Atrium Health
Wake Forest Baptist

# Biomarker Testing in Patient Care for Non-Small Cell Lung Cancer

Thomas W. Lycan Jr., DO, MHS

Lung Cancer Initiative Summit: Community of Hope
9/25/25

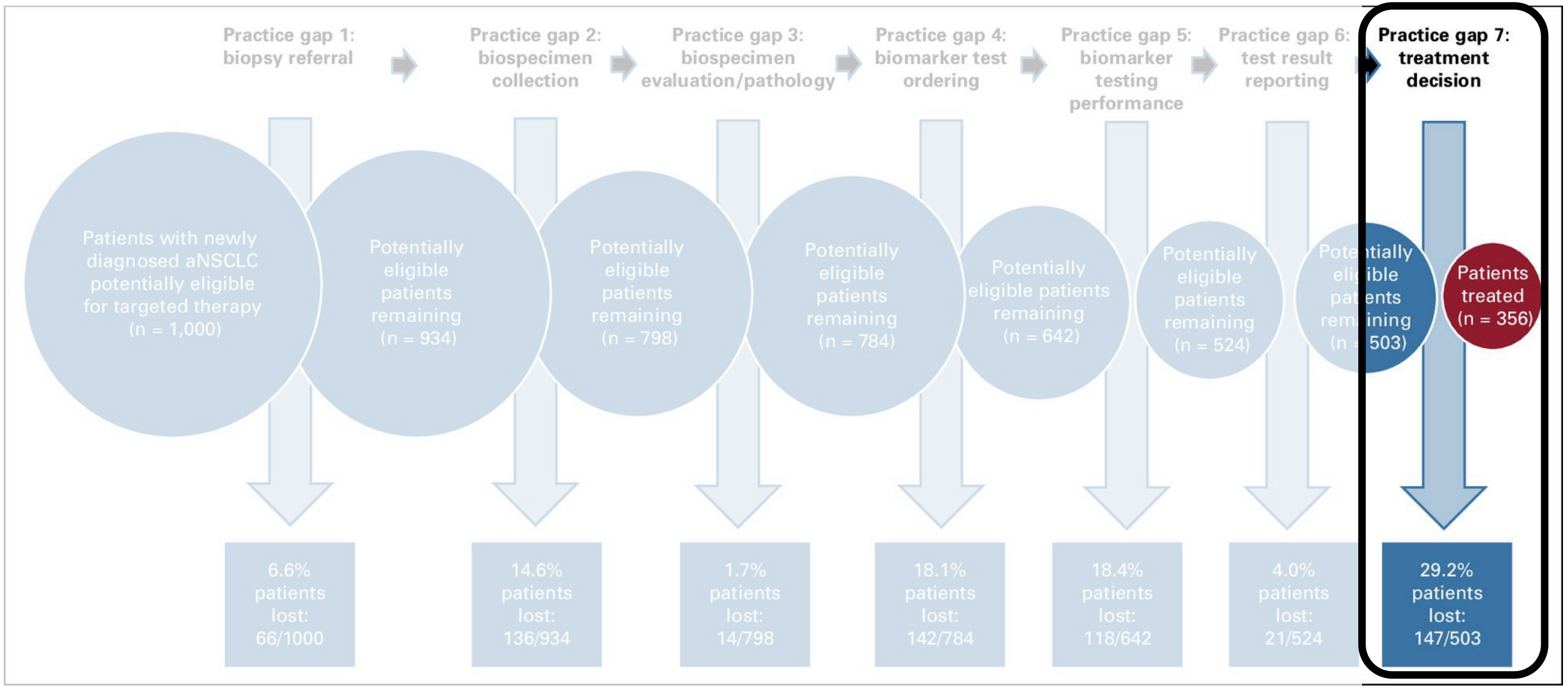
I have no conflicts of interest.

# Goal: Discuss the role of biomarkers in lung cancer care.

**Learning Objectives**: After this session, attendees should be able to…

1. Recognize that an increasing number of biomarker tests are critical to start cancer treatments for higher stages of non-small cell lung cancer (NSCLC).
2. Compare and contrast the use of three major drug classes (chemotherapies, immunotherapies, and targeted therapies) to treat NSCLC.
3. Understand how the “standard approach” to biomarker testing continues to evolve over time for patients who are newly diagnosed with NSCLC.

# Successful biomarker profiling includes treatment selection




Sadik, JCO Precis Oncol, 2022, PMID 36315914.

# Not all biomarkers have clinical utility

- In terms of treatment selection, biomarkers can be:
  - **Critical**: Associated with a preferred standard-of-care therapy.
  - **Actionable:** Associated with a standard-of-care therapy that has some evidence to support its use depending on circumstances.
  - **Informative**: Not associated with a standard-of-care therapy but may inform eligibility for a clinical trial or otherwise be predictive or prognostic.
- At a minimum, successful biomarker profiling needs to include all tests that are **critical** for treatment selection.

# Current State of Biomarkers (2025)

| | Stage | | | | |
|---|---|---|---|---|---|
| Biomarkers | IA | IB-IIIA | IIIB-IIIC | IV 1L | IV 2L+ |
| EGFR | Informative | **Critical** | **Critical** | **Critical** | **Critical** |
| ALK | Informative | **Critical** | **Actionable** | **Critical** | **Critical** |
| PD-L1* | Informative | **Critical** | **Actionable** | **Critical** | Informative |
| ROS1, BRAF, NTRK, METex14, RET | Informative | Informative | Informative | **Critical** | **Critical** |
| KRAS, METamp, ERBB2, NRG1, HER2*, cMET*, FGFR | Informative | Informative | Informative | **Actionable** | **Critical** |
| Others | Informative | Informative | Informative | Informative | **Actionable** |

*Expression is tested by IHC on tumor tissue and therefore cannot be obtained in peripheral blood.

