

INTEGRATE 7.0

QUALI ‘REGOLE’ NELLA GESTIONE INTEGRATA DELLA NEOPLASIA POLMONARE?

GAMES

VERONA

13-14 OTTOBRE 2025

II SESSIONE - Let’s start game

SITUAZIONE CLINICA EMBLEMATICA 1

NSCLC stadio III EGFR mutato: TKI in adiuvante o in mantenimento?

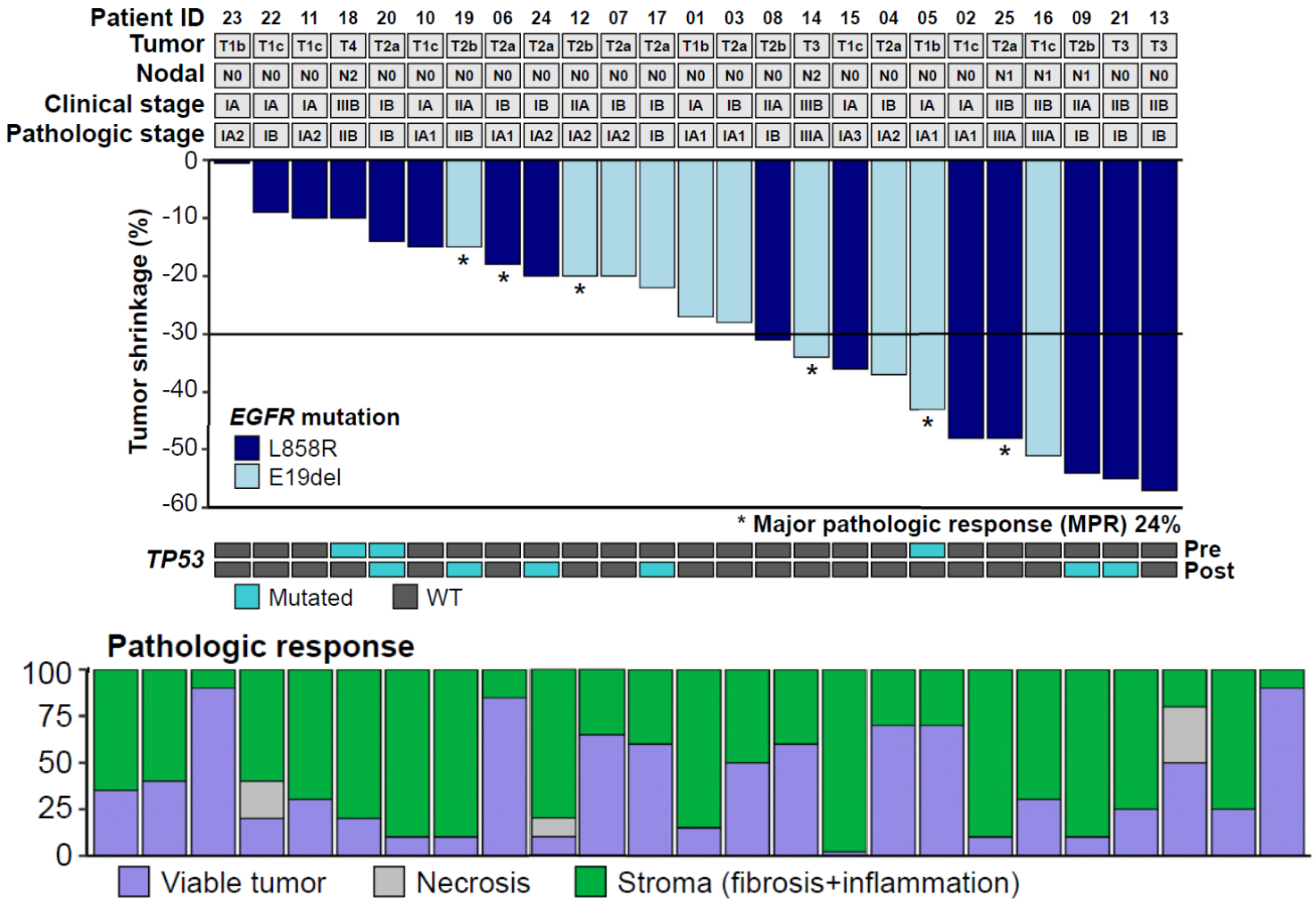
- **Pro radioterapia: Niccolò Giaj-Levra MD, PhD**

Advanced Radiation Oncology Department

IRCCS, Sacro Cuore Don Calabria Cancer Care Center,

Negrar di Valpolicella (VR), Italy

Radiotherapy, Yes! Why?



NORA study

- Neoadj and adju osimertinib
- Stage IA to IIIA (TNM 8th)
- MPR: 24%
- pCR: 0%

Lee JB et al., J Thorac Oncol 2025

Radiotherapy, Yes! Why?

