



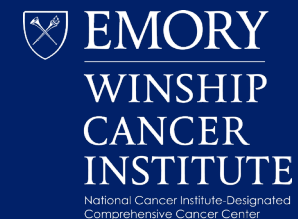
# NEW ERA OF PERIOPERATIVE THERAPY IN NSCLC

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**Emory University School of Medicine**



## Disclosures

FUNDING TO INSTITUTION: Amgen, AstraZenica, Ascentage Pharma, Black Diamond Therapeutics, Verastem

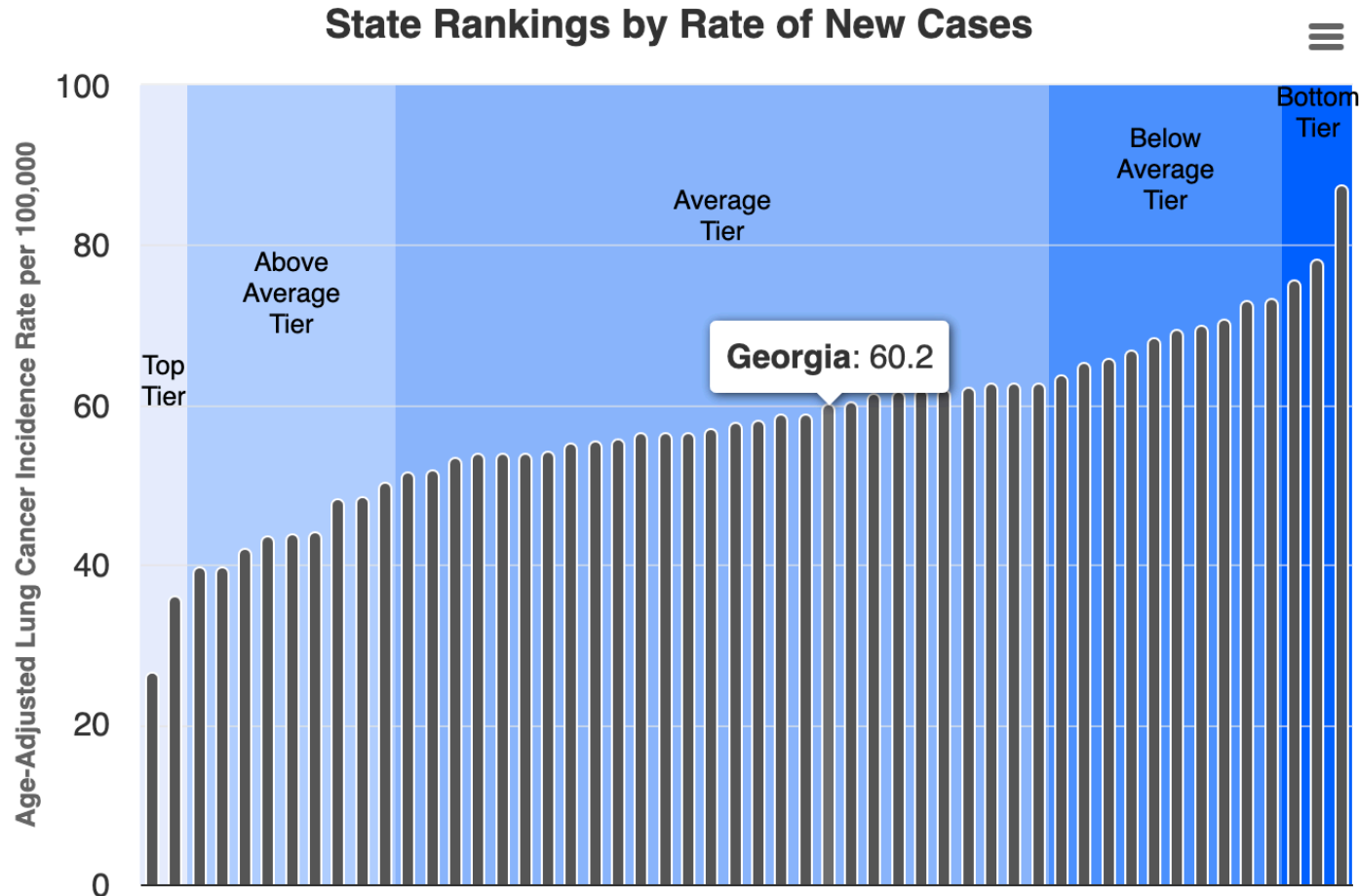
ADVISORY BORAD: Sanofi



# Perioperative Therapy for Resectable NSCLC

- ❑ Screening is underutilized
- ❑ Stage (IA) tumors
- ❑ Driver mutated NSCLC (EGFR, ALK, others)
- ❑ Non-driver mutated NSCLC: Neoadjuvant versus adjuvant
- ❑ Following Neoadjuvant therapy:
  - pathologic response
  - duration of adjuvant treatment (escalate or de-escalate?)

# American Lung Association: state of lung cancer 2022

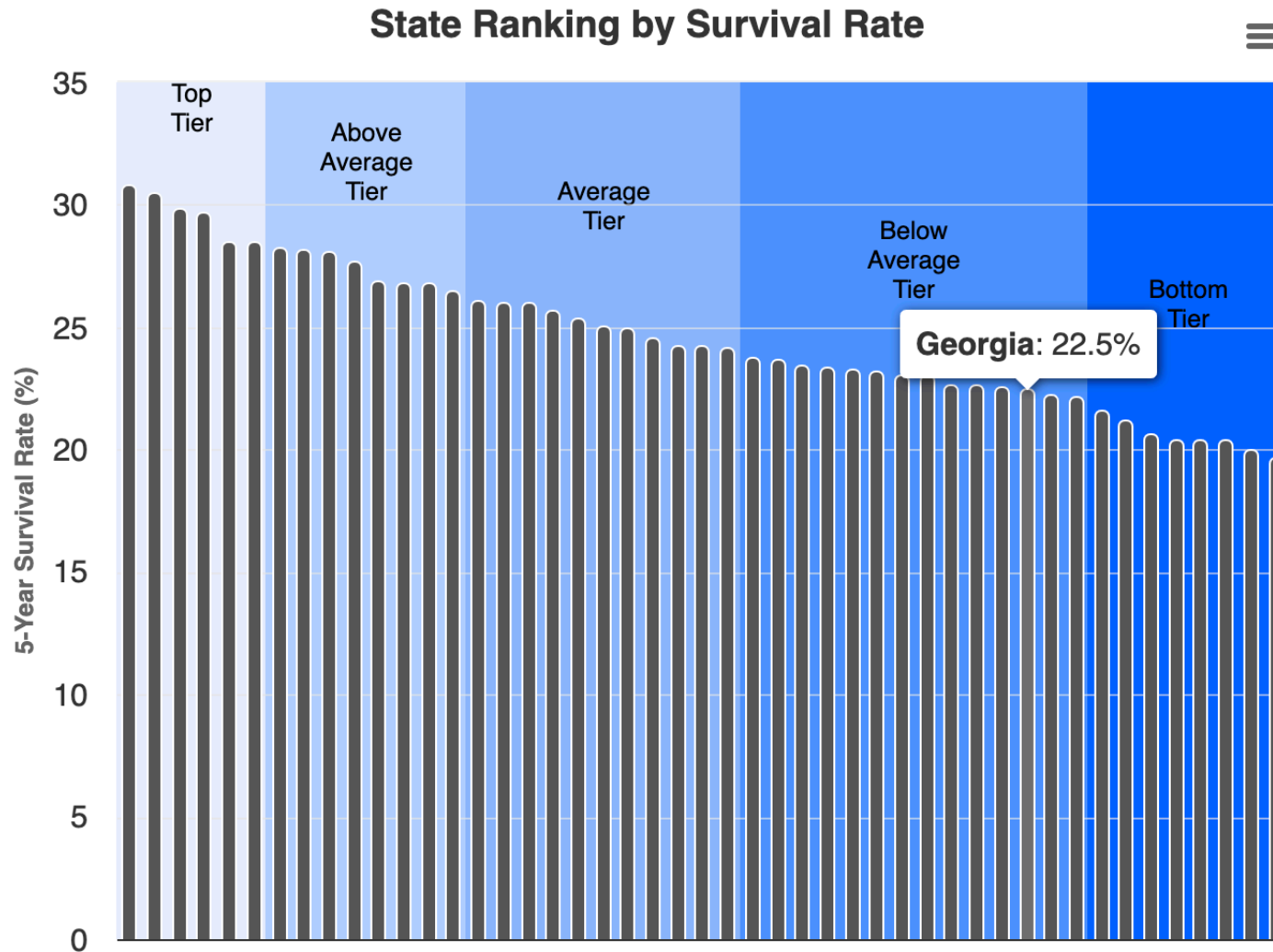


## New Cases:

- The rate of new lung cancer cases is **60** and **significantly higher** than the national rate of 57.
- Georgia ranks **29th** among all states, placing it in the **average tier**.
- Over the last five years, the rate of new cases **improved** by **11%**.

