

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

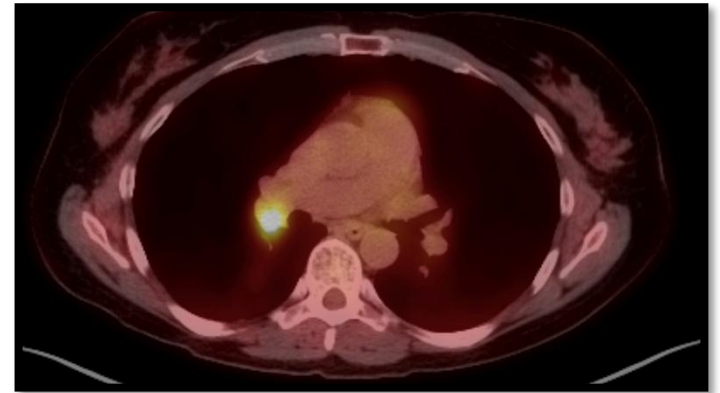
March 2025: CT chest showed a RLL mass measuring 2.3 x 1.6 cm

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

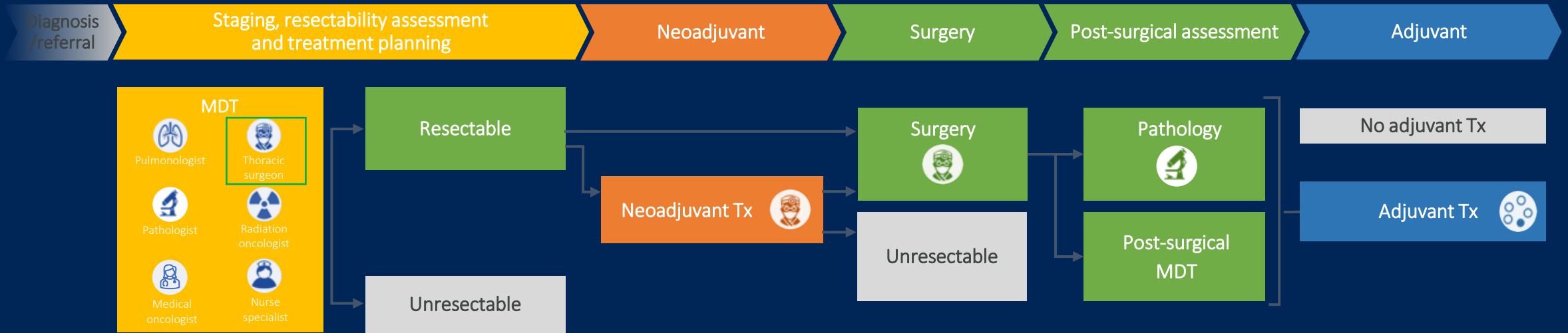
April 2025: Bronchoscopy confirmed metastatic adenocarcinoma in 4R, 10R, 11R Lymph Nodes. Level 4L, 11L, and 7 nodes were negative

Controlled hypertension, hyperlipidemia, COPD, osteoarthritis, PS 1

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



Management of Early-Stage NSCLC is Complex!

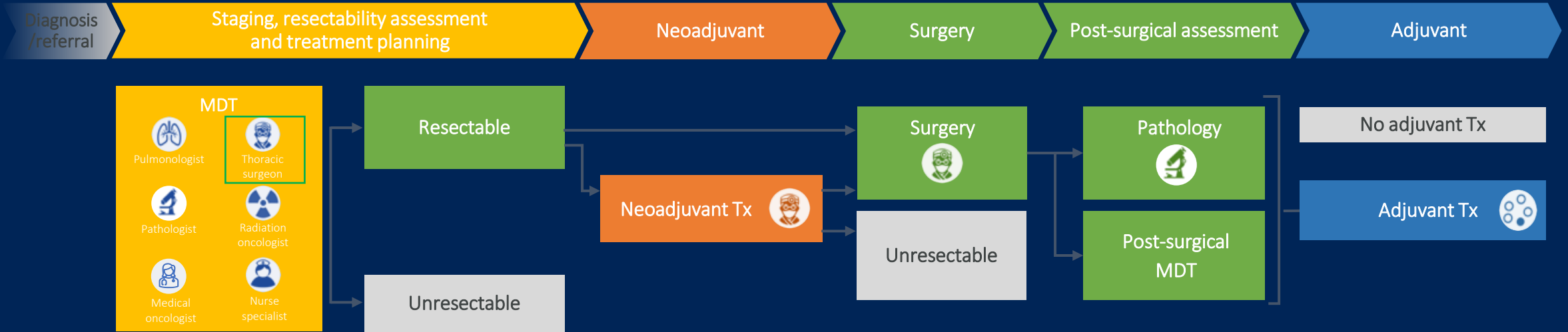



Current Approvals in Early-Stage NSCLC

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 <u>EGFR exon 19 deletions or exon 21 L858R</u>
Adjuvant	ALINA ⁴	Alectinib	April 18, 2024	Resected stage IB (tumors >4 cm), II, or IIIA <u>ALK-positive</u> 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) <u>without EGFR/ALK alterations</u>
Perioperative	CheckMate 77T ⁸	Nivolumab + Chemotherapy	October 3, 2024	Resectable NSCLC (tumors ≥4 cm and/or node-positive) <u>without EGFR/ALK alterations</u>

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

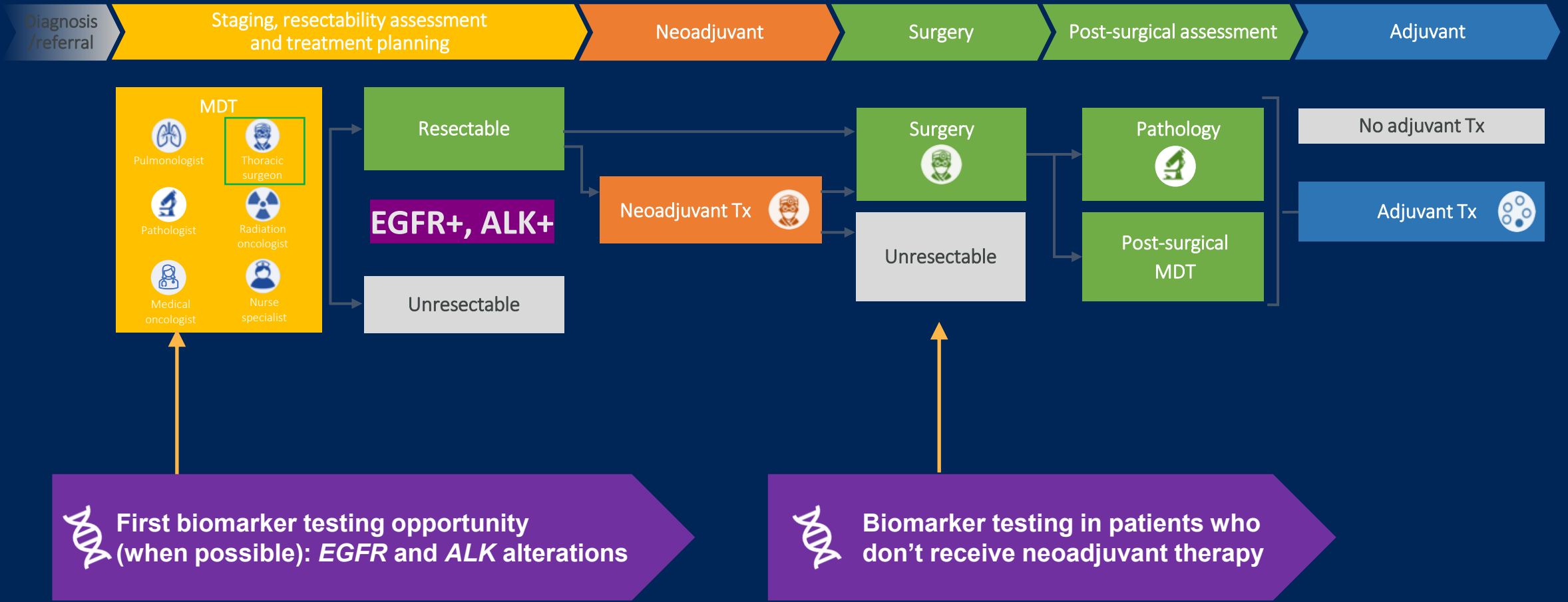
[NCCN Guidelines Index](#)
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PERIOPERATIVE SYSTEMIC THERAPY

