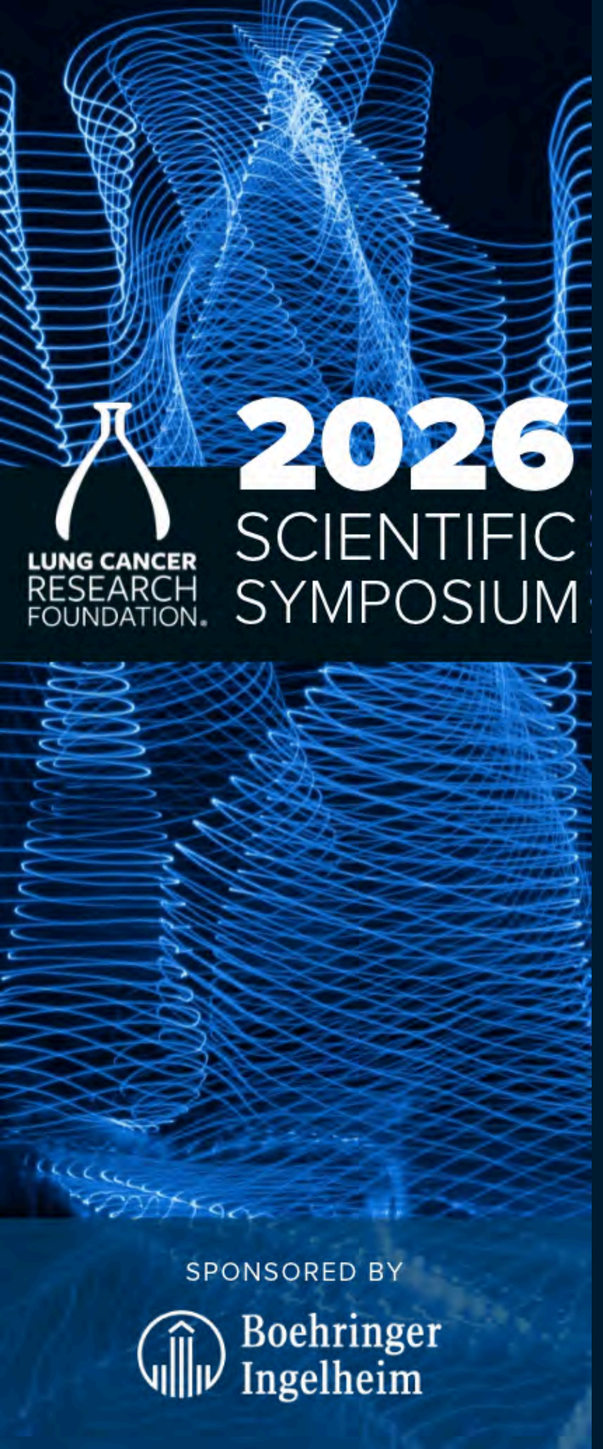


Today's schedule

All times listed are
United States
Eastern Standard Time

12:00 PM	**Welcome** *Kathryn O'Donnell, PhD, Chair, LCRF Scientific Advisory Board*
12:05 PM	**State of Lung Cancer Research** *Shirish Gadgeel, MBBS, FASCO*
12:35 PM	**Presentations** *Patient Advocacy: Colleen Conner Ziegler* *Leading Edge: AI and Machine Learning: Lecia Sequist, MD, MPH* *Early Detection: Liquid biopsy & ctDNA in clinical practice: Christian Rolfo, MD, PhD* *Overcoming Resistance: Brain Metastasis: Timothy Burns, MD, PhD*
1:45 PM	**Panel discussion with Q&A** *Moderators:* *Kathryn A. O'Donnell, PhD* *Isabel Preeshagul, DO, MBS*
2:25 PM	**Closing remarks** *Kathryn O'Donnell, PhD, Chair, LCRF Scientific Advisory Board*
2:30 PM	**Symposium ends**


The 2026 LCRF Scientific Symposium is supported by
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LUNG CANCER RESEARCH FOUNDATION.

2026 SCIENTIFIC SYMPOSIUM

SPONSORED BY

Boehringer Ingelheim

State of Lung Cancer Research

Shirish Gadgeel, MBBS, FASCO

Member, LCRF Scientific Advisory Board

Co-Chair, Protocol Review and Monitoring Committee,
Winship Cancer Institute of Emory University

Professor, Department of Hematology and Medical Oncology and Vice Chair for Clinical Research, Department of Hematology and Medical Oncology
Emory University School of Medicine





Where Science Becomes Hope

STATE OF LUNG CANCER RESEARCH- A CLINICIAN'S PERSPECTIVE

Shirish M. Gadgeel, MD, FASCO

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

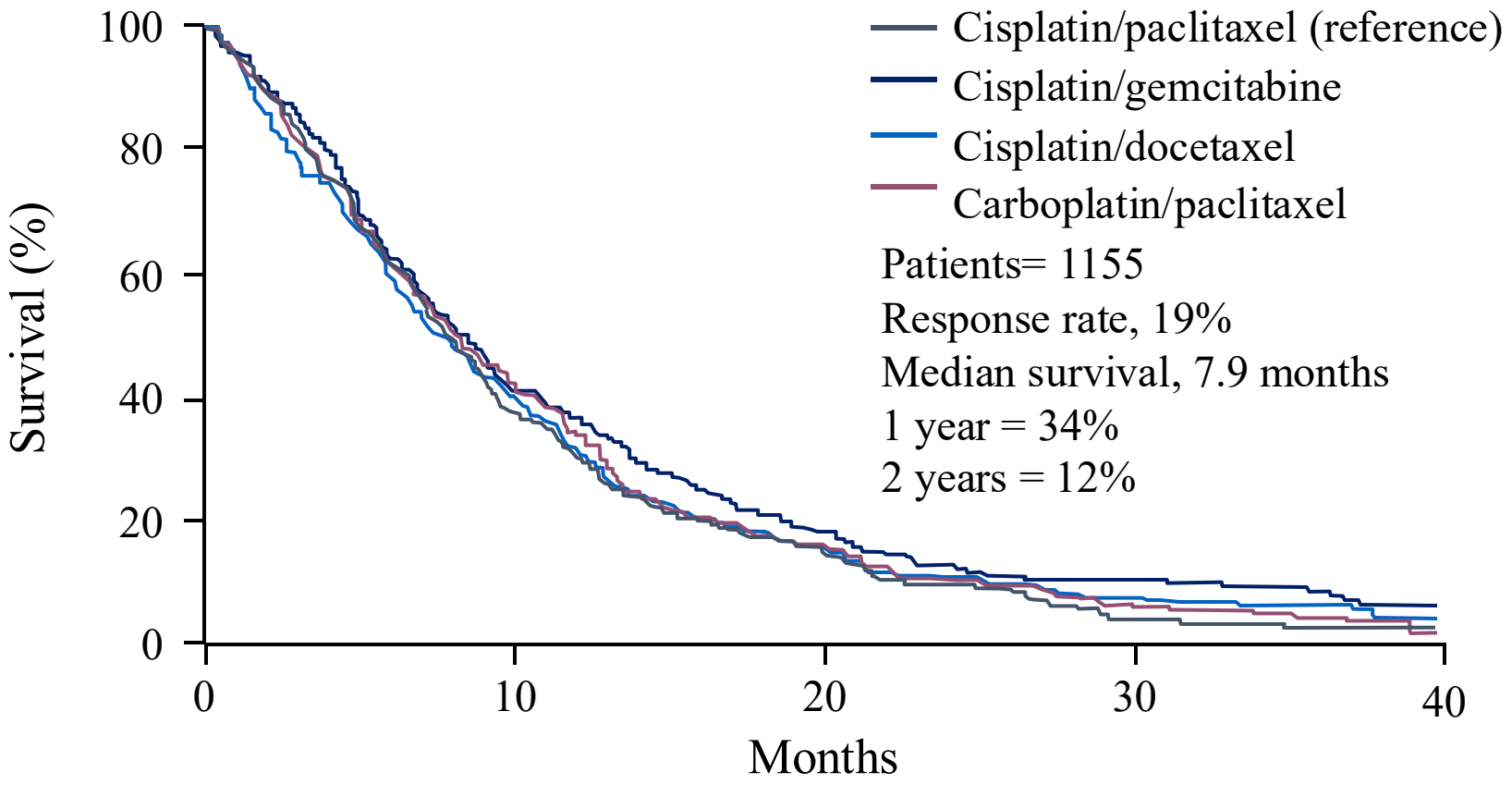
NCI Designated Comprehensive Cancer Center

DISCLOSURES

Advisory Board- Genentech/Roche, Amgen, Astra-Zeneca, Pfizer, Boehringer-Ingelheim, Bayer, Lilly, BMS, Daichii, Gilead, Johnson and Johnson, Abbvie, Sanofi, Summit, MBrace, Erasca, Astellas, GSK

IDMC- Astra-Zeneca

ECOG 1594

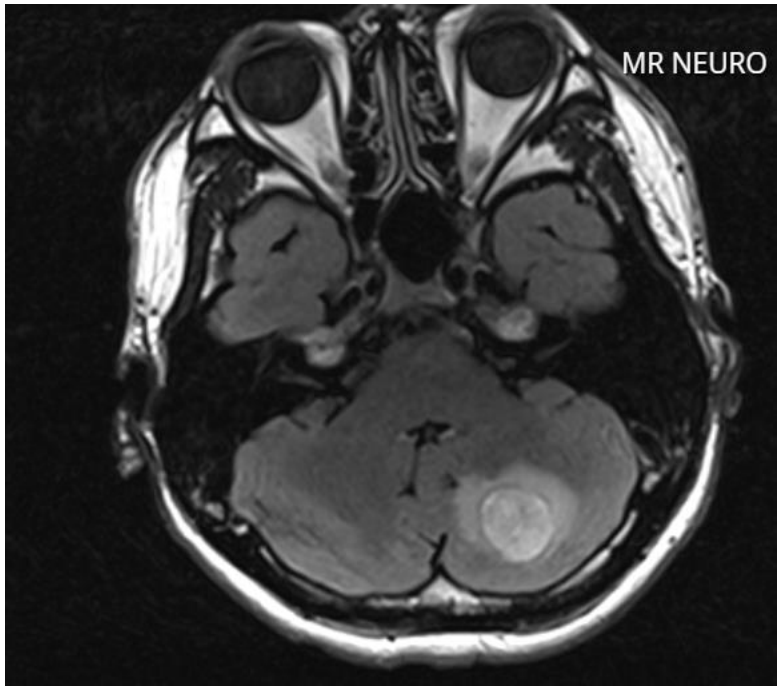


Schiller et al. *N Engl J Med*. 2002;346:92.

19-YEAR OLD MALE PATIENT



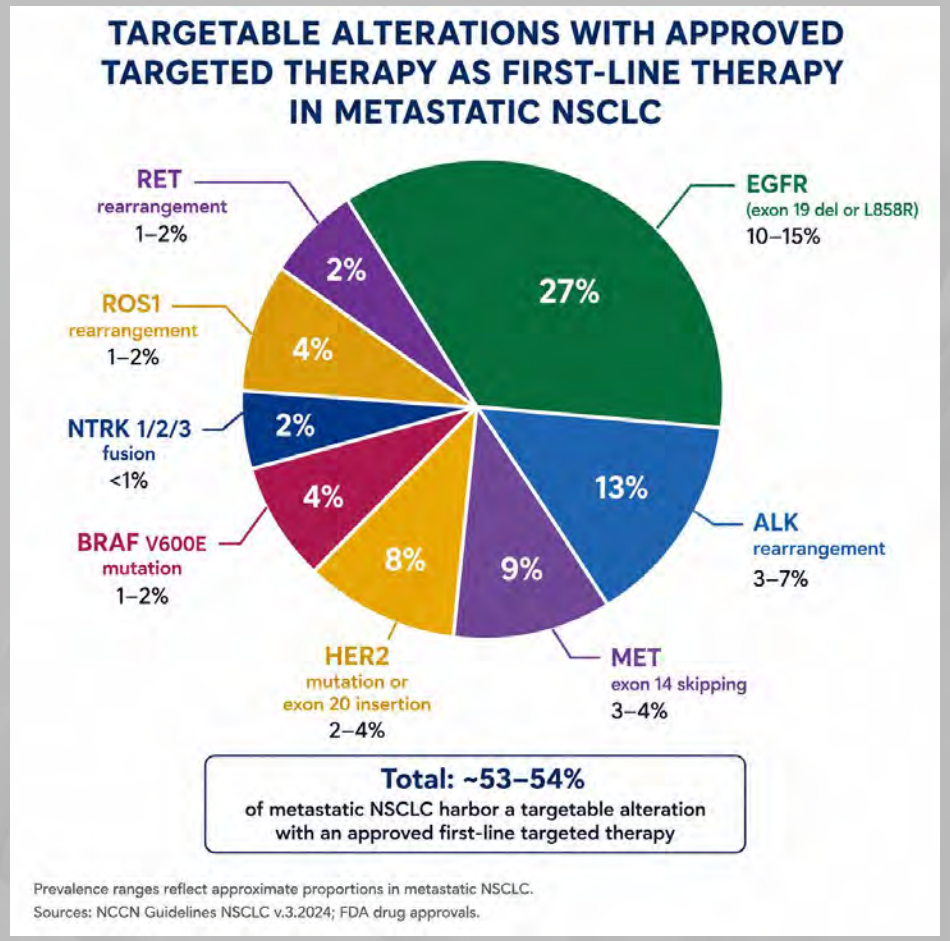
7/9/2026

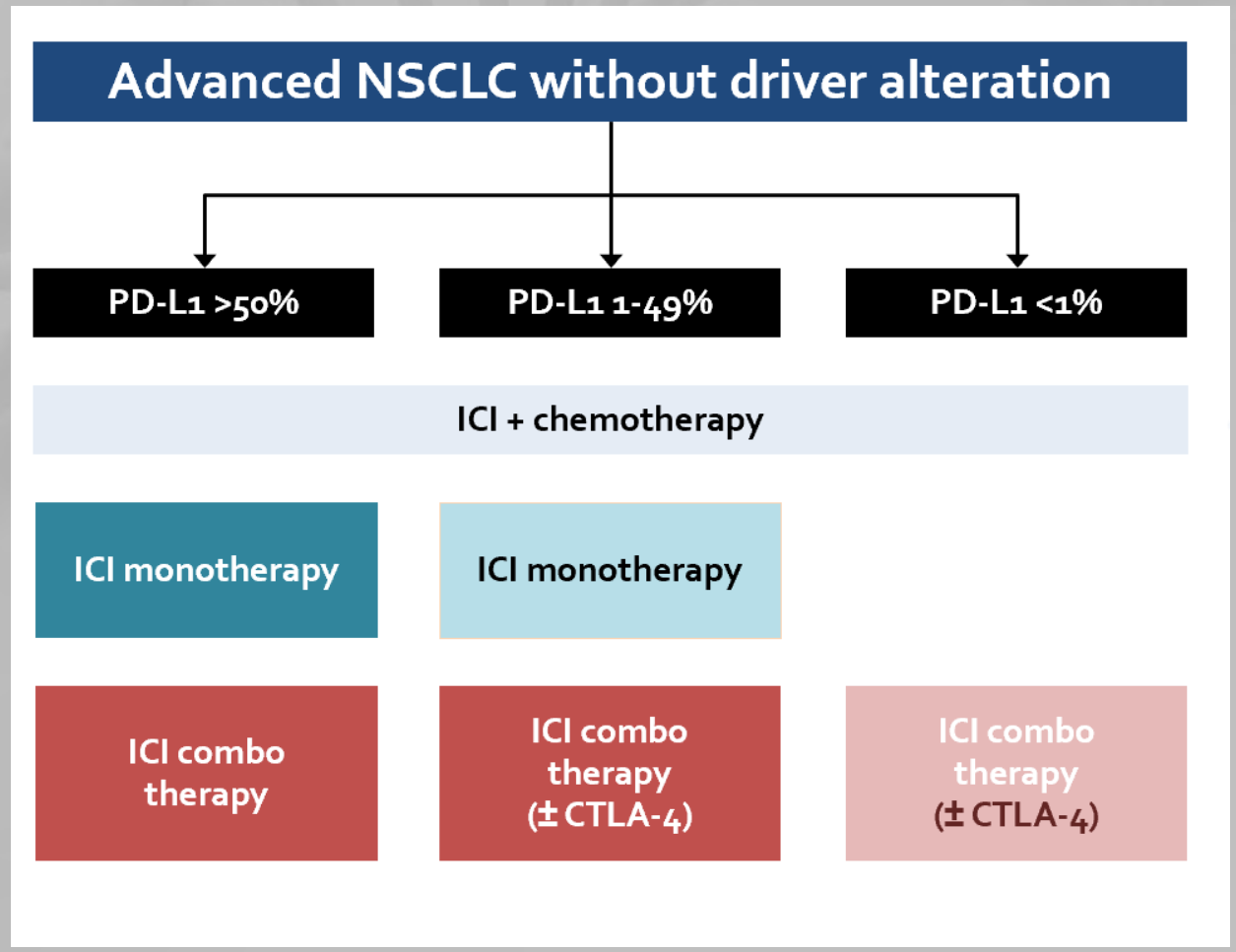


6/16/2026

19 year old male patient had persistent cough.
No symptoms related to brain met.

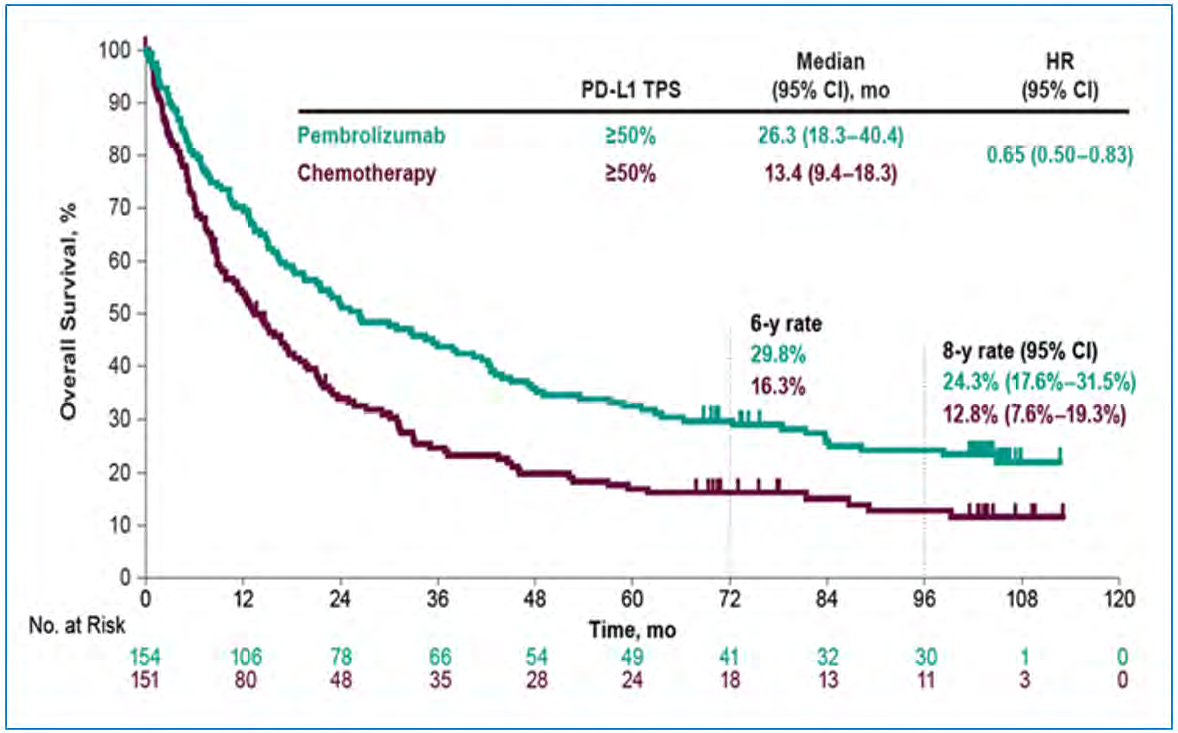
THERAPY FOR NSCLC



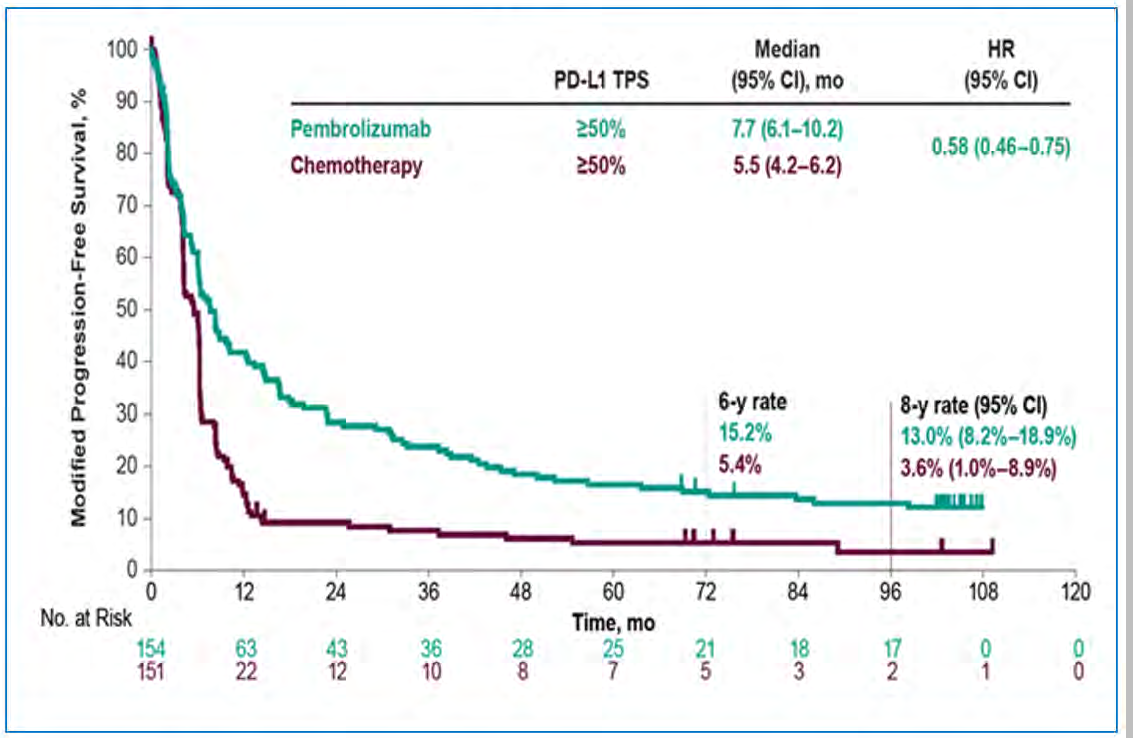


KEYNOTE-24- LONG TERM EFFICACY

OS



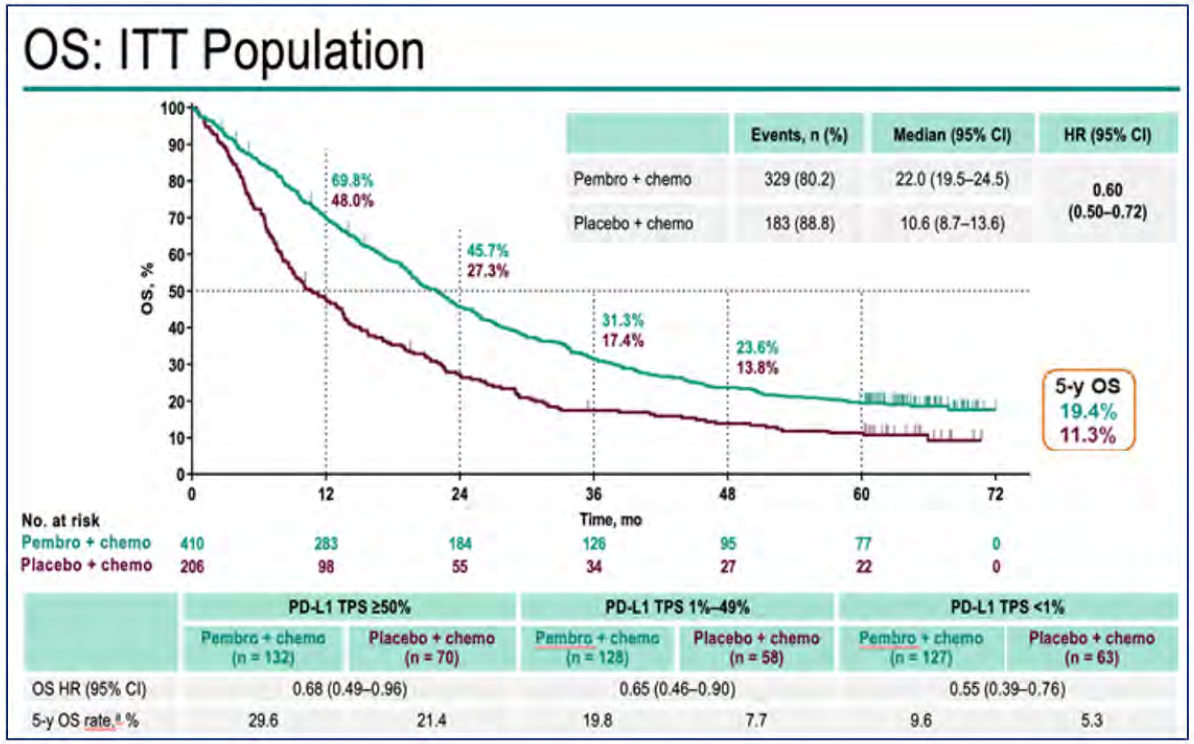
PFS

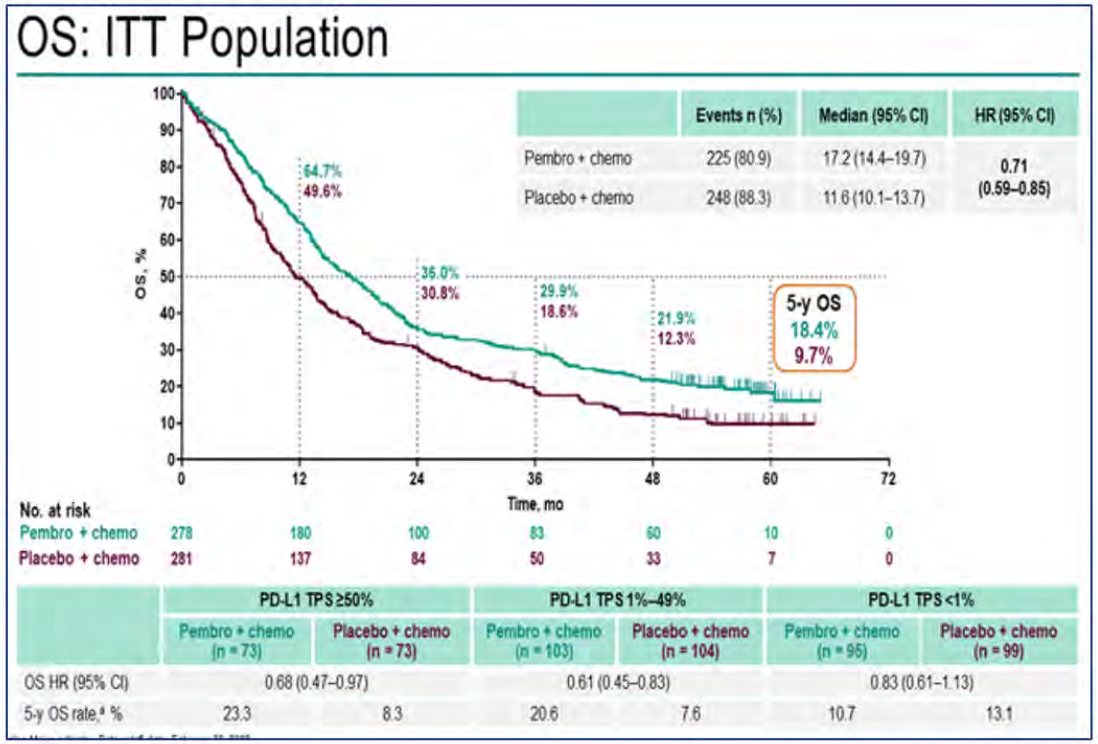


8 year OS: 24.3% vs 12.8% (HR 0.65)

Garon E et al, ESMO 2025

KN-189 AND KN-407- LONG TERM RESULTS





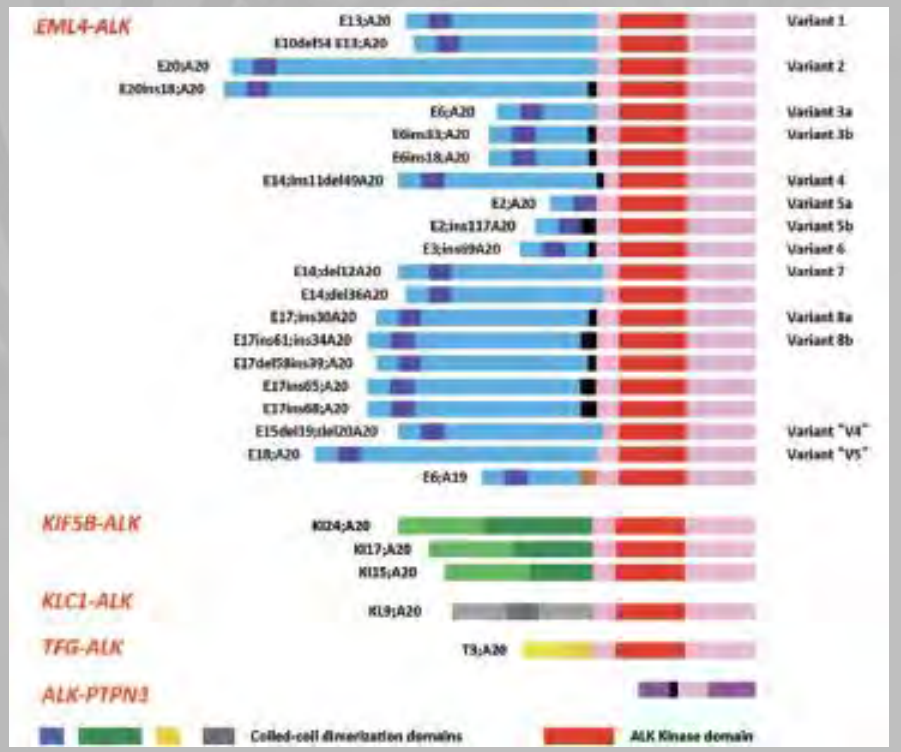
KN-189- 5 y OS 19.4% vs 11.3%, HR 0.6

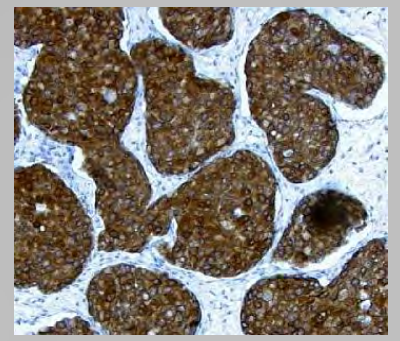
KN-407- 5 y OS 18.4% vs 9.7%, HR 0.71

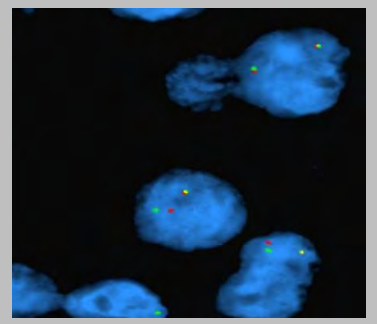
Garassino M, et al, ESMO 2022; J Clin Oncol 2023; Novell S, et al, ESMO 2022; J Clin Oncol 2023

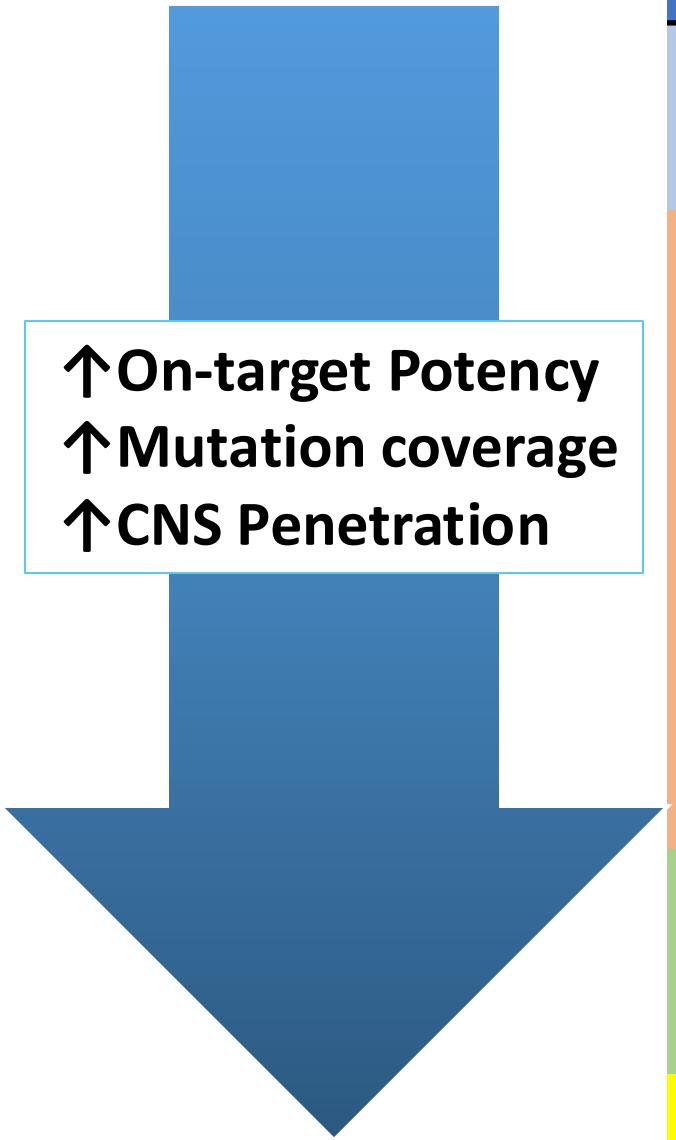
ALK GENE REARRANGEMENTS IN NSCLC

- ***EML4-ALK* and other ALK fusion variants present in 3-5% of NSCLC.**
  - Adenocarcinoma histology.
  - Typically (but not always!) younger & never smokers or light former smokers.
  - Propensity for brain metastases
  - Incidence very similar globally







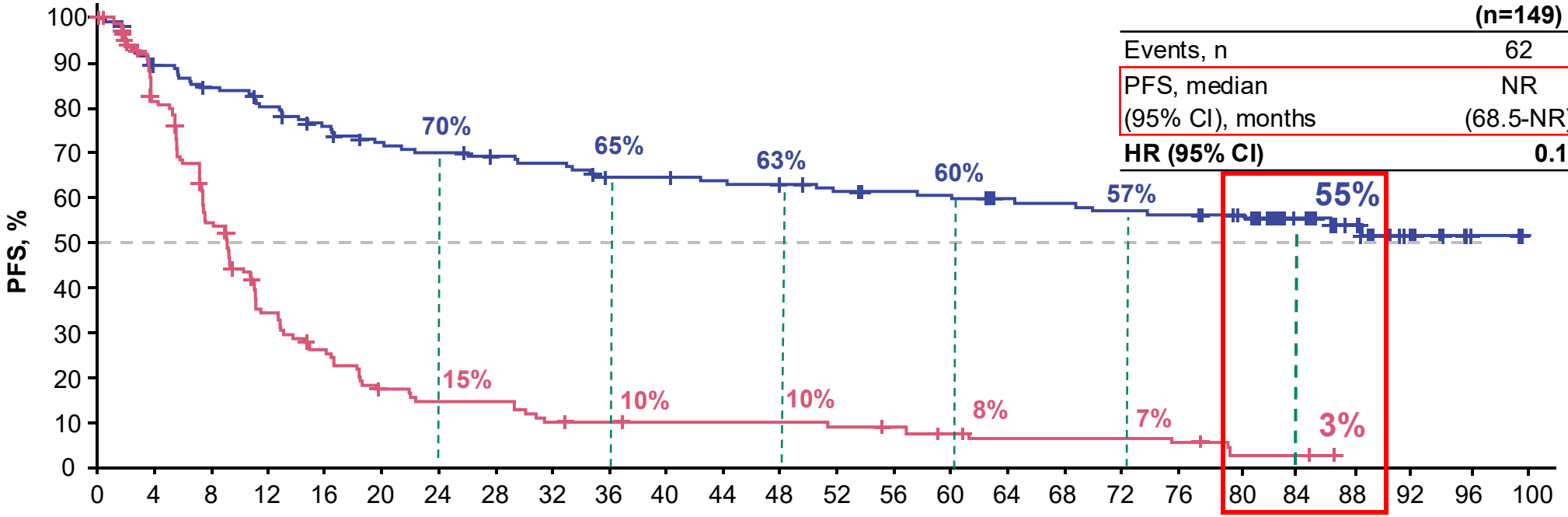


ALK TKI		STATUS
1st generation	Crizotinib	▪ FDA-approved, EMA-approved
2nd generation	Ceritinib	▪ FDA / EMA approved, post crizotinib ▪ FDA / EMA approved, first line
	Alectinib	▪ FDA / EMA approved, post crizotinib ▪ FDA / EMA approved, first line
	Brigatinib	▪ FDA / EMA approved, post crizotinib ▪ FDA/EMA approved, first line
	Ensartinib	▪ FDA approved
3rd generation	Lorlatinib	▪ FDA / EMA approved, in patients who have received 1 or more ALK inhibitors ▪ FDA/EMA approved firstline
4th Generation	Neladalkib (NVL-655)	▪ FDA Breakthrough designation

PFS IN THE ITT POPULATION (7-YEAR FOLLOW-UP)

The median duration of follow-up for PFS was **83.0 months** (95% CI, 81.2-86.3) in the lorlatinib arm and **77.2 months** (95% CI, 36.8-not evaluable) in the crizotinib arm

	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	62	119
PFS, median (95% CI), months	NR (68.5-NR)	9.1 (7.4-10.9)
HR (95% CI)	**0.19 (0.13-0.26)**	



No. at risk

Lorlatinib	149	126	118	111	103	96	93	89	87	81	81	79	78	75	73	71	69	68	66	65	62	38	28	9	2	0
Crizotinib	147	107	70	42	30	19	16	16	11	10	9	9	9	8	8	7	6	6	6	5	2	2	0	0	0	0

At the time of this analysis, median PFS by investigator was still not reached with lorlatinib

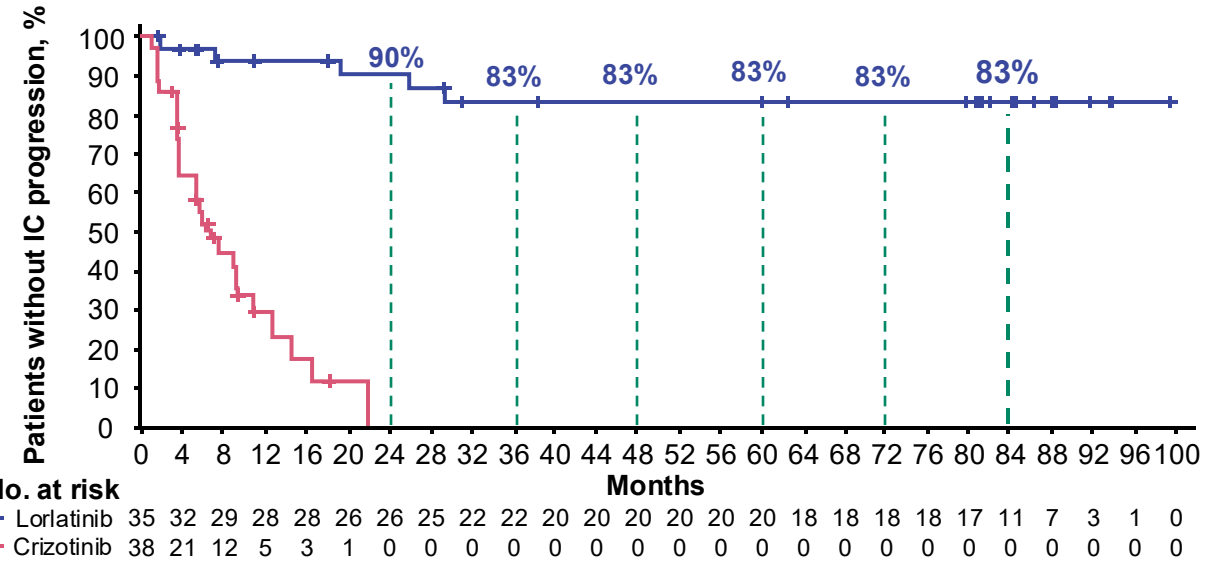
CI, confidence interval; HR, hazard ratio; ITT, intention to treat; NR, not reached; PFS, progression-free survival.