<https://www.lung.org/research/state-of-lung-cancer/states/georgia>

# American Lung Association: state of lung cancer 2022



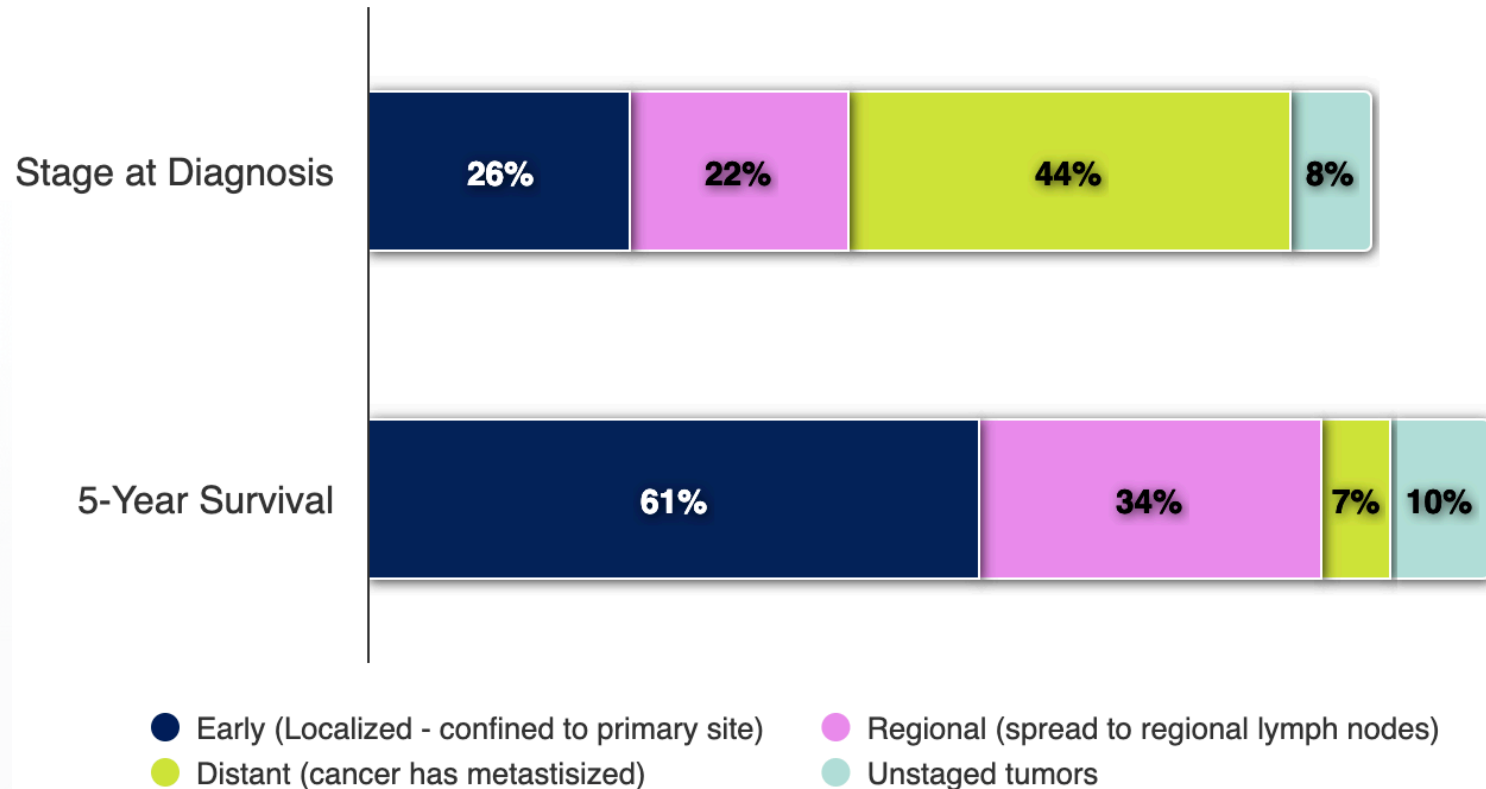
## 5-Year Survival Rate:

- The percent of people alive five years after being diagnosed with lung cancer (the survival rate) in Georgia is **23%**, which is **significantly lower** than the national rate of 25%.
- It ranks **36th** among the 46 states with survival data, placing it in the **below average tier**.
- Over the last five years, the survival rate in Georgia **improved** by **20%**.

<https://www.lung.org/research/state-of-lung-cancer/states/georgia>

# American Lung Association: state of lung cancer 2022

## Stage at Diagnosis and 5-Year Survival Rate



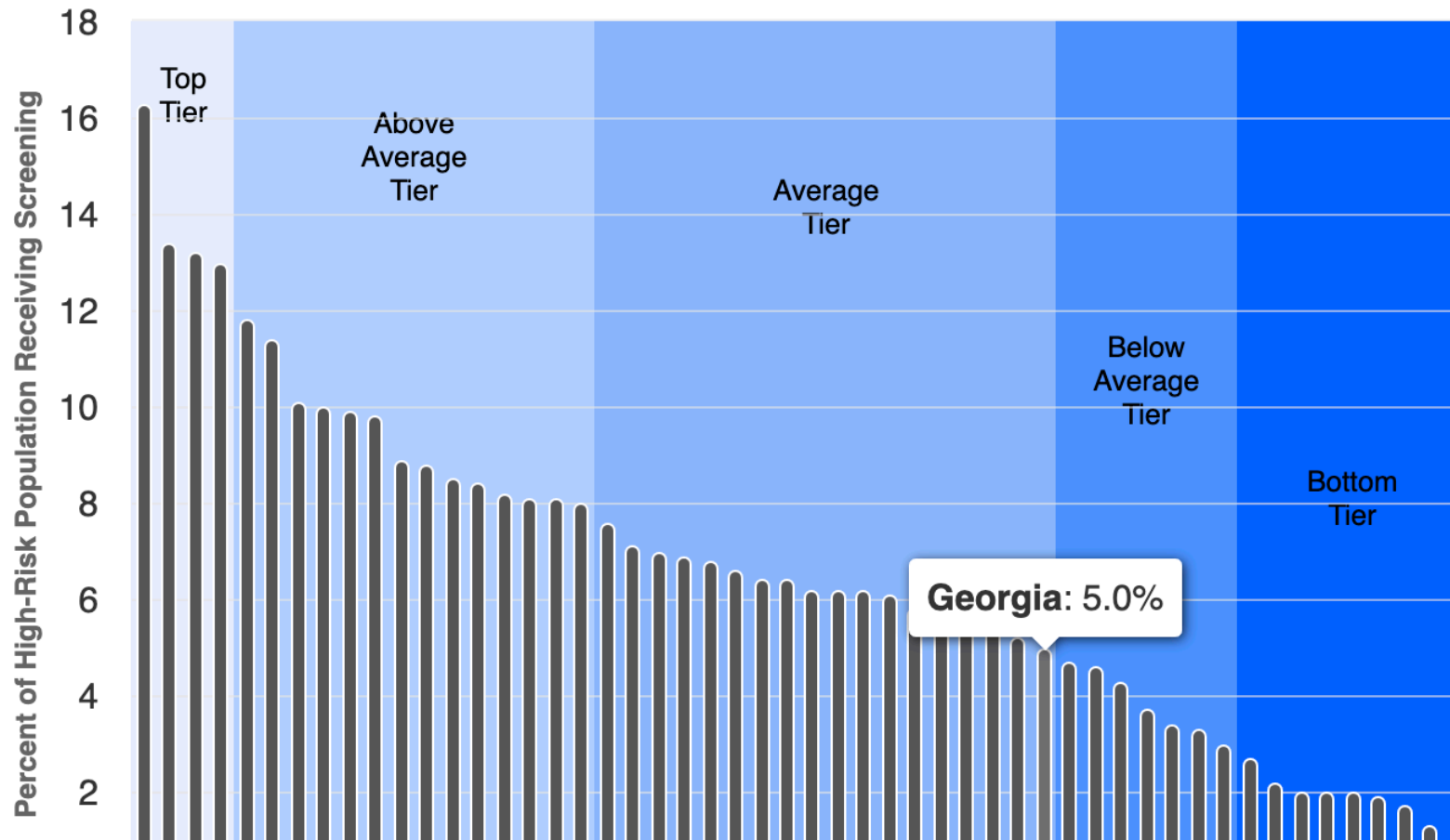
Highcharts.com

## Early Diagnosis:

- **24%** of cases are caught at an early stage, which is **significantly lower** than the national rate of 26%.
- It ranks **40th** among the 49 states with data on diagnosis at an early stage, placing it in the **below average tier**.
- Over the last five years, the early diagnosis rate in Georgia **improved** by **23%**.

