Welcome!

- Our program will begin at 3:00 PM 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 EVENT LEAD & MODERATOR

Kathryn O'Donnell, PhD

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

Associate Professor, Molecular Biology
UT Southwestern Medical Center

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Today's schedule

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

3:00 PM	**Welcome** *Kathryn O'Donnell, PhD, Chair, LCRF Scientific Advisory Board*
3:10 PM	**State of Lung Cancer Research** *Brendon Stiles, MD, Vice Chair, LCRF Scientific Advisory Board*
3:30 PM	**Lung Cancer Patient Advocacy** *Colleen Conner Ziegler, Chair, LCRF Board of Directors*
3:45 PM	**Presentations and panel discussion with Q&A** • *Hossein Borghaei, DO, MS – immuno-oncology* • *Lauren Averett Byers, MD – small cell lung cancer* • *Don Nguyen, PhD, BSc – brain metastasis* • *Joseph A. Greer, PhD – telemedicine and palliative care* • *Mark Awad, MD, PhD – KRAS*
5:45 PM	**Closing remarks** *Kathryn O'Donnell, PhD, Chair, LCRF Scientific Advisory Board*
6:00 PM	**Symposium ends**

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STATE OF LUNG CANCER RESEARCH

Brendon M. Stiles, MD

Vice Chair, LCRF Scientific Advisory Board
Vice Chair, LCRF Board of Directors

Chief, Division of Thoracic Surgery & Surgical Oncology
Associate Director, Surgical Services
Montefiore-Einstein Cancer Center
Professor, Cardiovascular & Thoracic Surgery
Albert Einstein College of Medicine
Montefiore Medical Center

LUNG CANCER PATIENT ADVOCACY

Colleen Conner Ziegler

Chair, Board of Directors
Member, LCRF Scientific Executive Committee

Patient and Research Advocate

CHAT MODERATOR

Isabel Preeshagul, DO, MBS

Chair, LCRF Education + Engagement Committee

Assistant Attending Physician, Thoracic Oncology
Memorial Sloan Kettering Cancer Center

State of Lung Cancer Research

Brendon M. Stiles, MD

Lung Cancer Patient Advocacy

Colleen Conner Ziegler

Chair, LCRF Board of Directors

Research Advocate

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**.

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

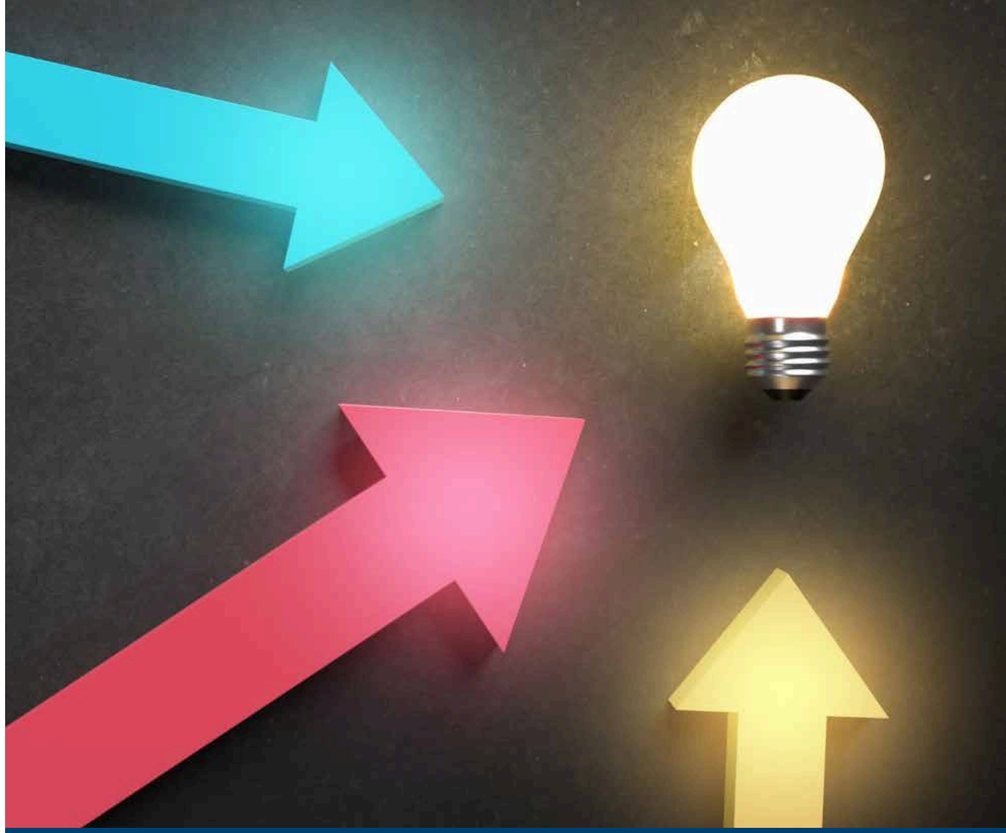
- Is about conducting research **‘with’ or ‘by’** people living with lung cancer.

  Patients often are used in initial and/or end stage of research. Understanding equity, respect, trust, empowerment, clarity on roles/expectations may facilitate patient involvement through all stages of research planning and conduct.

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**

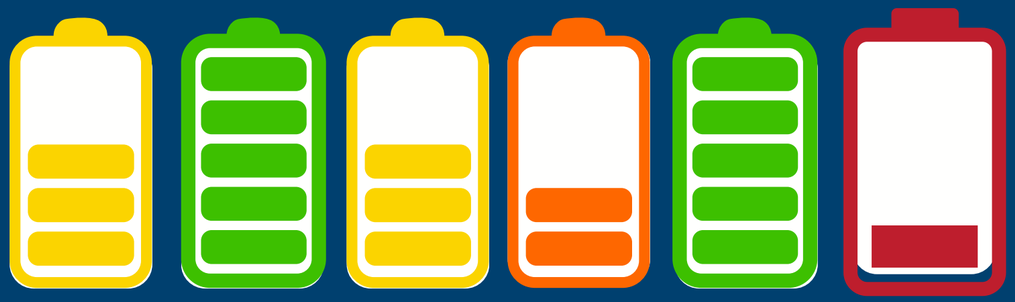
Advocacy that moves research forward

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.
Ask about trials that serve to move the science forward.

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



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.**

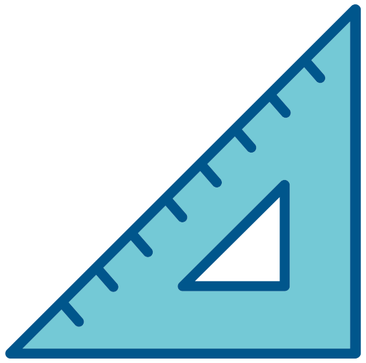
How to **connect** the research advocate with the research to be a partner.

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

Questions to consider

Defining engagement

- How are we engaging with research?
- How should we be engaged?
- What do we mean by meaningful engagement?



Measuring success

- How do we measure engagement?
- How do we make our engagement more methodical and consistent?

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.

Access to current research information.

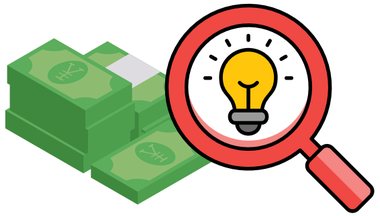
Opportunities for research advocacy training.

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.

Today's presenters + panelists

Hossein Borghaei, DO, MS

Fox Chase Cancer Center

Professor and Chief, Thoracic Oncology
The Gloria and Edmund M. Dunn Chair in Thoracic Oncology
Department of Hematology and Oncology

Lauren Averett Byers, MD

The University of Texas MD Anderson Cancer Center

Professor and Thoracic Section Chief
Department of Thoracic/Head and Neck Medical Oncology
Division of Cancer Medicine

Don Nguyen, PhD, BSc

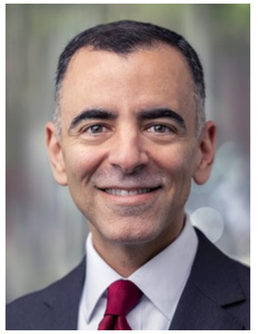
Yale University School of Medicine

Associate Professor of Pathology and Medical Oncology
Co-Leader, Cancer Signaling Networks, Yale Cancer Center

Joseph A. Greer, PhD

Massachusetts General Hospital Cancer Center

Assoc Professor of Psychology, Harvard Medical School
Co-Director, Cancer Outcomes Research & Education
Clinical Psychologist, Center for Psychiatric Oncology & Behavioral Sciences



Mark Awad, MD, PhD

Memorial Sloan Kettering

Chief of Thoracic Oncology Service
Solid Tumor Oncology,
Department of Medicine

Immuno-oncology

Hossein Borghaei, DO, MS

Immunotherapy in Metastatic Non-Small Cell Lung Cancer

Hossein Borghaei, MS, DO

Professor and Chief of Thoracic Oncology

The Gloria and Edmund M. Dunn Chair in Thoracic Oncology

Philadelphia

2024

FOX CHASE CANCER CENTER

TEMPLE HEALTH

Disclosures

- **Research Support (Clinical Trials):**
  - BMS/Lilly, Amgen
- **Advisory Board/Consultant:**
  - BMS, Lilly, Genentech, Pfizer, Merck, EMD-Serono, Boehringer Ingelheim, Astra Zeneca, Novartis, Genmab, Regeneron, BioNTech, Amgen, Axiom, PharmaMar, Takeda, Mirati, Daiichi, Guardant, Natera, Oncocyte, Beigene, iTEO, Jazz, Janssen, Puma, BerGenBio, Bayer, Iobiotech, Grid Therapeutics, RAPT, Gilead, Abbvie, Novocure
- **Scientific Advisory Board:**
  - Sonnetbio (Stock Options), Rgenix (Stock Options), Nucleai (Stock options)
- **Data and Safety Monitoring Board:**
  - University of Pennsylvania, CAR T Program, Takeda, Incyte, Springworks, Novartis
- **Employment:**
  - Fox Chase Cancer Center

FOX CHASE CANCER CENTER
TEMPLE HEALTH

Factors Affecting Treatment Decision

First-line treatment in patients without molecularly driven tumors (simplified)

PD-L1 ≥50%

- Checkpoint inhibitor alone
- Chemotherapy plus checkpoint inhibitor
- I-O/I-O combination (?)

PD-L1 <50%

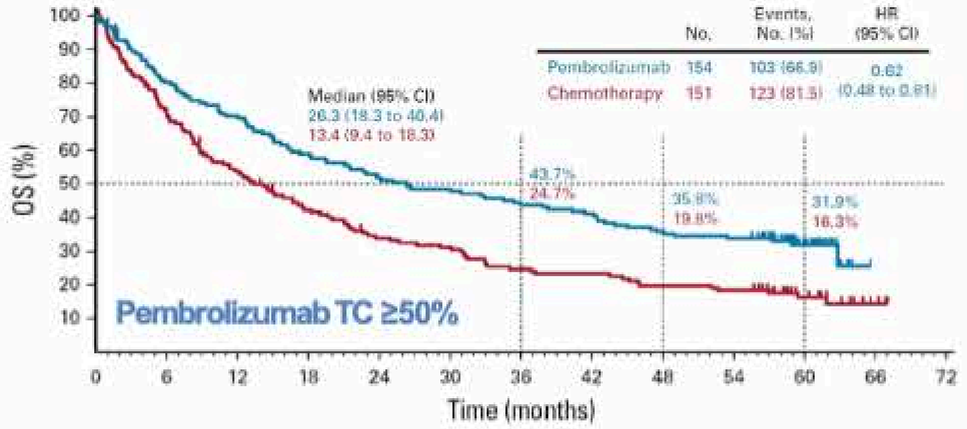
- Checkpoint inhibitor alone (?)
- Chemotherapy plus checkpoint inhibitor
- I-O/I-O combination (?)

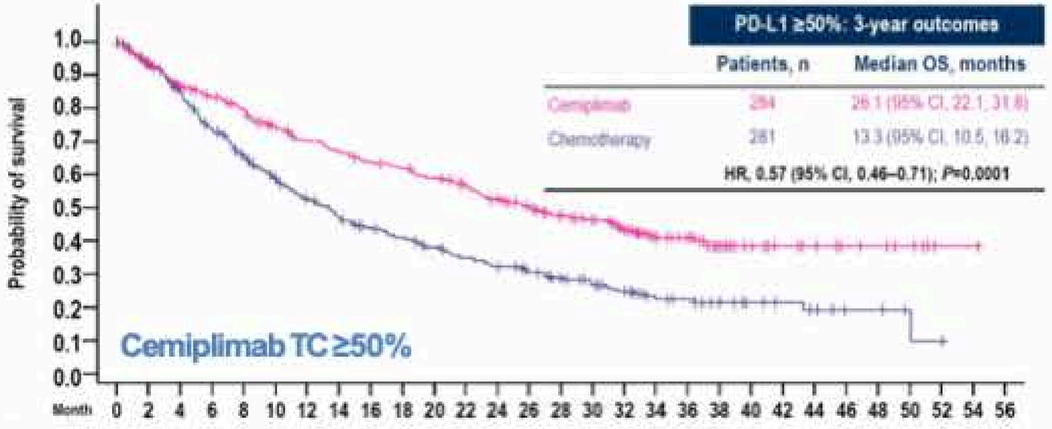
Genomic Data

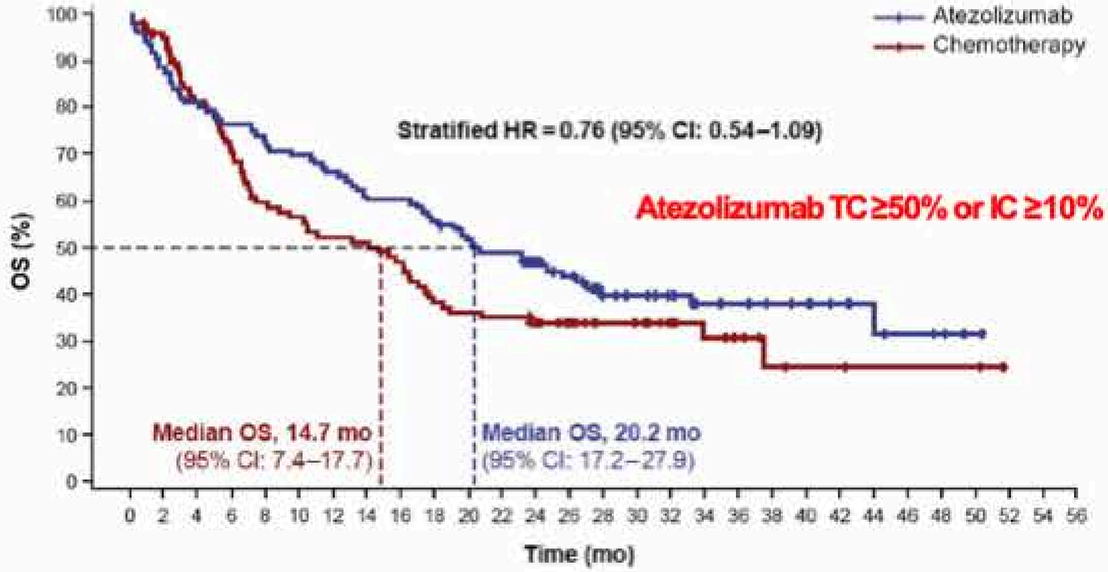
Molecular Determinants of Response

- STK11
- KEAP-1
- EGFR/ALK

PD-L1 ≥ 50% Associated with Response to Single Agent CPI

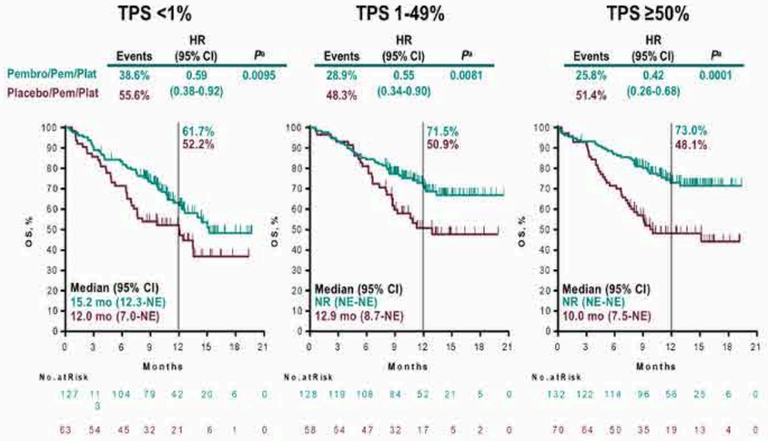






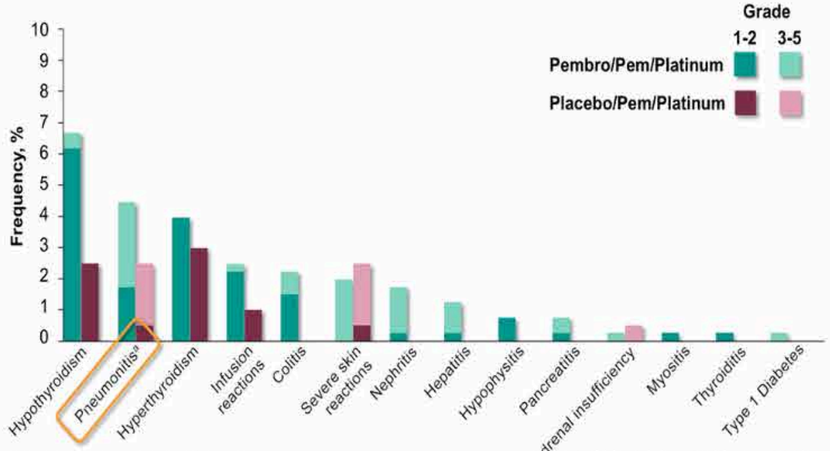
Reck, WCLC 2019; Brahmer, ESMO 2020; Aguilar, Ann Oncol 2019, Herbst, NEJM 2019

Overall Survival by PD-L1 TPS



Gandhi L, et al. AACR Annual Meeting; Chicago, Illinois, April 14-18, 2018; Abstract CT075

Immune-Mediated Adverse Events



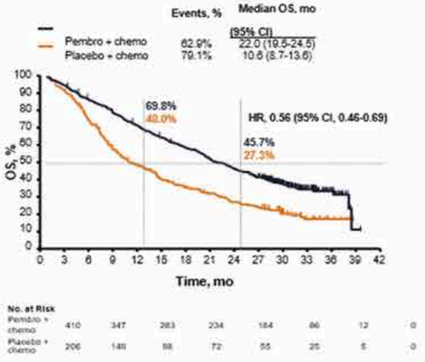
[a]Includes 3 grade 5 events. Data cutoff date: Nov 8, 2017.

Gandhi L, et al. AACR Annual Meeting; Chicago, Illinois, April 14-18, 2018; Abstract CT075

Acute kidney injury Incidence: 5.2%
in pembrolizumab/pemetrexed/platinum arm vs 0.5% in placebo/pemetrexed/platinum arm
Grade 3-5 incidence: 2.0% vs 0%
Grade 5 events: 2

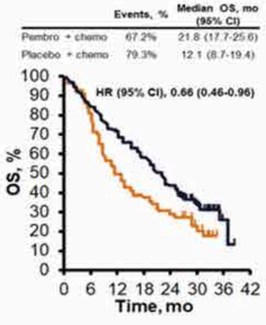
KEYNOTE-189 Final Analysis: OS by PD-L1 status[1]

OS PD-L1 ≥50%



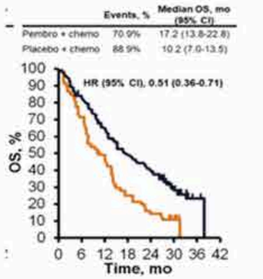
OS: HR = 0.58
(95% CI, 0.46-0.89
Median OS: 22 vs. 10.6 mo

