In resectable, early-stage ALK or EGFR-positive NSCLC, the induction TKIs should be standard of care? NO

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2025 ASCO ANNUAL MEETING

GOIRC
GRUPPO ONCOLOGICO ITALIANO DI RICERCA CLINICA

Alectinib as Neoadjuvant Treatment in Potentially Resectable Stage III ALK-positive NSCLC: Final Analysis of ALNEO Phase II Trial (GOIRC-01-2020-ML42316)

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PRESENTED BY: Marcello Tiseo, MD, PhD

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KNOWLEDGE CONQUERS CANCER

Why are induction TKIs attractive?

- Strong oncogenic dependence
- High response rates (in metastatic disease)
- Rapid tumor shrinkage
- Potential nodal downstaging
- Excellent tolerability
- Early eradication of micrometastatic disease

…But biological plausibility alone is not enough!!

What defines a standard of care?

- Phase III randomized evidence
- Superiority over existing strategies
- Overall survival benefit
- Reproducibility
- Surgical feasibility and safety
- Long-term follow-up

…data not all available for induction EGFR and ALK-TKIs

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EGFR and ALK-TKIs as induction Tx

Evidence in EGFR-mutated

- **EMERGING-CTONG1103:** Erlotinib vs CT: small study with improved PFS but no clear OS advantage
- **NeoAdaura trial:** data still immature; long-term cure impact unknown and OS benefit not yet demonstrated

We are still waiting for definitive evidence

Evidence in ALK-positive

- No randomized evidence
- **Only retrospective studies and several small trials** (n < 40 pts)
- No mature survival endpoints

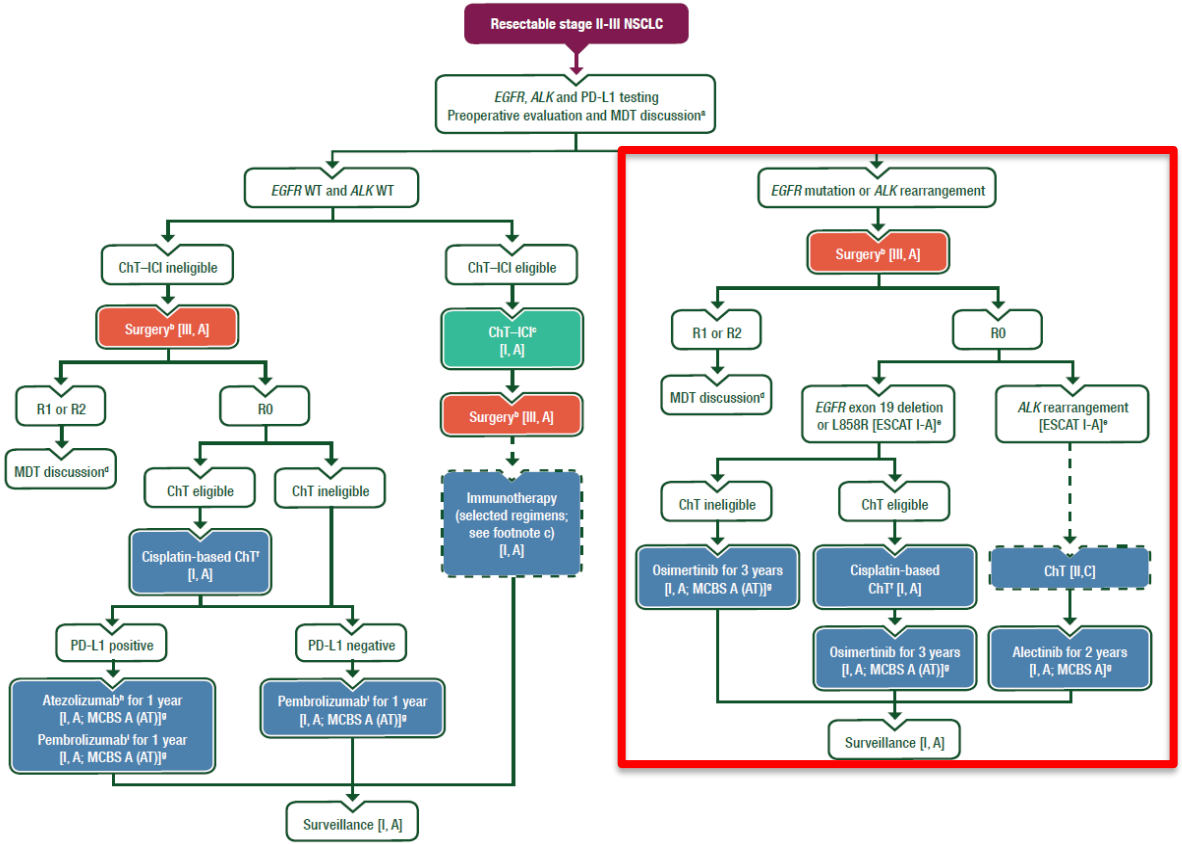
ALK neoadjuvant TKIs remain investigational

EGFR and ALK-TKIs as induction Tx: No, also because…

- **Pathological response is not enough**
- MPR and pCR are surrogate endpoints not fully validated in oncogene-addicted NSCLC
- A dramatic CT scan does not necessarily translate into long-term survival: **radiologic response ≠ cure**