Staging TNM

Study	Author	Year	Clinical trial Phase	Inclusion criteria stage	TNM edition	T	N	Stage
ADAURA	Wu YL	2020	III	II to **IIIA**	7 (2010)	T2a (41mm)	N2 (multi)	IIIA
LAURA	Lu S	2024	III	**IIIA** to IIIC	8 (2017)	T2b (41 mm)	N2 (multi)	IIIA



Radiotherapy, Yes! Why?

Staging TNM

In January 2025, TNM 9th edition is scheduled to take effect

8th Edition TNM Categories

T/M	Label	N0	N1	N2	N3
T1	T1a	IA1	IIB	IIIA	IIIB
	T1b	IA2	IIB	IIIA	IIIB
	T1c	IA3	IIB	IIIA	IIIB
T2	T2a Inv	IB	IIB	IIIA	IIIB
	T2a >3-4	IB	IIB	IIIA	IIIB
	T2b >4-5	IIA	IIB	IIIA	IIIB
T3	T3 >5-7	IIB	IIIA	IIIB	IIIC
	T3 Inv	IIB	IIIA	IIIB	IIIC
	T3 Same Lobe Nod	IIB	IIIA	IIIB	IIIC
T4	T4 >7	IIIA	IIIA	IIIB	IIIC
	T4 Inv	IIIA	IIIA	IIIB	IIIC
	T4 Ipsi Nod	IIIA	IIIA	IIIB	IIIC
M1	M1a Pl Dissem	IVA	IVA	IVA	IVA
	M1a Contr Nod	IVA	IVA	IVA	IVA
	M1b Single Les	IVA	IVA	IVA	IVA
	M1c Mult Les	IVB	IVB	IVB	IVB

9th Edition TNM Categories

T/M	Description	N0	N1	N2		N3
				N2a	N2b	
T1	T1a ≤1 cm	IA1	IIA	IIB	IIIA	IIIB
	T1b >1 to ≤2 cm	IA2	IIA	IIB	IIIA	IIIB
	T1c >2 to ≤3 cm	IA3	IIA	IIB	IIIA	IIIB
T2	T2a Visceral pleura / central invasion	IB	IIB	IIIA	IIIB	IIIB
	T2a >3 to ≤4 cm	IB	IIB	IIIA	IIIB	IIIB
	T2b >4 to ≤5 cm	IIA	IIB	IIIA	IIIB	IIIB
T3	T3 >5 to ≤7 cm	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Invasion	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Same lobe tumor nodule	IIB	IIIA	IIIA	IIIB	IIIC
T4	T4 >7 cm	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Invasion	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Ipsilateral tumor nodule	IIIA	IIIA	IIIB	IIIB	IIIC
M1	M1a Pleural/pericardial dissemination	IVA	IVA	IVA	IVA	IVA
	M1a Contralateral tumor nodule	IVA	IVA	IVA	IVA	IVA
	M1b Single extrathoracic lesion	IVA	IVA	IVA	IVA	IVA
	M1c1 Multiple lesions, 1 organ system	IVB	IVB	IVB	IVB	IVB
	M1c2 Multiple lesions, >1 organ system	IVB	IVB	IVB	IVB	IVB

N staging

- N2a: single station
- N2b: multiple station

Detterbeck FC, et al. Chest. 2024

Radiotherapy, Yes! Why?

Staging TNM

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ADAURA	Wu YL	2020	III	II to **IIIA**	7 (2010)	T2a (41mm)	N2 (multi)	IIIA
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LAURA	Lu S	2024	III	**IIIA** to IIIC	8 (2017)	T2b (41 mm)	N2 (multi)	IIIA
Case	Borghetti P	2024-2025	-	-	9	T2b	N2b	**IIIB**

According to TNM 9th edition, this patient can not be eligible to Osi after surgery

LAURA Phase 3 double-blind study design

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

Key inclusion criteria:
- ≥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

Treatment duration until BICR-assessed progression (per RECIST v1.1), toxicity, or other discontinuation criteria