OS PD-L1 1-49%



OS: HR = 0.66
(95% CI, 0.46-0.96)
Median OS: 21.8 vs 12.1 mo

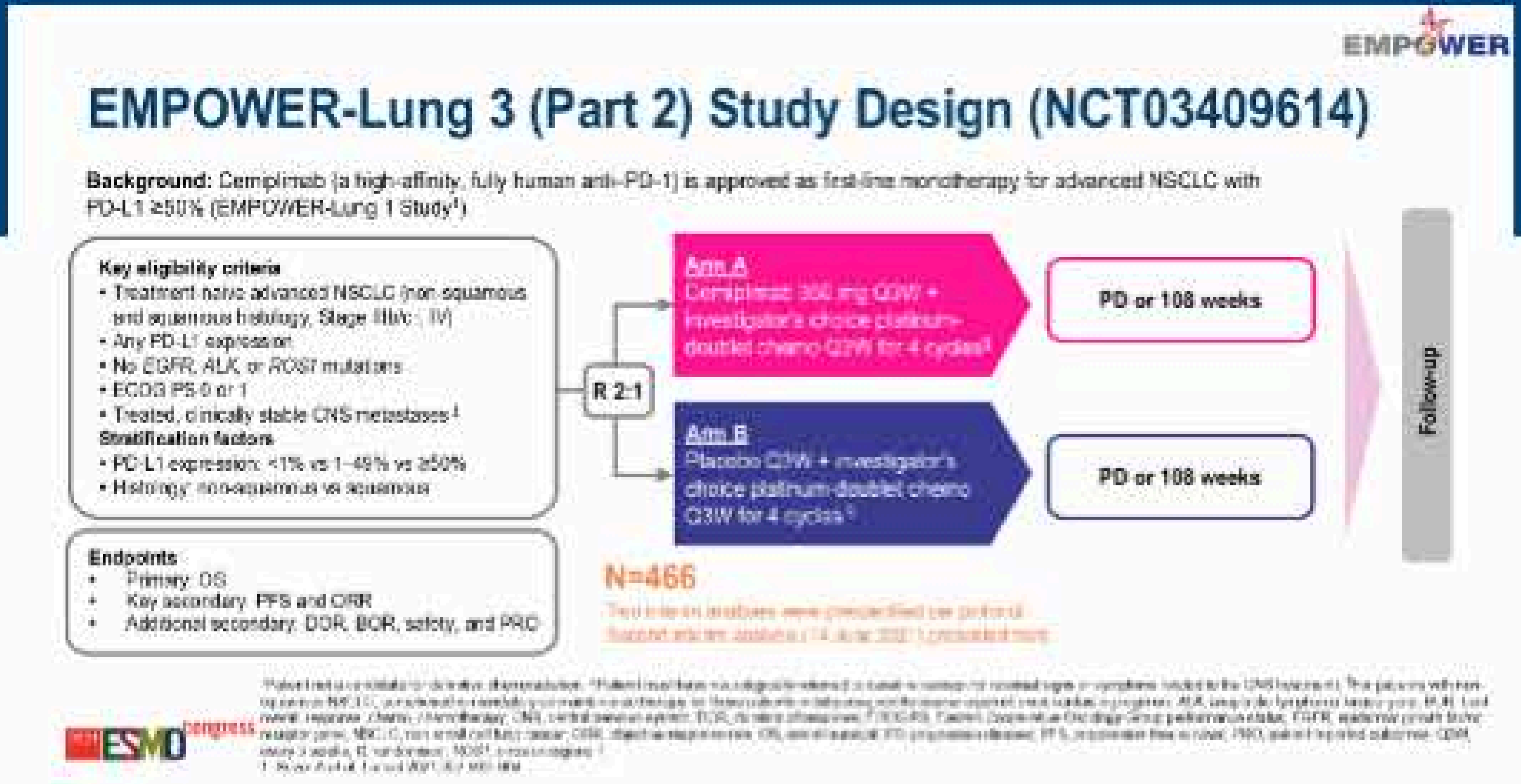
OS PD-L1 <1%

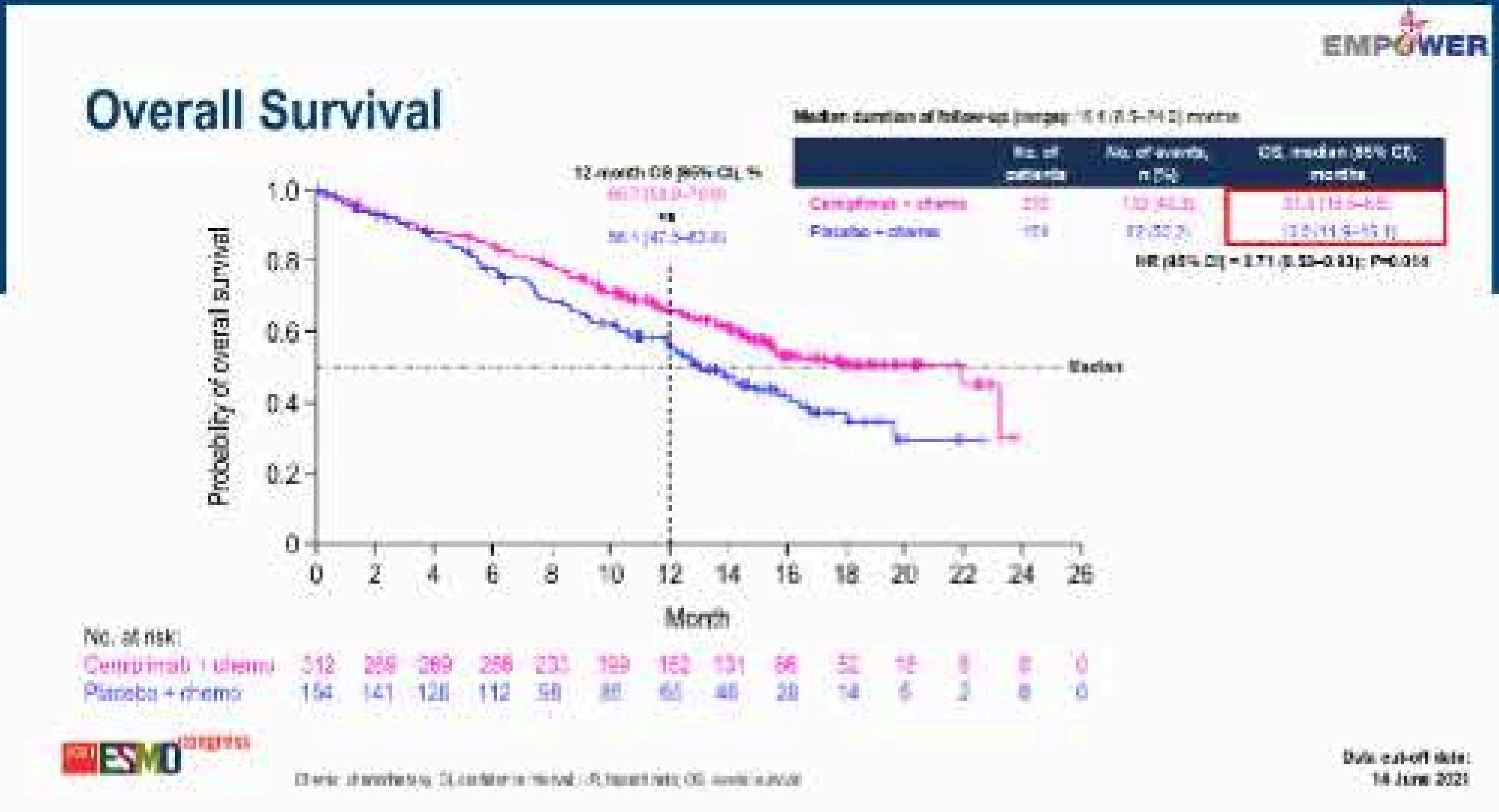


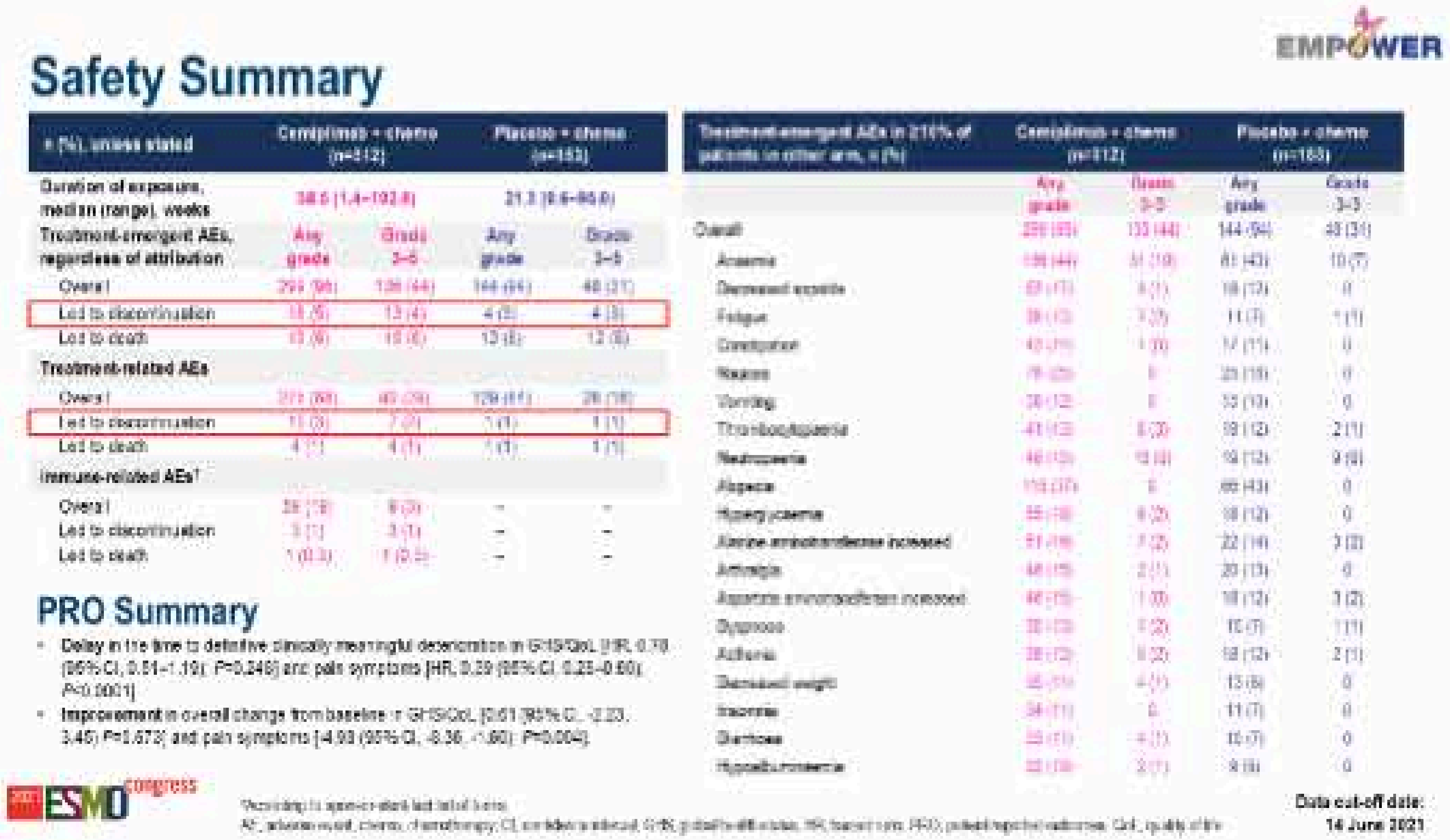
OS: HR = 0.51
(95% CI, 0.36-0.71)
Median OS: 17.2 vs 10.2 mo

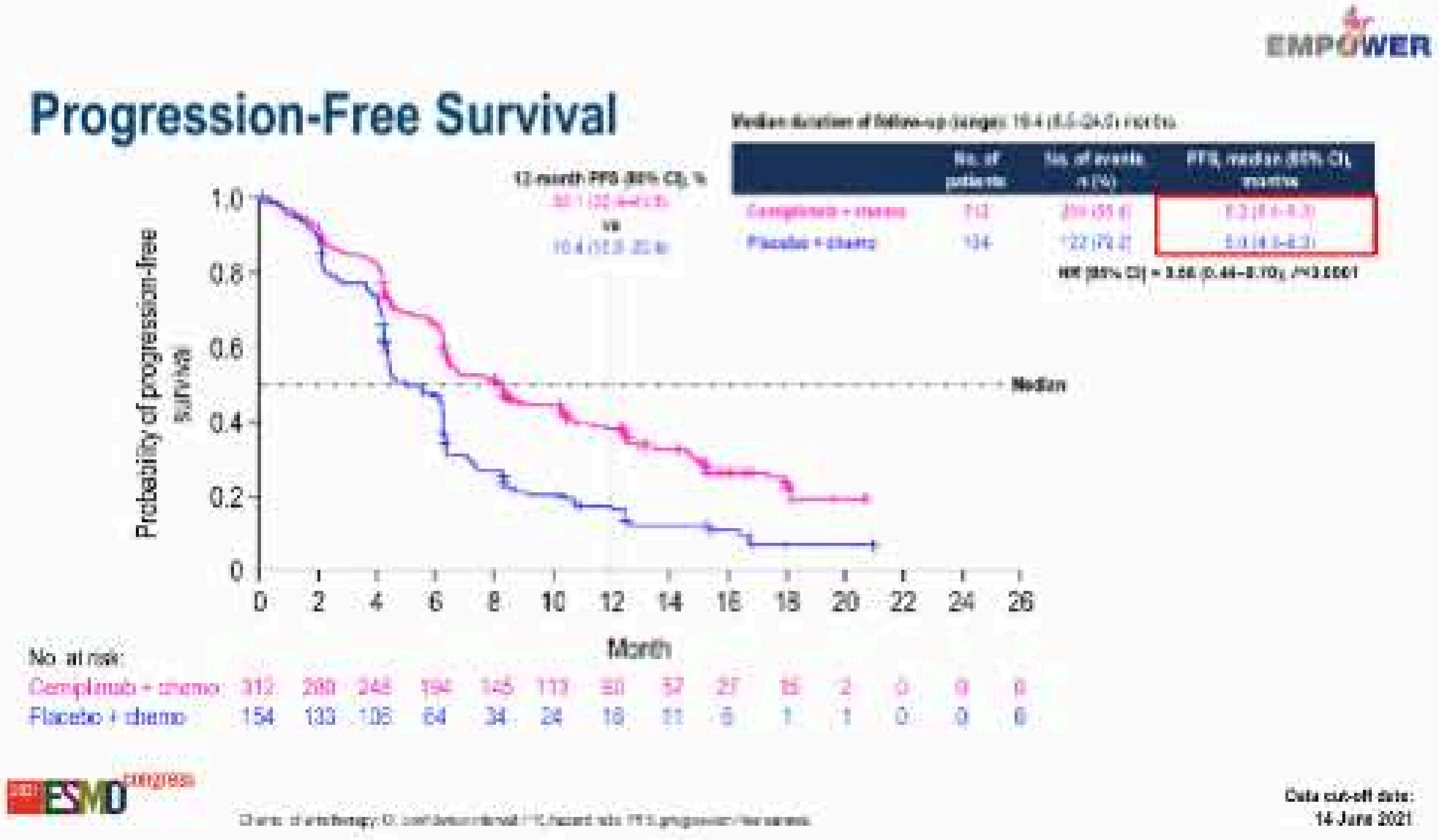
Forde, WCLC 2021

1. Rodriguez-Abreu D et al. ASCO 2020. Abstract 9582.



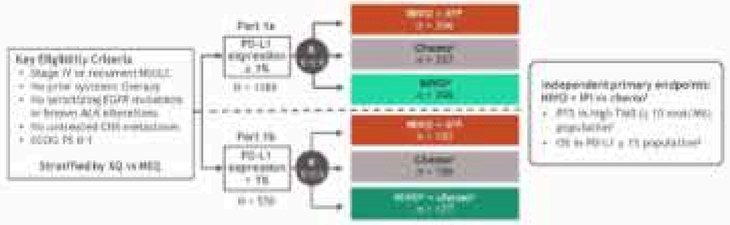




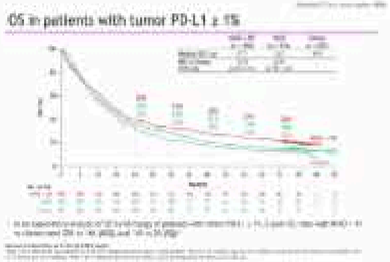


Gogishvili et al, ESMO 2021

CheckMate 227[a] Part 1 study design

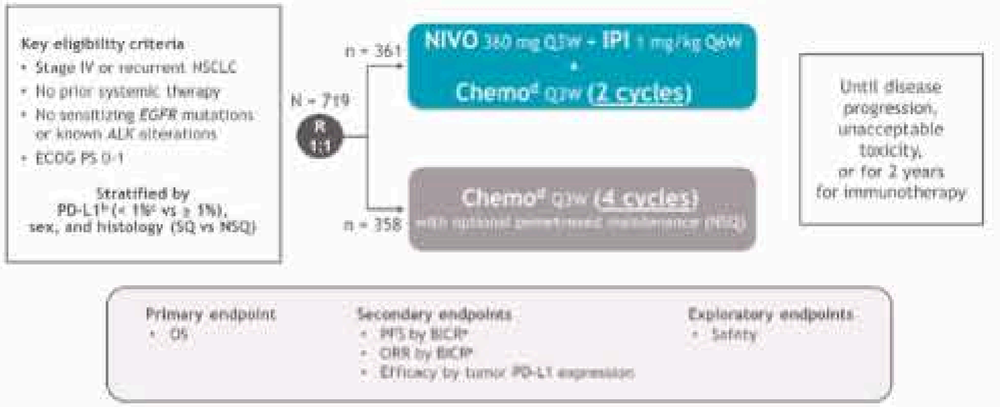


Six –year survival in Checkmate-227

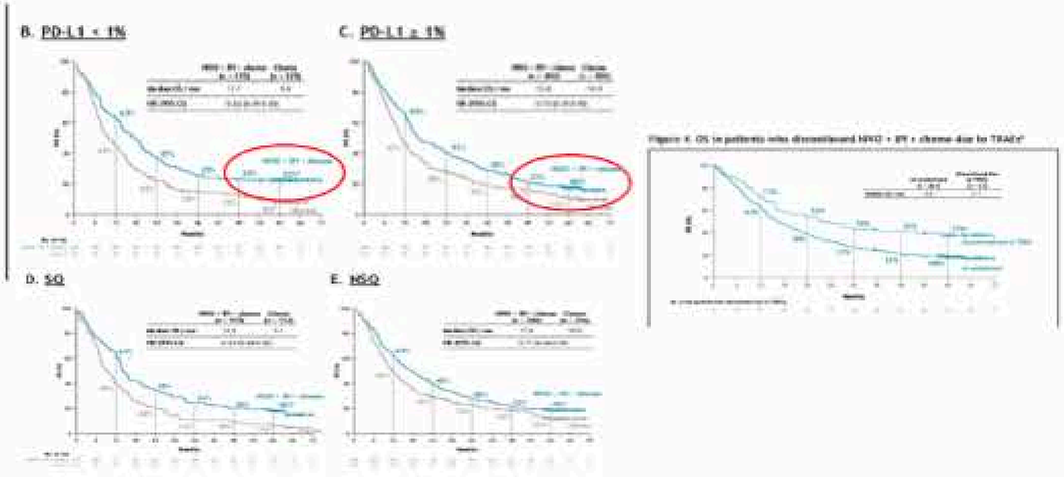


Ramalingam, IASLC Meeting, 2023

CheckMate 9LA study design[a]

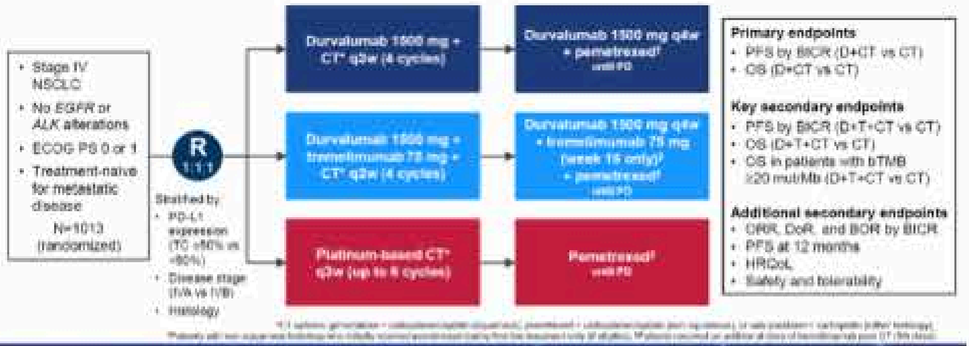


Five-year outcomes in Chekmate-9LA
Martin Reck, ASCO 2024, Poster 8560

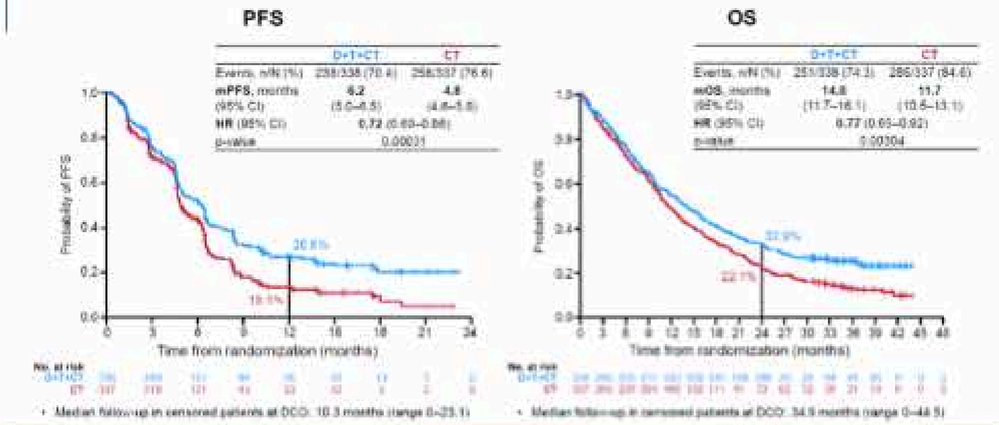


POSEIDON Study Design

Phase 3, global, randomized, open-label, multicenter study



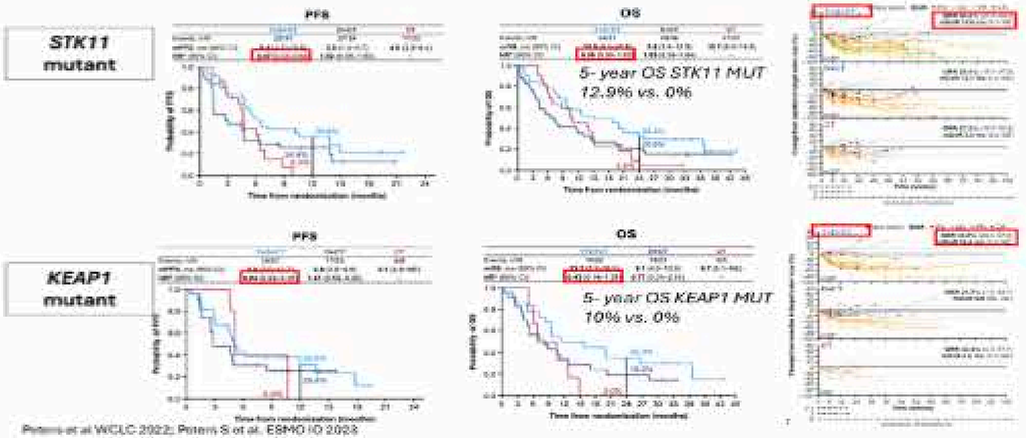
Durvalumab + Tremelimumab + CT vs CT: PFS and OS



• Median follow-up in censored patients at DCO: 10.3 months (range 0–23.1)

• Median follow-up in censored patients at DCO: 34.9 months (range 0–44.5)

POSEIDON: Durvalumab + Tremelimumab + Chemotherapy across *STK11* & *KEAP1* mutations



Peters et al WCLC 2022; Peters S et al. ESMO IO 2023

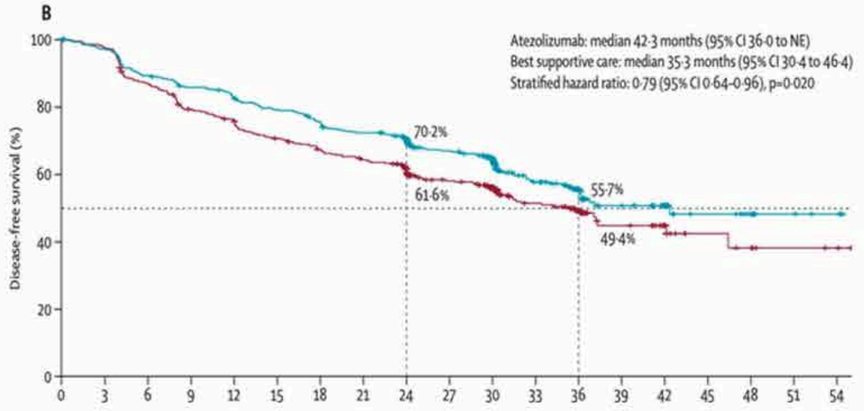
Overview of Reported Global Phase 3 Immunotherapy Trials in Resectable NSCLC

Neoadjuvant Immunotherapy (Approved)				Adjuvant Immunotherapy (Approved)	
CheckMate -816	Nivolumab + chemo x 3 cycles	→ SURGERY	FDA approved		
		SURGERY →	FDA approved	IMpower010	Chemo → atezolizumab ~1 y (PD-L1 ≥1%)
				KEYNOTE-091	Chemo (trial optional but label required) → pembrolizumab ~1 year

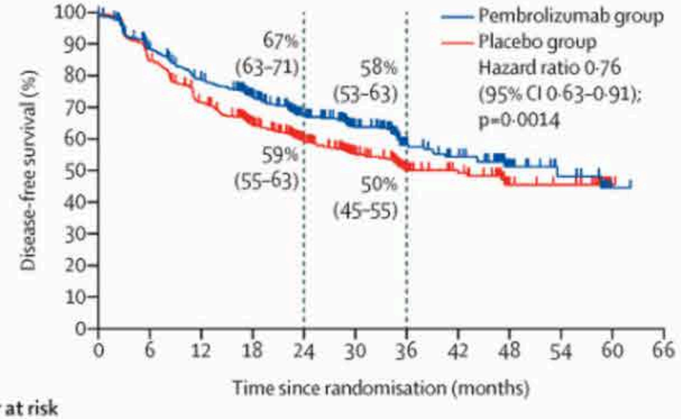
Study	Neoadjuvant Regimen	SURGERY	Adjuvant Regimen	
AEGEAN	Durvalumab + chemo x 4 cycles	→	Durvalumab ~1 year	FDA approved
KEYNOTE-671	Pembrolizumab + chemo x 4 cycles	→	Pembrolizumab ~1 year	FDA approved
CheckMate -77T	Nivolumab + chemo x 4 cycles	→	Nivolumab ~1 year	FDA approved

Disease Free Survival

IMpower 010
Stage 2-3A



Keynote-091



Median, mo (95% CI)
53.6 (39.2-NR)
42.0 (31.3-NR)

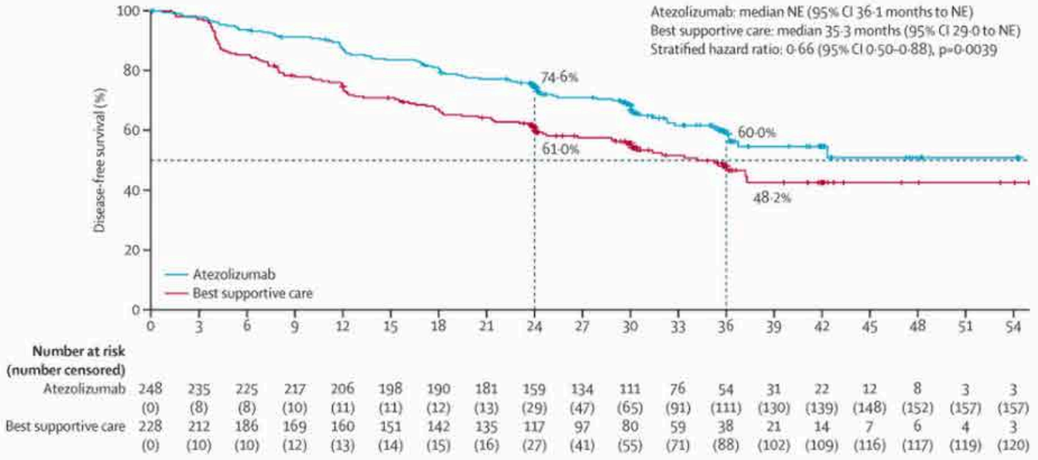
Number at risk (number censored)

Pembrolizumab	590 (0)	493 (30)	434 (36)	358 (84)	264 (150)	185 (216)	82 (306)	70 (313)	28 (352)	16 (363)	1 (377)	0 (378)
Placebo	587 (0)	493 (5)	409 (13)	326 (56)	241 (118)	160 (183)	72 (259)	57 (273)	22 (305)	18 (309)	1 (326)	0 (327)

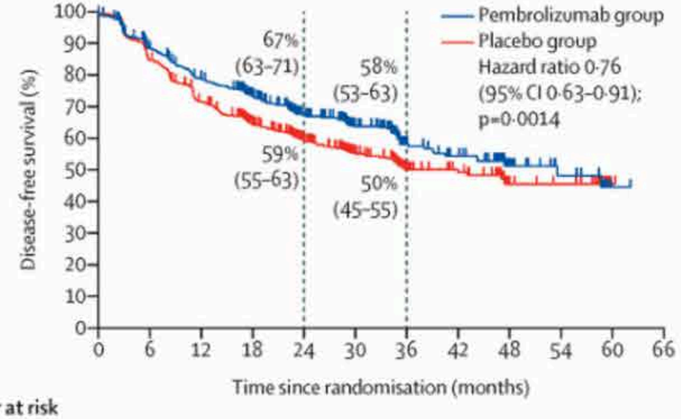
Felip E et al Lancet 2021, O'Brien M et al. Lancet Oncol. 2022

Disease Free Survival

IMpower 010
Stage 2-3A



Keynote-091



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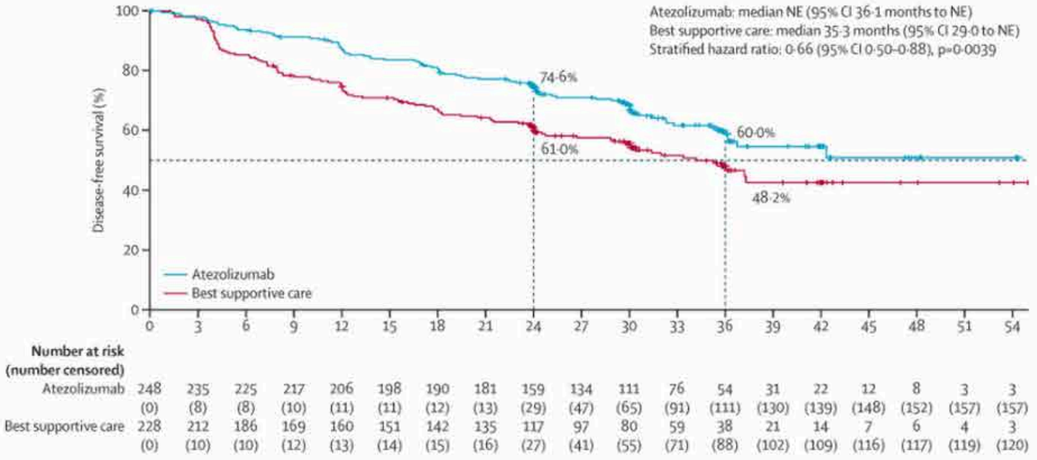
Felip E et al Lancet 2021, O'Brien M et al. Lancet Oncol. 2022