<https://www.lung.org/research/state-of-lung-cancer/states/georgia>

### Screening for High Risk:



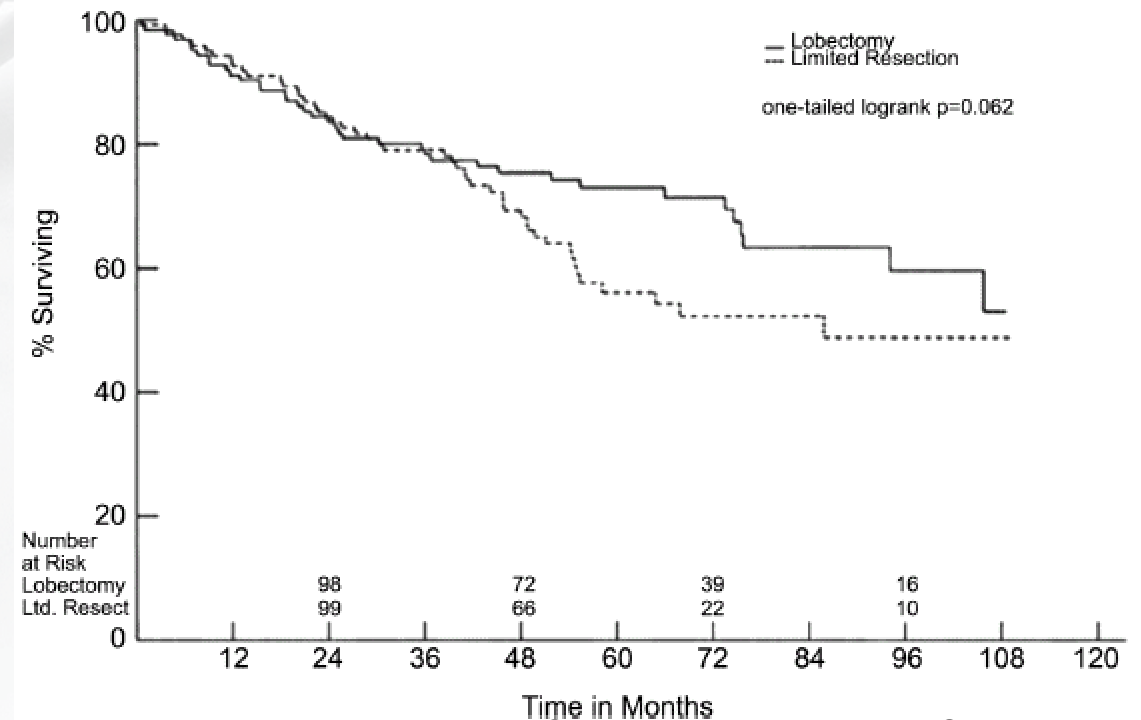
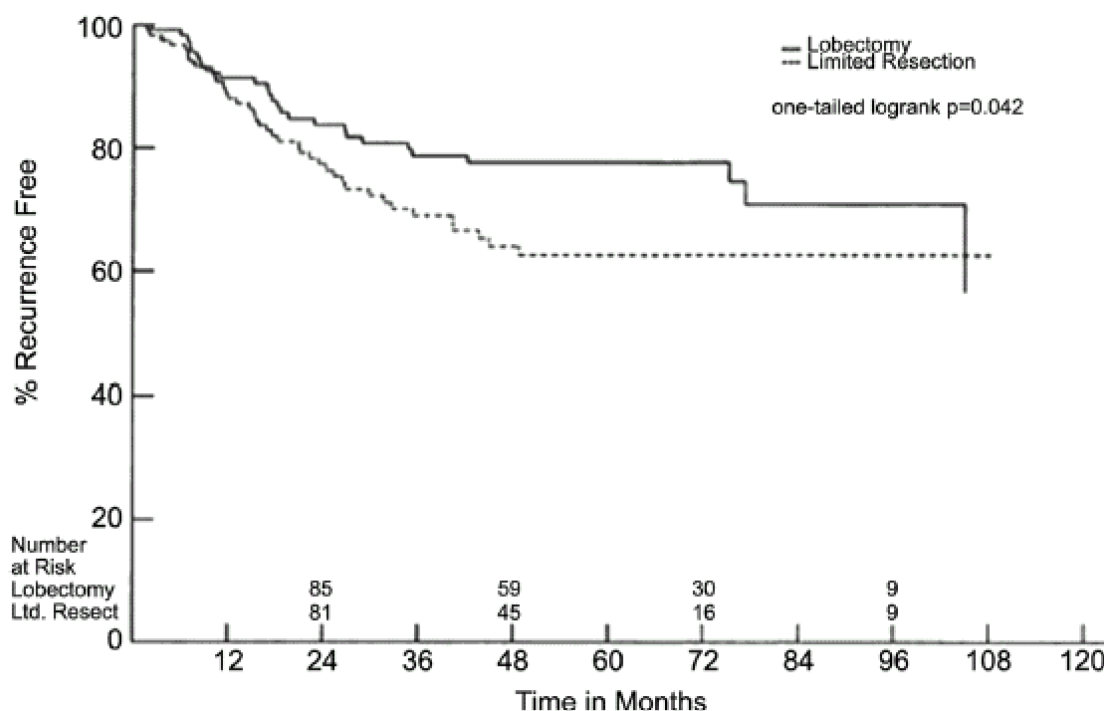
- In Georgia, **5%** of those at high risk were screened, which was not significantly different than the national rate of 6%.
- It ranks **35th** among all states, placing it in the **average tier**.
- Screening rates may be higher in states with large, regional managed care providers that did not share screening data.

7



# Lobectomy versus limited resection

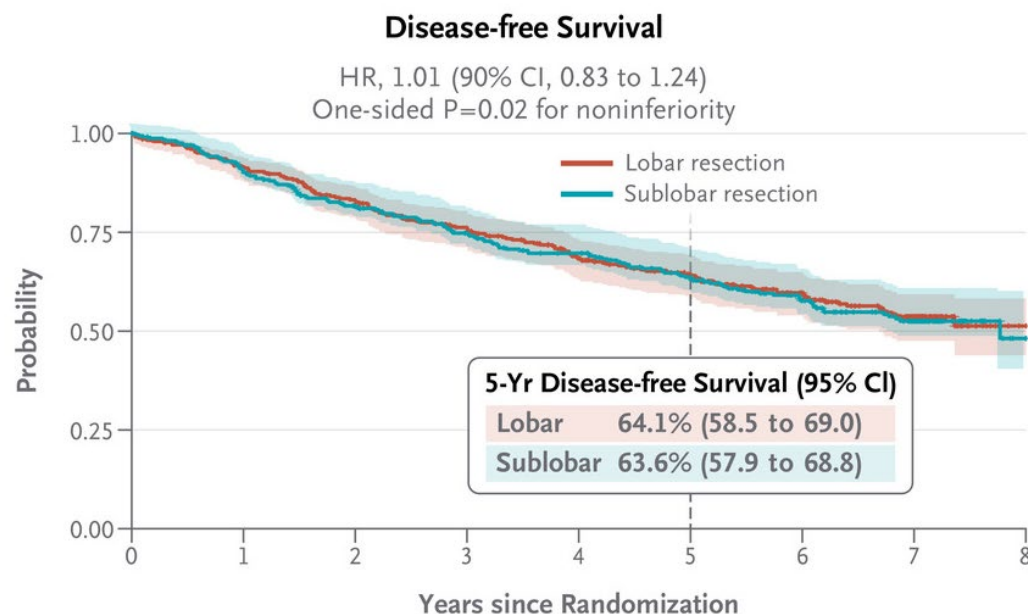
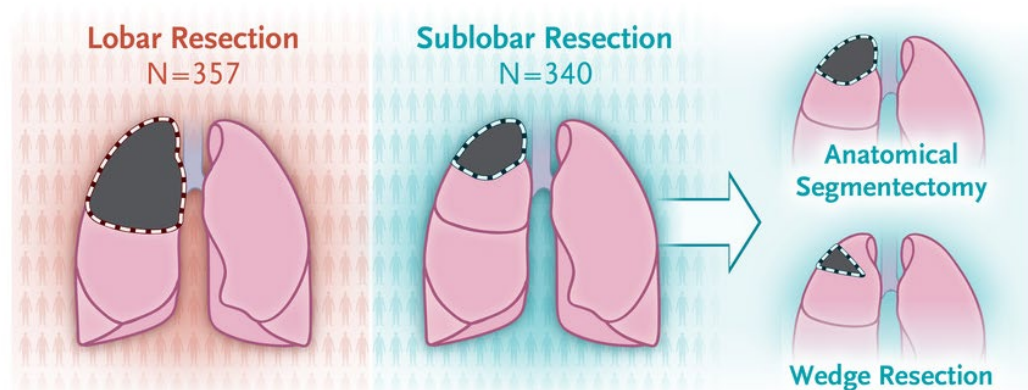
- Prospective Multi-institutional Randomized Trial (Lung Cancer Study Group)
- 247 patients with peripheral T1N0 NSCLC
- Limited resection group had observed 75% increase in recurrence rates ( $p = 0.02$ , one-sided) attributable to an observed tripling of the local recurrence rate ( $p = 0.008$  two-sided), an observed 30% increase in overall death rate ( $p = 0.08$ , one-sided), and an observed 50% increase in death with cancer rate ( $p = 0.09$ , one-sided) compared to lobectomy



Ginsberg et al. Ann Thorac Surg 1995; 60:615-23



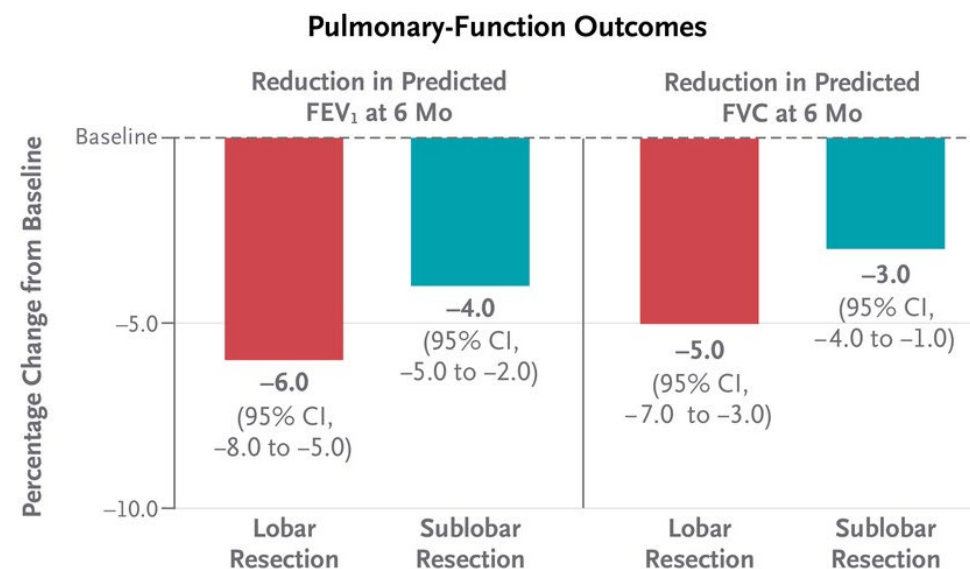
# Sub-lobar resection is non-inferior for stage IA (<2cm)



International phase III randomized non-inferiority study of 697 patients with stage IA peripheral NSCLC