Tony S. K. Mok, MD (tony@clo.cuhk.edu.hk)

TIME TO IC PROGRESSION BY BRAIN METASTASES

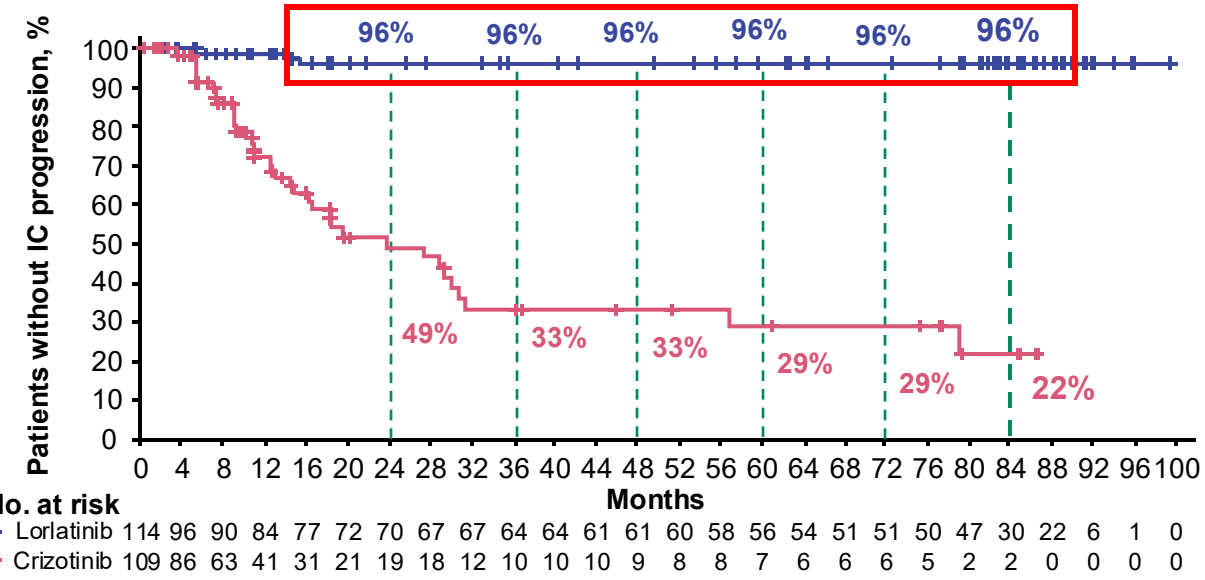
With baseline brain metastases

	Lorlatinib (n=35)	Crizotinib (n=38)
Events, n	5	26
Time to IC progression, months, median (95% CI)	NR (NR-NR)	7.2 (3.7-11.0)
HR (95% CI)	**0.03 (0.01-0.13)**	



Without baseline brain metastases

	Lorlatinib (n=114)	Crizotinib (n=109)
Events, n	4	40
Time to IC progression, months, median (95% CI)	NR (NR-NR)	23.9 (16.4-30.8)
HR (95% CI)	**0.04 (0.02-0.12)**	



Sustained plateau in time to IC progression indicates a prolonged protective effect against the development of new brain metastases and a sustained control of the existing ones

CI, confidence interval; HR, hazard ratio; IC, intracranial; NR, not reached.

Tony S. K. Mok, MD (tony@clo.cuhk.edu.hk)

TOMORROW'S PROMISE BUILT ON PAST ACHIEVEMENTS



Novel Therapeutics/Beyond Advanced Stage

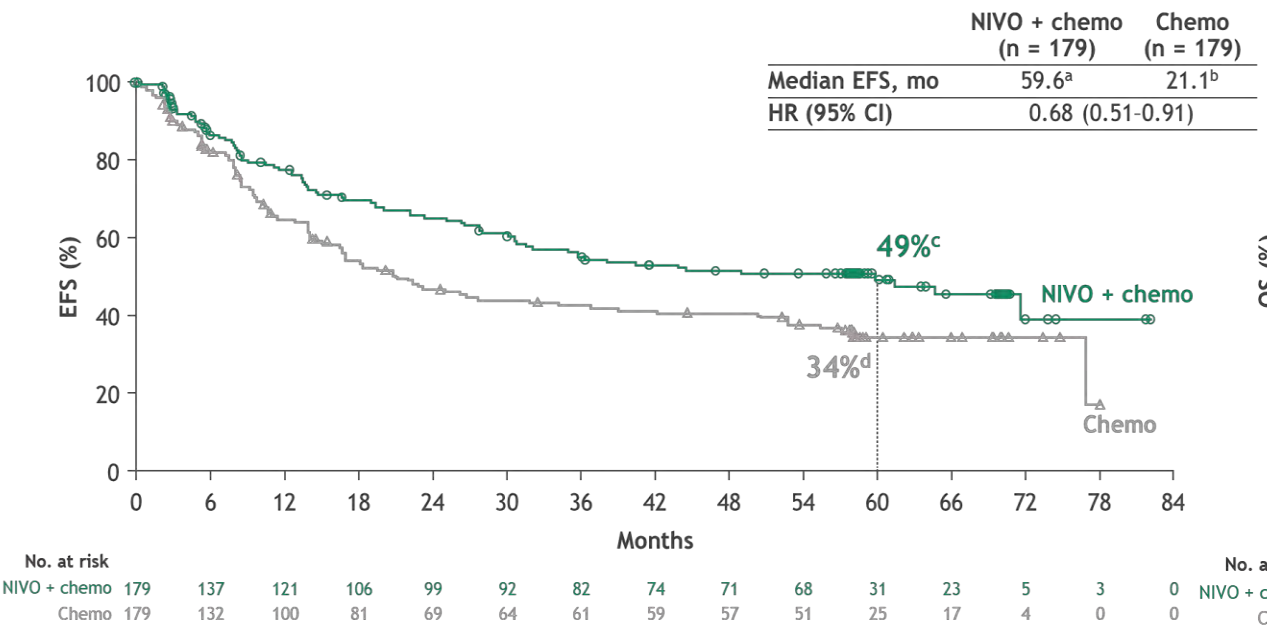
Mechanisms of Resistance

Biomarkers for Personalized Care

Healthy Survival/Survivorship

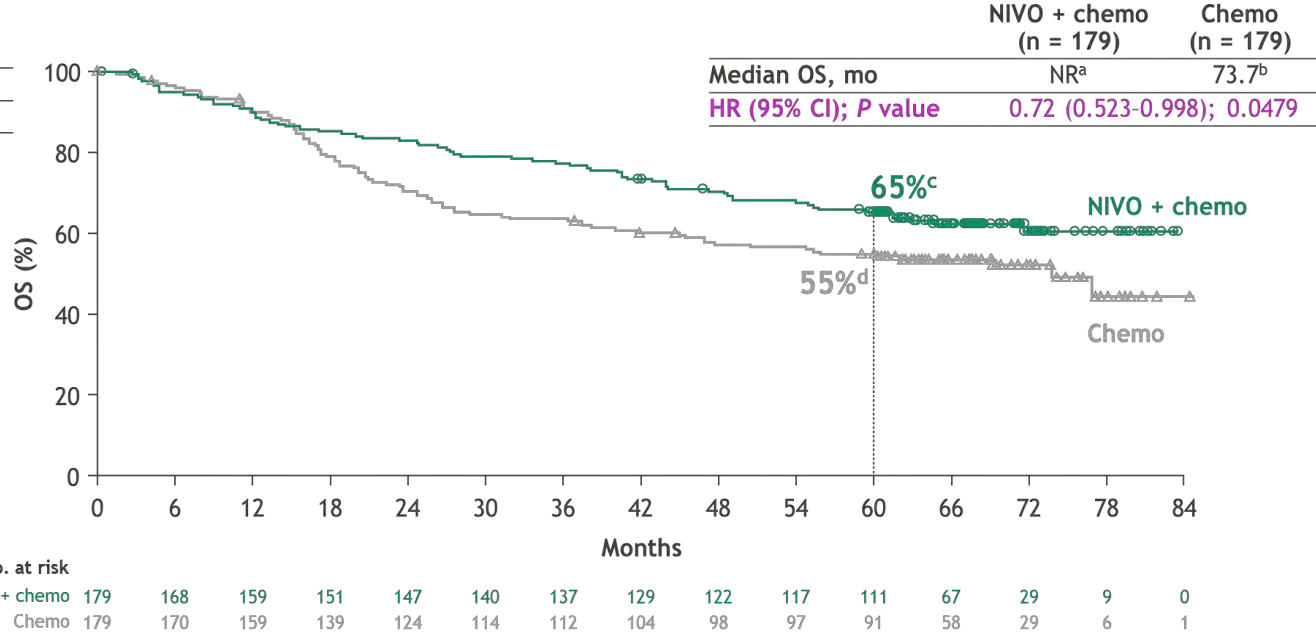
CheckMate 816: 5-year EFS and OS outcomes

Neoadjuvant Nivo plus CT: 5-year EFS



Minimum/median follow-up: 59.9/68.4 months
[a–d]95% CI: [a]31.6–NR; [b]16.5–36.8; [c]41–57; [d]27–42

Neoadjuvant Nivo plus CT : 5-year OS

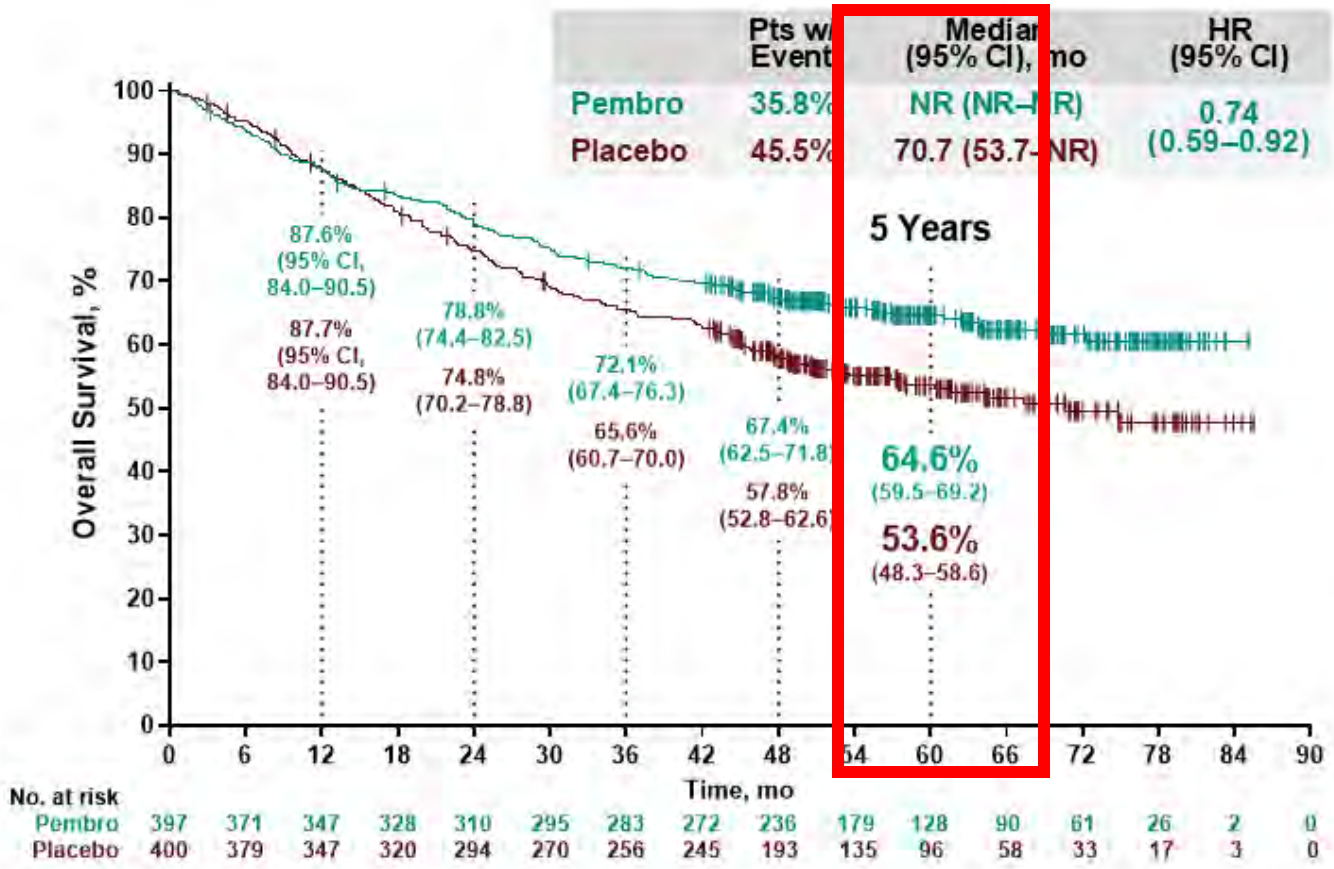


Minimum/median follow-up: 59.9/68.4 months
[a-d]95% CI: [a]NR; [b]47.3–NR; [c]58–72; [d]47–62

Forde P et al. *N Engl J Med.* 2022

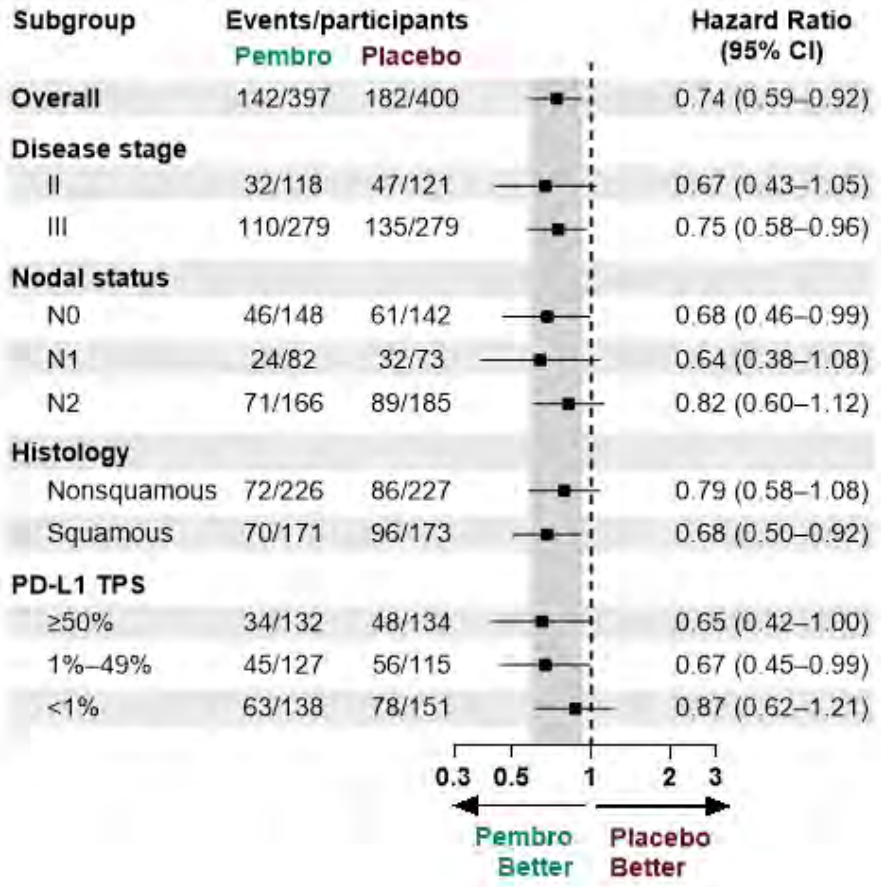
KEYNOTE-671: 5-year OS Updates

Overall Population



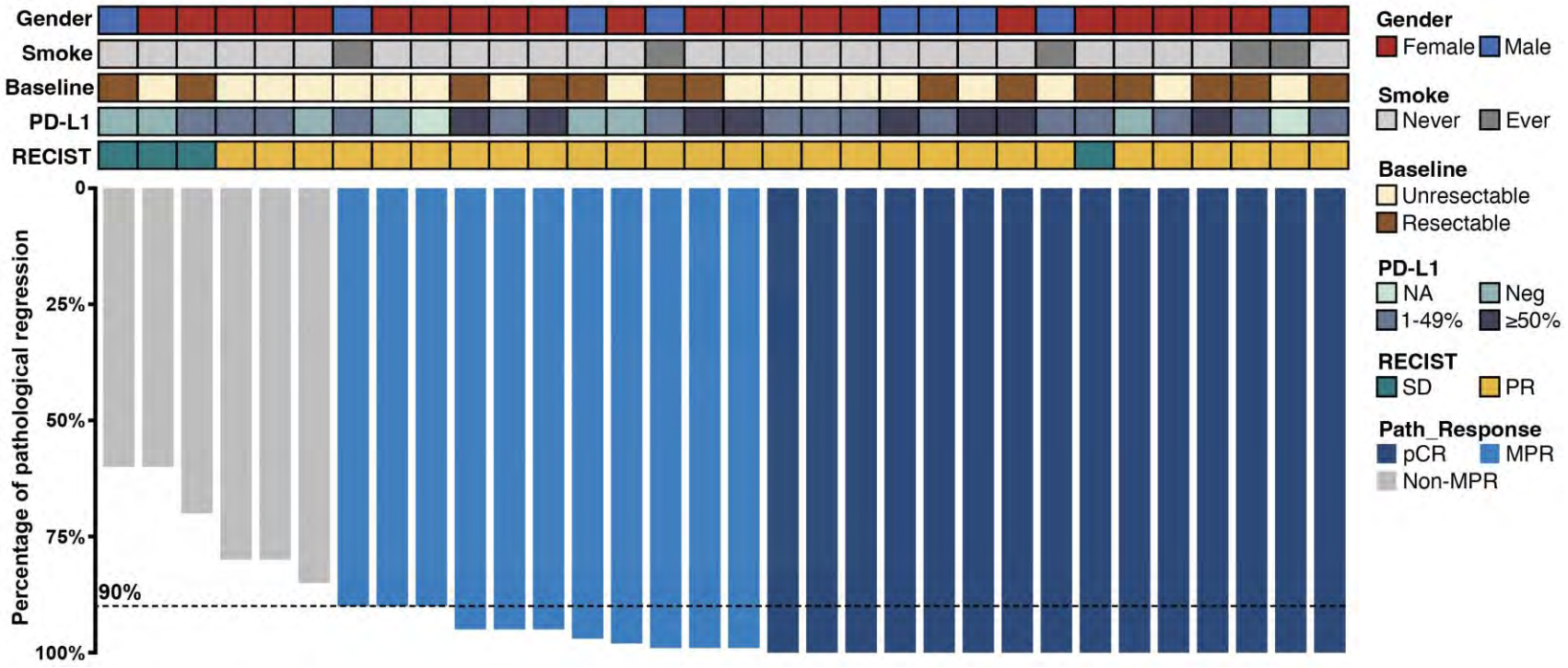
Median time from randomization to data cutoff was 60.4 (range, 42.6–85.8) months.
Data cutoff date: July 3, 2025.

Key Subgroups



Wakelee H et al. *Ann Oncol.* 2025;36(Suppl-2):LBA67.

LORIN: Primary Endpoint—pCR (Surgery)



Overall	N=32 (n, %)
pCR	**15 (47)**
MPR	26 (81)
Median/Mean RVT	**1%/7%**

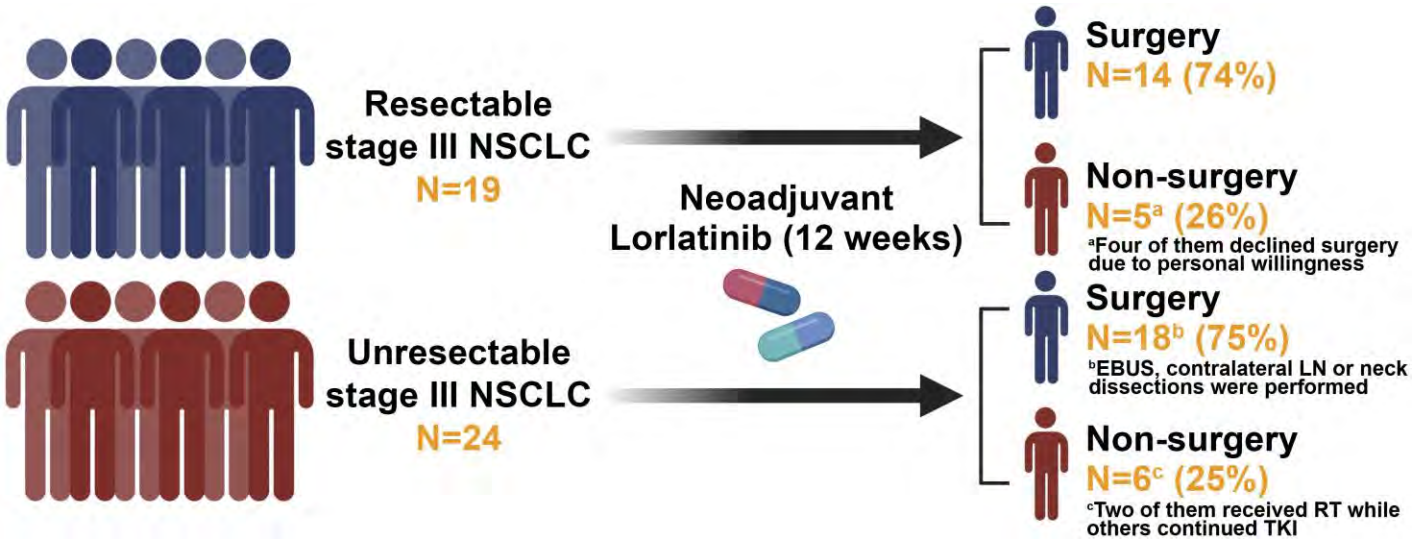
Resectability	pCR/MPR
Resectable	50%/86%
Unresectable	44%/78%

	Median PD-L1 exp.
MPR/pCR	25%
Non-MPR	1%
p value <0.01	

Among patients who underwent surgery, the pCR and MPR rates were **46.9% (15/32) (95%CI, 29.1%-65.2%) [34.9% for ITT]** and **81.3% (26/32) [60.5% for ITT]**, respectively, reaching the primary endpoint.

PR, partial response; SD, stable disease; pCR, pathological complete response; MPR, major pathological response; NA, not assessed; Neg, negative; RVT, residual viable tumor

LORIN: Surgical Outcomes



Overall pN downstaging **90%**

cN-pN shift	Num. (%)
cN3(n=18)→pN3	1 (6)
cN3(n=18)→pN1/N2	**4 (22)**
cN3(n=18)→pN0	**13 (72)**
cN2(n=12)→pN2	1 (8)
cN2(n=12)→pN1	**0 (0)**
cN2(n=12)→pN0	**11 (92)**

Operation	N=32
R0 resection, n (%)	31 (97)*
Types of surgery, n (%)	
VATS#/RATS/Open surgery	27(84) /2(7) /3(9)
Conversion to open surgery	3 (9)

Operation details	N=32
Median surgical duration	180mins (90-315)
Median harvested LNs	12 (7-31)
Median estimated blood loss	50ml (30-800)
Clavien-Dindo (grade II)	5 (16%)

*One patient had pathologically confirmed N3 positive after lorlatinib and surgery; #All patients underwent lobectomy with 3 underwent bilobectomy

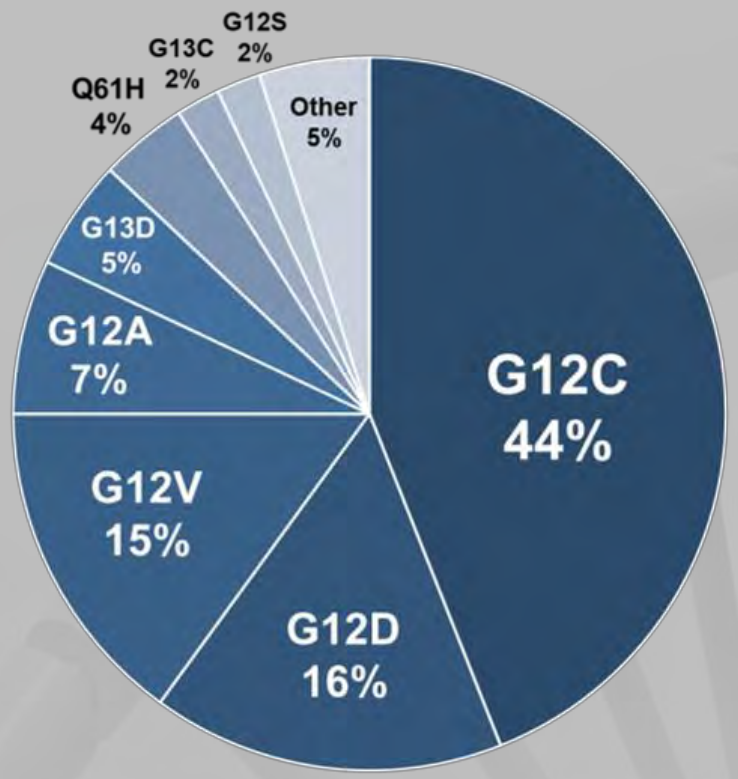
NOVEL THERAPEUTICS

1. New Targets- Driver Mutations and Co-Mutations

2. Drugs Targeting IO Resistance

3. Novel Drugs- Antibody Drug Conjugates, Bispecific Antibodies, Vaccines

KRAS MUTATIONS IN NSCLC



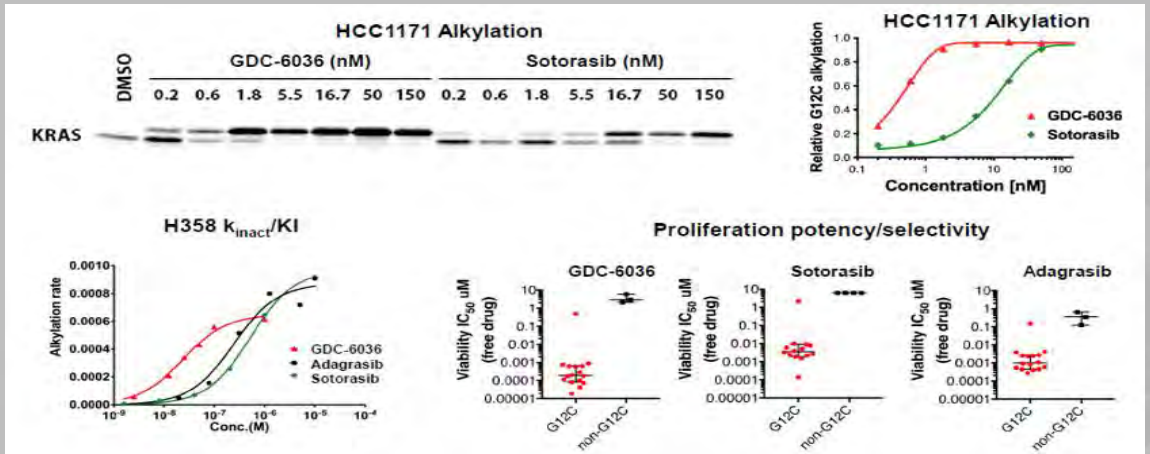
KRAS G12C incidence across the globe

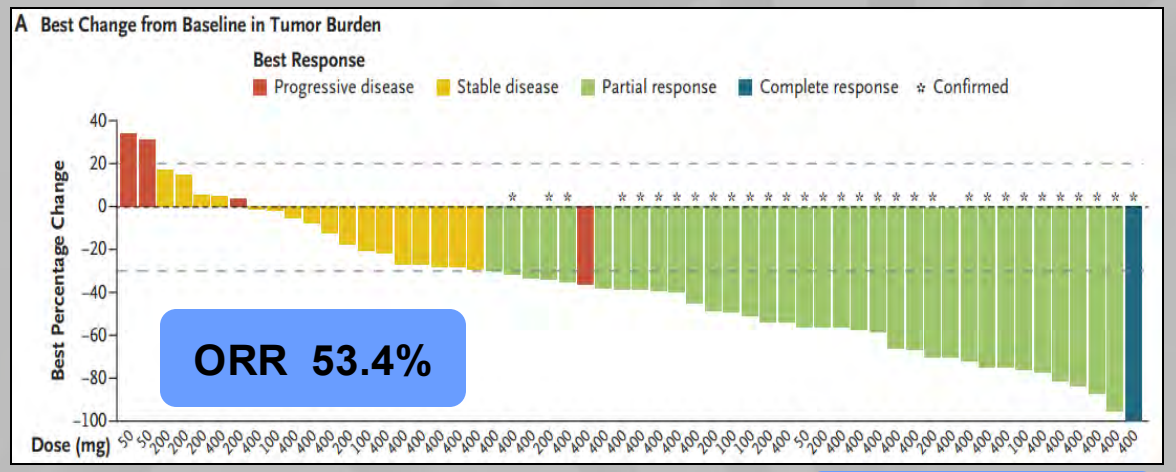
Region	KRAS G12C
North America and Europe	~ 13%
Latin America	~ 9%
Asia	~ 3%

KRAS mutations
25% of NSCLC patients
30 % of Adenocarcinomas
<5% of Squamous Cell Carcinomas

Lim TKH, et al, Lung Cancer 2023

DIVARASIB- POTENT 'OFF' INHIBITORS





mDOR= 14.1m

mPFS= 13.1m

TRAEs OVERALL (≥10% PATIENTS) & CORRESPONDING GRADE 3-5 TRAEs	NSCLC N=65	
	All TRAEs	Grade 3-5 TRAEs
Patients with at least one AE	61 (94%)	11 (17%)
Nausea	51 (79%)	1 (2%)
Vomiting	43 (66%)	0
Diarrhea	40 (62%)	2 (3%)
Fatigue	16 (25%)	1 (2%)
Decreased appetite	15 (23%)	0
Amylase increased	11 (17%)	0
ALT increased	10 (15%)	4 (6%)
Lipase increased	10 (15%)	2 (3%)
AST increased	9 (14%)	3 (5%)

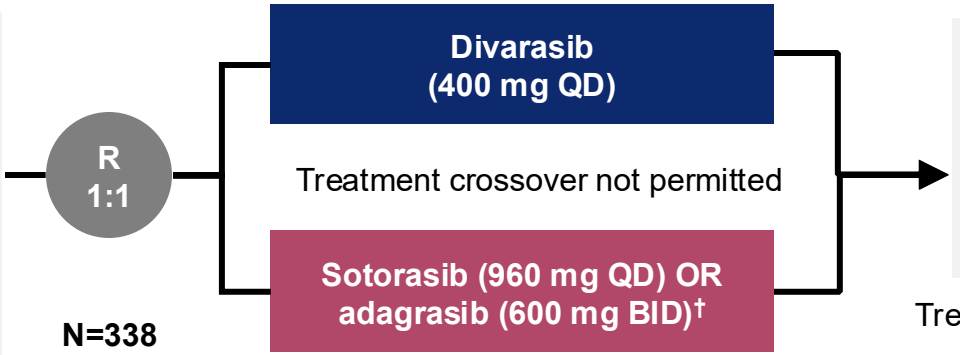
STUDY TREATMENT ACTION DUE TO TRAEs	NSCLC N=65
Patients with AEs resulting in divarasib modification (interruption/reduction/withdrawal)	25 (39%)
Patients with AEs resulting in divarasib reduction	15 (23%)
Patients with AEs resulting divarasib withdrawal	3 (5%)

Sacher A, et al, N Engl J Med 2023

Krascendo 1: a phase III, global, randomised, open-label trial in previously treated *KRAS* G12C-mutated advanced or metastatic NSCLC

Key eligibility criteria

- KRAS G12C inhibitor naive
- ECOG PS 0–1
- Advanced *KRAS* G12C-mutated NSCLC
- ≥1 but ≤3 lines of prior systemic therapy, including platinum-based chemo and a PD-(L)1 inhibitor*
- Measurable disease per RECIST v1.1
- Patients with active, untreated CNS metastases were excluded



Treatment until disease progression, unacceptable toxicity, death, withdrawal of consent, or study termination

Treatment beyond progression was permitted

Stratification factors
- History of CNS metastases
- Intended choice of control arm KRAS G12C inhibitor†
- *KEAP1* mutation status‡

Primary endpoint
- PFS per BICR

Key secondary endpoints
- OS
- Confirmed ORR per BICR
- TTCD

Other secondary endpoints
- DoR per BICR
- Safety
- Other PROs

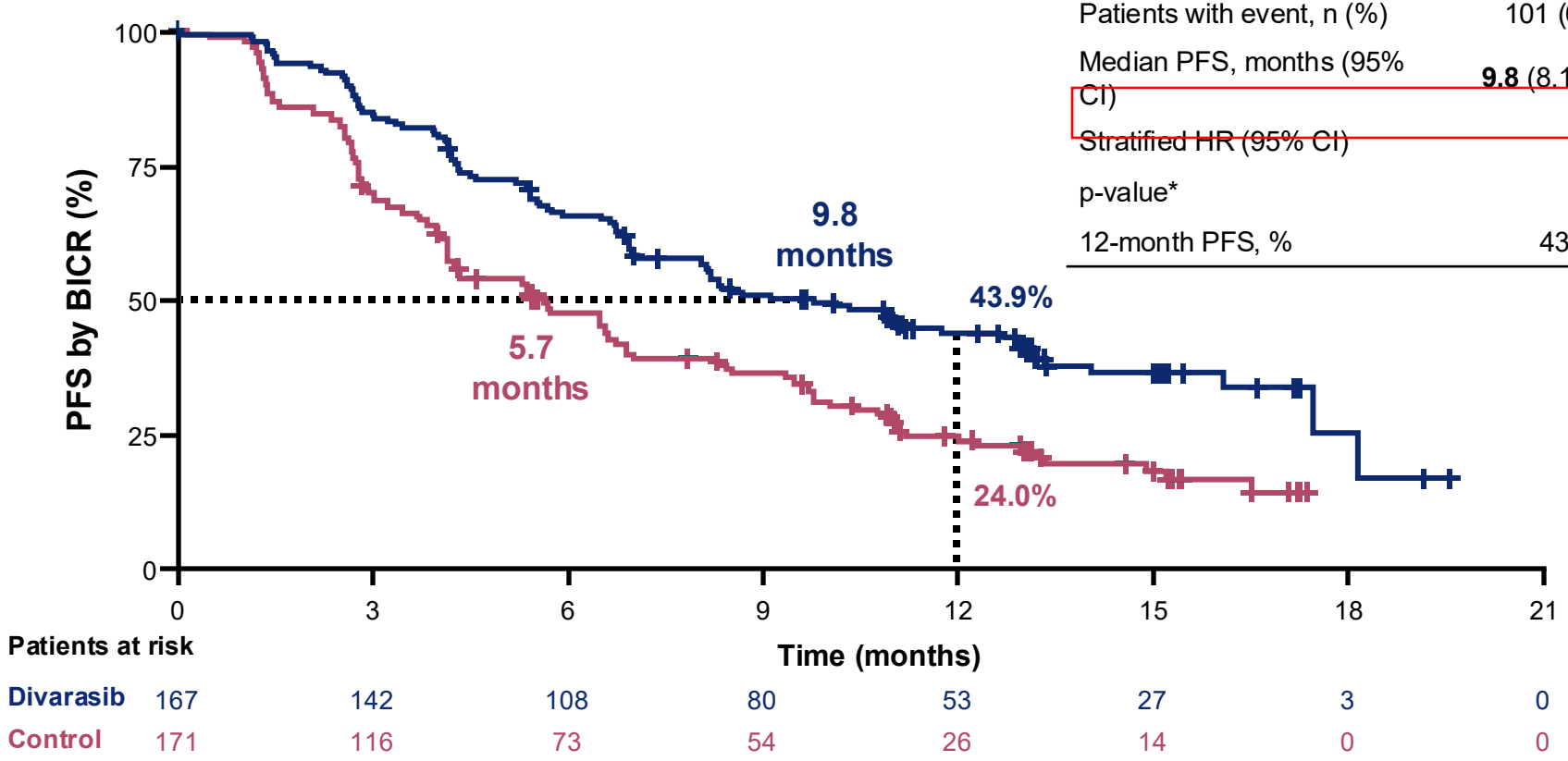
NCT06497556

PD-L1 all-comers population. *In the advanced or metastatic setting. †The control arm drug depended on local approvals and availability; if both drugs were locally approved and available, investigators designated their intended control drug for each patient prior to randomisation and patients received the same drug for the duration of the study. ‡Detected versus not detected/unknown. BICR, blinded independent central review; BID, twice a day; chemo, chemotherapy; CNS, central nervous system; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PROs, patient-reported outcomes; TTCD, time to confirmed deterioration; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors