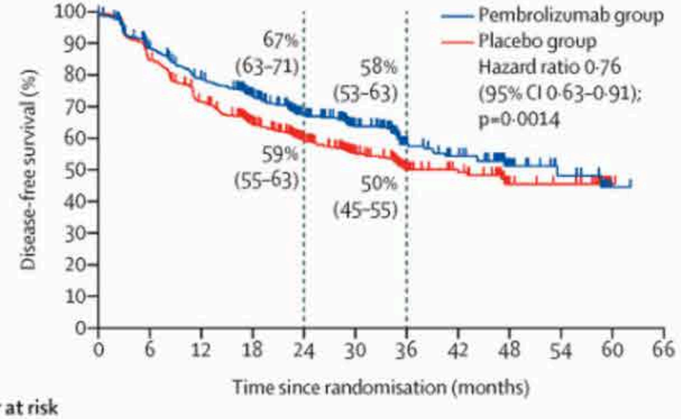
Disease Free Survival

IMpower 010
Stage 2-3A

PD-L1 ≥1%



Keynote-091



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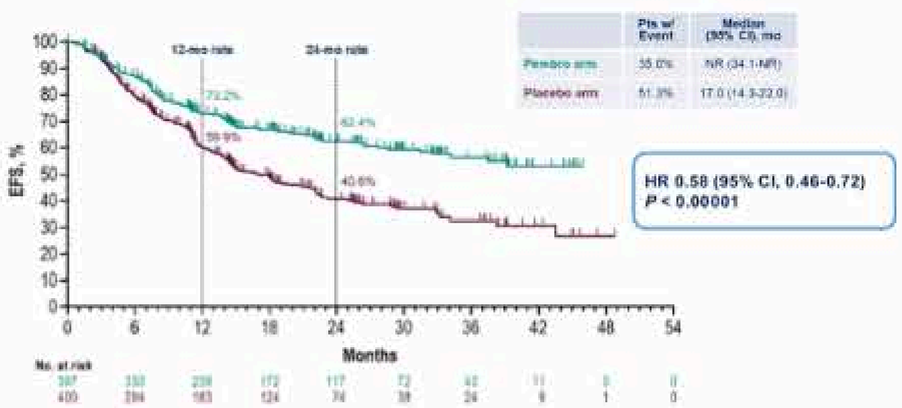
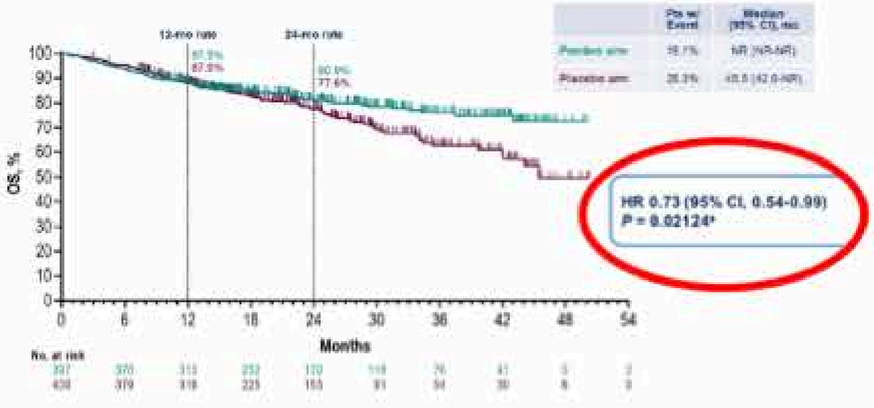
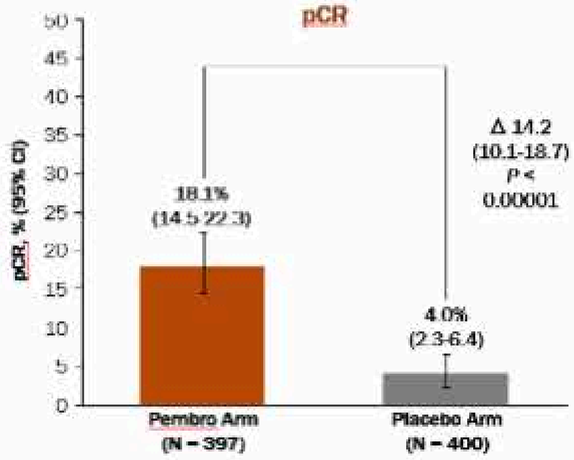
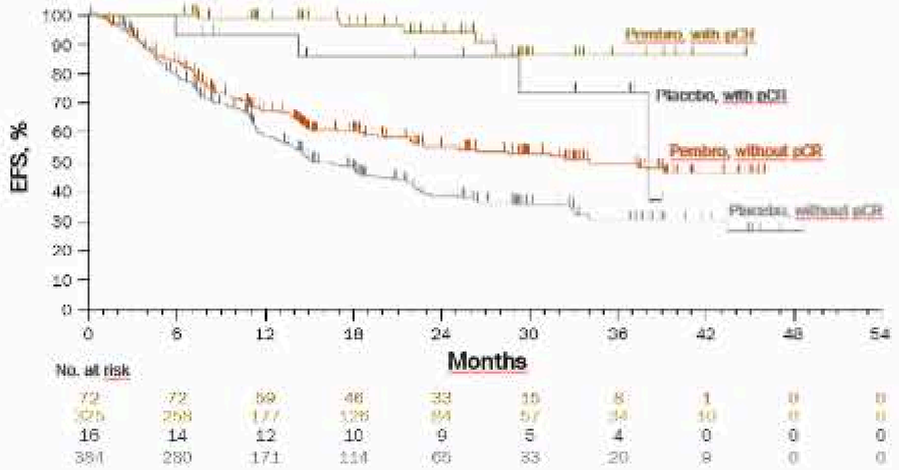
Felip E et al Lancet 2021, O'Brien M et al. Lancet Oncol. 2022

KeyNote 671 Pembrolizumab + Chemotherapy









With pCR
HR 0.33
(95% CI, 0.09-1.22)

Without pCR
HR 0.69
(95% CI, 0.55-0.85)

Wakelee H et al ASCO 2023

Questions that remain Unanswered

- What is the best treatment after First line treatment?
- Does every patient with metastatic disease need chemotherapy added to immunotherapy?
- Who benefits the most from treatment with two checkpoint inhibitors?
- In the early stage setting, do we have to give everyone a year of check point inhibitors?
- MORE RESEARCH IS NEEDED

Small cell lung cancer

Lauren Averett Byers, MD

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Lung Cancer: Addressing Unmet Needs

Advancing Precision Medicine in Small Cell Lung Cancer

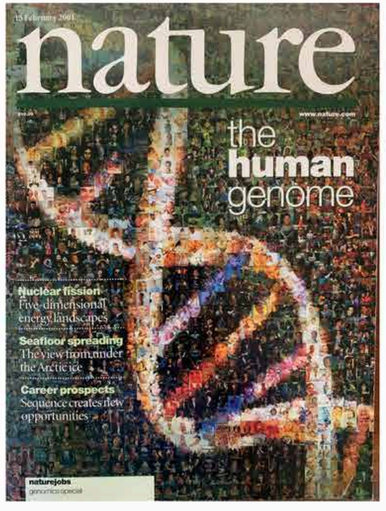
Lauren Averett Byers, MD
Professor and Thoracic Section Chief
MD Anderson Cancer Center

LCRF Annual Symposium

@LaurenByersMD
November 4, 2024

LUNG CANCER RESEARCH FOUNDATION®

Revolution in Cancer Care through Science



2001 – First Targeted Therapy

2001 - First Human Genome

2004 - First Targeted Lung Cancer Therapy (EGFR inhibitors)

2011 – First Immunotherapy

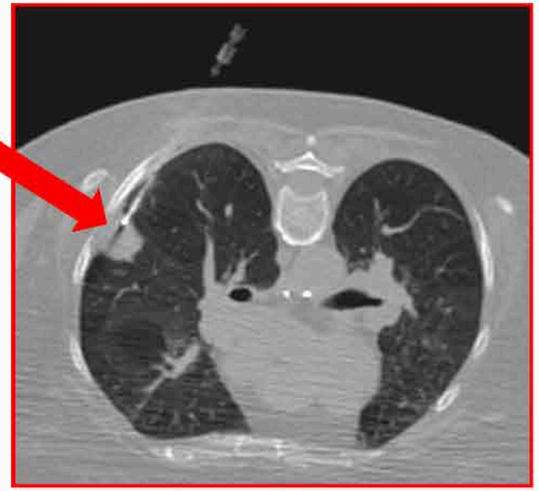
2019, 2020 *– Immunotherapies approved (with chemotherapy) for Frontline Extensive Stage SCLC*

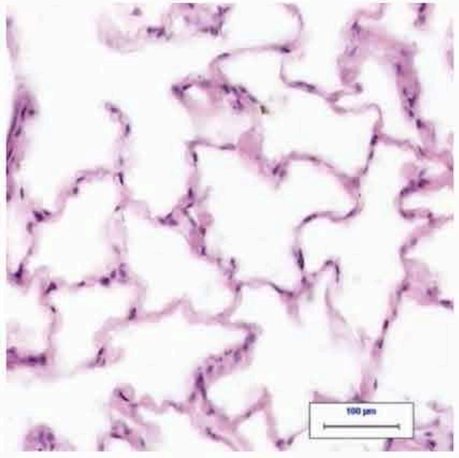
May 2024 *– Tarlatamab (T-cell engager targeting "DLL3" approved)*

Coming soon*... Approval of immunotherapy following chemo-radiation for Limited Stage SCLC (based on a 2-year improvement in survival)*

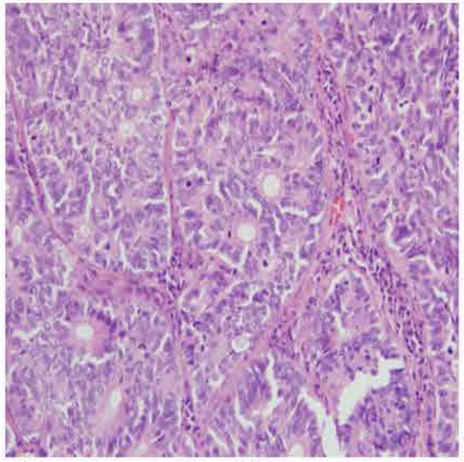
Lung cancer is many different diseases

Lung Biopsy

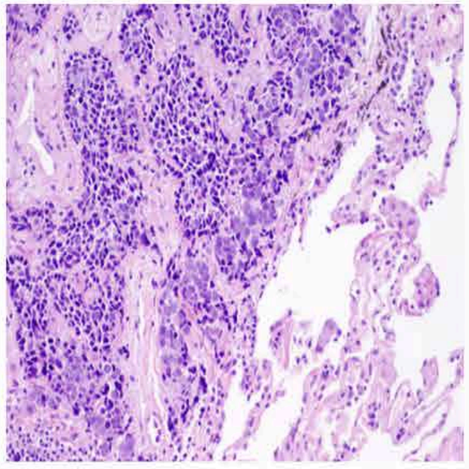




Normal Lung

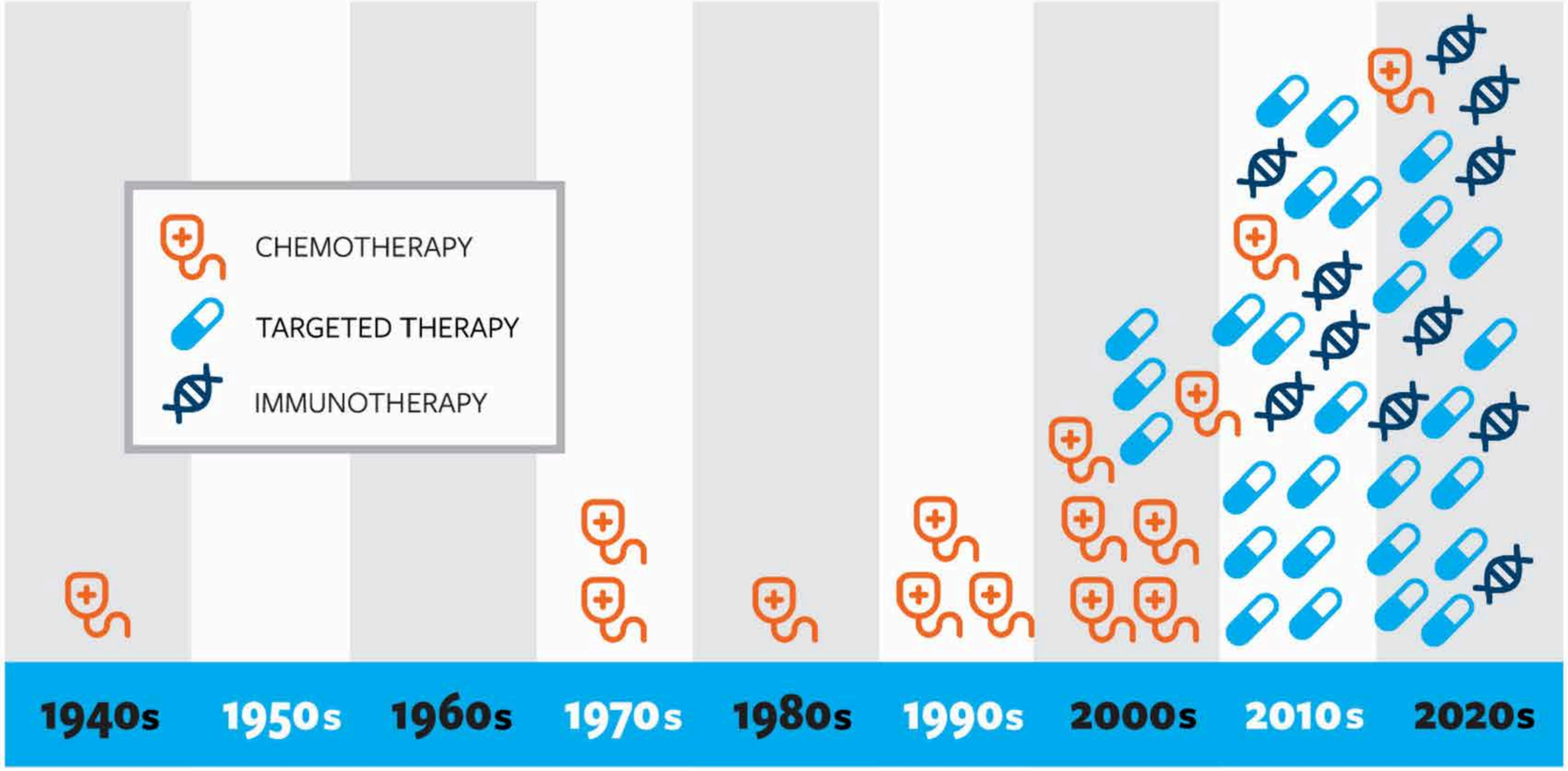


Non-small cell lung cancer
(Ex., Adenocarcinoma)



Small cell lung cancer

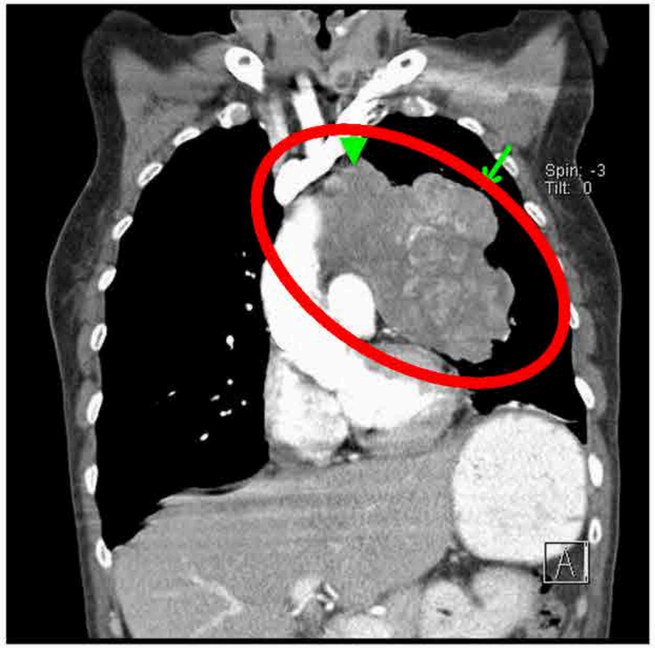
Remarkable progress for patients with lung cancer



Lung cancer treatment approvals over the decades

History of lung cancer treatment advances (updated 1/24); Lung Cancer Research Foundation

Small Cell Lung Cancer (SCLC)



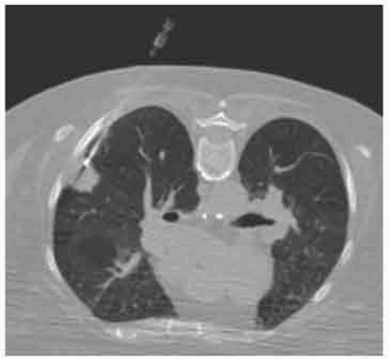
Small Cell Lung Cancer
(Farago et al, TLCR 2018)

- Most aggressive form of lung cancer
- 70% of patients have metastatic cancer
- Initially responds to chemotherapy and radiation, but drug resistance develops within a few months
- Median survival with current treatments is 1 year

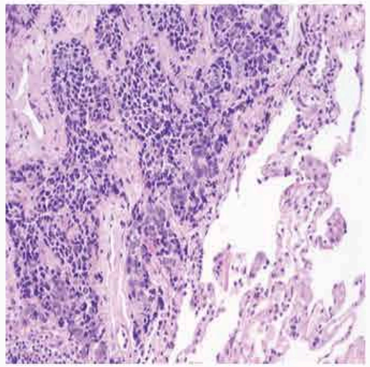
Govindan et al *J Clin Oncol* 2006 24(28): 4539-4544
Siegel et al, Cancer statistics, 2018. *CA: A Cancer Journal for Clinicians*, 68: 7-30
Farago and Keane, *Translational Lung Cancer Research*, 2018

Urgent need for **personalized, biomarker-driven** therapies for Small Cell Lung Cancer (SCLC)

Tumor Biopsy



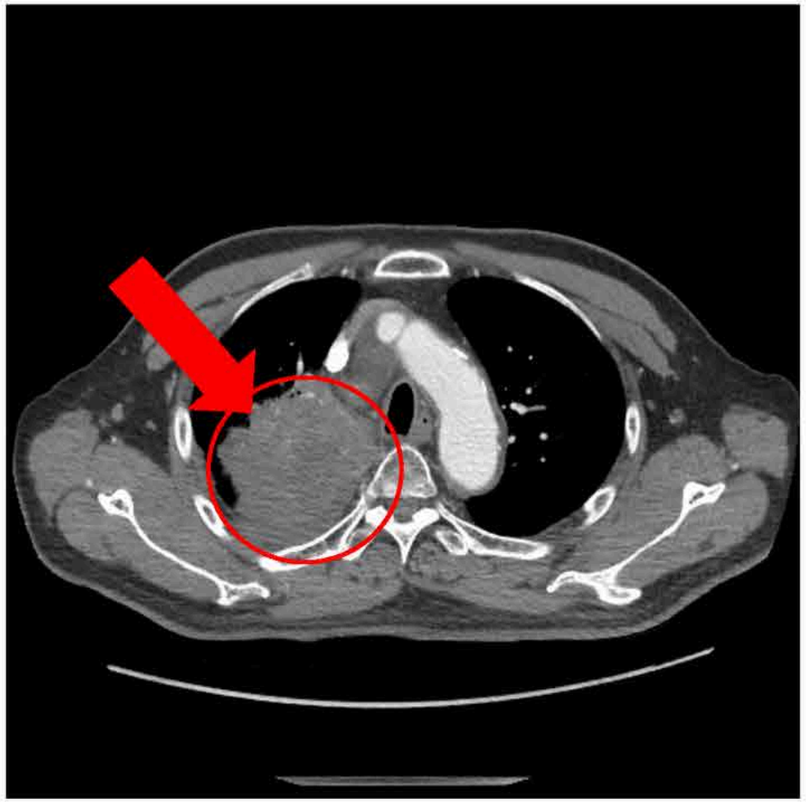
SCLC Diagnosis



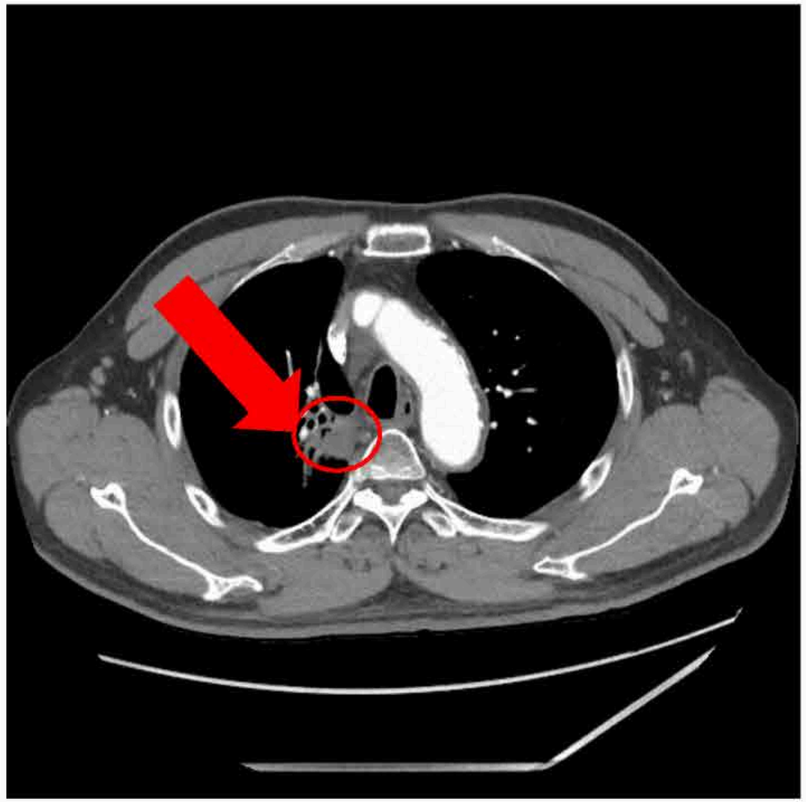
Historically treated as "One-size-fits-all"

(all patients treated the same)

A radical new way to fight cancer -- **Immunotherapy**



Before treatment



After immunotherapy

The New England
Journal of Medicine

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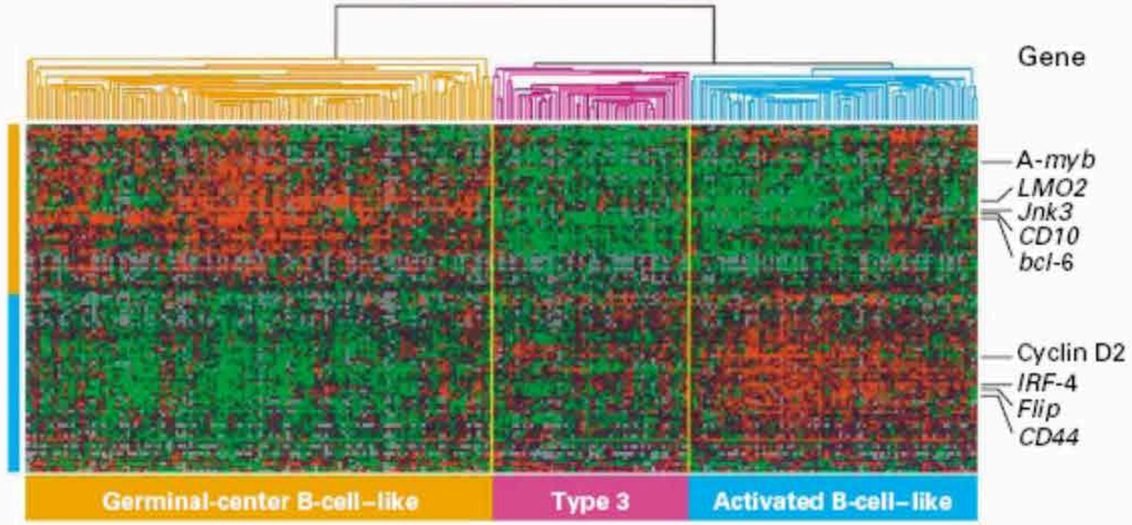
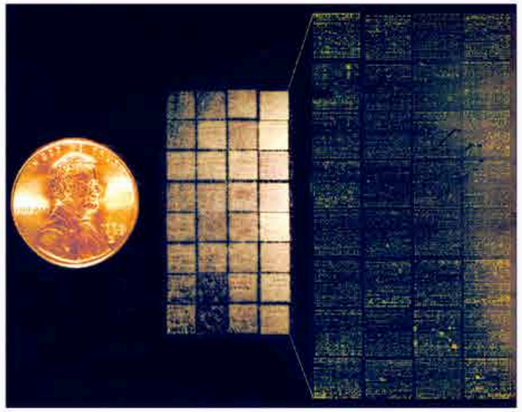
VOLUME 346 JUNE 20, 2002 NUMBER 25

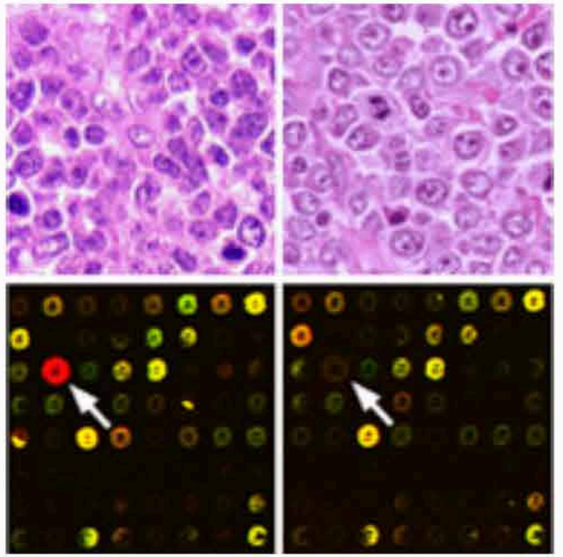
ORIGINAL ARTICLE

The Use of Molecular Profiling to Predict Survival after Chemotherapy for Diffuse Large-B-Cell Lymphoma

Andreas Rosenwald, M.D., George Wright, Ph.D., Wing C. Chan, M.D., Joseph M. Connors, M.D., Elias Campo, M.D., Richard I. Fisher, M.D., Randy D. Gascoyne, M.D., H. Konrad Muller-Hermelink, M.D., Erlend B. Smeland, M.D., Ph.D., Jena M. Giltnane, B.S., Elaine M. Hurt, Ph.D., Hong Zhao, M.S., Lauren Averett, B.A., Liming Yang, Ph.D., Wyndham H. Wilson, M.D., Ph.D., Elaine S. Jaffe, M.D., Richard Simon, D.Sc., Richard D. Klausner, M.D., John Powell, M.S., Patricia L. Duffey, R.N., Dan L. Longo, M.D., Timothy C. Greiner, M.D., Dennis D. Weisenburger, M.D., Warren G. Sanger, Ph.D., Bhavana J. Dave, Ph.D., James C. Lynch, Ph.D., Julie Vose, M.D., James O. Armitage, M.D., Emilio Montserrat, M.D., Armando López-Guillermo, M.D., Thomas M. Grogan, M.D., Thomas P. Miller, M.D., Michel LeBlanc, Ph.D., German Ott, M.D., Stein Kvaloy, M.D., Ph.D., Jan Delabie, M.D., Ph.D., Harald Holte, M.D., Ph.D., Peter Krajci, M.D., Ph.D., Trond Stokke, Ph.D., and Louis M. Staudt, M.D., Ph.D. for the Lymphoma/Leukemia Molecular Profiling Project

