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Early Stage NSCLC – EGFR Mutant NSCLC

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Clinical Scenario

55-year-old female with a 20 pack-year smoking history underwent a low dose screening CT chest that showed a concerning RLL mass

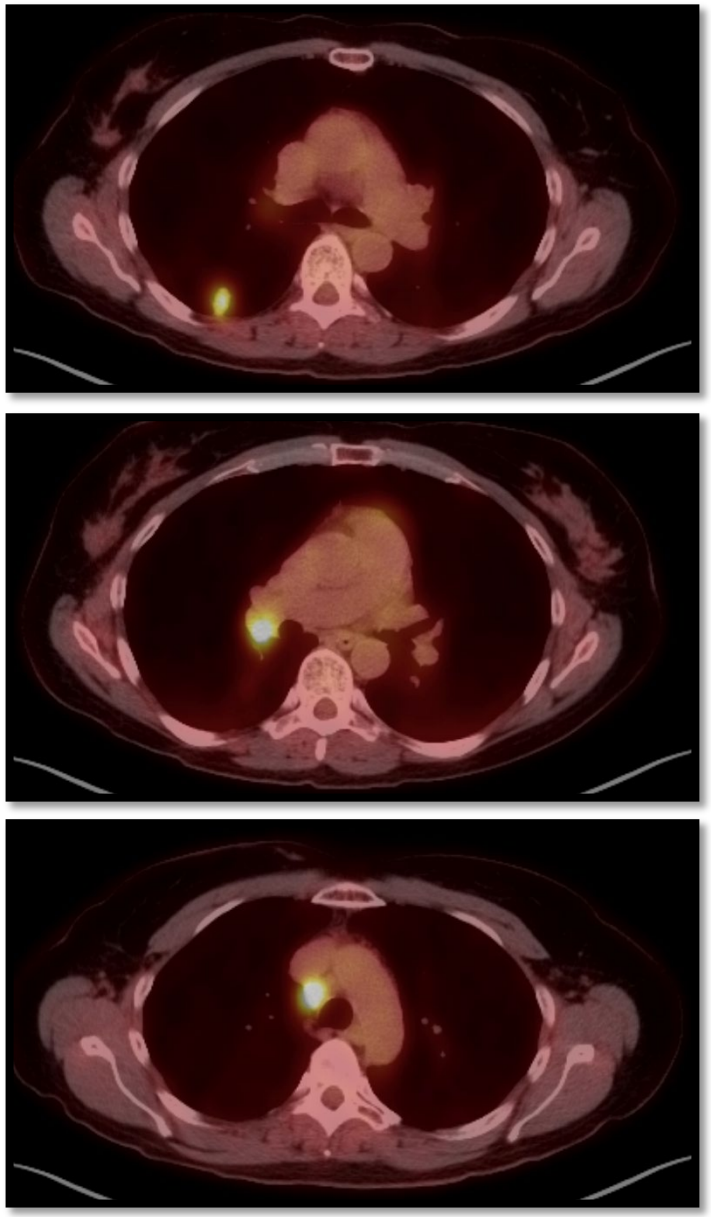
March 2025: CT chest showed a RLL mass measuring 2.3 x 1.6 cm

April 2025: PET/CT confirmed avidity in RLL, along with right hilar and paratracheal LN, MRI Brain Negative

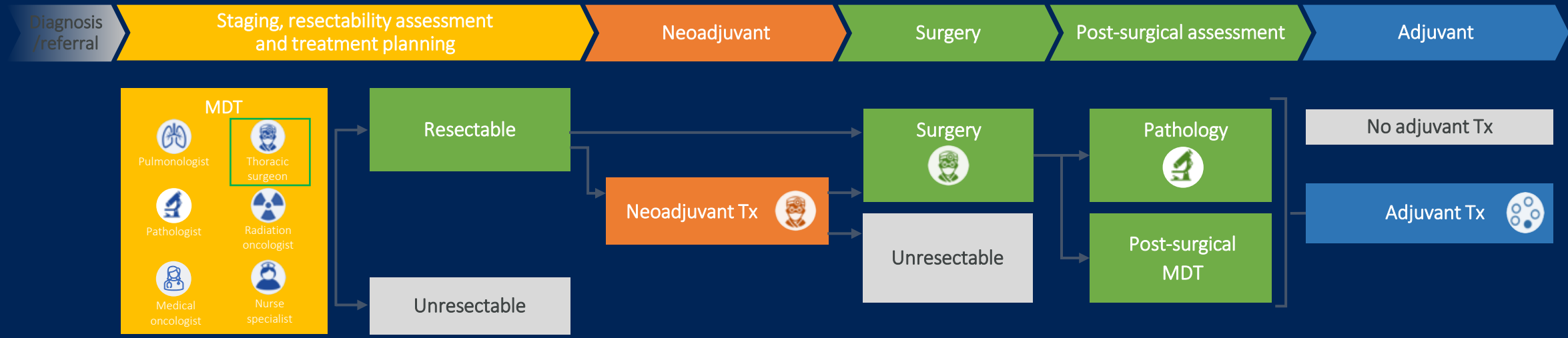
April 2025: Bronchoscopy confirmed metastatic adenocarcinoma in 4R, 10R, 11R Lymph Nodes. Level 4L, 11L, and 7 nodes were negative

Controlled hypertension, hyperlipidemia, COPD, osteoarthritis, PS 1

FEV1 1.2, normal exercise, cardiac, marrow/organ function



Management of Early-Stage NSCLC is Complex!

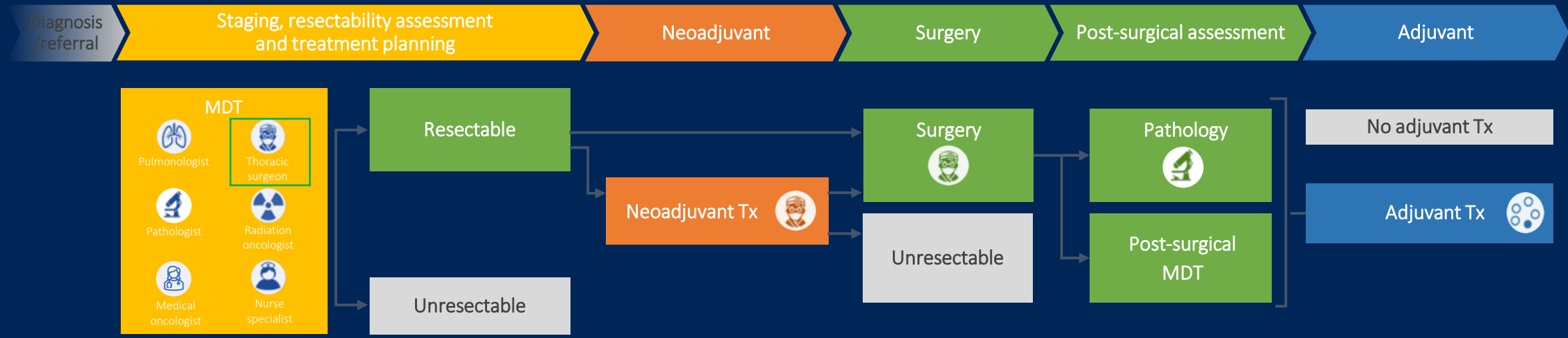


Current Approvals in Early-Stage NSCLC

Setting	Trial	Therapy	FDA Approval Date	Indication
Adjuvant	**IMpower010**[1]	Atezolizumab	October 15, 2021	Stage II–IIIA NSCLC with PD-L1 ≥1%, post-surgery and platinum-based chemotherapy
Adjuvant	**PEARLS/KEYNOTE-091**[2]	Pembrolizumab	January 26, 2023	Stage IB (≥4 cm), II, or IIIA NSCLC, post-surgery
Adjuvant	**ADAURA**[3]	Osimertinib	December 18, 2020	Stage IB–IIIA NSCLC post-surgery with **EGFR exon 19 deletions or exon 21 L858R**
Adjuvant	**ALINA**[4]	Alectinib	April 18, 2024	Resected stage IB (tumors >4 cm), II, or IIIA **ALK-positive** NSCLC
Neoadjuvant	**CheckMate 816**[5]	Nivolumab + Chemotherapy	March 4, 2022	Resectable NSCLC (tumors ≥4 cm or node-positive), pre-surgery
Perioperative	**KEYNOTE-671**[6]	Pembrolizumab + Chemotherapy	October 16, 2023	Resectable stage II–IIIB NSCLC, neoadjuvant and adjuvant treatment
Perioperative	**AEGEAN**[7]	Durvalumab + Chemotherapy	August 15, 2024	Resectable NSCLC (tumors ≥4 cm and/or node-positive) **without EGFR/ALK alterations**
Perioperative	**CheckMate 77T**[8]	Nivolumab + Chemotherapy	October 3, 2024	Resectable NSCLC (tumors ≥4 cm and/or node-positive) **without EGFR/ALK alterations**

Felip E et al Lancet 2021, O'Brien M, Lancet 2021, Tsuboi M et al NEJM 2023, Wu YL et al NEJM 2024,
Forde PM et al NEJM 2022, Wakelee H et al NEJM 2023, Heymach J et al NEJM 2023, Cascone T et al NEJM 2024

Management of Early-Stage NSCLC is Complex!