Median follow-up: 7 years

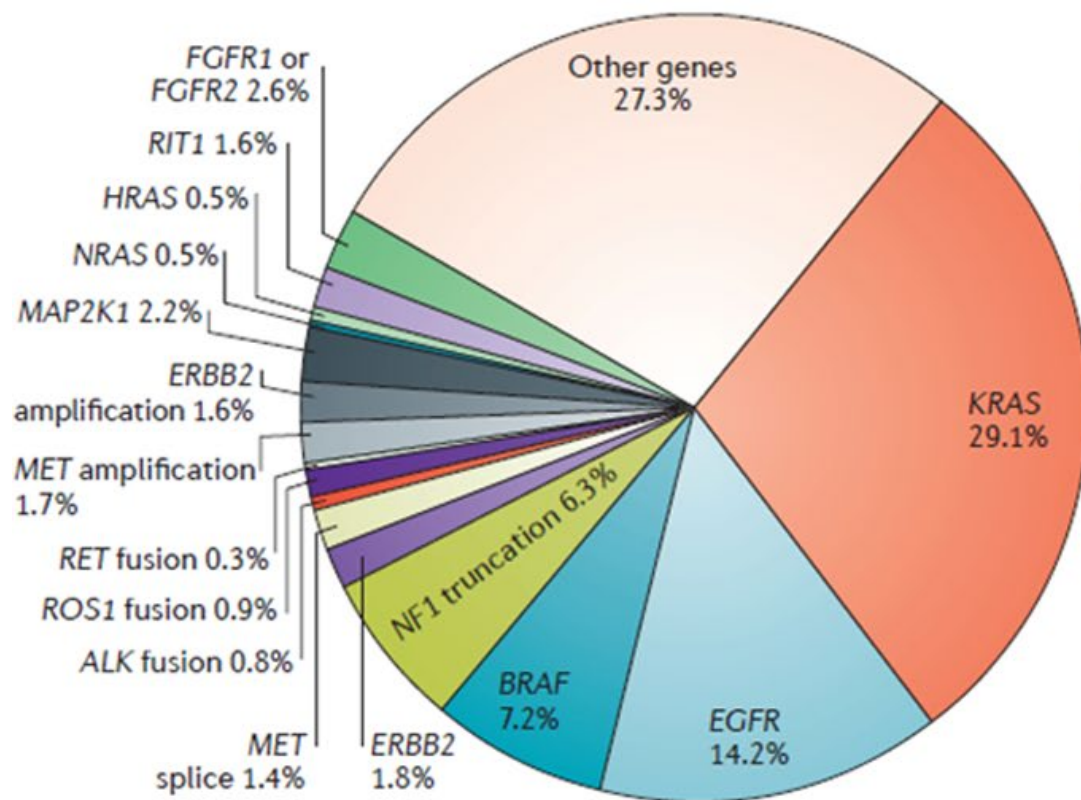
Improved pulmonary function



Altorki et al. NEJM, 2023; 388:489-498

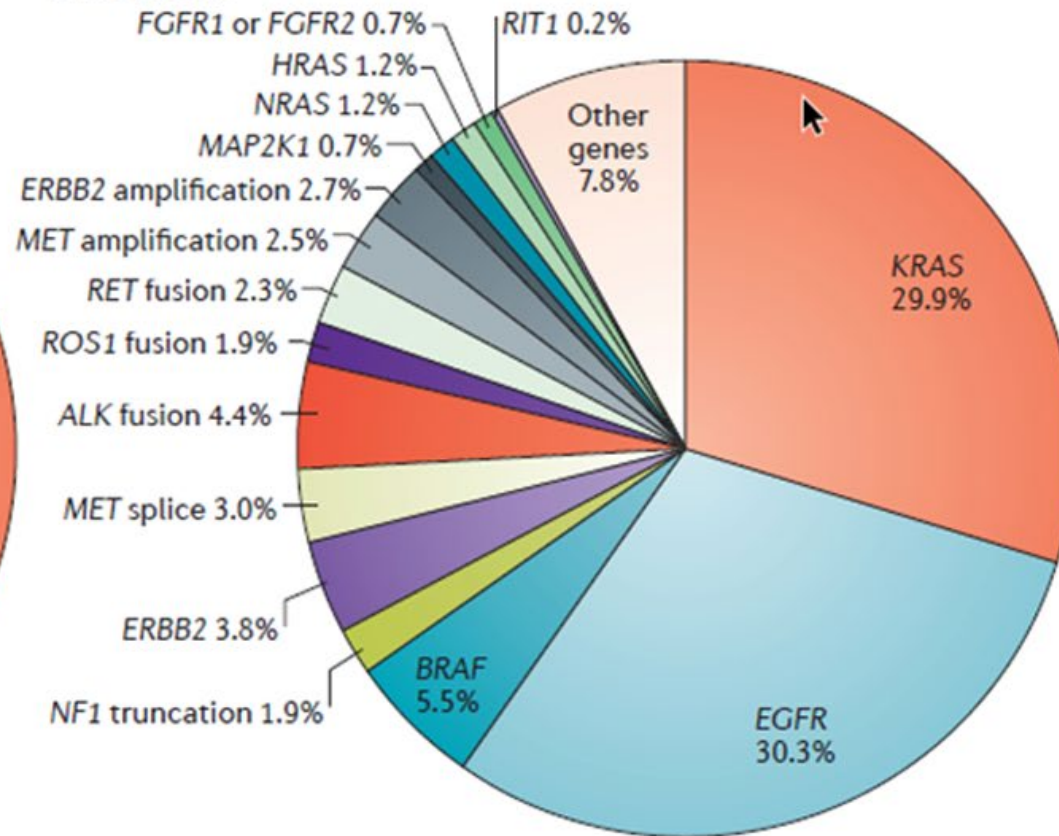
# Peri-operative therapy for driver mutated NSCLC

**a Early stage**



Data from TCGA (Sanchez-Vega et al.<sup>178</sup>, Ellrott et al.<sup>179</sup> and Hoadley et al.<sup>100</sup>), Imielinski et al.<sup>62</sup> and Kadara et al.<sup>133</sup> (n = 741)

**b Metastatic**



Data from MSK-IMPACT (Jordan et al.<sup>59</sup>) and FoundationOne (Frampton et al.<sup>15</sup>) panels (n = 5262)