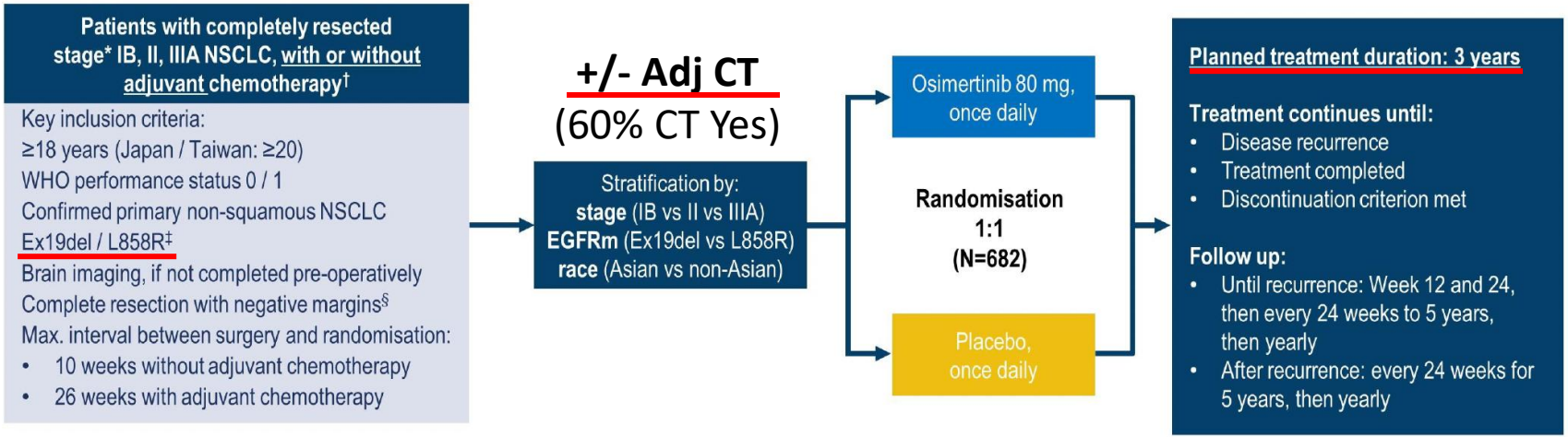
- Risk of delaying surgery
- **Emergence of resistant clones** and risk of disease progression during induction
- Surgical complexity and fibrosis (??)

Early and locally advanced NSCLC: ESMO Clinical Practice Guideline



Zer et al, Ann Oncol 2025

Adjuvant osimertinib: ADAURA trial



Endpoints

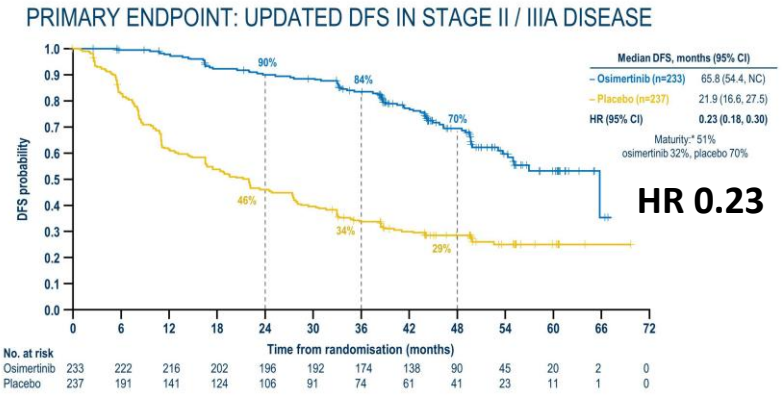
- **Primary endpoint:** DFS by investigator assessment in stage II / IIIA patients, designed for superiority under the assumed DFS HR of 0.70
- **Key secondary endpoints:** DFS in the overall population¶, DFS at 2, 3, 4, and 5 years, OS, safety, health-related quality of life
- **Pre-specified exploratory endpoints:** Patterns of recurrence, time to CNS disease recurrence or death (CNS DFS)

Neoadjuvant CT not permitted

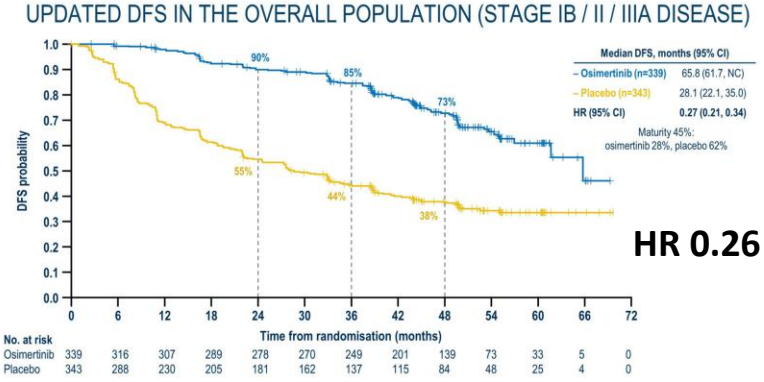
Wu YL et al, N Eng J Med 2020
Herbst R et al JCO 2023; Tsuboi M et al, NEJM 2023

