Masters in Thoracic Oncology Summit
November 22, 2024

# Which patients need adjuvant therapy?

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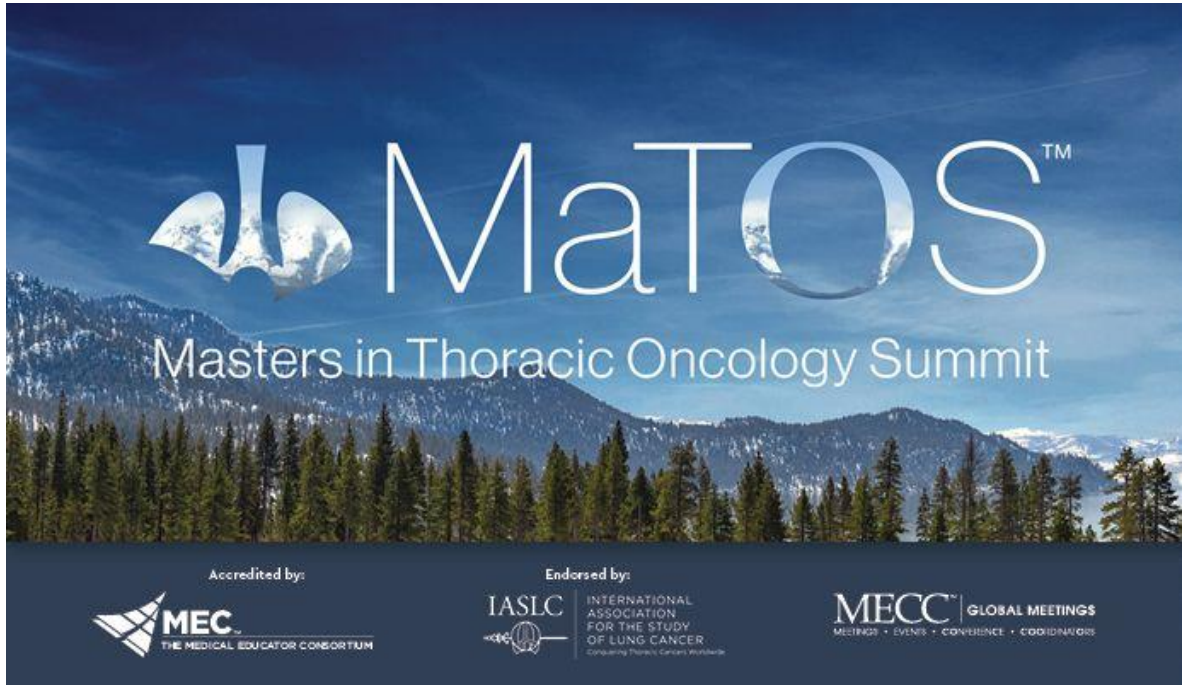

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# Relevance of Adjuvant therapy in 2024—5 Ps

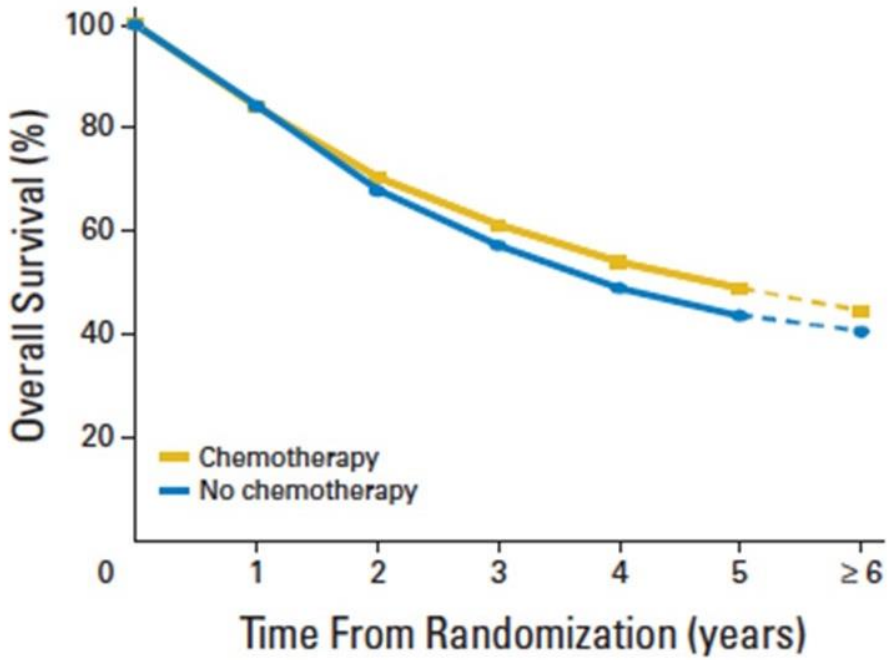
- **Possibility of cure**—the perception that resection will lead to cure is strong and 15-20% who receive neoadjuvant therapy may not have surgery
- **Preoperative staging**—patients can be upstaged at surgery
- **Patient selection**—patients with oncogenic driver alterations may derive more benefit from adjuvant therapy
- **Prolonged therapy**—short duration of neoadjuvant immunotherapy may not be sufficient for long-term benefits in most patients
- **Patterns of referral**—only patients referred prior to surgery will receive perioperative therapy

# Possibility of cure

# Adjuvant chemotherapy in early-stage NSCLC

High recurrence rates and poor survival in patients undergoing potentially curative resections for early-stage NSCLC.

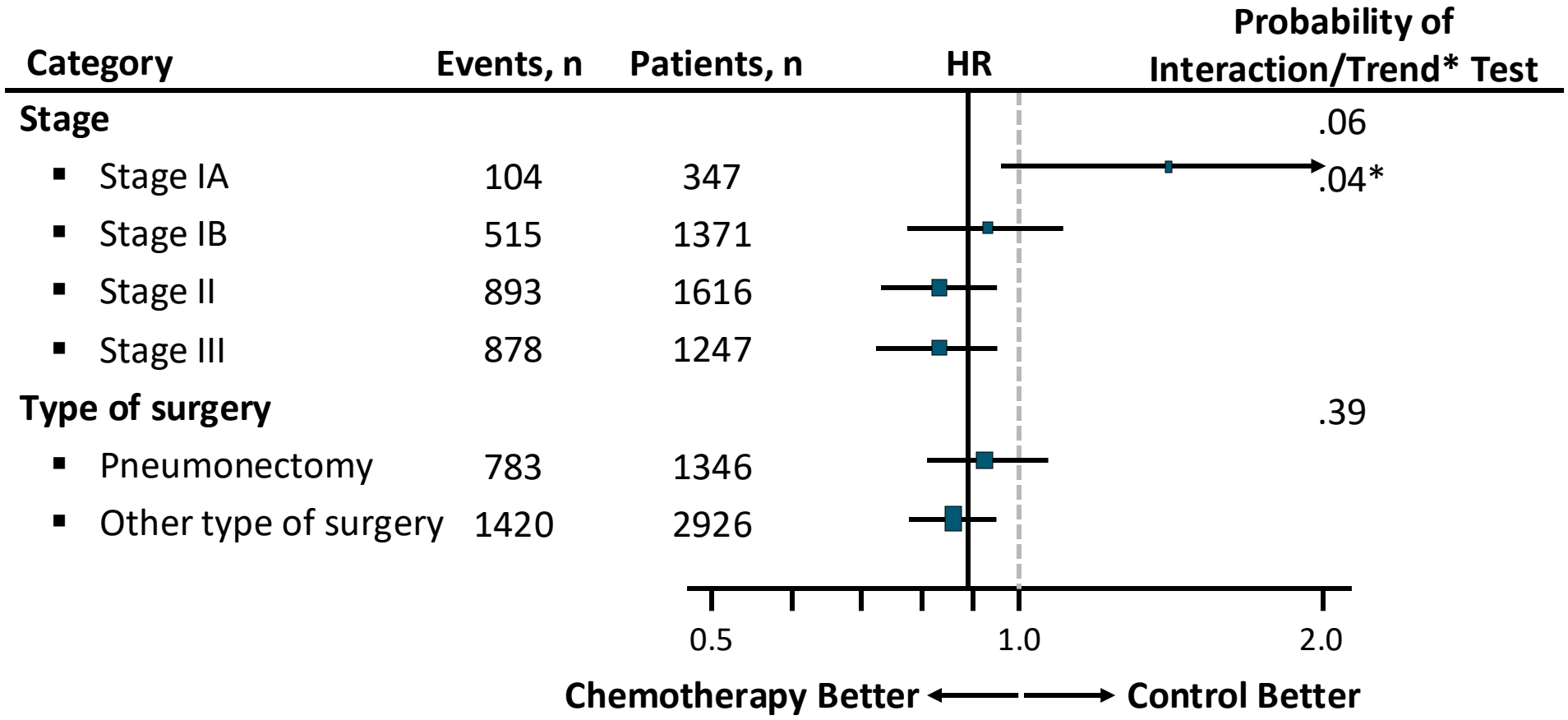
Absolute improvement in survival with **adjuvant cisplatin-based chemotherapy** of **5.4% at 5 years**