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

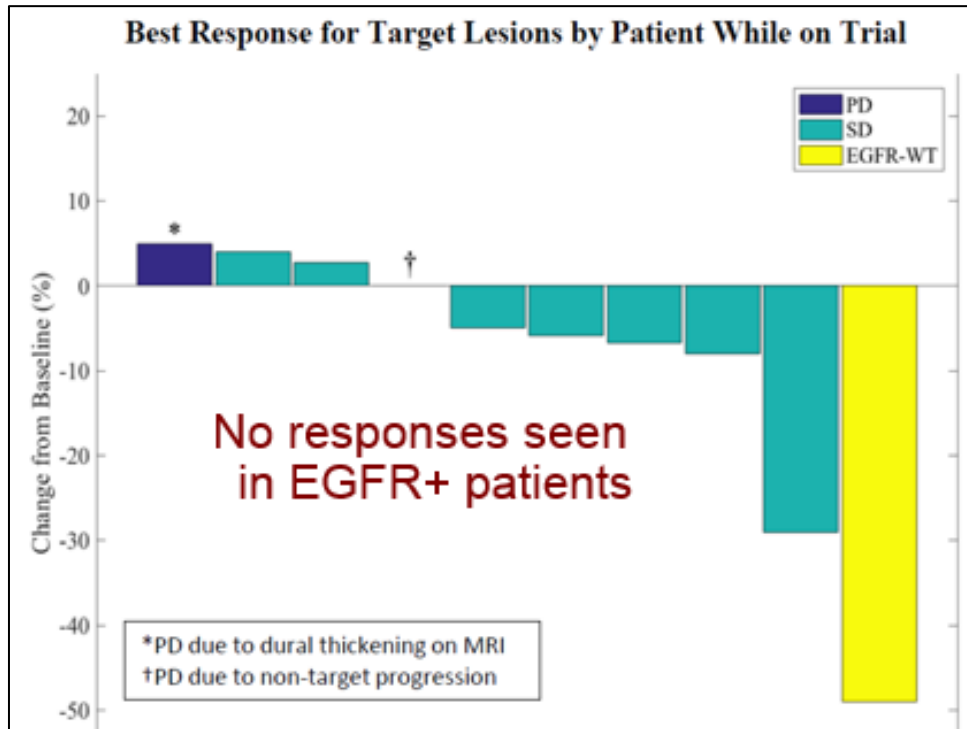
Biomarker Testing in Early-Stage NSCLC is Complex!



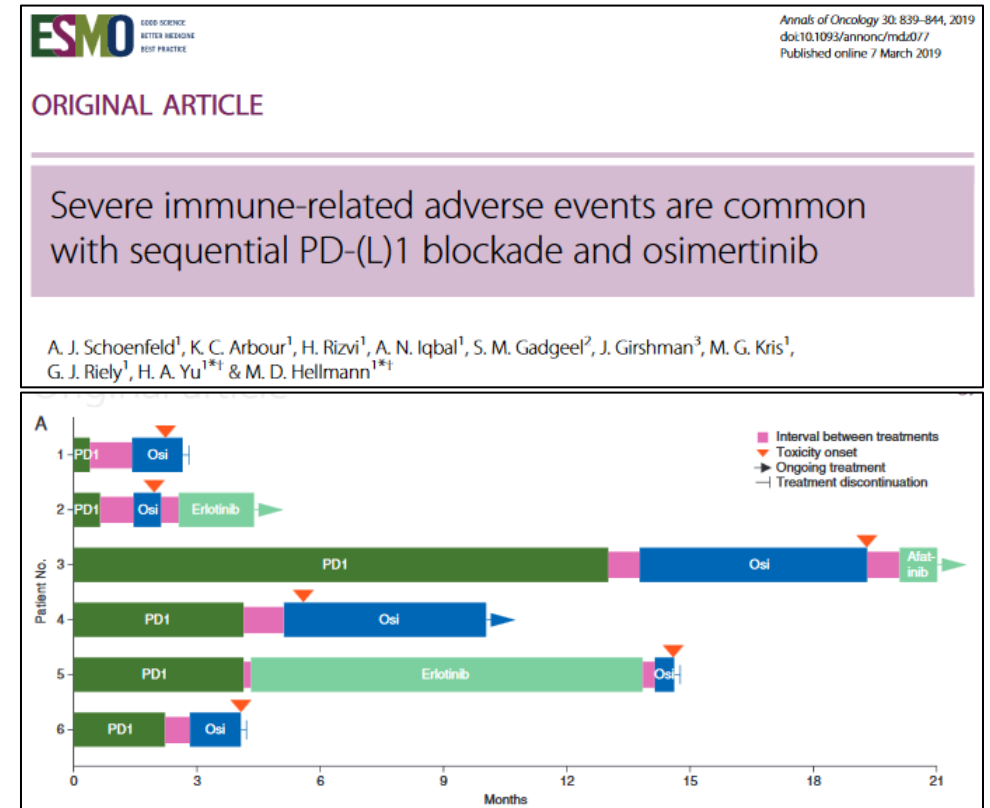
National Cancer Institute. Non-Small Cell Lung Cancer Treatment (PDQ®)—Health Professional Version. Accessed May 2025
<https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq>

Why is Biomarker Testing Important?

Immunotherapy is ineffective in some molecular subsets of NSCLC



Targeted therapy given after immunotherapy increases toxicity



Clinical Scenario (continued)

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

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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):

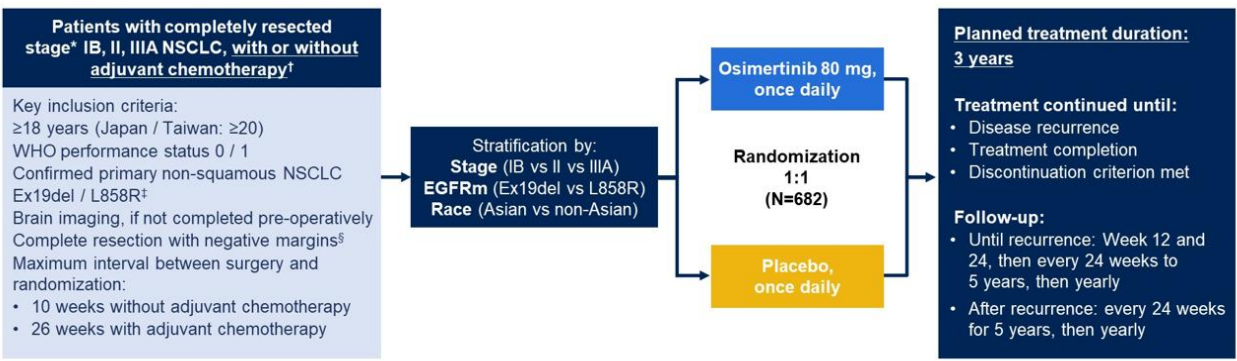
0.0 mutations per megabase (u/MB)
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Potential Treatment Options



