Avances en el tratamiento de la enfermedad precoz EGFR mutada

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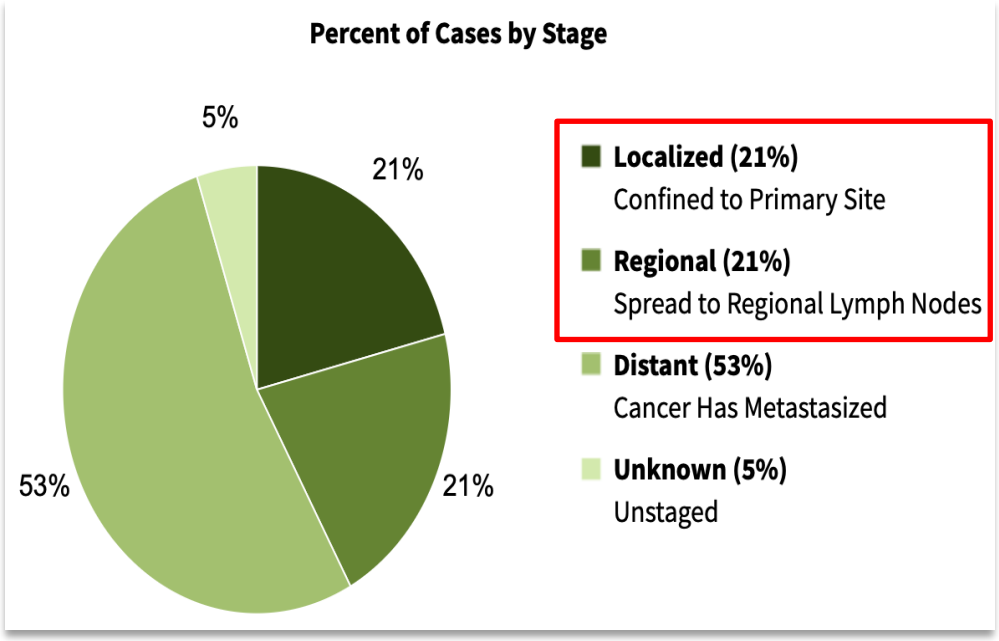
Disclosure Information

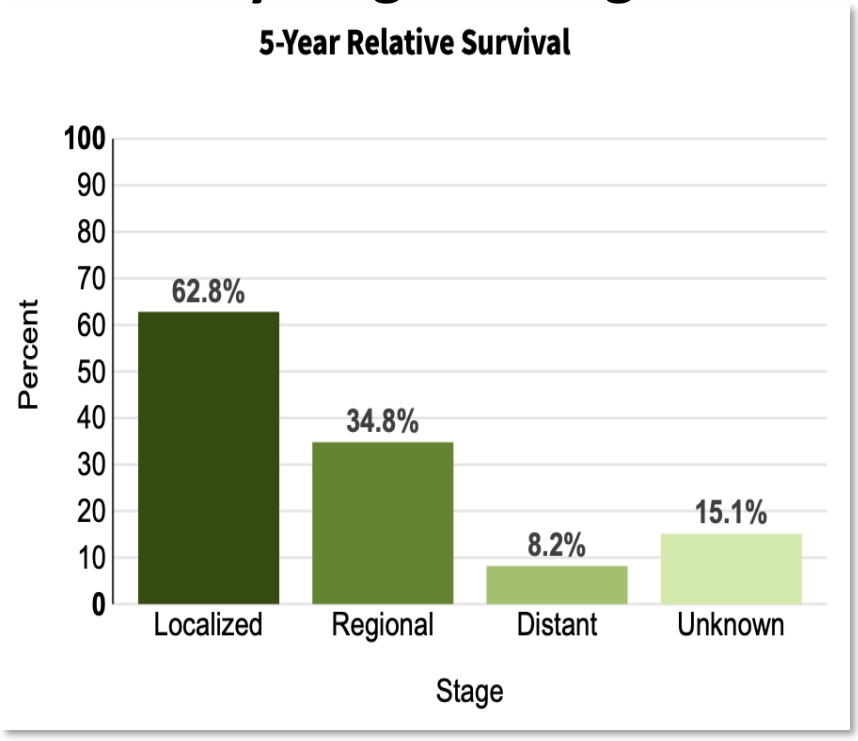
- **Personal fees/honoraria for consultancy/Advisory role and lectures** from Roche/Genentech, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Merck Sharp and Dohme, Merck Serono, Eli Lilly, Gilead, Incyte, Sanofi, Regeneron, Incyte, Pfizer, Takeda and Novartis

- **Travel expenses** from Roche, Bristol-Myers Squibb, Merck Sharp and Dohme, Sanofi, Regeneron and Novartis

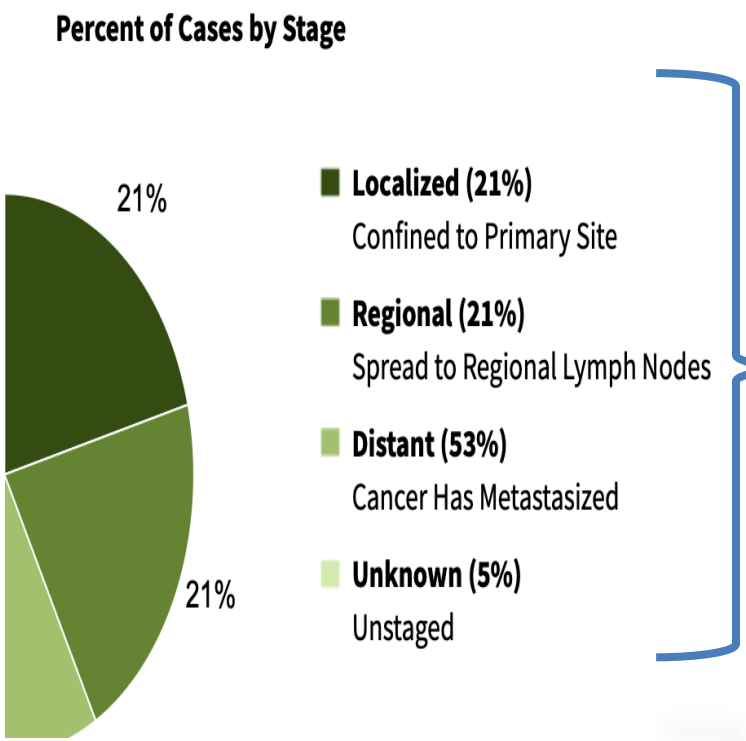
- **Grant support** for studies from BMS

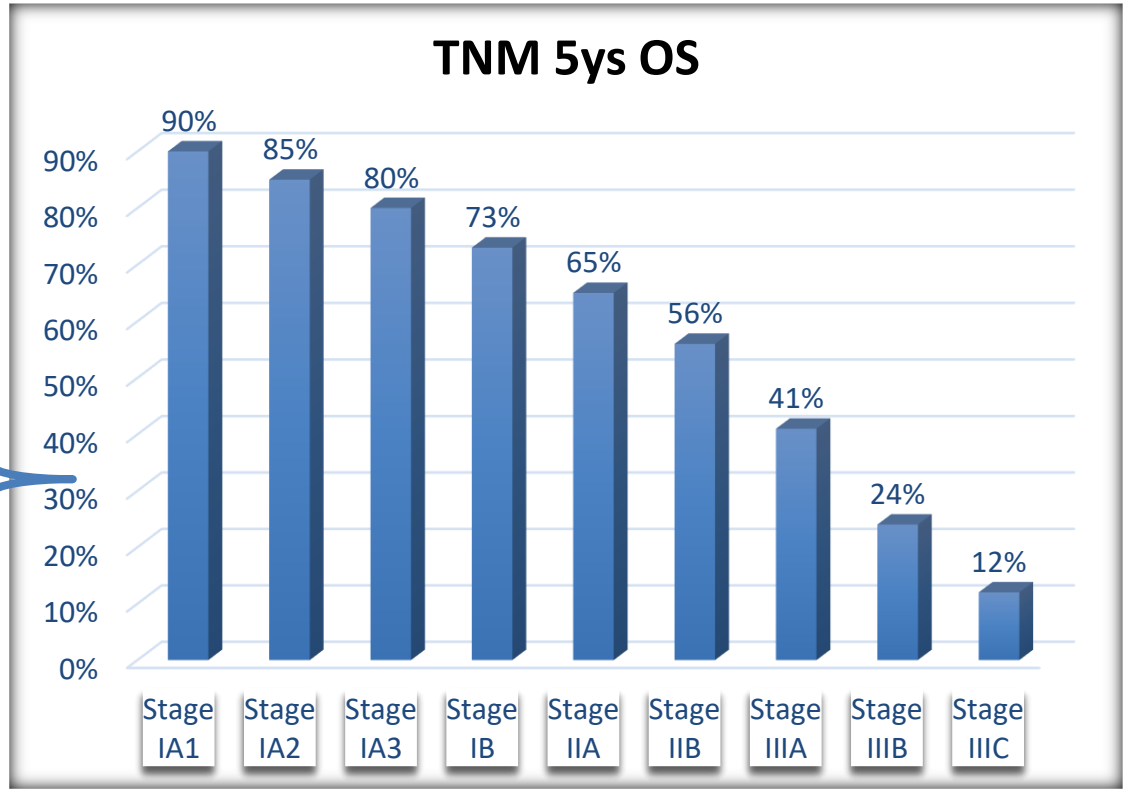
Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis





SEER Cancer Stat Facts: Lung and Bronchus Cancer. National Cancer Institute. Bethesda. https://seer.cancer.gov/statfacts/html/lungb.html





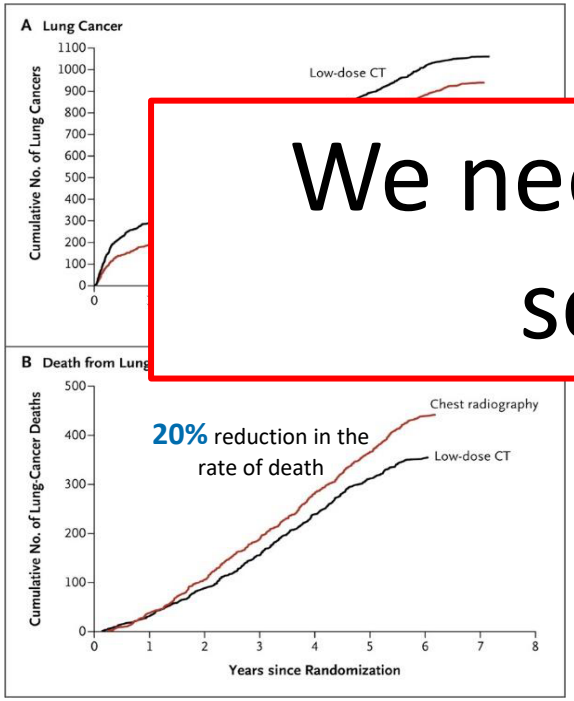
SEER Cancer Stat Facts: Lung and Bronchus Cancer. National Cancer Institute. Bethesda. https://seer.cancer.gov/statfacts/html/lungb.html