**LACE meta-analysis**

Pignon JCO 2008

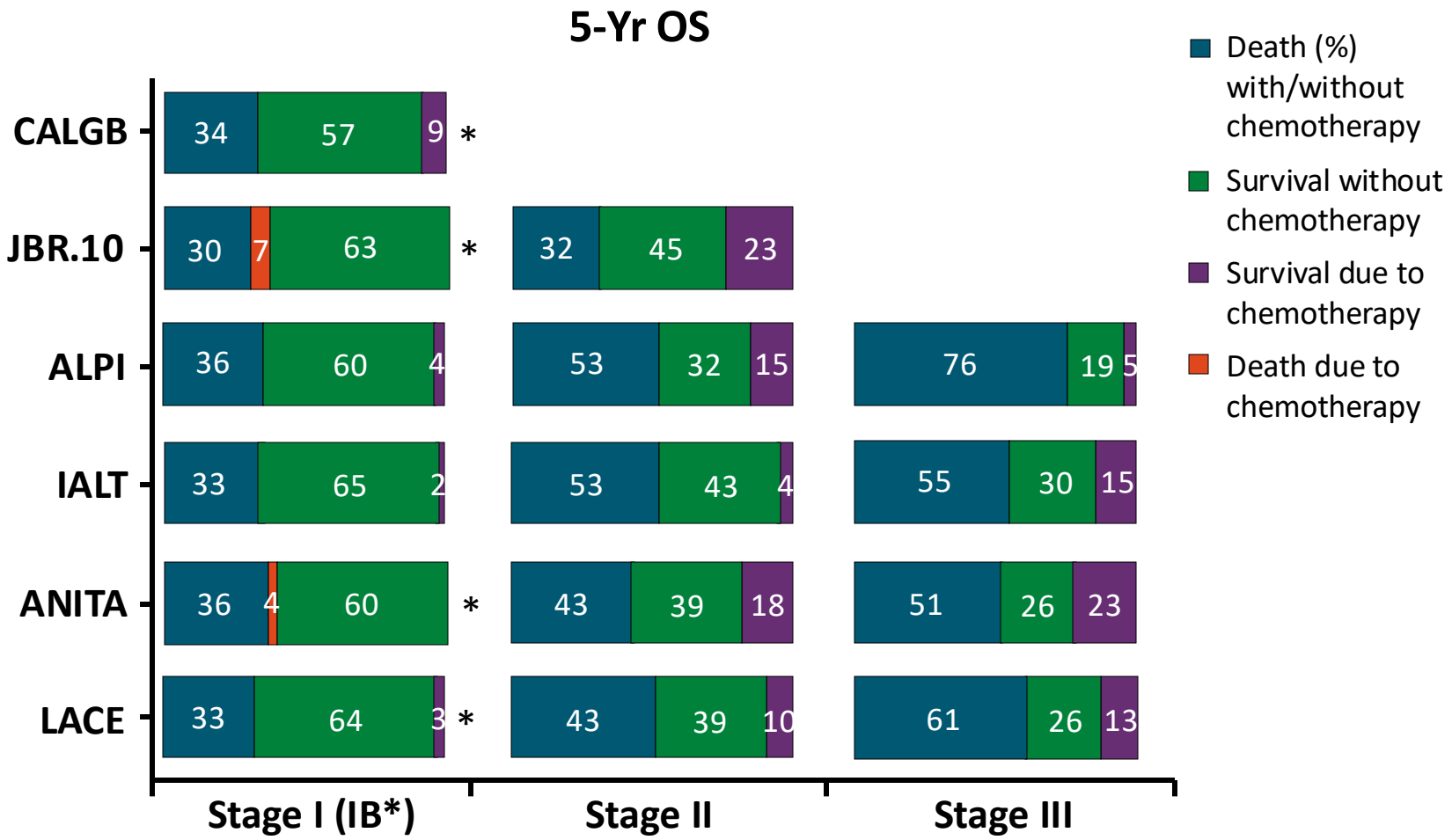
# LACE Meta-Analysis: OS by Stage and Type of Surgery




Pignon. JCO. 2016;26:3552.

# Impact of Adjuvant Therapy in Early-Stage NSCLC Depends on Stage

- Retrospective analysis of estimated absolute risk/benefit for 100 patients treated with surgery and adjuvant CT based on reported, stage-specific 5-yr OS rates in the control arms of each clinical trial

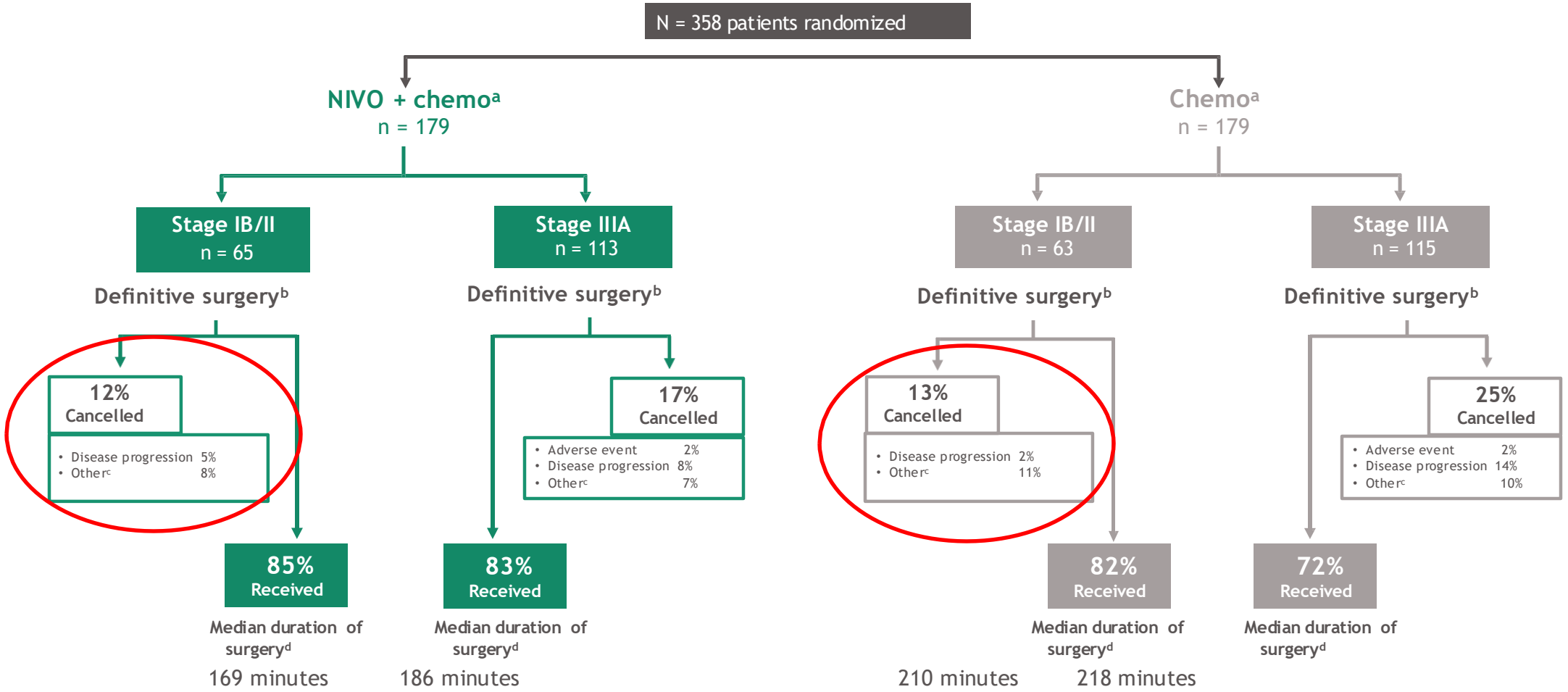



Kris. JCO. 2017;35:2960.

*Trials that only included stage IB; ALPI and IALT included both IA and IB.

