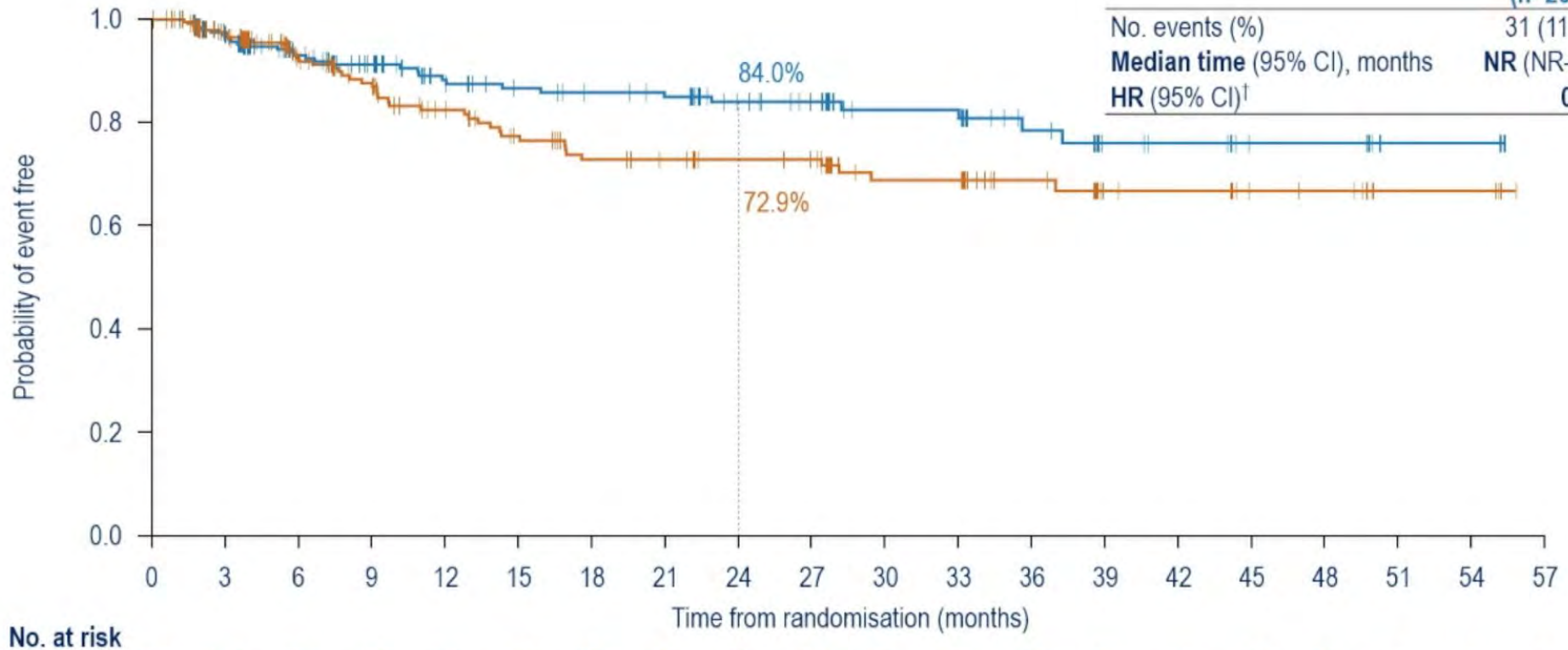
New extrathoracic lesions at first progression

	Durvalumab (n=264)	Placebo (n=266)
Any new extrathoracic lesion*, n (%)	52 (19.7)	79 (29.7)
No. of new organ locations, n (%)		
1	50 (18.9)	76 (28.6)
2	2 (0.8)	3 (1.1)
New lesions by organ location, n (%)		
Brain/CNS	18 (6.8)	33 (12.4)
PCI Yes	4 (2.8)†	9 (6.3)‡
PCI No	14 (11.5)†	24 (19.5)‡
Liver	14 (5.3)	16 (6.0)
Adrenal gland	9 (3.4)	8 (3.0)
Distant lymph node	5 (1.9)	8 (3.0)
Bone	2 (0.8)	6 (2.3)
Other§	6 (2.3)	11 (4.1)

Senan S, et al. ELCC 2025 MO297

Time to brain/CNS progression* or death

	Durvalumab (n=264)	Placebo (n=266)
No. events (%)	31 (11.7)	44 (16.5)
Median time (95% CI), months	**NR** (NR–NR)	**NR** (NR–NR)
HR (95% CI)†	**0.64** (0.40–1.01)	



No. at risk																				
Durvalumab	264	212	161	135	113	105	101	98	84	78	51	51	33	21	19	10	10	4	4	0
Placebo	266	208	146	122	100	88	79	76	71	69	47	47	34	23	22	15	14	5	5	0

Senan S, et al. ELCC 2025 MO297

CONCLUSIONS

ADRIATIC study

- ✓ Durvalumab after chemoradiation significantly improved EFS (median 16.6 mo *vs* 9.2 mo; HR=0.76 [0.61-0.95]
- ✓ PCI, carboplatin, RT twice daily or once daily fractionation
- ✓ OS was significantly improved with durvalumab (median 55.9 mo *vs* 33.4 mo; HR=0.73 [0.57-0.93]
- ✓ Durvalumab is approved for LS-SCLC as consolidation by FDA (Dec 2024) and EMA (Mar 2025)

K.Oselin

SUMMARY OF RECENT ADVANCES

- EARLY STAGE NSCLC, perioperative setting, no actionable genomic alterations

  ctDNA could be potential marker to guide treatment decisions after surgery

-

Not ready for clinical use

- LIMITED STAGE SCLC – IO post radiochemo

Contacts ESMO

European Society for Medical Oncology
Via Ginevra 4, CH-6900 Lugano
T. +41 (0)91 973 19 00
esmo@esmo.org

esmo.org

State-of-the-art therapies for patients with locally advanced unresectable NSCLC

Dr Ullas Batra
Co Director, Dept of Medical Oncology
Chief, Thoracic medical Oncology
Rajiv Gandhi Cancer Institute & Research Centre
Delhi

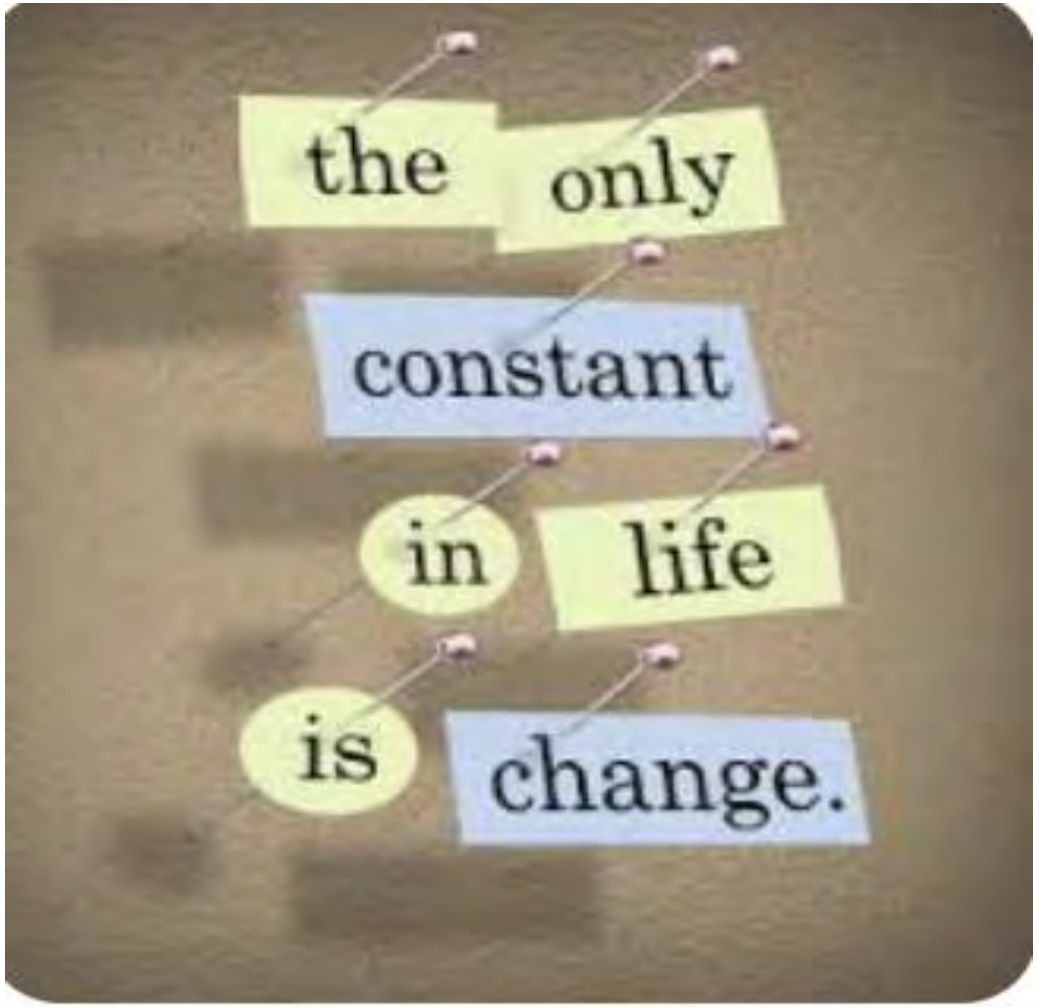
ESMO WEBINAR SERIES

ESMO IN FOCUS

DECLARATION OF INTEREST

Commercial Organizations	Relationship
AstraZeneca, Pfizer, Janssen, Roche, MSD, BMS, Guardant	Honorarium or Advisory Board Member
AstraZeneca, Pfizer, BMS	Research Grant to the Institute

My subsequent reactions(in 2025)

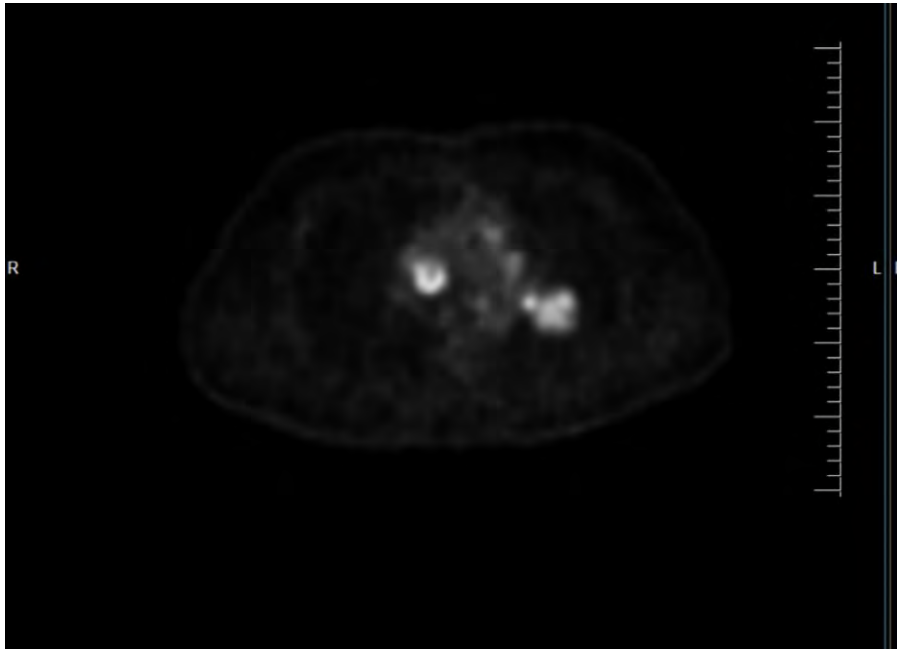


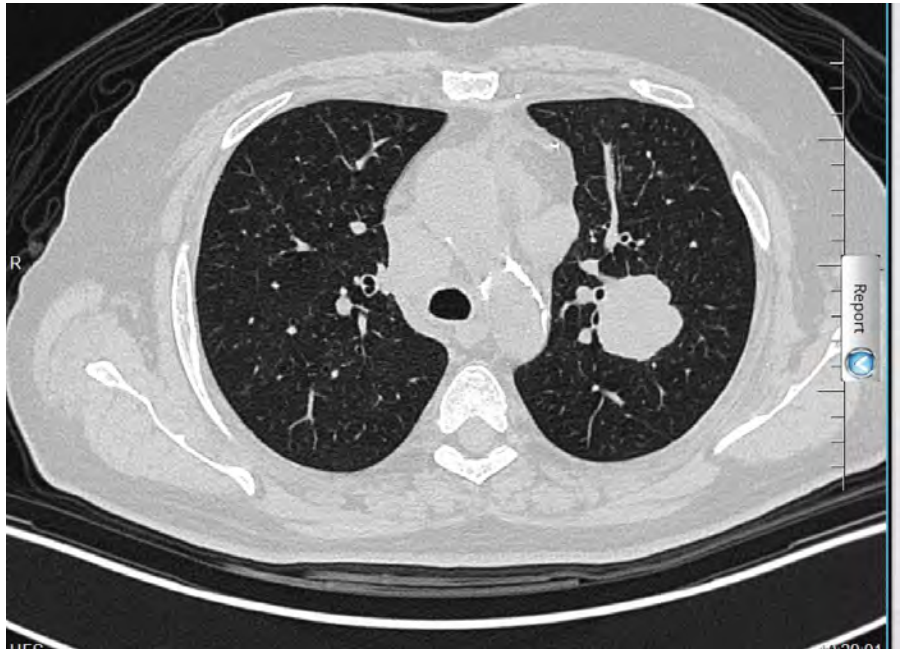
CASE SCENARIO -1

- 65 year old male , current smoker
- Presented with h/o cough with expectoration, breathlessness
- PET CT – Left lung mass with hilar and bilateral mediastinal lymphadenopathy. No evidence of distant metastases
- MRI Brain- No evidence of brain metastases
- Underwent EBUS and Bronchoscopy biopsy – adenocarcinoma, TTF 1 positive. Contralateral lymph node positive for adenocarcinoma cells
- Final stage of disease –cT2N3M0(bilateral multistation bulky mediastinal lymphadenopathy)

Speakers own case

THE CASE CONTINUES



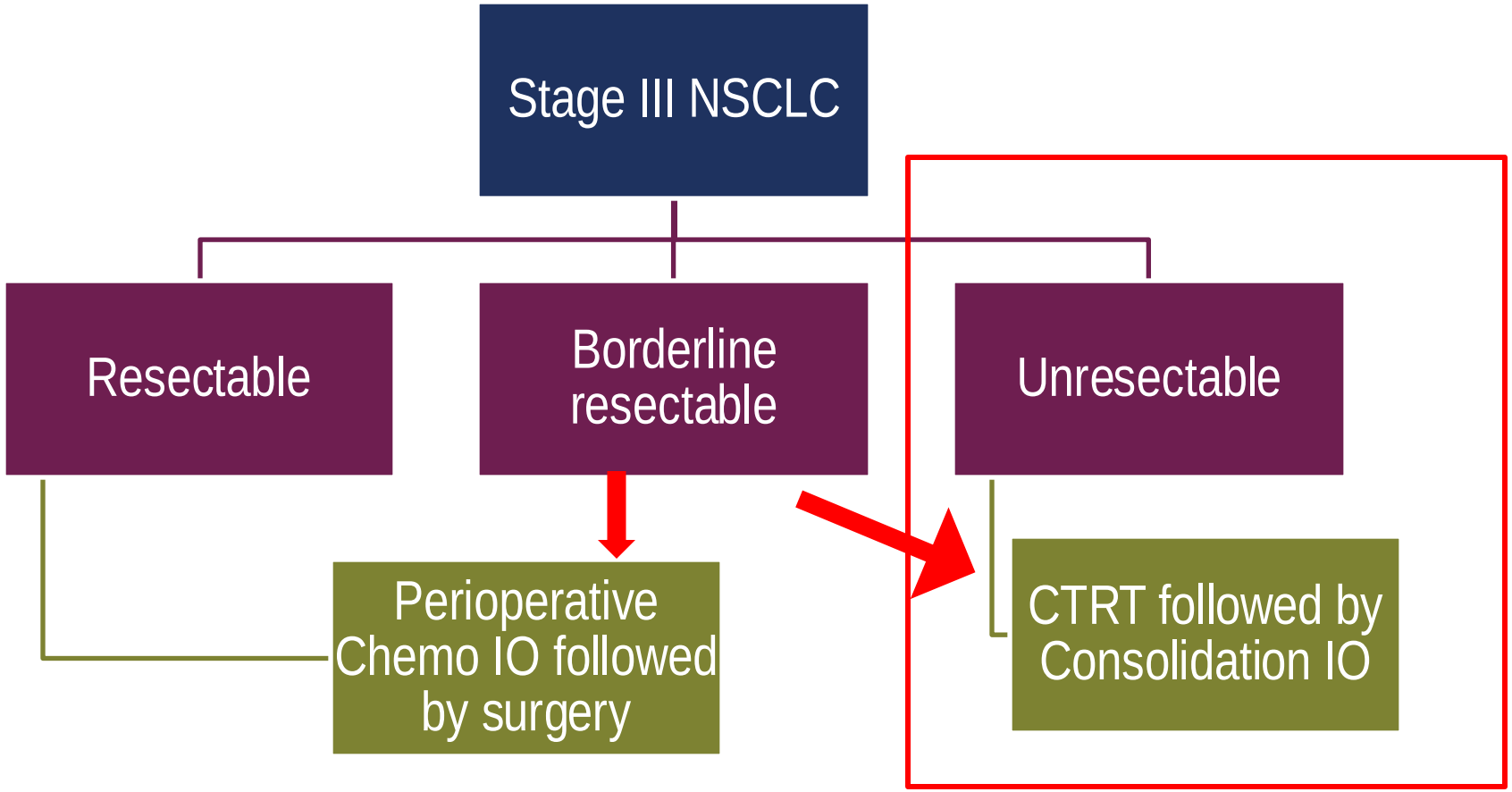


RT opinion- difficult to achieve dose constraints for organs at risk during radiation (eg: higher risk of esophagitis)

Speakers own case

MSC discussion- sequential chemotherapy followed by RT

STAGE III NSCLC- A HETEROGENOUS GROUP

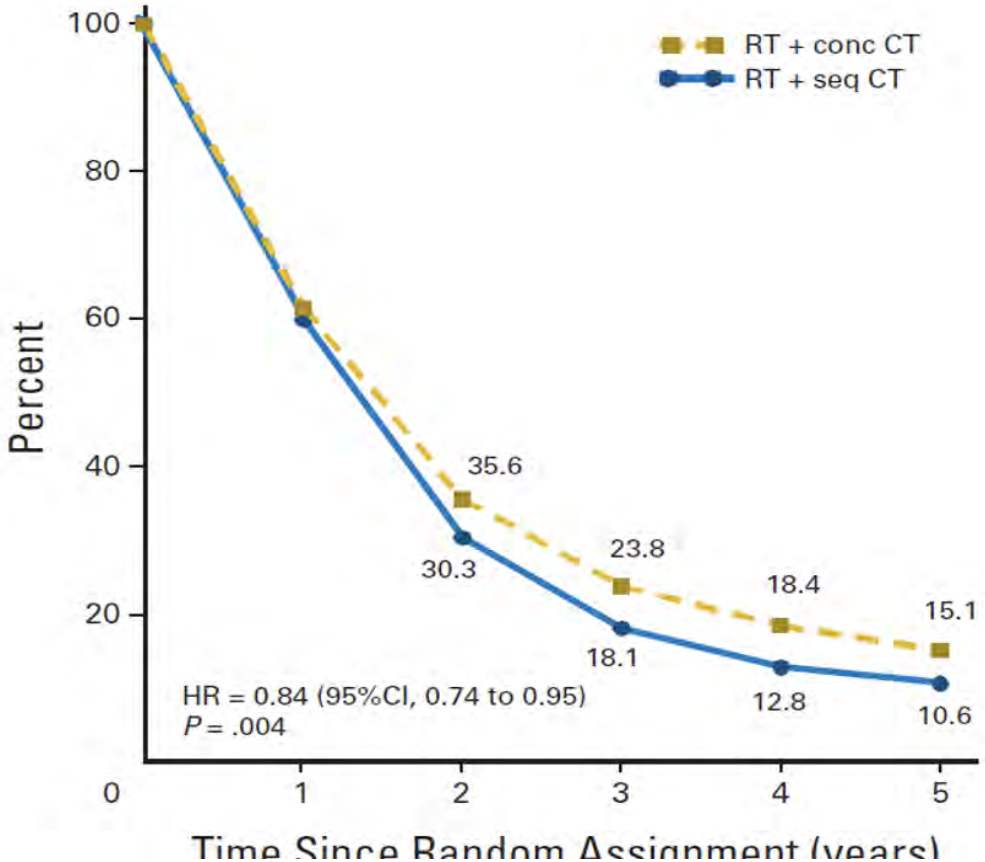


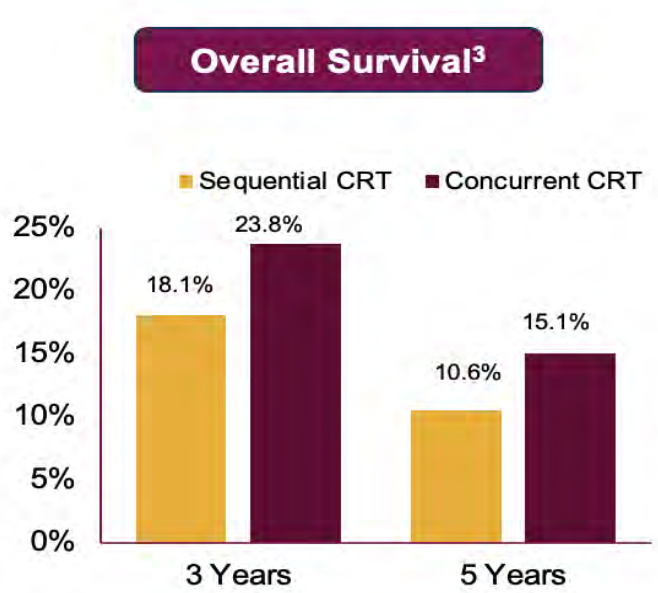
Topic for todays deliberation- management of unresectable NSCLC

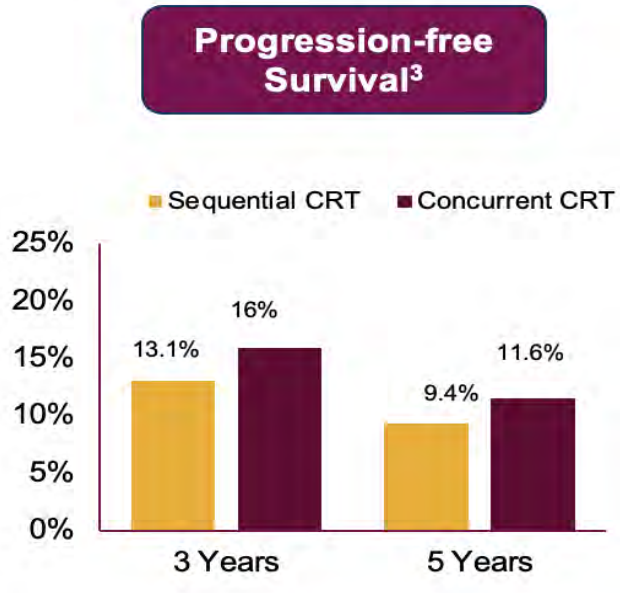
- Pre IO era
- IO era
- Probable answers to some Practical questions
- Future directions

A BRIEF HISTORY OF RT CT IN UNRESECTABLE NSCLC

(The pre Immunotherapy era)







Overall survival: absolute benefit		
2 years	3 years	5 years
5.3%	5.7%	4.5%

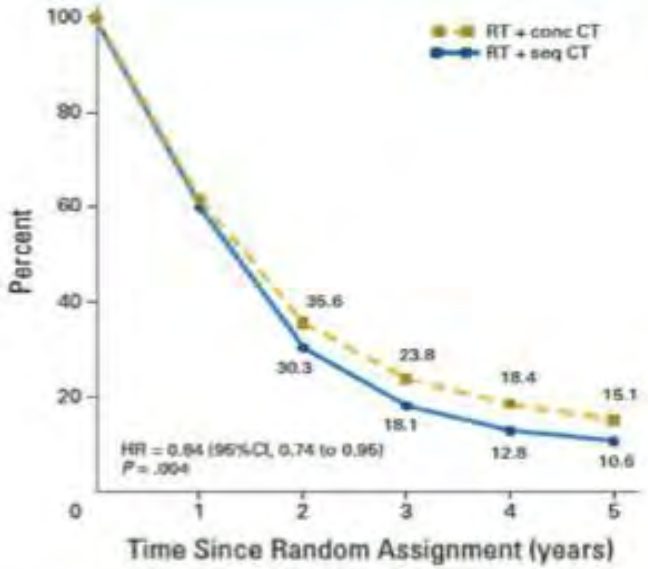
Anne Auperin et al, JCO 2010

CCRT is the treatment of choice for inoperable stage III NSCLC

CAN WE IMPROVE THE STANDARD TREATMENT ?

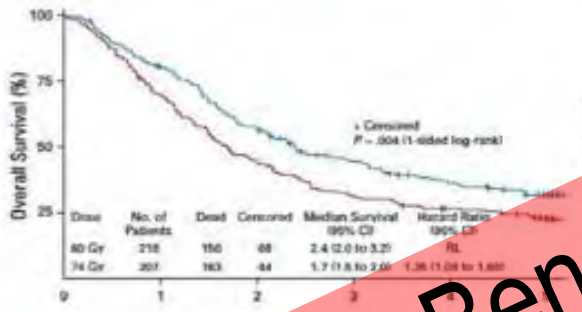
(The pre Immunotherapy era)

SoC: Concurrent CRT > Sequential CRT

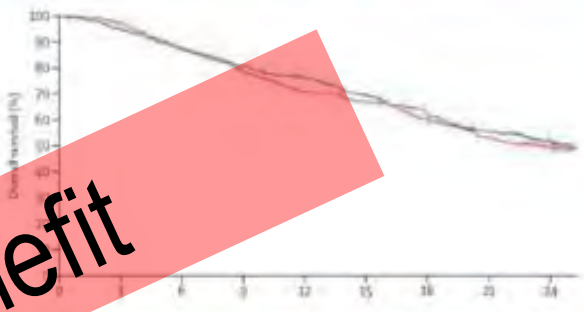


RTOG0617: cCTRT (60 Gy)
mOS: 28.7 months. 5-year OS rate: 32%
(Only 44% of patients suitable for cCTRT)

RTOG 0617: 60Gy *vs.* 74Gy

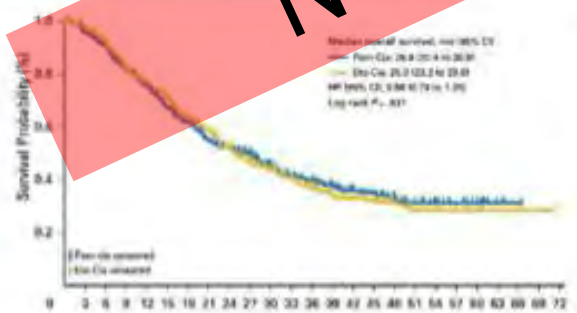


RTOG 0617: Cetuximab *vs.* No-cetuximab

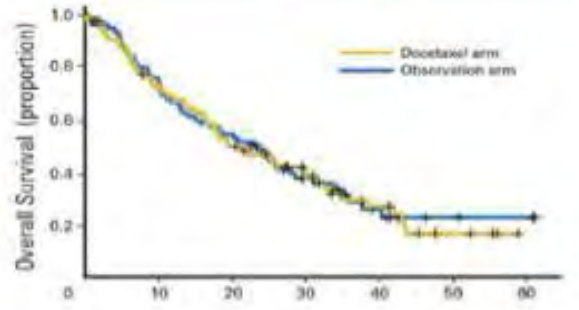


NO Benefit

PROCLAIM: Cis/Pem *vs.* ET/VP16

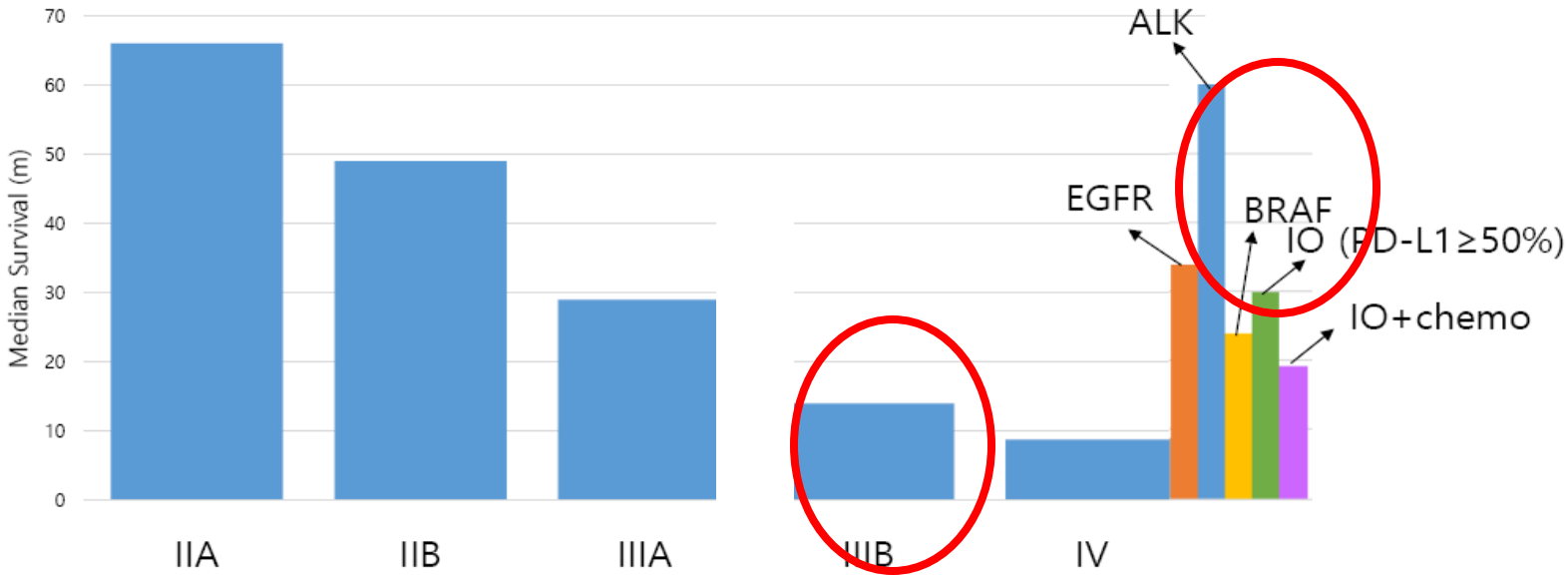


HOG: Consolidation Placebo *vs* Docetaxel



Aupérin – JCO 2010 * Senan – JCO 2016 * Bradley – JCO 2019 * Bradley – LO 2015 * Kelly – JCO 2008 * De Ruysscher – Ann Oncol 2009