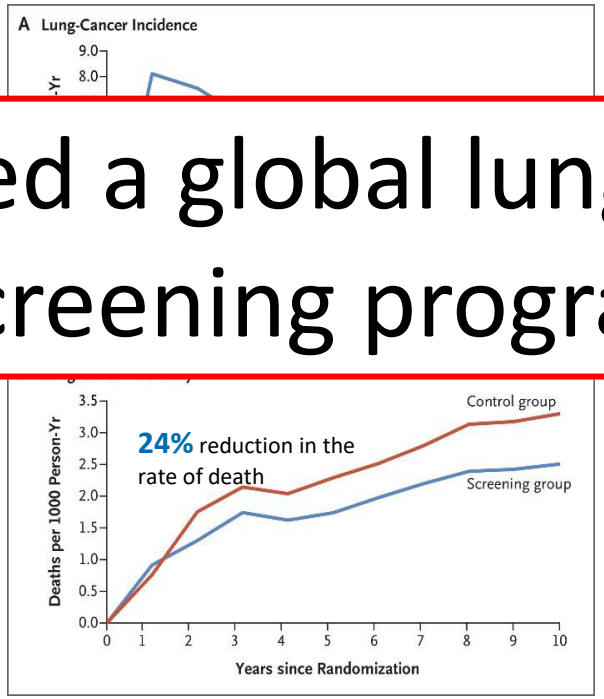
Early detection the better way to reduce mortality in lung cancer

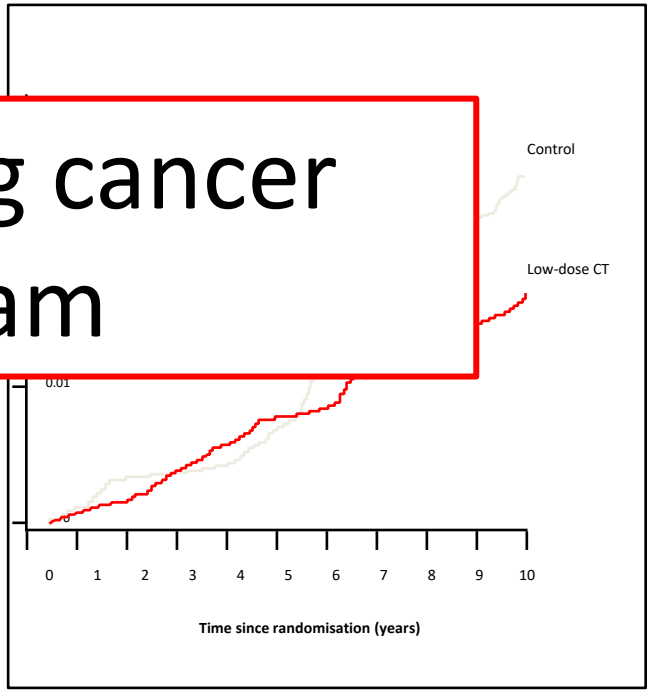
NLST[2] Large trial of >50,000 patients 3 rounds of low-dose CT versus 3 rounds of chest radiography over 2 years

NELSON[1] Medium trial of >15,000 patients 4 rounds of low-dose CT versus no screening over 5.5 years

MILD[3] Small trial of >4,000 patients 5+ rounds of low-dose CT versus no screening over 8–10 years







We need a global lung cancer screening program

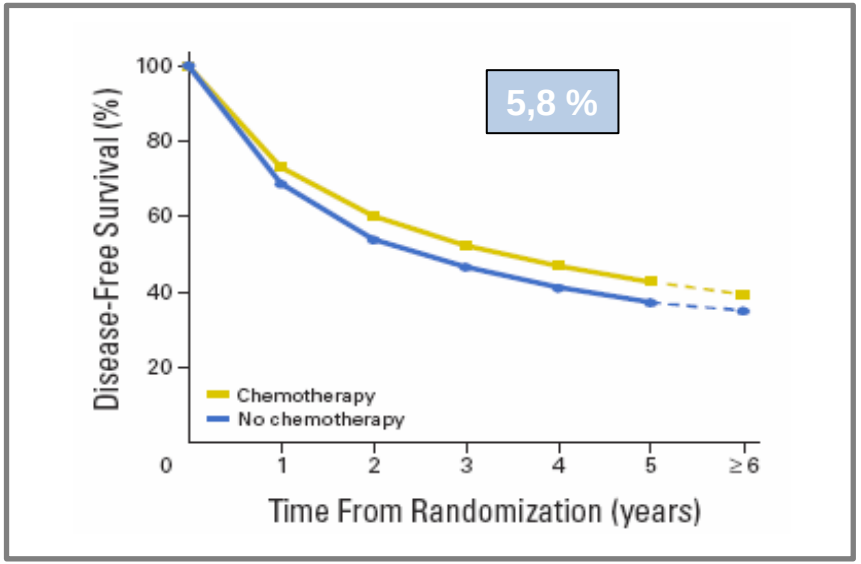
[1] de Koning, et al. N Engl J Med 2020 [2] National Lung Screening Trial Research Team. N Engl J Med 2011 [3] Pastorino, et al. Ann Oncol 2019

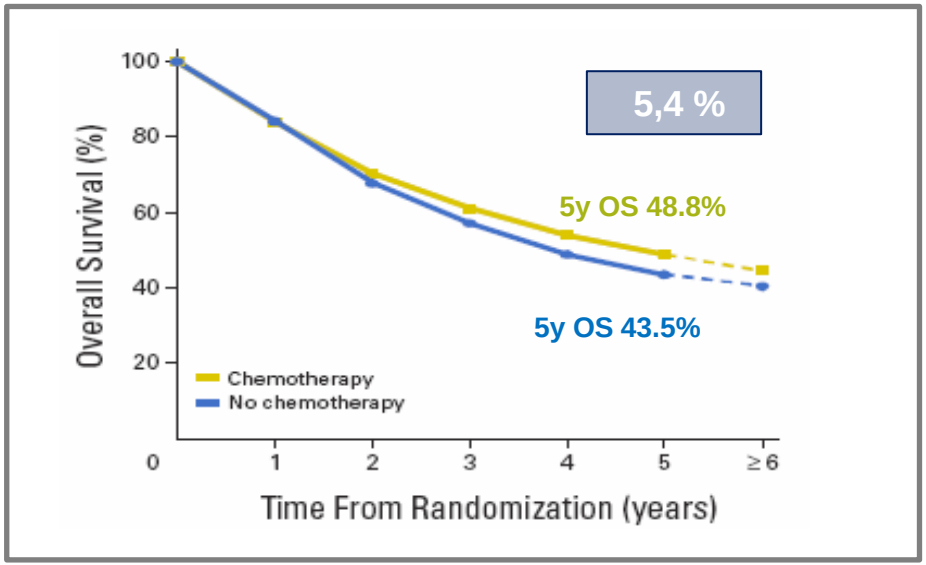
LACE Meta-analysis of Adjuvant Chemo:

Chemotherapy Effect and Stage

- In a retrospective European study, only 48% of patients with resected NSCLC received adjuvant chemotherapy.

DFS lead to OS benefit

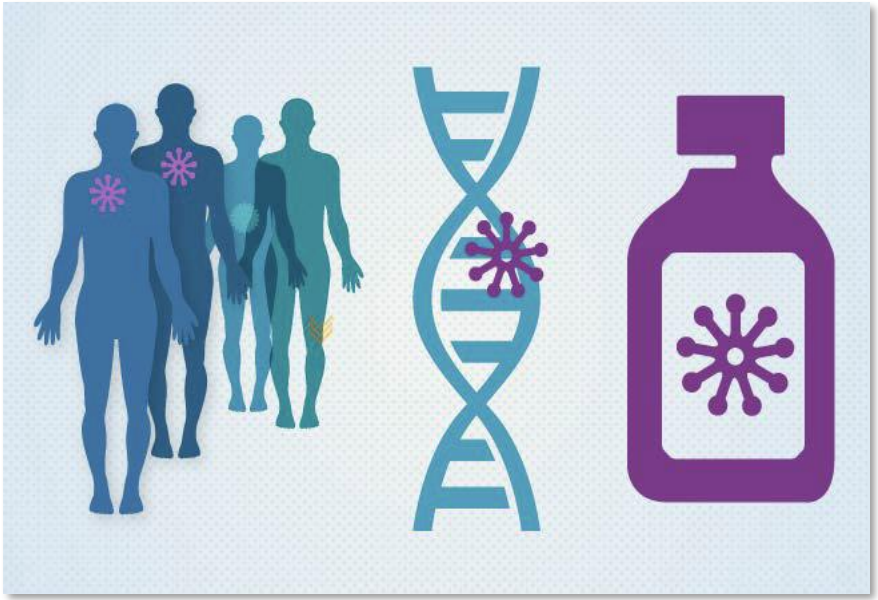




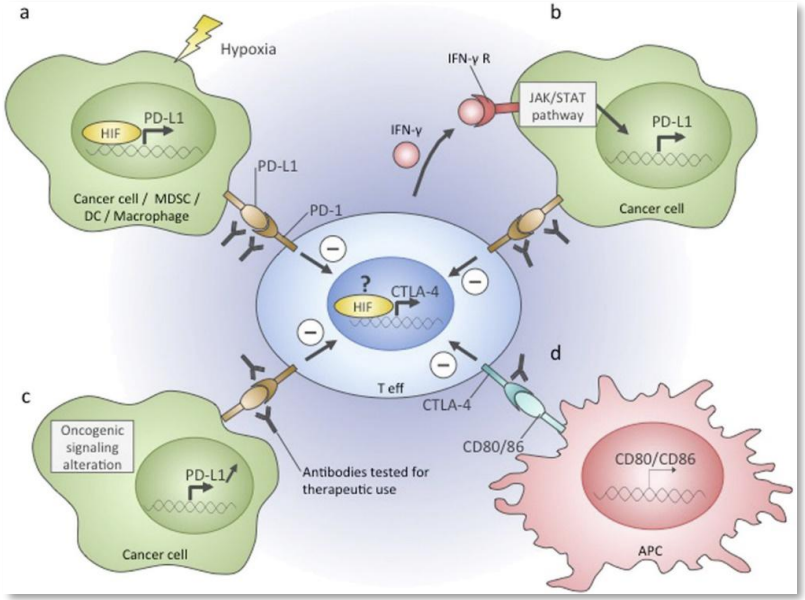
Pignon, JP *et al*. J Clin Oncol. 2008. Chouaid C, Lung Cancer 2018