National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2025
Non-Small Cell Lung Cancer

NCCN Guidelines Index
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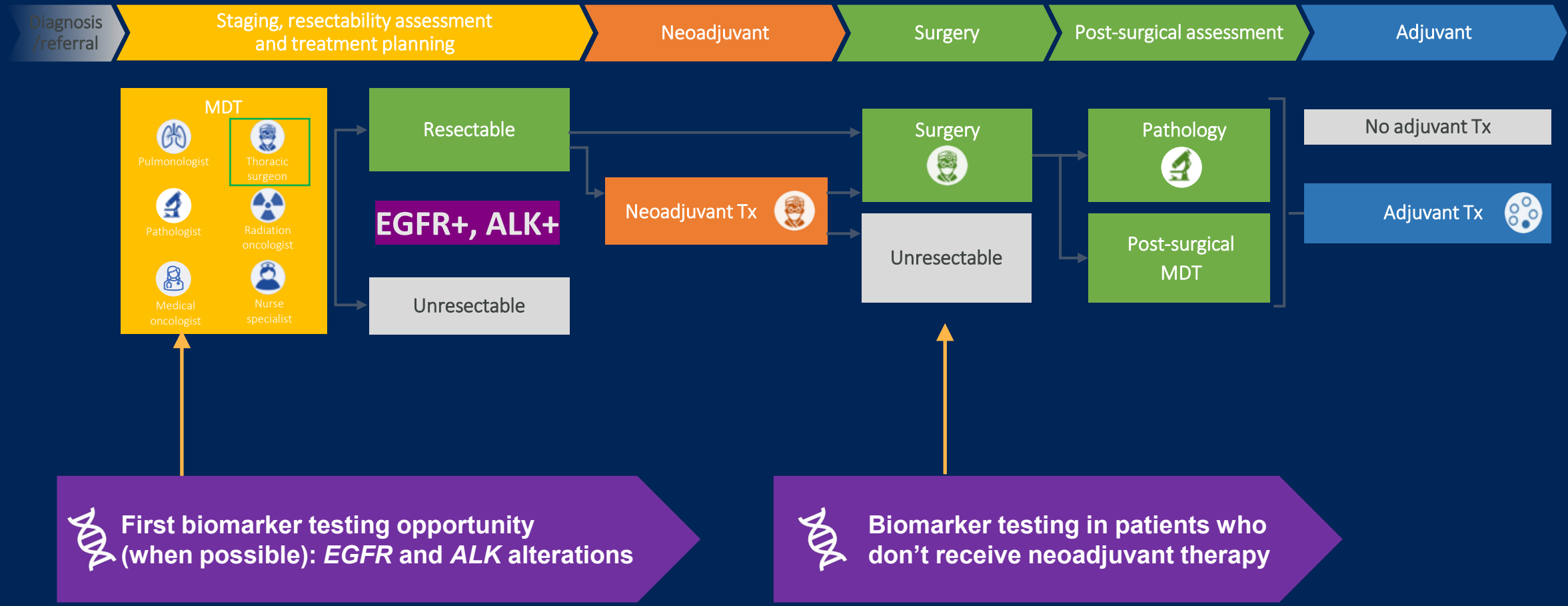
Discussion

PERIOPERATIVE SYSTEMIC THERAPY

Neoadjuvant Systemic Therapy[a]

- Patients with tumors ≥4 cm or node positive should be evaluated for preoperative therapy, with strong consideration for an immune checkpoint inhibitor + chemotherapy. Otherwise refer to the Neoadjuvant Systemic Therapy for Patients Who Are Not Candidates for Immune Checkpoint Inhibitors.
- Test for PD-L1 status, *EGFR* mutations, and *ALK* rearrangements (stages IB–IIIA, IIIB [T3–4, N2]). PD-L1 status can be incorporated with other

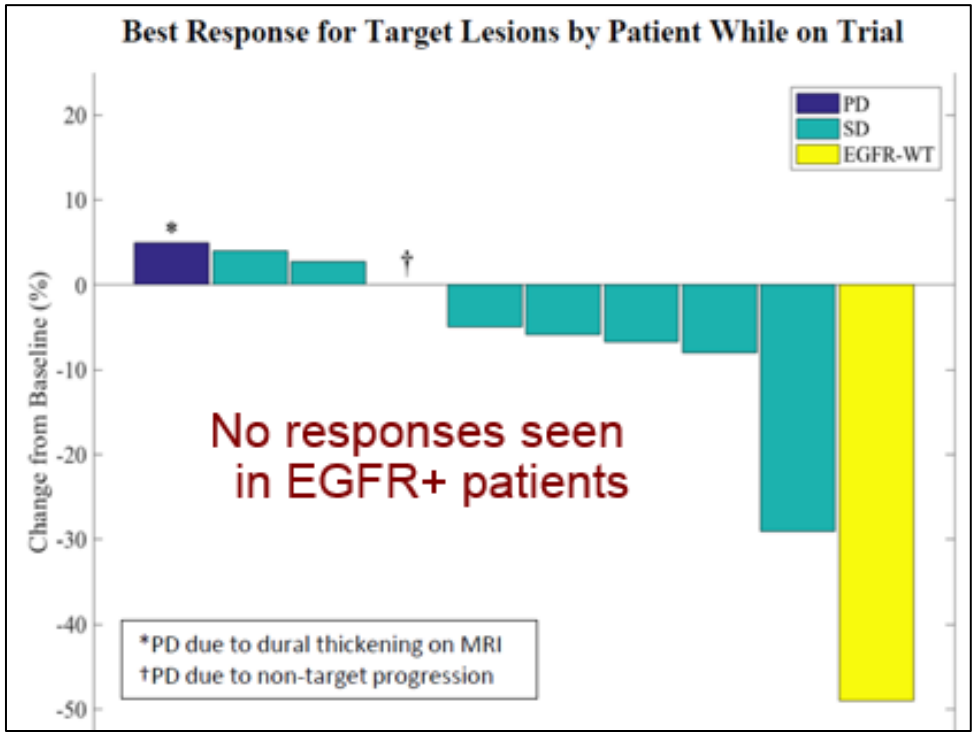
Biomarker Testing in Early-Stage NSCLC is Complex!