MEDIAN SURVIVAL BY STAGE – A PARADOXICAL EFFECT



Goldstraw P, JTO 2015; Mok TS, JCO 2018; Solomon BJ, JCO 2018; Planchard D, Lancet Oncol 2017; Brahmer JR, WCLC 2017; Lopes G, ASCO 2018; Socinski MA, NEJM 2018

Prior To IO usage, survival in stage IV in certain subsets > stage III disease

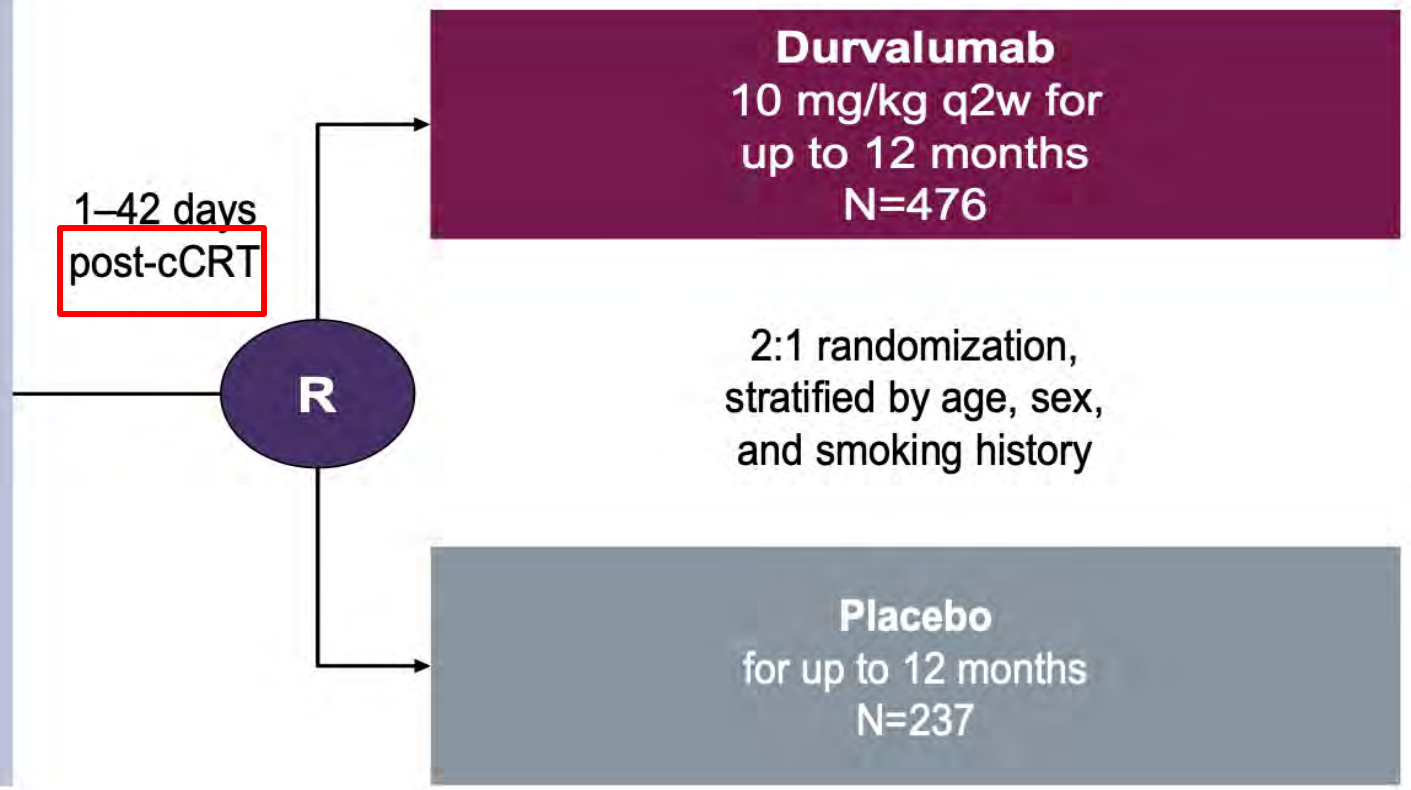
THE ADVENT OF IO IN STAGE III UNRESECTABLE NSCLC

The PACIFIC trial- IO era

- Unresectable, Stage III NSCLC without progression after definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- If available, archived pre-cCRT tumor tissue for PD-L1 testing*

All-comers population
(i.e. irrespective of PD-L1 status)

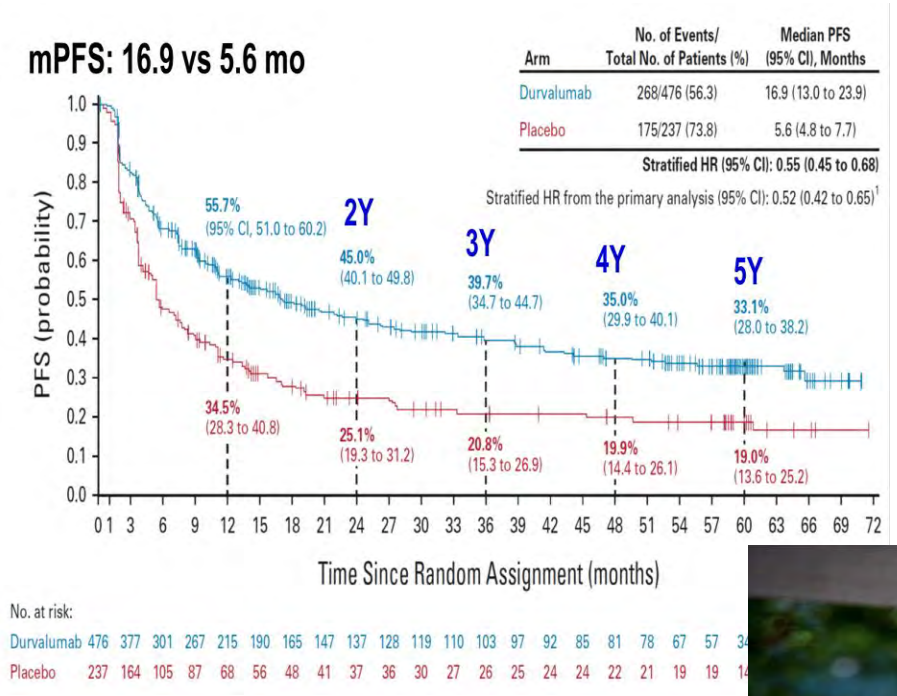
N=713 randomized

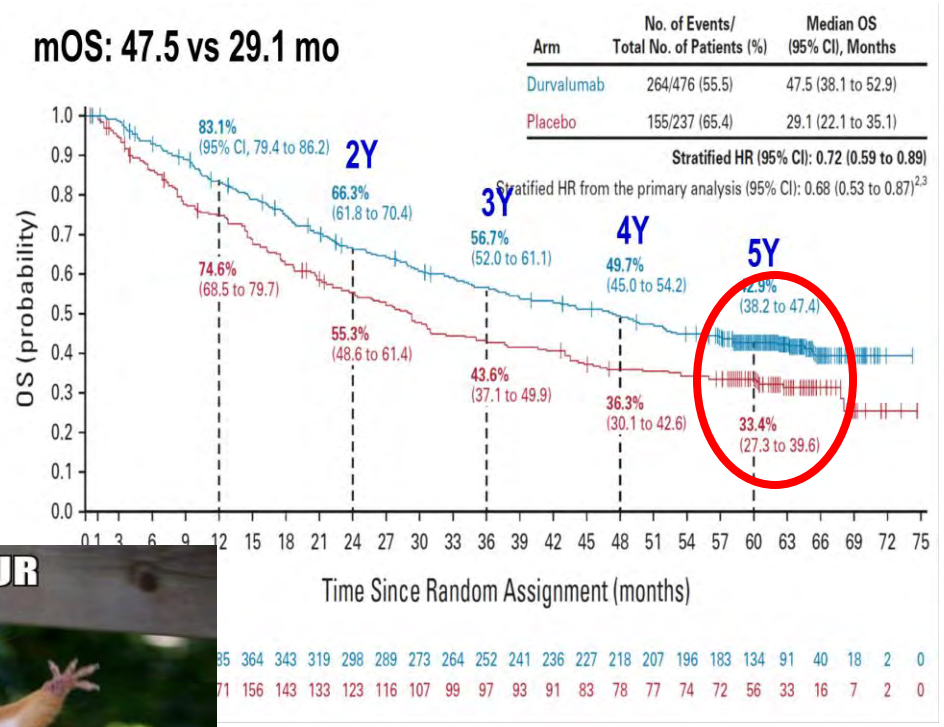


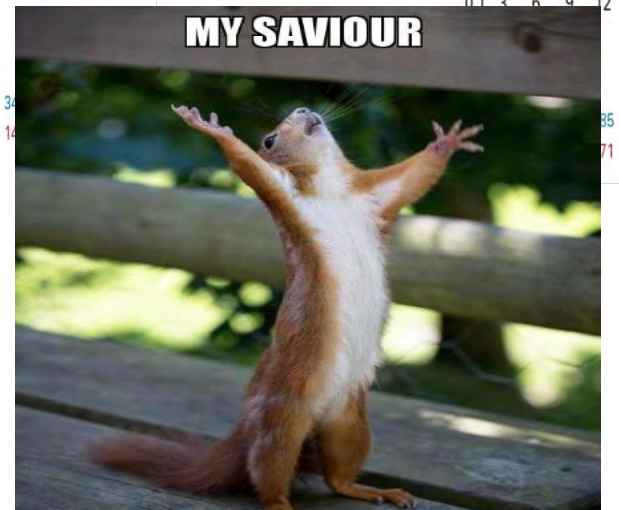
Antonio S, NEJM

Durvalumab After Chemoradiotherapy in Patients With Unresectable Stage III NSCLC (PACIFIC) (cCRT)

Updated 5 year survival data – PACIFIC (The IO era)







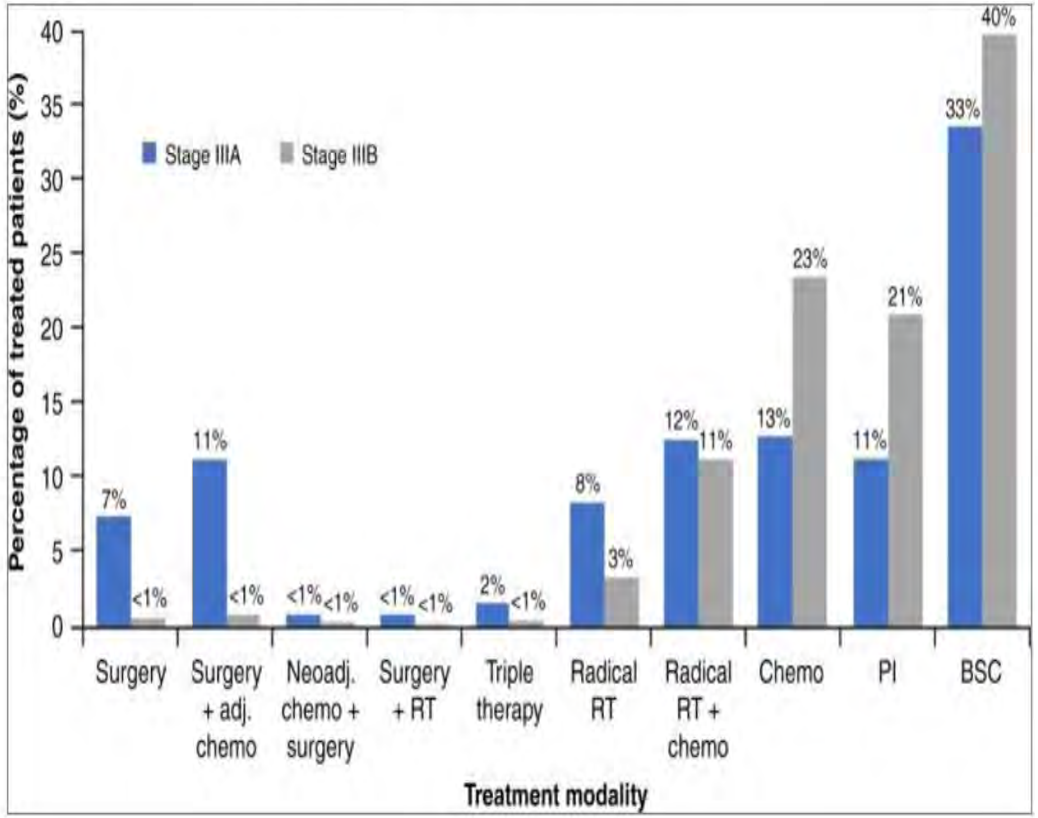
David R. Spigel et al, JCO 2022

FEW UNANSWERED QUESTIONS AFTER PACIFIC TRIAL

What is the benefit of Durvalumab after sequential CTRT ?	What is the ideal duration of Consolidation Durvalamab?	Can we incorporate Durvalumab as Concurrent radiation sensitizer	Does Consolidation Durvalamab work in oncogene addicted NSCLC ?
PACIFIC 5 and 6	PACIFIC 5 and 6	PACIFIC 2	LAURA trial

PACIFIC TRIAL APPLICABILITY IN THE REAL WORLD

UK: Treatment landscape for stage III in 2018



Stage IIIA
- Surgery: 22%
- RT: 23%

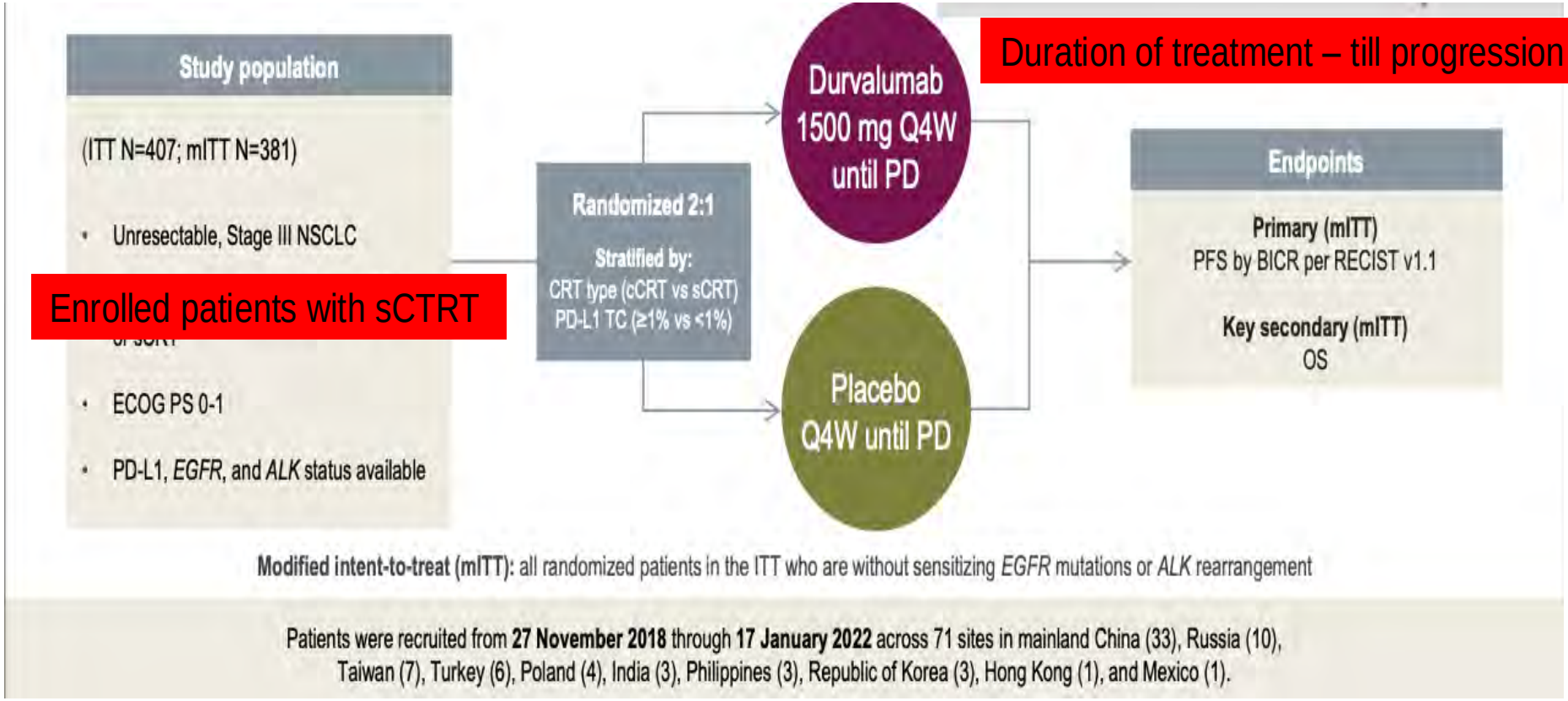
Stage IIIB
- Surgery: 5%
- RT: 16%

Real world incidence of Concurrent RT CT
Netherlands- 55%
Belgium -35%
UK-33%
Kindle study (Aian)-29.2%

Reasons for sequential / only RT
Poor PS
Comorbidities
Concerns about field of RT
Concerns about toxicity
Availability of RT machines

Walraven Clin Oncol 2017; Evison BJC 2020

PACIFIC 5 TRIAL DESIGN



Yi-Long Wu, ESMO ASIA 2024

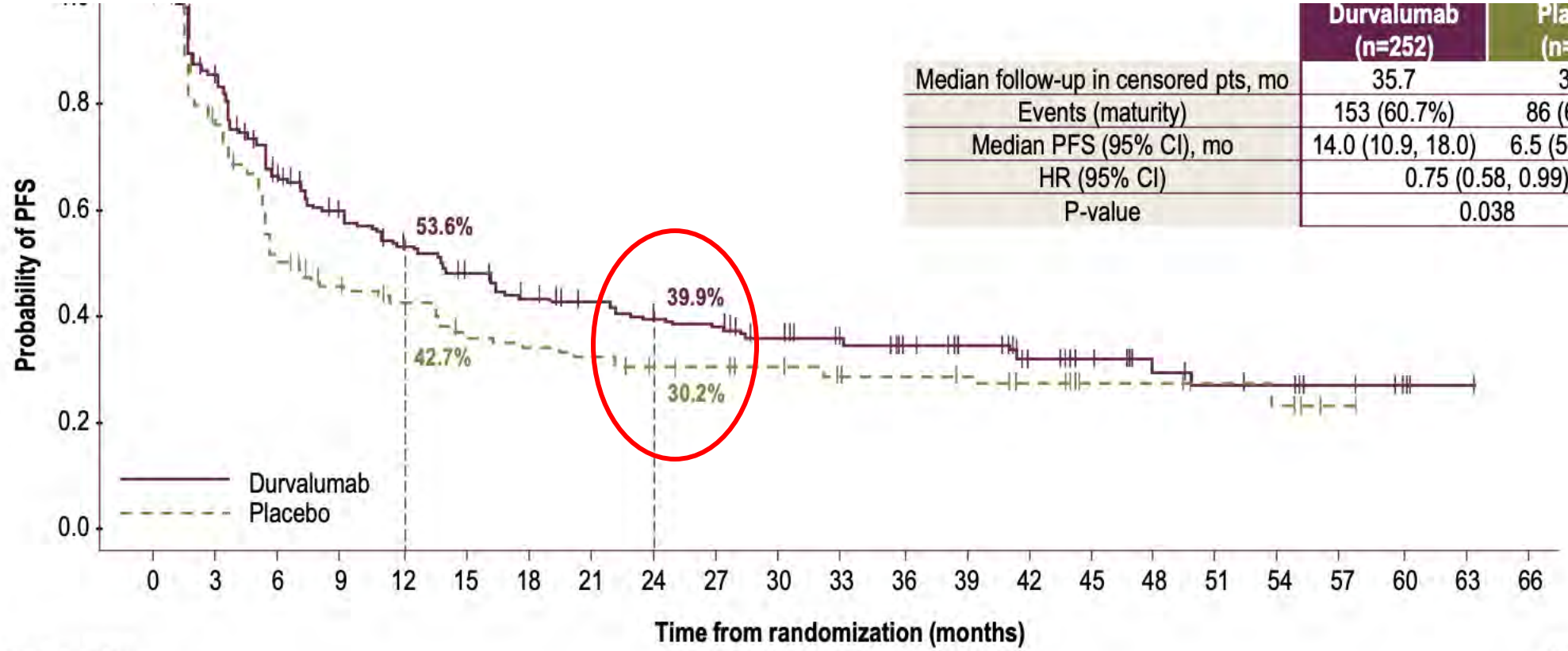
PACIFIC -5 PATIENT DISPOSITION

		Durvalumab (n=252)	Placebo (n=129)
Prior therapy, n (%)	cCRT	168 (66.7)	90 (69.8)
	sCRT	84 (33.3)	39 (30.2)
Best response to previous cCRT or sCRT, n (%)	Complete response	0	1 (0.8)
	Partial response	163 (64.7)	84 (65.1)
	Stable disease	89 (35.3)	44 (34.1)
	Progression	0	0
Platinum-based chemotherapy, n (%)	Cisplatin	122 (48.4)	64 (49.6)
	Carboplatin	124 (49.2)	62 (48.1)
	Cis/carbo	6 (2.4)	3 (2.3)
Time from last dose of radiation to randomization, days	Mean	22.6	22.8
	Median (range)	23.0 (3–42)	24.0 (7–32)
Time from last dose of radiation to randomization, n (%)	<14 days	26 (10.3)	14 (10.9)
	≥14 days	226 (89.7)	115 (89.1)
Definitive radiotherapy*, n (%)		252 (100.0)	129 (100.0)
Total radiation dose, Gy†	n	256	132
	Mean	60.2	59.7
	Median (range)	60.0 (10–66)	60.0 (5–66)
Total radiation dose, n (%)†	<54 Gy	3 (1.2)	3 (2.3)
	≥54–≤66 Gy	250 (99.2)	129 (100.0)
	>66–≤74 Gy	0	0
	>74 Gy	0	0

Yi-Long Wu, ESMO ASIA 2024

PFS BY BICR-ITT

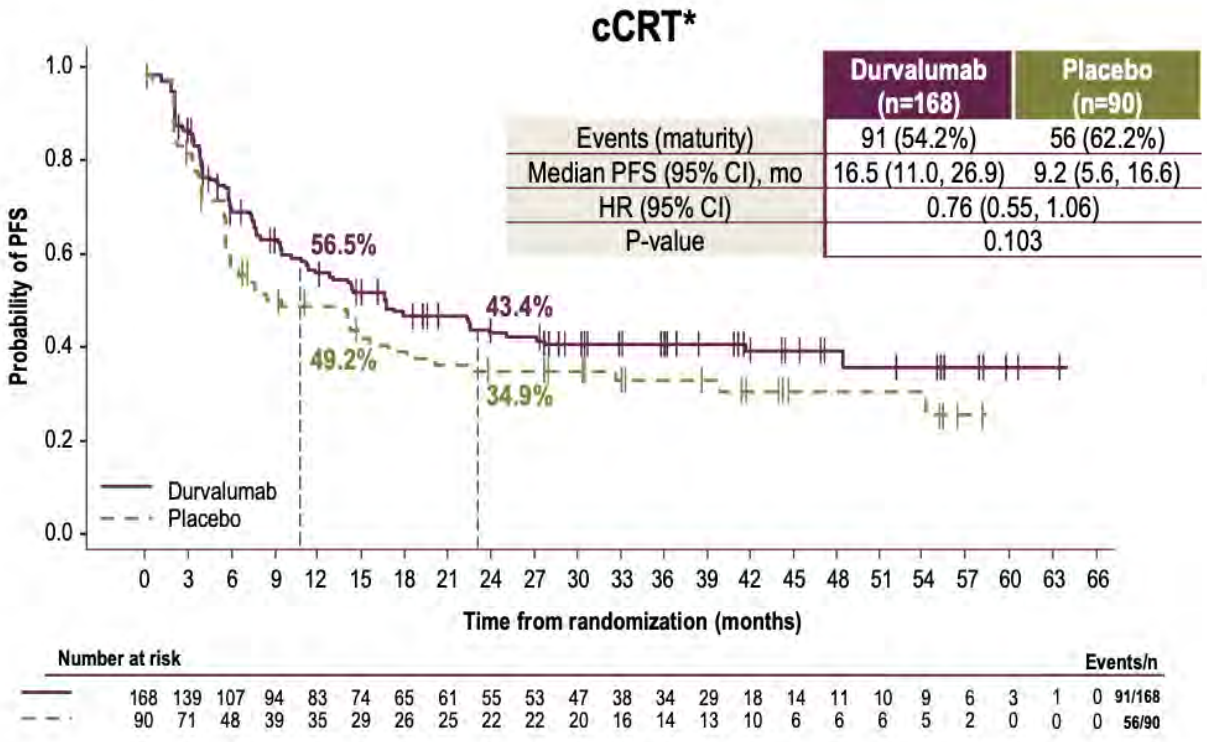
	Durvalumab (n=252)	Placebo (n=129)
Median follow-up in censored pts, mo	35.7	30.5
Events (maturity)	153 (60.7%)	86 (66.7%)
Median PFS (95% CI), mo	14.0 (10.9, 18.0)	6.5 (5.4, 13.8)
HR (95% CI)	0.75 (0.58, 0.99)	
P-value	0.038	

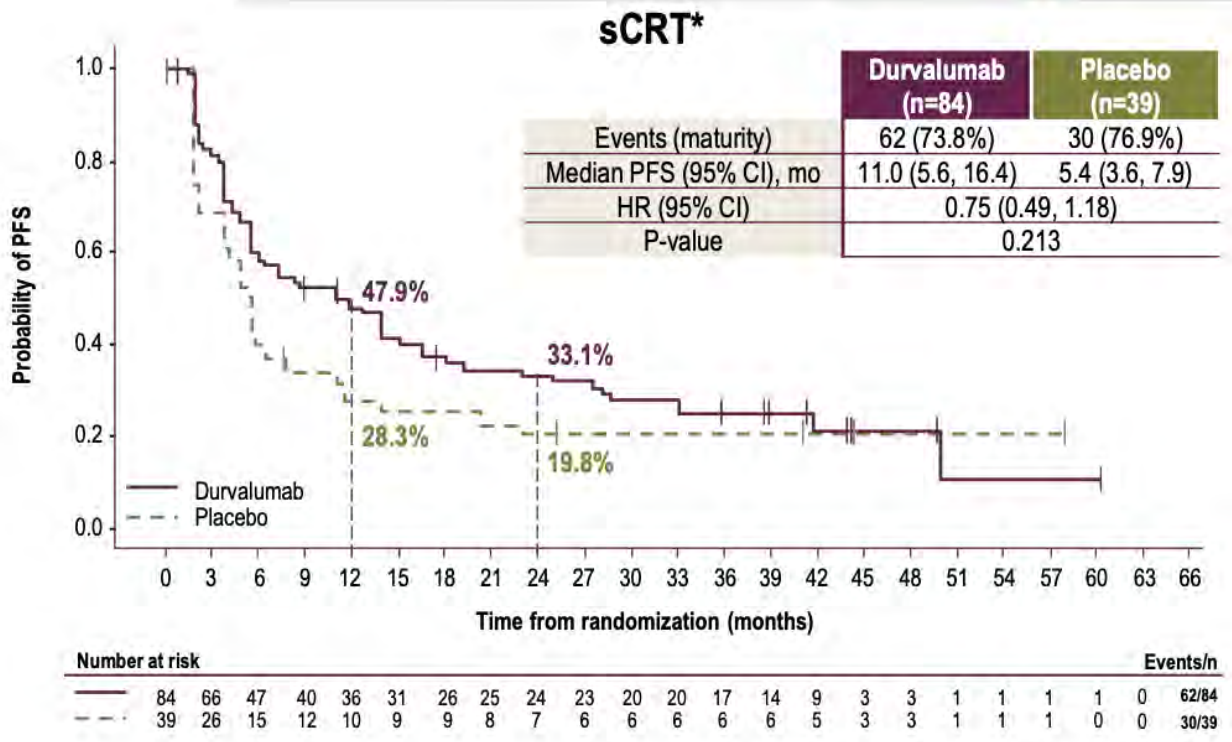


Number at risk																							Events/n
Durvalumab	252	205	154	134	119	105	91	86	79	76	67	58	51	43	27	17	14	11	10	7	4	1	0	153/252
Placebo	129	97	63	51	45	38	35	33	29	28	26	22	20	19	15	9	9	7	6	3	0	0	0	86/129

Yi-Long Wu, ESMO ASIA 2024

PFS BENEFIT – COMPARISION B/W CCRT AND CCTRT





Benefit similar to PACIFIC regimen
Is there any benefit of indefinite Durvalumab?

