16th CONGRESS Lung ON CANCER

BARCELONA 27 / 28 NOVEMBER 2025

GECP lung cancer research

TREATMENT STRATEGIES FOR LOCOREGIONAL DISEASE WITH ONCOGENIC DRIVER

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Declaration of Interests

Receipt of honoraria from: AstraZeneca, Regeneron, Janssen, Takeda, Pfizer, Amgen, Boehringer

Travel and Accommodation Expenses from: MSD, Roche, Pfizer, Janssen.

16th CONGRESS Lung ON CANCER

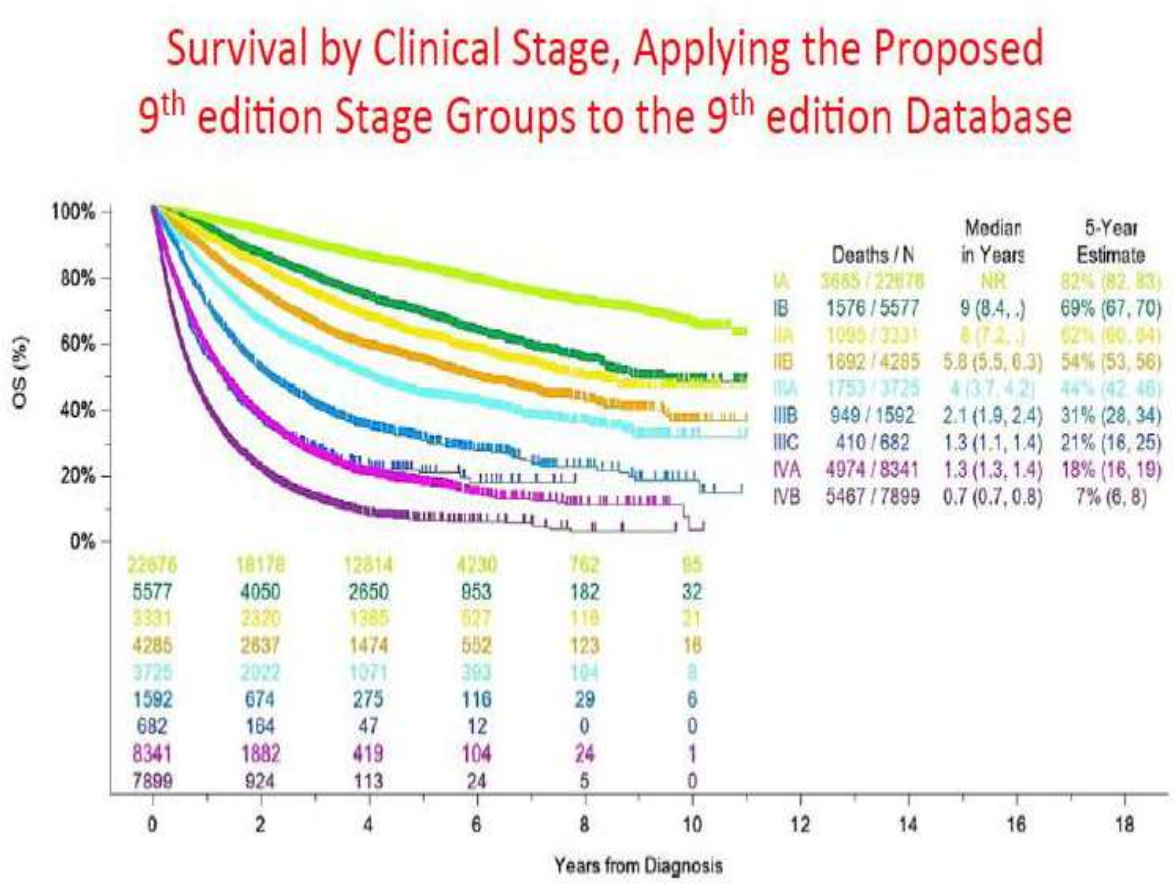
BARCELONA 27 / 28 NOVEMBER 2025

- Introduction
- Current standard of care with targetable alterations
- Specific treatment strategies
- Open questions and current challenges

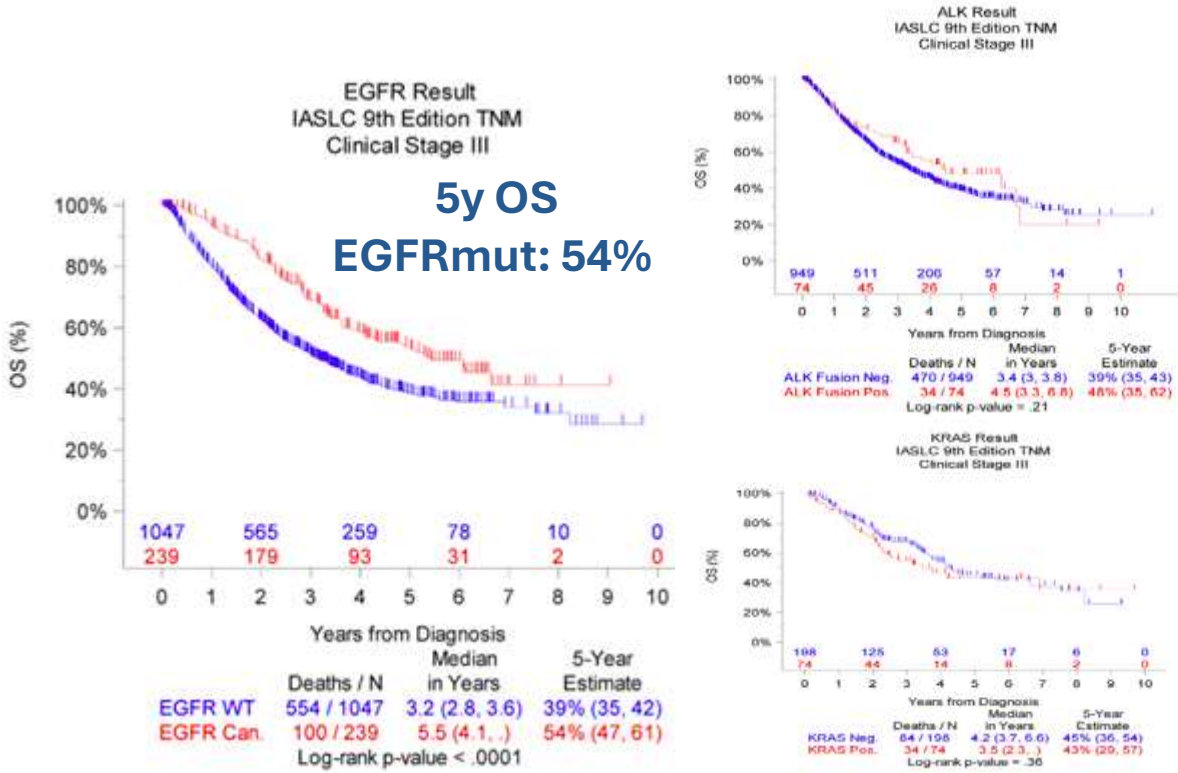
GECP lung cancer research

INTRODUCTION

5-year OS: 20-30%



The impact of common molecular alterations



Patients with EGFR-mutated tumors had improved OS regardless of stage, whereas an OS benefit was found in stage IV patients with ALK-positive tumors.

Porta et al. JTO 2024. Carbone DP. J Thorac Oncol. 2025;20:1423-1440.

UNRESECTABLE STAGE III: SoC

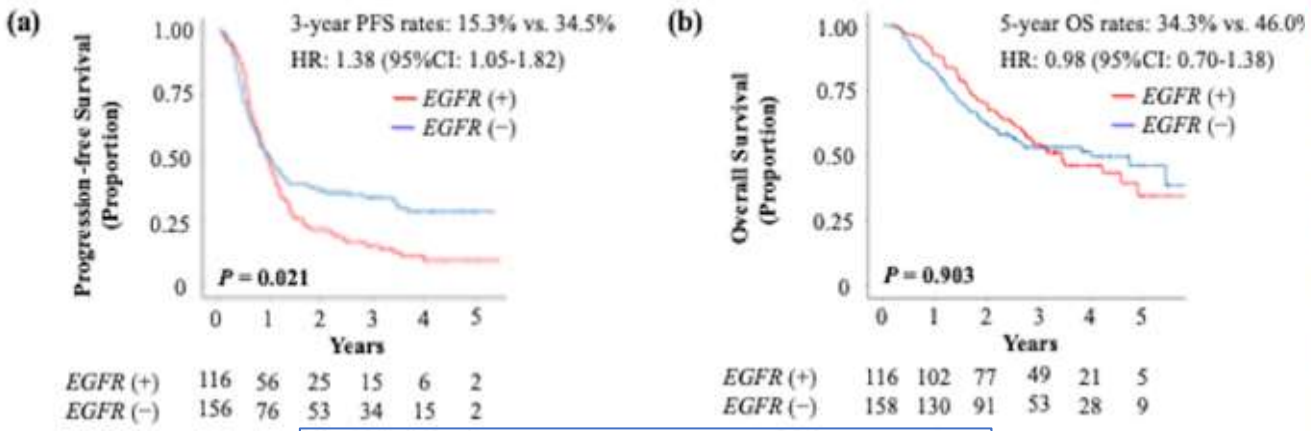
Unresectable stage III remains an important challenge given that only around **1/3** of patients treated with cCRT and ICIs remain **alive and progression-free** at 5 years.

… and also **20%** of patients without ICI

CAN WE IMPROVE THESE RESULTS IN SPECIFIC POPULATIONS?

Is cCRT equally effective in EGFRmut NSCLC?

EGFR-mutant NSCLC exhibited significantly higher ORR but shorter PFS than EGFR wildtype NSCLC



greater radiosensitivity ?

Table 3 Summary of Reported Results Regarding the EGFR Status and Recurrence Pattern

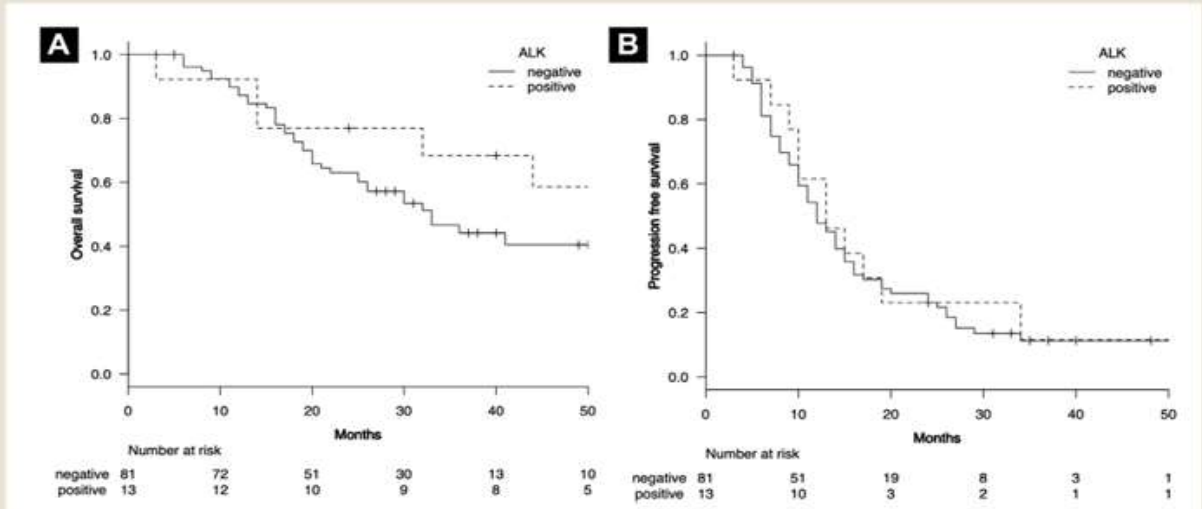
	Akamatsu et al	Yagishita et al	Tanaka et al	Lim et al	Our Study
Failure					
EGFR wild-type	84 (26/31)	79 (129/164)	71 (53/75)	NA	79 (110/139)
EGFR mutated	77 (10/13)	74 (25/34)	83 (24/29)	NA	94 (32/34)
ALK positive					85 (11/13)
Locoregional failure					
EGFR wild-type	32 (10/31)	33 (54/164)[a]	35 (26/75)	45 (31/69)[a]	45 (63/139)
EGFR mutated	15 (2/13)	15 (5/34)[a]	14 (4/29)	12 (3/26)[a]	21 (7/34)
ALK positive					54 (7/13)
Distant failure					
EGFR wild-type	58 (18/31)	63 (102/164)[b]	40 (30/75)	39 (27/69)[b]	61 (85/139)
EGFR mutated	69 (9/13)	71 (24/34)[b]	76 (22/29)	50 (13/26)[b]	79 (27/34)
ALK positive					46 (6/13)

Data from some studies suggest no significant differences in PFS and better OS for EGFRmut

Shinkichi Takamori et al. JTO Clinical and Research Reports 2025; 100897. Nakamura, M. et al. Clin. Lung Cancer 20, e256–e264 (2019). Masaki Nakamura et al. Clinical Lung Cancer May 2019

Is cCRT equally effective in ALK+ NSCLC?