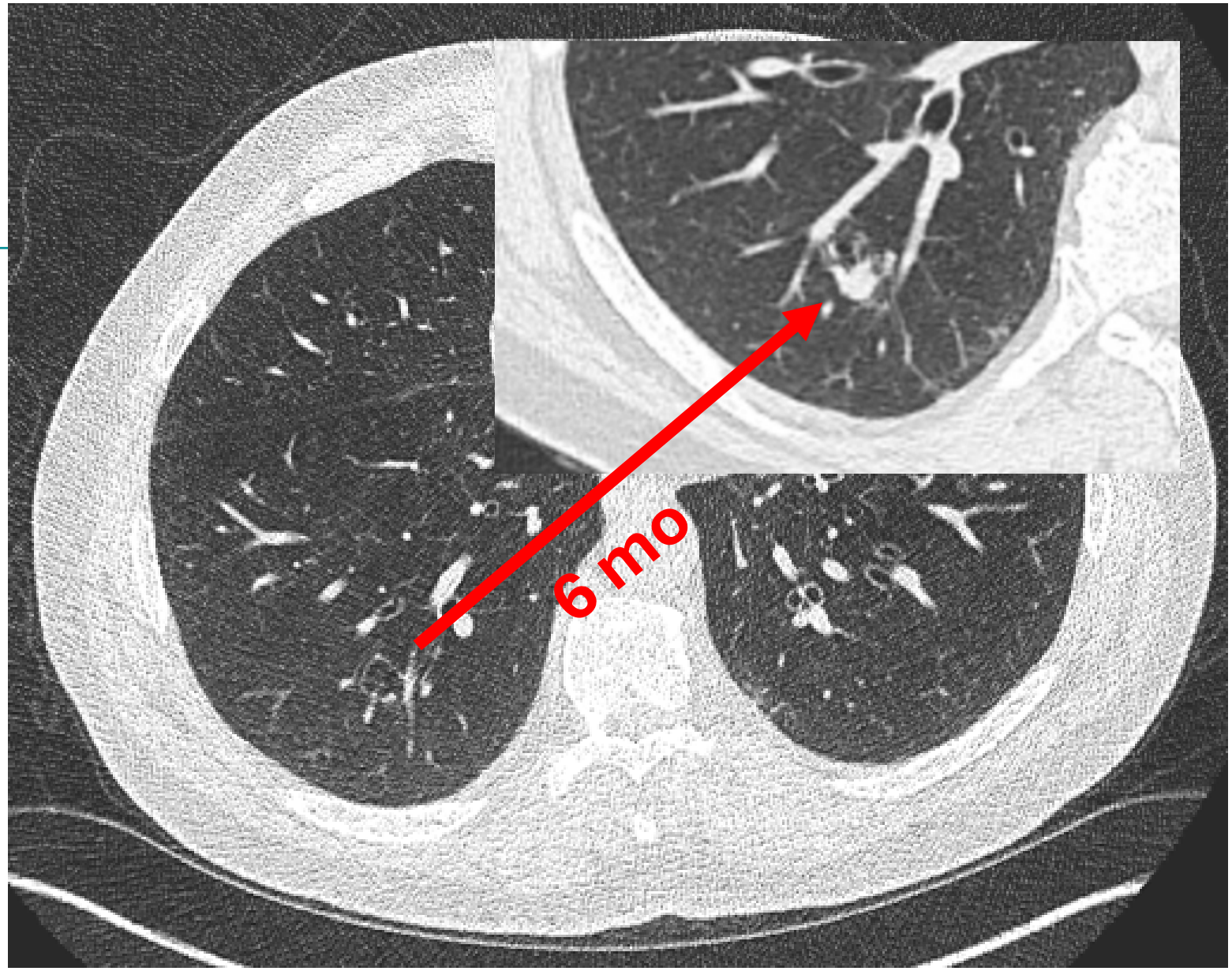
# Patient A

58yo WM trucker

Cigarettes 1PPD x 30yrs

Lung cancer screening finds 0.8cm RLL nodule

Increasing solid component



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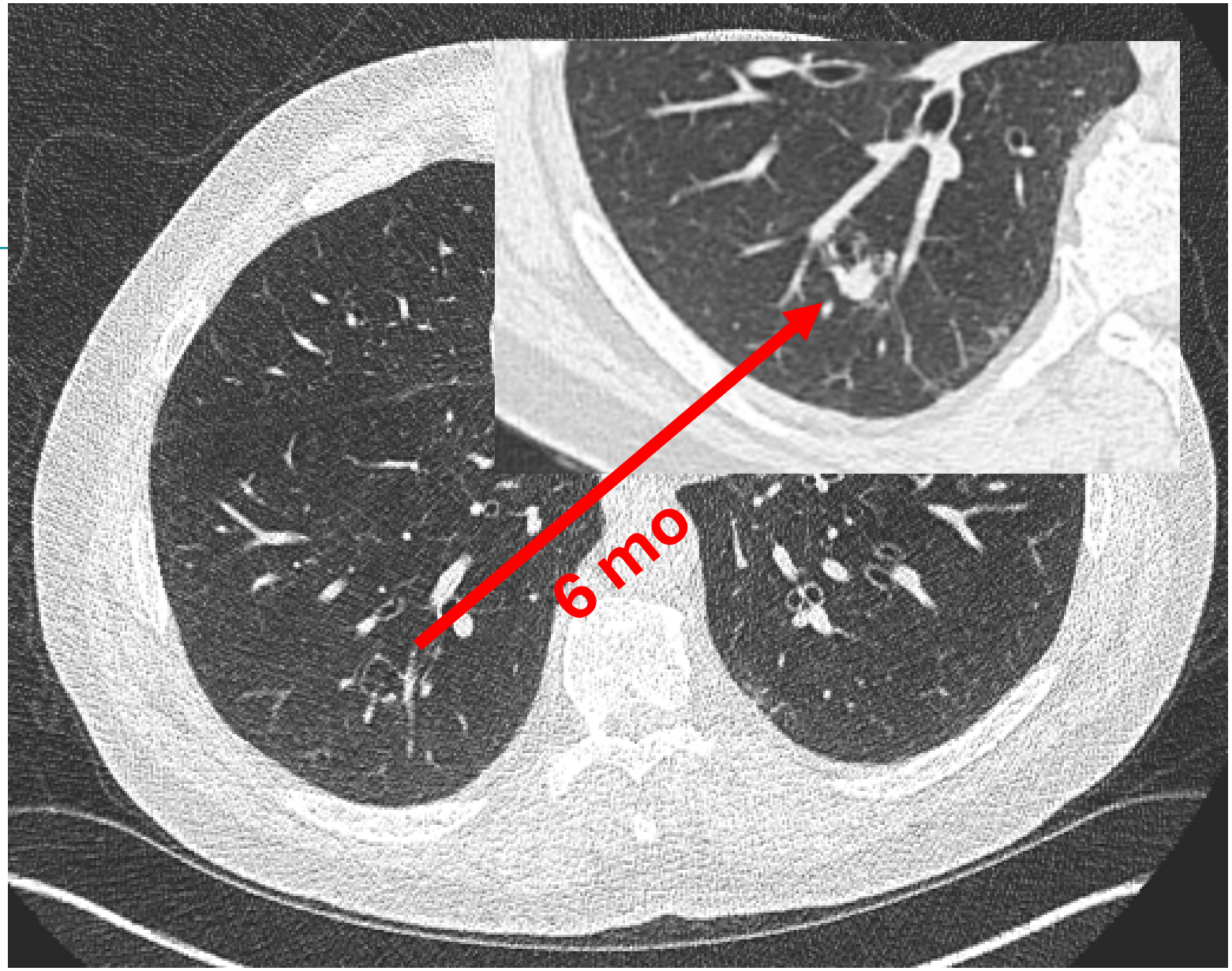
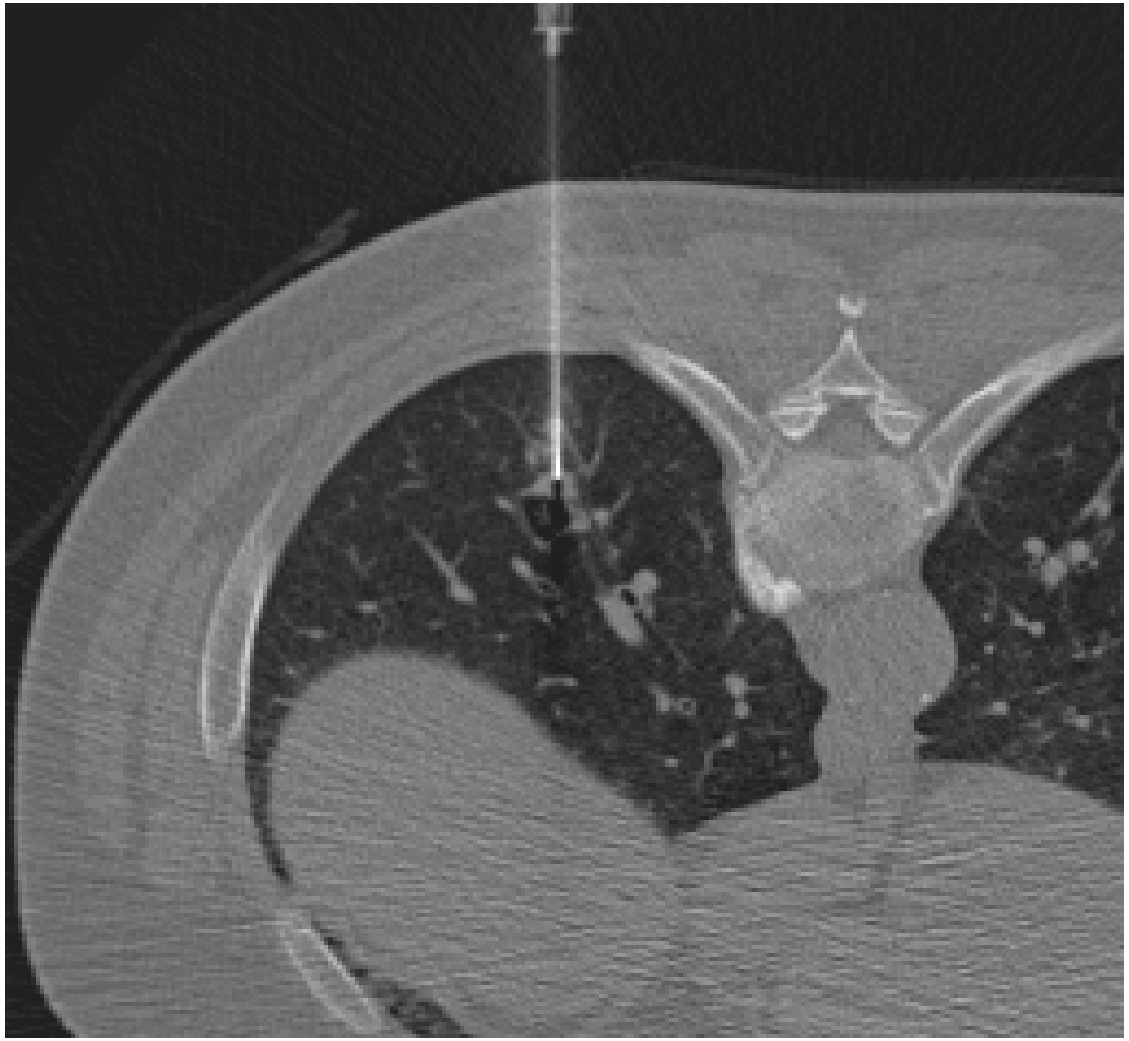
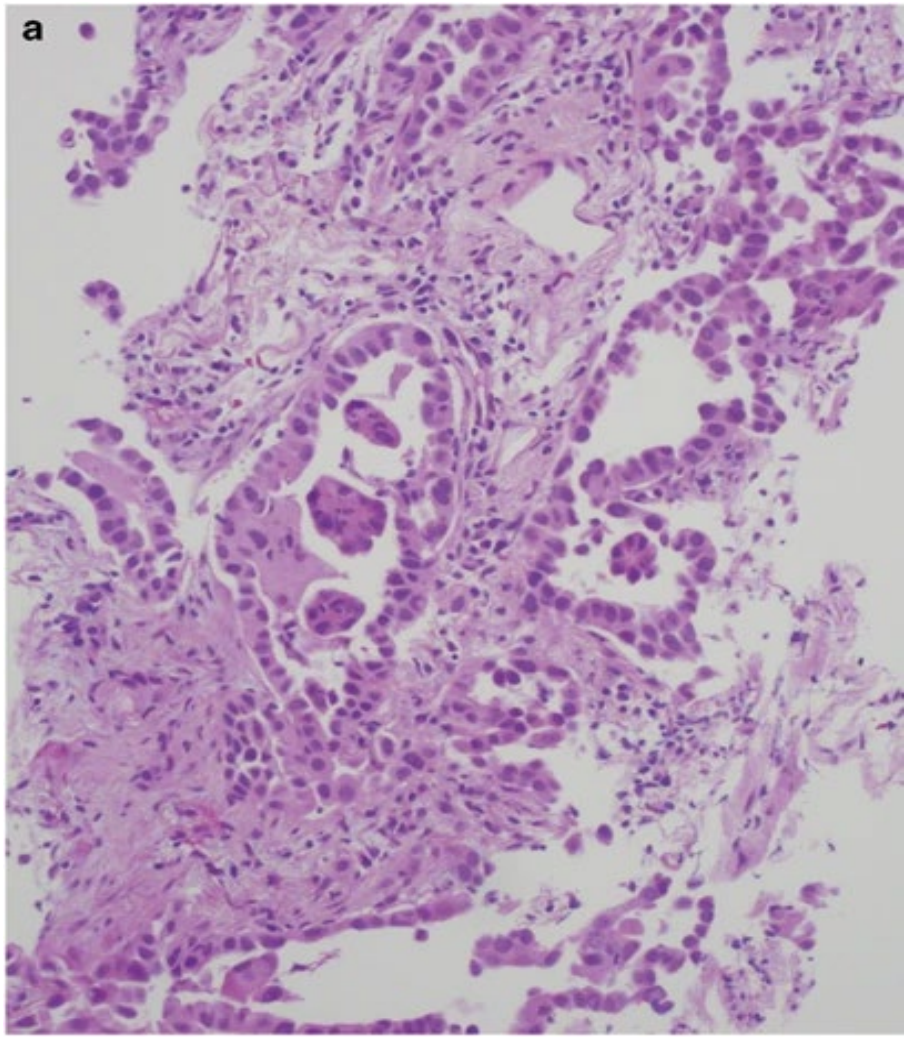


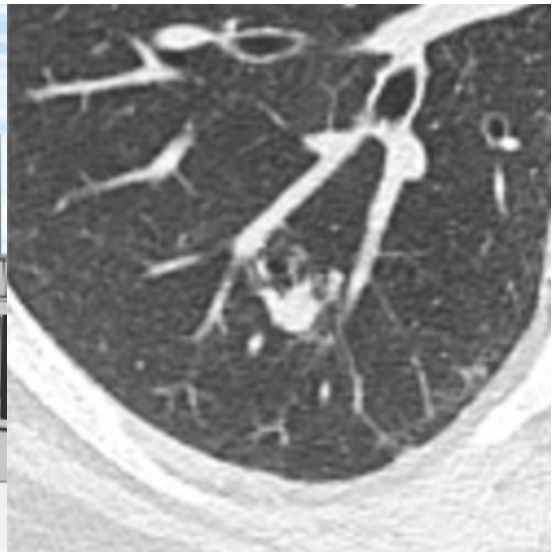
# Adenocarcinoma






PMID 22214970

# Patient A / Question #1



58yo p/w stage IA2 NSCLC (T1bN0M0).

Insufficient tissue for biomarker testing.

**What is your recommendation?**

---

1) Repeat lung biopsy for NGS testing on tumor tissue.
2) Peripheral blood for NGS testing of circulating tumor DNA.
3) Surgical resection.
4) Watchful waiting.

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| Others | Informative | Informative | Informative | Informative | Actionable |

*PD-L1 + HER2 expression is tested by IHC on tumor tissue and therefore cannot be obtained in peripheral blood.