Dr Ferdinandos Skoulidis

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Progression-free survival by BICR



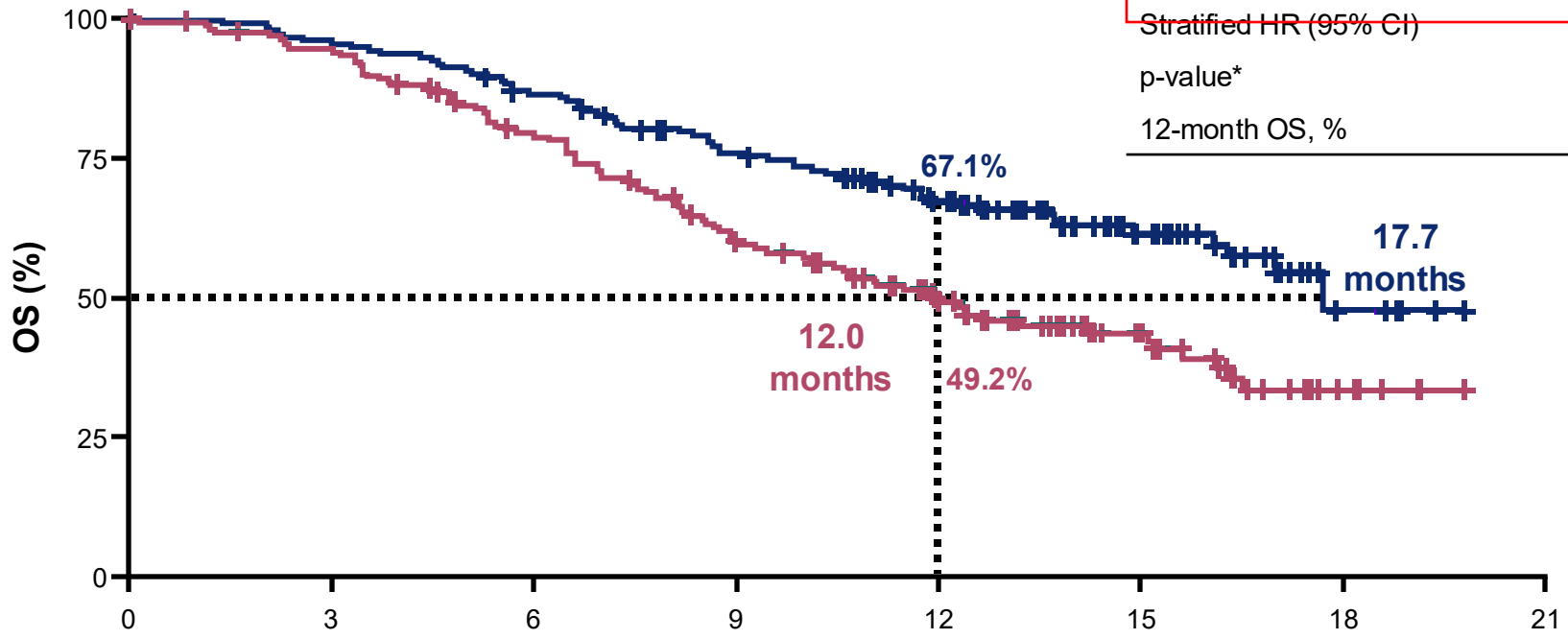
	Divarasib (n=167)	Control (n=171)
Patients with event, n (%)	101 (60.5)	128 (74.9)
Median PFS, months (95% CI)	**9.8** (8.1–12.9)	**5.7** (4.2–6.8)
Stratified HR (95% CI)	**0.58** (0.44–0.76)	
p-value*	<0.0001	
12-month PFS, %	43.9	24.0

Data cut-off: 19 May 2026. Median duration of follow up: 14.3 months. Minimal duration of follow up: 5.6 months. Control arm included treatment with sotorasib or adagrasib
*Stratified log-rank test. CI, confidence interval

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Overall survival

	Divarasib (n=167)	Control (n=171)
Patients with event, n (%)	63 (37.7)	93 (54.4)
Median OS, months (95% CI)	**17.7** (16.3–NE)	**12.0** (10.0–15.2)
Stratified HR (95% CI)	**0.56** (0.41–0.78)	
p-value*	0.0005	
12-month OS, %	67.1	49.2



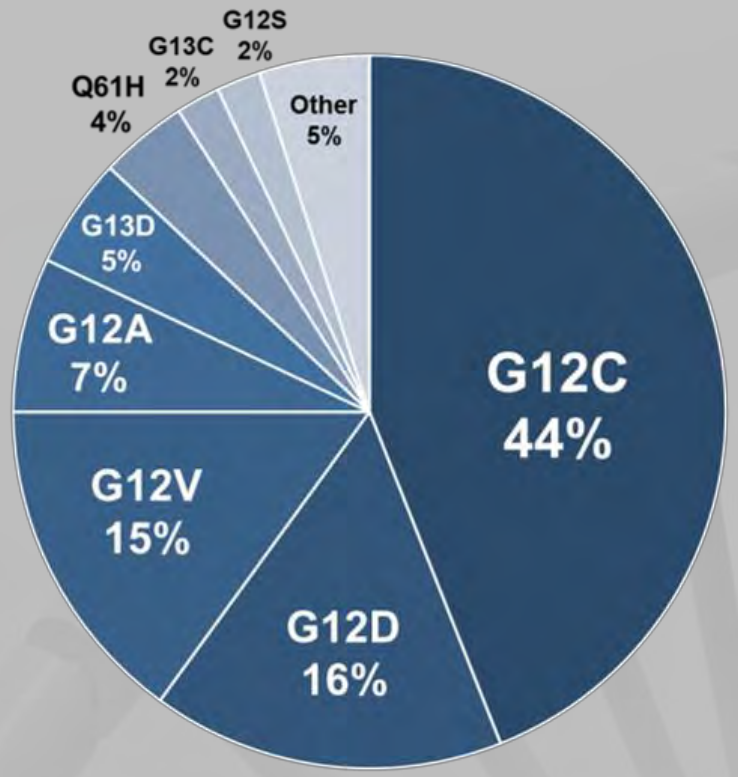
Patients at risk

Divarasib	167	160	142	120	95	41	6	0
Control	171	159	128	94	65	31	6	0

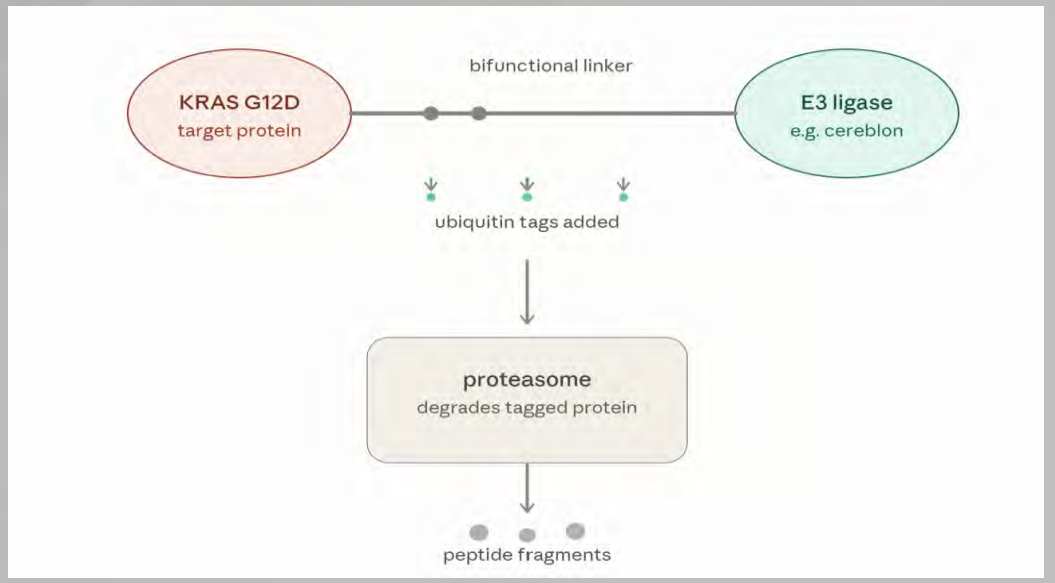
Data cut-off: 19 May 2026. Median duration of follow up: 14.3 months. Minimal duration of follow up: 5.6 months. Control arm included treatment with sotorasib or adagrasib
*Stratified log-rank test. NE, not estimable

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KRAS INHIBITORS IN NSCLC

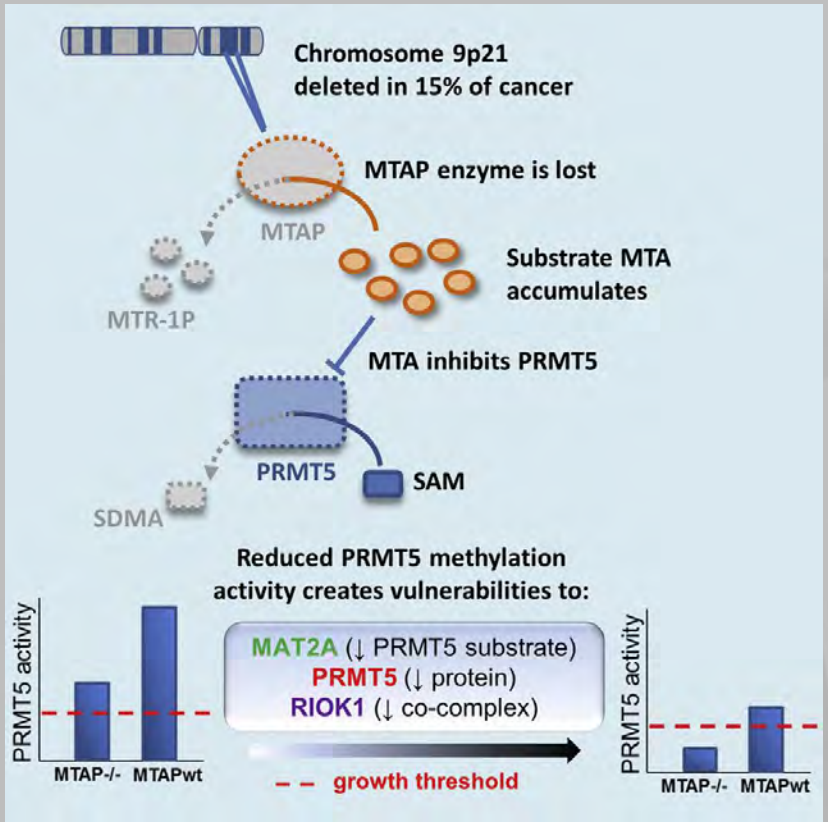


Allele Specific Inhibitors and Degraders
KRAS G12D, G12V
PAN- RAS Inhibitors and Degraders



Lim TKH, et al, Lung Cancer 2023

CO-MUTATIONS- MTAP DELETION



MTAP is involved in methionine salvage pathway

Loss of MTAP leads to accumulation of MTA

MTA inhibits PRMT5 which regulates gene expression and cell cycle.

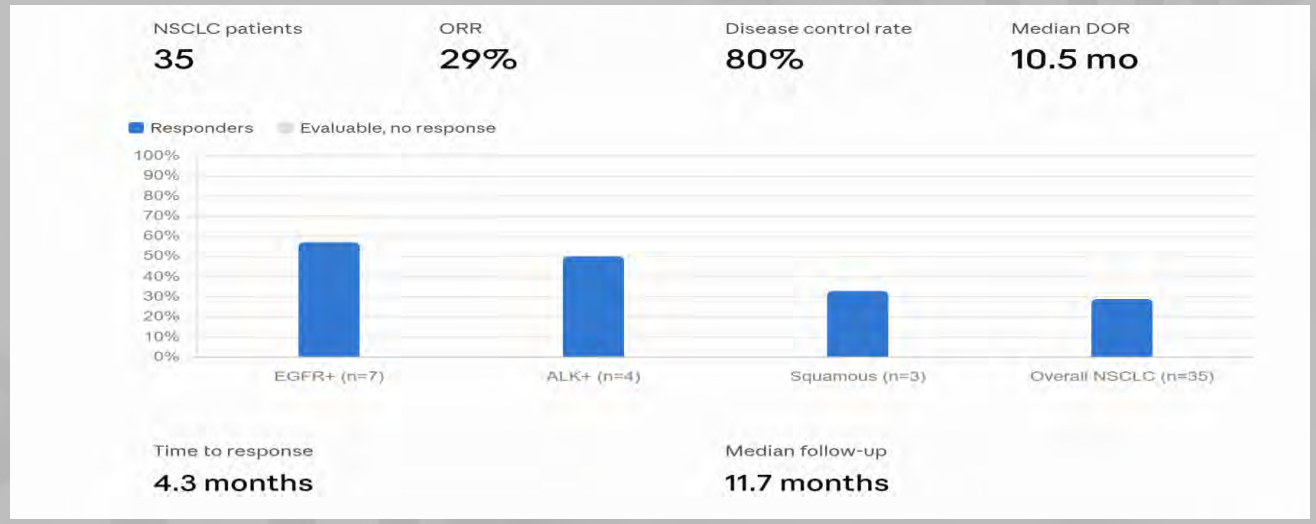
Cancer cells with MTAP deletion makes them sensitive to further PRMT5 inhibition

Rate of MTAP deletion is about 25% in NSCLC

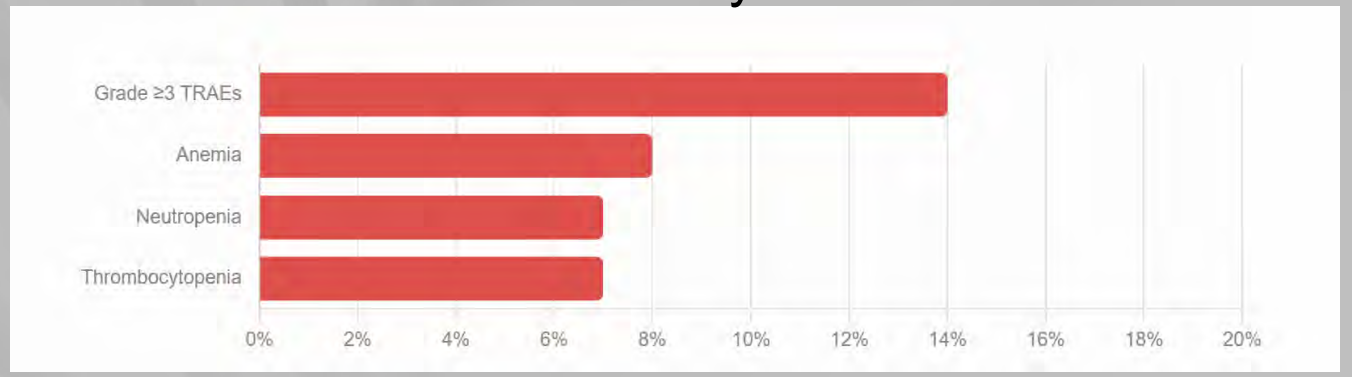
Marjon K, Cell Reports 2016; Ikushima, H ESMO Open 2025; Gadgeel AACR 2026

NAVLIMETOSTAT (BMS-986504)

Efficacy



Toxicity

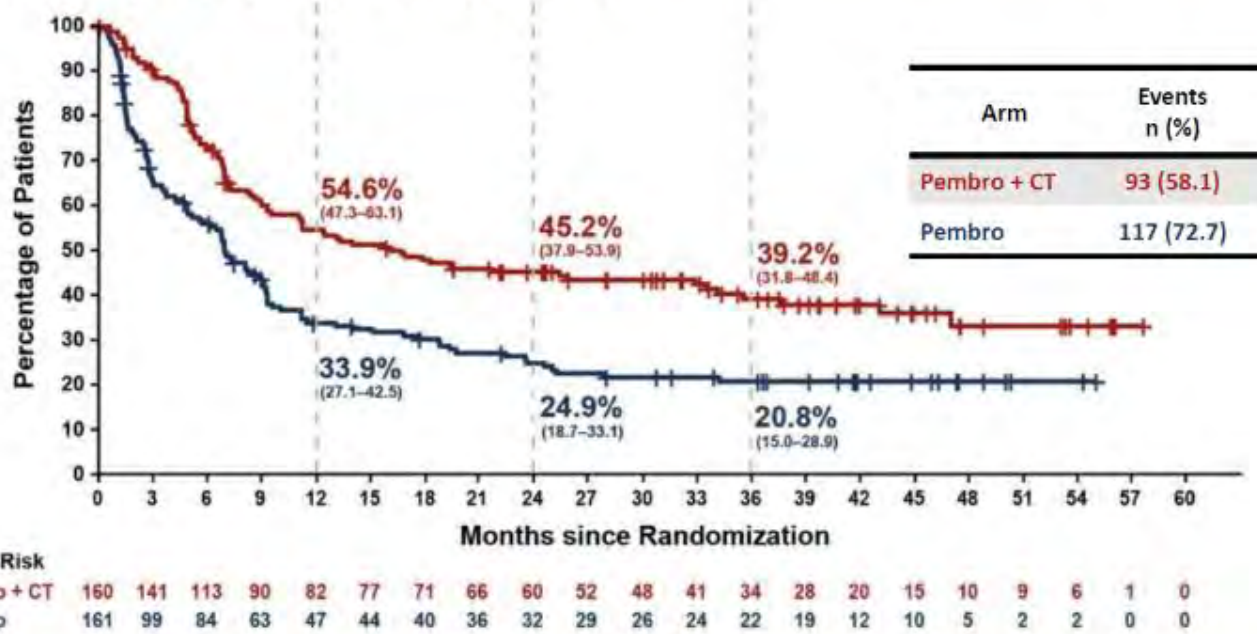


Janne, et al, WCLC 2025

PERSEE TRIAL- CHEMO AND PEMBRO IN PDL1 HIGH

Primary endpoint: PFS by BCR (RECIST 1.1)

Median follow-up was 38.7 (35.3-41.6) months



Arm	Events n (%)	Median PFS (95% CI), months	HR (95% CI) Two-sided P value
Pembro + CT	93 (58.1)	16.1 (11–34.1)	0.56 (0.43–0.74)
Pembro	117 (72.7)	6.9 (5.5–9.3)	P < 0.001

No. at Risk

Pembro + CT	160	141	113	90	82	77	71	66	60	52	48	41	34	28	20	15	10	9	6	1	0
Pembro	161	99	84	63	47	44	40	36	32	29	26	24	22	19	12	10	5	2	2	0	0

PFS assessed by BCR was significantly longer in the pembro-CT group than in the pembro group, with a clinically meaningful benefit sustained over time.

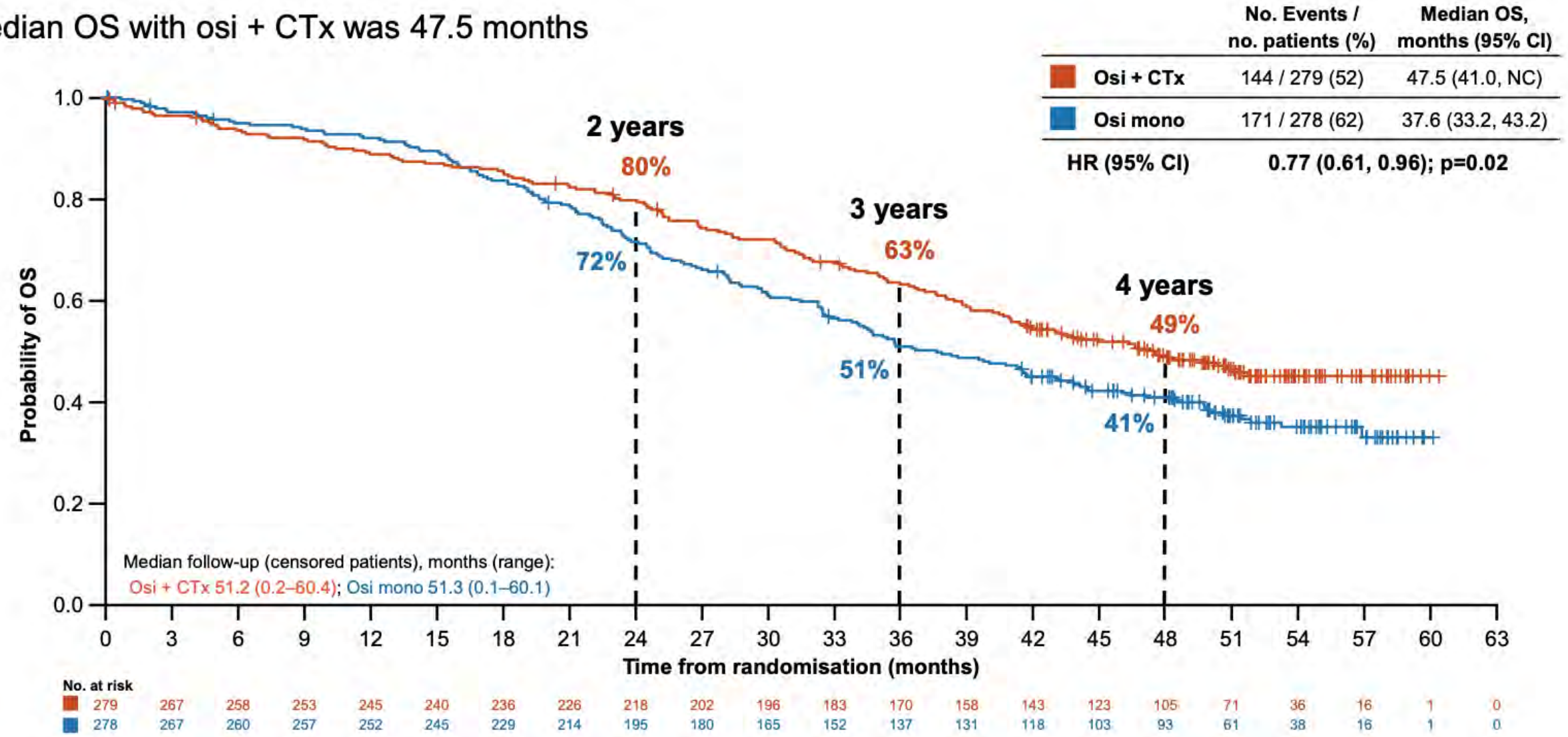
The PFS benefit was consistent with investigators assessment with a **HR 0.59 (0.46-0.77).**

Chantal Decroisette

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FLAURA2: FINAL OVERALL SURVIVAL

Median OS with osi + CTx was 47.5 months



David Planchard, IASLC WCLC 2025

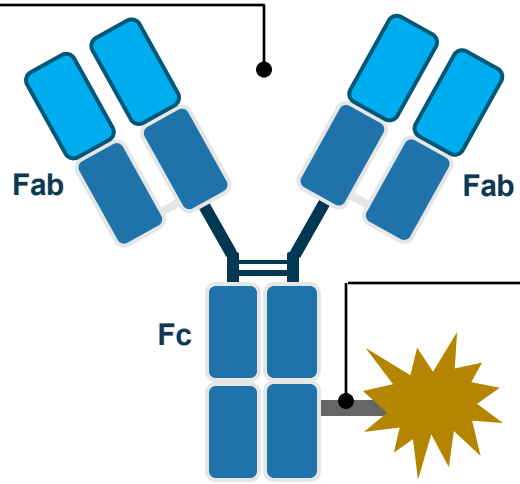
ANTIBODY-DRUG CONJUGATES
NEW KIDS ON THE BLOCK

Important Properties of the ADC Components and Target Antigen

Antigen
- High homogeneous expression on tumor
- Low or no expression on healthy tissues
- High affinity and avidity for antibody recognition

Antibody
- High affinity and avidity for tumor antigen
- Chimeric or humanized to decrease immunogenicity
- Long half-life and high molecular weight

Cytotoxic Payload
- Highly potent agents:
  - Calicheamicin
  - Maytansine derivative (DM1 or DM4)
  - Auristatin (MMAE or MMAF)
  - SN-38
  - DXd topoisomerase I inhibitor
- Optimal DAR (range: 2 to 8)



Linker
- Stable in circulation
- Efficient release of payload at target site
- Prevents premature release of payload at nontarget tissue
- Efficient linker technology **(cleavable vs noncleavable)**
- Site of conjugation
- DAR affects drug distribution and pharmacokinetics

Cleavable Linkers
Depend on physiological conditions:
pH, proteolysis, or high intracellular glutathione
Noncleavable Linkers
Depend on lysosomal degradation

© Medscape, LLC

Courtesy- Benjamin Levy, MD @benlevylungdoc

Chau CH, et al. Lancet. 2019;394:793-804.

OPTITROP-LUNG06 TRIAL

OptiTROP-Lung06 Study Design

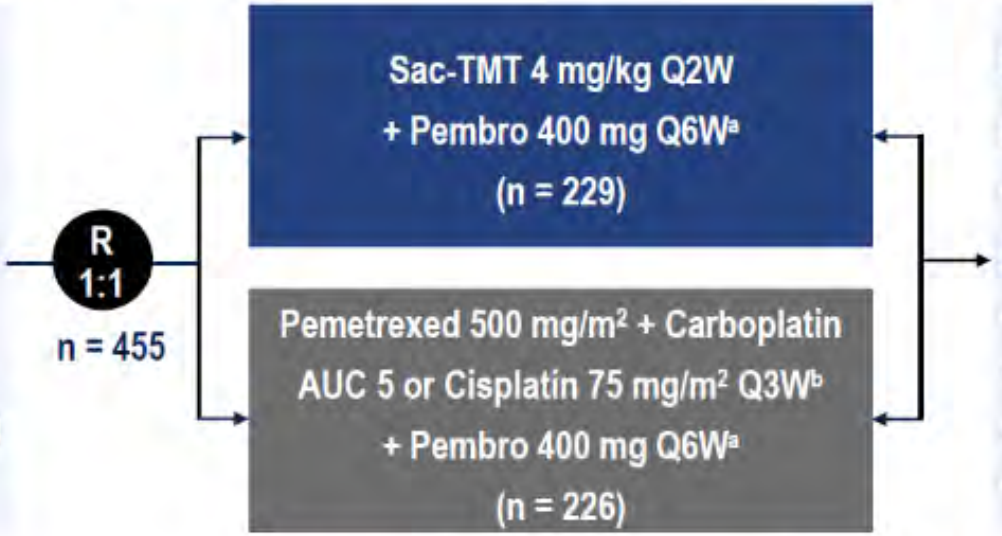
Randomized, multicenter, open-label, phase 3 trial (NCT06711900)

Key eligibility criteria

- Locally advanced (stage IIIB/IIIC) or metastatic (stage IV) nsq-NSCLC
- No prior systemic therapy for advanced disease
- No sensitizing *EGFR* or *ALK* alteration
- PD-L1 TPS< 1% (IHC 22C3, central lab)
- ECOG PS score 0 or 1

Stratification factors

- Sex (male vs. female)
- ECOG PS score (0 vs. 1)
- Disease stage (IIIB/IIIC vs. IV)



Treatment until disease progression or unacceptable toxicity

Endpoints [c]

Primary

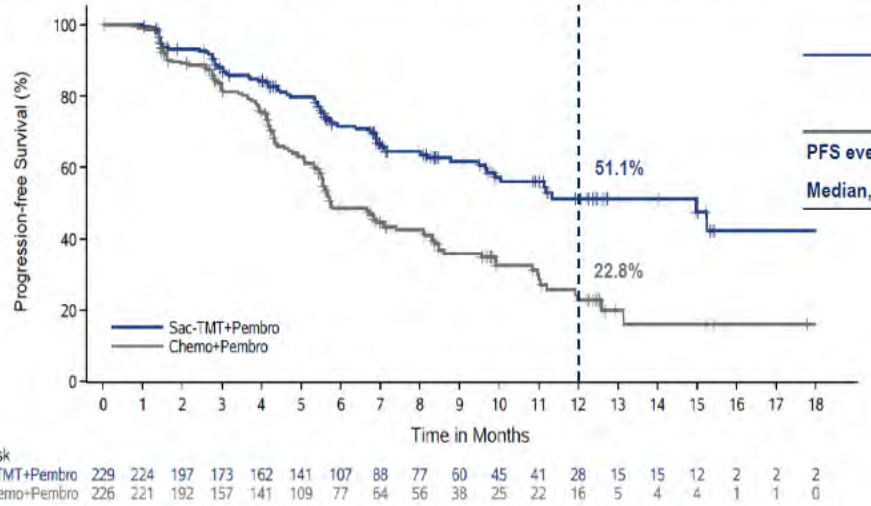
- PFS assessed by BICR

Secondary endpoints included

- OS
- PFS assessed by investigator
- ORR, DCR, DOR
- Safety

PFS by BICR

Sac-TMT + pembro significantly improved PFS vs. Chemo + pembro, with a 51% reduction in risk of disease progression or death.



At Risk

Sac-TMT+Pembro	229	224	197	173	162	141	107	88	77	60	45	41	28	15	15	12	2	2	2
Chemo+Pembro	226	221	192	157	141	109	77	64	56	38	25	22	16	5	4	4	1	1	0

	Sac-TMT + Pembro (n = 229)	Chemo + Pembro (n = 226)
PFS events, n (%)	79 (34.5)	126 (55.8)
Median, mo (95% CI)	15.0 (9.9–NE)	5.7 (5.5–7.4)

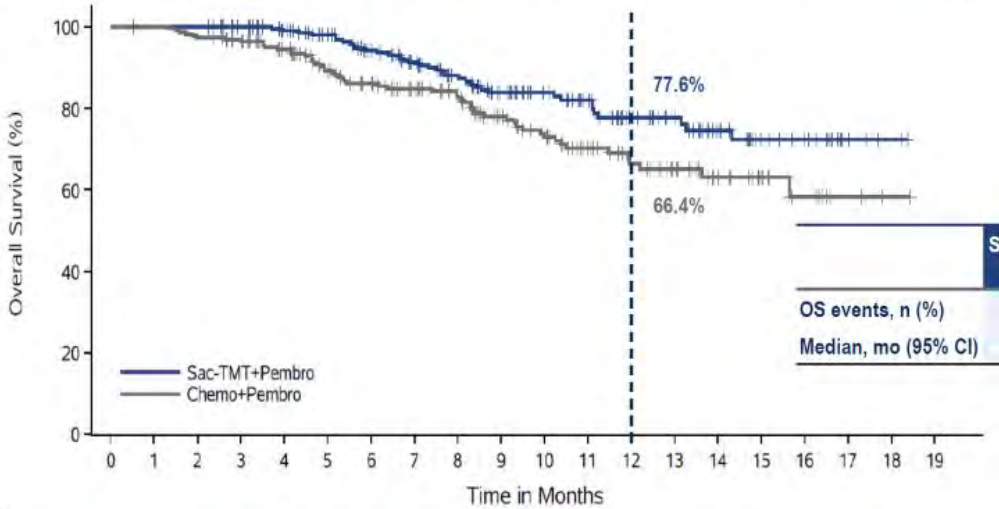
HR 0.49 (95% CI: 0.36–0.65)

P < 0.0001[a]

PFS by investigator assessment was consistent with the results of BICR: HR 0.52 (95% CI: 0.40-

[a] Updated efficacy boundary (corresponding to 205 actual PFS events by BICR): 0.0160 (2-sided).
NE, not estimable

A favorable trend in overall survival was observed with sac-TMT + pembro over chemo + pembro.



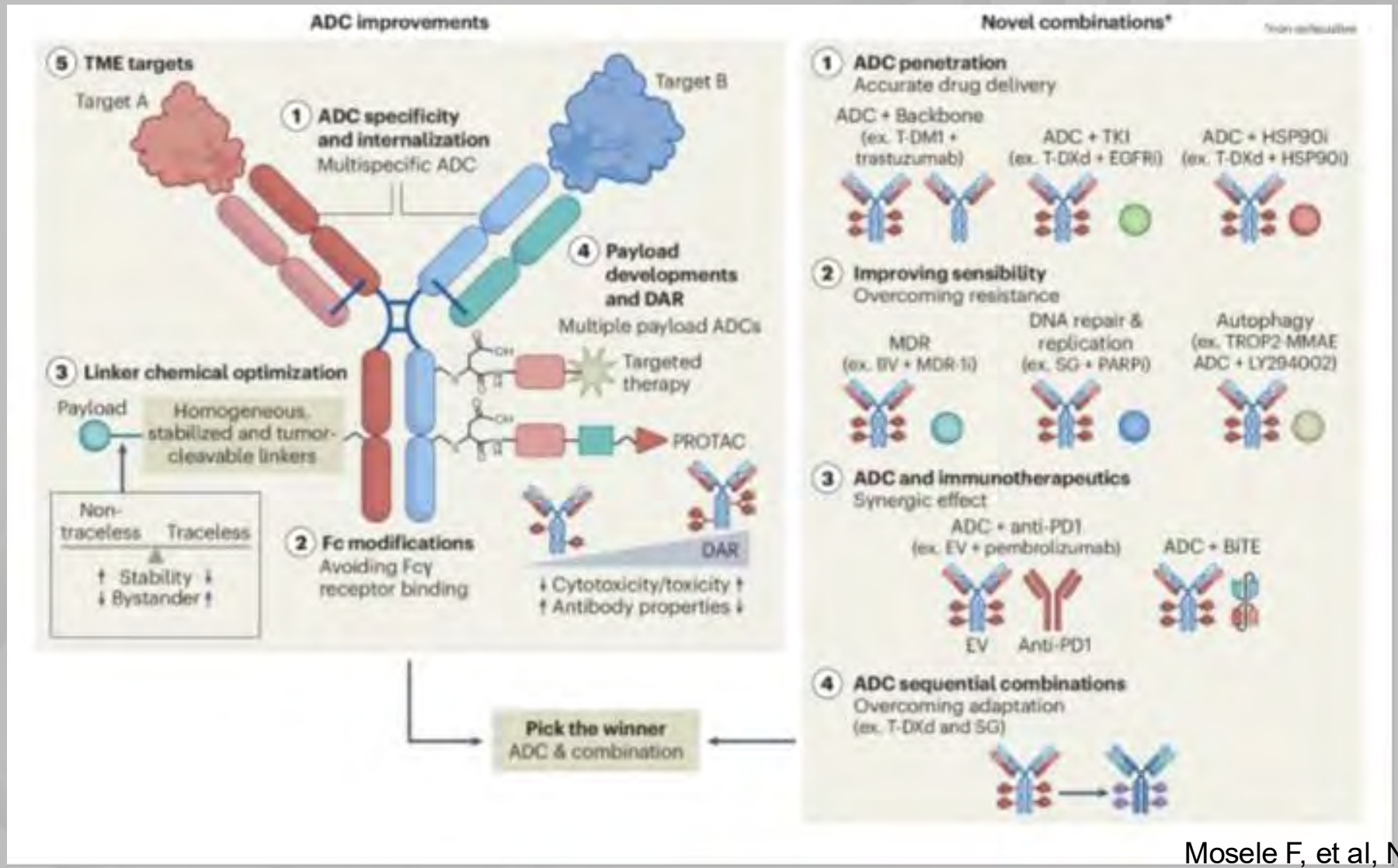
At Risk

Sac-TMT+Pembro	229	228	228	215	200	184	166	148	130	109	92	79	60	51	36	24	21	7	4
Chemo+Pembro	226	226	220	210	188	167	152	136	122	98	85	67	51	39	25	17	10	3	1

	Sac-TMT + Pembro (n = 229)	Chemo + Pembro (n = 226)
OS events, n (%)	36 (15.7)	55 (24.3)
Median, mo (95% CI)	NR (NE–NE)	NR (15.6–NE)

HR 0.58 (95% CI: 0.38–0.88)

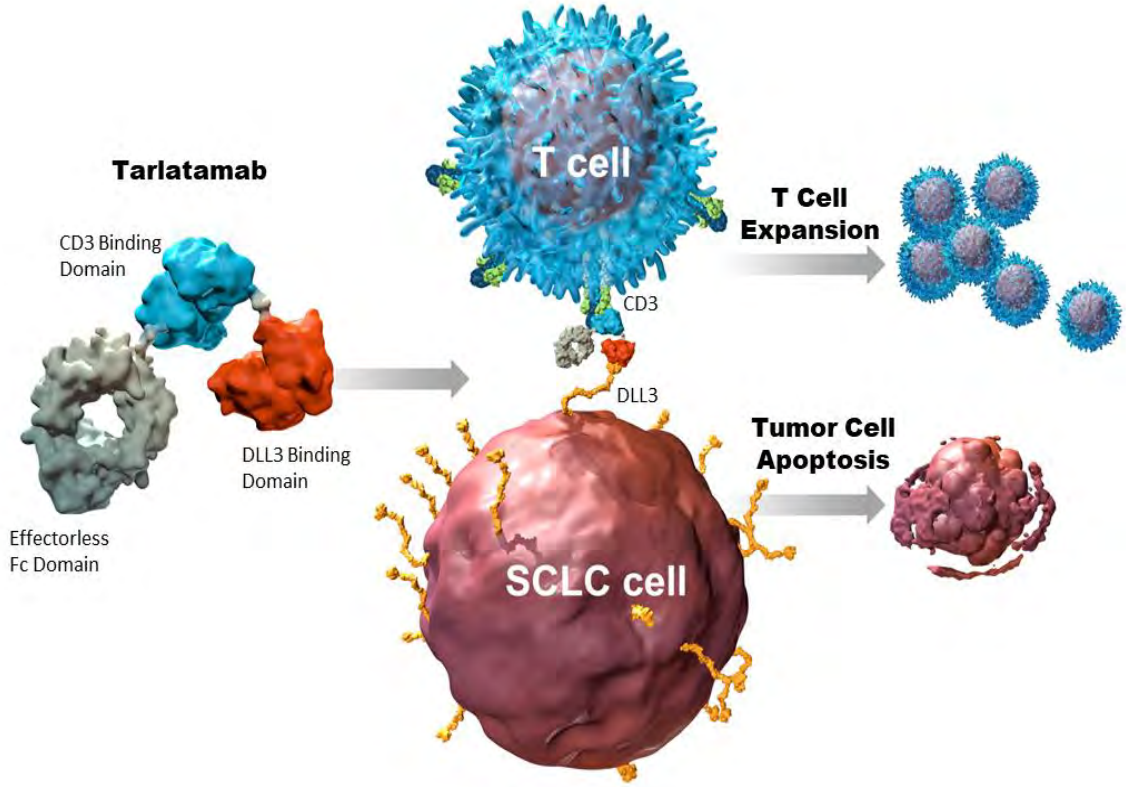
NEXT GENERATION OF ADCS



Mosele F, et al, Nature Medicine, 2026

Tarlatamab

- Tarlatamab is a BiTE® (bispecific T-cell engager) immunotherapy that directs cytotoxic T cells to cancer cells expressing delta-like ligand 3 (DLL3)
- Tarlatamab demonstrated encouraging clinical activity in both the phase 1 DeLLphi-300[1] and phase 2 DeLLphi-301 studies[2] in patients with previously treated small cell lung cancer (SCLC)

