
# Welcome!

- Our program will begin at 1:00 PM US ET.
- Please stay muted unless you are called on during the Q&A.
- We invite you to use the chat function to introduce yourself!

## MEET TODAY'S HOST

**Kathryn O'Donnell, PhD**

*Chair, LCRF Scientific Advisory Board*
*Member, LCRF Board of Directors*

Associate Professor, Molecular Biology
Co-leader, Development and Cancer Program,
Simmons Comprehensive Cancer Center
UT Southwestern Medical Center

*The 2025 LCRF Scientific Symposium is supported by*

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# Today's schedule

*All times listed are*
***United States***
***Eastern Standard Time***

| | |
|---|---|
| 1:00 PM | **Welcome**<br>*Kathryn O'Donnell, PhD, Chair, LCRF Scientific Advisory Board* |
| 1:05 PM | **State of Lung Cancer Research**<br>*Sarah Goldberg, MD, MPH* |
| 1:25 PM | **Presentations**<br>*Patient Advocacy: Colleen Conner Ziegler*<br>*Screening: Chi-Fu Jeffrey Yang, MD*<br>*Overcoming Resistance: Don L. Gibbons, MD, PhD*<br>*Innovation: James DeGregori, PhD* |
| 2:20 PM | **Panel discussion with Q&A**<br>*Moderators:*<br>*Kathryn A. O'Donnell, PhD*<br>*Isabel Preeshagul, DO, MBS* |
| 2:55 PM | **Closing remarks**<br>*Kathryn O'Donnell, PhD, Chair, LCRF Scientific Advisory Board* |
| 3:00 PM | **Symposium ends** |


# State of Lung Cancer Research

## Sarah Goldberg, MD, MPH

*Member, LCRF Scientific Advisory Board*

*Recipient, 2025 LCRF | Bayer Research Award on Innovative Therapeutic Strategies to Treat Lung Cancers Harboring HER2 Mutations and/or Other HER2 Alterations*

**Yale School of Medicine**
Associate Professor of Internal Medicine (Medical Oncology)
Associate Director, Hematology/ Oncology Fellowship Program
Research Director, Center for Thoracic Cancers

# State of Lung Cancer Research

LCRF Symposium
November 2025


**Sarah Goldberg, MD, MPH**

**Professor of Medicine (Medical Oncology)**
**Division Chief, Thoracic Oncology**
**Co-Director, Center for Thoracic Cancers**
**Yale School of Medicine and Yale Cancer Center**

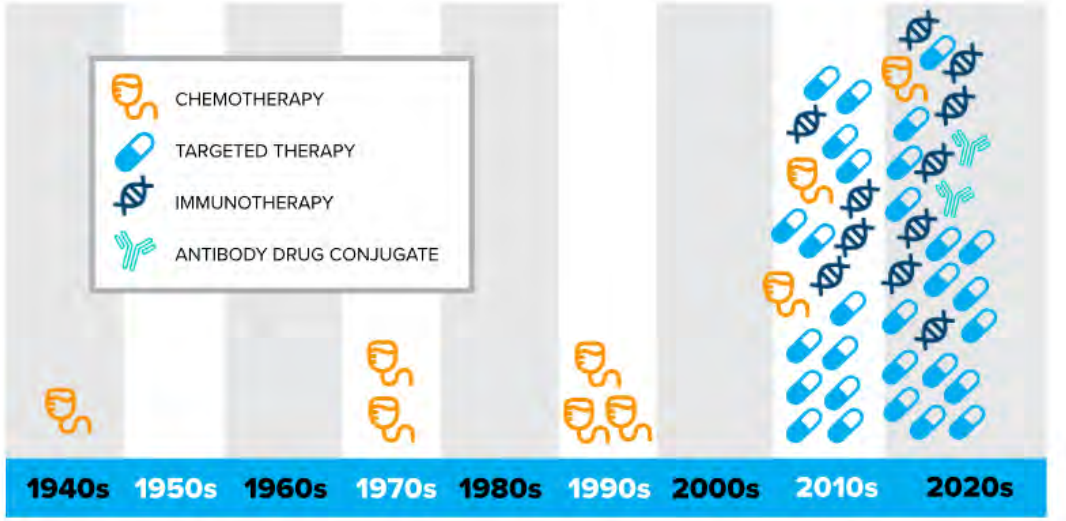
YaleNewHavenHealth
Smilow Cancer Hospital

Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

Yale SCHOOL OF MEDICINE

# WHAT A YEAR!!!

- 2025 was an exciting year in lung cancer research!
- 6 new drugs approved by the FDA for lung cancer
- Progress in our understanding of how to best treat patients
- Many exciting treatment strategies moving forward in trials

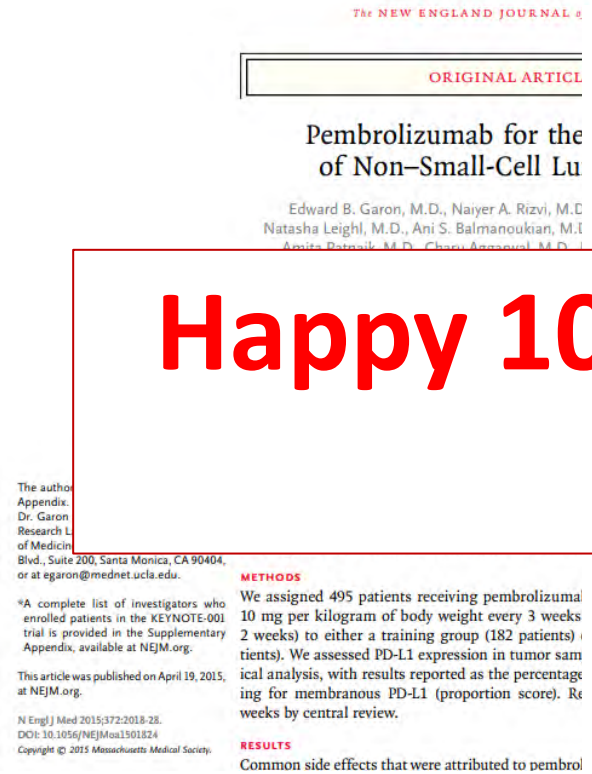


# Advances in 2025 that I will highlight

- Novel immunotherapies
  - Bispecific antibodies
  - T-cell engagers
- Targeted therapy
  - First-line treatment for EGFR
  - Overcoming resistance
  - Emerging HER2 therapies
- Antibody-drug conjugates

# A decade of PD-1/PD-L1 inhibitors

**Happy 10th anniversary to immunotherapy for lung cancer!**


The NEW ENGLAND JOURNAL

ORIGINAL ARTICL

Pembrolizumab for the
of Non–Small-Cell Lu

Edward B. Garon, M.D., Naiyer A. Rizvi, M.D
Natasha Leighl, M.D., Ani S. Balmanoukian, M.D

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*A complete list of investigators who enrolled patients in the KEYNOTE-001 trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on April 19, 2015, at NEJM.org.

N Engl J Med 2015;372:2018-28.
DOI: 10.1056/NEJMoa1501824
Copyright © 2015 Massachusetts Medical Society.

METHODS

We assigned 495 patients receiving pembrolizumab
10 mg per kilogram of body weight every 3 weeks
2 weeks) to either a training group (182 patients)
tients). We assessed PD-L1 expression in tumor sam
ical analysis, with results reported as the percentage
ing for membranous PD-L1 (proportion score). Re
weeks by central review.

RESULTS

Common side effects that were attributed to pembrol


NIH NATIONAL CANCER INSTITUTE

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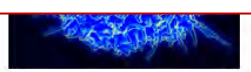
Home › News & Events › Cancer Currents Blog › FDA Approves First Immunotherapy Treatment for Lung Cancer

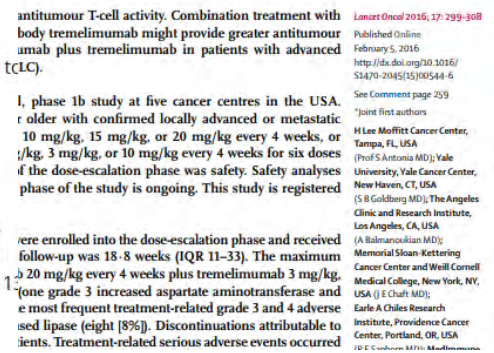
melanoma, is the first immunotherapy drug to be approved to treat lung cancer. It works by inhibiting a protein receptor called PD-1 on T cells, a type of immune cell.

PD-1 belongs to a family of so-called checkpoint proteins that, when activated, serve as a brake on the immune system. Nivolumab prevents tumor cells from communicating through the PD-1 protein to inactivate T cells, allowing the immune system to attack the tumor cells.

The FDA based the approval on findings from a randomized phase III trial that enrolled 272 patients with advanced non-small cell lung cancer who were assigned to receive either nivolumab or the chemotherapy drug docetaxel.

Results from the phase III trial have yet to be published or presented at a scientific meeting, but, according to the FDA, participants who received nivolumab had a 41% reduction in the risk of death and lived on average 3.2 months longer than those who received docetaxel. Approximately 30 percent of patients treated with nivolumab were alive 2 years after beginning treatment compared to 1
percent of patients treated with docetaxel.




E Sanborn, Ashok Gupta, Rajesh Narwal, Keith Steele, Yu Gu,

antitumour T-cell activity. Combination treatment with
body tremelimumab might provide greater antitumour
umab plus tremelimumab in patients with advanced
LC).

l, phase 1b study at five cancer centres in the USA.
r older with confirmed locally advanced or metastatic
10 mg/kg, 15 mg/kg, or 20 mg/kg every 4 weeks, or
/kg, 3 mg/kg, or 10 mg/kg every 4 weeks for six doses
f the dose-escalation phase was safety. Safety analyses
phase of the study is ongoing. This study is registered

ere enrolled into the dose-escalation phase and received
follow-up was 18·8 weeks (IQR 11–33). The maximum
20 mg/kg every 4 weeks plus tremelimumab 3 mg/kg,
(one grade 3 increased aspartate aminotransferase and
e most frequent treatment-related grade 3 and 4 adverse
sed lipase (eight [8%]). Discontinuations attributable to
ients. Treatment-related serious adverse events occurred

Lancet Oncol 2016; 17: 299-308
Published Online
February 5, 2016
http://dx.doi.org/10.1016/
S1470-2045(15)00544-6

See Comment page 259

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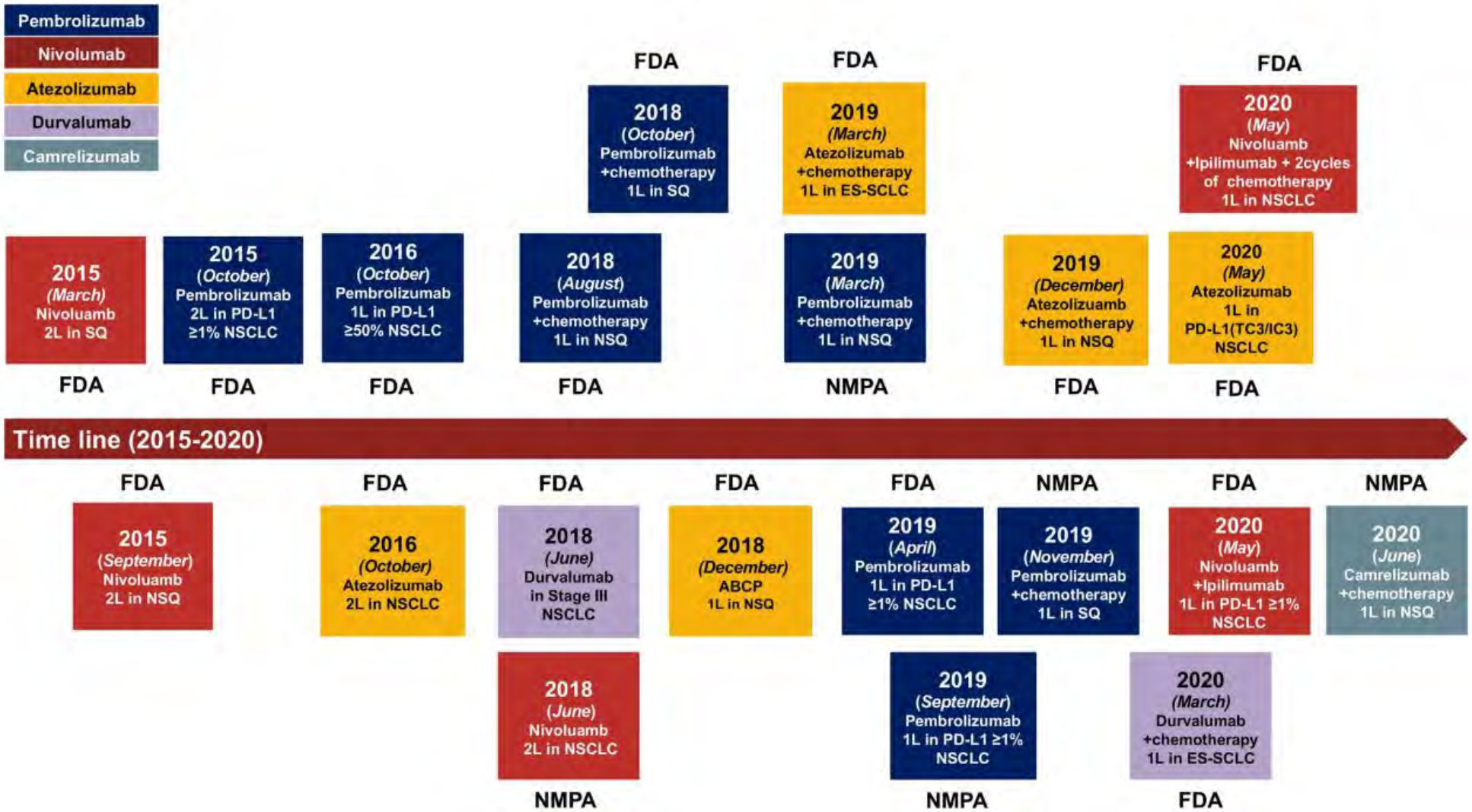
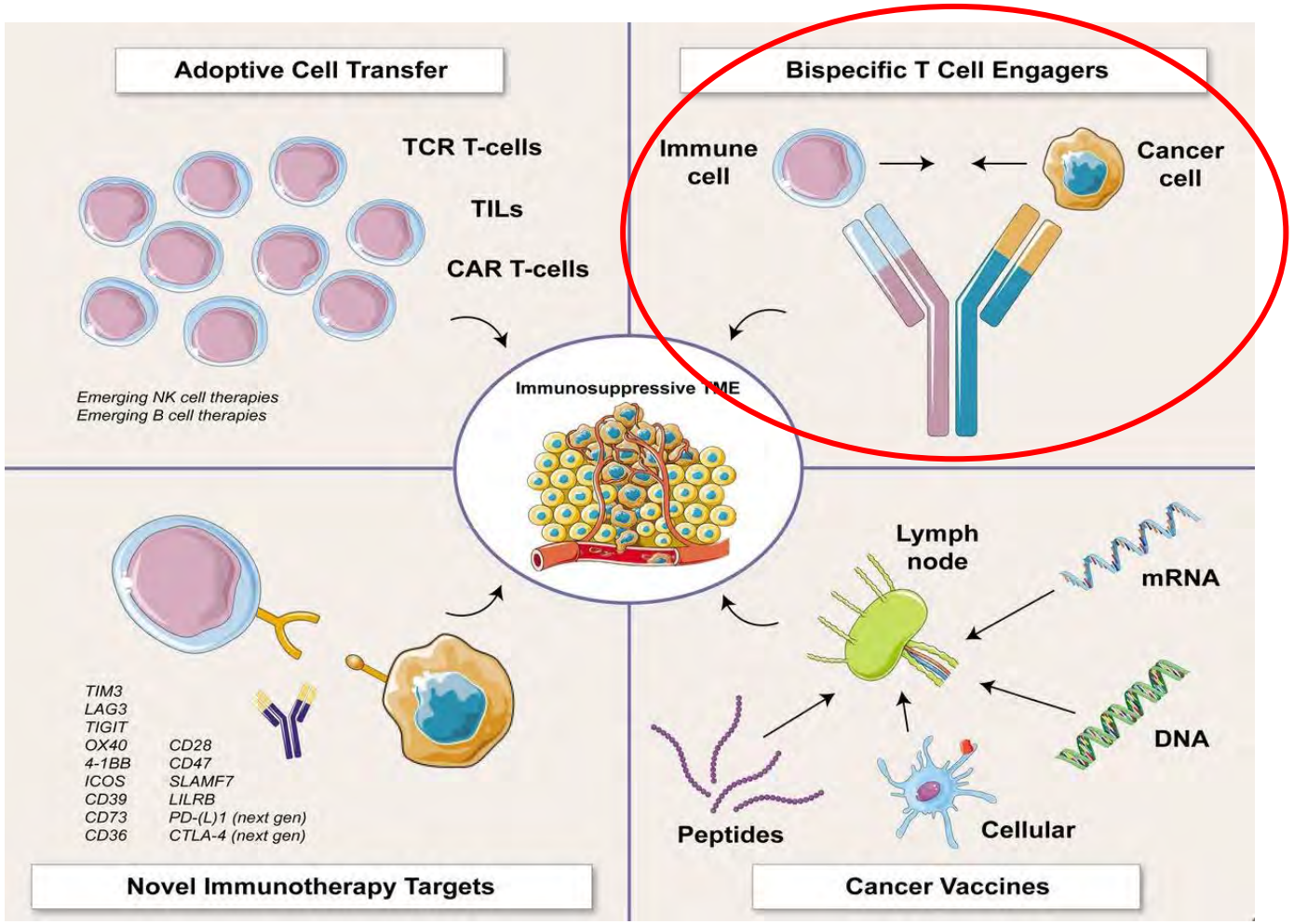

Pembrolizumab
Nivolumab
Atezolizumab
Durvalumab
Camrelizumab
2015 (March) Nivoluamb 2L in SQ
FDA
2015 (October) Pembrolizumab 2L in PD-L1 ≥1% NSCLC
FDA
2016 (October) Pembrolizumab 1L in PD-L1 ≥50% NSCLC
FDA
2018 (August) Pembrolizumab +chemotherapy 1L in NSQ
FDA
2018 (October) Pembrolizumab +chemotherapy 1L in SQ
FDA
2019 (March) Pembrolizumab +chemotherapy 1L in NSQ
NMPA
2019 (March) Atezolizumab +chemotherapy 1L in ES-SCLC
FDA
2019 (December) Atezolizuamb +chemotherapy 1L in NSQ
FDA
2020 (May) Nivoluamb +Ipilimumab + 2cycles of chemotherapy 1L in NSCLC
FDA
2020 (May) Atezolizumab 1L in PD-L1(TC3/IC3) NSCLC
FDA
Time line (2015-2020)
FDA
2015 (September) Nivoluamb 2L in NSQ
FDA
2016 (October) Atezolizumab 2L in NSCLC
FDA
2018 (June) Durvalumab in Stage III NSCLC
FDA
2018 (June) Nivoluamb 2L in NSCLC
NMPA
FDA
2018 (December) ABCP 1L in NSQ
FDA
2019 (April) Pembrolizumab 1L in PD-L1 ≥1% NSCLC
NMPA
2019 (September) Pembrolizumab 1L in PD-L1 ≥1% NSCLC
NMPA
NMPA
2019 (November) Pembrolizumab +chemotherapy 1L in SQ
FDA
2020 (March) Durvalumab +chemotherapy 1L in ES-SCLC
FDA
2020 (May) Nivoluamb +Ipilimumab 1L in PD-L1 ≥1% NSCLC
NMPA
2020 (June) Camrelizumab +chemotherapy 1L in NSQ

# Novel immunotherapy strategies

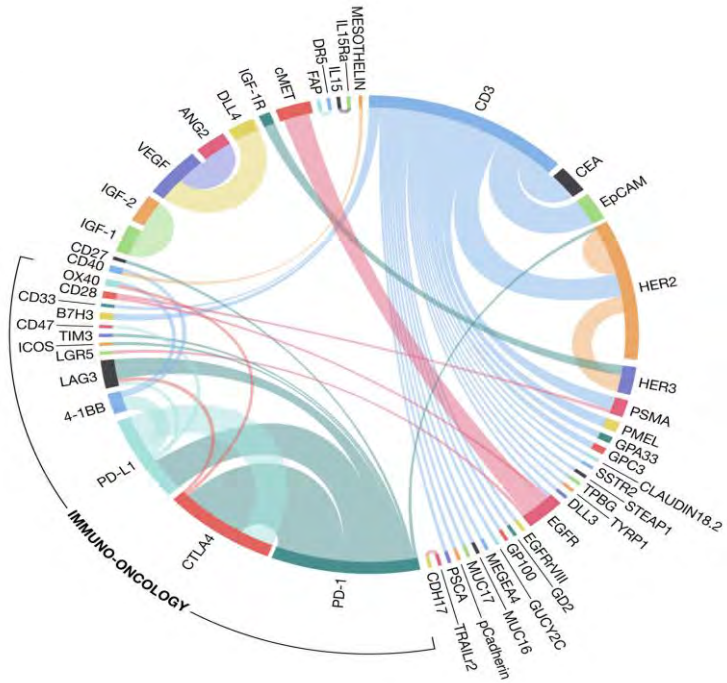


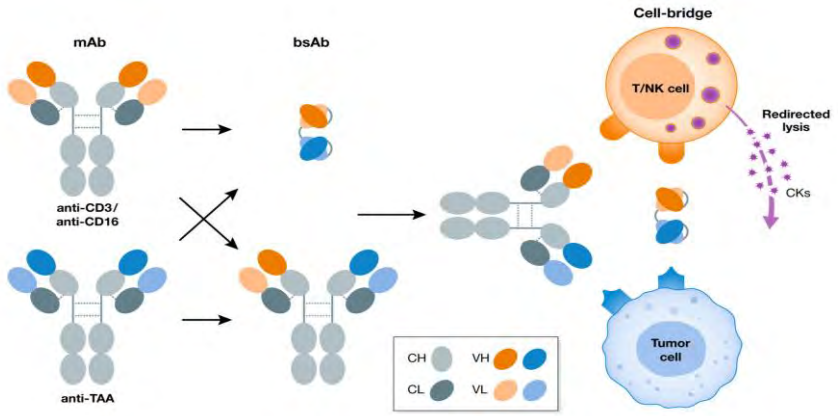

Many others including intratumoral therapy, cytokines, oncolytic viruses, myeloid targeting therapy, …

Emens LA, et al. JITC 2024

# Bispecific antibodies

- Bispecific antibodies bind two targets with one molecule
- Two general classes:
  - Cell-bridging
    - Often link immune cells to tumor cells to recruit and activate immune cells within the tumor
  - Antigen-crosslinking
    - Typically block two signals of cell growth/survival or activate immune cells



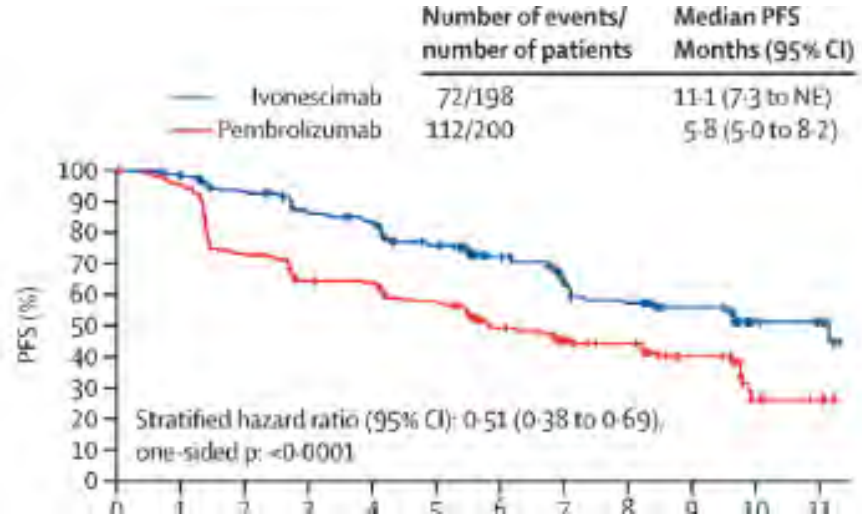



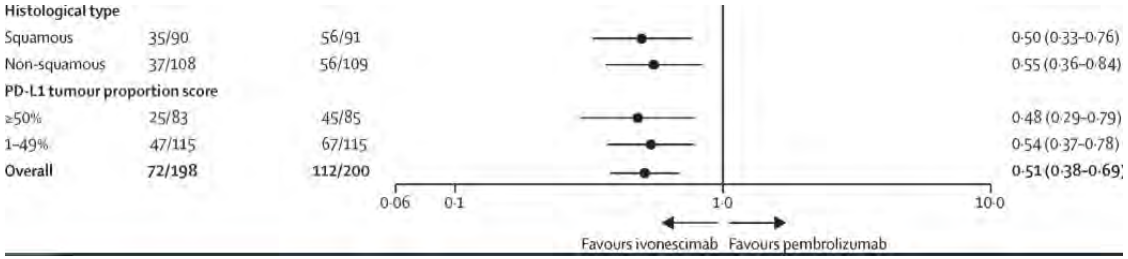

Wang S, et al. EMBO Mol Med 2021; Surrs FV, et al. Pharmacology & Therapeutics 2019.

# Ivonescimab

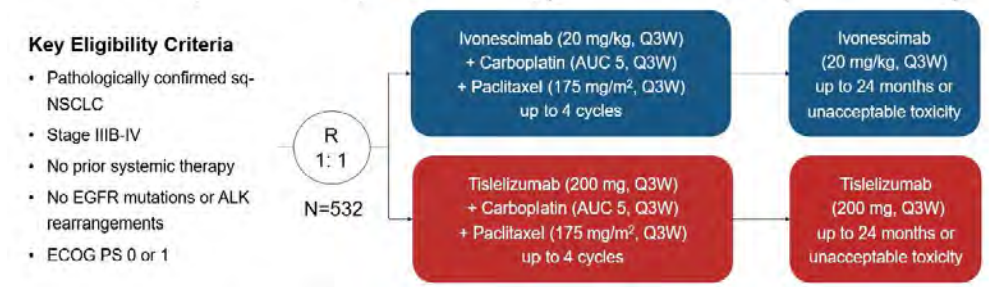

Bispecific antibody that blocks PD1 and VEGF

## First-line NSCLC with PD-L1 ≥ 1%

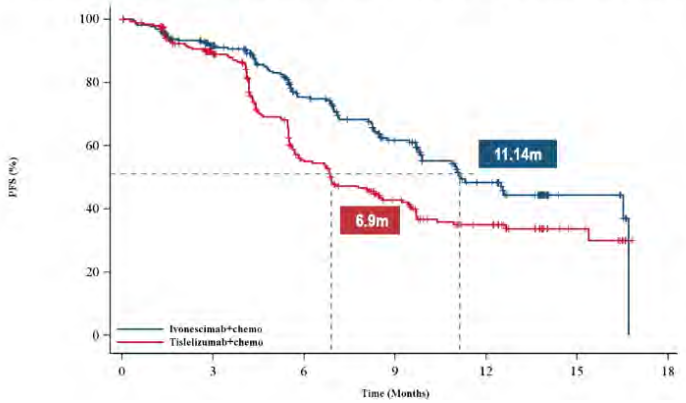



## First-line NSCLC in combination with chemo




Ivonescimab+chemo demonstrated a statistically significant improvement in PFS vs. tislelizumab+chemo with HR=0.60, representing a 4.2 months improvement in mPFS.



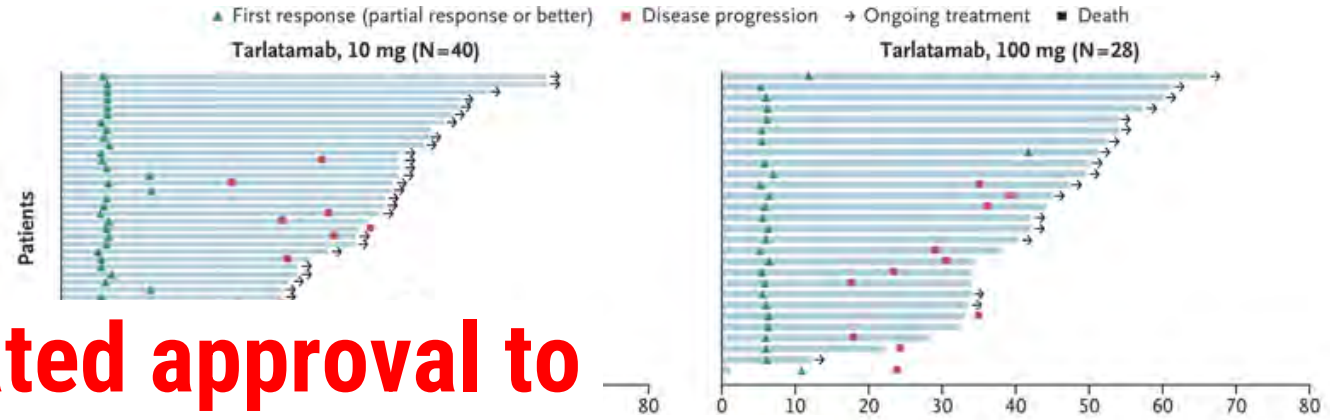

| | Ivonescimab + chemo (N=266) | Tislelizumab + chemo (N=266) |
|---|---|---|
| mPFS, months (95% CI) | 11.14 (9.86, NE) | 6.90 (5.82, 8.57) |
| Stratified HR (95% CI) | 0.60 (0.46, 0.78) | |
| p-value | <0.0001 | |

Median Follow-up: 10.28 months

Xiong A, et al. Lancet 2025
Lu S, ESMO 2025

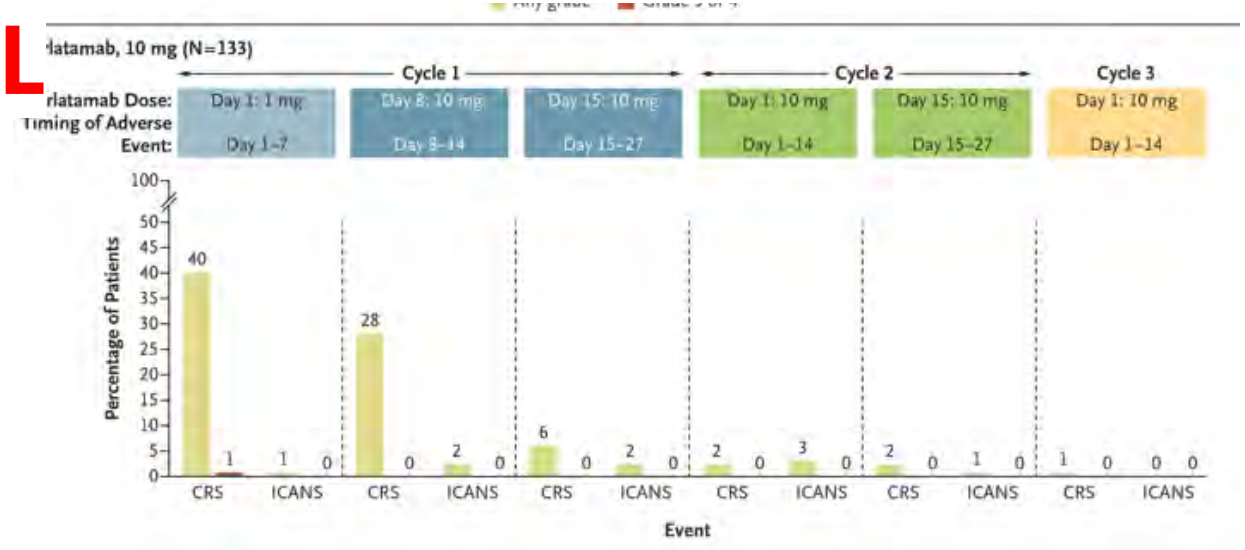
# Tarlatamab for SCLC

- Bispecific antibody that binds DLL3 and CD3


**FDA grants accelerated approval to tarlatamab-dlle for extensive stage small cell lung cancer in ≥ 2L on May 16, 2024**

| Outcome | 0 mg = 88) |
|---|---|
| **Objective response rate**, n (%) (97.5% CI) | 40 (40.0) (29.1, 51.7) | 28 (31.8) (21.1, 44.1) |
| Observed duration of response ≥ 6 months, n/N (%) | 23/40 (58) | 17/28 (61) |
| **Disease control rate**, n (%) (95% CI) | 70 (70.0) (60.0, 78.8) | 55 (62.5) (51.5, 72.6) |




Ahn MJ, et al. NEJM 2023

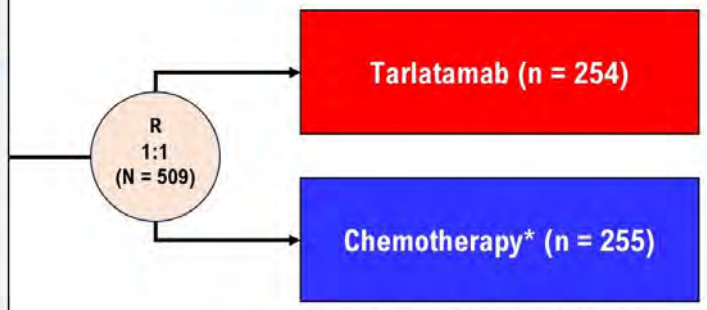
# Tarlatamab for second-line treatment of SCLC

**Key inclusion criteria**

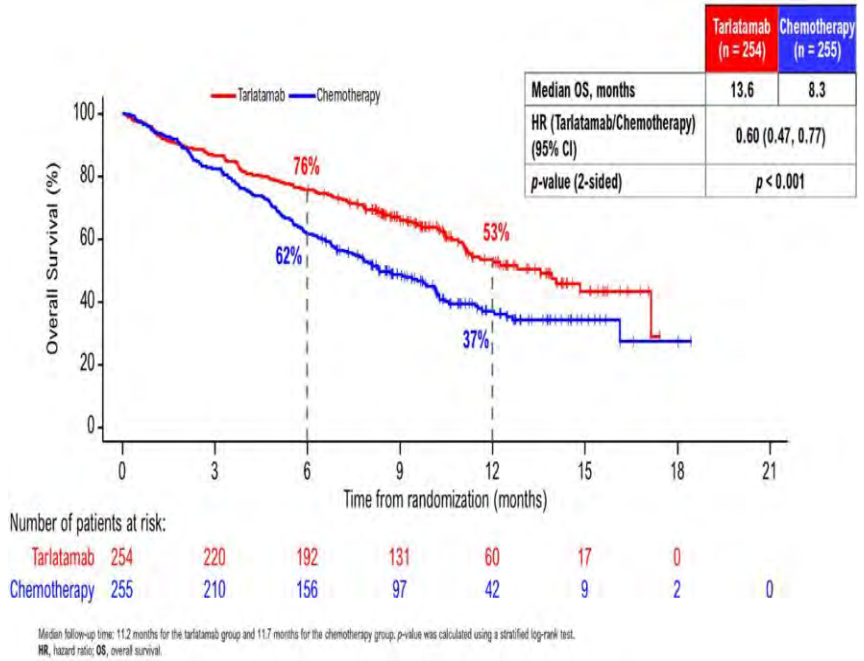
- Histologically or cytologically confirmed SCLC
- Progression after 1L platinum-based chemotherapy +/- anti-PD-(L)1
- ECOG PS 0 or 1
- Asymptomatic, treated or untreated brain metastases

**Randomization stratified by**

- Prior anti-PD-(L)1 exposure (yes/no)
- Chemotherapy-free interval (< 90 days vs ≥ 90 to < 180 days vs ≥ 180 days)
- Presence of (previous/current) brain metastases (yes/no)
- Intended chemotherapy (topotecan/amrubicin vs lurbinectedin)

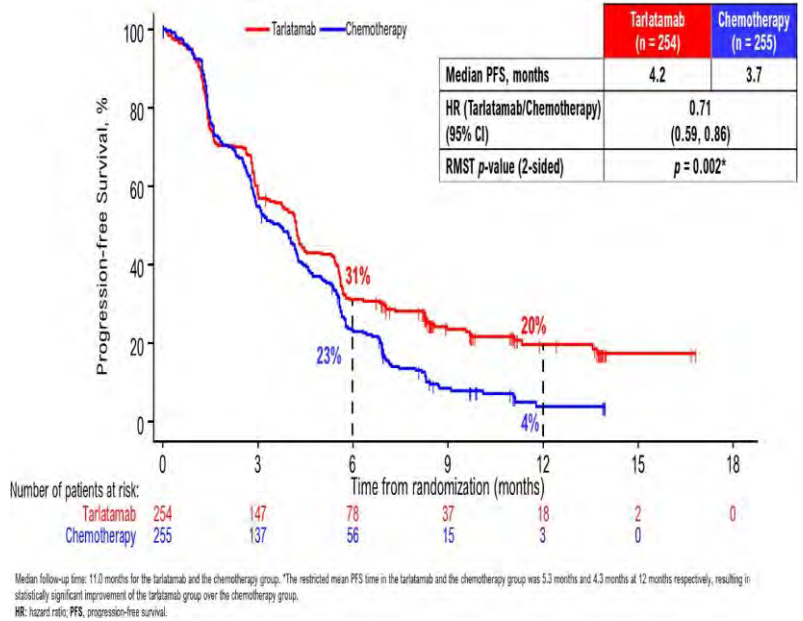



Topotecan (n = 185); Lurbinectedin (n = 47); Amrubicin (n = 23)




| | Tarlatamab (n = 254) | Chemotherapy (n = 255) |
|---|---|---|
| Median OS, months | 13.6 | 8.3 |
| HR (Tarlatamab/Chemotherapy) (95% CI) | 0.60 (0.47, 0.77) | |
| *p*-value (2-sided) | *p* < 0.001 | |

Median follow-up time: 11.2 months for the tarlatamab group and 11.7 months for the chemotherapy group. *p*-value was calculated using a stratified log-rank test.
**HR**, hazard ratio; **OS**, overall survival.




| | Tarlatamab (n = 254) | Chemotherapy (n = 255) |
|---|---|---|
| Median PFS, months | 4.2 | 3.7 |
| HR (Tarlatamab/Chemotherapy) (95% CI) | 0.71 (0.59, 0.86) | |
| RMST *p*-value (2-sided) | *p* = 0.002* | |

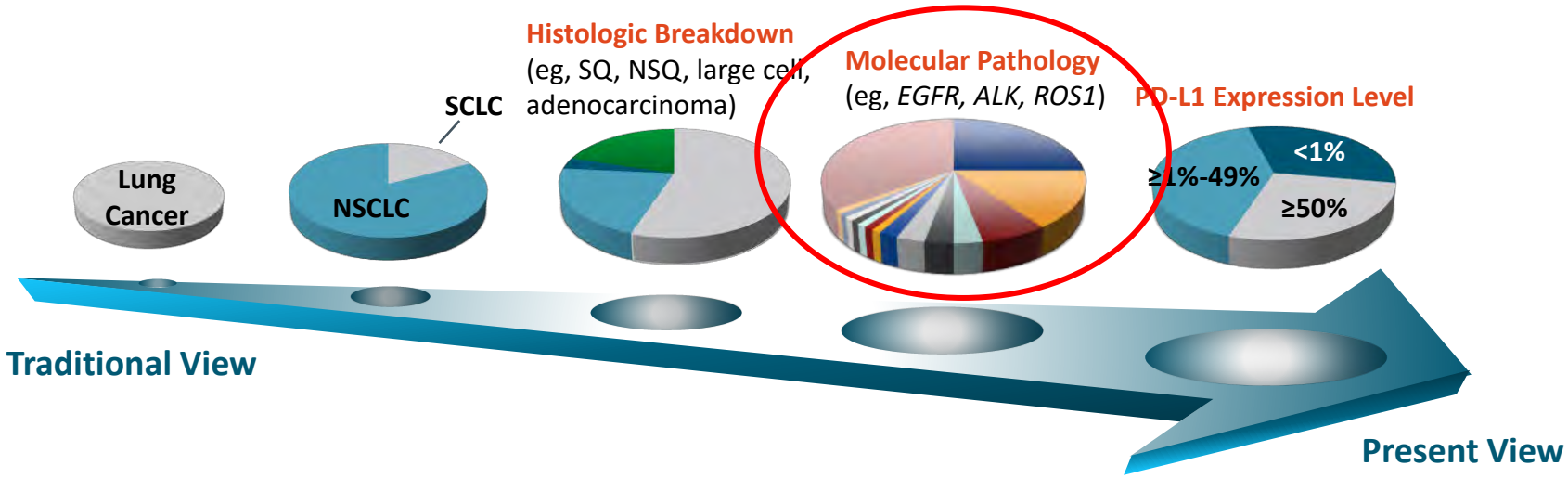
Median follow-up time: 11.0 months for the tarlatamab and the chemotherapy group. *The restricted mean PFS time in the tarlatamab and the chemotherapy group was 5.3 months and 4.3 months at 12 months respectively, resulting in statistically significant improvement of the tarlatamab group over the chemotherapy group.
**HR**: hazard ratio; **PFS**, progression-free survival.