# CM 816—Definitive surgery

## Surgery Summary: By Baseline Stage of Disease




[a]1 patient with stage IV in each arm; [b]Patients with definitive surgery not reported: NIVO + chemo, 3% (stage IB/II), 0 (stage IIIA); chemo, 5% (stage IB/II), 3% (stage IIIA); [c]Other reasons included patient refusal, unresectability, and poor lung function; [d]Patients (n) with reported duration of surgery: NIVO + chemo, 46 (stage IB/II), 76 (stage IIIA); chemo, 47 (stage IB/II), 74 (stage IIIA); IQR for median duration of surgery: NIVO + chemo, 126.0-275.0 (stage IB/II) and 134.5-245.5 (stage IIIA); chemo, 150.0-267.0 (stage IB/II) and 147.0-290.0 (stage IIIA).

Forde PM et al. N Engl J Med 2022

# NO surgery following neoadjuvant therapy

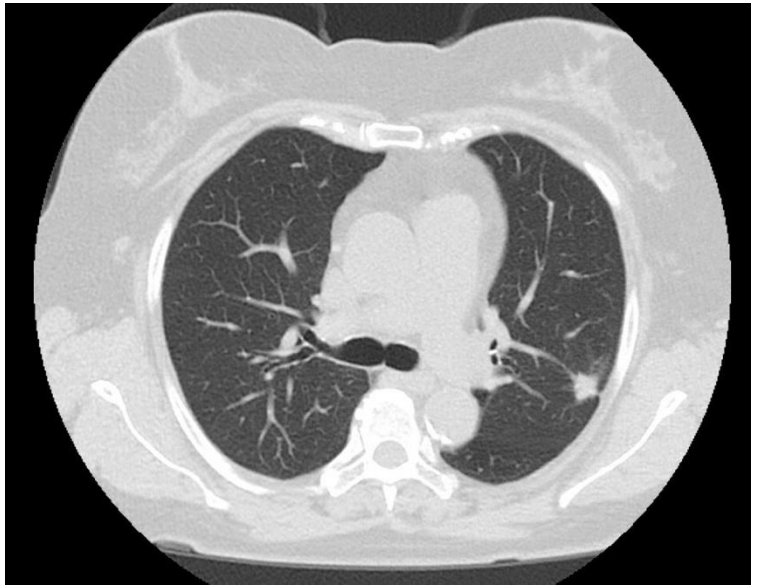
| TRIAL | STAGES | % completing surgery |
|---|---|---|
| CM816 | 6% IB, 31% II, 63% III | 84% |
| AEGEAN | 29% II, 71% III | 78% |
| NEOTORCH | Only III presented | 82% |
| KN671 | 30% II, 70% III | 82% |
| CM77T | 35% II, 65% III | 78% |
| RATIONALE-315 | 41% II, 58% III | 84% |

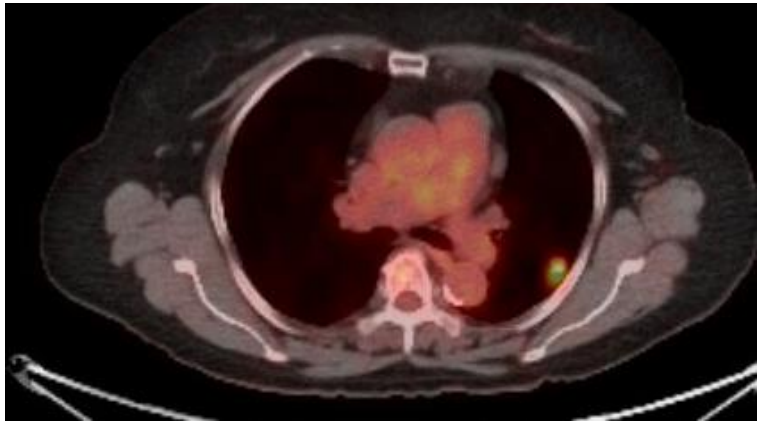
**16-22% NO surgery**

# Preoperative staging

# Case: Early-Stage NSCLC

- 64 yo female presented with chest discomfort and cardiac work up was negative.
- CT chest
  - 1.3 cm left upper lobe nodule
  - No abnormal lymphadenopathy
- CT A/P without evidence of disease
- Bronchoscopy with FNA of the left upper lobe nodule
  - Non-small cell carcinoma, consistent with adenocarcinoma
- PET/CT with uptake in the left upper lobe
- MRI brain was normal
- **Preoperative clinical staging: cT1bN0M0—Stage IA2**





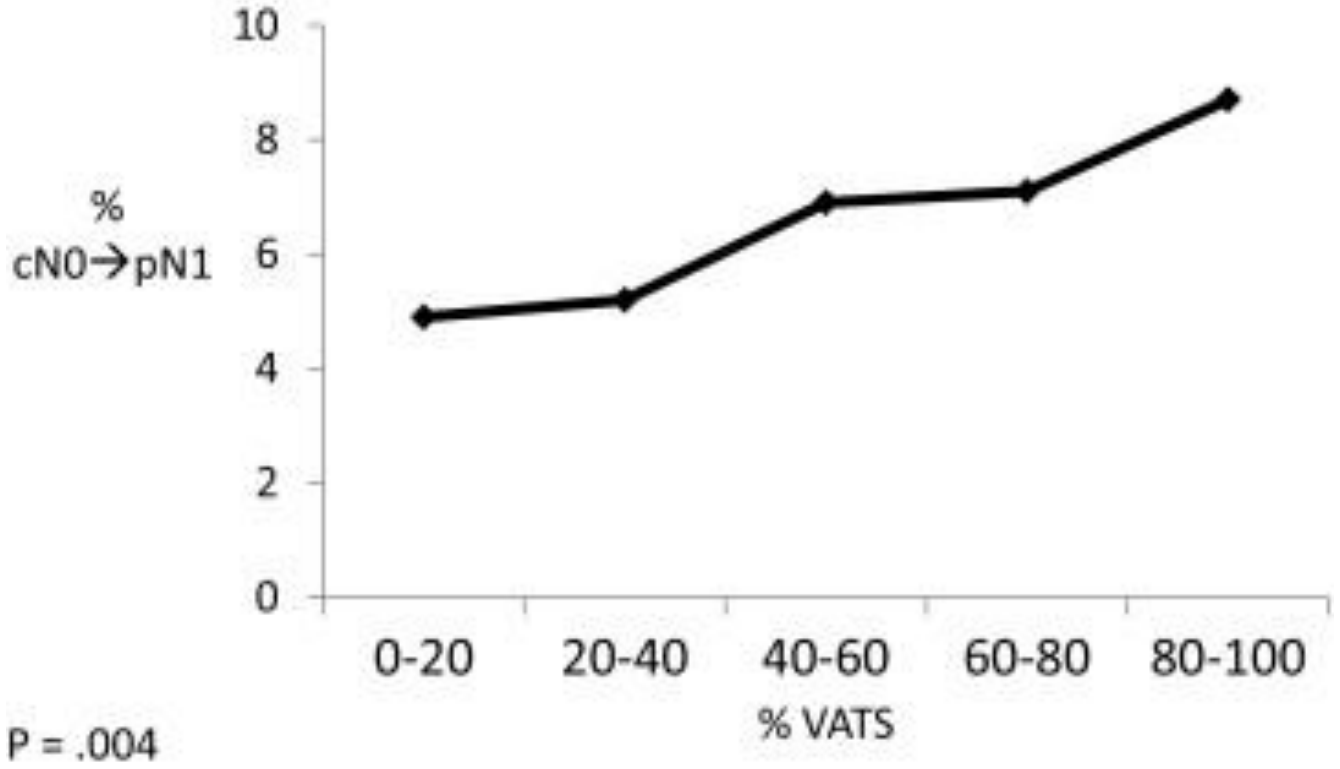
# Early-Stage NSCLC

- Robotic VATS left upper lobectomy and lymph node dissection

- **Pathology showed poorly differentiated adenocarcinoma, 1cm**
  - **Focal pleural invasion**
  - **1 level 11LN involved**
- **PD-L1: 10%**
- **ALK fusion positive**
- **Pathologic stage: pT2aN1M0, stage IIB**

# Pre-operative staging for NSCLC

- Nodal upstaging occurs in 10-25%
- 30-55% will develop recurrence and die despite resection