Figure 3 Overall Survival (A) and Progression-free Survival (B) Rates in Groups Stratified by the ALK Status



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ALK positive					46 (6/13)

Masaki Nakamura et al. Clinical Lung Cancer May 2019

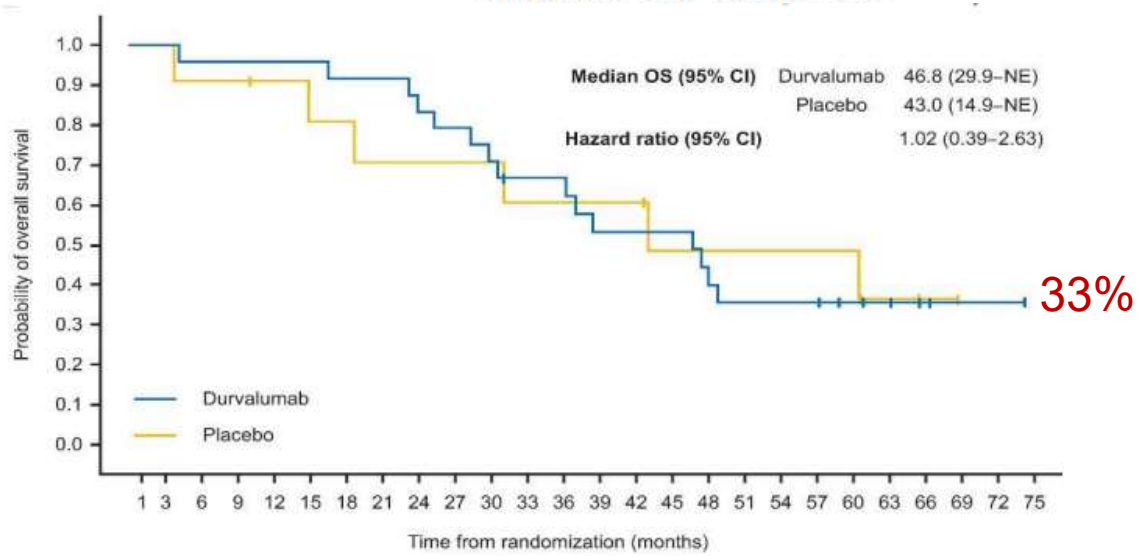
Is DURVALUMAB equally effective in EGFRmut or ALK+ NSCLC?

35 EGFR mut
8 ALK +

PACIFIC trial

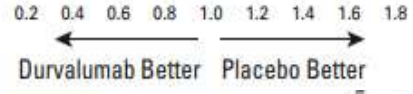
Updated OS by prespecified and exploratory, post hoc subgroups

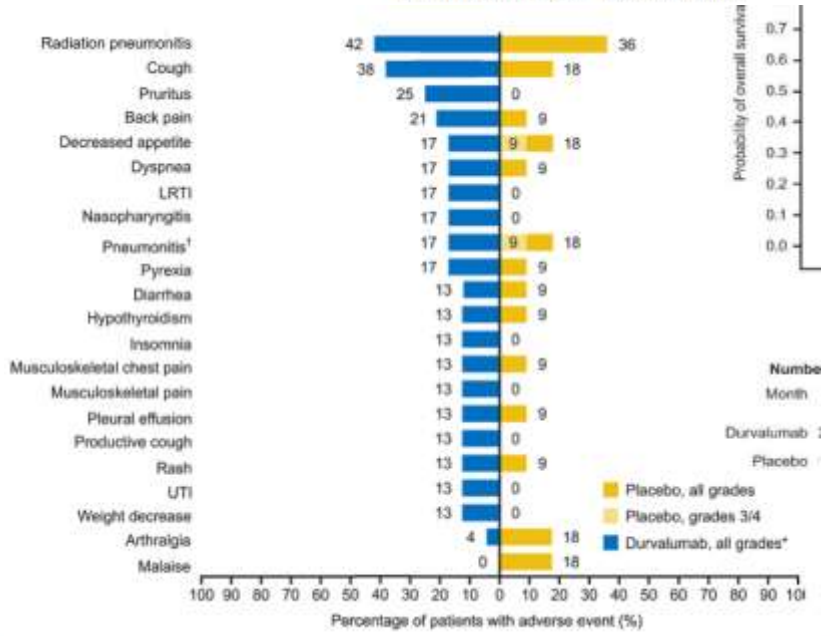
Group	No. of Events / No. of Patients (%) Durvalumab	Placebo	Unstratified HR (95% CI)
EGFR or *ALK* aberration status			
Positive[d]	17/29 (58.6)	8/14 (57.1)	0.85 (0.37 to 1.97)
Negative	166/317 (52.4)	109/165 (66.1)	0.66 (0.52 to 0.84)
Unknown	81/130 (62.3)	38/58 (65.5)	0.85 (0.57 to 1.24)



33%

Group	No. of Events / No. of Patients (%) Durvalumab	Placebo	Unstratified HR (95% CI)
EGFR or *ALK* aberration status			
Positive[d]	21/29 (72.4)	11/14 (78.6)	0.82 (0.39 to 1.71)
Negative	169/317 (53.3)	124/165 (75.2)	0.52 (0.41 to 0.65)
Unknown	78/130 (60.0)	40/58 (69.0)	0.74 (0.51 to 1.09)



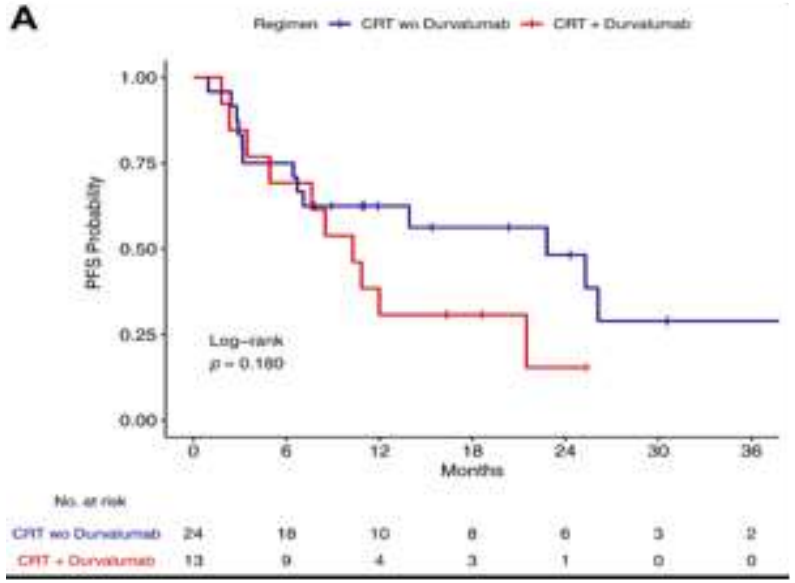


David R Spiegel et al. J Clin Oncol 40:1301-1311. Naidoo, J et al. J Thor Oncol 2023; 2023;18(5):657-663.

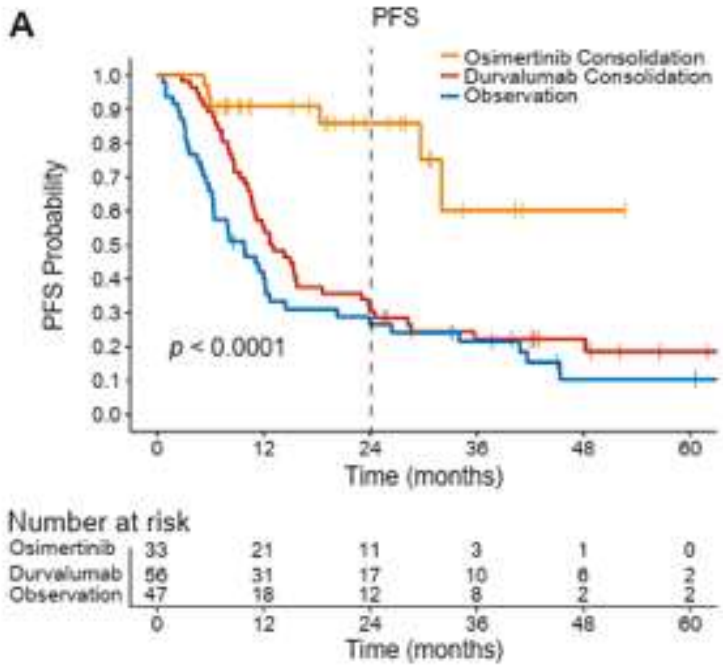
Is DURVALUMAB equally effective in EGFRmut or ALK+ NSCLC?

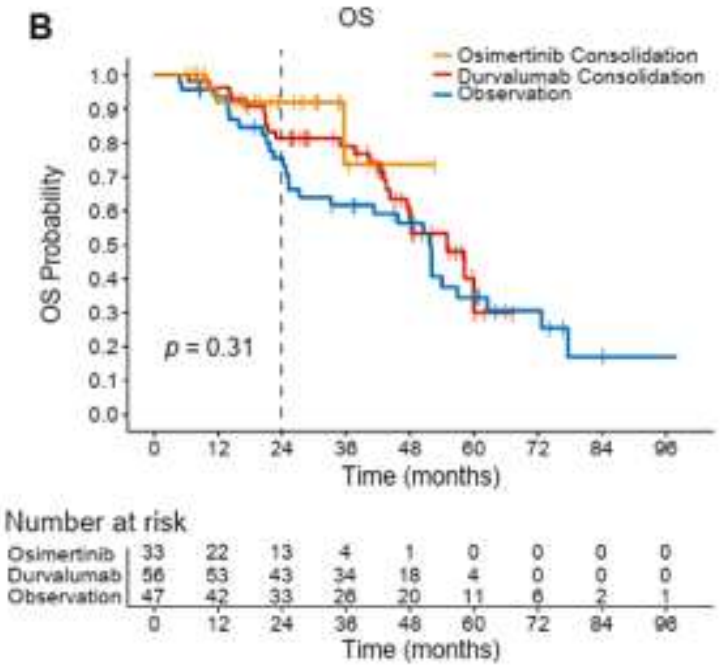
REAL WORLD DATA

No benefit rwPFS with durvalumab compared to observation



Consolidation osimertinib was associated with a significantly longer rwPFS compared to durvalumab or observation



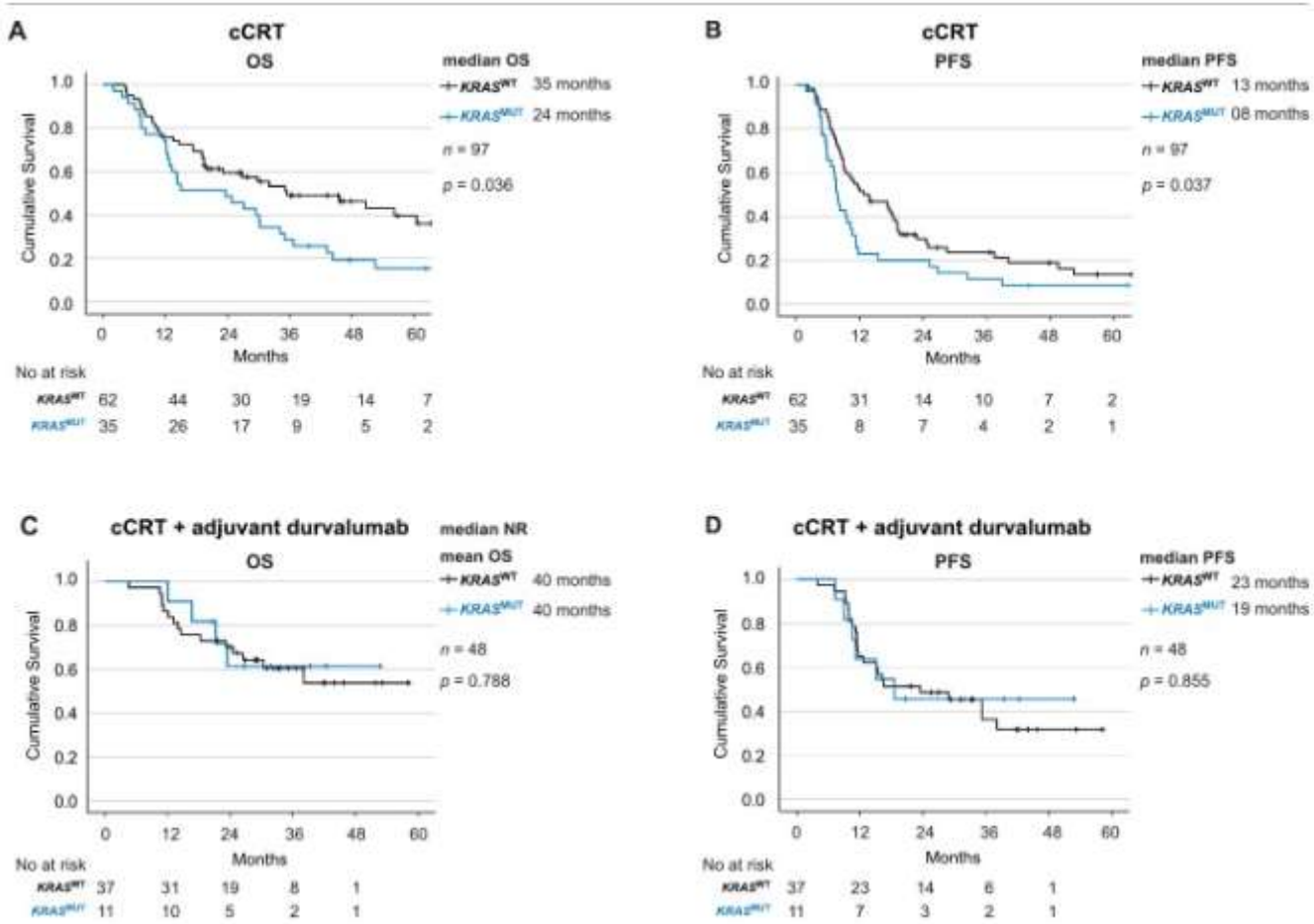


Jacqueline V. Aredo et al. J Thor Oncol 2021: 16(6): 1030-1041. Nassar et al. J. Thor Oncol. 2024; 19 (6): 928–940

Is SoC equally effective in KRASmut NSCLC?