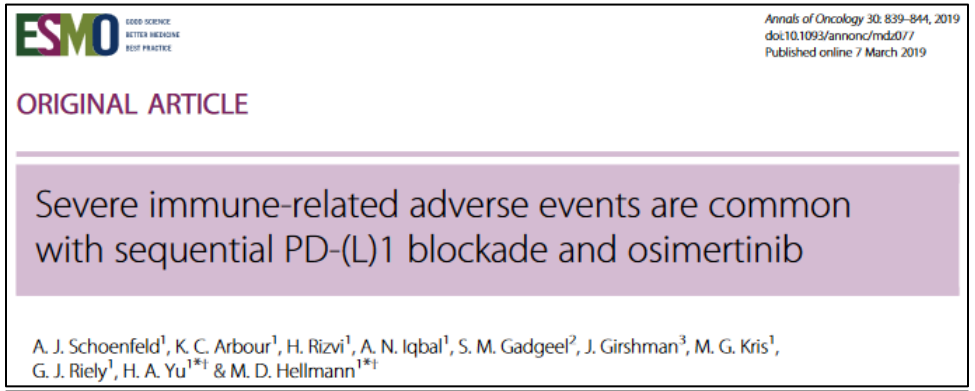
National Cancer Institute. Non-Small Cell Lung Cancer Treatment (PDQ®)–Health Professional Version. Accessed May 2025 https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq

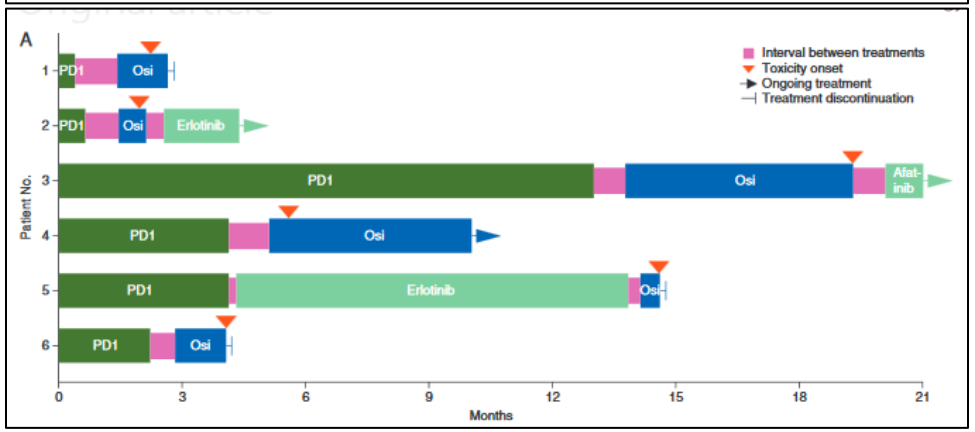
Why is Biomarker Testing Important?

Immunotherapy is ineffective in some molecular subsets of NSCLC



Targeted therapy given after immunotherapy increases toxicity





Lisberg et al, JTO 2018
Schoenfeld et al, Ann Onc, 2019

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Clinical Scenario (continued)

- Seen by MDT team
- Medically operable
- Surgically resectable
- PD-L1 90%
- Molecular testing is performed
- **How should this patient be treated?**

Tissue Source: Lung, Right Middle and Lower Lobe
Specimen Identifier: HS-21-20519
Block: 6M
Estimated Tumor Percentage: >=40%
Indication for Study: Invasive pulmonary adenocarcinoma

Abnormal Report

DISEASE ASSOCIATED VARIANTS (see interpretation and comments):

GENE PROTEIN CHANGE cDNA CHANGE

exon 19
EGFR p.E746_S752delinsV c.2237_2255delinsT

SMAD4 p.L23Ffs*2 c.67_68dup

TUMOR MUTATIONAL BURDEN (TMB; see interpretation and comments):

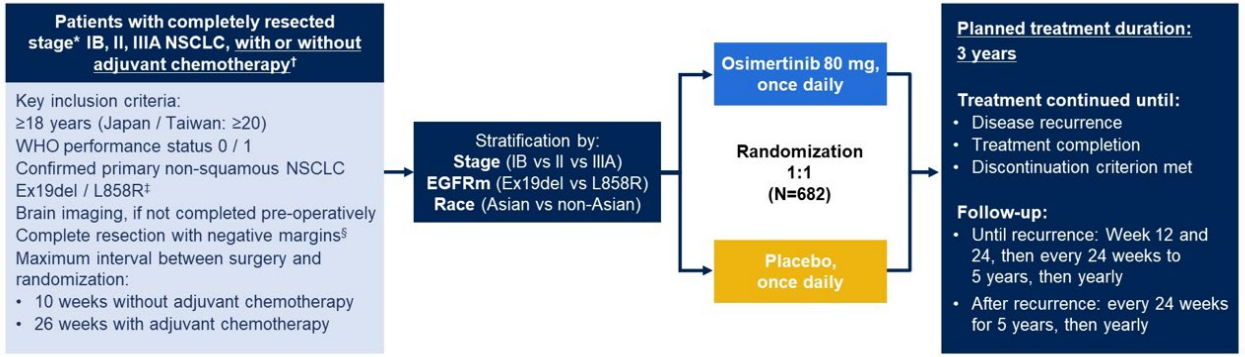
0.0 mutations per megabase (u/MB)

Potential Treatment Options

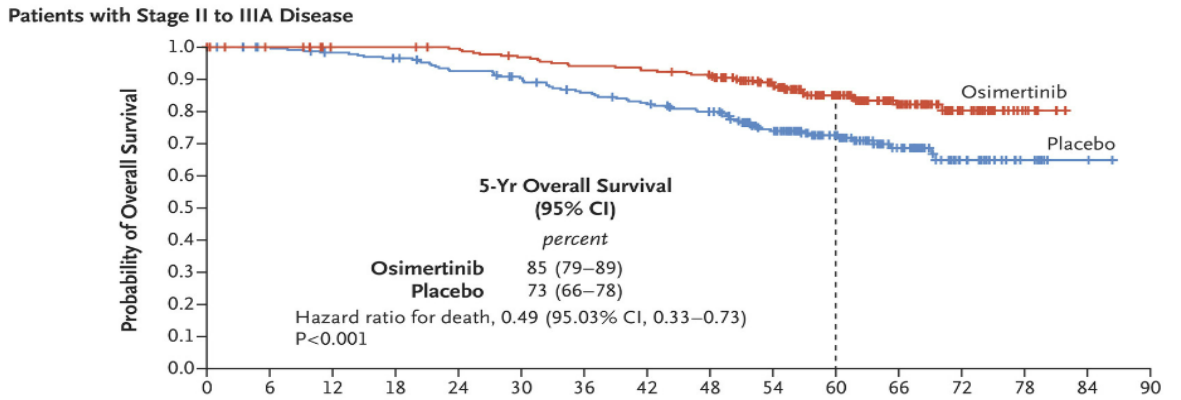
1. Surgery → Adjuvant
2. Neoadjuvant → Surgery → Adjuvant
3. Neoadjuvant → Surgery

EGFR TKIs in the Adjuvant Setting

NCT00049543	III	Adjuvant	*EGFR* in 4%	Stage IB-IIIA	503	Gefitinib daily × 2 years *v* placebo	OS	No difference (HR, 1.24)	Completed
ADJUVANT-CTONG1104 (NCT01405079)	III	Adjuvant	*EGFR*	Stage II-IIIA	222	Gefinitib daily × 2 years *v* vinorelbine + cisplatin × four cycles	DFS	30.8 *v* 19.8 months (HR, 0.56)	Completed
EVAN (NCT01683175)	II	Adjuvant	*EGFR*	Stage IIIA	94	Erlotinib daily × 2 years *v* vinorelbine + cisplatin × four cycles	2-year DFS	81.4% *v* 44.6% (RR, 1.8)	Completed
SELECT (NCT00567359)	II	Adjuvant	*EGFR*	Stage IA-IIIA	100	Erlotinib daily × 2 years after adjuvant chemotherapy/ radiotherapy	2-year DFS	90%	Completed
RADIANT (NCT00373425)	III	Adjuvant	*EGFR* expression/ amplification, *EGFR* mutation in 16.5%	Stage IB-IIIA	1,252	Erlotinib daily × 2 years *v* placebo	DFS	50.5 *v* 48.2 months (HR, 0.90 [95% CI, 0.74 to 1.10])	Completed