**mOS: 13.6 v 8.3 mo; HR 0.6**

**mPFS: 4.2 v 3.7 mo; HR 0.71**

Rudin CM et al. ASCO 2025
Mountzios G et al. N Engl J Med. 2025

# Lung Cancer: Not one disease, but many

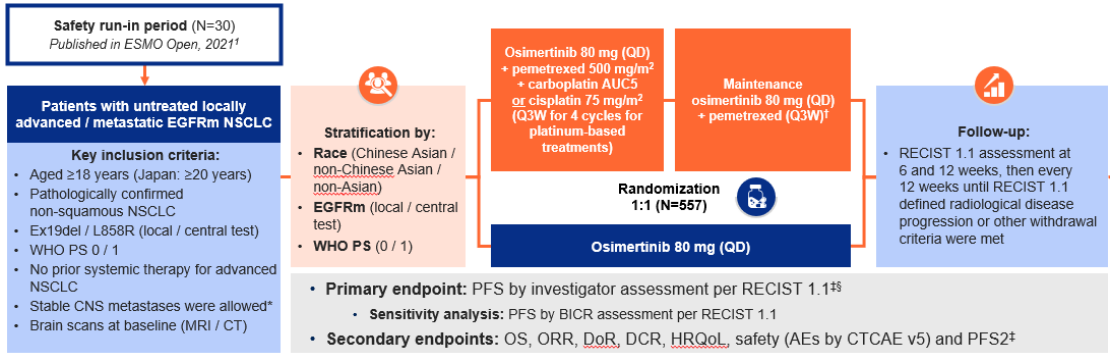


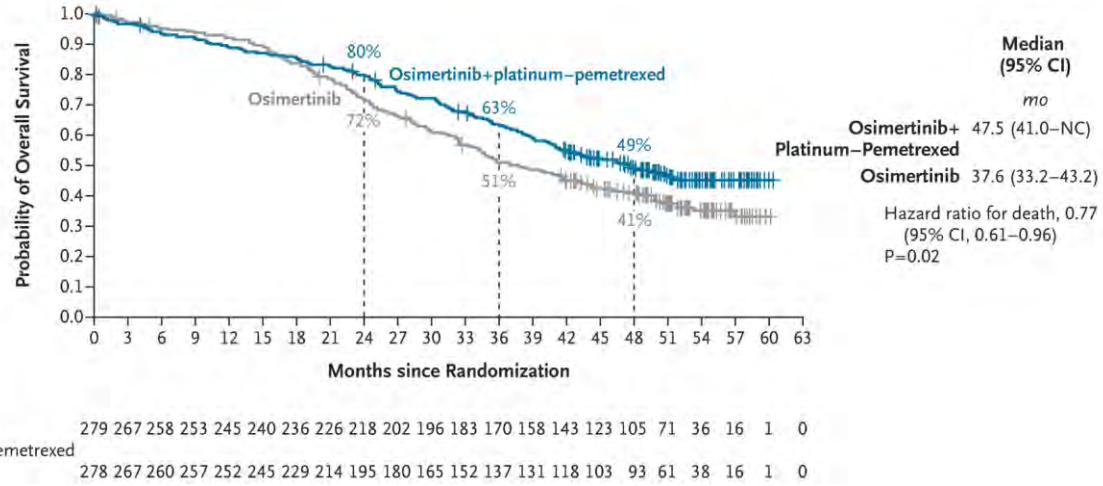

The characteristics of the tumor – stage, histology, mutations, PD-L1 expression – dictate the most appropriate therapy

Cooper. Pathology. 2011;43:103. Langer. JCO. 2010;28:5311. Galon. Immunity. 2013;39:11. Pao. Lancet Oncol. 2011;12:175. Krigsfeld. AACR 2017. Abstr CT143.

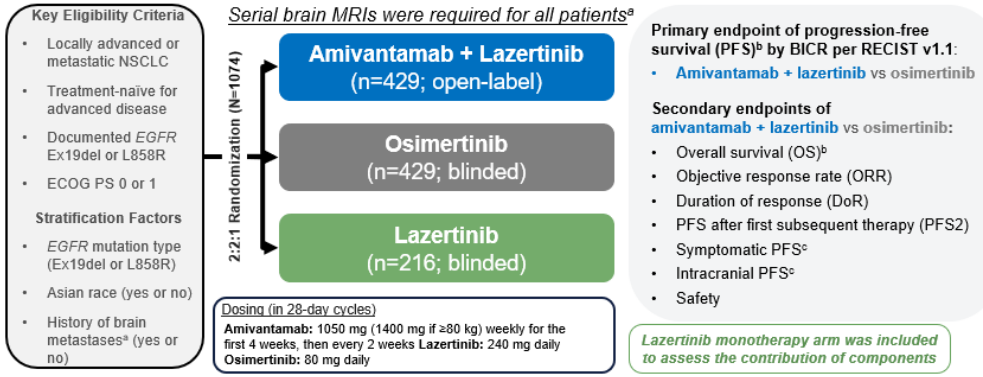
# Combination therapy can improve survival in first-line treatment of EGFR-mutant lung cancer

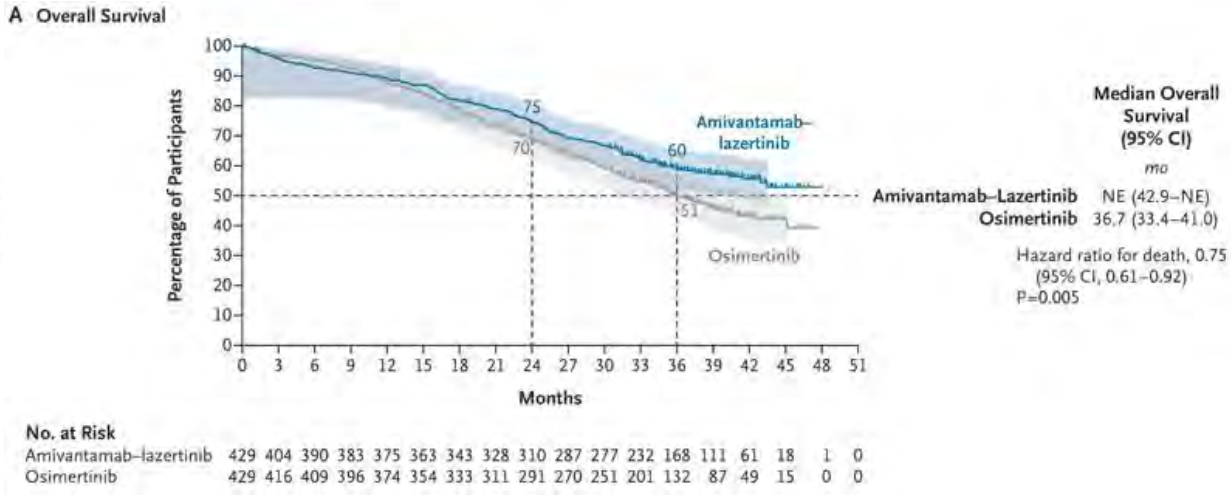
## Osimertinib plus chemotherapy (FLAURA2)




## Amivantamab plus Lazertinib (MARIPOSA)

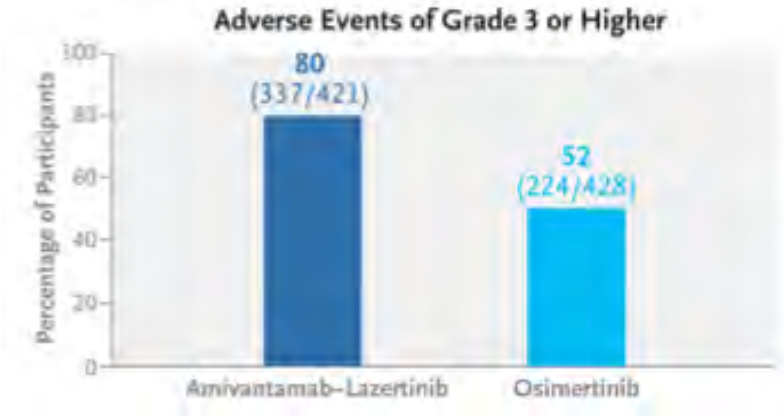


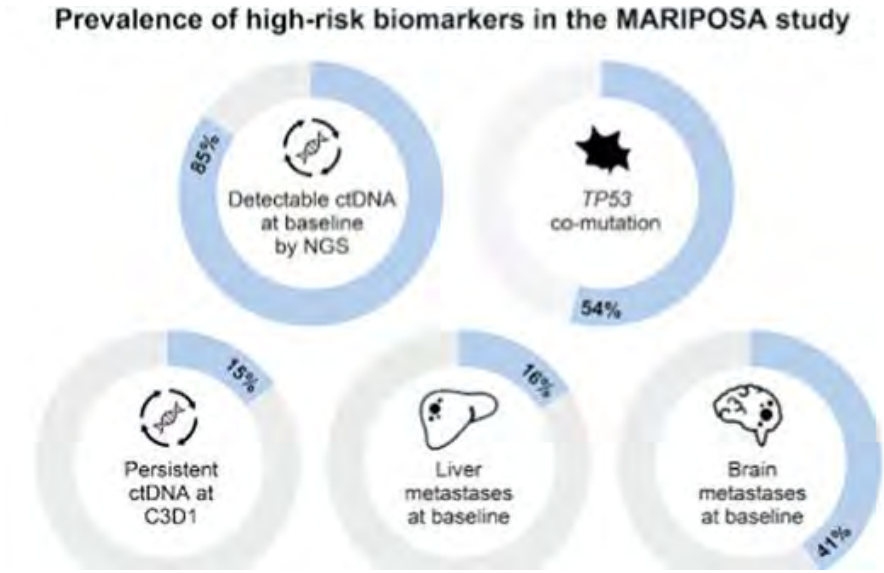



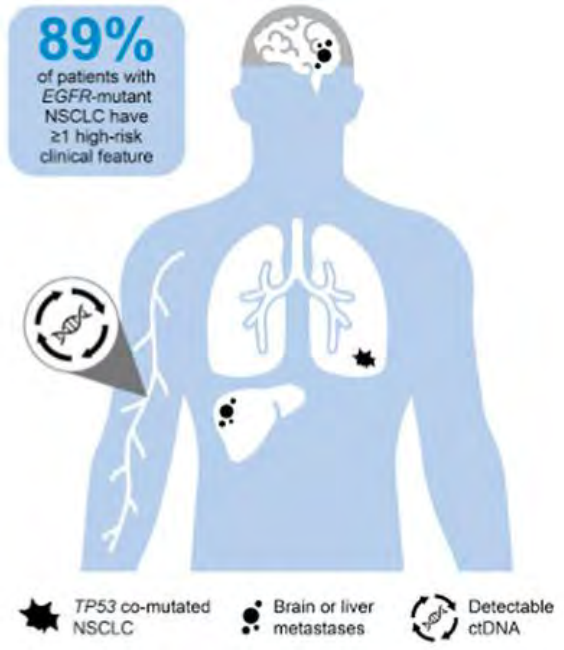

Janne P, et al. NEJM 2025
Yang J, et al. NEJM 2025.

# Is combination therapy right for everyone?

- No!
- More drugs = more side effects
- Some people have excellent disease control with osimertinib alone for years – but how do we figure out who they are in advance?



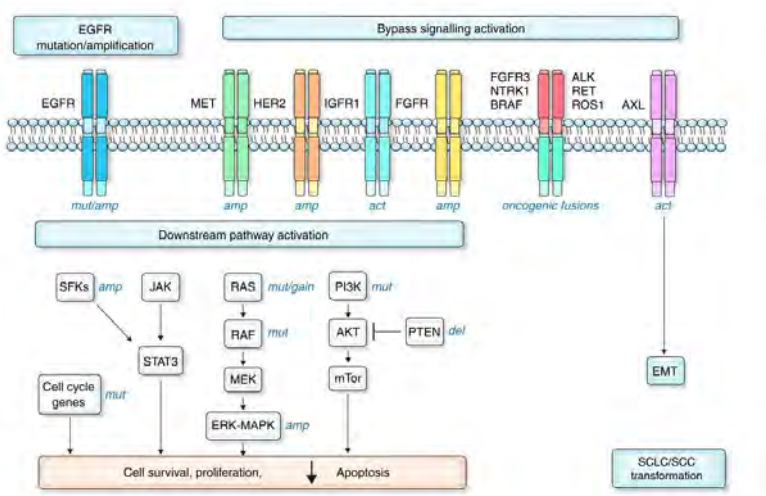



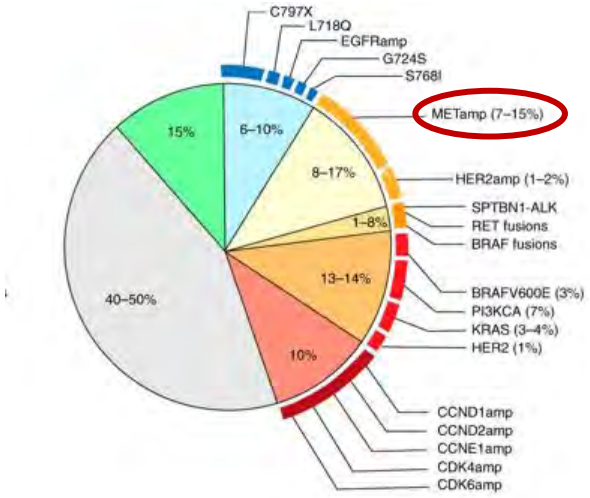




Yang J, et al. NEJM 2025
Felip E. Ann Oncol 2024

# Overcoming resistance in EGFR-mutant lung cancer

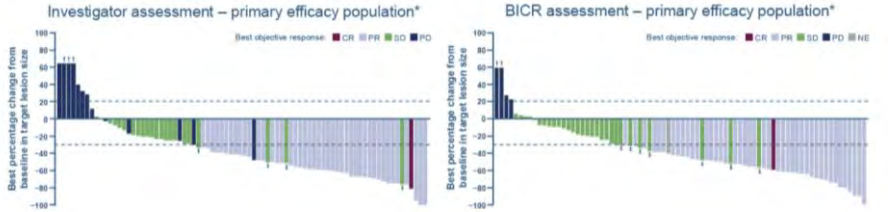
- MET amplification is a known mechanisms of resistance to EGFR targeted therapies
- Targeting MET with a MET TKI has demonstrated benefit in several trials




Osimertinib plus savolitinib in patients with EGFR-mutant NSCLC with MET amplification or overexpression (SAVANNAH)

| | Primary efficacy population (n=80)* | |
|---|---|---|
| | Investigator assessment | BICR assessment |
| Confirmed ORR, % (95% CI) | 56 (45, 67) | 55 (43, 66) |
| CR, % | 1 | 1 |
| PR, % | 55 | 54 |
| Median DoR, months (95% CI) | 7.1 (5.6, 9.6) months | 9.9 (6.0, 13.7) months |
| Median time to onset of response, weeks (IQR) | 6.1 (6.0–6.7) weeks | 6.0 (5.7–6.6) weeks |




Leonetti A, et al. BJC 2019
Ahn M-J, et al. ELCC 2025

# Overcoming MET-mediated resistance

## SACHI: Randomized, open-label, multi-center phase 3 study conducted across 68 centers in China.

- Unresectable or metastatic NSCLC
- EGFRm, PD on first-line EGFR-TKI
  - 1st /2nd G: T790M-, METamp;
  - 3rd G: METamp
- METamp (FISH+) confirmed by central lab
- ECOG PS 0-1

1:1

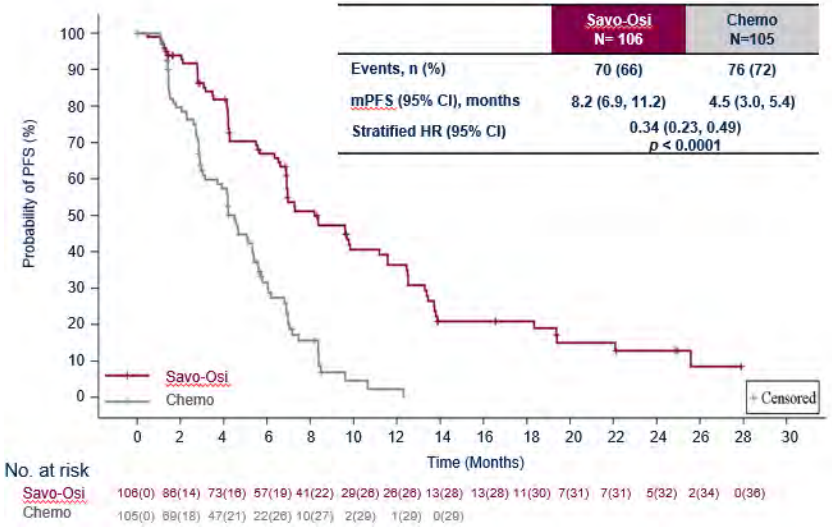
Savolitinib 600mg (BW≥50kg), or 400mg (BW<50kg) QD + Osimertinib 80mg QD
N = 106

→ Until PD or intolerable toxicity

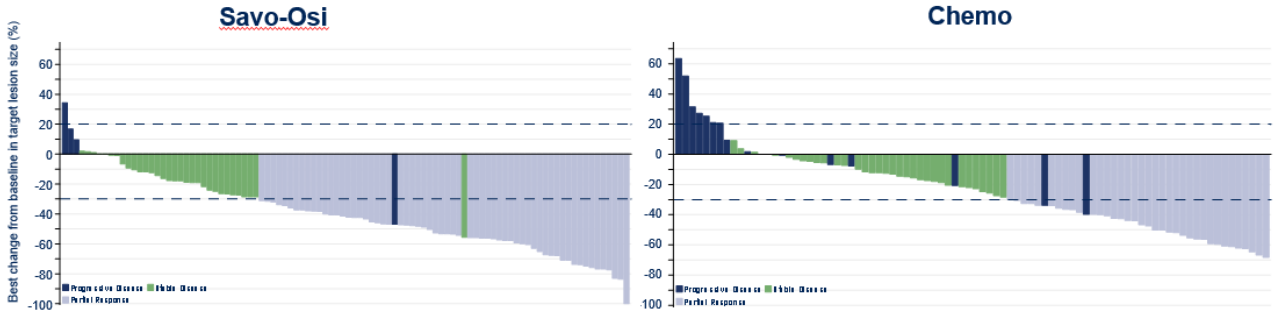
Platinum +Pemetrexed 4~6 cycle then Pemetrexed maintenance
N = 105

→ Until PD or intolerable toxicity

### ITT population



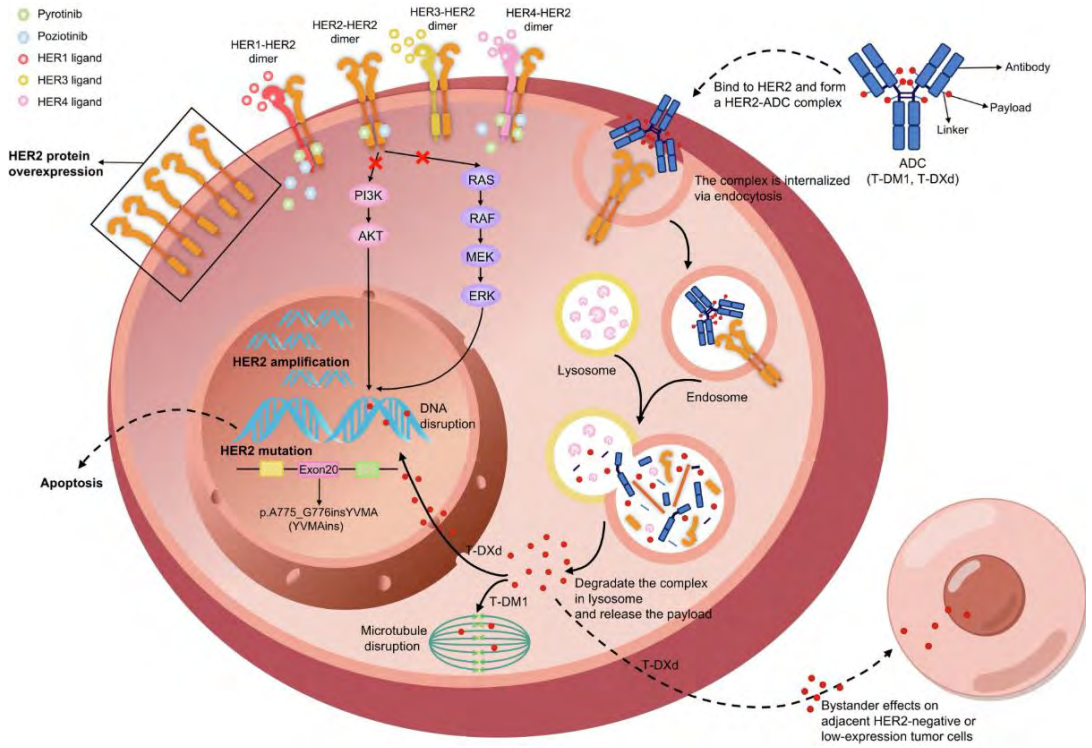

| | Savo-Osi N= 106 | Chemo N=105 |
|---|---|---|
| Events, n (%) | 70 (66) | 76 (72) |
| mPFS (95% CI), months | 8.2 (6.9, 11.2) | 4.5 (3.0, 5.4) |
| Stratified HR (95% CI) | 0.34 (0.23, 0.49) $p < 0.0001$ | |

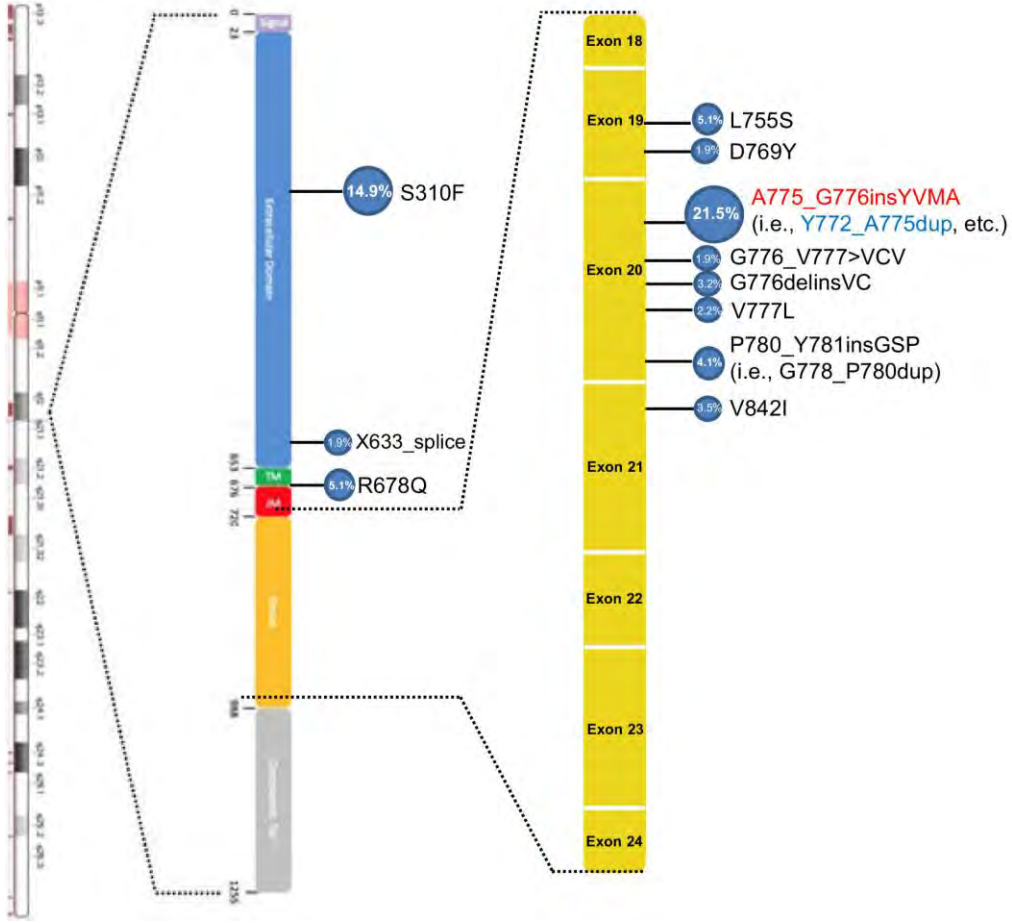



| | Savo-Osi N=106 | Chemo N=105 | Stratified OR (95% CI) |
|---|---|---|---|
| ORR, % (95% CI) | 58 (49-68) | 34 (25-44) | 2.74 (1.50-4.98) $p$=0.0004 |
| DCR, % (95% CI) | 89 (81-94) | 67 (57-76) | 3.98 (1.81-8.82) $p$=0.0001 |
| Median DoR, month (95% CI) | 8.4 (5.9-11.1) | 3.2 (2.8-4.2) | - |

Lu S, et al. ASCO 2025

# HER2 alterations in lung cancer



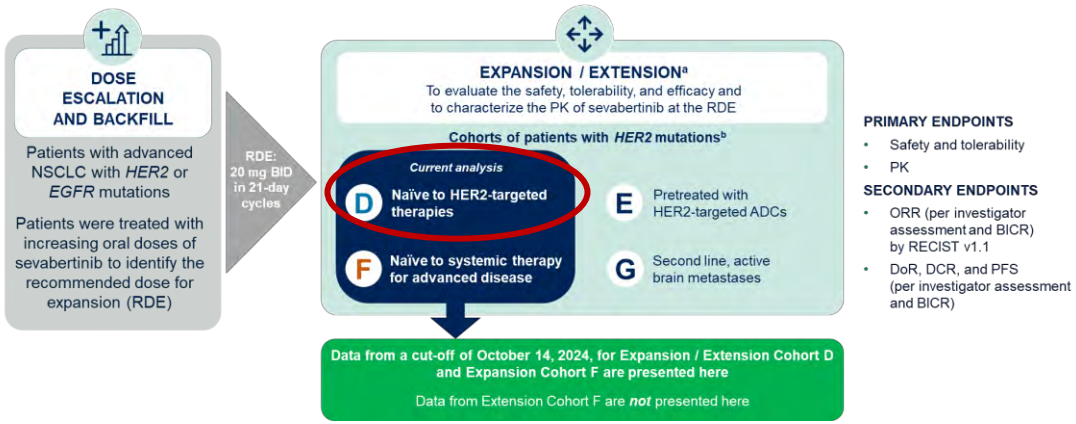

- HER2 mutations occur in 2-4% of lung adenocarcinomas
- Most common are insertion mutations in the tyrosine kinase domain in exon 20

Yu Y, et al. Anti-tumor Treatment 2023
Zeng J, et al. JNCCN 2021

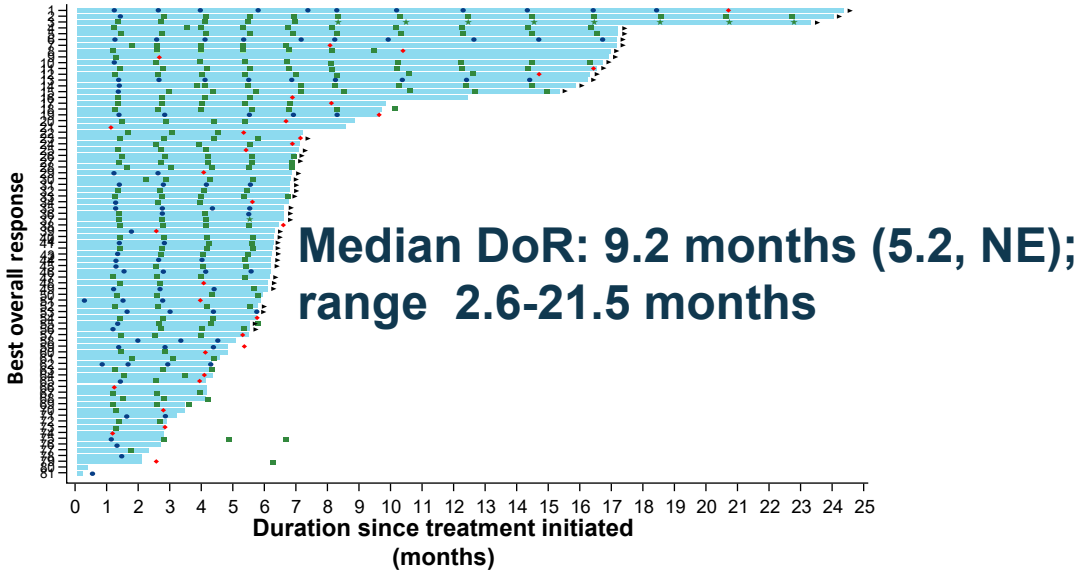
# Sevabertinib in patients with HER2-mutant NSCLC

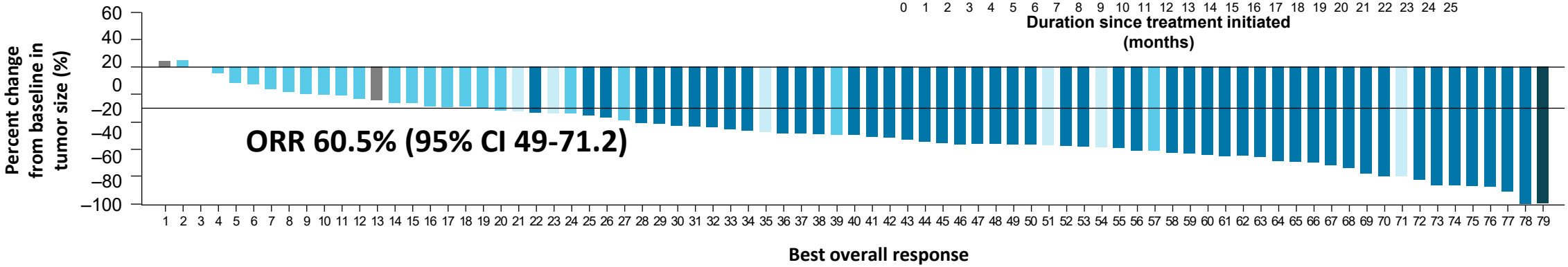
- Oral, reversible TKI that potently inhibits HER2-activating mutations

## SOHO-01 study design (NCT05099172)




## Cohort D (*n*=81), naïve to HER2-targeted therapy

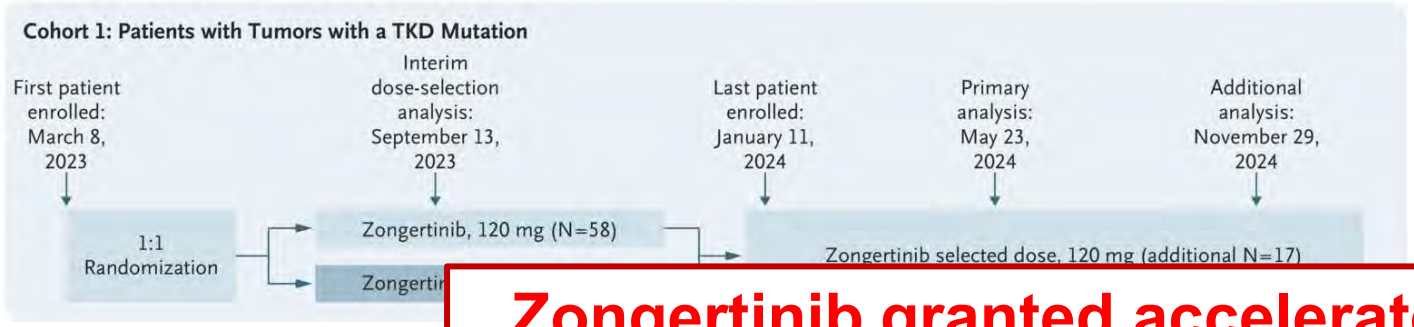


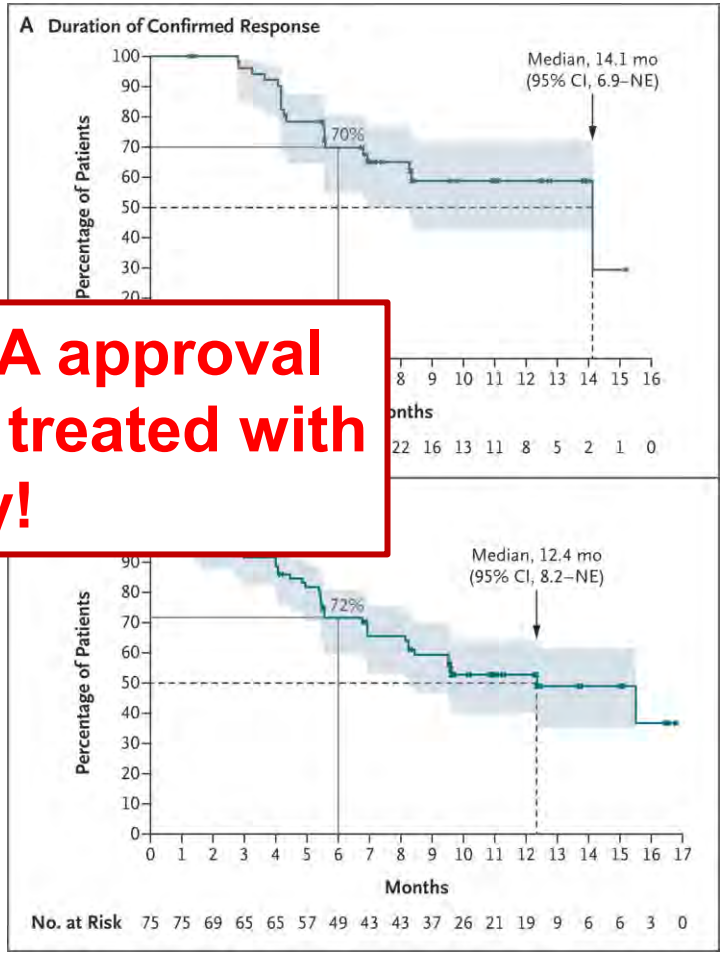

Loong HH, et al. ASCO 2025.

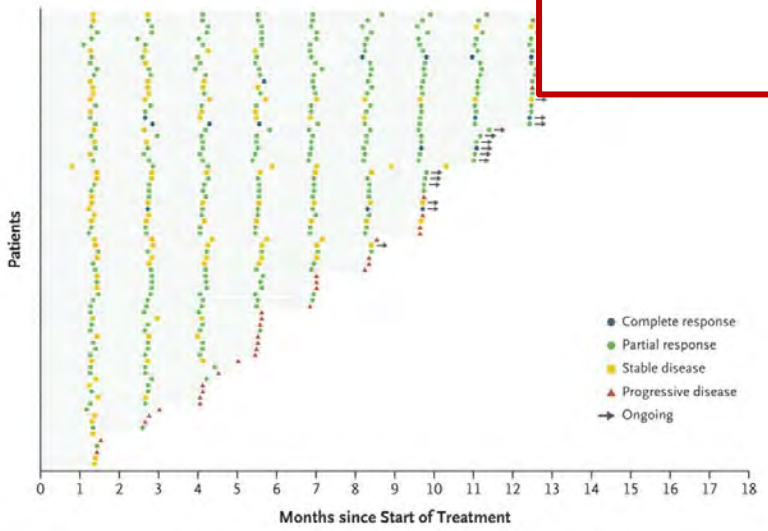
# Zongertinib in HER2-mutant NSCLC

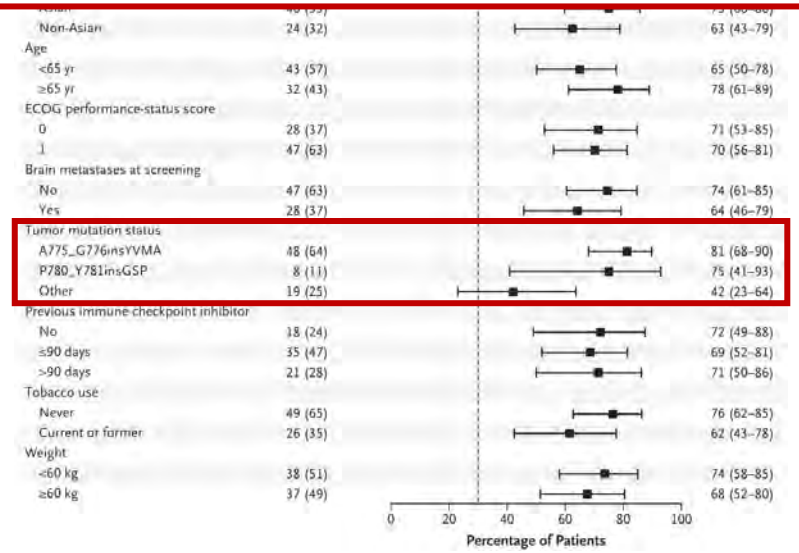
- Oral, irreversible, HER2-selective TKI




**Zongertinib granted accelerated FDA approval 8/25 for HER2 TKD mutation patients treated with previous systemic therapy!**

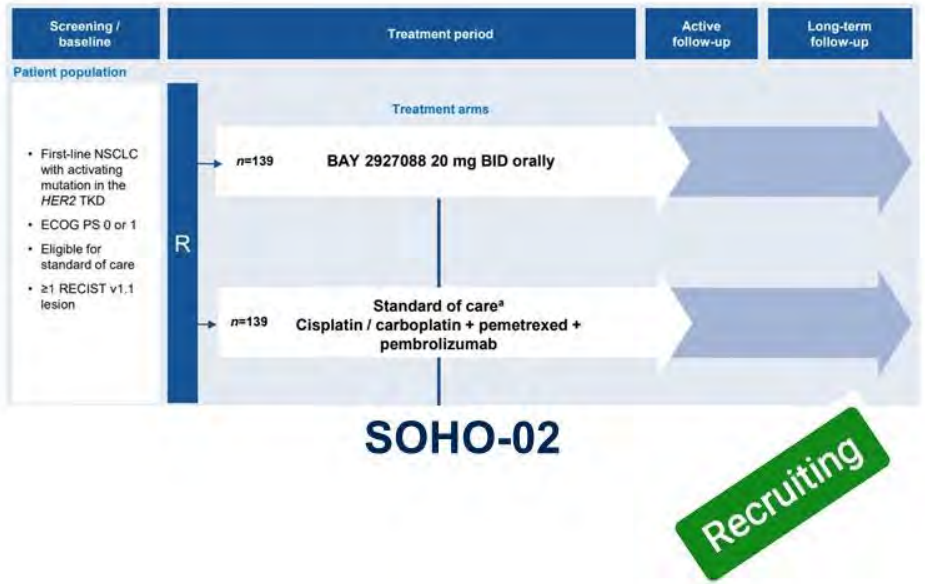


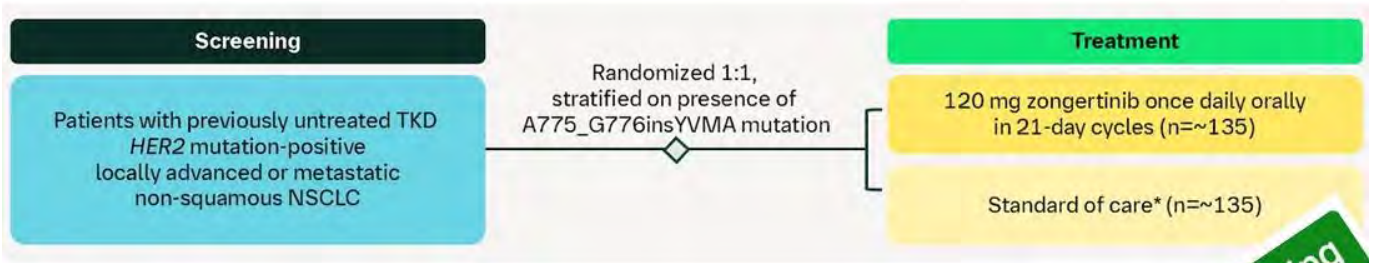

Heymach JV, et al. NEJM 2025.