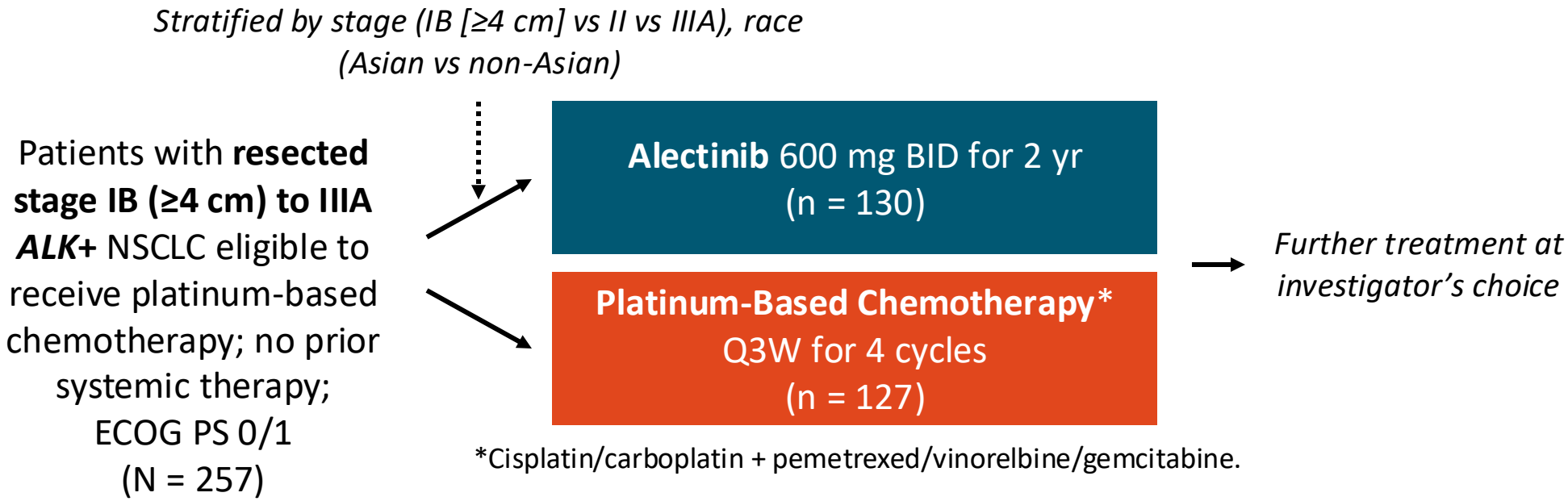



Boffa, DJ. et al. Ann Thorac Surg 2012; 94:347 – 353. Hoffman PC, Mauer AM, Vokes EE. Lancet 2000;355:479-85

# Patient selection

# ALINA: Adjuvant Alectinib for Early-Stage *ALK* Fusion-Positive NSCLC

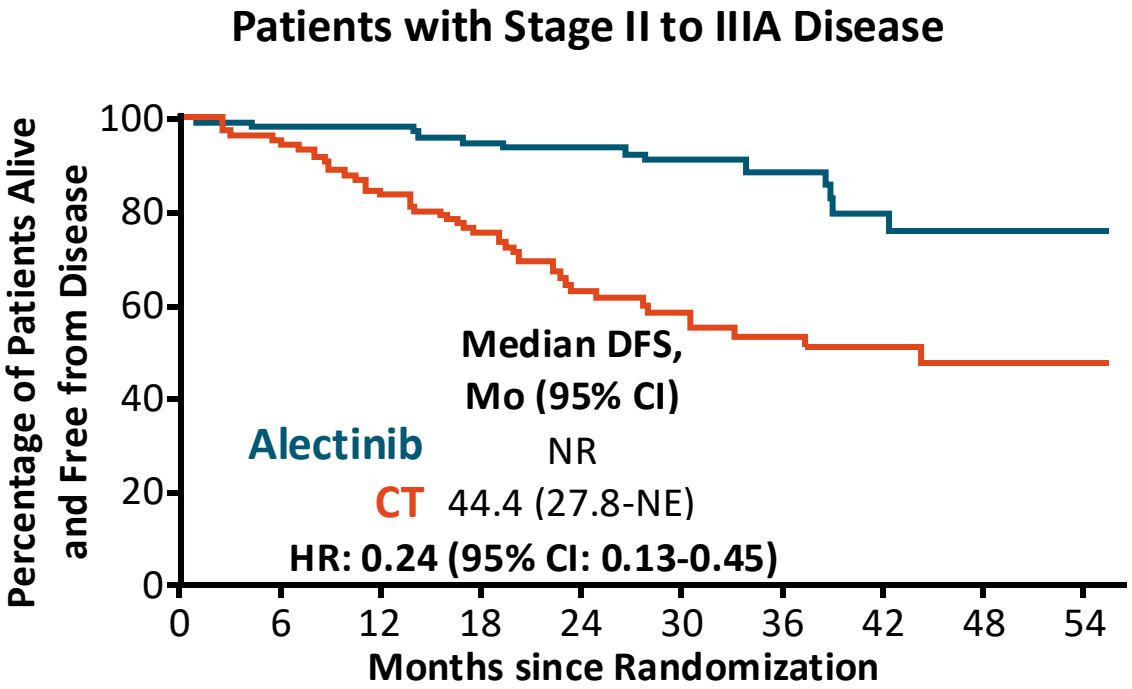
- International, randomized, open-label phase III trial

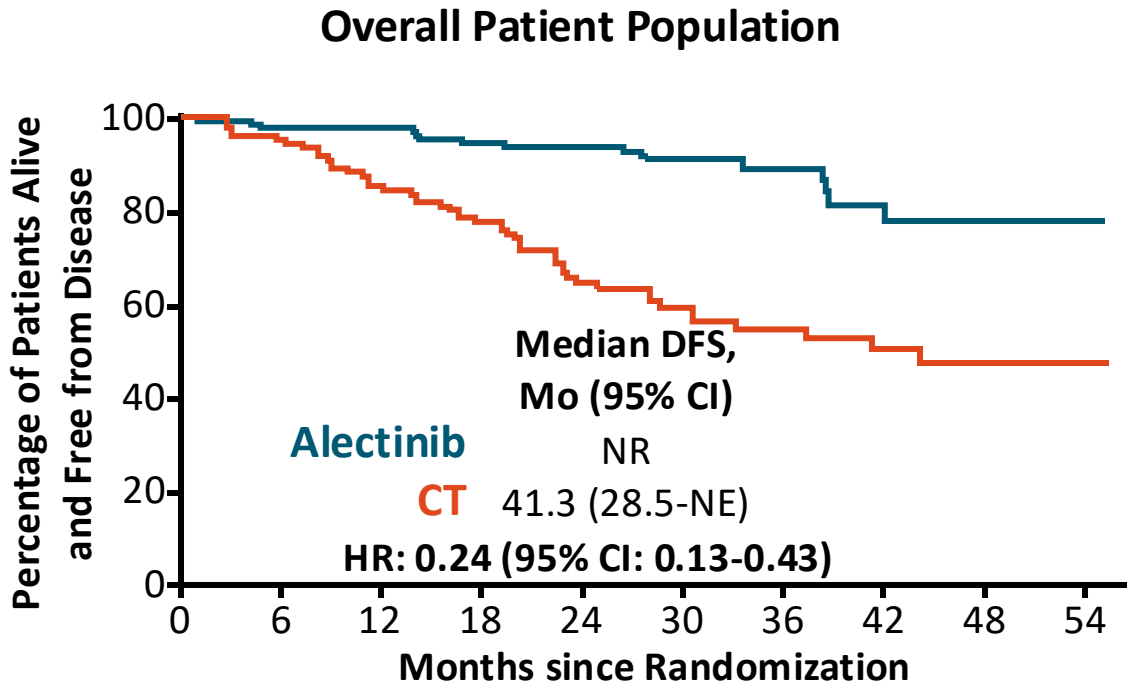



- **Primary endpoint:** DFS per investigator (hierarchical: stage II-IIIA; then stage IB-IIIA [ITT population])
- Secondary endpoints: CNS DFS, OS, safety

Wu. NEJM. 2024;390:1265. NCT03456076.