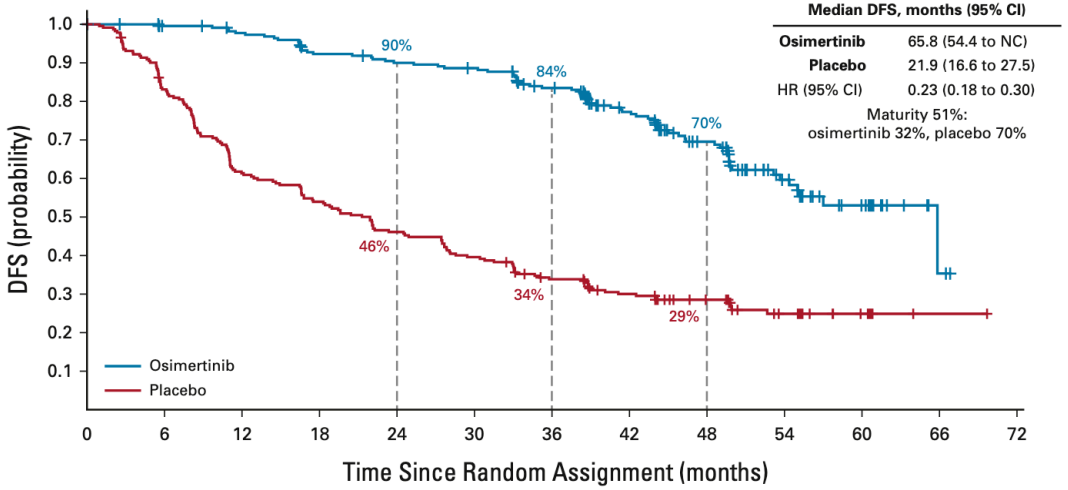
Endpoints
- **Primary endpoint:** DFS by investigator assessment in stage II–IIIA patients
- **Key secondary endpoints:** DFS in the overall population (stage IB–IIIA), landmark DFS rates, OS, safety, health-related quality of life



Adjuvant Osimertinib improves OS in EGFR Mutant Early Stage NSCLC

Voruganti T et al ASCO Education Book 2025, Tsuboi M et al NEJM 2023, Wu Y et al NEJM 2020

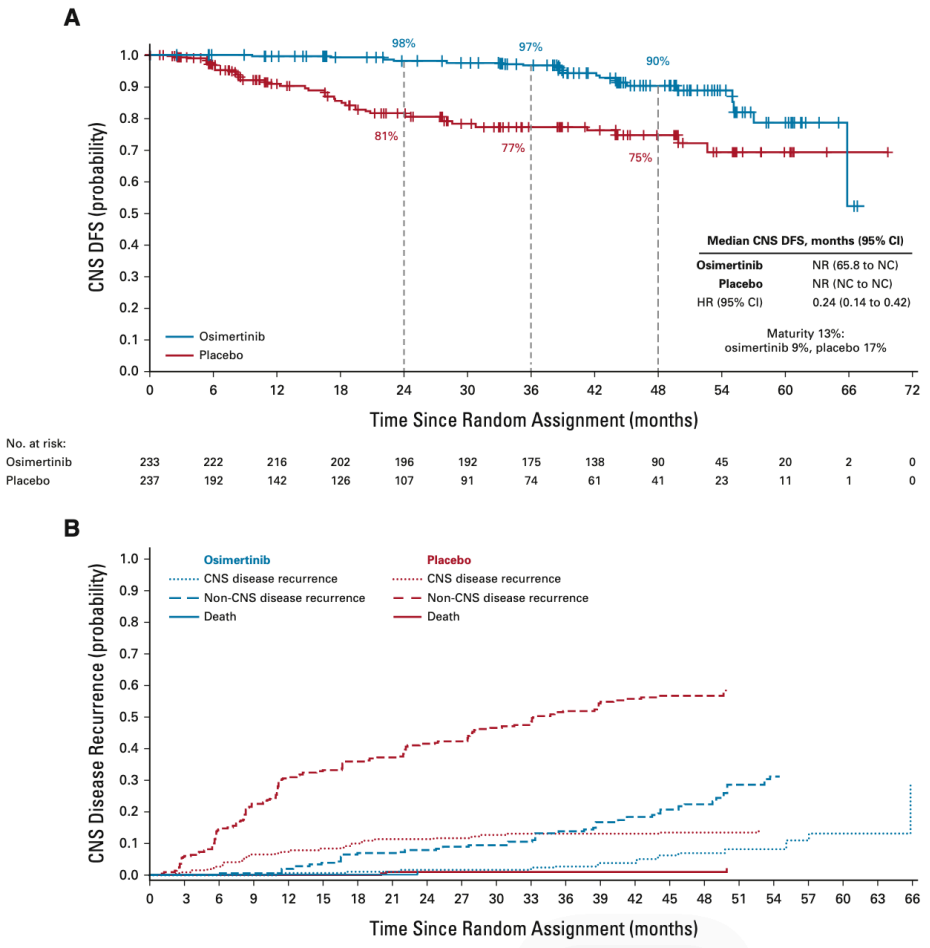
Updated DFS Analysis from ADAURA



No. at risk:

Osimertinib	233	222	216	202	196	192	174	138	90	45	20	2	0
Placebo	237	191	141	124	106	91	74	61	41	23	11	1	0

Sustained DFS benefit beyond 3 years



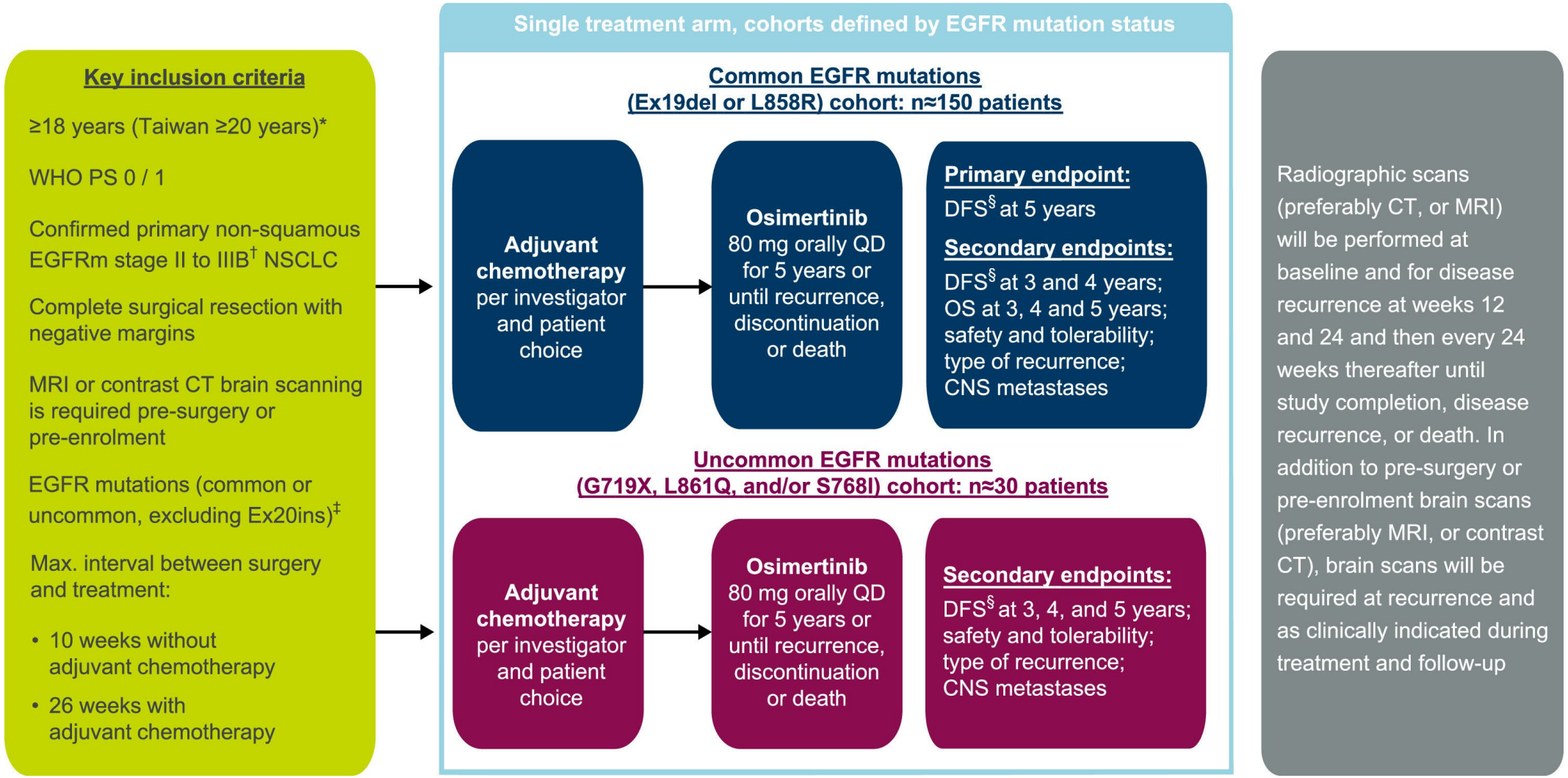
No. at risk:

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

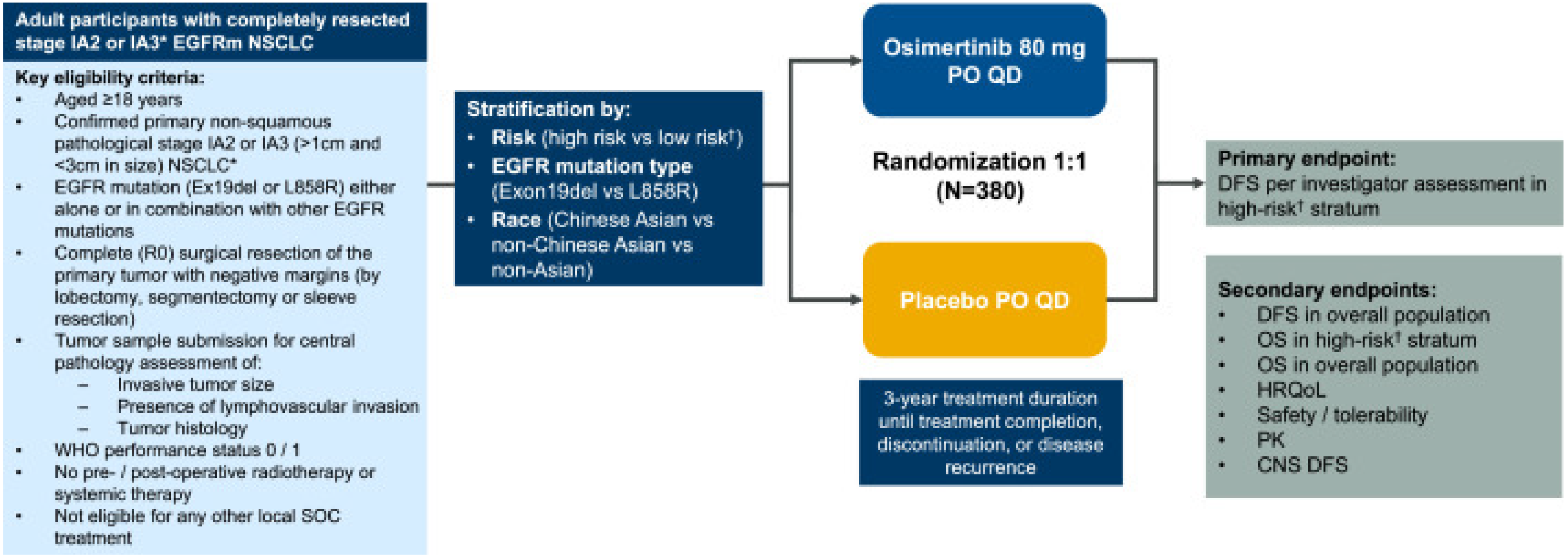
CNS Benefit

In patients with II-IIIA disease, 15/18 CNS recurrences occurred after stopping Osimertinib

Duration of Osimertinib – TARGET Study



Osimertinib in Stage I – ADAURA2 Study



Potential Treatment Options

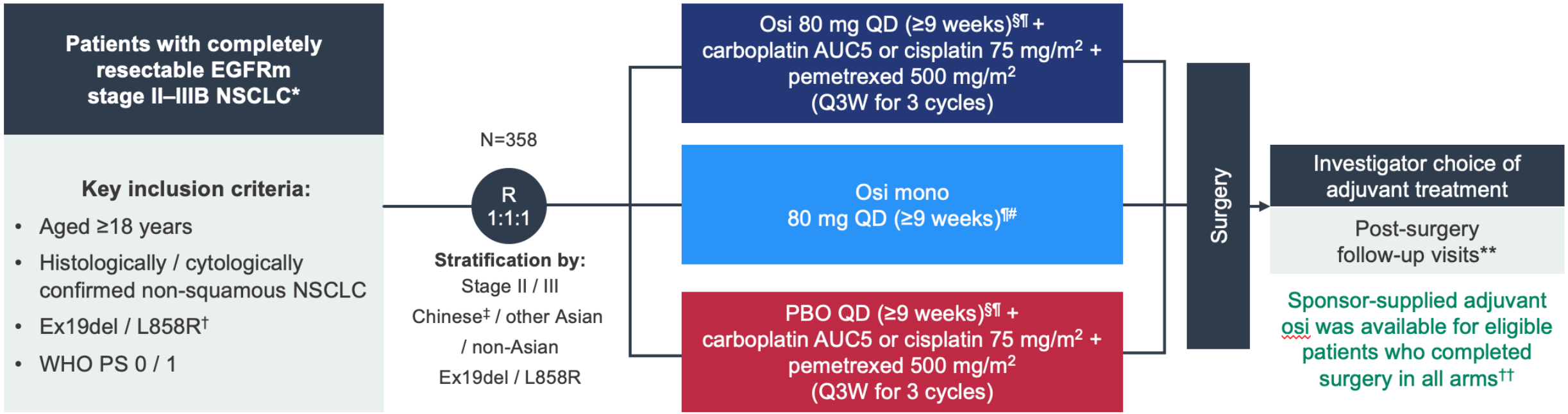
1. Surgery → Adjuvant

2. Neoadjuvant → Surgery → Adjuvant

   Neoadjuvant TKI?

3. Neoadjuvant → Surgery

NeoADAURA: global, randomized, Phase 3 controlled study



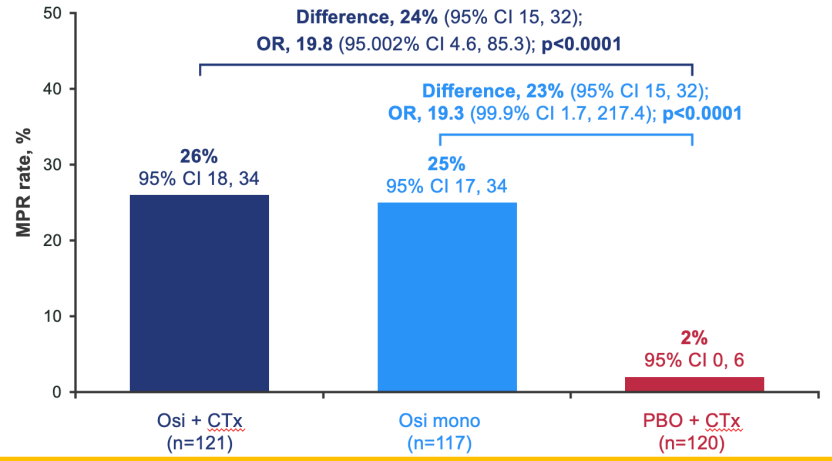
Endpoints:

- **Primary: major pathological response (MPR; by blinded central pathology review)**
- Secondary: event-free survival, pathological complete response, nodal downstaging and safety