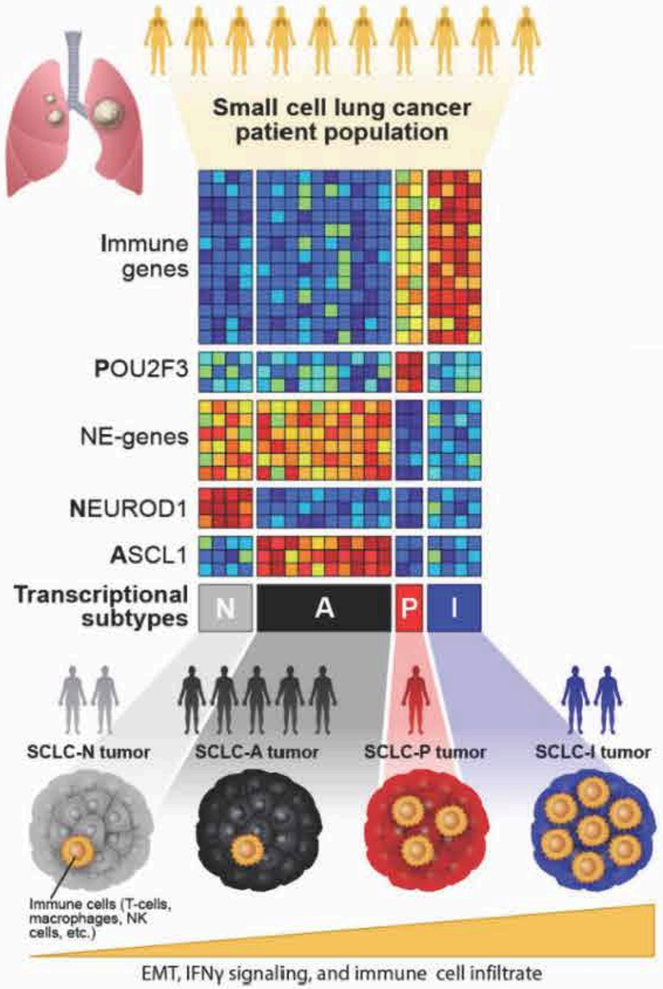




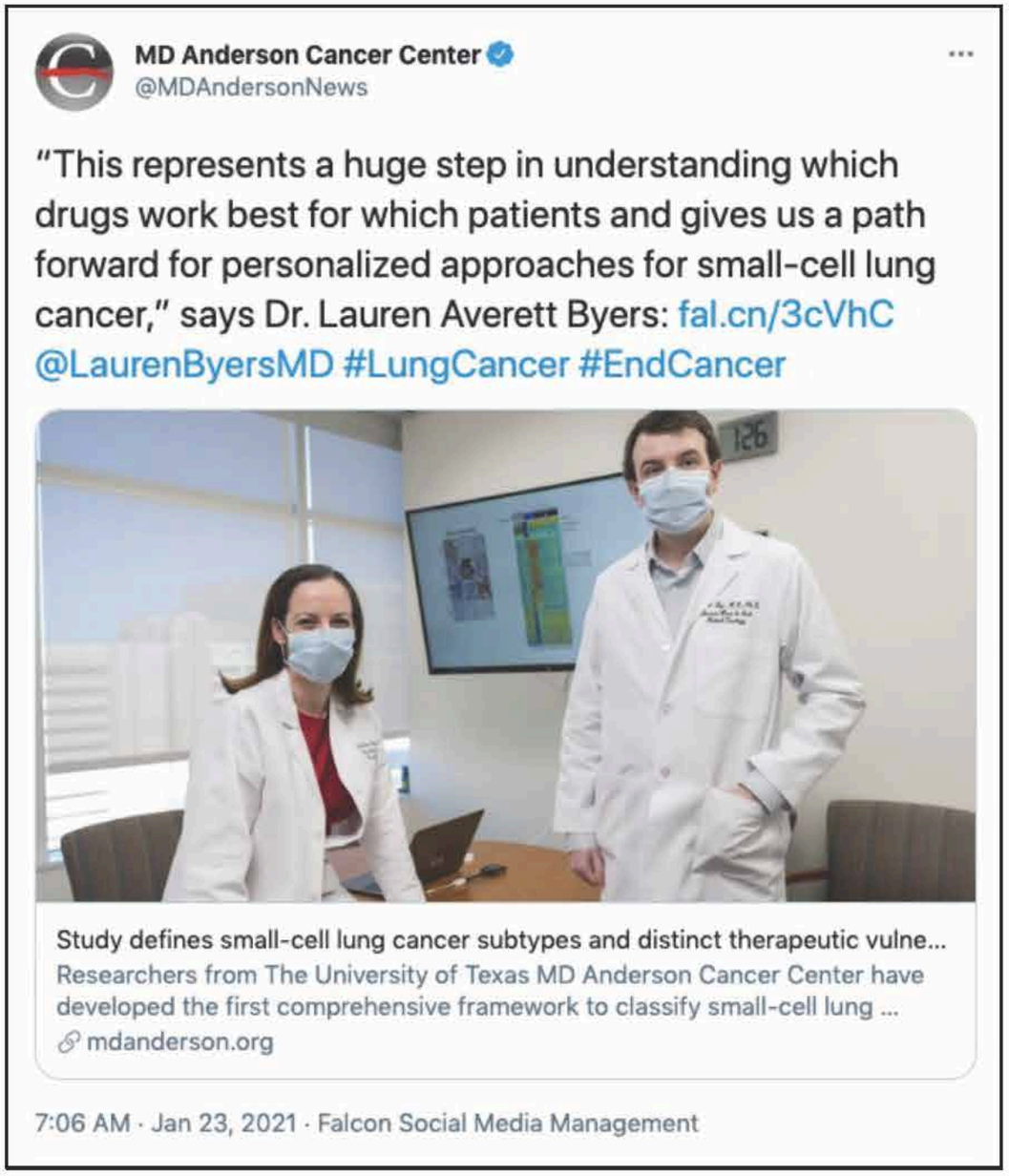


Cancer Cell

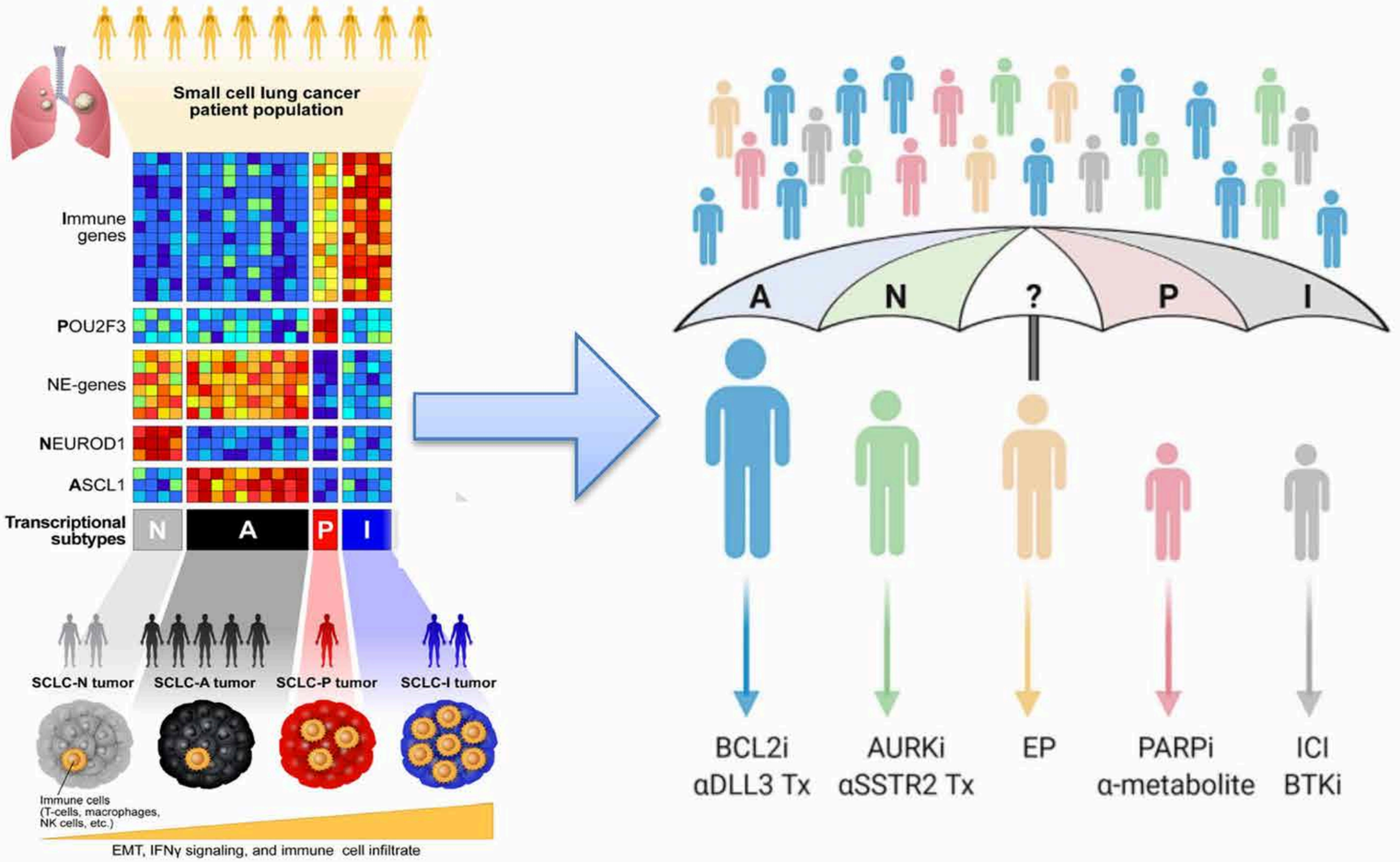
Patterns of transcription factor programs and immune pathway activation define four major subtypes of SCLC with distinct therapeutic vulnerabilities

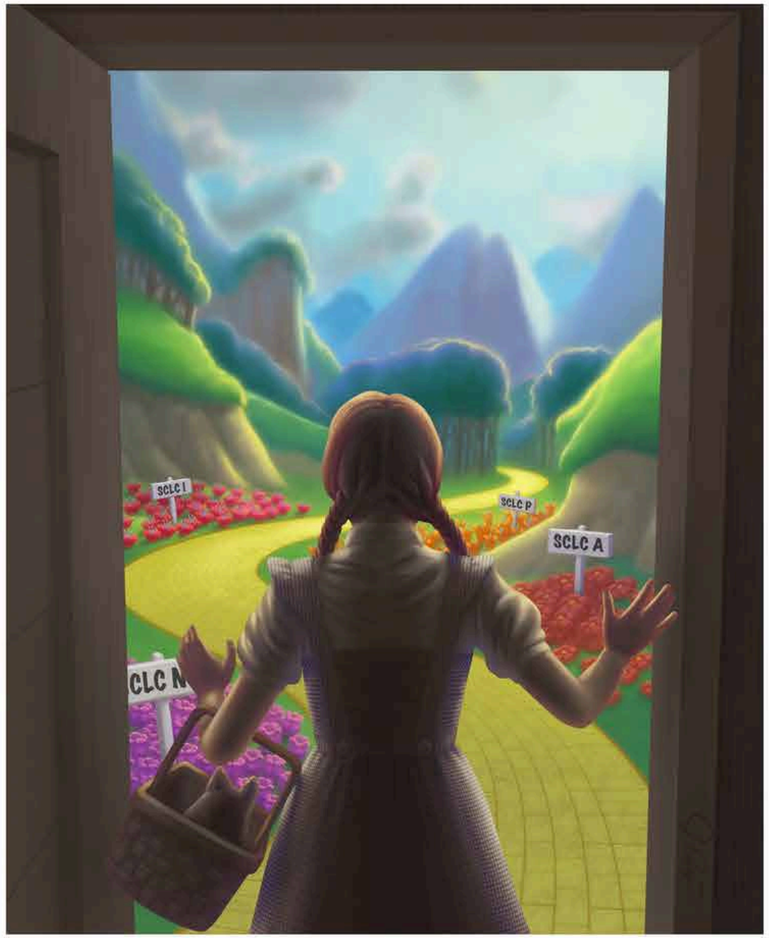


Gay, et al, Cancer Cell 2021



Distinct drug targets in each **SCLC subtype** opens the door to personalized treatments for patients

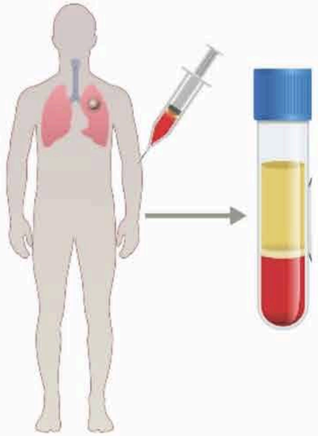


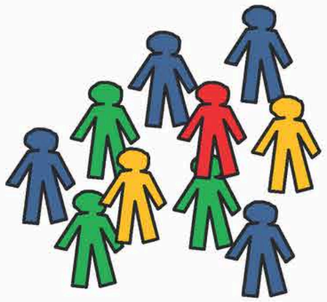


Gay, Stewart, Park et al, Cancer Cell 2021
SWOG PRISM Trial will be the first SCLC Subtype-matched clinical trial

Personalized SCLC Treatment: *Clinical Trials*

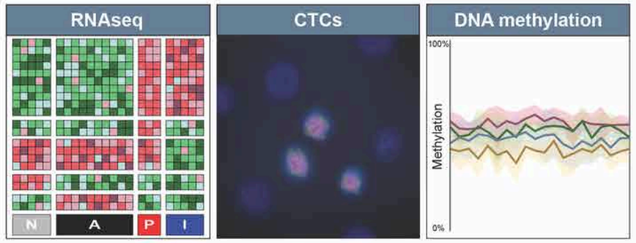
Collect patient blood





"Liquid Biopsy"
e.g., ctDNA methylation profiling for SCLC subtype/target expression

Patients matched to treatment based on SCLC subtype and other biomarkers



Targeted Treatment 1

Targeted Treatment 2

Targeted Treatment 3

Targeted Treatment 4

Small Cell Lung Cancer "sheds" cancer DNA (ctDNA) into the blood and can be used as a biomarker

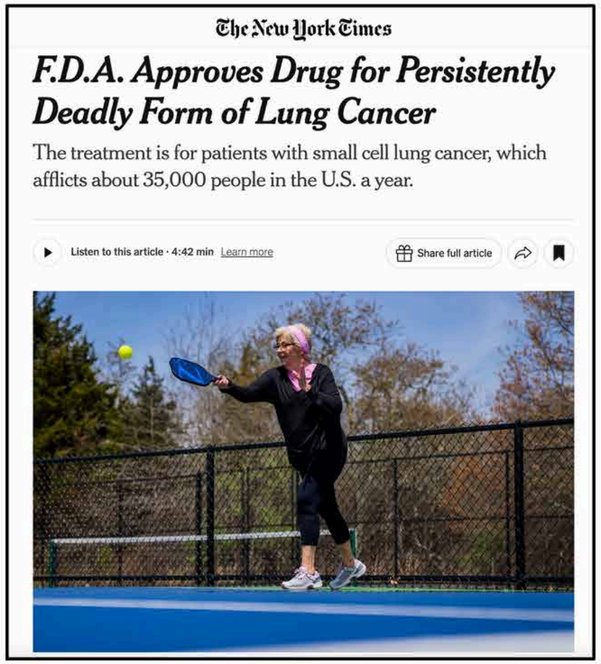
Our goal is to transform SCLC treatment through New, Personalized Therapeutics and "Liquid" Biomarkers (blood tests)

Mapping the **tumor surface** for anti-cancer therapies

ADC – **A**ntibody **D**rug **C**onjugate; antibody binds to tumor cell and delivers chemotherapy payload

CAR – **C**himeric **A**ntigen **R**eceptor; engineered immune cell that is attracted to tumor cell

Bi-specific **T**-cell **E**ngager (**BiTE**) – binds to both immune cells and tumor cell to bring the two together.

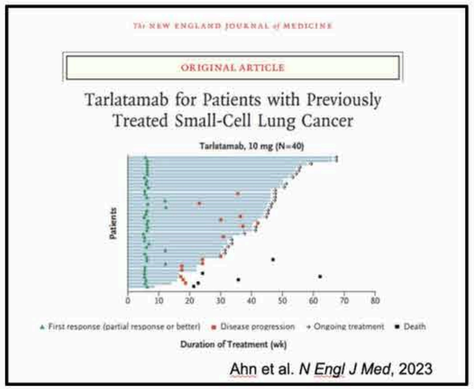

The New York Times

F.D.A. Approves Drug for Persistently Deadly Form of Lung Cancer

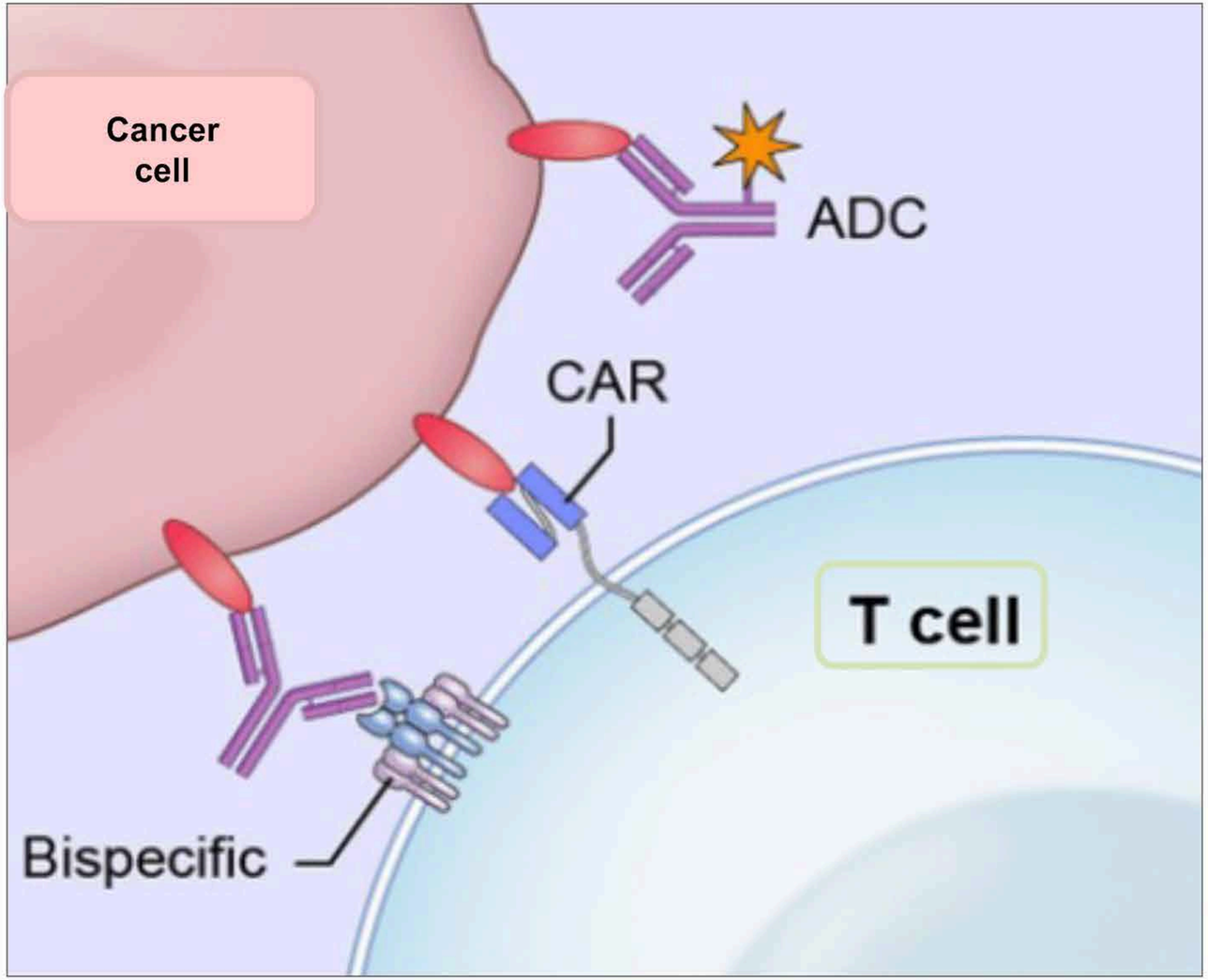
The treatment is for patients with small cell lung cancer, which afflicts about 35,000 people in the U.S. a year.

Listen to this article · 4:42 min Learn more

Share full article



Ahn et al. *N Engl J Med*, 2023



Overview of “CAR” T-cell therapy – a “living drug”

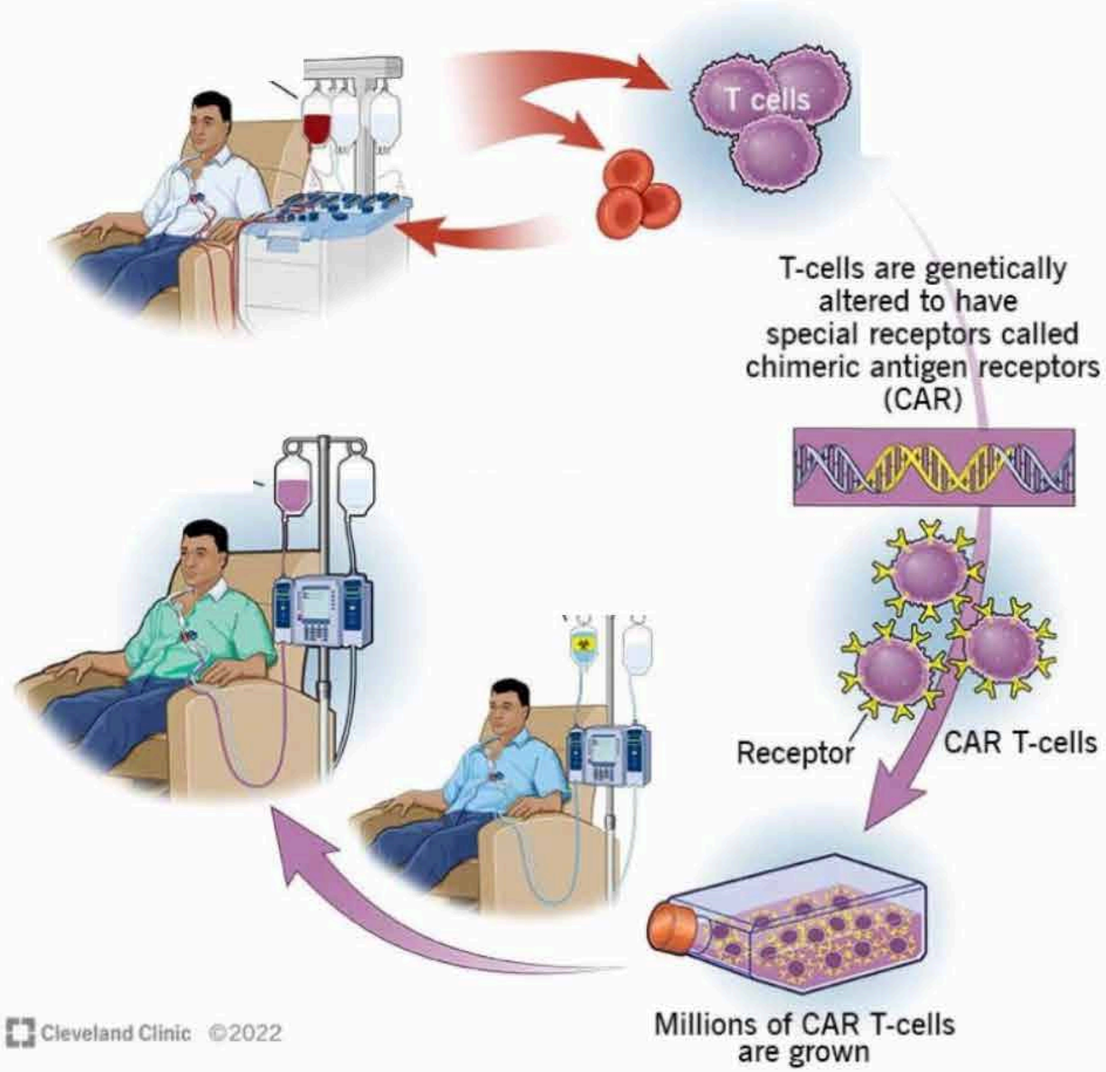
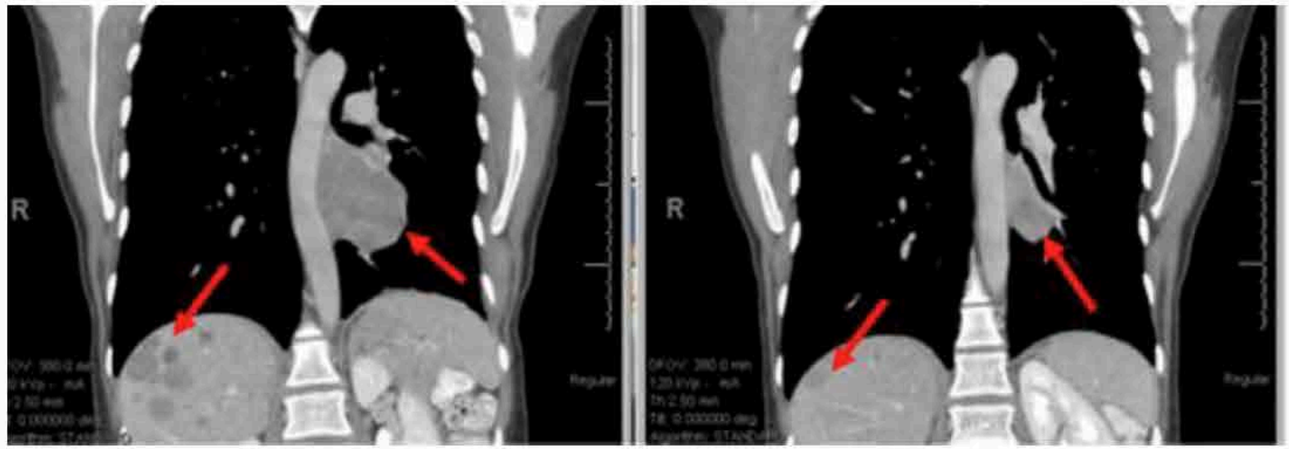


Image from Clevelandclinic.org

Before treatment

1 month after CAR-T



Byers, et al. SITC 2022

II

112TH CONGRESS
2D SESSION

S. 3560

To provide for scientific frameworks with respect to recalcitrant cancers.

IN THE SENATE OF THE UNITED STATES

SEPTEMBER 19, 2012

Mr. WHITEHOUSE (for himself, Mr. LUGAR, Ms. MIKULSKI, Mr. GRASSLEY, Mr. AKAKA, Ms. COLLINS, Mr. REED, Mr. PRYOR, Ms. STABENOW, Mr. BROWN of Massachusetts, Mr. LAUTENBERG, Mr. BLUNT, Mr. BROWN of Ohio, Mr. RUBIO, Mr. BLUMENTHAL, Mr. WICKER, Mr. TESTER, and Mr. WARNER) introduced the following bill; which was read twice and referred to the Committee on Health, Education, Labor, and Pensions

---

A BILL

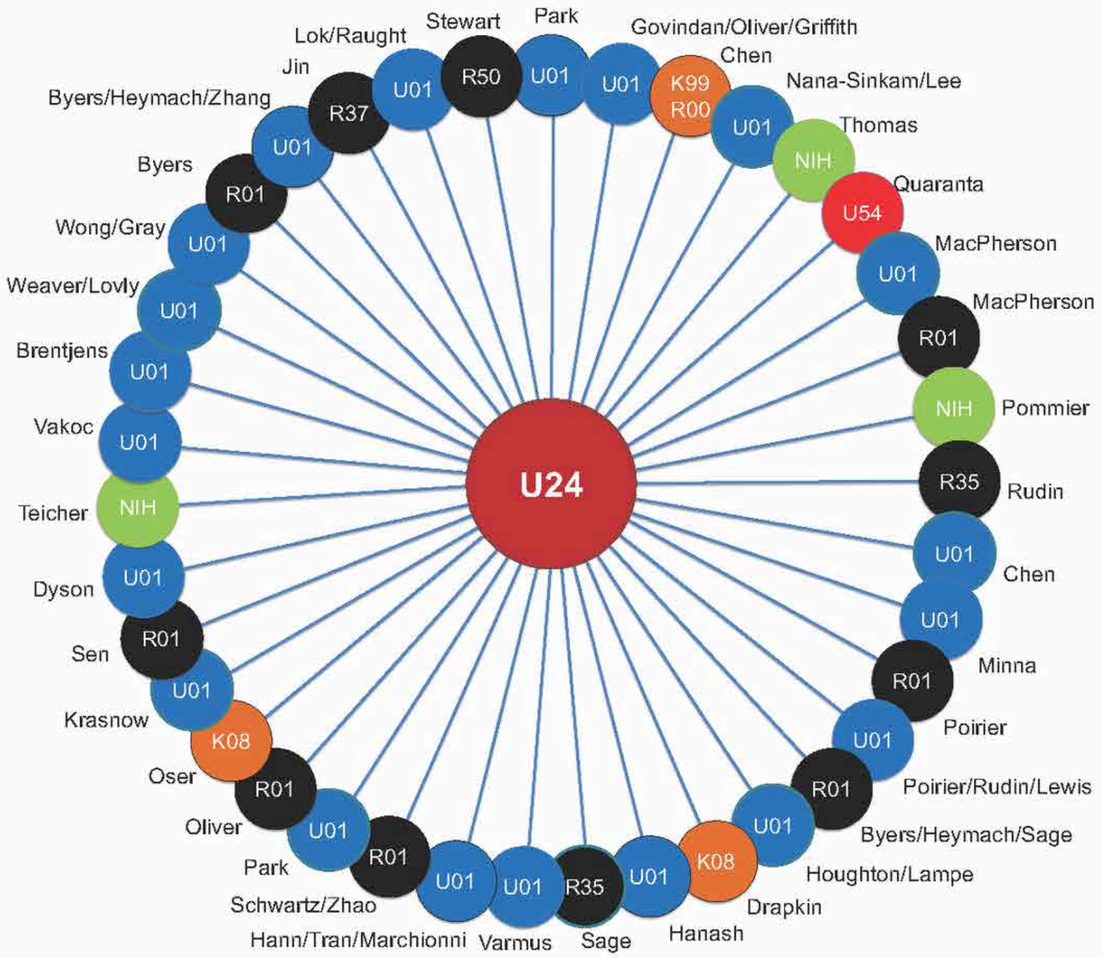
To provide for scientific frameworks with respect to recalcitrant cancers.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "Recalcitrant Cancer Research Act of 2012".