# Clinical trial in progress – ADAURA2

**Adult participants with completely resected stage IA2 or IA3* EGFRm NSCLC**

**Key eligibility criteria:**

- Aged ≥18 years
- Confirmed primary non-squamous pathological stage IA2 or IA3 (>1cm and <3cm in size) NSCLC*
- EGFR mutation (Ex19del or L858R) either alone or in combination with other EGFR mutations
- Complete (R0) surgical resection of the primary tumor with negative margins (by lobectomy, segmentectomy or sleeve resection)
- Tumor sample submission for central pathology assessment of:
  - Invasive tumor size
  - Presence of lymphovascular invasion
  - Tumor histology
- WHO performance status 0 / 1
- No pre- / post-operative radiotherapy or systemic therapy
- Not eligible for any other local SOC treatment

**Stratification by:**

- **Risk** (high risk vs low risk†)
- **EGFR mutation type** (Exon19del vs L858R)
- **Race** (Chinese Asian vs non-Chinese Asian vs non-Asian)

**Osimertinib 80 mg PO QD**

**Randomization 1:1 (N=380)**

**Placebo PO QD**

3-year treatment duration until treatment completion, discontinuation, or disease recurrence

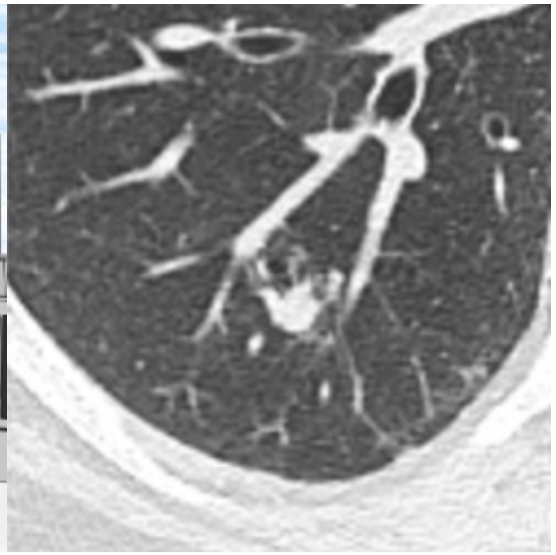
**Primary endpoint:**
DFS per investigator assessment in high-risk† stratum

**Secondary endpoints:**

- DFS in overall population
- OS in high-risk† stratum
- OS in overall population
- HRQoL
- Safety / tolerability
- PK
- CNS DFS

Tsutani, Clin Lung Cancer, 2023, PMID 36872181.

# Patient A



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Insufficient tissue for biomarker testing.

**What is your recommendation?**

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3) Surgical resection.
4) Watchful waiting.

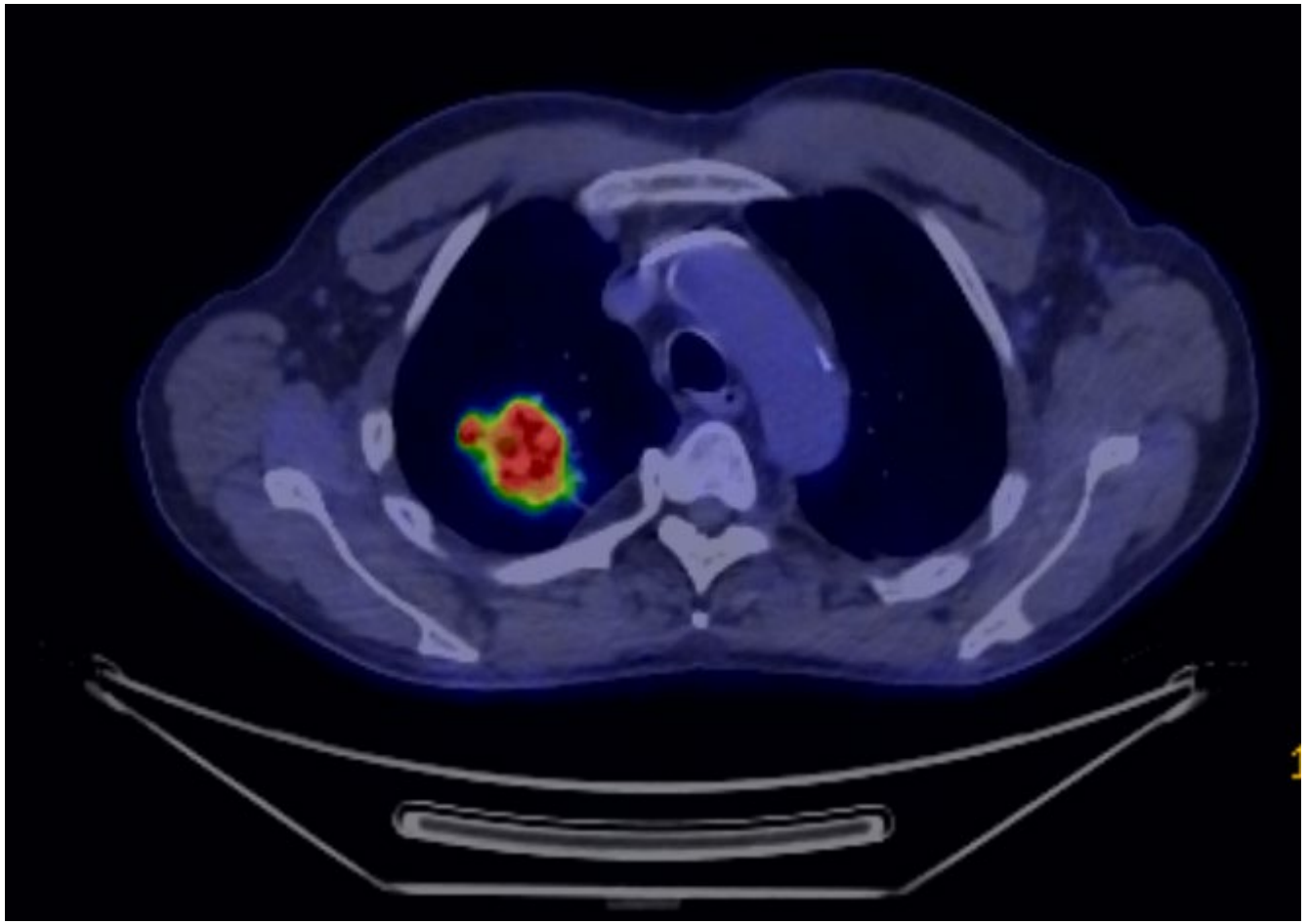
# Patient B

46yo office administrator

Minimal smoking history.

Incidentally found R lung mass that is 4.5cm.

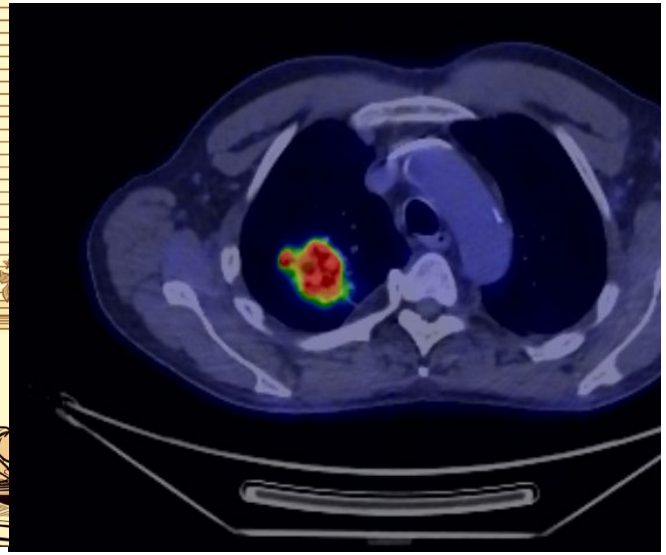
Biopsies by bronchoscopy return as non-small cell lung cancer, adenocarcinoma.



# Question #2

46yo p/w stage IIB adeno NSCLC (cT2bN0M0) that is surgically resectable.

**What do you recommend as the next step?**



1) Surgical resection.
2) Neoadjuvant platinum chemotherapy + immunotherapy.
3) Neoadjuvant platinum chemotherapy.
4) Request biomarker tests (e.g., EGFR, ALK, PD-L1).

# Current State of Biomarkers (2025)

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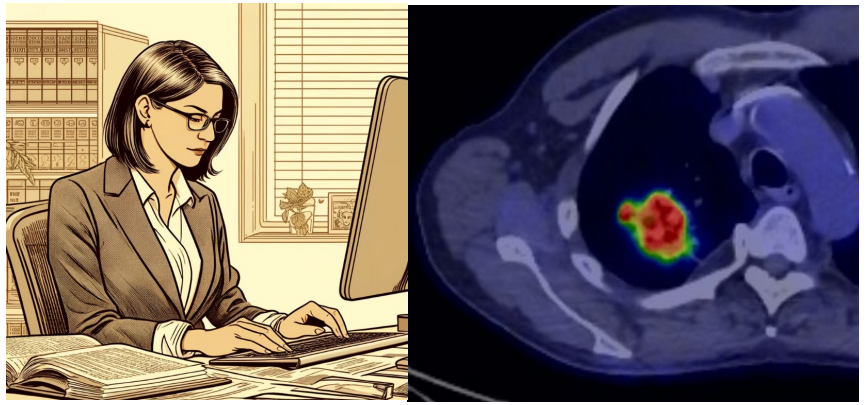
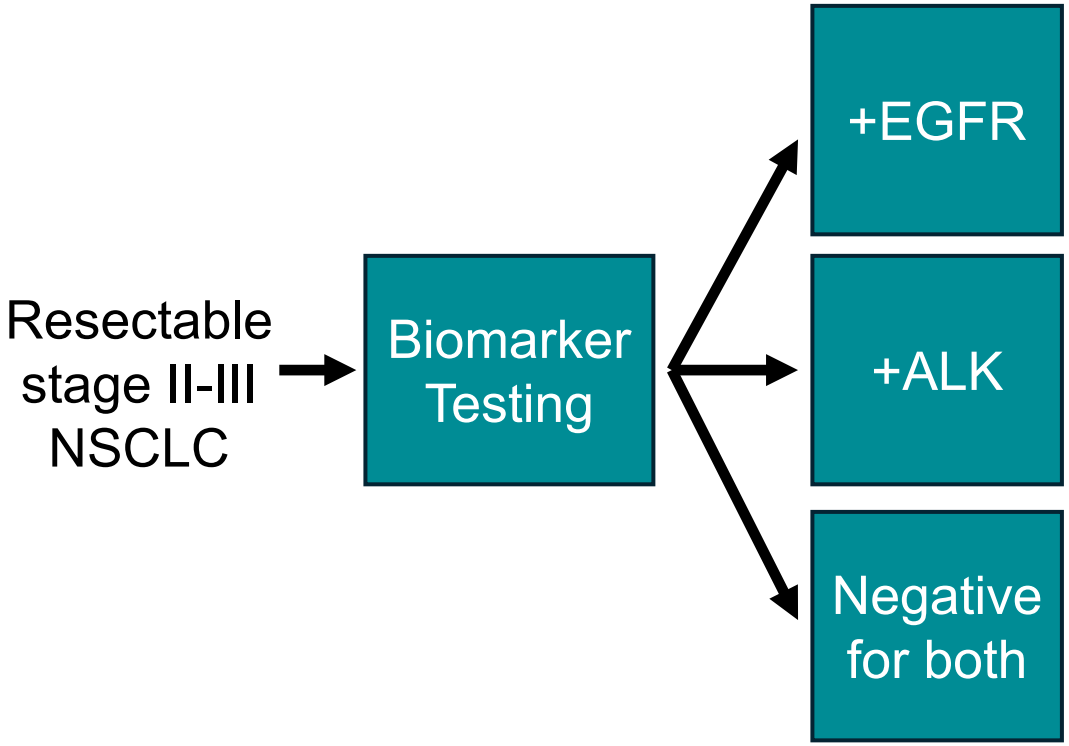
*PD-L1 + HER2 expression is tested by IHC on tumor tissue and therefore cannot be obtained in peripheral blood.

# Treatment Approach

58yo presenting with resectable stage IIB (cT2bN0M0) adenocarcinoma non-small cell lung cancer (NSCLC)






Spicer et al, J Thorac Oncol, 2024, PMID 38901648.