Late censoring seen
? To consider starting with IO chemo and consolidate with RT later

Yi-Long Wu, ESMO ASIA 2024

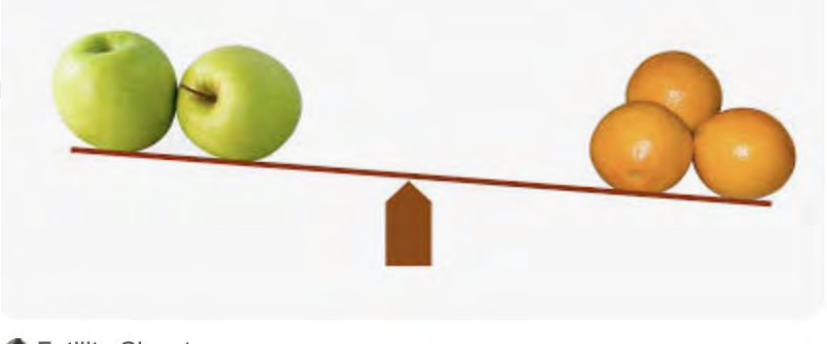
THE TOXICITY PROFILE OF DURVALUMAB VS PLACEBO

Preferred term, n (%)	Durvalumab (n= 271)	Placebo (n=134)
Any	257 (94.8)	112 (83.6)
Pneumonitis* or radiation pneumonitis	**107 (39.5)**	**54 (40.3)**
Grade 1	42 (15.5)	20 (14.9)
Grade 2	51 (18.8)	30 (22.4)
Grade 3	10 (3.7)	3 (2.2)
Grade 4	0	0
Grade 5	4 (1.5)	1 (0.7)
Pneumonia	51 (18.8)	15 (11.2)
Hypothyroidism	51 (18.8)	10 (7.5)
Anemia	41 (15.1)	20 (14.9)
COVID-19	35 (12.9)	15 (11.2)
Cough	32 (11.8)	16 (11.9)
Upper respiratory tract infection	31 (11.4)	16 (11.9)
Hyperthyroidism	33 (12.2)	8 (6.0)
Alanine aminotransferase increased	27 (10.0)	6 (4.5)

Consistent safety profile with no new safety signals

Yi-Long Wu, ESMO ASIA 2024

LETS DO THE CARDINAL SIN OF MEDICAL ONCOLOG CROSS TRIAL COMPARISONS



Consolidation therapy trials with concurrent CRT regimen

	PACIFIC	PACIFIC-R	GEMSTONE-301 (cCRT)	PACIFIC-5 (All)	PACIFIC-5 (cCRT)
n	713	1071	254	407	258
Drug	Durvalumab	Durvalumab	Sugemalimab	Durvalumab	Durvalumab
mPFS (mo, IO vs Control)	16.8 vs 5.6	23.7	10.5 vs 6.4	14 vs 6.5	16.5 vs 9.2
HR PFS (95%)	0.52 (0.42-0.65)	NA	0.68 (0.45-1.01)	0.75 (0.58 – 0.99)	0.76 (0.55-1.06)
% Cisplatin	55.4%	51.2%	50.1% across cCRT and SCRT	48.8% across cCRT and sCRT	48.8% across cCRT and sCRT
Discontinuation	15.4%	16.5% across cCRT and SCRT	11% across cCRT and sCRT	14.4% across cCRT and sCRT	14.4% across cCRT and sCRT
G3+ pneumonitis (%)	3.4%	3.3% across cCRT and sCRT	3% across cCRT and sCRT	5.2% across cCRT and sCRT	5.2% across cCRT and sCRT

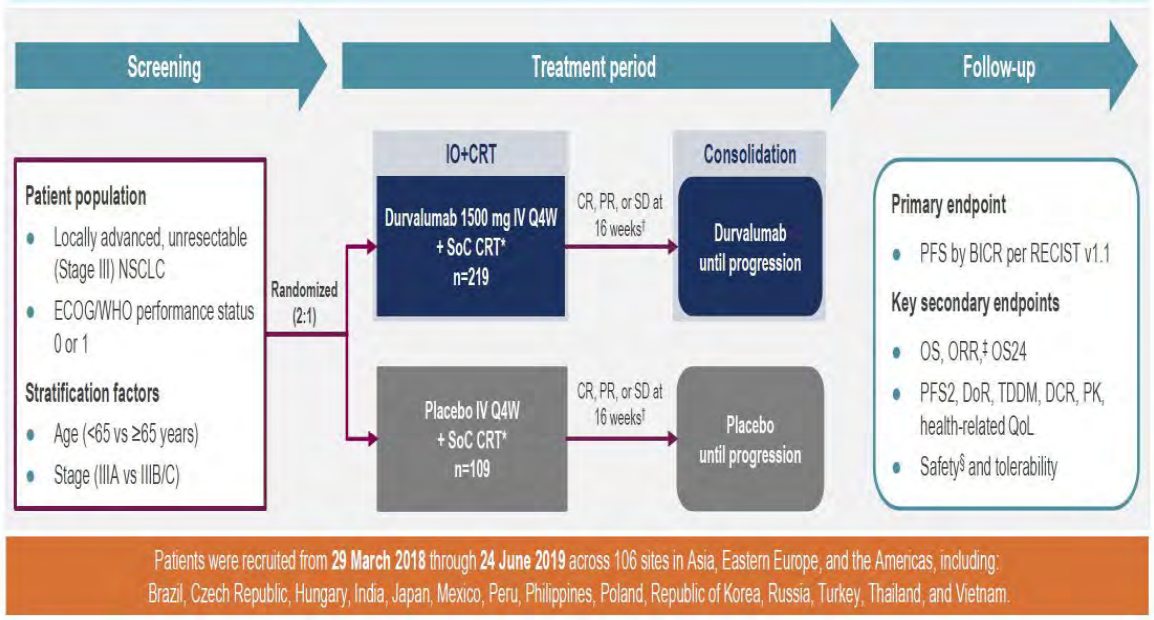
CONSOLIDATION THERAPY TRIALS WITH SEQUENTIAL CRT REGIMEN

	PACIFIC-R (sCRT)	GEMSTONE -301 (sCT)	PACIFIC-6 (sCRT)	PACIFIC-5 (all)	PACIFIC-5 (sCRT)
n	201	127	117	407	123
Drug	Durvalumab	Sugemalimab	Durvalumab	Durvalumab	Durvalumab
mPFS (mo, IO vs Control)	19.3	8.1 vs 4.1	10.9	14 vs 6.5	11 vs 5.4
HR PFS (95%)	NA	0.60 (0.39-0.93)	NA	0.75 (0.58 – 0.99)	0.75 (0.49-1.18)
% Cisplatin	47.3%	50.1% across cCRT and SCRT	27.4%	48.8% across cCRT and sCRT	48.8% across cCRT and sCRT
Discontinuation	16.5% across cCRT and SCRT	11% across cCRT and sCRT	21.4%	14.4% across cCRT and sCRT	14.4% across cCRT and sCRT
G3+ pneumonitis (%)	3.3% across cCRT and sCRT	3%across cCRT and sCRT	1.7%	5.2% across cCRT and sCRT	5.2% across cCRT and sCRT

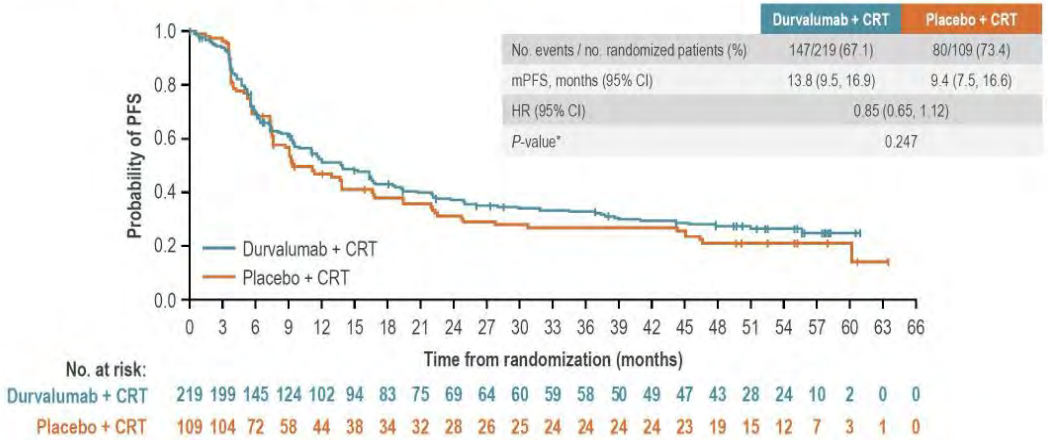
WHAT ABOUT CONCURRENT RT CT AND IO

PACIFIC-2

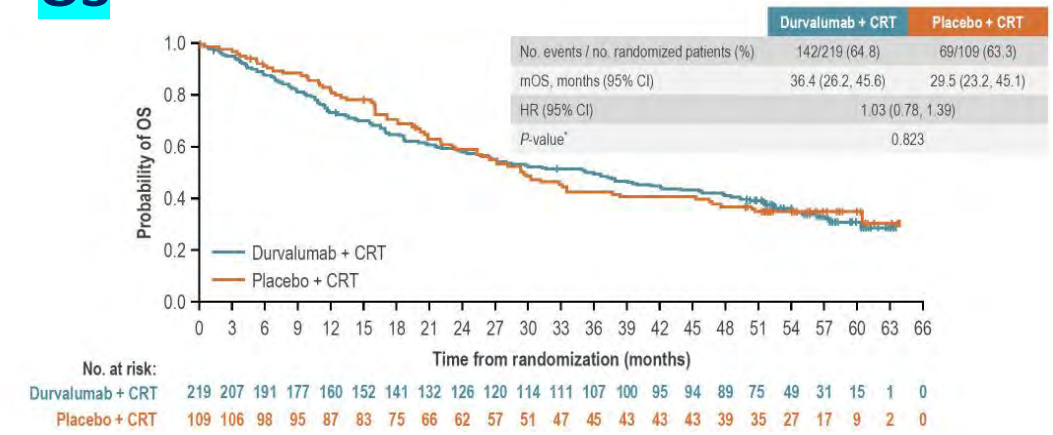
Durvalumab + cRT



PFS by BIRC

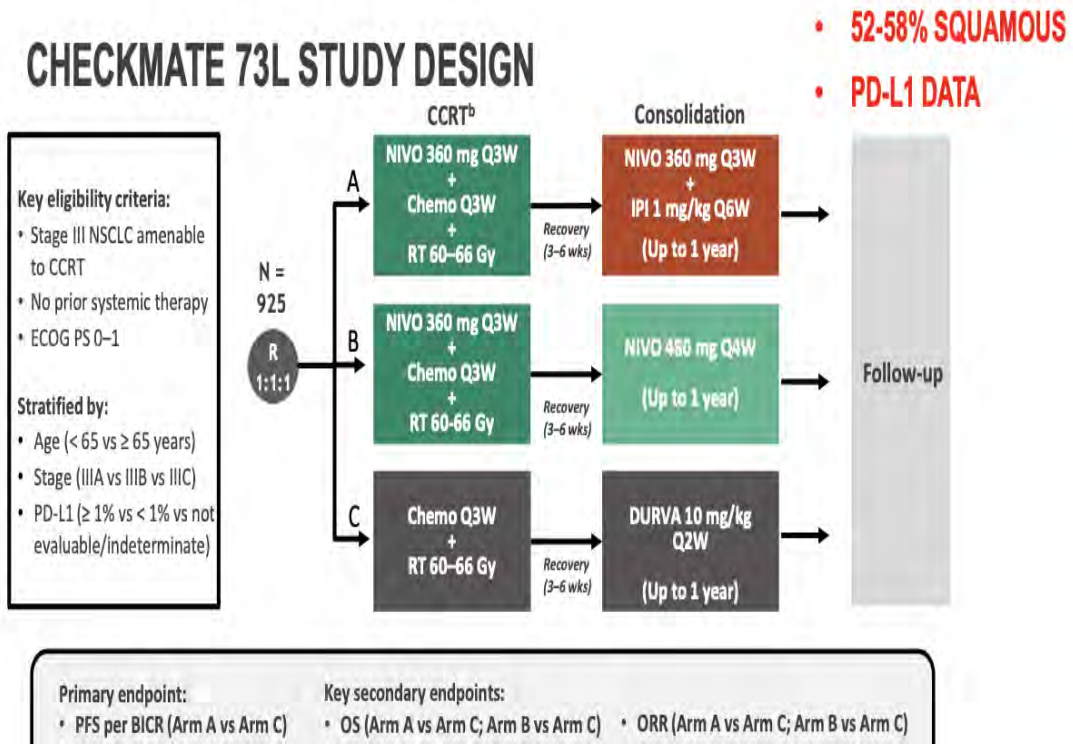


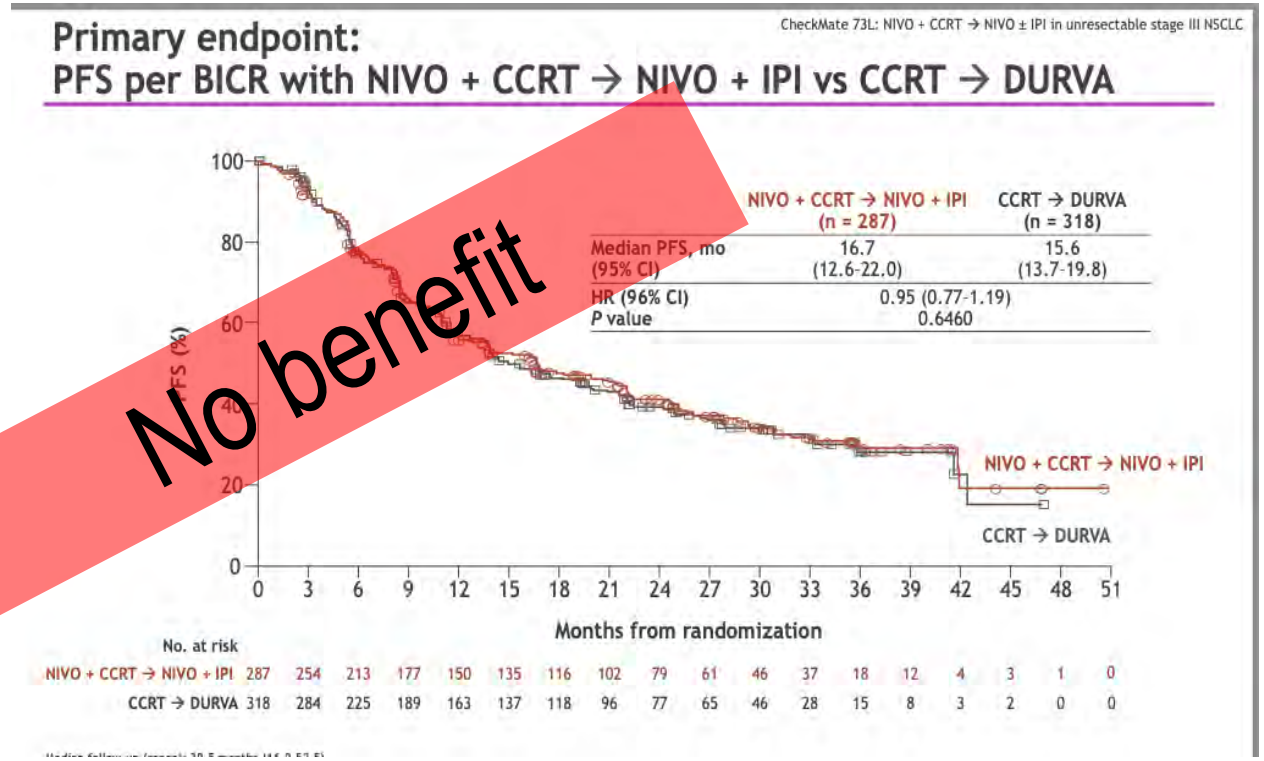
OS



Bradley et al. ELCC (2024)

CheckMate 73L: phase 3 study comparing nivolumab + concurrent chemoradiotherapy followed by nivolumab ± ipilimumab vs concurrent chemoradiotherapy followed by durvalumab for previously untreated, locally advanced stage III NSCLC





Peters S, ESMO Immuno oncology conf 2024

THE STORY CONTINUES….

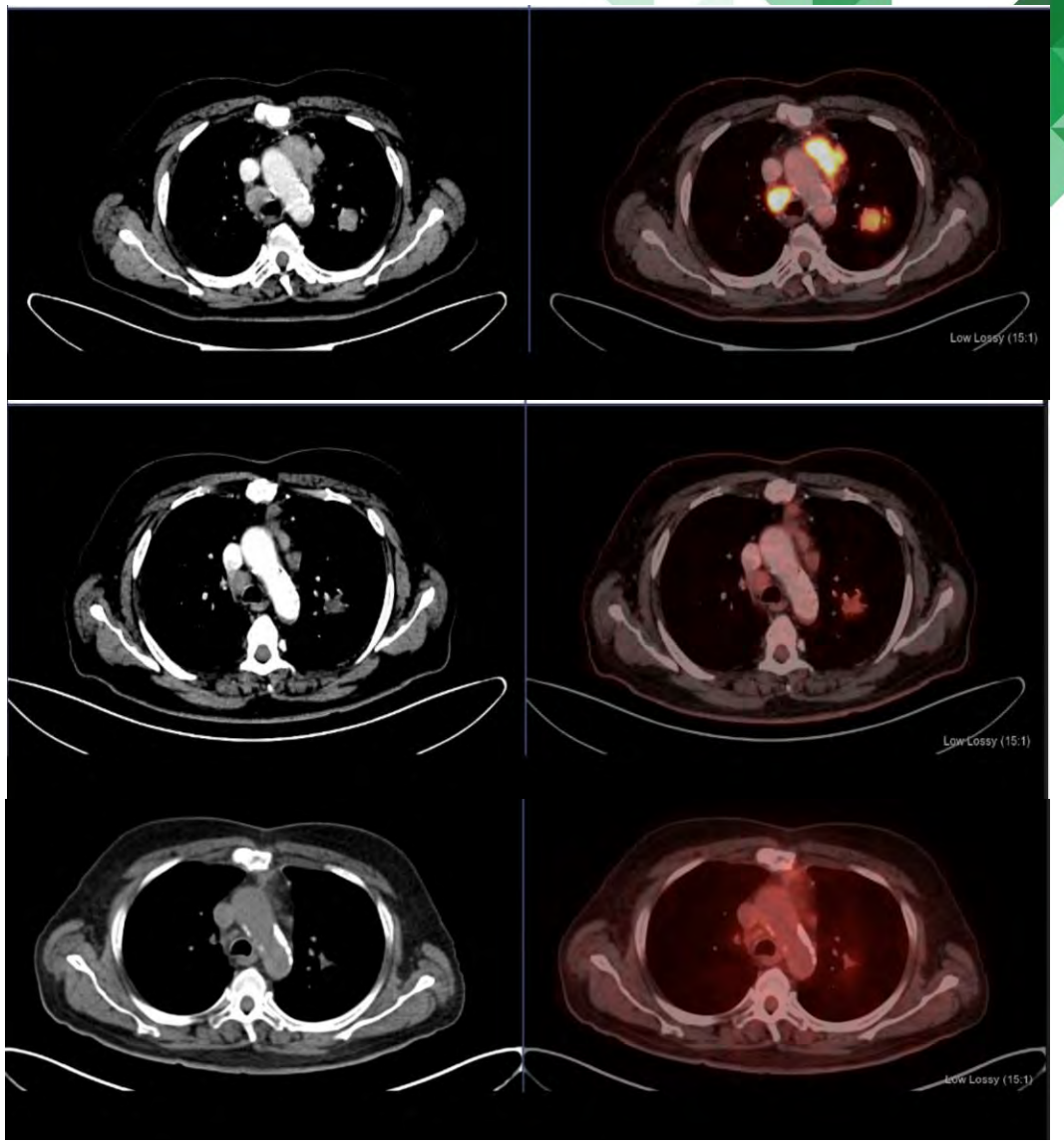
Patient received chemotherapy followed by Radiotherapy

Tolerability well

No dose delays/ drug intensity maintained

Started on Maintenance Durvalumab

In clinical and radiological remission now



MY CONCLUSIONS ABOUT PACIFIC

CTRT followed by Consolidation Durvalumab remains the standard of care in stage III unresectable NSCLC

1 year of consolidation Durvalumab is standard

Magnitude of benefit is more in patients who receive CCRT than patients who receive sequential RT CT

Concurrent IO with RT has not shown improvement in PFS /OS

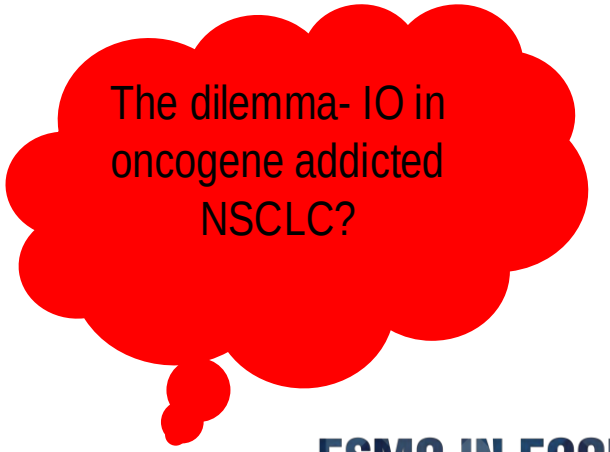
PACIFIC regimen is reasonably well tolerated with manageable safety profile

However , not all patients benefit from PACIFIC regimen

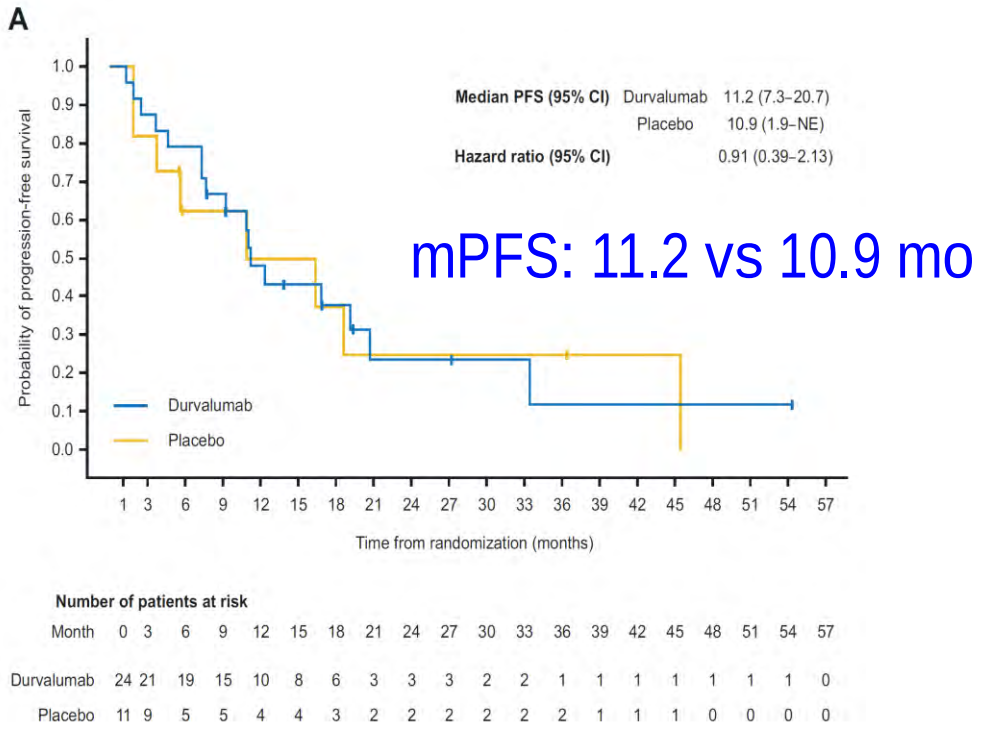
What about role of Durvalumab in oncogene directed stage III NSCLC??

CASE SCENARIO 2

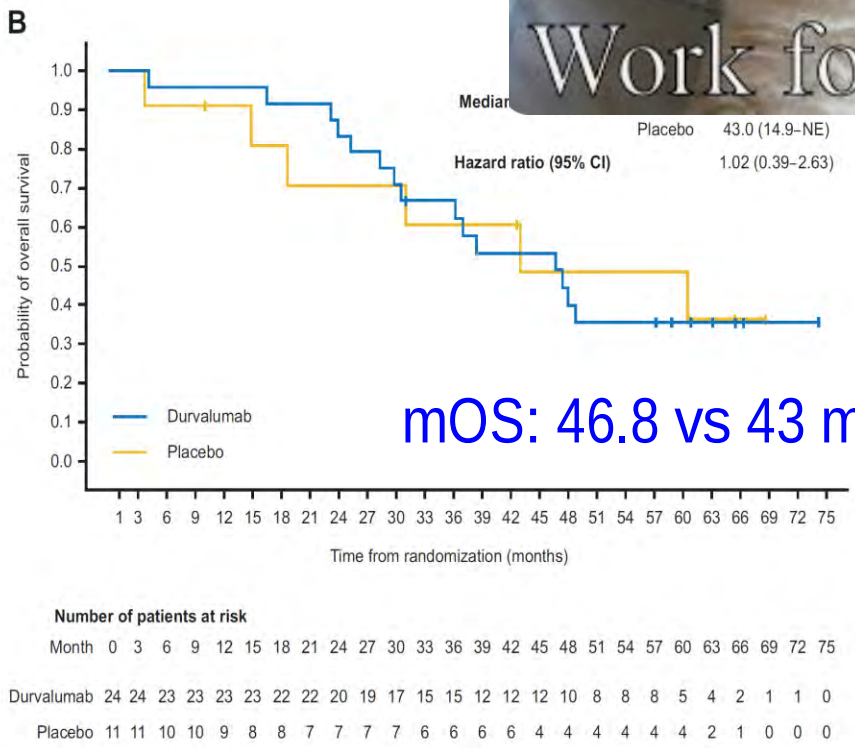
- 55 year old female , never smoker
- Presented with h/o cough with expectoration, breathlessness
- PET CT – Right Hilar mass with bilateral mediastinal lymphadenopathy
- MRI Brain- No evidence of brain metastases
- Underwent EBUS and Bronchoscopy biopsy – adenocarcinoma, TTF 1 positive ,
- Final stage of disease –cT2N3M0(bilateral mediastinal lymphadenopathy)
- Started on CCRT
- NGS report – EGFR del 19, PDL1-50%



PFS AND OS IN THE PACIFIC EGFR MUTATION SUBGRO



mPFS: 11.2 vs 10.9 mo



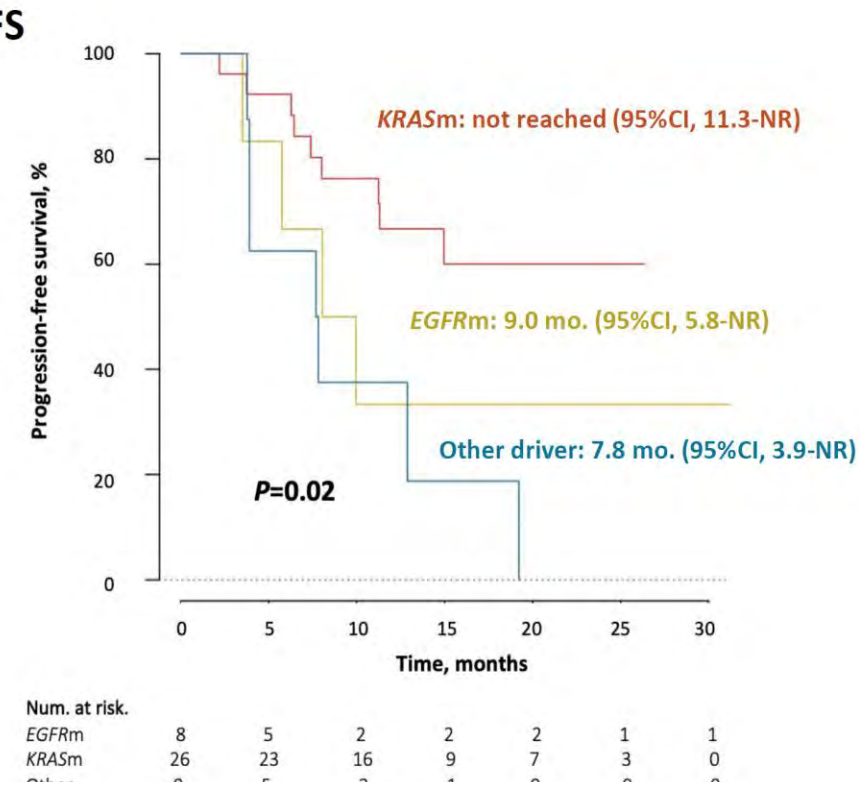
mOS: 46.8 vs 43 mo

Jarushka Naidoo et al, JTO 2023

Durvalumab consolidation in patients with unresectable stage III NSCLC with driver genomic alterations

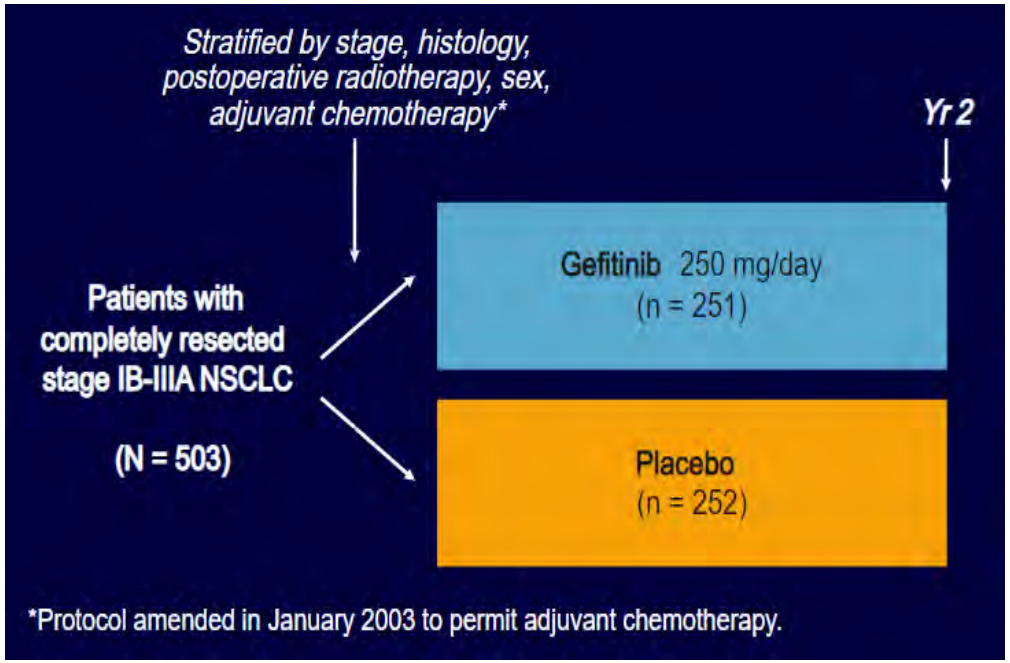
Median FU: 18.5 mo. (95%CI, 16.9-21.0)

	Median PFS mo. (95% CI)	OS rate at 18 mo. % (95% CI)
Overall dGA (N=43)	14.9 (8.1-NR)	93.4 (84.7-100)
*KRAS*m (N=26)	NR (14.9-NR)	89.7 (76.8-100)
***KRAS*m G12C** (N=8)	**NR** (11.3-NR)	87.5 (67.3-100)
*EGFR*m (N=8)	9.0 (5.8-NR)	100 (NR-NR)
***EGFR*m del19/ex21** (N=6)	**8.1** (5.8-NR)	100 (NR-NR)
*BRAF*m (N=5)	3.9 (3.9-NR)	100 (NR-NR)
BRAF*m *V600E (N=4)	**8.4** (3.9-NR)	100 (NR-NR)
***ALK*r** (N=4)	**7.8** (7.7-NR)	100 (NR-NR)

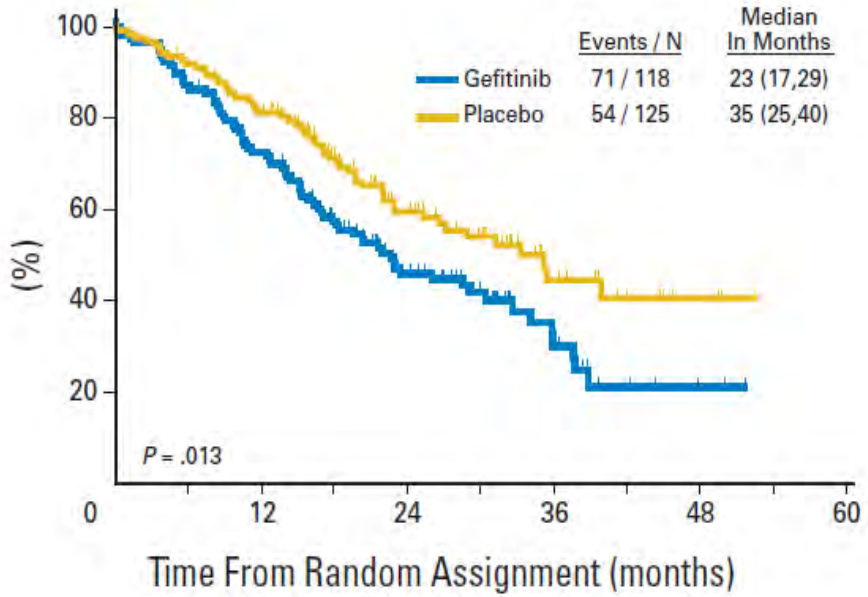


TKIS IN STAGE III NSCLC- A NEW STORY ??