National Cancer Institute established the **Small Cell Lung Cancer Consortium** in 2012 to accelerate research advances



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Thank you!

Byers Lab:
C. Allison Stewart
Robert Cardnell
Kavya Ramkumar
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Runsheng Wang
Ali Ibrahim
Kyle Concannon
Bing Zhang
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Yuanxin (Fred) Xi
Li Shen
Qi Wang
Pan Tong (Former)
Lerong Li (Former)

MD Anderson:
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John Heymach
Simon Heeke
Don Gibbons
Marcelo Vailati Negrao
Billy Wang
Bonnie Glisson
Junya Fujimoto
Ignacio Wistuba
Bob Bast
Waun Ki Hong

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NIH/NCI U01- Heymach, Sage, Byers
NIH/NCI U01 – Byers, Heymach, Zhang
NIH/NCI U24
MD Anderson Cancer Center CCSG (P30-CA01667)
University of Texas SPORE in Lung Cancer (P5-CA070907)
NIH/NCI T32 CA009666
NIH/NCI R50-CA243698 (Allison Stewart)
MD Anderson Cancer Center Small Cell Lung Cancer Working Group and Abell Hangar Foundation Distinguished Professor Endowment
Through generous philanthropic contributions to The University of Texas MD Anderson Cancer Center Lung Cancer Moonshot Program
The Rexanna Foundation for Fighting Lung Cancer
The Andrew Sabin Family Fellowship
The Department of Defense (LC170171)
The Hope Foundation SWOG/ITSC Pilot Program (w/ Paul Robson)
LUNGevity Foundation

Lung Cancer Research Foundation

NIH NATIONAL CANCER INSTITUTE

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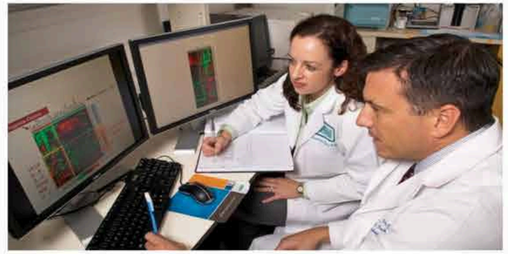
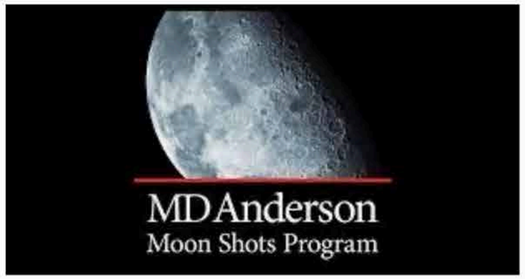


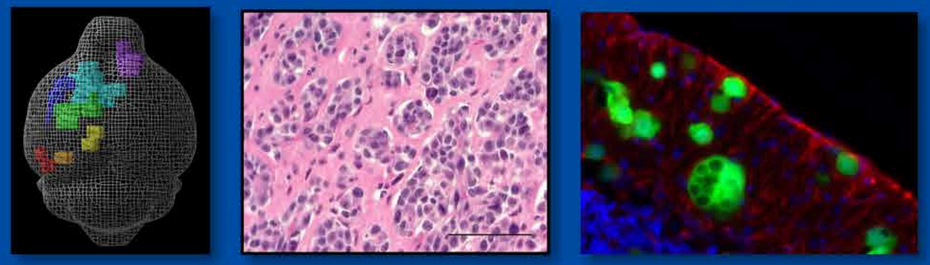
Lauren Averett Byers, M.D., and John Heymach, M.D., Ph.D., worked together to better understand gene response to Tarceva. Photo: Karen Hensley



Brain metastasis

Don Nguyen, PhD, BSc

NSCLC Metastasis to the Central Nervous System: Progress and Unmet Needs



Don X. Nguyen

LCRF Annual Symposium

November 4th, 2024

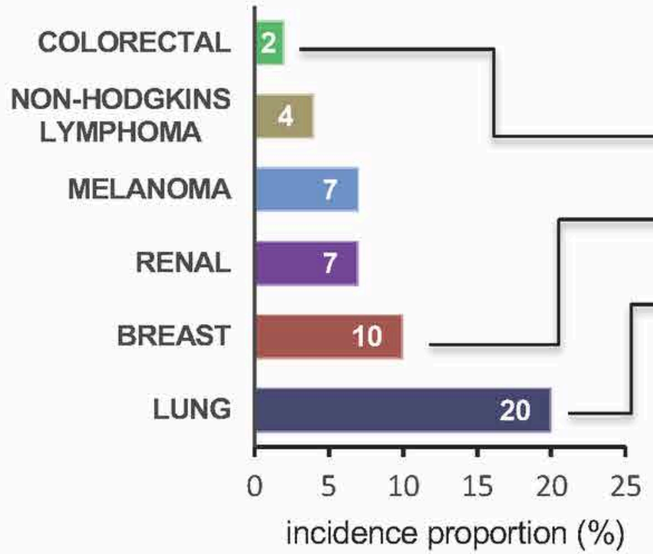
Yale SCHOOL OF MEDICINE

Disclosures

I have the following financial relationships to disclose:

- Grant/research support from AstraZeneca, Inc

Evolving Clinical Landscape of Brain Metastasis

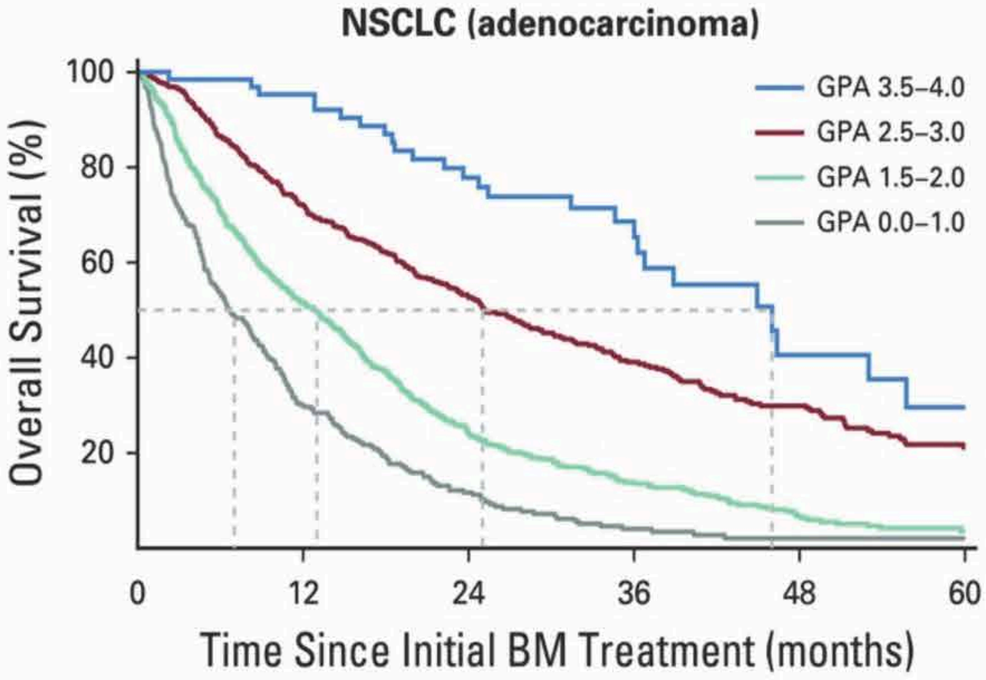


- ⬆ 2 fold b/w 1987-2006 (Smedby et. al.,2009)
- ⬆ 6-7 fold in patients on clinical trials (Shindorf et. al., 2020)
- ⬆ 2-3 fold In HER2+ and TNBC. ⬆ 2 fold in ER+/HER2− (w/*PI3K*mut) (Fitzgerald et. al., 2019)
- ⬆ 1.5-2 fold with targeted therapy (Offin et. al., 2019)

⬆ Disparities in diagnosis and access to care

2010-2016	Lung Brain Metastasis (n = 29,502)		
Characteristic	**aHR***	**95% CI**	***P* Value**
Yost quintile			
Fifth	1.00	—	—
Fourth	1.07	1.03–1.12	**0.001**
Third	1.17	1.12–1.22	**<0.001**
Second	1.18	1.14–1.23	**<0.001**
First	1.22	1.17–1.27	**<0.001**

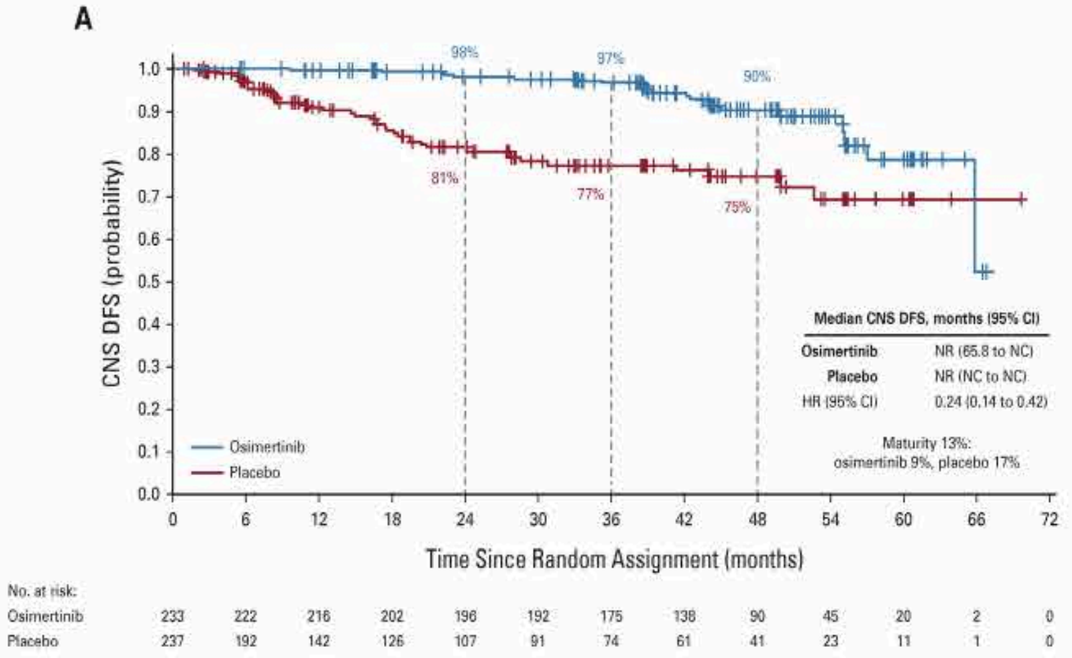
Rodrigues et. al., 2021



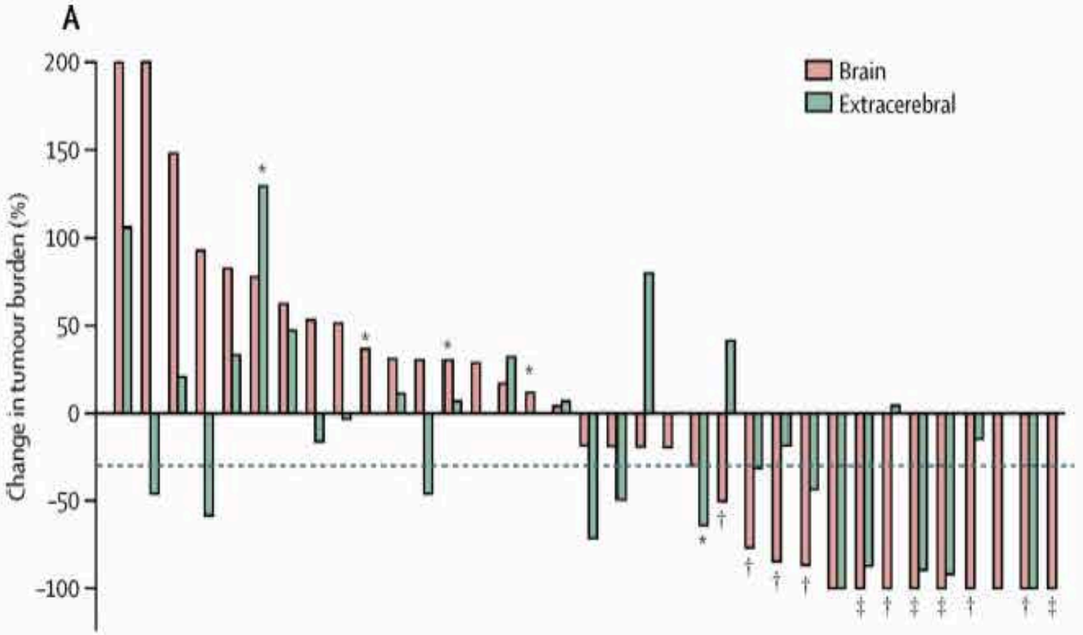
Sperduto PW et al, JCO, 2020

Is the Brain (Still) a Sanctuary Site in Non-Small Cell Lung Cancer?

- Historically, few systemic therapies were available for patients with NSCLC brain metastasis.



Herbst et al., 2023



Goldberg et al., 2020

Overview

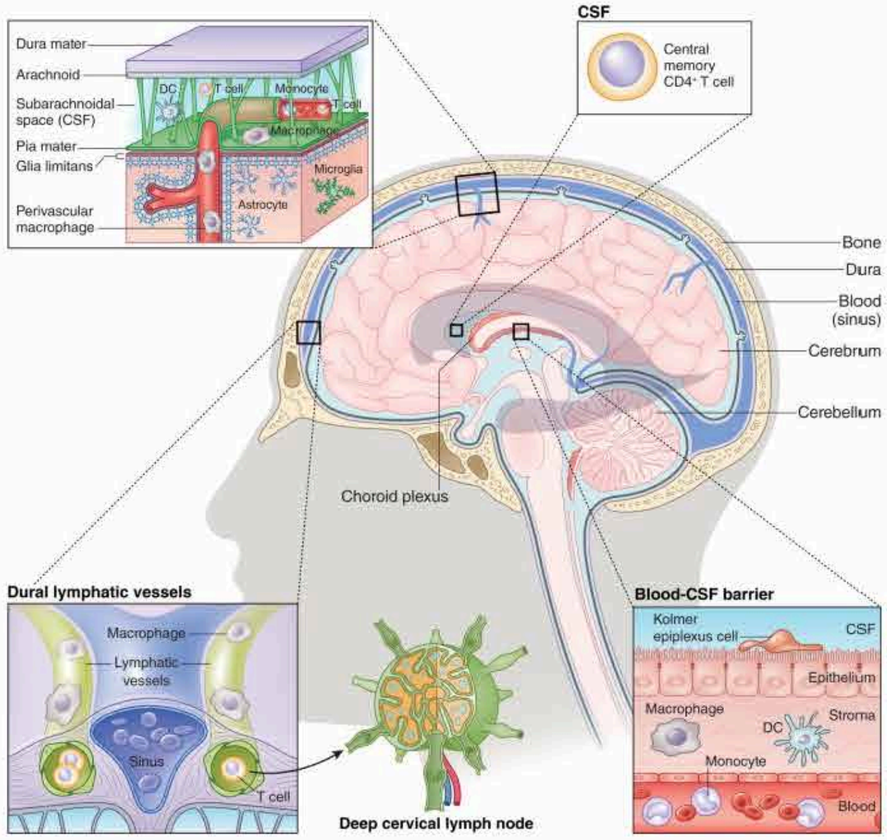
NSCLC Metastasis to the Central Nervous System (CNS)

I. Heterogeneity of CNS metastasis and response to immunotherapy

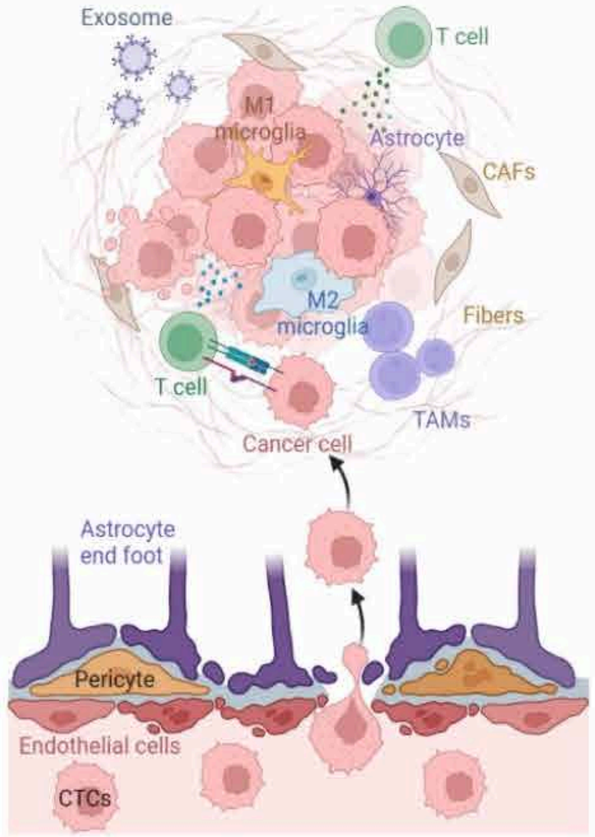
II. Mechanistic link between targeted therapy resistance and CNS metastasis

Location, Location, Location...

- **Cancer cells form metastasis in different regions of the CNS.**
- **The microenvironment surrounding tumor cells in the brain is unique.**



Pinz et al., 2017



Feng et al., 2024

Addressing the Issue of Tissue:
The Yale CNS Metastasis Biorepository

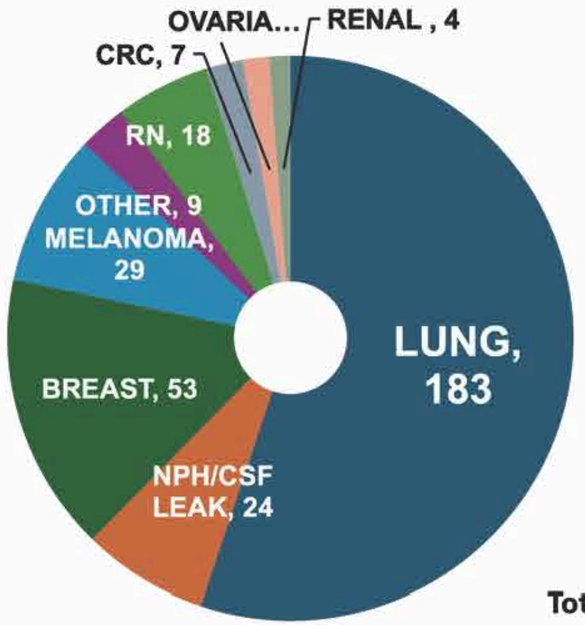
CNS Biorepository Team

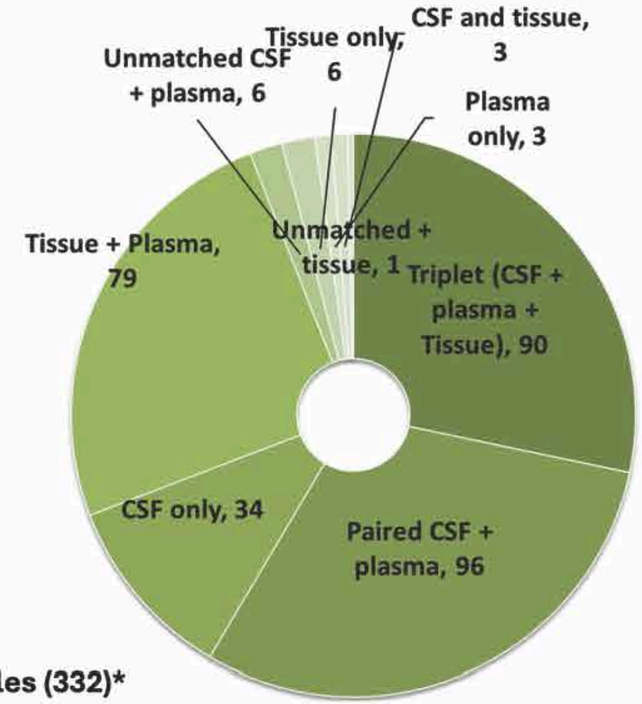
Veronica Chiang
Nicholas Blondin
Sarah Goldberg

Rocco Carbone

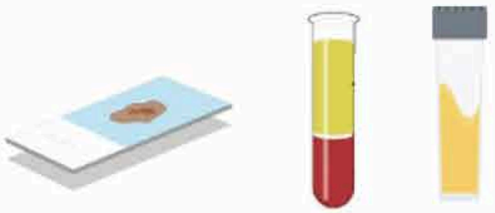
Sampada Chande
Tang Tang
Savannah Kandigian
Yuchen Huo
Anna Arnal Estapé

➢ ***Patients@ Smilow***



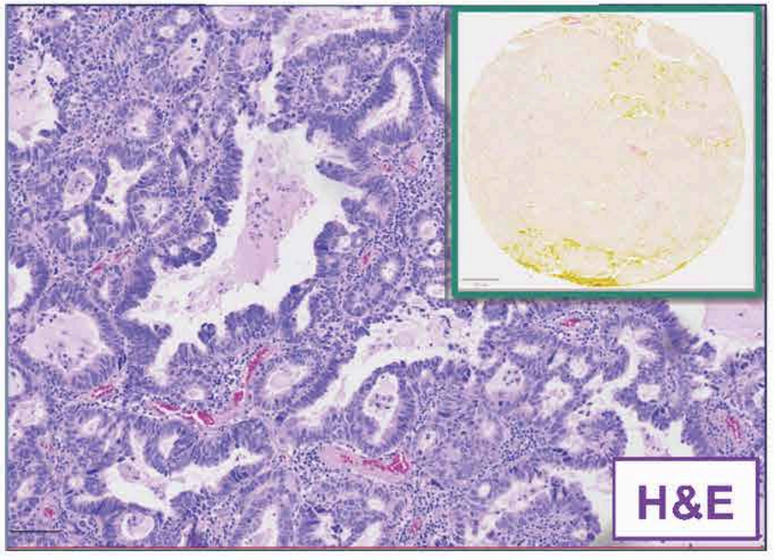


Total: samples (332)*
* includes serial samples



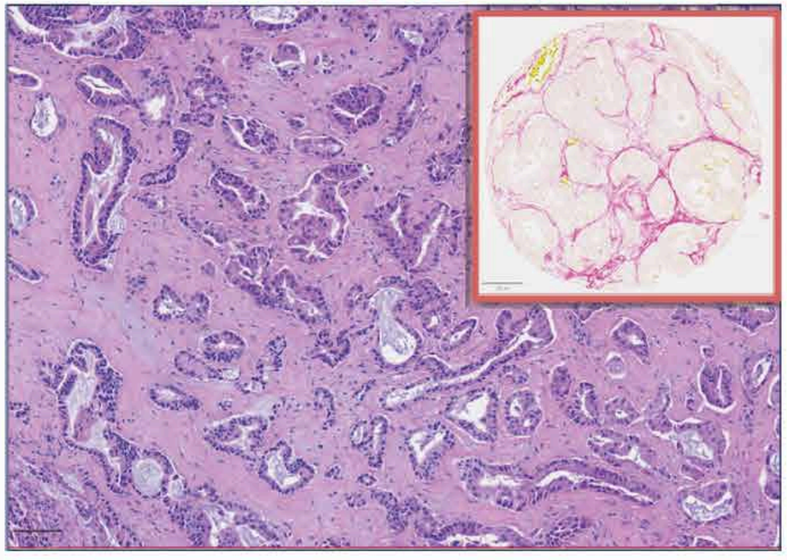
NSCLC Brain Metastases Are Not all the Same