# ALINA: Disease-Free Survival (Primary Endpoint)




No. at Risk

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Alectinib | 116 | 111 | 111 | 107 | 67 | 49 | 35 | 21 | 10 | 3 |
| CT | 115 | 102 | 88 | 79 | 48 | 35 | 23 | 17 | 10 | 2 |

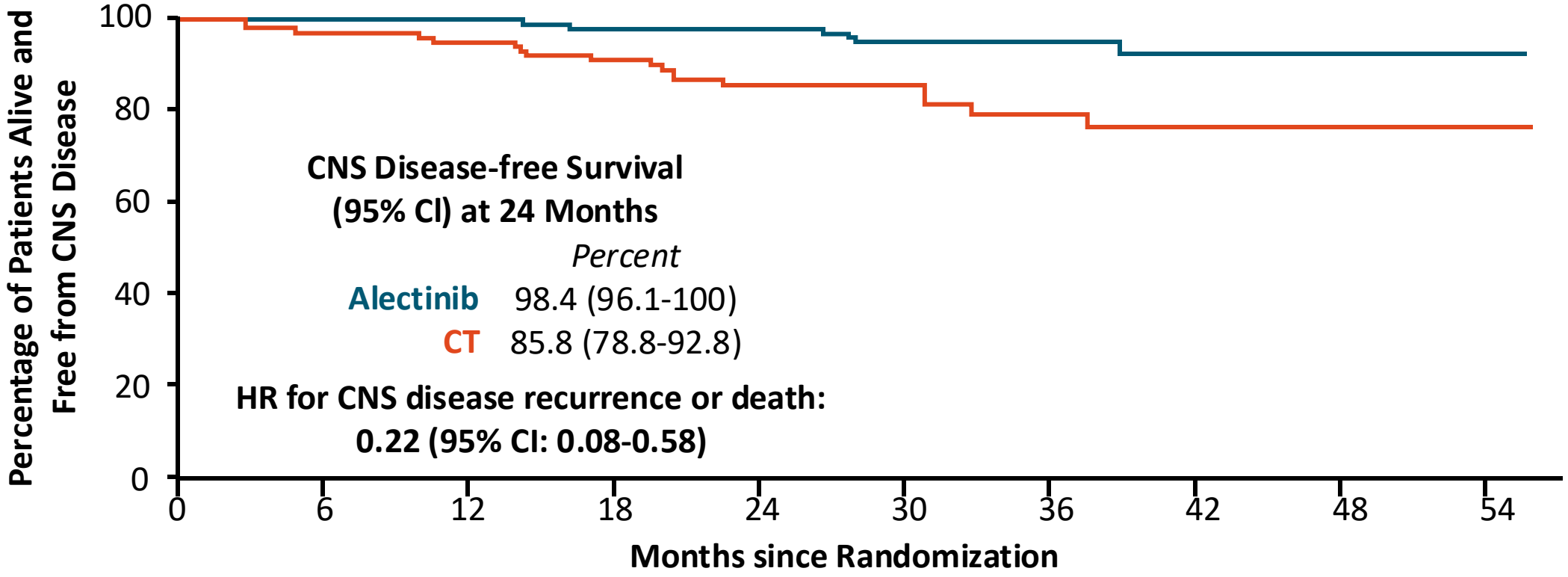
No. at Risk

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Alectinib | 130 | 123 | 123 | 118 | 74 | 55 | 39 | 22 | 10 | 3 |
| CT | 127 | 112 | 98 | 89 | 55 | 41 | 27 | 18 | 11 | 2 |

- DFS benefit with alectinib vs chemotherapy observed across all subgroups of the ITT population, including age, sex, race, baseline ECOG PS, tobacco use history, tumor stage, and regional LN status

Wu. NEJM. 2024;390:1265.

# ALINA: CNS Disease-free Survival




| No. at Risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Alectinib | 130 | 124 | 124 | 118 | 74 | 55 | 39 | 22 | 10 | 3 |
| CT | 127 | 113 | 98 | 90 | 57 | 43 | 27 | 18 | 11 | 2 |

Wu. NEJM. 2024;390:1265.

# ALINA: Safety

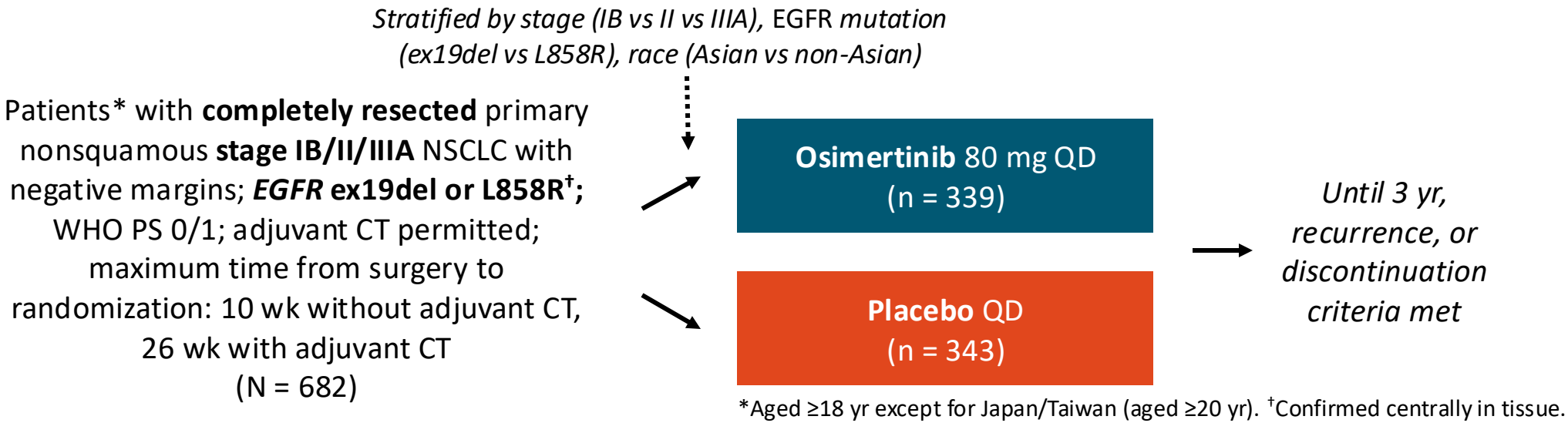
| Safety Outcome | Alectinib (n = 128) | CT (n = 120) |
|---|---|---|
| Median treatment duration, mo | 23.9 | 2.1 |
| Any AE, % | 98.4 | 93.3 |
| Any grade 3/4 AE, % | 29.7 | 30.8 |
| Death due to AE, % | 0 | 0 |
| Serious AE, %<br>▪ Related to treatment | 13.3<br>1.6 | 8.3<br>6.7 |
| AEs leading to dose reduction, % | 25.8 | 10.0 |
| AEs leading to dose interruption, % | 27.3 | 18.3 |
| AEs leading to discontinuation, % | 5.5 | 12.5 |

- Most frequent AEs:
  - **Alectinib:** increased CPK, constipation, increased AST, increased ALT, increased bilirubin
  - **Chemotherapy:** nausea, constipation, decreased appetite, anemia, vomiting
- No grade 5 AEs in either arm
- At data cutoff, 20.3% of patients in alectinib arm remain on treatment

Wu. NEJM. 2024;390:1265.

# ADAURA: Adjuvant Osimertinib for Early-Stage *EGFR*-Mutated NSCLC

- International, randomized, double-blind phase III trial (data cutoff for final OS analysis: 1/27/2023)

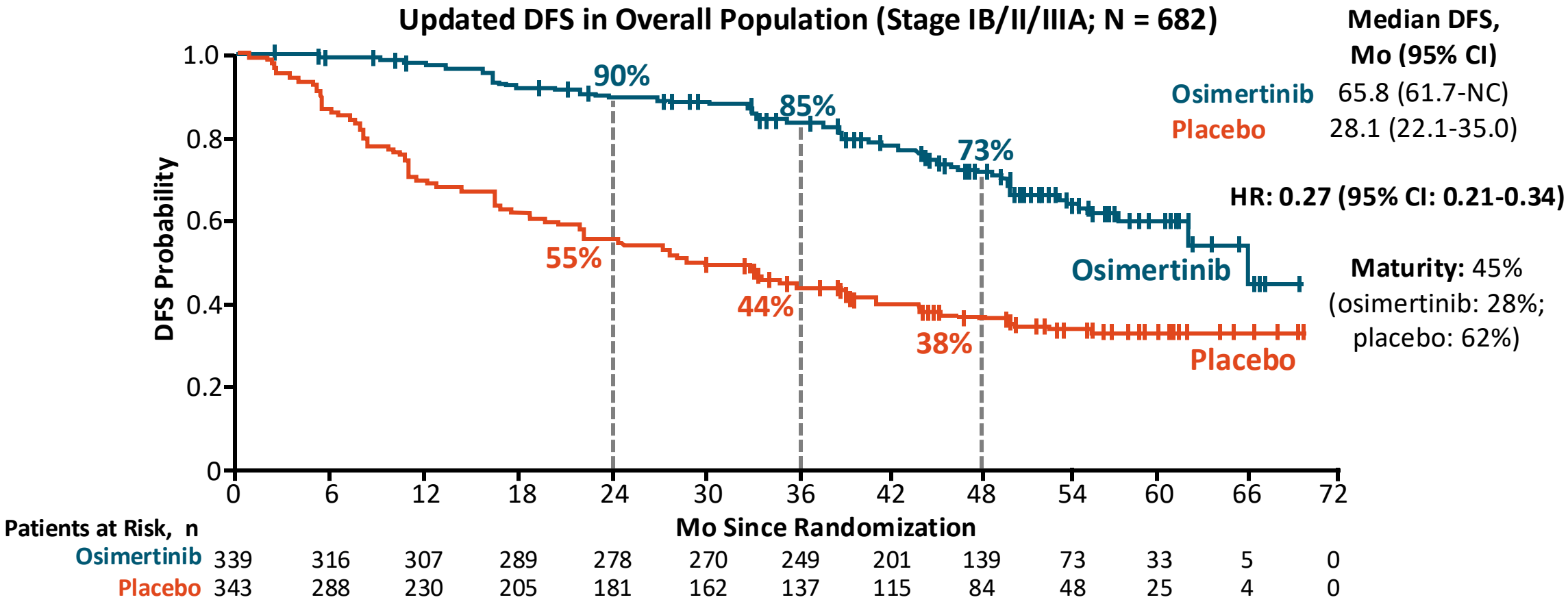



*Aged ≥18 yr except for Japan/Taiwan (aged ≥20 yr). †Confirmed centrally in tissue.