KRAS-mut groups showed worse prognosis than wildtype after treatment with cCRT alone (p = 0.036).

Addition of durvalumab: No longer any significant differences in survival outcomes (p = 0.788)

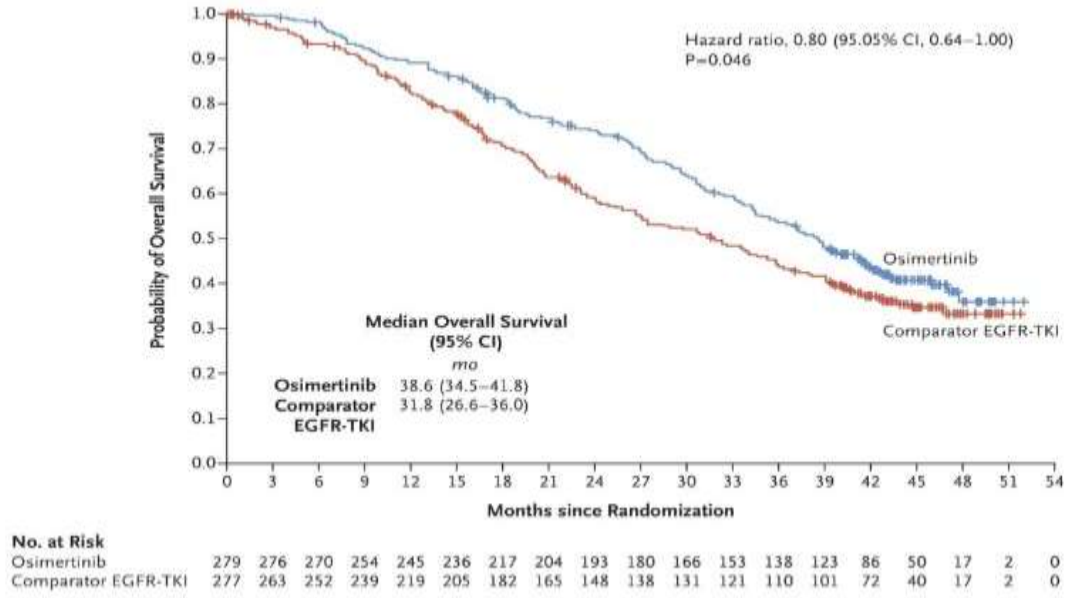


Ella A. Eklund et al. Lung cancer. 2025; 204

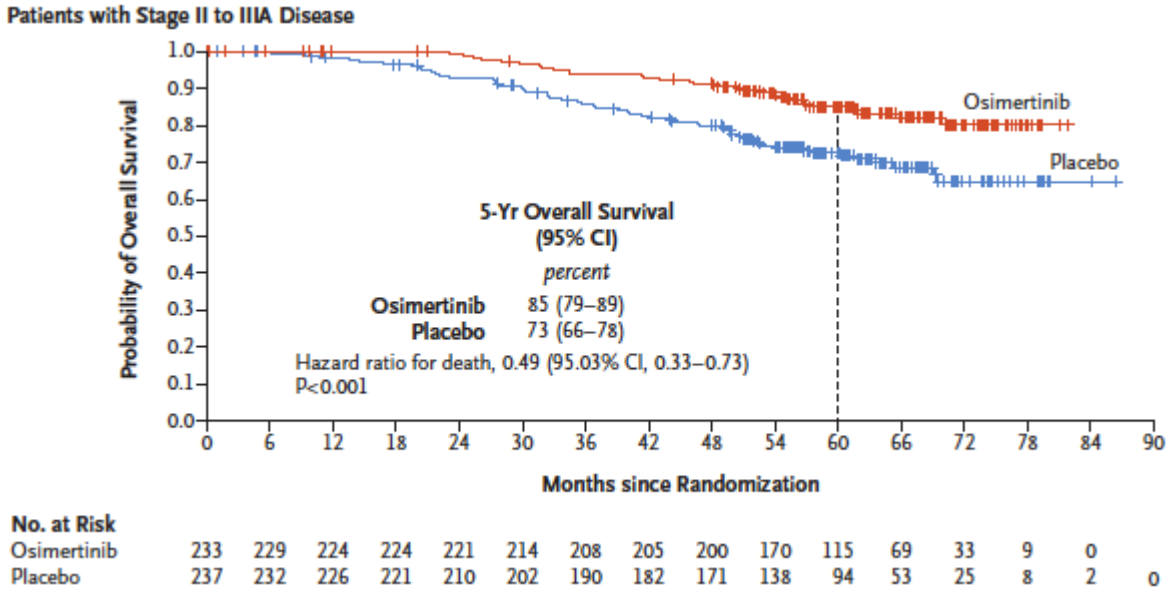
HOW TO IMPROVE OUTCOMES?

TARGETED THERAPY

FLAURA: Phase 3 trial of a targeted therapy in Untreated, EGFR-Mutated Advanced NSCLC



ADAURA is the first phase 3 trial of a targeted therapy in the adjuvant setting for NSCLC to demonstrate an overall survival Benefit

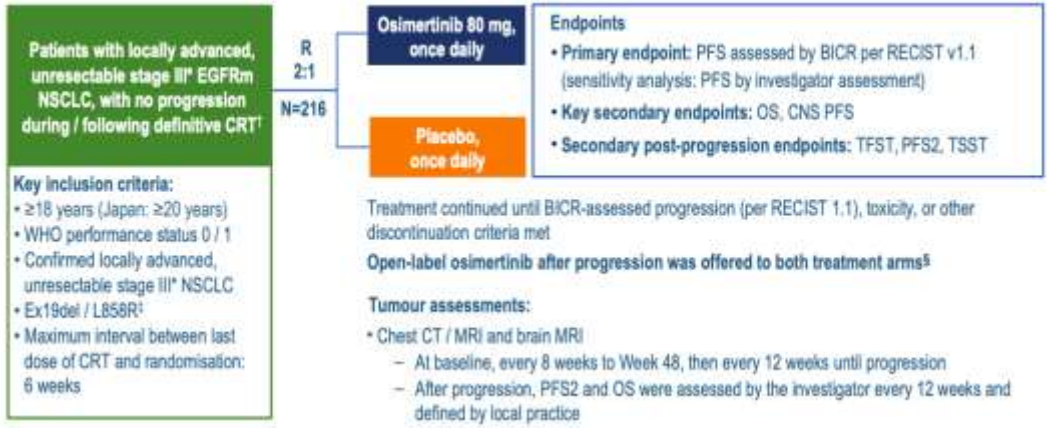


M. Tsuboi NEJM 2023. Ramalingam et al. NEJM 2020

EGFR TKI CONSOLIDATION

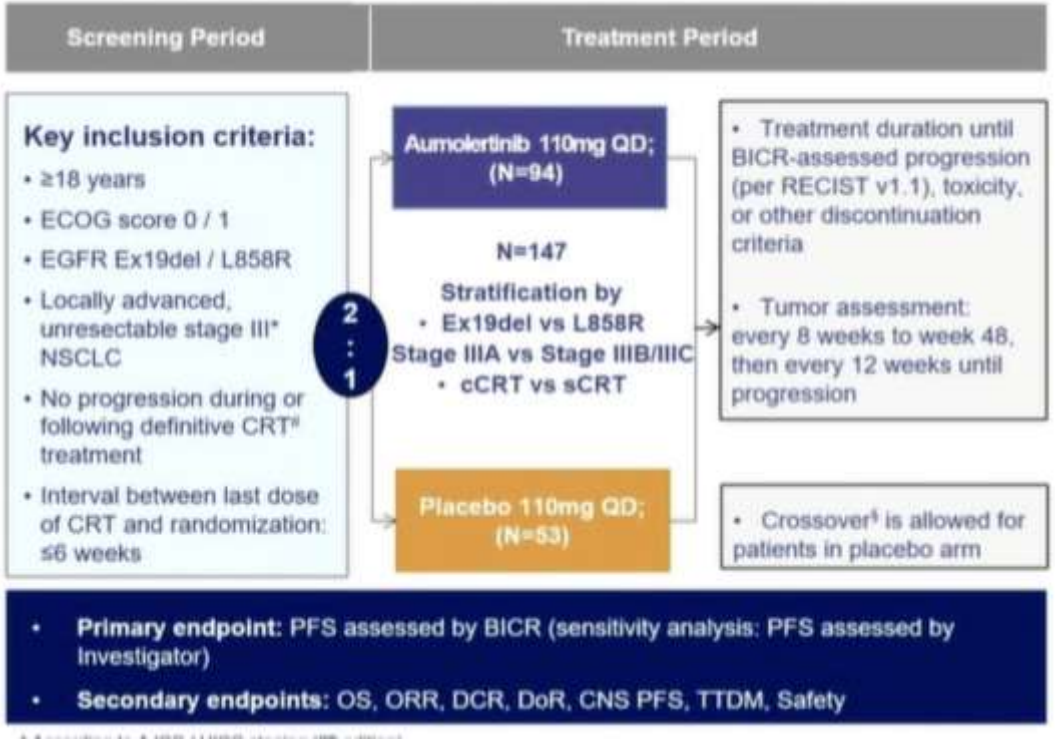
LAURA STUDY

Phase 3, double-blind, placebo-controlled trial with Osimertinib in patients with unresectable EGFR-mutated stage III NSCLC without progression during or after chemoradiotherapy



POLESTAR STUDY

phase 3, double-blind, placebo-controlled trial with Aumolertinib after chemoradiotherapy in Stage III, unresectable EGFRm NSCLC.