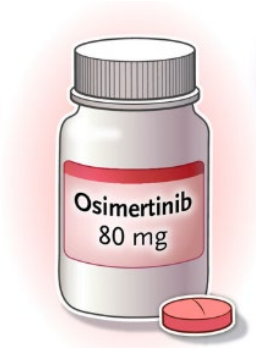
# ADAURA: Adjuvant therapy for resected **(+)EGFR** NSCLC

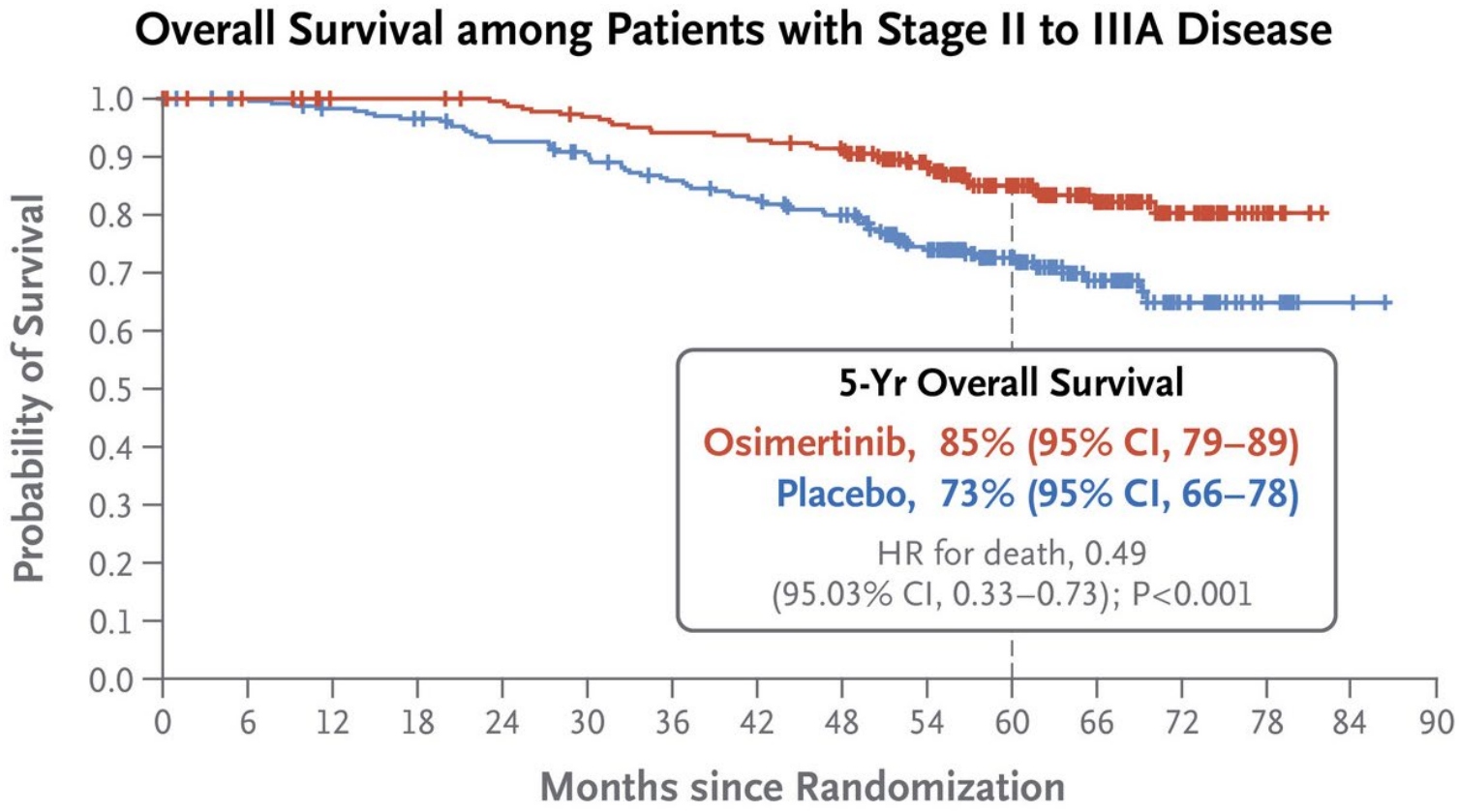
Stage IB (≥4cm), II, IIIA s/p R0

+/-



Placebo



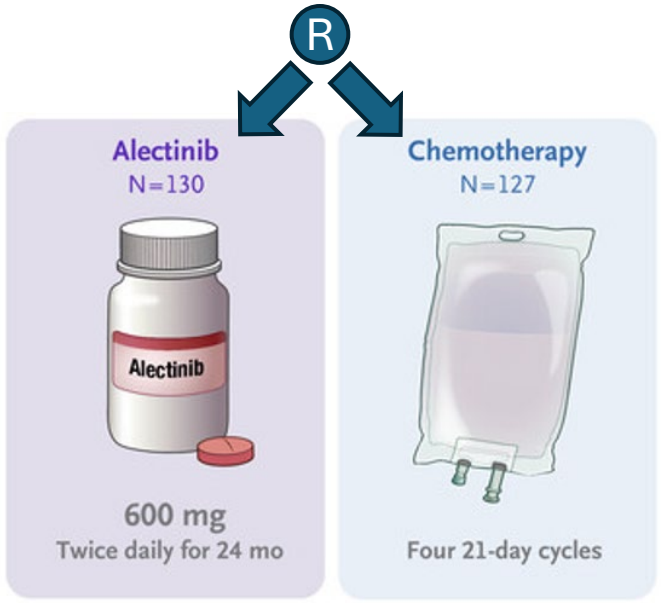




12/18/20: FDA approval

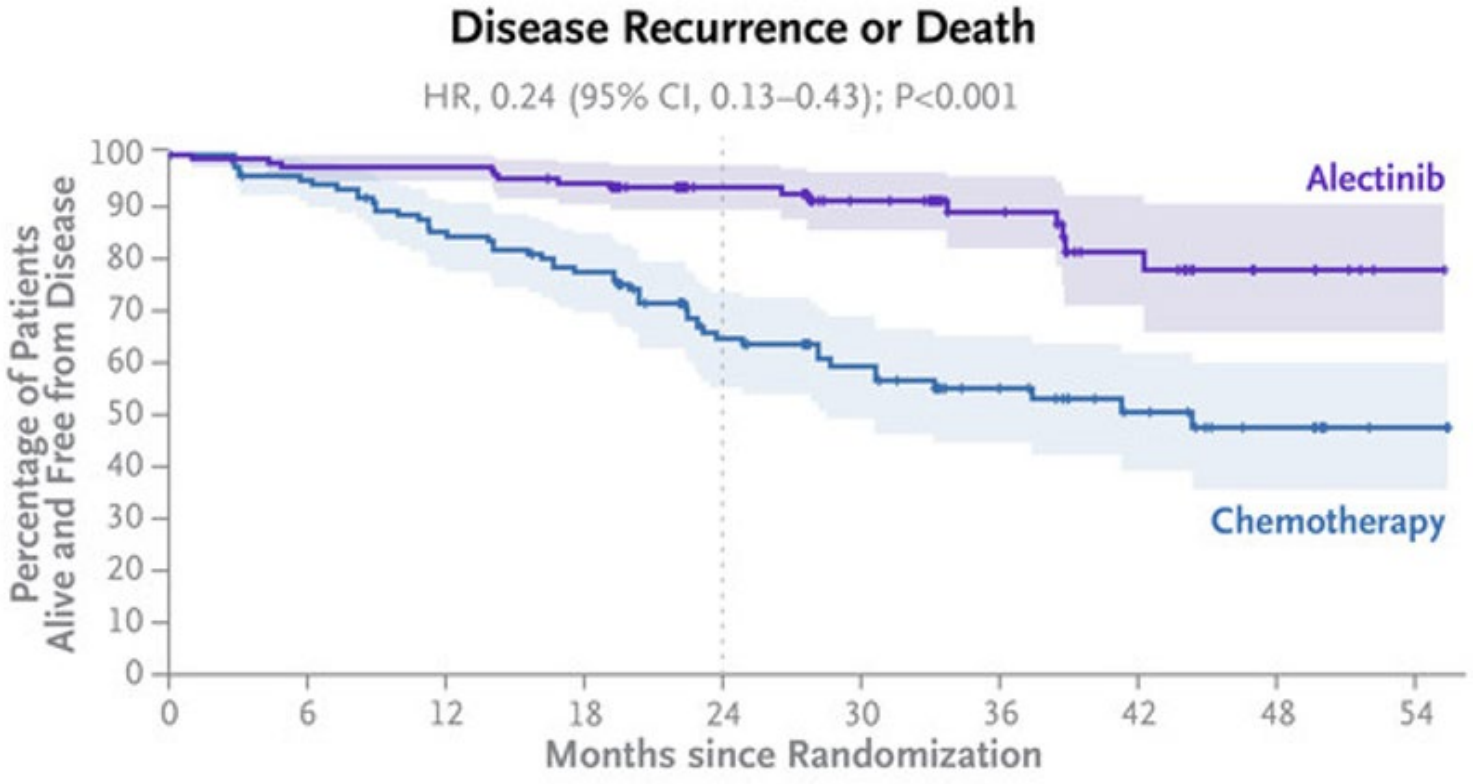
Tsuboi, N Engl J Med, 2023, PMID 37272535.

# ALINA: Adjuvant therapy for resected **(+)ALK** NSCLC

Stage IB (≥4cm), II, IIIA s/p R0




4/18/24: FDA approval



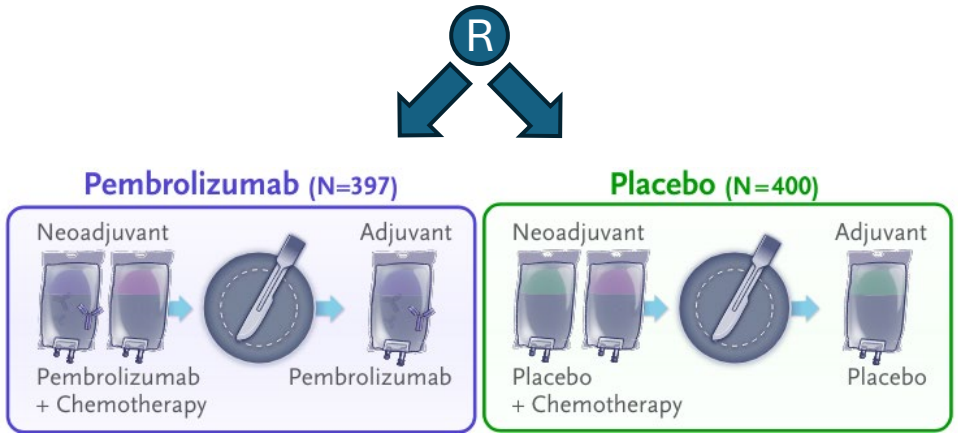

Wu, N Engl J Med, 2024, PMID 38598794.