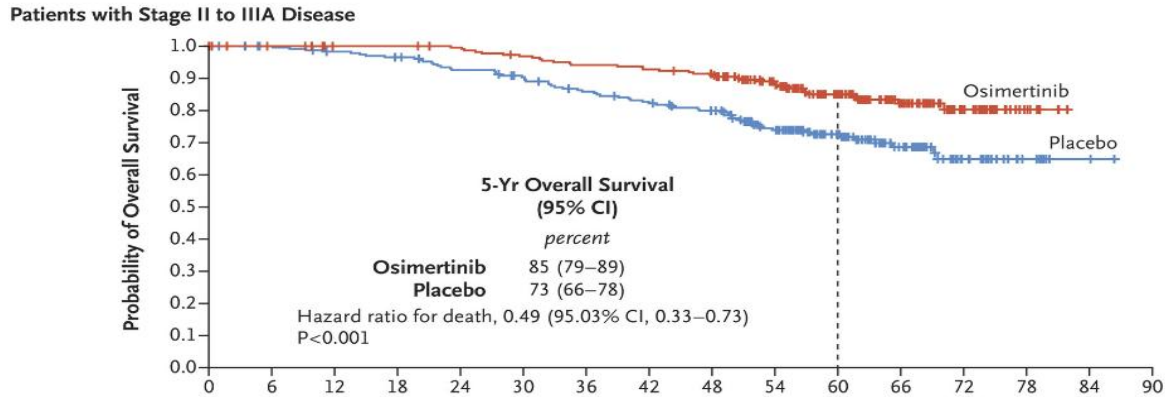
EGFR TKIs in the Adjuvant Setting

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	Gefitinib 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

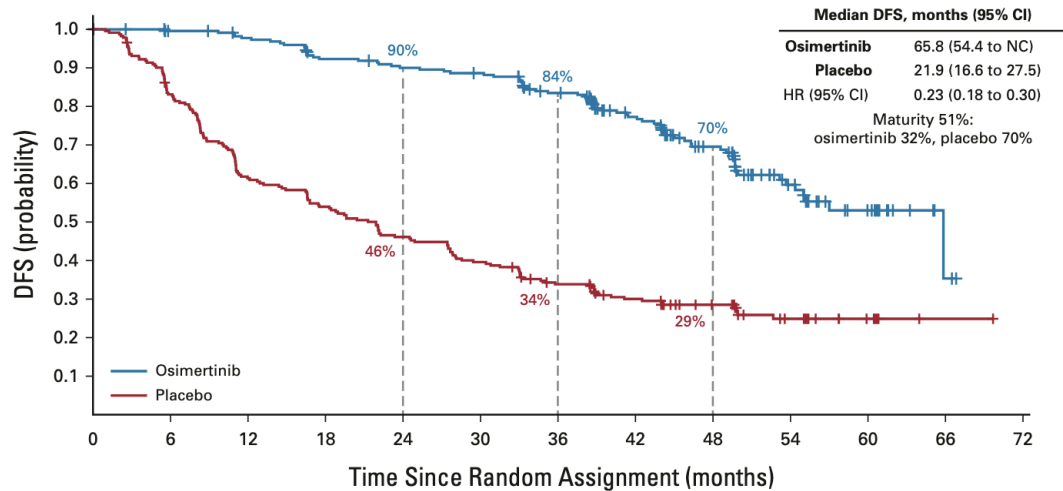
- **Primary endpoint:** DFS by investigator assessment in stage II–IIIa patients
- **Key secondary endpoints:** DFS in the overall population (stage IB–IIIa), landmark DFS rates, OS, safety, health-related quality of life



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

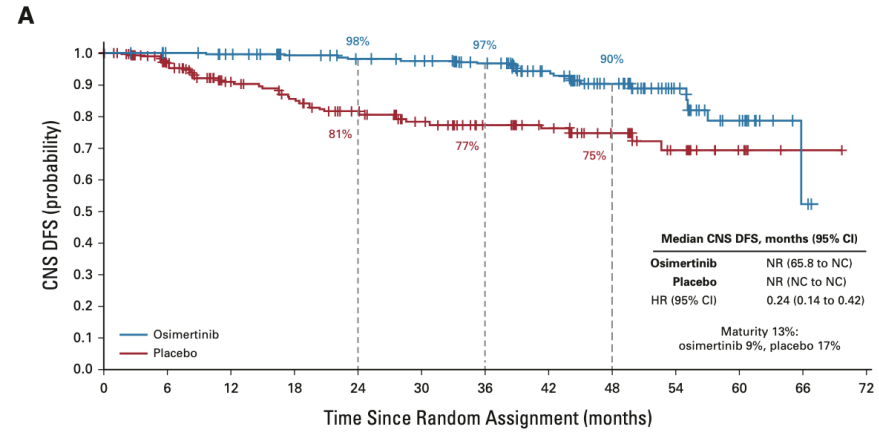
Updated DFS Analysis from ADAURA



No. at risk:

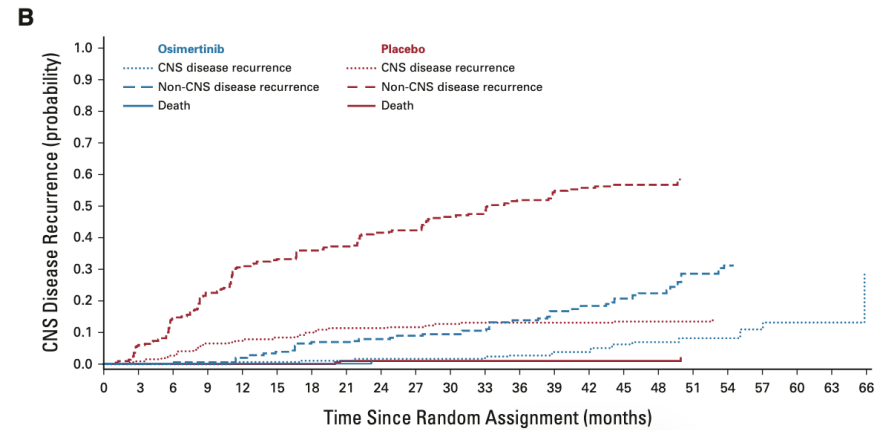
Osimertinib	233	222	216	202	196	192	174	138	90	45	20	2	0
Placebo	237	191	141	124	106	91	74	61	41	23	11	1	0