May reflect referral bias in the metastatic cohort

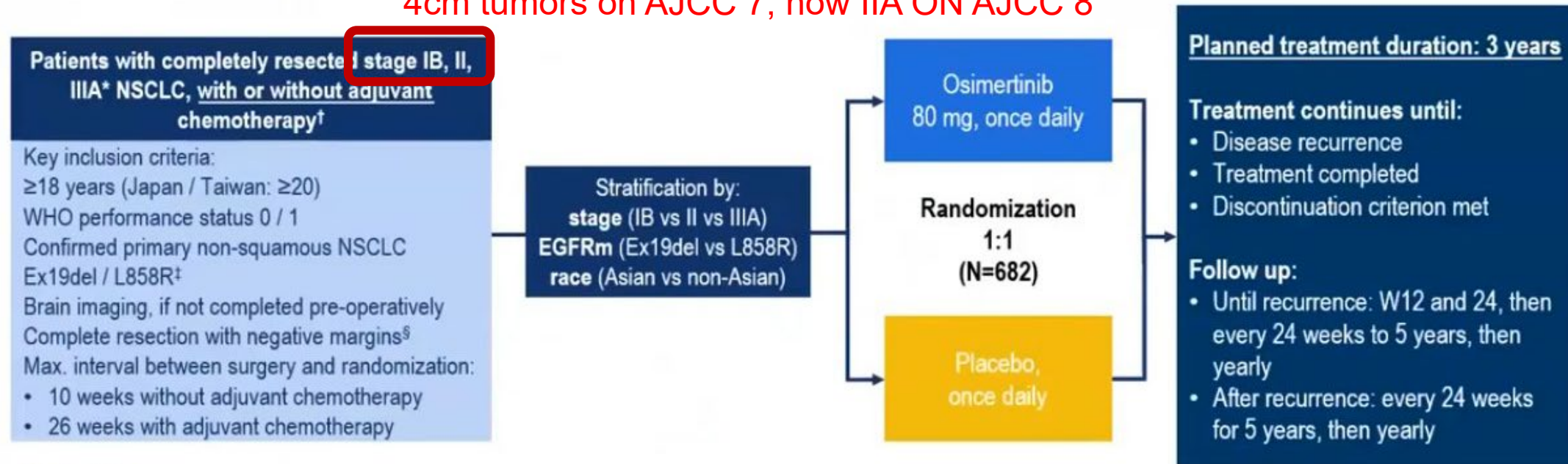
Skiloudis & Haymach Nat Rev Cancer 2019



# EGFR mutant NSCLC (exon 19 del, L858R)

## ADAURA Phase III double-blind study design

4cm tumors on AJCC 7, now IIA ON AJCC 8



### Endpoints

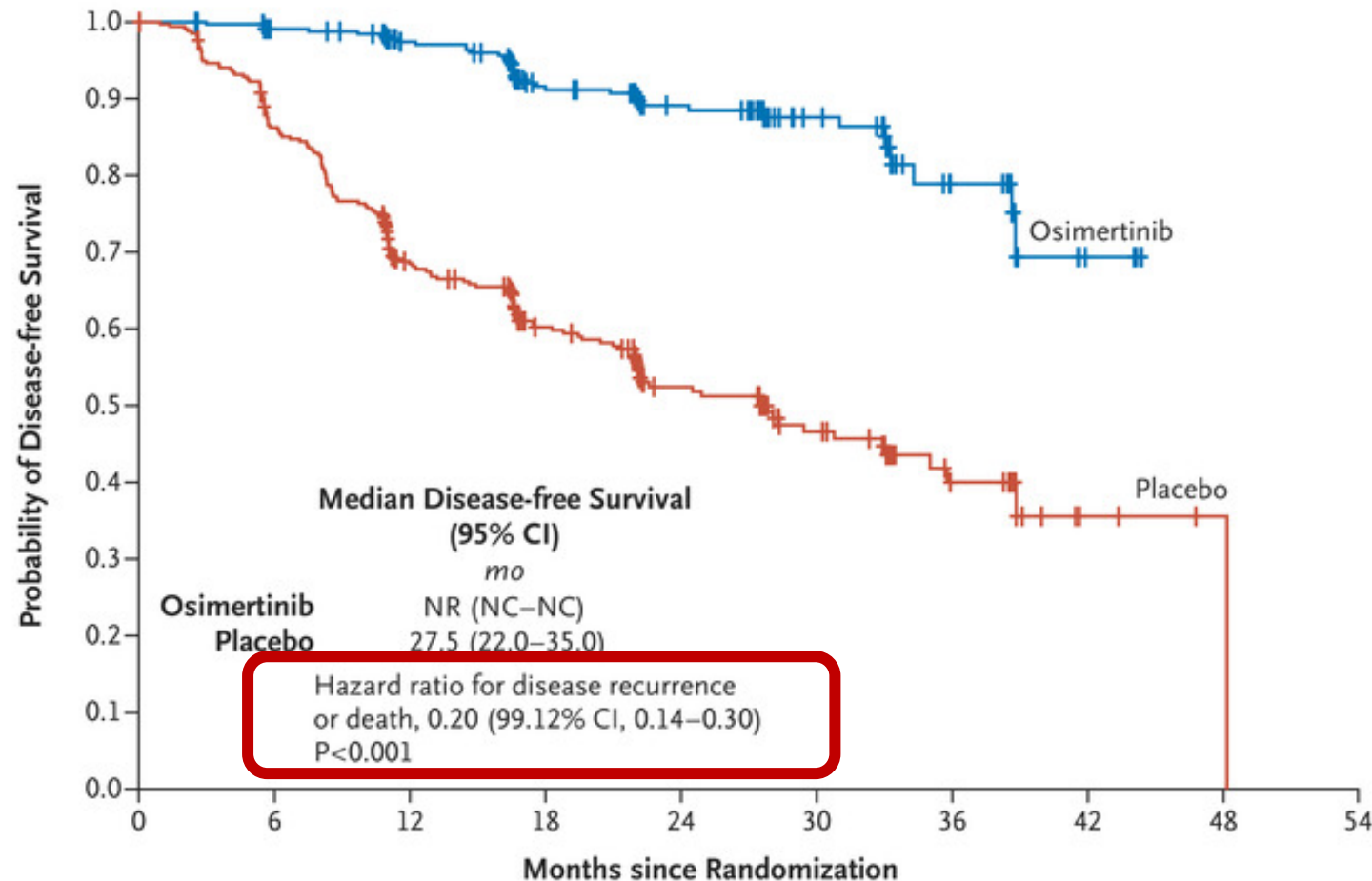
- **Primary:** DFS, by investigator assessment, in stage II—IIIA patients
- **Secondary:** DFS in the overall population<sup>¶</sup>, DFS at 2, 3, 4, and 5 years, OS, safety, quality of life

- Following IDMC recommendation, the study was unblinded early due to efficacy; here we report an unplanned interim analysis
- At the time of unblinding the study had completed enrollment and all patients were followed up for at least 1 year



# ADAURA: adjuvant Osimertinib improved PFS

B Patients with Stage IB to IIIA Disease



FDA approved 12/18/20 for AJCC8 stage II-IIIa following complete resection +/- chemo

Are we just delaying recurrence and preventing CNS disease with added cost?

Wu et al. N Engl J Med 2020; 383:1711-1723

# ADAURA: adjuvant Osimertinib delays CNS disease

- CNS metastases are a poor prognostic factor among patients with NSCLC, and are associated with deterioration in quality of life<sup>1</sup>

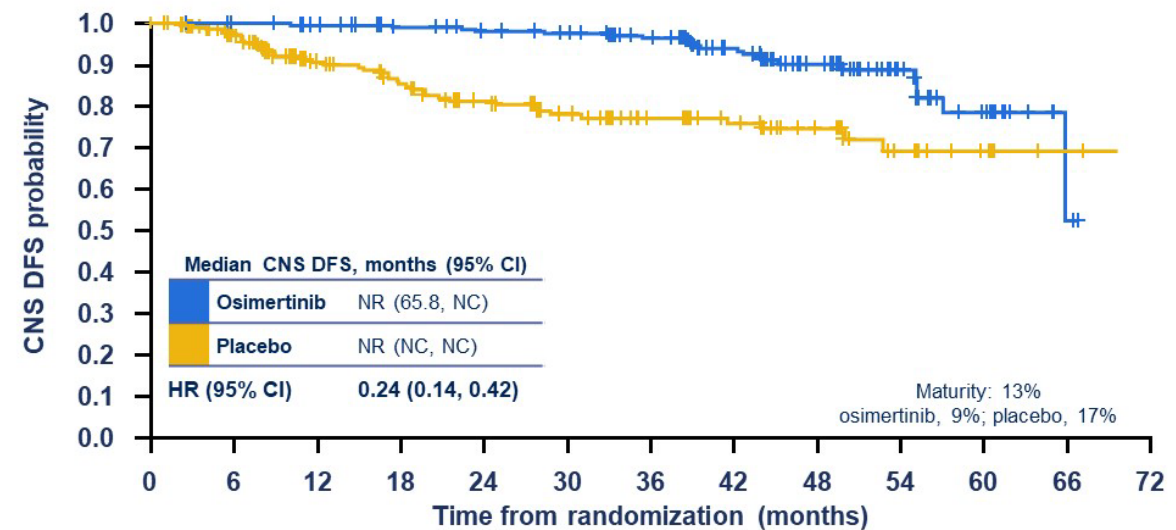
## Improved CNS efficacy with osimertinib treatment



- Osimertinib has shown greater penetration of the blood-brain barrier and higher exposure in the brain compared with other EGFR-TKIs<sup>2-4</sup>
- Adjuvant osimertinib demonstrated CNS DFS\* benefit vs placebo in both the stage II–IIIA and IB–IIIA populations<sup>5,6</sup>

## ADAURA updated CNS DFS analysis<sup>5,6</sup> (stage II–IIIA)

JCO January 2023



No. at risk												
Osimertinib	233	222	216	202	196	192	175	138	90	45	20	2
Placebo	237	192	142	126	107	91	74	61	41	23	11	1

Data cut-off: April 11, 2022.

1. Peters et al. Cancer Treat Rev 2016;45:139–162; 2. Colclough et al. Eur J Cancer 2016;69:S28; 3. Ballard et al. Clin Cancer Res 2016;22:5130–5140; 4. Vishwanathan et al. Cancer Res 2018;78:CT013; 5. Herbst et al. J Clin Oncol 2023;41:1830–1840; 6. Tsuboi et al. Ann Oncol 2022;33(Suppl 7): abstract / oral LBA47.

2023 ASCO  
ANNUAL MEETING

#ASCO23

PRESENTED BY: Roy S. Herbst

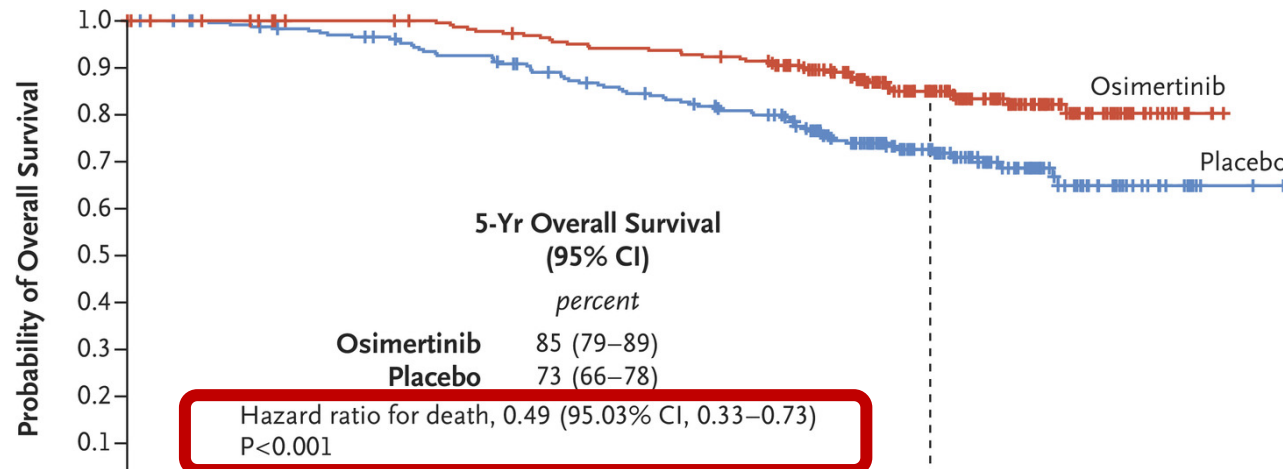
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CI, confidence interval; CNS, central nervous system; DFS, disease-free survival; EGFR, epidermal growth factor receptor; EGFRm, EGFR-mutated; EGFR-TKI, EGFR-tyrosine kinase inhibitor; HR, hazard ratio; NC, not calculable; NR, not reached; NSCLC, non-small cell lung cancer