The **BIG 2** in the Treatment of NSCLC and Now even in Early Stage

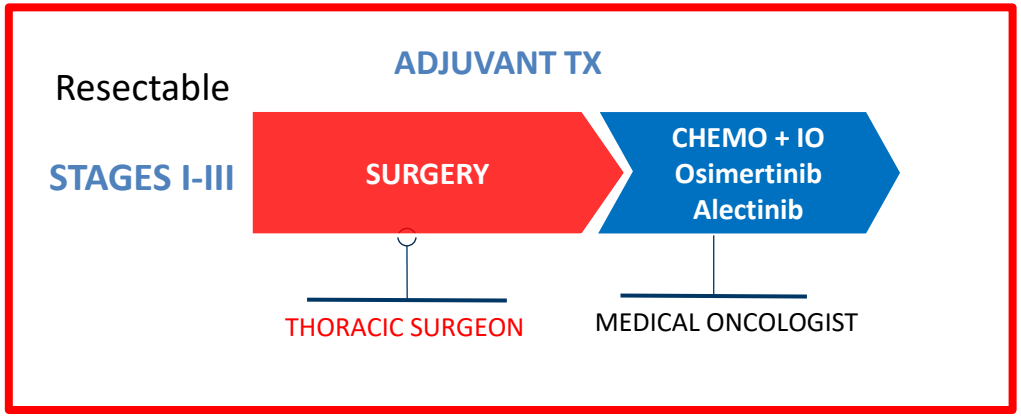
Targeted Therapy

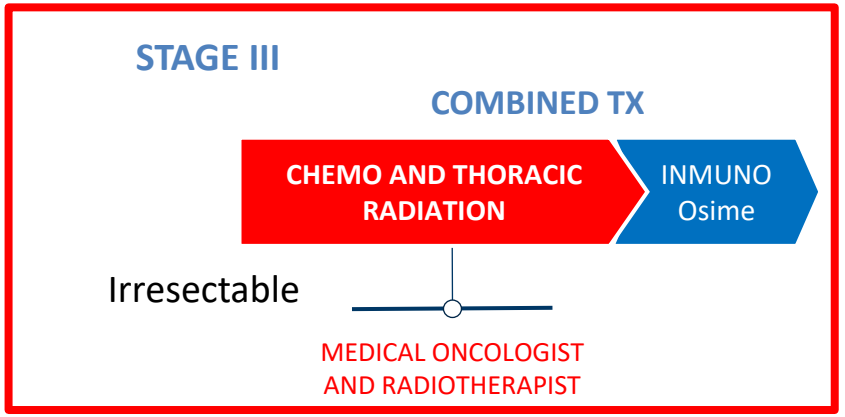


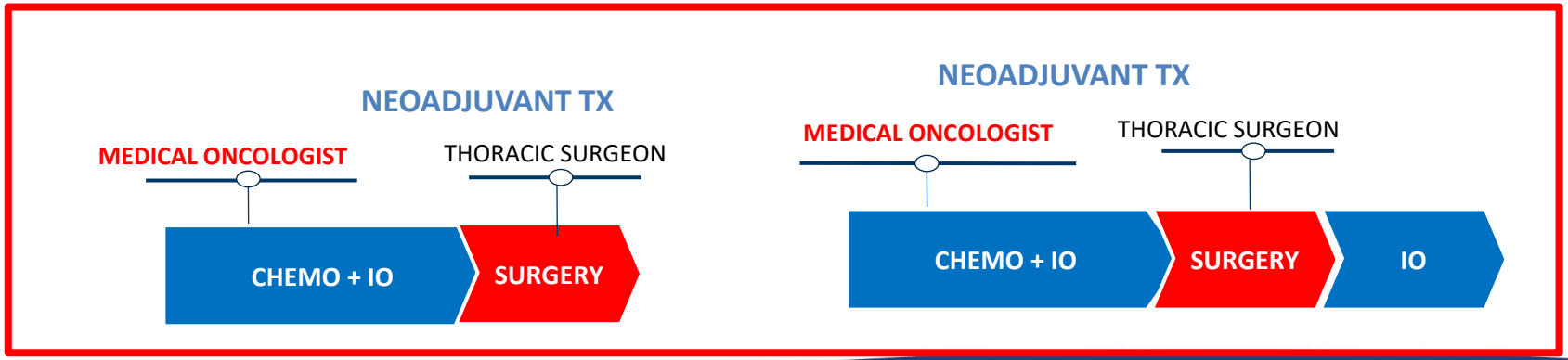
Immunotherapy



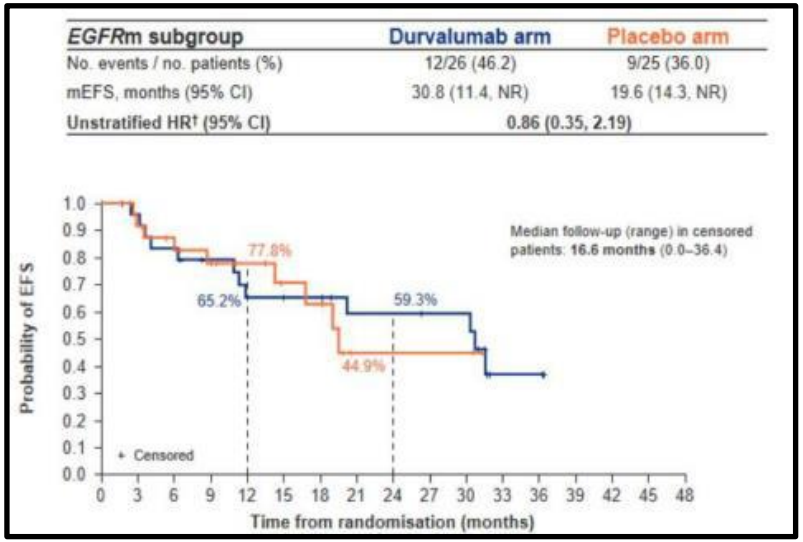
Treatment paradigm for Early-Stage NSCLC



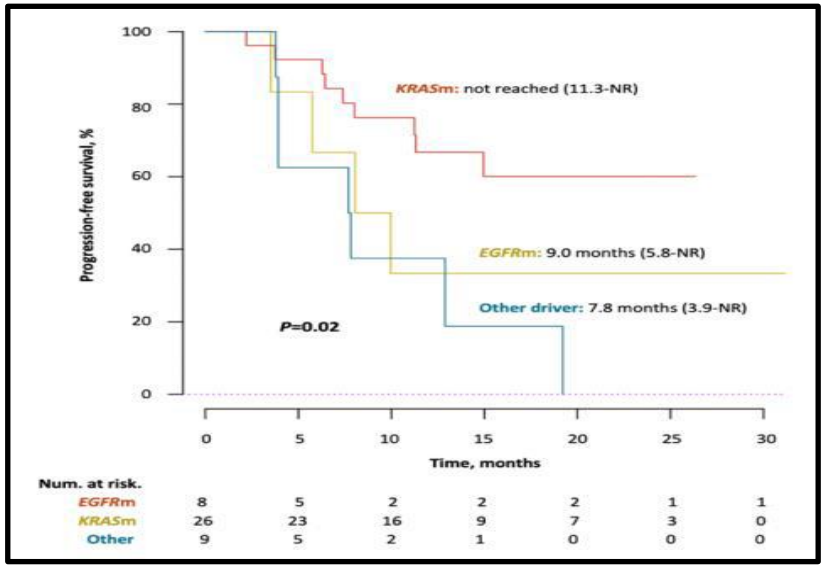




But, in patients with driver mutation always less benefit



AEGEAN, perioperative treatment



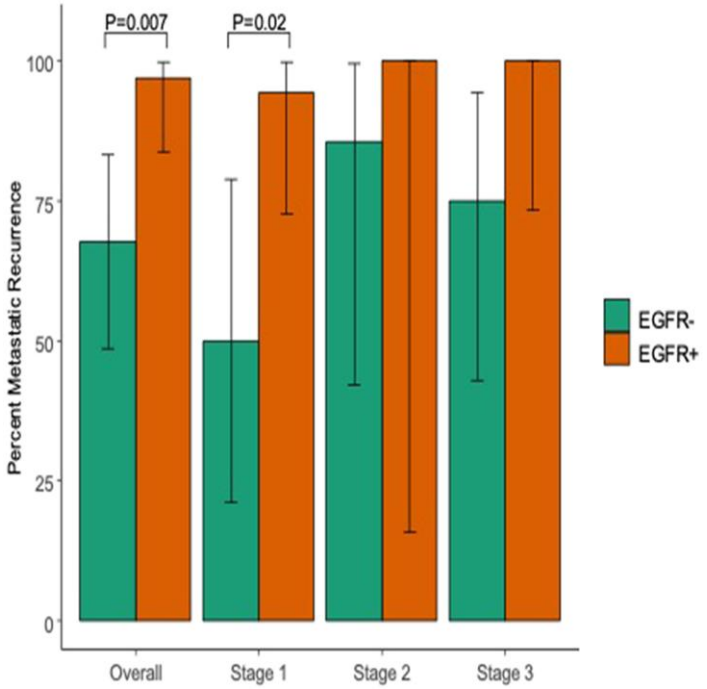
RWD, durvalumab consolidation

Riudavets, M et al, EurJ Cancer 2022, Harpole D, WCLC 2023

But we still needing a good biomarker!!!!

Why is important to search for driver mutations in early-stage NSCLC?

- Generate a different natural history and prognosis.
- Identify patients where immunotherapy may not be as effective (EGFR, ALK)
- Provide information which save time and money at disease recurrence, allowing the next treatment decision to be made earlier
- Provide information which help us to do a better follow up (risk stratification for disease relapse)
- Provide the opportunities of inclusion in many current ongoing clinical trials



Higher rates of metastatic relapse in EGFR mut vs EGFR WT.