Up-date trial ADAURA: DFS

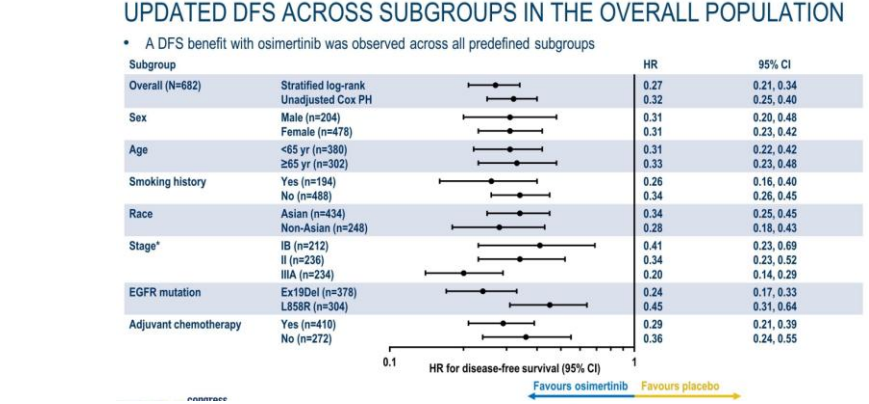
Median FU Osimertinib 44.2 months



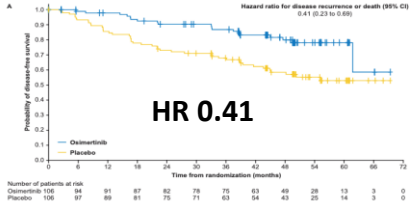
HR 0.23



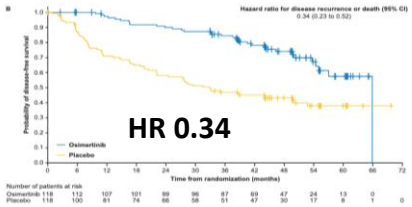
HR 0.26



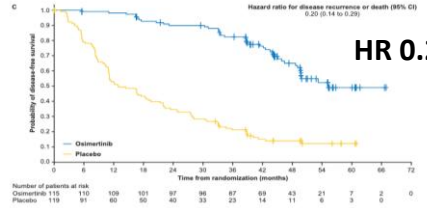
IB



II



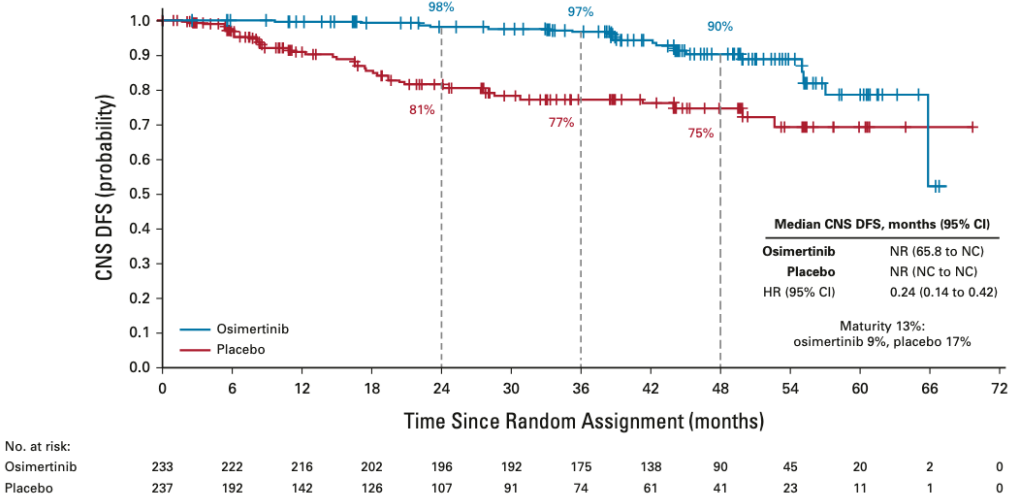
IIIA



Tsuboi M et al, ESMO 2022 and Herbst R et al, JCO 2023

ADAURA: CNS outcomes

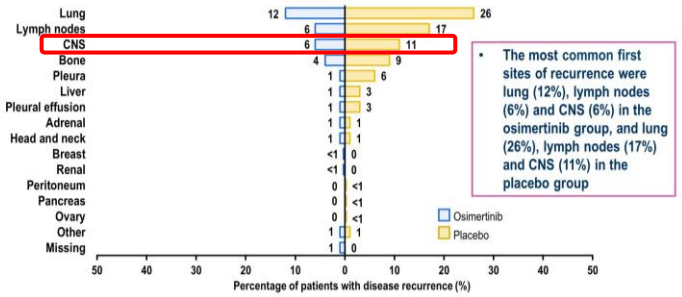
CNS DFS

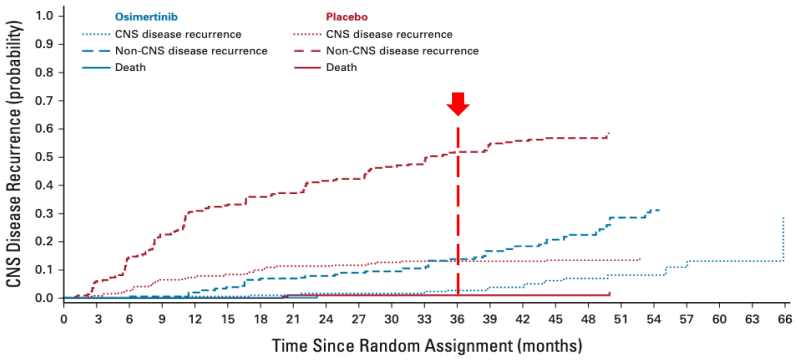


No. at risk:

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

CNS Risk of Recurrence





Tsuboi M et al, ESMO 2022 and Herbst R et al, J Clin Oncol 2023

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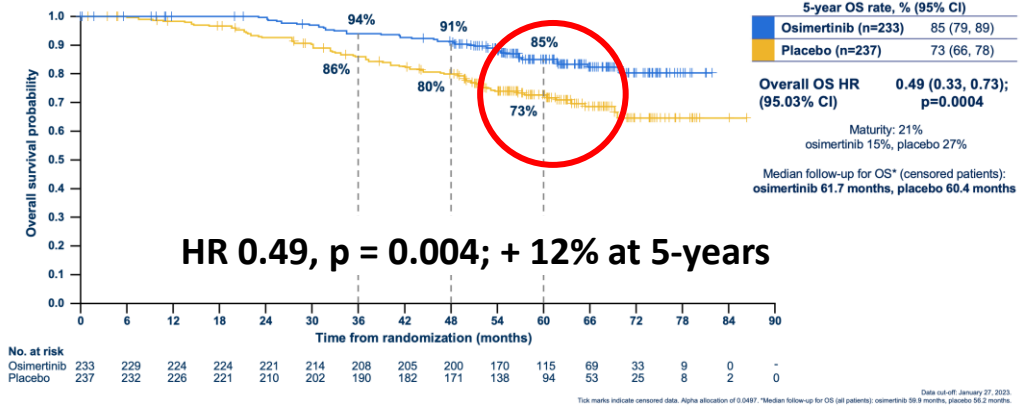
OS trial ADAURA

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



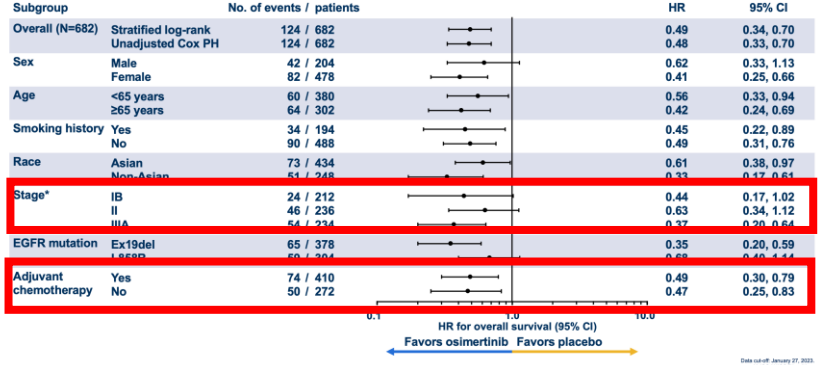
5-year OS rate, % (95% CI)	
Osimertinib (n=233)	85 (79, 89)
Placebo (n=237)	73 (66, 78)
Overall OS HR (95.03% CI)	0.49 (0.33, 0.73); p=0.0004

Maturity: 21%
osimertinib 15%, placebo 27%

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

HR 0.49, p = 0.004; + 12% at 5-years

OS across subgroups: patients with stage IB / II / IIIA disease

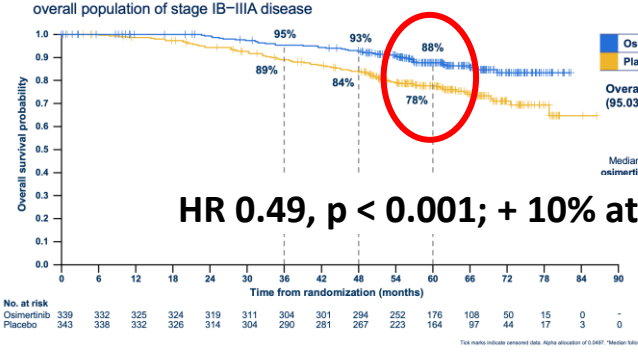


Subgroup		No. of events / patients	HR	95% CI
Overall (N=682)	Stratified log-rank	124 / 682	0.49	0.34, 0.70
	Unadjusted Cox PH	124 / 682	0.48	0.33, 0.70
Sex	Male	42 / 204	0.62	0.33, 1.13
	Female	82 / 478	0.41	0.25, 0.66
Age	<65 years	60 / 380	0.56	0.33, 0.94
	≥65 years	64 / 302	0.42	0.24, 0.69
Smoking history	Yes	34 / 194	0.45	0.22, 0.89
	No	90 / 488	0.49	0.31, 0.76
Race	Asian	73 / 434	0.61	0.38, 0.97
	Non-Asian	51 / 248	0.33	0.17, 0.61
Stage*	IB	24 / 212	0.44	0.17, 1.02
	II	46 / 236	0.63	0.34, 1.12
	IIIA	54 / 234	0.37	0.20, 0.64
EGFR mutation	Ex19del	65 / 378	0.35	0.20, 0.59
	L858R	50 / 304	0.68	0.40, 1.14
Adjuvant chemotherapy	Yes	74 / 410	0.49	0.30, 0.79
	No	50 / 272	0.47	0.25, 0.83

Data cut-off: January 27, 2023.
*ADCI / UICC 7th edition.

Overall survival: patients with stage IB / II / IIIA disease

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



5-year OS rate, % (95% CI)	
Osimertinib (n=339)	88 (83, 91)
Placebo (n=343)	78 (73, 82)
Overall OS HR (95.03% CI)	0.49 (0.34, 0.70); p<0.0001