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

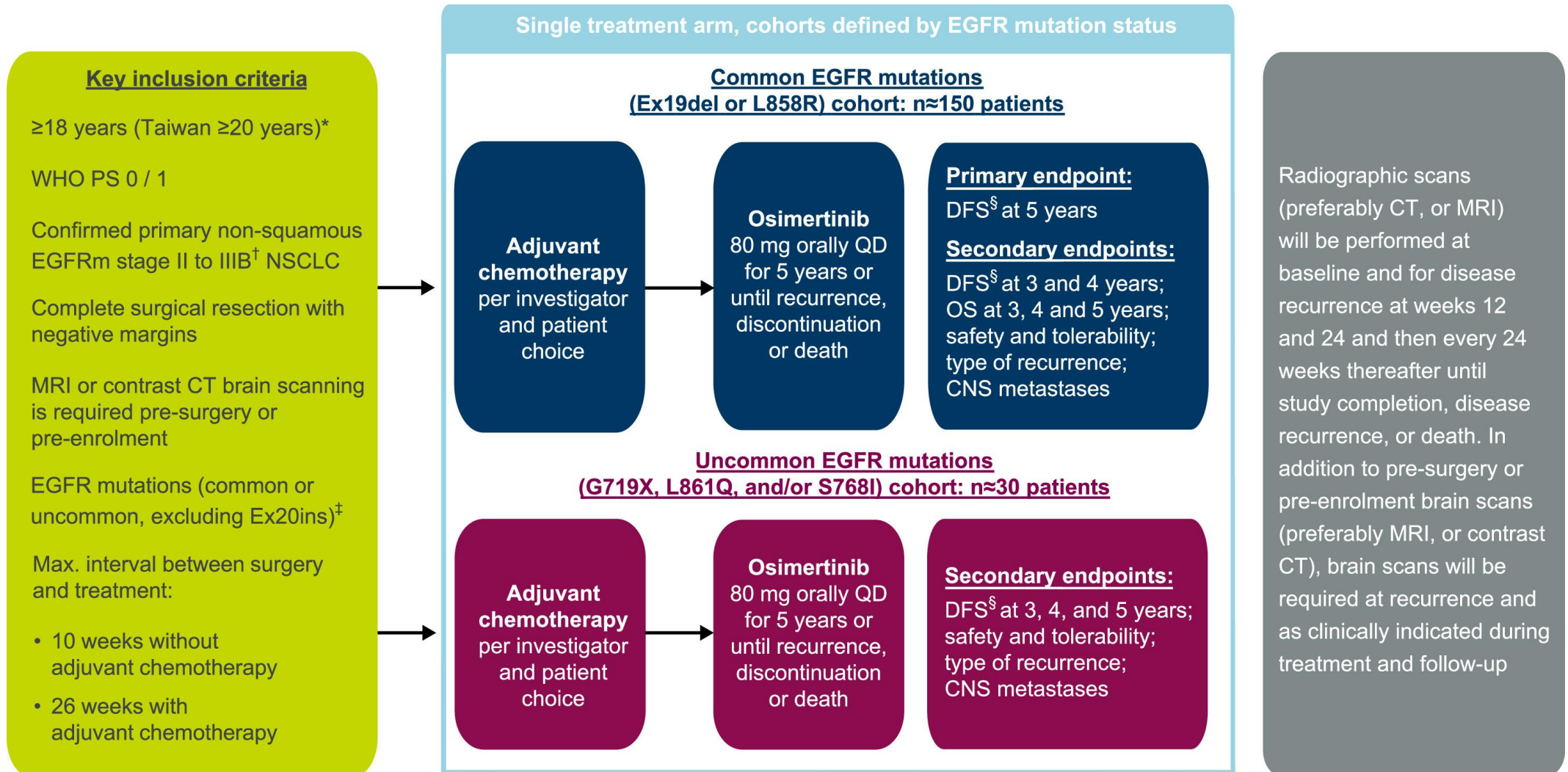


Penn Medicine
University of Pennsylvania Health System

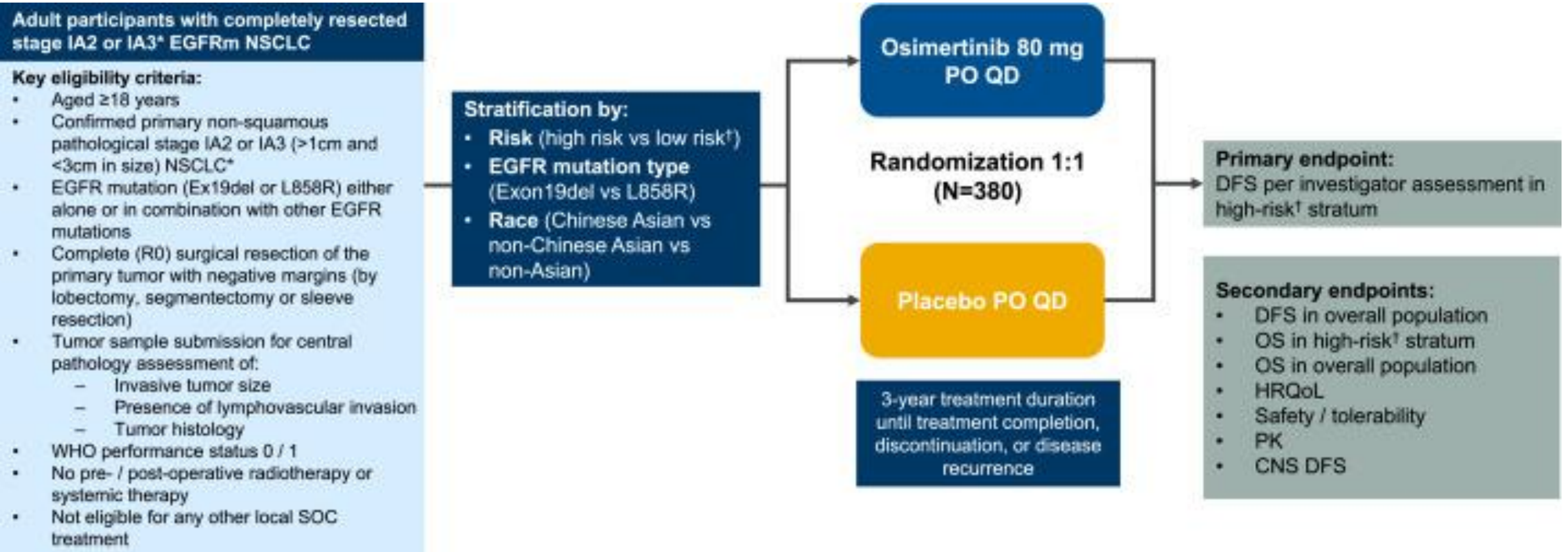


Penn Medicine

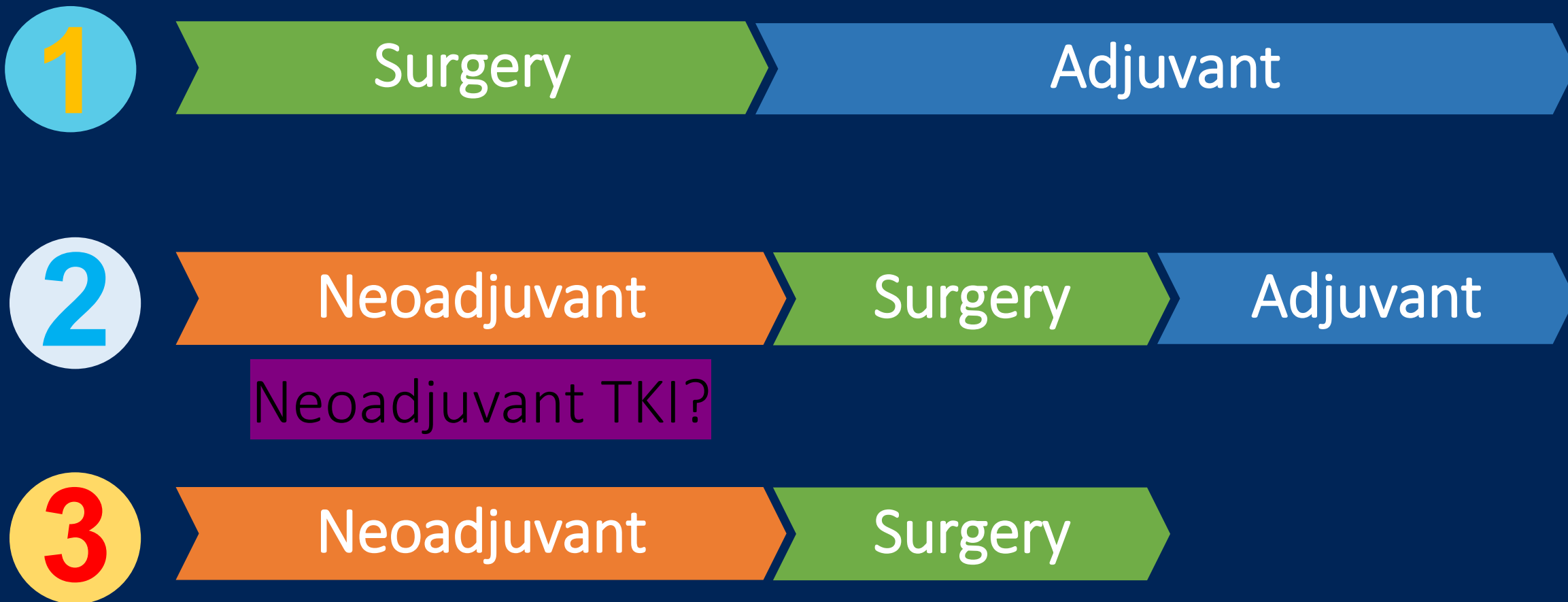