- **Primary endpoint:** investigator-assessed DFS in patients with stage II-IIIA NSCLC
- **Key secondary endpoints:** DFS in overall population; landmark DFS rates at Yr 2, 3, and 5; OS; HRQoL; safety
- **Exploratory endpoints:** patterns of recurrence; CNS DFS

Tsuboi. NEJM 2023;389:137. NCT02511106.

# ADAURA: Disease-free Survival in Patients With Stage IB-IIIA NSCLC



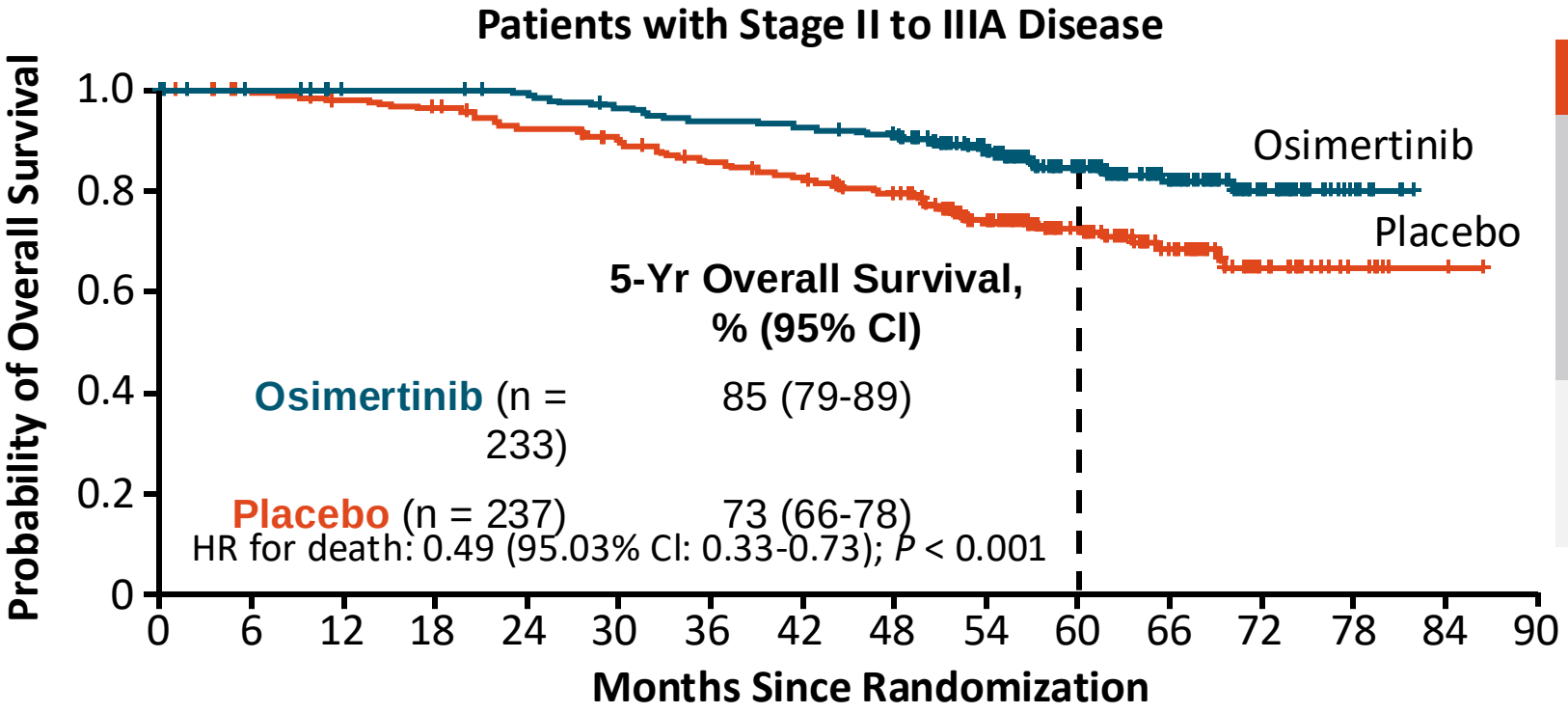

- FDA approved in December 2020 for adjuvant treatment of adults with stage IB-IIIA *EGFR+* (del19 or L585R) NSCLC following tumor resection ± adjuvant chemotherapy

Herbst. J Clin Oncol. 2023;41:1830. Osimertinib PI.