Maturity: 18%
osimertinib 12%, placebo 24%

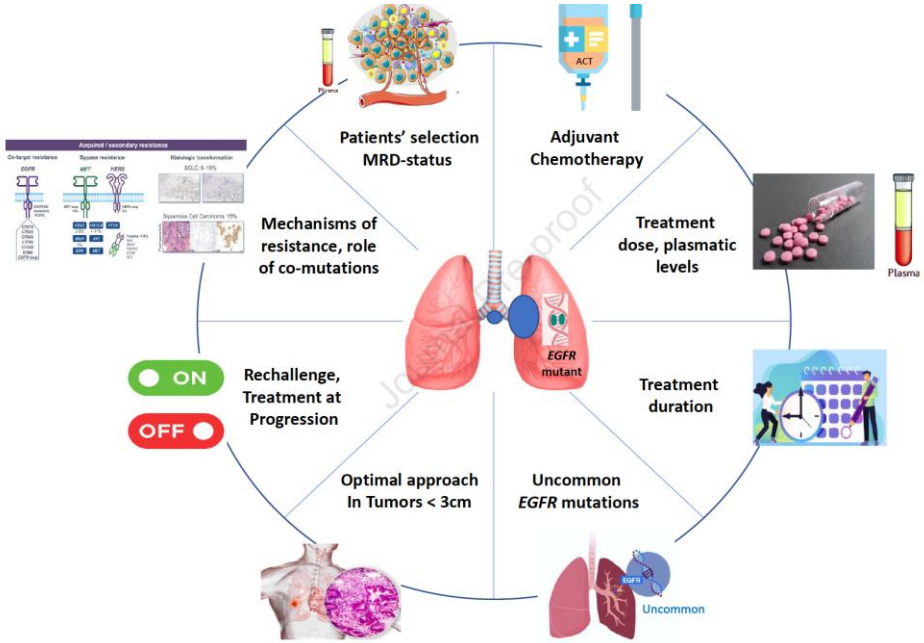
Median follow-up for OS* (censored patients):
osimertinib 61.5 months, placebo 61.5 months

HR 0.49, p < 0.001; + 10% at 5-years

Herbst R et al, ASCO 2023 and Tsuboi M et al, NEJM 2023

Unresolved Issues Regarding Adjuvant Osimertinib

- Should all early-stage cases be treated?
- Adjuvant CT?
- Adjuvant RT?
- Duration of treatment?
- Rare mutations?
- Mechanisms of resistance?
- Treatment for relapse?
- MRD?



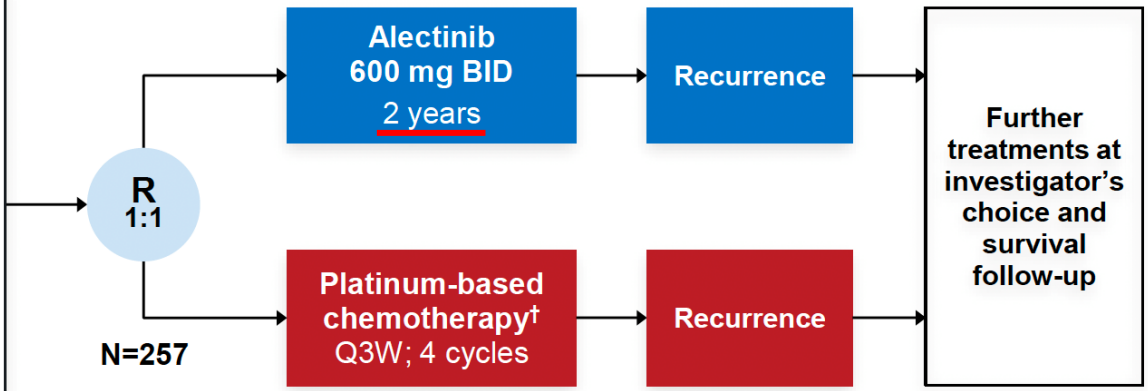
Remon et al, JTO 2023

ALINA: adjuvant alectinib in ALK+

Resected Stage IB (≥4cm)–IIIA *ALK*+ NSCLC
per UICC/AJCC 7th edition

Other key eligibility criteria:
- ECOG PS 0–1
- Eligible to receive platinum-based chemotherapy
- Adequate end-organ function
- No prior systemic cancer therapy

Stratification factors:
- Stage: IB (≥ 4cm) vs II vs IIIA
- Race: Asian vs non-Asian



Primary endpoint
- DFS per investigator,‡ tested hierarchically:
  - Stage II–IIIA → ITT (Stage IB–IIIA)

Other endpoints
- CNS disease-free survival
- OS
- Safety

Disease assessments (including brain MRI)§ were conducted: at baseline, every 12 weeks for year 1–2, every 24 weeks for year 3–5, then annually