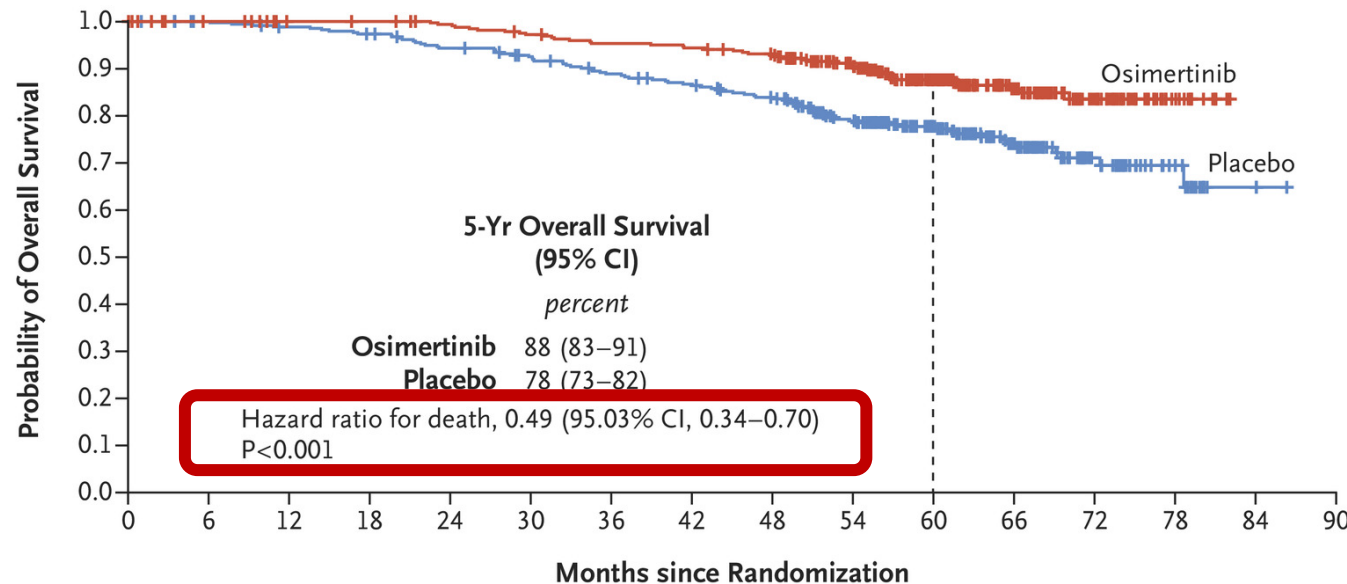
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# ADAURA: adjuvant Osimertinib improves OS

A Patients with Stage II to IIIA Disease



B Patients with Stage IB to IIIA Disease



## No. at Risk

Osimertinib	339	332	325	324	319	311	304	301	294	252	176	108	50	15	0	
Placebo	343	338	332	326	314	304	290	281	267	223	164	97	44	17	3	0

Absolute benefit at 5 years:

12% (II-IIIa)

10% (Ib-IIIa)

Regardless of prior chemotherapy

Exon 19 deletions do better than L858R

Tsubi et al. N Engl J Med June 2023  
DOI: 10.1056/NEJMoa2304594



# Questions following ADAURA

Are they cured?

## How can therapy be optimized:

What is the optimal duration of osimertinib therapy?

Is chemotherapy necessary for all patients?

What about neoadjuvant osimertinib?

NEO-ADAURA: Randomize to chemo,  
chemo+osi, or osi for 9 weeks prior to surgery

## Who may benefit:

Will pts with Stage IA disease or locally advanced disease benefit?

What about *EGFR* mutations other than Exon19del/L858R?

Role of ctDNA?

ADAURA2: Osi for Stage IA2-IA3 NSCLC  
Following Complete Tumor Resection

## What happens after relapse?

Do tumors retain sensitivity to EGFR TKIs?

What are mechanisms of resistance?

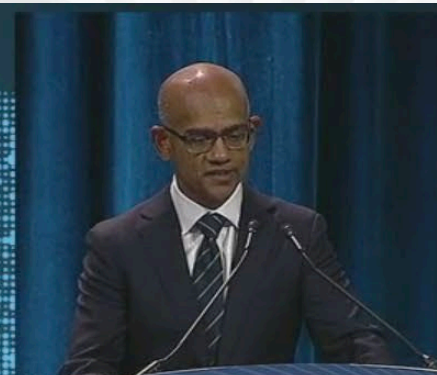
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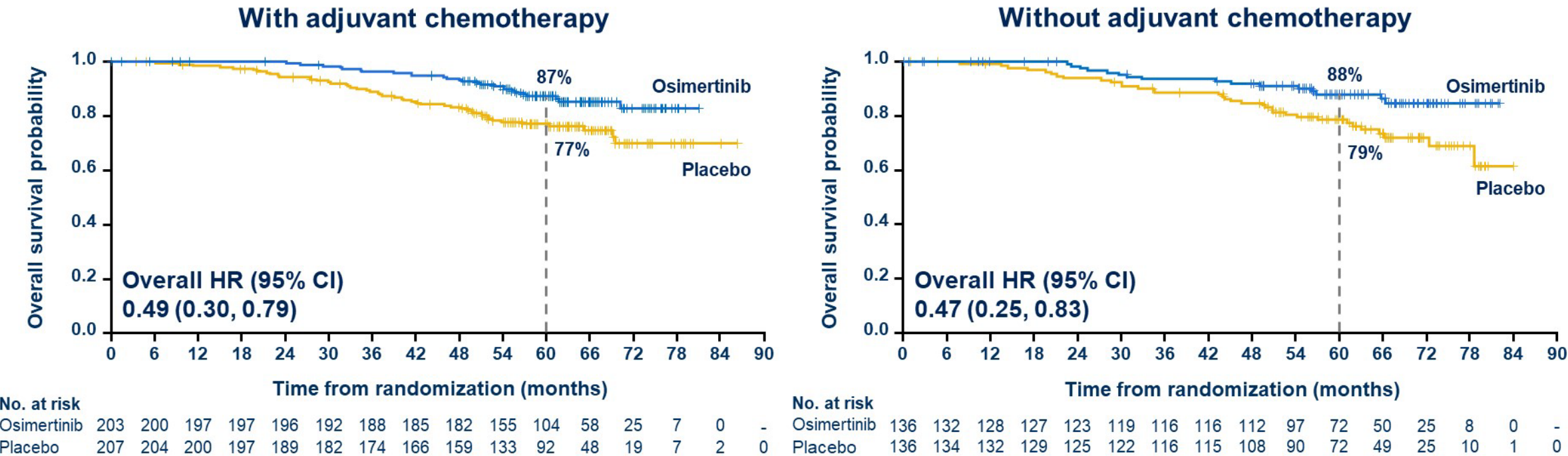
PRESENTED BY: Benjamin Solomon MBBS, PhD

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# ADAURA: OS with and without chemotherapy



60% of patients received chemotherapy, no difference between arms

Presented by Roy Herbst, ACO 2023; Tsubi et al. N Engl J Med June 2023 DOI: 10.1056/NEJMoa2304594

# Take-aways from ADAURA

- ❑ Molecular testing of early-stage NSCLC is mandatory
- ❑ Rather than piecemeal testing, NGS preferred
- ❑ Given FDA approved option for neoadjuvant chemo-IO, need NGS at diagnosis to avoid chemo-IO in patients with EGFR to avoid toxicity with adjuvant osimertinib following IO (pneumonitis)

 How much can we extrapolate to other driver mutations?



# Early stage ALK trials...are languishing

Trial	Study design	Control	Primary endpoint	Target enrollment	Trial dates
ALCHEMIST (33), NCT02201992	Phase III; resected stage IB (>4 cm)- IIIA; adjuvant crizotinib x2 years	Placebo	OS	168 patients	Start date: 8/2014; completion date: 2036
ALINA (34), NCT03456076	Phase III; resected stage IB-IIIA; adjuvant alectinib x2 years	Platinum-based chemotherapy	DFS	257 patients	Start date: 3/2018; completion date: 2026
NCT05241028 (35)	Phase II; stage IB-IIIA; adjuvant ensartinib x3 years	None	DFS	80 patients	Not yet recruiting
RTOG 1306 (40), NCT01822496	Phase II; unresectable stage III; neoadjuvant crizotinib x12 weeks	Placebo	PFS	59 patients (actual enrollment 16 patients)	Start date: 11/2013; completion date: 6/2018
SAKULA (41), UMIN00017906	Phase II; resectable stage II-III; neoadjuvant ceritinib x12 weeks	None	mPR	19 patients (actual enrollment 7 patients)	Start date: 3/2015; completion date: 10/2019
ARM (42), NCT03088930	Phase II; resectable stage IA-IIIA; neoadjuvant crizotinib x6 weeks	None	ORR	26 patients (actual enrollment 3 patients)	Start date: 3/2017; completion date: 2/2022
ALNEO (39), NCT05015010	Phase II; resectable stage III; neoadjuvant alectinib x8 weeks followed by adjuvant alectinib x96 weeks	None	mPR	33 patients	Start date: 8/2021; completion date: 5/2026
NAUTIKA1 (43), NCT04302025	Phase II; resectable stage IB-III; neoadjuvant alectinib x8 weeks followed by adjuvant alectinib x104 weeks	None	mPR	80 patients	Start date: 3/2020; completion date: 2/2029

ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; OS, overall survival; DFS, disease free survival; PFS, progression free survival; mPR, major pathologic response; ORR, objective response rate.