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

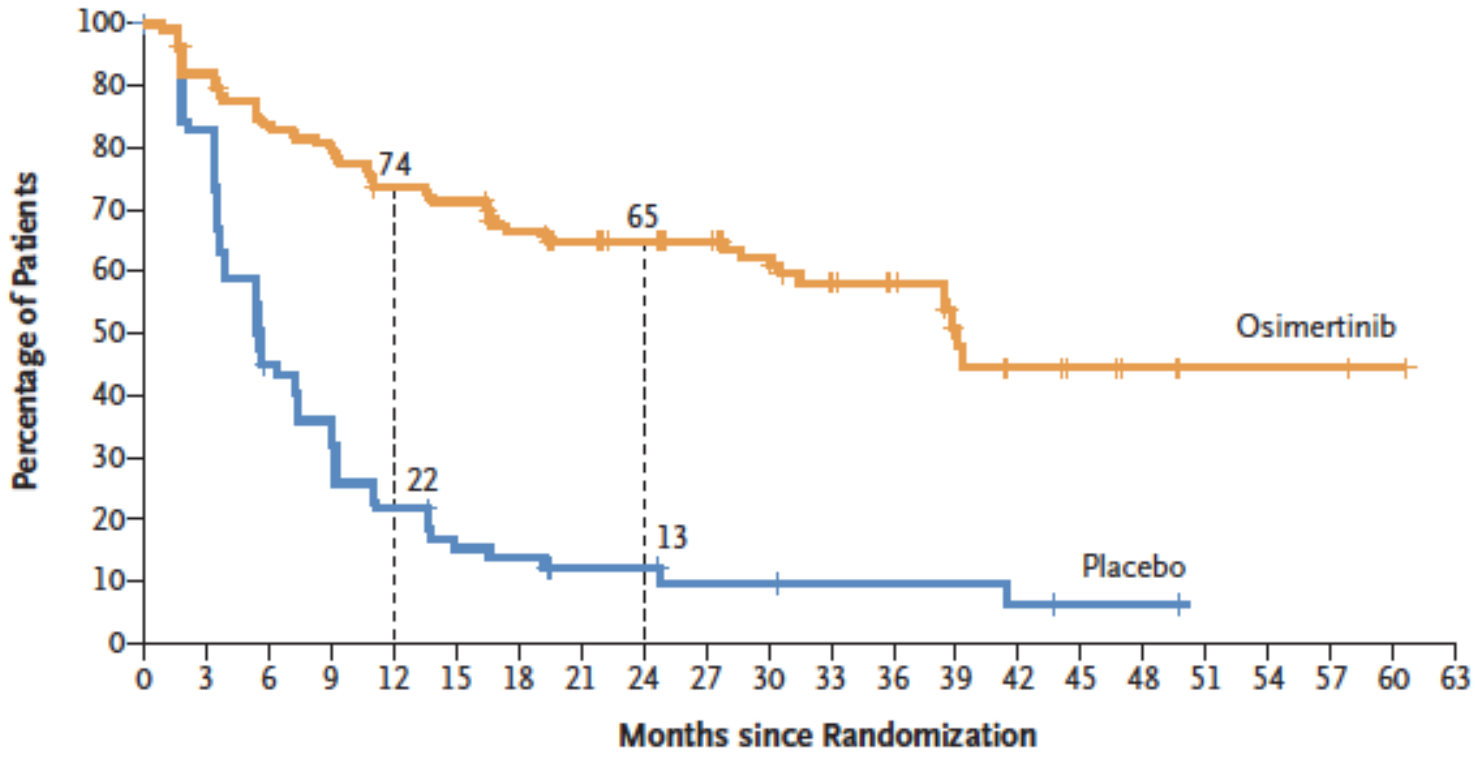
*According to AJCC / UICC staging (8th edition);
†Concurrent or sequential CRT comprising ≥2 cycles of platinum-based chemotherapy (or 5 doses of weekly platinum-based chemotherapy) and a total dose of radiation of 60 Gy ±10%;
‡Central or FDA-approved local testing (from a CLIA-approved laboratory, or accredited local laboratory for sites outside of USA) based on tissue;
§If deriving clinical benefit (osimertinib arm); by the judgement of treating physician (placebo arm).

AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; CLIA, Clinical Laboratory Improvement Amendments; CNS, central nervous system; CRT, chemoradiotherapy; CT, computed tomography; EGFRm, epidermal growth factor receptor-mutated; Ex19del, exon 19 deletion; FDA, Food and Drug Administration; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; UICC, Union for International Cancer Control; WHO PS, World Health Organization performance status

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Radiotherapy, Yes! Why?

LAURA



No. at Risk																					
Osimertinib	143	127	114	109	99	96	83	76	69	61	49	37	28	16	9	6	4	2	2	2	1	0
Placebo	73	59	31	25	15	10	9	6	6	4	4	3	3	3	2	1	1	0	0	0	0	0

Median Progression-free Survival (95% CI)	*mo*
Osimertinib	39.1 (31.5–NC)
Placebo	5.6 (3.7–7.4)

Hazard ratio for disease progression or death, 0.16 (95% CI, 0.10–0.24)
P<0.001

Lu S, et al. NEJM. 2024

Baseline characteristics

- Baseline characteristics were generally well-balanced between treatment arms[1]

Characteristics, %	Osimertinib (n=143)	Placebo (n=73)
Sex: male / female	37 / 63	42 / 58
Age: median (range), years	62 (36–84)	64 (37–83)
Age group: <65 / ≥65 years	57 / 43	53 / 47
Smoking history: formerly / currently / never	26 / 3 / 71	32 / 1 / 67
Race: Asian / non-Asian	81 / 19	85 / 15
WHO performance status: 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: cCRT / sCRT‡	92 / 8	85 / 15
Response to prior CRT: CR / PR / SD / PD / NE	3 / 47 / 43 / 0 / 8	4 / 37 / 51 / 0 / 8

Data cut-off: January 5, 2024.