# What's next: moving HER2 inhibitors into first-line




**SOHO-02**

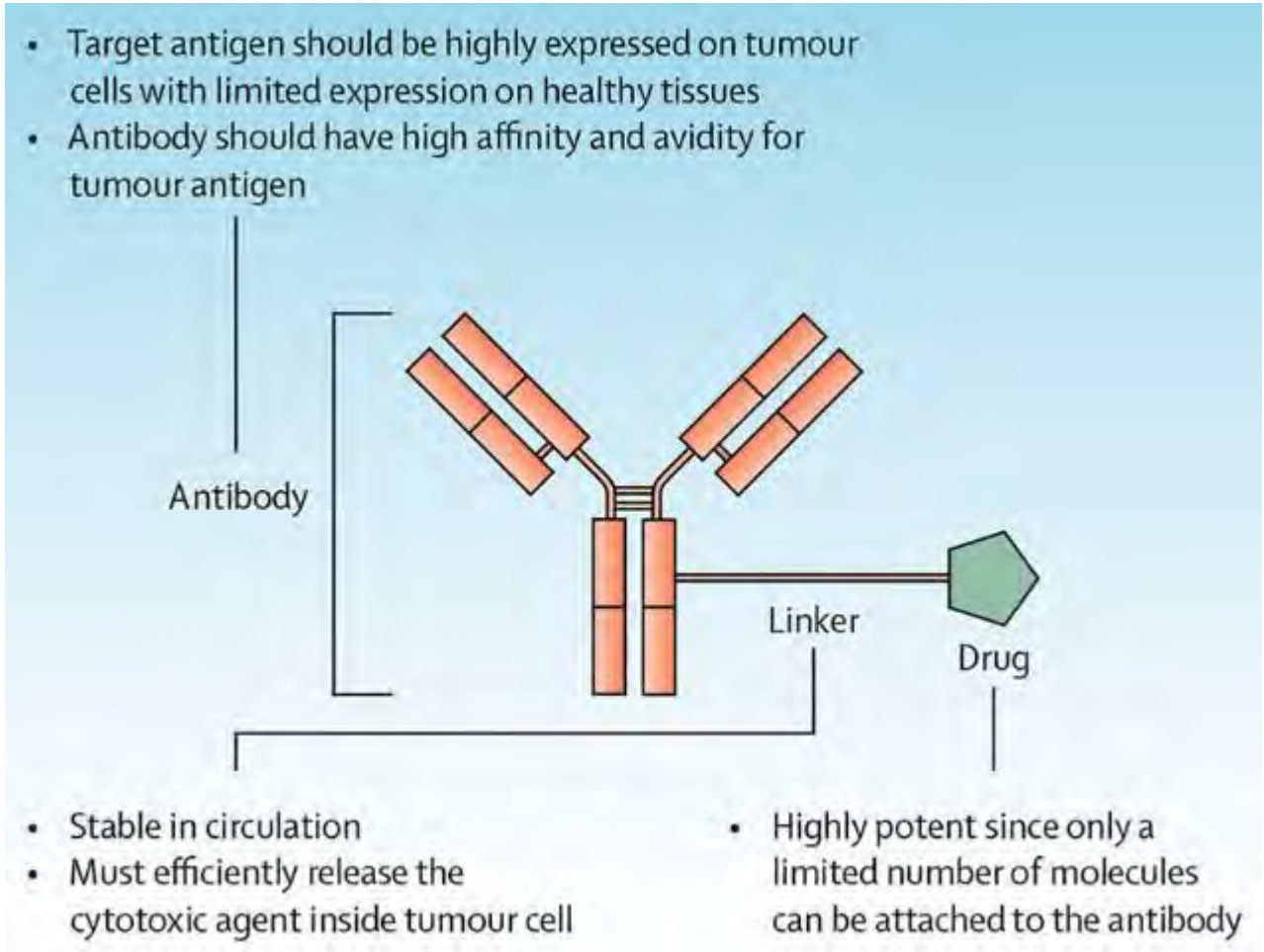
Recruiting




**Beamion-Lung 02**

Recruiting

# Antibody-Drug Conjugates



# ADCs: established and emerging

## Telisotuzumab vedotin

### FDA grants accelerated approval to telisotuzumab vedotin-tllv for NSCLC with high c-Met protein overexpression

On May 14, 2025, the Food and Drug Administration granted accelerated approval to telisotuzumab vedotin-tllv (Emrelis, AbbVie Inc.), a c-Met-directed antibody and microtubule inhibitor conjugate, for adults with locally advanced or metastatic, non-squamous non-small cell lung cancer (NSCLC) with high c-Met protein overexpression [≥50% of tumor cells with strong (3+) staining], as determined by an FDA-approved test, who have received a prior systemic therapy.

FDA also approved the VENTANA MET (SP44) RxDx Assay (Roche Diagnostics) as a companion diagnostic test to aid in detecting c-Met protein overexpression in patients with non-squamous NSCLC who may be eligible for treatment with Emrelis.

## Datopotomab deruxtecan

### FDA grants accelerated approval to datopotamab deruxtecan-dlnk for EGFR-mutated non-small cell lung cancer

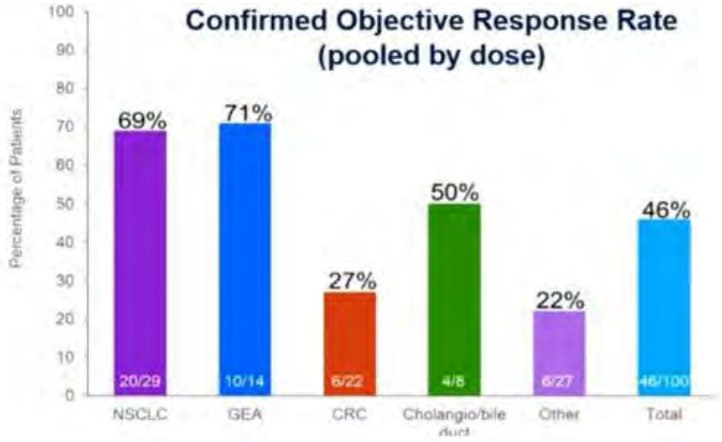
On June 23, 2025, the Food and Drug Administration granted accelerated approval to datopotamab deruxtecan-dlnk (Datroway, Daiichi Sankyo, Inc.) for adults with locally advanced or metastatic epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC) who have received prior EGFR-directed therapy and platinum-based chemotherapy.

Full prescribing information for Datroway will be posted on Drugs@FDA.

**Efficacy and Safety**

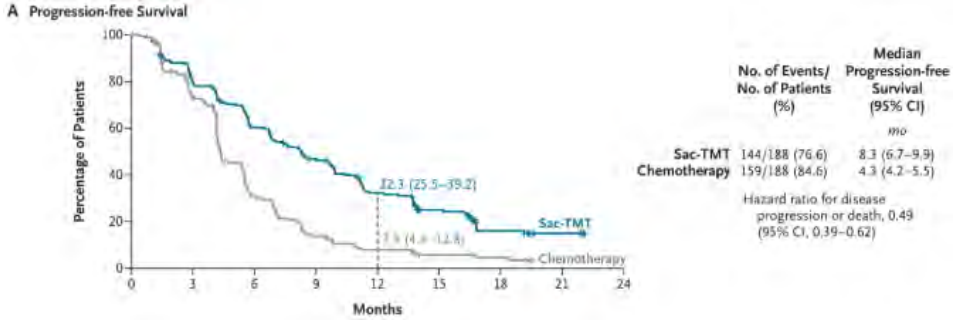
Efficacy was evaluated in a pooled subgroup of 114 patients with locally advanced or metastatic EGFR-mutated NSCLC who had received prior treatment with an EGFR-directed therapy and platinum-based chemotherapy and received datopotamab deruxtecan-dlnk at the recommended dose across two clinical trials: TROPION-Lung05

## Teliso adizutecan




| | NSCLC (n=29) |
|---|---|
| Median DOR, months (95% CI) | 13.0 (7.0–22.1) |
| Median PFS, months (95% CI) | 11.0 (7.7–15.1) |
| Median OS, months (95% CI) | NR |

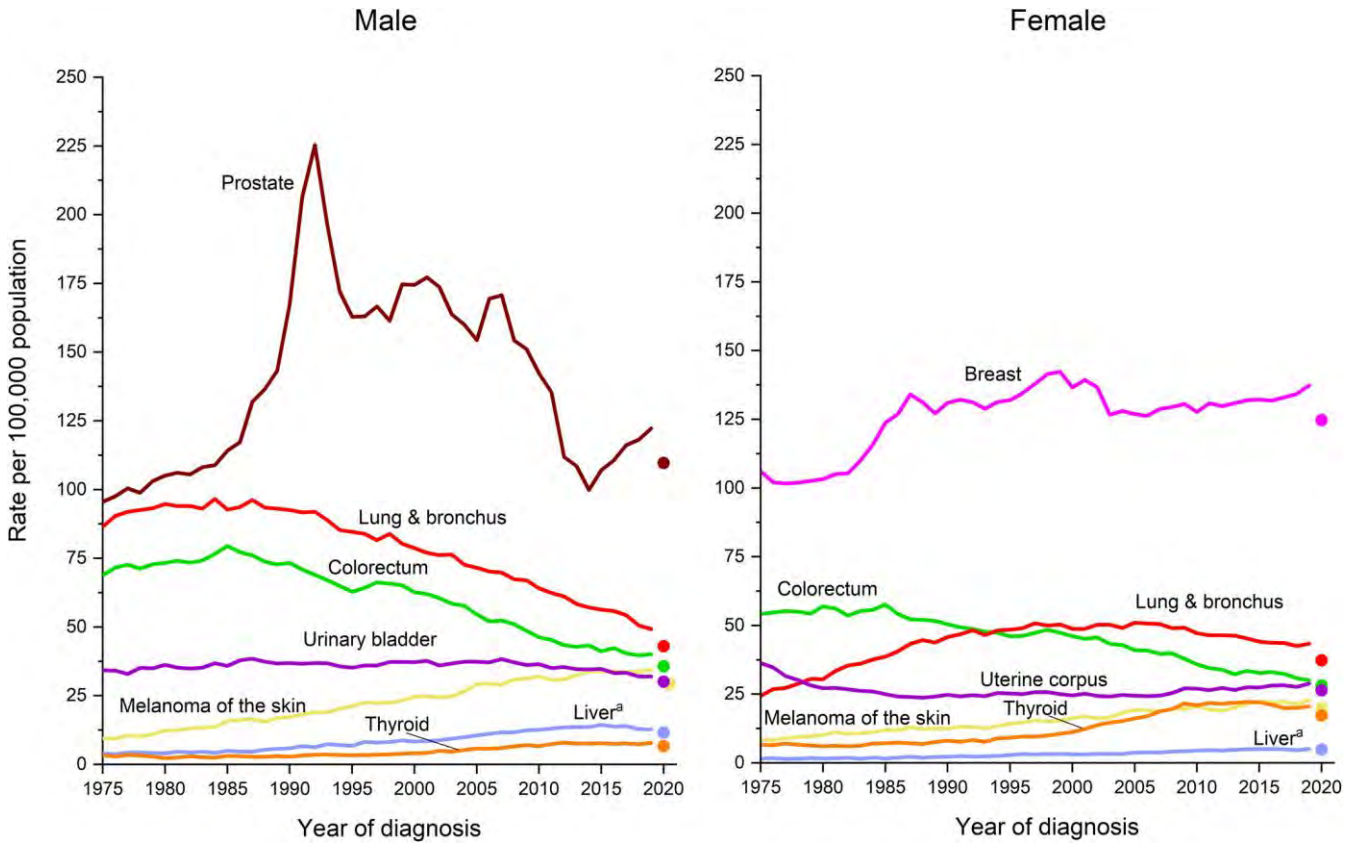
## Sacituzumab tirumotecan

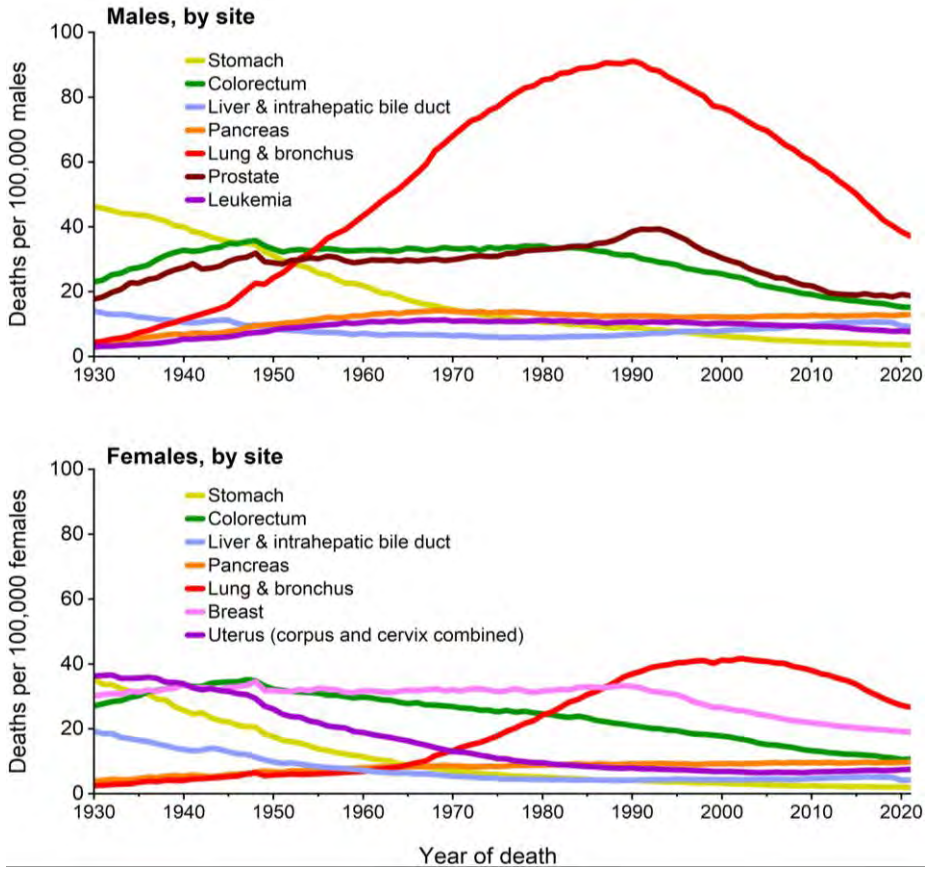



Camidge DR, et al. JCO 2024
Ahn M-J, et al. JTO 2025

Murciano-Goroff YR, et al. EMSO 2025
Fang W, et al. NEJM 2025

# We have made incredible progress over the last few decades… but still have more to go



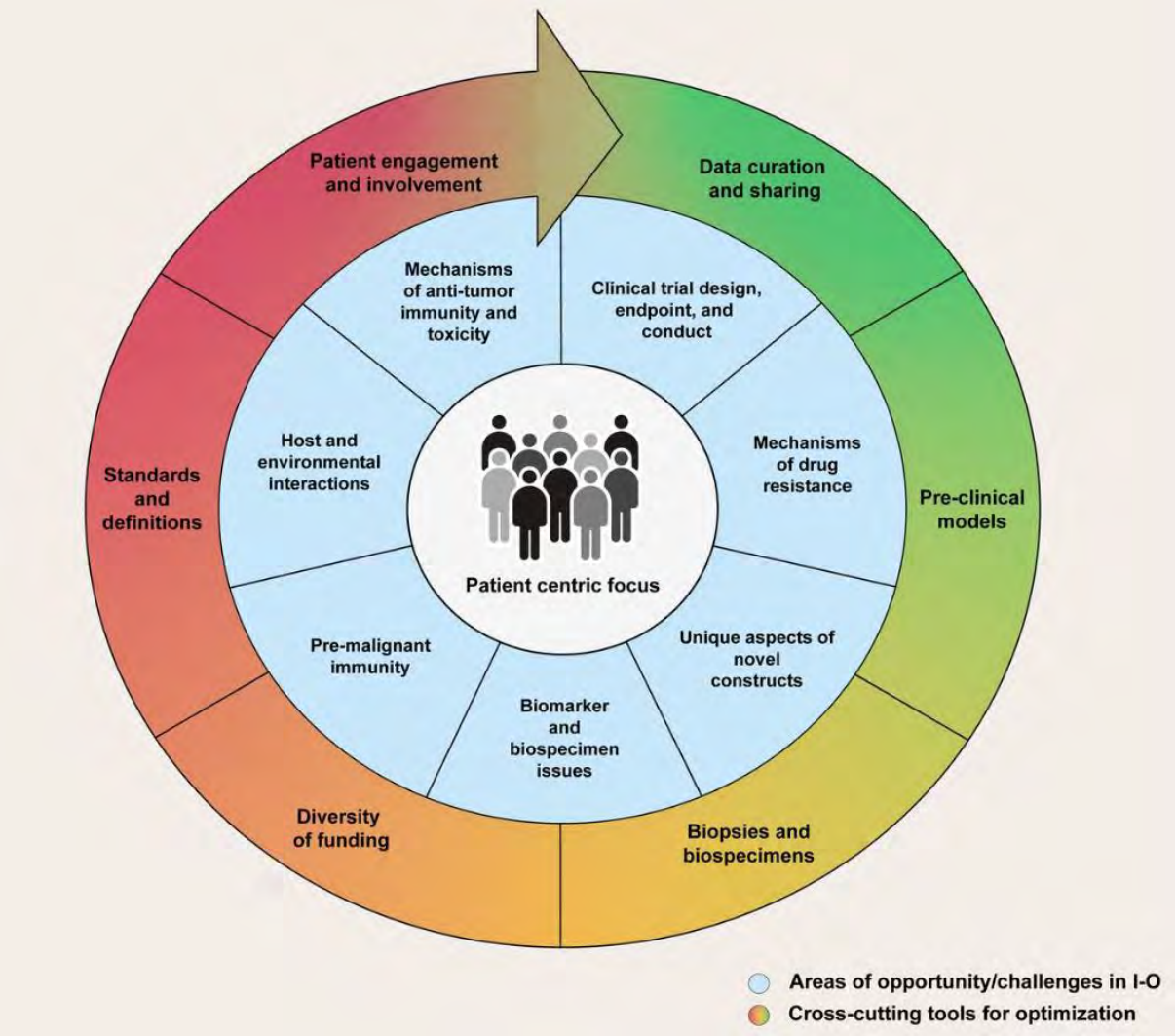




Improvement likely due to:

- Reductions in smoking
- Increased screening
- Improvement in therapy

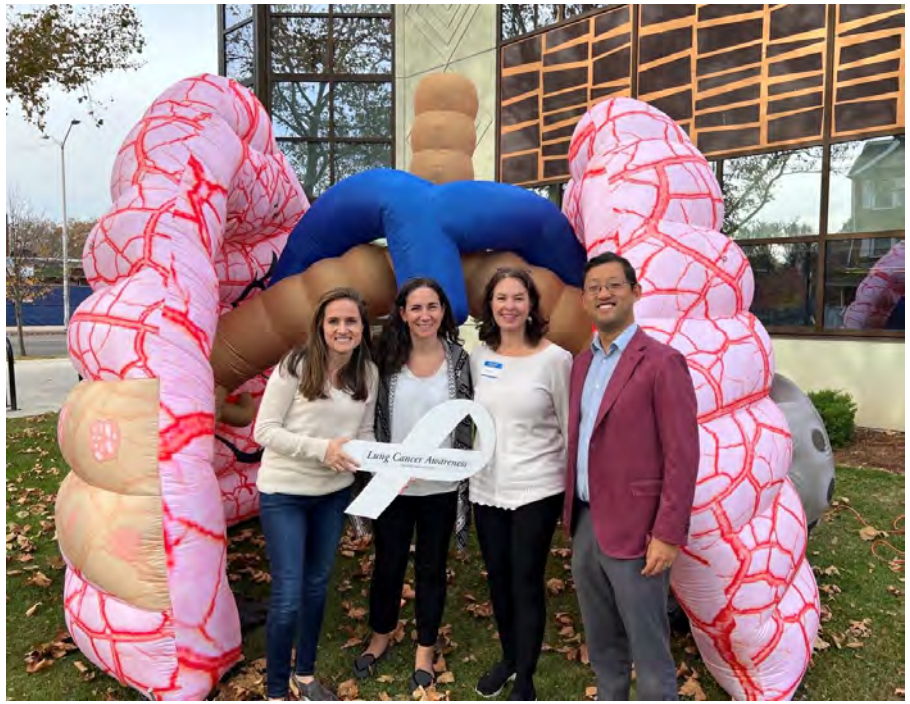
CA A Cancer J Clinicians, 2024

# How do we continue to make progress?




Emens LA, et al. JITC 2024

# Thank you so much for your attention and support!


# Today's presenters + panelists

## Colleen Conner Ziegler

**Patient Advocate**

Chair, LCRF Board of Directors

## Chi-Fu Jeffrey Yang, MD

**Massachusetts General Hospital**

Thoracic Surgeon

Founding Director, MGH CAIIRE

Founder and Chair, American Lung Cancer Screening Initiative

Associate Professor of Surgery, Harvard Medical School

## Don L. Gibbons, MD, PhD

**MD Anderson Cancer Center**

Isaiah J. Fidler Professorship in Cancer Research, Professor & Deputy Chair

Director, Translational Genetic Models Laboratory

Co-Leader, Lung Cancer Moon Shot Program

Dept. Thoracic/Head and Neck Medical Oncology, Dept. Molecular & Cellular Oncology

## James DeGregori, PhD

**University of Colorado Anschutz**

Professor, Biochemistry and Molecular Genetics

Courtenay C. and Lucy Patten Davis Endowed Chair in Lung Cancer Research

Deputy Director, University of Colorado Cancer Center


# Lung Cancer Patient Advocacy

Colleen Conner Ziegler

*Chair, LCRF Board of Directors*

*Research Advocate*

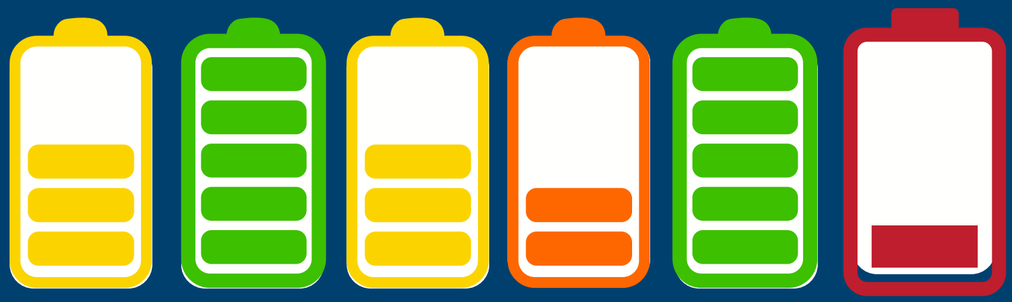
# Advocacy that moves research forward

**Be informed.**
Avail yourself of educational programs and conferences, in person or virtually. Ask questions.

**Be involved.**
Connect with LCRF and other groups to raise awareness/ funding for research.

**Be proactive.**
Engage in building new skills, knowledge, and mutual learning.

**Engagement happens on a continuum.**
Not everyone will participate at the same level, but every patient should be an advocate for themself.



# Why is patient participation important in research?

- Our experiences are all different but as a collective, we share what works best for the patient community to ensure **relevance** and **relatability**.

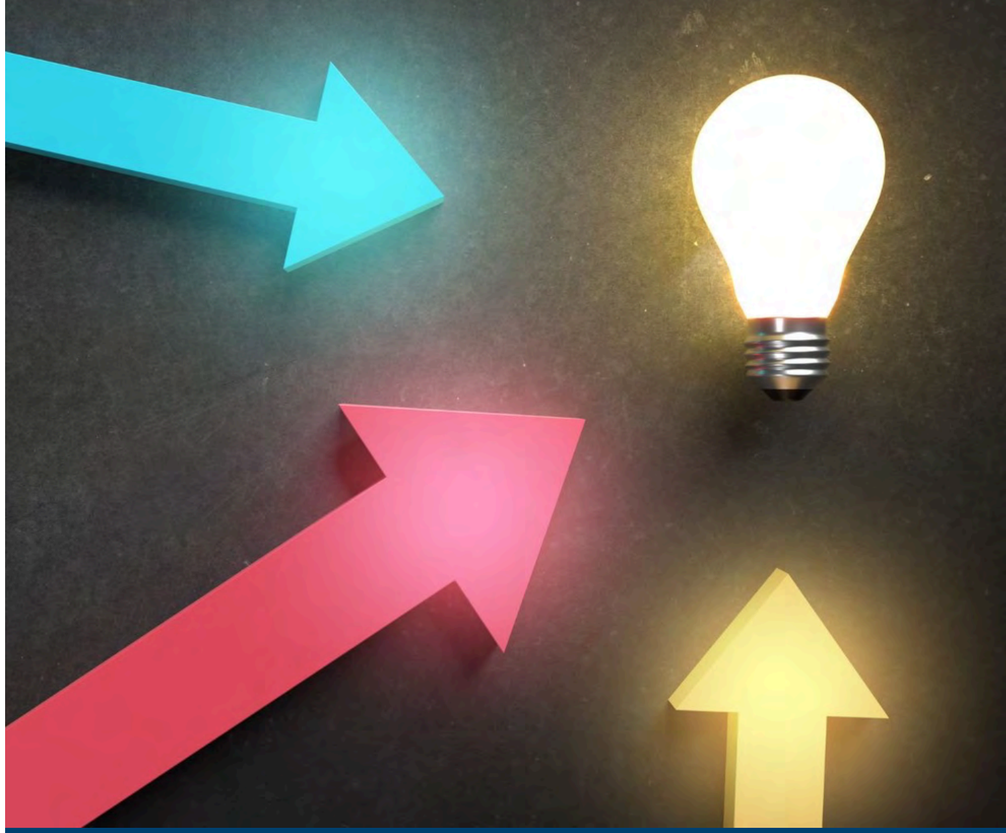
- Is about conducting research **‘with’ or ‘by’** people living with lung cancer.

- Helps to explore **barriers** and **solutions**.

# What does patient participation in research look like?

- Patients as **research partners & principals** have progressively become more **important**.

- Patient involvement has **gained momentum** in the last decade, with patients identifying and prioritizing topics, reviewing grant applications, analyzing and interpreting data, and disseminating findings.



Formalize engagement of Patient Advocates in clinical trial design and development:

- **Input** on clinical design
- Inclusion/exclusion **criteria**
- **Endpoints**

# Challenges integrating research advocacy into lung cancer research and clinical trials

Research advocates as partners with researchers in cancer research has been **expanding**, but **challenges still exist.**

How to **connect** the research advocate with the research to be a partner.

**Greater diversity and opportunities.** Patient advocates should be pulled from the population being studied.

# For clinicians and scientists

**Recognize advocates' skill sets.** Before our diagnoses, we were people from every walk of life.

**View research advocates as equitable partners in research process, not only clinical trial participants.** Advocates can contribute at all steps in the process.

**Embrace collaboration for mutual benefit.**

- *Advocates* enrich ongoing research initiatives as they learn about scientific developments and future possibilities.
- *Researchers* understand priorities of those affected by the disease and focus on areas relevant to patients' needs.

# Research advocacy and barriers to participation

**Conference participation.** Advocates are often responsible for the expenses associated with conference attendance.

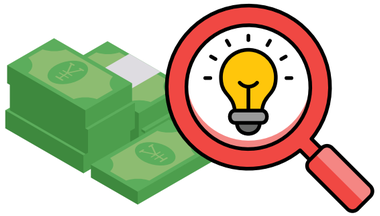
**Opportunities** for research advocacy training.

**Initiating and maintaining connection** with researchers/scientists.

**Physical** – challenges of living with lung cancer.

# Positive trends in research advocacy

People with lung cancer are often **living longer**, and because of this more are engaging in advocacy.



Patient/research advocates have taken on a **greater role in the funding of research**, raising significant funds both as individuals and members of patient organizations.


**Expanding range of advocacy activities** including grant reviews, focus groups, steering committees, advisory committees, clinical trial protocol – and in some cases, the engagement of a research advocate is a requirement for research funding.

# Research and the patient perspective

Research informed by the perspectives of people directly affected by lung cancer leads to more **meaningful discoveries**, **greater impact**, and **increased survival**.

***How LCRF's research program incorporates the patient perspective:***

- Research advocates are **fully integrated** in LCRF's research program.
- Mid-career and team science grant applicants ***must*** **incorporate** patients / advocates into their research teams.
- LCRF recommends that patients / advocates **should be compensated** for participation in research teams.

# Opportunities for Research Advocate participation and training

**Lung Cancer Research Foundation (LCRF)**
***Research Advocate program***

---

**International Association for the Study of Lung Cancer** (IASLC)
*STARs program*

---

**American Society of Clinical Oncology** (ASCO)
*serve on ASCO committees, guideline panels (must be a member)*

---

**American Association for Cancer Research** (AACR)
*Scientist - Survivor program*

---

**Advocates for Collaborative Education** (ACE)


# Screening

## Chi-Fu Jeffrey Yang, MD

**Massachusetts General Hospital**
Thoracic Surgeon

Founding Director, MGH CAIIRE

Founder and Chair, American Lung Cancer Screening Initiative

Associate Professor of Surgery, Harvard Medical School

# Updating Who We Screen: Rethinking Lung Cancer Screening Eligibility in 2025

Lung Cancer Research Foundation
Annual Scientific Symposium
November 5th, 2025

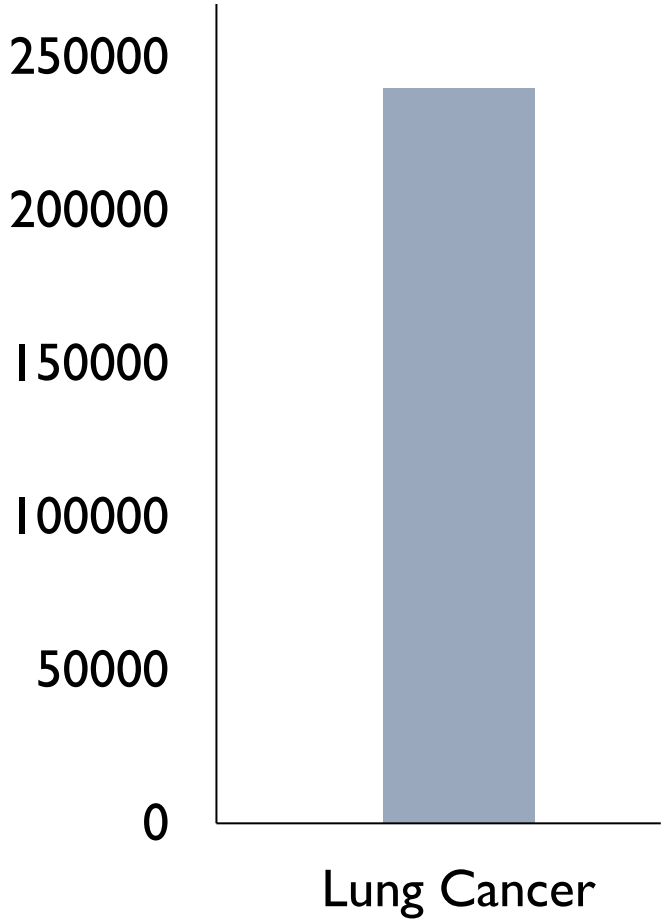
Chi-Fu Jeffrey Yang
Massachusetts General Hospital

# Disclosures

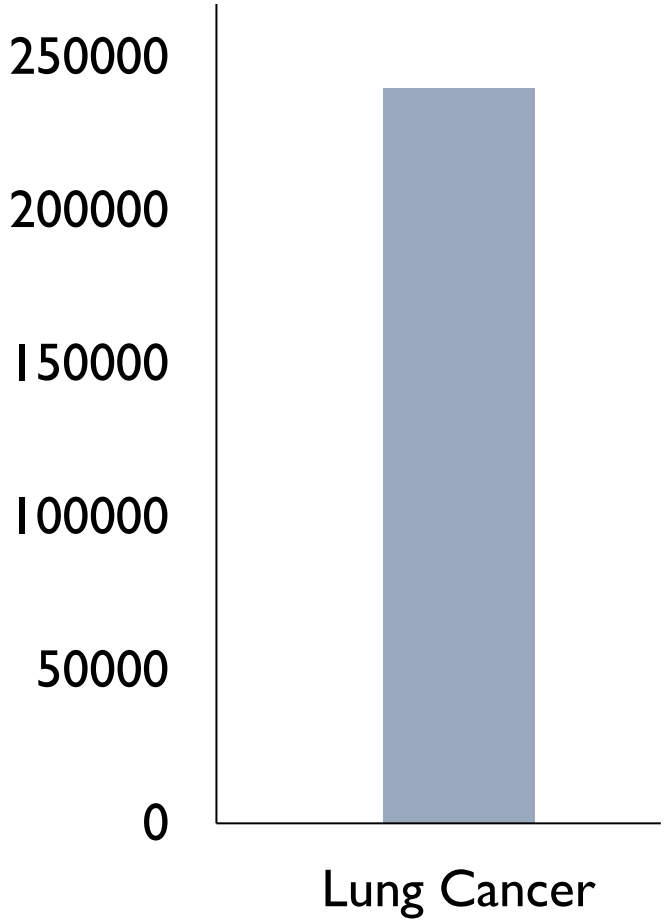
- Founder of the American Lung Cancer Screening Initiative

- Member of the advisory board for AstraZeneca and Genentech and have received honorarium from AstraZeneca and Genentech.

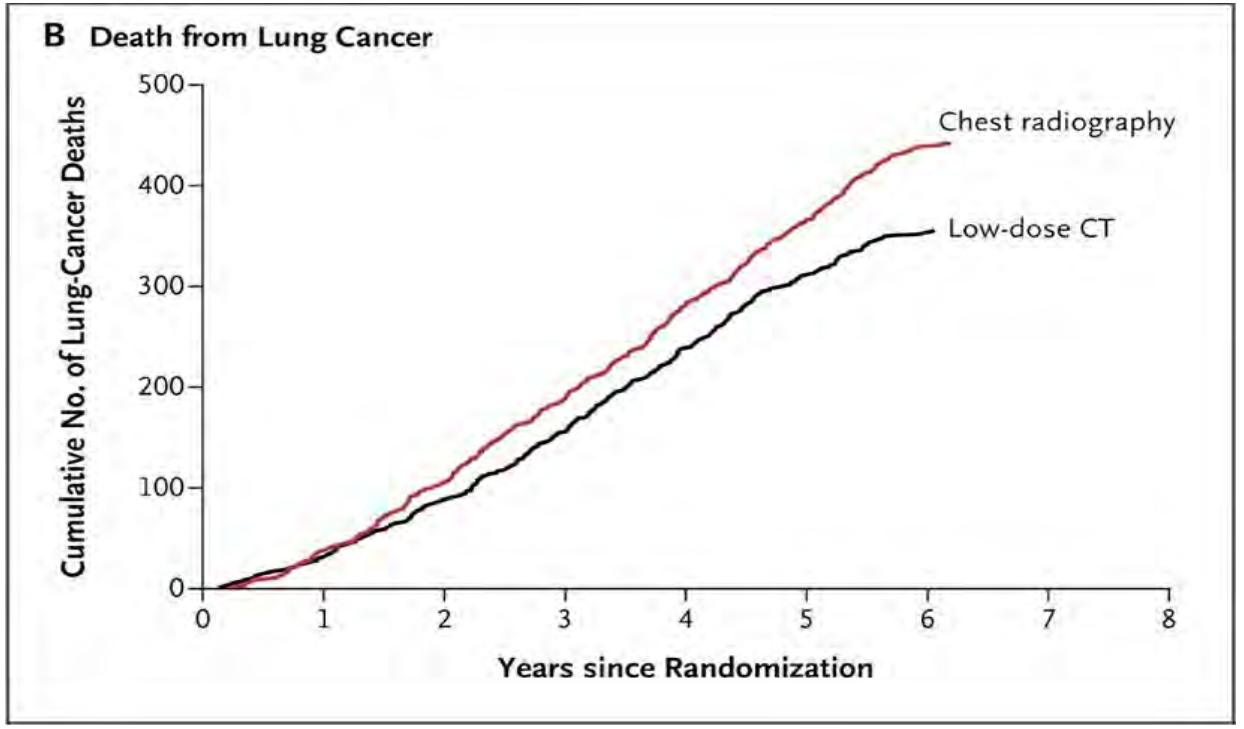
# U.S. Lung Cancer Estimates 2025



# U.S. Lung Cancer Estimates 2025

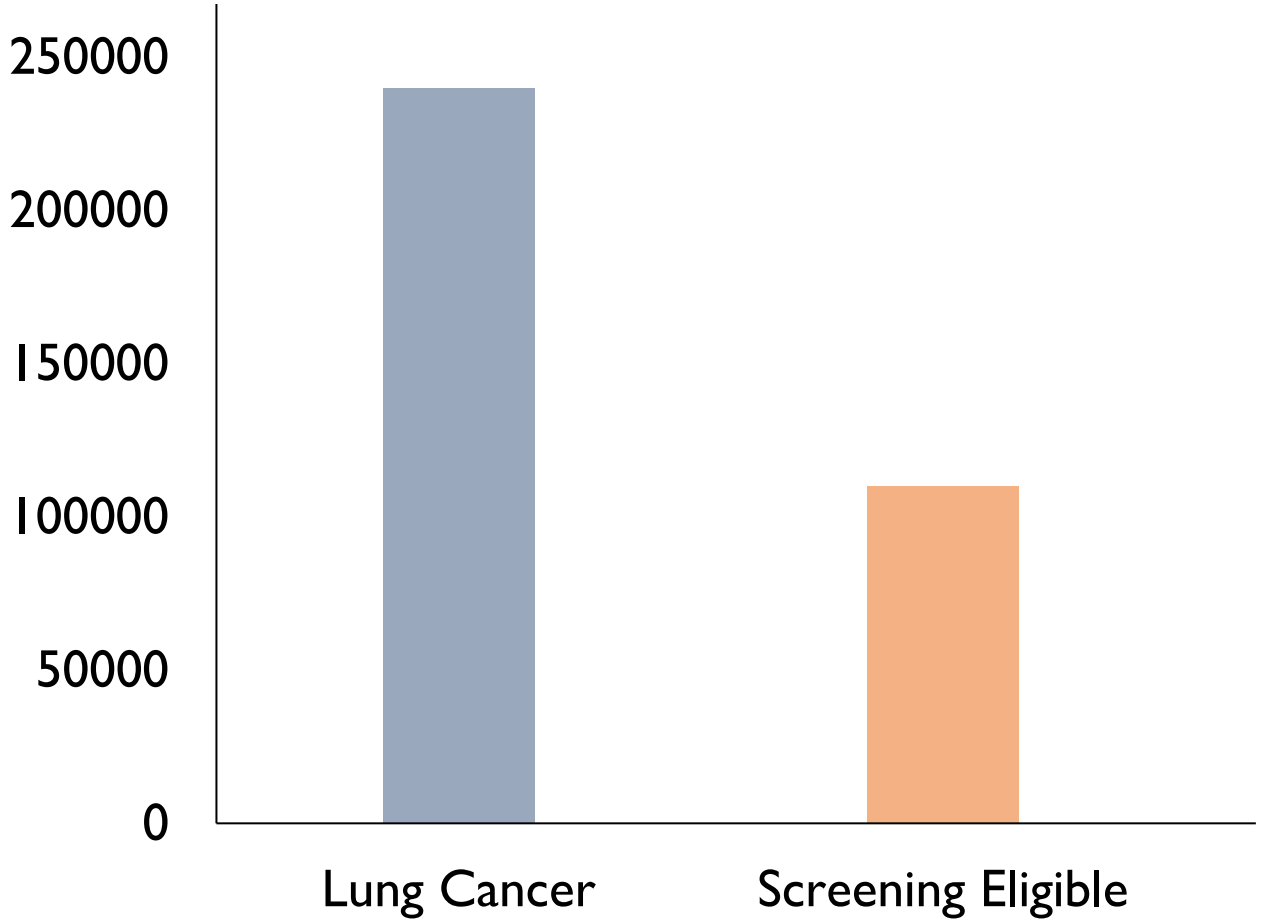



## Lung Cancer Screening Saves Lives

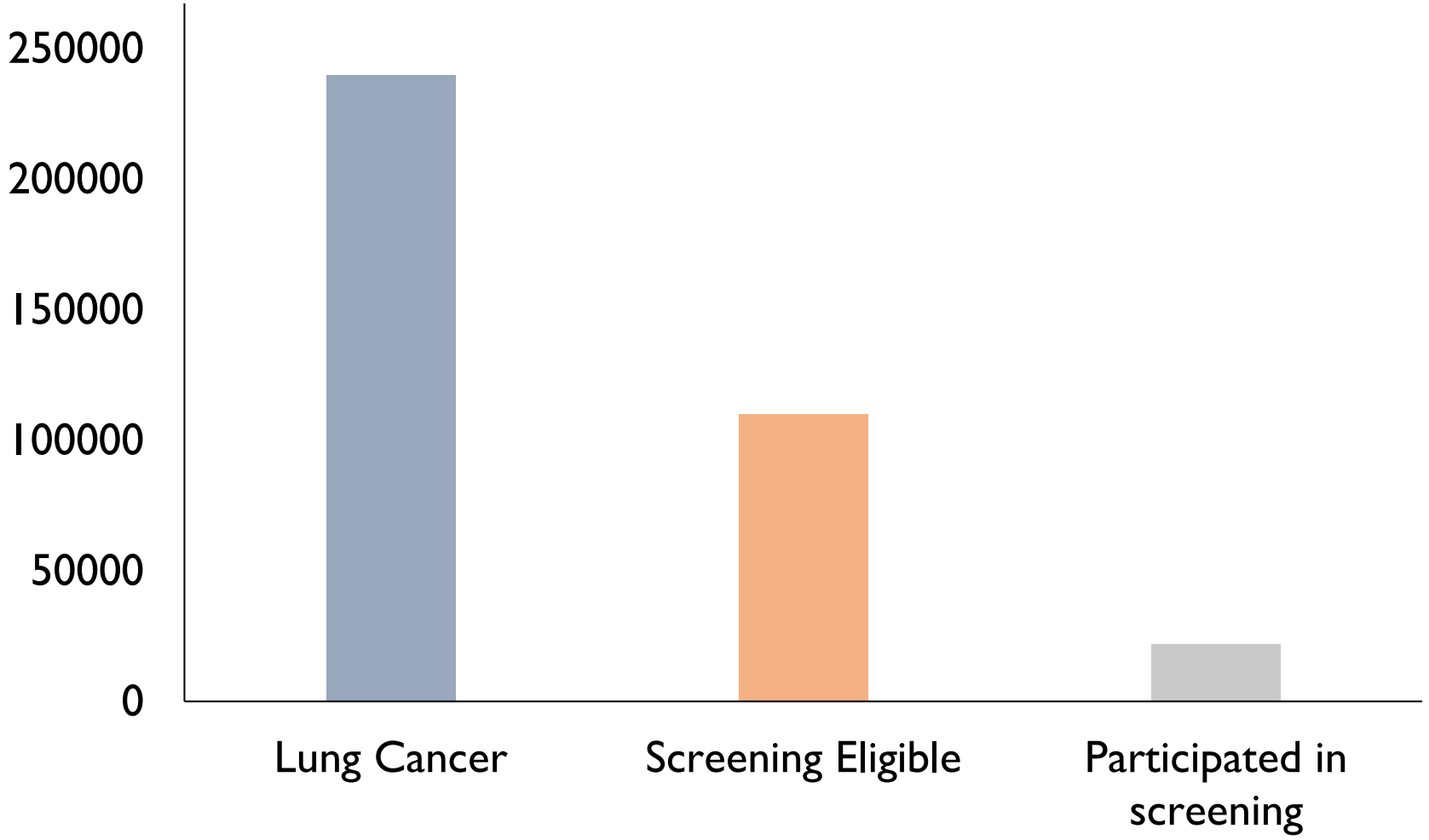



*Aberle et. al, New England Journal of Medicine, 2011*

# U.S. Lung Cancer Estimates 2025



# U.S. Lung Cancer Estimates 2025



# Outline

I. Lung cancer screening eligibility criteria

# 2021 USPSTF Criteria for Lung Cancer Screening

- The U.S. Preventive Services Task Force currently recommends lung cancer screening for the following individuals:

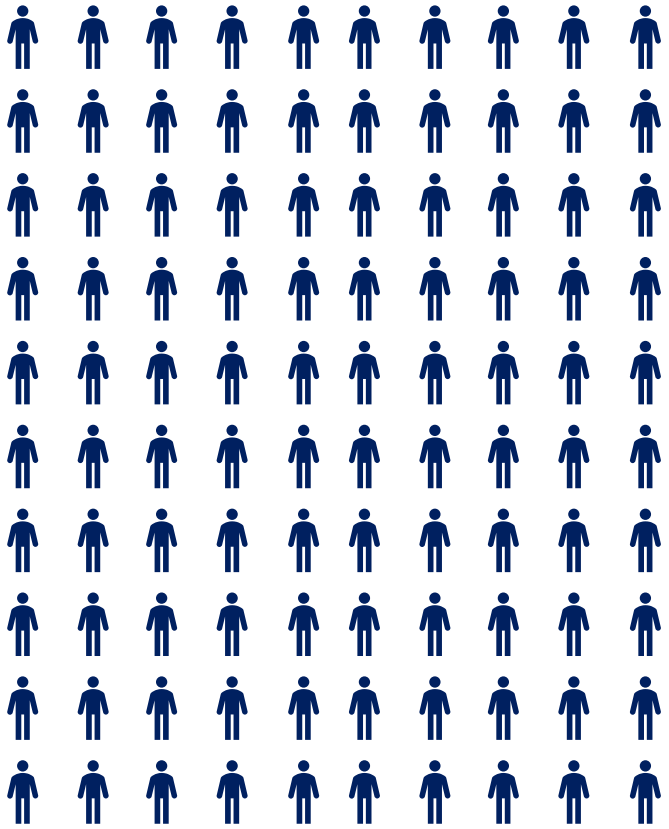
I. Age 50 – 80

II. ≥ 20 pack-year cigarette smoking history

III. Currently smoke cigarettes or quit smoking within the past 15 years

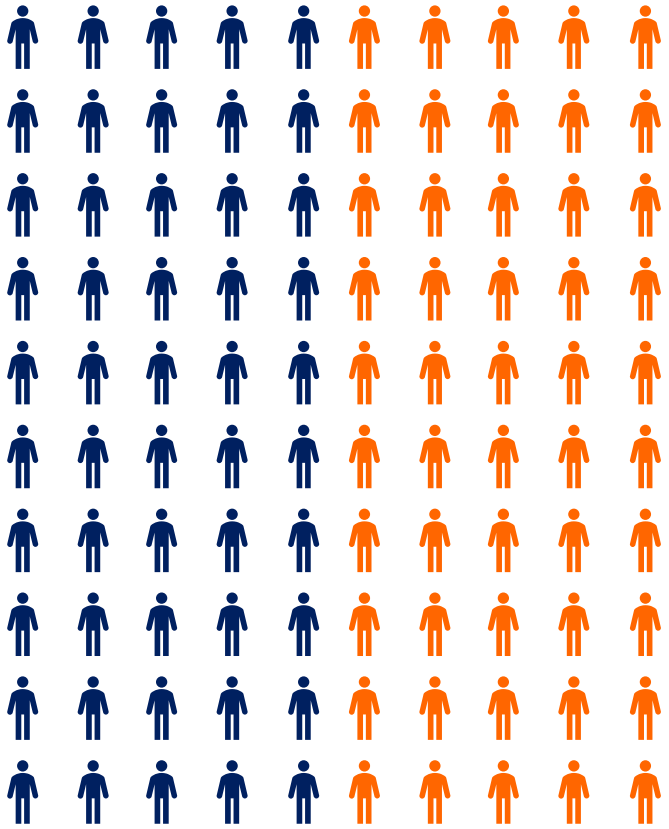
# How well do lung cancer screening eligibility criteria identify individuals at risk of developing lung cancer?

# How well do the 2021 USPSTF criteria identify people at risk of developing lung cancer?



Among patients newly diagnosed with lung cancer…

# How well do the 2021 USPSTF criteria identify people at risk of developing lung cancer?



Among patients newly diagnosed with lung cancer…

**~50% of patients would have been ineligible for lung cancer screening**[1-4]

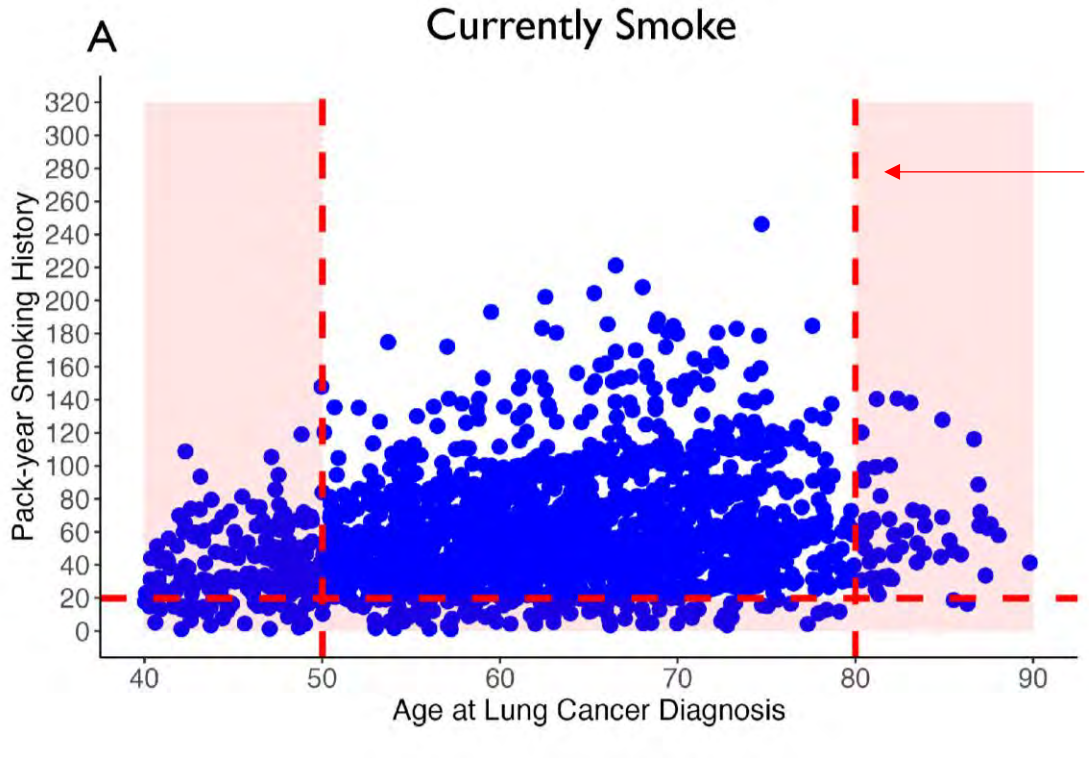

1. Potter et al, *Journal of Clinical Oncology*, 2024
2. Potter et al, *Annals of Thoracic Surgery*, 2025
3. Smeltzer et al, *Journal of Thoracic Oncology*, 2023
4. Cooley-Rieders et al, *JTCVS* 2023

# Evaluating Lung Cancer Screening Eligibility in the Boston Lung Cancer Study

- **Study Design:** Analysis of 7,186 patients diagnosed with lung cancer in the Boston Lung Cancer Study from 1992-2024
- **Objective:** To evaluate the proportion that would have qualified for lung cancer screening and the reasons for ineligibility
- **Key Finding:** Only **46%** of patients diagnosed with lung cancer would have met the 2021 USPSTF lung cancer screening criteria

## Who do the USPSTF criteria miss?

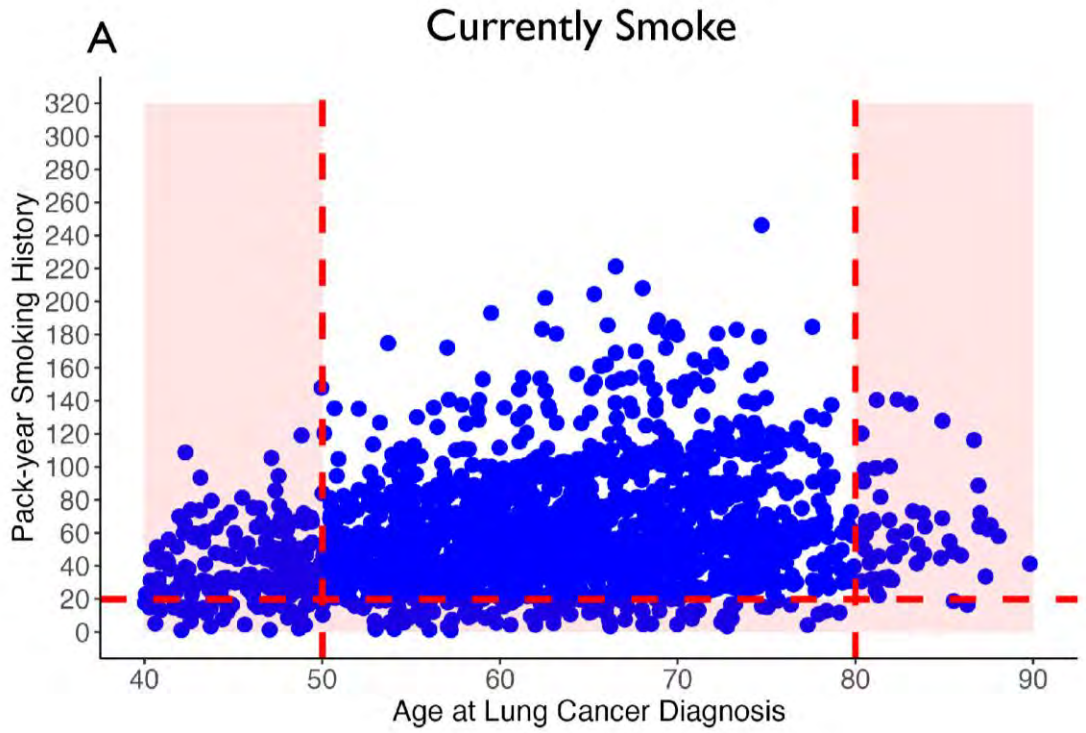
# Evaluating Lung Cancer Screening Eligibility in the Boston Lung Cancer Study

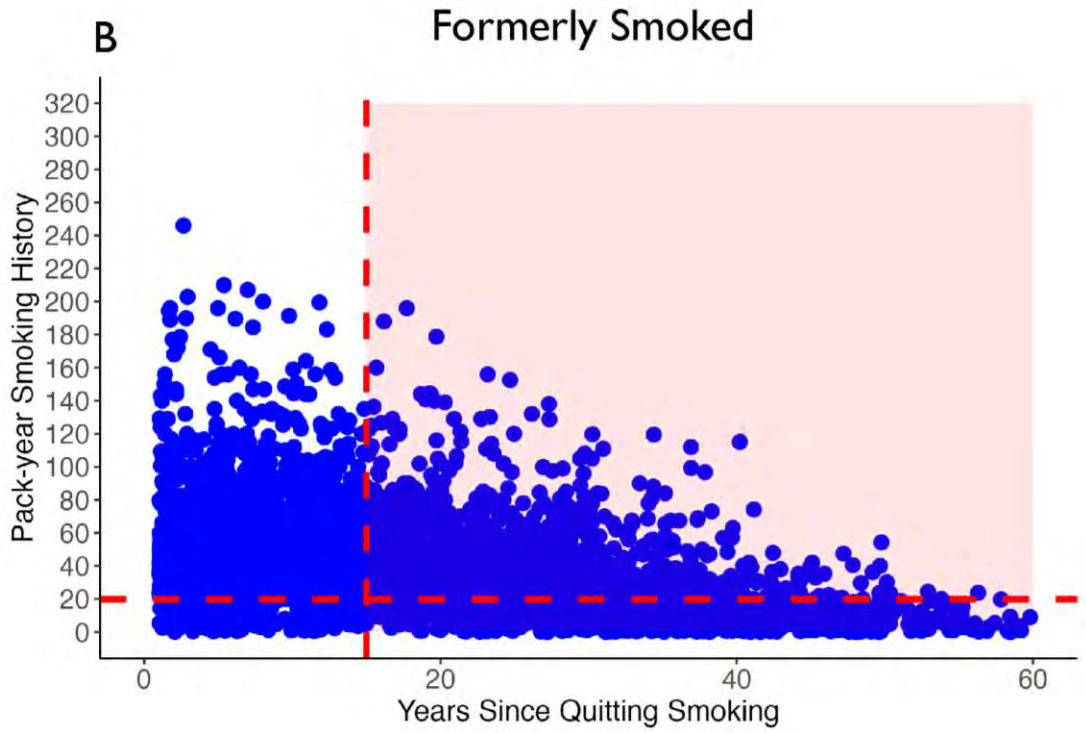



Red-shaded regions denote ineligibility for lung cancer screening under the 2021 USPSTF Guideline

**81% of patients who currently smoked at diagnosis would have qualified**

# Evaluating Lung Cancer Screening Eligibility in the Boston Lung Cancer Study




**81% of patients who currently smoked at diagnosis would have qualified**

**36% of patients who formerly smoked would have qualified**

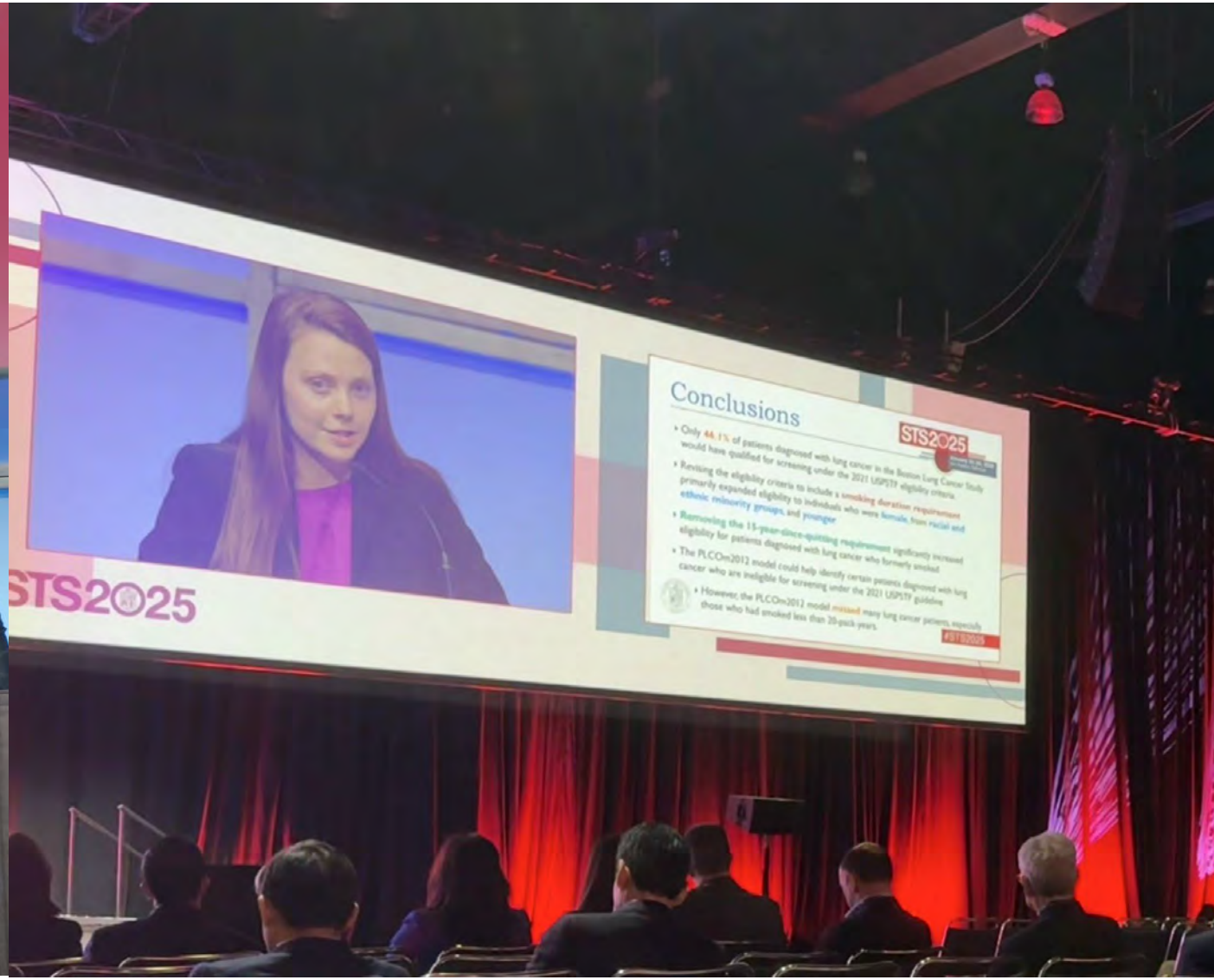
Potter et al, *Annals of Thoracic Surgery*, 2025

# Evaluating Lung Cancer Screening Eligibility in the Boston Lung Cancer Study

| Reason for Ineligibility | Patients with Lung Cancer Ineligible for Screening (n=3,872) |
|---|---|
| Years Since Quitting >15 | 54.4% |
| <20 Pack-years | 29.4% |
| Never Smoked | 26.9% |
| Age <50 | 15.6% |
| Age >80 | 14.3% |

*Categories are not mutually exclusive

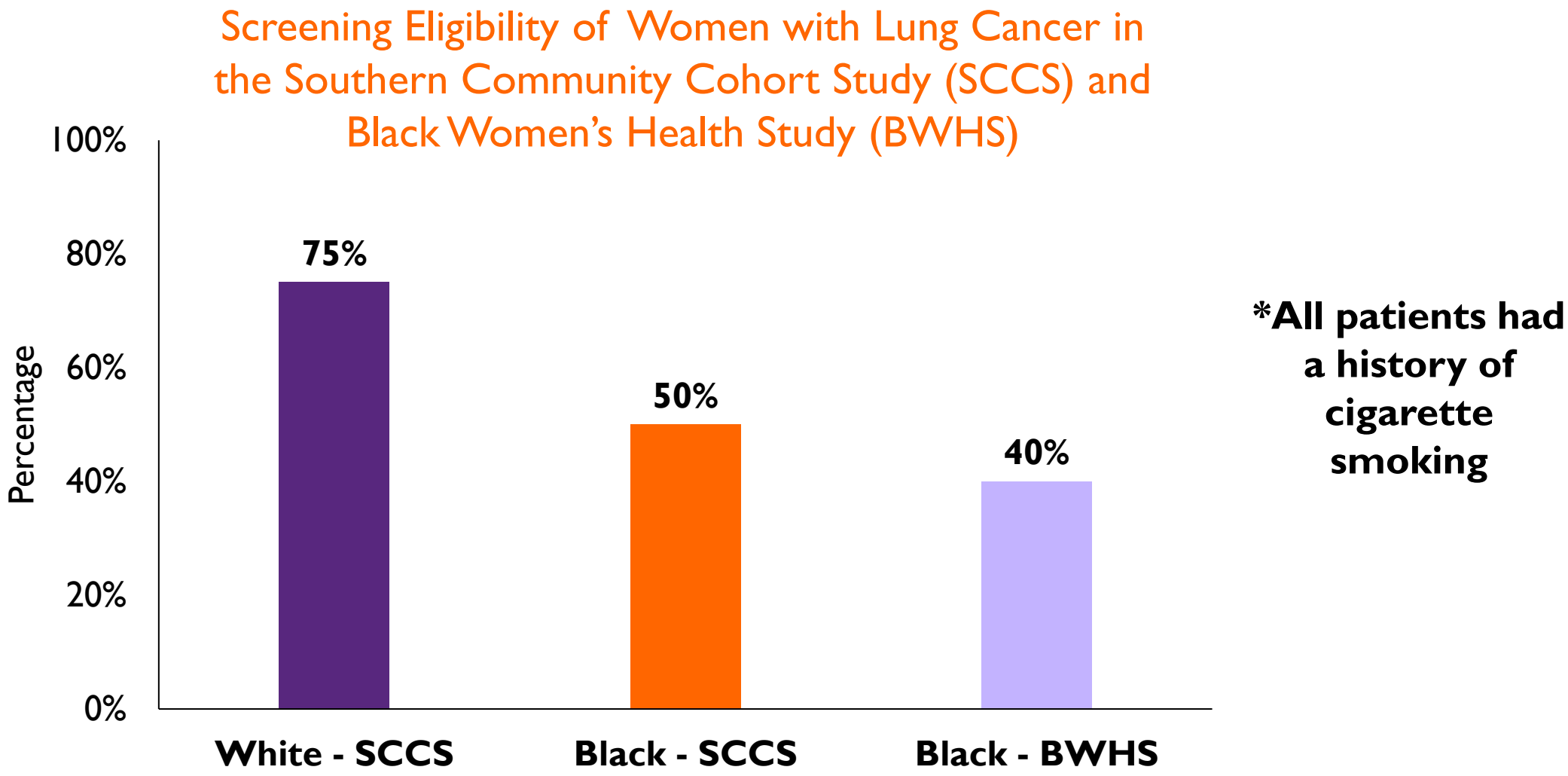
# STS Plenary Presentation, Maxwell Chamberlain Paper

# Lung Cancer Screening Eligibility in Other Cohorts

- Southern Community Cohort Study (SCCS)
  - Prospective cohort of ~85,000 predominately low-income Black and white adults from 12 Southeastern U.S. states from March 2002 to September 2009
- Black Women's Health Study (BWHS)
  - Largest prospective cohort of self-identified Black women in the U.S. (n= ~59,000) from predominantly metropolitan regions, which began in 1995

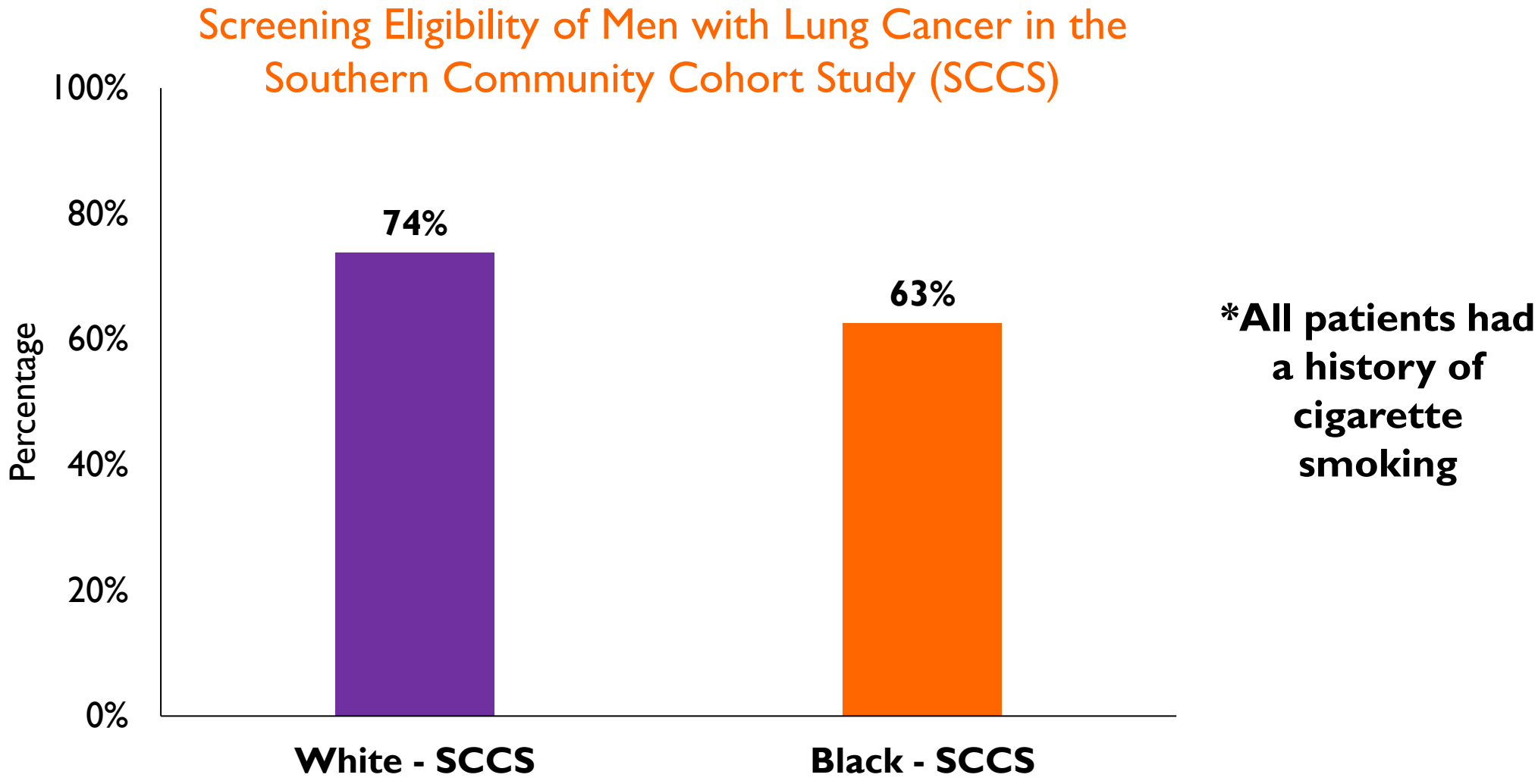
# Under the 2021 USPSTF guideline, only **40-50%** of Black women diagnosed with lung cancer would have been eligible for lung cancer screening




Potter et al. *JAMA Oncology.* 2022 8(1):163-164.

Potter et al. *Journal of Thoracic and Cardiovascular Surgery.* 2023 168(1):248-260.e2.

# Under the 2021 USPSTF guideline, only **63%** of Black men diagnosed with lung cancer would have been eligible for lung cancer screening




Potter et al. *JAMA Oncology.* 2022 8(1):163-164.

Potter et al. *Journal of Thoracic and Cardiovascular Surgery.* 2023 168(1):248-260.e2.

# Reasons for Ineligibility Under the 2021 USPSTF Criteria

## Black Women's Health Study

| Reason for Ineligibility | Black Women (n=284) |
|---|---|
| <20 Pack-years | 75.0% |
| Years Since Quitting >15 | 29.6% |
| Age <50 | 17.6% |
| Age >80 | 5.3% |

## Southern Community Cohort Study

| Reason for Ineligibility | White (n=195) | Black (n=532) |
|---|---|---|
| <20 Pack-years | 50.3% | 82.5% |
| Years Since Quitting >15 | 39.0% | 16.5% |
| Age <50 | 20.5% | 11.8% |
| Age >80 | 10.3% | 6.0% |

*Categories are not mutually exclusive

Potter et al. *JAMA Oncology.* 2022 8(1):163-164.

Potter et al. *Journal of Thoracic and Cardiovascular Surgery.* 2023 168(1):248-260.e2.

What revisions to the USPSTF criteria can **improve** the identification of individuals ultimately diagnosed with lung cancer?

# 2021 USPSTF Criteria for Lung Cancer Screening

- The U.S. Preventive Services Task Force currently recommends lung cancer screening for the following individuals:

I. Age 50 – 80

II. ≥ 20 pack-year cigarette smoking history

III. Currently smoke cigarettes or quit smoking within the past 15 years

# Pack-Year Smoking History

$$\text{Pack-year Smoking History} = \underbrace{\frac{\text{Cigarettes per Day}}{20}}_{\text{Smoking Intensity}} \times \underbrace{\text{Total Number of Years Smoked}}_{\text{Smoking Duration}}$$

- The pack-year assumes that smoking duration and smoking intensity have equal importance in determining lung cancer risk
- Smoking duration is more strongly associated with lung cancer risk compared to smoking intensity[1-3]
  - Pack-year smoking history **underestimates** lung cancer risk among individuals who smoke less intensely


1. Doll, *J Epidemiology Community Health, 1978*
2. Remen, *BMC Cancer,* 2018
3. Bach, *JNCI,* 2003

# Objective

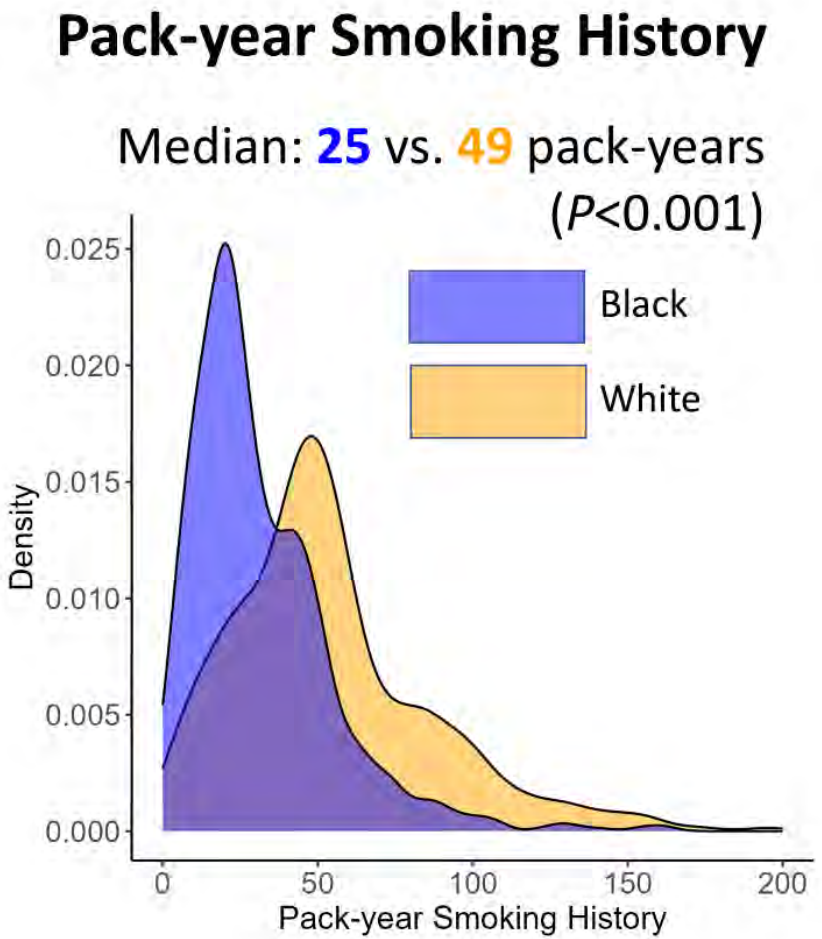
- To evaluate the impact of using a 20-year smoking duration cutoff, instead of a 20-pack-year cutoff, as a selection criterion for lung cancer screening

| **2021 USPSTF Lung Cancer Screening Guidelines** |
|---|
| 1) Aged **50-80**, and |
| 2) Have a ≥ **20** pack-year smoking history, and |
| 3) Currently smoke or have quit within the past **15** years |

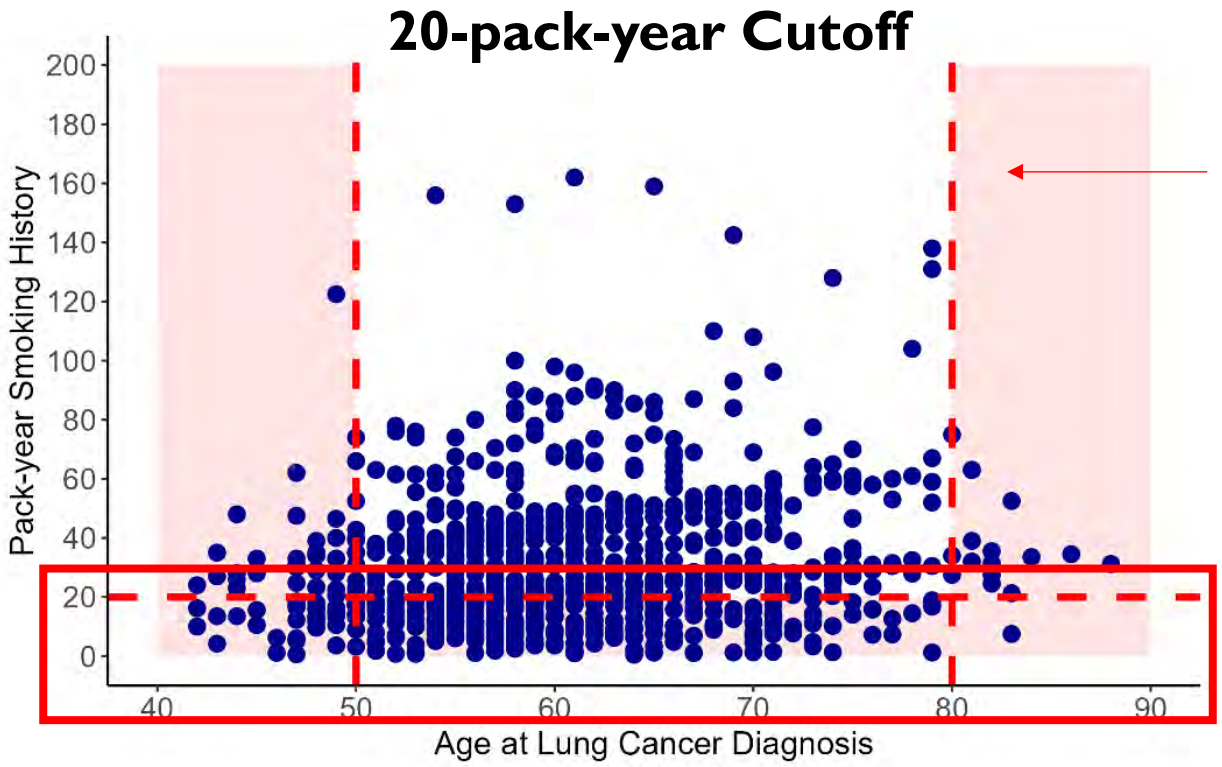
vs

| **Duration Guideline** |
|---|
| 1) Aged **50-80**, and |
| 2) Have a ≥ **20** year smoking duration, and |
| 3) Currently smoke or have quit within the past **15** years |

# Black Lung Cancer Patients Smoked Fewer Pack-years at Lung Cancer Diagnosis Compared to White Lung Cancer Patients: Southern Community Cohort Study