Stage III post chemo-RT: in all-comers, TKIs are detrimental, S0023 trial



HR=0.633, (0.44-0.91), p=0.013



Kelly et al. JCO (2008)

LAURA- PHASE 3 DOUBLE BLIND STUDY

Both sequential and concurrent CTRT allowed

Dose of RT -60 Gy

PET CT scan not mandatory

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

Osimertinib 80 mg, once daily

Randomization 2:1 (N=216)

Stratification by:
Concurrent vs sequential CRT
Stage IIIA vs stage IIIB/IIIC
China vs non-China

Placebo, once daily

Duration of Osimertinib – till progression ??
Duration in ADAURA – 3 years ?
Duration in PACIFIC – 1 year?

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

Tumor assessments:

- Chest CT / MRI and brain MRI
- At baseline, every 8 weeks to Week 48, then every 12 weeks until BICR-assessed progression

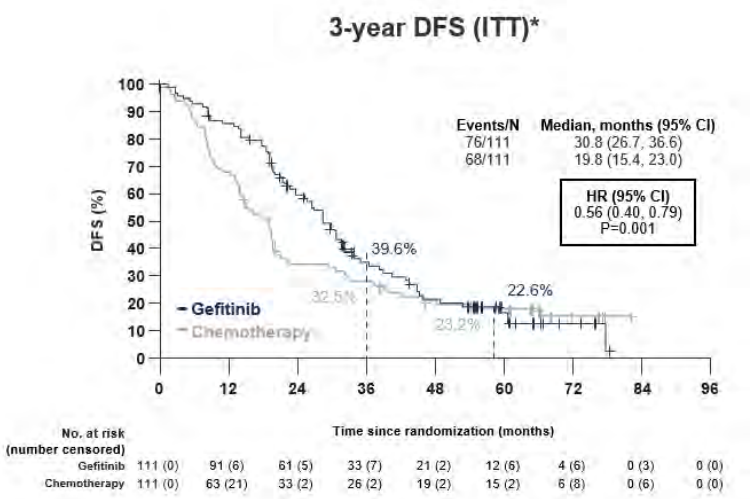
Endpoints

- **Primary endpoint:** PFS assessed by BICR per RECIST v1.1 (sensitivity analysis: PFS by investigator assessment)
- **Secondary endpoints included:** OS, CNS PFS, safety

S.S.Ramalingam et al, ASCO 2024

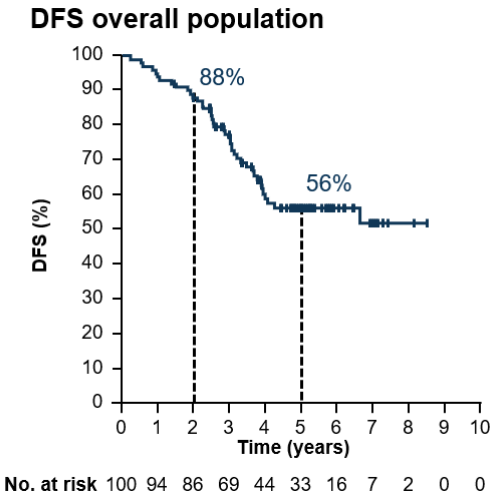
RATIONALE FOR INDEFINITE DOSE

ADJUVANT trial – Adjuvant gefitinib



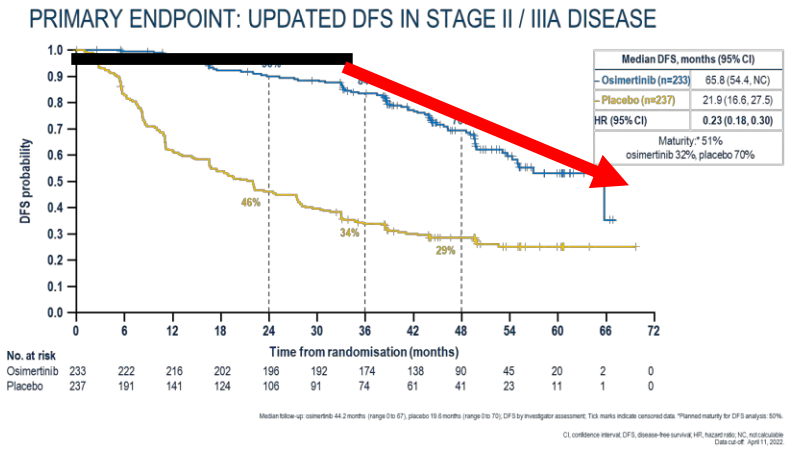
After 24 months, DFS curve began to converge, meeting by 36 months

SELECT trial– Adjuvant erlotinib



After 24 months, DFS curve began to converge and tailed at 48 months

ADAURA trial– Adjuvant osimertinib



After 36 months, a sharp drop in DFS curve is seen

Baseline characteristics

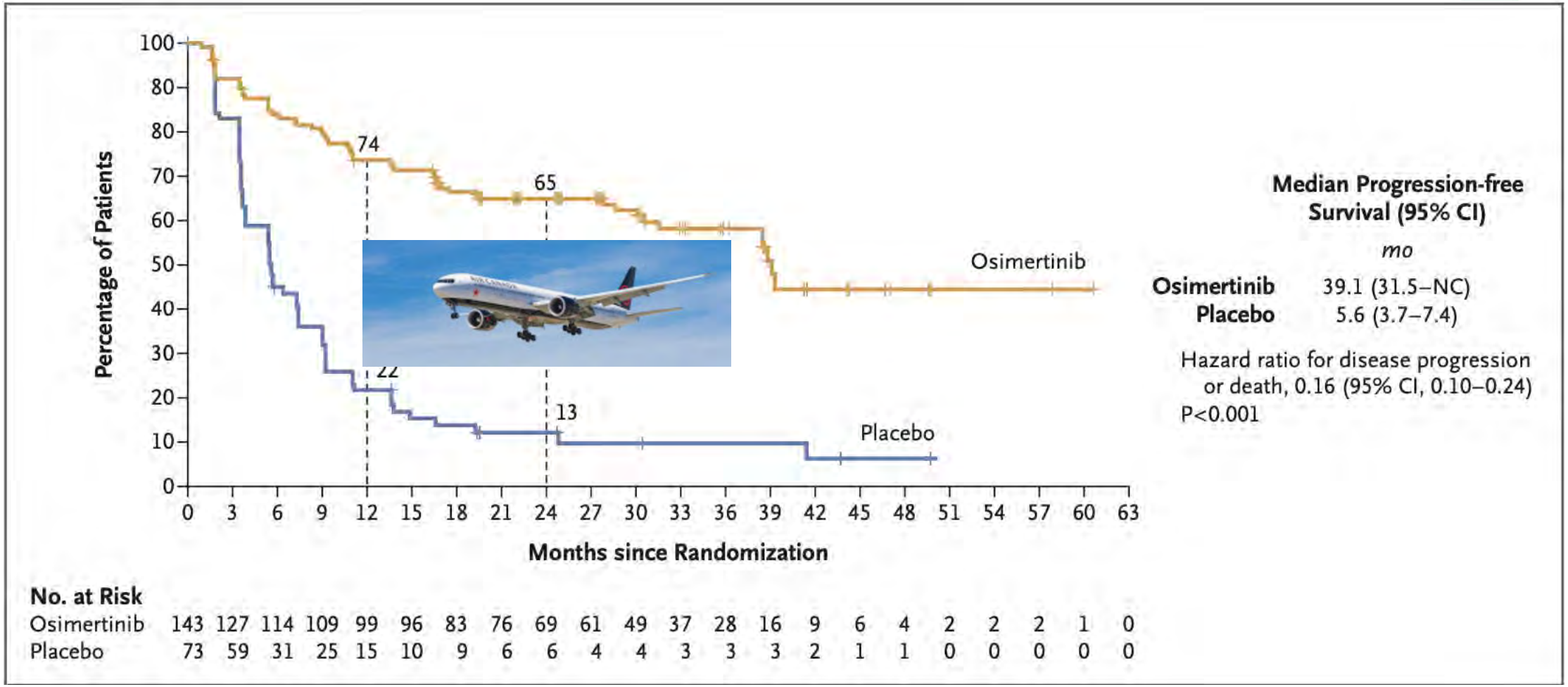
Characteristics, %	Osimertinib (n=143)	Placebo (n=73)
Sex: male / female	37 / 63	42 / 58
Age: median (range), years	62 (36–84)	64 (37–83)
Smoking history: formerly / currently / never	26 / 3 / 71	32 / 1 / 67
Race: Asian / non-Asian	81 / 19	85 / 15
WHO PS: 0 / 1	56 / 44	42 / 58
AJCC / UICC staging (8th edition) at diagnosis: IIIA / IIIB / IIIC	36 / 47 / 17	33 / 52 / 15
Histology: adenocarcinoma / other	97 / 3	95 / 5
EGFR mutation at randomization:* Ex19del / L858R	52 / 48†	59 / 41
Type of CRT: concurrent CRT / sequential CRT	92 / 8	85 / 15
Response to prior CRT: CR / PR / SD / PD / NE	3 / 47 / 43 / 0 / 8	4 / 37 / 51 / 0 / 8
Target lesion size by BICR:‡ mean (SD), mm	33 (18)	36 (17)

Real world applicability

Most patients got CTRT

S.S.Ramalingam et al, ASCO 2024

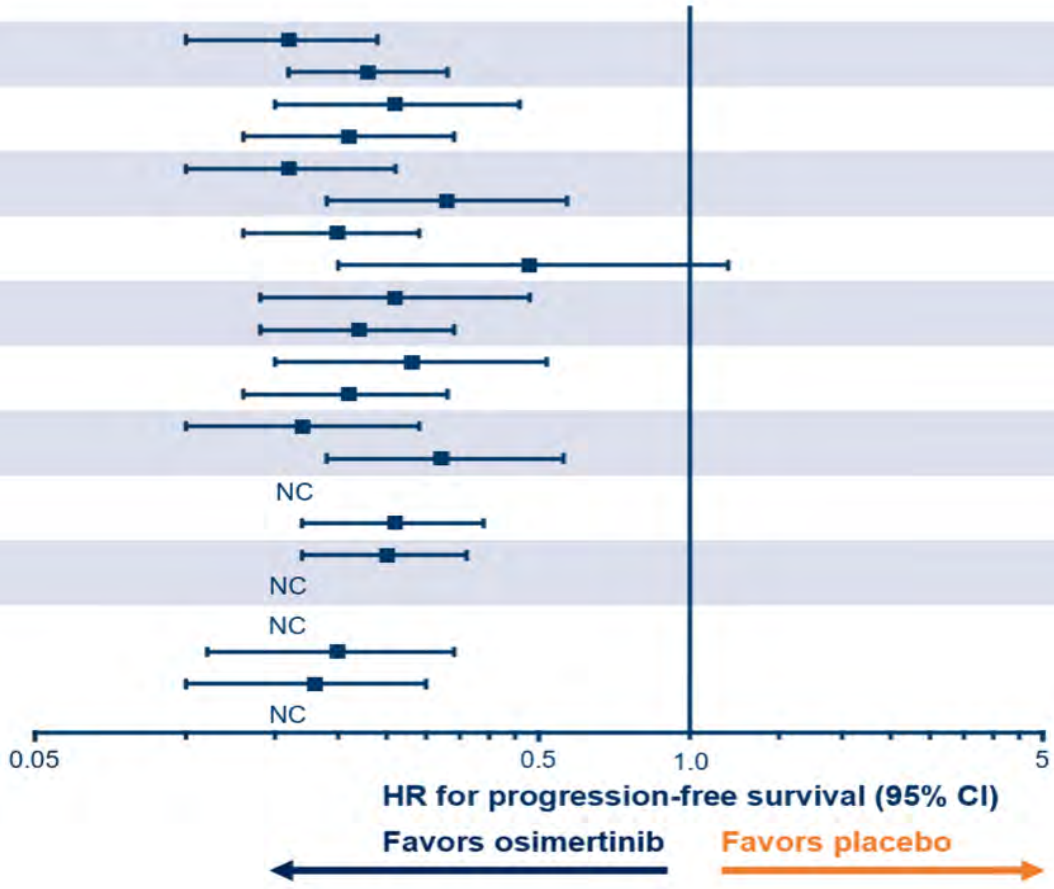
PFS CURVES



Lu S. NEJM 2024

PFS BY BICR ACROSS SUBGROUPS

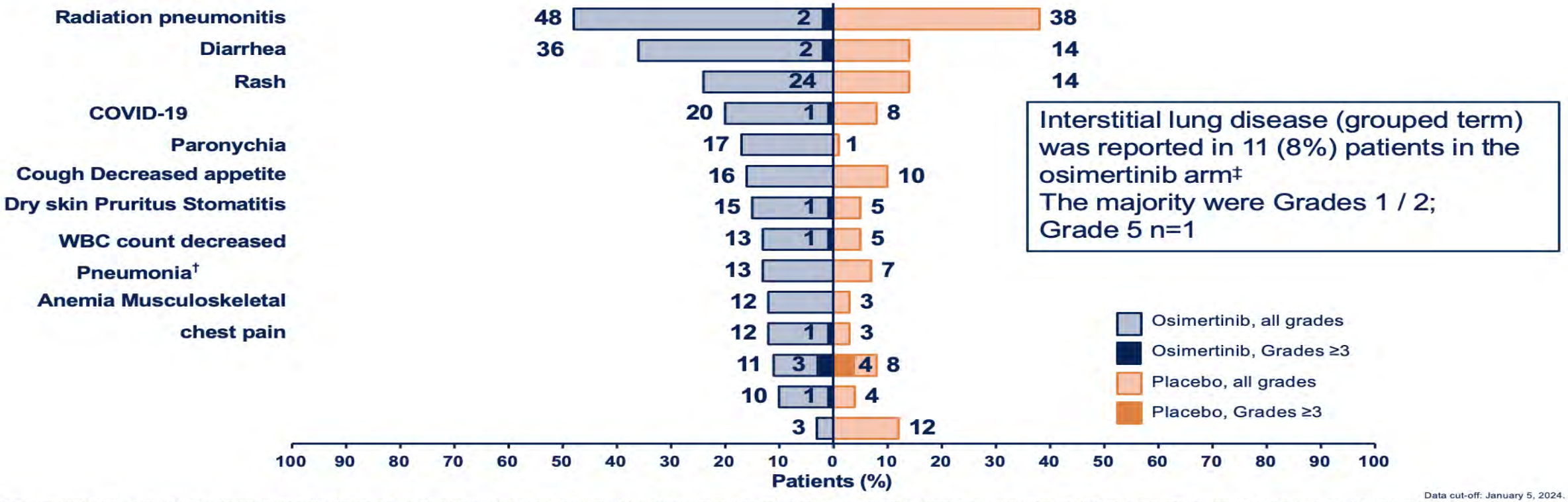
Subgroup		No. of events / patients	HR	95% CI
Overall (N=216)	Stratified log-rank	120 / 216	0.16	0.10, 0.24
	Unadjusted Cox PH	120 / 216	0.23	0.16, 0.33
Sex	Male	50 / 84	0.26	0.15, 0.46
	Female	70 / 132	0.21	0.13, 0.34
Age	<65 years	67 / 120	0.16	0.10, 0.26
	≥65 years	53 / 96	0.33	0.19, 0.57
Race	Asian	98 / 178	0.20	0.13, 0.29
	Non-Asian	22 / 38	0.48	0.20, 1.19
Smoking history	Current / former (yes)	42 / 65	0.26	0.14, 0.48
	Never (no)	78 / 151	0.22	0.14, 0.34
Stage*	IIIA	42 / 76	0.28	0.15, 0.52
	IIIB / IIIC	78 / 140	0.21	0.13, 0.33
EGFR mutation†	Ex19del	65 / 117	0.17	0.10, 0.29
	L858R	55 / 98	0.32	0.19, 0.56
China cohort	Chinese	18 / 40	NC	NC, NC
	Non-Chinese	102 / 176	0.26	0.17, 0.39
Chemoradiotherapy	Concurrent	107 / 193	0.25	0.17, 0.36
	Sequential	13 / 23	NC	NC, NC
Response to prior CRT	Complete response	3 / 7	NC	NC, NC
	Partial response	53 / 94	0.20	0.11, 0.34
	Stable disease	58 / 98	0.18	0.10, 0.30
	Non-evaluable	6 / 17	NC	NC, NC



S.S.Ramalingam et al, ASCO24

ALL CAUSALITY ADVERSE EVENTS

- The most common AE in both arms was radiation pneumonitis; the majority were low grade, non-serious and manageable.

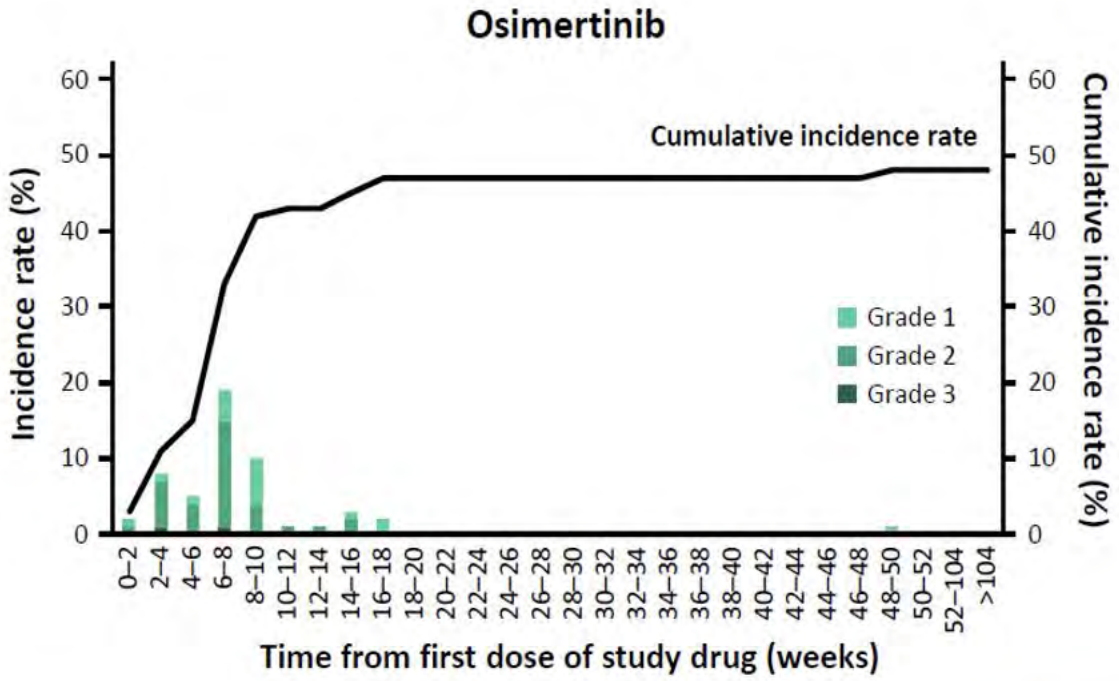


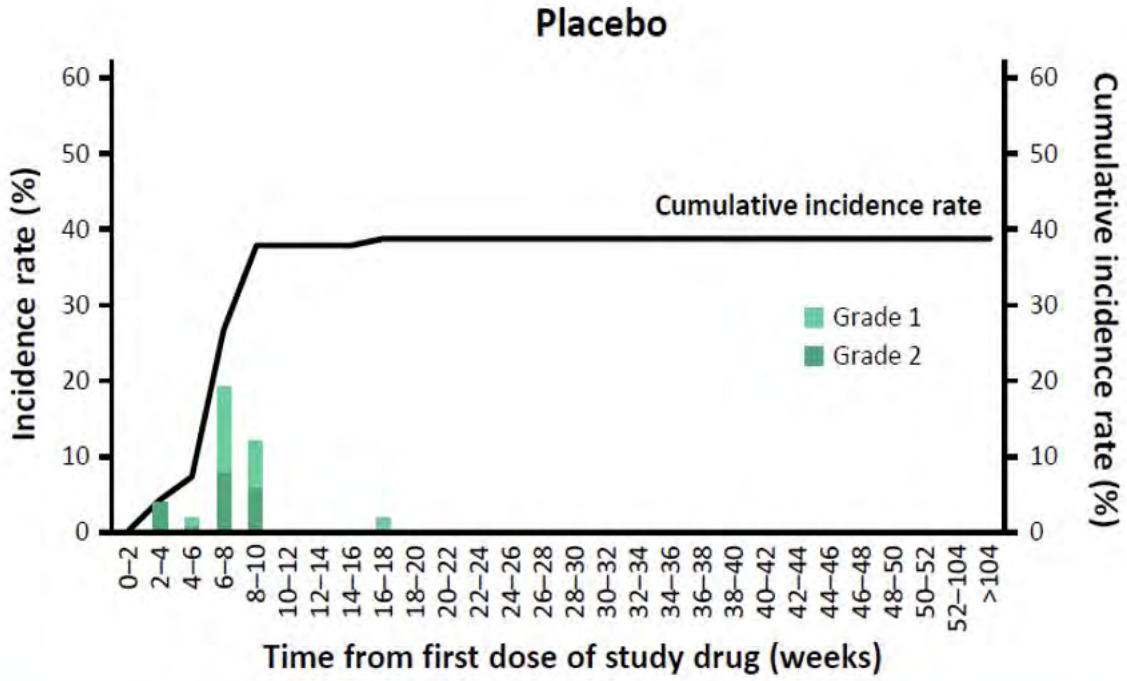
Data cut-off: January 5, 2024.

*AEs with incidence of 10% or more in either treatment arm are shown. Patients with multiple events in the same category counted only once in that category. Patients with events in more than one category are counted once in each of those categories. Incl udes AEs with an onset date on or after the date of first dose and up to and including 28 days following the discontinuation of study treatment and before starting subsequent cancer therapy; †One grade 5 AE of pneumonia was reported in the osimertinib arm; ‡Interstitial lung disease (grouped term) was reported in 1 patient (1%) in placebo arm; AE was pneumonitis, Grade 1.

S.S.Ramalingam et al, ASCO24

TIME TO RADIATION PNEUMONITIS





Time to onset of radiation pneumonitis, median (range), days	Osimertinib (n=69)	Placebo (n=28)
From first dose of study drug	52 (10–676)	54 (15–113)
From last dose of prior CRT	76 (38–694)	81 (47–136)

Terufumi Kato | WCLC 2024 |

SOME UNANSWERED QUESTIONS (POST ASCO 2024)

What was the benefit of Osimertinib in patients who underwent PET scan vs patients who did not undergo PET scan at staging ?

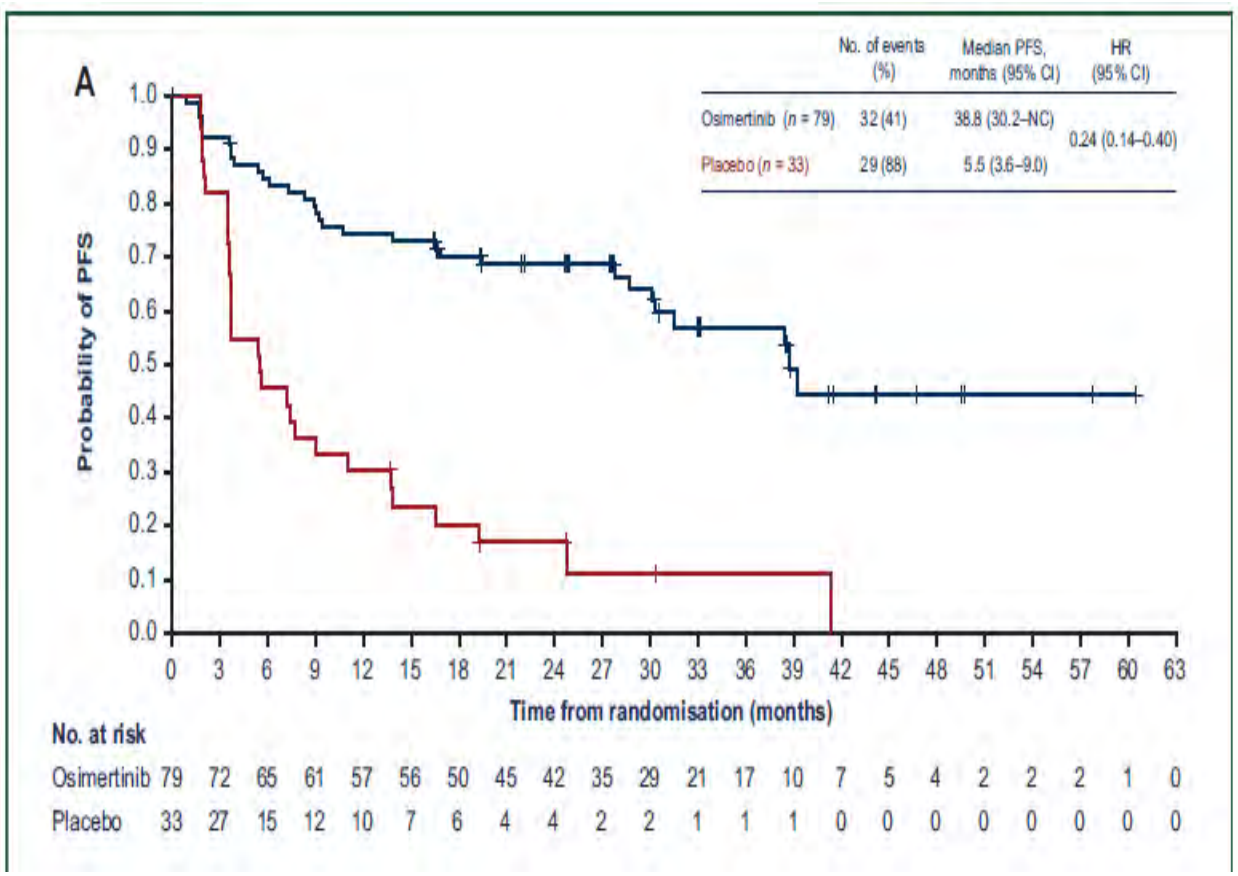
What was the impact of Osimertinib on local Control vs distant control ?

Was the incidence of CNS metastases decreased in the experimental arm ?

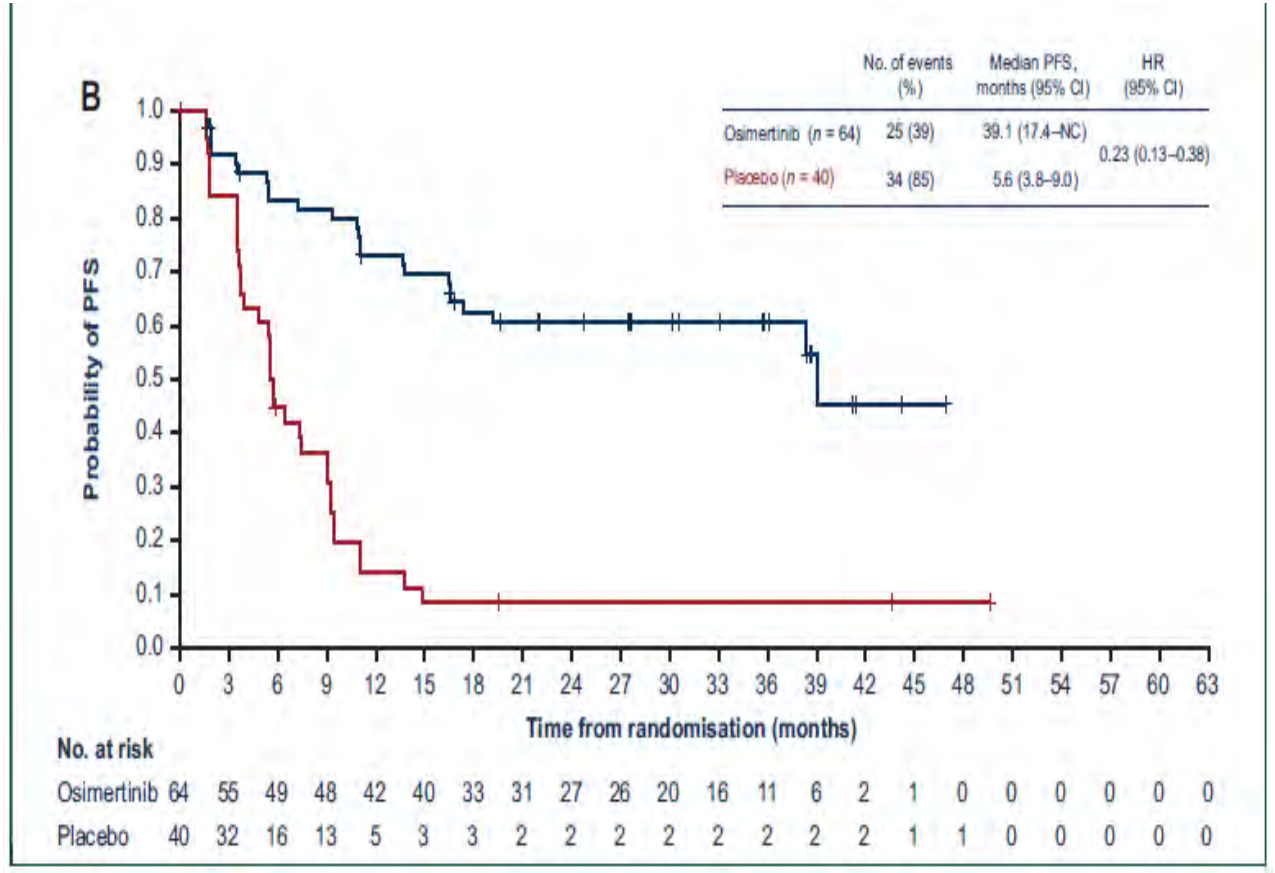
With such high cross over regimen, is there a survival advantage ?