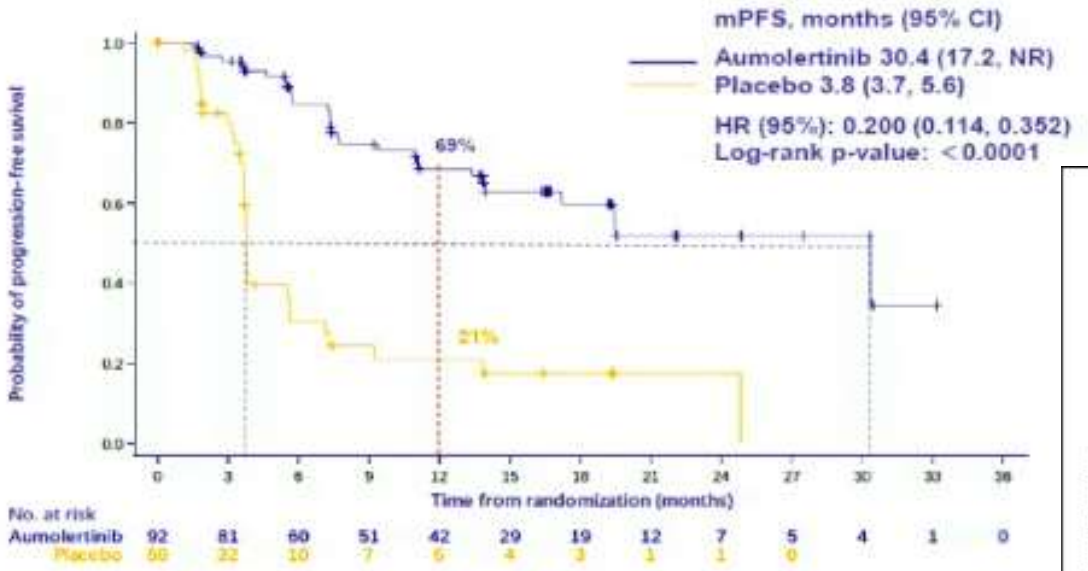


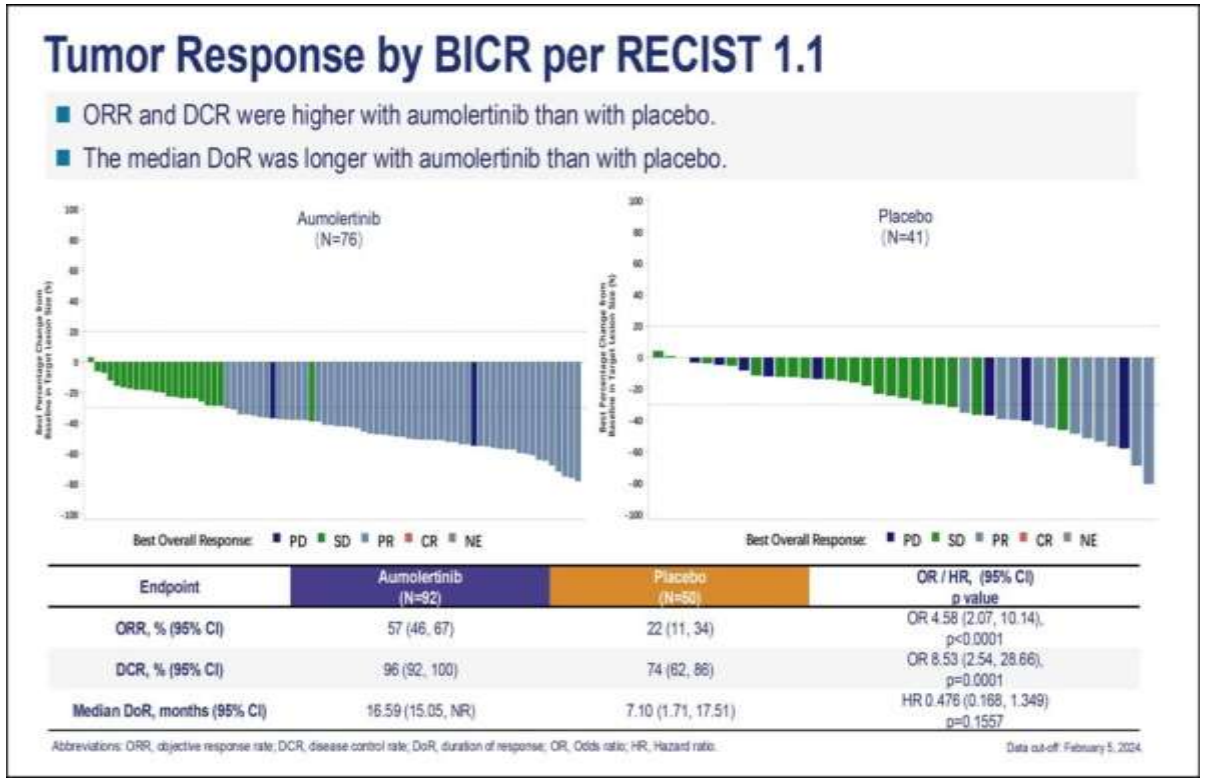
Lu et al. N Engl J Med 2024;391:585–597. Xiangjiao et al. WCLC 2024

EGFR TKI CONSOLIDATION

POLESTAR STUDY

LIFETIME AUMOLERTINIB



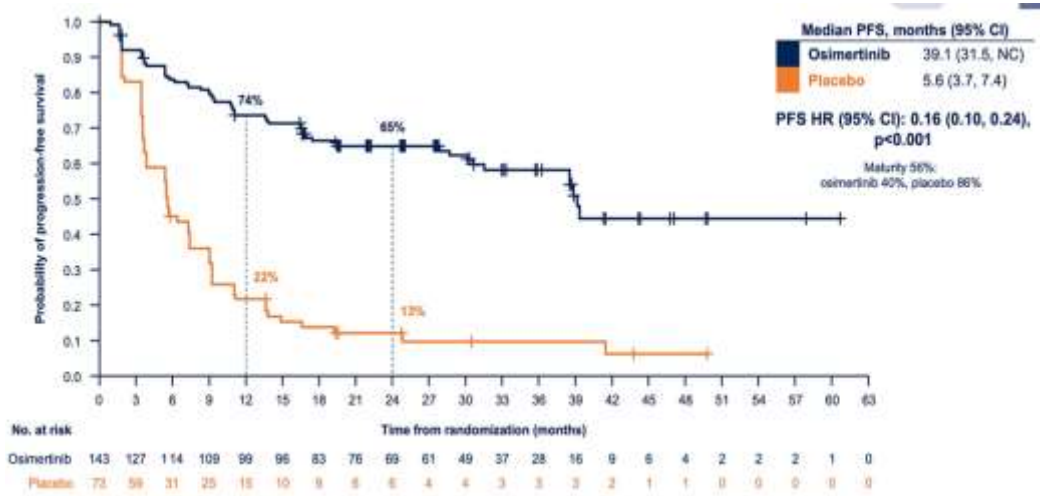


Xiangjiao et al. WCLC 2024

EGFR TKI CONSOLIDATION

LAURA STUDY

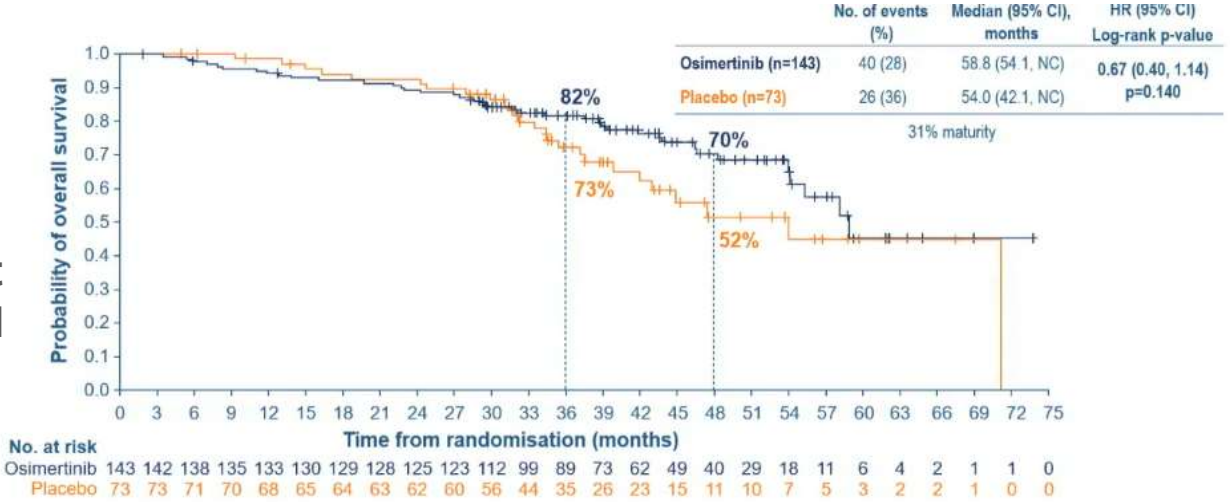
Osimertinib significantly improved PFS over placebo



LIFETIME OSIMERTINIB

80% received 3rd EGFR TKI (77% osimertinib)

Trend towards OS benefit at updated analysis



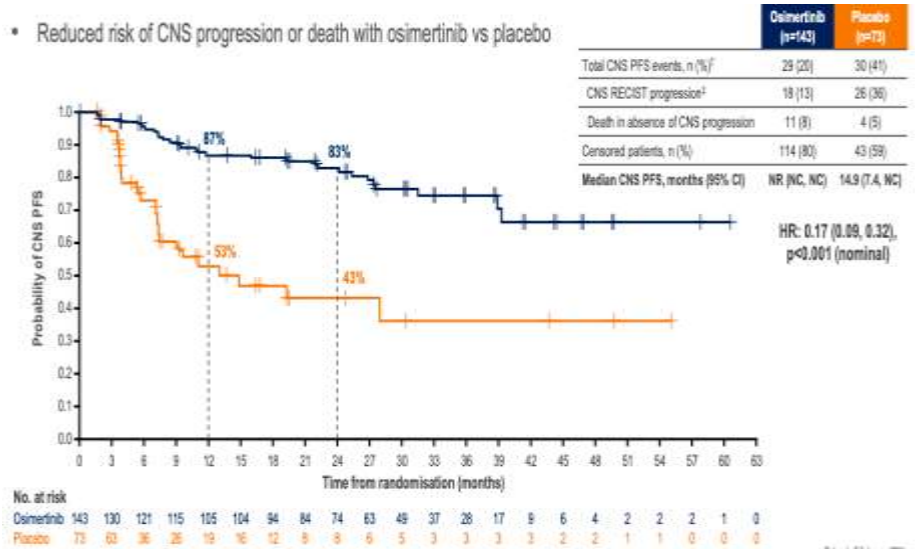
1. Lu et al. N Engl J Med 2024;391:585–597. Suresh S. Ramalingam ELCC 2025

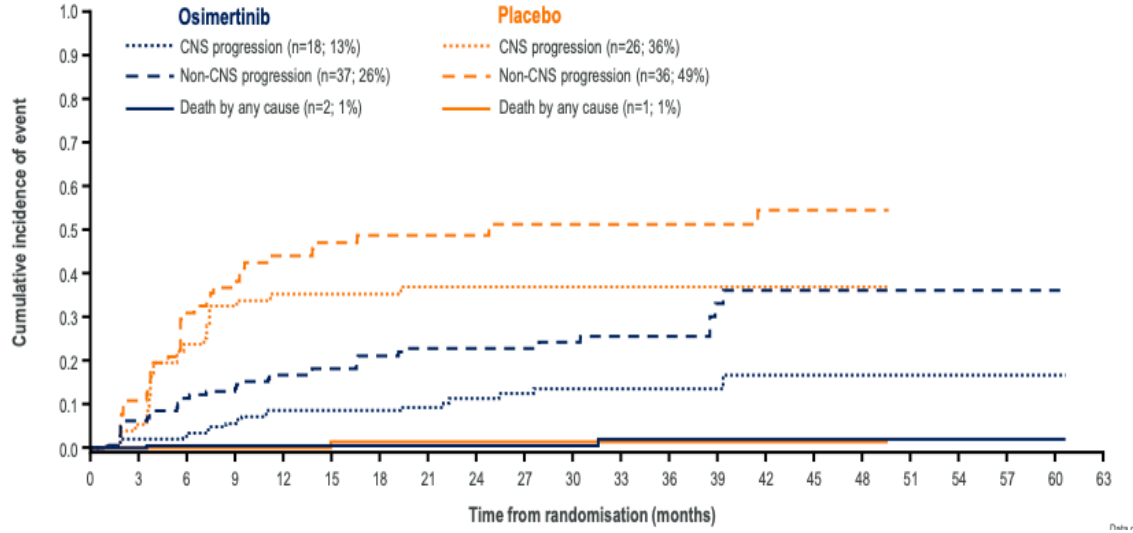
EGFR TKI CONSOLIDATION

LOWER RISK OF CNS PD

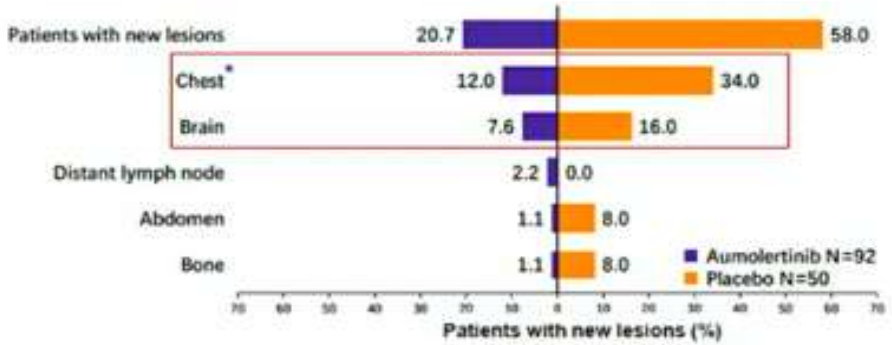
12-month brain metastases 9% vs 36%

LAURA





POLESTAR



Endpoint	Aumolertinib (N=92)	Placebo (N=50)	HR, 95% CI) p value
Median CNS PFS#, months (95% CI)	NR (NR, NR)	NR (NR, NR)	0.33 (0.12-0.92) p=0.0270
Median TTDM§, months (95% CI)	NR (NR, NR)	NR (3.84, NR)	0.21 (0.09, 0.49), p<0.0001

CNS PFS: survival without progression of CNS disease.
§ TTDM: time to death or distant metastasis.