Chaft J et al, ASCO Annual Meeting 2025

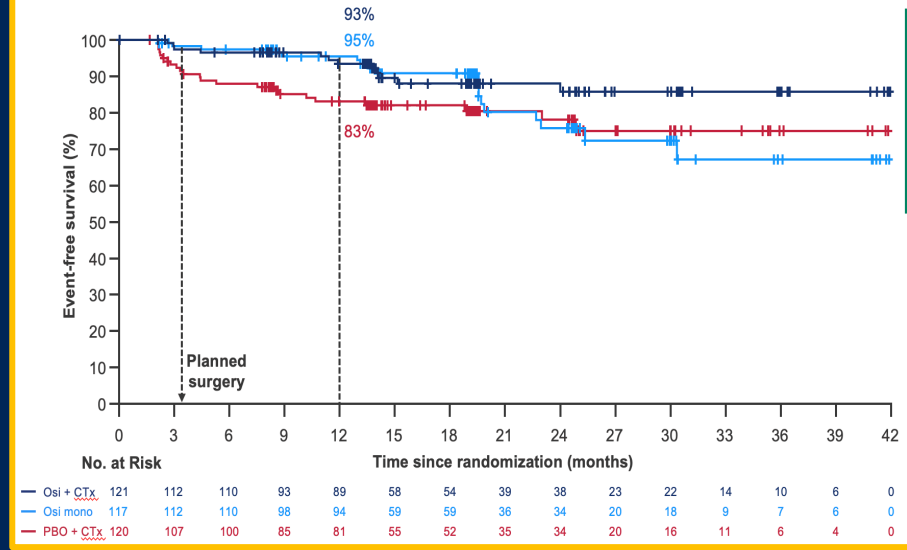
NeoADAURA – A Phase III Study

The MPR rate was statistically significantly higher with both osi-containing regimens



Neoadjuvant osi, with or without CTx, should be considered when planning treatment for patients with resectable EGFRm stage II–IIIB NSCLC

Interim EFS analysis (15% maturity)



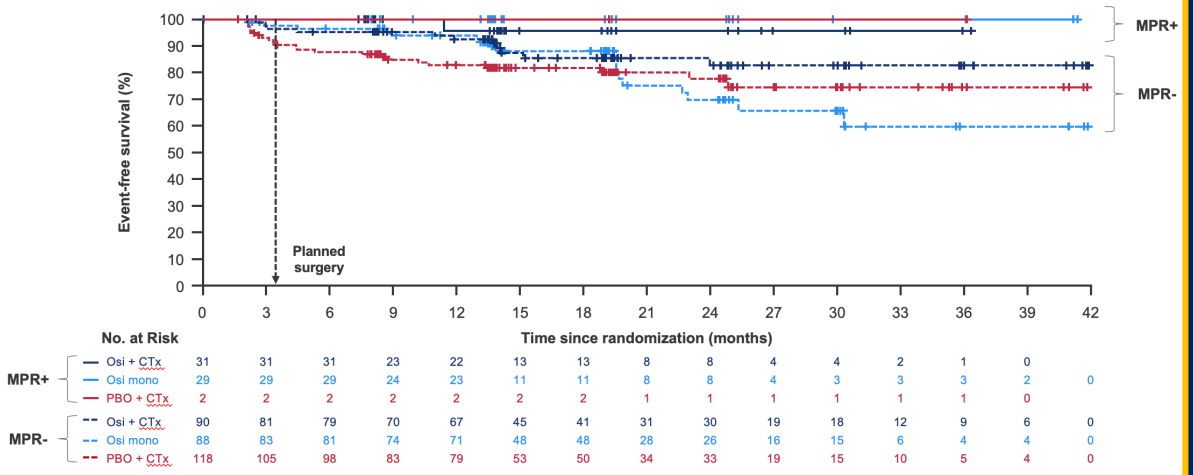
EFS HR vs PBO + CTx

Osi + CTx: 0.50
(99.8% CI 0.17, 1.41); p=0.0382*

Osi mono: 0.73
(95% CI 0.40, 1.35)†

Median follow-up, months‡
osi + CTx 14.3, osi mono 18.3,
PBO + CTx 14.3

EFS by MPR status



EFS events were reported in 2% (1/62) of patients with an MPR vs 18% (52/296) of patients without an MPR

Chaft J et al, ASCO Annual Meeting 2025

Potential Treatment Options

1. Surgery → Adjuvant

2. Neoadjuvant → Surgery → Adjuvant

   Neoadjuvant Chemo-IO?

3. Neoadjuvant → Surgery

Peri-operative Immunotherapy in EGFRm NSCLC?

		AEGEAN[1] (Perioperative)	CheckMate 816[2] (neoadjuvant only)	KEYNOTE-671[3,4] (Perioperative)	CheckMate 77T[5,6] (Perioperative)
N		740	358	797	451
Stage		Stage II, IIIA, and IIIB (N2) *By AJCC 8th ed*	Stage IB (≥4 cm), II, IIIA *By AJCC 7th ed*	Stage II, IIIA, and IIIB (N2) *By AJCC 8th ed*	Stage IIA (>4 cm) to IIIB (N2) *By AJCC 8th ed*
Regimen	Neoadjuvant	Durva + CT (Q3W x 4 cycles)	Nivo + CT (Q3W x 3 cycles)	Pembro + CT (Q3W up to 4 cycles)	Nivo + CT (Q3W x 4 cycles)
	Adjuvant	Durva (Q4W x 12 cycles)	N/A	Pembro (Q4W x 13 cycles)	Nivo (Q4W X 12 cycles)
Platinum backbone		Cisplatin/carboplatin	Cisplatin/carboplatin	Cisplatin	Cisplatin/carboplatin
Planned pneumonectomy permitted at baseline?		Amended to exclude	Yes	Yes	No specified
T4 invasion		Excluded	Included	Included	Excluded
EGFRm/ALK alterations		**Excluded from mITT analysis**	**Excluded patients with known EGFR/ALK alterations**	**Included**	**No EGFRm/no known ALK alterations**

	Chemo+IO	Chemotherapy
Known EGFR mutation n, (%)	**14 (3.5)**	**19 (4.8)**
Known ALK translocation n, (%)	12 (3.0)	9 (2.3)

Heymach J, et al. *NEJM 2023*; Forde PM, et al. *NEJM 2022*; Wakelee HA, et al. *NEJM 2023;* Cascone T, et al. *NEJM 2024*

Potential Treatment Options

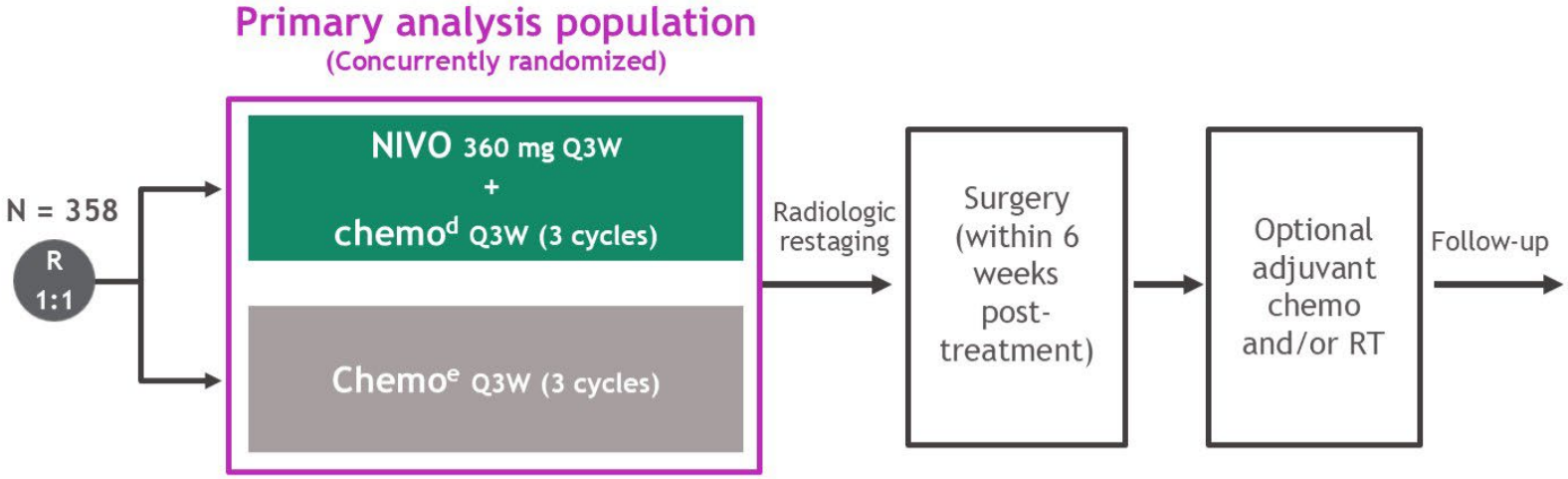
1. Surgery → Adjuvant
2. Neoadjuvant → Surgery → Adjuvant
3. Neoadjuvant → Surgery