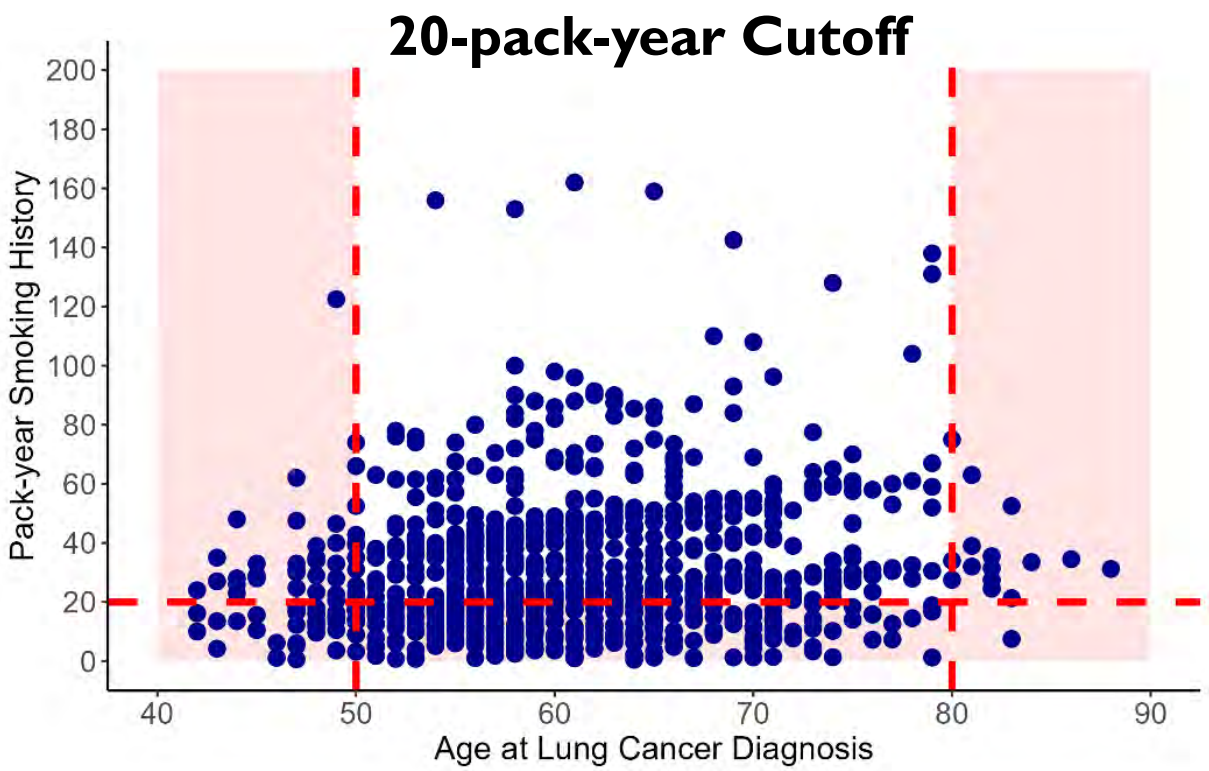
# Use of a 20-year Smoking Duration Cutoff Significantly Increases the Proportion of Black Lung Cancer Patients that Currently Smoke Who Would Have Qualified for Lung Cancer Screening: SCCS Analysis

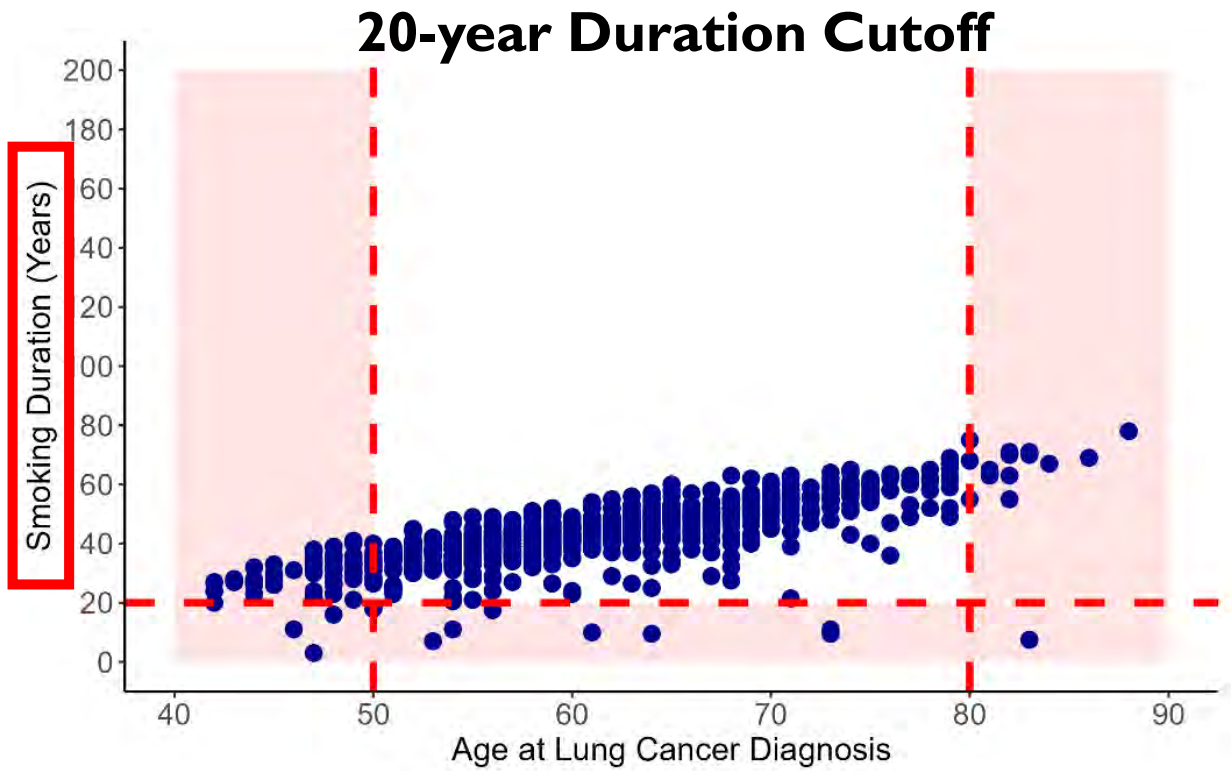



Red-shaded regions denote ineligibility for lung cancer screening under the 2021 USPSTF Guideline

**61.8% of Black Lung Cancer Patients Who Currently Smoked Would Have Qualified**

# Use of a 20-year Smoking Duration Cutoff Significantly Increases the Proportion of Black Lung Cancer Patients that Currently Smoke Who Would Have Qualified for Lung Cancer Screening: SCCS Analysis



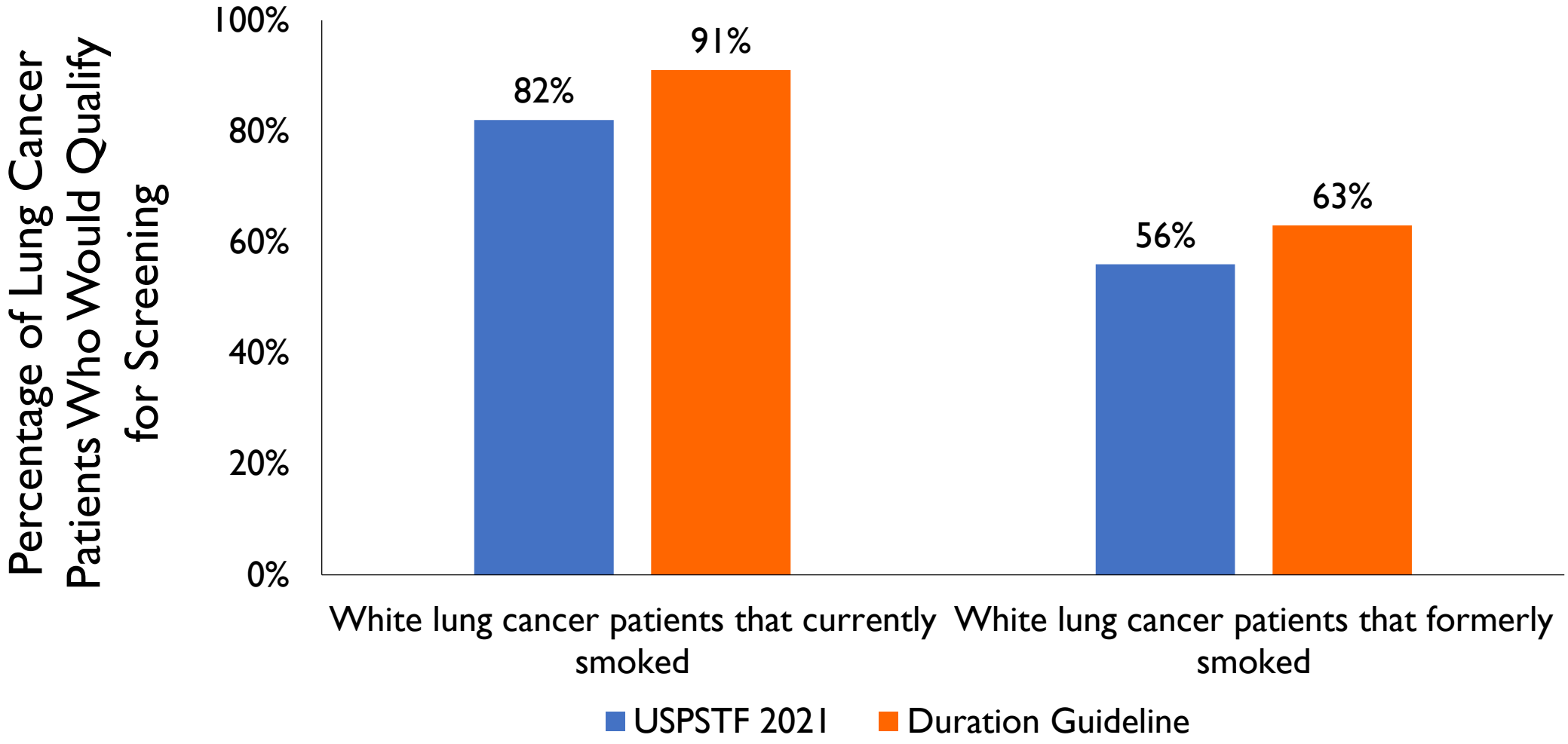

**61.8% of Black Lung Cancer Patients Who Currently Smoked Would Have Qualified**

**92.0% of Black Lung Cancer Patients Who Currently Smoked Would Have Qualified**

McNemar's $P < 0.001$

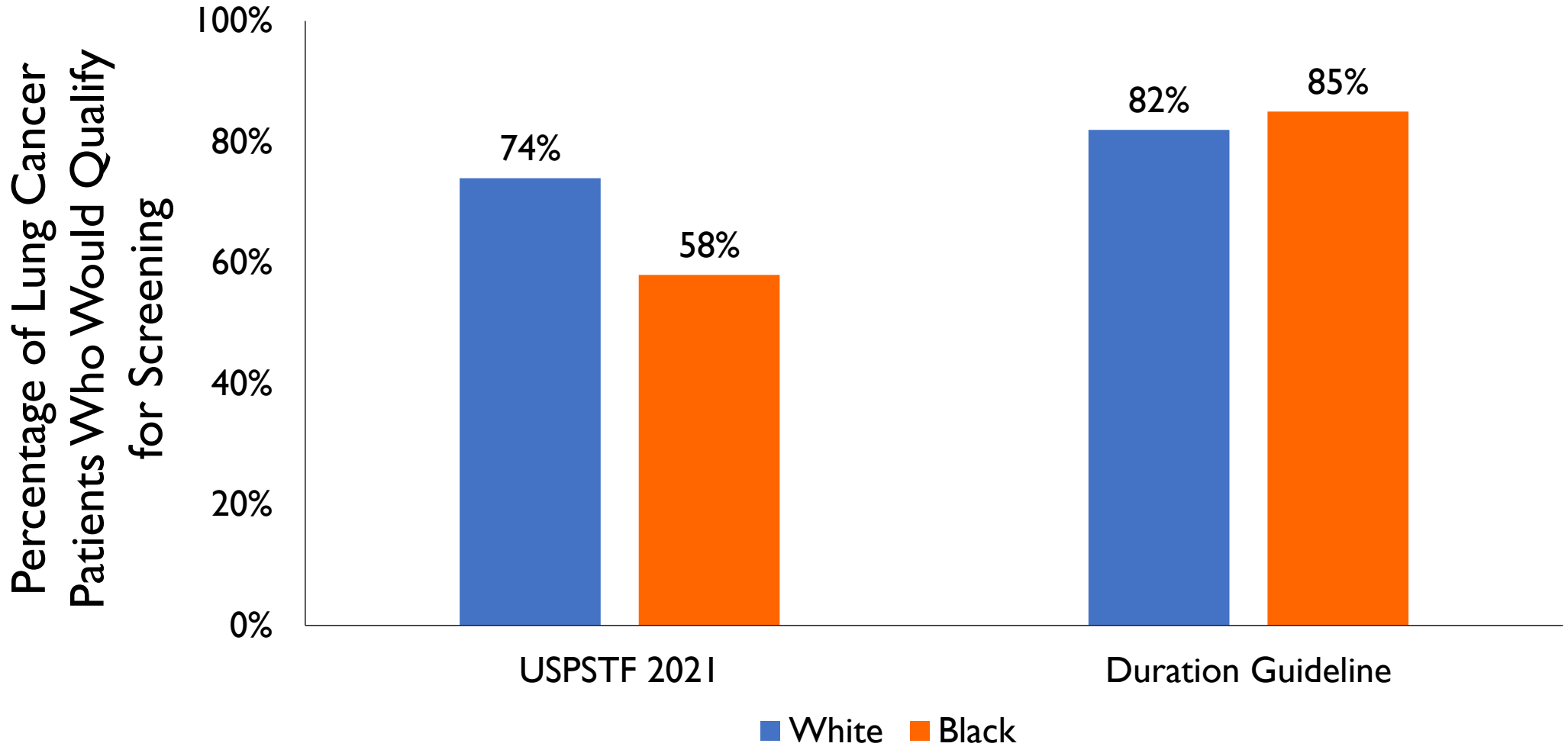
Potter et al. *Journal of Clinical Oncology.* 2024 42(17):2026-2037

# Use of a 20-year Smoking Duration Cutoff Significantly Increases the Proportion of White Lung Cancer Patients Who Would Have Qualified for Lung Cancer Screening




Potter et al. *Journal of Clinical Oncology.* 2024 42(17):2026-2037

# Use of a 20-year Smoking Duration Cutoff Eliminated Racial Disparities in Screening Eligibility




Potter et al. *Journal of Clinical Oncology.* 2024 42(17):2026-2037

# Using Smoking Duration, Instead of Pack-Years, as a Lung Cancer Screening Selection Criteria is More Equitable

- Including a smoking duration threshold as a selection criterion for lung cancer screening, instead of a smoking pack-year threshold, has been shown to reduce racial and ethnic disparities in lung cancer screening eligibility in the:
  - Multi-ethnic Cohort Study[1] (Black, White, Latino, Japanese American, Native Hawaiian/Other Pacific Islander)
  - Deluge Cohort (Detecting Early Lung Cancer in the Mississippi Delta Cohort)[2] (Black vs. White and Male vs. Female)



1. Su et al, Impact of Using Smoking Duration in Place of Pack-Years as Eligibility Criteria for Lung Cancer Screening to Reduce Racial and Ethnic Disparities, World Conference on Lung Cancer 2024

2. Smeltzer et al, Smoking History Requirement and Lung Cancer Screening Eligibility Disparities, ASCO 2024

# What is the impact of including a 20-year duration requirement?

- More patients who smoke long durations, but less intensely, **become eligible** for screening
- Racial and ethnic differences in screening eligibility are **reduced or eliminated**

# NCCN Guidelines Version 1.2025
# Lung Cancer Screening

NCCN Guidelines Index
Table of Contents
Discussion

**RISK ASSESSMENT[a,b,c]**

- Cigarette smoking history[d]
- Radon exposure[e]
- Occupational exposure[f]
- Cancer history[g]
- Family history of lung cancer in first-degree relatives
- Disease history (chronic obstructive pulmonary disease [COPD] or pulmonary fibrosis)
- Cigarette smoking exposure[h] (second-hand smoke)
- Risk calculator to enhance determination of risk status[i,j]

**Patients not eligible for lung cancer screening:**

- Symptoms of lung cancer (see NCCN Guidelines for Non-Small Cell Lung Cancer)
- Previous lung cancer (see Surveillance in the NCCN Guidelines for Non-Small Cell Lung Cancer)
- Functional status and/or comorbidity that would prohibit curative intent treatment[k] (see Principles of Surgery in the NCCN Guidelines for Non-Small Cell Lung Cancer and Principles of Radiation Therapy in the NCCN Guidelines for Non-Small Cell Lung Cancer)

**RISK STATUS**

**High risk[i,l,m]**
- Age ≥50 y (category 1) and
- ≥20 pack-year history of smoking cigarettes (category 1) or ≥20 year history of smoking cigarettes[1] (category 2B)

**Low risk**
- Age <50 y and/or
- <20 pack-year history of smoking cigarettes or <20 year history of smoking cigarettes[1] (category 2B)

**SCREENING**

In candidates for screening, shared patient/provider decision-making is recommended, including a discussion of benefits/risks[c,j] → Low-dose CT (LDCT)[n] (category 1) → Screening Findings (LCS-2)

Lung cancer screening not recommended

[1] Potter AL, Xu NN, Senthil P, et al. Pack-year smoking history: An inadequate and biased measure to determine lung cancer screening eligibility. J Clin Oncol 2024;42:2026-2037.

# 2021 USPSTF Criteria for Lung Cancer Screening

- The U.S. Preventive Services Task Force currently recommends lung cancer screening for the following individuals:

I. Age 50 – 80

II. ≥ 20 pack-year cigarette smoking history

III. Currently smoke cigarettes or quit smoking within the past 15 years

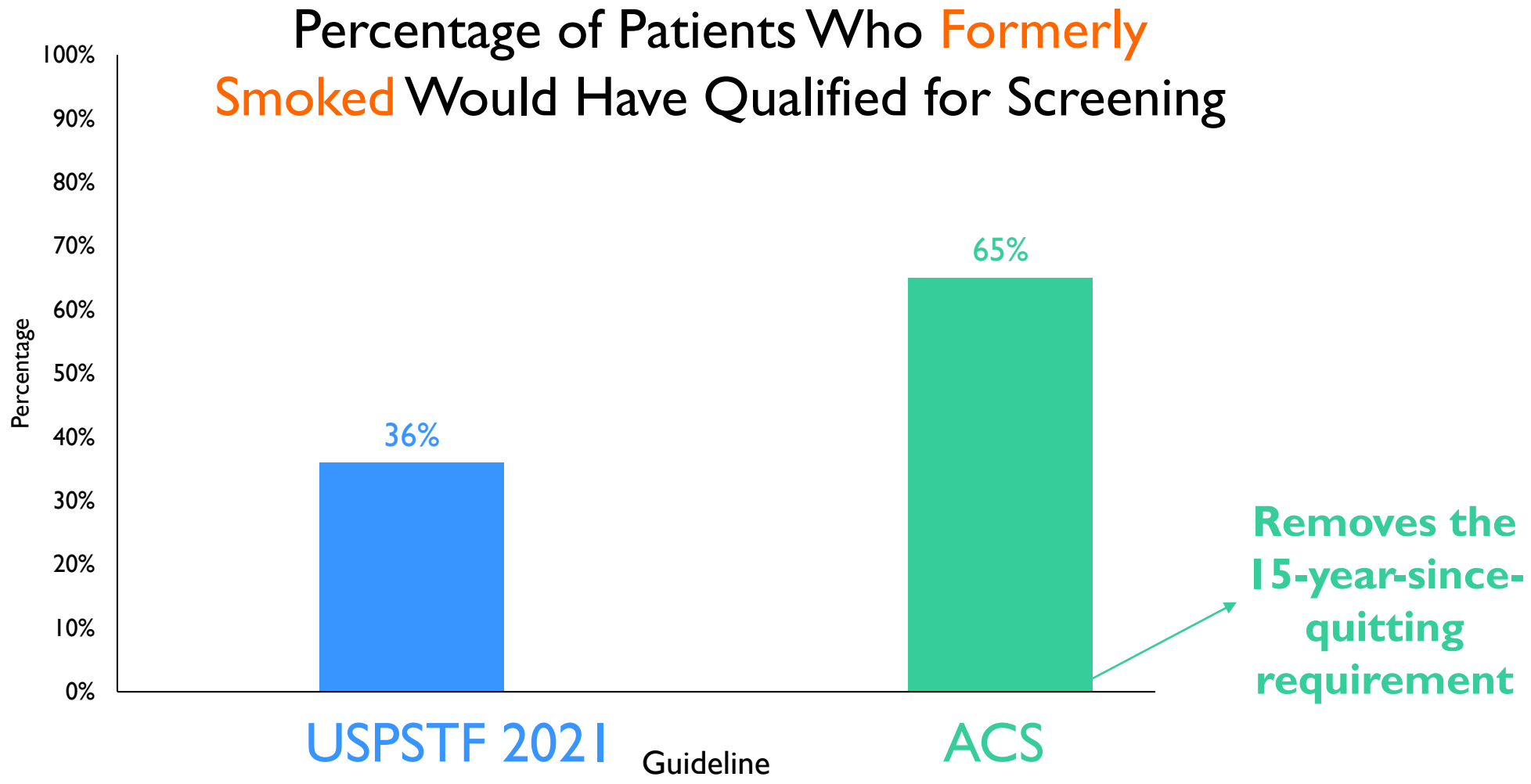
## "the 15-Year-Since-Quit" Requirement

# Removing the 15-Year-Since-Quitting Requirement

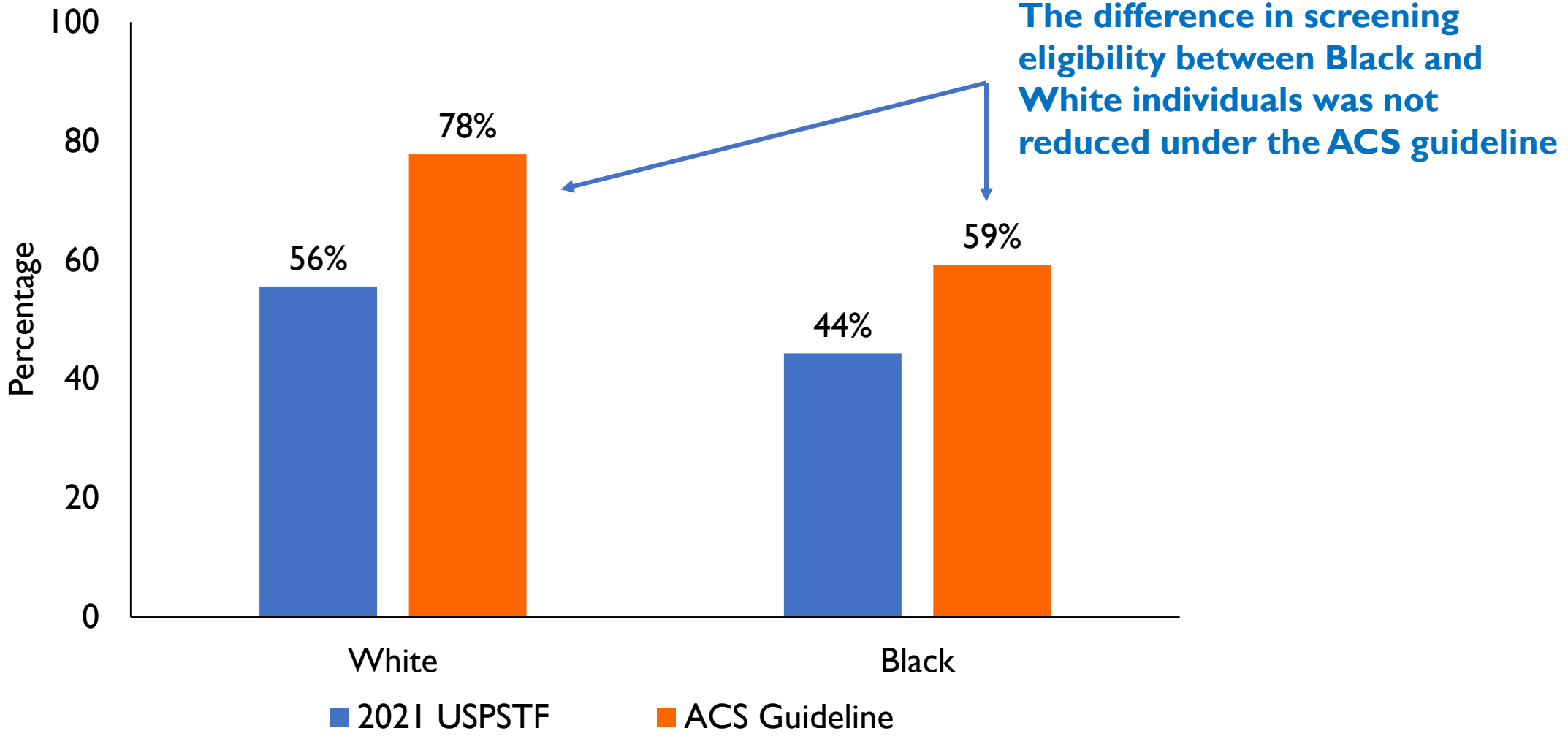
- Previous studies have shown that the risk of lung cancer remains significantly elevated even after 15 years since stopping smoking[1,2]
- 33-77% of lung cancer diagnoses among people who formerly smoked occur >15 years after stopping smoking[3]
- The National Comprehensive Cancer Network and American Cancer Society have removed the 15-year-since-quitting criterion from their lung cancer screening recommendations

[1]Landy et al, *Cancer*, 2024
[2]Pinsky et al, *Journal of Medical Screening*, 2015
[3]Pu et al, *JAMA Oncology*, 2022

# Impact of Removing the 15-Year-Since-Quitting Requirement on Eligibility: Boston Lung Cancer Study Analysis



# Impact of Removing the 15-Year-Since-Quitting Requirement on Eligibility: Southern Community Cohort Study Analysis




Potter et al, Submitted

# What is the impact of removing the 15-year-since-quitting requirement?

- Removing the 15-year-since-quitting requirement significantly **increases** eligibility for patients diagnosed with lung cancer who **formerly smoked**

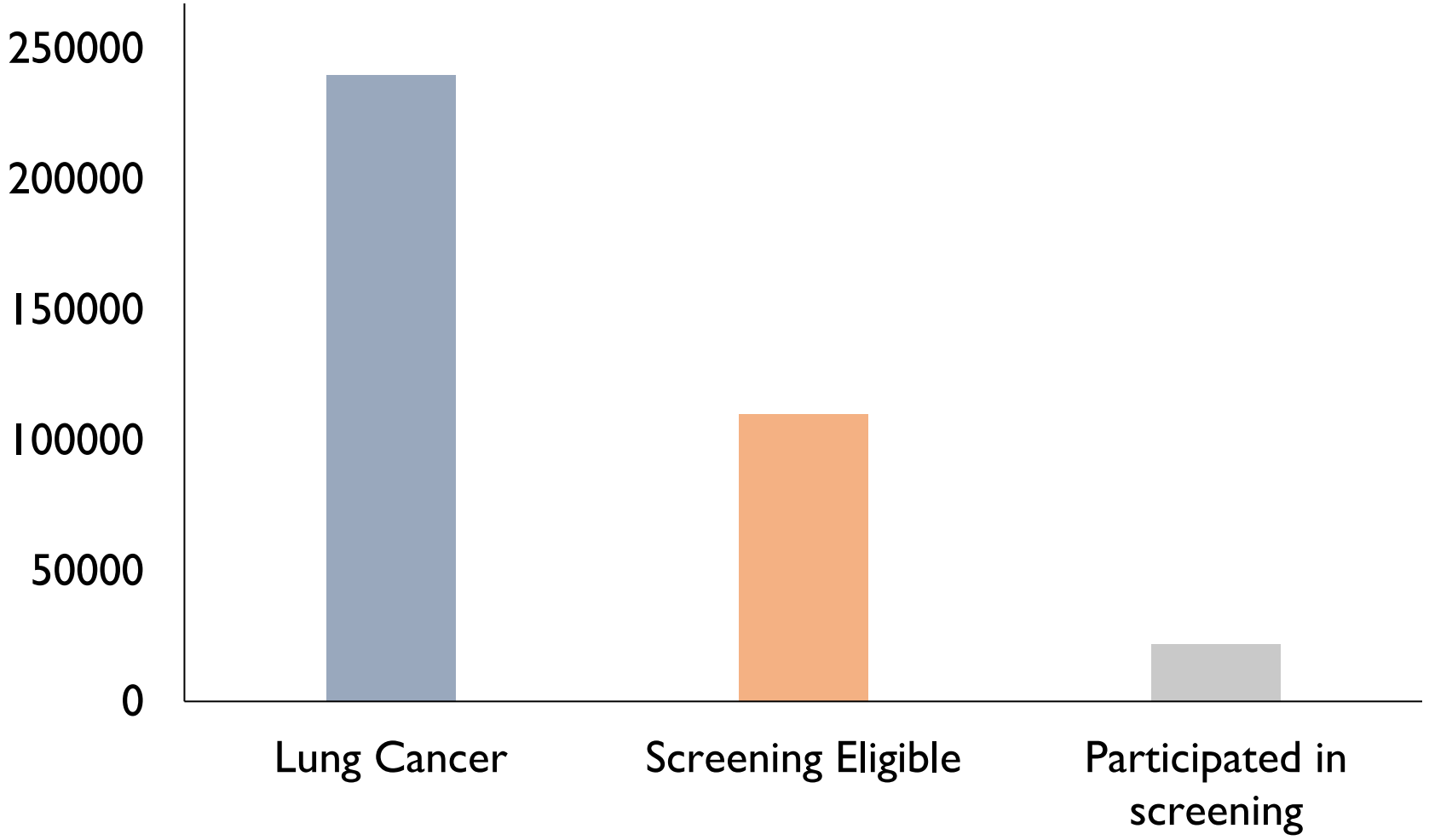
- Removing the 15-year-since-quitting requirement does **not** reduce differences in lung cancer screening eligibility between Black and White individuals

# Investigating Screening in Populations at High Risk to Improve Equity: INSPIRE

R18 HS029430-01
Contact PI and Project Leader
3-year Award: $1,499,336

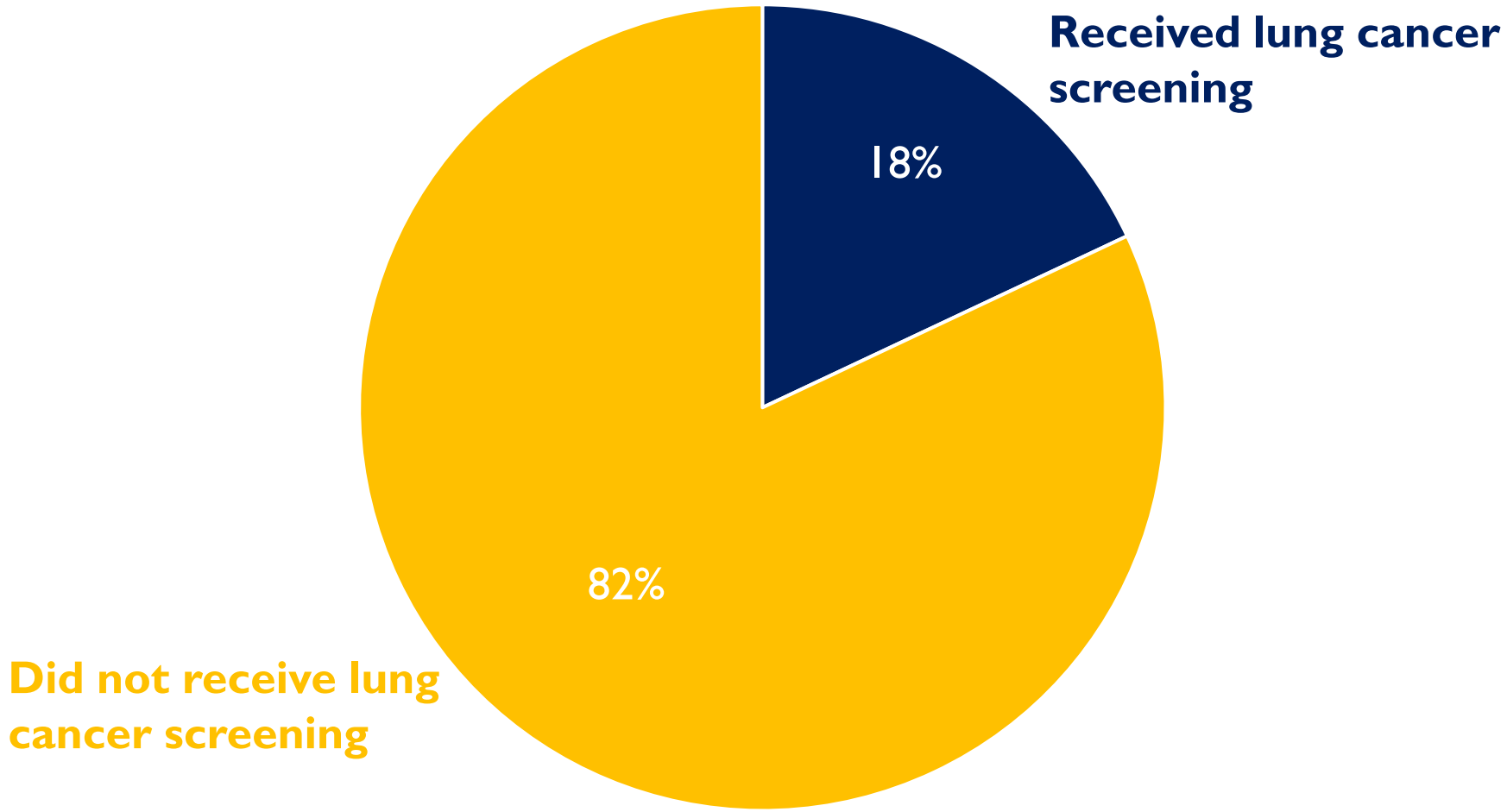
Agency for Healthcare Research and Quality

# U.S. Lung Cancer Estimates 2025

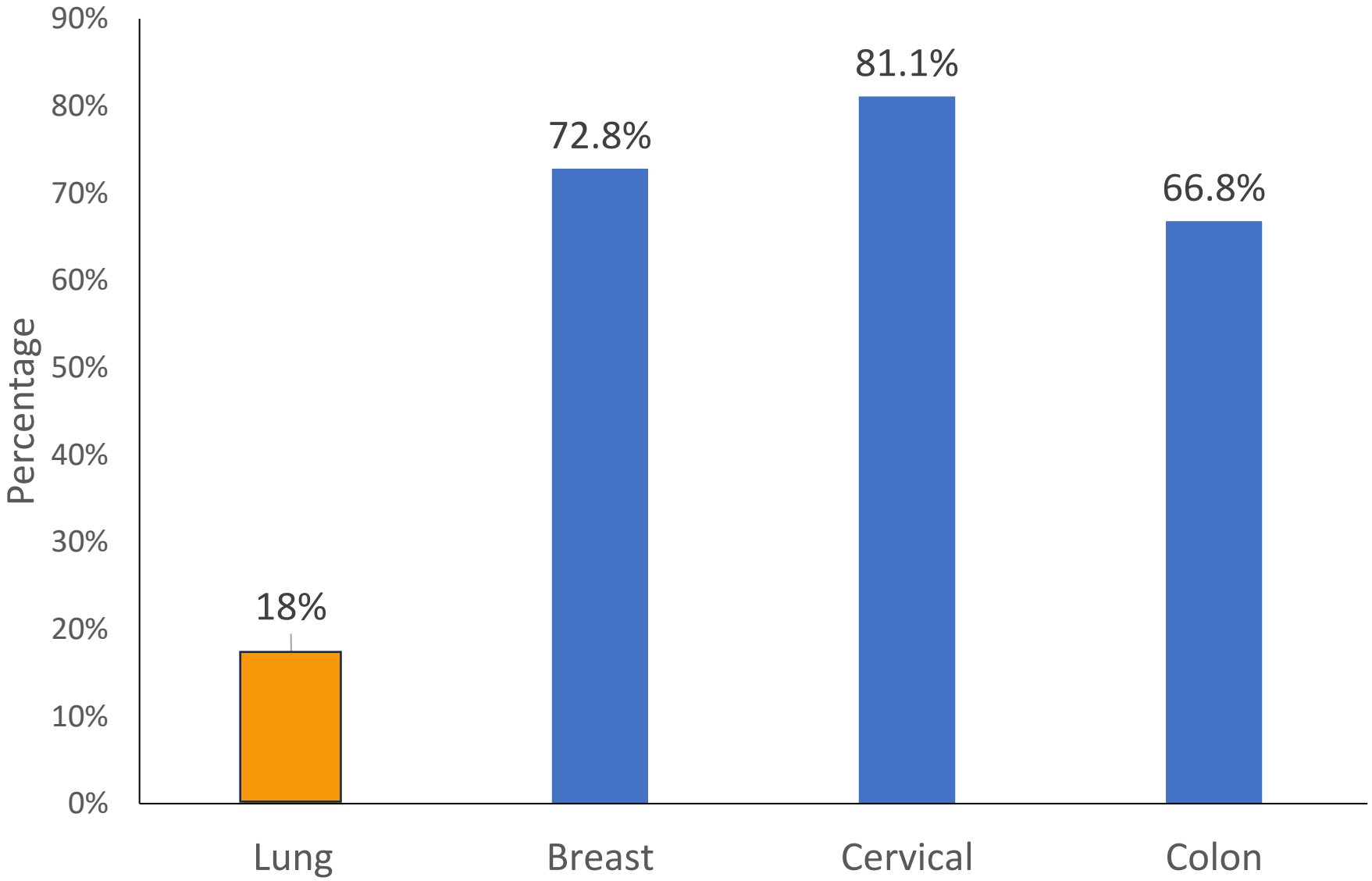


# Myth Busting: Patients eligible for lung cancer screening are “hard to reach”

# 82% of Individuals Eligible for Lung Cancer Screening Are Not Getting Screened



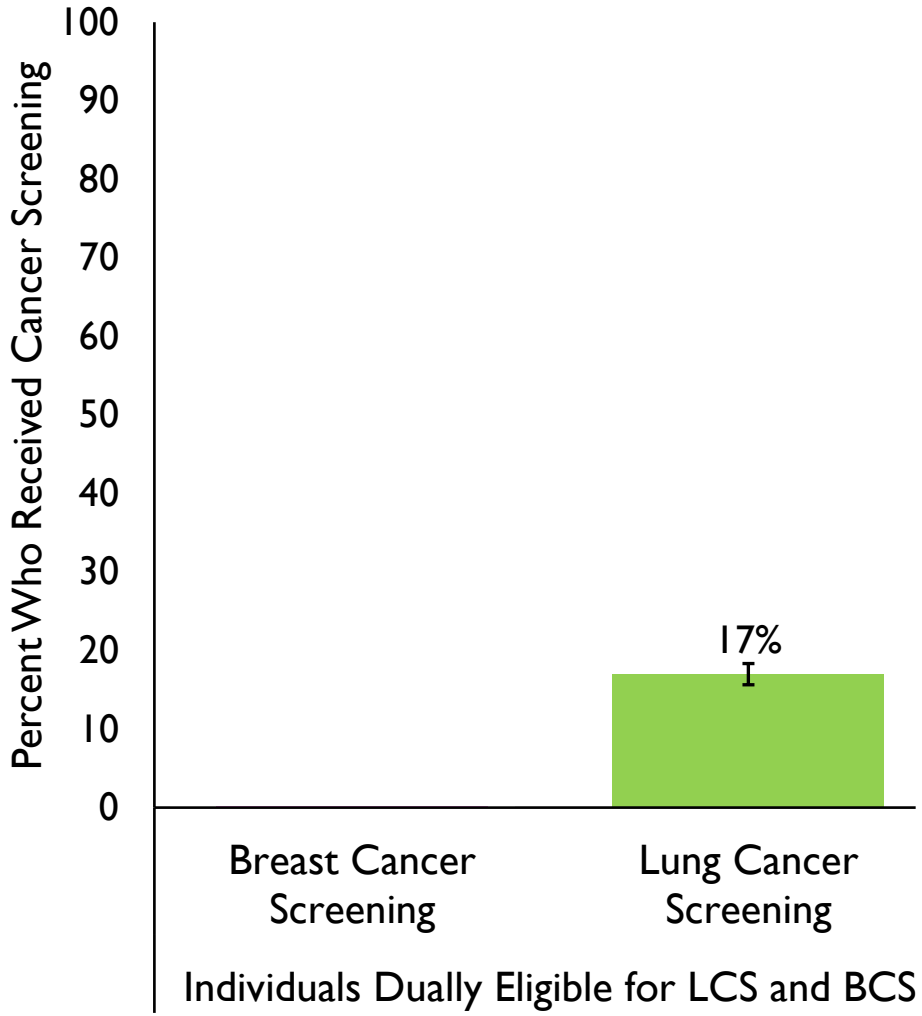
# Percentage of Eligible Individuals Undergoing Screening in the U.S.