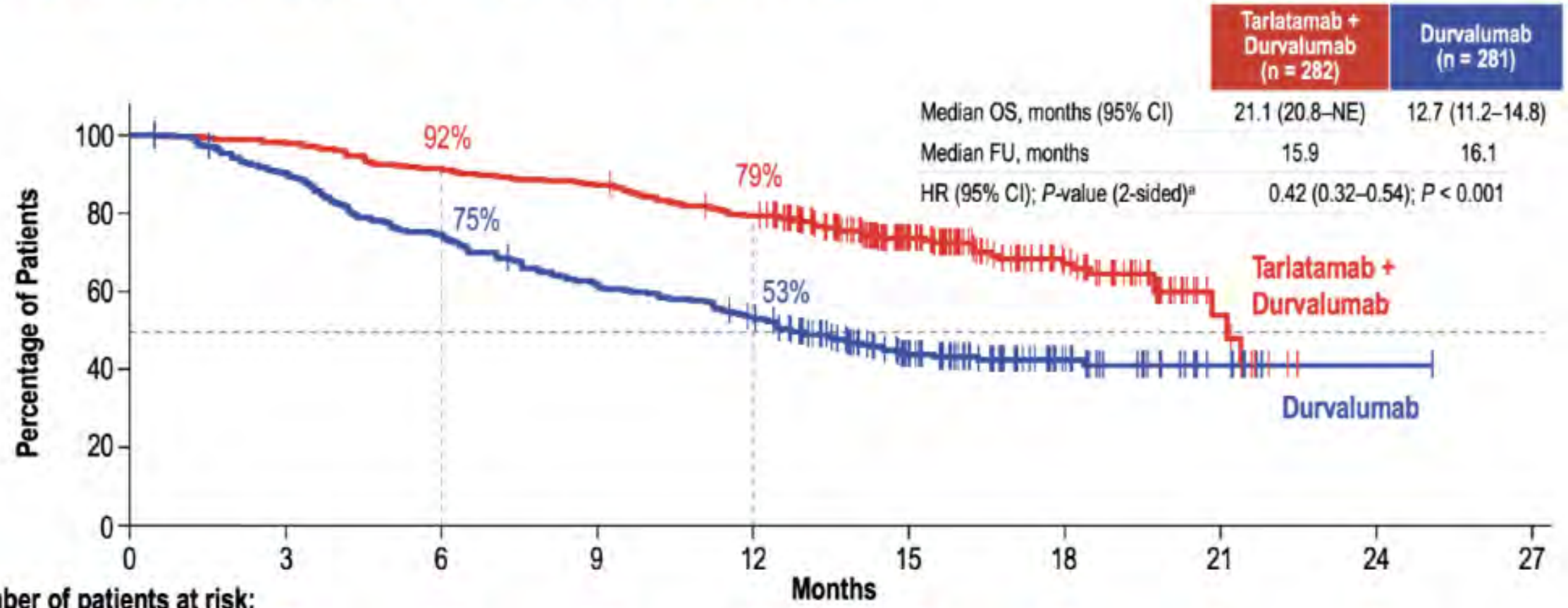


Here we report long-term outcomes and intracranial activity of tarlatamab from fully enrolled cohorts of patients treated with clinically relevant doses of tarlatamab (≥ 10 mg) in the DeLLphi-300 phase 1 study

1. Paz-Ares et al. *J Clin Oncol*. 2023; 41:2893-2903. 2. Ahn M-J et al. *N Engl J Med*. 2023; 389:2063-2075.

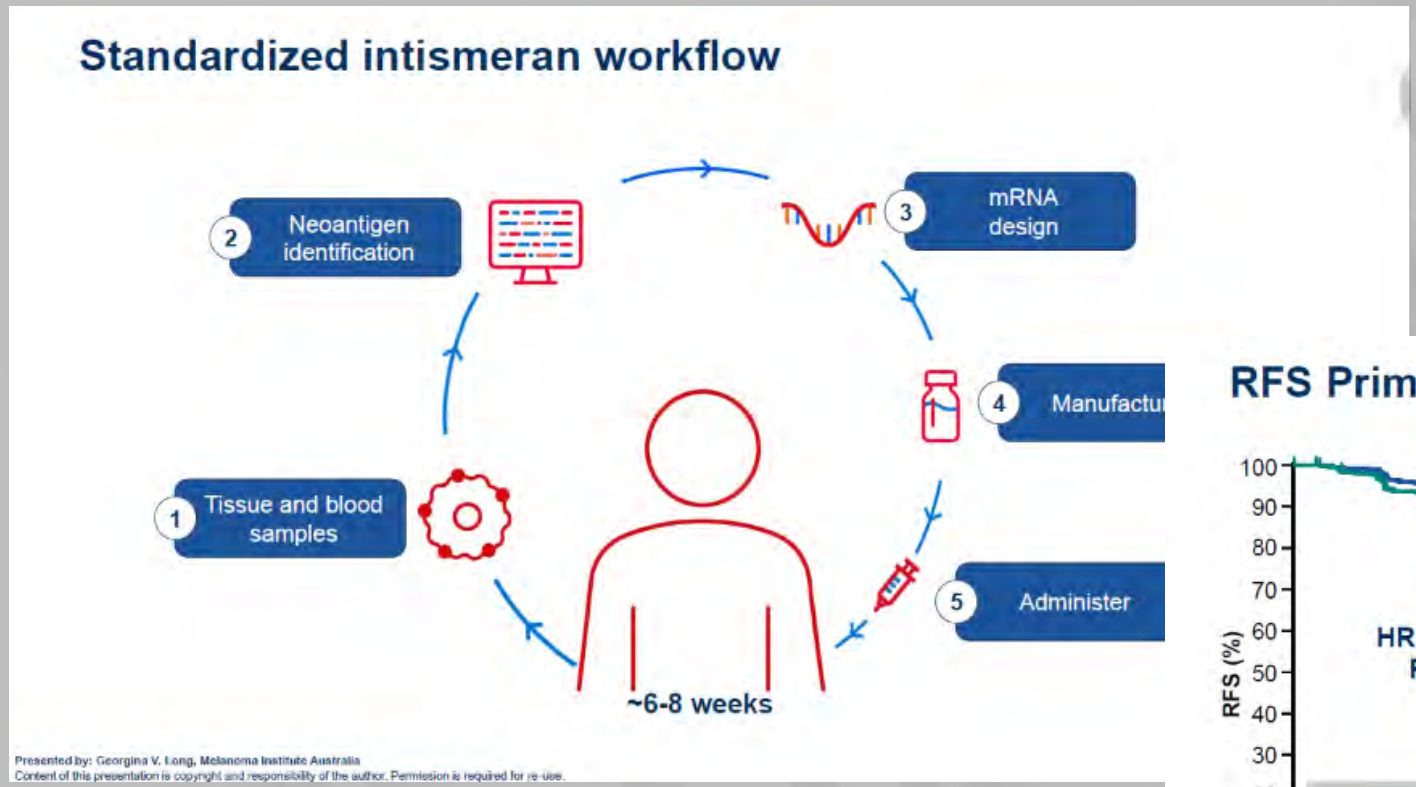
CD3: cluster of differentiation 3; Fc domain: fragment crystallizable domain

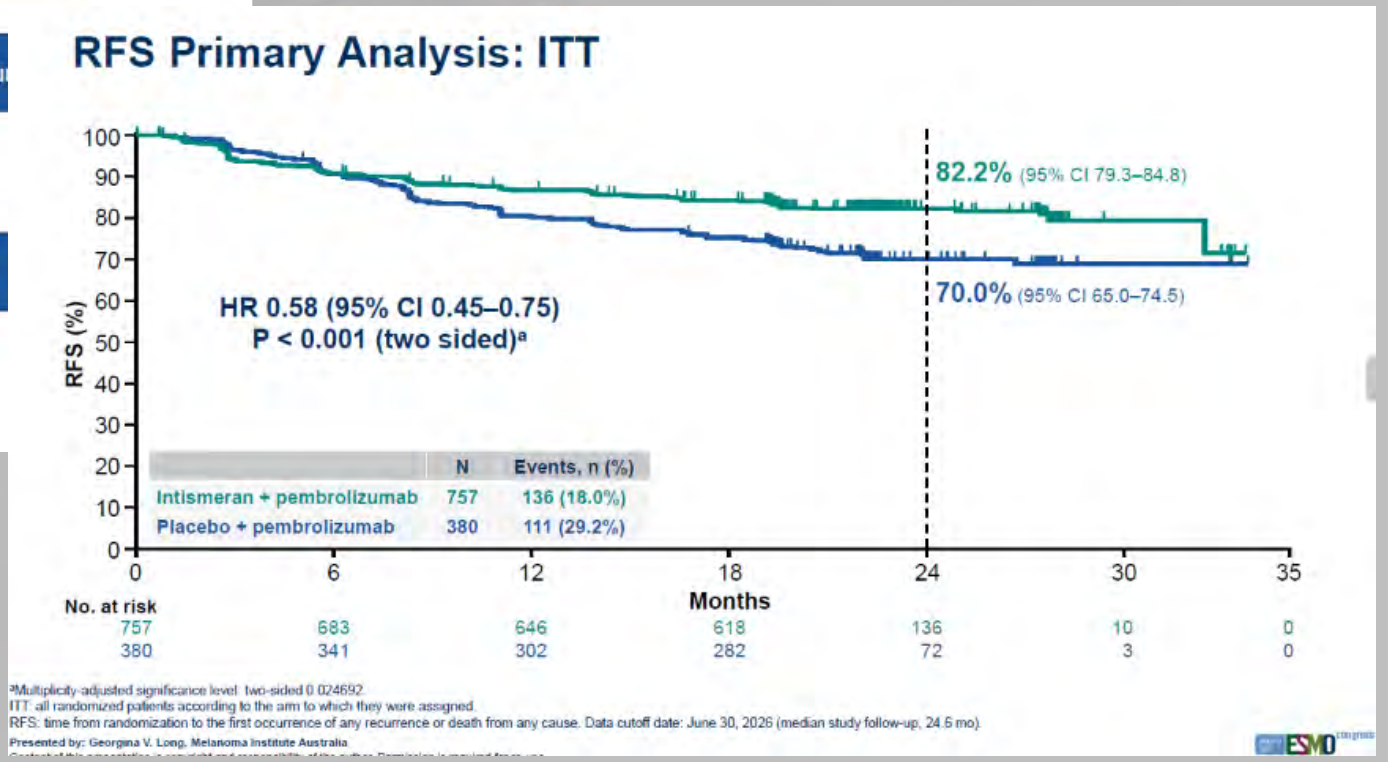
Tarlatamab: DeLLphi-305: Survival



Sands, ESMO 2026

MRNA VACCINE- INTERPATH-001 MELANOMA TRIAL

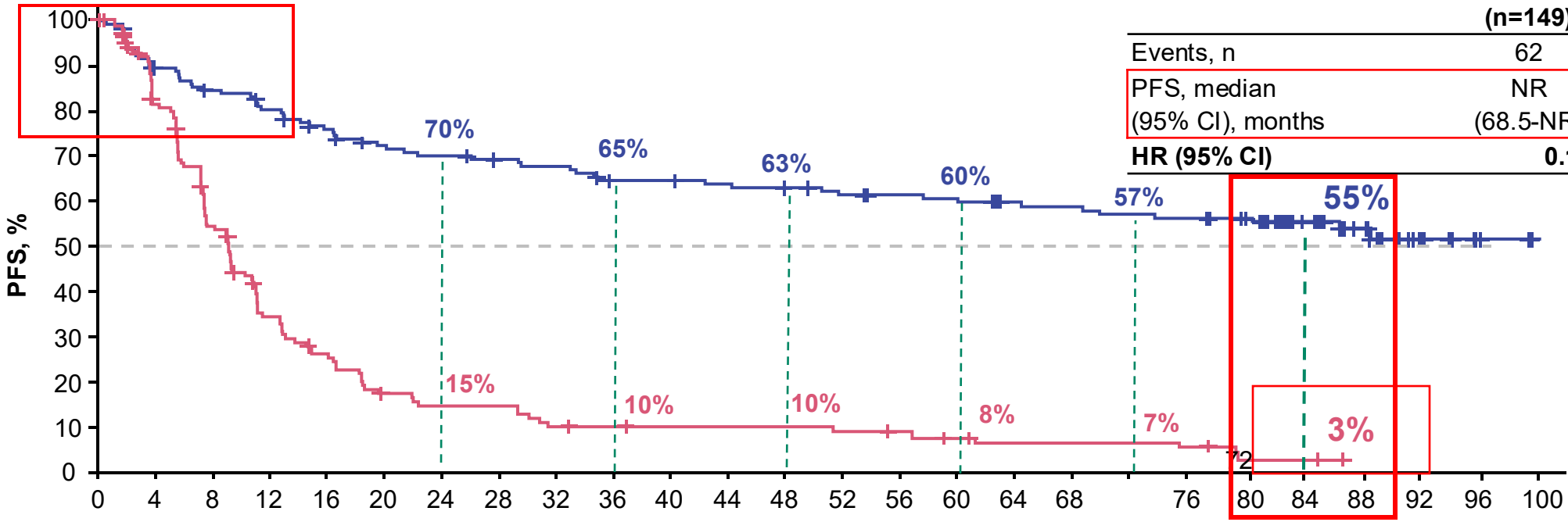




PFS IN THE ITT POPULATION (7-YEAR FOLLOW-UP)

The median duration of follow-up for PFS was **83.0 months** (95% CI, 81.2-86.3) in the lorlatinib arm and **77.2 months** (95% CI, 36.8-not evaluable) in the crizotinib arm

	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	62	119
PFS, median (95% CI), months	NR (68.5-NR)	9.1 (7.4-10.9)
HR (95% CI)	**0.19 (0.13-0.26)**	



36 year old female died within 11 months of diagnosis. Tumor had MET amplification

No. at risk

Lorlatinib	149	126	118	111	103	96	93	89	87	81	81	79	78	75	73	71	69	68	66	65	62	38	28	9	2	0
Crizotinib	147	107	70	42	30	19	16	16	11	10	9	9	9	8	8	7	6	6	6	5	2	2	0	0	0	0

At the time of this analysis, median PFS by investigator was still not reached with lorlatinib

CI, confidence interval; HR, hazard ratio; ITT, intention to treat; NR, not reached; PFS, progression-free survival.

Tony S. K. Mok, MD (tony@clo.cuhk.edu.hk)

BIOMARKERS- PERSONALIZATION OF THERAPY

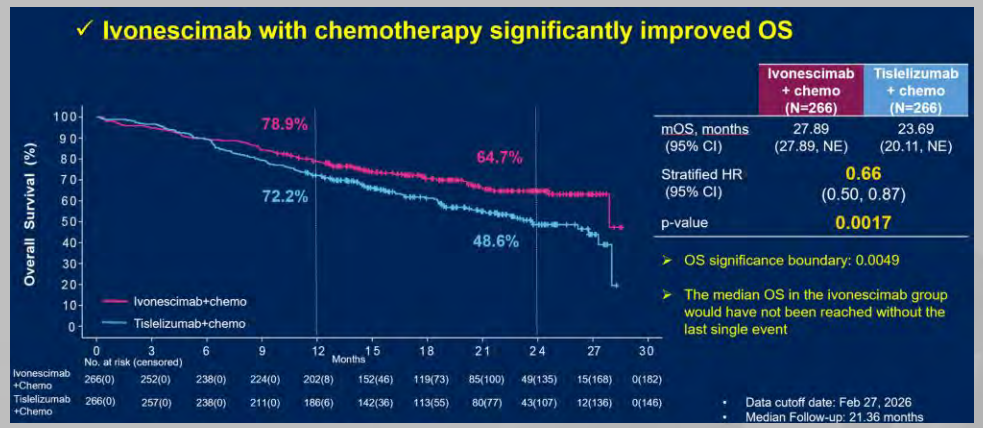
1. Prognostic Utility

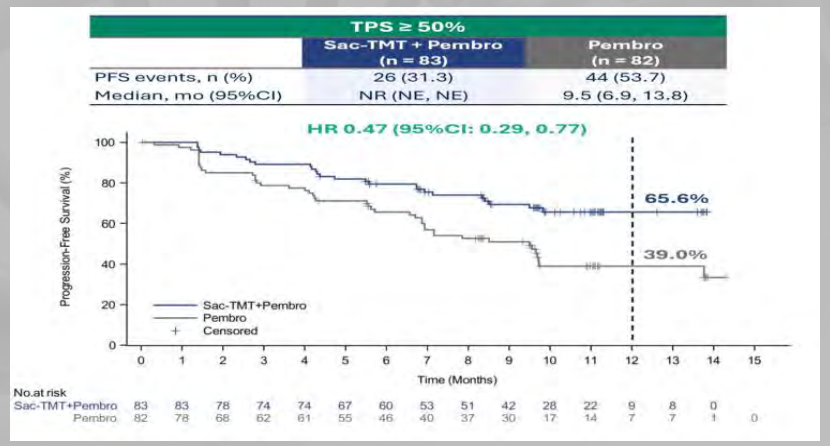
2. Predictive Capacity

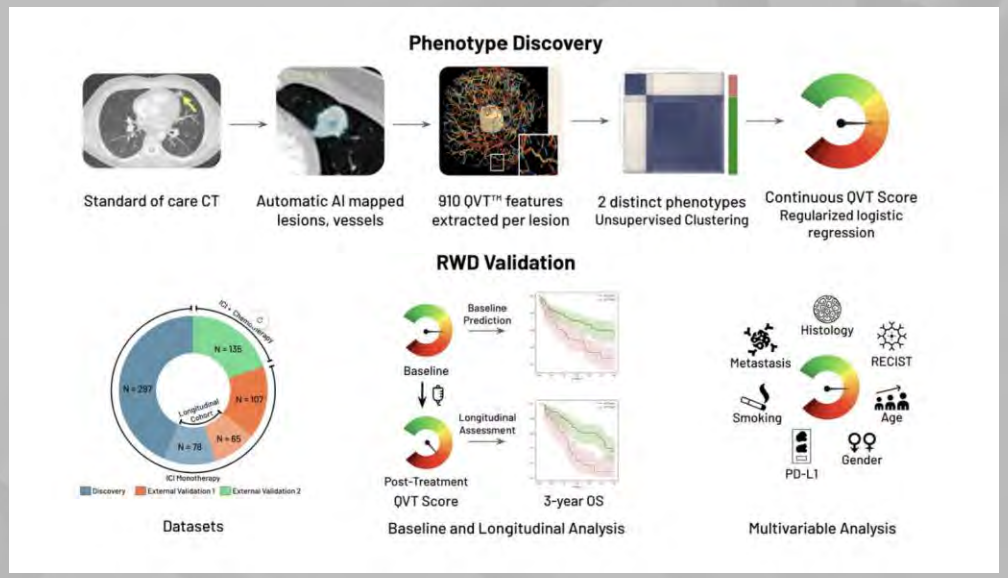
3. Mechanisms of Resistance

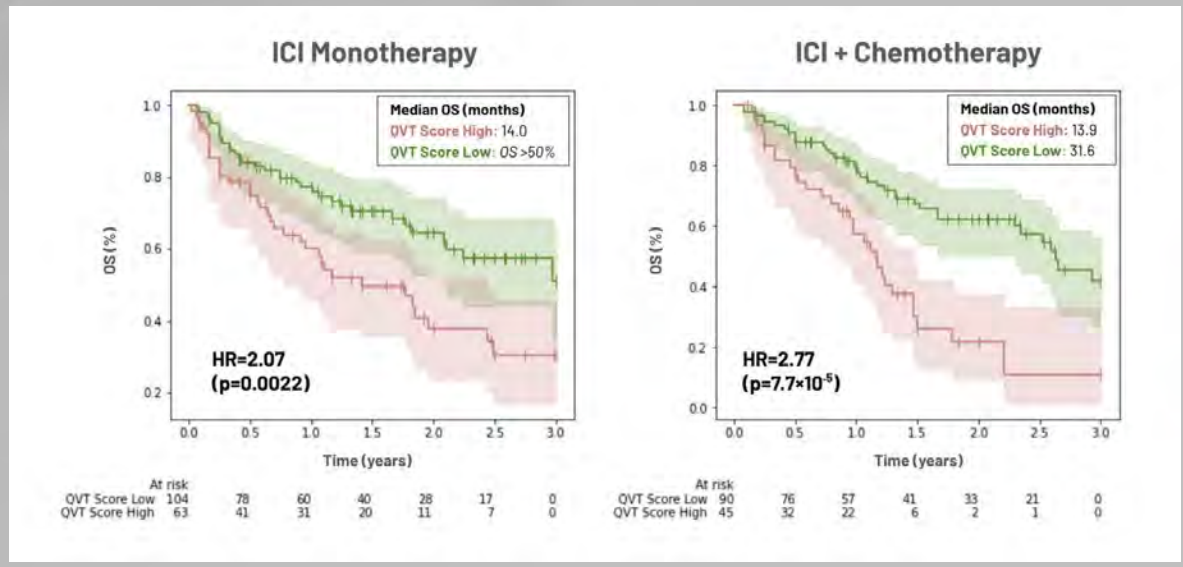
4. Screening

PERSONALIZED THERAPY





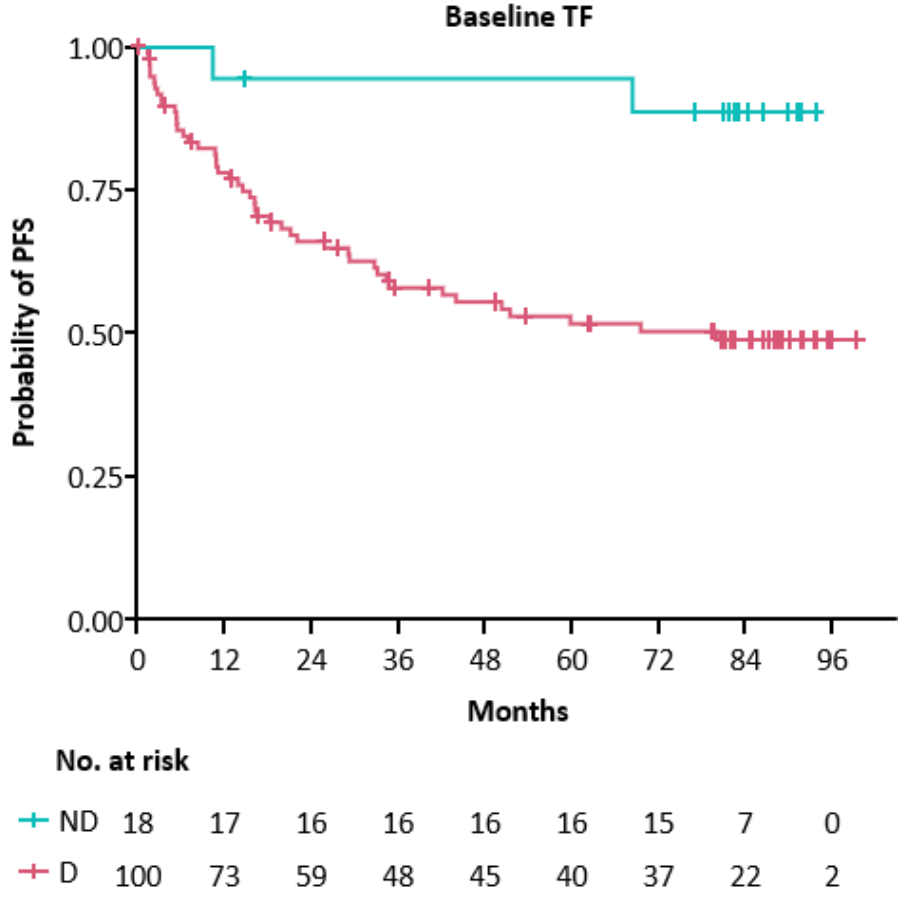




Chae, Y, **Madabhushi A**, Braman N, et al JTC 2026

7-year PFS by baseline methylation-based TF detection in the lorlatinib group

- *The Guardant Infinity ctDNA next-generation sequencing assay assesses genomic alterations across 755 genes and uses a non-destructive methylation-based technology to quantify tumor fraction*
- *Baseline methylation-based TF level was prognostic for PFS, with longer PFS in patients with TF ND vs D at baseline[a]*



	ND n=18	D n=100
PFS, median (95% CI), months	*NR (NR-NR)*	*80.3 (34.6-NR)*
HR (95% CI), ND vs D	*0.17 (0.04-0.69)*	

D, detected; HR, hazard ratio; ND, not detected; NR, not reached; PFS, progression-free survival; TF, tumor fraction.

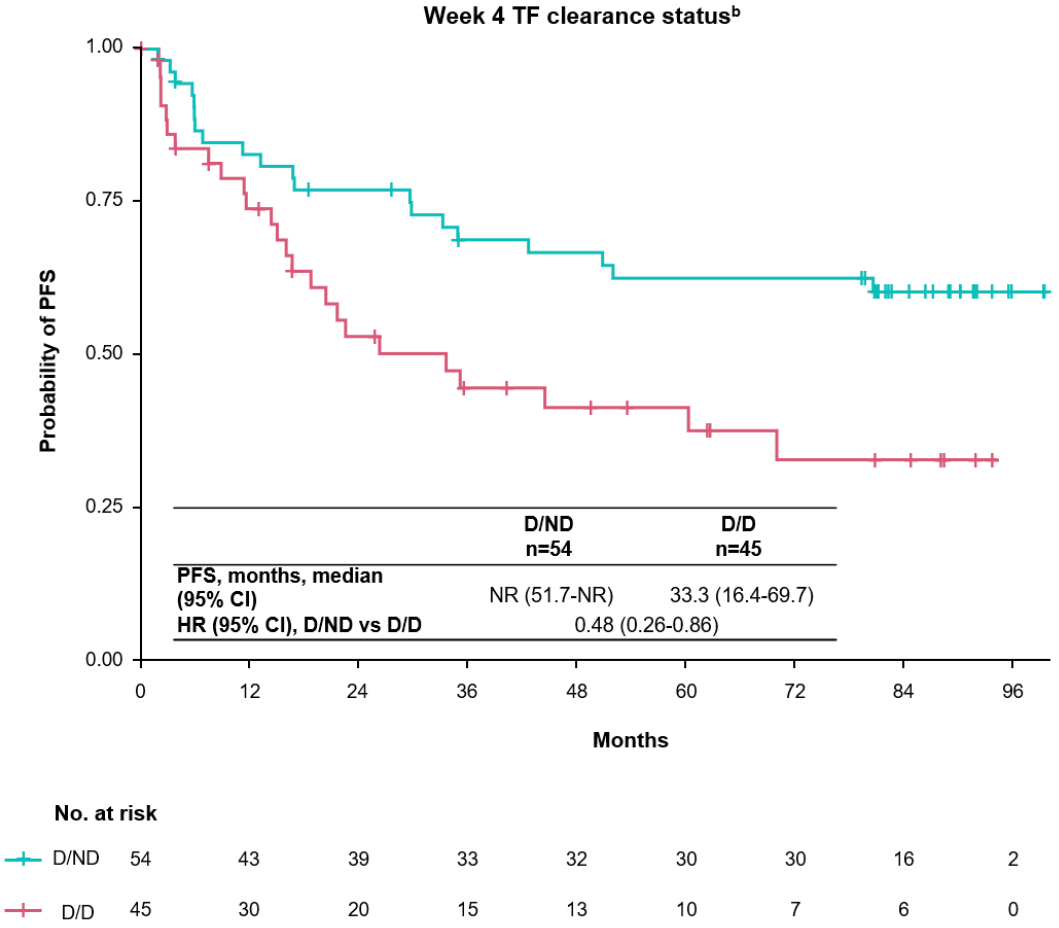
[a]TF is defined as the ratio of observed tumor-specific methylation signals to methylation levels across constitutively methylated and unmethylated regions. ND means TF=0.

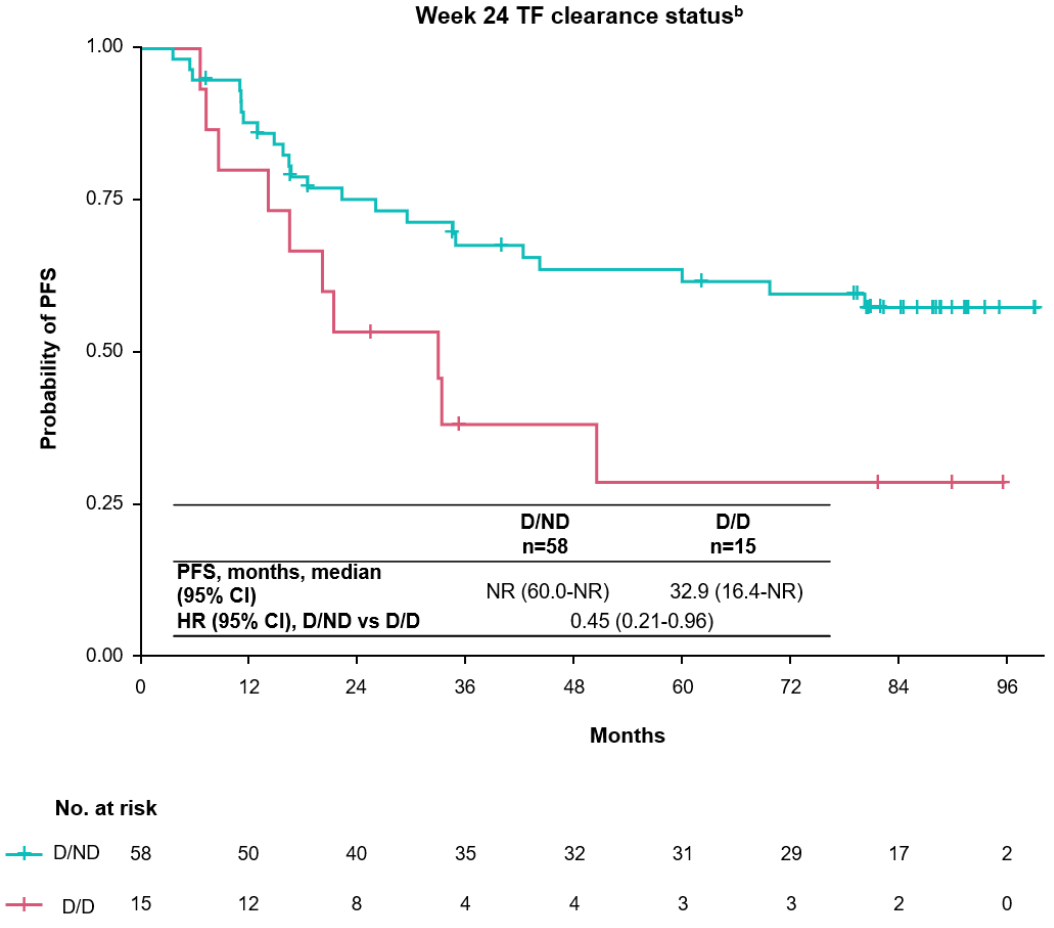
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MADRID 2026 ESMO congress

7-year PFS by on-treatment TF clearance in the lorlatinib group

- *Among patients with TF detected at baseline, TF clearance (D/ND) was associated with longer PFS vs persistent TF detected (D/D) as early as week 4 (HR 0.48) and the association held at week 24 (HR 0.45)[a]*





D, detected; HR, hazard ratio; ND, not detected; NR, not reached; PFS, progression-free survival; TF, tumor fraction.

[a]TF is defined as the ratio of observed tumor-specific methylation signals to methylation levels across constitutively methylated and unmethylated regions. ND means TF=0.

[b]The clearance analyses at Week 4 and Week 24 are based on patients with both a detectable baseline sample and an evaluable paired sample at the respective visit.

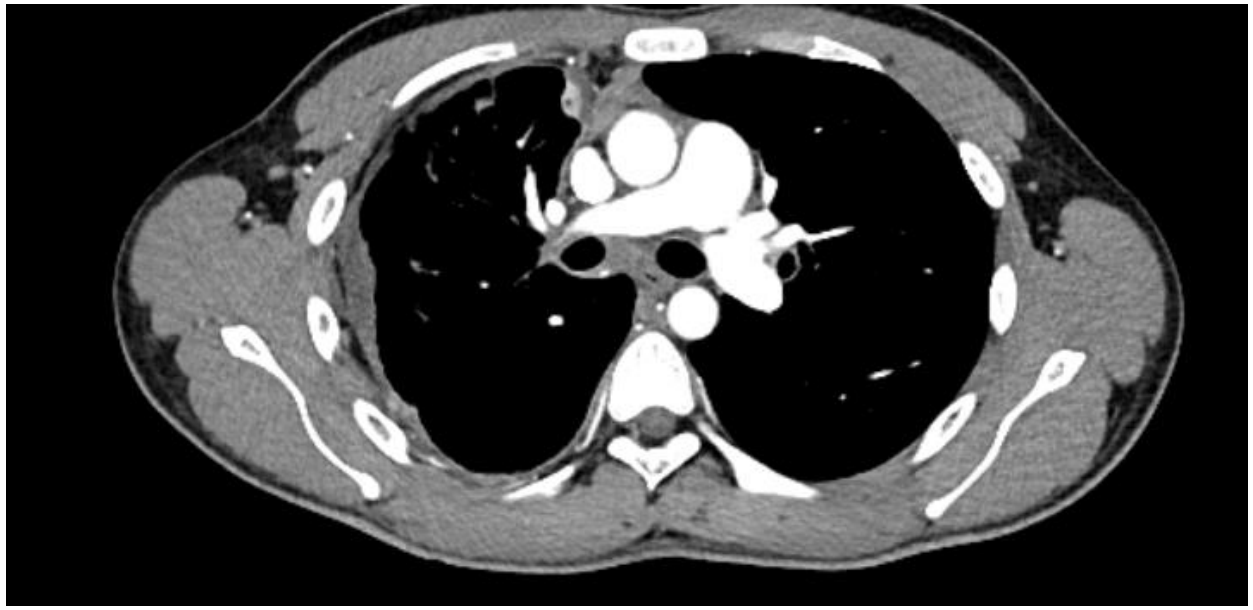
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19-YEAR OLD MALE PATIENT



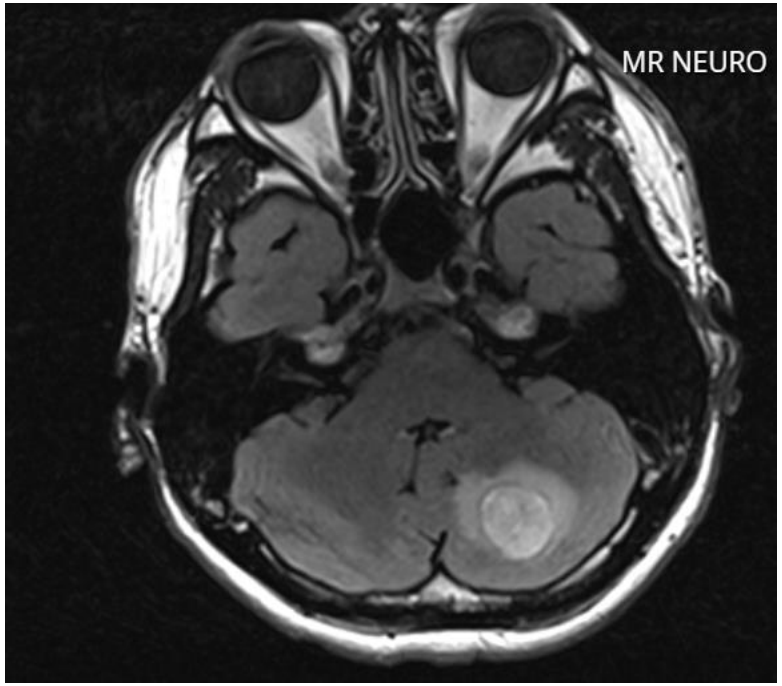
7/9/2026



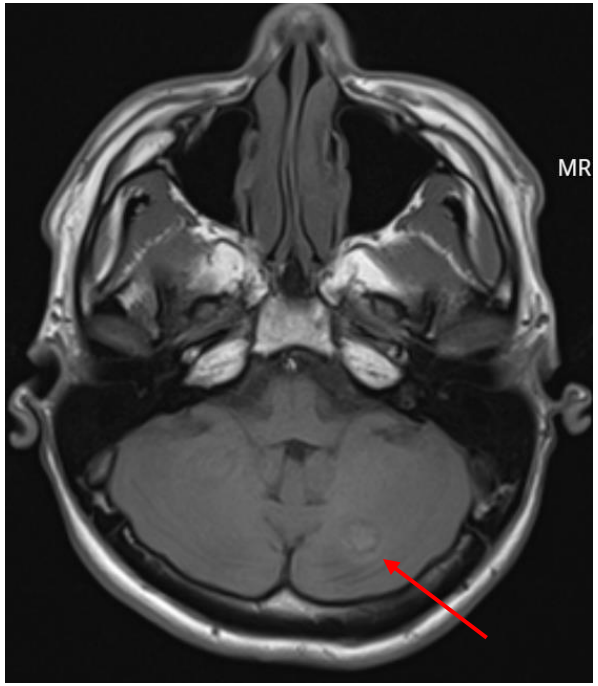
8/23/2026

19 year old male patient had persistent cough.
No symptoms related to brain met.