Chen & Chافت, TLCR  
Feb 2023

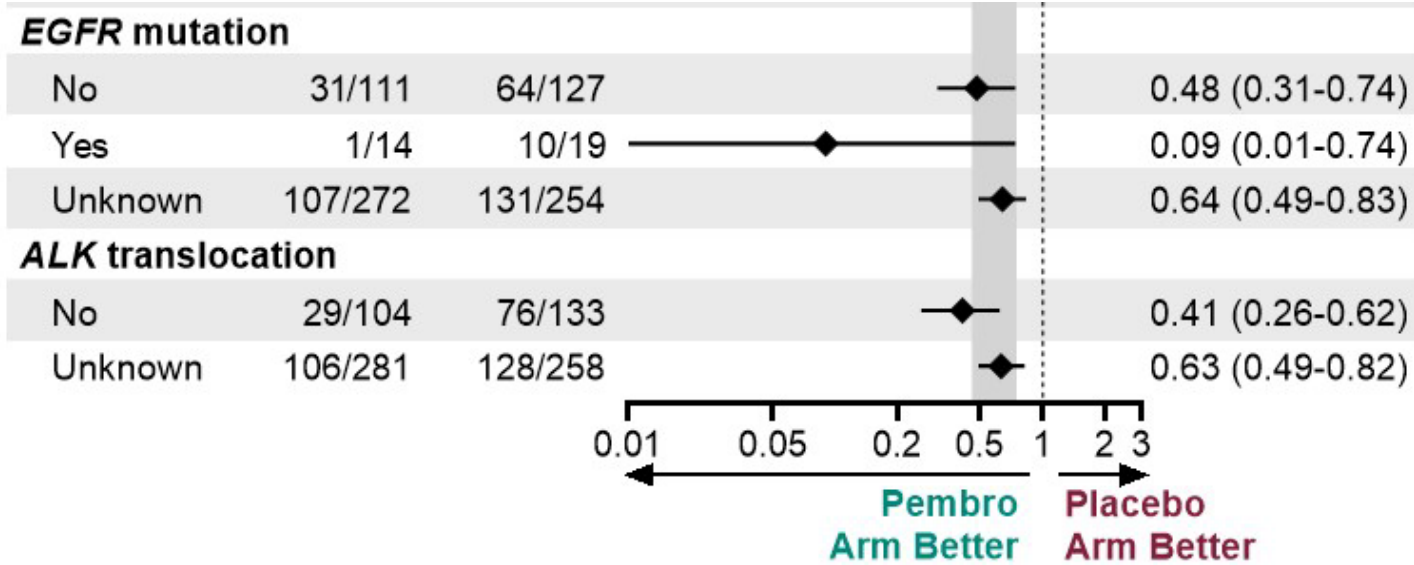
# Other Molecular targets

## Neoadjuvant + Adjuvant:

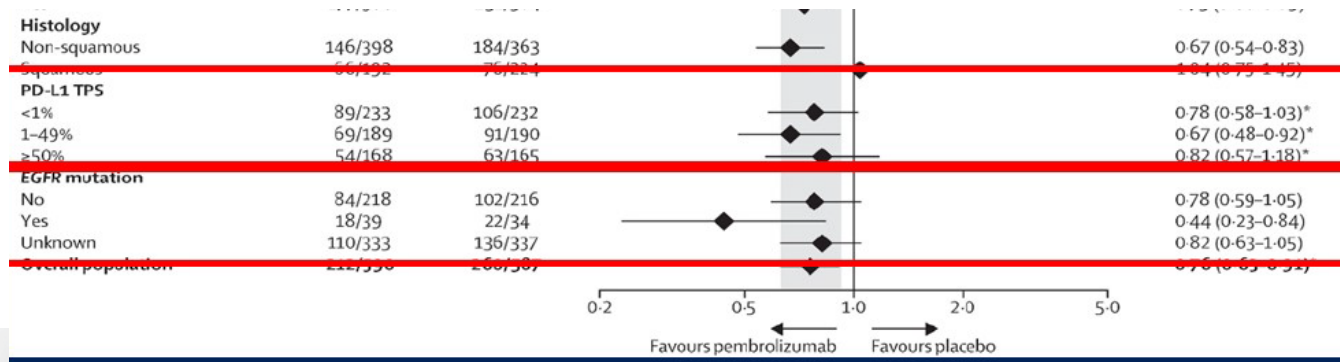
- osimertinib (EGFR, NeoADAURA, NCT04351555)
- divarasil (KRASG12C, NAUTIKA-1, NCT04302025)
- alectinib (ALK, ALNEO, NCT05015010)
- capmatinib (MET, Geometry-N, NCT04926831)
- entrectinib (ROS1, NTRK, NAUTIKA-1, NCT04302025)
- vemurafenib/cobimetinib (BRAF, NAUTIKA-1, NCT04302025)
- pralsetinib (RET, NAUTIKA-1, NCT04302025)
- etc

# Chemo-IO in driver mutated NSCLC – EGFR?

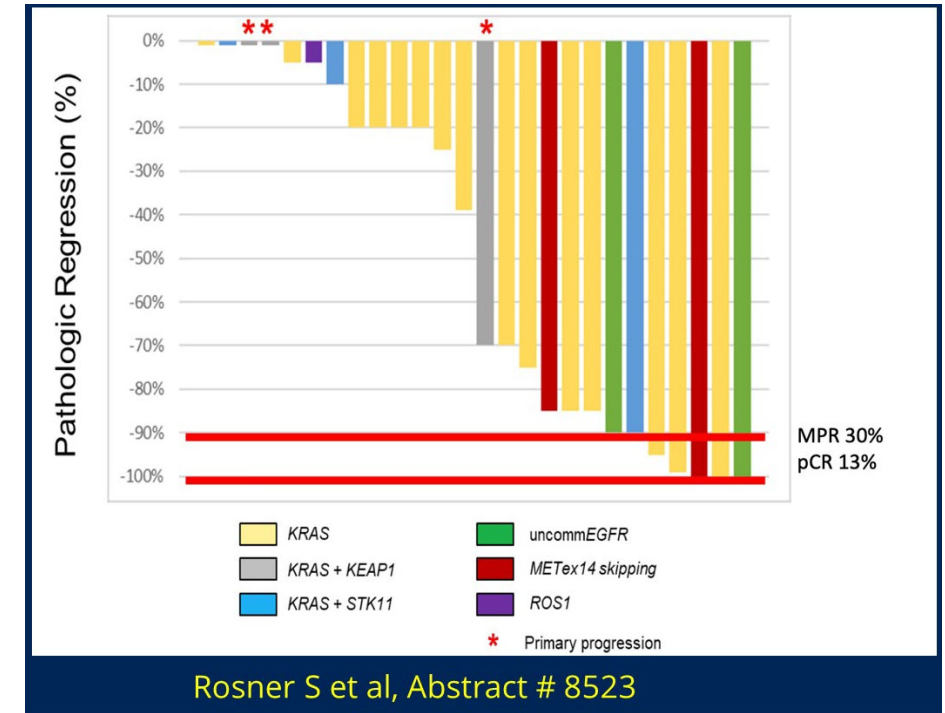
## KEYNOTE-671



## KEYNOTE-091



## MOSTLY NEOADJUVANT NIVO

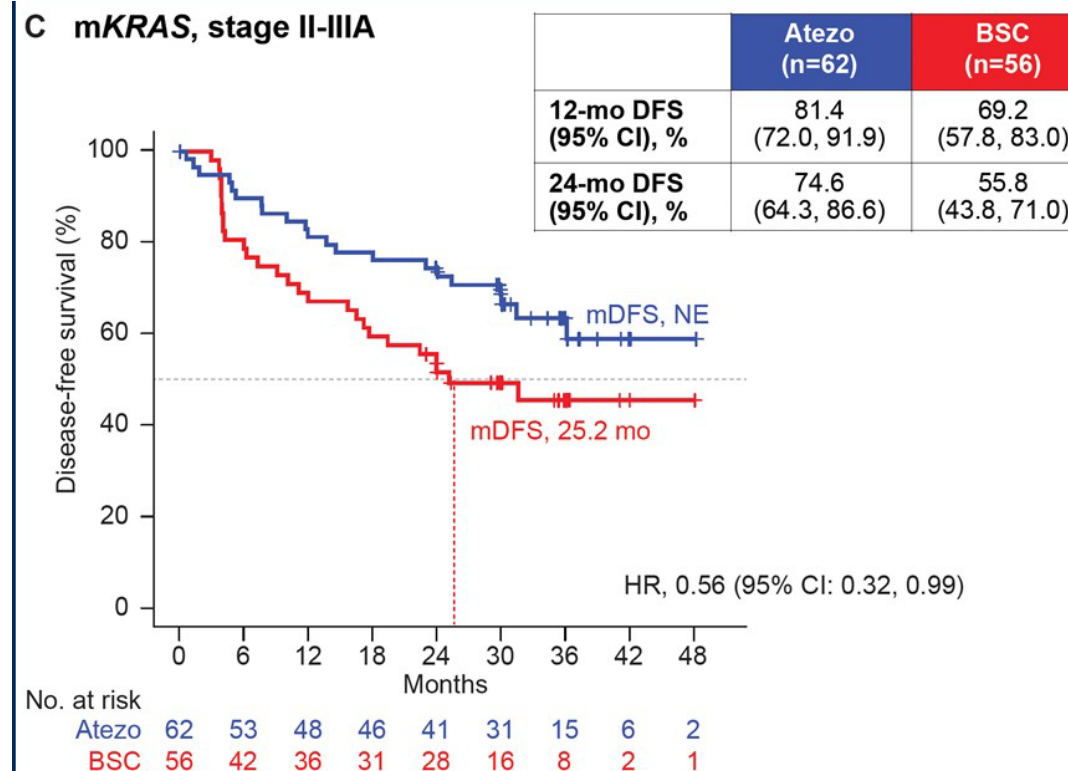
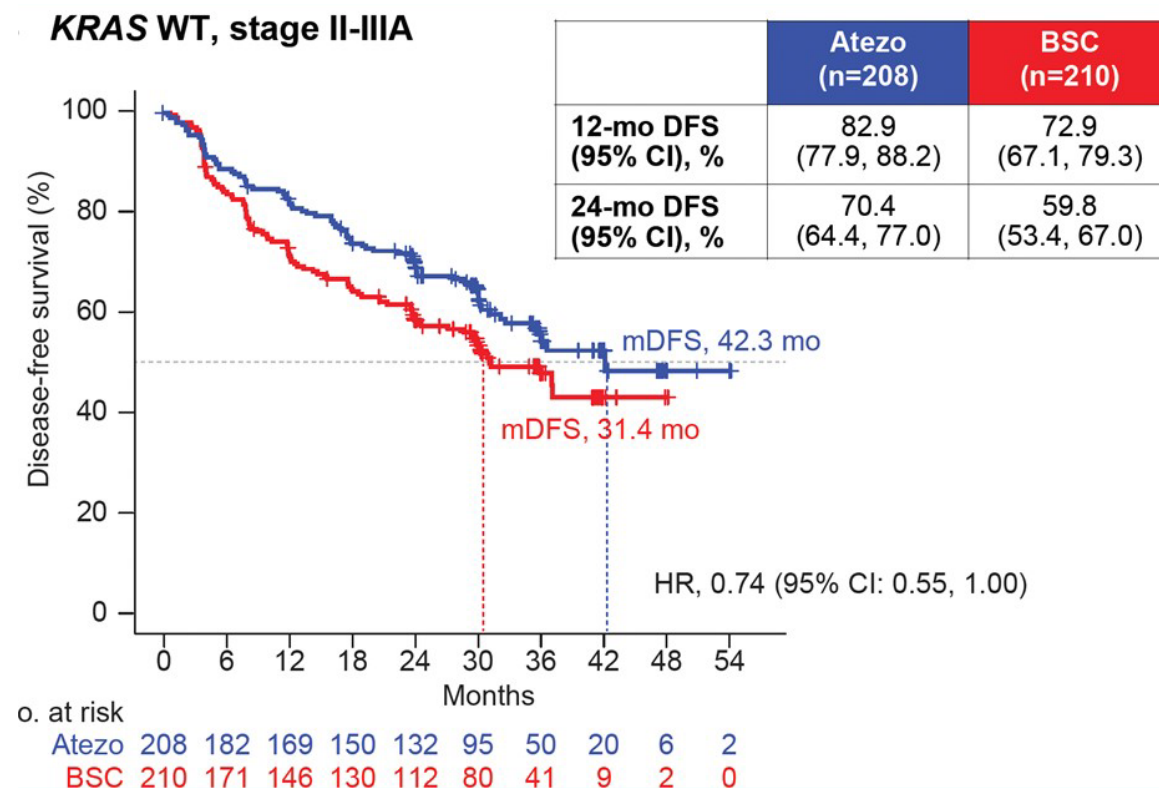