Y.-L. Zhang. Oncotarget 7-2016. NCCN 2023. ESMO guideline 2023. Skoulidis, Nat Rev Cancer 2019, Galvez Oncotarget2020

SUMMARY OF PROSPECTIVE TRIALS IN ADJUVANT SETTING USING EGFR TKIS

Study	Phase Sample size	Stage	EGFR mutation status	AdCT/ Percentage of patients receiving adCT	Treatment regimen	Primary endpoint	DFS in EGFR mutant	OS in EGFR mutant
RADIANT	Phase III 973 161 EGFR mut	IB-IIIA	EGFR+ by IHC and/ or FISH; 161 EGFR mut	Optimal 52.9	Erlotinib vs placebo for 2y	DFS	46.4 vs 28.5 m HR 0.61	NR
SELECT	Phase 2 100	IA-IIIA	EGFR mut	As per staging NR	Erlotinib for 2 y	2y DFS	2 years DFS 88%	NR HR 0.16 P 0.0013
EVAN	Phase II 102	IIIA					42.4m vs 21 m HR 0.27 p<0.0001	NR
CTONG-1104 ADJUVANT	Phase III 222	II-IIIA	EGFR mut	50	Cisplatin+Vnb 4 cy vs Gefitinib 2y	DFS	28.7 vs 18m HR 0.60; p=0.0054	5y OS 53.2% vs 51.2% HR 0.92 p=0.674
EVIDENCE	Phase III 322	II-IIIA	EGFR mut	50	Platinum-dB 4 cy Vs Icotinib 2y	DFS	46.9 vs 22.1 HR 0.36 p<0.001	HR 0.91
IMPACT	Phase III 234	II-III	EGFR mut	50	Cisplatin-VNB 4cy Vs Gefitinib 2 y	DFS	36 vs 25.2m HR 0.92 p 0.63	5y OS 78% vs 74.6% HR 1.03, P 0.89

DFS benefit did NOT correlate with OS

Kelly K, et al. J Clin Oncol 2015; Pennell NA, et al. J Clin Oncol 2019; Yue D, et al. Lancet Respir Med 2018; ; Zhong WZ et al, J Clin Oncol 2021; He J, et al. Lancet Respir Med 2021. Tada H, et al. J Clin Oncol 2022

18 Dec 2020 | 26 Apr 2021 | 1 Dec 2022

ADAURA

Objectives

Updated results of the Phase 3 ADAURA trial, exploring adjuvant osimertinib therapy vs placebo. Reported here are updated exploratory analyses of DFS, recurrence patterns, and safety after 2 years added follow-up.

ADAURA study design

Key eligibility criteria

- Patients with completely* resected stage IB – IIIA *EGFR*-mutant (exon19del/L858R[†]) NS-NSCLC
- With or without adjuvant chemotherapy[‡]
- WHO performance status 0/1
- 10 (adjuvant chemotherapy) and 26 (no adjuvant chemo) weeks maximum interval between surgery and randomisation

Osimertinib 80mg OD

Randomisation 1:1 (N=682)

Placebo OD

Primary endpoint: DFS by investigator assessment in stage II/IIIA patients

Secondary endpoints: DFS in overall population[§], DFS at 2, 3, 4, and 5 years, OS, safety, health-related QoL

Pre-specified exploratory endpoints: Patterns of recurrence, CNS DFS

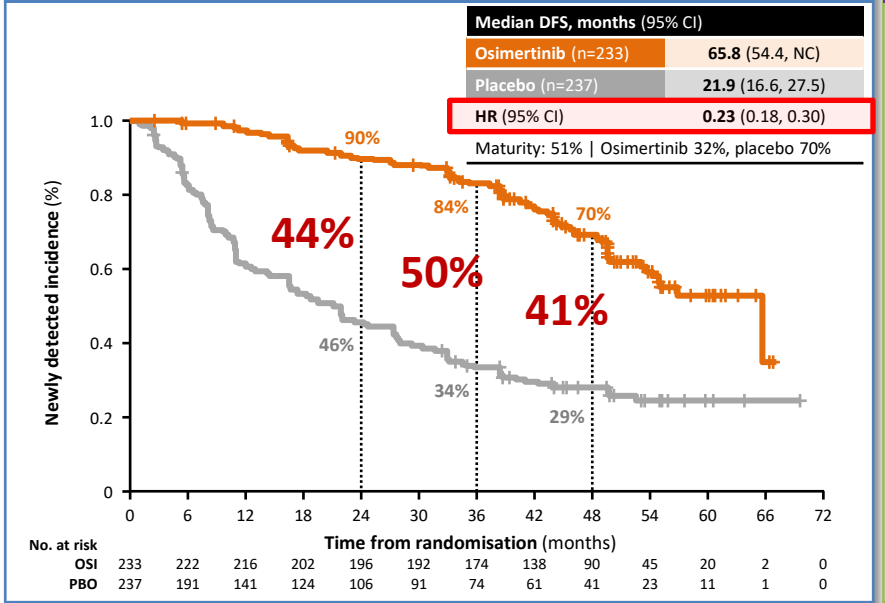
Baseline characteristics

	Osi (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[ll] / no	32 / 68	25 / 75
Race: Asian / non-Asian	64 / 36	64 / 36
WHO PS: 0 / 1	63 / 37	64 / 36
AJCC/UICC staging at diagnosis (7th edition): **IA / IB / II / IIIA / IIIB**	1 / 32 / 33 / 35 / 0	0 / 31 / 34 / 35 / 0
Histology: Adenocarcinoma/other	96 / 4	97 / 3
***EGFR* mutation at randomisation: exon19del / L859R**	55 / 45	55 / 45
Adjuvant chemo: yes / no	60 / 40	60 / 40

Tsuboi M, et al. ESMO 2022

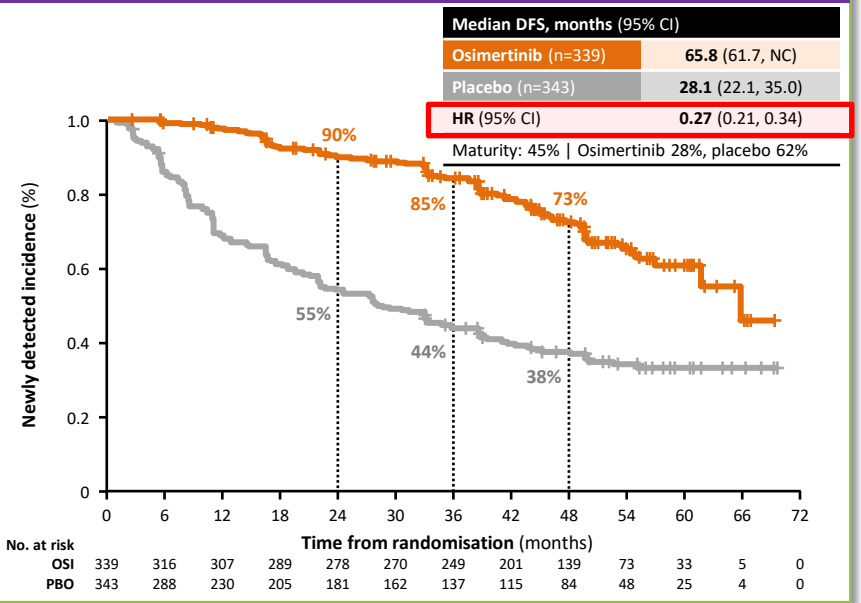
Updated DFS in stage II / IIIA population and overall population

Updated DFS in stage II / IIIA disease*† (primary endpoint)



77% reduction in risk of **disease recurrence** or **death** in **stage II / IIIA** population

Updated DFS in stage IB / II / IIIA disease*§ (overall population)



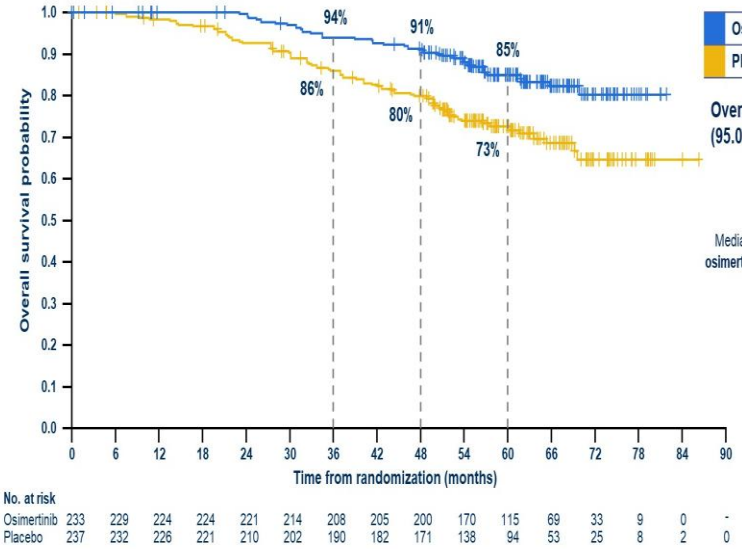
73% reduction in risk of **disease recurrence** or **death** in **overall population**

Tsuboi M, et al. NEJM 2023

Updated OS ADAURA

Overall survival: patients with stage II / IIIA disease

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



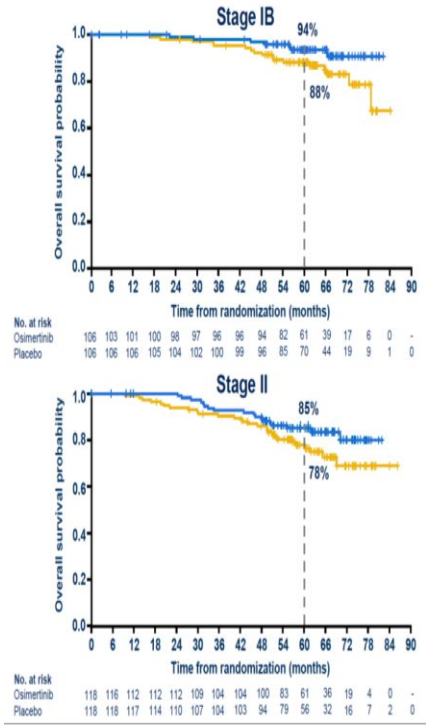
5-year OS rate, % (95% CI)	
Osimertinib (n=233)	85 (79, 89)
Placebo (n=237)	73 (66, 78)

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

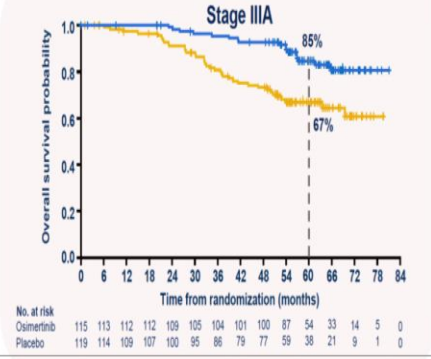
Maturity: 21%
osimertinib 15%, placebo 27%