19-YEAR OLD MALE PATIENT



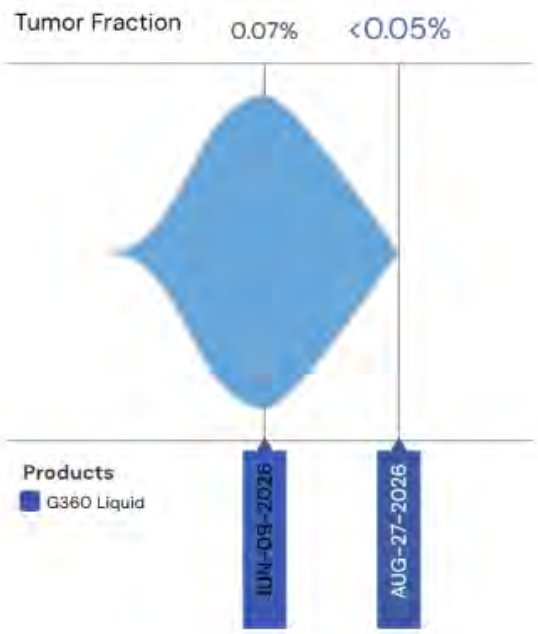
6/16/2026



8/23/2026

19 year old male patient had persistent cough.
No symptoms related to brain met.

CT DNA CHANGES



EML4-ALK Fusion

and 1 other alterations

Amplifications not graphed.

	ND n=18	D n=100
PFS, median (95% CI), months	*NR (NR-NR)*	*80.3 (34.6-NR)*
HR (95% CI), ND vs D	*0.17 (0.04-0.69)*	

ADVANCED LUNG CANCER SURVIVORSHIP

Advanced lung cancer survivorship

Physical symptoms
Dyspnea, fatigue, pain

Psychological
Anxiety and distress

Financial toxicity
Costs and income loss

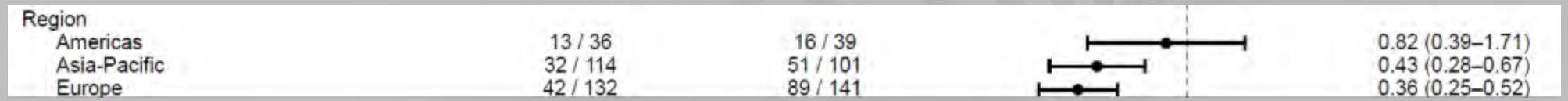
Social & role changes
Relationship and caregiver strain

Ongoing surveillance
Scans, specialists, monitoring

CANCER CLINICAL TRIALS IN USA



Geographic region	Europe	209	106	8.3	103	4.3	0.54 (0.39–0.75)
	North America	55	28	10.9	27	5.7	0.79 (0.38–1.64)
	Rest of World	74	33	13.2	41	6.9	0.52 (0.29–0.92)



Region			
Americas	13 / 36	16 / 39	0.82 (0.39–1.71)
Asia-Pacific	32 / 114	51 / 101	0.43 (0.28–0.67)
Europe	42 / 132	89 / 141	0.36 (0.25–0.52)



The New York Times https://www.nytimes.com/2026/09/04/opinion/clinical-trials-drugs-science.html

OPINION
GUEST ESSAY

This Is the Biggest Obstacle to New Cancer Cures

▶ Listen · 17:20 min

By Ruxandra Teslo

Dr. Teslo is a biotechnology editor at Works in Progress magazine and a nonresident fellow at the Institute for Progress.

Regulatory Oversight, Legal Concerns, Cost Structure

CONCLUSIONS

1. Major advance in therapeutics is sustained and long-term benefit in a proportion of patients

2. Novel Therapeutics- Drugs targeting driver mutations and co-mutations; ADCs, T-cell engagers, vaccines

3. Biomarkers to personalize therapy

4. Survivorship Research

6. Providing access to clinical trials is of paramount importance.

ACKNOWLEDGMENT

HOST



Kathryn A. O'Donnell, PhD
Associate Professor, Dept. of Molecular Biology, UT Southwestern Medical Center;
Co-leader, Development and Cancer Program, Simmons Comprehensive Cancer Center
Chair, LCRF Scientific Advisory Board

MODERATOR



Isabel Preeshagul, DO, MBS
Assistant Attending Physician, Thoracic Oncology, Memorial Sloan Kettering Cancer Center
Chair, LCRF Education and Engagement Committee

PRESENTERS



Shirish M. Gadgeel, MD, MBBS, FASCO
Co-Chair, Protocol Review and Monitoring Committee, Winship Cancer Institute of Emory University
Professor, Department of Hematology and Medical Oncology and Vice Chair for Clinical Research, Department of Hematology and Medical Oncology, Emory University School of Medicine
Member, LCRF Scientific Advisory Board



Colleen Conner Ziegler
Patient Advocate
LCRF Research Advocate
Chair, LCRF Board of Directors



Christian Rolfo, MD, PhD
Professor of Medicine, Division Director of Medical Oncology; Associate Director for Early Phase Clinical Trials
The James Comprehensive Cancer
The Ohio State University



Lecia Sequist, MD
Landry Family Professor of Medicine, Field of Medical Oncology, Harvard Medical School; Associate Physician, Medicine-Hematology and Medical Oncology, Massachusetts General Hospital



Timothy Burns, MD, PhD
Professor of Medicine, Division of Medical Oncology, The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute



ADVANCED ALK+VE NSCLC PATIENT



Patient has provided verbal permission to show picture

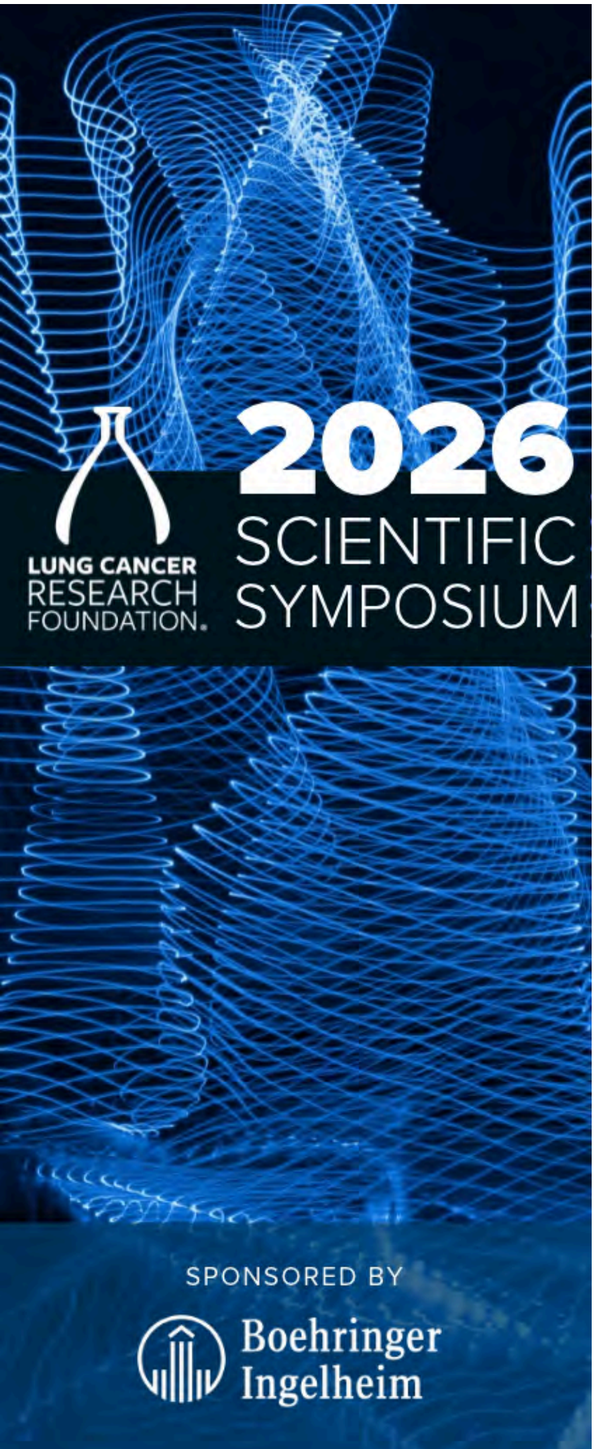
THANK YOU

Thoracic Oncology Team
Winship Cancer Institute/Emory University



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@ShirishGadgeel



Today's presenters + panelists



Colleen Conner Ziegler
Patient Advocate
Former Chair, LCRF Board of Directors



Lecia Sequist, MD, MPH, FASCO
Director, Cancer Early Detection & Diagnostics Program; Mass General Brigham Cancer Institute

The Landry Family Professor of Medicine; Harvard Medical School



Christian Rolfo, MD, PhD
Professor, Department of Internal Medicine, Division of Medical Oncology
The Ohio State University

Director of the Division of Medical Oncology; Associate Director for early phase clinical trials
The Ohio State University Comprehensive Cancer Center



Timothy Burns, MD, PHD
Professor of Medicine, Division of Medical Oncology
The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute

Member, LCRF Scientific Advisory Board



Lung Cancer Patient Advocacy

Colleen Conner Ziegler
Former Chair, LCRF Board of Directors
Research Advocate



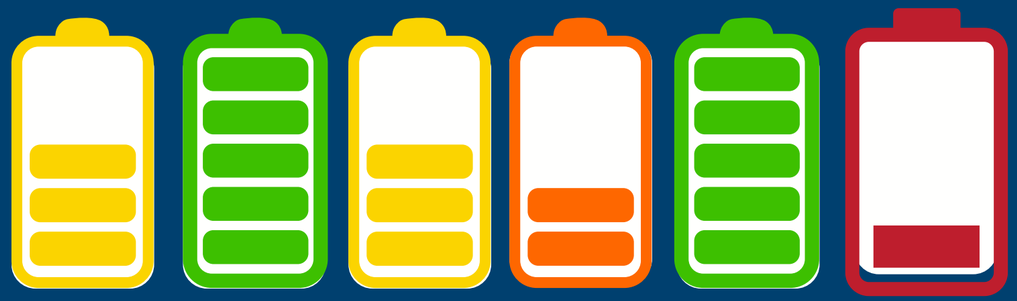
Advocacy can take many forms

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 research patient participation important?

- 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**.



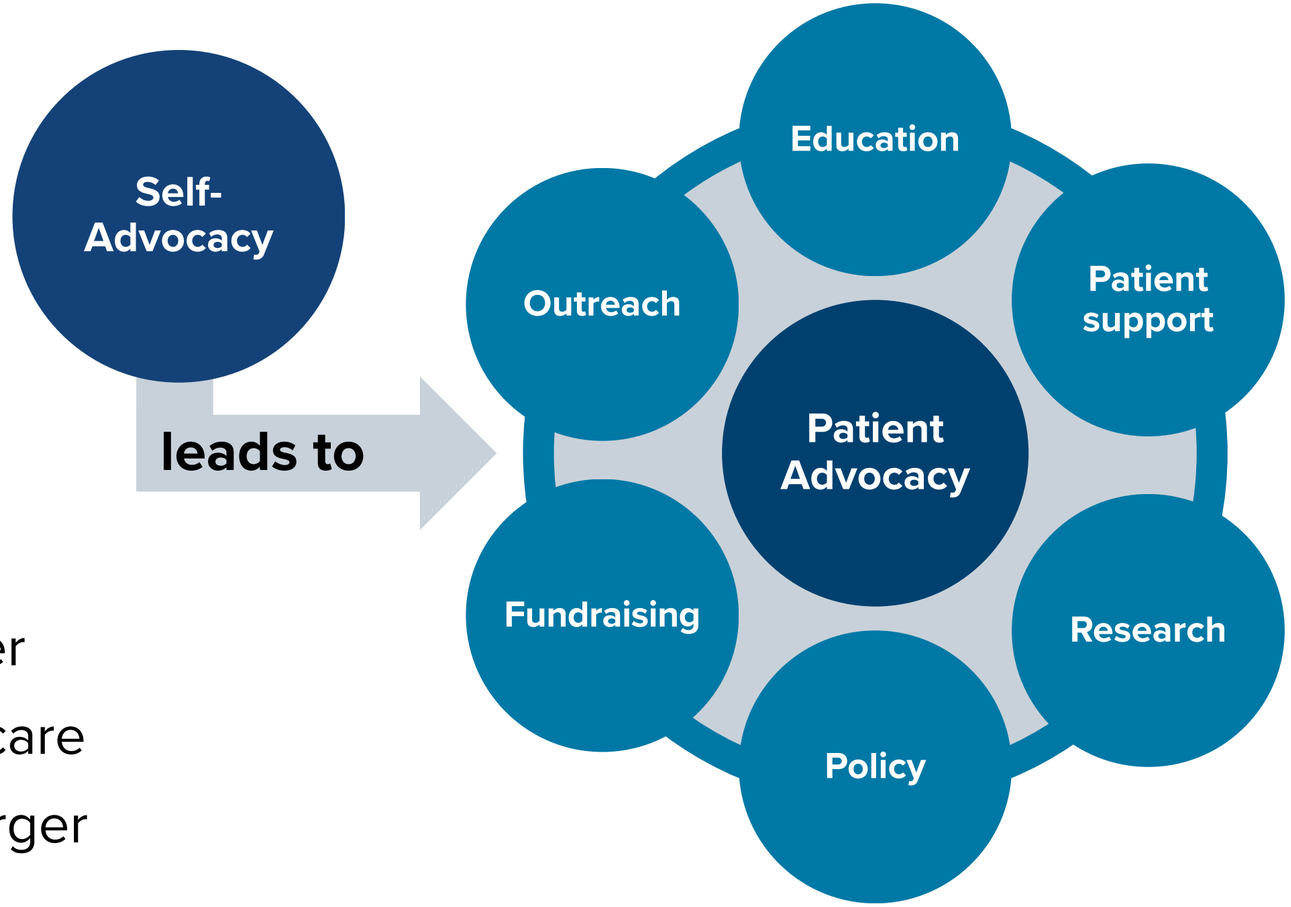
Patient advocacy takes many forms

Patient/Self Advocates:

- Treatment for themselves or a family member
- Participate in patient groups to learn more about the diagnosis

Patient/Research Advocate:

- In-depth knowledge of lung cancer
- Influence research and/or health care
- Advocacy work is focused on a larger community



Specialized types of patient advocacy

Research Advocate

- Translates research into outcomes
- Represents the perspective of the lung cancer community in partnership with researchers



Policy Advocate

- Influences governmental and healthcare policies that benefit patients



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.

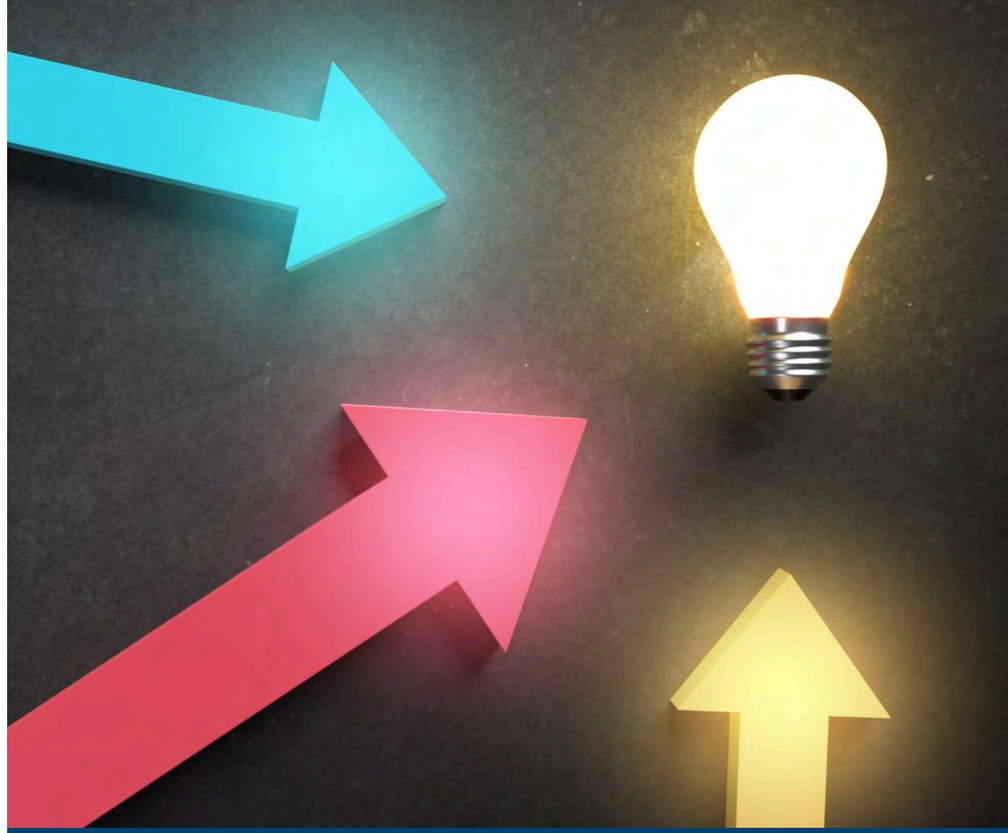


Expanding range of advocacy activities including grant reviews, focus groups, steering committees, advisory committees, clinical trial protocol – and in some cases, the engagement of a research advocate is a requirement for research funding.

What does research patient participation 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



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.

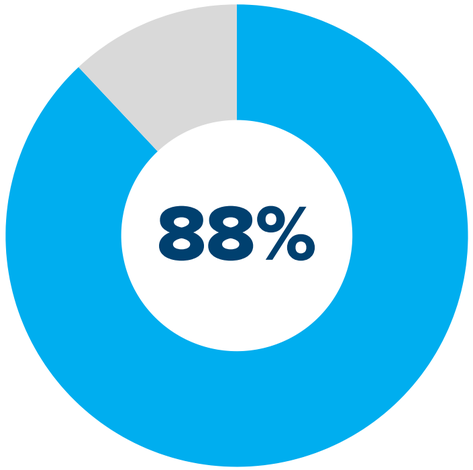
Greater diversity and opportunities. Patient advocates should be pulled from the population being studied.

How do researchers experience RA engagement?

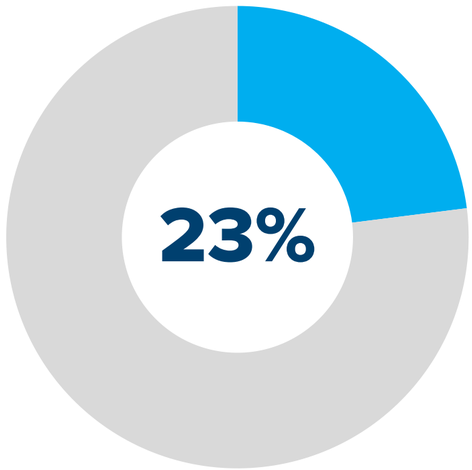
Source: Jill Feldman, 2026 IASLC presentation

Experiences working with a Research Advocate:

n=95



Have **worked with** a PRA



Included a **budget item** to **compensate** PRA time

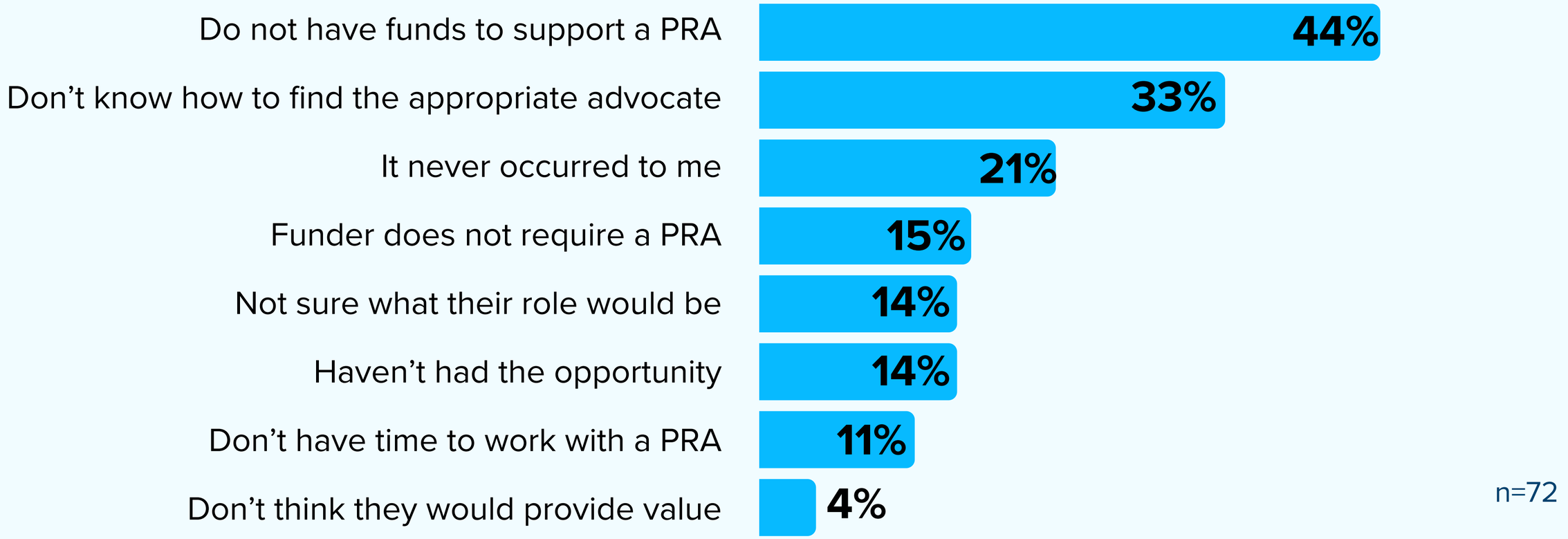


Rated the experience **very/somewhat beneficial**

Barriers to engaging

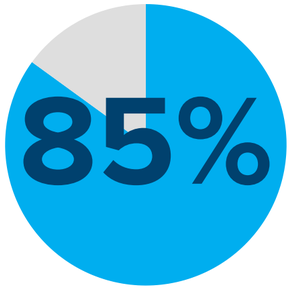
Source: Jill Feldman, 2026 IASLC presentation



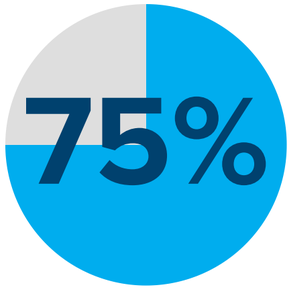


What would encourage engagement?

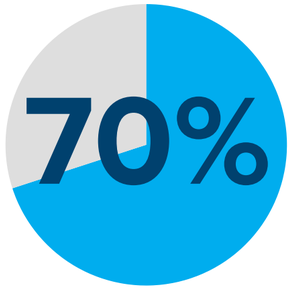
Source: Jill Feldman, 2026 IASLC presentation



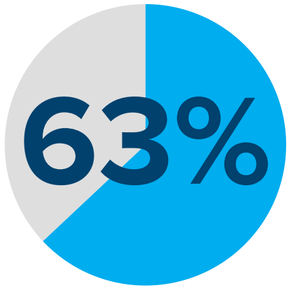
Dedicated funds to support PRAs



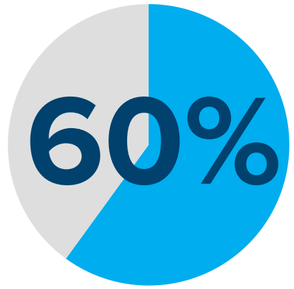
Easier **access**/ PRA contact list



Training on **best practices**



Clear **guidelines** and **policies**



More **time** for engagement

n=94

> Patient research advocates help ensure that lung cancer research is **grounded in the real questions, priorities, and experiences** of people living with the disease.

> We need **funding, guidance, and infrastructure** so meaningful patient partnerships become the **norm** in lung cancer research.

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.



Research and the LCRF 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)

NCI Advocate/OAR Office of Advocacy Relations

FDA patient engagement

CDMRP LCRP consumer grant reviewer

PCORI Advisory Panel member

LUNG CANCER RESEARCH FOUNDATION.

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Leading Edge: AI and Machine Learning

Lecia Sequist, MD, MPH, FASCO

Director, Cancer Early Detection & Diagnostics Program; Mass General Brigham Cancer Institute

The Landry Family Professor of Medicine; Harvard Medical School

Recipient of 2010 UALC award on resistance to targeted therapy



Mass General Brigham
Cancer Institute

Leading Edge: AI and Machine Learning in Lung Cancer Screening

Lecia V. Sequist, MD, MPH, FASCO
Director, Early Detection & Diagnostics Program
Mass General Brigham Cancer Institute
The Landry Family Professor of Medicine
Harvard Medical School

November 2026



Disclosures, Acknowledgements

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Thank you to Allison Chang, MD, PhD
for help with many of the graphics

Lung Cancer Screening

- Large randomized controlled trial (>50K subjects) confirmed an overall survival benefit for lung cancer screening
- The test is very efficient

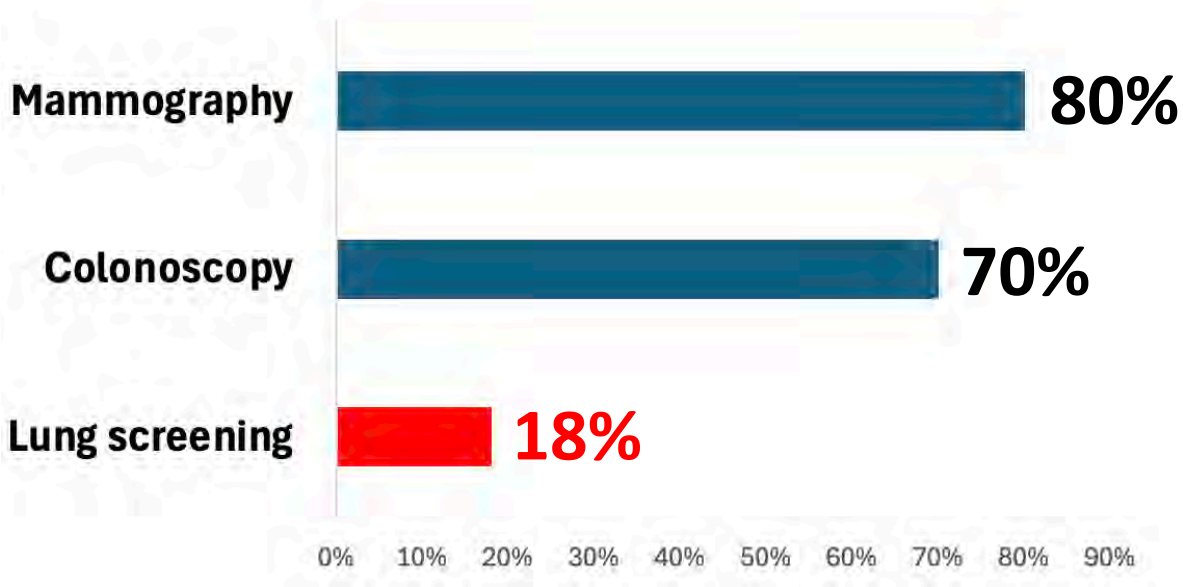
Cancer	Screening Modality	NNS
Lung cancer	LDCT	~300
Colon cancer	Colonoscopy	~1,000
Colon cancer	FOBT	~450
Breast cancer	Mammogram	~800-2,000
Cervical cancer	Pap smear	~2,560

The New York Times

America's Deadliest Cancer Has Abysmal Screening Rates

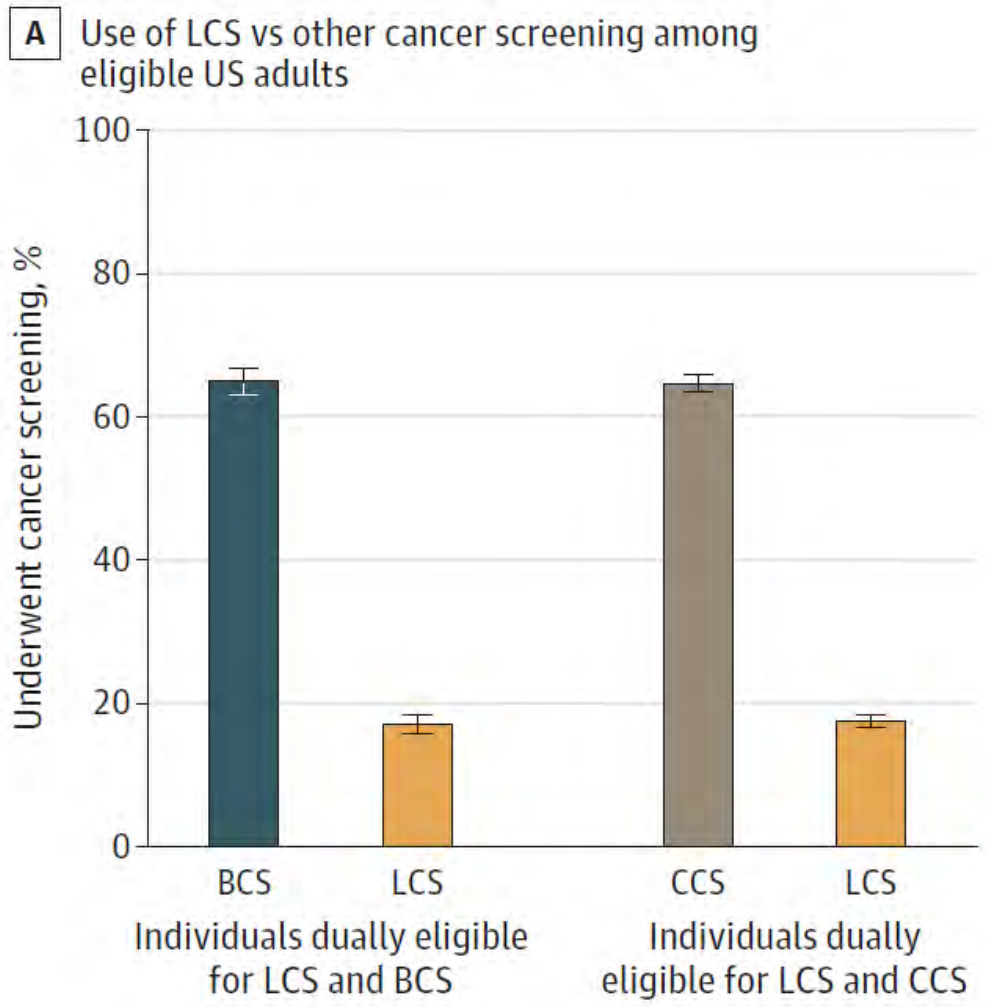
If everyone eligible had a lung cancer screening, 62,000 lives would be saved over five years, a new study shows.





NY Times, Nov 19, 2025
JAMA, Nov 19, 2025

Hard to Reach or Hardly Reached?



Potter at al, JAMA 2025



Alexandra Potter

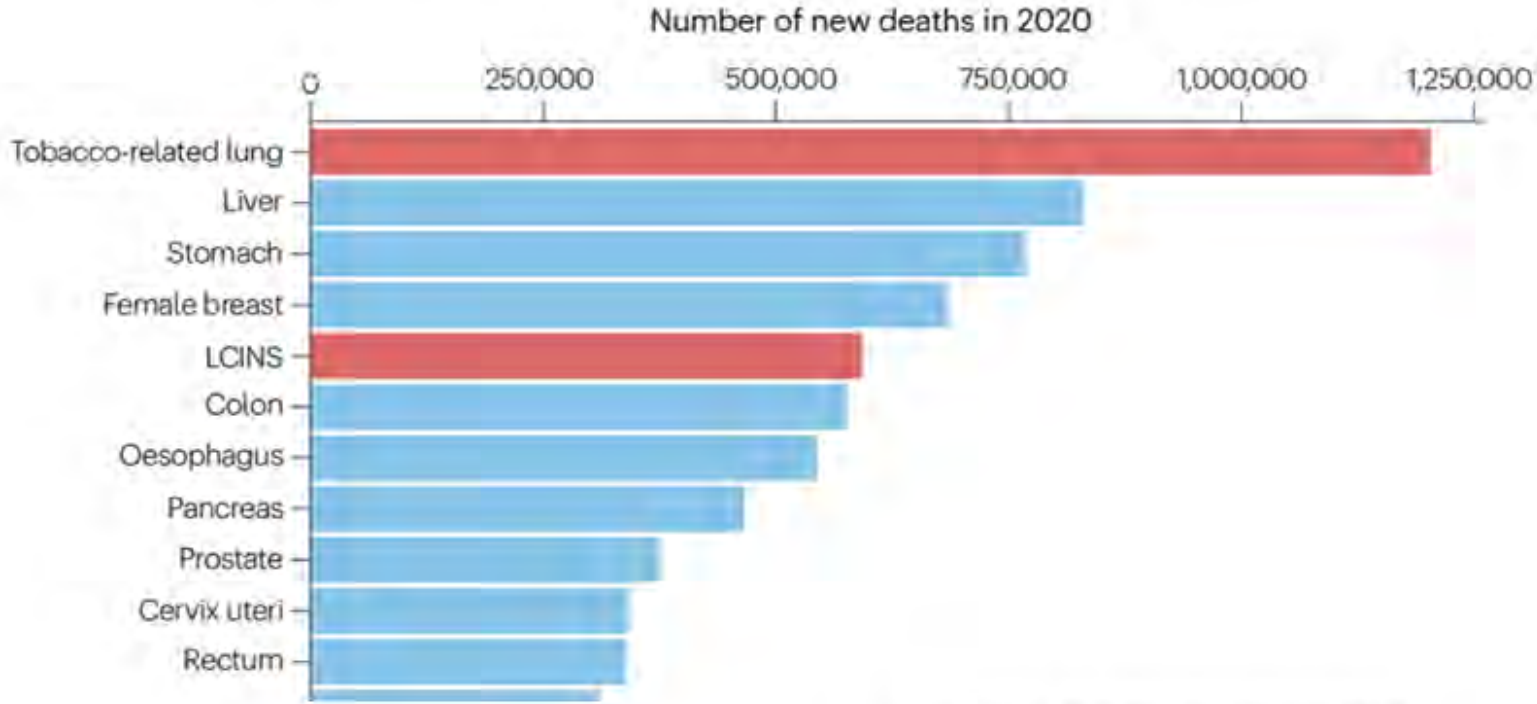


How to reconcile these opposing ideas?