Shun Lu et al. ESMO 2024. Xiangjiao et al. WCLC 2024

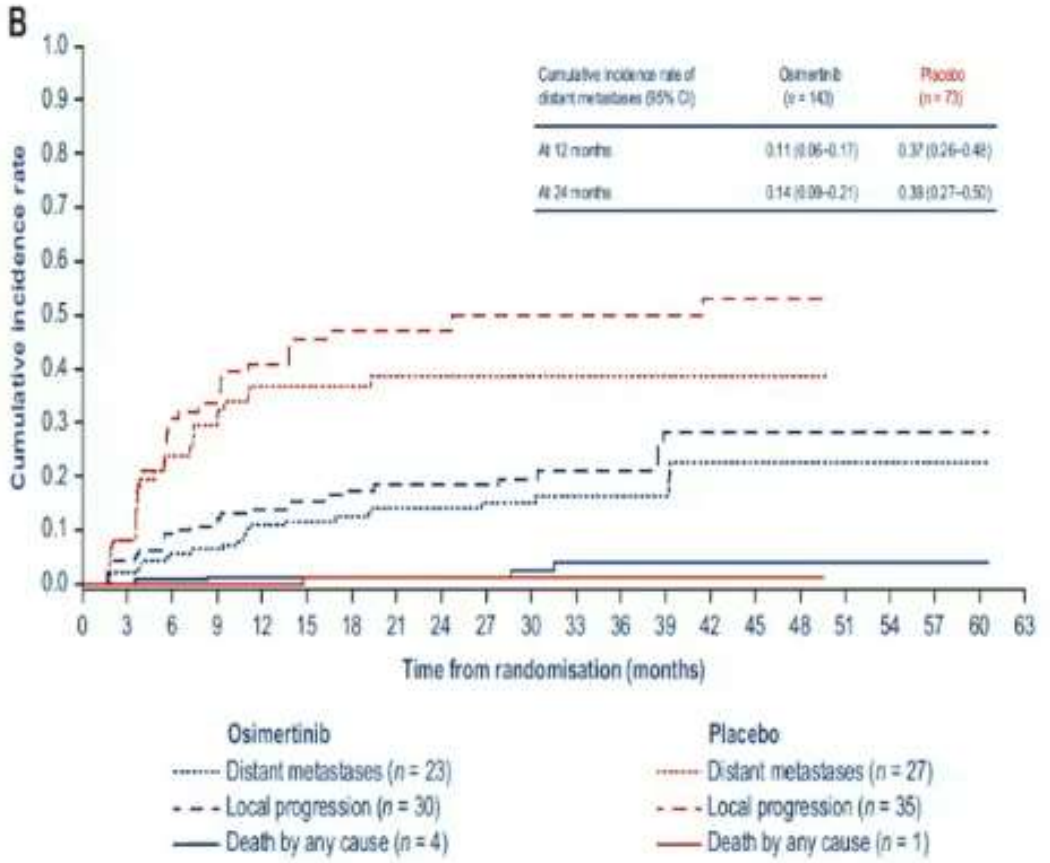
EGFR TKI CONSOLIDATION

LOCAL PROGRESSION

LAURA STUDY

Table 3. TTDM events by BICR, competing risk analysis (all randomised patients)

	Osimertinib (n = 143)	Placebo (n = 73)
Patients with an event, n (%)	57 (40)	63 (86)
Distant metastases[a]	23 (16)	27 (37)
Local progression[b]	30 (21)	35 (48)
Death in the absence of distant metastases or local progression	4 (3)	1 (1)
Censored patients, n (%)[c]	86 (60)	10 (14)



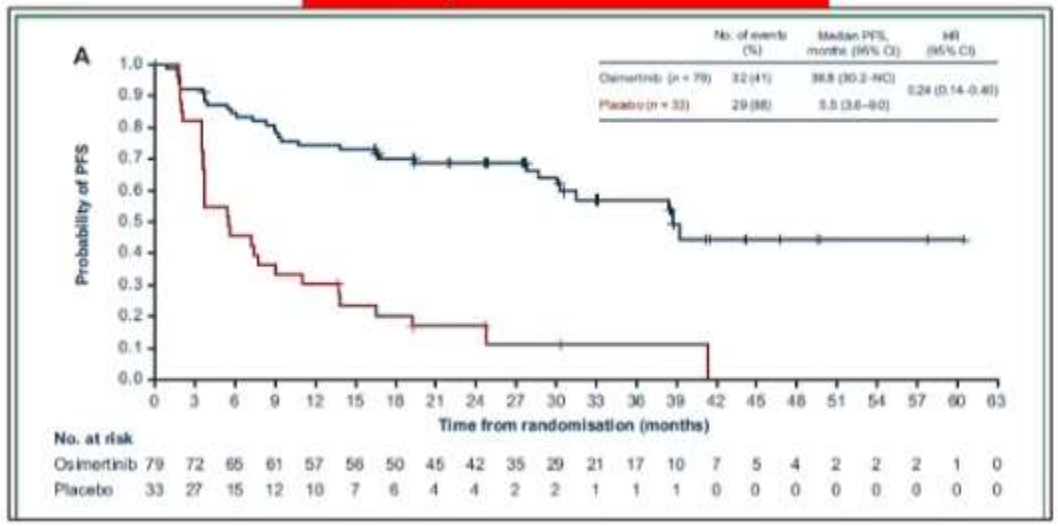
Lu et al. N Engl J Med 2024;391:585–597. Suresh S. Ramalingam ELCC 2025

EGFR TKI consolidation

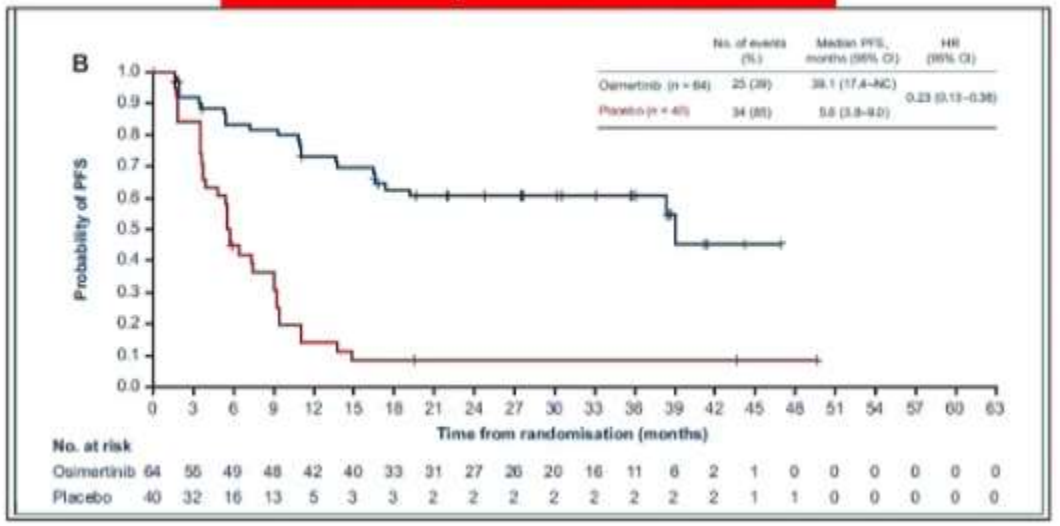
LAURA TRIAL

IMPORTANT ASPECTS AND OPEN QUESTIONS

WITH pre-CRT PET scan



WITHOUT pre-CRT PET scan



Difficult to know the TNM of study population (included after CRT)

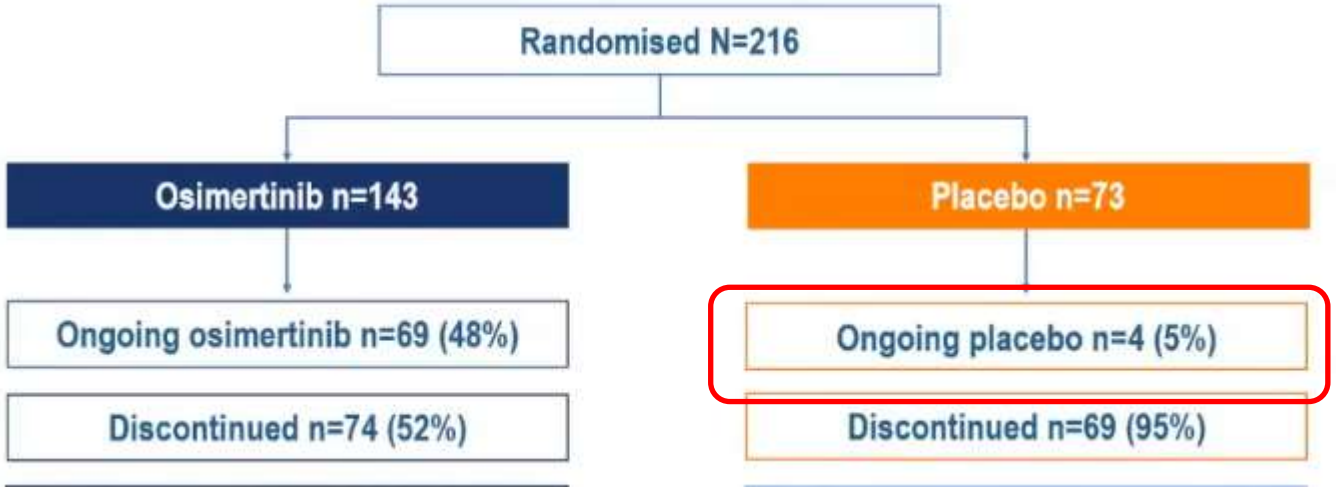
Lu et al. N Engl J Med 2024;391:585–597.

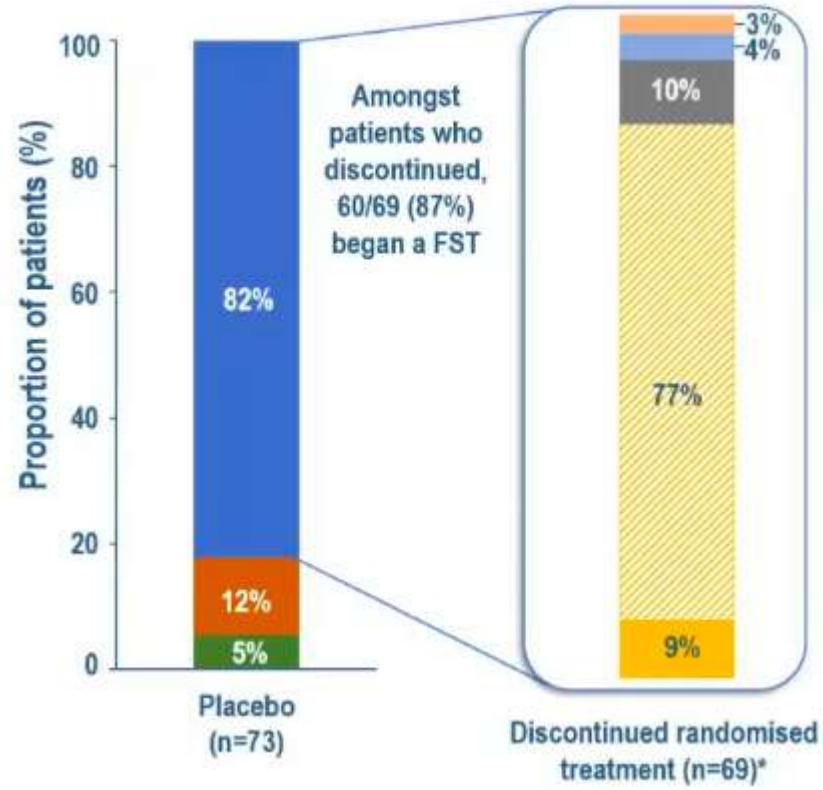
EGFR TKI consolidation

LAURA TRIAL

IMPORTANT ASPECTS AND OPEN QUESTIONS

In the CONTROL arm, only 5% pts ongoing. Does stage III really "exist" in EGFR?