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

Data cut-off: January 27, 2023



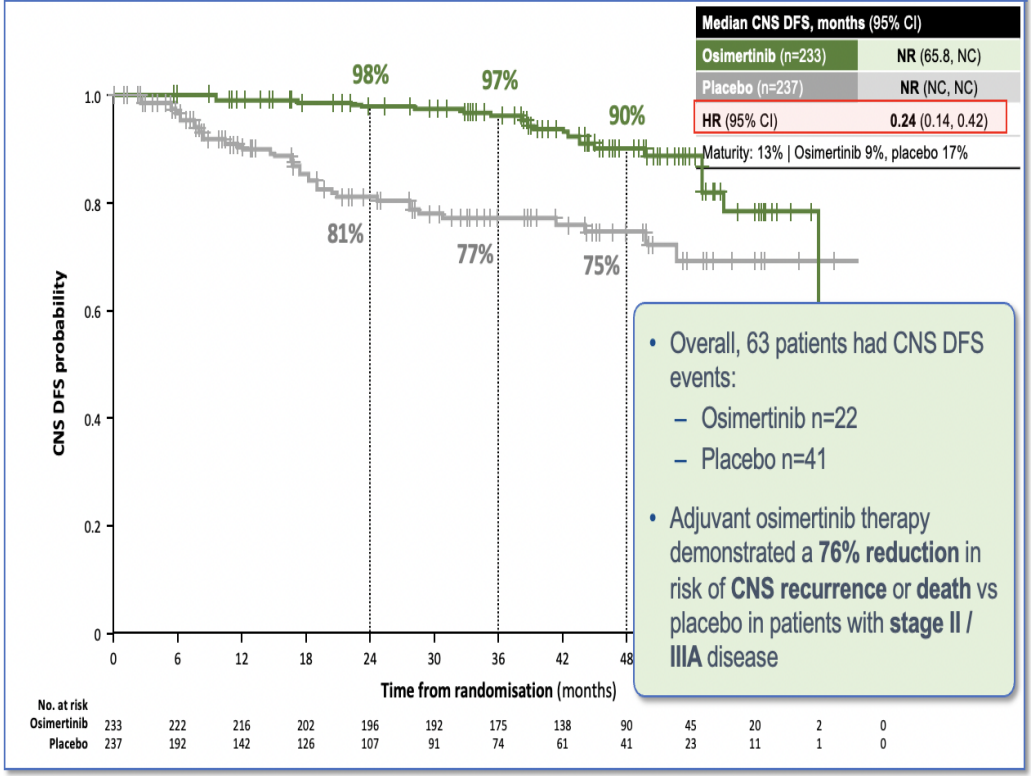
	Stage IB	Stage II	Stage IIIA
5 year OS rate, % (95% CI)			
Osimertinib	94 (86, 97)	85 (77, 91)	85 (76, 91)
Placebo	88 (80, 93)	78 (69, 85)	67 (57, 75)
Overall HR (95% CI)	0.44 (0.17, 1.02)	0.63 (0.34, 1.12)	0.37 (0.20, 0.64)



Herbst et al, ASCO 2023; Tsuboiet al, NEJM 2023

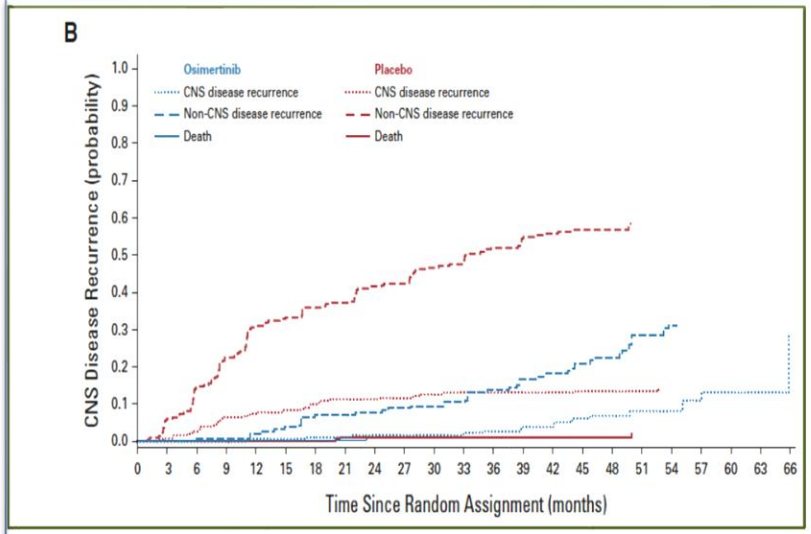
Updated CNS DFS and Toxicity

Updated CNS DFS in stage II / IIIA disease†



- Overall, 63 patients had CNS DFS events:
  - Osimertinib n=22
  - Placebo n=41
- Adjuvant osimertinib therapy demonstrated a **76% reduction** in risk of **CNS recurrence** or **death** vs placebo in patients with **stage II / IIIA** disease

CNS -Recurrence

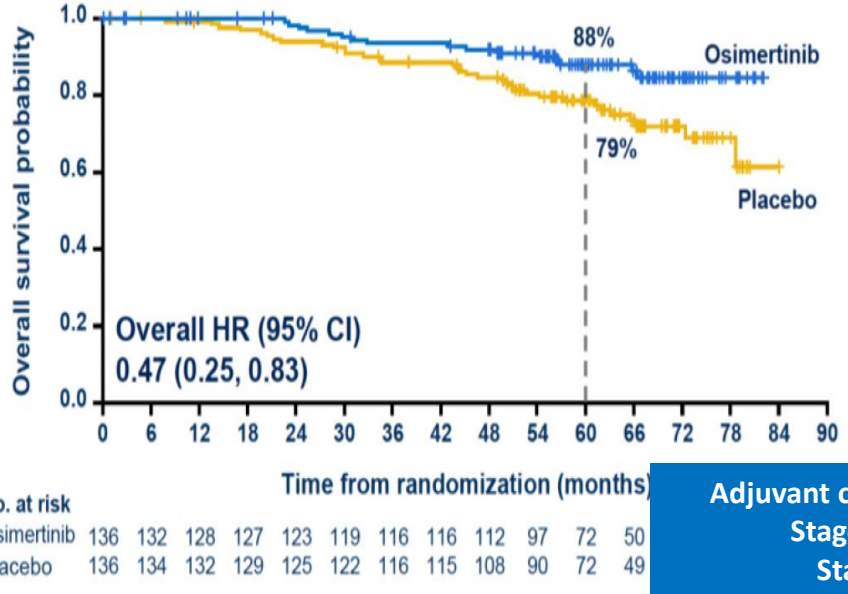


Probability of observing CNS and non-CNS recurrence: an estimated probability of observing CNS recurrence at 3 years of 2% with osimertinib vs 13% with placebo

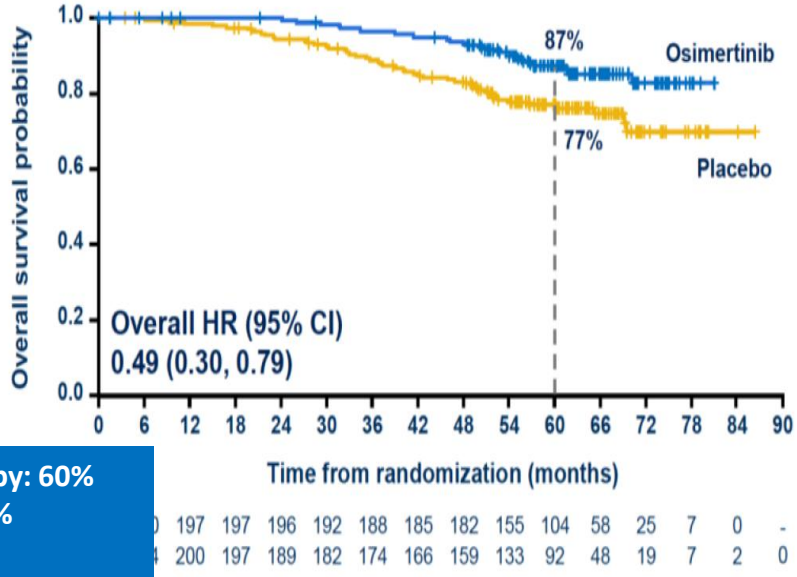
Herbst et al, JCO 2023

Is adjuvant CT still need in ressected EGFR mutant patients?

NO adjuvant chemo (40%)



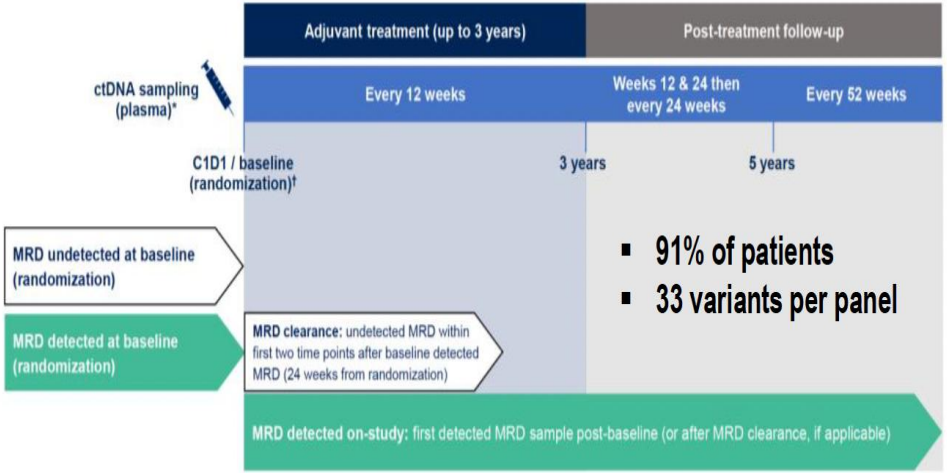
Adjuvant chemo (60%)

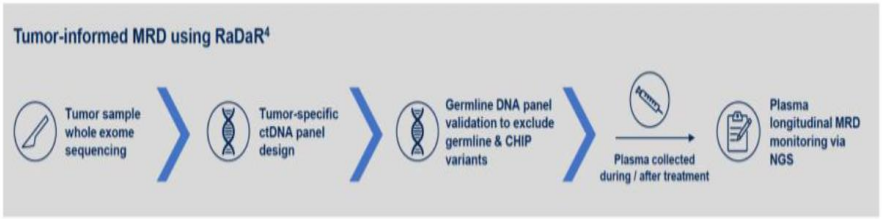


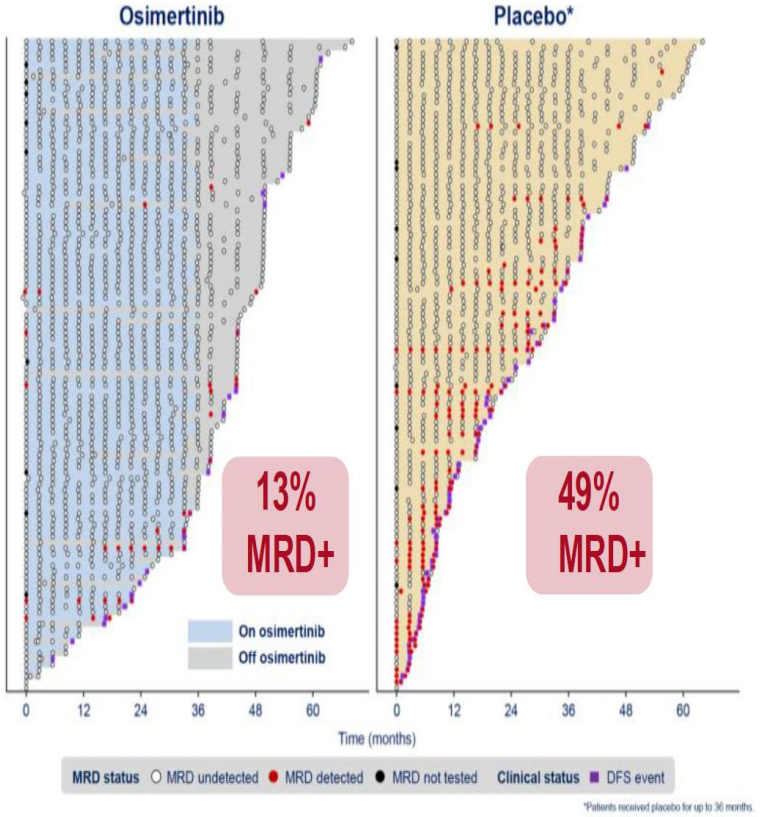
Adjuvant chemotherapy: 60%
Stage II–IIIA: 76%
Stage IB: 26%
CT was not a stratification factor