Traditional concept of risk:
One factor



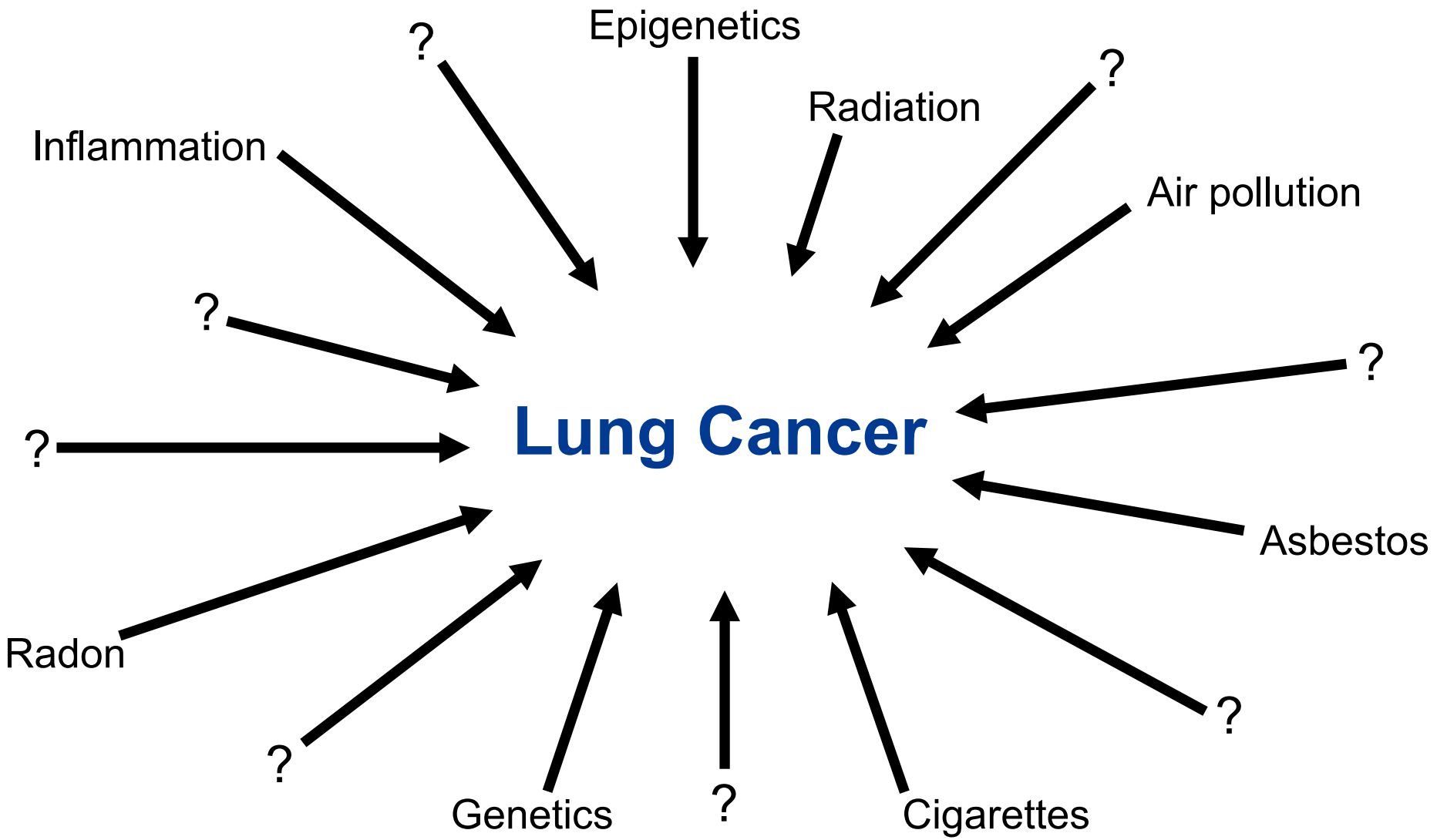
But.. lung cancer in tobacco non-users is also a common global disease



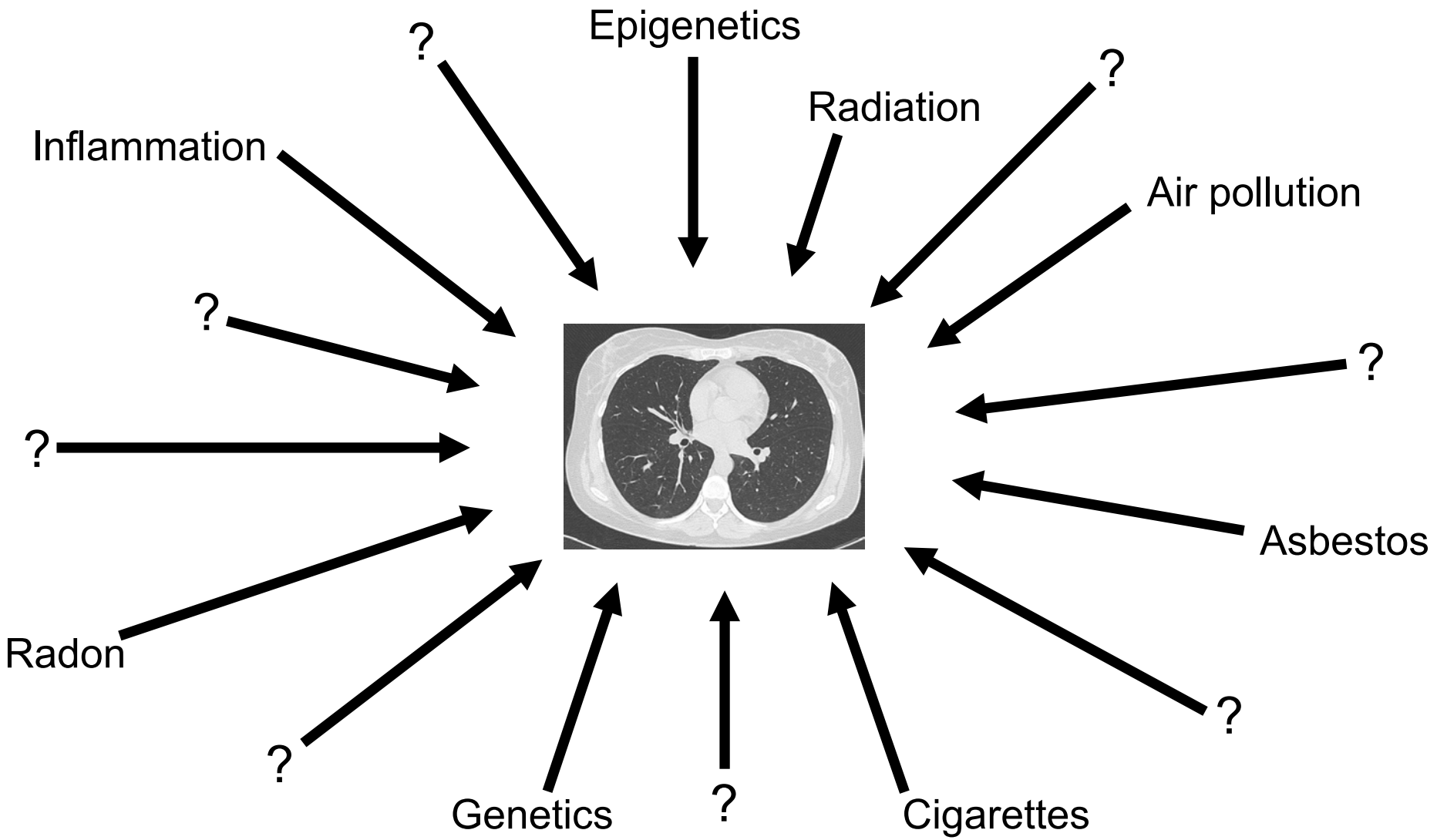
LoPiccolo, *Nat Rev Clin Oncol* 2024

In the US, 50-60% of people diagnosed with lung cancer could **not** have accessed lung screening because of strict eligibility

Lung cancer risk factors are complex

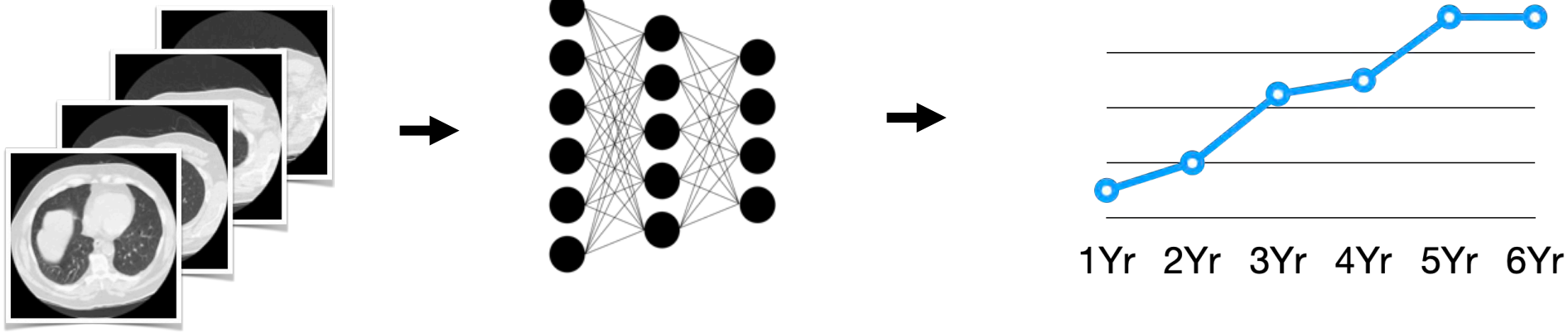


Can chest imaging capture how these factors have combined to affect the lungs



Sybil: A Convolutional Neural Network

> 44K LDCT exams from
> 15K subjects in NLST trial





<u>Key Advantages</u>

- No image annotation
- No clinical data needed
- Instant readouts
- Multi-year <u>future</u> risk stratification from single CT
- Code is open source



Mikhael, *J Clin Oncol* 2023

Sybil Implementation Consortium



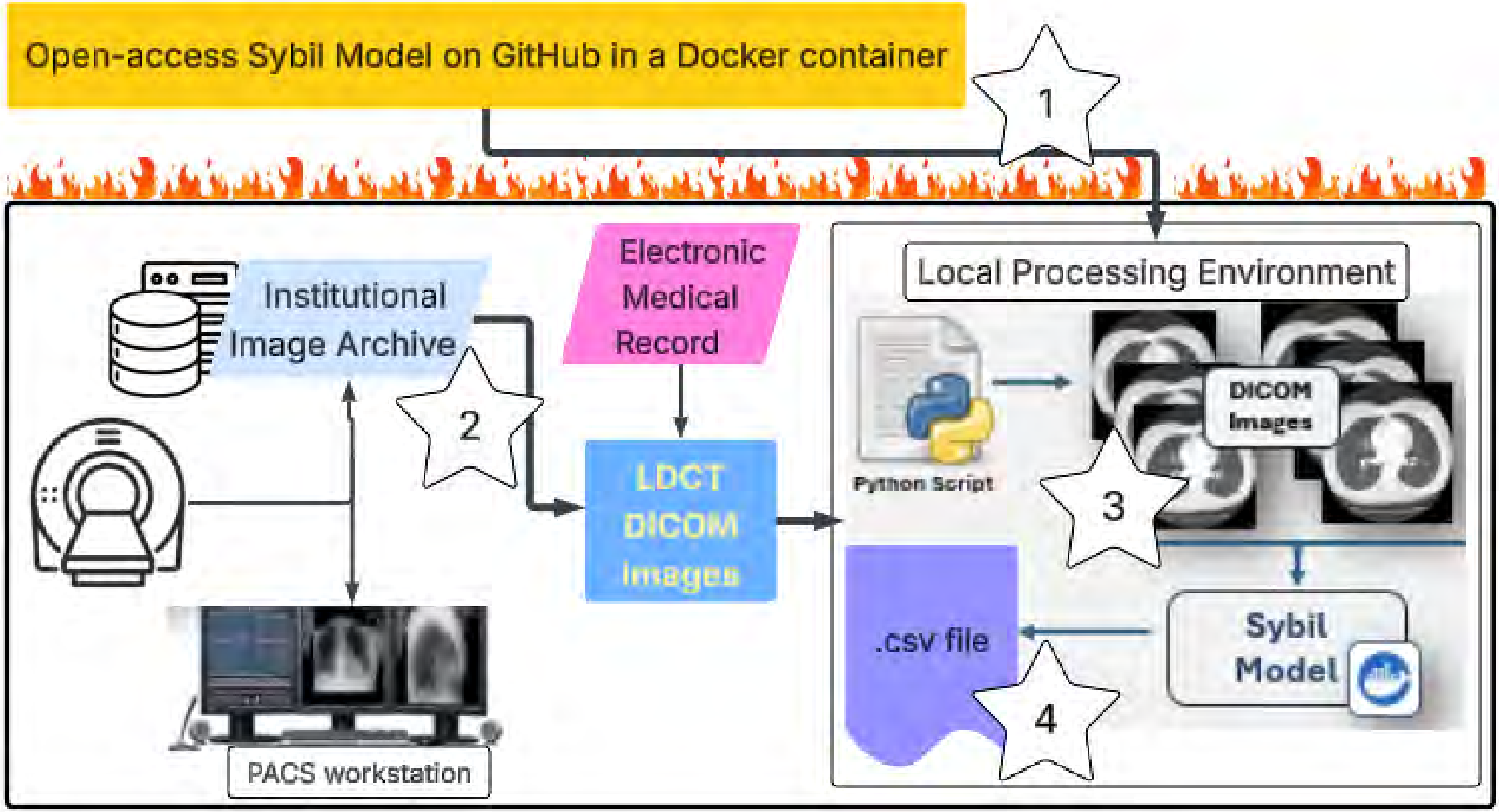






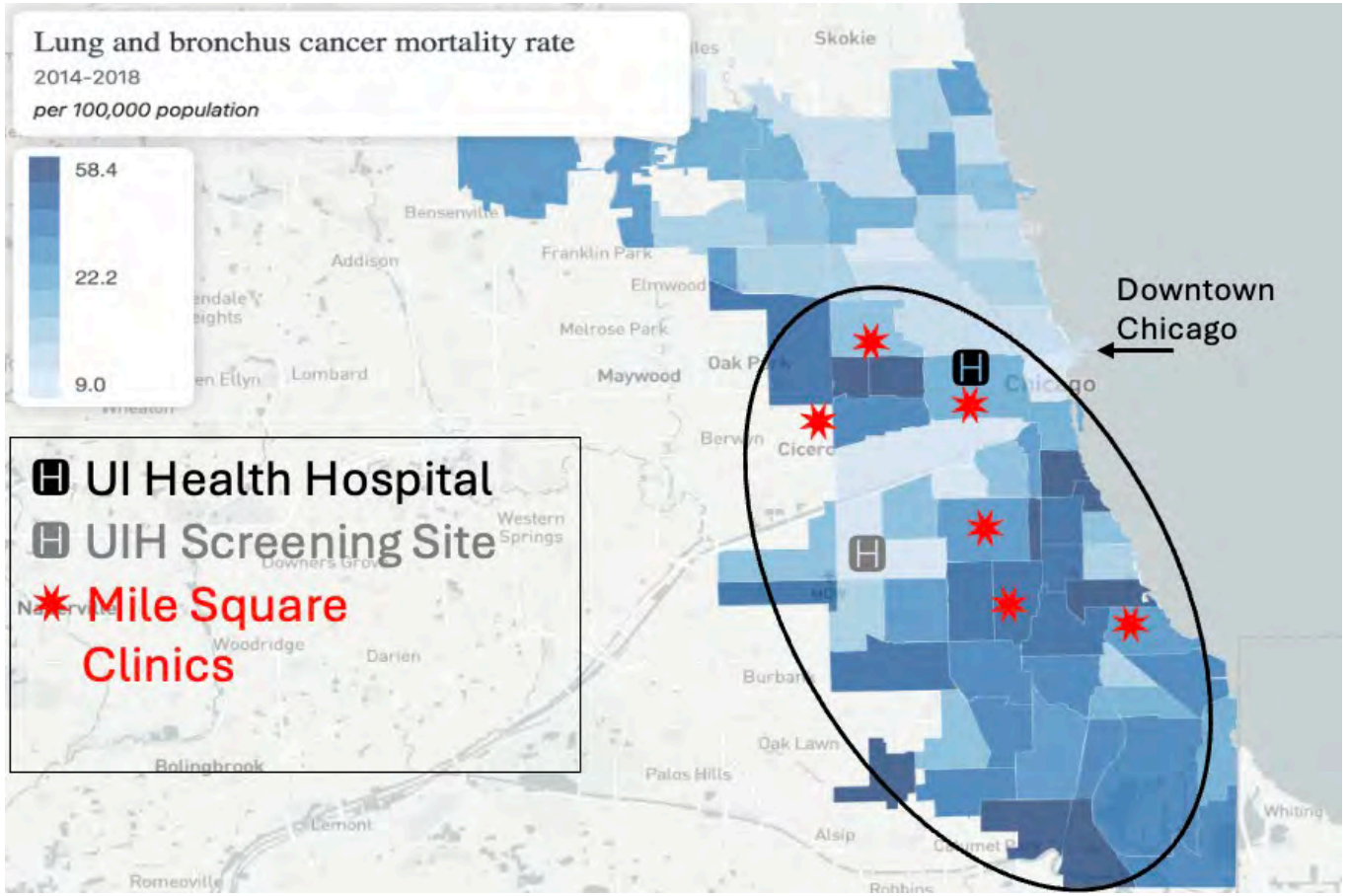




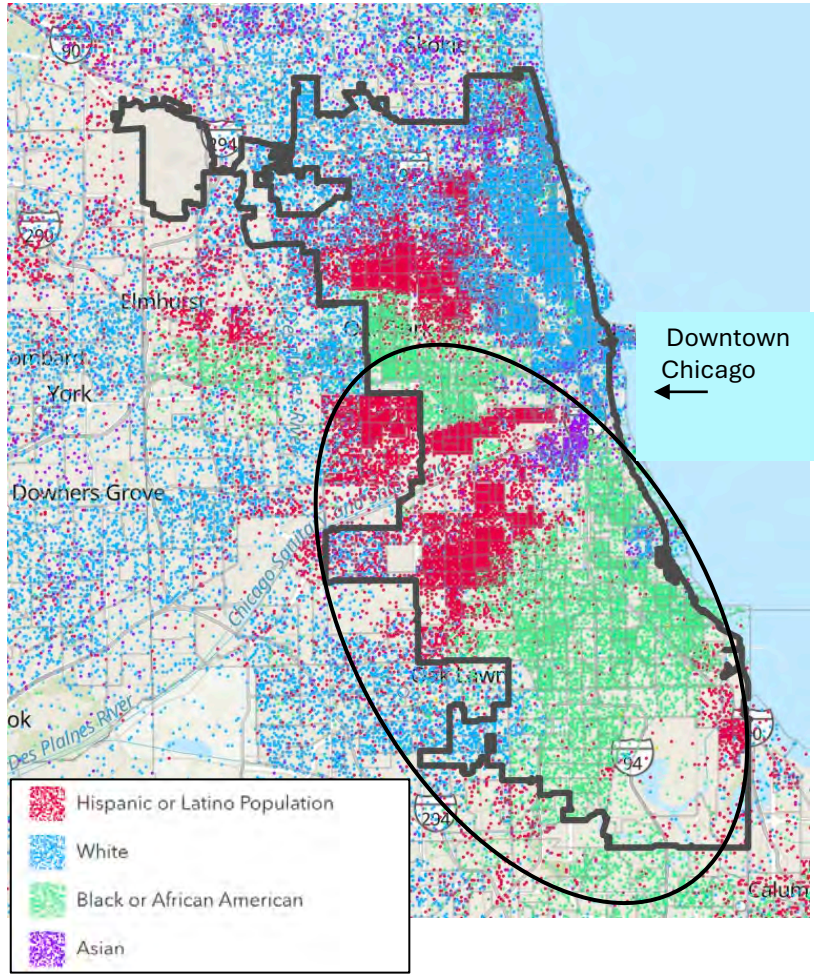

Open-access Sybil Model on GitHub in a Docker container
1
Institutional Image Archive
2
Electronic Medical Record
LDCT DICOM Images
PACS workstation
Local Processing Environment
Python Script
DICOM Images
3
.csv file
4
Sybil Model

University of Illinois Chicago (UIC)/UI Health Service Area

UI Health Serves is a safety net hospital, serving a primarily minority population living in lower socioeconomic communities on the south and west side of Chicago



Lung Cancer Mortality Map – Chicago

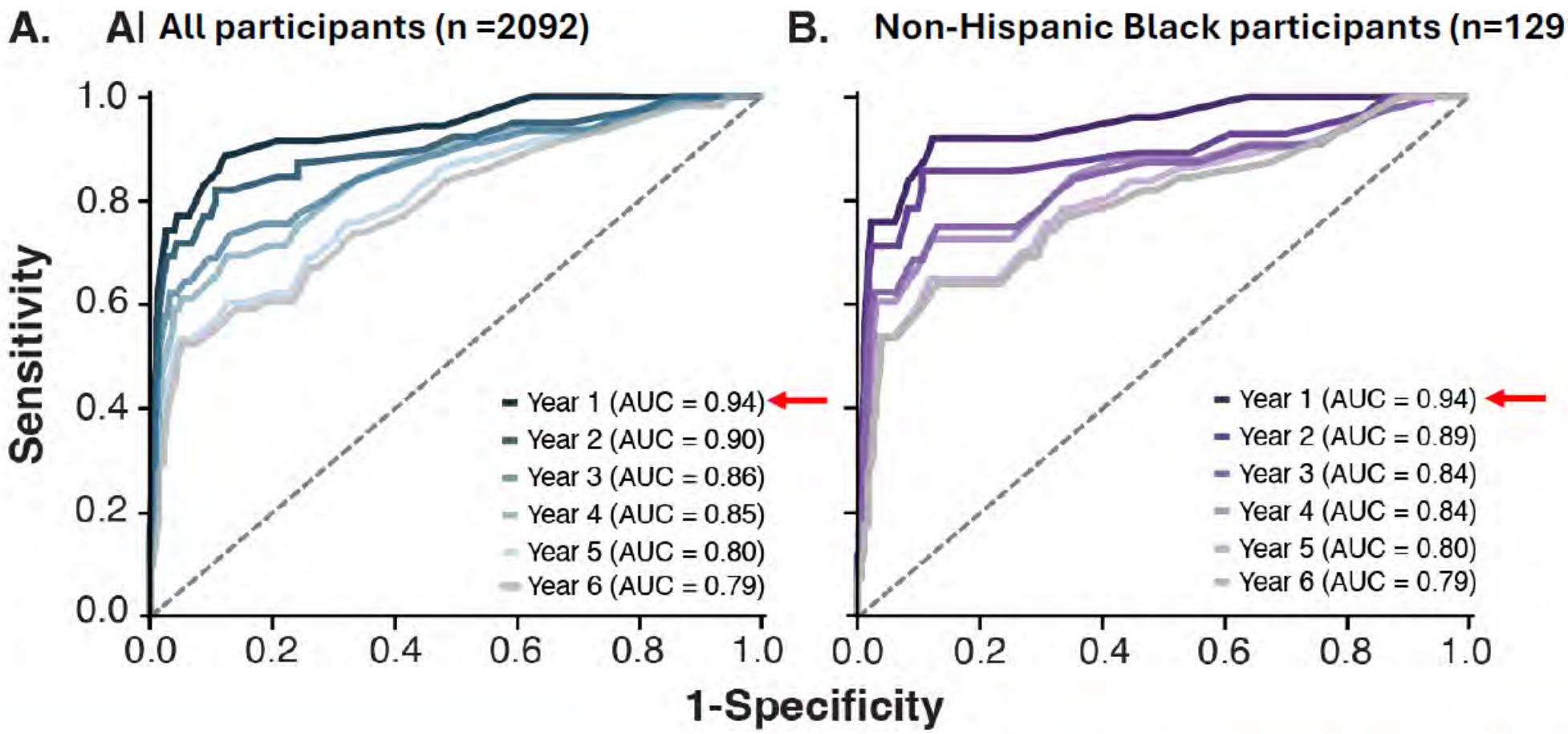


Race/Ethnicity Map – Chicago

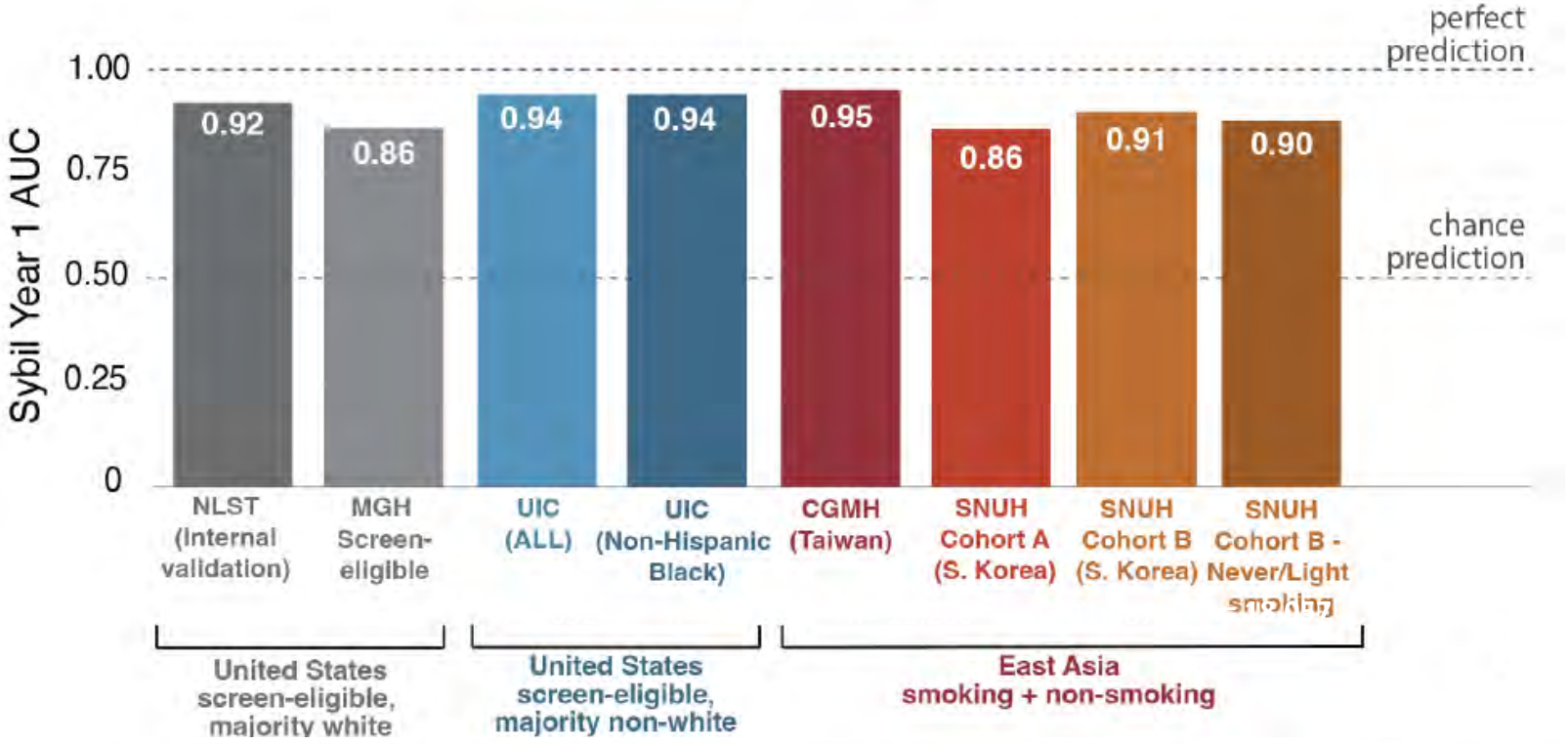
Chicago Health Atlas; Chicago Racial Dot Map 2020, ArcGIS Online

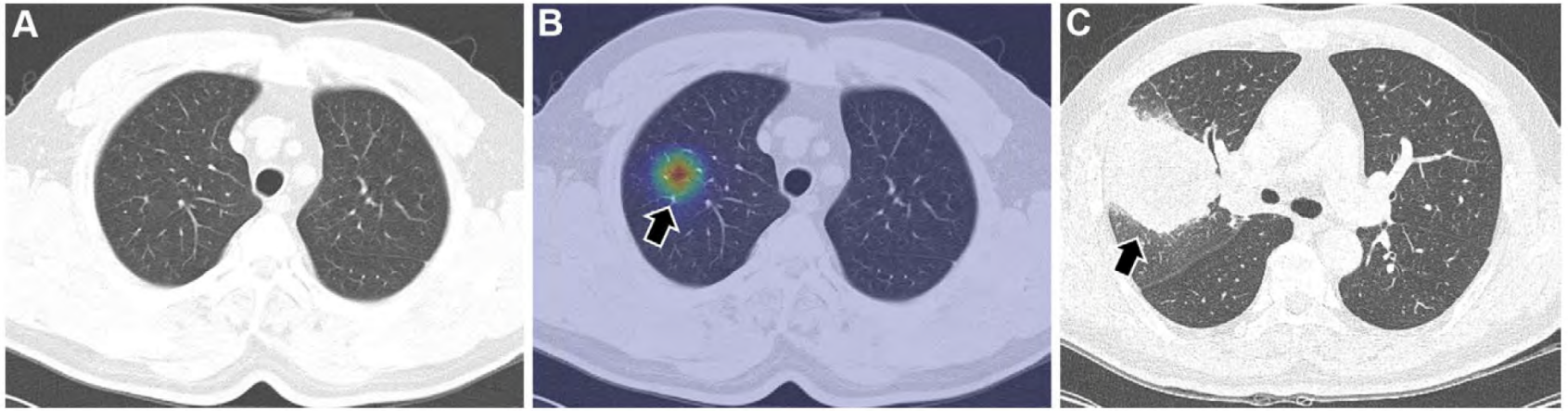
Pasquinelli, et al WCLC 2025

Results: Calibrated risk scores predicting lung cancer risk from 1 to 6 years post baseline LDCT



Snapshot of Global Sybil Studies





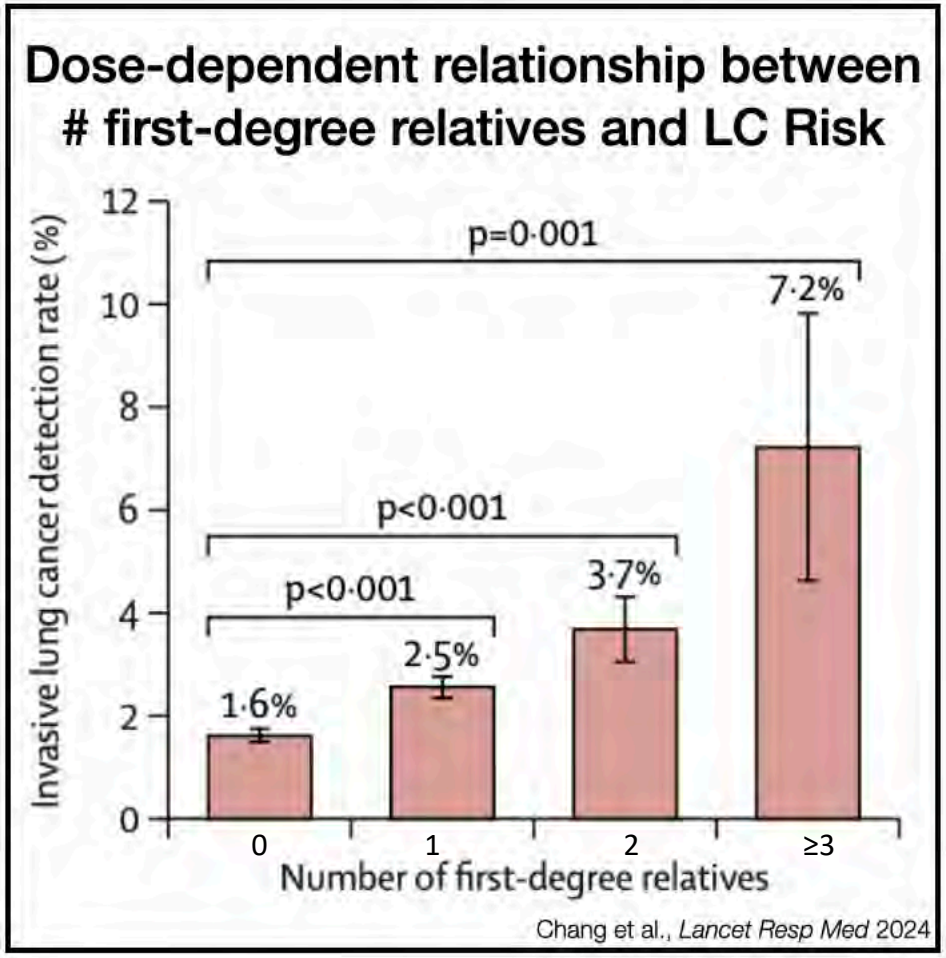
Mikhael, JCO 2023
Pasquinelli, JTO 2026
Kim, CHEST 2026
Lee, Radiology 2025

Example Use Cases for Sybil

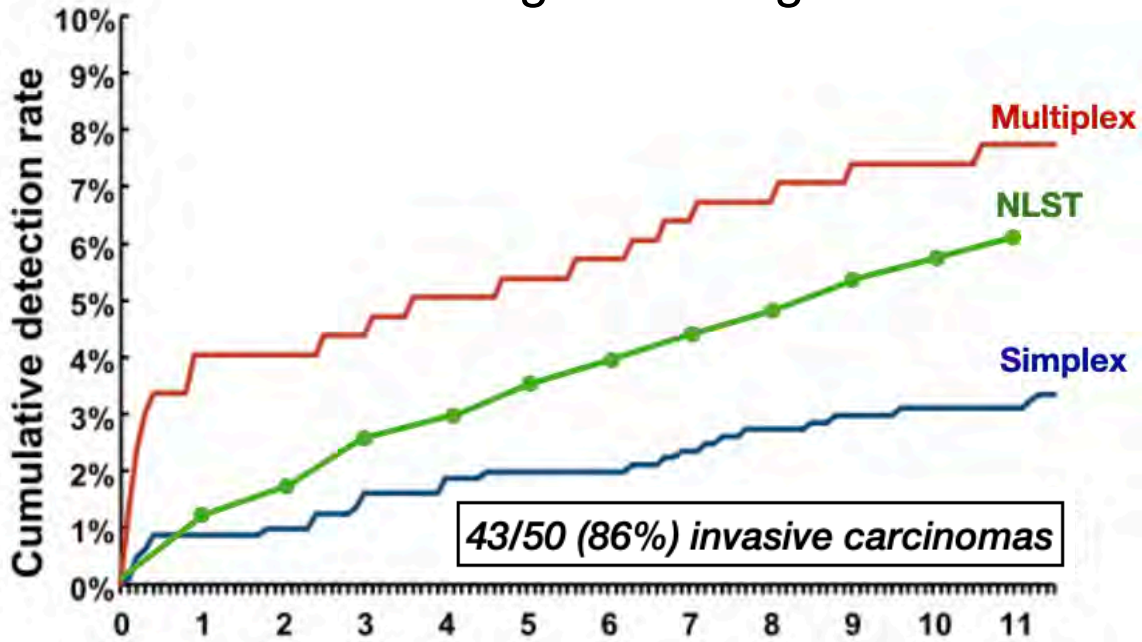
- Improve USPSTF Screening: personalize frequency, increase adherence
- Expand Access to Screening: identify people at highest risk
- Refine Management of Pulmonary Nodules
- Tailor Surveillance of Post-Surgical Lung Cancer Patients
- Many other globally-relevant ideas are under exploration by colleagues



A family history of lung cancer significantly increases lung cancer risk

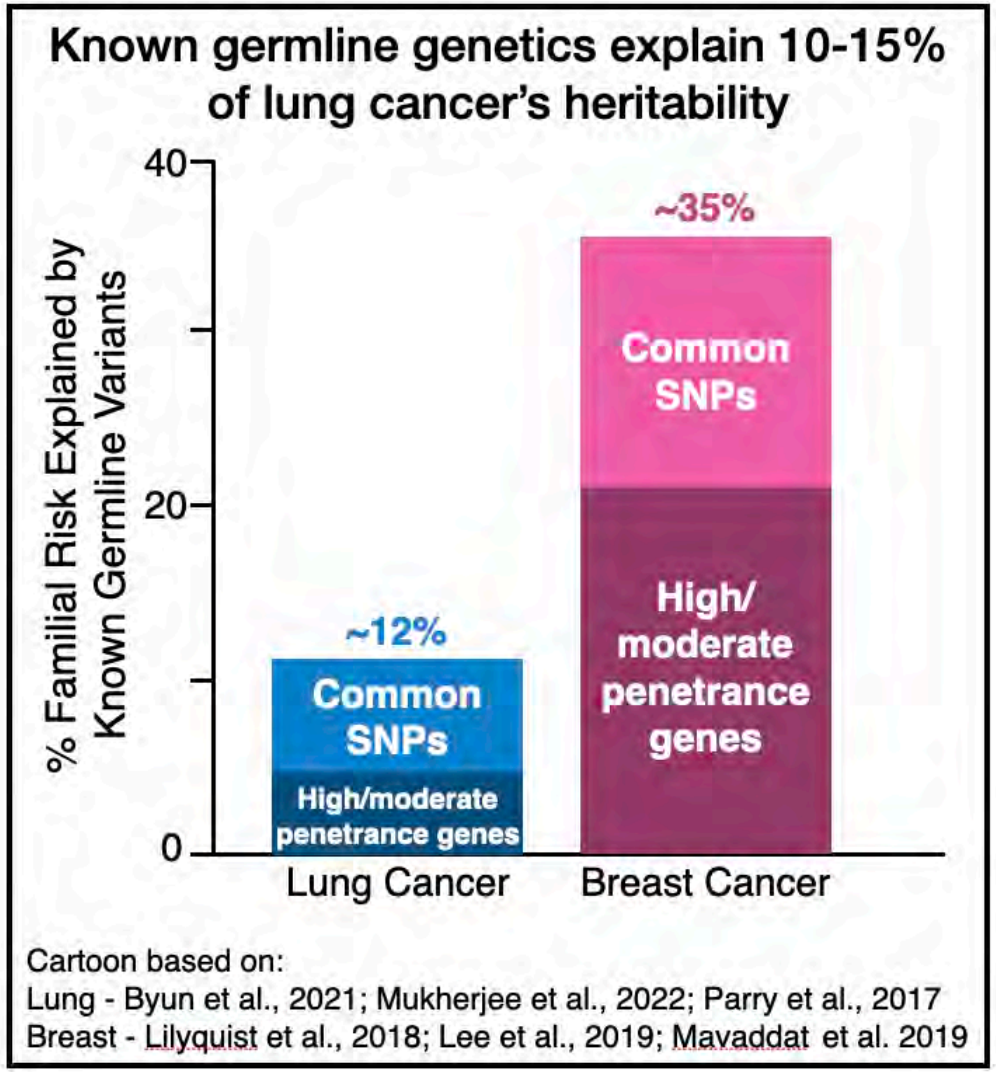


With >1 first- and/or second-degree relatives, lung cancer risk is comparable to the that in the National Lung Screening Trial



Wang et al., *JTO* 2023
Aberle et al., *JTO 2020*

Germline genetics do not fully explain why lung cancer clusters in families

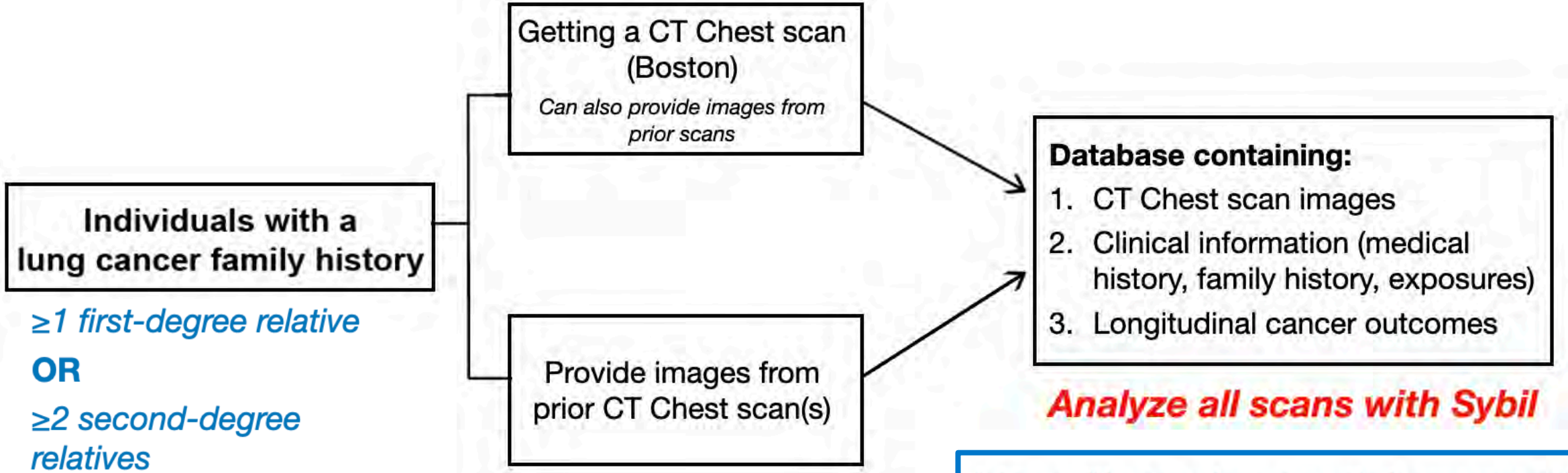


We are still learning about the genetics of lung cancer risk.

- **INHERIT Trial - Jaclyn LoPiccolo + Pasi Janne (Dana-Farber Cancer Institute)**

INHERIT
Investigating Hereditary Risk in Thoracic Cancers

LEGACY: A large, prospective trial to validate Sybil in individuals with a lung cancer family history



https://legacylung.mgh.harvard.edu

Goal enrollment: ≥2500 participants

Global, remote enrollment permitted!