Wakelee et al, NEJM, 2023  
 Rosner et al, ASCO 2023  
 O'Brien, Lancet Oncology, 2022



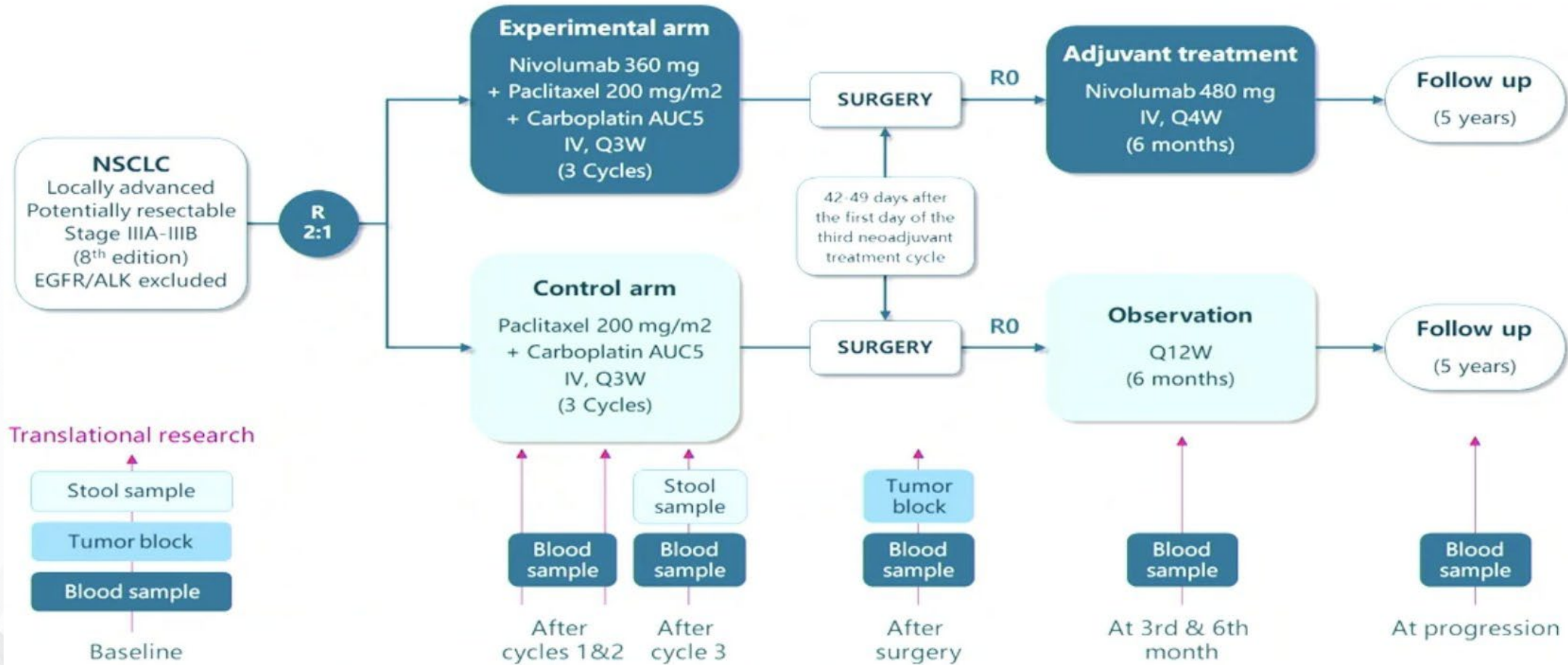
# Chemo-IO in KRAS subgroups

## IMpower010: DFS benefit regardless of KRAS mutation



Reck et al, ASCO 2023

# NADIMII: Duration adjuvant IO after neoadjuvant chemo-IO

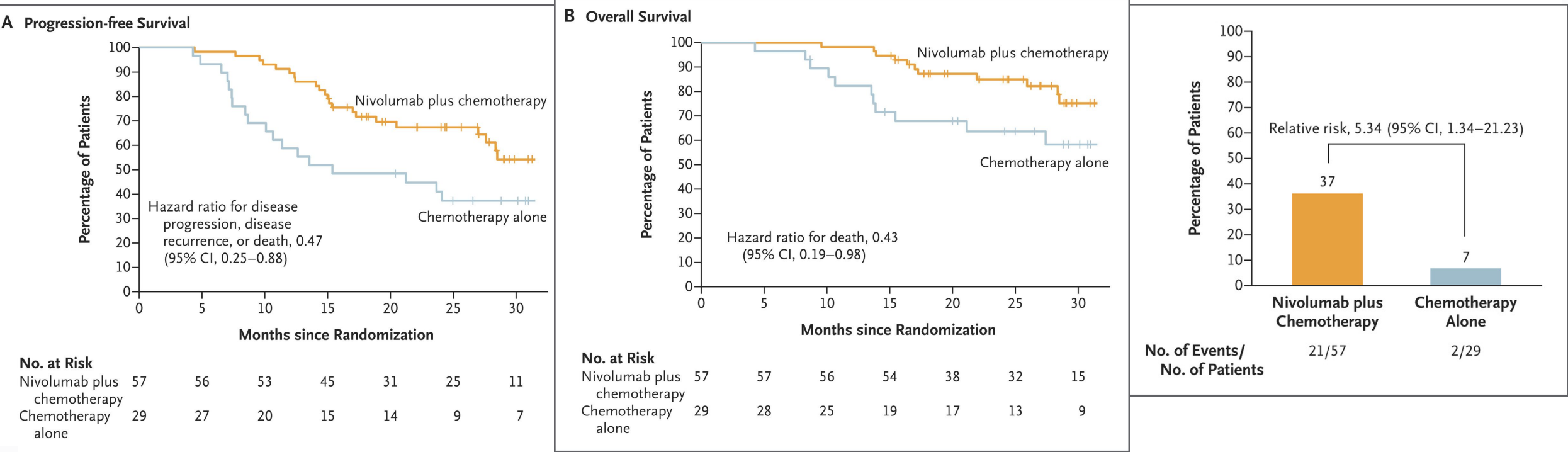


Provencio et al, WCLC, 2022

Provencio, Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain

# NADIMII: Efficacy with 6 months adjuvant nivolumab

hazard ratio for death, 0.43; 95% CI, 0.19 to 0.98



Surgery was performed in 93% of the patients in the experimental group and in 69% in the control group (relative risk, 1.35; 95% CI, 1.05 to 1.74)

Provencio et al, NEJM, 2023



# Pathologic complete response rates with chemo IO

Trial	IO Agent	PCr% Treatment (95%CI)	PCr% Control (95% CI)	P value
Keynote-671	Pembrolizumab	18.1% (14.5-22.3)	4.0% (2.3-6.4)	<0.0001
NEOTORCH	Toripalimab	28.2% (22.1-35)	1.0% (0.1-3.5)	<0.0001
AGEAN	Durvalumab	17.2%	4.3%	0.000036
CheckMate-816	Nivolumab	24.0%	2.2%	<0.0001
NADIMII	Nivolumab	37%	7%	relative risk, 5.34; 95%CI (1.34 to 21.23) P=0.02

# Proposed ideal workflow:

Suspicious lung mass biopsy shows NSCLC

Reflex NGS\* and PD-L1, any clinical stage  
(ordered by pathology)

PET +/- Brain MRI  
(ordered by IP/PMD)

*Clinical Pre-review for Multidisciplinary clinic*

Stage I

PFTs  
Surgery  
+/- Rad  
onc

Stage II-IIIB

Surgery, Rad onc, Med onc

*Resectable  
Driver negative  
Candidate for IO*

**Neoadjuvant  
> Adjuvant**

*Resectable  
Driver +  
EGFR/ALK*

**Surgery,  
chemo +/- OSI**

*Not surgical  
candidate*

Stage IIIC /  
unresectable

Rad onc  
Med onc

**CRT ->  
Durvalumab  
\*discuss if EGFR**

Stage IV

Med onc  
+/- Rad onc