*Tissue tested by central or FDA-approved local test from a CLIA-approved laboratory or accredited local laboratory outside of the USA; †One patient in the osimertinib arm had a missing EGFR mutation status; ‡Summarized on the basis of data entered in the electronic case-report form.

1. Lu et al. N Engl J Med 2024;391:585–597.

AJCC, American Joint Committee on Cancer; cCRT, concurrent CRT; CLIA, Clinical Laboratory Improvement Amendments; CR, complete response; CRT, chemoradiotherapy; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; FDA, Food and Drug Administration; NE, not evaluable; PD, progressive disease; PR, partial response; sCRT, sequential CRT; SD, stable disease; UICC, Union for International Cancer Control; WHO, World Health Organization

BASELINE CHARACTERISTICS (OVERALL POPULATION)

- Demographics and characteristics were generally well balanced between treatment arms
- Proportion of stages was similar when ADAURA patients were re-staged by AJCC 8th edition staging manual

Characteristics, %	Osimertinib (n=339)	Placebo (n=343)
Sex: male / female	32 / 68	28 / 72
Age: median (range), years	64 (30–86)	62 (31–82)
Smoking history: yes* / no	32 / 68	25 / 75
Race: Asian / non-Asian	64 / 36	64 / 36
WHO PS: 0 / 1	63 / 37	64 / 36
AJCC staging at diagnosis (7th edition): IA / IB / II / IIIA / IIIB	0 / 32 / 33 / 35 / 0	0 / 31 / 34 / 35 / 0
AJCC staging at diagnosis (8th edition)†: IA / IB / II / IIIA / IIIB	1 / 30 / 33 / 32 / 3	<1 / 29 / 35 / 34 / 2
Histology: Adenocarcinoma / other	96 / 4	97 / 3
EGFR mutation at randomisation‡: Ex19del / L858R	55 / 45	55 / 45
Adjuvant chemotherapy: yes / no	60 / 40	60 / 40

Masahiro Tsuboi, MD

*Formerly: osimertinib n=104 (31%), placebo n=83 (24%); currently: osimertinib n=4 (1%), placebo n=3 (1%). †Disease stage IV: osimertinib n=0, placebo n=1 (<1%); missing: osimertinib n=2 (1%), placebo n=2 (1%). ‡Central test.

1. Wu et al. N Engl J Med 2020;383:1711–1723; 2. Herbst et al. J Clin Oncol 2020;38:18_suppl:LBA5.

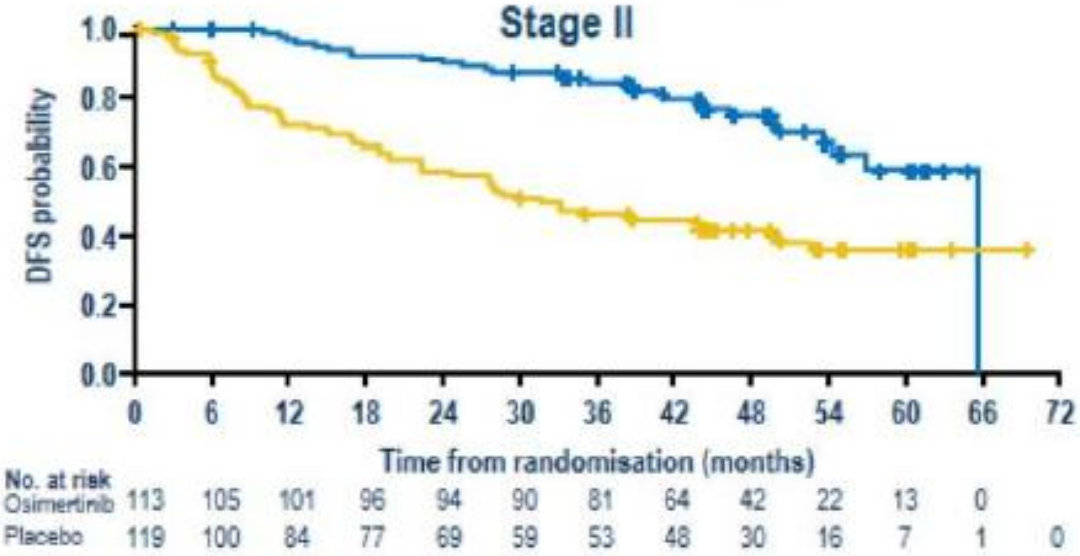
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AJCC, American Joint Committee on Cancer; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; PS, performance status; WHO, World Health Organization