https://progressreport.cancer.gov/detection

American Lung Association | American Lung Association

# Hard to Reach or Hardly Reached? Use of Preventive Healthcare Among Adults Eligible for Lung Cancer Screening




Potter et al, *JAMA*, 2025

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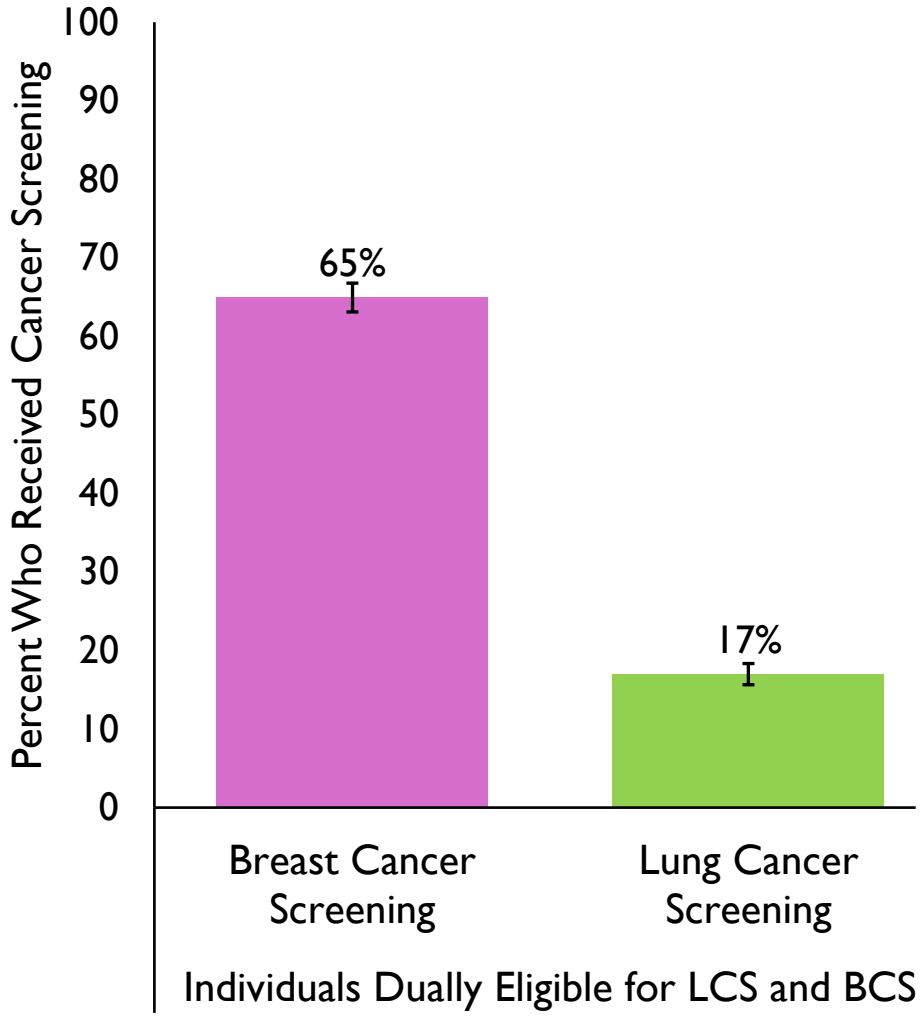


Potter et al, *JAMA*, 2025

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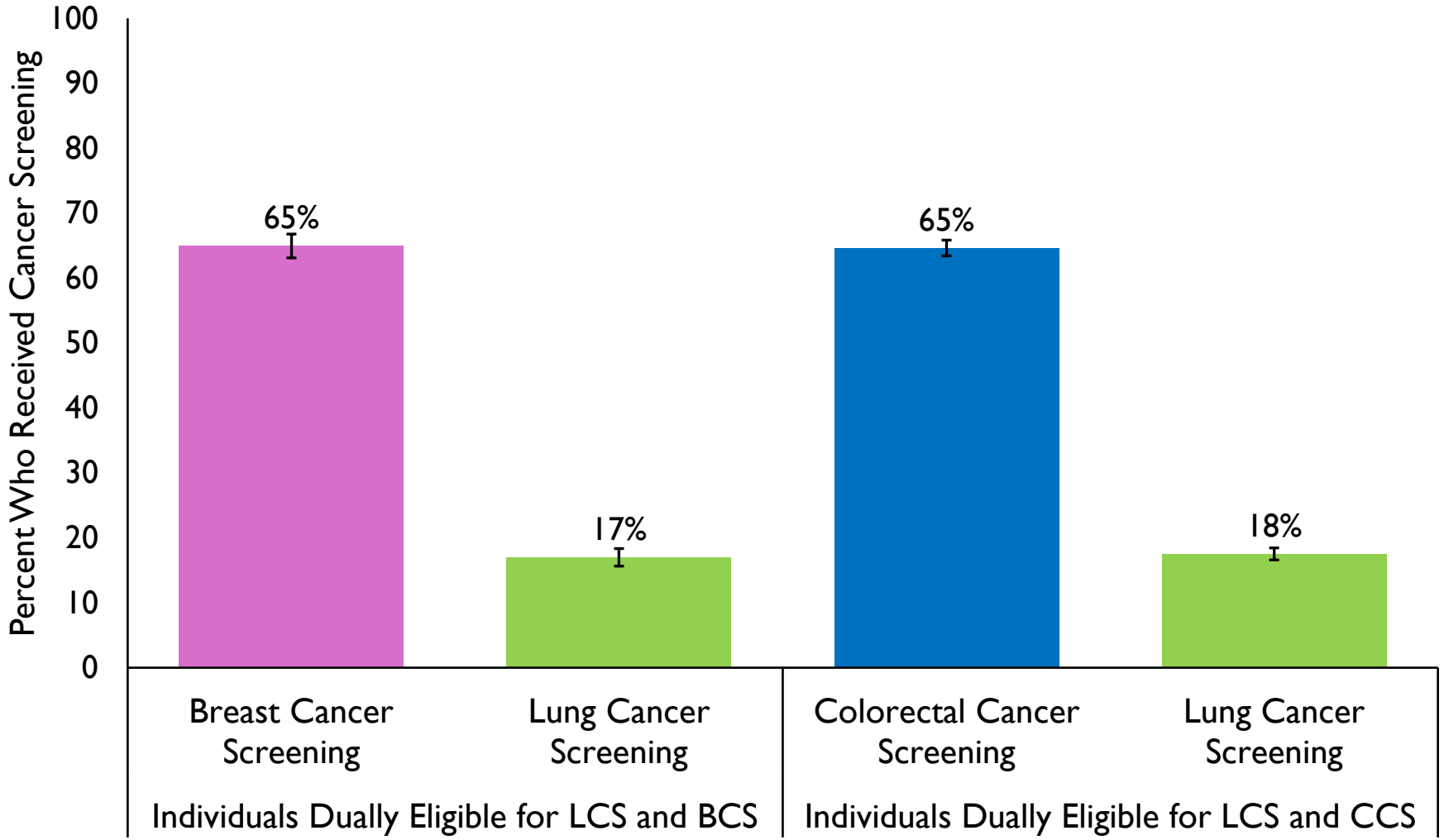



Potter et al, *JAMA*, 2025


# Mission

ALCSI

1. To raise awareness of lung cancer and lung cancer screening.
2. To increase access to lung cancer screening among high-risk individuals.

# Engaging Students to Increase Awareness

## 103 ALCSI Chapters across the U.S.

# Teaching the Community: 1000+ Community Events

Health Fairs


Campus Events

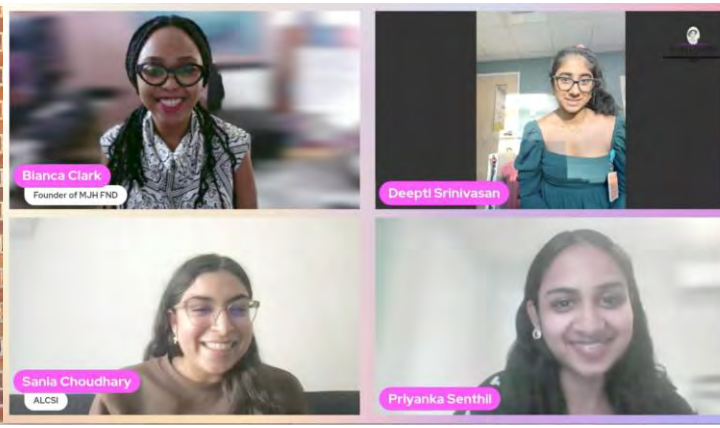
Canvassing at Bus Stops and Subways

Tabling at Community Events


Food Pantries

Canvassing at Parks

White Ribbon Builds



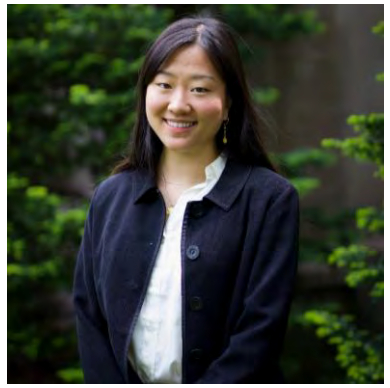

Virtual Presentations

# Plus One Campaign

- Student-driven grassroots initiative to teach friends, family members, and local community members how to identify if they or someone they know is eligible for lung cancer screening and, if they qualify, how to get screened

**Riley Hurr**

**Priyanka Senthil**



**Donna Tong**

**Zachary Davis**

LUNG CANCER RESEARCH FOUNDATION®

Living. Breathing. Science.™

**Launched at 50 chapters!**

**350+ Plus One events**

**Taught over 25,000 individuals about lung cancer screening**


# Overcoming Resistance

## Don L. Gibbons, MD, PhD

**MD Anderson Cancer Center**

Isaiah J. Fidler Professorship in Cancer Research,
Professor & Deputy Chair

Director, Translational Genetic Models Laboratory

Co-Leader, Lung Cancer Moon Shot Program

Dept. Thoracic/Head and Neck Medical Oncology,
Dept. Molecular & Cellular Oncology,

# KRAS Inhibitors and Resistance in NSCLC

## Lung Cancer Research Foundation Scientific Symposium

**Don L. Gibbons, MD, PhD**
Professor & Deputy Chair
Isaiah J. Fidler Professorship in Cancer Research
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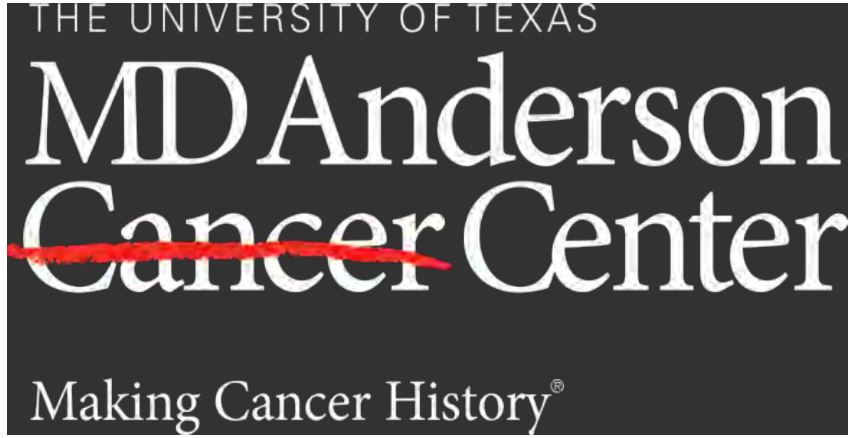
Co-Leader, Lung Cancer Moon Shot Program
Dept. of Thoracic/Head and Neck Medical Oncology
Dept. of Molecular and Cellular Oncology

November 5, 2025



# Disclosures

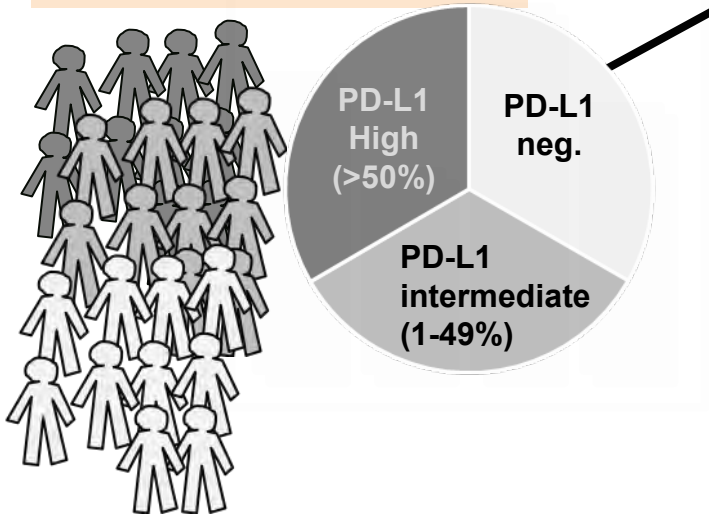
- Research Funding: NGM Biopharmaceuticals, AstraZeneca, Boehringer Ingelheim, BMS/Mirati, Eli Lilly

- Consulting/Advisory Board: Sanofi, Eli Lilly, Menarini Richerche, 4D Pharma, Onconova, Aktis Oncology

- This won't be a comprehensive review or overview of the research area & my apologies to investigators whose work is left out.

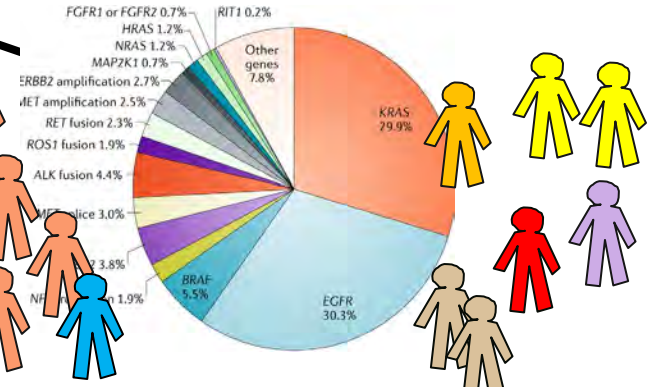
# The treatment landscape of NSCLC in 2025 continues to evolve rapidly

**Driver negative: the immune pie (60%)**




**NSCLC**

**Driver positive: the genomic pie (40%)**




Classical EGFR (10%)

EGFR T790M

EGFR Exon20 (2%)

EGFR atypicals (3%)

ALK fusion (4%)

KRAS G12C 12-14%

G12V 6-7.5%

G12D ~4%

Other

HER2 mutant (3%)

BRAF mutant (3%)

ROS1 mutant (1%)

MET exon14 (3%)

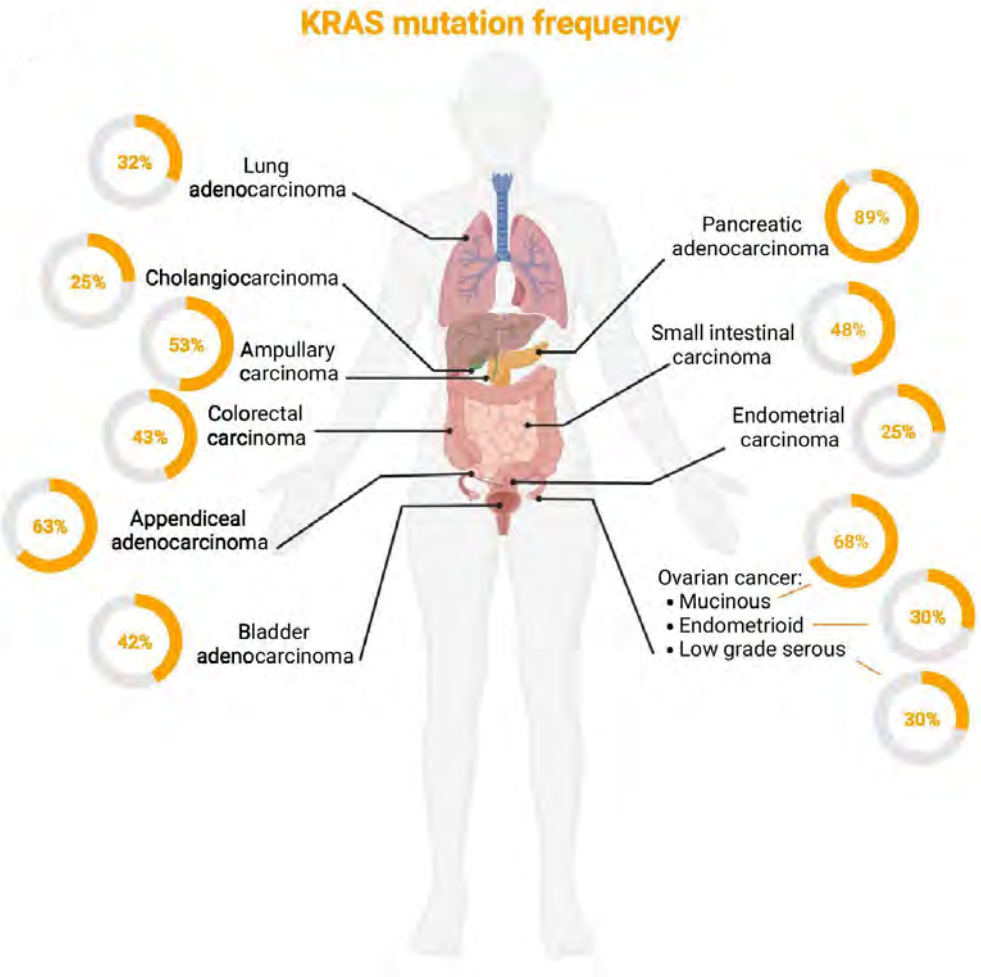
RET fusion (1%)

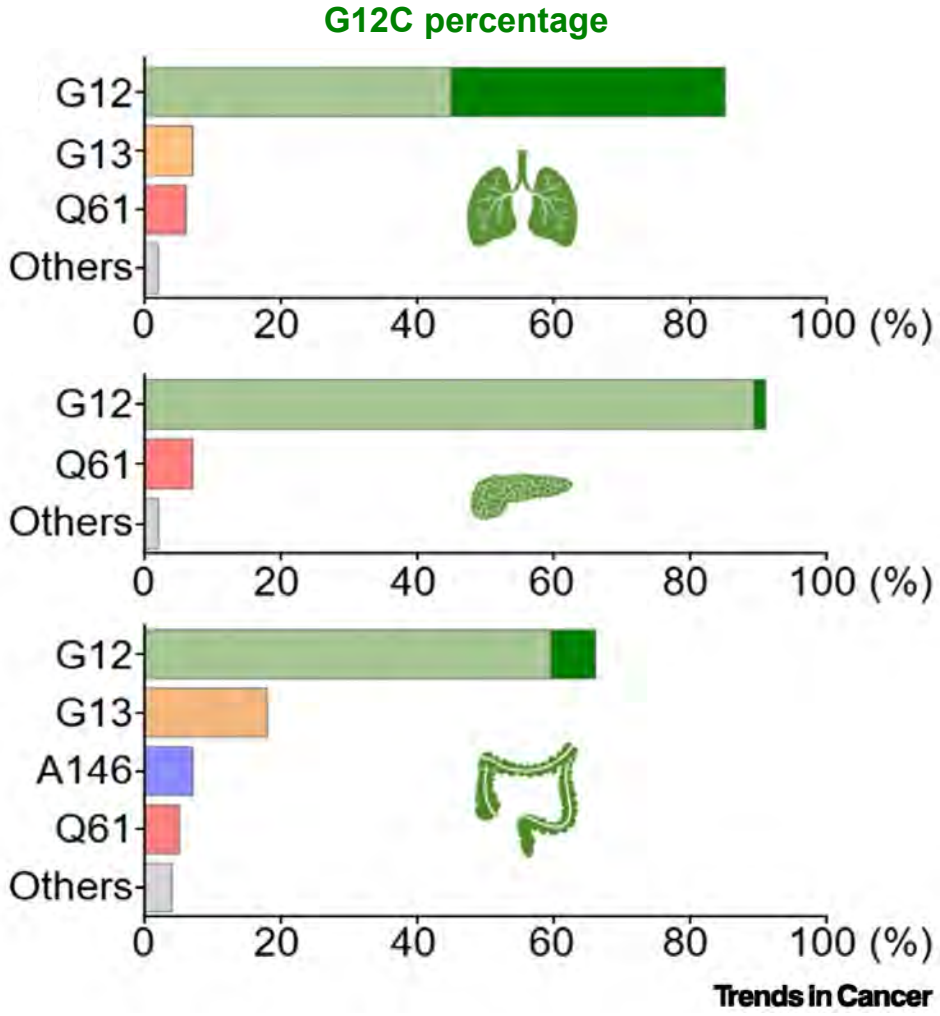
NTRK mutant (1%)

<u>On the horizon:</u>

-ADCs (TROP2, CEACAM5, etc)
-Radio-ligands
-Tailoring based on co-mutations
-TCRs, CAR-Ts, TILs
-Vaccines

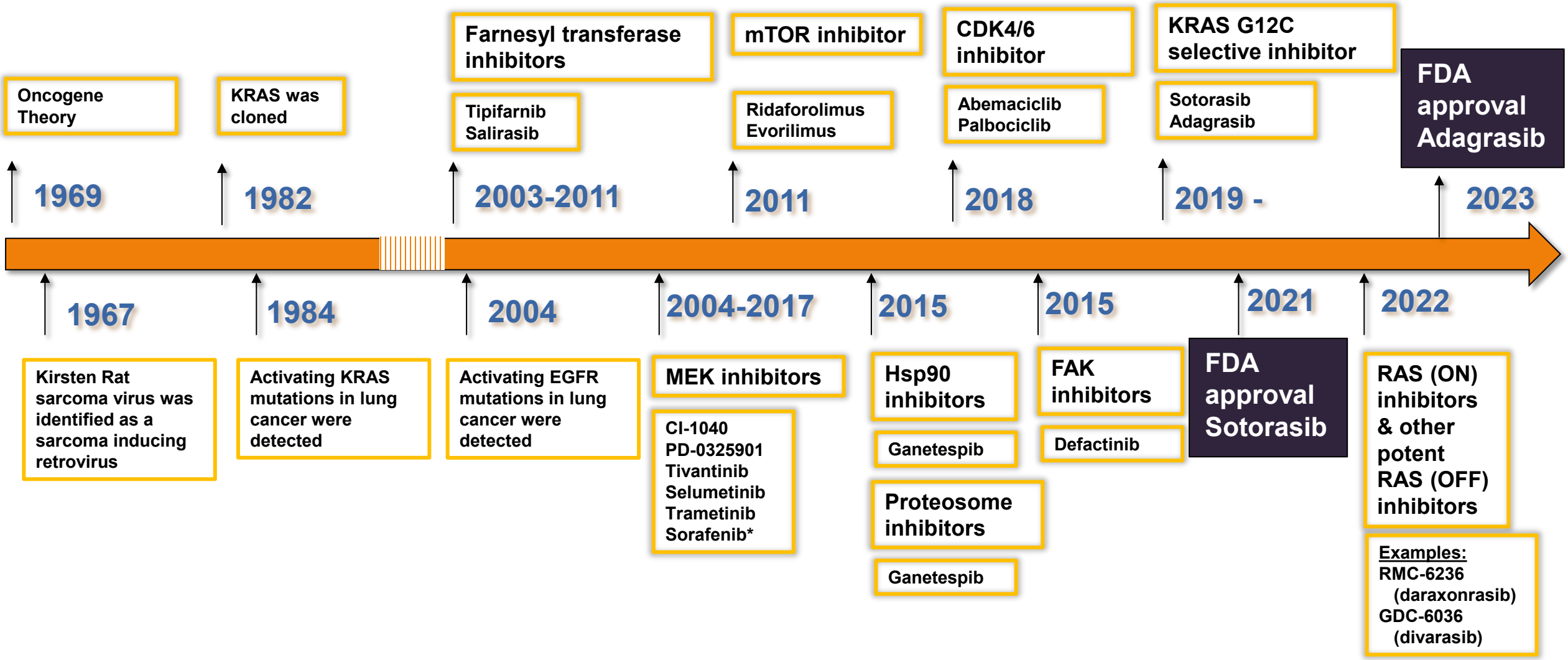
# KRAS mutations found across multiple cancers including NSCLC




Zeissig et al., *Trends in Cancer*, 2023
Isermann et al., *Trends in Cancer*, 2024

# Historical Overview of KRAS Targeted Therapies



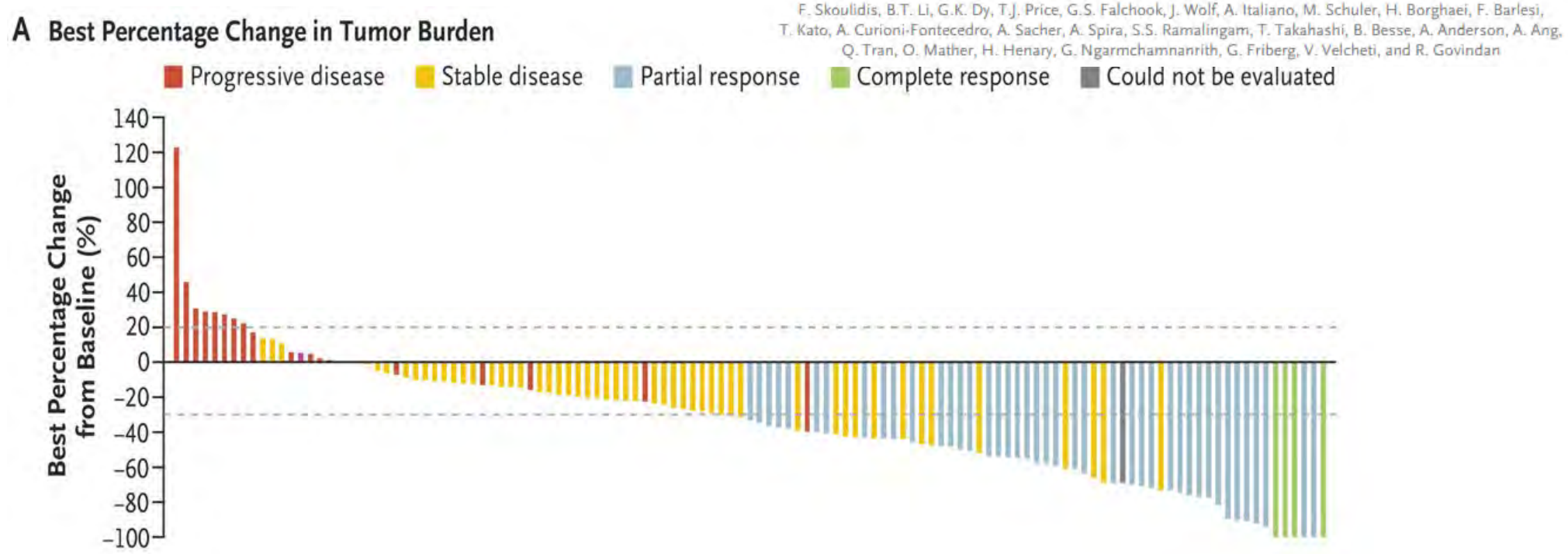
# Phase 2 CodeBreaK 100: Sotorasib therapy produces clinical benefit in KRAS G12C mutant NSCLC

**ORR 37.1%**
**mPFS 6.8 months**; mDOR 11.1m
mOS 12.5m

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JUNE 24, 2021 VOL. 384 NO. 25

## Sotorasib for Lung Cancers with *KRAS* p.G12C Mutation

F. Skoulidis, B.T. Li, G.K. Dy, T.J. Price, G.S. Falchook, J. Wolf, A. Italiano, M. Schuler, H. Borghaei, F. Barlesi, T. Kato, A. Curioni-Fontecedro, A. Sacher, A. Spira, S.S. Ramalingam, T. Takahashi, B. Besse, A. Anderson, A. Ang, Q. Tran, O. Mather, H. Henary, G. Ngarmchamnanrith, G. Friberg, V. Velcheti, and R. Govindan



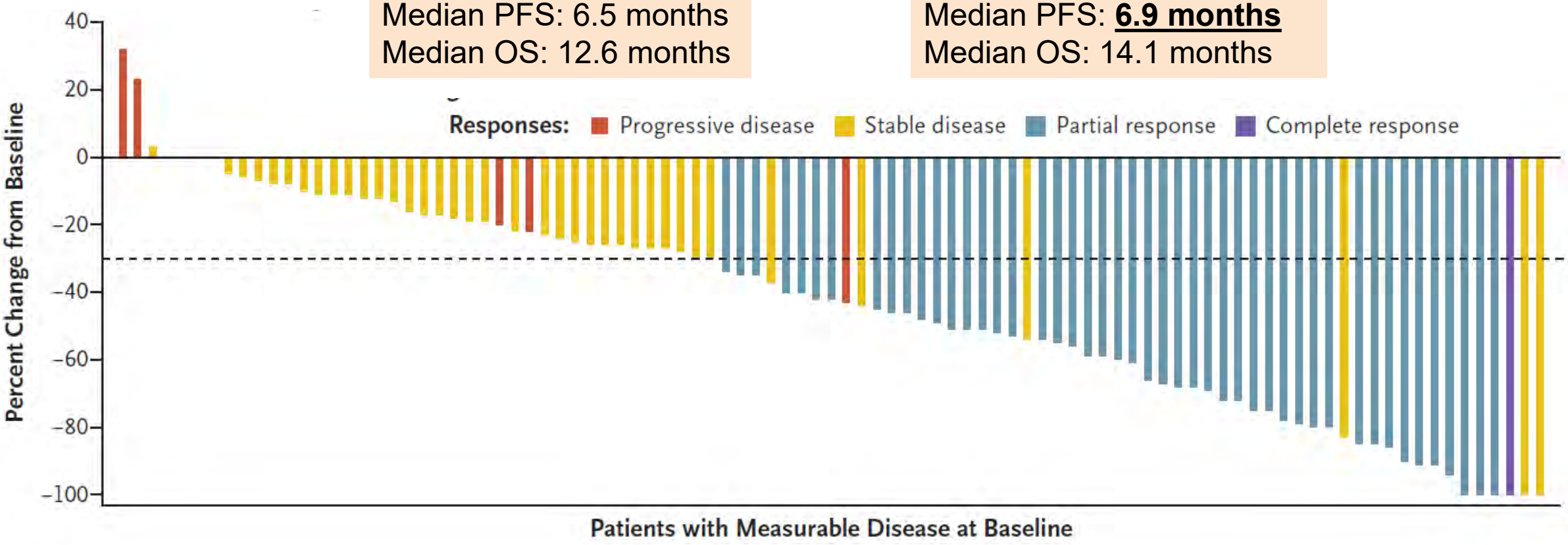

May 28, 2021: FDA granted accelerated approval for sotorasib for advanced NSCLC patients with KRAS G12C mutation who received one prior systemic therapy.

# Phase 2 KRYSTAL-1 trial: Adagrasib in previously-treated KRAS$^{G12C}$ mutant NSCLC

**Confirmed ORR: 42.9%**
Median PFS: 6.5 months
Median OS: 12.6 months

IASLC 2023 update

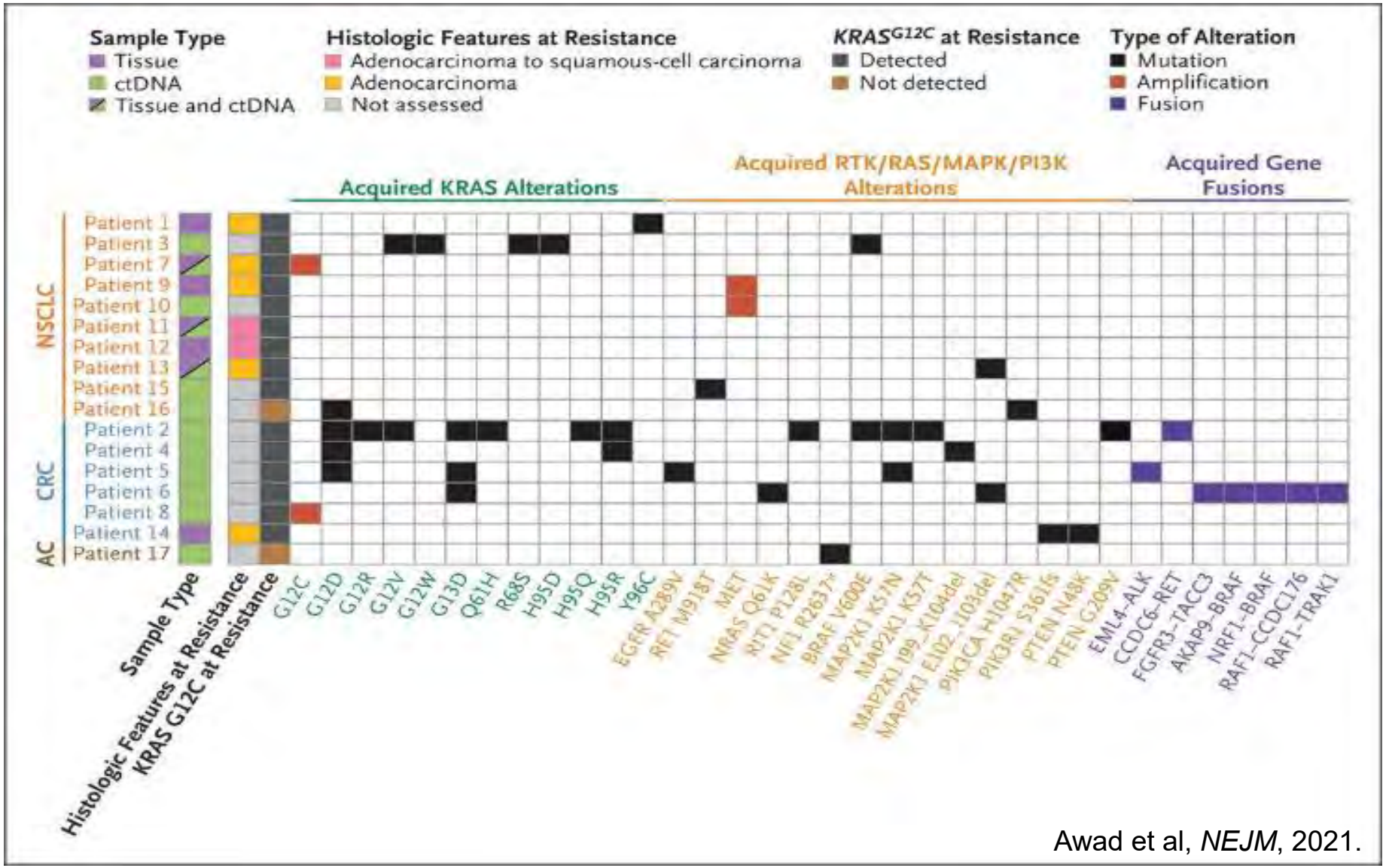
**Confirmed ORR: 43%**
Median PFS: **6.9 months**
Median OS: 14.1 months




December 12, 2022: FDA granted accelerated approval for adagrasib for advanced NSCLC patients with KRAS G12C mutation who received one prior systemic therapy.

Jänne et al., *NEJM*, 2022; Gadgeel et al., WCLC, 2023.

# Putative mechanisms of acquired resistance to adagrasib treatment




Awad et al, *NEJM*, 2021.

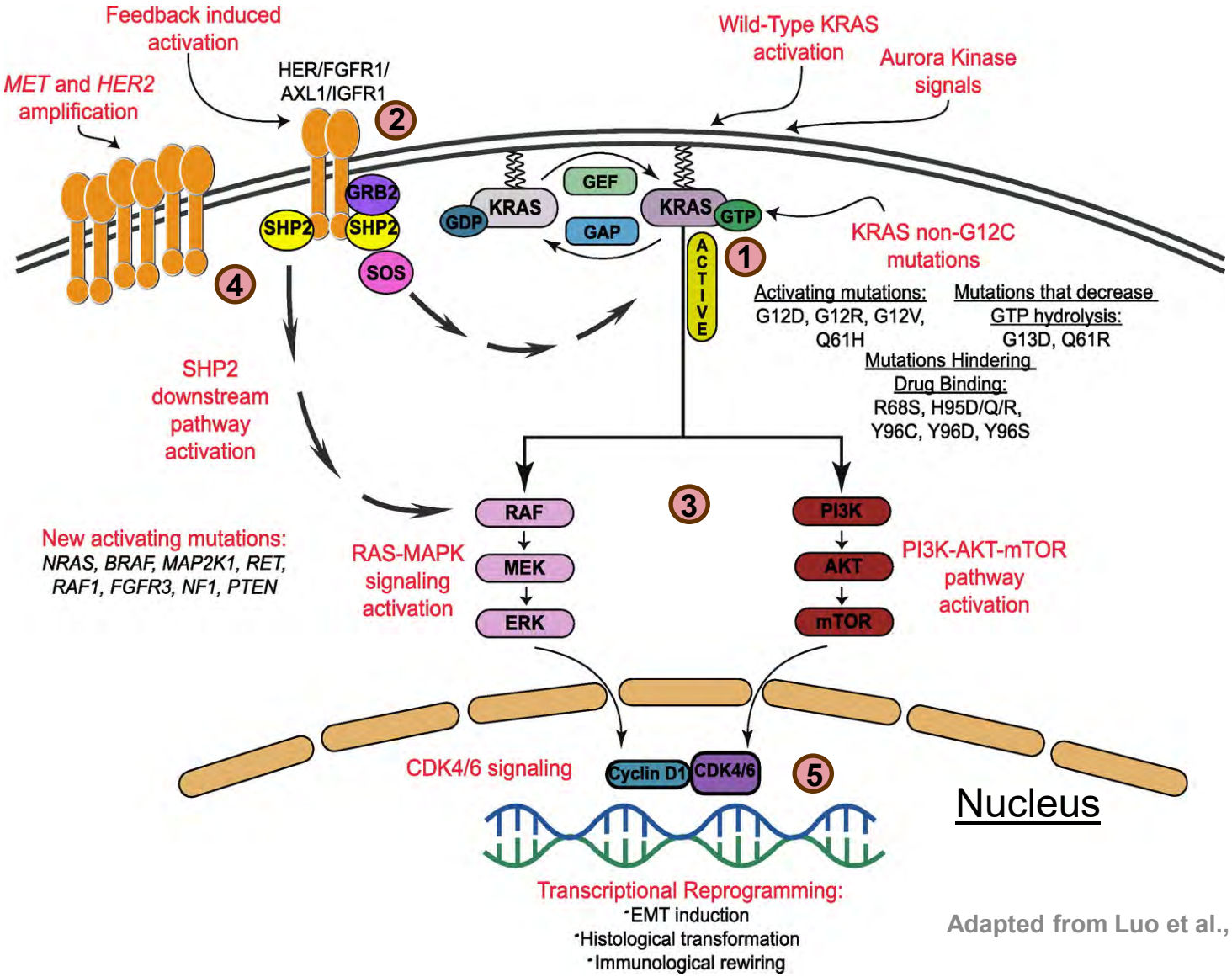
# Mechanisms of resistance to KRAS inhibition

## Population Level

Drug

Drug

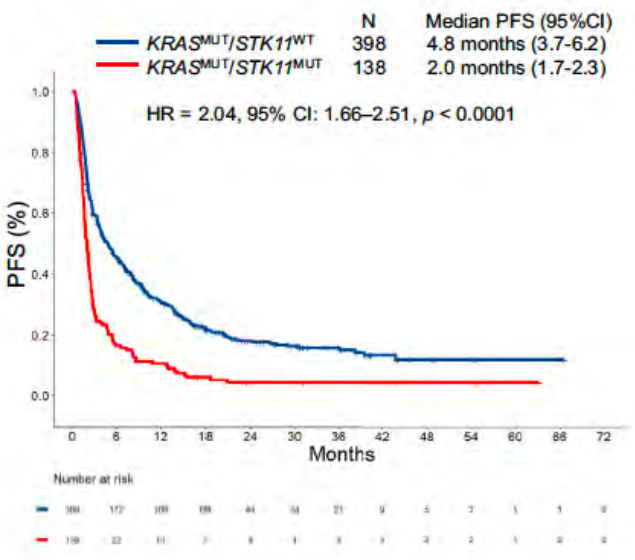
## Cellular Level



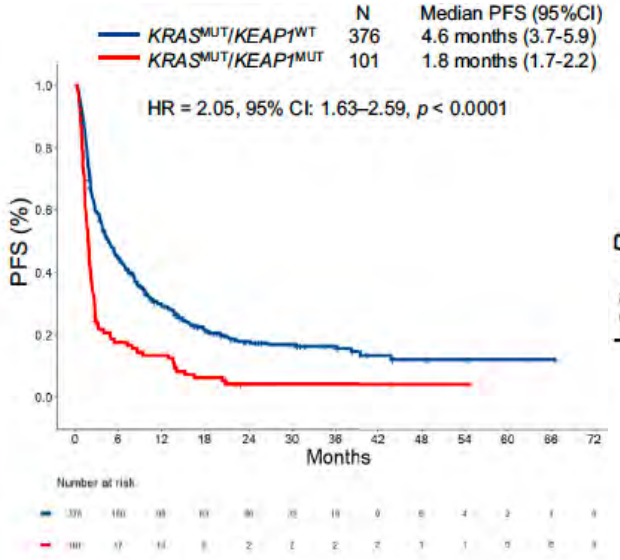

Adapted from Luo et al., *ASCO Publications*, 2022.