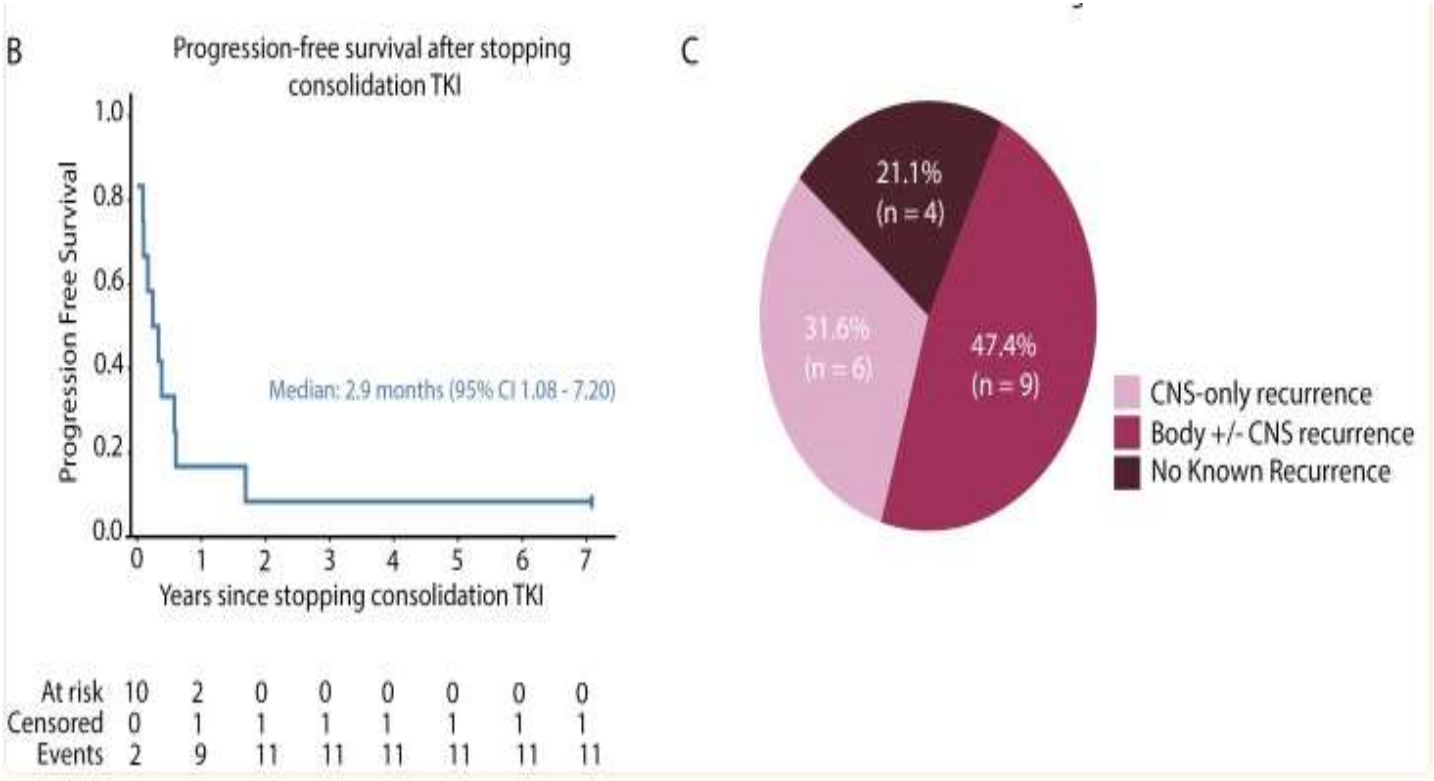


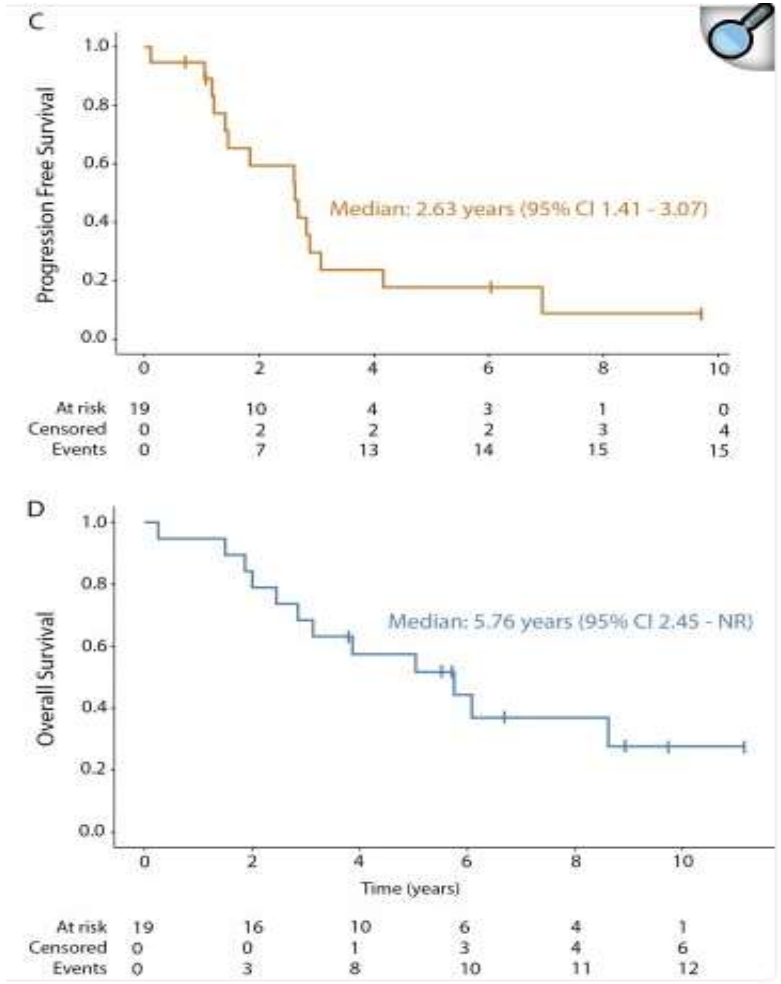


Suresh S. Ramalingam ELCC 2025

Unresectable stage III

Phase II ACENT trial

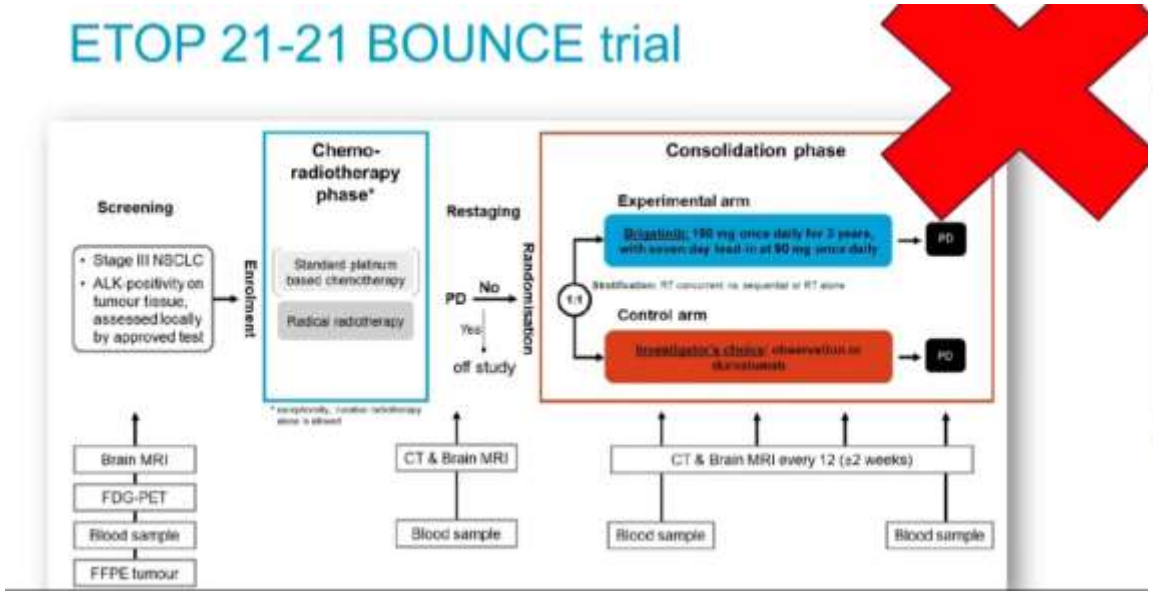




Chang, A. E. B. et al. Oncologist 29, 609–618 (2024).

UNRESECTABLE STAGE III: ALK+

BOUNCE



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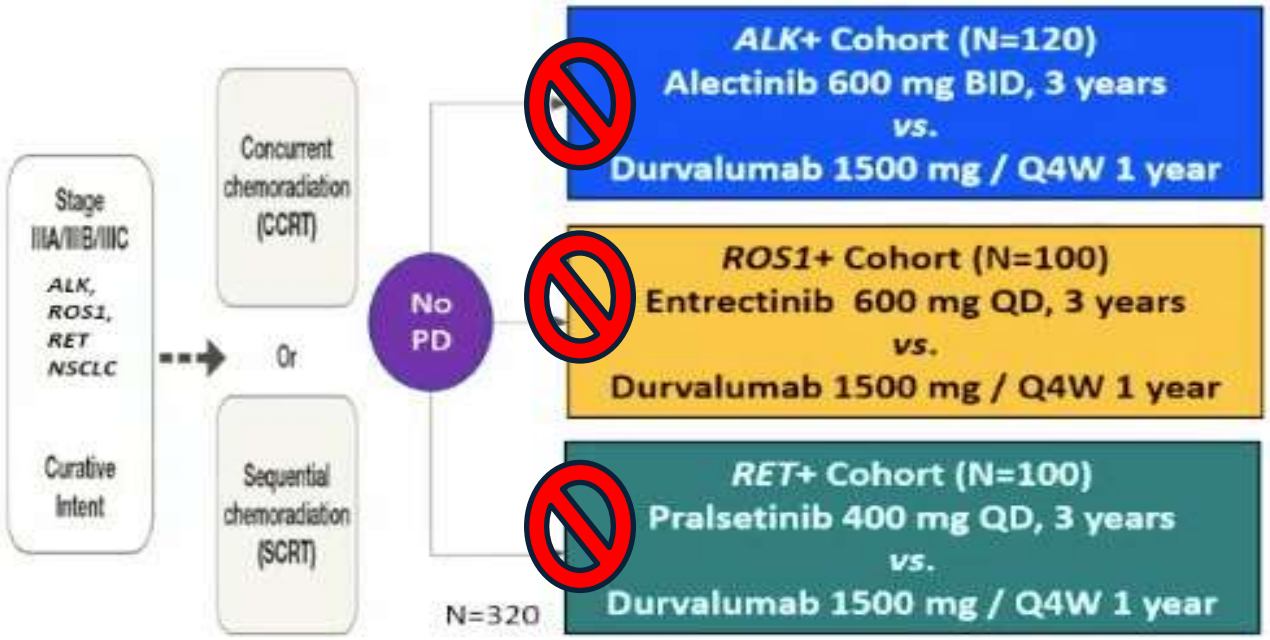
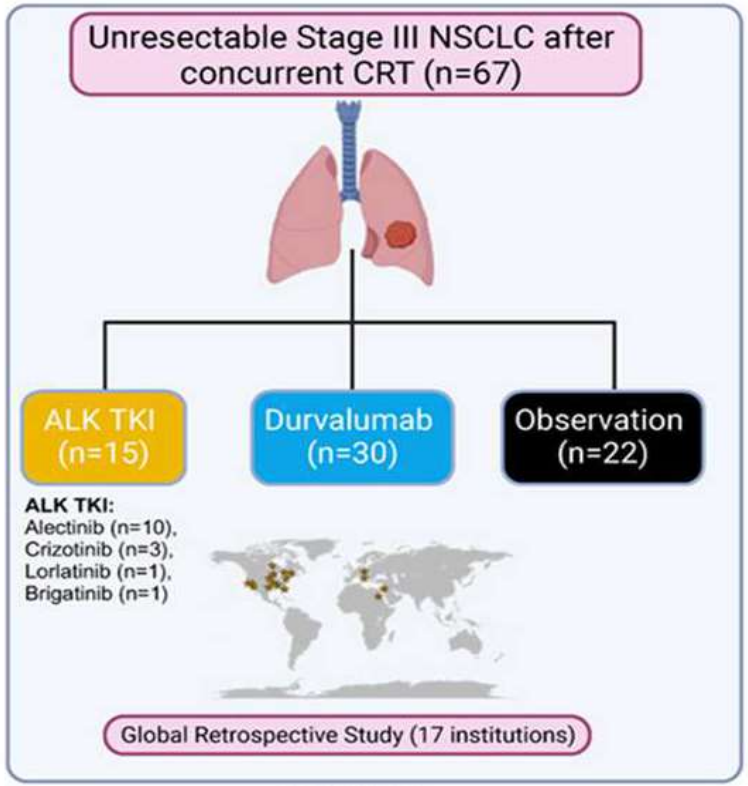