Solomon BJ et al, ESMO 2023 and Wu YL et al, NEJM 2024

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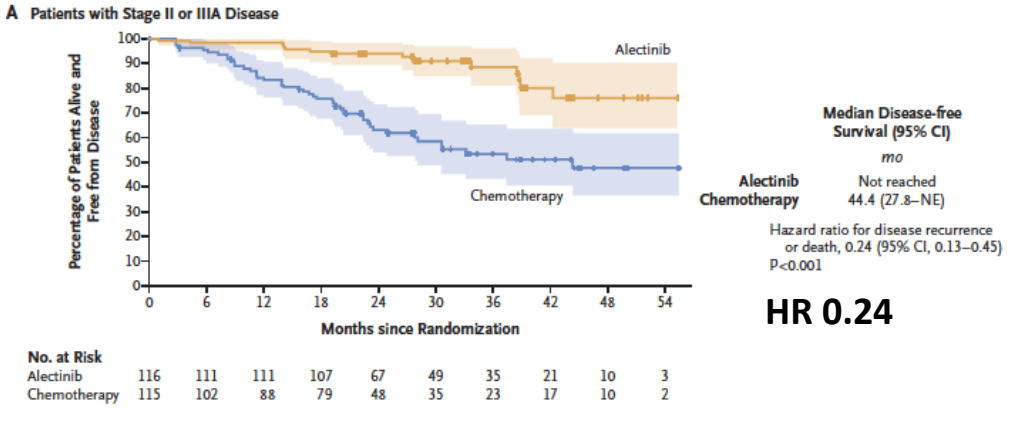
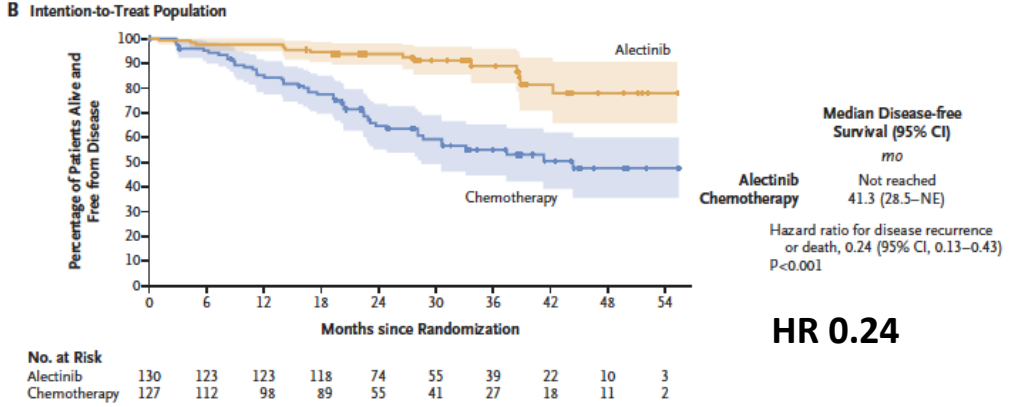
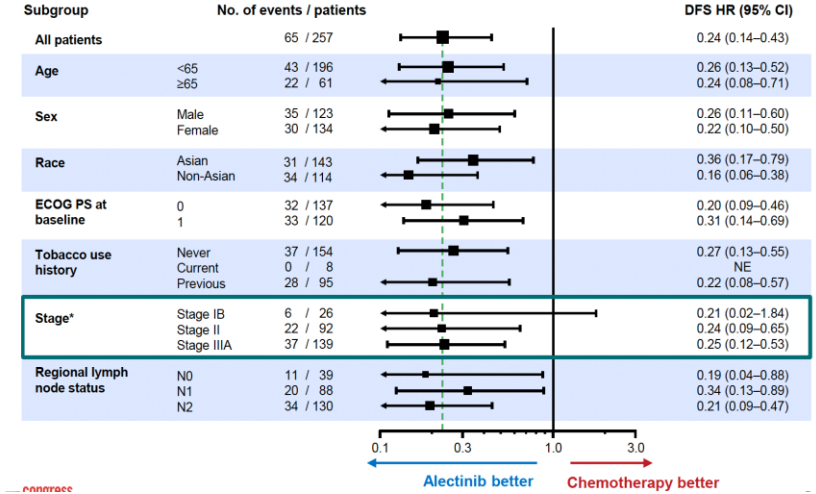
Adjuvant Alectinib in ALK +: ALINA trial







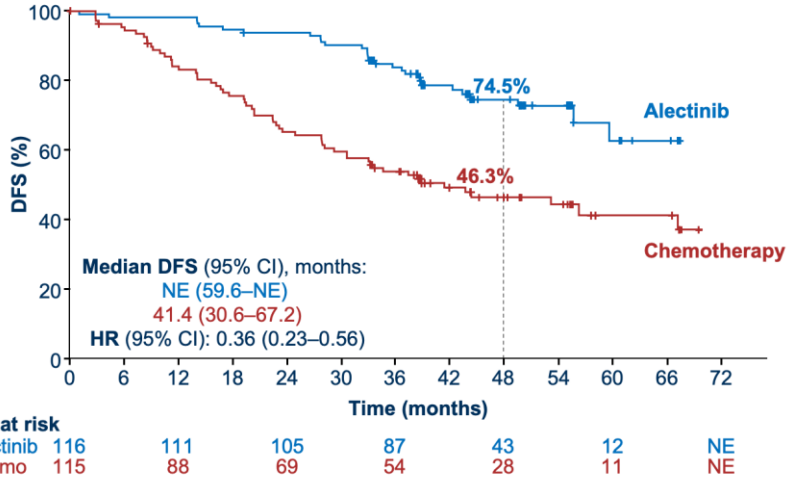
2-year DFS rate, % (95% CI)	Stage IB (n=26)	Stage II (n=92)	Stage IIIA (n=139)
Alectinib	92.3 (77.8, 100.0)	95.6 (89.5, 100.0)	92.7 (86.4, 98.9)
Chemotherapy	71.6 (44.2, 99.0)	66.3 (51.7, 81.0)	60.7 (47.9, 73.5)
HR† (95% CI)	0.21 (0.02, 1.84)	0.24 (0.09, 0.65)	0.25 (0.12, 0.53)

Solomon BJ et al, ESMO 2023 and Wu YL et al, NEJM 2024

Resected ALK + NSCLC – ALINA trial, up-dated analysis

- updated data with a median follow-up of 4 years
- All patients in the alectinib arm had completed 2 years of treatment with ≥ 1 year of follow-up