Minimal fibrosis



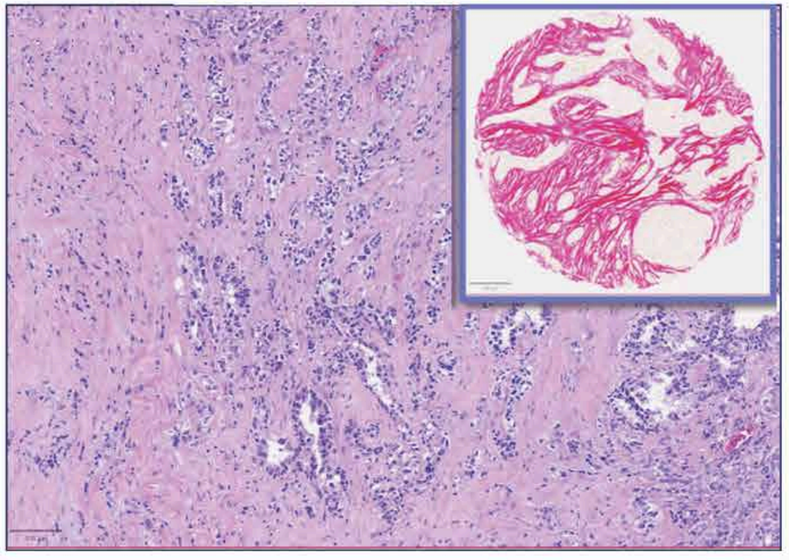
40% of cases

Fibrotic/Organizing stroma

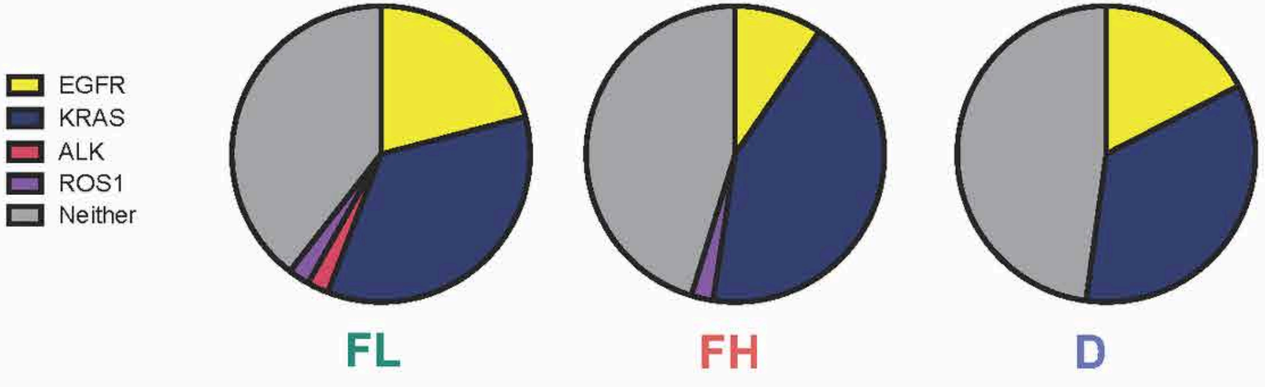


39% of cases

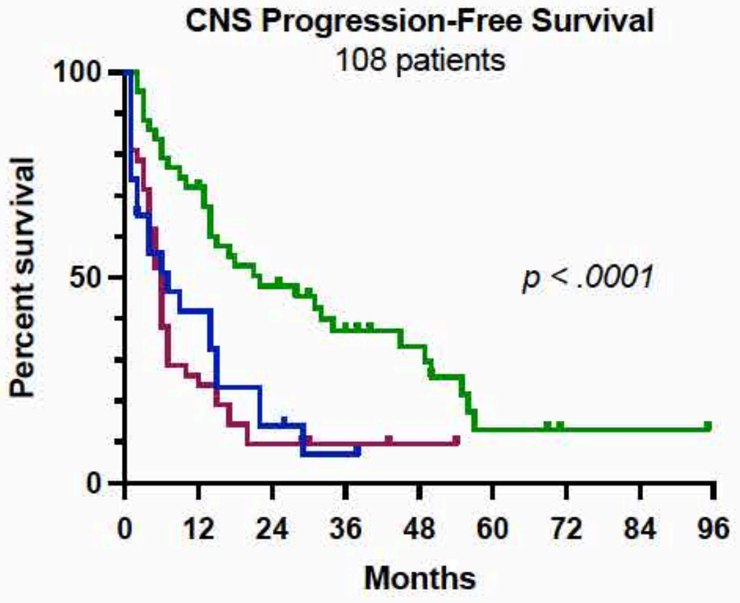
Dural involvement

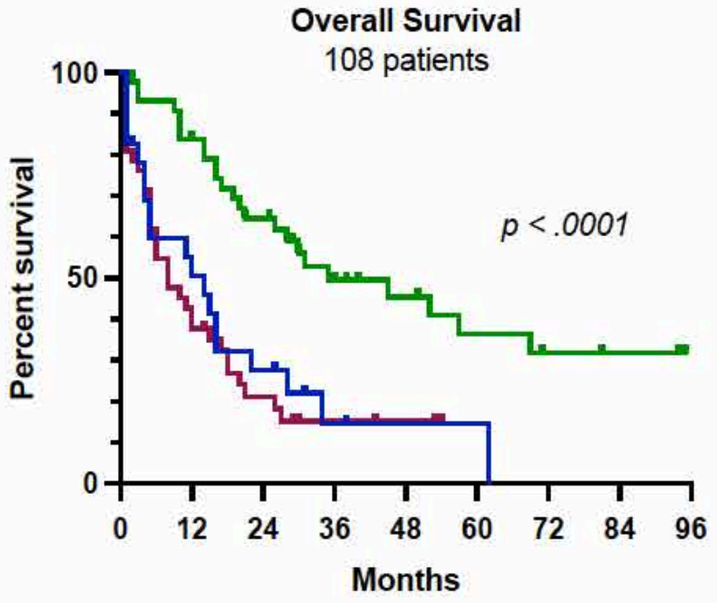


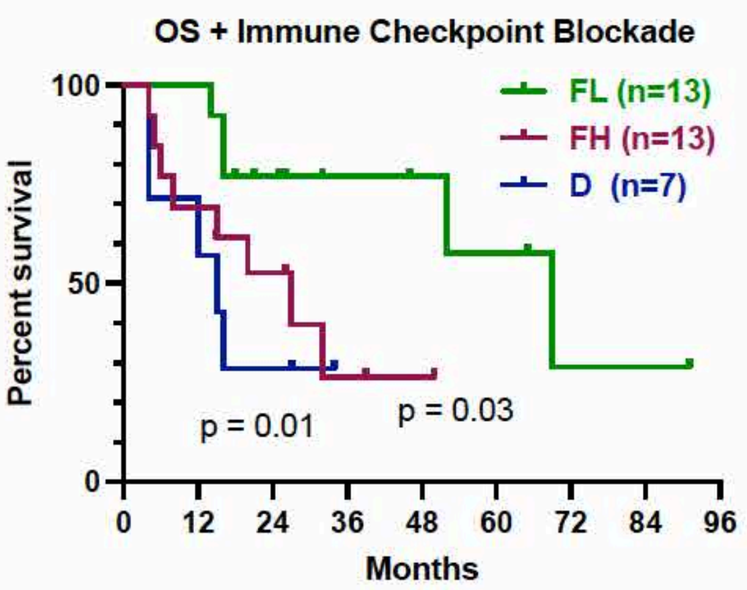
21% of cases

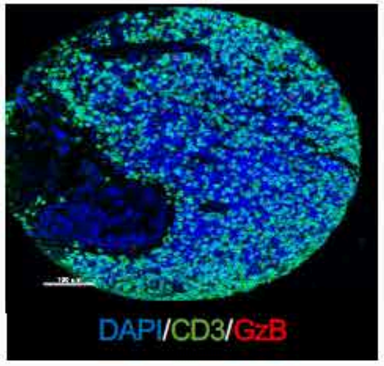


Fibrotic and Dural Metastases are Associated with Poor Outcome

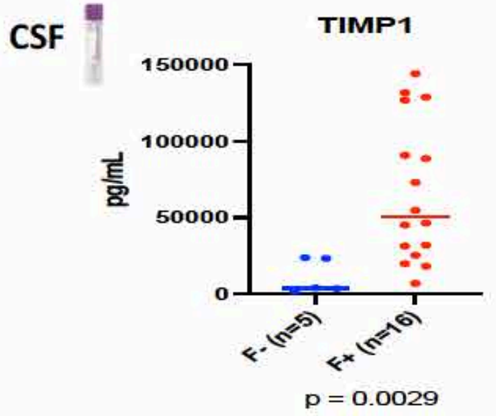




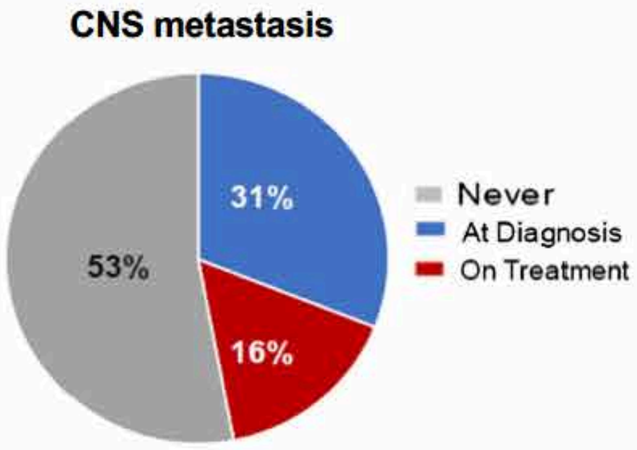




- Evidence of T cell dysfunction in tissue biopsies
- Detection of extracellular matrix proteins in cerebral spinal fluid (CSF) of patients

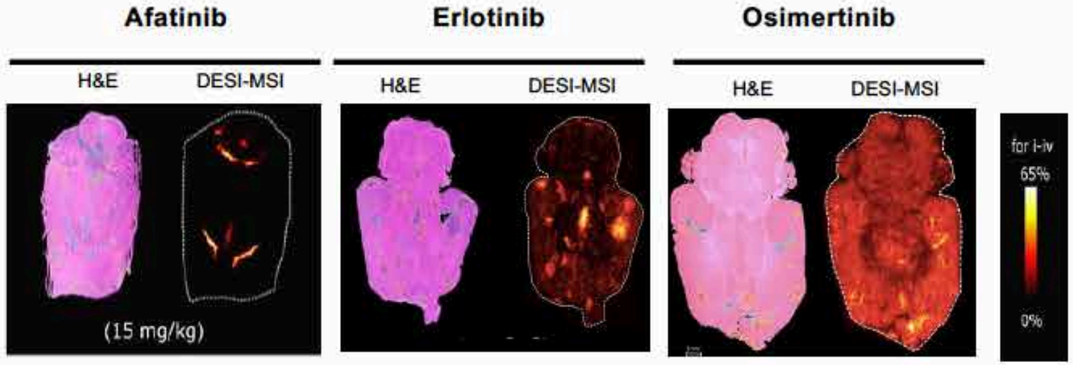


The EGFR mutant NSCLC Paradigm



Adapted from Offin, et al (2019)

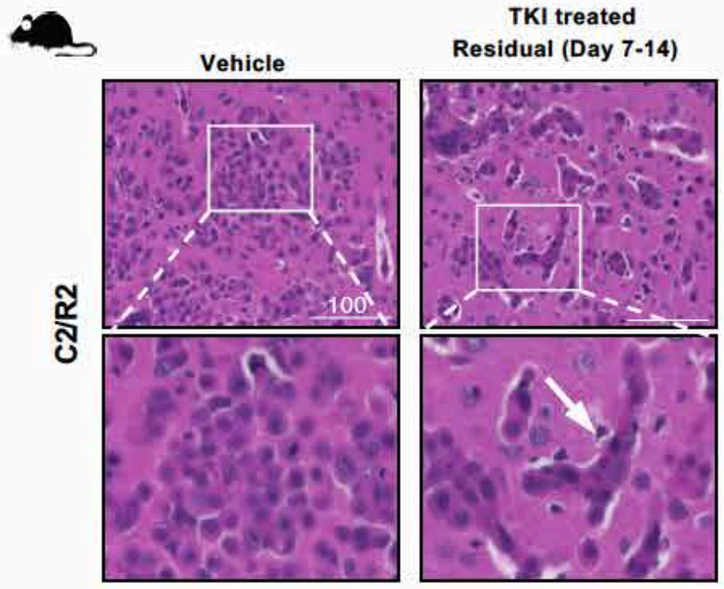
- 3rd Gen **brain penetrant** TKIs **osimertinib** is effective as first line therapy for EGFR mutant NSCLC:



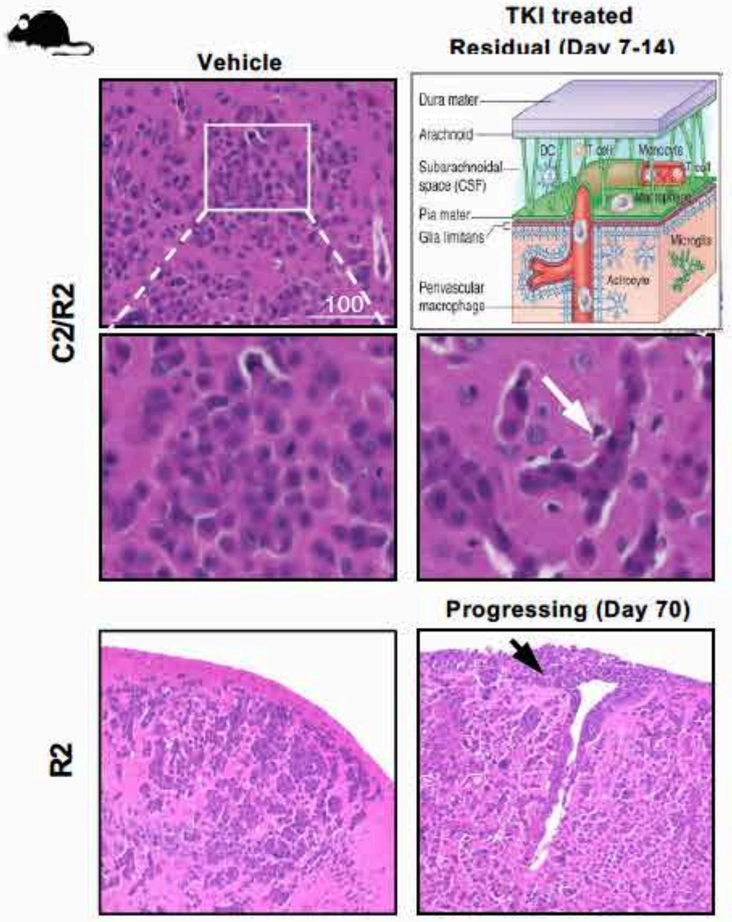
Colclough et al., 2021

- **What are the mechanism(s) linking osimertinib resistance and CNS relapse?**
- **How can we overcome drug resistance in the CNS?**

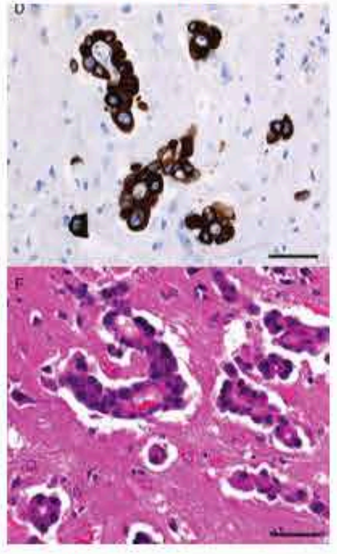
Resistance to anti-EGFR Therapy and Leptomeningeal Metastasis are linked to Changes in the Microenvironment



Resistance to anti-EGFR Therapy and Leptomeningeal Metastasis are linked to Changes in the Microenvironment

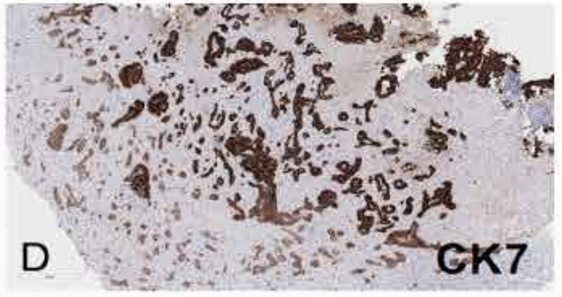


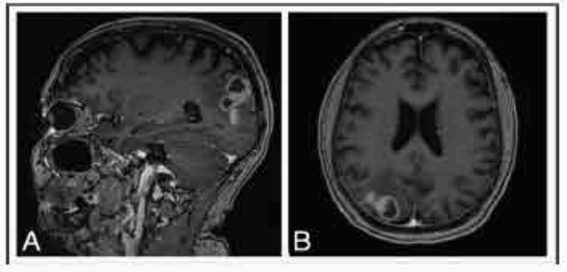
Miliary brain metastasis
in EGFR mut LUAD



Kiruhara, 2019
Wu, 2013; Sekine, 2012;
Togahsi , 2011; Poonia, 2011

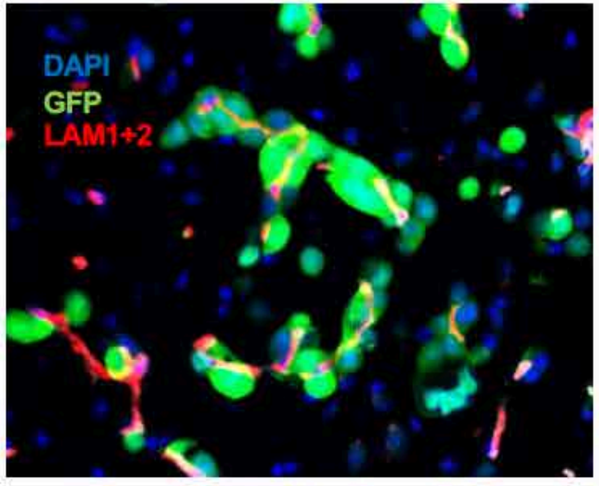
Concomitant with
Leptomeningeal Disease (LMD)



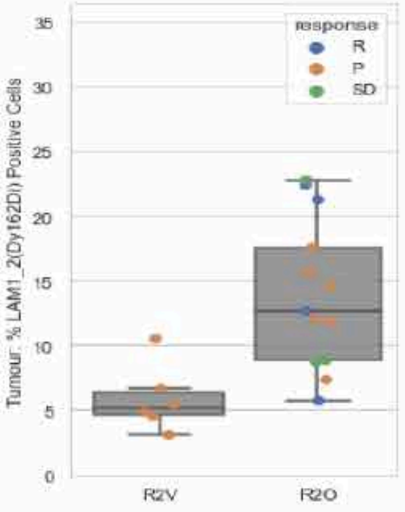


Dasgupta, 2020

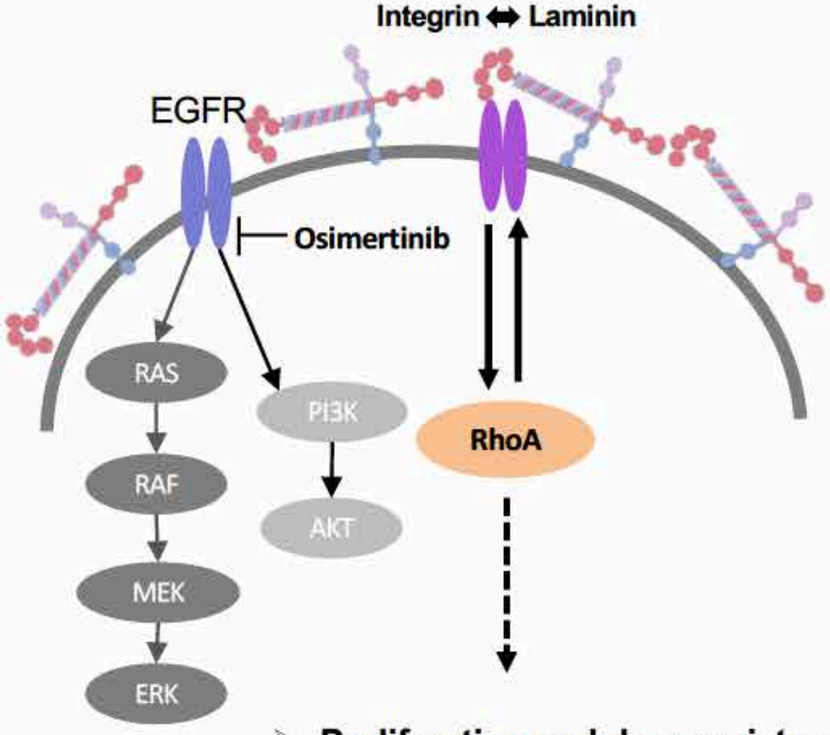
Vascular Co-option Precedes Leptomeningeal Metastasis



Adua et al., 2022



c/o Heather Hulme



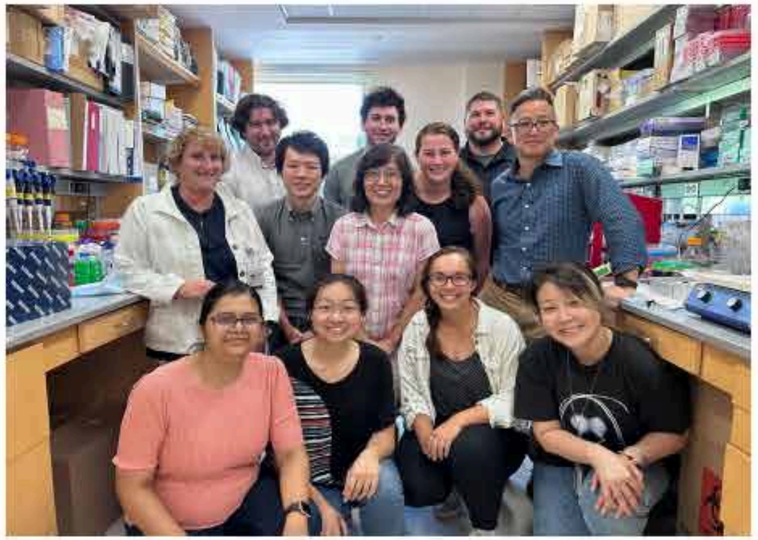
- **Proliferation and drug resistance**
- **Leptomeningeal disease?**

Summary

- **Identified distinct subtypes of CNS metastasis based on morphology, location, and stromal content.**
- Fibrotic ”high” parenchymal metastasis and dural metastasis have poor outcome.
- Biomarkers of fibrotic high tumors are detected in the CSF.
- Genomic and proteomic characterization of distinct CNS metastases is ongoing.

- Brain penetrant drugs when administered early increase depth of therapeutic response.
- **Recurrence eventually develops due to changes in the CNS microenvironment.**
- This is linked to increased peri-vascular laminin deposition.
- Invasion along perivascular spaces may lead to leptomeningeal metastasis following acquired resistance to Tagrisso.

Acknowledgements



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- Patients@ Smilow

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AstraZeneca

Yale University School of Medicine

Yale CANCER CENTER

Telemedicine and palliative care

Joseph A. Greer, PhD

CORE Cancer Outcomes Research & Education

Use of Telehealth for Delivering Early Integrated Palliative Care

Joseph Greer, PhD

Co-Director, Cancer Outcomes Research & Education Program,
Massachusetts General Hospital

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HARVARD MEDICAL SCHOOL

Benefits of Early and Longitudinal Palliative Care in the Outpatient Care Setting

- Enhances quality of life
- Increases use of adaptive coping strategies
- Reduces symptoms of depression
- Improves understanding of prognosis
- Increases communication about care preferences
- Decreases caregiver distress

Early integrated palliative and oncology care in the outpatient setting improves the experience and outcomes of patients diagnosed with advanced cancers and their caregivers

Monthly visits in the outpatient setting can be challenging to implement for both patients and clinicians.

What Are the Barriers to Implementing the Early In-Person Palliative Care Model?

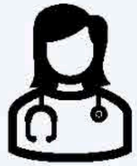
Patient Barriers

Added time in the outpatient clinic

Burden of travel and costs from monthly visits

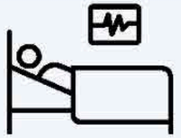
Discomfort of clinic setting and difficulties for family to attend visits

Palliative Care Barriers



Insufficient numbers of clinicians

Inadequate resources



Challenges of balancing the needs of acute patients

Increasing Accessibility and Patient-Centeredness of Early Palliative Care

- Can we design palliative care delivery models that are more scalable (tailored, person-centered, and convenient)?
- One promising solution is the use of telehealth
  - Helps overcomes access barriers
  - Reduces financial burden
  - Increases efficiency

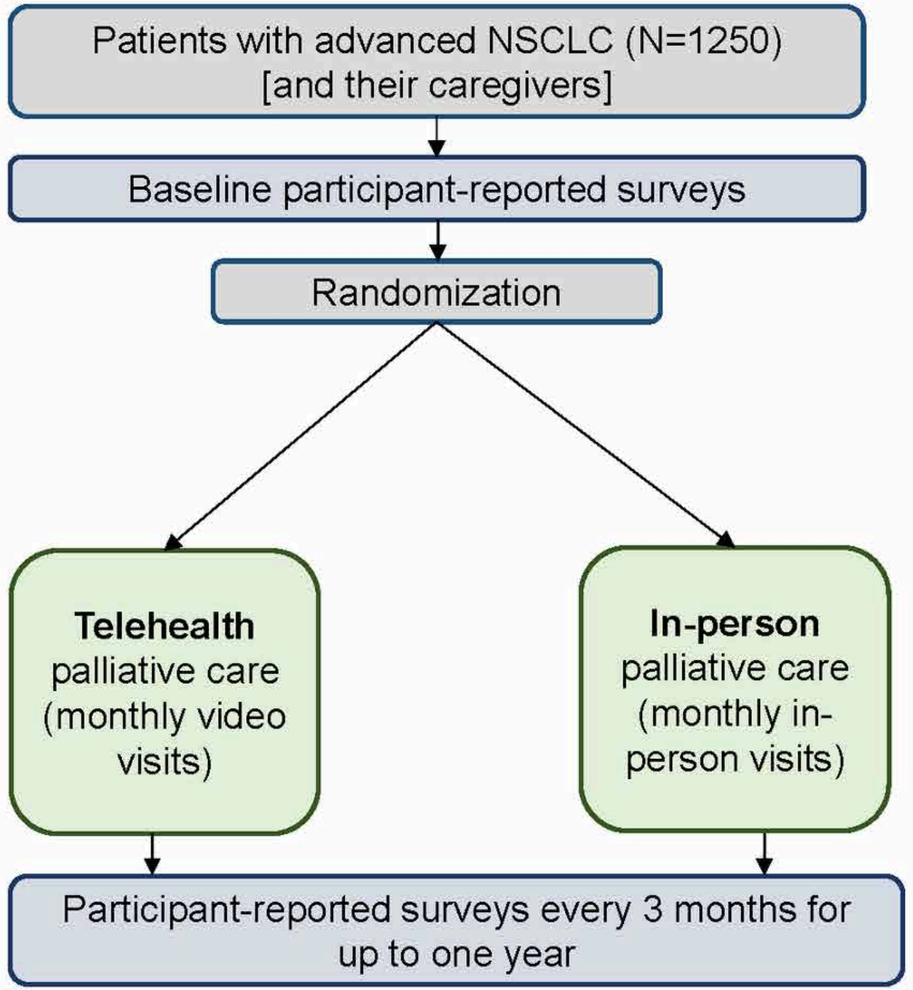
Are Video Visits an Effective Way To Deliver Palliative Care?