# KEYNOTE-671: Pembrolizumab before and after surgery

**Oct 2023**

Resectable stage II-IIIB by AJCC 8th edition

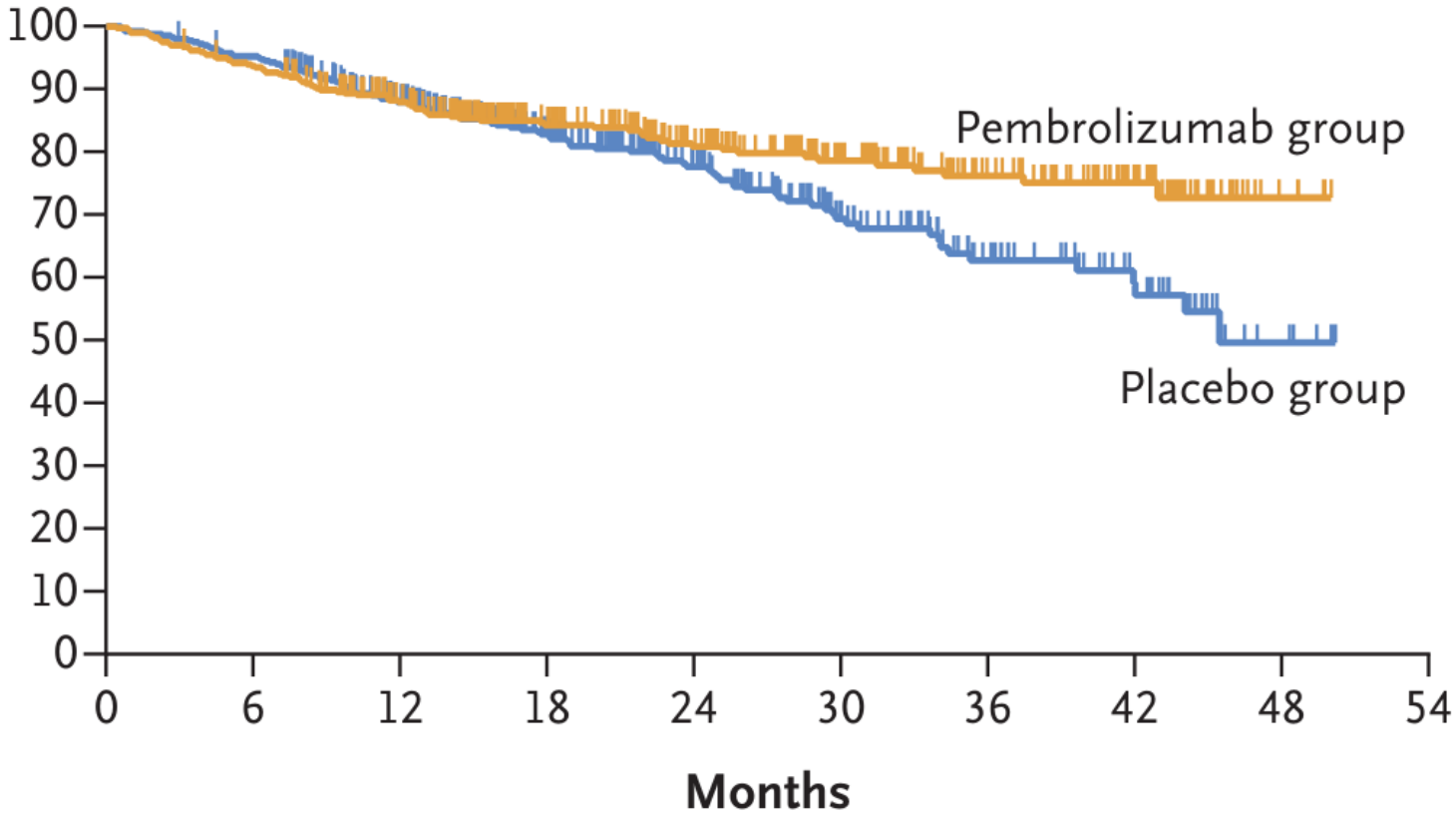
(i.e., T≥4cm and N0-2)




Pathological complete response

18% vs 4% placebo

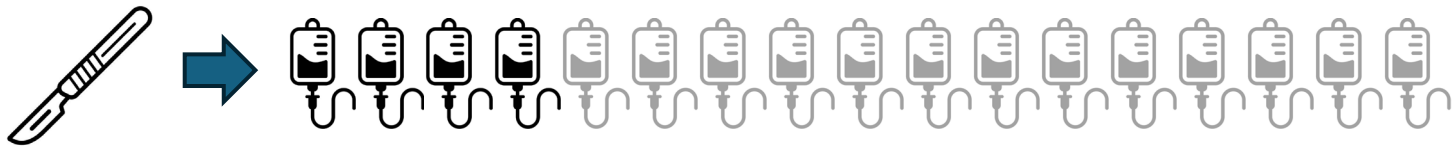
24mo overall survival 81% vs 78% (follow-up met significance)



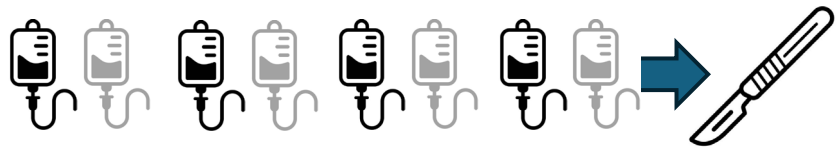

Wakelee, N Engl J Med, 2023, PMID 37272513.

# Peri-operative chemo + immunotherapy: multiple options to choose from

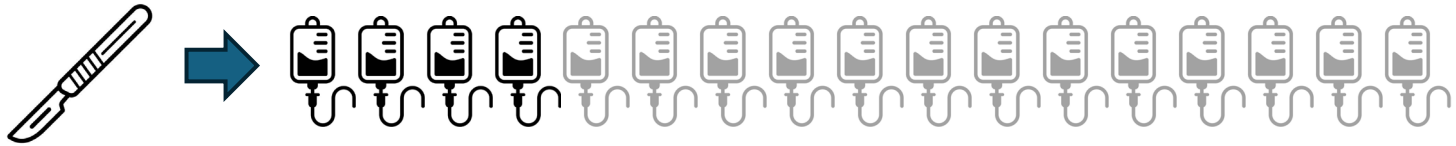
**Oct 2021** **IMpower010**
Adjuvant atezo x1 year



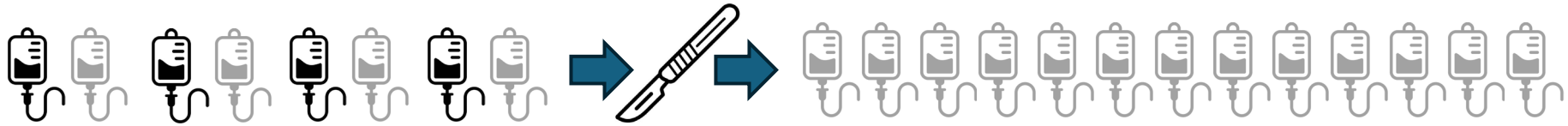
**Mar 2022** **CheckMate 816**
Neo nivo/chemo x3



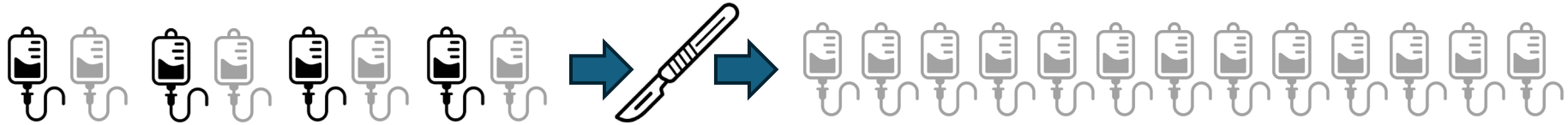
**Jan 2023** **KEYNOTE-091 (PEARLS)**
Adjuvant pembro x1 year



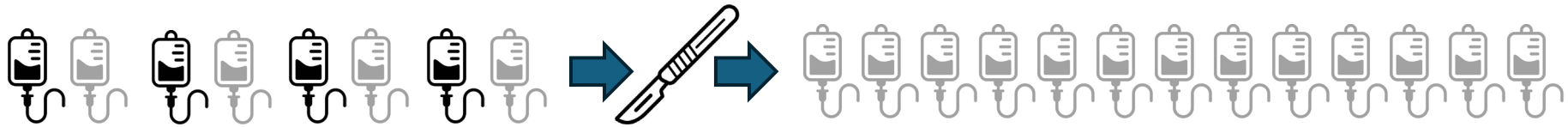
**Oct 2023** **KEYNOTE-671***
Periop pembro



**Aug 2024** **AEGEAN**
Periop durva

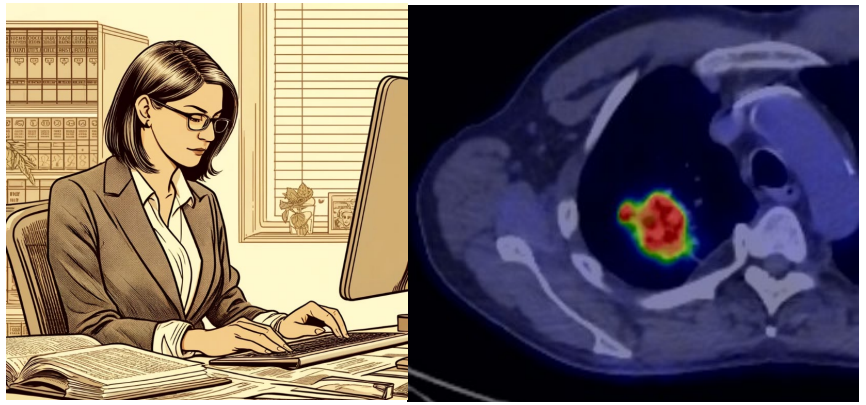


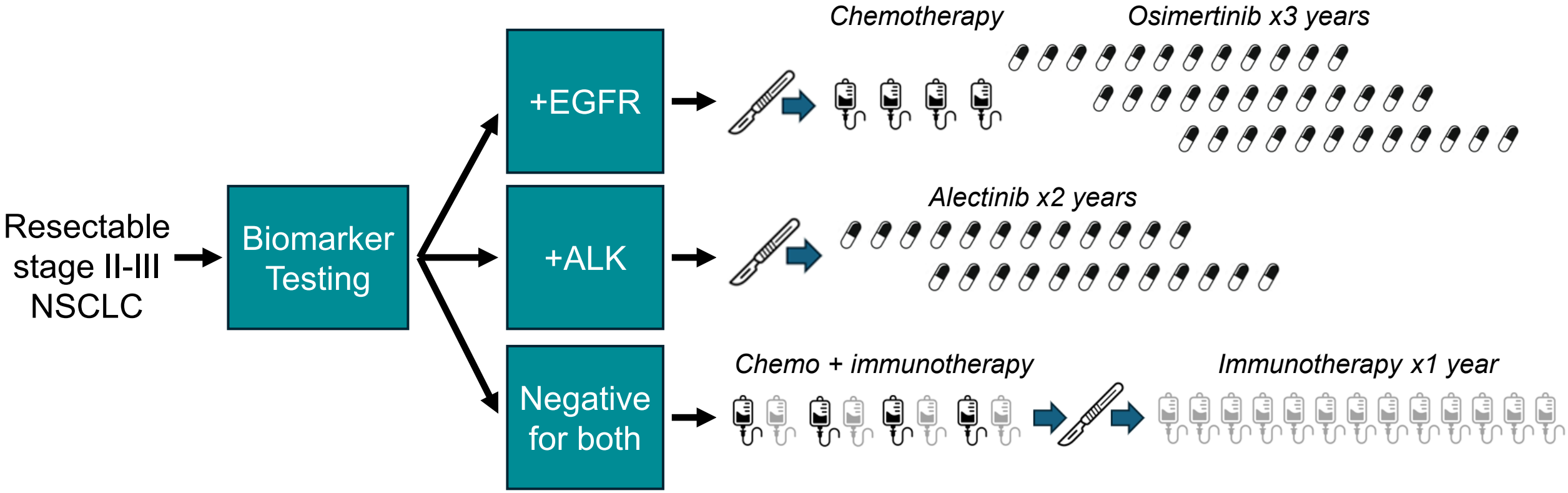
**Oct 2024** **CheckMate 77T**
Periop nivo



# Treatment Approach

58yo presenting with resectable stage IIB (cT2bN0M0) adenocarcinoma non-small cell lung cancer (NSCLC)



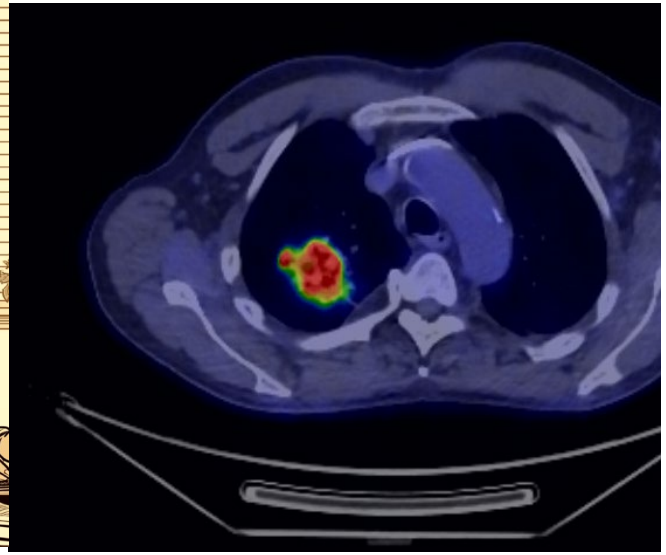



Spicer et al, J Thorac Oncol, 2024, PMID 38901648.