IMPACT OF BASELINE PET SCAN STAGING

With baseline PET scan



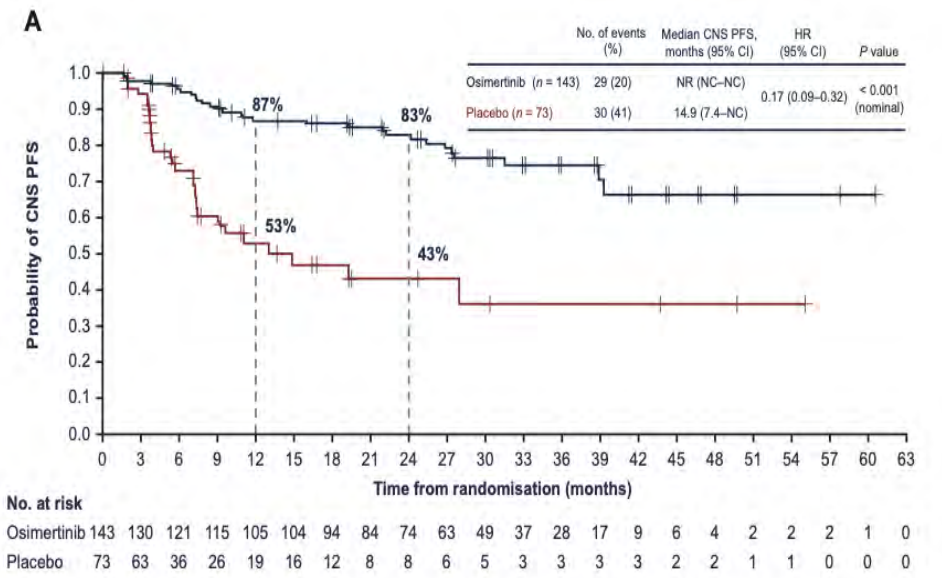
Without baseline PET scan

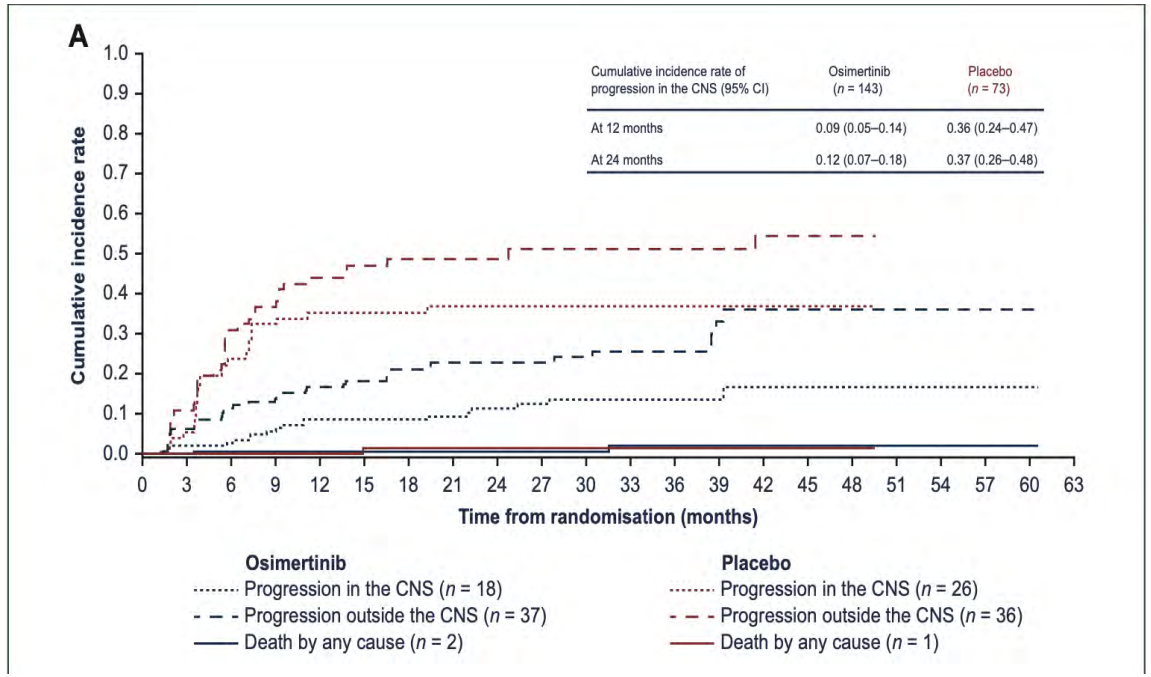


Lu et al. Ann Oncol (2024)

HR – 0.24/0.23

TIME TO CNS PFS

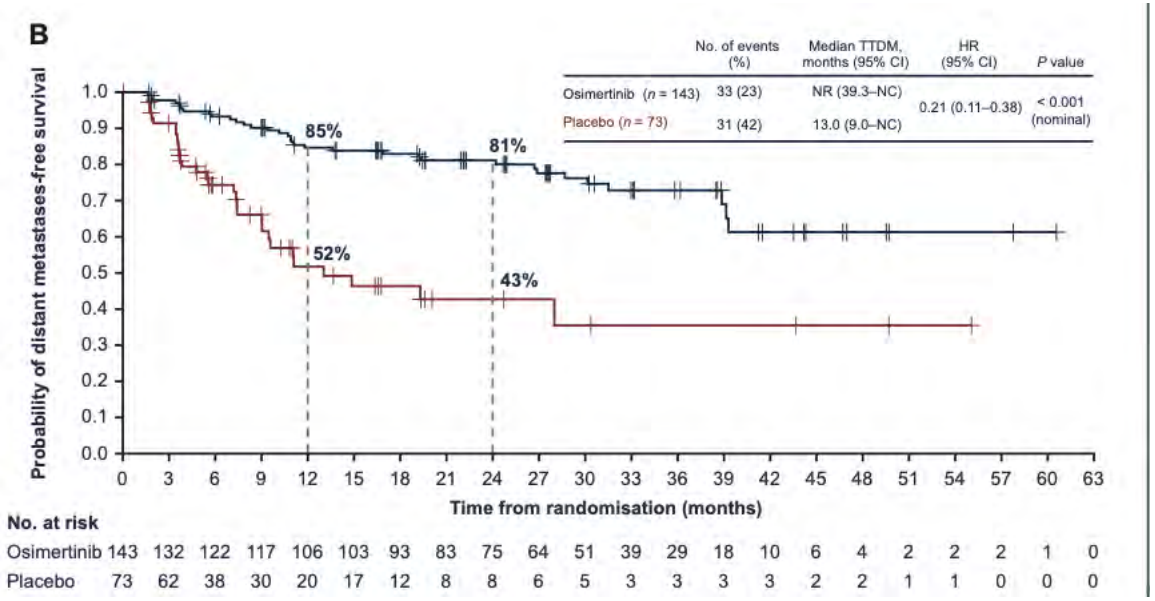


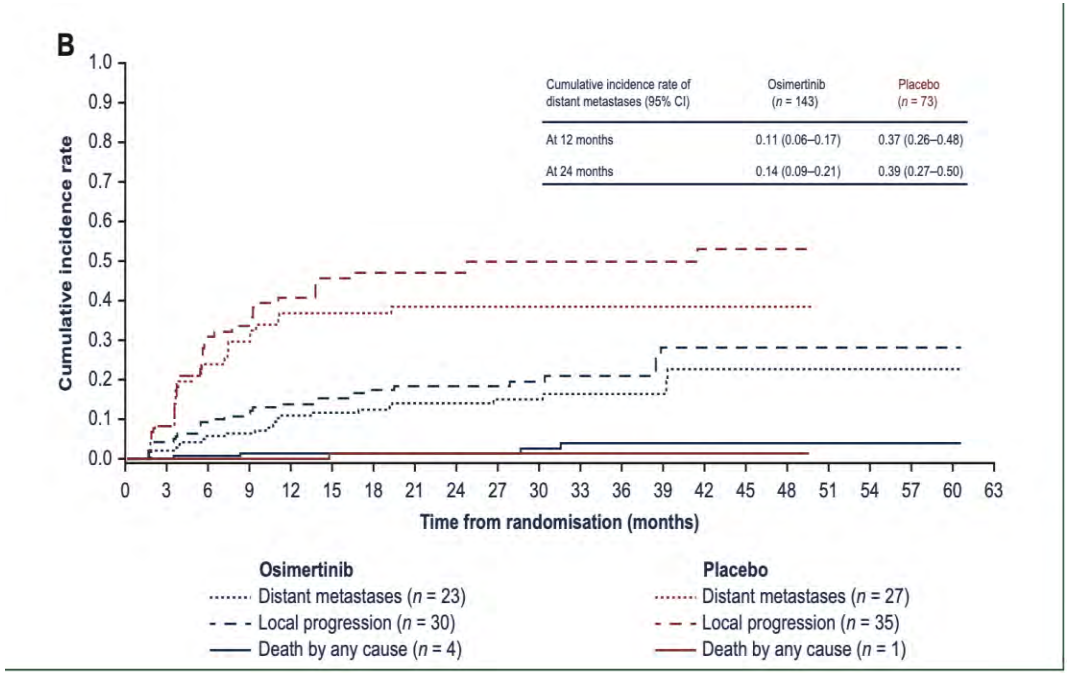


Lu et al. Ann Oncol (2024)

Incidence of brain mets at 12 months – 9% vs 36%
HR 0.17

TIME TO DISTANT METASTASES





Lu et al. Ann Oncol (2024)

Incidence of Distant mets at 12 months- 11% vs 37%
HR for TTDM- 0.21

SOME UNANSWERED QUESTIONS(POST ASCO 2024)

ANSWERED IN ESMO 2024

What was the benefit of Osimertinib in patients who underwent PET scan vs patients who did not undergo PET scan at staging ?

Benefit almost similar in patients irrespective of baseline PET SCAN

What was the impact of Osimertinib on local Control vs distant control ?

Osimertinib reduces Time to distant mets as well as time to CNS mets

Was the incidence of CNS metastases decreased in the experimental arm ?

With such high cross over regimen, is there a survival advantage ?

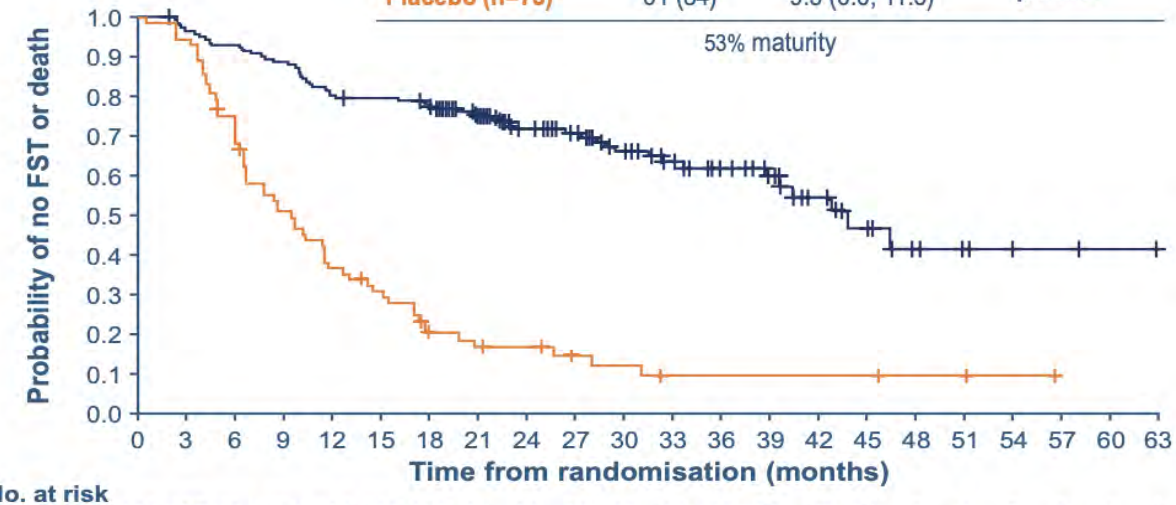
Answered in ELCC 2025

UPDATED SURVIVAL DATA PRESENTED AT ELCC 2025

TFST

	No. of events (%)	Median (95% CI), months	HR (95% CI) Nominal p-value
Osimertinib (n=143)	53 (37)	43.8 (38.9, NC)	0.13 (0.08, 0.21) p<0.001
Placebo (n=73)	61 (84)	9.5 (6.6, 11.5)	

53% maturity



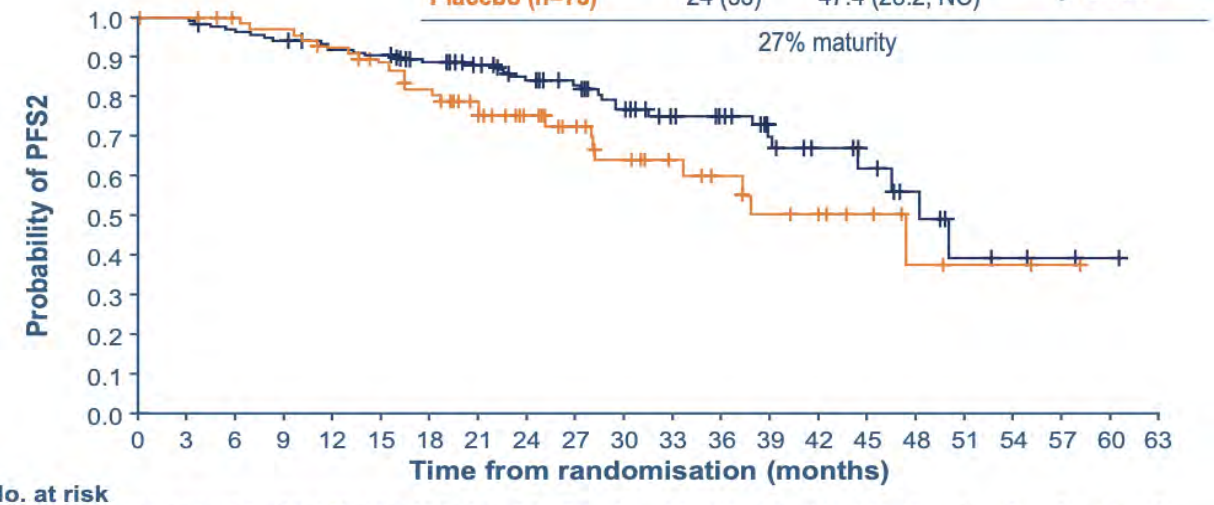
No. at risk

Osimertinib	143	137	132	126	114	112	108	94	80	70	55	44	36	26	17	11	6	4	2	2	1	0
Placebo	73	69	51	36	26	20	12	10	9	6	5	3	3	3	3	3	2	2	1	0	0	0

PFS2

	No. of events (%)	Median (95% CI), months	HR (95% CI) Nominal p-value
Osimertinib (n=143)	34 (24)*	48.2 (44.4, NC)	0.62 (0.35, 1.08) p=0.088
Placebo (n=73)	24 (33)	47.4 (28.2, NC)	

27% maturity



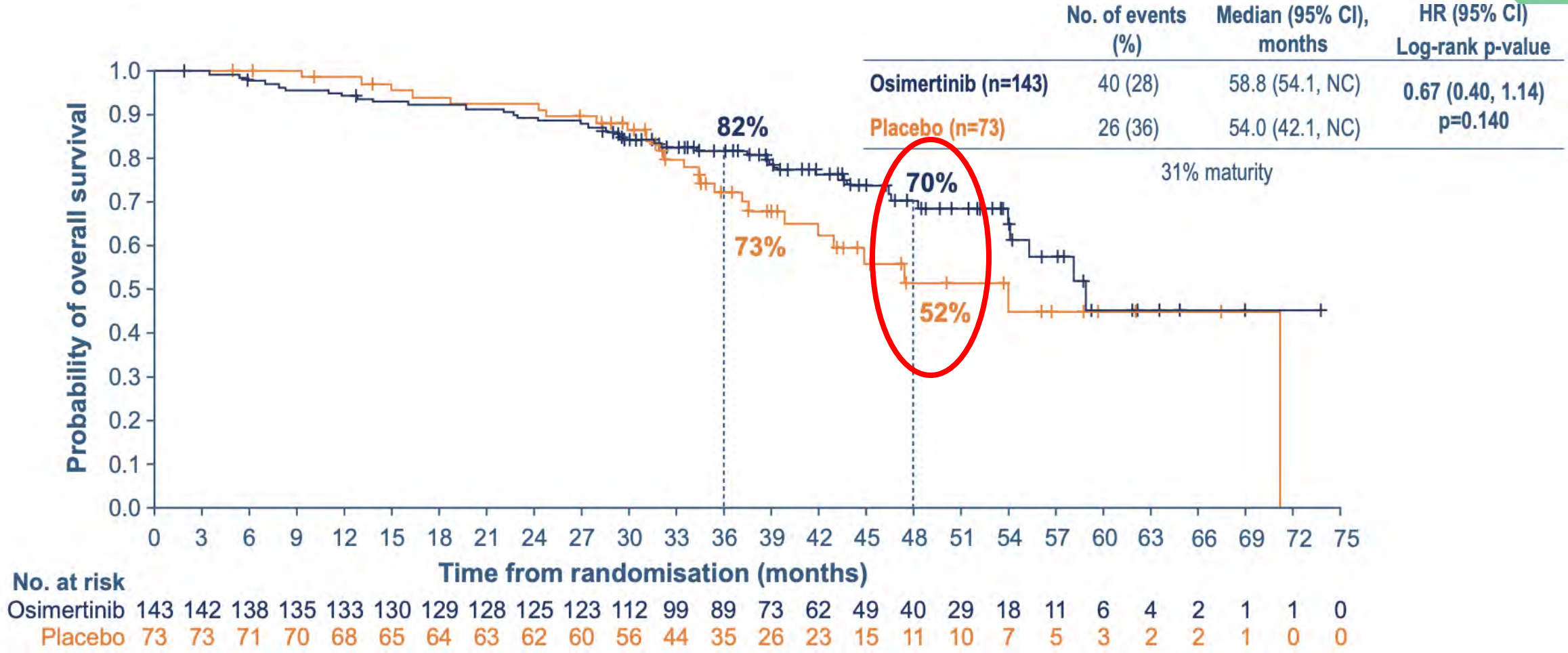
No. at risk

Osimertinib	143	140	134	130	123	121	109	99	86	76	59	47	37	24	16	12	8	4	3	2	1	0
Placebo	73	72	68	66	62	57	52	41	34	28	22	16	13	10	8	6	3	2	2	1	0	0

- Median TSST was NR in the osimertinib arm and 47.4 months in the placebo arm; HR 0.51 (95% CI 0.28, 0.91); p=0.022†

Ramalingam S, ELCC 2025

UPDATED SURVIVAL DATA PRESENTED AT ELCC 2025



Ramalingam S, ELCC 2025

80% of patients in the placebo subfroup got Osimertinib at progression

LAURA TRIAL- SOME MORE PRACTICAL QUESTIONS STILL NOT ANSWERED

Stage III A patients in ADAURA trial - Duration of therapy 3 years vs indefinite?

Role of Molecular testing to predict which patients can stop treatment ?

What about other oncogene addicted NSCLC stage III?

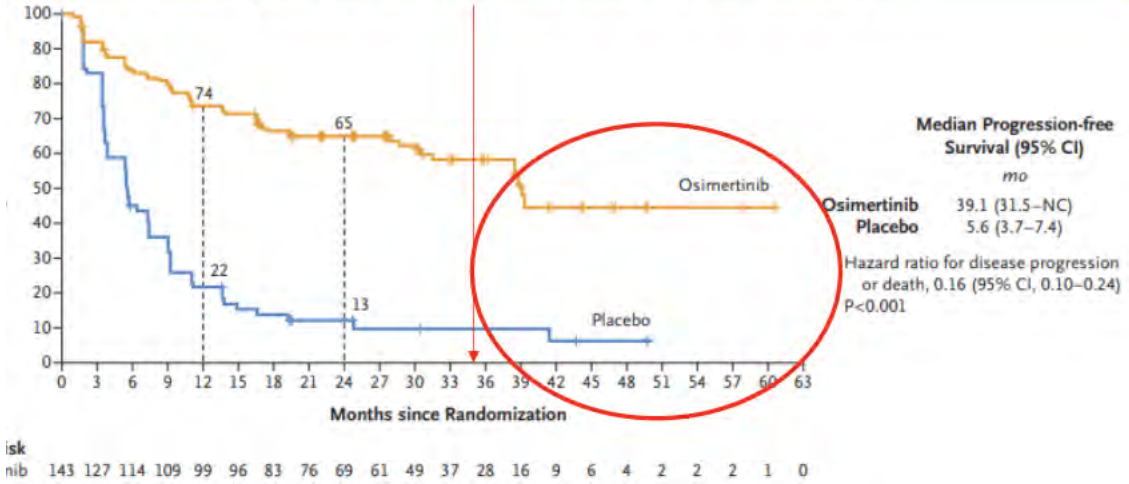
How will we treat at progression ?

What about Neoadjuvant TKIs?

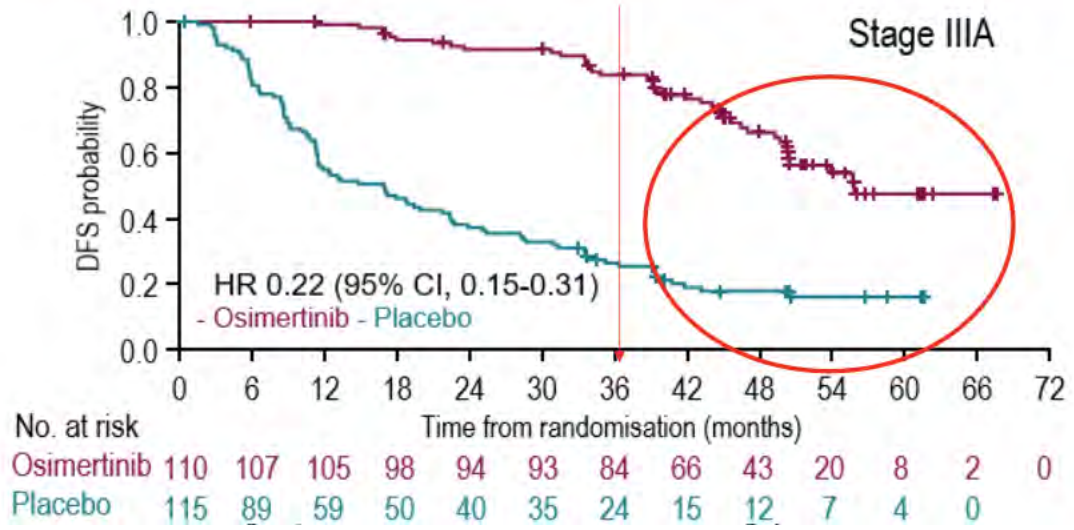
Any role of deescalating RT fields?

DURATION OF OSIMERTINIB- ADAURA VS LAURA ?

LAURA: Osimertinib after Chemoradiotherapy in Stage III EGFR-Mutated NSCLC (cont. Osi)
Stage IIIA (HR 0.28), IIIB/IIIC (HR 0.21)



ADAURA: Osimertinib in Stage IIIA EGFR-Mut (3Y)



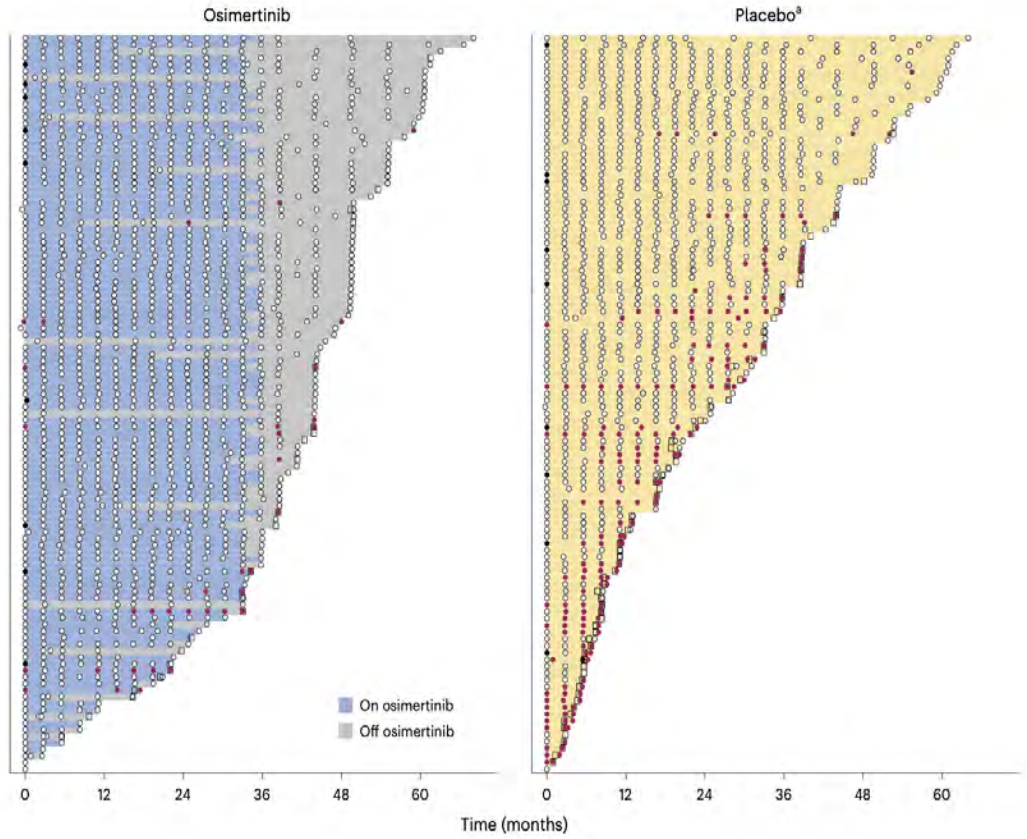
Hye Ryun Kim, ELCC 2025

Continue Osimertinib in stage III resected NSCLC??

MOLECULAR MEDICINE TO RESCUE ??

Molecular residual disease analysis of adjuvant osimertinib in resected *EGFR*-mutated stage IB–IIIA non-small-cell lung cancer

MRD preceded imaging DFS events by a median of 5 months

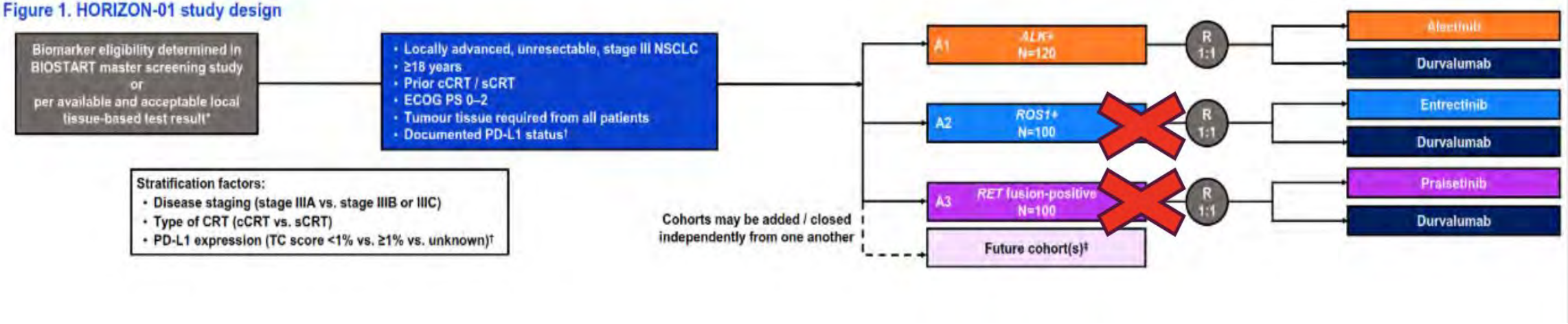


Herbst R, Nature 2025

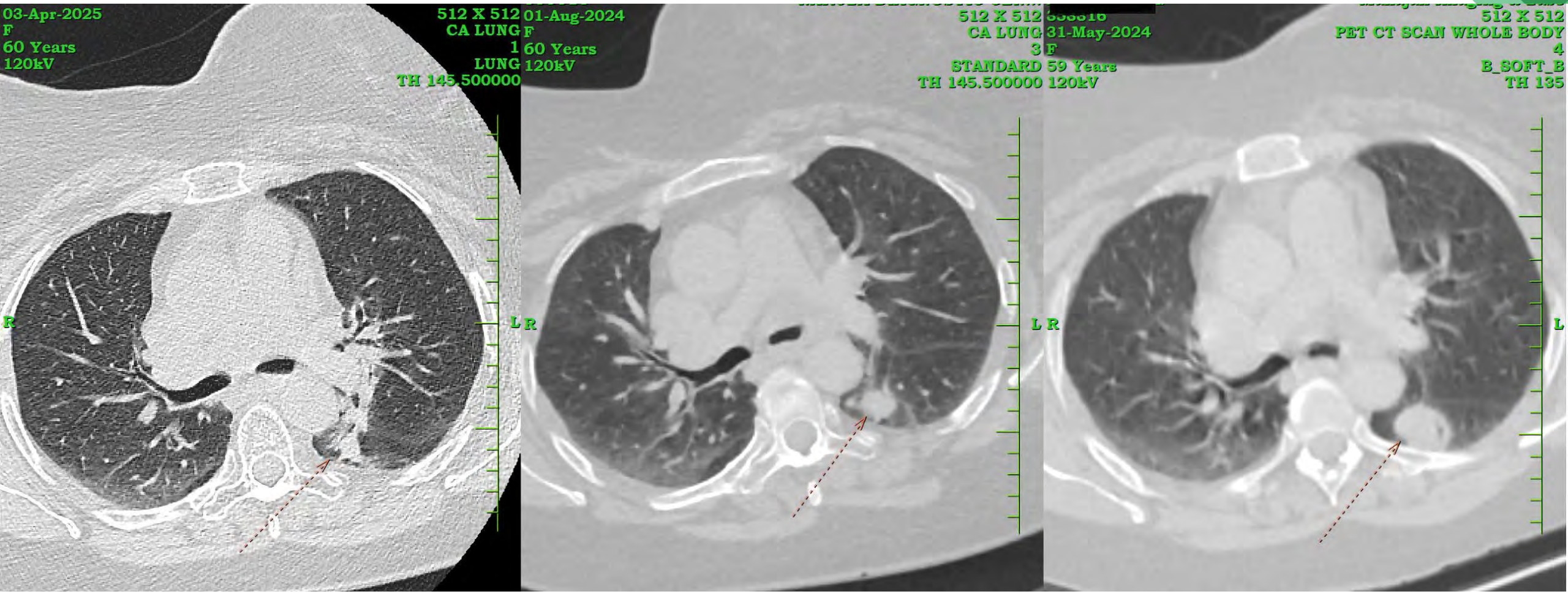
CLINICAL TRIALS UNDERWAY

NEOLA trial: A Phase II, Open-label, Single-arm Study of Osimertinib as Induction Therapy Prior to CRT and Maintenance Osimertinib in Patients with Epidermal Growth Factor Receptor (EGFR) Mutation-positive, Stage III, Unresectable Non-small Cell Lung Cancer (NEOLA) [NCT06194448]

Figure 1. HORIZON-01 study design



WHAT HAPPENED TO OUR PATIENT ?