Prospective Trials Incorporating Sybil

CREST-AI*

Potter Criteria (smoking duration)

Mary Pasquinelli + Frank Weinberg



LEGACY*

Family history of lung cancer

Allison Chang + Lecia Sequist



INSPIRE

Black women

Jeff Yang + Alex Potter





Home Base Study

Veterans

Mass General Brigham



Fire Health Study

Firefighters

Erica Warner + Lecia Sequist



RESOLVE

Pulmonary nodules

Sybil Implementation Consortium

Acknowledgments

Sybil Implementation Consortium

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Meridith Ray
David Cheng
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Carrie Fehnel
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Teri Hill
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MGBCI Early Detection & Diagnostics Program

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Judie Panagiotopoulos
Allison Chang
Apryl Bilodeau
Angie Frank
Kristin Anderson
Emily Ranaghan
Mary Beth Metelenis
Tara Soumerai
David Miller
Mike Rainone
Joel Schwartz
Christine Engle
Tish Conway
Jill Thornton
Elaina Chan
Julius Chiang
Abby Moore
Jen Clow
Chetan Shulka

MGH Fire Health Study

Erica Warner
Elaina Chan
Julius Chiang
Audra Hite

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Rising Tide Foundation
HCC and MIT Bridge Program
Conquer Cancer Foundation
Upstage Lung Cancer
The BMS Foundation
The V Foundation
SU2C
The Bralower Family
The Landry Family
LUNGSTRONG





LUNG CANCER RESEARCH FOUNDATION.

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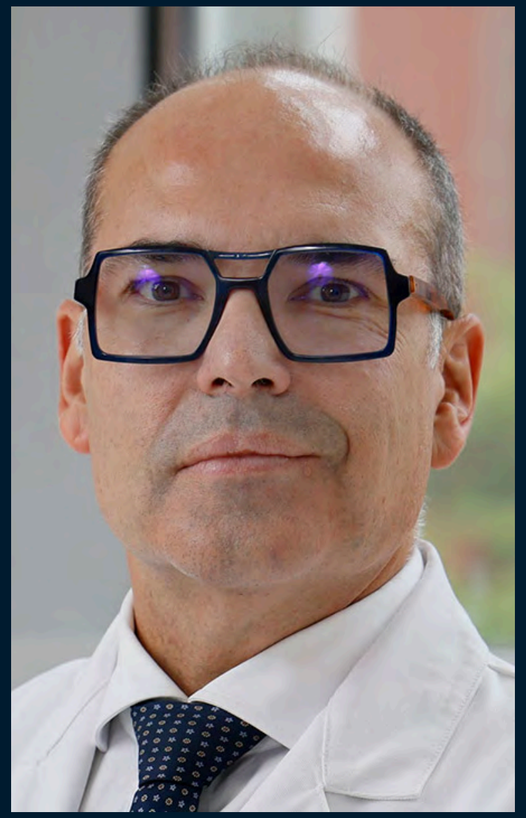
Early Detection: Liquid biopsy and ctDNA in clinical practice

Christian Rolfo, MD, PhD

Professor, Department of Internal Medicine, Division of Medical Oncology
The Ohio State University

Director of the Division of Medical Oncology; Associate Director for early phase clinical trials
Ohio State University Comprehensive Cancer Center

Recipient of 2019 LCRF Lung Cancer Treatment Focused Research Grant Program



Liquid biopsy for early cancer detection

Christian Rolfo, MD, PhD, MBA, Dr.hc.
Director Division Medical Oncology
Associate Director for Early Phase Clinical Trials

The James

THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

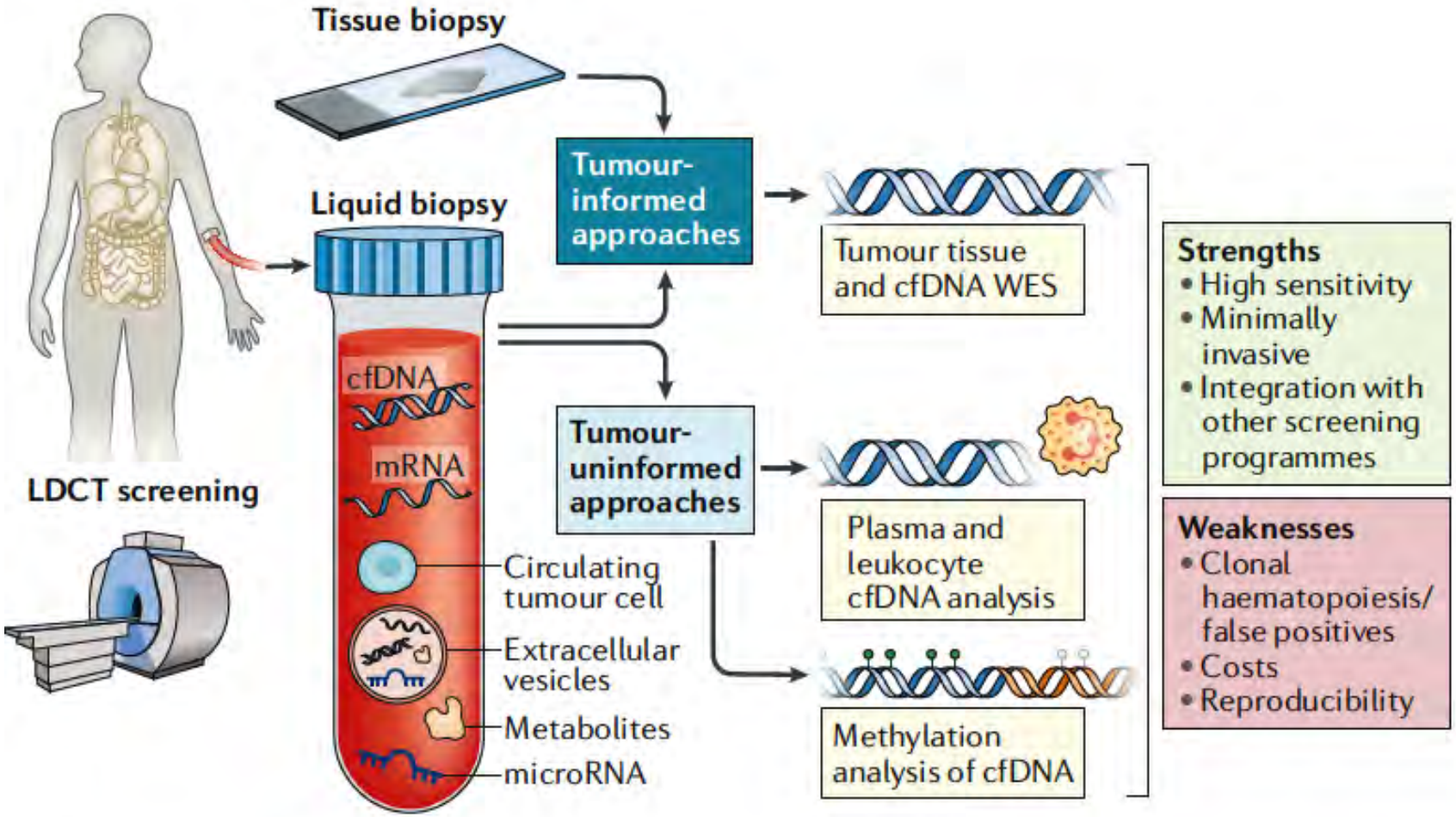


ISLB
INTERNATIONAL SOCIETY OF LIQUID BIOPSY

Disclosures

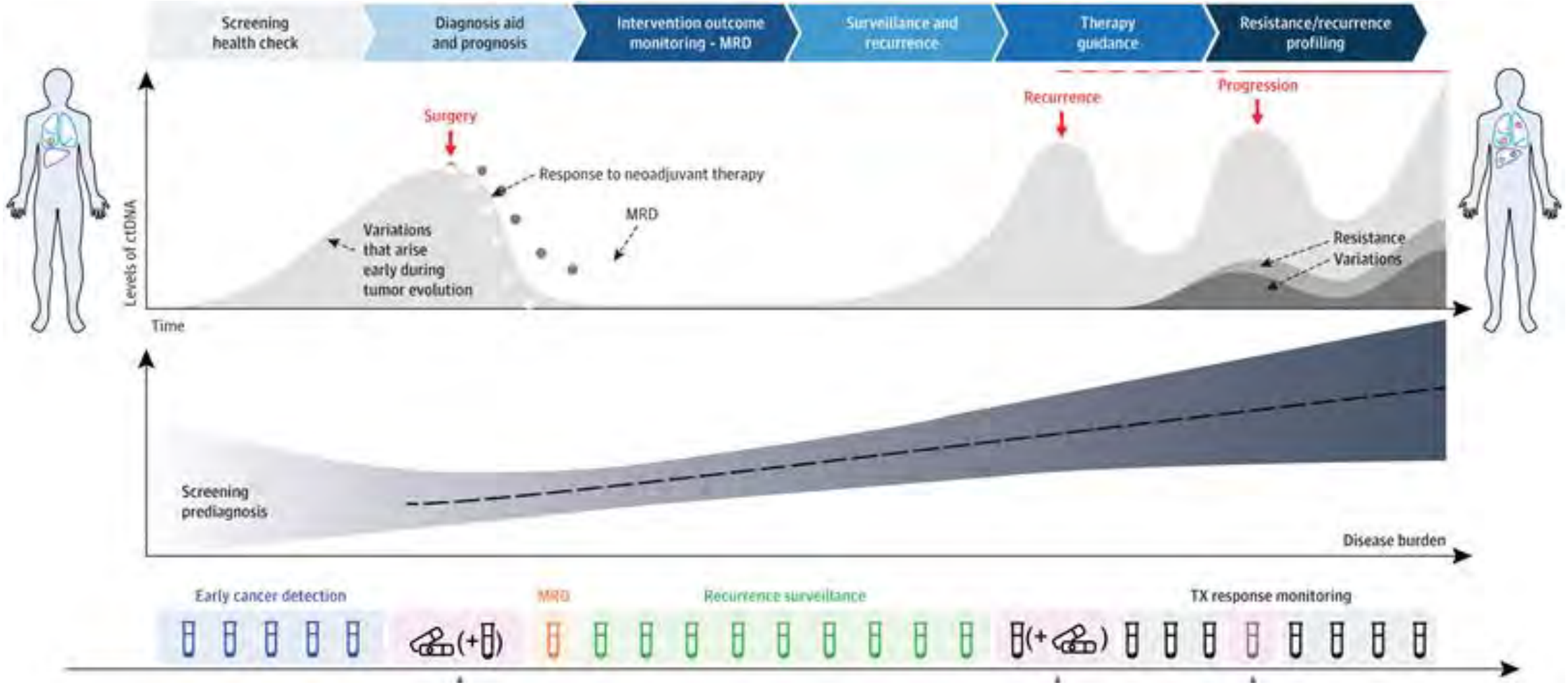
- Advisory Board: AstraZeneca, Daiichi Sankyo, Regeneron and Novocure; Bristol-Myers Squibb (BMS), Novartis, Invitae, Guardant Health,COR2ED, Bayer, Boehringer Ingelheim, Abbvie, Invitae, Janssen, EMD Serono, BioNtech
- Research Grant: Astra Zeneca, Thermo Fisher, Lung Cancer Research Foundation, National Foundation for Cancer Research, and U54 (National Institute of Health)
- Research collaboration: GuardantHealth, Foundation Medicine, Roche Diagnostics, EMD Serono
- Leadership roles: in International Society of Liquid Biopsy, The European School of Oncology, International Association for Study of Lung Cancer, and Oncology Latin American Association.
- Editor role: Editor in chief of CROH and Honorary editor at Journal of Liquid Biopsy Elsevier. Editorial board Lung Cancer and ILCN (IASLC).

Liquid biopsy & early detection



Rolfo C & Russo A. Nat Rev Clin Oncol 2020;17:523-524.

Liquid biopsy can provide clinically-valuable information along the whole patient journey

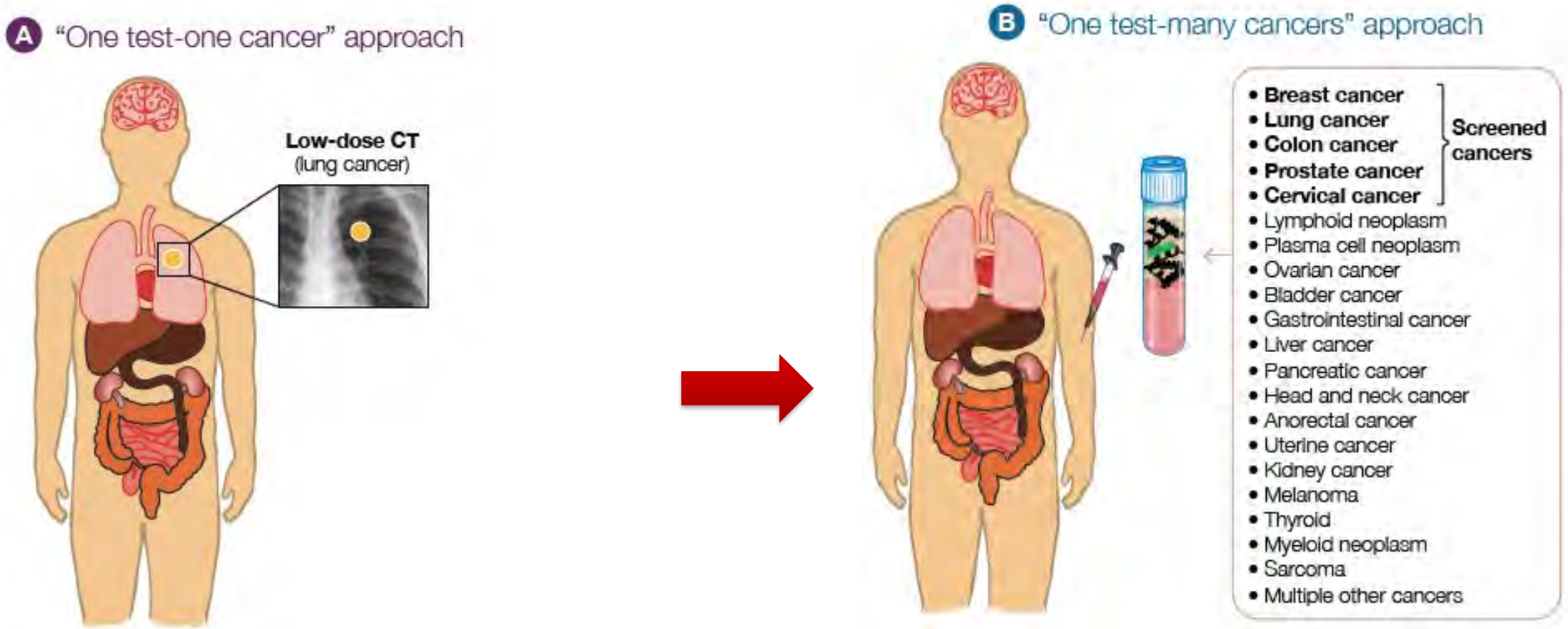


Krebs M. Malapelle..(Rolfo) et al, JAMA Oncology October 2022

The James

The Ohio State University
Comprehensive Cancer Center

A changing paradigm: Multicancer detection tests

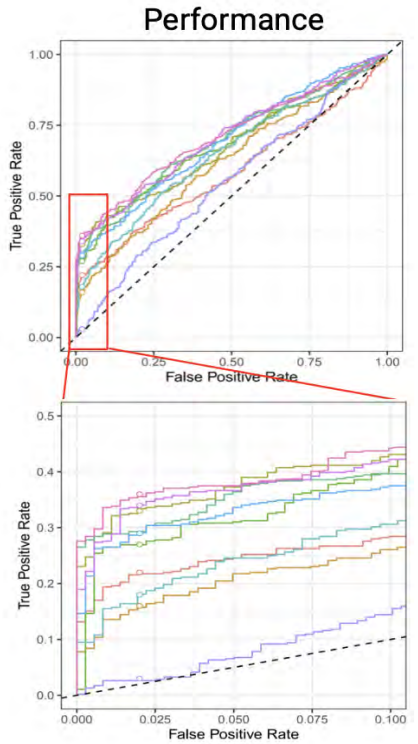


Questions / concerns we still have:

- Same specificity and Sensitivity in all the tumor?
- Interpatient variability in the same tumor type is alredy know
- One fit for all approach ?

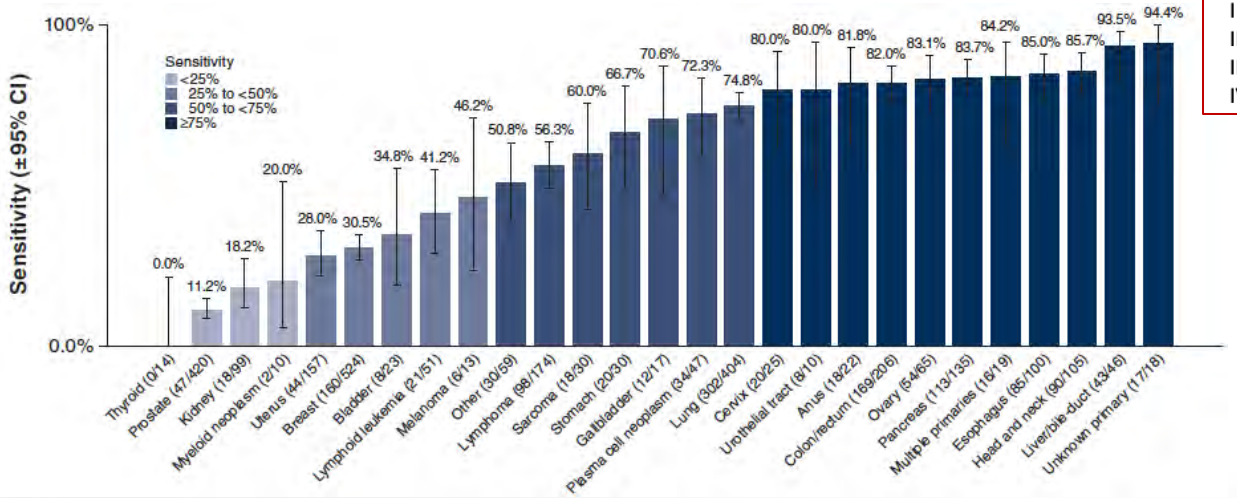
MCED test performance for cancer signal detection

Sensitivity at 98% specificity	WGBS	WG methylation	34% (30%-39%)	158/464



	Cancer	Non-cancer	Total
	2823	1254	4077
Test positive	1453	6	1459
Test negative	1370	1248	2618
	Sensitivity = 1453/2823 51.5% (49.6%-53.3%)	Specificity = 1248/1254 99.5% (99.0%-99.8%)	

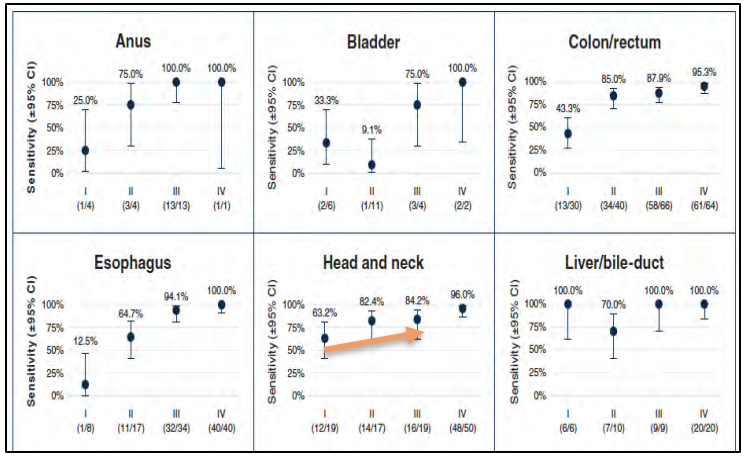
Two-sided 95% Wilson confidence intervals were calculated.

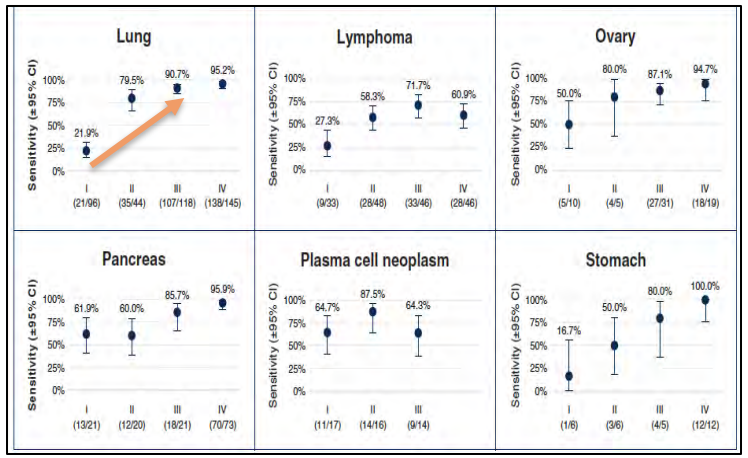


Confirmed status analysis set, *n* = 4077
cancer, *n* = 2823; non-cancer, *n* = 1254

Clinical cancer stage, *n* (%)	
I	849 (30.1)
II	703 (24.9)
III	566 (20.0)
IV	618 (21.9)

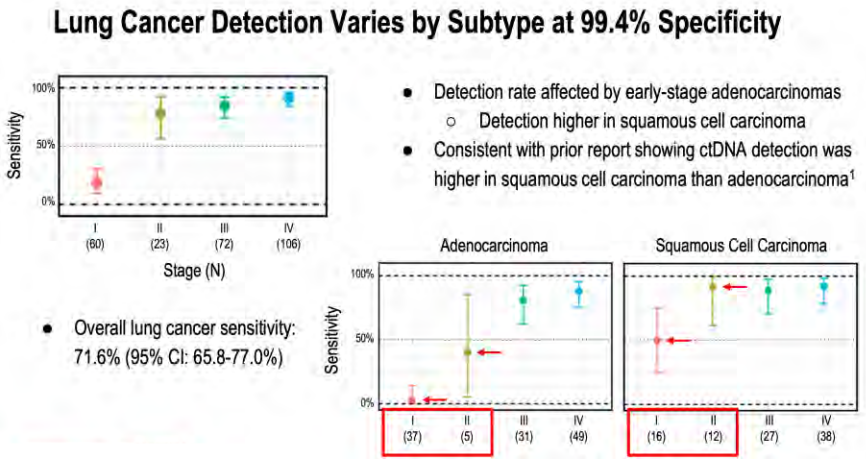
Klein EA, et al. Ann Oncol 2021

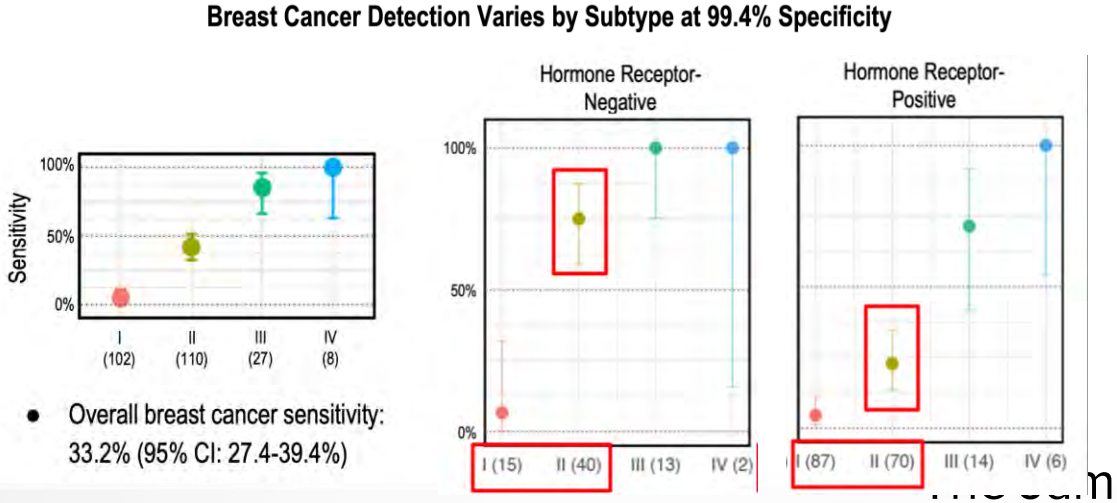




Clinical stage	Total *N*	Test positive	Sensitivity % (95% CI)[a]
All	2823	1453	51.5 (49.6% to 53.3%)
I	849	143	16.8 (14.5% to 19.5%)
II	703	284	40.4 (36.8% to 44.1%)
III	566	436	77.0 (73.4% to 80.3%)
IV	618	557	90.1 (87.5% to 92.2%)
I-II	1552	427	27.5 (25.3% to 29.8%)
I-III	2118	863	40.7 (38.7% to 42.9%)
I-IV	2736	1420	51.9 (50.0% to 53.8%)
III-IV	1184	993	83.9 (81.7% to 85.9%)
Not expected to be staged	67	23	34.3 (24.1% to 46.3%)
Missing	20	10	50.0 (29.9% to 70.1%)

MCED: All subtypes have the same sensitivity?



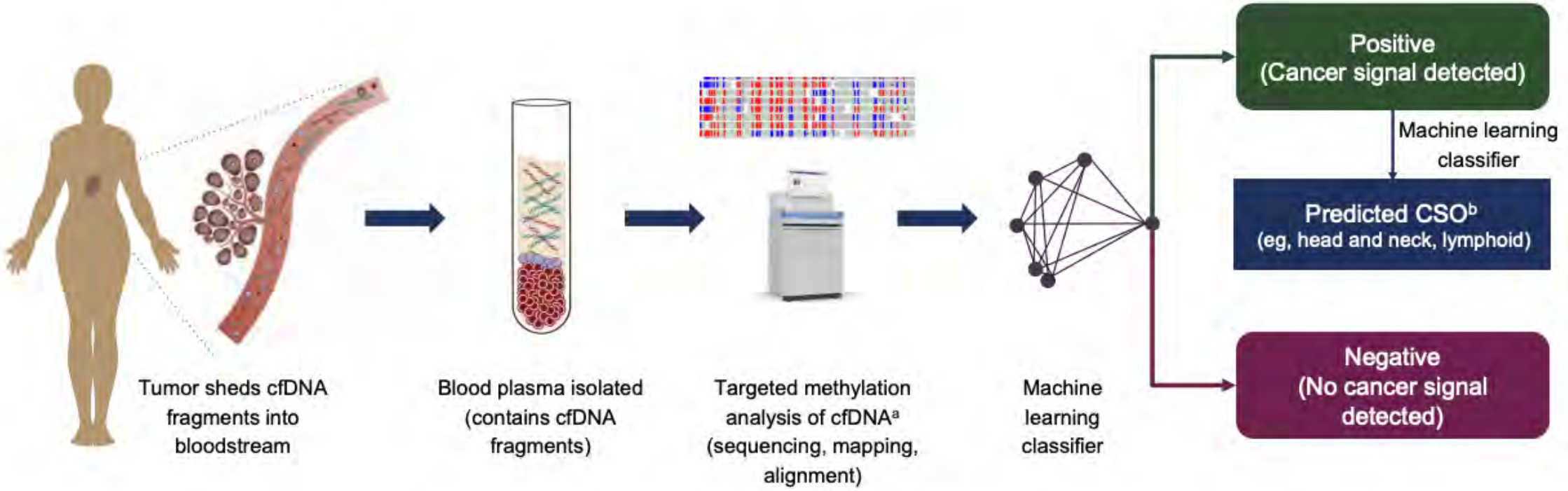


Oxnard et al, ESMO 2019, Klein EA, et al. Ann Oncol 2021

PATHFINDER 2: The Largest Interventional MCED Study Conducted in the US to Date

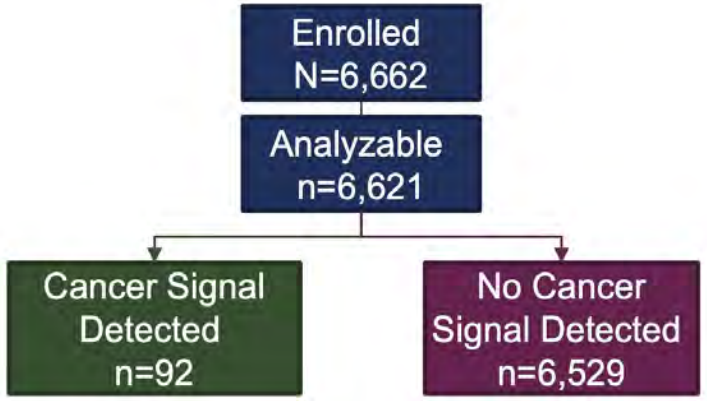
MCED Blood-Based Targeted Methylation Test

Detects cancer signals from cfDNA and predicts cancer signal origin to guide diagnostic evaluation



Adapted from Nima Nabavizadeh. ESMO 2025

	With Additional Risk[a] n = 3,681	Without Additional Risk n = 2,940	Total N = 6,621
Age[b], in years, mean (SD)	64.7 (8.7)	61.6 (8.1)	63.4 (8.6)
Female	65%	62%	63%
White, Non-Hispanic	93%	89%	92%
College Degree or Higher	59%	71%	65%
Up to Date With Standard Cancer Screening Prior to MCED Testing			
Colorectal Cancer[c]	91%	92%	92%
Breast Cancer[d]	78%	83%	80%

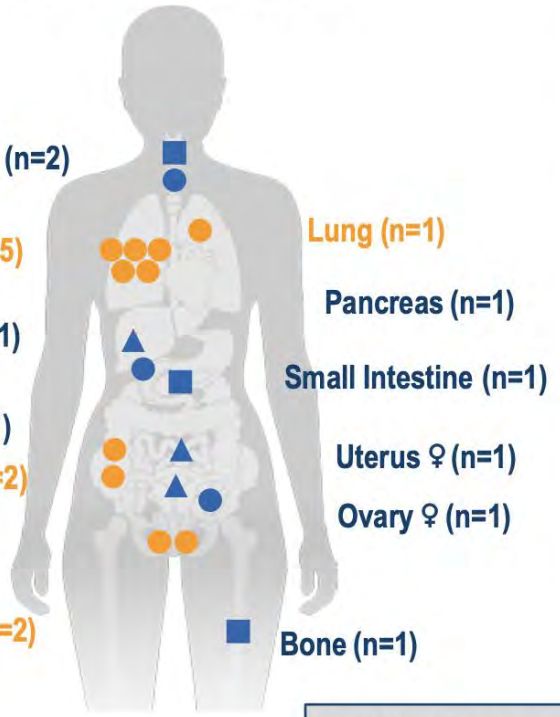


	With Additional Risk[a] n = 3,681	Without Additional Risk n = 2,940	Total N = 6,621
Signal Detected	1.5%	1.2%	**1.4%**
No Signal Detected	98.5%	98.8%	98.6%

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Cancers Diagnosed After a True Positive MCED Signal

19 Solid Tumors

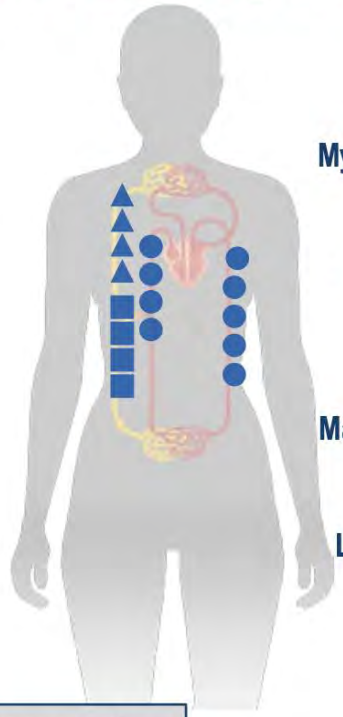


35 people were diagnosed with 36 cancers

- 24 in high-risk cohort
- 11 in not-high-risk cohort

- 7 recurrent cancers
- 14 early-stage cancers
- 26 cancers lacking standard screening

17 Hematologic Cancers



Plasma Cell Myeloma/Disorders (n=1)

Lymphoid Leukemia (n=2)

Waldenstrom Macroglobulinemia (n=2)

Lymphoma (n=12)

AJCC Staging: ▲ Stage I ■ Stage II ● Stage III/IV/No Stage/Recurrent

Available Screening: USPSTF cancer screening or No standard screening

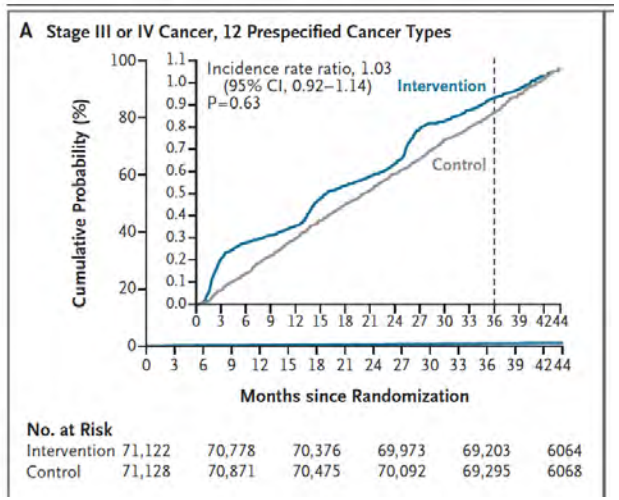
Deb Schrag, ESMO 2022

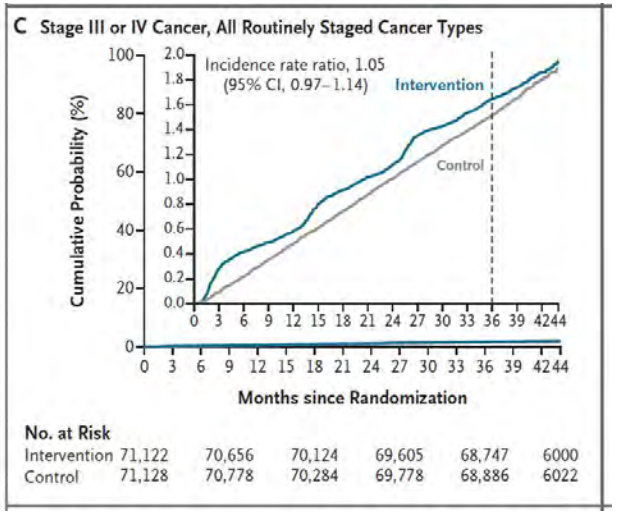
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Effect of Screening with MCED on Late-Stage Cancer Diagnosis

TRIAL DESIGN

142,250 adults | Age 50–77 years | 3 annual blood draws | **MCED + usual care vs usual care**





PRIMARY ENDPOINT

Stage III–IV cancer

IRR 1.03

95% CI 0.92–1.14 • P = 0.63

706 vs 688 cases | No significant reduction

CLINICAL INTERPRETATION

MCED increased cancer detection, but clinical utility for reducing late-stage (III–IV) diagnoses remains unproven.

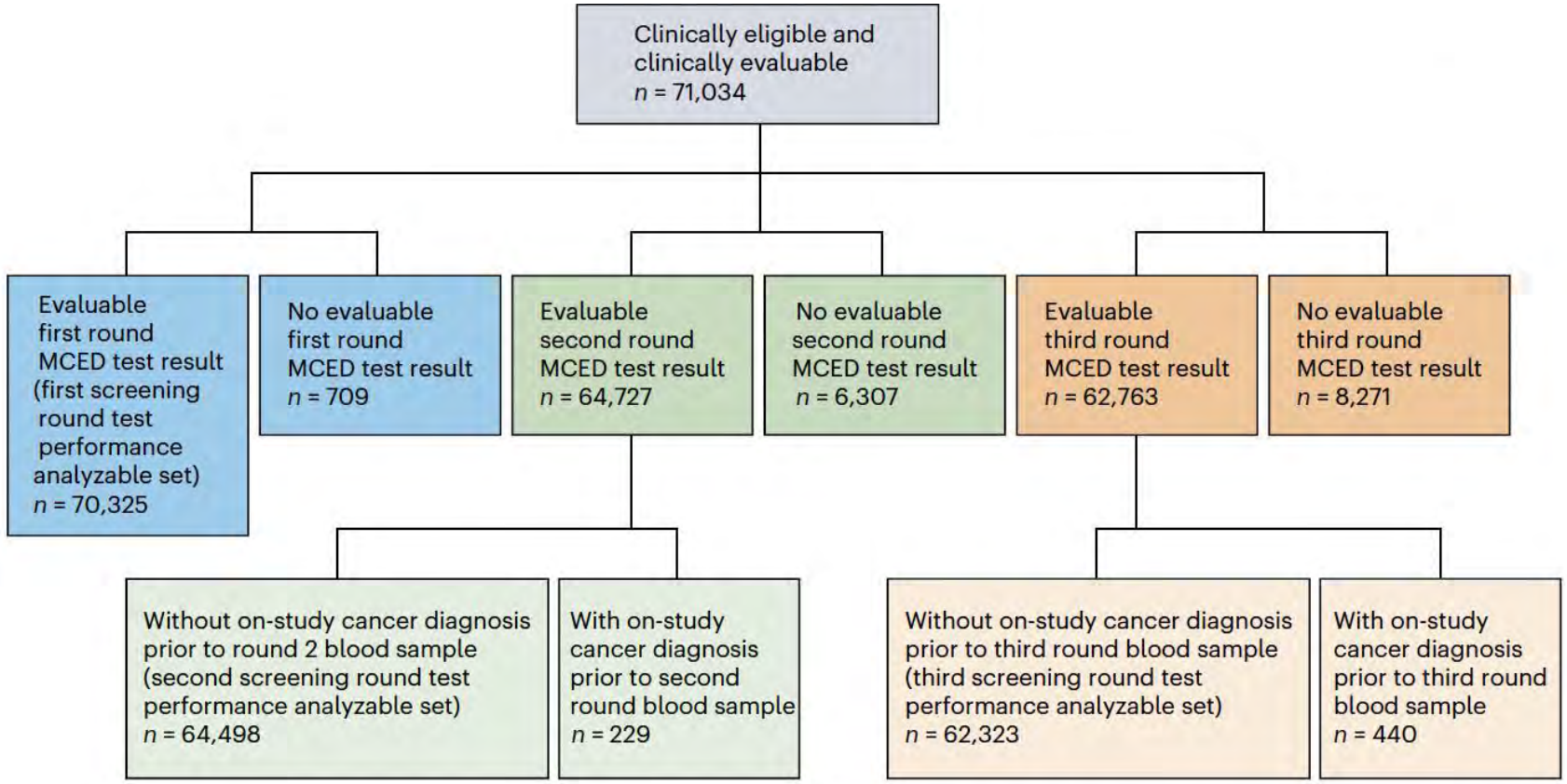
Stage IV signal is hypothesis-generating; secondary comparisons were not adjusted for multiplicity. Longer follow-up is needed.