# Question #2

46yo p/w stage IIB adeno NSCLC (cT2bN0M0) that is surgically resectable.

**What do you recommend as the next step?**



1) Surgical resection.
2) Neoadjuvant platinum chemotherapy + immunotherapy.
3) Neoadjuvant platinum chemotherapy.
4) Request biomarker tests (e.g., EGFR, ALK, PD-L1).

# Patient A: Biomarker Testing

## PD-L1 (22C3) SemiQuant IHC, Manual

**Interpretation**

Brain, right temporal , specimen for PD-L1 immunohistochemistry proprietary detection system) (WFS23–4729-B1):

30% tumor cells are positive for PD-L1 (membranous positivity).

## Biomarker Findings

**Tumor Mutational Burden** - 17 Muts/Mb

**Microsatellite status** - MS-Stable

## Genomic Findings

*For a complete list of the genes assayed, please refer to the Appendix.*

***KRAS*** amplification - equivocal, G12C†

***ATM*** splice site 4437-1G>T

***MYC*** amplification - equivocal†

***DNMT3A*** K140*

***JAK2*** V617F - subclonal†

***KDM5C*** E686*

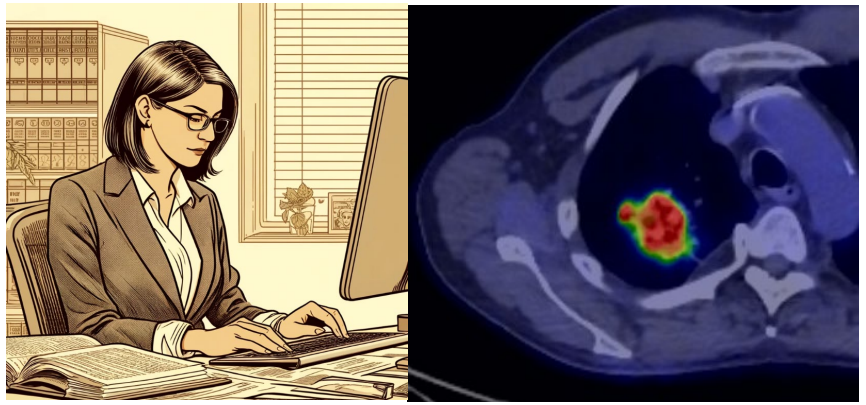
***NFKBIA*** amplification

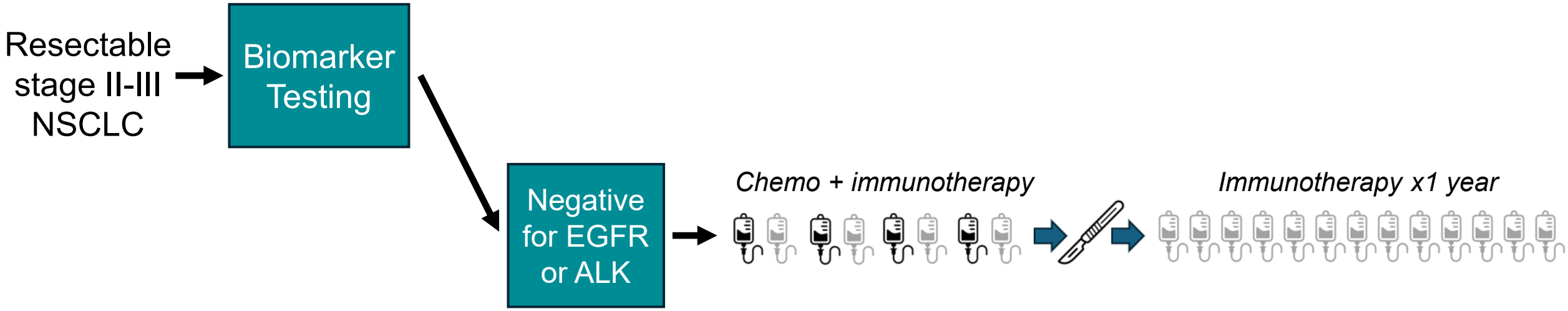
***NKX2-1*** amplification

**7** Disease relevant genes with no reportable alterations: ***ALK, BRAF, EGFR, ERBB2, MET, RET, ROS1***

# Treatment Approach

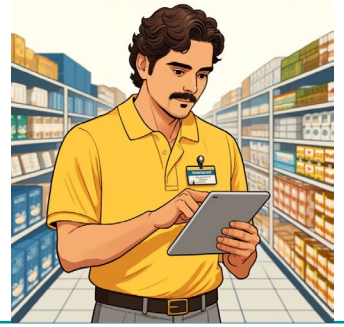
In the absence of a high-level alteration, perioperative chemo/immunotherapy should be considered for resectable stage II-III NSCLC.



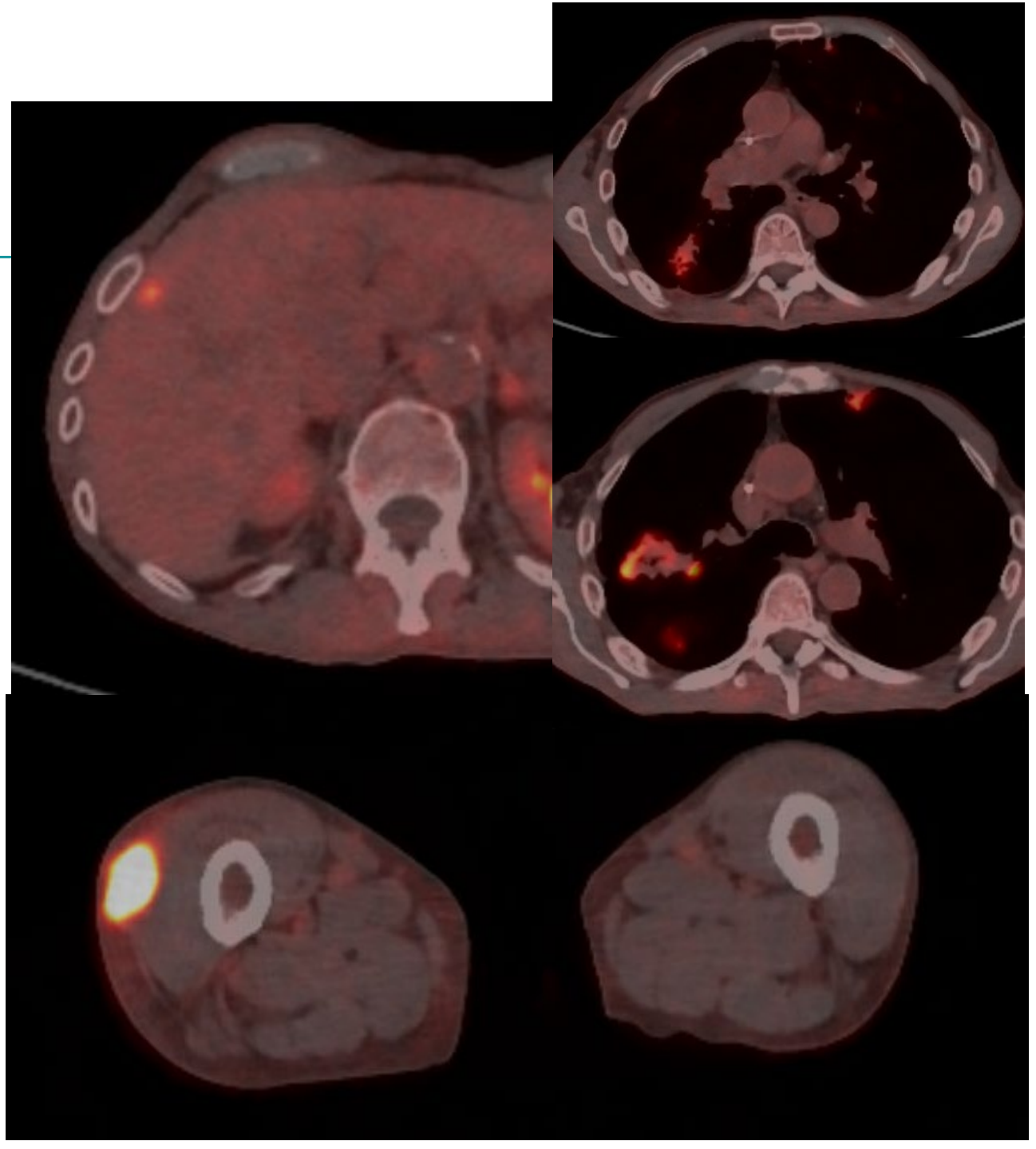



Spicer et al, J Thorac Oncol, 2024, PMID 38901648.

# Patient C



- 60yo grocery store employee presents with severe back pain due to bone metastases from a new diagnosis of stage IV non-small cell lung adenocarcinoma.
- He undergoes urgent palliative radiation therapy to a painful vertebral metastasis.
- He has no autoimmune comorbidities.
- His goals of care are in favor of aggressive treatment options.



# Question #3

60yo with a new diagnosis of stage IV adeno NSCLC with metastases to liver, soft tissue, bone.

PCR testing is negative for EGFR.

**What is the next step in management?**

1) Immunotherapy.
2) Platinum chemotherapy + immunotherapy.
3) Selective biomarker testing for EGFR, ALK, and PD-L1.
4) Broad molecular profiling of tumor.