Wu et al. J Thorac Oncol 2021 Zhong et al. J Clin Oncol 2021

Exploratory endpoint – Feasibility of MRD – during/after adjuvant T



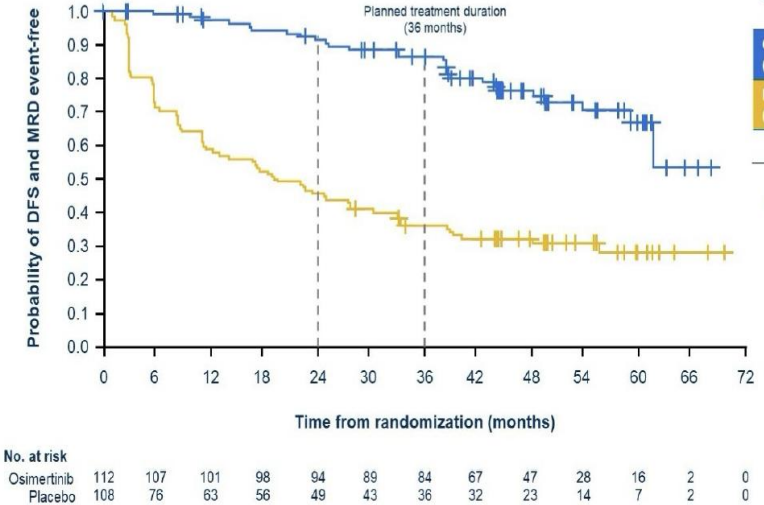




MRD events were detected more frequently with placebo vs osimertinib

John T, ASCO 2024

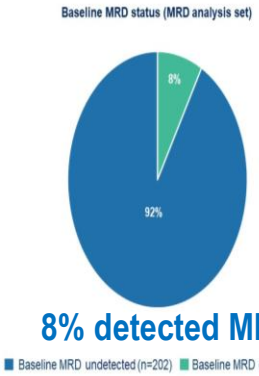
ADAURA: molecular residual disease (MRD)

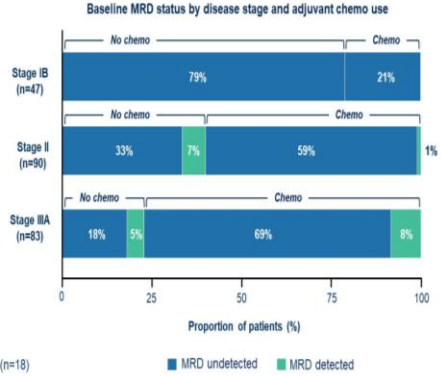


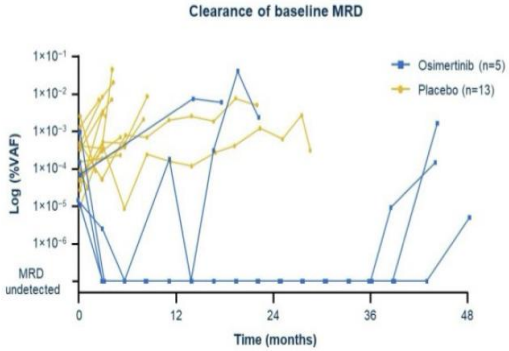
% (95% CI)	DFS and MRD event-free rate	
	24 months	36 months
Osimertinib (n=112)	91 (84, 95)	86 (78, 92)
Placebo (n=108)	46 (36, 55)	36 (27, 45)
HR (95% CI) 0.23 (0.15, 0.36)†		

Median follow-up time, months (95% CI):
osimertinib 44.2 (42.4, 49.1), placebo 19.1 (11.1, 28.3)

Majority of patients were MRD undetected at baseline







- Detected MRD at baseline was associated with poor outcomes
- Patients receiving osimertinib were more likely to be DFS and MRD event free vs placebo

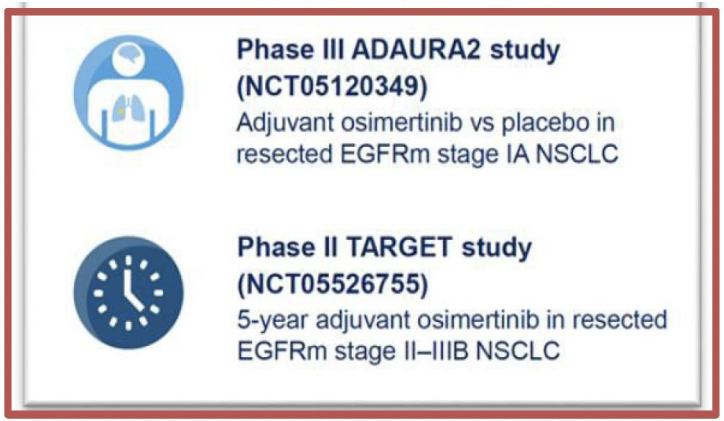
- Of 18 patients with detected MRD at baseline
  - 4 / 5 patients receiving osimertinib cleared MRD
  - 0 / 13 patients receiving placebo cleared MRD

John T, ASCO 2024

And with the OS positive, do we need to extend treatment with Osimertinib?

TARGET TRIAL (NCT05526755): An Open-label, Single-arm, Phase II, Multinational, Multicentre Study to Assess the Efficacy and Safety of 5 Years of Osimertinib in Participants With EGFRm-positive Stage II-IIIB NSCLC, Following Complete Tumour Resection With or Without Adjuvant Chemotherapy

- Phase 2 trial
- Stage II-IIIA-IIIB
- 40 or 80 mg daily x 5 years
- Primary endpoint: DFS



NEOADJUVANT Therapy in *EGFR*m NSCLC: Osimertinib

Study design

NEOS (ChiCTR1800016948):

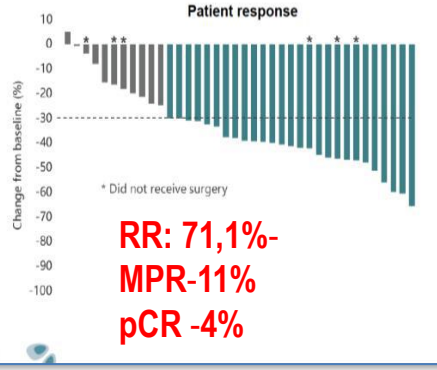
Phase II, multicenter study of neoadjuvant osimertinib in EGFRm resected NSCLC

Key inclusion criteria
- Resectable lung carcinoma
- Stage II–IIIB N2 (AJCC v8)
- EGFRm NSCLC (Ex19del/L858R)
- ECOG PS 0-1

N=40 → Osimertinib 80mg PO QD (6 weeks) → Surgical Resection

Endpoints

Primary: Objective response rate (ORR) assessed by investigator per RECIST v1.1.
Secondary: Safety, R0 resection rate, major pathologic response (MPR) rate, pathological complete response (pCR) rate, N2 downstaging rate, quality of life.



RR: 71,1%-
MPR-11%
pCR -4%

Endpoint		N=38
Tumor Response, n (%)	CR	0 (0%)
	PR	27 (71%)
	SD	11 (29%)
	PD	0 (0%)
ORR		71% (27/38)
DCR		100% (38/38)
R0 resection		94% (30/32)
MPR		11% (3/28)
pCR		4% (1/28)
Pathological response ≥50%		46% (13/28)

- ORR: objective response rate; DCR: disease control rate
- MPR: major pathological response rate, defined as the proportion of patients with no more than 10% residual viable tumor cells.
- pCR: pathological complete response rate, defined as the proportion of patients without residual viable tumor cells evaluated by pathologists.

Lyu C, ELCC 2023

Multi-institutional Phase II Trial

UCSF UCDAVIS HEALTH

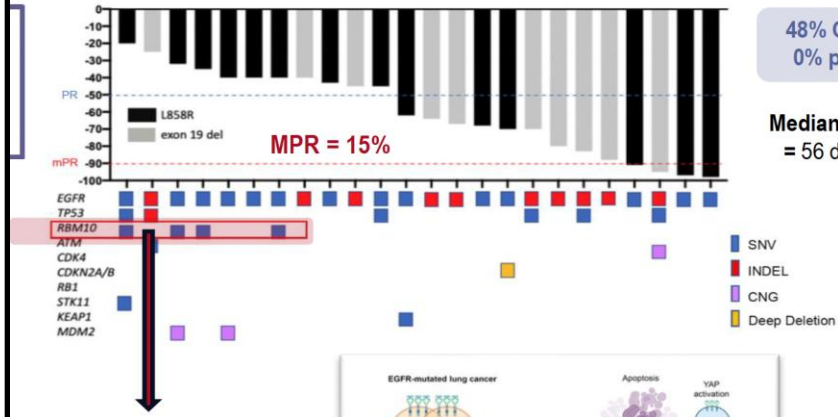
- Surgically resectable NSCLC
- Stage I-IIIIA (AJCC V7)
- Documented *EGFR* mutation (ex19del, L858R)

N=27

Osimertinib 1-2 mo.