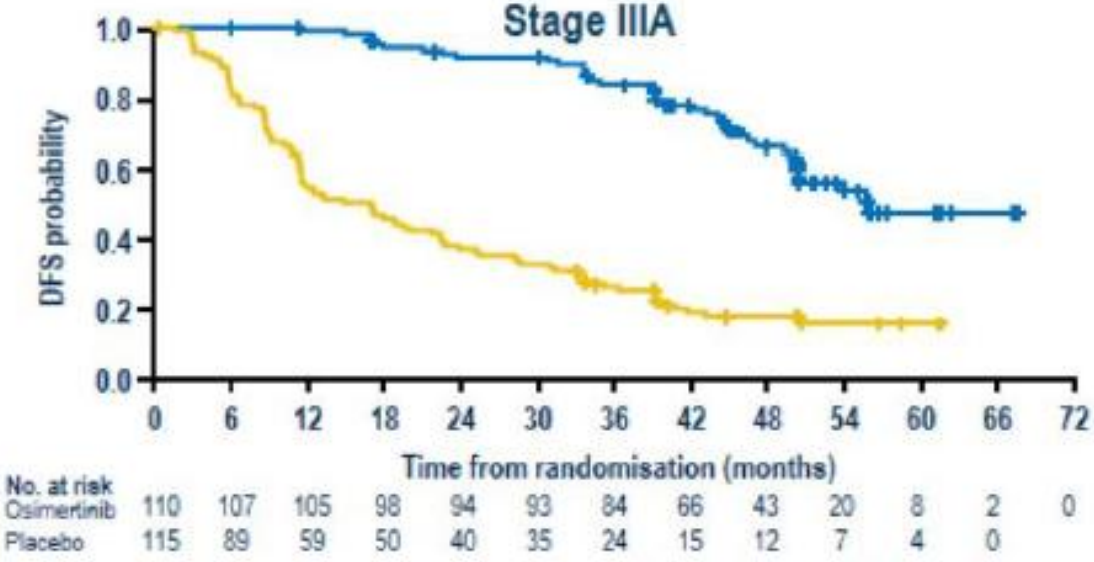
Data cut-off: April 11, 2022.

UPDATED DFS BY STAGE (AJCC 8TH EDITION*)





	Stage IB	Stage II	Stage IIIA
4 year DFS rate, % (95% CI)			
– Osimertinib	80 (69, 87)	75 (65, 83)	66 (55, 75)
– Placebo	60 (49, 69)	43 (34, 52)	16 (10, 24)
Overall HR (95% CI)	**0.44 (0.25, 0.76)**	**0.33 (0.21, 0.50)**	**0.22 (0.15, 0.31)**



DFS by investigator assessment; Tick marks indicate censored data.
*Re-staging based on data captured in the Pathology at Diagnosis AJCC 8th edition manual, per investigator assessment requested before the primary analysis.

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AJCC, American Joint Committee on Cancer; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio
Data cut-off: April 11, 2022.

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In both studies N2 multistation percentace is unknow … but… LAURA enrolled IIIA, IIIB and IIIC

cN2 multistation LAURA > pN2 multistation ADAURA

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In ADAURA study > 95% received lobectomy, < 5% other surgery (about 2% pneumonectomy)

Is pneumonectomy correct in stage IIIA EGFR mutated or better RT?



Radiotherapy, Yes! Why?