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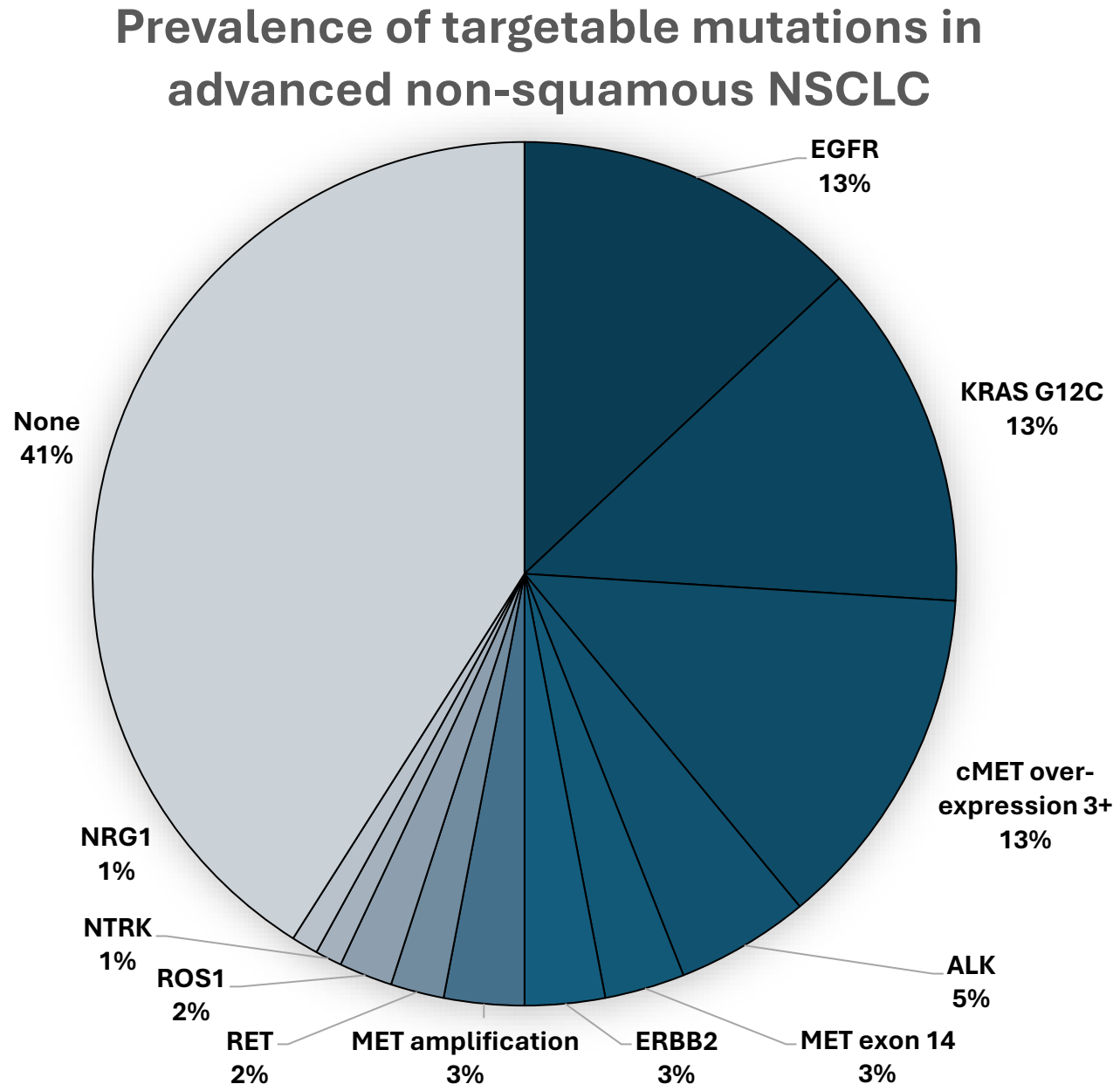
*PD-L1 + HER2 expression is tested by IHC on tumor tissue and therefore cannot be obtained in peripheral blood.

# New drug development increases the number of actionable biomarkers

- Selective biomarker tests for single alterations (“a la carte”) miss other actionable biomarkers and are not as cost effective.
- Broad molecular profiling is most commonly done with DNA-based next-generation sequencing



NCCN v3.2025

| Alteration | Targeted Therapy Options |
|---|---|
| EGFR exon 19 deletion, exon 21 L858R | 1L osimertinib +/- chemotherapy; 1L amivantamab + lazertinib, etc |
| EGFR S768I, L861Q, G719X | 1L afatinib; 1L osimertinib |
| EGFFR exon 20 insertion | 1L amivantamab + chemotherapy |
| KRAS G12C | 2L sotorasib; 2L adagrasib |
| ALK rearrangement | 1L alectinib; 1L brigatinib; 1L lorlatinib; 1L ensartinib |
| ROS1 rearrangement | 1L/2L entrectinib; 1L/2L repotrectinib; 1L crizotinib; 2L lorlatinib |
| BRAF V600E | 1L/2L dabrafenib + trametinib; 1L/2L encorafenib + binimetinib |
| NTRK 1/2/3 gene fusion | 1L larotrectinib; 1L entrectinib; 1L repotrectinib |
| MET exon 14 skipping mutation | 1L capmatinib; 1L tepotinib |
| MET amplification (high-level, CN >10) | 2L capmatinib, 2L tepotinib, 2L crizotinib (emerging) |
| cMET over-expression (IHC 3+) | 2L telisotuzumab vedotin-tllv |
| RET rearrangement | 1L selpercatinib; 1L pralsetinib |
| ERBB2 (HER2) mutation | 2L fam-trastuzumab deruxtecan; 2L ado trastuzumab emtansine |
| NRG1 fusion | 2L zenocutuzumab-zbco |
| HER2 overexpression (IHC 3+) | 2L trastuzumab deruxtecan |
| FGFR alteration | Erdafitinib |

# Question #3

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NCCN v3.2025

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|---|---|
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| ALK rearrangement | 1L alectinib; 1L brigatinib; 1L lorlatinib; 1L ensartinib |
| ROS1 rearrangement | 1L/2L entrectinib; 1L/2L repotrectinib; 1L crizotinib; 2L lorlatinib |
| BRAF V600E | 1L/2L dabrafenib + trametinib; 1L/2L encorafenib + binimetinib |
| NTRK 1/2/3 gene fusion | 1L larotrectinib; 1L entrectinib; 1L repotrectinib |
| MET exon 14 skipping mutation | 1L capmatinib; 1L tepotinib |
| MET amplification (high-level, CN >10) | 2L capmatinib, 2L tepotinib, 2L crizotinib (emerging) |
| cMET over-expression (IHC 3+) | 2L telisotuzumab vedotin-tllv |
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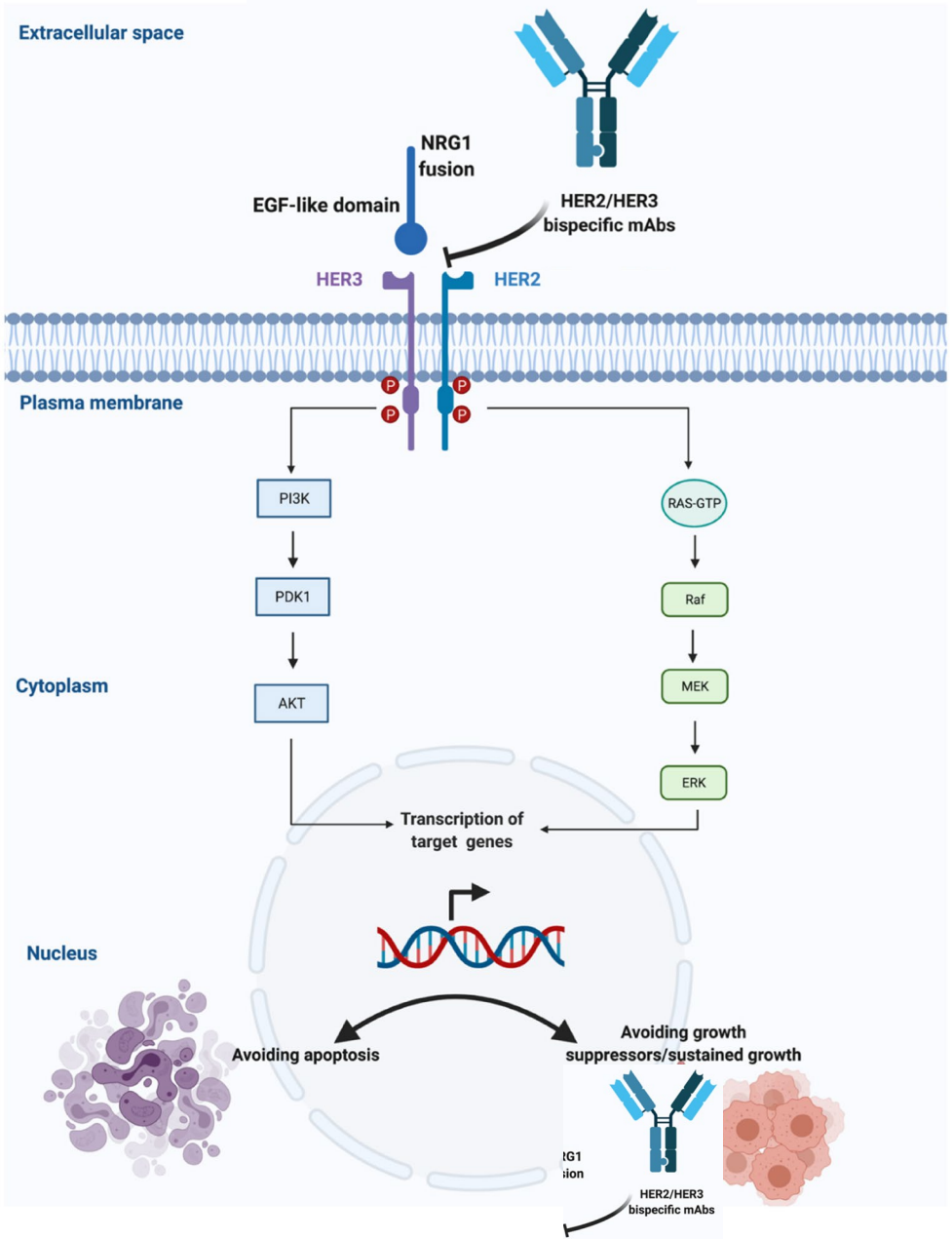
| ERBB2 (HER2) mutation | 2L fam-trastuzumab deruxtecan; 2L ado trastuzumab emtansine |
| NRG1 fusion | 2L zenocutuzumab-zbco |
| HER2 overexpression (IHC 3+) | 2L trastuzumab deruxtecan |
| FGFR alteration | Erdafitinib |

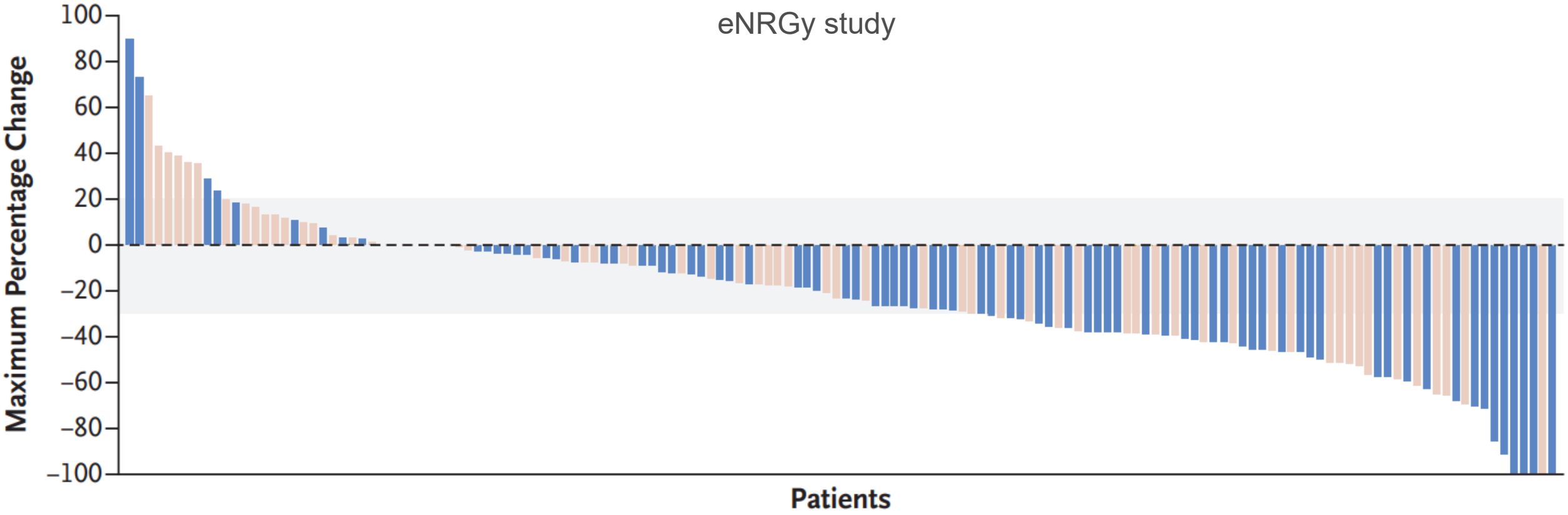
# NRG1 fusion (<1% of NSCLC)




- NRG1 fusion creates proteins that bind and activate HER2 and HER3.
- Zenocutuzumab is a first-in-class, humanized, full-length IgG1 bispecific antibody directed against HER2 and HER3.