Slide credit: ProCE.com and clinicaloptions.com

# ADAURA: Overall Survival in Patients With Stage II-IIIA NSCLC

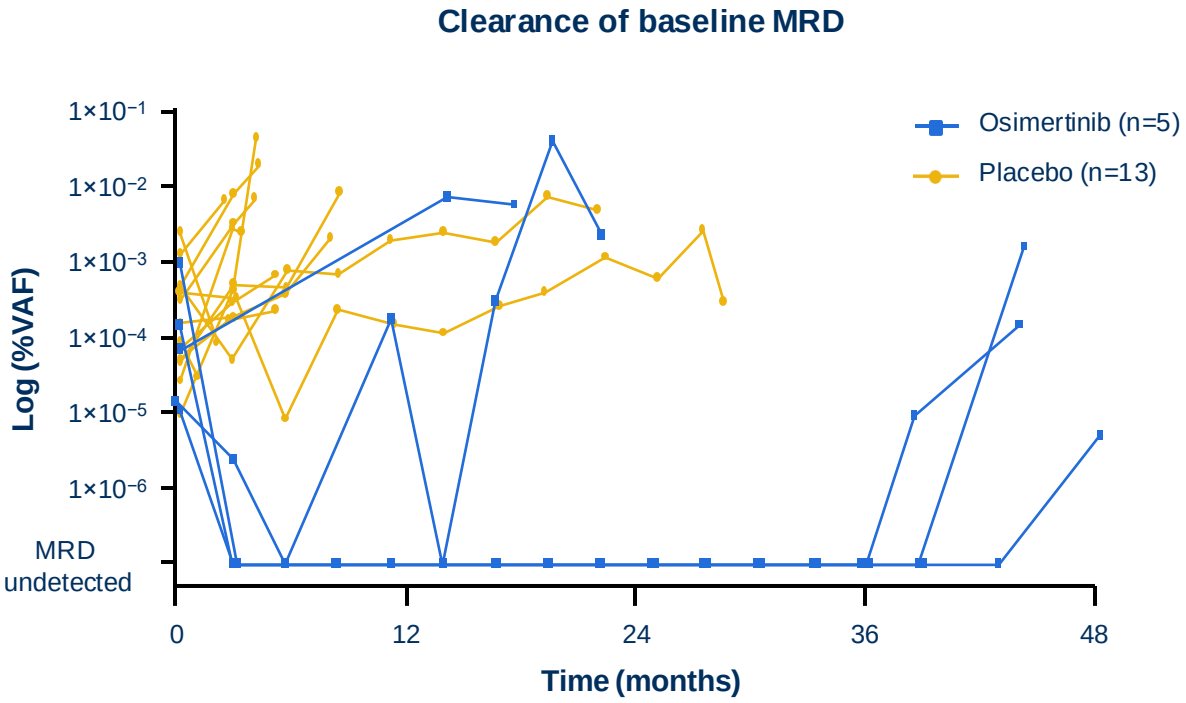
- Median follow-up for OS: 61.5 mo



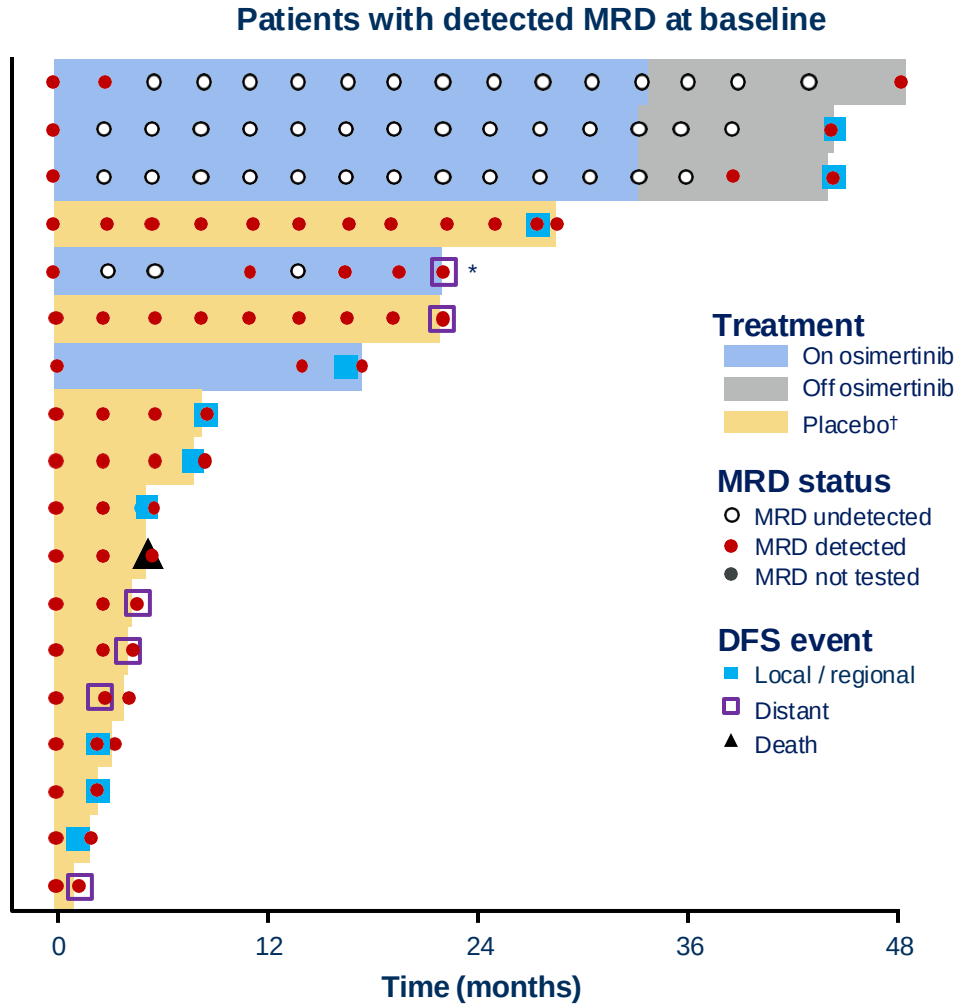

| 5-Yr OS, % | Osi | Pbo | HR |
|---|---|---|---|
| Disease stage | | | |
| ▪ IB | 94 | 88 | 0.44 |
| ▪ II | 85 | 78 | 0.63 |
| ▪ IIIA | 85 | 67 | 0.37 |
| Adjuvant CT | | | |
| ▪ Yes | 87 | 77 | 0.49 |
| ▪ No | 88 | 79 | 0.47 |

Tsuboi. NEJM. 2023;389:137. Herbst. ASCO 2023. Abstr LBA3.

# ADAURA: Detected MRD at baseline was associated with poor outcomes




- Of 18 patients with detected MRD at baseline
  - 4 / 5 patients receiving osimertinib cleared MRD
  - 0 / 13 patients receiving placebo cleared MRD




*CNS only DFS event. †Patients received placebo for up to 36 months.

CNS, central nervous system; DFS, disease-free survival; MRD, molecular residual disease; VAF, variant allele frequency

John et al. ASCO24 #8005

# ADAURA: Safety Summary

| AEs by Final DFS Analysis, n (%) | Osimertinib (n = 337) | Placebo (n = 343) |
|---|---|---|
| Any cause | 330 (98) | 309 (90) |
| ▪ Grade ≥3 | 79 (23) | 48 (14) |
| ▪ Leading to death | 1 (<1) | 2 (1) |
| ▪ Serious | 68 (20) | 47 (14) |
| ▪ Leading to d/c | 43 (13) | 9 (3) |
| ▪ Leading to dose reduction | 42 (12) | 3 (1) |
| ▪ Leading to dose interruption | 91 (27) | 43 (13) |
| Possibly causally related* | | |
| ▪ Any | 308 (91) | 199 (58) |
| ▪ Grade ≥3 | 36 (11) | 7 (2) |
| ▪ Leading to death | 0 | 0 |
| ▪ Serious | 10 (3) | 2 (1) |
| ▪ Leading to d/c | 35 (10) | 5 (1) |

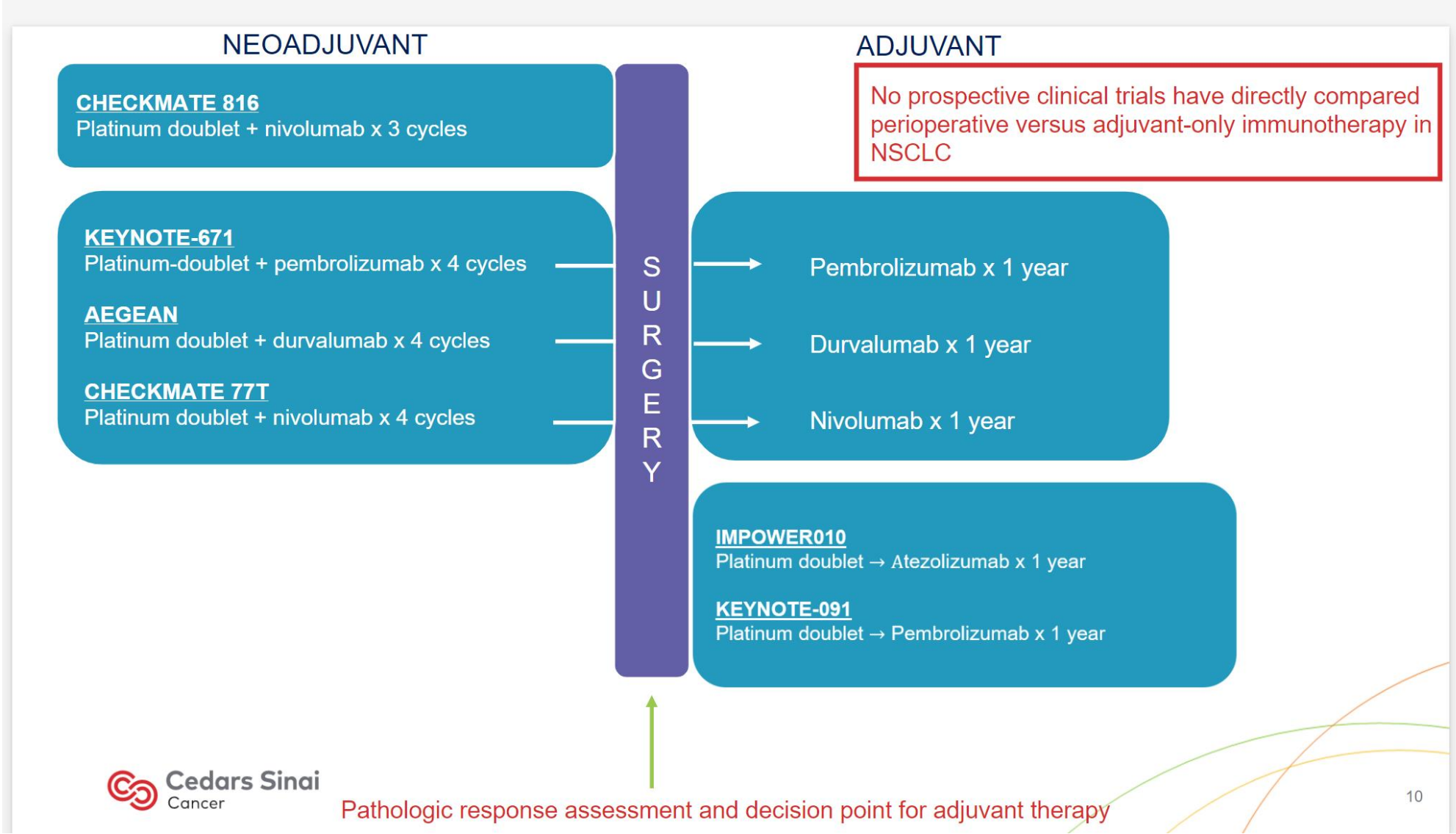
*Assessed by investigator.