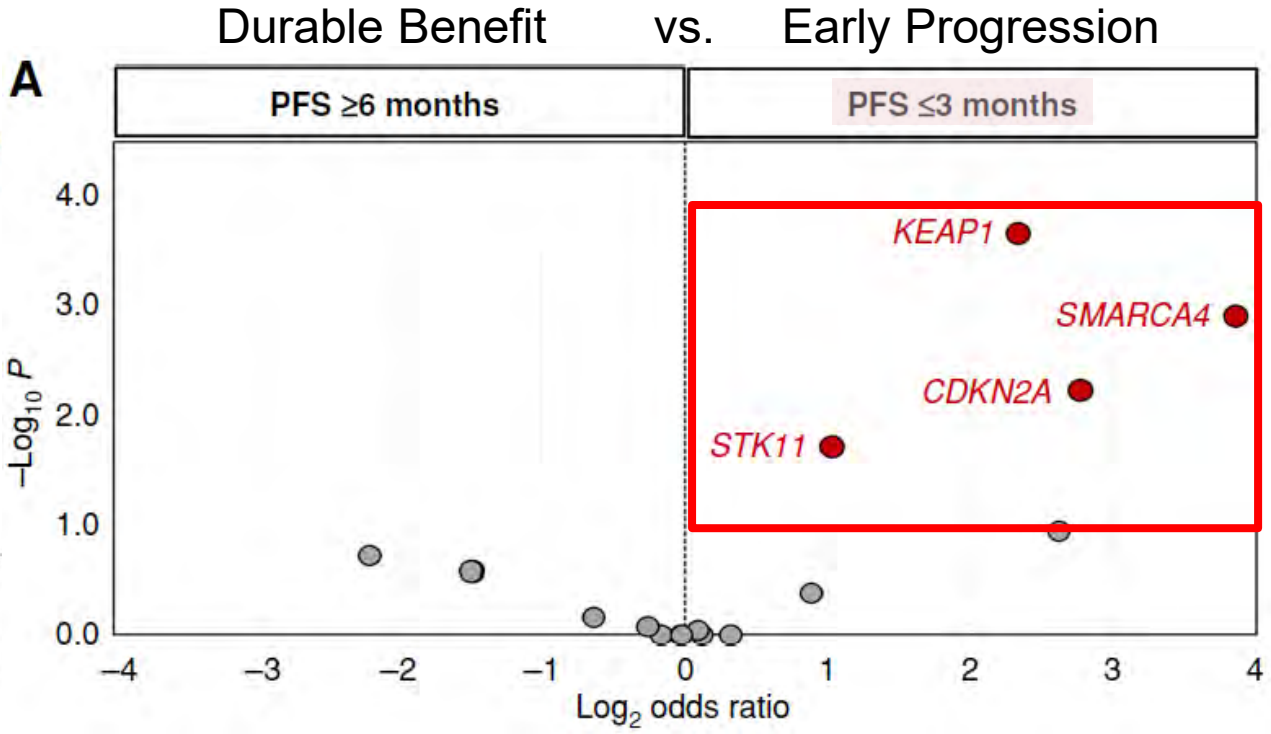
# Impact of KRAS co-mutations on response to KRAS G12C inhibitors

STK11 mutations
PFS HR 2.04




KEAP1 mutations
PFS HR 2.05



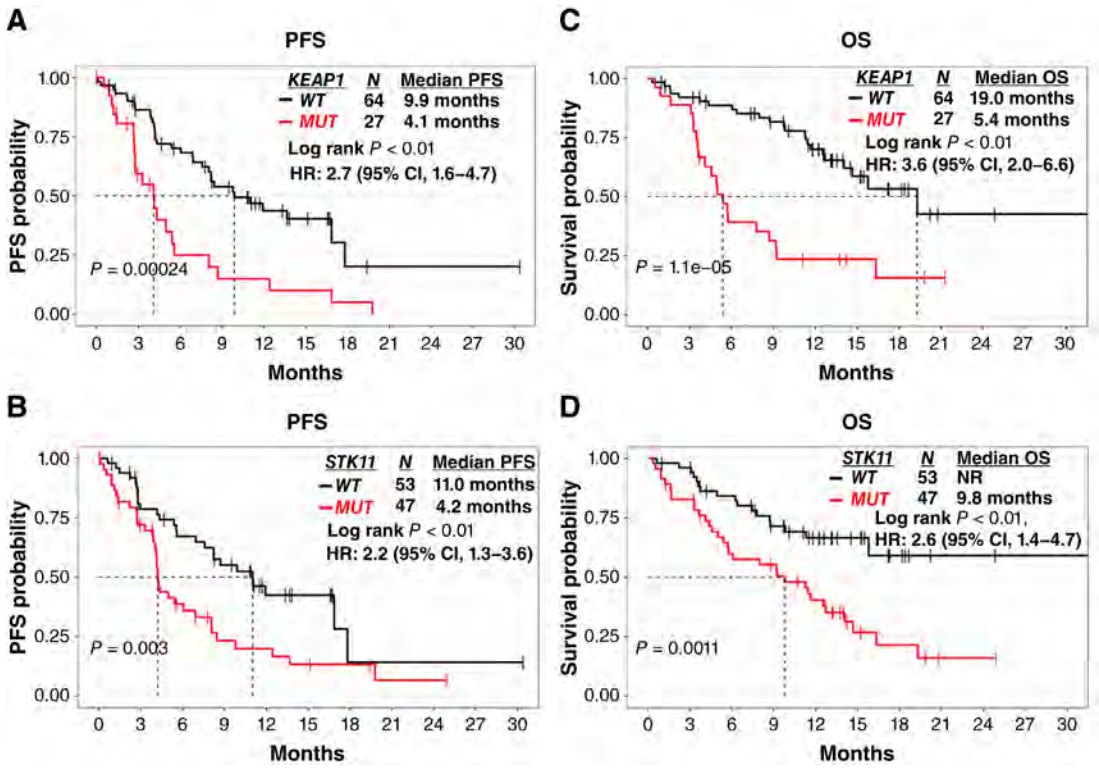




- 21 International centers; 424 patients
- Real World Sotorasib or Adagrasib treatment
- Identifies ~49% of patients with early progression

Since these co-mutations are associated with different drug sensitivities, they may be useful for guiding KRAS G12C inhibitor combinations

Negrao et al, *Cancer Discovery,* 2023.

# KRYSTAL-1 trial patients with co-mutated STK11 or KEAP1 have worse outcomes & higher squamous component



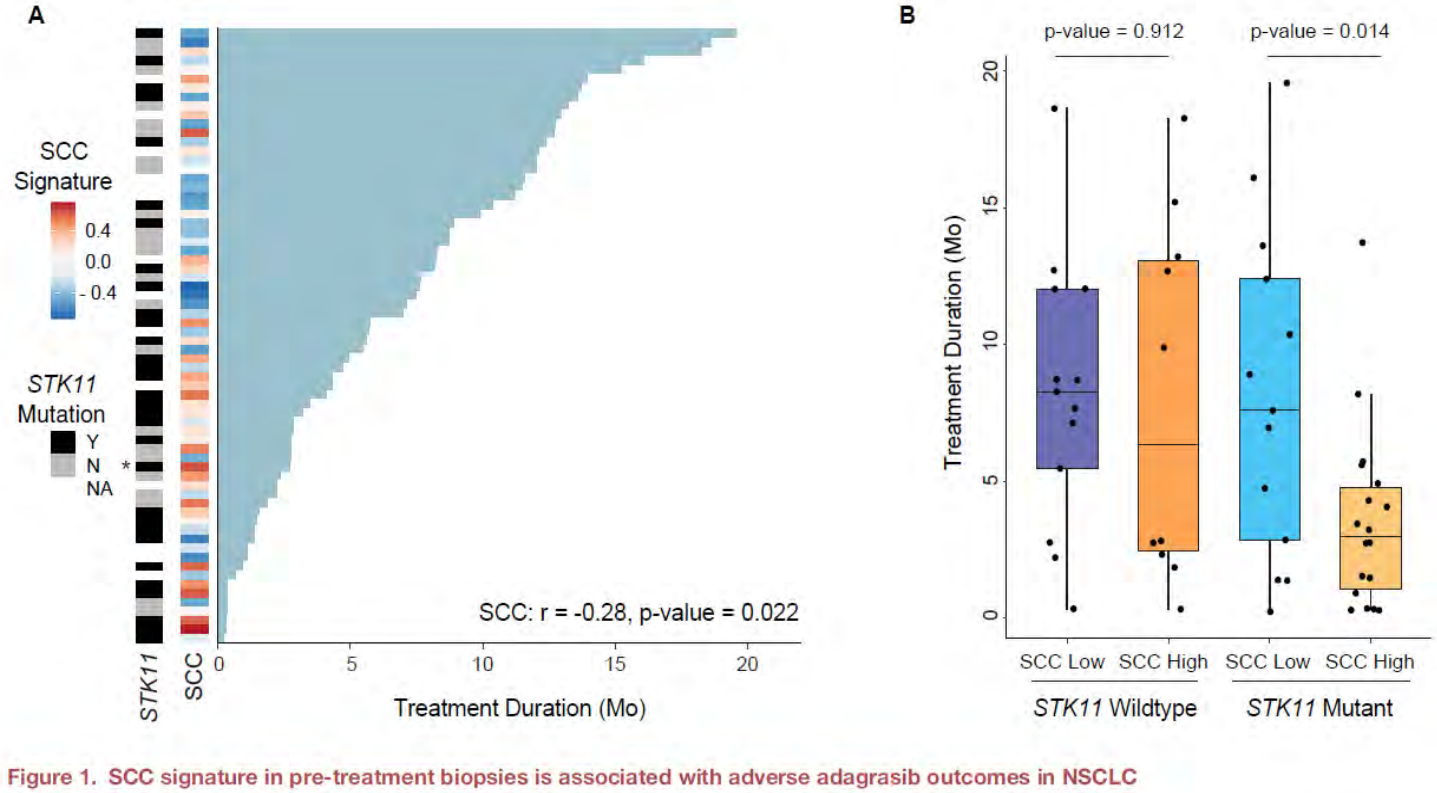
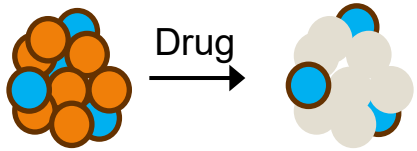




Figure 1. SCC signature in pre-treatment biopsies is associated with adverse adagrasib outcomes in NSCLC

Negrao et al, *Clin. Cancer Research*, 2025.

Tong et al, *Cancer Cell*, 2024.



# YAP/TEAD pathway has been identified as a resistance mechanism to KRAS-G12Ci treatment in NSCLC

TRANSLATIONAL CANCER BIOLOGY | DECEMBER 15 2023

**Genome-Wide CRISPR Screens Identify Multiple Synthetic Lethal Targets That Enhance KRAS$^{G12C}$ Inhibitor Efficacy** FREE

Suman Mukhopadhyay; Hsin-Yi Huang; Ziyan Lin; Michela Ranieri; Shuai Li; Soumyadip Sahu; Yingzhuo Liu; Yi Ban; Kayla Guidry; Hai Hu; Alfonso Lopez; Fiona Sherman; Yi Jer Tan; Yeuan Ting Lee; Amanda P. Armstrong; Igor Dolgalev; Priyanka Sahu; Tinghu Zhang; Wenchao Lu; Nathanael S. Gray; James G. Christensen; Tracy T. Tang; Vamsidhar Velcheti; Alireza Khodadadi-Jamayran; Kwok-Kin Wong; Benjamin G. Neel

TRANSLATIONAL CANCER BIOLOGY | DECEMBER 15 2023

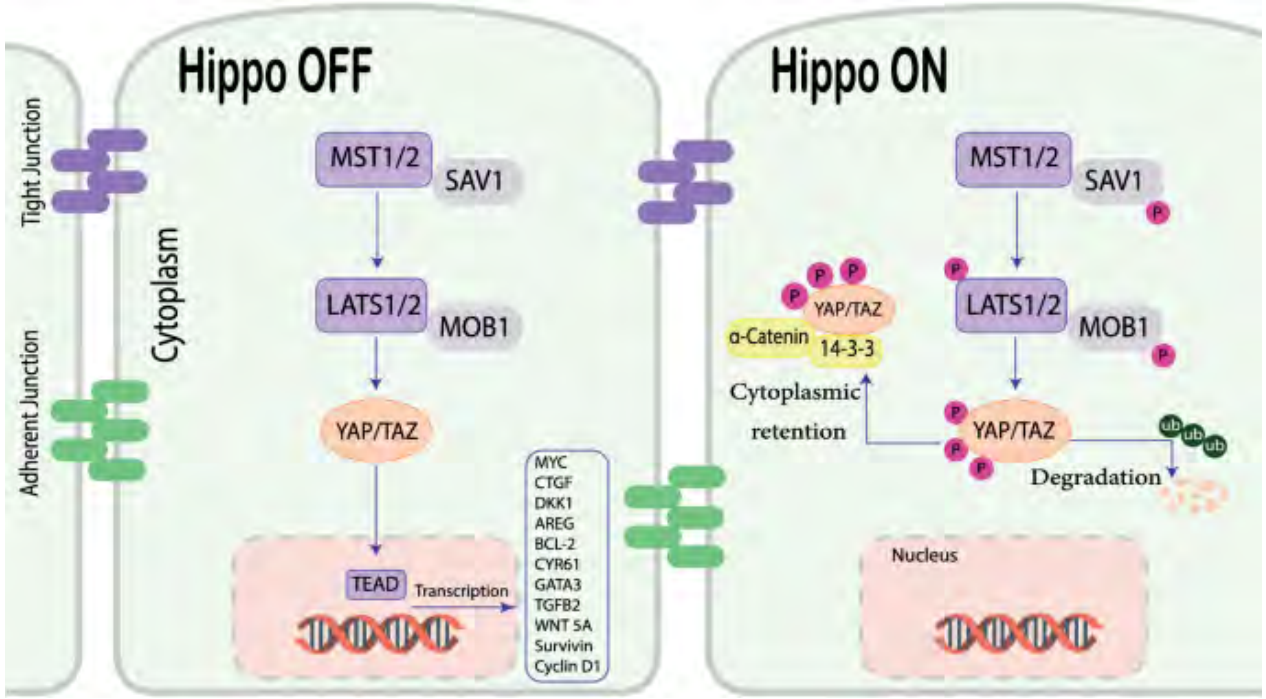
**TEAD Inhibition Overcomes YAP1/TAZ-Driven Primary and Acquired Resistance to KRAS$^{G12C}$ Inhibitors** FREE

A. Cole Edwards; Clint A. Stalnecker; Alexis Jean Morales; Khalilah E. Taylor; Jennifer E. Klomp; Jeffrey A. Klomp; Andrew M. Waters; Niranjan Sudhakar; Jill Hallin; Tracy T. Tang; Peter Olson; Leonard Post; James G. Christensen; Adrienne D. Cox; Channing J. Der

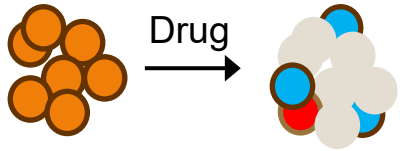
**YAP/TAZ mediates resistance to KRAS inhibitors through inhibiting proapoptosis and activating the SLC7A5/mTOR axis**

Wang Yang,[1,2,3] Ming Zhang,[2,3] Tian-Xing Zhang,[4] Jia-Hui Liu,[2,3] Man-Wei Hao,[4] Xu Yan,[5] Haicheng Gao,[4] Qun-Ying Lei,[6,7,8] Jiuwei Cui,[1] and Xin Zhou[1,2,3]

Published December 20, 2024 - More info

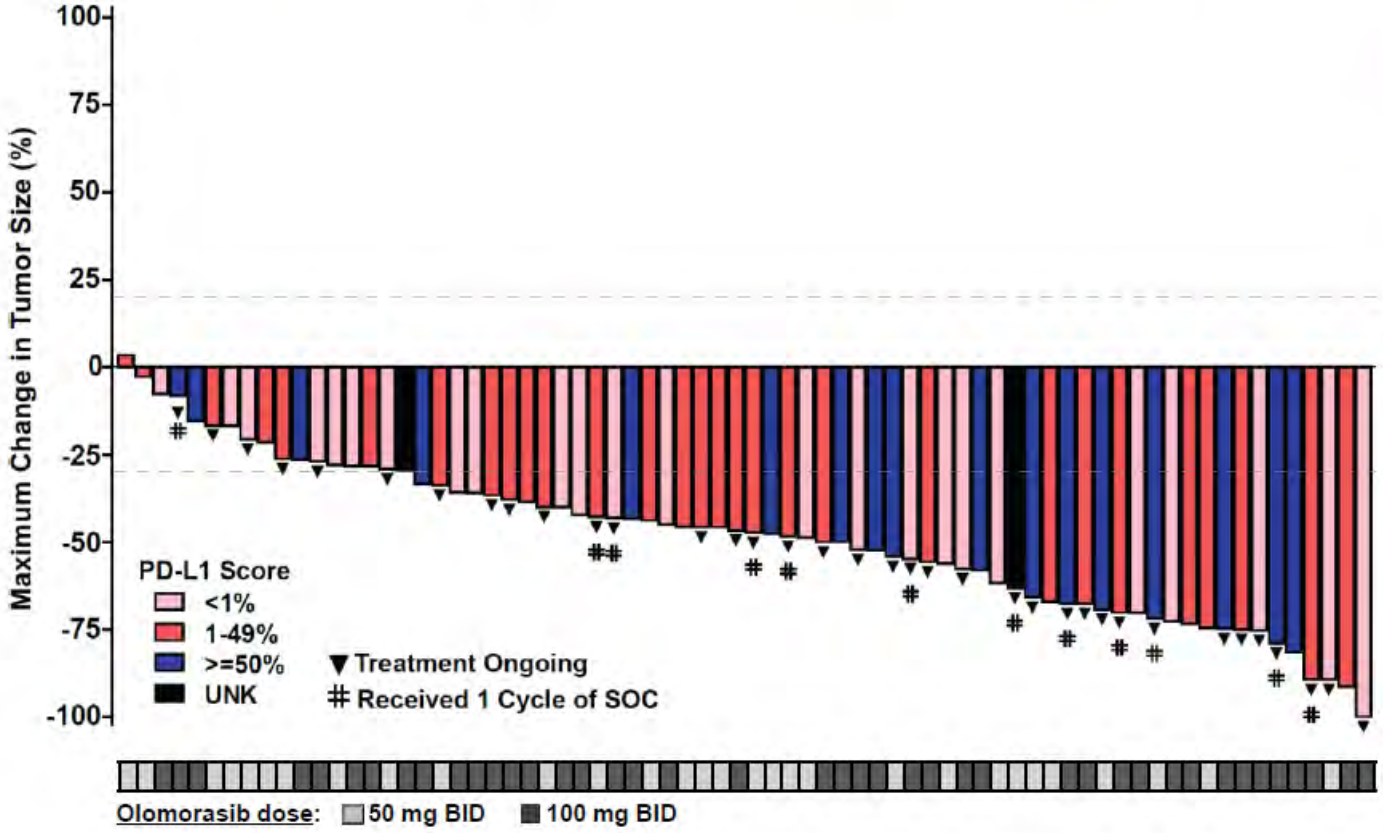



Noorbakhsh et al., *Cancer Cell International*, 2021



# Multiple G12C inhibitors in combination testing for frontline treatment with good efficacy and safety

## Efficacy of 1L Olomorasib + Pembrolizumab + Pemetrexed + Platinum



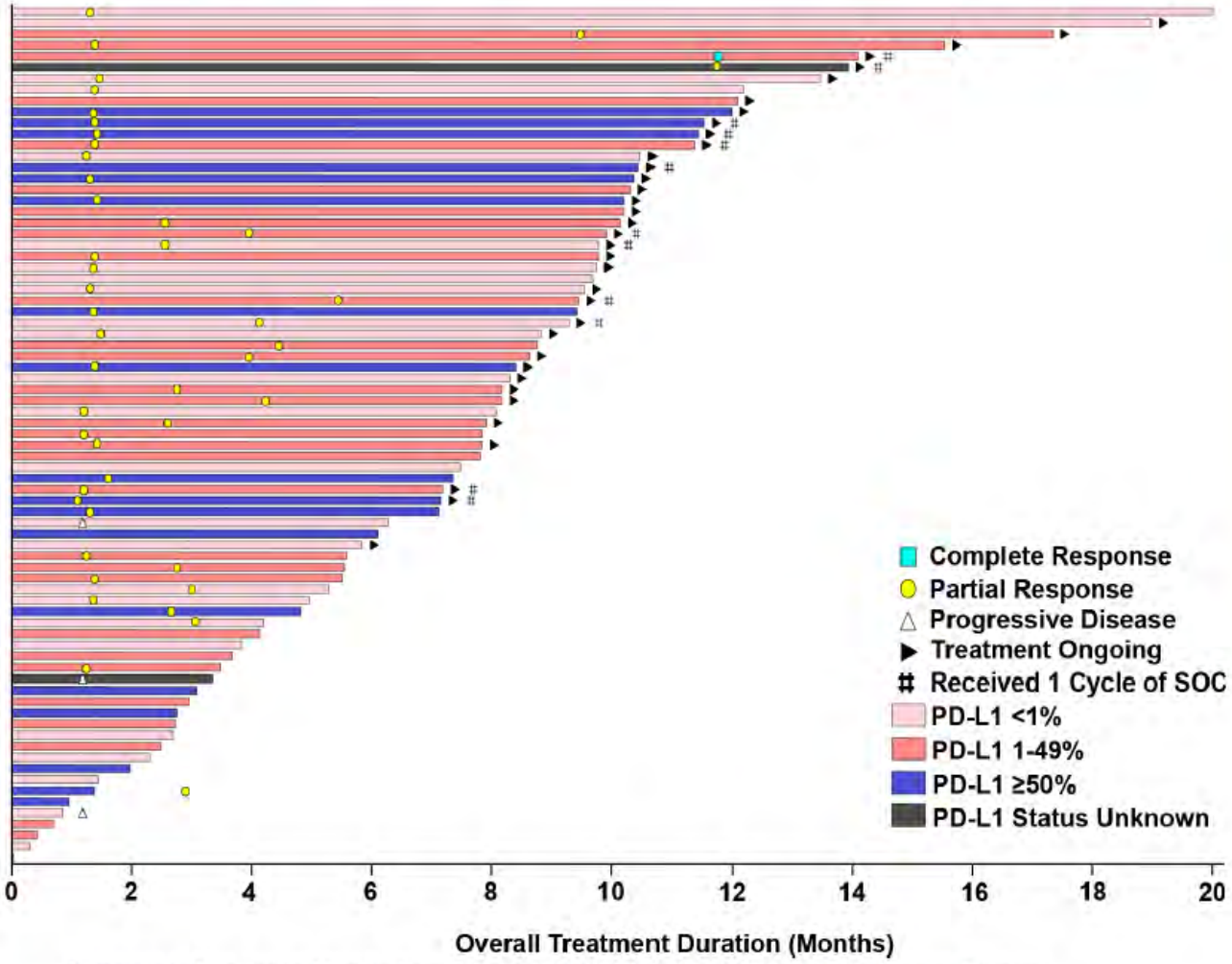

| Olomorasib + Pembrolizumab + Pemetrexed + Platinum | | | | |
|---|---|---|---|---|
| Efficacy Evaluable Patients[a] | All pts PD-L1 0-100% N = 77[b] | Pts with PD-L1 <1% N = 26 | Pts with PD-L1 1-49% N = 31 | Pts with PD-L1 ≥50% N = 18 |
| ORR, (%) (95% CI) | 61 (49.2, 72.0) | 50 (29.9, 70.1) | 68 (48.6, 83.3) | 67 (41.0, 86.7) |
| BOR, n (%) | | | | |
| CR | 1 (1) | - | 1 (3) | - |
| PR[b] | 46 (60) | 13 (50) | 20 (65) | 12 (67) |
| SD | 22 (29) | 9 (35) | 8 (26) | 5 (28) |
| PD | 3 (4) | 2 (8) | - | - |
| NE | 5 (7) | 2 (8) | 2 (7) | 1 (6) |
| DCR, (%) (95% CI) | 90 (80.6, 95.4) | 85 (65.1, 95.6) | 94 (78.6, 99.2) | 94 72.7, 99.9) |

Negrao et al, WCLC, 2025.

Combined data from LOXO-RAS-20001 & SUNRAY-01 Trials (n=77 patients)

# Multiple G12C inhibitors in combination testing for frontline treatment with good durability of response

## Treatment duration: 1L Olomorasib + Pembrolizumab + Pemetrexed + Platinum



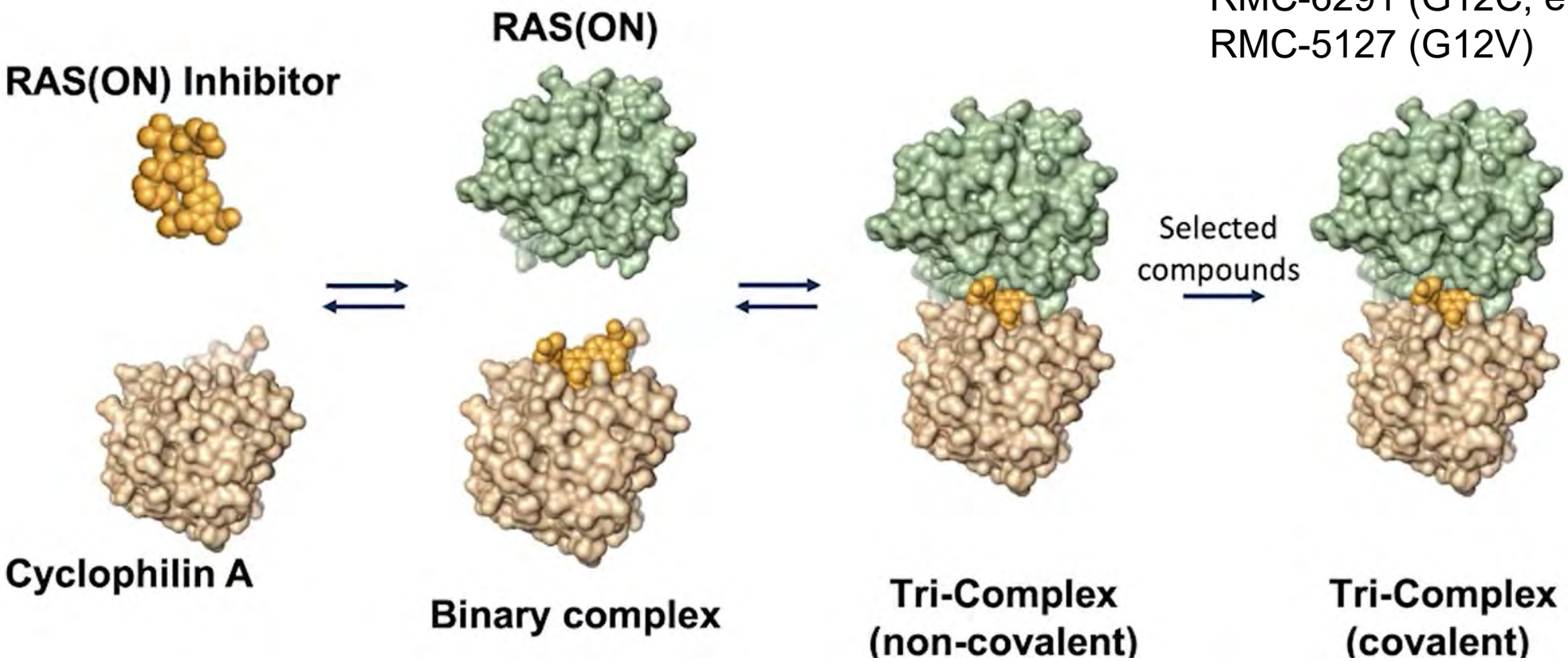

Responses on the swimmer plot are best overall response. Abbreviations: 1L, first-line: TTR, Time to treatment response.

- Median follow-up time: 9.7 months
- 64% of patients with ≥ 6 months of treatment, and ongoing.
- Most patients responded early (mTTR: 1.4 months, 95% CI 1.4, 2.6).
- Responses observed regardless of prior cycle of SOC.
- Durable responses in PD-L1 0-49% and in PD-L1 ≥50%.

Negrao et al, WCLC, 2025.

# A unique class of RAS(ON) inhibitors block signaling through formation of inhibitory tri-complexes

RMC-6236 (multi-RAS; daraxonrasib)
RMC-9805 (G12D; zoldonrasib)
RMC-6291 (G12C; elironrasib)
RMC-5127 (G12V)




Stephen Kelsey, Revolution Medicines, AACR-NCI-EORTC 2021.

# RMC-6236: tri-complex RAS-MULTI(ON) inhibitor in patients with KRAS mutant NSCLC and PDAC

- 40 patients with previously treated RAS G12X mutant NSCLC
- ORR 38% (confirmed)
- Median PFS 9.8 months
- Median OS 17.7 months
- ctDNA clearance from baseline was associated with response or stable disease.
- Grade 3 treatment-related adverse events (TRAEs) were: rash (6.8%), vomiting (2.7%), anemia (2.7%). No Grade 4 or 5 TRAEs.
- Similar efficacy/safety data presented for the PDAC cohort of this Phase I trial
- RASolve 301, global Phase 3, randomized trial in NSCLC (May 2025)

Luo et al, AACR 2025, abstract LB218.

# Clinical development progress of RMC-6236: tri-complex RAS-MULTI(ON) inhibitor in PDAC

Revolution Medicines

## Revolution Medicines' RAS(ON) Multi-Selective Inhibitor Daraxonrasib Granted U.S. FDA Orphan Drug Designation in Pancreatic Cancer

October 27, 2025

REDWOOD CITY, Calif., Oct. 27, 2025 (GLOBE NEWSWIRE) -- Revolution Medicines, Inc. (Nasdaq: RVMD), a late-stage clinical oncology company developing targeted therapies for patients with RAS-addicted cancers, today announced that the U.S. Food and Drug Administration (FDA) has granted Orphan Drug Designation to daraxonrasib, the company's RAS(ON) multi-selective inhibitor, for the treatment of pancreatic cancer.

## Revolution Medicines Awarded Voucher for Daraxonrasib (RMC-6236) Under FDA Commissioner's National Priority Voucher Pilot Program

October 16, 2025

REDWOOD CITY, Calif., Oct. 16, 2025 (GLOBE NEWSWIRE) -- Revolution Medicines, Inc. (Nasdaq: RVMD), a late-stage clinical oncology company developing targeted therapies for patients with RAS-addicted cancers, today announced that the U.S. Food and Drug Administration (FDA) has granted a non-transferrable voucher for daraxonrasib (RMC-6236), the company's RAS(ON) multi-selective inhibitor, under the Commissioner's National Priority Voucher (CNPV) pilot program.

Daraxonrasib is being studied in two global Phase 3 clinical trials, RASolute 302 in patients with previously treated metastatic pancreatic ductal adenocarcinoma and RASolve 301 in patients with previously treated metastatic non-small cell lung cancer.

# KRAS Inhibitors: Take Home Messages

1. KRAS G12C inhibitors available for 2nd-line treatment.
   - Sotorasib, adagrasib have FDA approval. 1st-line testing underway.
   - Divarasib, olomorasib and others show promising activity with greater selectivity/potency/combinability. Moving through combination trials.
2. New types of allele-specific or pan-(K)RAS inhibitors (G12D, tricomplex, others) will broaden the patient population that can be treated & will likely alter resistance patterns.
3. Co-mutations (STK11, KEAP1, CDKN2A, SMARCA4) impact the biology & response and may help guide combination development.
4. Diverse resistance mechanisms are observed, including other KRAS mutations, RAF/MEK pathway alterations & YAP/TEAD activation, may also help guide combination development.

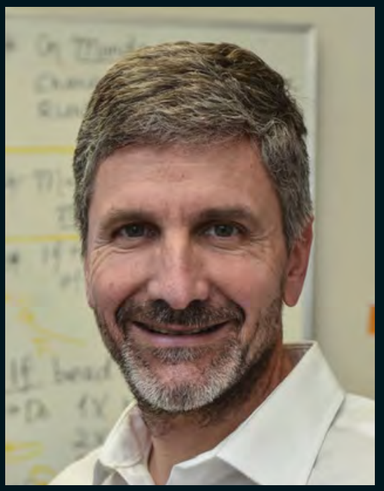

# Innovation

James DeGregori, PhD

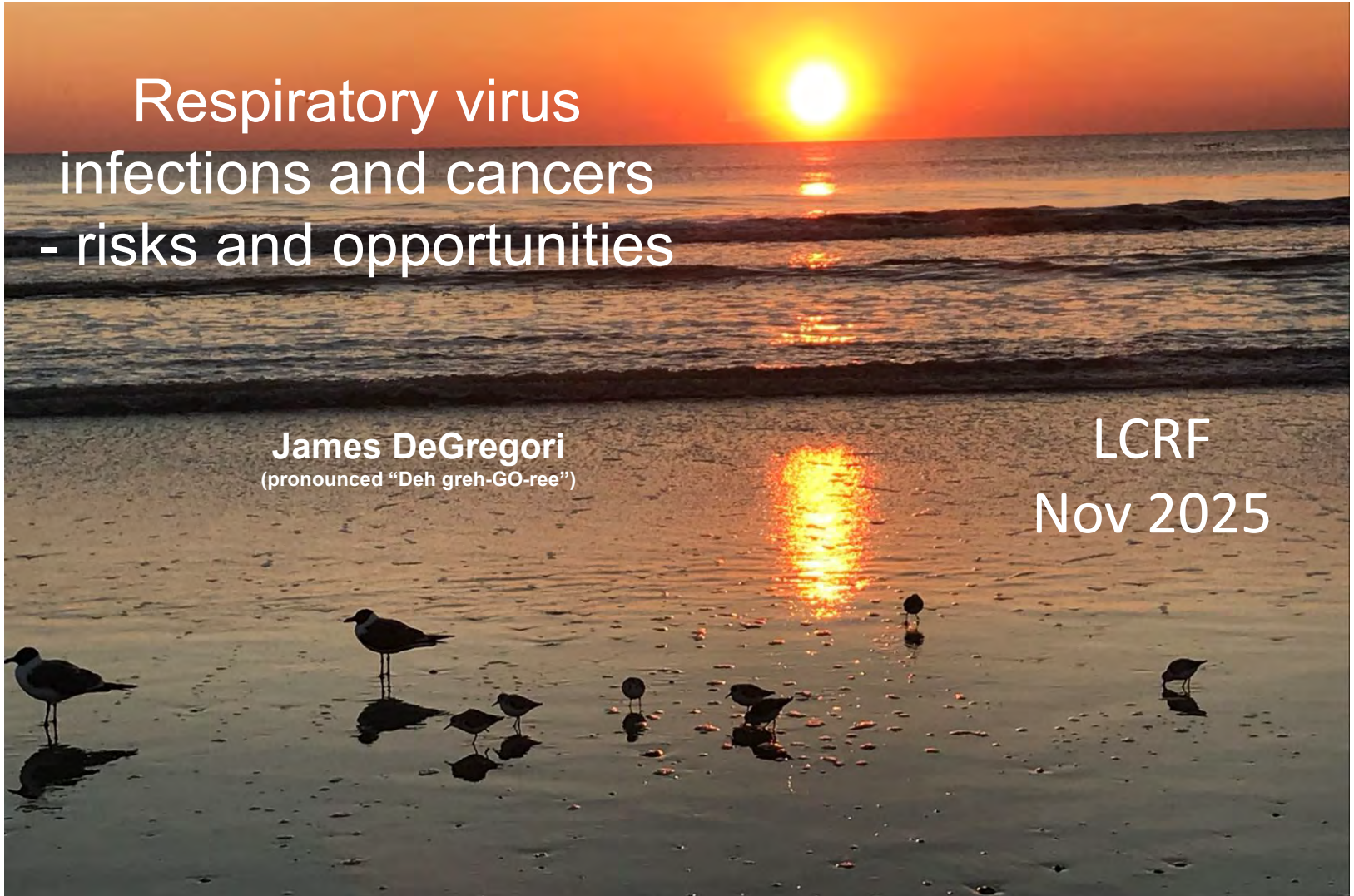
**University of Colorado Anschutz**
Professor, Biochemistry and Molecular Genetics

Courtenay C. and Lucy Patten Davis Endowed Chair in Lung Cancer Research

Deputy Director, University of Colorado Cancer Center



# Respiratory virus infections and cancers - risks and opportunities

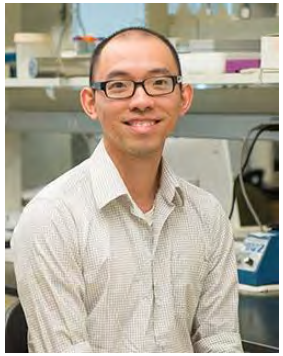


**James DeGregori**
(pronounced “Deh greh-GO-ree”)

LCRF
Nov 2025

Cancer Center
NCI-DESIGNATED COMPREHENSIVE CANCER CENTER

Bryan Johnson



Shi Biao Chia

Mercedes Rincon

Julio Aguirre-Ghiso

Roel Vermeulen

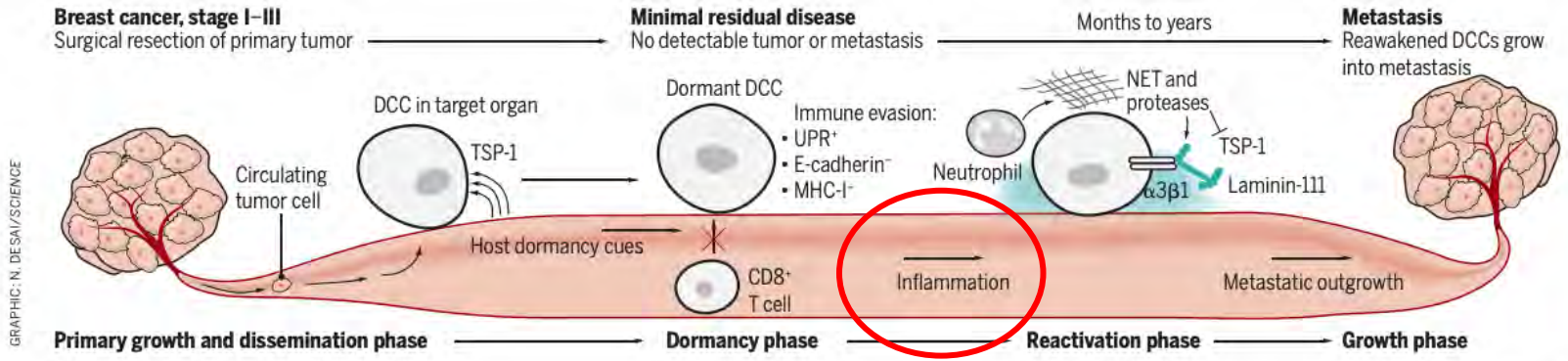
Shi B. Chia[1]*, Bryan J. Johnson[1]*, Junxiao Hu[4,6], Felipe Valença-Pereira[2], Marc Chadeau-Hyam[7,9,10], Fernando Guntoro[9,10,11], Hugh Montgomery[12], Meher P. Boorgula[5,6], Varsha Sreekanth[3,6], Andrew Goodspeed[5,6], Bennett Davenport[2], Marco De Dominici[1], Vadym Zaberezhnyy[1], Wolfgang E. Schleicher[1], Dexiang Gao[4,6], Andreia N. Cadar[13,14], Lucia Petriz-Otaño[15], Michael Papanicolaou[15], Afshin Beheshti[16,17,18], Stephen B. Baylin[16,19,20], Joseph W. Guarnieri[21], Douglas C. Wallace[21,22], James C. Costello[3,6], Jenna M. Bartley[13,14], Thomas E. Morrison[2], Roel Vermeulen[7,8,9,#], Julio A. Aguirre-Ghiso[15,#], Mercedes Rincon[2,6,#], James DeGregori[1,2,4,6,#]