Primary Aim:

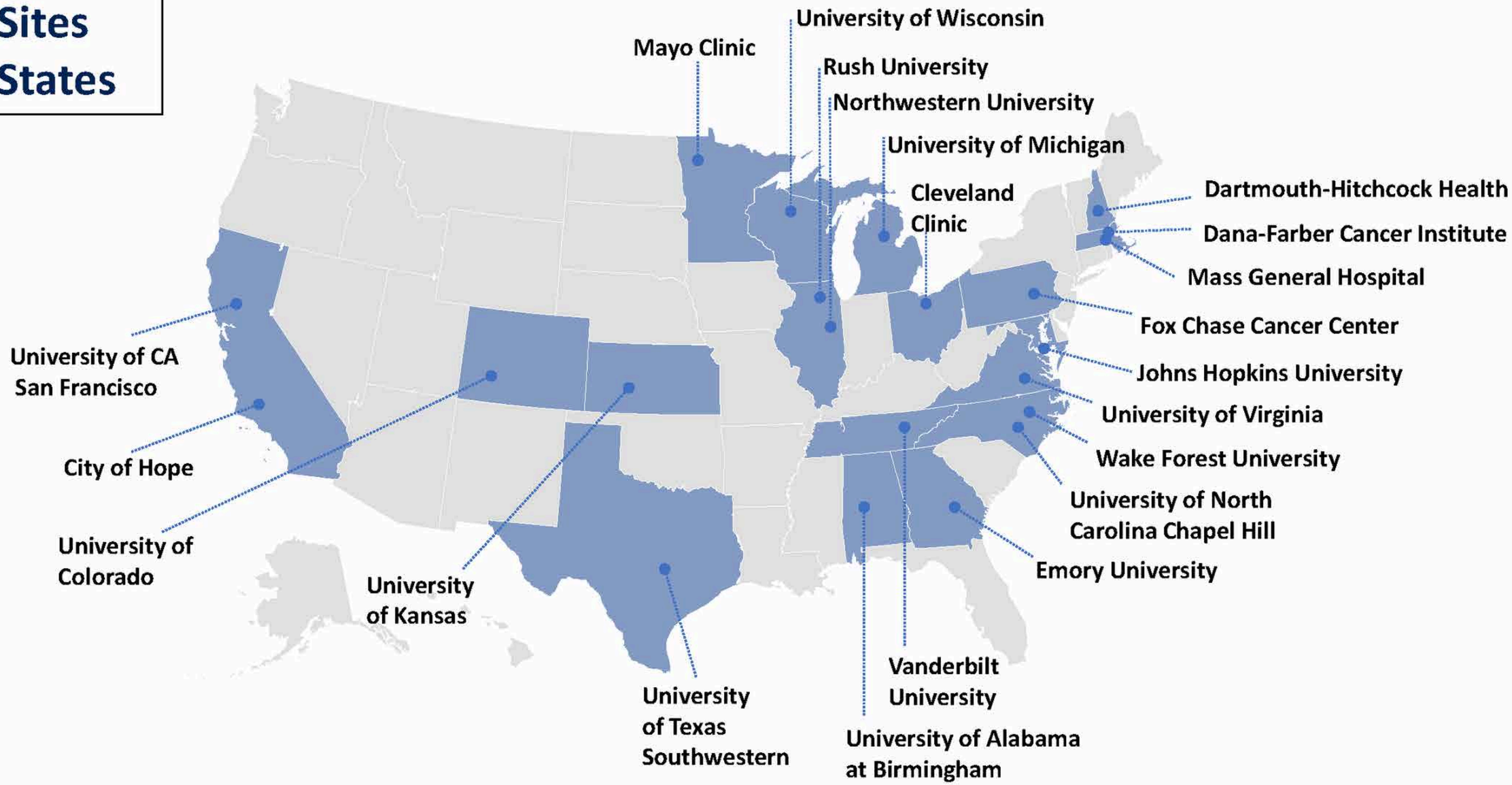
- To evaluate the equivalence of the effect of delivering early palliative care using video versus in-person visits on patient-reported quality of life

Secondary and Exploratory Aims:

- Satisfaction with care
- Caregiver attendance at study visits
- Mood symptoms

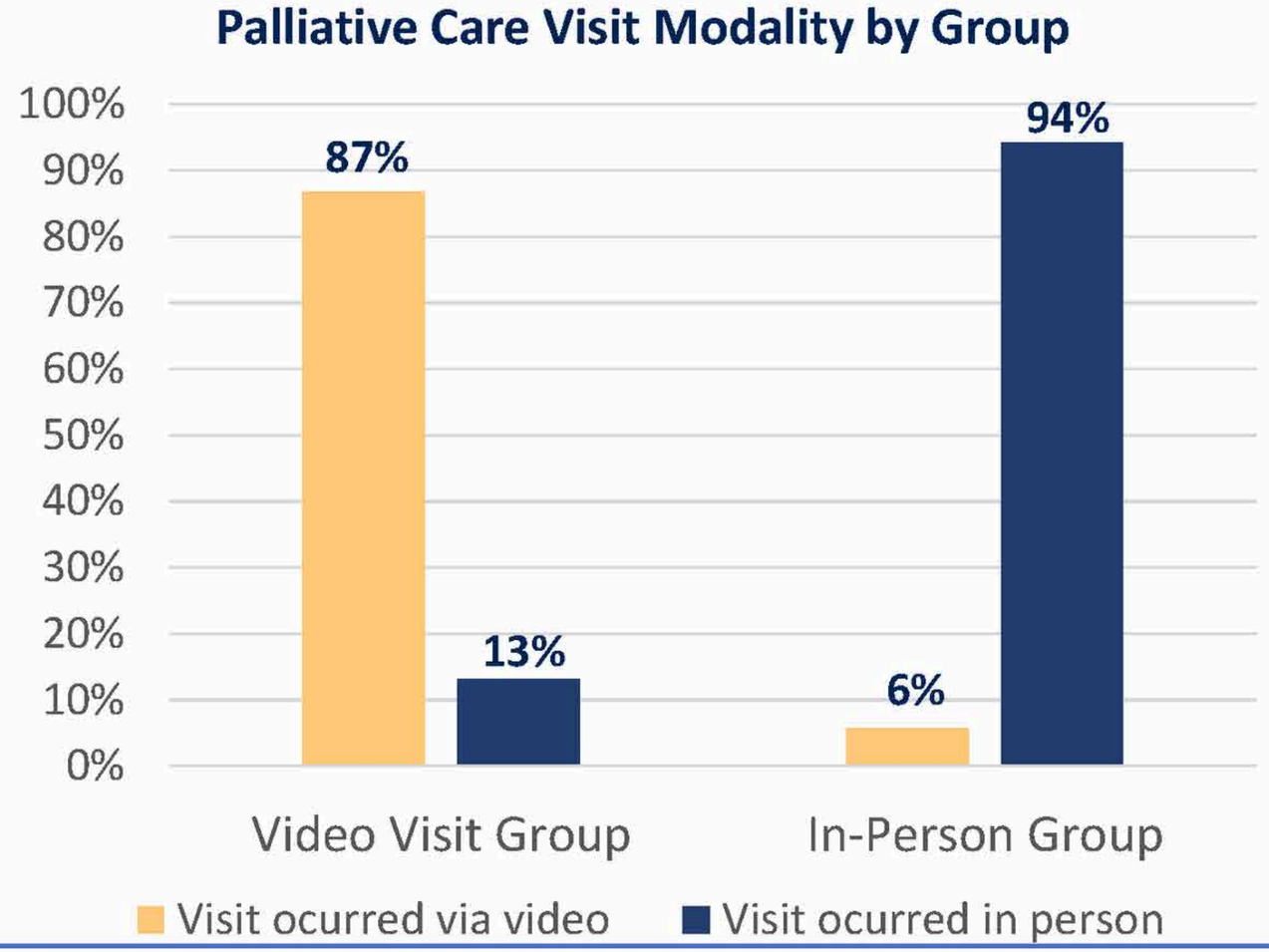


22 Sites
18 States



Intervention Delivery

Number of Palliative Care Visits by 24 Weeks Mean (SD)	
Video Visit	In-Person
4.7 (2.5)	4.9 (2.7)

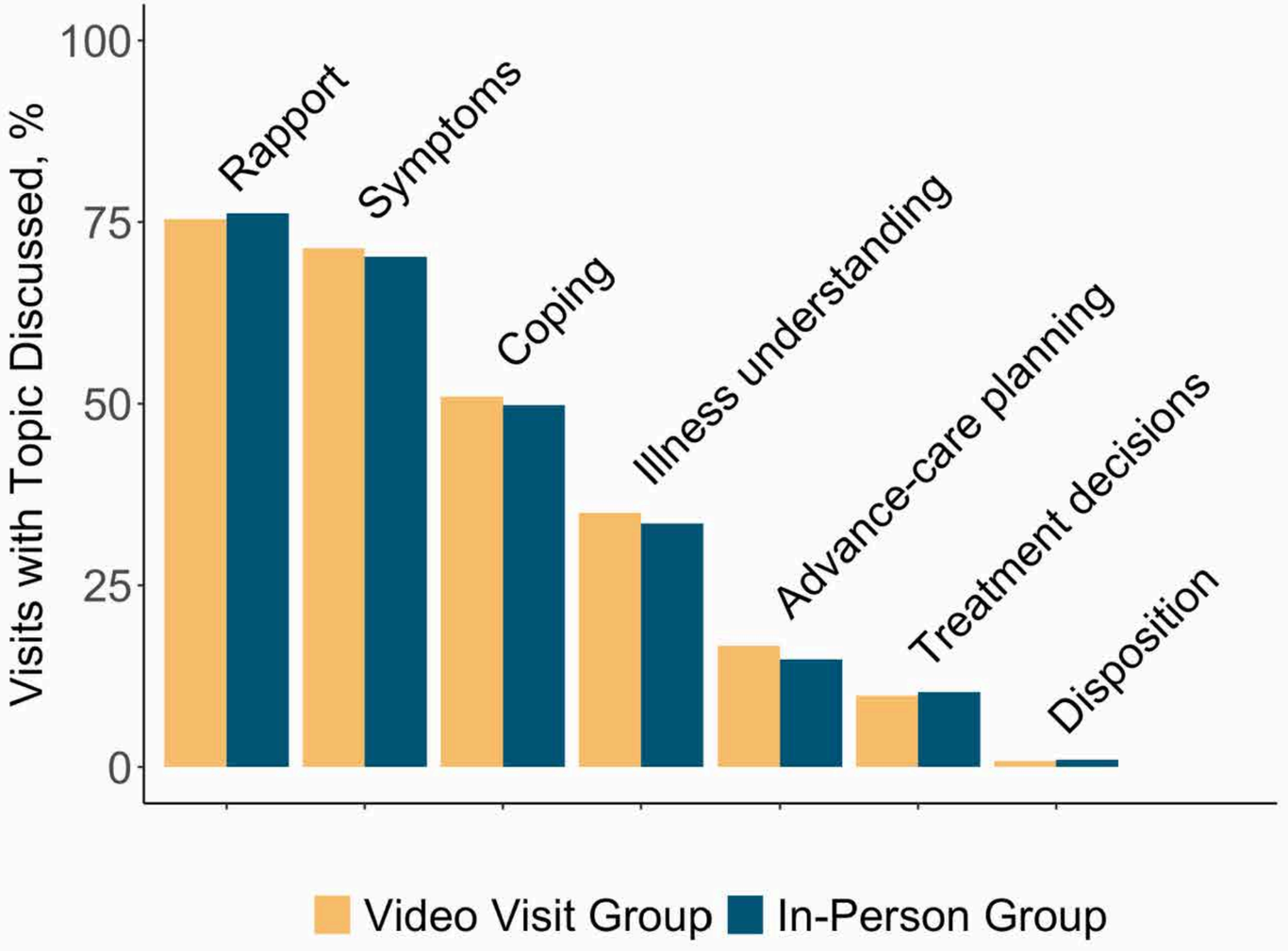


Intervention Delivery

Clinician Documented Topics Discussed in Palliative Care Visits

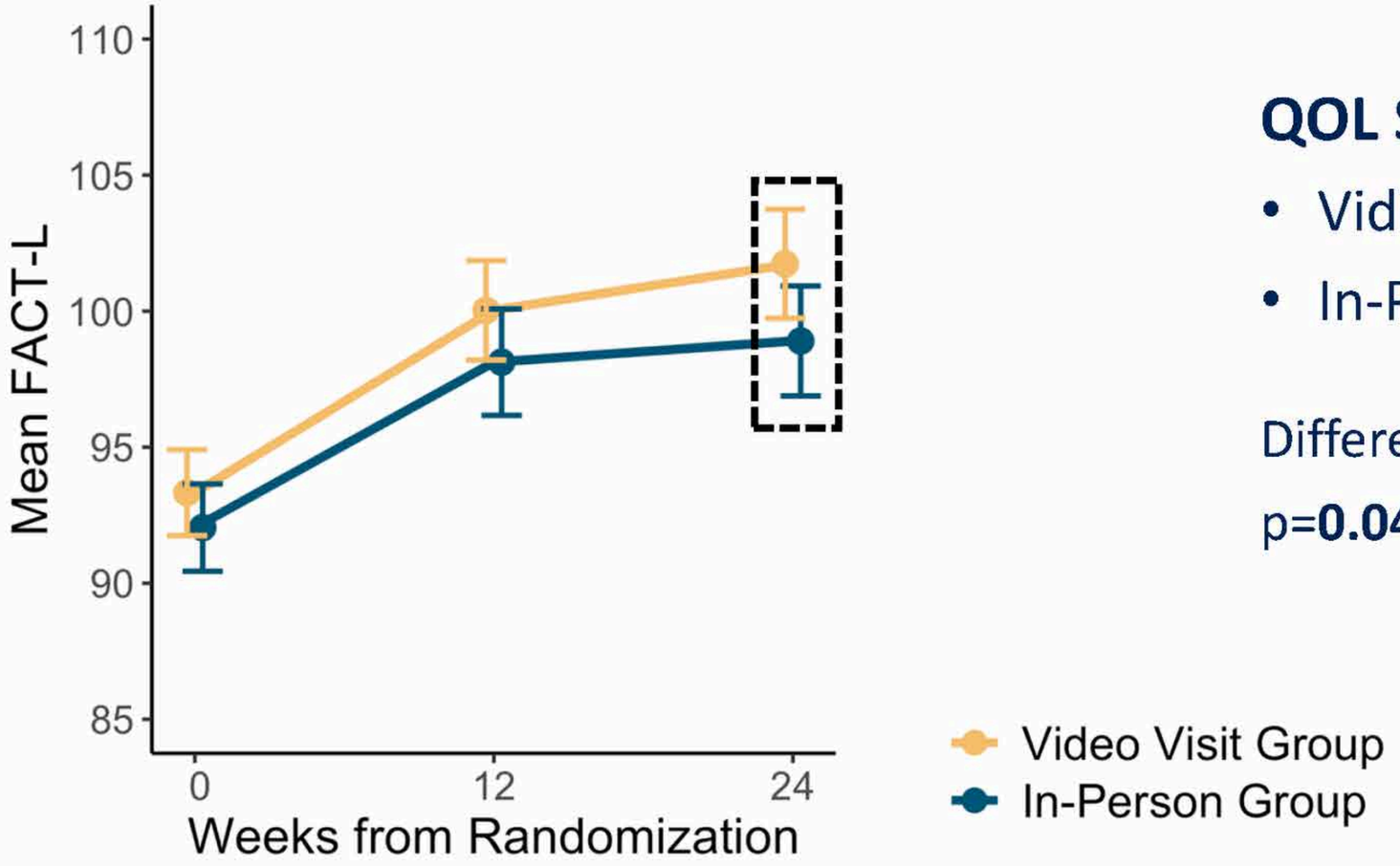
Visit Summary Forms

N=5,219



Results: Patient Quality of Life (QOL)

Higher scores indicate better QOL (range: 0-136)



QOL Scores at 24 Weeks:

- Video Visit Group: **99.7**
- In-Person Group: **97.7**

Difference (90% CI): **2.0 (0.1, 3.9)**

p=**0.04 for equivalence**

Results: Satisfaction with Care & Caregiver Attendance in Visits

Outcome Measure	Video Visit Group Estimated Mean/Proportion	In-Person Group Estimated Mean/Proportion	Difference 95% (CI)
Satisfaction with Care†			
Patient report, mean	41.3	41.0	0.3 (-1.0, 1.7)
Caregiver report, mean	37.2	36.8	0.4 (-1.5, 2.3)
Attendance of Caregiver at Visits			
proportion	36.6%	49.7%	-13.0% (-17.6, -8.6)

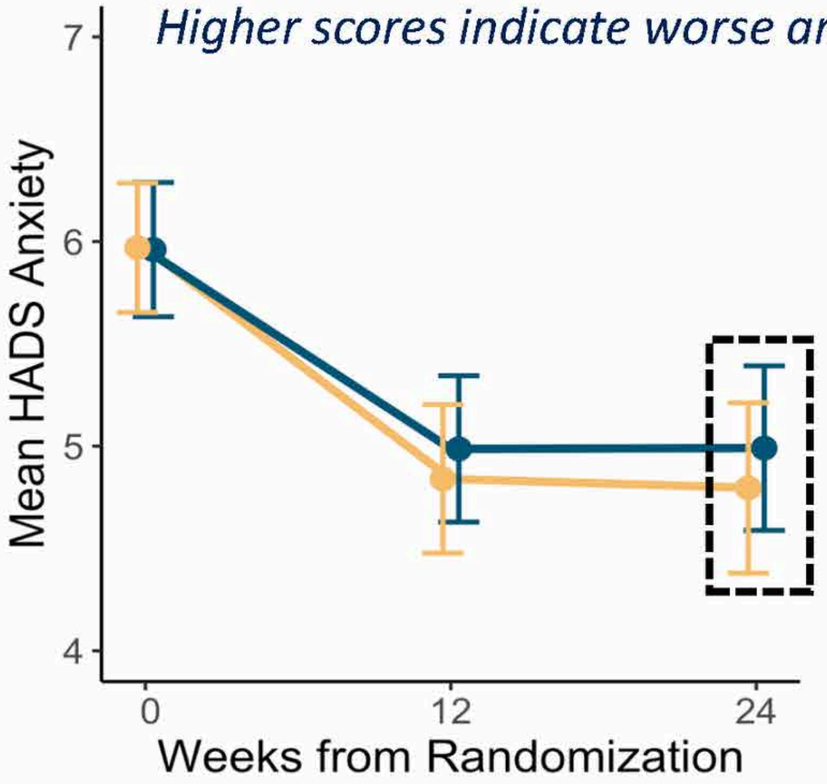
†*Higher scores on the Satisfaction and Care Delivery Questionnaire indicate greater satisfaction*

Results: Patient Anxiety & Depression

Anxiety Symptoms

Difference (95% CI) = -0.2 (-0.6, 0.3)

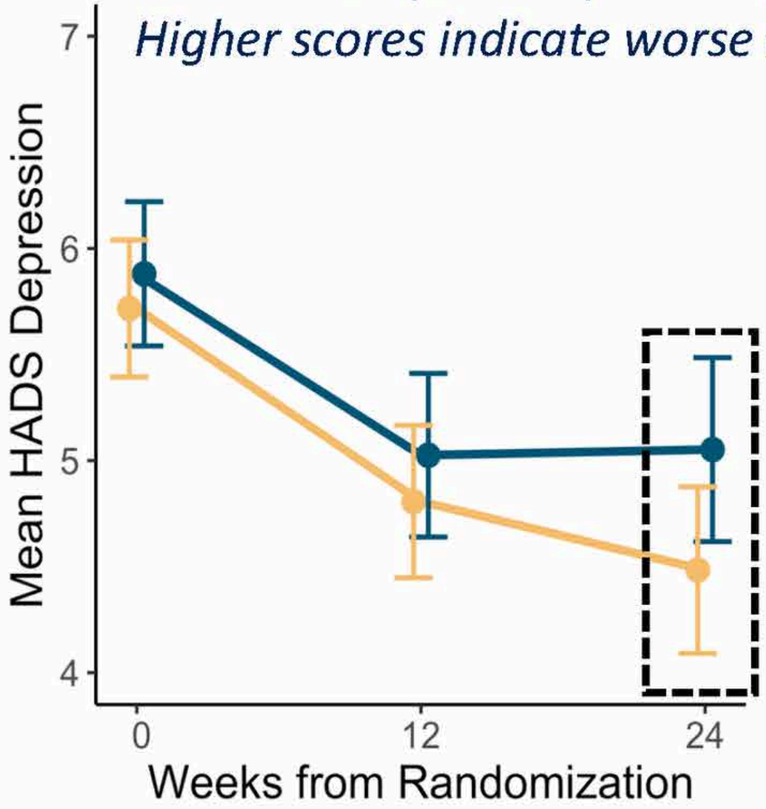
Higher scores indicate worse anxiety



Depression Symptoms

Difference (95% CI) = -0.4 (-0.9, 0.1)

Higher scores indicate worse depression



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Video Visit Group

In-Person Group

CORE

Efficiency of Care Delivered via Telehealth

- Less costly
  - Patients
  - Healthcare Systems
- Less time consuming
- Better for the environment

Summary

- The role of early palliative care for patients with serious cancers is established, but workforce and healthcare system barriers make implementation challenging.
- Palliative care delivered via telehealth may be a more scalable way to deliver early palliative care.
- Moving forward, we are evaluating additional care models to improve access to early palliative care:
  - Teaching oncology clinicians to provide palliative care skills
  - Using digital health interventions (e.g., mobile apps) to provide education, symptom management, and coping support

Thank you!

Participating Sites & Stakeholders

- Patients and Caregivers
- Palliative Care Clinicians
- Thoracic Oncology Clinicians
- Research Staff

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KRAS

Mark Awad, MD, PhD

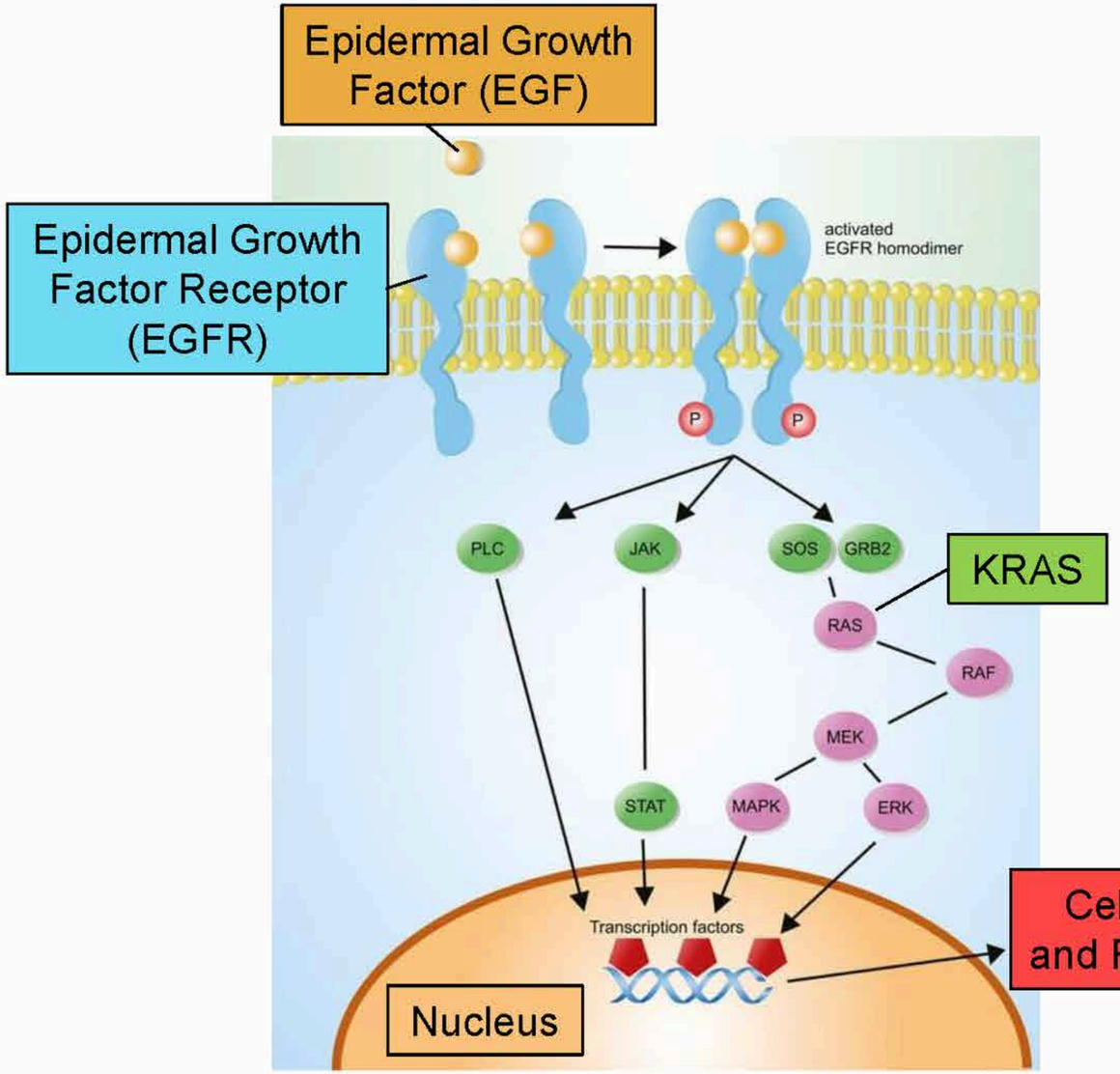
Targeting KRAS-mutant lung cancer and overcoming drug resistance

Mark M. Awad, MD, PhD
Chief, Thoracic Oncology
Memorial Sloan Kettering Cancer Center

Lung Cancer Research Foundation
Scientific Symposium: Addressing Unmet Needs in Lung Cancer
November 4, 2024

Memorial Sloan Kettering Cancer Center

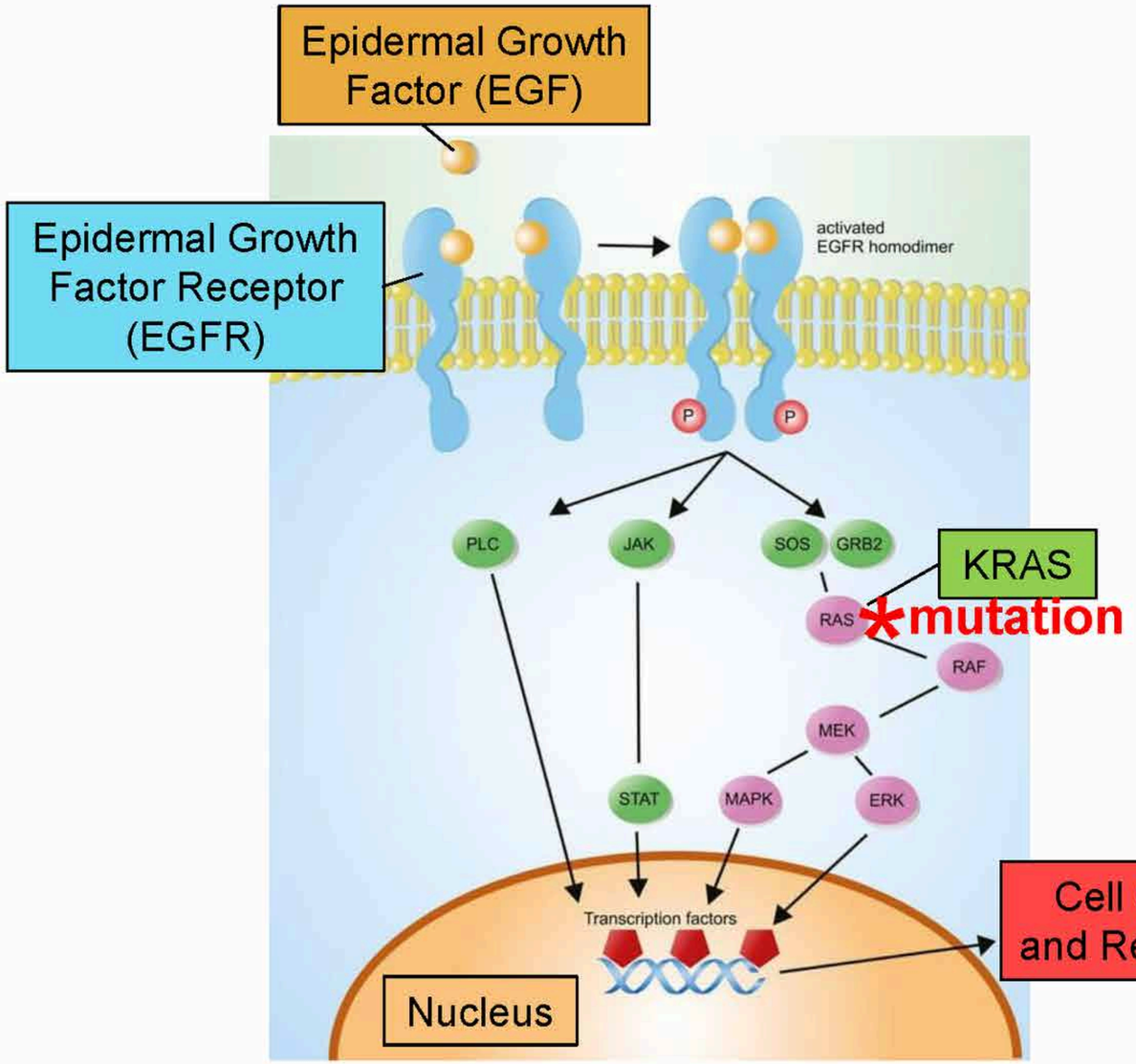
What is KRAS?