CheckMate 816 study design[a]

Key Eligibility Criteria

- Newly diagnosed, resectable, stage IB (≥ 4 cm)-IIIA NSCLC (per TNM 7th edition)
- ECOG PS 0-1
- No known sensitizing *EGFR* mutations or *ALK* alterations

Stratified by
Stage (IB-II vs IIIA), PD-L1[b] (≥ 1% vs < 1%[c]), and sex



Minimum/median follow-up: 59.9/68.4 months

Primary endpoints
- pCR by BIPR
- EFS by BICR

Key secondary endpoints
- OS
- MPR by BIPR
- TTDM

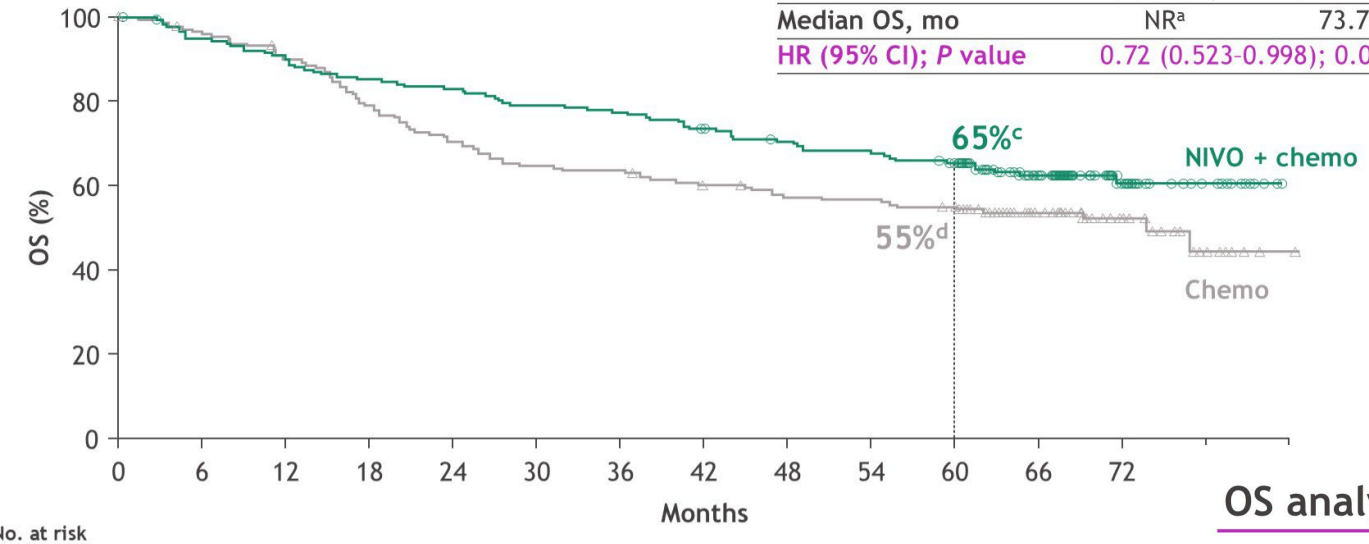
Exploratory analyses
- OS by pCR, ctDNA clearance
- Lung cancer-specific survival

Database lock: January 23, 2025. From *The New England Journal of Medicine*, Forde PM, et al, Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer, 2022;386:1973-1985. Copyright © 2022 Massachusetts Medical Society. Adapted with permission from Massachusetts Medical Society. [a]NCT02998528. [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako). [c]Included patients with PD-L1 expression status not evaluable and indeterminate. [d]Nonsquamous: pemetrexed + cisplatin or paclitaxel + carboplatin; squamous: gemcitabine + cisplatin or paclitaxel + carboplatin. [e]Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (squamous only), pemetrexed + cisplatin (nonsquamous only), or paclitaxel + carboplatin.

Forde P et al, NEJM 2025

Final analysis: OS with neoadjuvant NIVO + chemo vs chemo

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median OS, mo	NR[a]	73.7[b]
HR (95% CI); *P* value	0.72 (0.523-0.998); 0.0479	



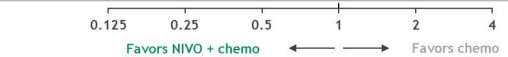
No. at risk

NIVO + chemo	179	168	159	151	147	140	137	129	122	117	111	67	29
Chemo	179	170	159	139	124	114	112	104	98	97	91	58	29

Minimum/median follow-up: 59.9/68.4 months.
[a-d]95% CI: [a]NR; [b]47.3-NR; [c]58-72; [d]47-62.

OS analysis by key subgroups

	Median OS, mo		Unstratified HR (95% CI)	Unstratified HR
	NIVO + chemo (n = 179)	Chemo (n = 179)		
Overall (N = 358)	NR	73.7		0.71
Male (n = 255)	NR	61.8		0.76
Female (n = 103)	NR	NR		0.52
White (n = 169)	NR	73.7		0.91
Black or African American (n = 7)	NR	20.9		
Asian (n = 179)	NR	76.8		0.52
North America (n = 91)	NR	73.7		0.83
Europe (n = 66)	NR	38.3		0.64
Asia (n = 177)	NR	76.8		0.54
ECOG PS 0 (n = 241)	NR	76.8		0.70
ECOG PS 1 (n = 117)	71.6	45.3		0.76
Stage IB-II (n = 126)	NR	76.8		0.77
Stage IIIA (n = 229)	NR	73.7		0.70
Squamous (n = 182)	NR	73.7		0.71
Nonsquamous (n = 176)	NR	NR		0.72
PD-L1 < 1% (n = 155)	NR	61.8		0.89
PD-L1 ≥ 1% (n = 178)	NR	73.7		0.51
PD-L1 1%-49% (n = 98)	NR	73.7		0.66
PD-L1 ≥ 50% (n = 80)	NR	76.8		0.33
Cisplatin (n = 258)	NR	76.8		0.81
Carboplatin (n = 72)	NR	37.2		0.39