University of Colorado Anschutz Medical Campus, Utrecht University, Imperial College London, University College London, University of Connecticut School of Medicine, Albert Einstein College of Medicine

# Disseminated Cancer Cells (DCCs) and Dormancy

- Metastasis is the leading cause of cancer related deaths
- Metastatic relapse frequently occurs years to decades after diagnosis and treatment
- This process is mediated by the reawakening of dormant DCCs

**What keeps these cells dormant and what awakens them?**




(Julio A. Aguirre-Ghiso,2018)

# Aging, smoking, stress and chemo can promote metastatic outgrowth

nature cancer

Article

https://doi.org/10.1038/s43018-023-00525-y

## Age-associated microenvironmental changes highlight the role of PDGF-C in ER$^+$ breast cancer metastatic relapse

Received: 18 March 2022

Accepted: 7 February 2023

Frances K. Turrell[1], Rebecca Orha[1], Naomi J. Guppy[2], Andrea Gillespie[1], Matthew Guelbert[3], Chris Starling[2], Syed Haider[1] & Clare M. Isacke[1]

Article

## Stromal changes in the aged lung induce an emergence from melanoma dormancy

https://doi.org/10.1038/s41586-022-04774-2

Received: 17 August 2020

Accepted: 19 April 2022

Published online: 1 June 2022

Mitchell E. Fane[1,2], Yash Chhabra[1,2], Gretchen M. Alicea[1,2], Devon A. Maranto[2], Stephen M. Douglass[1,2], Marie R. Webster[1], Vito W. Rebecca[1,2], Gloria E. Marino[1,2], Filipe Almeida[4], Brett L. Ecker[4,5], Daniel J. Zabransky[1,2], Laura Hüser[1,2,6,7], Thomas Beer[4], Hsin-Yao Tang[4], Andrew Kossenkov[4], Meenhard Herlyn[4], David W. Speicher[4], Wei Xu[8], Xiaowei Xu[8], Elizabeth M. Jaffee[2], Julio A. Aguirre-Ghiso[8,9,10,11] & Ashani T. Weeraratna[1,2,12]

RESEARCH

RESEARCH ARTICLE SUMMARY

CANCER

## Neutrophil extracellular traps produced during inflammation awaken dormant cancer cells in mice

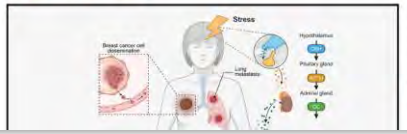
Jean Albrengues, Mario A. Shields, David Ng, Chun Gwon Park, Alexandra Ambrico, Morgan E. Poindexter, Priya Upadhyay, Dale L. Uyeminami, Arnaud Pommier, Victoria Küttner, Emilis Bružas, Laura Maiorino, Carmelita Bautista, Ellese M. Carmona, Phyllis A. Gimotty, Douglas T. Fearon, Kenneth Chang, Scott K. Lyons, Kent E. Pinkerton, Lloyd C. Trotman, Michael S. Goldberg, Johannes T.-H. Yeh, Mikala Egeblad*

Cancer Cell

Report

## Chronic stress increases metastasis via neutrophil-mediated changes to the microenvironment

Graphical abstract




Authors

Xue-Yan He, Yuan Gao, David Ng, ..., Christopher R. Vakoc, Linda Van Aelst, Mikala Egeblad

Correspondence

mikala.egeblad@jhmi.edu

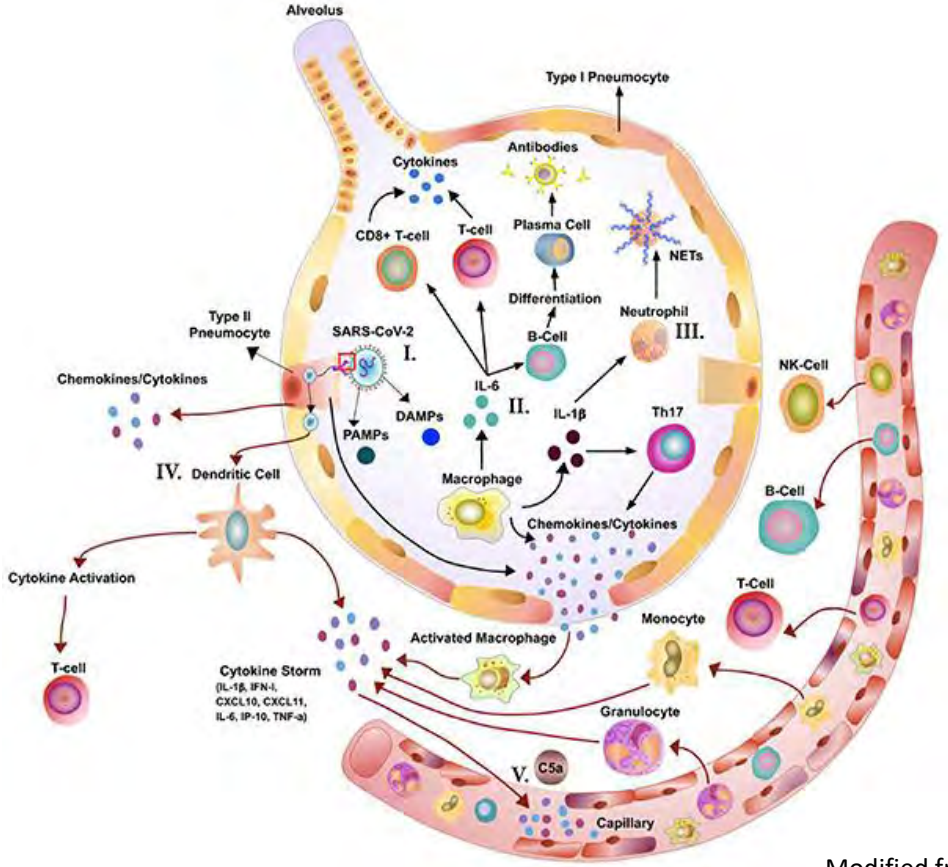
PLOS BIOLOGY

RESEARCH ARTICLE

## Taxane chemotherapy induces stromal injury that leads to breast cancer dormancy escape

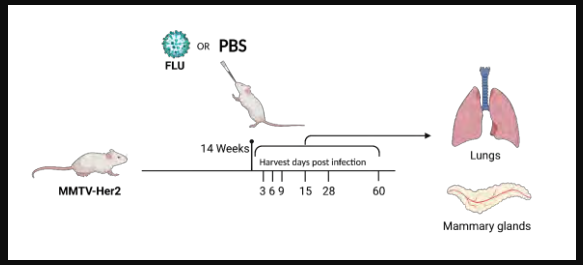
Ramya Ganesan[1]*, Swati S. Bhasin[2,3], Mojtaba Bakhtiary[2,3], Upaasana Krishnan[2,4], Nagarjuna R. Cheemarla[5,6], Beena E. Thomas[2,3], Manoj K. Bhasin[2,3,4,7,8,9], Vikas P. Sukhatme[1,8,9]*

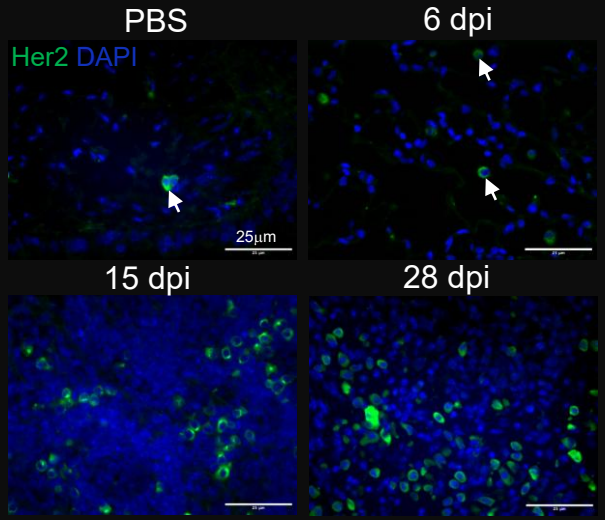
# Respiratory viral infections induce massive inflammatory responses in the lungs

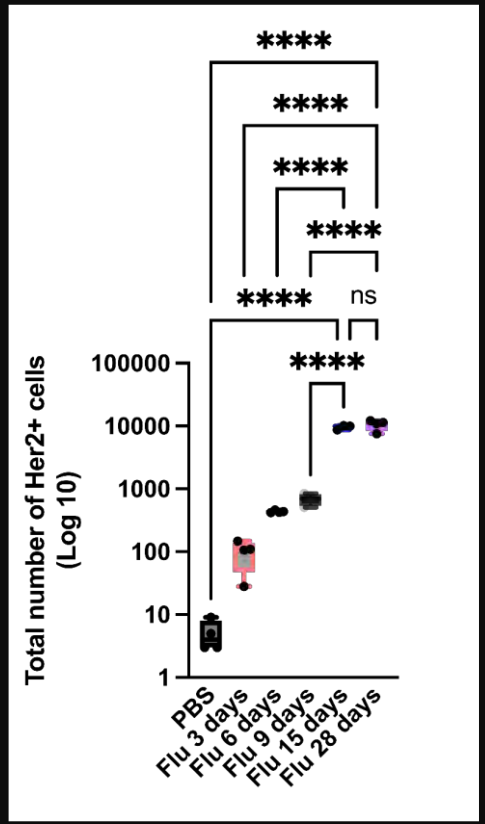


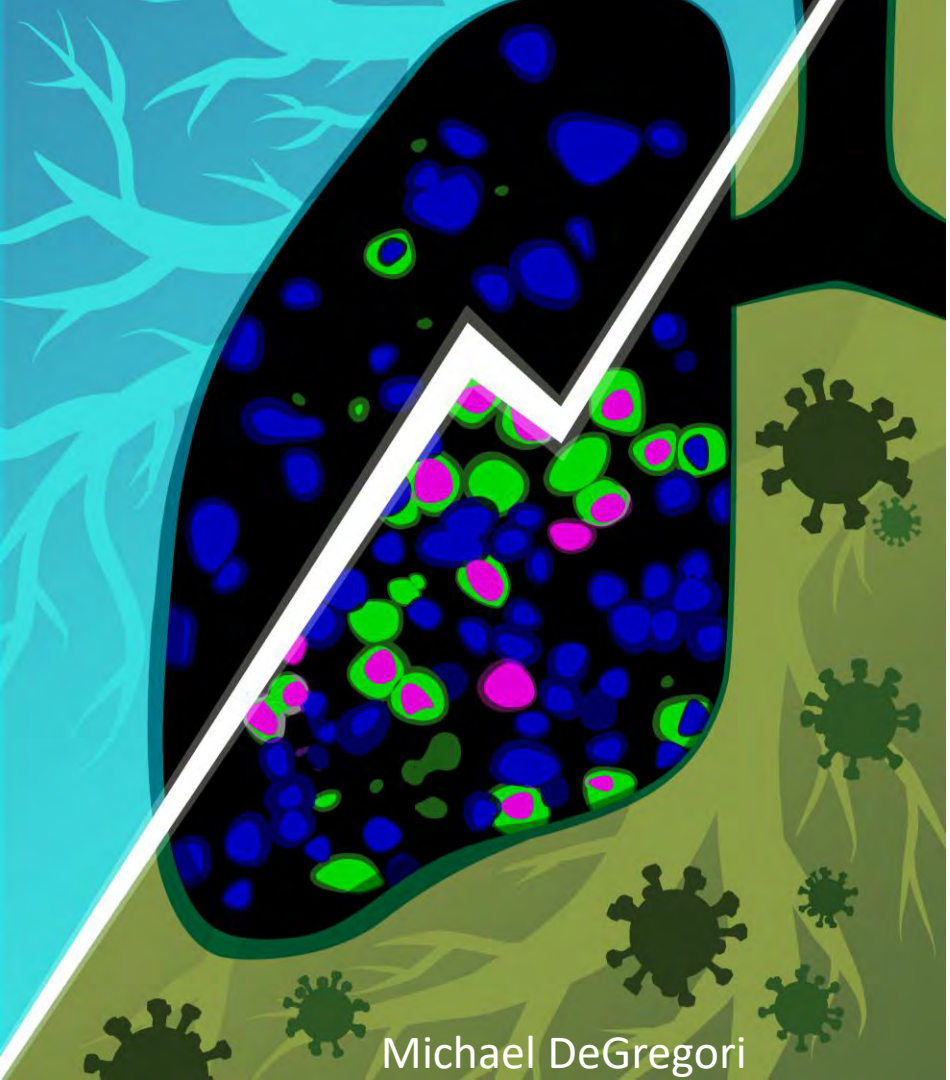

Modified from Ahmed-Hassan et al. Front Immunol. 2020.

# Influenza virus infection results in the awakening of breast disseminated cancer cells (DCC) in the lungs



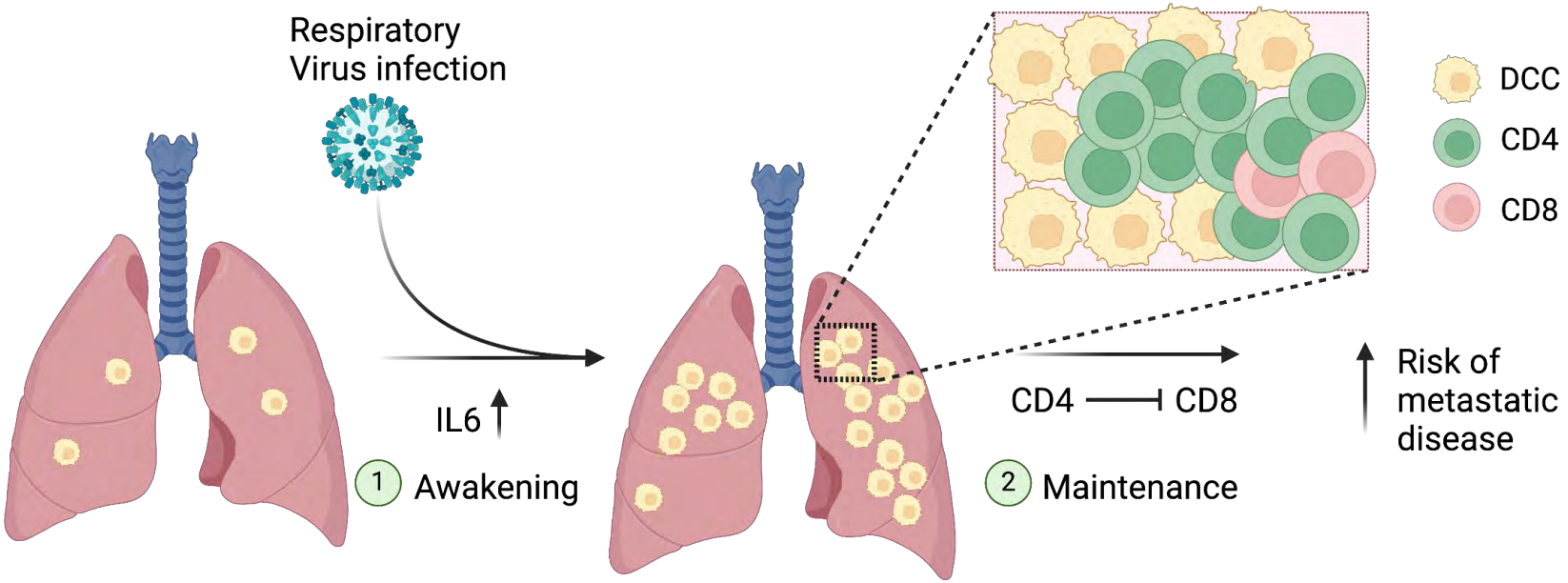






- Influenza and COVID virus infections induce metastatic awakening in the lungs, with substantial (>100 fold) expansion of tumor cells.

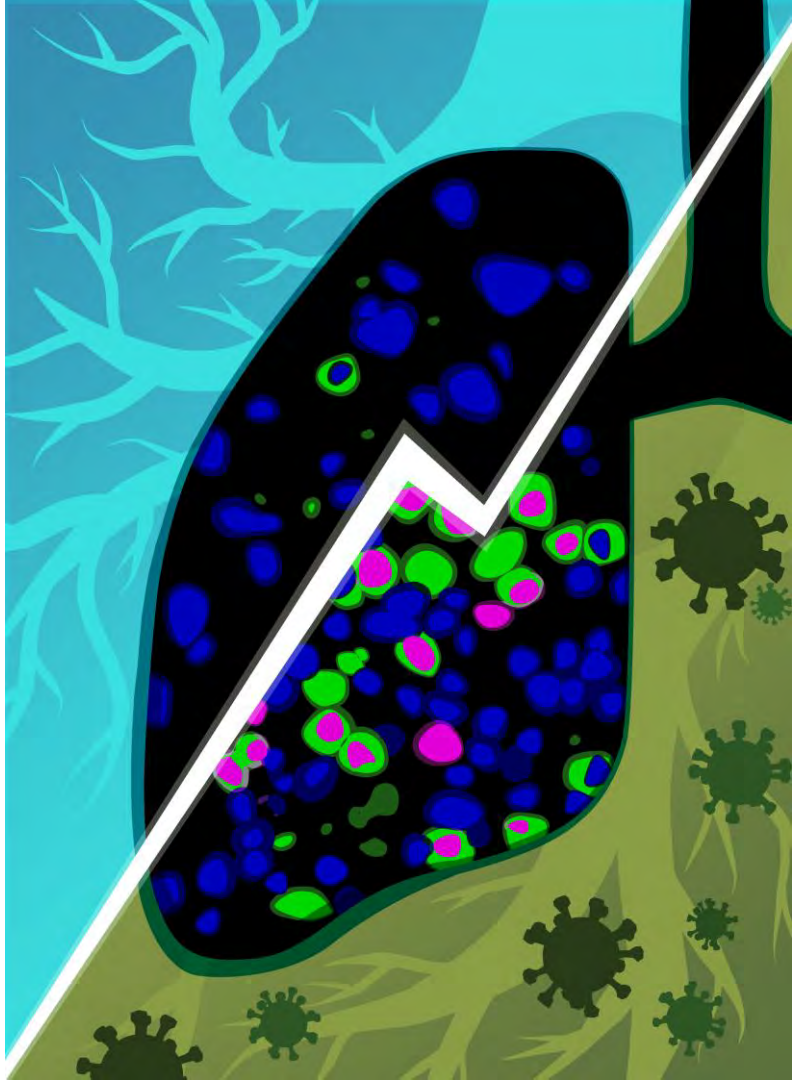
- IL-6 is required for awakening and expansion of the disseminated cancer cells (DCC).

- The DCC suppress the killer T-cells that would otherwise eliminate the cancer.

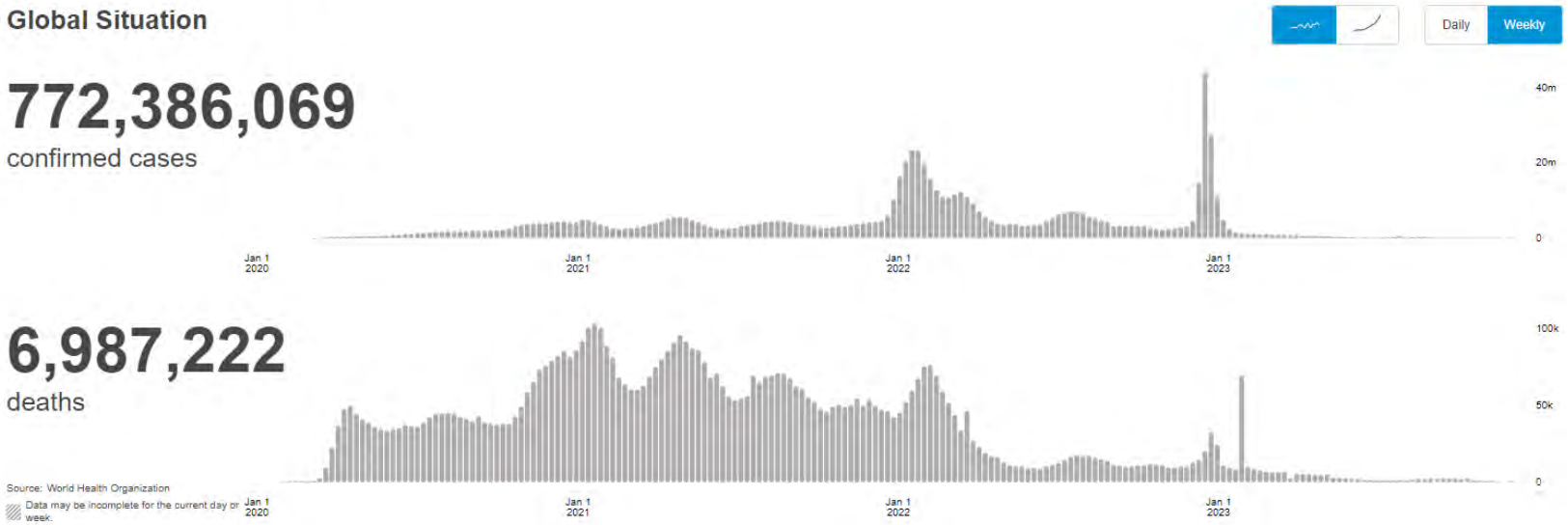

Respiratory
Virus infection
IL6
1 Awakening
2 Maintenance
CD4
CD8
Risk of
metastatic
disease
DCC
CD4
CD8

# Next Steps

- Test whether inhibition of the IL-6 signaling pathway during or after infection can prevent virus induced awakening and metastatic progression.
- Identify the mechanisms of DCC-mediated immune suppression and how it can be reversed.
- Determine whether other infections and at other sites can promote dormant DCC awakening and disease progression.
- Determine how prior infections or vaccination might attenuate virus induced DCC expansion.



# Does COVID alter the risk of breast cancer progression to metastatic disease in lungs?




https://covid19.who.int/

Fernando Guntoro

Marc Chadeau-Hyam

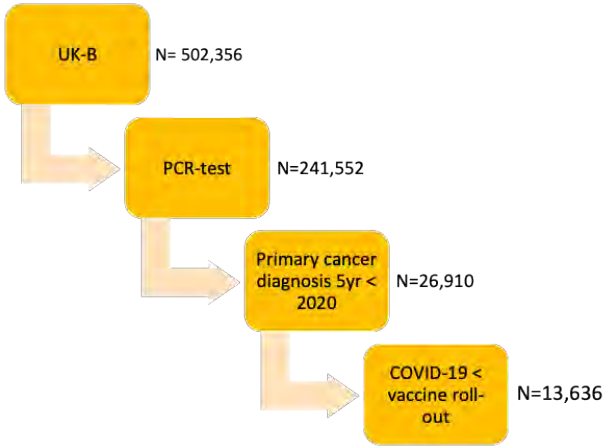
Roel Vermeulen

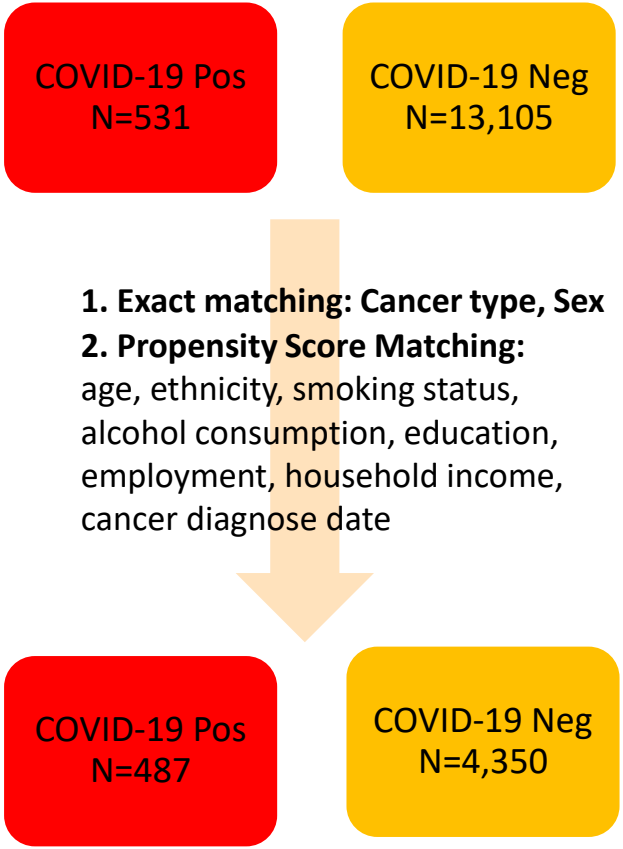
UK-B N= 502,356

PCR-test N=241,552

Primary cancer diagnosis 5yr < 2020 N=26,910

COVID-19 < vaccine roll-out (Dec 2020) N=13,636



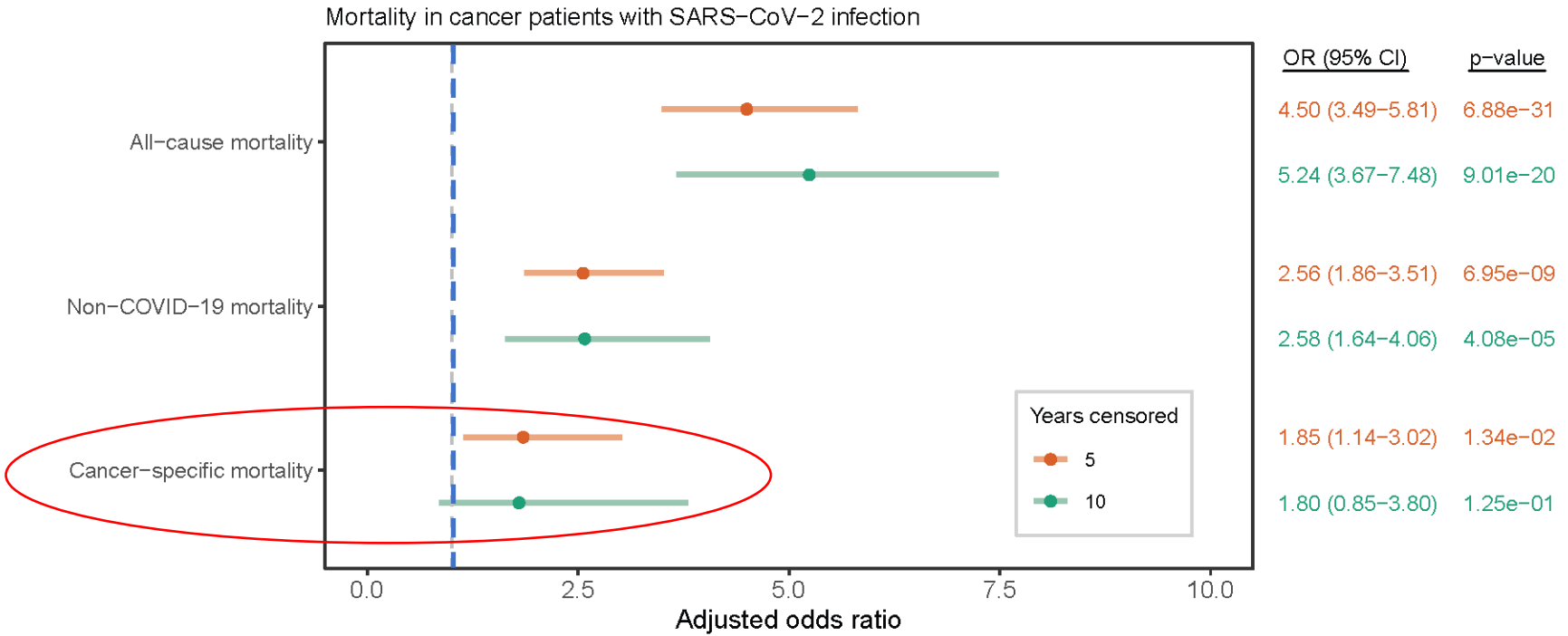




-Main analyses: Unconditional logistic regression: All cause, Non-COVID-19, and Cancer mortality

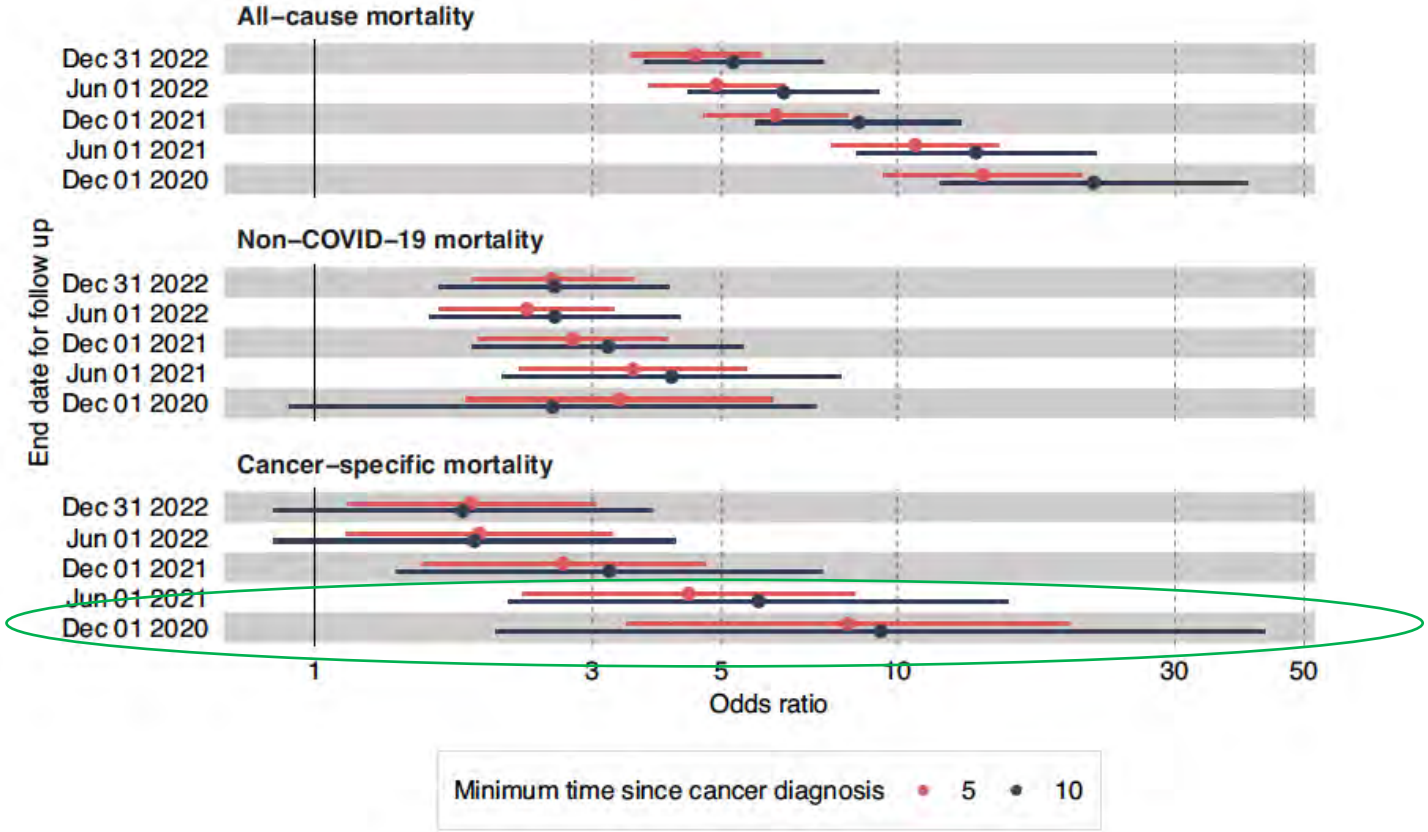
-Sensitivity analyses: Cancer Diagnosis > 10 years before COVID-19 pandemic

Decreasing censoring date by 6 months from 31st 2022 to 1st June 2020

# For patients with a prior diagnosis of cancer, SARS-CoV-2 substantially increases the risk of cancer-specific mortality



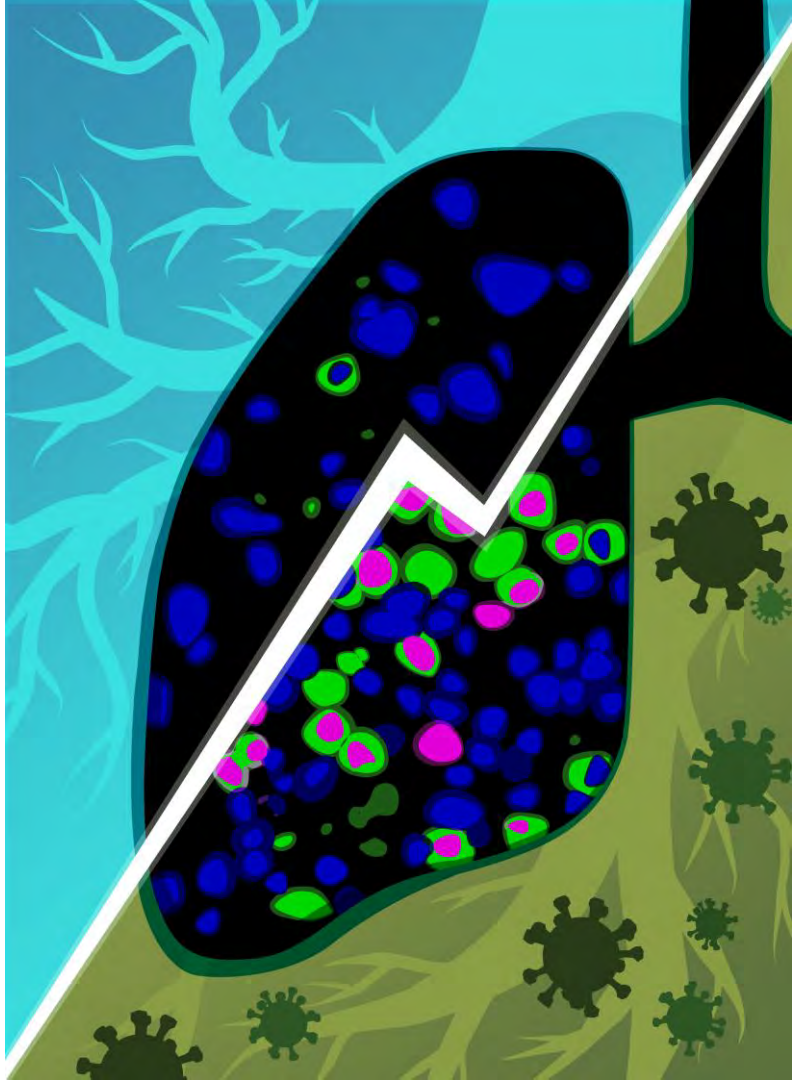
# The excess cancer risk is greatest in the months following SARS-CoV-2 infection



# Conclusions

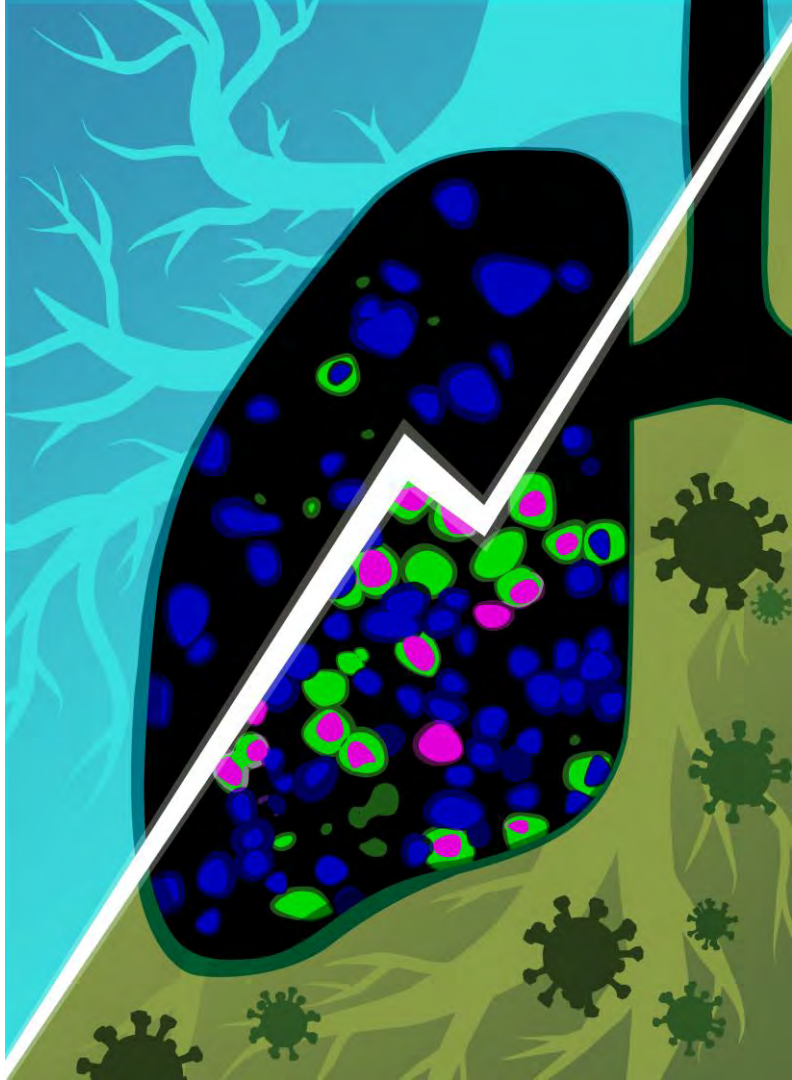
- For patients with a prior diagnosis of cancer, SARS-CoV-2 substantially increases the risk of cancer-specific mortality

- The excess cancer risk is greatest in the months following SARS-CoV-2 infection



# Next Steps

- Extend analyses to other cancers and other sites.
- Explore the impact of prior exposures and vaccination.
- Determine how therapies received during COVID-19 infections alters the risk of cancer relapse (IL6/Jak inhibitors, anti-virals, dex, controlling for severity).
- Extend to other infections (pneumonia, etc).



## Respiratory viral infections prime accelerated lung cancer growth

Wei Qian1,2,#, Xiaoqin Wei1,2,#, Andrew J Barros3, Xiangyu Ye4, Qing Yu1, Samuel P Young1,2,5, Eric V Yeatts1, Yury Park1, Chaofan Li1,2, Gislane Almeida-Santos1,2, Jinyi Tang1,2, Harish Narasimhan1,2,5, Nicole A Kirk5, Ying Li6, Li Li7, Peter Chen8, Jeffrey M Sturek3, Kwon-Sik Park5, Wei Chen4,9, In Su Cheon1,2, Jie Sun1,2,*

https://doi.org/10.1101/2025.09.02.672566

- Respiratory virus infections can promote lung cancers, and vaccination can prevent this.
- Promote a pro-tumor and immune suppressed lung environment.

## SARS-CoV-2 mRNA vaccines sensitize tumours to immune checkpoint blockade

Adam J. Grippin, Christiano Marconi, Sage Copling, Nan Li, Chen Braun, Cole Woody, Elliana Young, Priti Gupta, Min Wang, Annette Wu, Seong Dong Jeong, Dhruvkumar Soni, Frances Weidert, Chao Xie, Eden Goldenberg, Andrew Kim, Chong Zhao, Anna DeVries, Paul Castillo, Rishabh Lohray, Michael K. Rooney, Benjamin R. Schrank, Yifan Wang, Yifan Ma, D3CODE Team, …Steven H. Lin

https://www.nature.com/articles/s41586-025-09655-y#Sec11

- COVID-19 mRNA vaccines render cancers more responsive to immune checkpoint inhibitors (ICI) – *cold to hot!*
- The vaccine boosted anti-tumor immunity by triggering strong type I interferon responses and activating T cells.
- Cancer patients who received a mRNA vaccine within 100 days before starting ICI therapy had significantly better survival.

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**LCRF.org/quicklinks**

Find information about resources, trials, patient groups, and more

**(844) 835-4325**
**or support@LCRF.org**

Lung Cancer Support Line:
Ask questions, get guidance and support