Duration of Osimertinib – TARGET Study



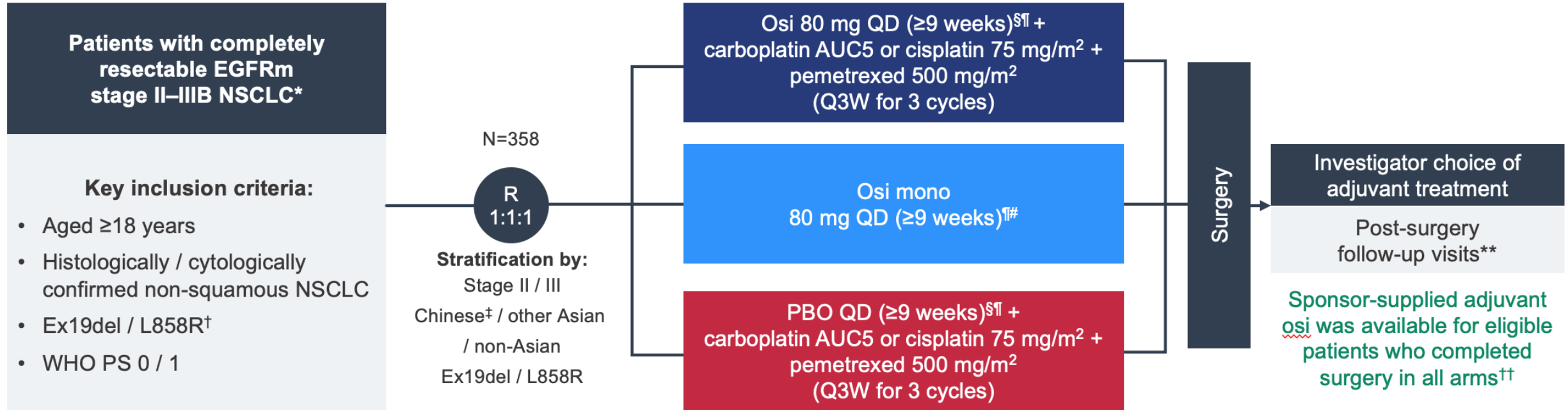
Osimertinib in Stage I – ADAURA2 Study



Potential Treatment Options



NeoADAURA: global, randomized, Phase 3 controlled study



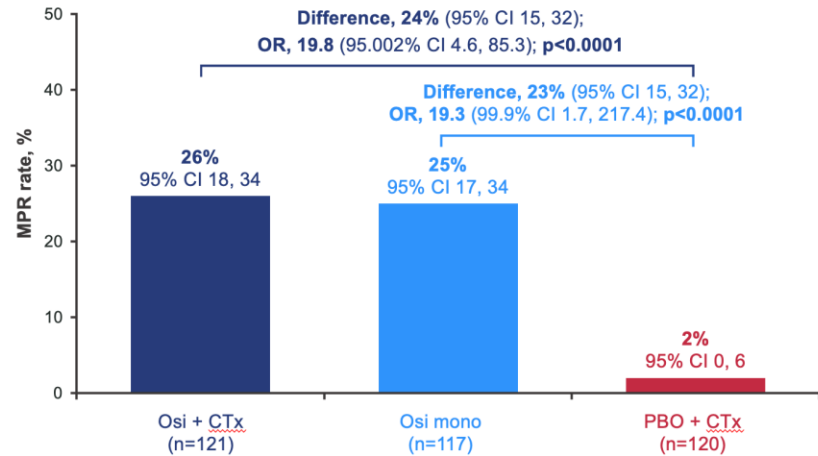
Endpoints:

- **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

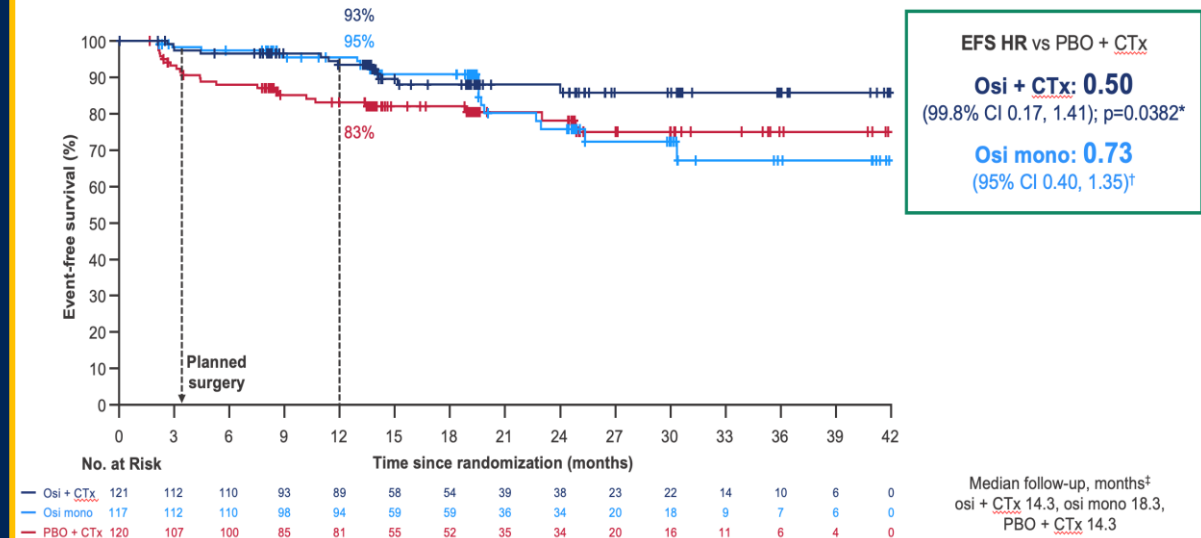
NeoADAURA – A Phase III Study

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

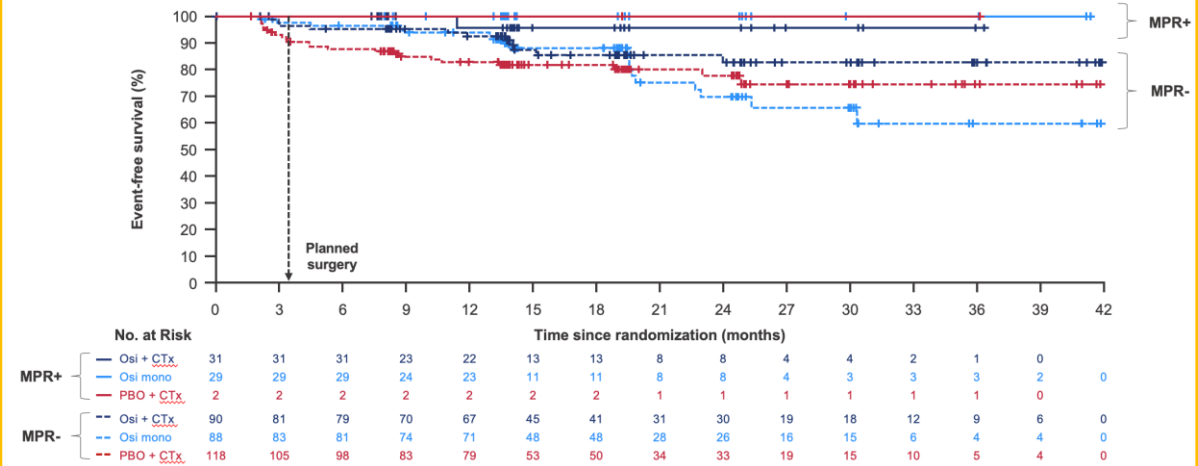


Neoadjuvant osi, with or without CTx, should be considered when planning treatment for patients with resectable EGFRm stage II–IIIB NSCLC

Interim EFS analysis (15% maturity)

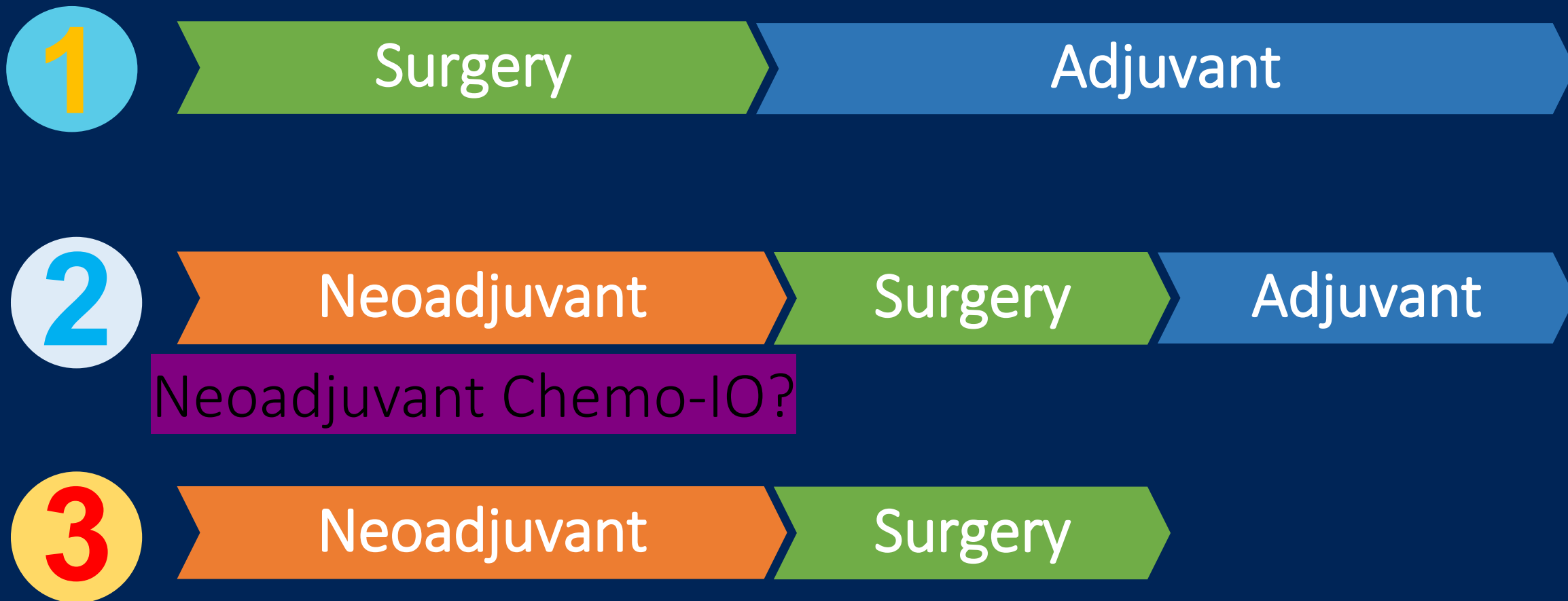


EFS by MPR status



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

Potential Treatment Options



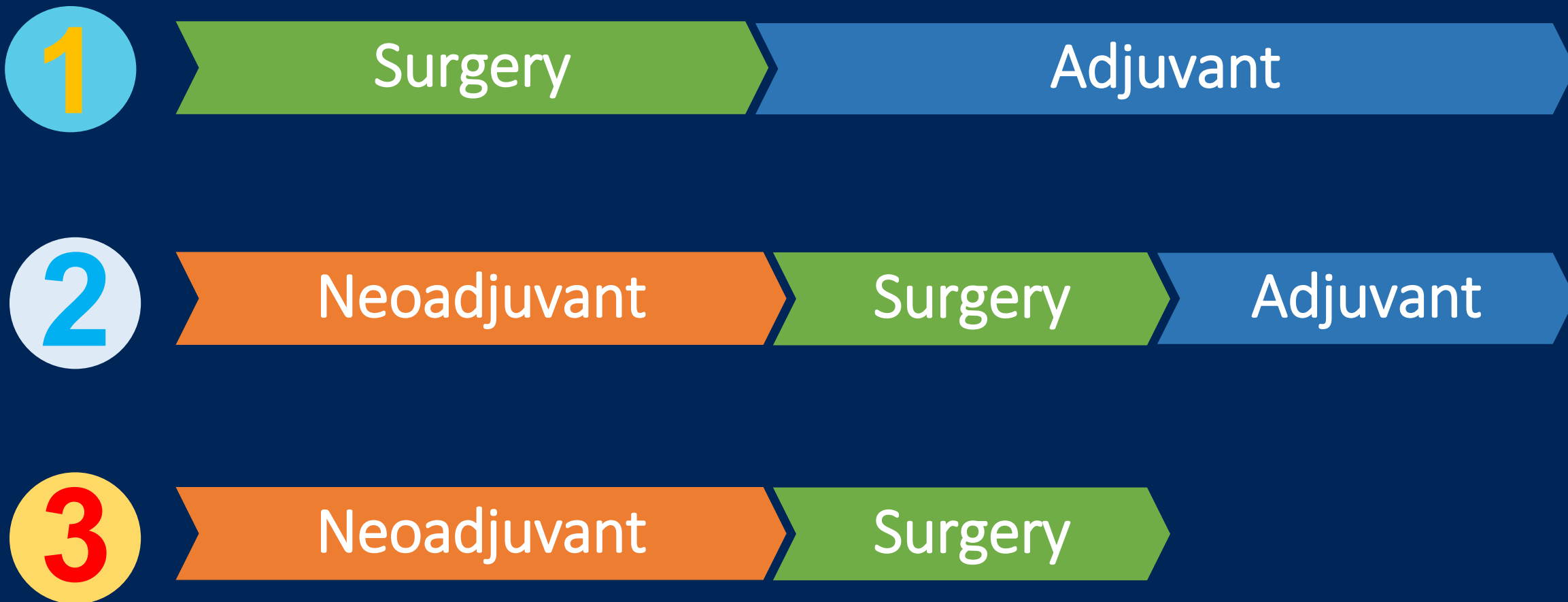
Peri-operative Immunotherapy in EGFRm NSCLC?