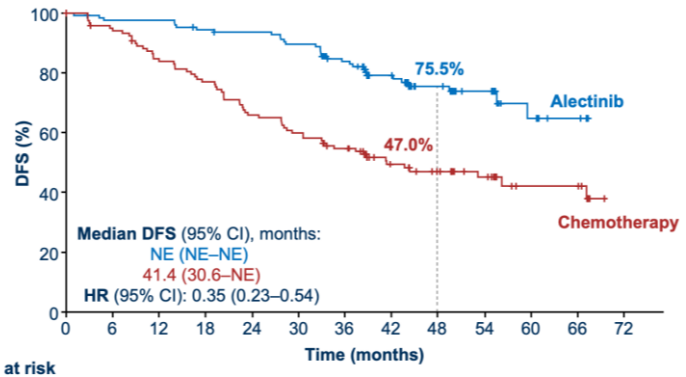
DFS in stage II–IIIA*



No. at risk							
Alectinib	116	111	105	87	43	12	NE
Chemo	115	88	69	54	28	11	NE

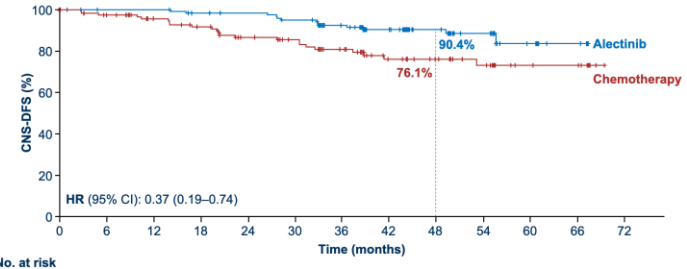
Positive trend in OS; HR 0.40 (95%CI 0.12–1.32)

DFS in stage IB–IIIA (ITT)*



No. at risk							
Alectinib	130	123	116	97	48	13	NE
Chemo	127	98	77	61	33	12	NE

CNS disease-free survival (ITT)



No. at risk							
Alectinib	130	124	117	98	49	13	NE
Chemo	127	99	80	61	33	13	NE

Median follow-up (ITT): alectinib, 48.0 months; chemotherapy, 47.4 months

Marcello Tiseo, MD, PhD; University Hospital of Parma, Italy

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Dziadziuszko et al, ESMO 2025

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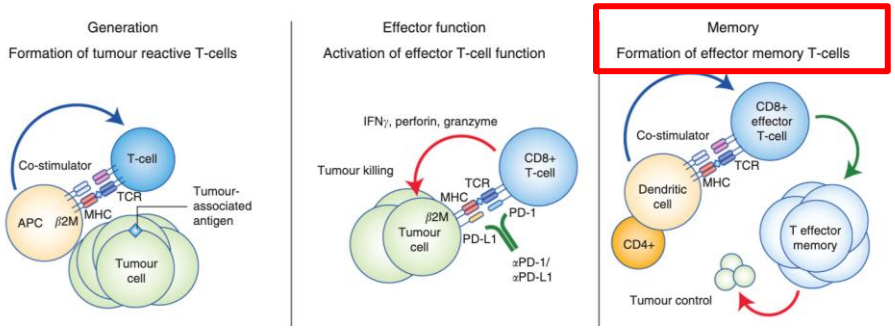
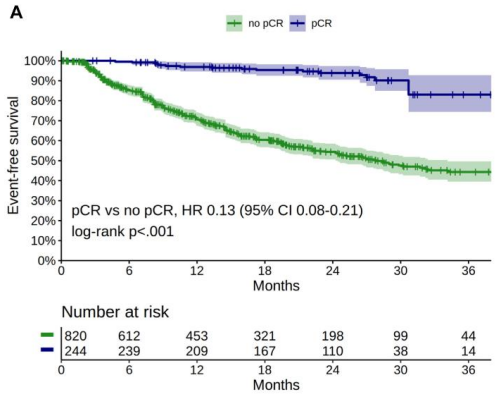
Neoadjuvant Tx
in oncogene *vs* non-oncogene: same aim?

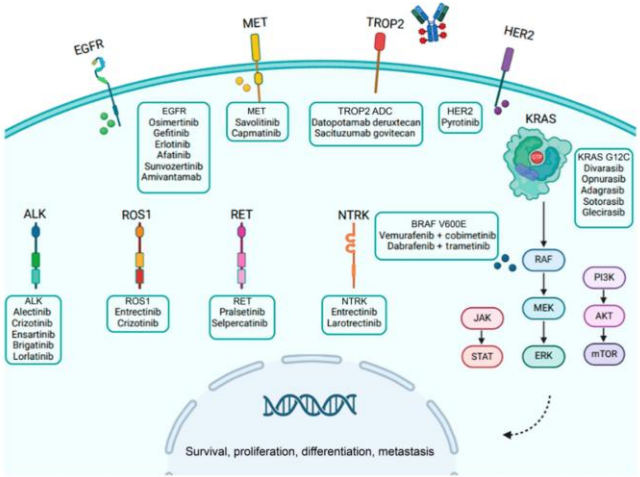
CT-IO





vs

TKIs



MPR: 30-60%
pCR: 18-25%

MPR: 15-40%
pCR: 0-10%

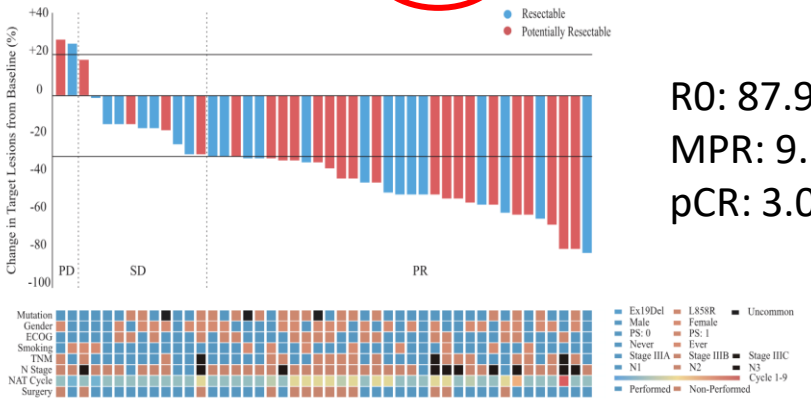
Jentkins RW et al, BJC 2018; Marinelli D et al, JTO 2025; Voruganti T et al, JCO 2025

Could TKI convert unresectable to resectable?