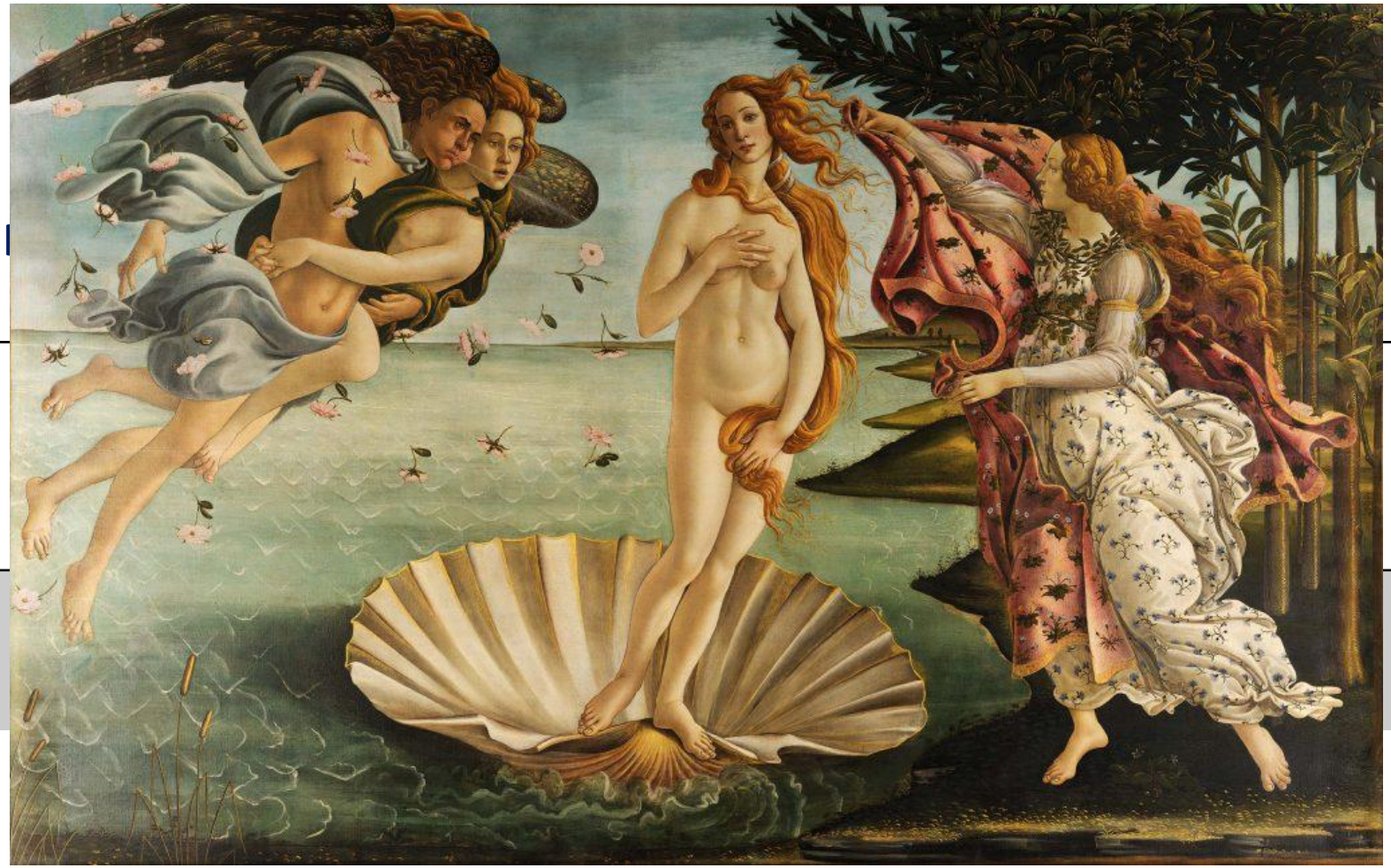
Clinical cases discussion – EORTC LCG

	N0 (total n / % resectable)	N1 (total n / % resectable)	N2 SINGLE (total n / % resectable)	N2 MULTI (total n / % resectable)	N2 BULKY / INVASIVE (total n / % resectable)	N3 (total n / % resectable)
T1-2	N/A	N/A	13 / 100% **RESECTABLE**	2 / 0% **UNRESECTABLE**	6 / 17% **UNRESECTABLE**	7 / 14% **UNRESECTABLE**
T3 SIZE / SATELLITE / INVASION	N/A	5 / 100% **RESECTABLE**	3 / 100% **RESECTABLE**	3 / 0% **UNRESECTABLE**	5 / 0% **UNRESECTABLE**	3 / 0% **UNRESECTABLE**
T4 SIZE/SATELLITE	11 / 100% **RESECTABLE**	(no cases)	3 / 100% **RESECTABLE**	2 / 0% **UNRESECTABLE**	2 / 0% **UNRESECTABLE**	1 / 0% **UNRESECTABLE**
T4 INVASION	12 / 33% **NO CONSENSUS**	5 / 0% **UNRESECTABLE**	2 / 0% **UNRESECTABLE**	8 / 0% **UNRESECTABLE**	6 / 0% **UNRESECTABLE**	8 / 0% **UNRESECTABLE**