Adapted from Rosas et al, Cancers (Basel), 2021, PMID 34680187.

# 12/4/24: Zenocutuzumab-zbco approved for +NRG1 NSCLC 2L

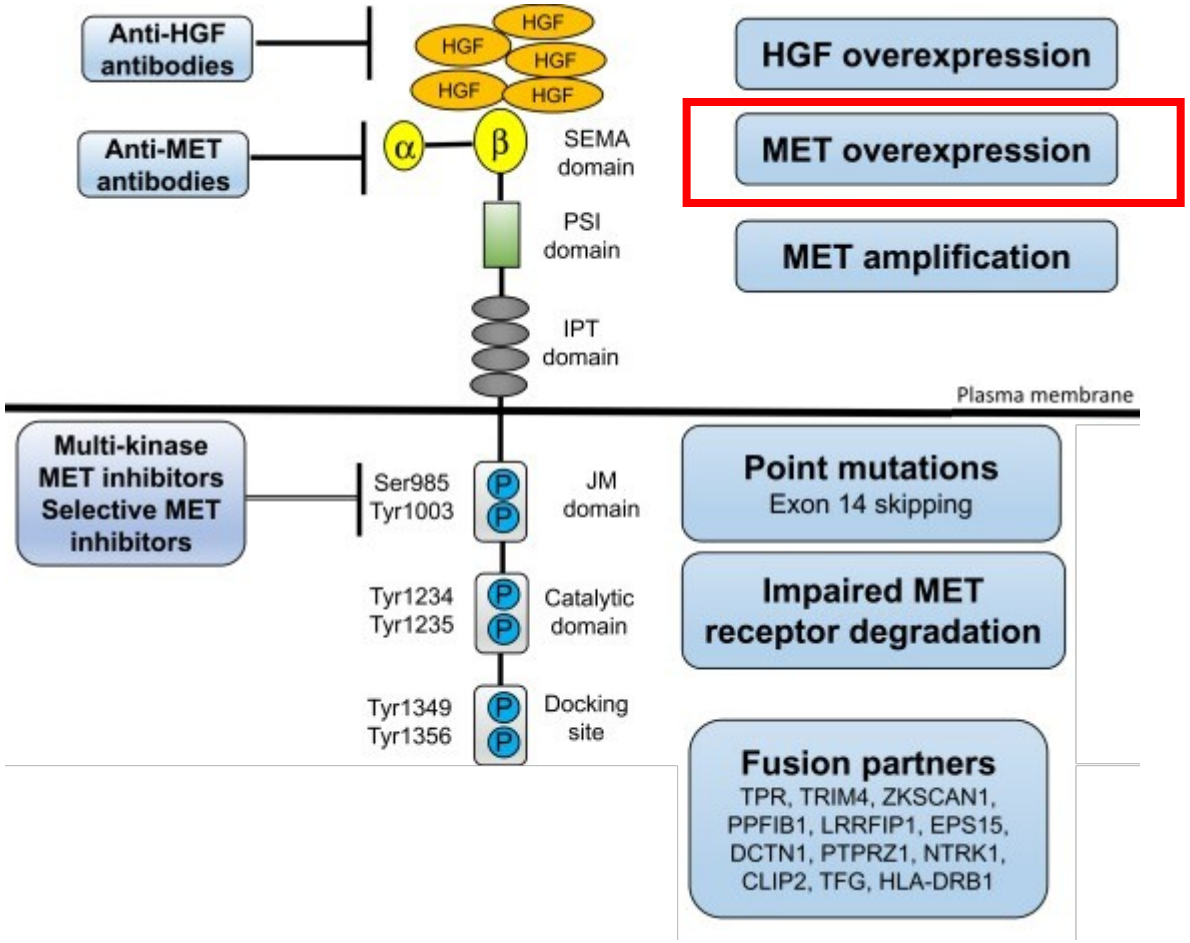



Maximum change in tumor burden from baseline according to tumor type (blue = non-small cell lung cancer, pink = any other type)

NSCLC ORR 29%, DOR 12.7mo, treatment discontinuation due to trAE 1% (G2 pneumonitis)

Adapted from Schram, N Engl J Med, 2025, PMID 39908431.

# cMET over-expression (12% of NSCLC)

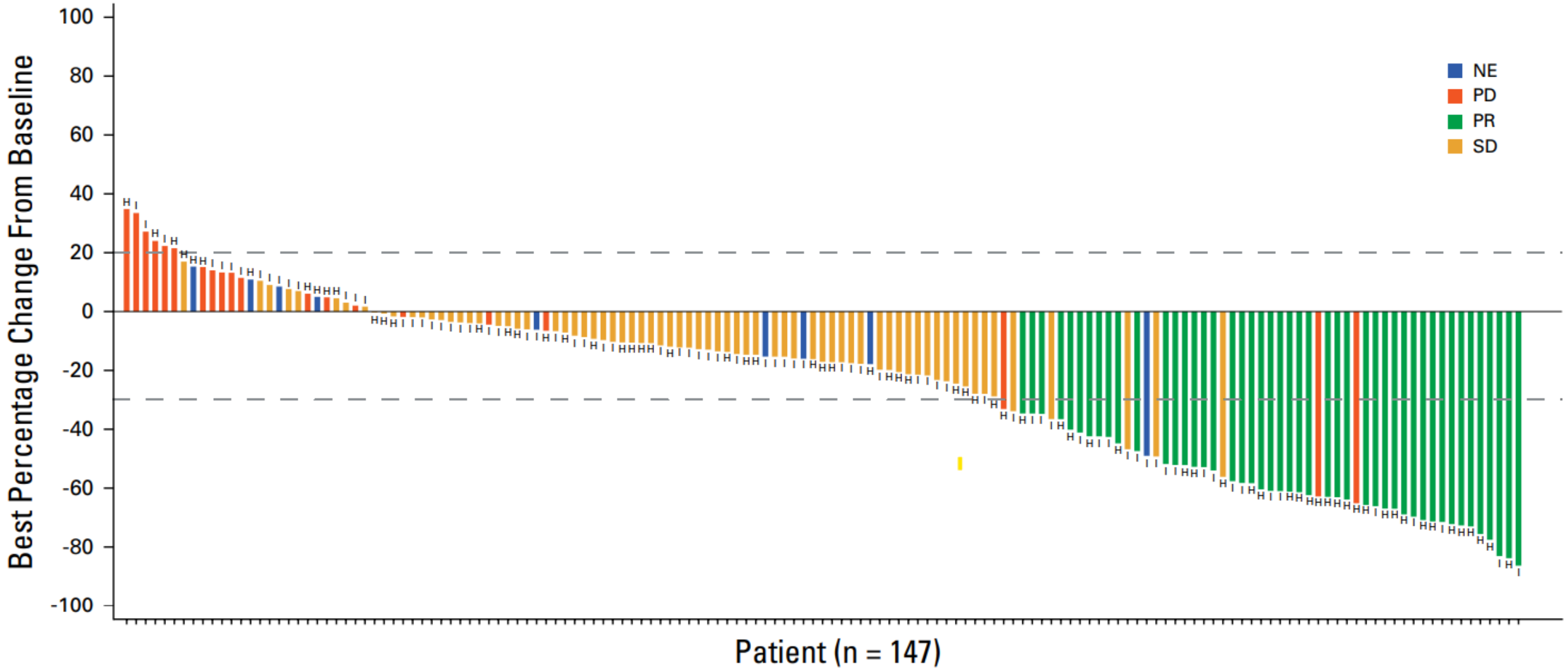



- cMET protein is over-expressed due to a variety of alterations in NSCLC
- High expression of cMET is measured by IHC and defined as ≥50% tumor cells with strong 3+ staining.

- Telisotuzumab vedotin (Teliso-V) is a c-Met–directed antibody-drug conjugate with a monomethyl auristatin E cytotoxic payload.

Adapted from Liang, Onco Targets Ther, 2020, PMID 32273721.

# 5/14/25: Telisotuzumab vedotin-tllv approved for cMET 3+ NSCLC 2L




cMET 3+ ORR 35%, median PFS 5.5mo, median OS 14.6mo
Treatment-related discontinuation rate 22% (neuropathy, ILD);
two patients died due to adverse events possibly treatment-related (ILD).

Camidge, J Clin Oncol, 2024, PMID 38843488.

# 1st line tx for stage IV NSCLC: which modality? TT vs IO vs CT/IO vs IO/IO vs CT

**Targeted tx**: If drug w efficacy (durable RR >50%) + safety (<25% TRAE d/c)

**Immunotherapy**: High PD-L1 (>50%).

**Immuno + chemo**: Absent PD-L1 (0%), high burden of disease.

**Immuno + immuno**: Absent PD-L1 (0%), chemo contraindication or stigma.

**Chemotherapy**: Urgent start or other options contraindicated or uncertain.

**Other considerations:**

- Chemotherapy: **many drug options** with widely variable toxicity.

- Targeted therapies: **few drug options** with variable toxicity.

- Immunotherapy: many drug options but **little variability in toxicity**.

- Match efficacy + toxicity to clinical status, comorbidities, goals of care.

- Plan ahead: OK to hope for the best but plan next steps (2L, 3L, etc).

# Current State of Biomarkers (2025)

| | Stage | | | | |
|---|---|---|---|---|---|
| Biomarkers | IA | IB-IIIA | IIIB-IIIC | IV 1L | IV 2L+ |
| EGFR | Informative | **Critical** | **Critical** | **Critical** | **Critical** |
| ALK | Informative | **Critical** | **Actionable** | **Critical** | **Critical** |
| PD-L1* | Informative | **Critical** | **Actionable** | **Critical** | Informative |
| ROS1, BRAF, NTRK, METex14, RET | Informative | Informative | Informative | **Critical** | **Critical** |
| KRAS, METamp, ERBB2, NRG1, HER2*, cMET*, FGFR | Informative | Informative | Informative | **Actionable** | **Critical** |
| Others | Informative | Informative | Informative | Informative | **Actionable** |

*Expression is tested by IHC on tumor tissue and therefore cannot be obtained in peripheral blood.

NCCN v3.2025

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Thank you for your attention!

Questions?

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