Primary endpoint: MPR (≈ 50%)
Secondary: safety, ORR, PCR, DFS

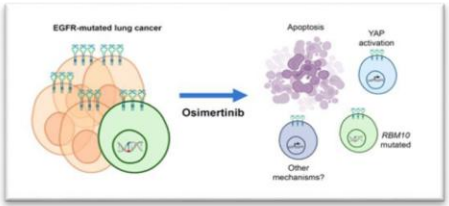
Median DFS = 32,4 mo (95% CI 25.9-NR)



48% ORR
0% pCR

Median time = 56 days

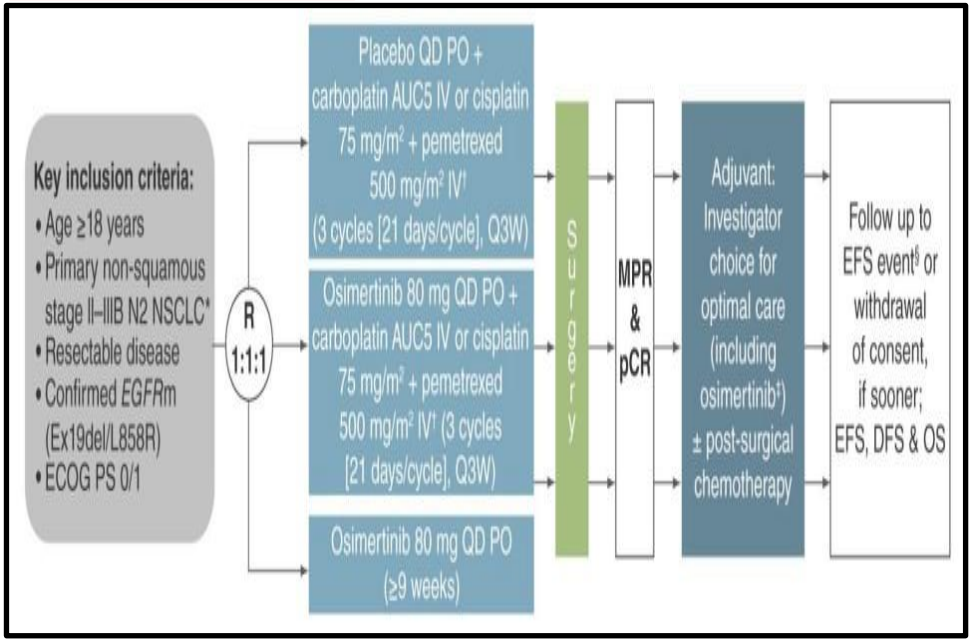
***RBM10* Loss-of-function mut.** identified in non-responders



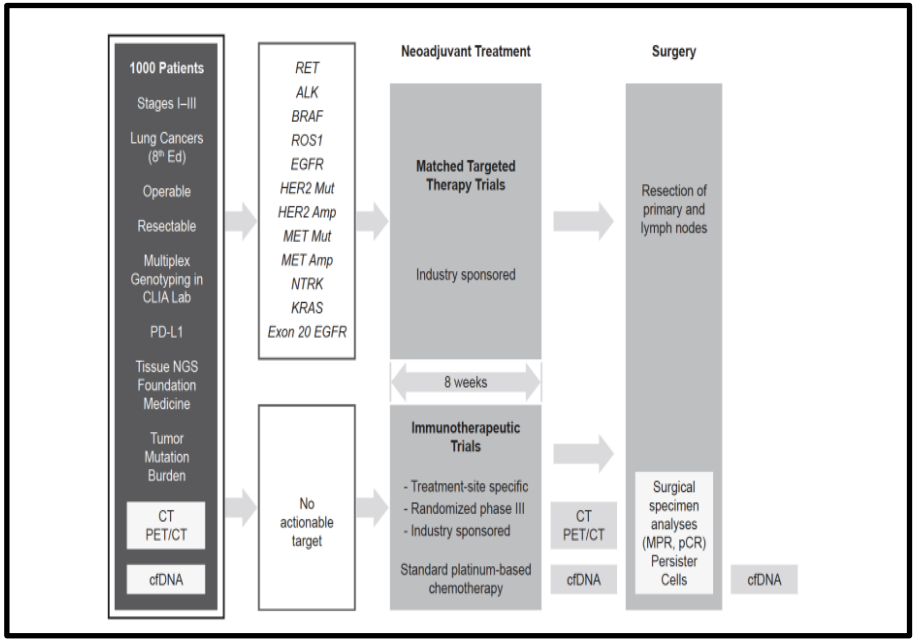
Aredo JV, ASCO 2023

ONGOING STUDIES FOR EGFRm IN THE NEOADJUVANT SETTING

NEOADAURA



LCMC Leader study, neoadjuvant



Primary endpoint: MPR
Secondary endpoints: EFS, pCR, nodal downstaging, DFS, OS

UNRESECTABLE NSCLC

PACIFIC

- 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 tumour tissue for PD-L1 testing†

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

N=713 randomised

1–42 days post-cCRT

R

2:1 randomisation, stratified by age, sex, and smoking history

Durvalumab
10 mg/kg q2w for up to 12 months
N=476

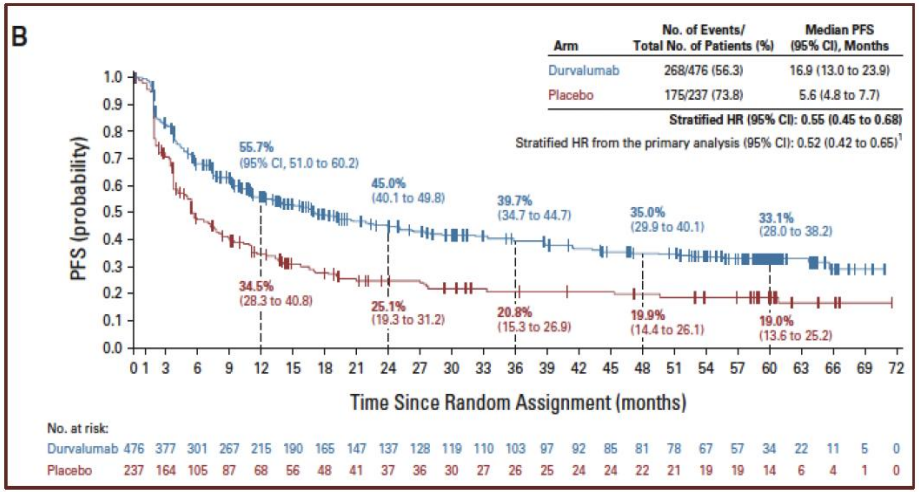
Placebo
q2w for up to 12 months
N=237

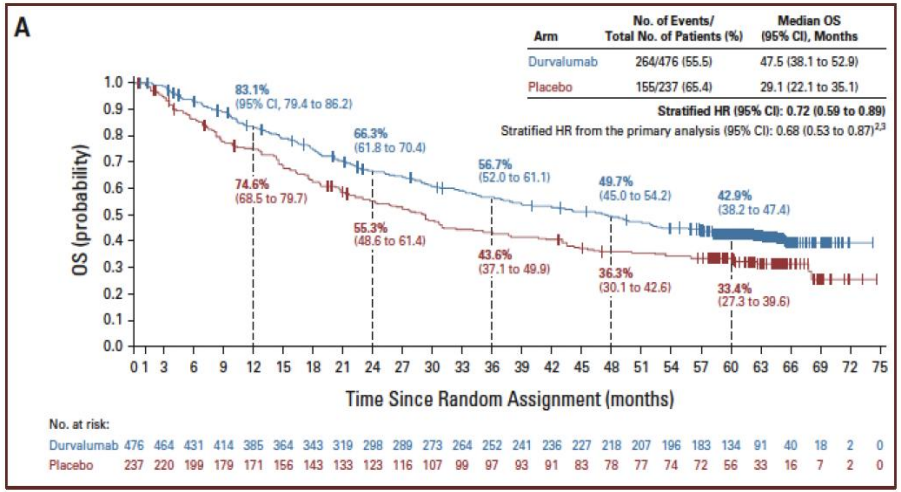
Primary endpoints

- PFS by BICR using RECIST v1.1‡
- OS

Key secondary endpoints

- ORR, DoR, and TTDM by BICR using RECIST v1.1
- Safety
- PROs

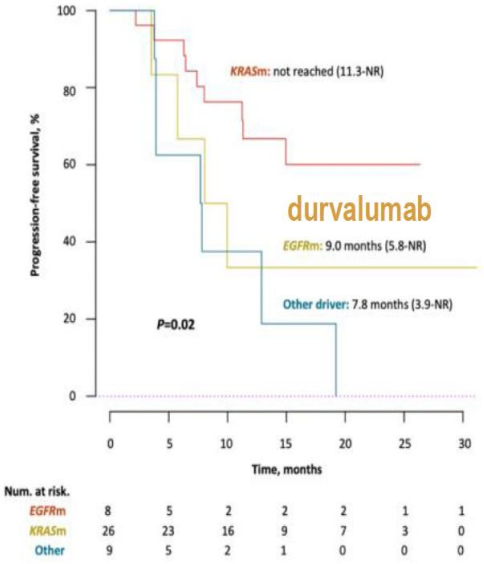




Spiegel DR, et al. J Clin Oncol 2022;40(12):1301-11

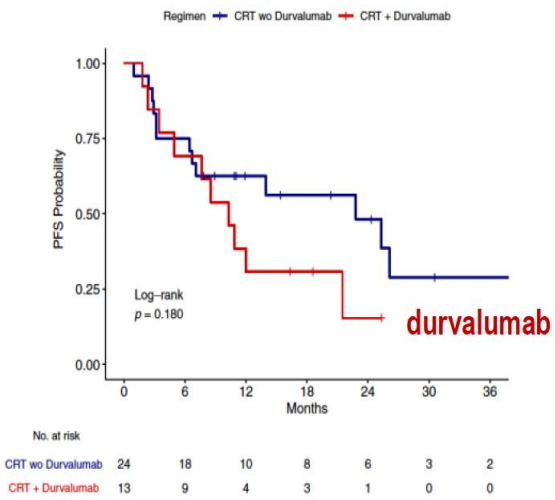
CONSOLIDATION: NO benefit of durvalumab, with high frequency of irAEs in *EGFR*m population

Retrospective cohort, n=8 *EGFR*m



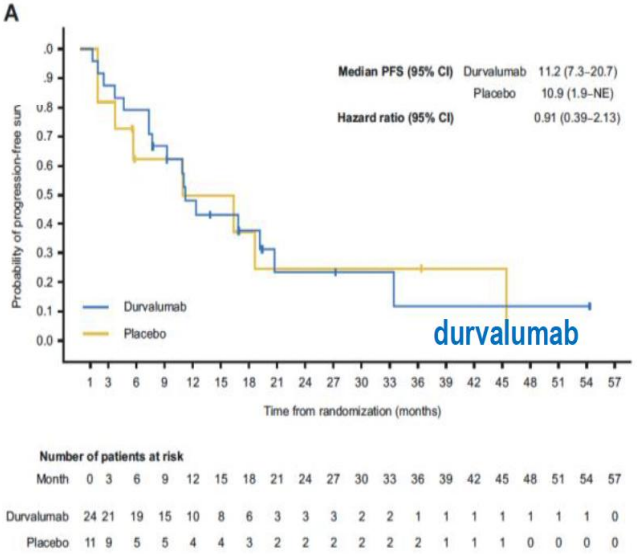
mPFS = 9 mo.

Retrospective cohort, n=37 *EGFR*m



mPFS = 10.3 mo.