MY CONCLUSIONS FROM THE LAURA TRIAL

Is the Trial an unmet need?

Yes , definitely an unmet need .
Experimental arm was appropriate

Is there a good scientific rationale for the experimental arm?

Was the study design appropriate and the control arm standard of care?

The trial design was appropriate especially,
allowing for cross over to SOC on progression

Were the end points justified?

Did the trial meet its primary end point ?

The trial met its primary end point
with numerically and clinically significant improvement
and manageable toxicity profile

Is the improvement clinically significant ?

How is the toxicity profile ??

Is it a PCT(practice changing trial)?

Definitely practice changing trial

TO CONCLUDE…

Medicine is not only a science, it is also an art.

Optimal front-line therapeutic approaches for patients with EGFRmt metastatic NSCLC

James Chih-Hsin Yang M.D., Ph.D.
楊志新教育部國家講座及台大講座教授
National Chair Professor,
Graduate Institute of Oncology, NTU
台灣大學醫學院腫瘤醫學研究所

Superintendent,
National Taiwan University Cancer Center
台大醫院癌醫中心分院院長

ESMO WEBINAR SERIES

ESMO IN FOCUS

DISCLOSURE OF CONFLICT OF INTEREST

Dr. Yang reports personal fees and other from Amgen, grants, personal fees and other from AstraZeneca, personal fees and other from Bayer, personal fees and other from Boehringer Ingelheim, personal fees and other from Bristol Myers Squibb, other from Daiichi Sankyo, other from Eli Lilly, other from Merck KGaA, Darmstadt, Germany, other from Merck Sharp & Dohme, other from Novartis, from Ono Pharmaceuticals, from Pfizer, grants and other from Roche/Genentech, other from Takeda Oncology, other from Yuhan Pharmaceuticals, other from Janssen Pharmaceuticals, other from Gilead Sciences Inc, other from GSK, other from BeiGene, other from Regeneron Pharmaceutical, other from Taiho Pharmaceutical, other from ArriVent, other from AnHeart Therapeutics,

CHOICES : THINGS TO CONSIDER

- Patients' expectation, OS, RR, DOR, QOL over treatment, PFS, treatment/work/life balance, financial
- Oncologists' expectation : OS, PFS, RR, DOR, brain metastasis, function preservation, ease of administration, less complication, any difference in subsets?
- Physician Scientists' expectation : OS consisting of several lines of treatment: best come first? Save some best? resistance pattern induced by treatment, tumor evolution, combinations to kill……

MARIPOSA

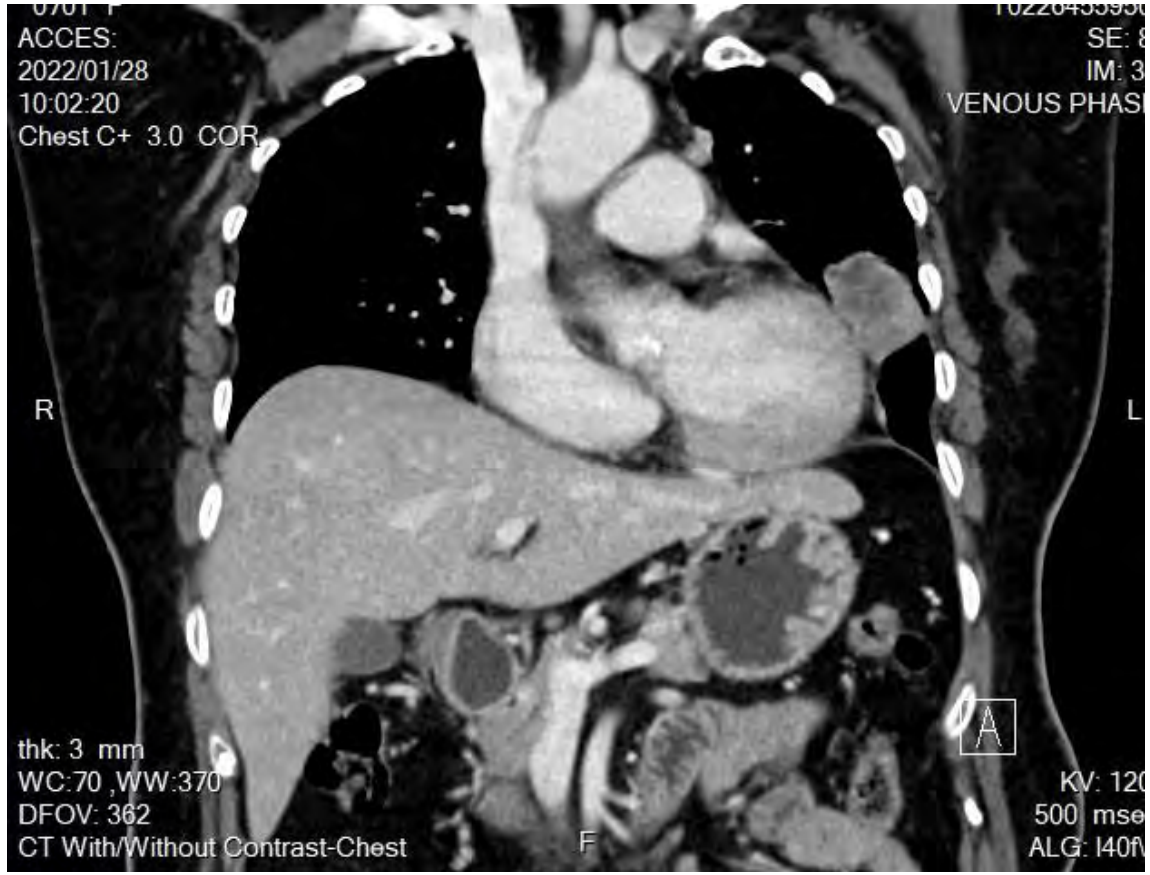
73 y/o Female, Lung adenocarcinoma, LUL with pleural and lung mets, cT4N2M1a, stage IVA, TTF-1 (+), EGFR: L858R, ALK (-), ROS-1(-), BRAF (-), PD-L1 IHC 22C3 pharmDx: 70 %.

Lazertinib + Amivantamab: 16/FEB/2022~ongoing, best response: PR

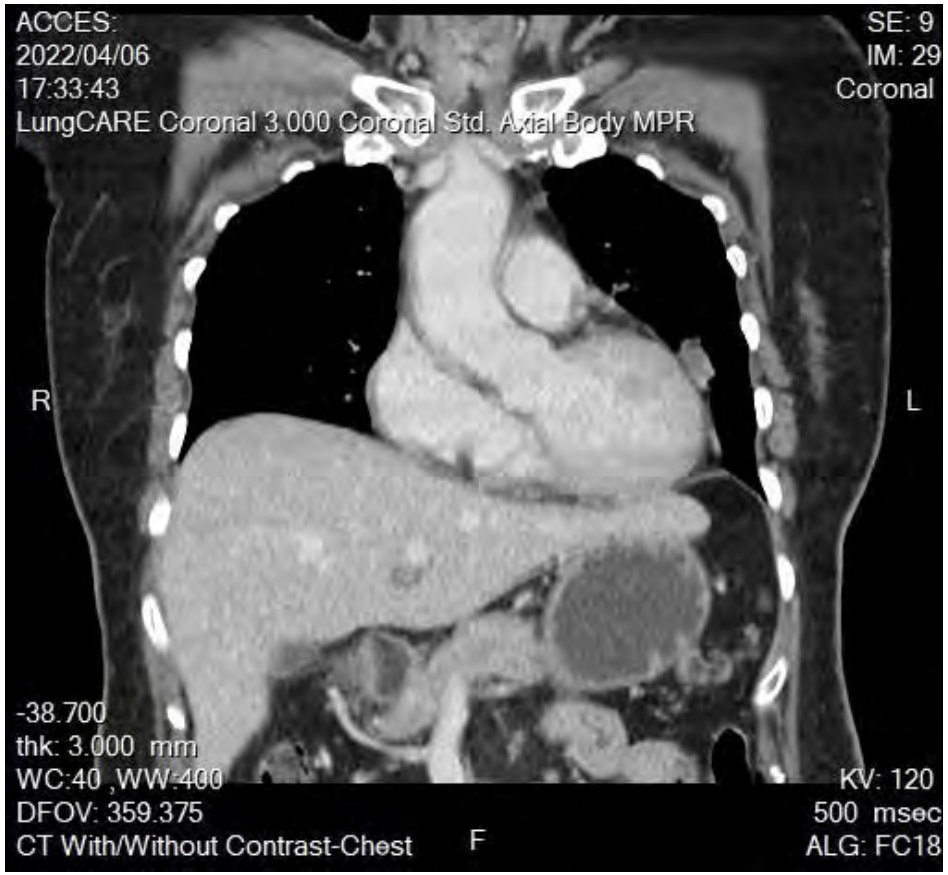
AE:

- Skin rash
- Paronychia
- Oral mucositis
- Pulmonary embolism

- Baseline: 28/Jan/2022



- Week 12: 06/Apr/2022

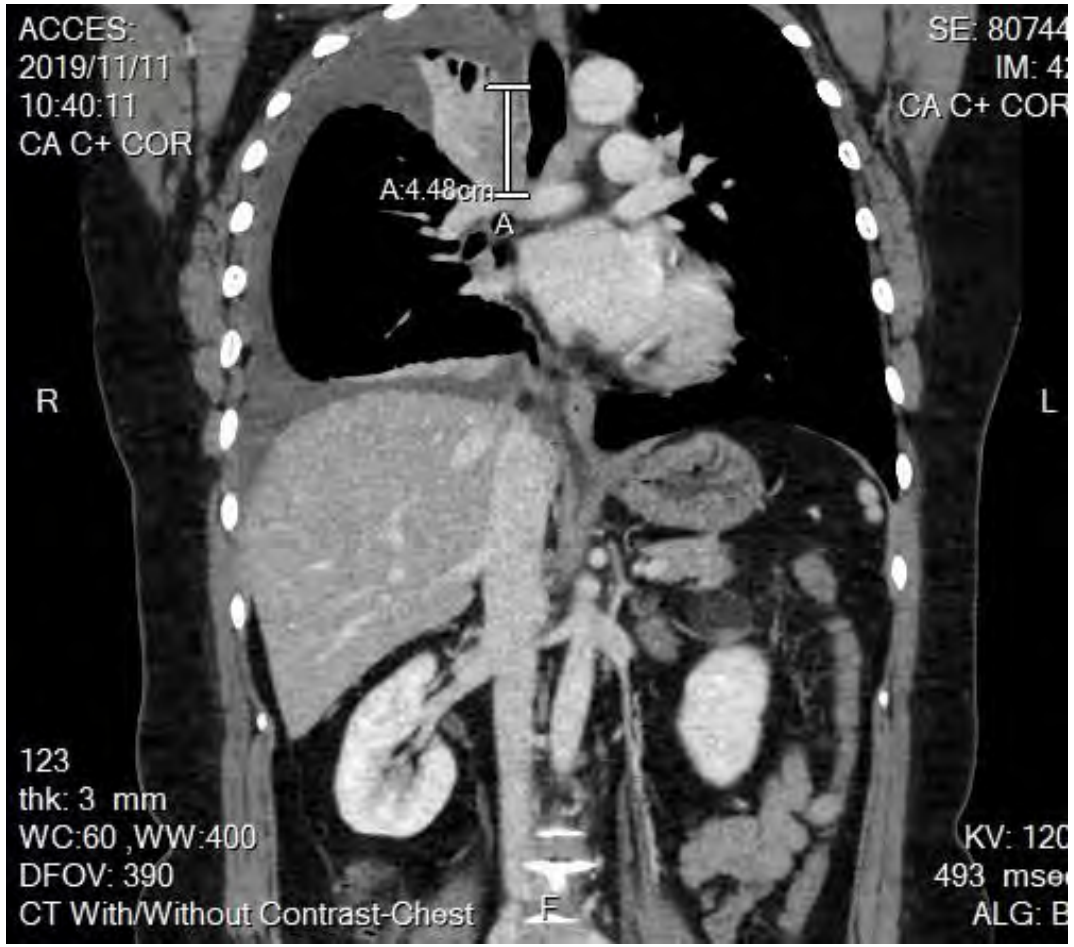


FLAURA2

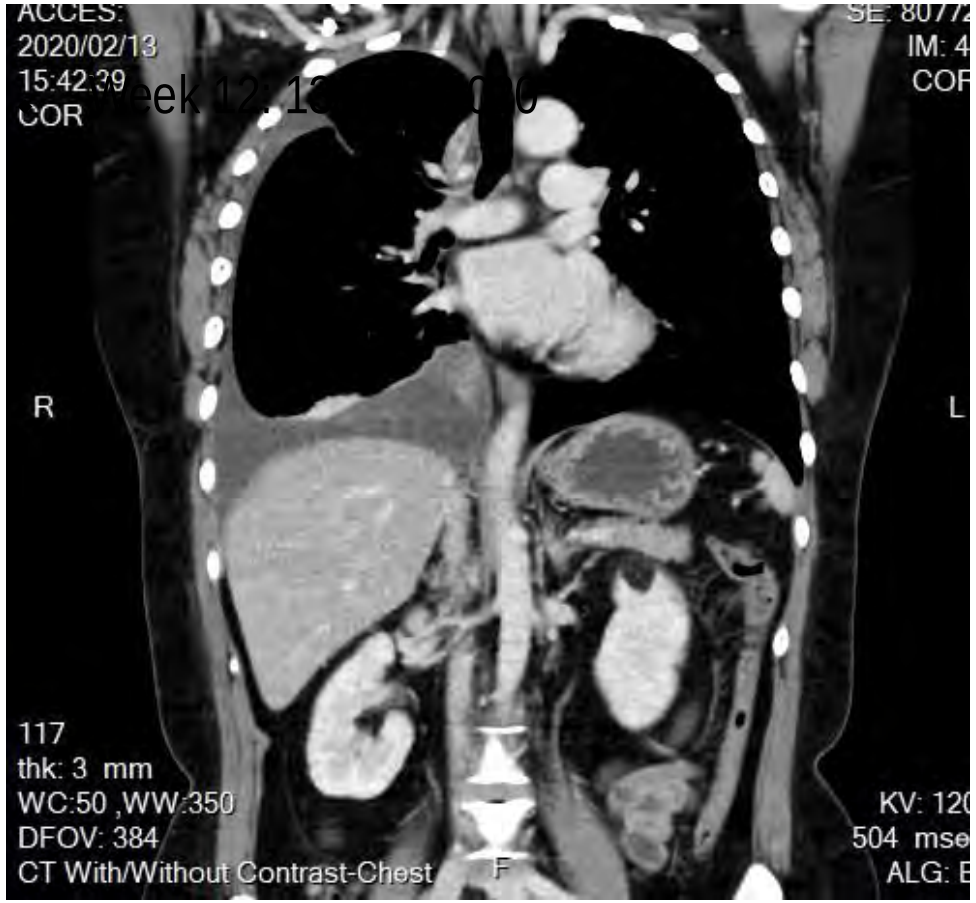
- 53y/o Female, Lung adenocarcinoma, cT2bN2M1c stage IVB with brain and bone mets., TTF-1 and CK7(+), EGFR: Exon 19 del., ALK (-), PD-L1 IHC 22C3 pharmDx: 70 %.

- Osimertinib, Pemetrexed and Carboplatin: 25/NOV/2019~07/NOV/2022, best response: PR

- Baseline: 11/NOV/2019



- Week 12: 13/FEB/2020



POST PROGRESSION

Radiotherapy: T7 – T9: 16/JUN/2022~29/JUN/2022, 3000cGy 10Fx

Osimertinib and Pemetrexed (treat beyond progression) till 06/NOV/2022

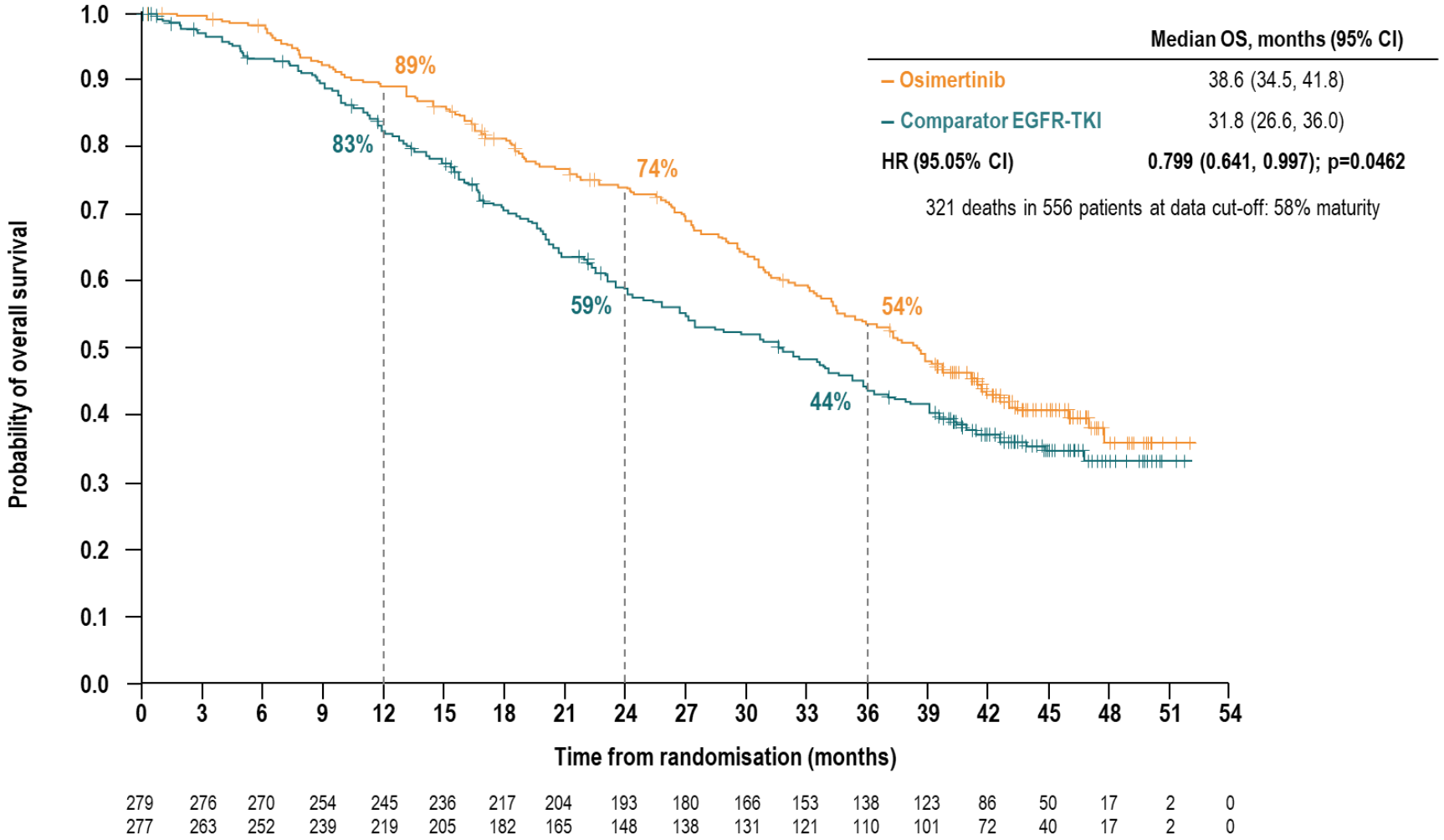
MRI on 31/OCT/2022: Multiple varying-sized marrow-replacing lesions with heterogeneous enhancement at multiple of the thoracolumbar spine, including T5, T8, and L1 vertebrae

NGS of pleural effusion (AlphaLiquid):

EGFR exon 19 del. (34.94%), EGFR amplification (CN:4.2), CDK4 amplification (CN:19.0), FGFR2: A511T (84.13%), FGFR1: Y380C (49.17%), MDM2 amplification (CN32.2), RET: T946A (1.39%), BRAF D565E(0.87%), CHEK2 D82_E86(0.13%), DPYD: I62M (0.13%)

TMB: 15.73 muts/Mb, MSI: MSS

FLAURA FINAL ANALYSIS: OVERALL SURVIVAL



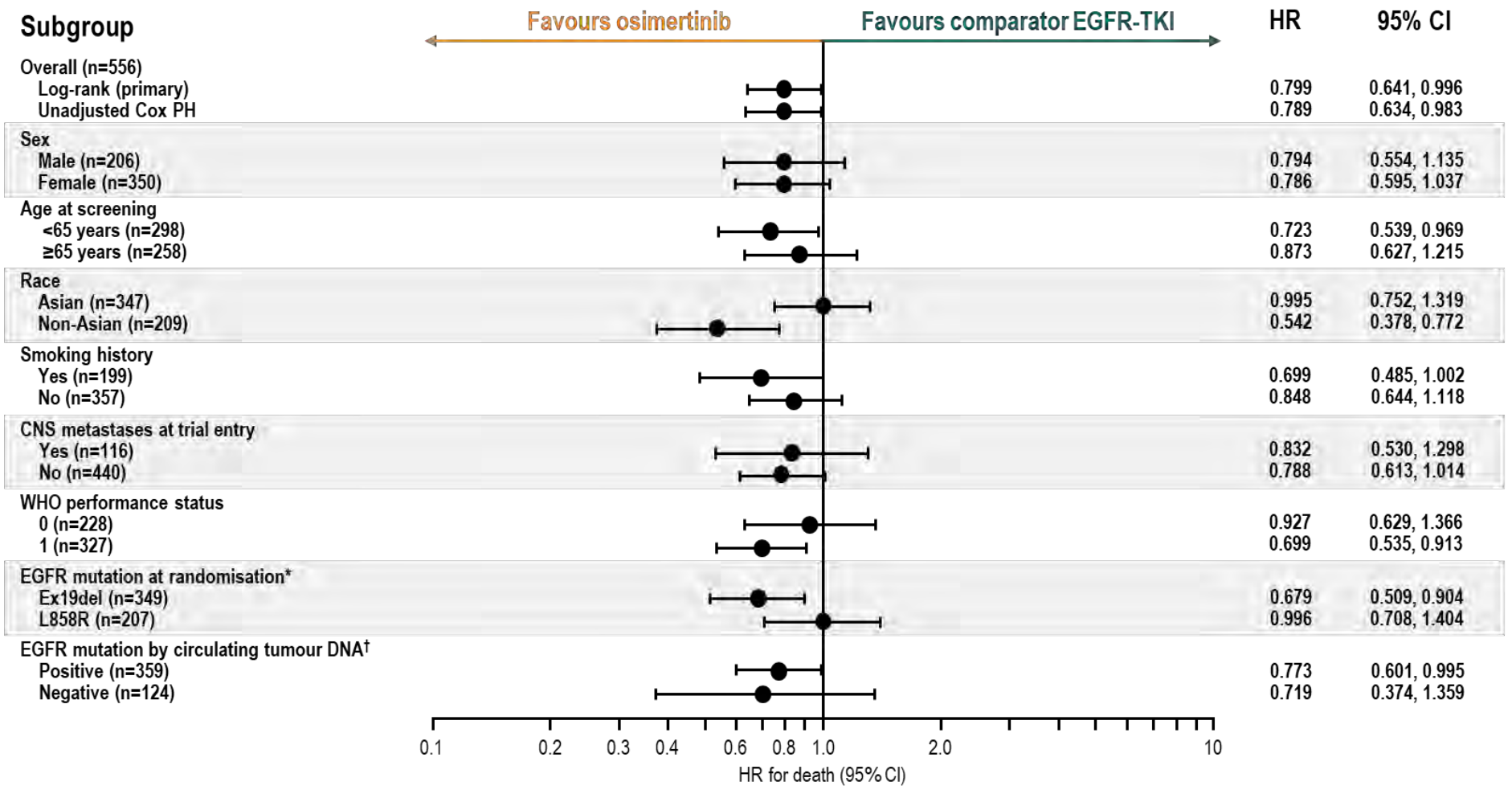
	Median OS, months (95% CI)
– Osimertinib	38.6 (34.5, 41.8)
– Comparator EGFR-TKI	31.8 (26.6, 36.0)
HR (95.05% CI)	**0.799 (0.641, 0.997); p=0.0462**

321 deaths in 556 patients at data cut-off: 58% maturity

Data cut-off: 25 June 2019

For statistical significance, a p-value of less than 0.0495, determined by O'Brien-Fleming approach, was required

FLAURA:
OVERALL SURVIVAL ACROSS SUBGROUPS



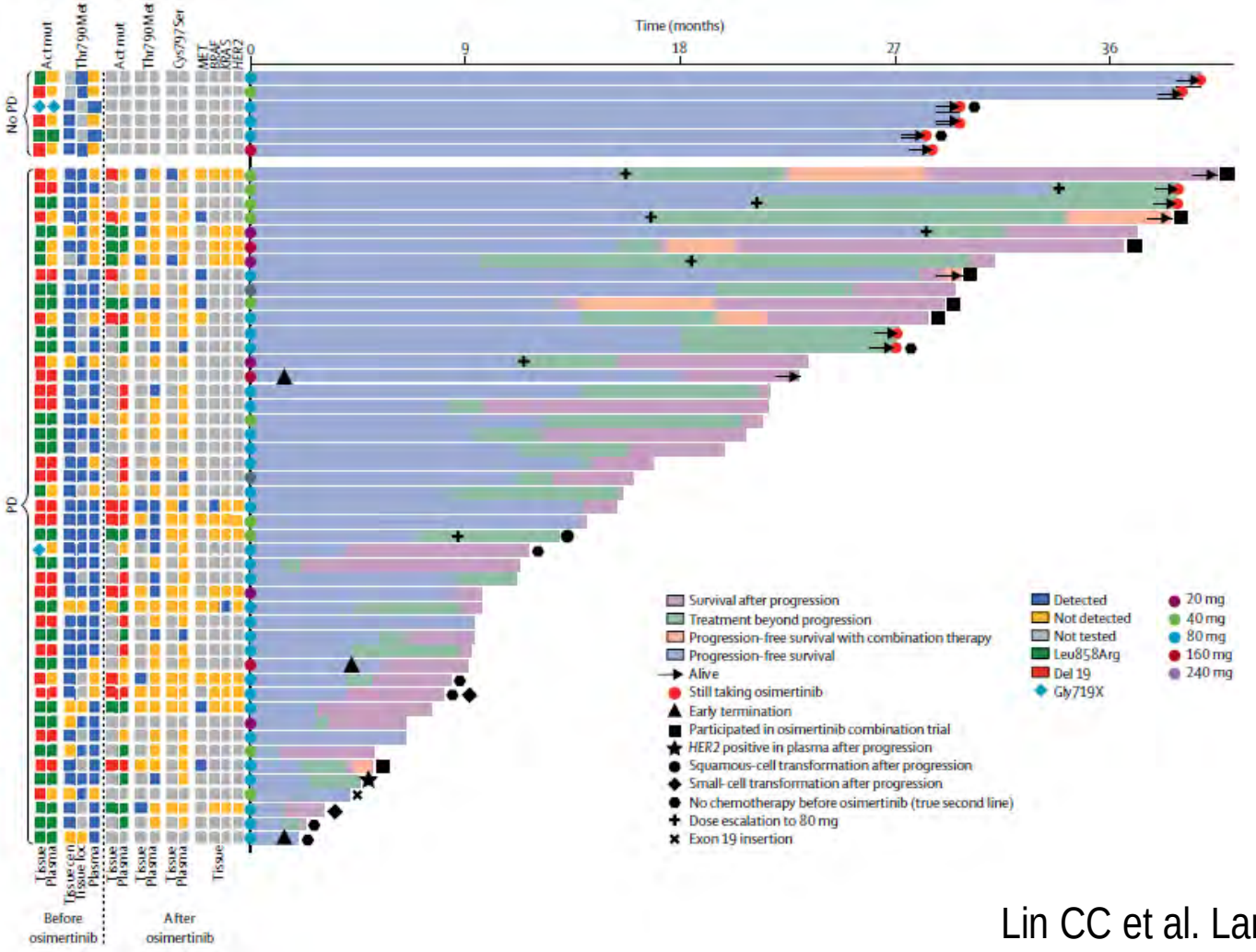
Data cut-off: 25 June 2019

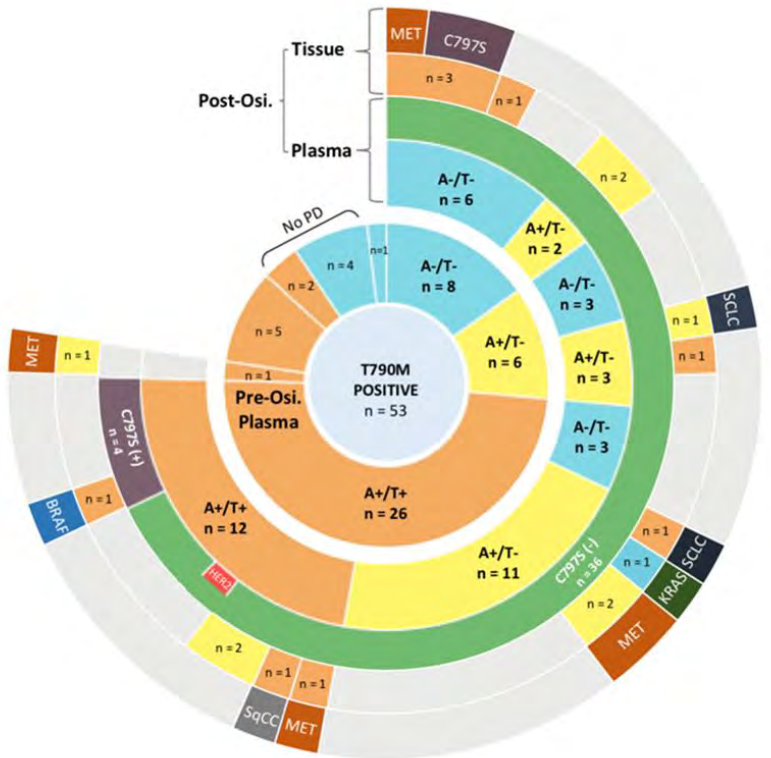
Hazard ratio <1 implies a lower risk of death on osimertinib