		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) <i>By AJCC 8th ed</i>	Stage IB (≥4 cm), II, IIIA <i>By AJCC 7th ed</i>	Stage II, IIIA, and IIIB (N2) <i>By AJCC 8th ed</i>	Stage IIA (>4 cm) to IIIB (N2) <i>By AJCC 8th ed</i>
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

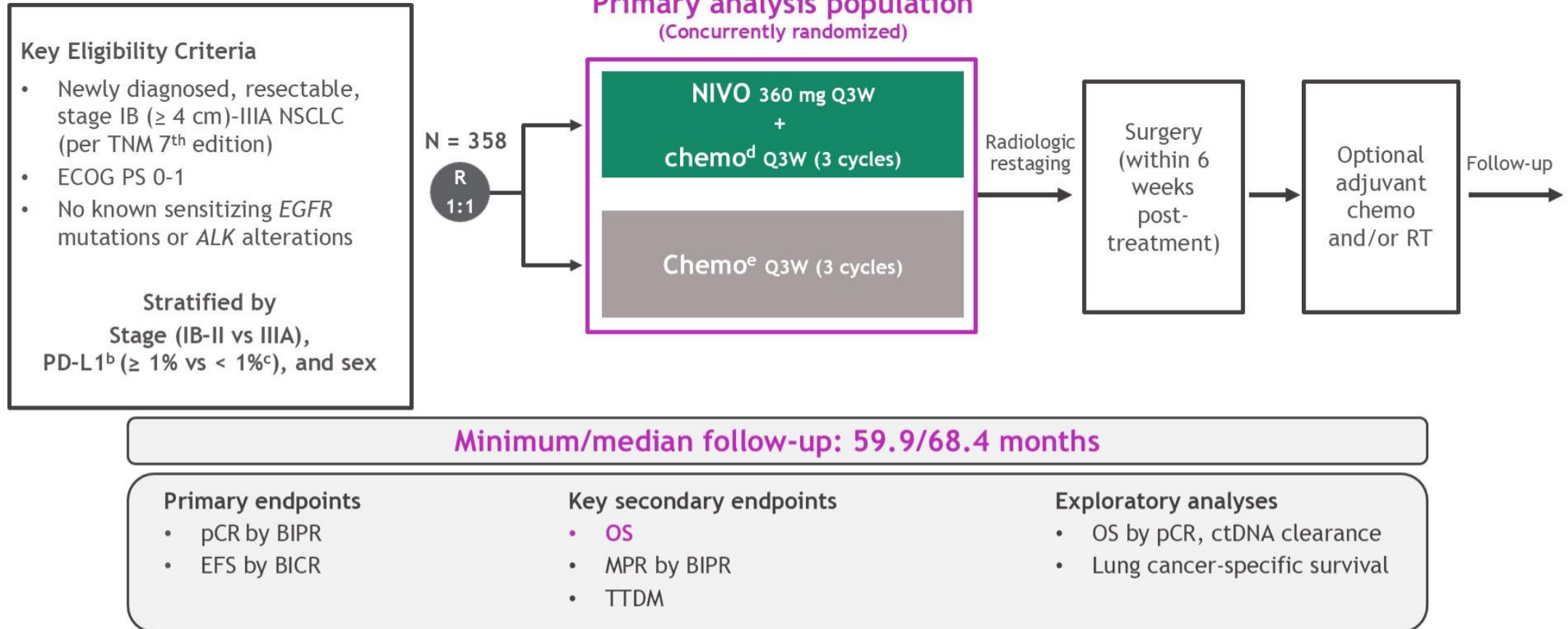
	Chemo+IO	Chemotherapy
Known EGFR mutation n, (%)	14 (3.5)	19 (4.8)
Known ALK translocation n, (%)	12 (3.0)	9 (2.3)

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

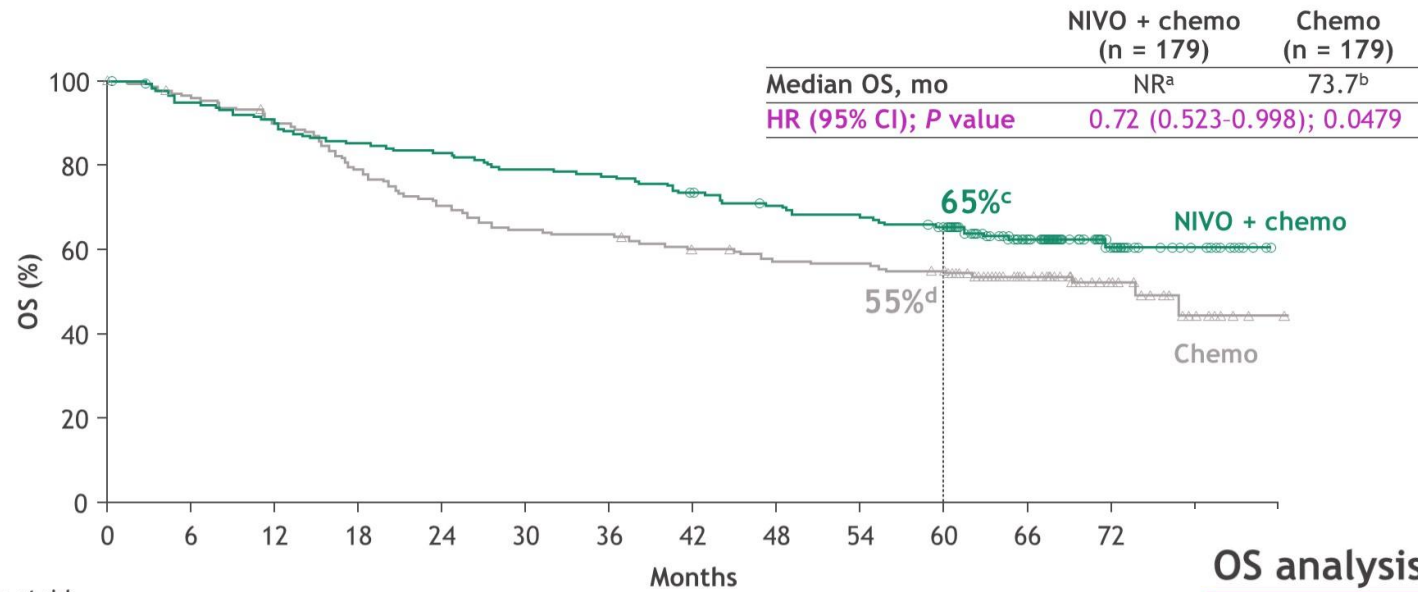


CheckMate 816 study design^a



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. ^aNCT02998528. ^bDetermined by the PD-L1 IHC 28-8 pharmDx assay (Dako). ^cIncluded patients with PD-L1 expression status not evaluable and indeterminate. ^dNonsquamous: pemetrexed + cisplatin or paclitaxel + carboplatin; squamous: gemcitabine + cisplatin or paclitaxel + carboplatin. ^eVinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (squamous only), pemetrexed + cisplatin (nonsquamous only), or paclitaxel + carboplatin.