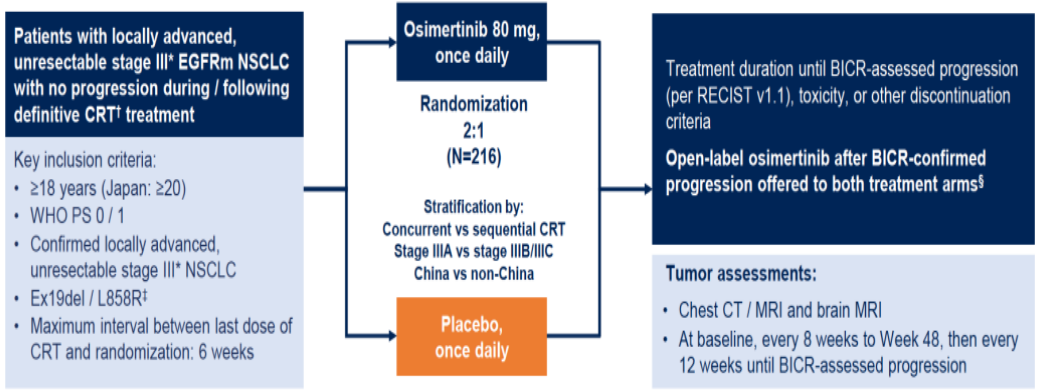
PACIFIC Post Hoc analysis, n=35 *EGFR*m



mPFS = 11.2 mo.

Riudavets M, EJC 2022, Aredo JV, JTO 2021 Naidoo, JTO 2023

LAURA Phase 3 double-blind study design



Endpoints

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

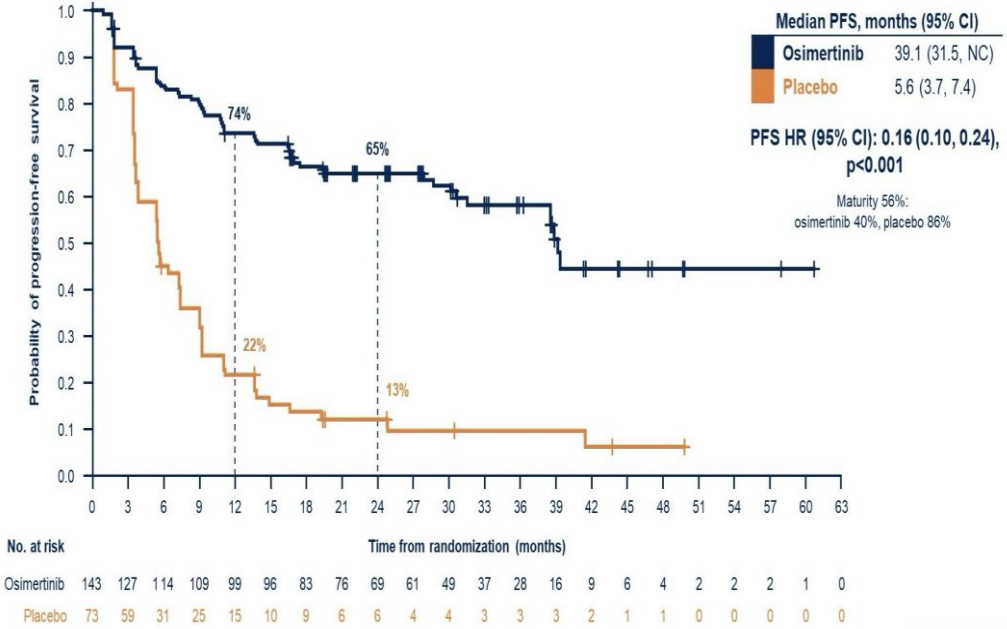
Baseline characteristics

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)

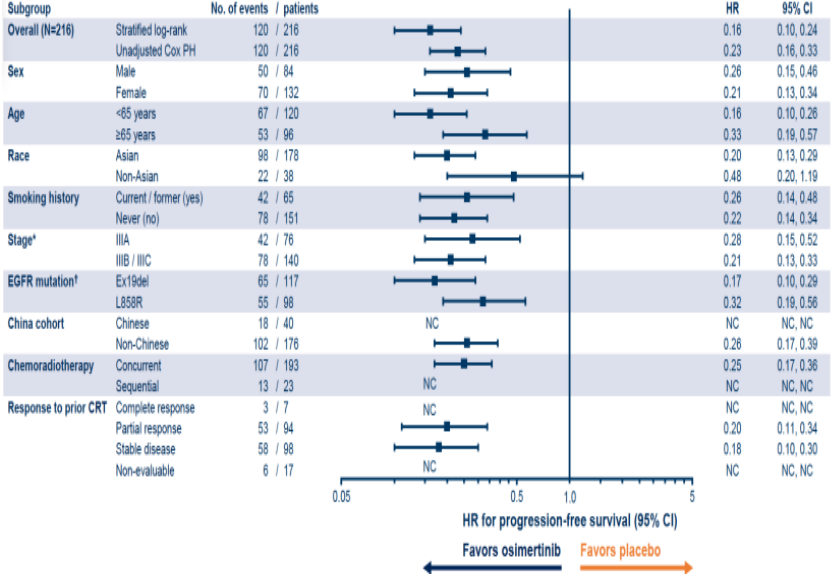
Data cut-off: January 5, 2024.
*Tissue tested by central or FDA-approved local test from a CLIA-approved laboratory, or accredited local laboratory for sites outside the USA.
†One patient in the osimertinib arm had missing EGFR mutation.
‡Post-CRT.

Ramalingam, ASCO 2024; Lu S, NEJM 2024

Progression-free survival by BICR

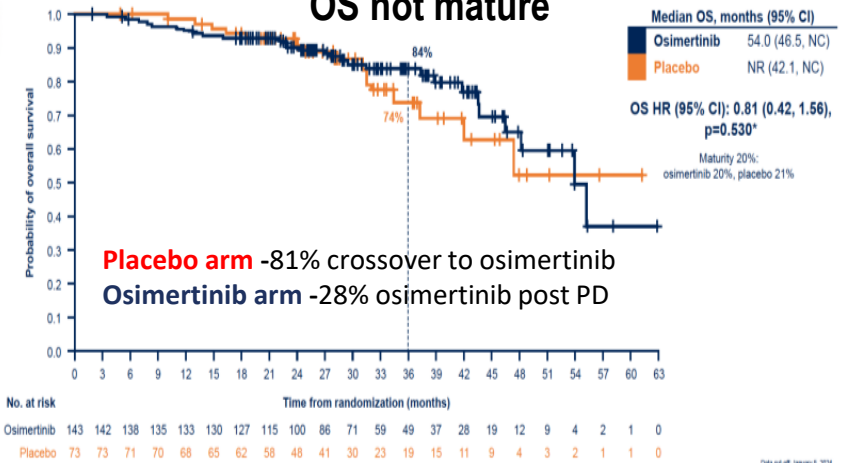


Progression-free survival by BICR across subgroups



Ramalingam, ASCO 2024; Lu S, NEJM 2024

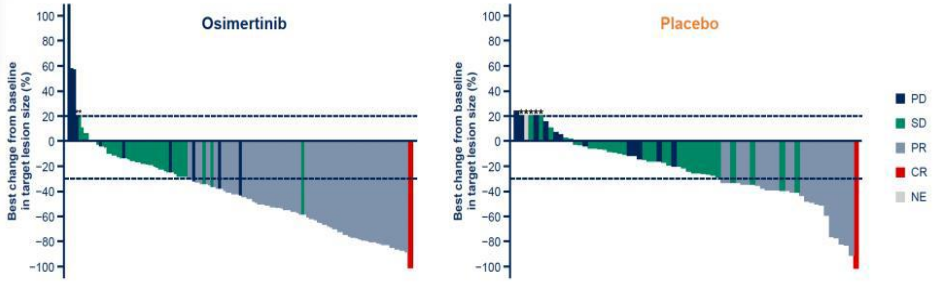
OS not mature



Placebo arm -81% crossover to osimertinib

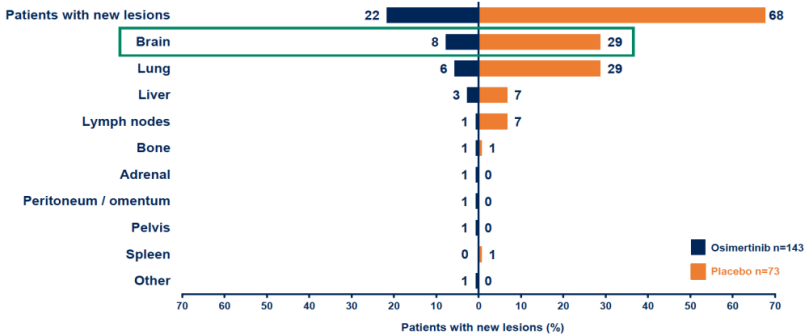
Osimertinib arm -28% osimertinib post PD

Tumor response by BICR



	Osimertinib (n=143)	Placebo (n=73)
Objective response rate, % (95% CI)	57 (49, 66)	33 (22, 45)
Disease control rate, % (95% CI)	89 (83, 94)	79 (68, 88)
Median duration of response, months (95% CI)	36.9 (30.1, NC)	6.5 (3.6, 8.3)

Sites of new lesions by BICR

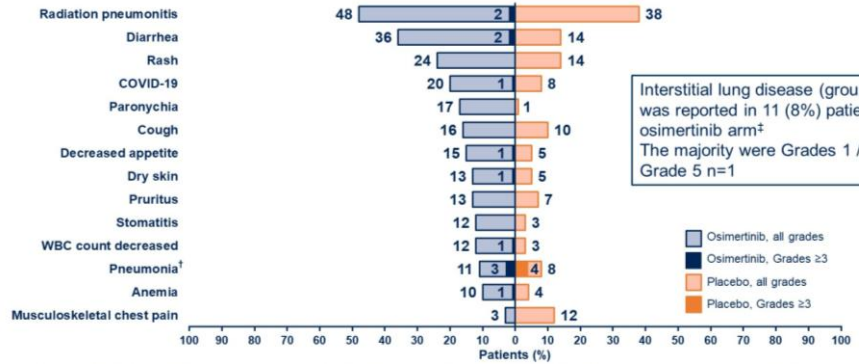


Percentages based on number of patients in each treatment arm. Patients can have more than one new lesion site. Based on BICR assessments according to RECIST v1.1 and includes all new lesions at any time (including those whose RECIST progression event had been censored).

Data cut-off: January 5, 2024.

All-causality adverse events (≥10%)*

The most common AE in both arms was radiation pneumonitis; the majority were low grade (no Grade 4 / 5), non-serious and manageable



Interstitial lung disease (grouped term) was reported in 11 (8%) patients in the osimertinib arm‡
The majority were Grades 1 / 2; Grade 5 n=1

Take Home Message

- Search always for driver mutations in early-stage NSCLC, mainly EGFR and ALK, prior to treatment.
- Osimertinib is the SoC after surgery in S-Ib-IIIA EGFRm (Adaura DFS and OS)
- For unresectable case, CRT followed by osimertinib is the SoC (Laura-DFS)
- Neoadjuvant TKI in clinical trial.
- We still needing better clinical trial base in biomarkers


Thank you