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

Outcomes in patients with non-small-cell lung cancer and acquired Thr790Met mutation treated with osimertinib: a genomic study

Chia-Chi Lin, Jin-Yuan Shih, Chong-Jen Yu, Chao-Chi Ho, Wei-Yu Liao, Jih-Hsing Lee, Tzu-Hsiu Tsai, Kang-Yi Su, Min-Shu Hsieh, Yih-Leong Chang, Ya-Ying Bai, Derek De-Rui Huang, Kenneth S Thress, James Chih-Hsin Yang





Lin CC et al. Lancet Res Med 2018:6, 107-16

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)

Randomization 1:1 (N=557)

Osimertinib 80 mg (QD) + pemetrexed 500 mg/m² + carboplatin AUC5 or cisplatin 75 mg/m² (Q3W for 4 cycles for platinum-based treatments)

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

Osimertinib 80 mg (QD)

Follow-up:

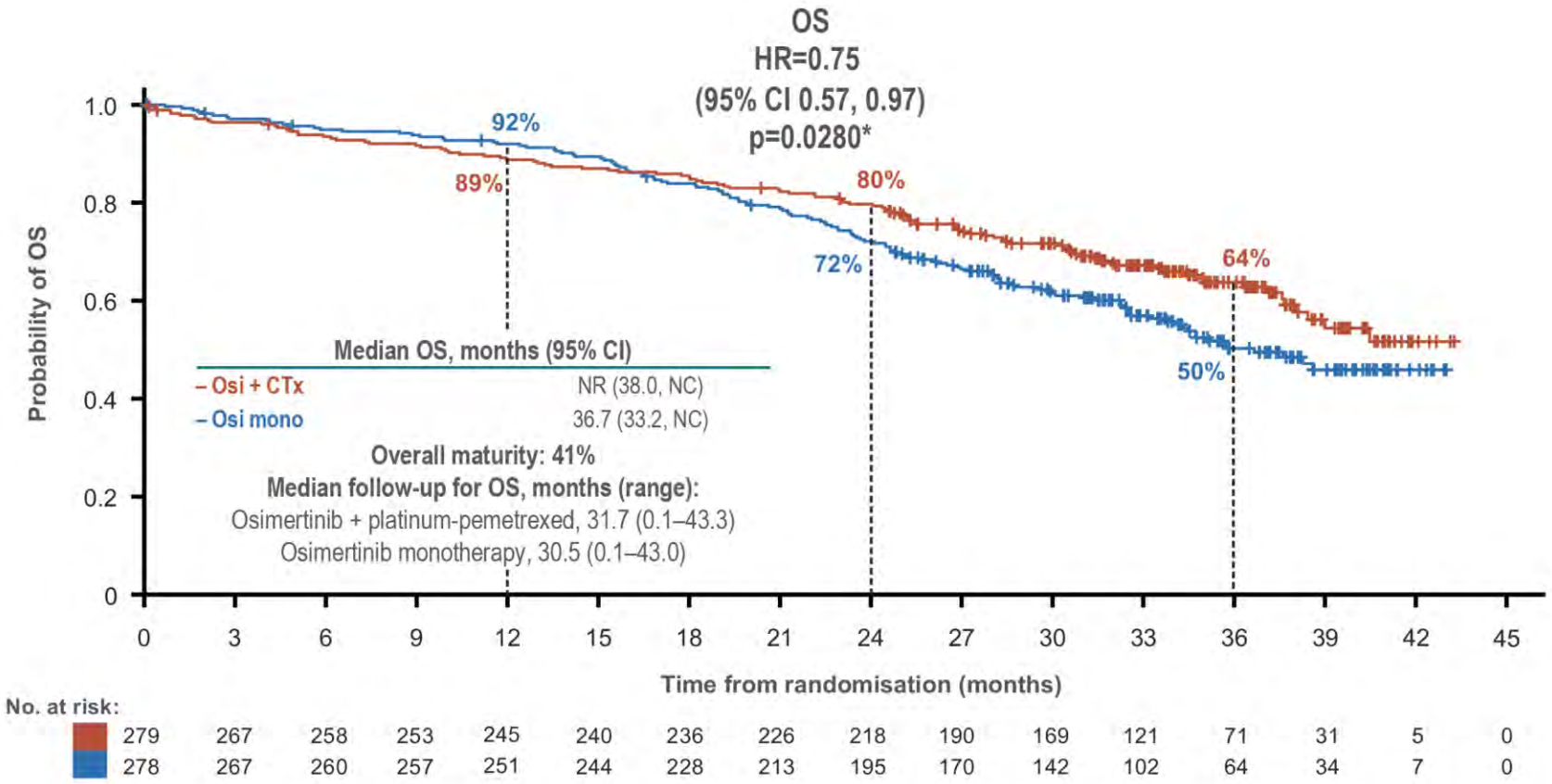
- RECIST 1.1 assessment at 6 and 12 weeks, then every 12 weeks until RECIST 1.1 defined radiological disease progression or other withdrawal criteria were met

- **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‡

1. Planchard et al. ESMO Open 2021;6:100271

*Not requiring steroids for at least two weeks; †Pemetrexed maintenance continued until a discontinuation criterion was met; ‡Efficacy analyses in the full analysis set, defined as all patients randomized to study treatment regardless of the treatment actually received, and safety analyses in the safety analysis set, defined as all randomized patients who received ≥1 dose of study treatment – one patient who was randomized to osimertinib plus platinum-pemetrexed received only osimertinib and was therefore included in the osimertinib monotherapy safety analysis set; §The study provided 90% power to demonstrate a statistically significant difference in PFS assuming HR=0.68 at 5% two-sided significance level

FLAURA2 SECOND INTERIM OVERALL SURVIVAL ANALYSIS



*A p-value of ≤0.000001 was required for statistical significance at this second interim analysis
CI, confidence interval; CTx, chemotherapy; HR, hazard ratio; mono, monotherapy; NC, not calculable; NR, not reached; OS, overall survival; osi, osimertinib

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) V	10 (10)	7 (6)
	Other uncommon	1 (1) V	4 (4)	5 (5)
RTK amplifications	MET amplification	8 (12)	11 (11)	17 (16)
	ERRB2 amplification	3 (4)	1 (1) V	2 (2)
MAPK / PI3K mutations	BRAF V600E	1 (1) V	5 (5)	3 (3)
	KRAS mutation	2 (3) V	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) V	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)	–

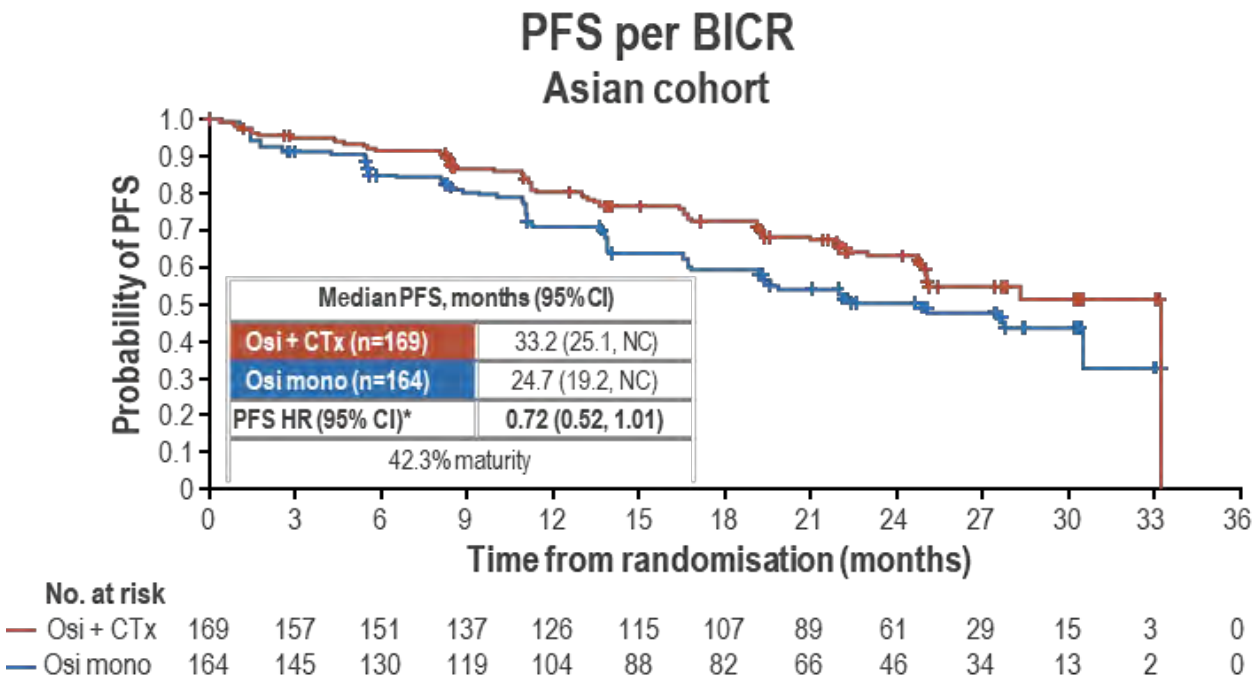
James Chih-Hsin Yang | FLAURA2: Resistance, and impact of baseline TP53 alterations in patients treated with 1L osimertinib ± platinum-pemetrexed

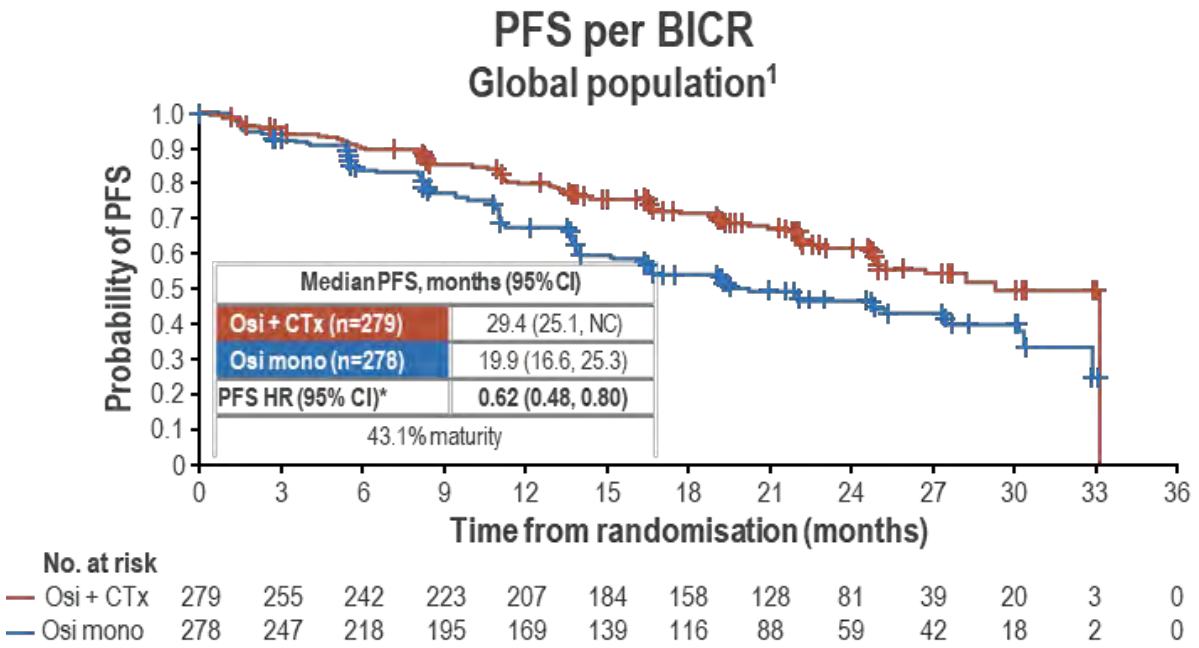
BASELINE CHARACTERISTICS WERE BALANCED ACROSS THE TREATMENT ARMS IN THE ASIAN COHORT

	Asian cohort (n=333)		Global population (N=557)[1]	
Characteristic	Osi + CTx (n=169)	Osi mono (n=164)	Osi + CTx (n=279)	Osi mono (n=278)
Sex, male / female, %	38 / 62	43 / 57	38 / 62	39 / 61
Age, median (range), years	61 (34–83)	61 (32–79)	61 (26–83)	62 (30–85)
Race, Asian / non-Asian, %	100 / 0	100 / 0	64 / 36	63 / 37
WHO PS, 0 / 1*, %	37 / 63	37 / 63	37 / 62	37 / 63
Histology, adenocarcinoma† / adenosquamous / other, %	99 / 1 / 0	98 / 0 / 2	99 / 1 / 1	99 / 0 / 1
EGFR mutation at randomisation,‡ Ex19del / L858R, %	53 / 46	61 / 38	61 / 38	60 / 38
Locally advanced / metastatic, %	5 / 95	3 / 97	5 / 95	3 / 97
CNS metastases, %	47	42	42	40
Extra-thoracic metastases, %	58	51	53	54
Baseline tumour size, mean (SD) / median (range), mm	61 (40) / 52 (11–220)	57 (34) / 50 (13–164)	65 (42) / 57 (10–284)	64 (39) / 57 (11–221)

Yang JC ESMO Asia 2024 6630MO

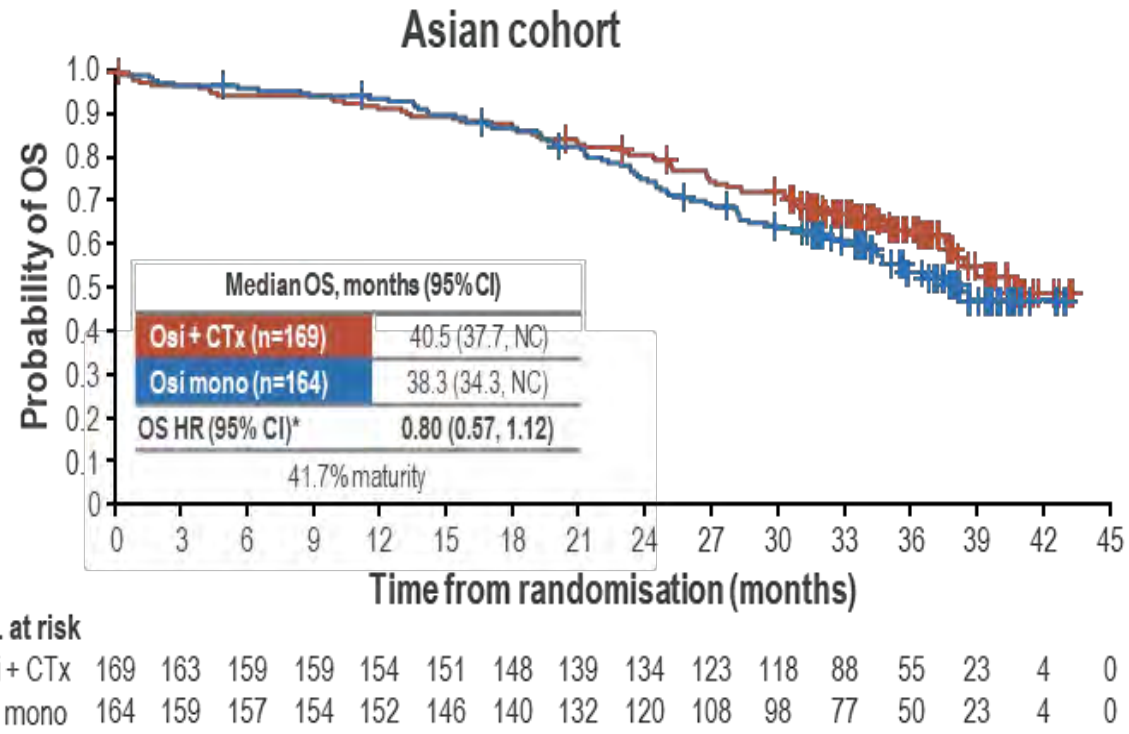
OSIMERTINIB WITH THE ADDITION OF CTX WAS ASSOCIATED WITH A CLINICALLY MEANINGFUL PFS BENEFIT VS OSIMERTINIB MONOTHERAPY IN THE ASIAN COHORT

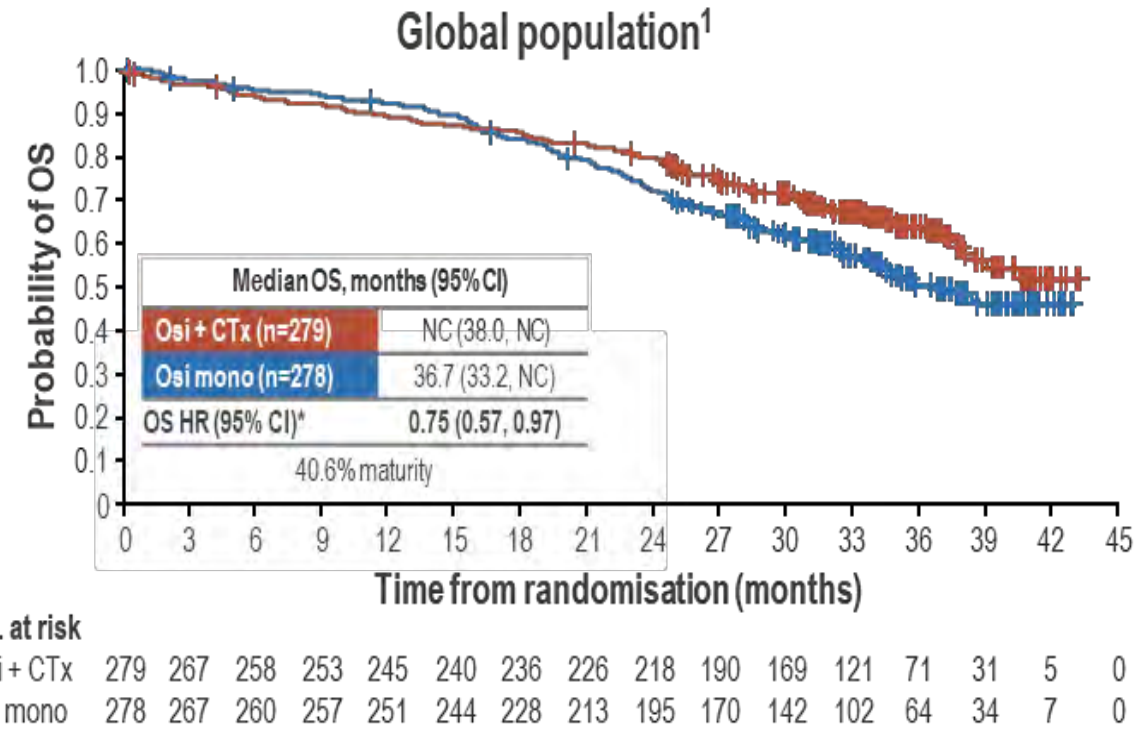




Yang JC ESMO Asia 2024 6630MO

OSIMERTINIB WITH THE ADDITION OF CTX SHOWED A TREND TOWARDS AN OS BENEFIT AT THE SECOND INTERIM OS ANALYSIS IN THE ASIAN COHORT





Yang JC ESMO Asia 2024 6630MO

ANAEMIA WAS THE MOST COMMON AE IN THE OSIMERTINIB PLUS CTX ARM OF THE ASIAN COHORT

- There were no instances of grade 4 / 5 ILD / pneumonitis‡ in the osimertinib + CTx arm
- The frequency of any grade ILD / pneumonitis‡ in the osimertinib + CTx arm of the Asian cohort (n=7, 4%) was consistent with the global study population (n=9, 3%)[1]

Yang JC ESMO Asia 2024 6630MO

All-causality AEs (≥25% patients in either arm; safety analysis set; Asian cohort)*

	Osi + CTx (n=167)			Osi mono (n=164)		
AEs, n (%)	Any grade†	Grade 3	Grade 4	Any grade†	Grade 3	Grade 4
Anaemia	84 (50)	37 (22)	0 (0)	19 (12)	0 (0)	0 (0)
Diarrhoea	65 (39)	5 (3)	0 (0)	67 (41)	1 (<1)	0 (0)
Nausea	62 (37)	3 (2)	0 (0)	10 (6)	0 (0)	0 (0)
Neutrophil count decrease	56 (34)	23 (14)	6 (4)	15 (9)	1 (<1)	0 (0)
Decreased appetite	55 (33)	7 (4)	0 (0)	14 (9)	2 (1)	0 (0)
Stomatitis	52 (31)	1 (<1)	0 (0)	41 (25)	0 (0)	0 (0)
Constipation	50 (30)	1 (<1)	0 (0)	14 (9)	0 (0)	0 (0)
Paronychia	47 (28)	2 (1)	0 (0)	49 (30)	0 (0)	0 (0)
Platelet count decrease	47 (28)	17 (10)	3 (2)	16 (10)	0 (0)	0 (0)
Rash	45 (27)	1 (<1)	0 (0)	32 (20)	0 (0)	0 (0)
WBC count decrease	43 (26)	8 (5)	1 (<1)	17 (10)	0 (0)	0 (0)
ALT increase	43 (26)	3 (2)	0 (0)	14 (9)	1 (<1)	0 (0)
Vomiting	43 (26)	1 (<1)	0 (0)	11 (7)	0 (0)	0 (0)

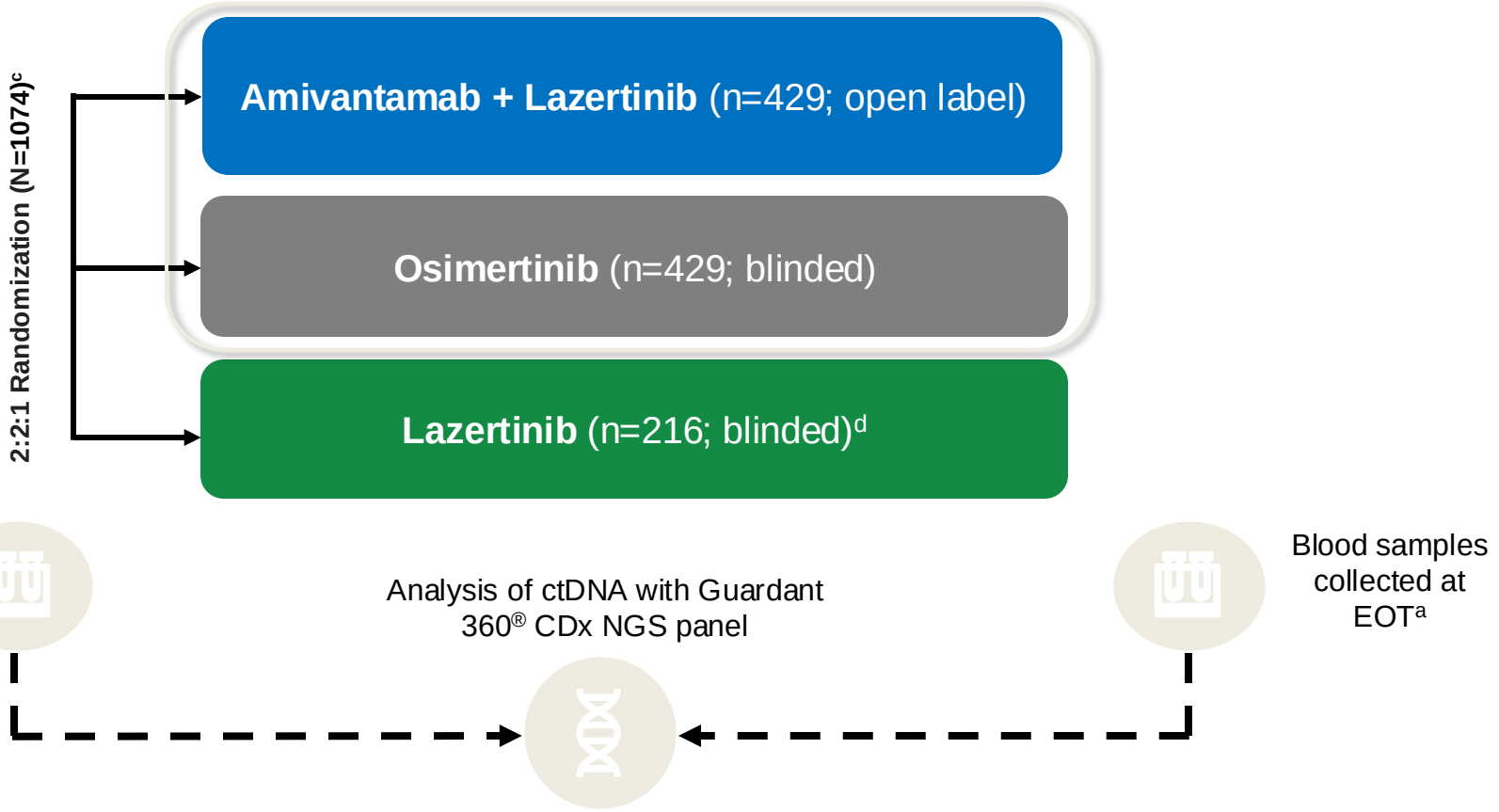
MARIPOSA STUDY DESIGN

Paired blood samples were collected at baseline and EOT[a] for analysis of detectable ctDNA by NGS[b]

Focus of this presentation

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



MARIPOSA (ClinicalTrials.gov Identifier: NCT04487080) enrollment period: November 2020 to May 2022. Last EOT sample was collected Feb 2024.

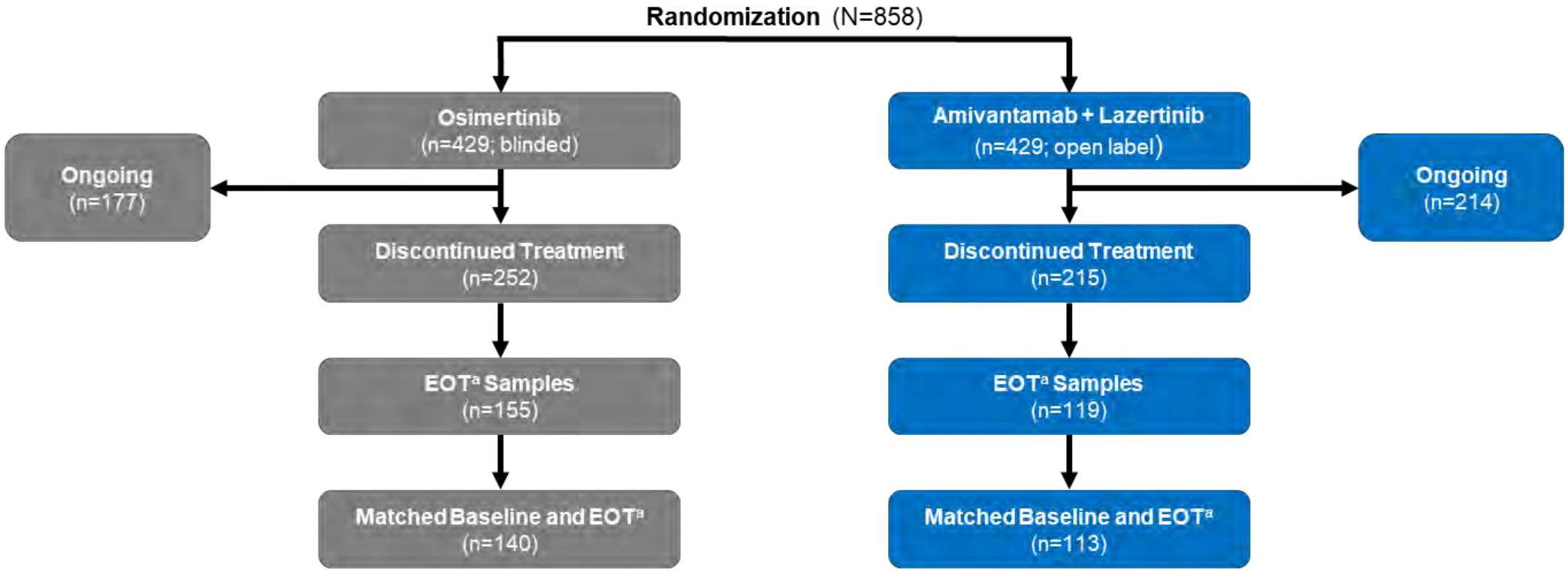
[a]Defined as at disease progression/treatment discontinuation or within 90 days of discontinuation. [b]Using Guardant 360® companion diagnostics. [c]Stratification factors included *EGFR* mutation type (Ex19del or L858R), Asian race (yes or no), and history of brain metastases (yes or no). [d]Lazertinib monotherapy arm was included to assess the contribution of components.

ctDNA, circulating tumor DNA; EOT, end of treatment; Ex19del, exon 19 deletion; NGS, next-generation sequencing.

Besse B. et al. ESMO 2024

CT-DNA ANALYSIS FOR ACQUIRED RESISTANCE

Among patients who discontinued treatment, 140/252 (56%) for osimertinib and 113/215 (53%) for amivantamab + lazertinib had matched baseline and EOT ctDNA data



- Demographic and baseline clinical characteristics were similar between both groups

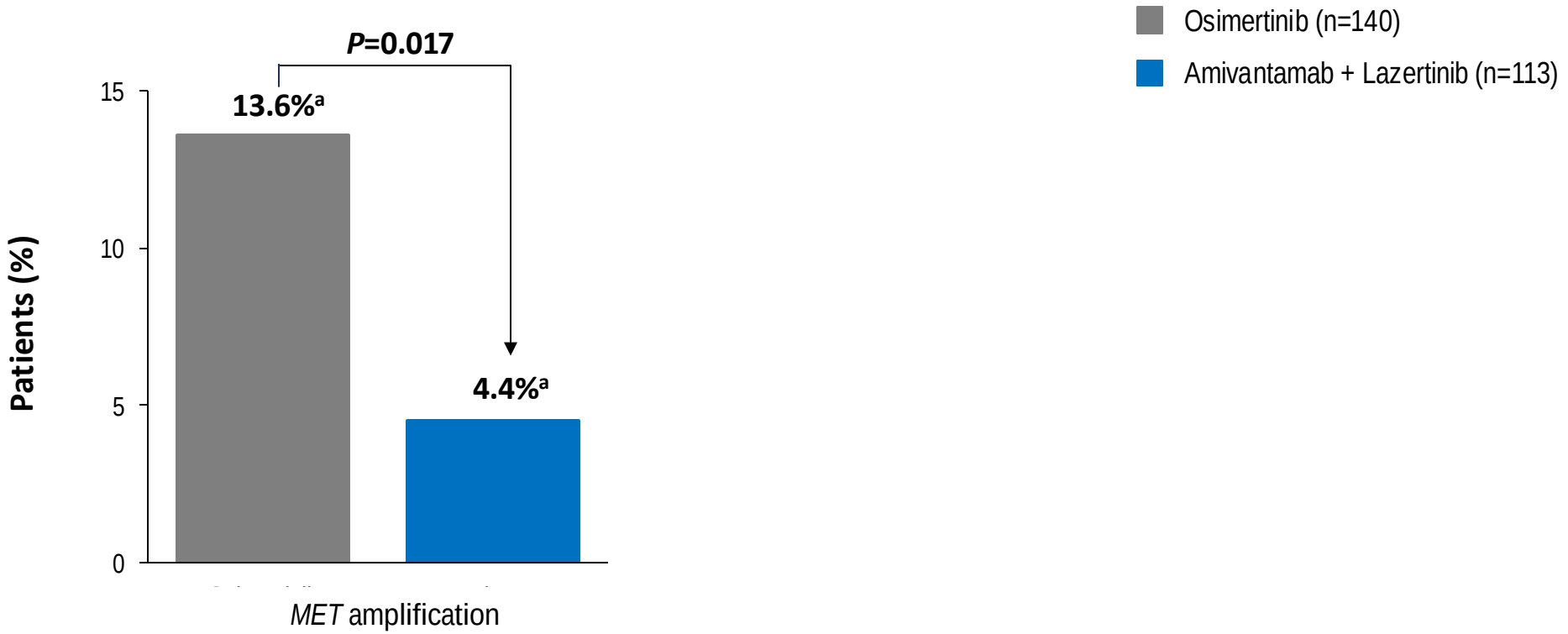
[a]Sample taken within 90 days of discontinuation if EOT sample was not available. Last EOT sample was collected Feb 2024. Median follow-up was 32.6 months.
ctDNA, circulating tumor DNA; EOT, end of treatment.