0 / 15 cases with multiple N2 considered as resectable

Dingemans AM, … Giaj-Levra N et al. 2025 under review

How long ca



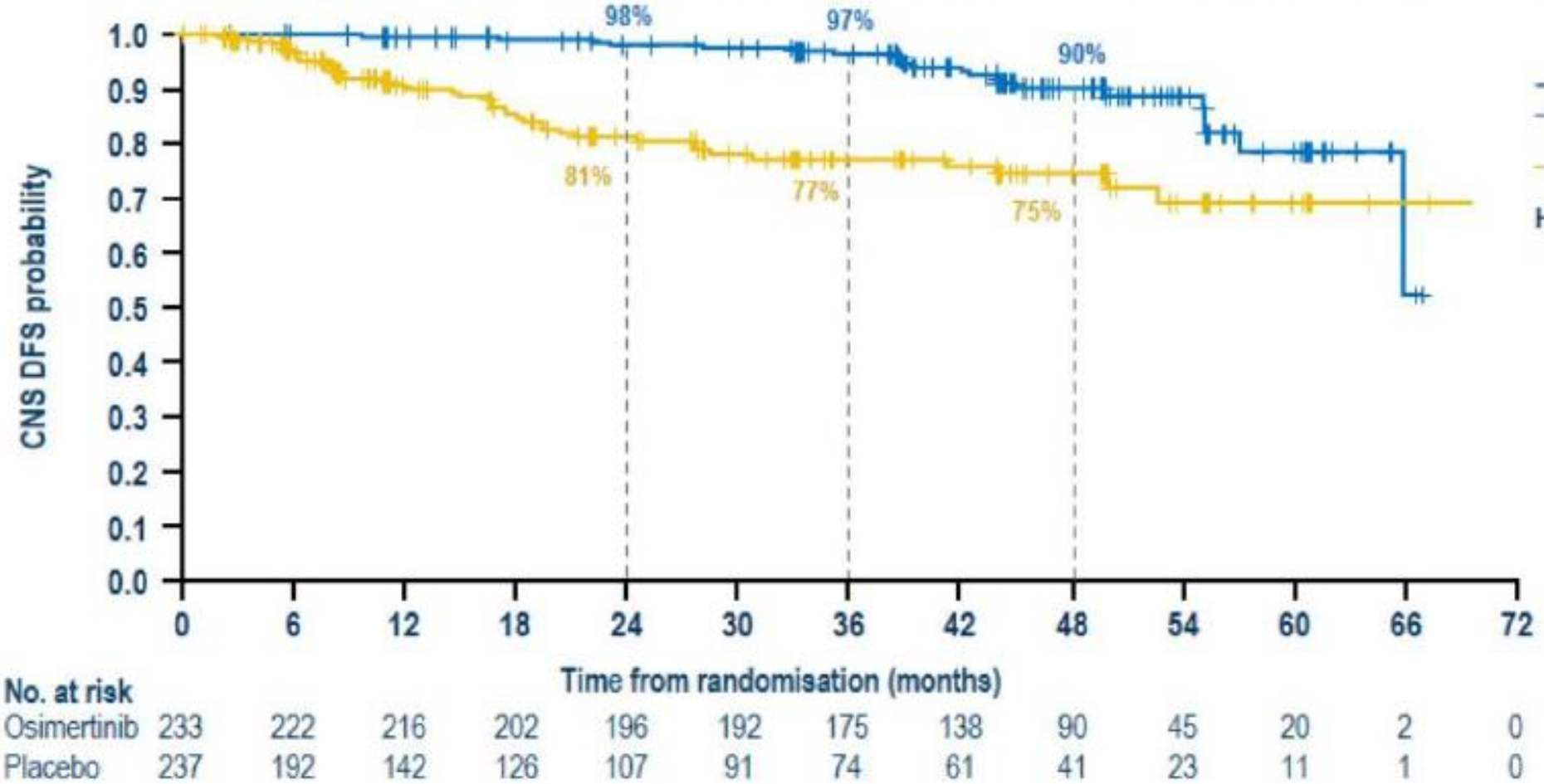
Study	Max time for Osi prescription
ADAURA	3 years or PD or toxicity
LAURA	PD or toxicity

Isn’t it appealing to be able to prescribe osimertinib until disease progression?
We can also help you manage oligoprogression

Botticelli, 1485 La nascit di Venere, dea dell'amore, della bellezza

UPDATED CNS DFS IN PATIENTS WITH STAGE II / IIIA DISEASE

- Overall, 63 patients (osimertinib n=22, placebo n=41) had CNS DFS events:*
  - 3 (14%) patients were on treatment at the time of CNS recurrence with osimertinib, versus 29 (71%) with placebo



Median CNS DFS, months (95% CI)	
– Osimertinib	NR (65.8, NC)
– Placebo	NR (NC, NC)
HR (95% CI)	**0.24 (0.14, 0.42)**

Maturity 13%:
osimertinib 9%, placebo 17%

No. at risk													
Osimertinib	233	222	216	202	196	192	175	138	90	45	20	2	0
Placebo	237	192	142	126	107	91	74	61	41	23	11	1	0