- Protein that transmits a signal telling cells when to divide during normal growth and development
- Usually a controlled, regulated process in the body
- KRAS signal is typically only turned “on” when growth factors are present and is otherwise turned “off”

Diagram from: https://researchoutreach.org/articles/understanding-egfr-mutation-aids-fight-lung-cancer/

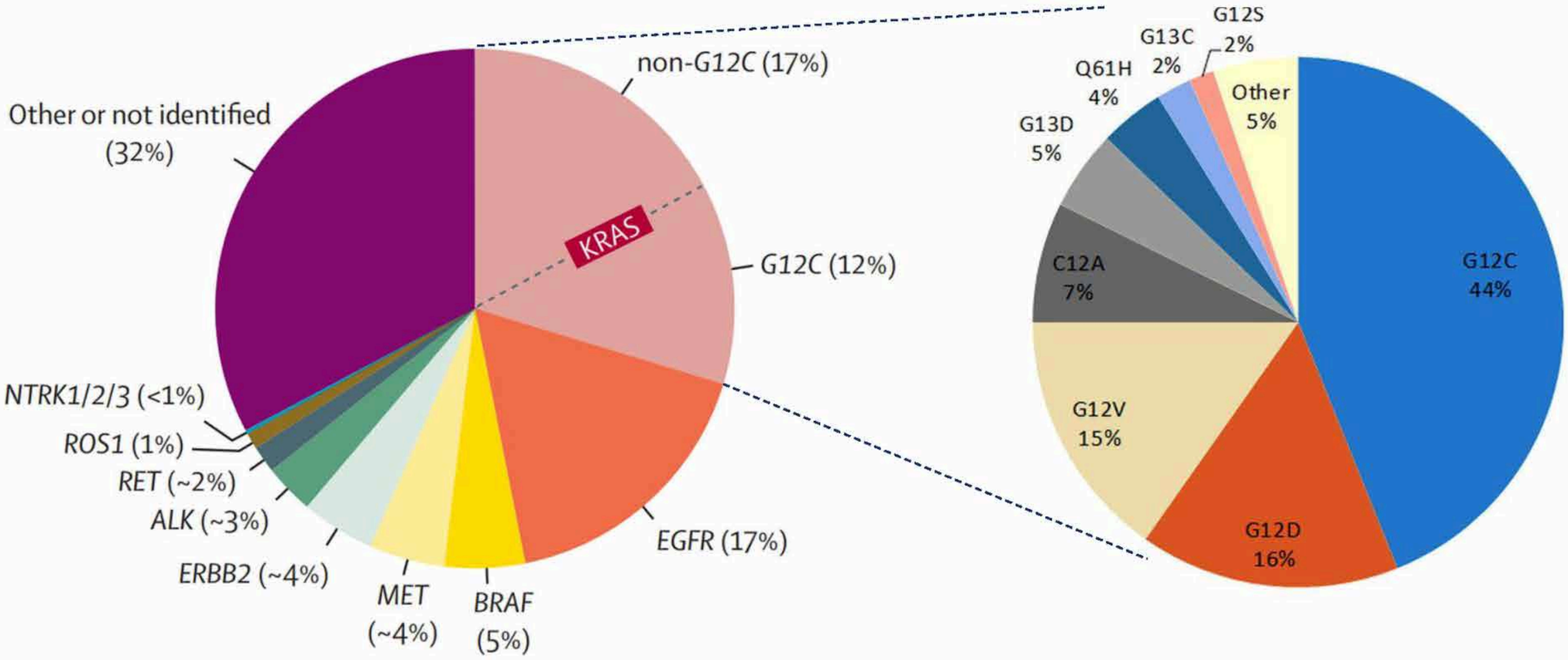
What are KRAS mutations?



- DNA mutations in cancer cells that cause changes to the KRAS protein ( ) *
- "Activating" or "Driver" mutations
- Causes abnormal signaling within the cell even in the absence of growth factors
- Results in abnormal cell growth, division, and spread in many cancers, including lung cancer
- We can test for KRAS mutations ("biomarkers") using DNA/genomic sequencing techniques

Diagram from: https://researchoutreach.org/articles/understanding-egfr-mutation-aids-fight-lung-cancer/

Different types of KRAS mutations



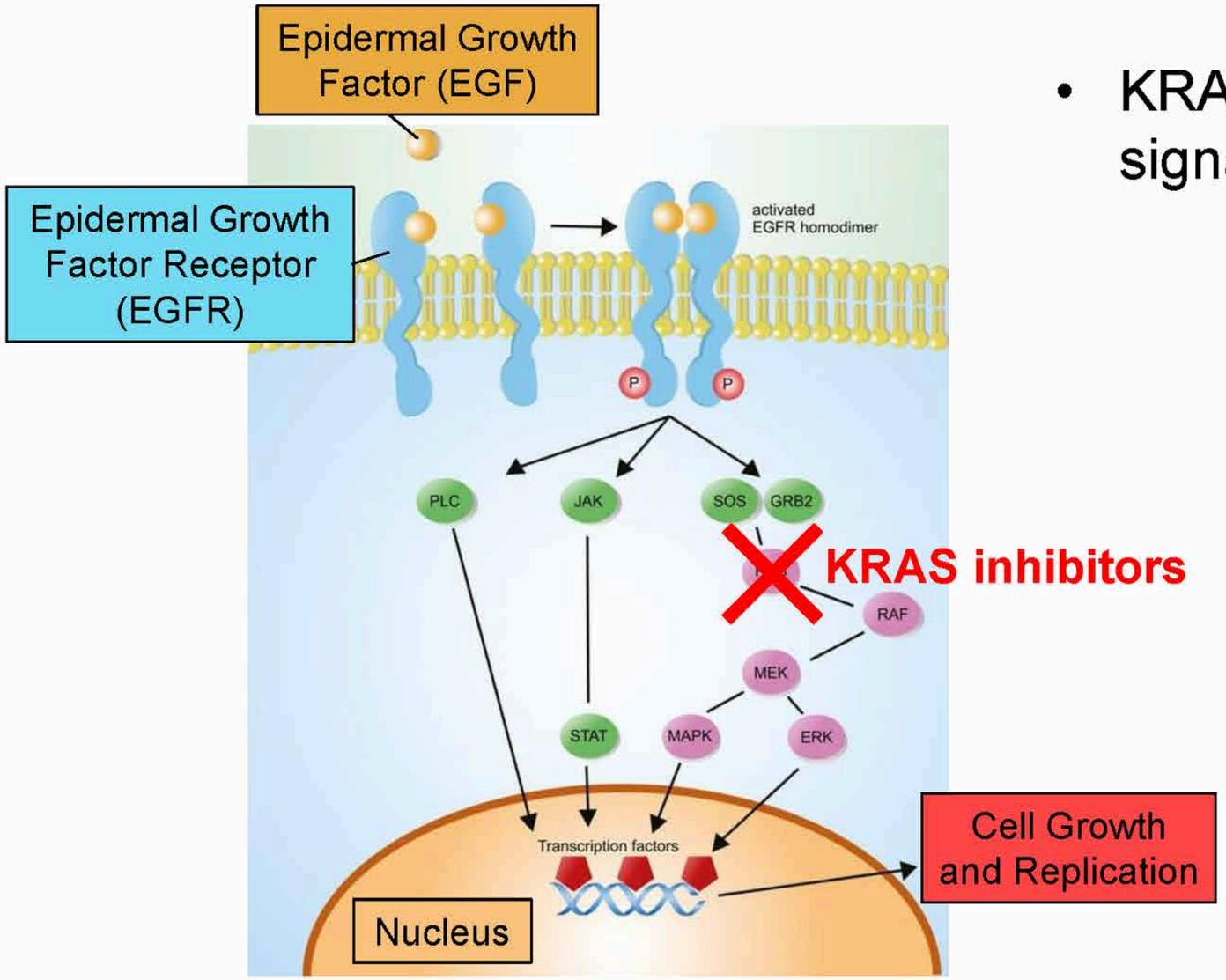
Two approved drugs for KRAS G12C:

- Sotorasib
- Adagrasib

Thai AA, et al, *Lancet* 2021; 398: 535–54

Arbour KC, et al, *Clin Cancer Res*. 2018 Jan 15;24(2):334-340.

KRAS inhibitors

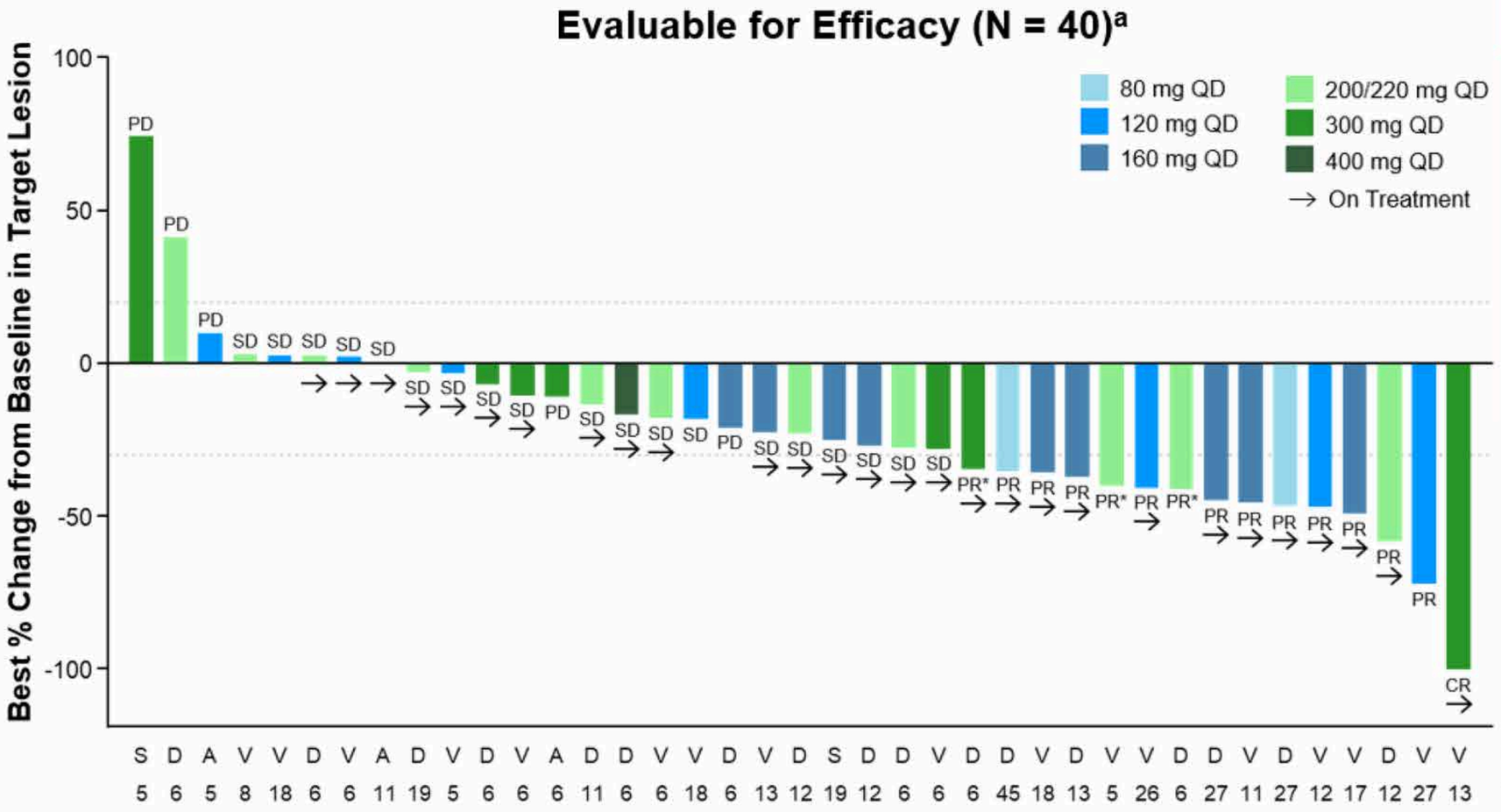


- KRAS inhibitors block the abnormal signaling

Diagram from: https://researchoutreach.org/articles/understanding-egfr-mutation-aids-fight-lung-cancer/

New KRAS inhibitors on the horizon

KRAS^{G12X} NSCLC: Best Response



Tumor Response (per RECIST 1.1)	
Best overall response, n (%)	
CR	1 (3)
PR	14 (35)
SD	19 (48)
PD	5 (13)
NE[b]	1 (3)
ORR, n (%)	15 (38)
Confirmed, n	12
DCR (CR+PR+SD), n (%)	34 (85)

*Unconfirmed PR per RECIST 1.1.

[a]Patients who received first dose of RMC-6236 at least 8 weeks prior to data extract date.

[b]One subject withdrew from study without post-baseline scans.

Arbour KC, et al, ESMO 2023 Annual Meeting.

Lung cancers can become resistant to KRAS inhibitors

- The time to development of resistance is variable from one person to another
- Cancer can regrow at sites where it was previously known to be, or spots of cancer can appear in new locations
- Continuation of current treatment + incorporation of radiation to a small number of limited sites (“oligoprogression”) can be considered in some circumstances
- How cancer develops resistance (ie the “mechanism” of resistance) differs between patients and can also differ between various spots of cancer in the same patient
- When safe and feasible, we try to determine the resistance mechanism with repeat tissue and/or blood biopsies

Mechanisms of Resistance

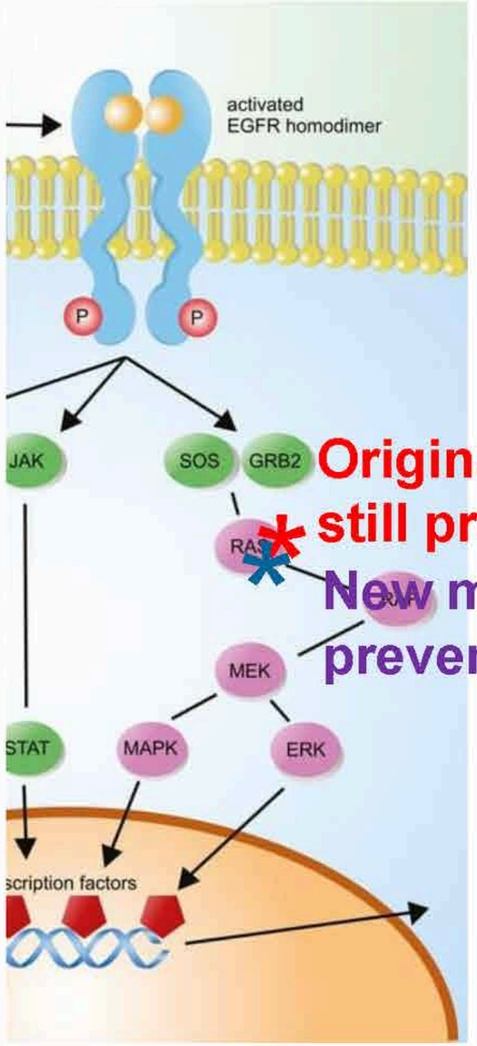
1. **"On Target":** KRAS gene can mutate again
   - Examples: KRAS Y96C, KRAS R68S, etc.
   - KRAS inhibitor drugs can no longer bind to target

2. **"Bypass":** Another gene besides KRAS mutates
   - Examples: MET amplification, ALK fusion, BRAF mutation, etc.
   - KRAS inhibitor still blocks KRAS properly, but other genes become abnormal to work around KRAS and turn the growth signal back on

3. **Histologic transformation:** Type of lung cancer changes
   - Examples: adenocarcinoma → squamous cell carcinoma
   - Can only be detected with tissue biopsy (not blood/liquid biopsy)

4. **Unknown**

“On Target” Resistance



Original activating mutation still present (eg KRAS G12C)

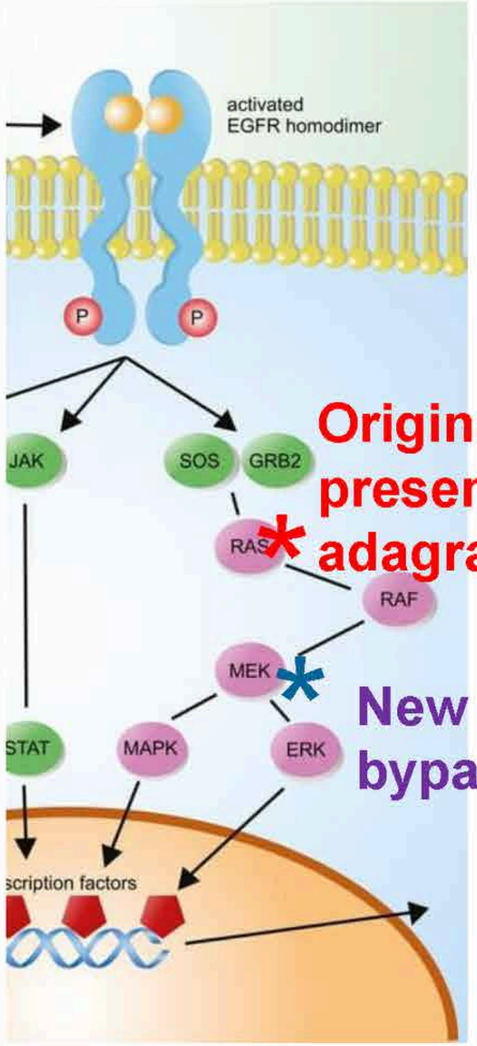
New mutation (eg KRAS Y96C) prevents asagrasib from binding

Switch to Chemotherapy

Strategies in Development:

- RMC-6236
- “Pan-KRAS” inhibitors
- And others

“Bypass” Resistance



Original activating mutation still present (eg KRAS G12C); adagrasib can still block KRAS

New mutation (eg MEK mutation) bypasses around KRAS

Switch to Chemotherapy

Add 2nd targeted therapy?

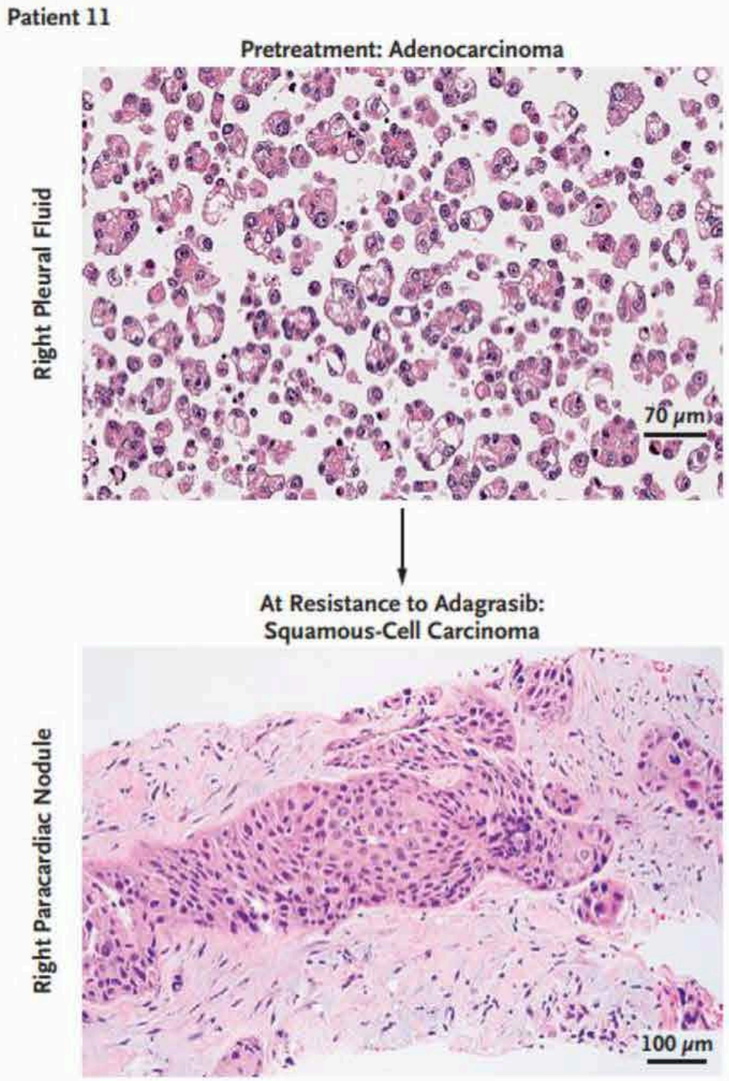
- ?MEK inhibitor for MEK mutations
- ?BRAF inhibitor for BRAF mutations
- ?ALK inhibitor for ALK fusions
- etc

Histologic Transformation

Adenocarcinoma (Non-small cell lung cancer)

↓

Small cell carcinoma

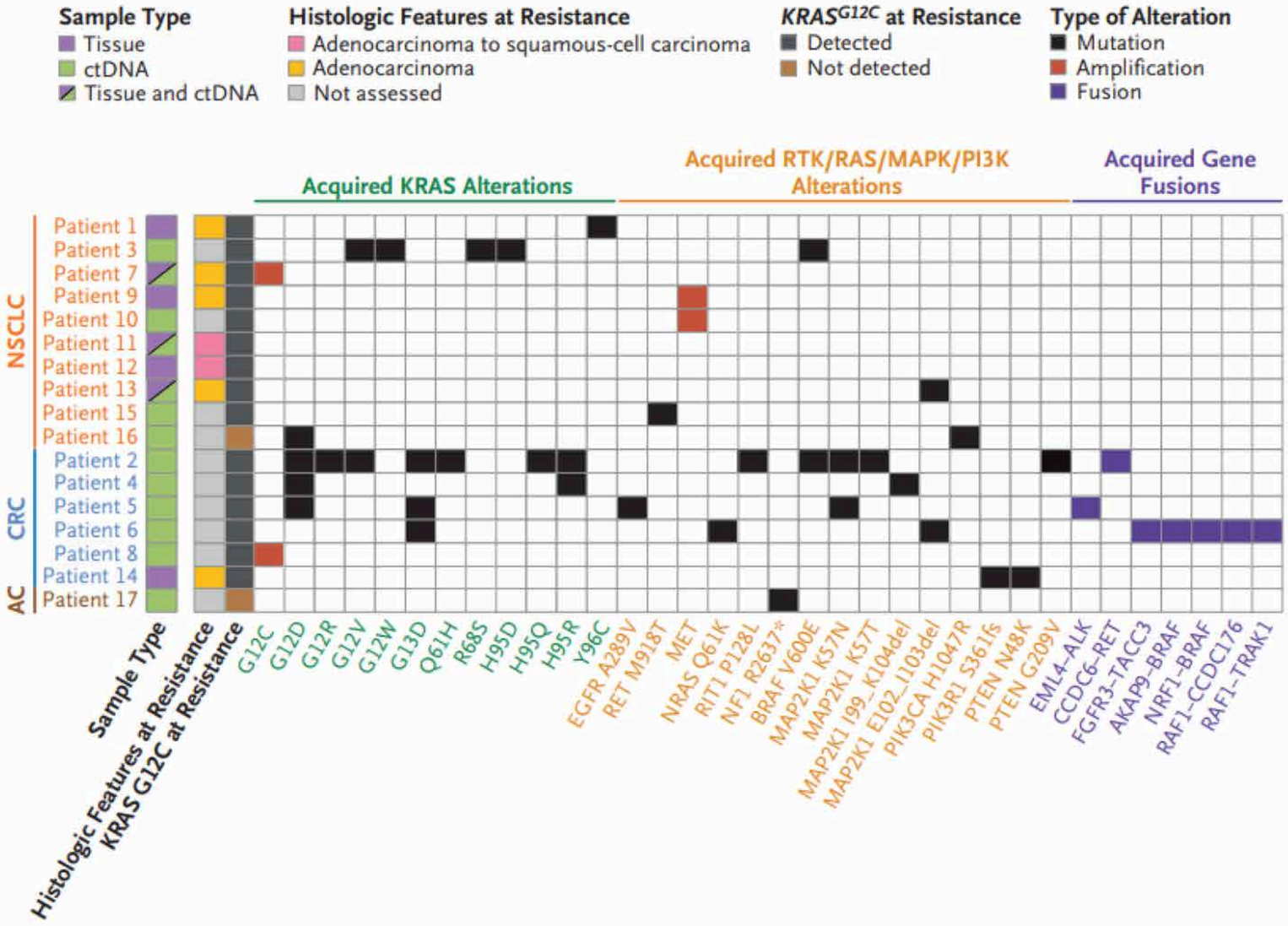


Switch to squamous chemotherapy

- carboplatin/paclitaxel

Awad MM, Liu S, et al, *N Engl J Med* 2021; 384:2382-2393.

Multiple resistance mechanisms can develop



Awad MM, Liu S, et al, *N Engl J Med* 2021; 384:2382-2393.

Strategies to delay/overcome resistance

Ongoing trials investigating a number of strategies to combine KRAS inhibitors with:

- Immunotherapy (some combinations do not appear to be safe)
- Chemotherapy
- Chemotherapy + immunotherapy
- Radiation
- EGFR inhibitors
- RAF/MEK inhibitors
- SOS1 or SHP2 inhibitors
- And many other strategies

Conclusions

- Approved and investigational KRAS inhibitors represent a major advance for patients with *KRAS*-mutant cancers
- Activity of $KRAS^{G12C}$ inhibitors is limited by baseline co-mutations and the emergence of complex acquired resistance mechanisms
- Several open questions remain about the optimal sequencing of therapies in *KRAS*-mutant NSCLC
- Additional studies are needed to determine if KRAS inhibitors can safely be combined and are synergistic with other therapies

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