Besse B. et al. ESMO 2024

MET and *EGFR*-based Resistance Mechanisms

MARIPOSA
Ami + Laz in
1L *EGFR*+ NSCLC

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



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

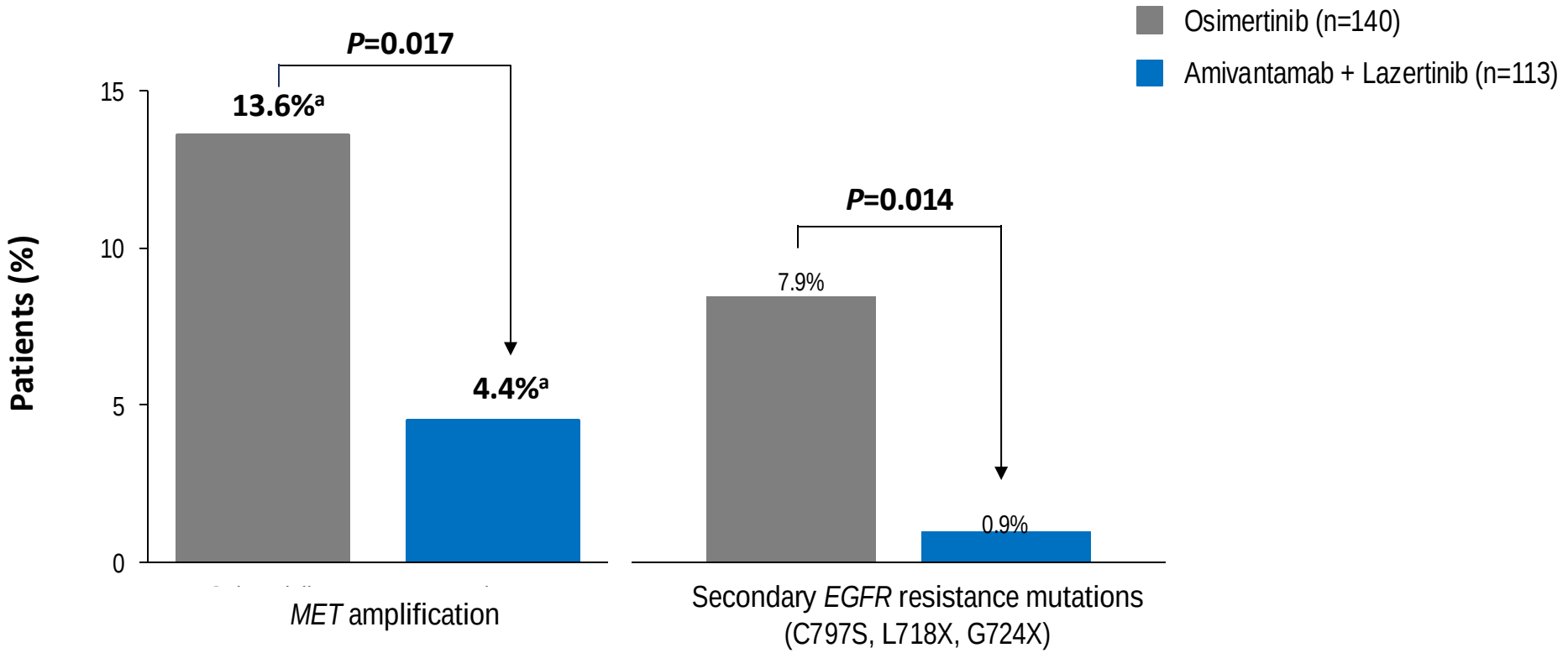
BARCELONA 2024 ESMO congress

[a]9.3% of patients in the osimertinib arm had focal *MET* amplifications vs 1.8% in the amivantamab + lazertinib arm. *MET* amplifications are defined as >2.2 copy number alterations.

MET and *EGFR*-based Resistance Mechanisms

MARIPOSA
Ami + Laz in
1L *EGFR*+ NSCLC

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



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

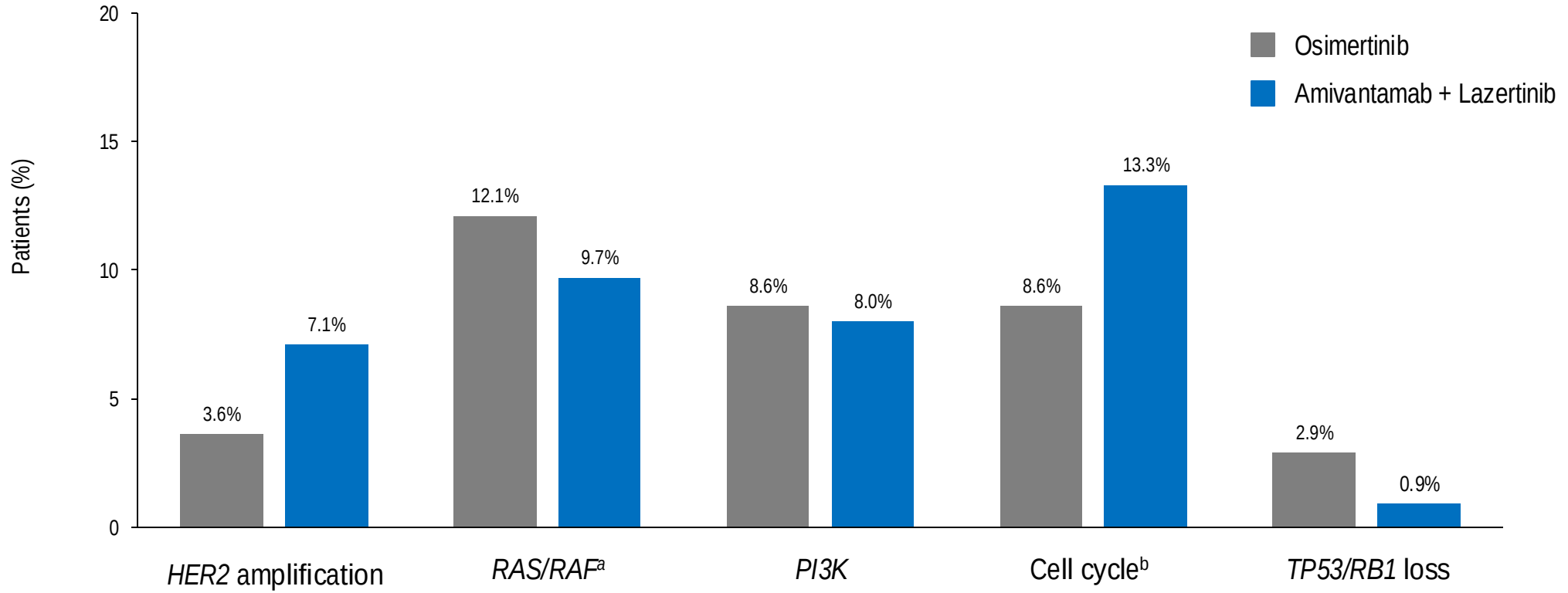
BARCELONA 2024 ESMO congress

[a]9.3% of patients in the osimertinib arm had focal *MET* amplifications vs 1.8% in the amivantamab + lazertinib arm. *MET* amplifications are defined as >2.2 copy number alterations.

MET and *EGFR* Independent Resistance Mechanisms

MARIPOSA
Ami + Laz in
1L *EGFR*+ NSCLC

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



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

BARCELONA 2024 ESMO congress

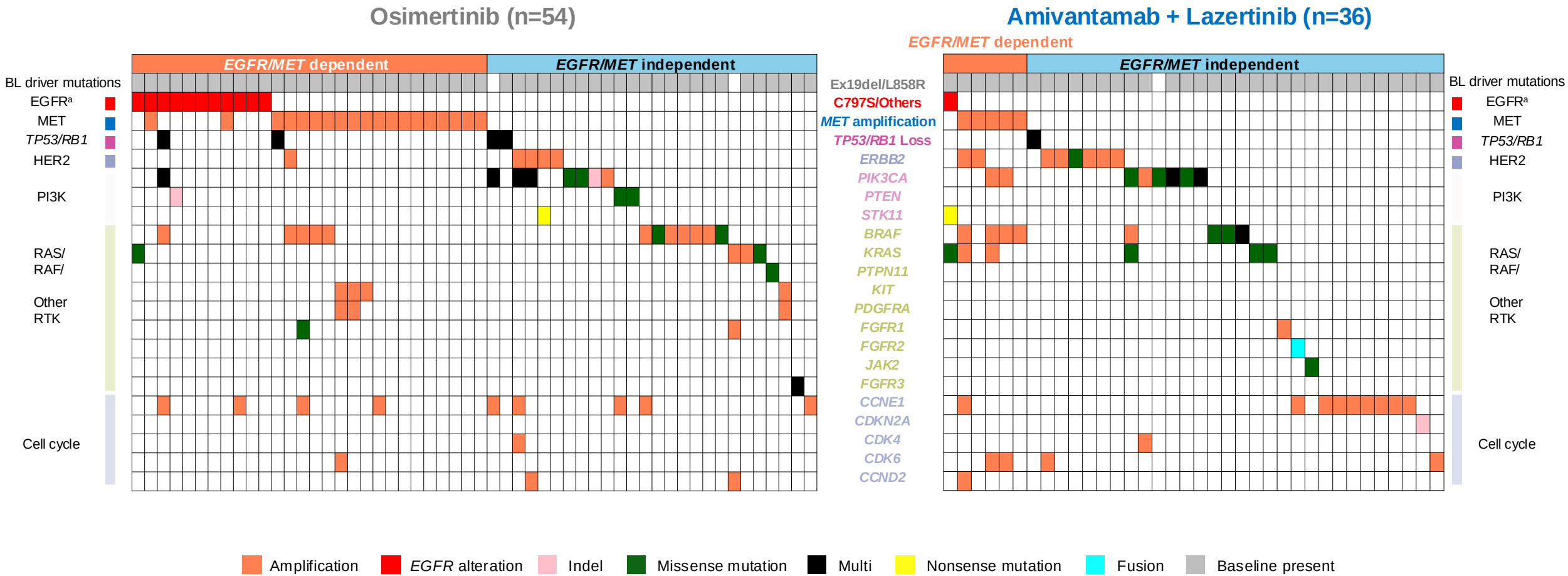
[a]Includes *BRAF* and *KRAS*. [b]Includes *CCNE1*, *CDKN2A*, *CDK4*, *CDK6,* and *CCND2*.

1. Offin M, et al. *J Thorac Oncol*. 2019;14(10):1784–1793.

Acquired Resistance Mutational Landscape

MARIPOSA
Ami + Laz in 1L *EGFR*+ NSCLC

- No clear resistance mechanisms (unknown) were detected in 86 (61%) for osimertinib and 77 (68%) for amivantamab + lazertinib
- Among patients with known resistance mechanisms, osimertinib had a more heterogeneous mutational landscape than amivantamab + lazertinib



[a]For osimertinib, *EGFR* mutations included C797S/L718X/G724X. For, amivantamab + lazertinib, only one *EGFR* C797S mutation was detected.

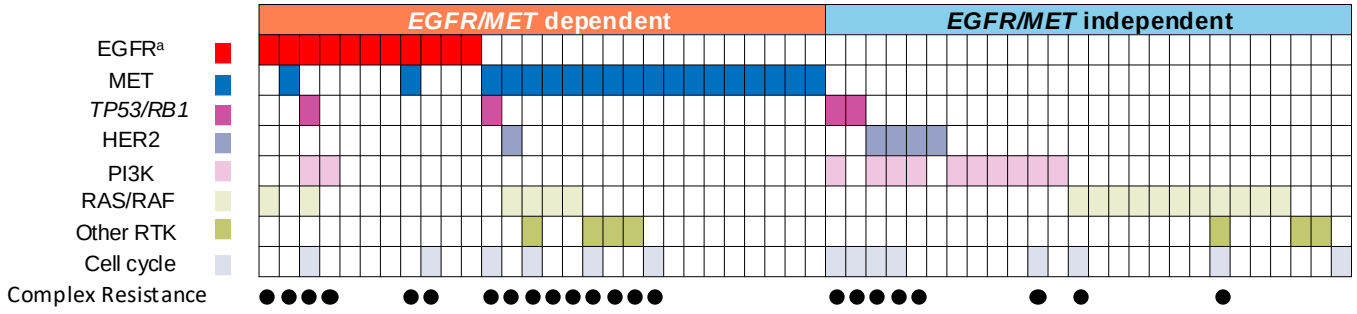
Ex19del, exon 19 deletion

Frequency of Complex Resistance

MARIPOSA
Ami + Laz in
1L *EGFR*+ NSCLC

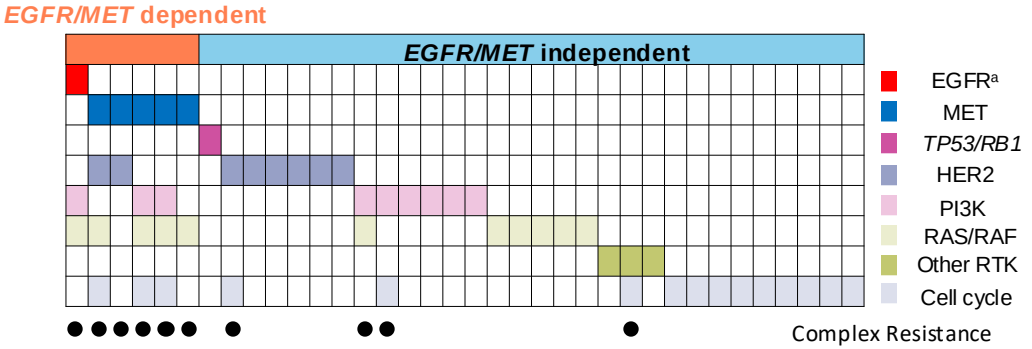
Complex resistance was defined as having 2 or more resistance pathway alterations detected by ctDNA

Osimertinib (n=54)



42.6% had alterations in ≥2 resistance pathways

Amivantamab + Lazertinib (n=36)



27.8% had alterations in ≥2 resistance pathways

Osimertinib had a higher frequency of complex resistance than amivantamab + lazertinib (42.6% vs 27.8%)

BARCELONA 2024 ESMO congress

[a]For osimertinib, *EGFR* mutations included C797S/L718X/G724X. For, amivantamab + lazertinib, only one *EGFR* C797S mutation was detected.

ctDNA, circulating tumor DNA.

Detection of *EGFR* Driver Mutations

MARIPOSA
Ami + Laz in 1L *EGFR*+ NSCLC

Lower rates of Ex19del or L858R detected in ctDNA were seen with amivantamab + lazertinib vs osimertinib at EOT

Osimertinib

Ex19del/L858R at BL (**82.9%**)

Amivantamab + Lazertinib

Ex19del/L858R at BL (**78.8%**)

Amivantamab + lazertinib had deeper and more sustained *EGFR* inhibition than osimertinib[a]

BARCELONA 2024 ESMO congress

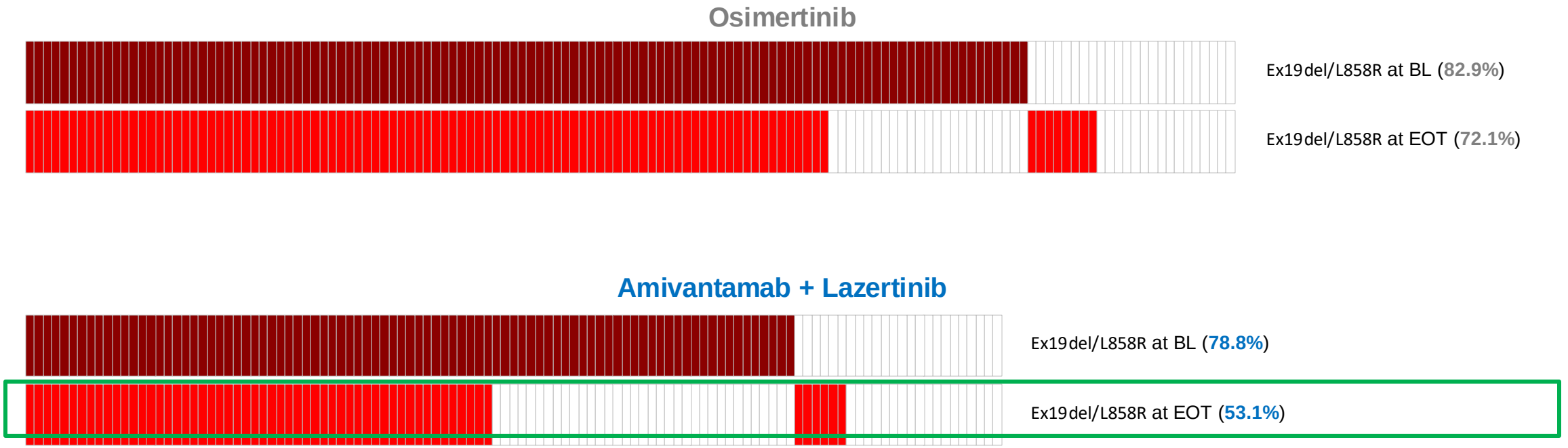
[a]*P*=0.003.

BL, baseline; ctDNA, circulating tumor DNA; EOT, end of treatment; Ex19del, exon 19 deletion.

Detection of *EGFR* Driver Mutations

MARIPOSA
Ami + Laz in
1L *EGFR*+ NSCLC

Lower rates of Ex19del or L858R detected in ctDNA were seen with amivantamab + lazertinib vs osimertinib at EOT



Amivantamab + lazertinib had deeper and more sustained *EGFR* inhibition than osimertinib[a]

BARCELONA 2024 ESMO congress

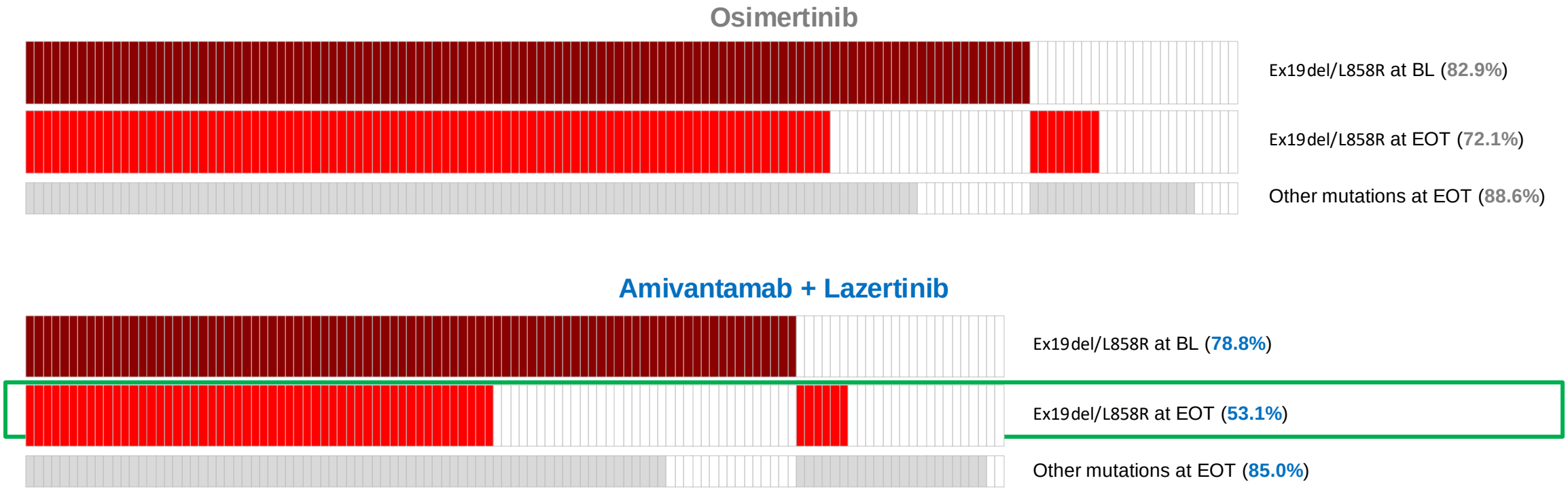
[a]*P*=0.003.

BL, baseline; ctDNA, circulating tumor DNA; EOT, end of treatment; Ex19del, exon 19 deletion.

Detection of *EGFR* Driver Mutations

MARIPOSA
Ami + Laz in
1L *EGFR*+ NSCLC

Lower rates of Ex19del or L858R detected in ctDNA were seen with amivantamab + lazertinib vs osimertinib at EOT



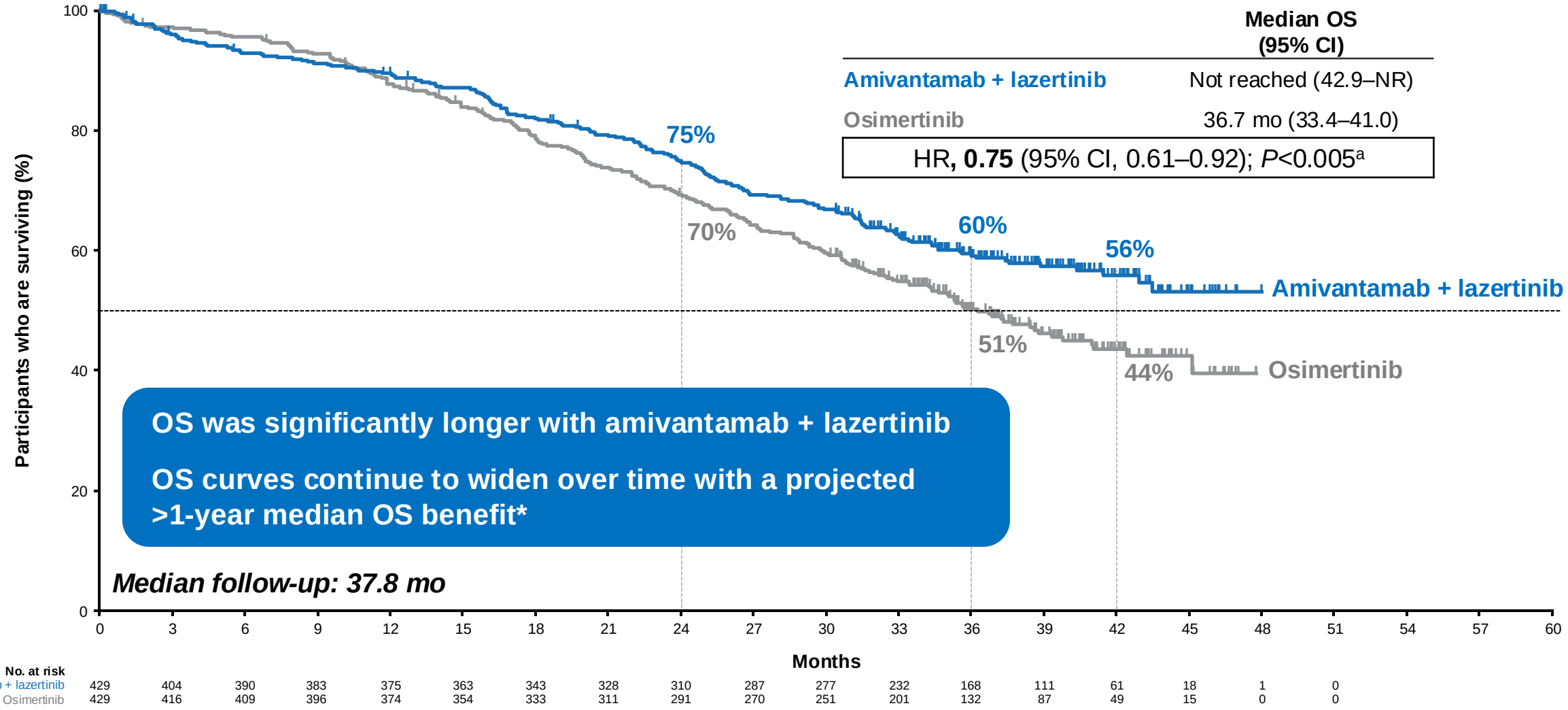
Amivantamab + lazertinib had deeper and more sustained *EGFR* inhibition than osimertinib[a]

BARCELONA 2024 ESMO congress

[a]*P*=0.003.

BL, baseline; ctDNA, circulating tumor DNA; EOT, end of treatment; Ex19del, exon 19 deletion.

MARIPOSA: Overall Survival



Based on an exponential distribution assumption of OS in both arms, the improvement in median OS is projected to exceed 1 year.

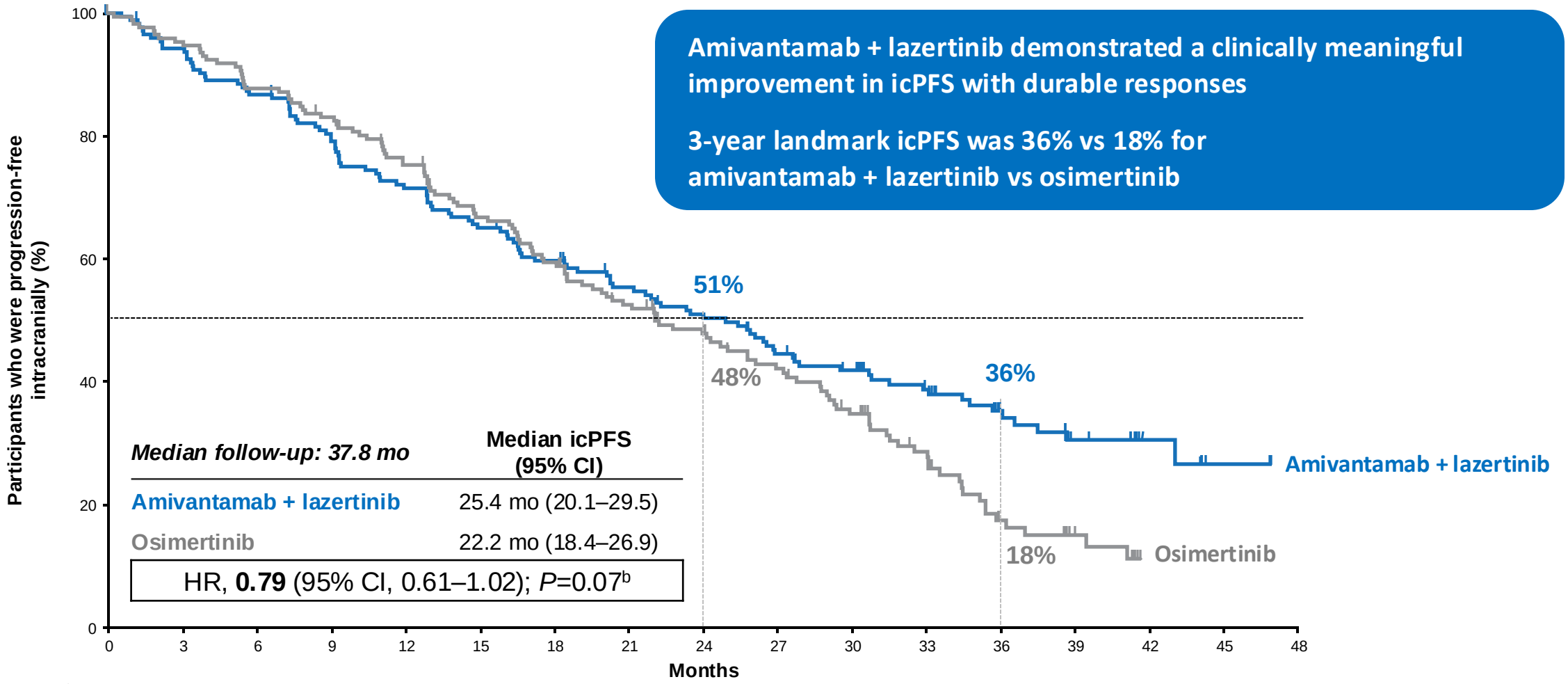
Note: Last participant was enrolled in May 2022. Clinical cutoff date was December 4, 2024. In total, 390 deaths had occurred in the amivantamab + lazertinib (173 deaths) and osimertinib (217 deaths) arms.

[a]*P*-value was calculated from a log-rank test stratified by mutation type (Ex19del or L858R), race (Asian or Non-Asian), and history of brain metastasis (present or absent). Hazard ratio was calculated from a stratified Cox regression model.

Intracranial PFS[a]

Amivantamab + lazertinib demonstrated a clinically meaningful improvement in icPFS with durable responses

3-year landmark icPFS was 36% vs 18% for amivantamab + lazertinib vs osimertinib



[a]Intracranial PFS was defined as time from randomization until the date of intracranial disease progression (progression of brain metastasis or occurrence of new brain lesions) or death, based on BICR using RECIST v1.1 among participants with a history of brain metastases. [b]*P*-value was calculated from a log-rank test stratified by mutation type (Ex19del or L858R) and race (Asian or Non-Asian). Hazard ratio was calculated from a stratified Cox regression model.


A
門診
Clinic
聯合服務中心

NTU CANCER CENTER
台大癌醫中心

Teaching Research

Thank you

Presented by: 楊志新 James Chih-Hsin Yang