Final analysis: OS with neoadjuvant NIVO + chemo vs chemo

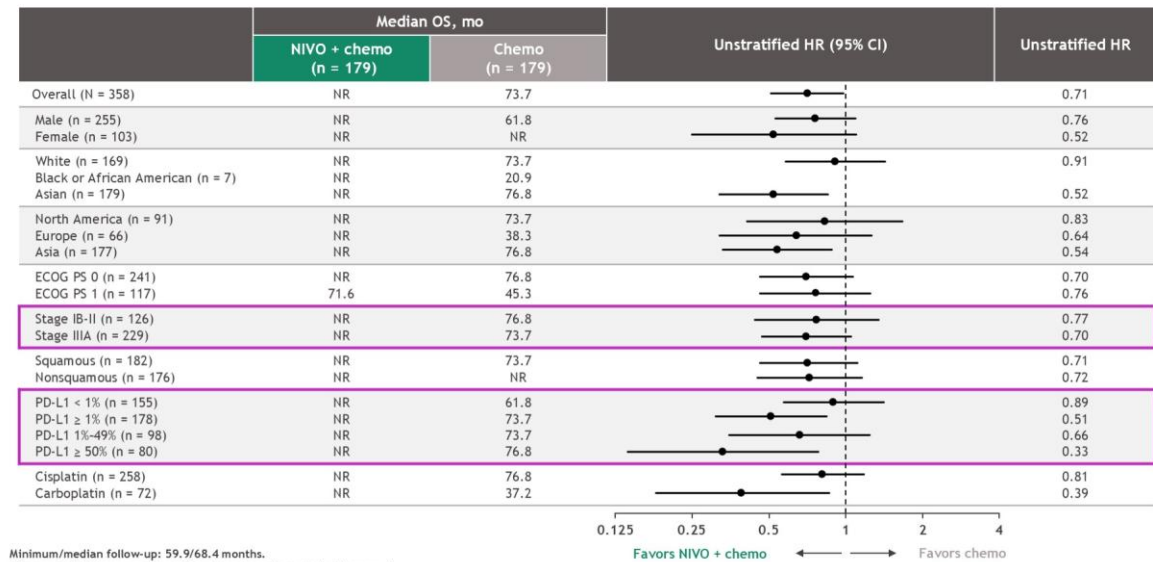


No. at risk	0	6	12	18	24	30	36	42	48	54	60	66	72
NIVO + chemo	179	168	159	151	147	140	137	129	122	117	111	67	29
Chemo	179	170	159	139	124	114	112	104	98	97	91	58	29

Minimum/median follow-up: 59.9/68.4 months.
^a=95% CI; ^bNR; ^c47.3-NR; ^d58-72; ^e47-62.

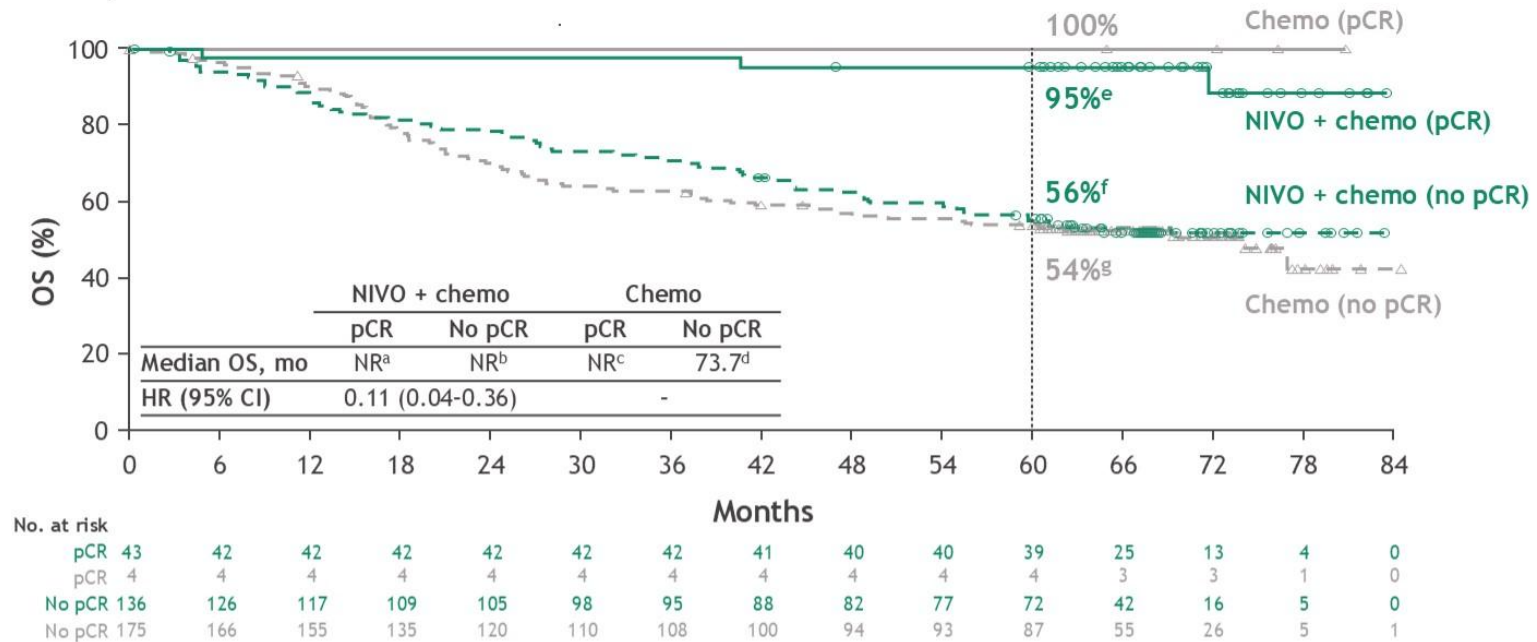
CheckMate 816: 5-y OS final analysis

OS analysis by key subgroups



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 pCR¹



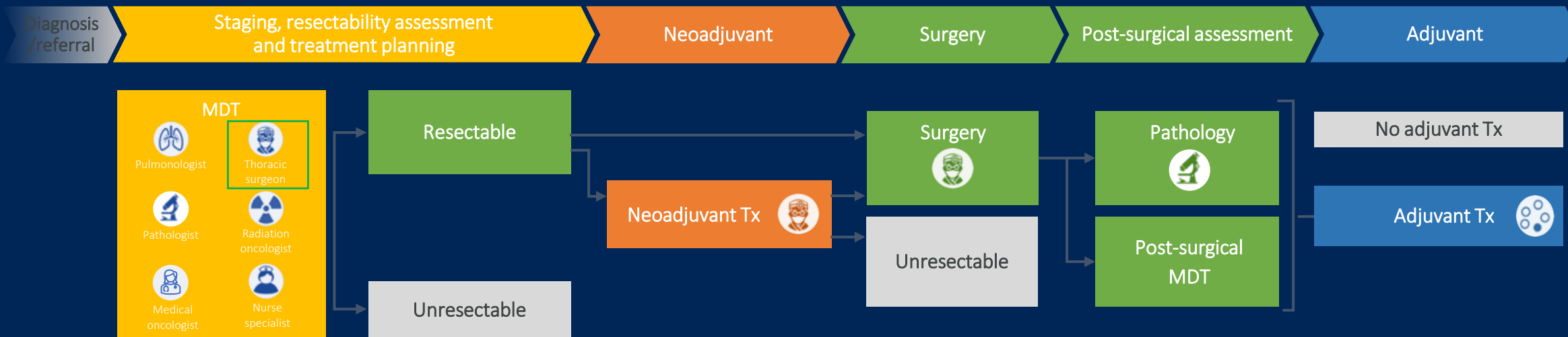
In the NIVO + chemo arm:

- 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 diseaseⁱ

Minimum/median follow-up: 59.9/68.4 months.

HRs were NC if there was an insufficient number of events (< 10 per arm). ^a=95% CI; ^aNR; ^b53.9-NR; ^cNR; ^d46.7-NR; ^e83-99; ^f47-64; ^g46-61. ^hIn the chemo arm, there were no deaths in patients with pCR. ⁱIn 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 – NeoAaura