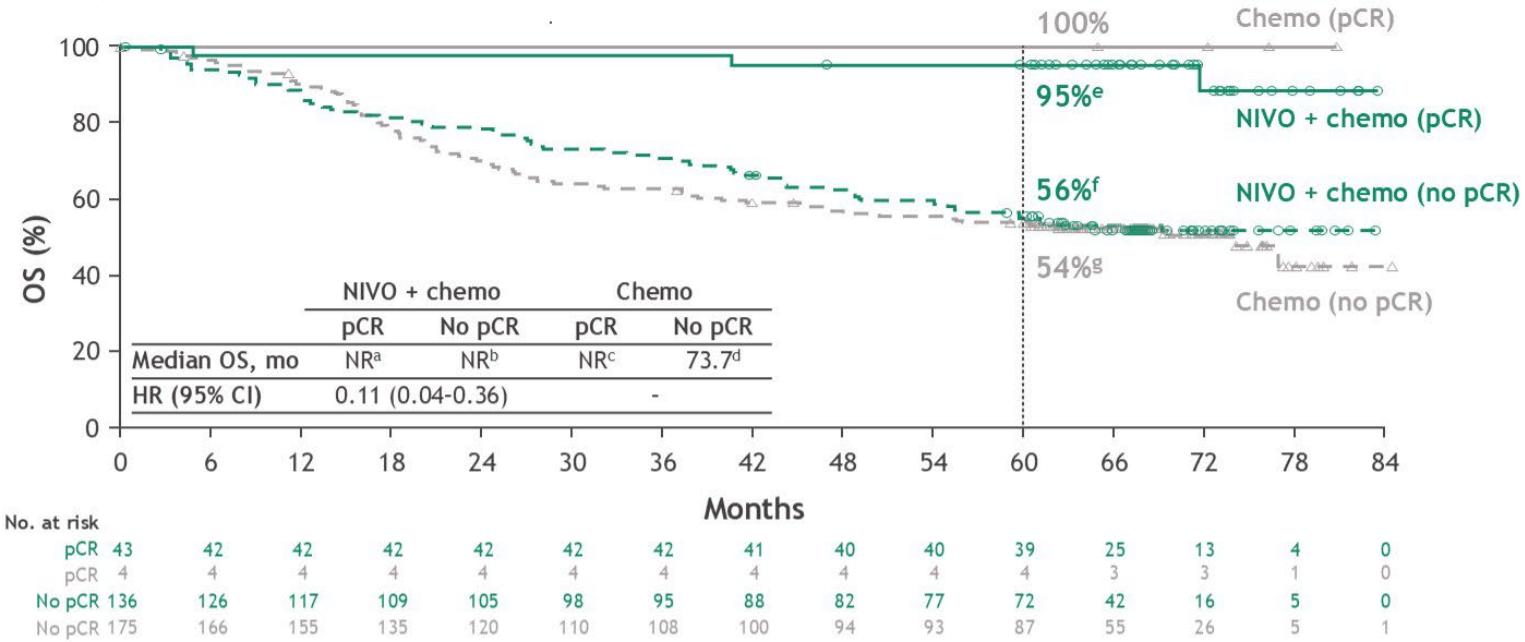


Minimum/median follow-up: 59.9/68.4 months.
HRs were NC if there was an insufficient number of events (< 10 per arm).

Forde P et al, NEJM 2025

Exploratory analysis: OS by pCR status

- Among concurrently randomized patients, 43/179 (24%) patients in the NIVO + chemo arm and 4/179 (2%) patients in the chemo arm had pCR[1]



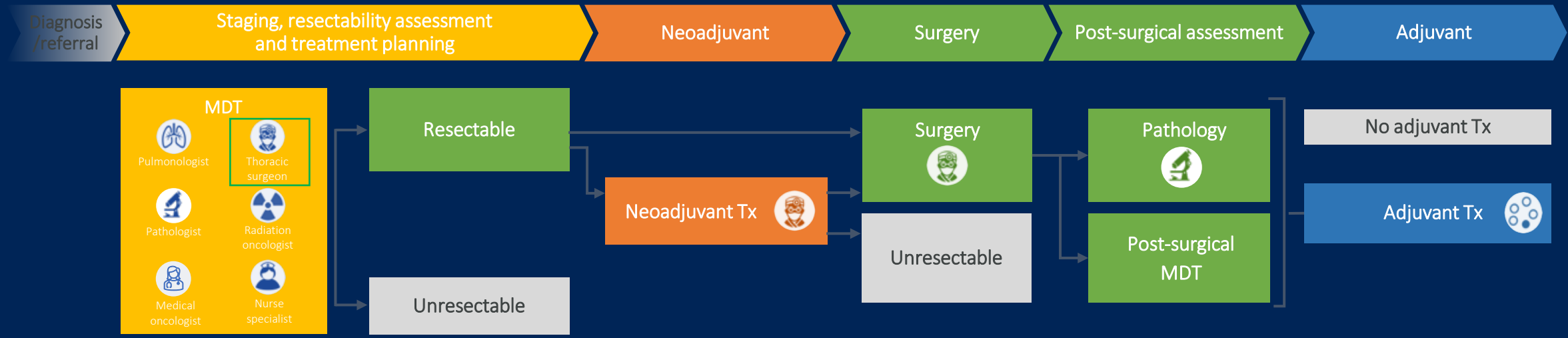
	NIVO + chemo		Chemo	
	pCR	No pCR	pCR	No pCR
Median OS, mo	NR[a]	NR[b]	NR[c]	73.7[d]
HR (95% CI)	0.11 (0.04-0.36)		-	

In the NIVO + chemo arm:

- Among patients with pCR, death occurred in 3 patients; none were due to disease[h]
- Among patients with no pCR, there were a total of 62 (46.6%) deaths; 44 (33.1%) were due to disease[i]

Minimum/median follow-up: 59.9/68.4 months.
HRs were NC if there was an insufficient number of events (< 10 per arm). [a-g]95% CI: [a]NR; [b]53.9-NR; [c]NR; [d]46.7-NR; [e]83-99; [f]47-64; [g]46-61. [h]In the chemo arm, there were no deaths in patients with pCR. [i]In the chemo arm, there were 82 (47.7%) deaths; 60 (34.9%) were due to disease. 1. Forde PM, et al. *N Engl J Med* 2022;386:1973-1985.

Early-Stage NSCLC



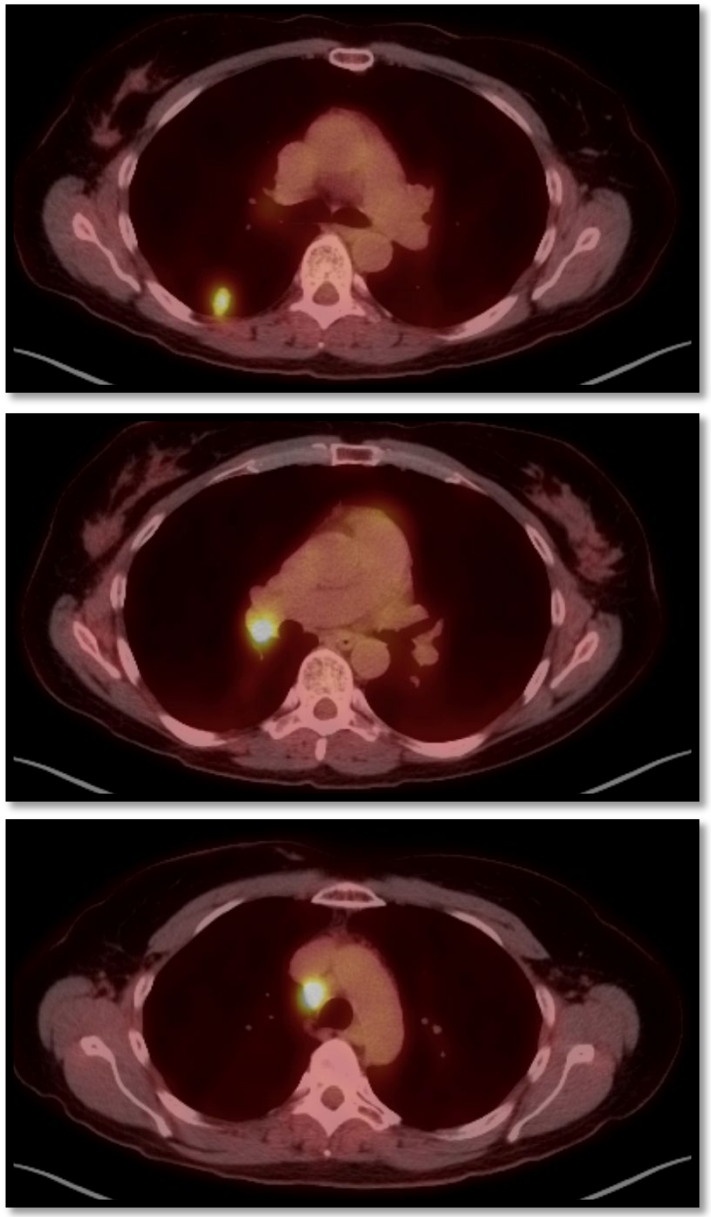
Molecular Testing is critical
If EGFR/ALK – Avoid ChemoIO

Neoadj Chemo + TKI – option sometimes

Neoadj ChemoIO w/ an OS benefit
Unclear if Periop >>Neoadj ChemoIO

Probably Ok to stop if pCR

Clinical Scenario



RLL T1cN2aM0, Stage IIB Lung Adenocarcinoma with an *EGFR* activating mutation

- ✓ **Adjuvant osimertinib provides a proven overall survival benefit**
- ✓ **Avoid neoadjuvant chemo-immunotherapy in patients with *EGFR*-mutant NSCLC**
- ✓ **Consider neoadjuvant chemo plus TKI – NeoAdaura**