TEAM-LungMate 004

Neoadj <u>afatinib</u> in stage III EGFRmut
(resectable + potentially resectable)

ORR: 70.2%
Conversion rate: 56%

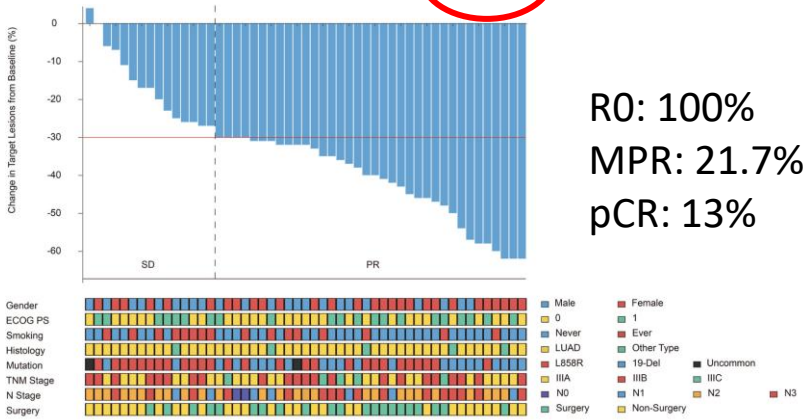


R0: 87.9%
MPR: 9.1%
pCR: 3.0%

LungMate 007

Neoadj <u>aumolertinib</u> in stage III EGFRmut
(unresectable)

ORR: 70.6%
Conversion rate: 45.1%

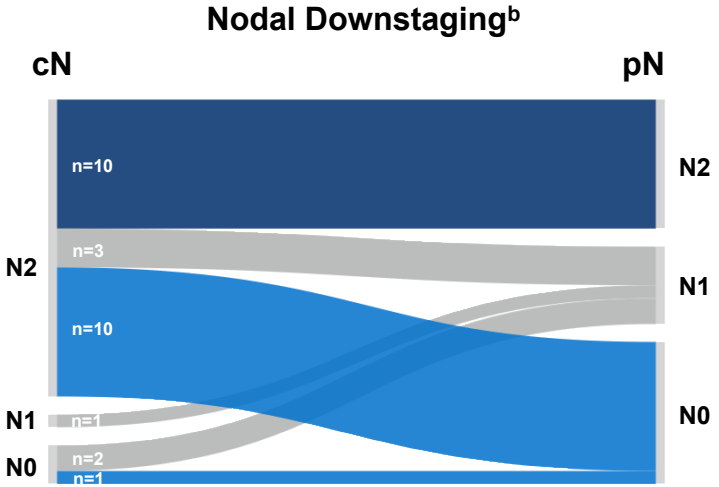


R0: 100%
MPR: 21.7%
pCR: 13%

Bian D et al, Nat Commun 2023; Bian D et al, Nat Commun 2025

ALNEO and NAUTIKA1 trials: Surgery and N Downstaging

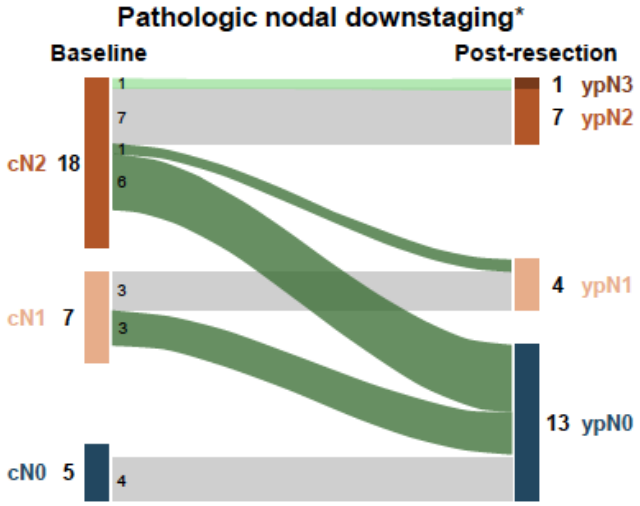
ALNEO trial



- **13/27 (48%) assessable pts had nodal downstaging**
- **R0 surgery: 86%** (24/28)
- Type of surgery: lobectomy in 64% (21/28)
- mfollow-up of 26.8 months, mEFS, DFS and OS were not reached

Tiseo et al, ASCO 2025

NAUTIKA1 trial



- **10/30 (33%) pts had nodal downstaging**
- **R0 surgery: 92.6%** (25/27)

Lee et al, WCLC 2025

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Conclusions

- Neoadjuvant TKIs are promising in oncogene-driven NSCLC
- However, current evidence remains insufficient to support induction TKIs as standard of care in resectable EGFR- or ALK-positive NSCLC
- Strong biology does not equal established standard
- **Adjuvant osimertinib and alectinib are already validated and represent standard of care in resectable EGFR- or ALK-positive NSCLC**
- Today, neoadjuvant TKIs use should preferably remain within clinical trials or carefully selected multidisciplinary settings
- **Neoadjuvant TKIs are promising — but not yet ready for prime time**

In resectable, early-stage ALK or EGFR-positive NSCLC, the induction TKIs should be standard of care?

NOT YET

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Grazie per l'attenzione

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