PARIS 2022 ESMO congress

Masahiro Tsuboi, MD

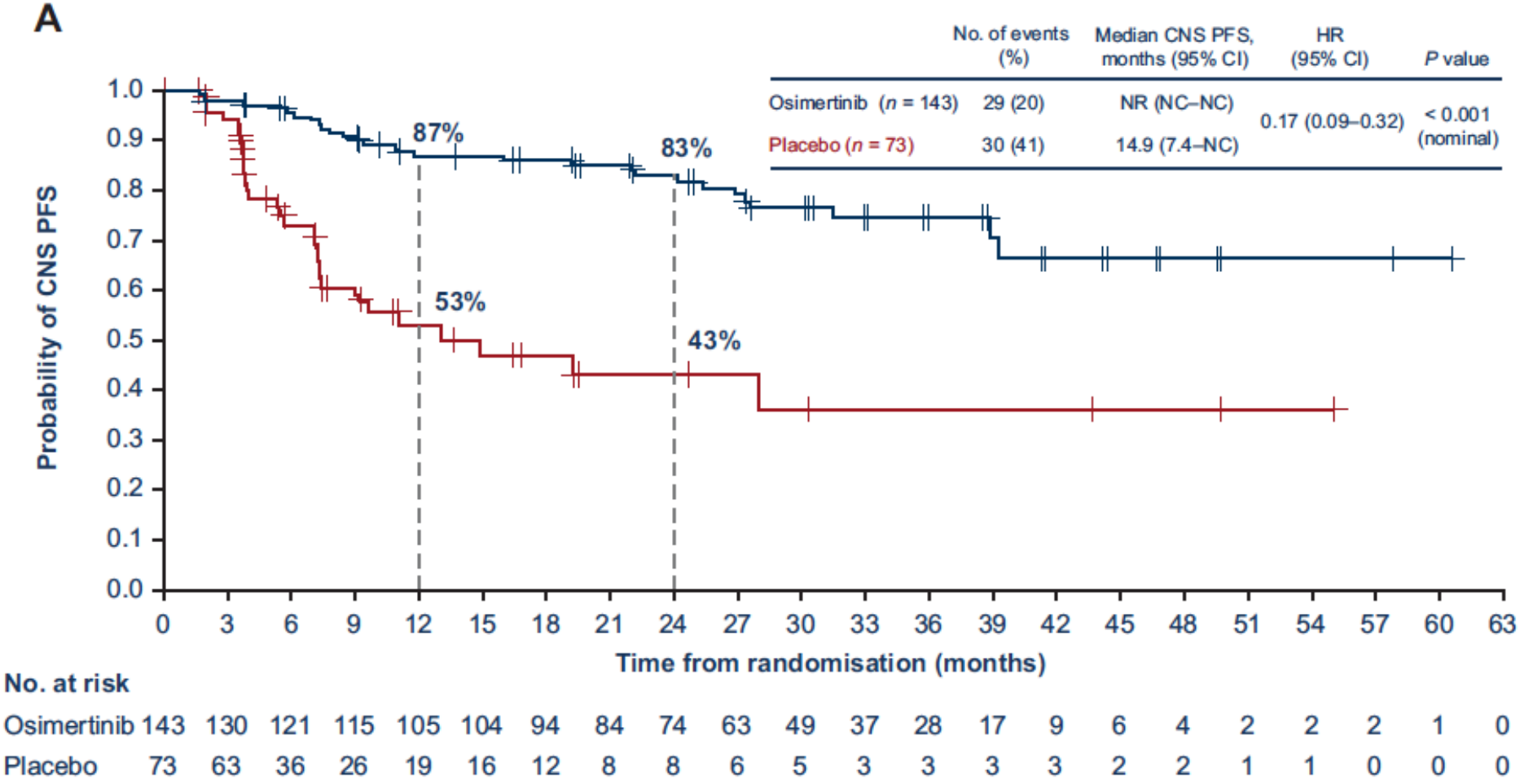
Median follow-up: osimertinib 44.2 months, placebo 20.4 months; DFS by investigator assessment; Tick marks indicate censored data.
*Defined as CNS as the first site of disease recurrence, or death without any disease recurrence.

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

Radiotherapy, Yes! Why?

CNS recurrence in LAURA trial



Lu S. et al. Ann Oncol. 2024

Radiotherapy, Yes! Why?

Conclusions

- The probability of achieving MPR and pCR is limited in patients with EGFR-mutated NSCLC.
- The clinical course of EGFR-mutated NSCLC appears to differ from that of PD-L1–positive NSCLC
- According to TNM 9th , this case is IIIB and not eligible to Osi
- None of the patients progressed following chemoradiotherapy
- The prescription on Osi until PD is very attractive
- CNS recurrence is an important issue after the end of Osi
- Pneumonectomy is used infrequently, and data are lacking to confirm its effect on clinical outcomes relative to standard lobectomy

IN RADIOTHERAPY WE TRUST!!