Primary Endpoint: PFS by BIRC

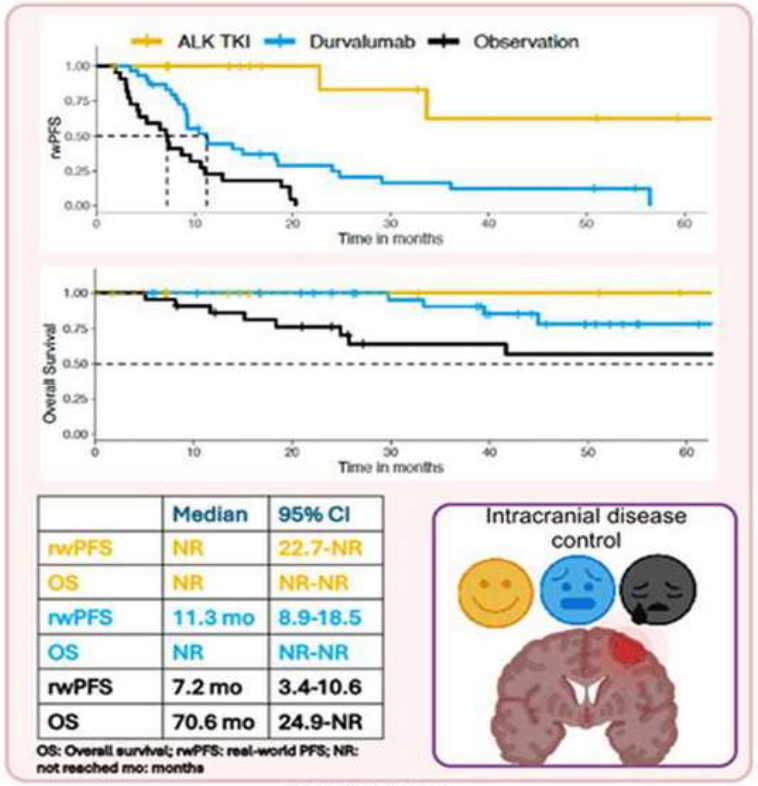
Secondary Endpoints: CNS PFS, Response Rate, OS, safety, and tolerability

UNRESECTABLE STAGE III

Consolidation ALK Tyrosine Kinase Inhibitors Versus Durvalumab or Observation After Chemoradiation in Unresectable Stage III ALK-Positive NSCLC

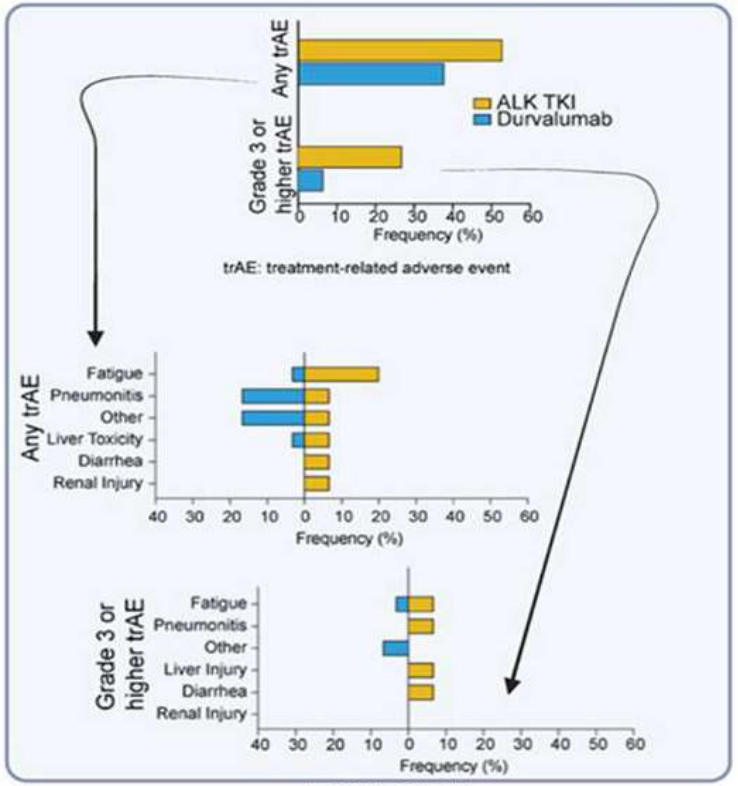


COHORT



	Median	95% CI
rwPFS	NR	22.7-NR
OS	NR	NR-NR
rwPFS	11.3 mo	8.9-18.5
OS	NR	NR-NR
rwPFS	7.2 mo	3.4-10.6
OS	70.6 mo	24.9-NR

SURVIVAL



TOXICITY

After adjusting for stage, age, and nodal status, median rwPFS was significantly longer for ALK TKI versus durvalumab or observation

Nassar et al. J Thor Oncol 2024

UNRESECTABLE STAGE III: KRAS G12C

SUNRAY 02

Part B

Stage III unresectable *KRAS* G12C mutant NSCLC
- No disease progression following concurrent platinum-based chemotherapy and radiation therapy

R 1:1

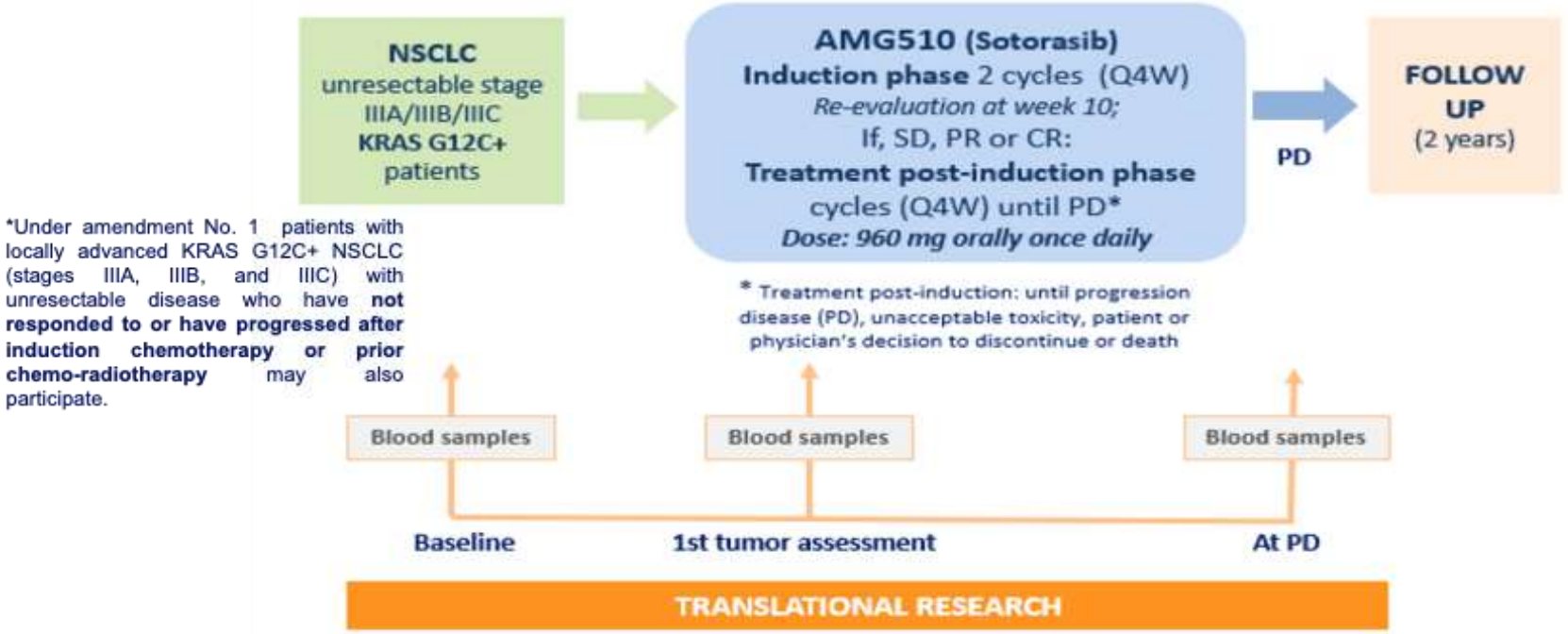
N ~ 300

- Olomorasib PO BID x 3 years + Durvalumab IV Q4W x 1 year
- Placebo PO BID x 3 years + Durvalumab IV Q4W x 1 year

Primary Endpoint: PFS

Abbreviations: BID = twice daily; IO = immune-oncology therapy; IV = intravenous; *KRAS* = *KRAS* oncogene; Q3W = every 3 weeks; Q4W = every 4 weeks

MERIT Lung



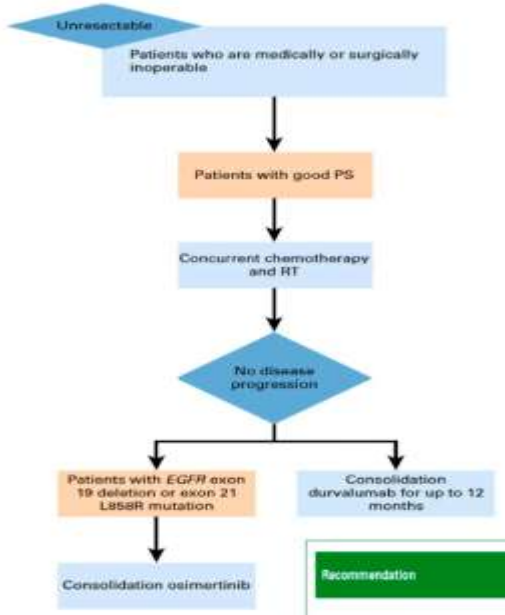
Nadal et al. J Thor Oncol 2025

GUIDELINES

How to treat with molecular targets

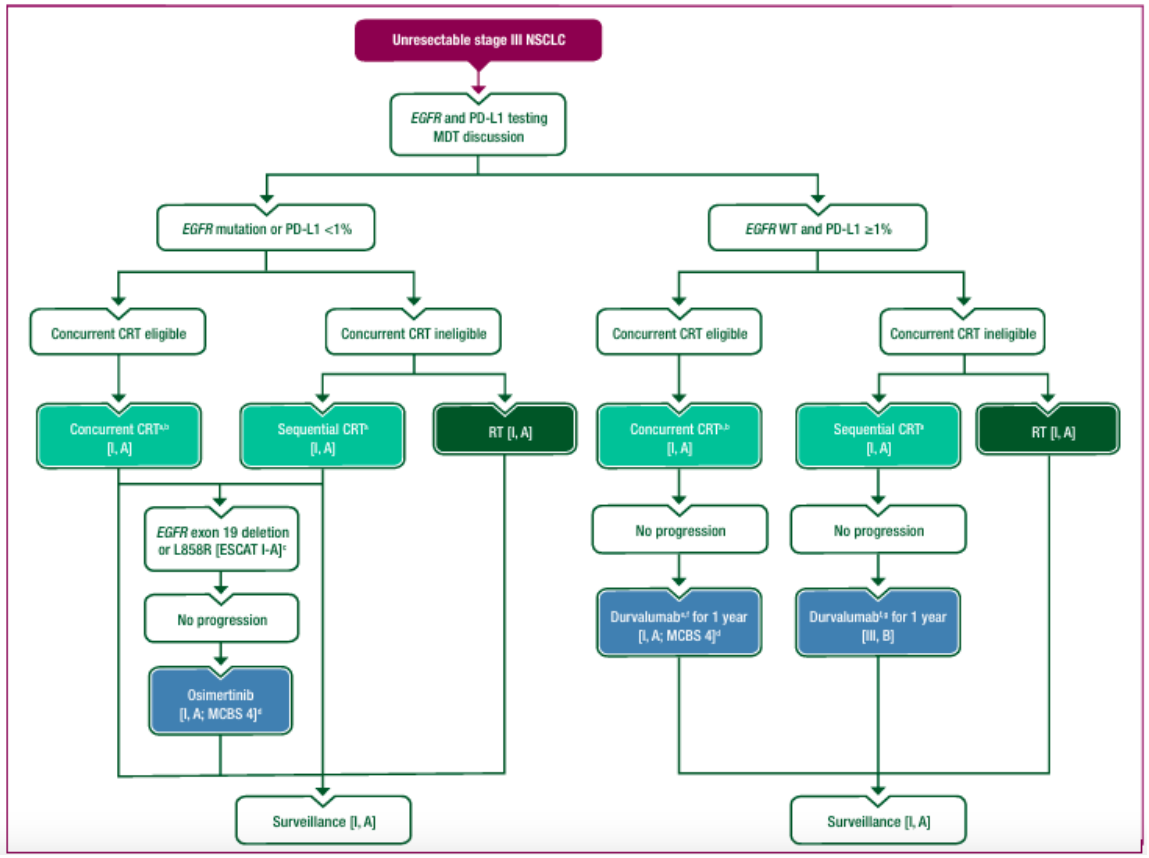
EGFR is the ONLY EXCEPTION

ASCO



Recommendation	Evidence Quality	Strength
5.8. Patients with unresectable stage III NSCLC with an *EGFR* exon 19 deletion or exon 21 L858R mutation may be offered consolidation osimertinib after definitive chemoradiotherapy (platinum-based chemotherapy and thoracic radiation given concurrently or sequentially).	M	S