- All patients had completed or discontinued study treatment at final DFS analysis (data cutoff: 4/11/2022)
- Safety profile was consistent with that seen in primary analysis
- Patients with AEs occurring >28 days after treatment discontinuation (n = 15) at OS data cutoff (1/27/2023)
  - Osimertinib arm (n = 10)
  - Placebo arm (n = 5)
- At OS data cutoff, 1 additional serious AE was reported (COVID-19 pneumonia)
  - Occurred >28 days after treatment discontinuation; deemed unrelated to treatment, and patient made full recovery

Tsuboi. NEJM. 2023; 389:137. Herbst. ASCO 2023. Abstr LBA3.

# Prolonged therapy

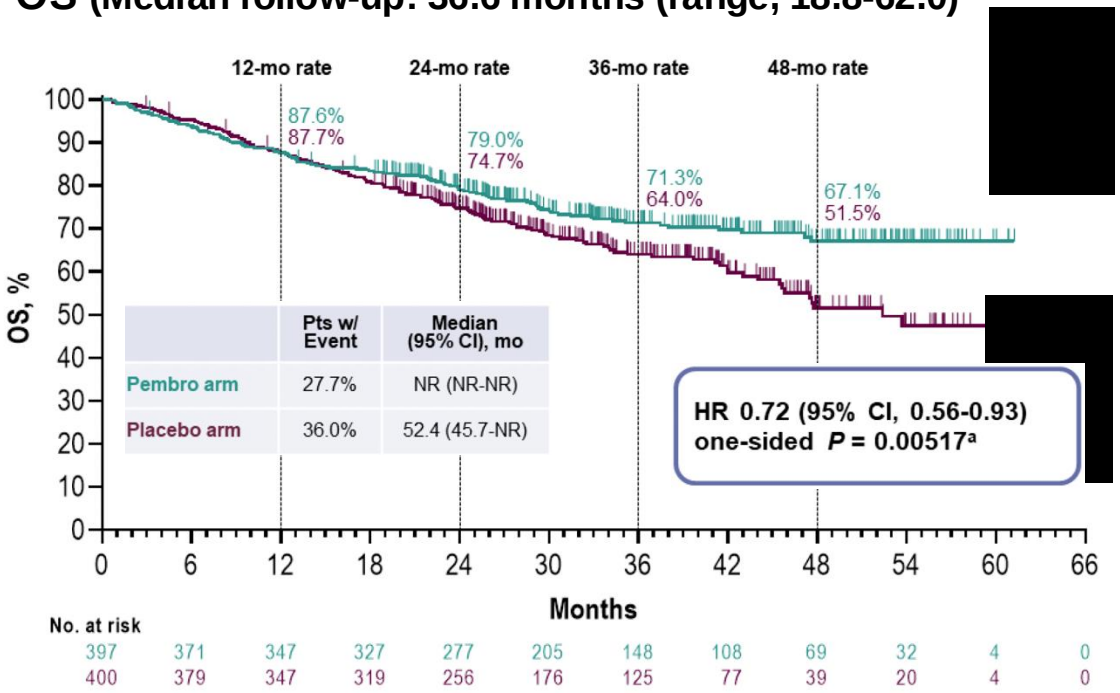
# Current state for immunotherapy in early-stage NSCLC



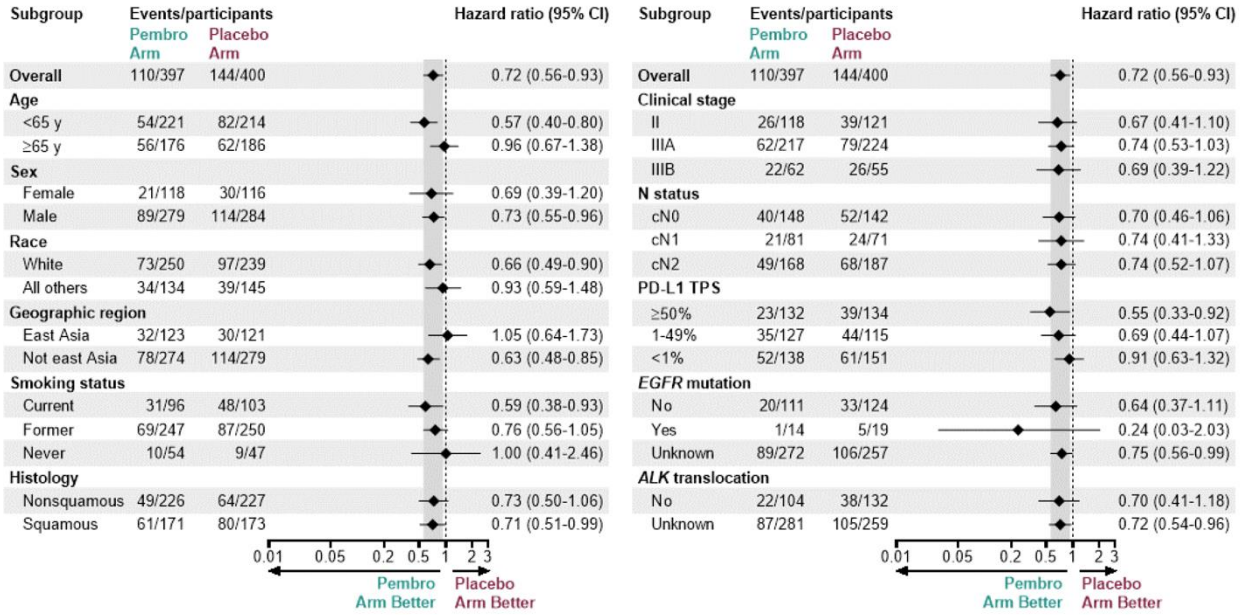

Cedars Sinai Cancer

# Phase 3 KEYNOTE-671: Overall Survival

## OS (Median follow-up: 36.6 months (range, 18.8-62.0)




## OS in Subgroups




Spicer JD, et al. ESMO 2023. Abstract LBA56.

# Patterns of referral

# Patterns of referral

- Practice patterns for patients with stage I-III NSCLC still suggest most patients do not receive neoadjuvant (or adjuvant therapy)
- Systemic review included 20 studies across North America, Europe and Asia

**Table 3. Proportion of patients by treatment modality (with timing) in resected stages I–III non-small-cell lung cancer.** (Table view)

| Study (year) | Country | Study period | Total (n) | Patients, n (%) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | S (±RT) | | Neo-CT/CRT | | Adj-CT/CRT | |
| | | | | n | % | n | % | n | % |
| **Stage I** | | | | | | | | | |
| Arnold (2016) | USA | 2003–2009 | 4293 | 3581 | 83.4† | 108 | 2.5‡ | 604 | 14.1‡ |
| Rajaram (2016) | USA | 2002–2011 | 55,016 | 44,563 | 81.0§ | 1540 | 2.8‡,¶ | 8913 | 16.2‡ |
| **Stage II** | | | | | | | | | |
| Arnold (2016) | USA | 2003–2009 | 5407 | 2737 | 50.6† | 766 | 14.2‡ | 1904 | 35.2‡ |
| Moore (2020) | Canada | 2005–2012 | 245 | 112 | 45.7§ | 7 | 2.9‡ | 126 | 51.4‡ |
| **Stage III** | | | | | | | | | |
| Arnold (2016) | USA | 2003–2009 | 5547 | 1909 | 34.4† | 2,053 | 37.0‡ | 1585 | 28.6‡ |
| Moore (2019) | Canada | 2005–2012 | 133 | 29 | 21.8# | 59 | 44.4‡‡ | 45 | 33.8‡‡ |
| Vinod (2012) | Canada | 2000–2007 | 250 | 148 | 59.2§ | 34 | 13.6‡,†† | 68 | 27.2‡,†† |

Waser et al. Future oncol 2022 18(12): 15

# Patients Who Need Adjuvant therapy in 2024

- **Possibility of cure**—some may need to go directly to surgery for risk of not undergoing resection
- **Preoperative staging**—some will appear to have stage I NSCLC with upstaging at surgery
- **Patient selection**—patients with oncogenic driver alterations may derive more benefit from adjuvant therapy
- **Prolonged therapy**—longer definitive therapy in the adjuvant setting may lead to greater duration of benefit for many patient both with immunotherapy and targeted treatments
- **Patterns of referral**—patterns of care show that many will not be evaluated for neoadjuvant therapy

# Thank you!