ESMO



Shingh et al. J Clin Oncol 2024.
Zer et al. Ann Oncol 2025;36(11)

OPEN QUESTIONS AFTER LAURA RESULTS EGFR

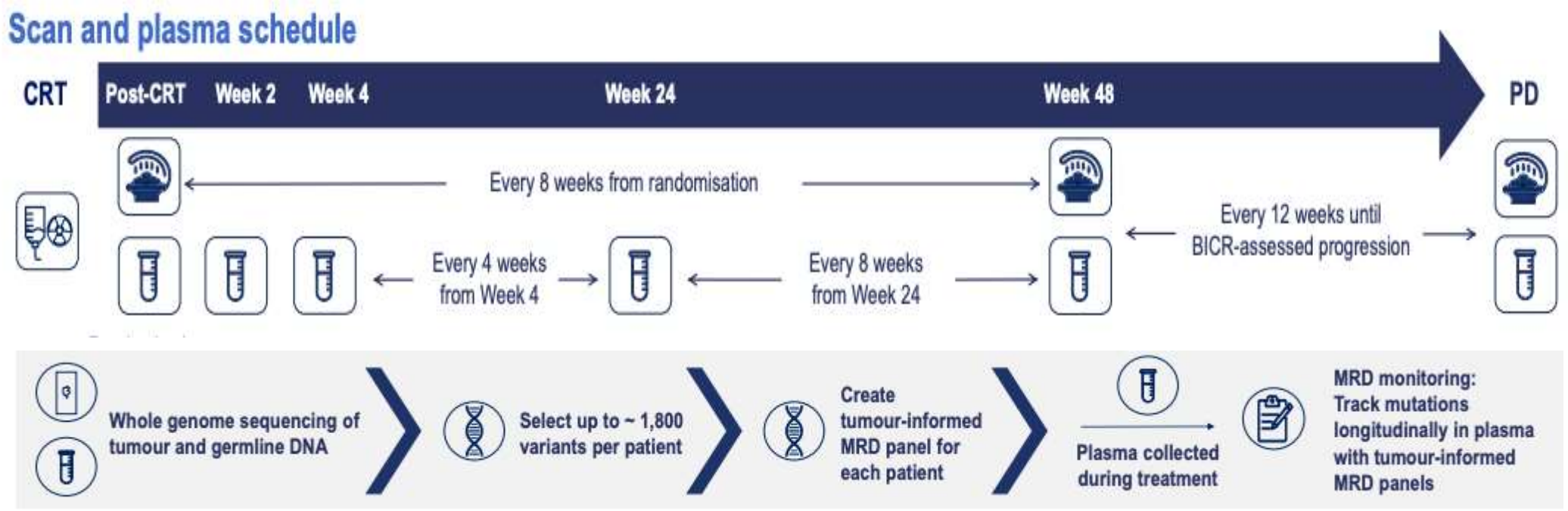
- **Is chemo-radiation therapy necessary in all patients with EGFRmut stage III NSCLC?**

  Local relapse is the most frequent PD

- **Is it necessary to continue osimertinib indefinitely?**

  Is CRT enough for some patient?

Molecular residual disease (MRD) analysis from the LAURA study

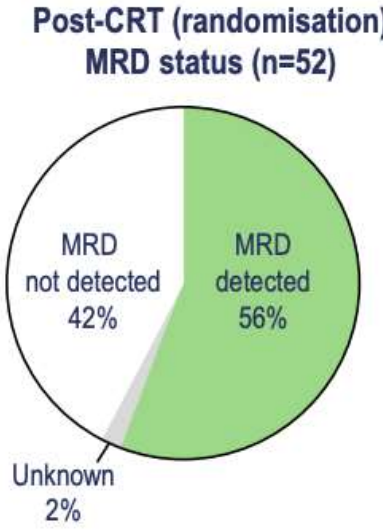


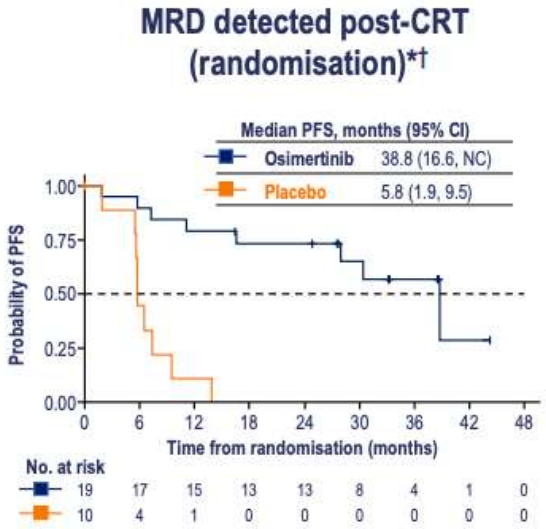
Clinical success rate: **54%**

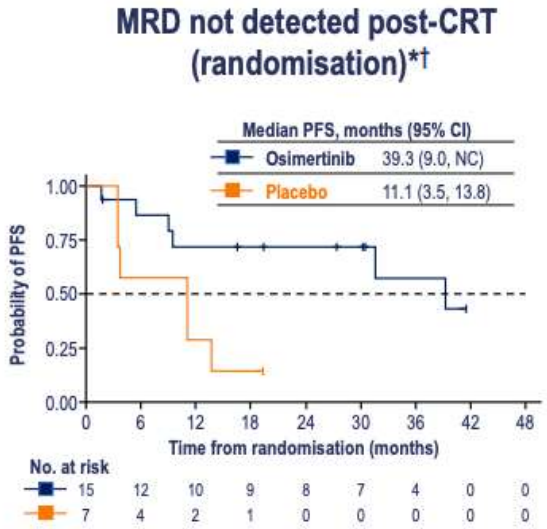
- **MRD clearance**: 10-fold ctDNA decrease from post-CRT (randomisation) levels or undetected MRD for 2 consecutive timepoints by Week 12
- **Molecular progression / MRD event:** 100% increase in ctDNA at a single time point or detected MRD above the LLOQ

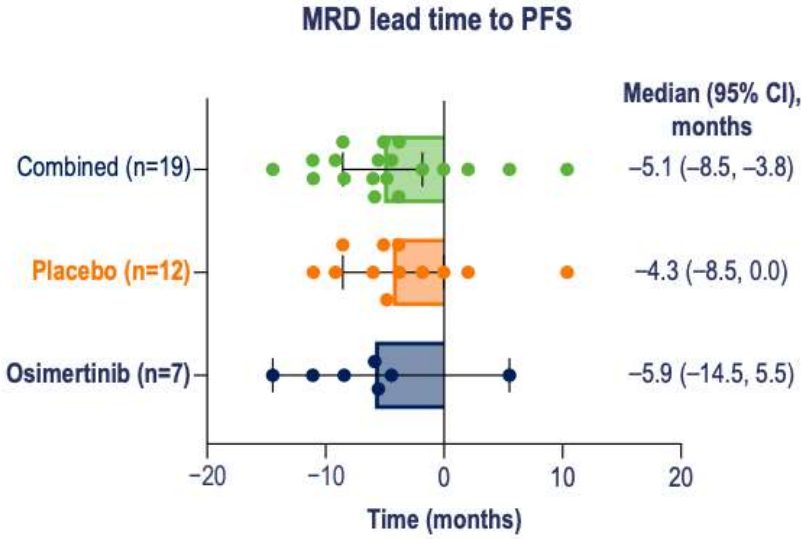
Arriola E et al. ESMO 2025

Molecular residual disease (MRD) analysis from the LAURA study









Concordance of MRD with PFS
SENSITIVITY 63%
SPECIFICITY 86%

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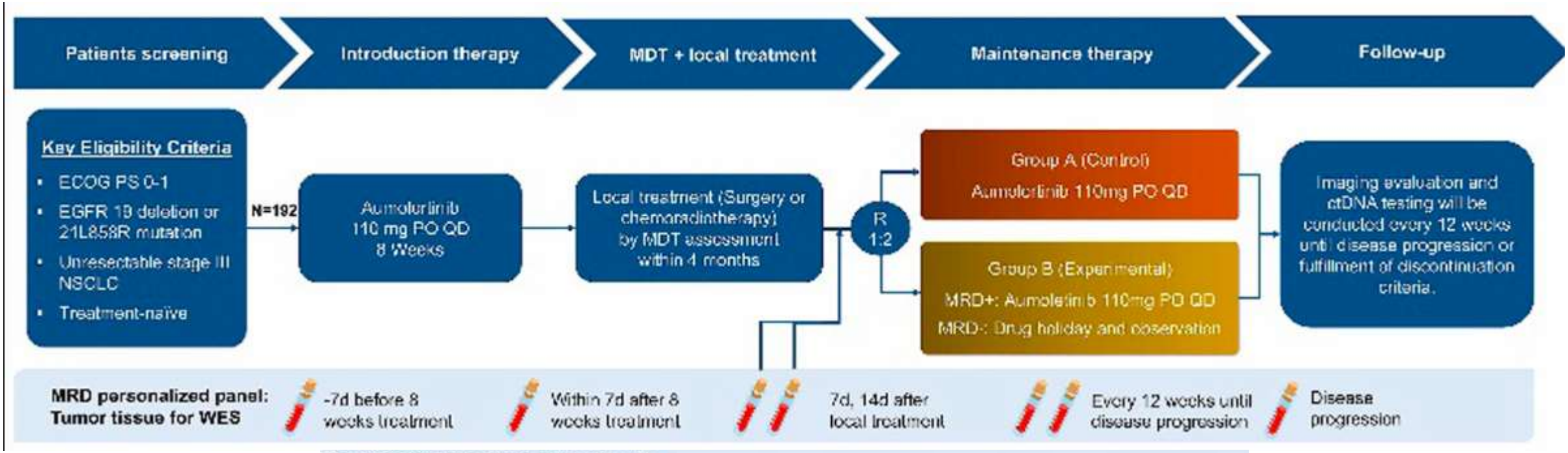
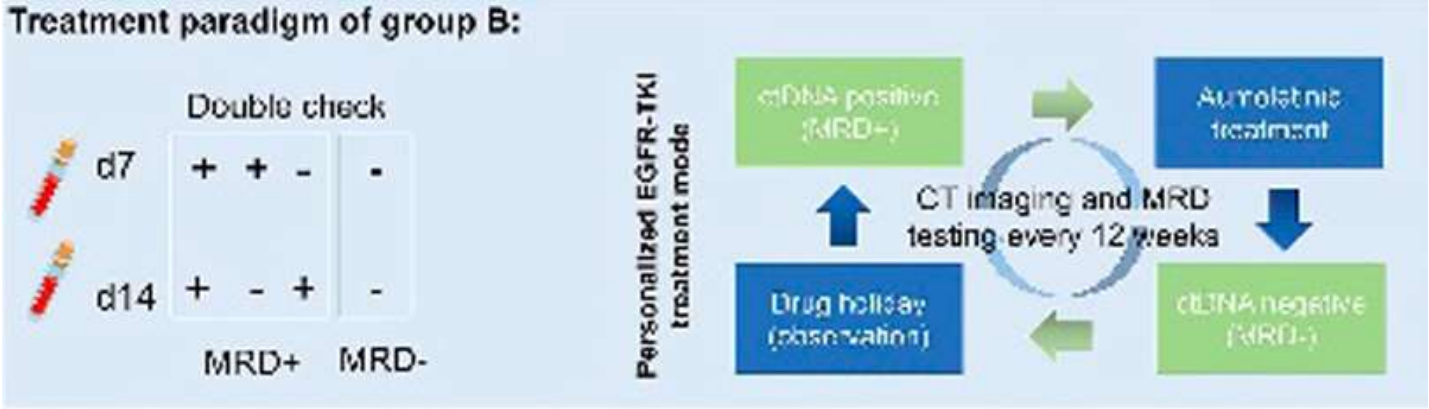
CURRENT CHALLENGES

APPROACH TRIAL





CONCLUSIONS

- Consolidation treatment with osimertinib after CRT improves PFS and reduces risk of brain metastases
- Lack of prognostic/predictive markers: role of MRD and adaptive ctDNA-guided strategies
- Resistance patterns for lifelong drugs after CRT
- Generate evidence on strategies in less frequent groups : ALK, ROS1, RET...

16th CONGRESS Lung ON CANCER

BARCELONA 27 / 28 NOVEMBER 2025

THANK YOU!

GECP lung cancer research