Sasieni P, et al. N Engl J Med. 2026;395:1374–1386. doi:10.1056/NEJMoa2505723 | NHS-Galleri (NCT05611632)

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Performance of a MCED in the randomized controlled NHS-Galleri trial



Primary endpoint: reduction in the incidence rate of stage III or IV cancer diagnoses across 12 prespecified cancer types, comparing Galleri multicancer early detection (MCED) testing plus usual care versus usual care alone, after three annual screening rounds.

142,250 randomized | Intervention: 71,122 | 197,146 evaluable tests across 3 rounds (not unique individuals)

Sasieni et al. Nature Medicine (2026), doi:10.1038/s41591-026-04652-8

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Performance of a MCED in the randomized controlled NHS-Galleri trial

937

MCED-detected primary cancers

Across 3 screening rounds

99.55%

Specificity

Aggregate false-positive rate: 0.45%

52.0%

Positive predictive value

Aggregate episode sensitivity: 30.7%

PERFORMANCE BY SCREENING ROUND

Metric	Round 1	Round 2	Round 3
Participants tested	70,325	64,498	62,323
Cancer detection rate	0.60%	0.40%	0.41%
Positive predictive value	58.0%	50.4%	45.8%
Episode sensitivity (all cancers)	**37.2%**	**27.1%**	**26.7%**
Cancer signal origin accuracy*	93.6%	92.3%	91.1%

Interpretation: High specificity and accurate tissue-of-origin prediction, but limited sensitivity; the randomized trial did not meet its primary stage III/IV endpoint.

Sasieni et al. Nature Medicine (2026), doi:10.1038/s41591-026-04652-8

The Most Studied MCED Test with Intended-Use Validation

1	CCGA (n=15,254)	Develop and validate a cell-free DNA-based MCED test *Enrollment: complete, published*	*Annals of Oncology* and *Cancer Cell* 2020-2023[1-3]
2	PATHFINDER (n=6,662)	Evaluate clinical implementation and perceptions of MCED test *Enrollment: complete, published*	*The Lancet* 2023[4]
3	PATHFINDER 2 (n=35,878)	Evaluate MCED test performance in eligible screening population *Enrollment: complete*	
4	SYMPLIFY (n=6,238)	Assess MCED test in individuals with signs/symptoms of cancer *Enrollment: complete, published*	*Lancet Oncology* 2023[5]
5	NHS-GALLERI (n≈142,321)	Assess clinical utility of MCED for population screening in the UK *Enrollment: complete*	
6	REFLECTION (n≈14,000)	Understand the real-world experience of Galleri® in clinical settings *Enrollment: complete*	
7	REACH (n≈50,000)	Understand health equity impact of Galleri in a Medicare population *Enrollment: ongoing*	
8	SUMMIT (n=13,035)	Clinical validation in individuals at high risk of lung cancer *Enrollment: complete*	
9	STRIVE (n=99,481)	Observational study in women undergoing mammography screening *Enrollment: complete*	

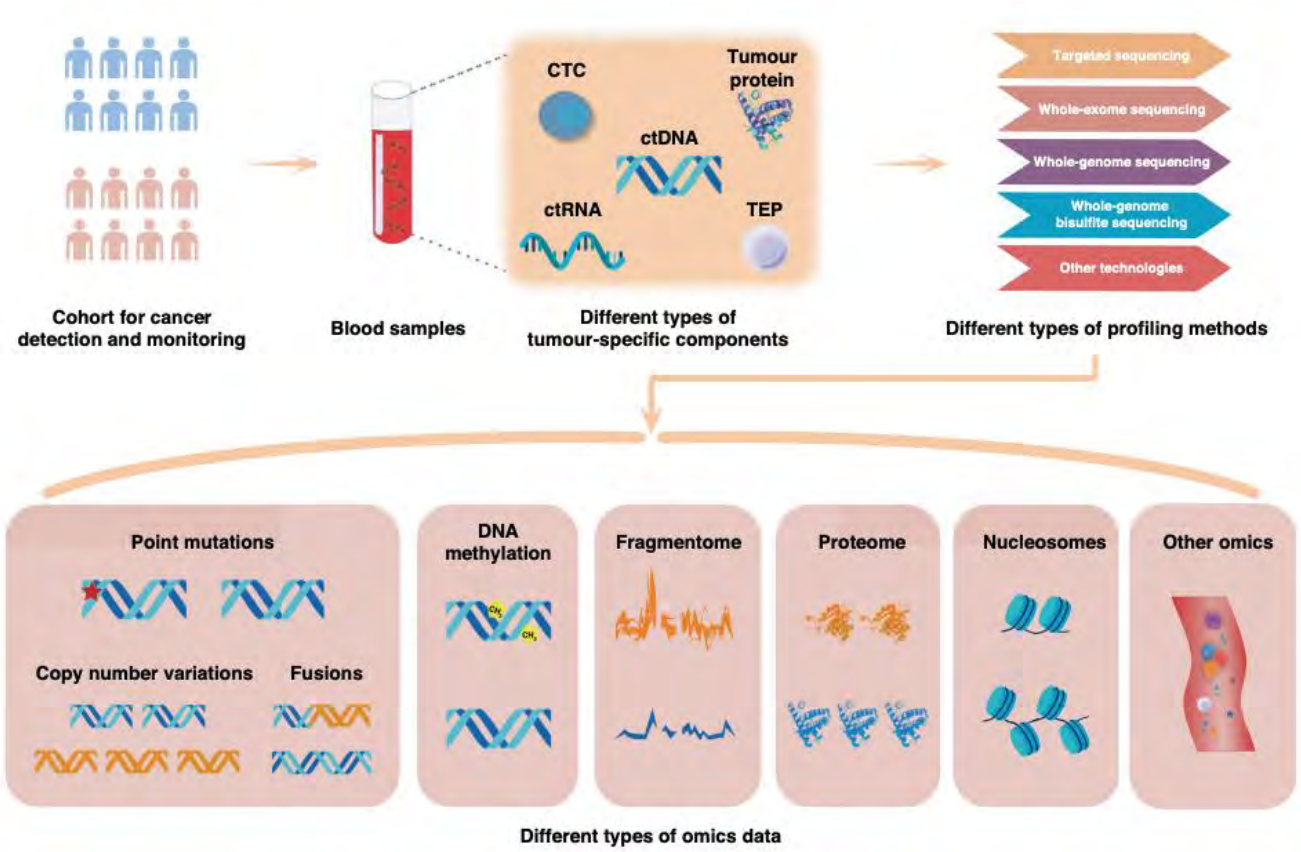


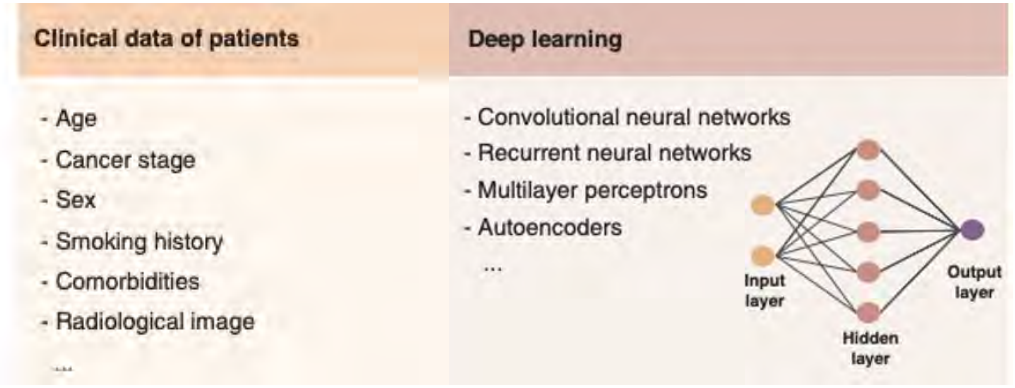
Nima Nabavizadeh. ESMO 2025

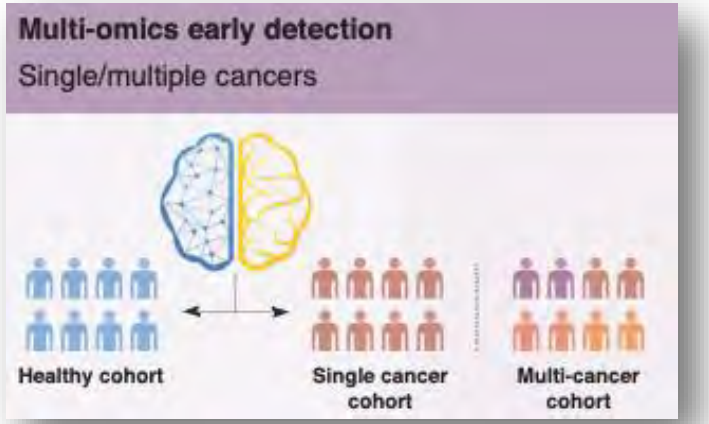
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The next frontier of early lung cancer detection: Is multiomics the solution?





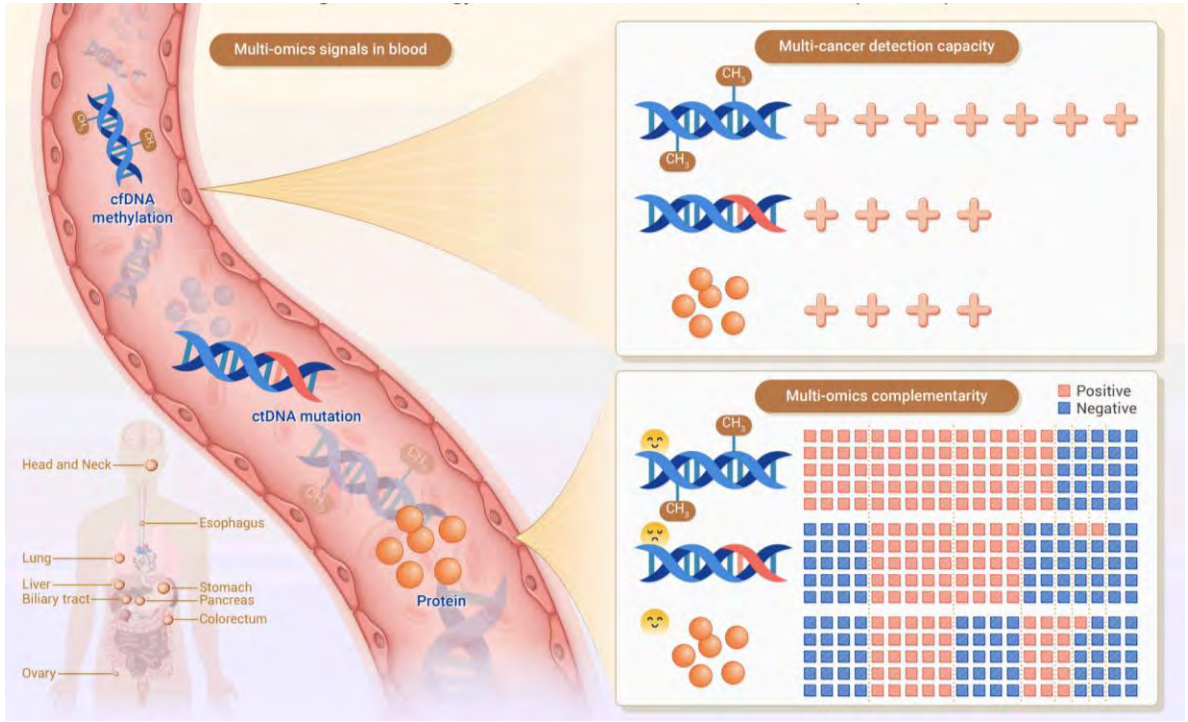


Adapted from: Geng Chen, et al. Br J Cancer 2023

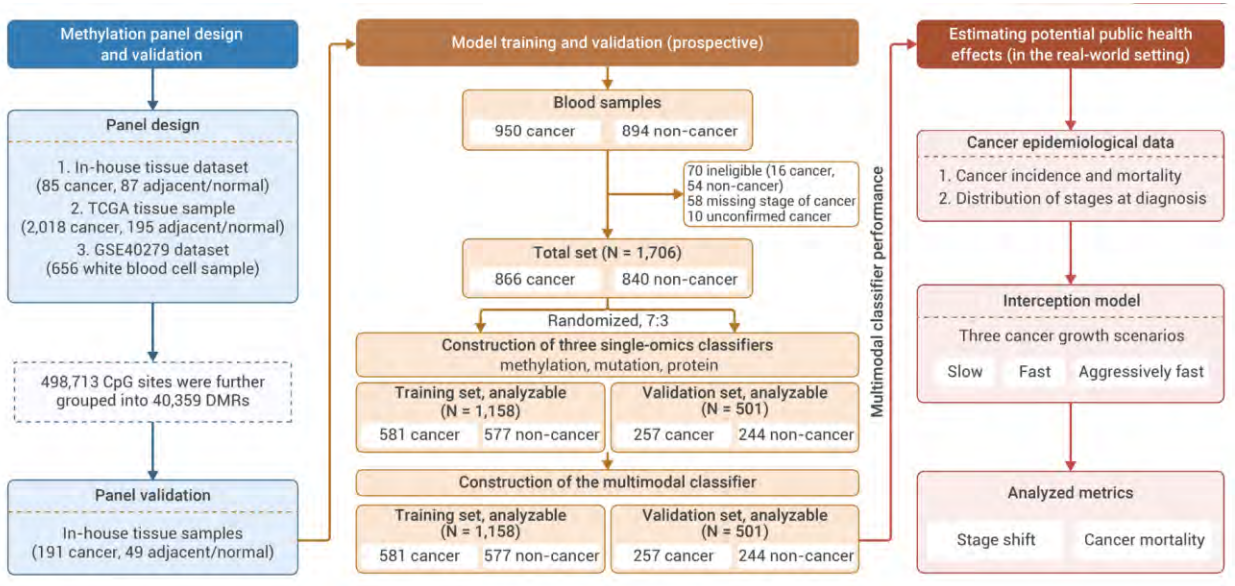
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PROMISE study: multi-omics liquid biopsy approaches for multi-cancer early detection



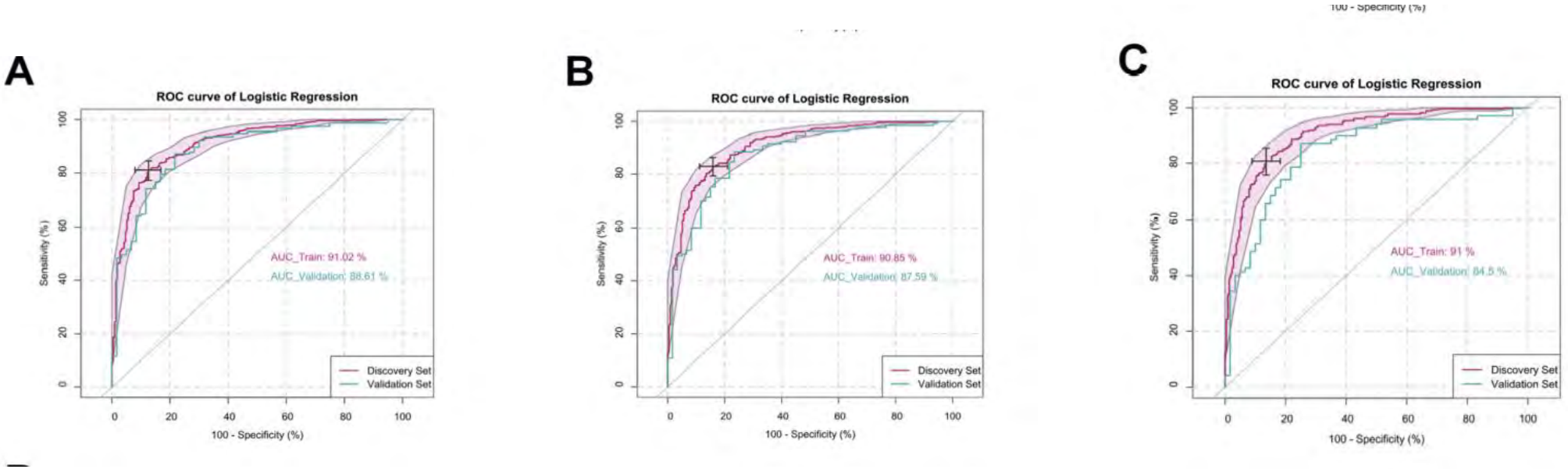
1,706 participants (840 non-cancer; 866 cancer)
9 cancer types



- ✓ The PROMISE study explored multi-omics liquid biopsy strategy for multi-cancer early detection.
- ✓ Multimodal approach combining **Methylation and Protein features** exhibited: sensitivity 75.1% and specificity of 98.8% in cancer detection.

Duan J, et al. The Innovation (Cell Press) 2026

Clinical Validation of Plasma Metabolite Markers for Early Lung Cancer Detection (using targeted, quantitative mass spectrometry)



- Discovery cohort: 680 archived plasma samples from biopsy-confirmed NSCLC patients and controls (including healthy individuals and patients with non-cancerous lung diseases)
- Validation cohort: 216 plasma samples

AUROC values of 93.63%, 93.74%, and 93.91% for distinguishing all-stage, stage I–II, and stage I NSCLC patients from controls, respectively.

Incorporating smoking history further improved model performance.

Zhang et al Int. J. Mol. Sci. 2025, 26, 4519

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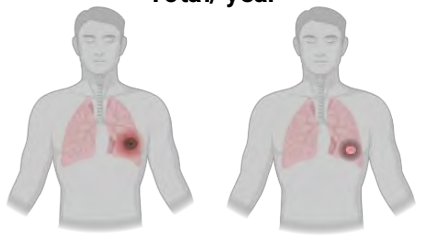
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Current **James Lung Cancer Early Detection Program**

Cases/ year	LCS (high-risk individuals)	ILN & LNC (6-30 mm or >4 RADS)
Early-Stage Lung cancer (I-IIIa)	75	140
Benign nodules	100	400



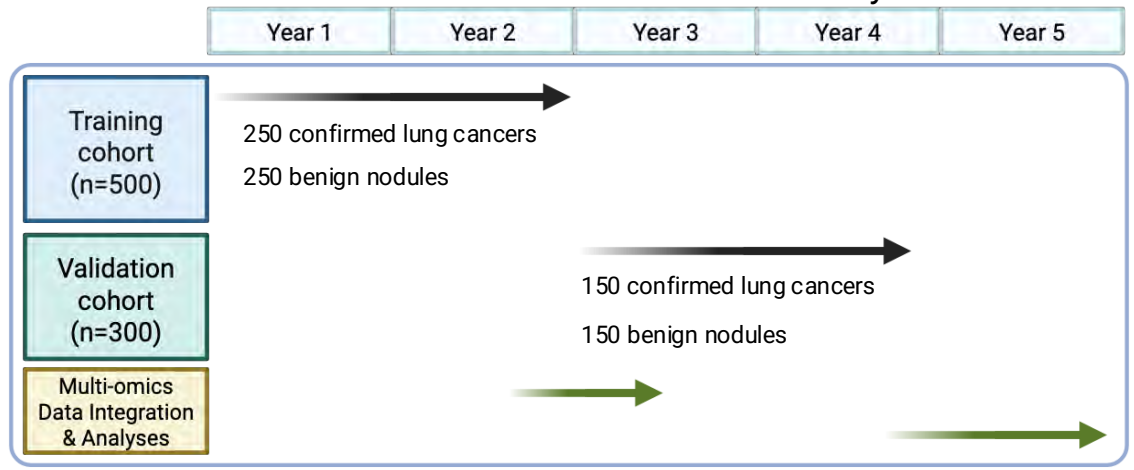
Total/ year



215 Early stage lung cancers (I-IIIa)

500 Benign nodules

Planned enrollment and analysis



Sample collection

OSUCCC - Total Cancer Care® (TCC) program

Processing & de-identification

Sample analysis



Peripheral blood



Plasma



- LDCT scan images from LCS program
- CT scan images from ILN & LNC programs

Aim 1A: Metabolomics



Plasma (500µL)

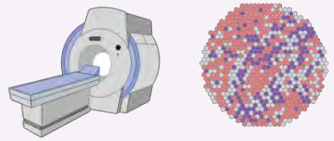
Aim 1B: EV proteomics



Plasma (3mL)

EVs

Aim 2: Radiomics



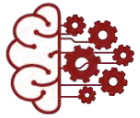
Radiomics features

Aim 3: Multi-omics approach



Multi-omics Data Integration & Analyses

Multi-omics Data Integration & Analyses



Aim 1: Liquid Biopsy

Multi-omics Data Integration & Analyses

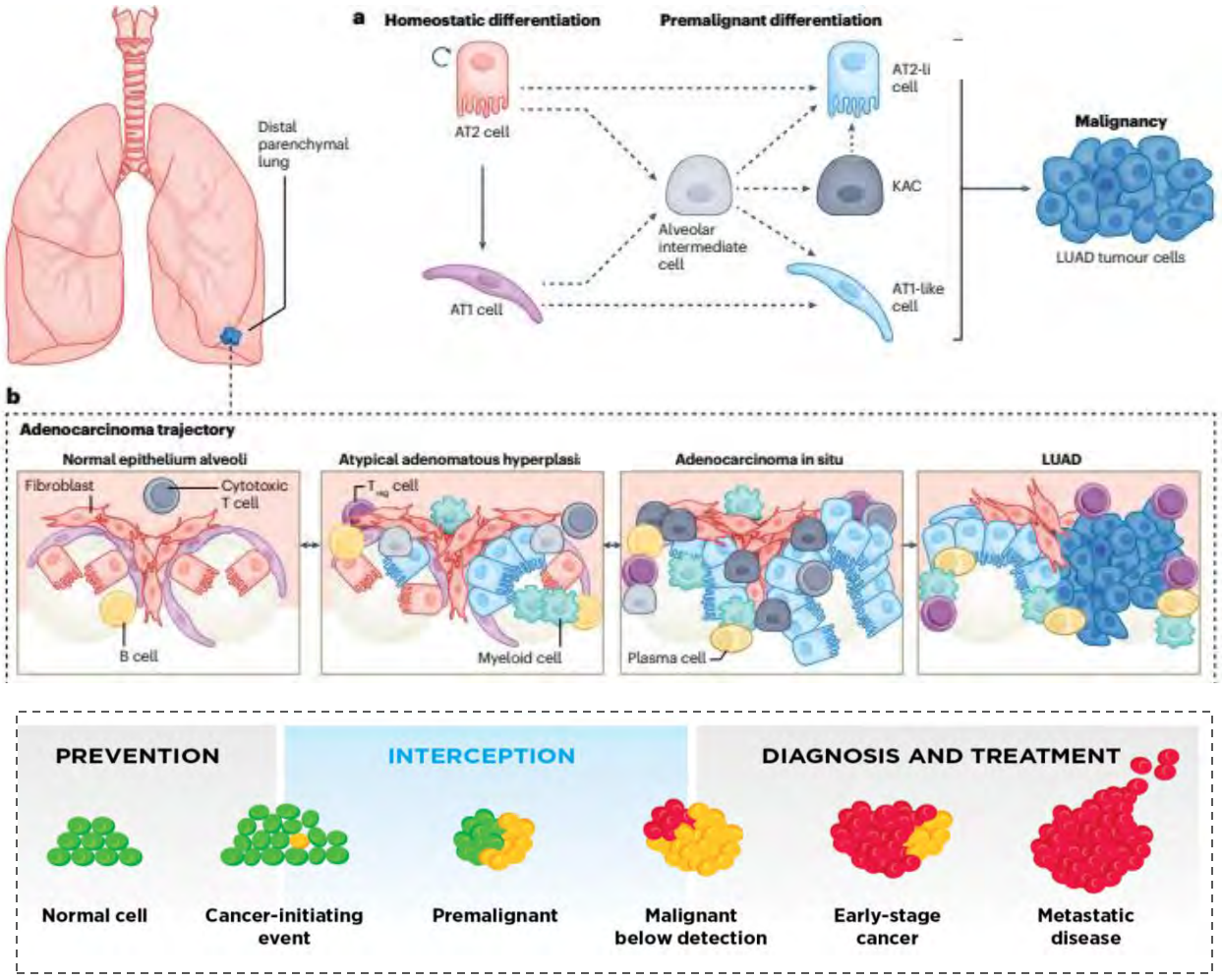


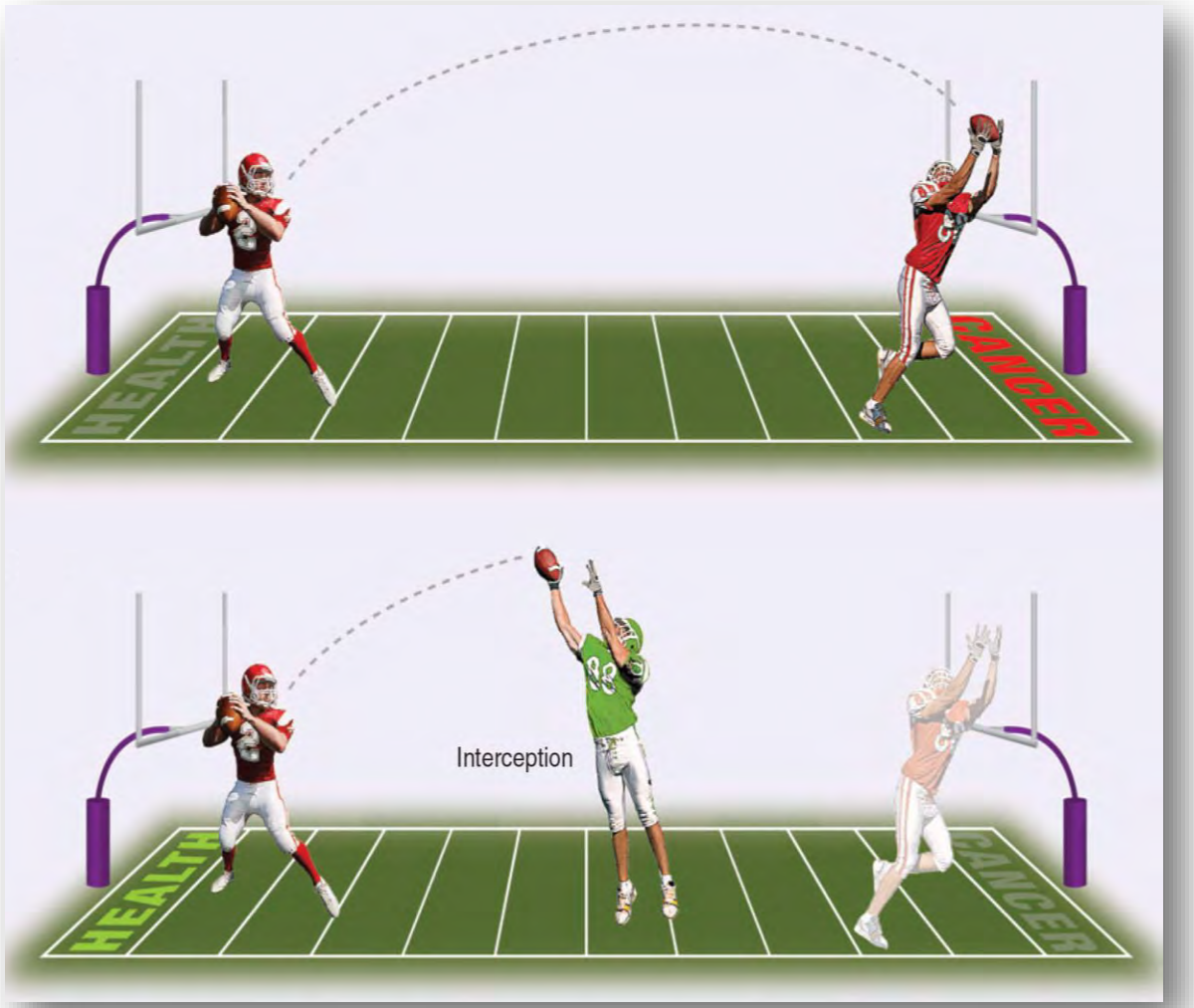
Aim 3: Metabolomics, Proteomics, & Radiomics

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Lung Cancer Interception: a Team Effort





Adapted from: AACR Progress Report 2025 and Sarah A. Mazzilli SA, Nat Rev Cancer. 2025

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Take home messagges

- Early detection is crucial to increase survival rates in cancer
- Liquid Biopsy is an ideal tool to make it possible
- We need methods to complement the screening programs
- But also methods standing by their self
- Multi-cancer detection or single tumor? Not clear yet
- Important to include risk populations in trials
- We are not yet in the best scenario that we could be…
- But we are not far to get it!

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THE OHIO STATE UNIVERSITY
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NATIONAL FOUNDATION FOR CANCER RESEARCH
Research for a Cure

LUNG CANCER RESEARCH FOUNDATION
Living. Breathing. Science.

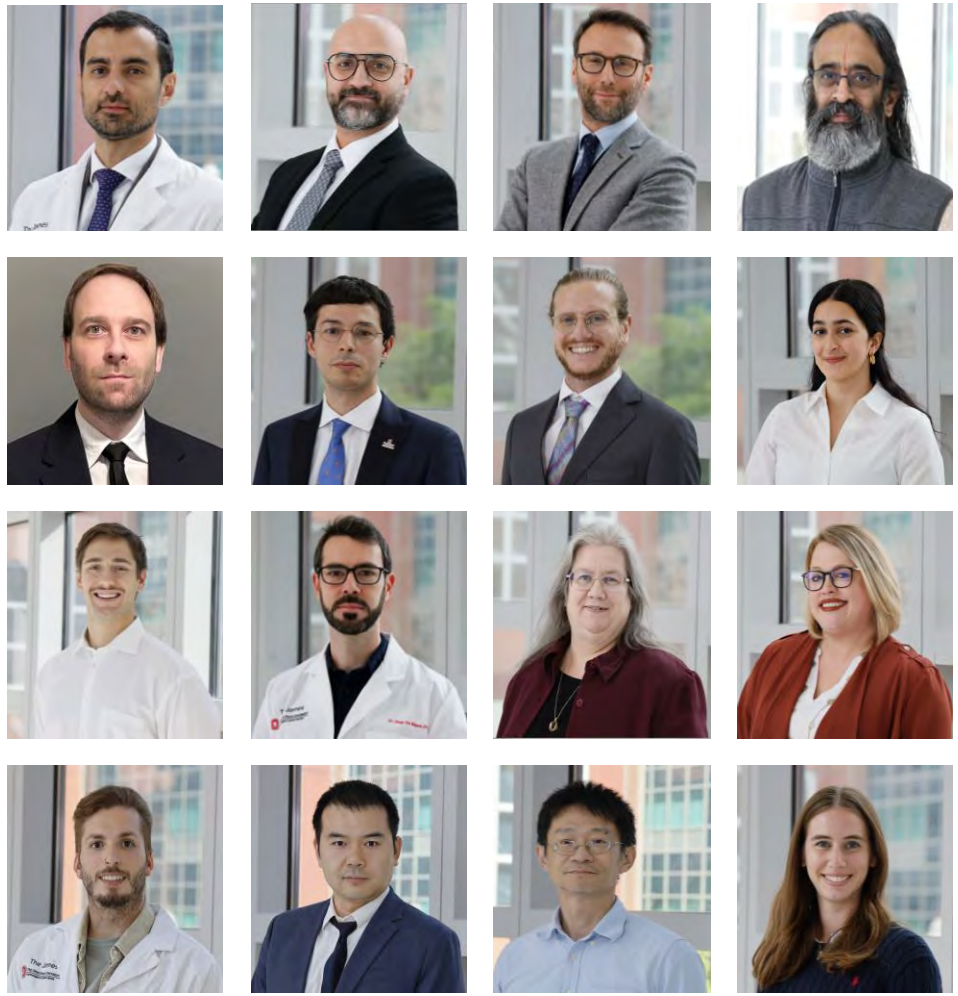
PELOTONIA

American Lung Association.

NIH

Rolfo Lab



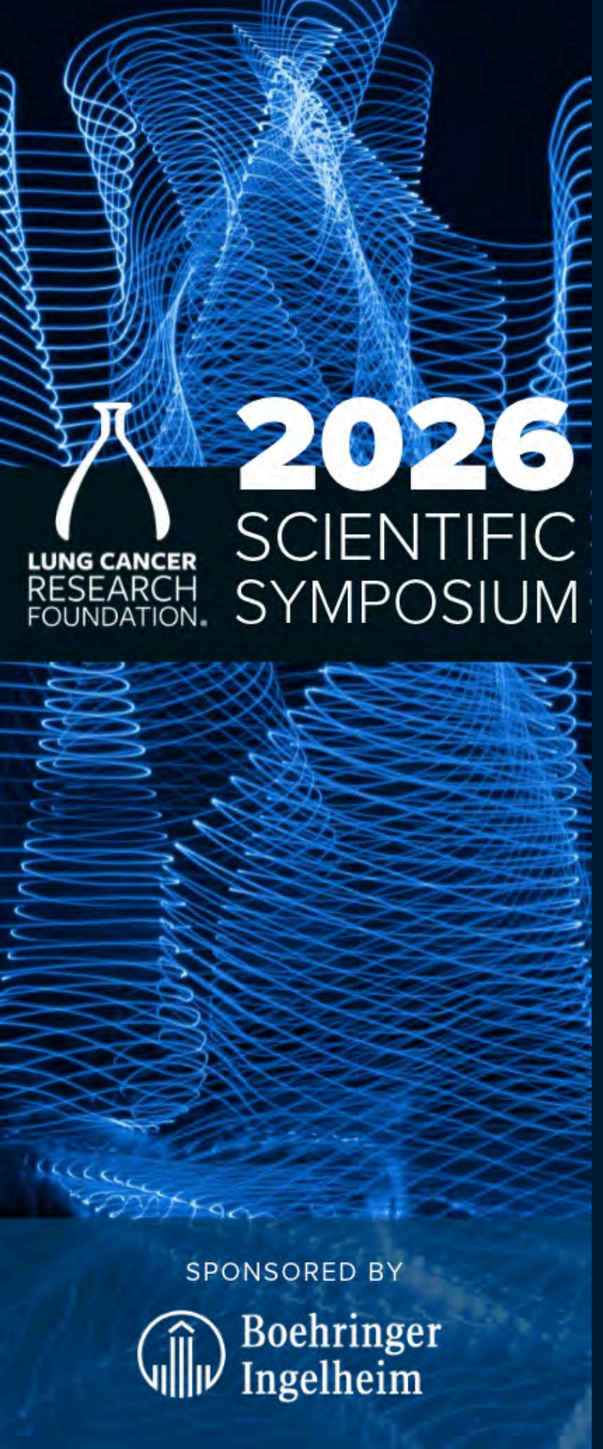


@ChristianRolfo

@RolfoLab

Thank you for your attention

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Overcoming Resistance: Brain Metastasis

Timothy Burns, MD, PHD

Professor of Medicine, Division of Medical Oncology
The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute

Member, LCRF Scientific Advisory Board

Recipient of 2022 LCRF and MET Crusaders Research Grant on MET-Driven Lung Cancer



Overcoming resistance in brain metastases: We need to start looking!

Timothy F. Burns, M.D./Ph.D.
Professor of Medicine
Division of Medical Oncology
Disease Specific Research Group (DSRG) Leader for Thoracic
The James – The Ohio State University Comprehensive Cancer Center
November 5th, 2026

Disclosures in past 24 months

DSMB: Advarra, Inc (Lantern Pharma)

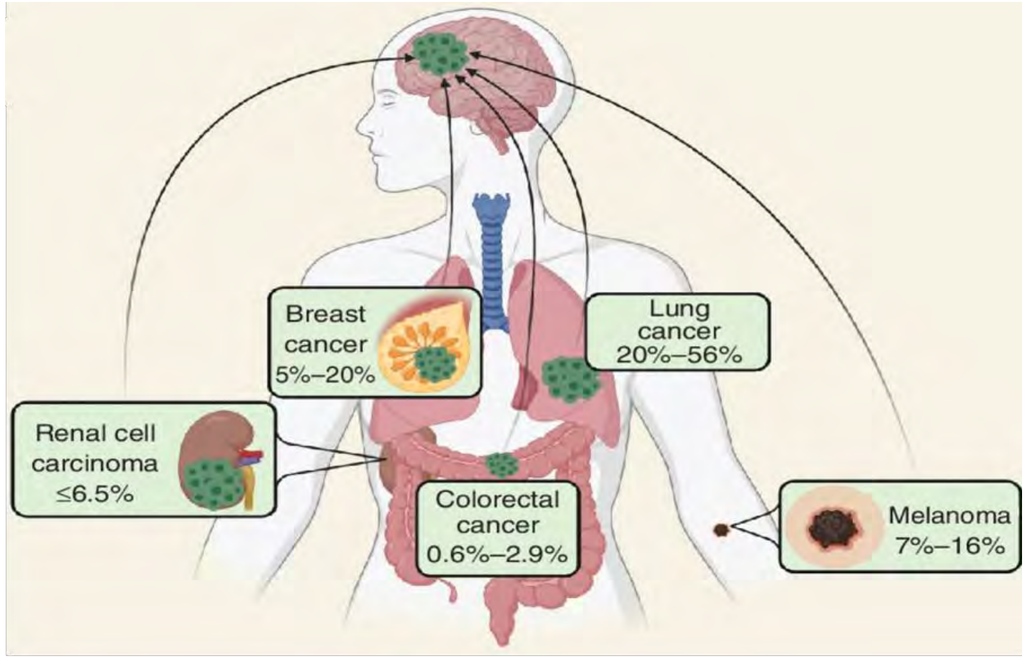
Scientific Advisory Board: (no stock) Janssen Scientific Affairs, LLC, Eli Lilly, Inc., Genentech, Caris Life Sciences, Adcendo Aps, Bristol-Myers Squibb, Erasca and Nuvation Bio

Steering Committees: Eli Lilly, Inc: SUNRAY-01

Consultant: N/A

Off-label use of FDA approved agents as well as agents in currently in clinical trials may be discussed during this presentation.

Brain metastases are a frequent complication of lung cancer



- NSCLC has the highest frequency of brain metastases (BMs).
- ~50% of patients with metastatic NSCLC develop BMs.
- Prognosis has significantly improve for brain metastases patients with targeted oncogenic drivers and/or PD-L1 expression.
- **Median survival is only 3-6 months for oncogene driver brain metastases.**
- The brain is often the site of progression despite systemic disease control.
- After radiation, there are no effective therapies, and no brain-specific targeted therapies exist.
- Current non-invasive strategies to detect resistance mechanisms in BM are limited.

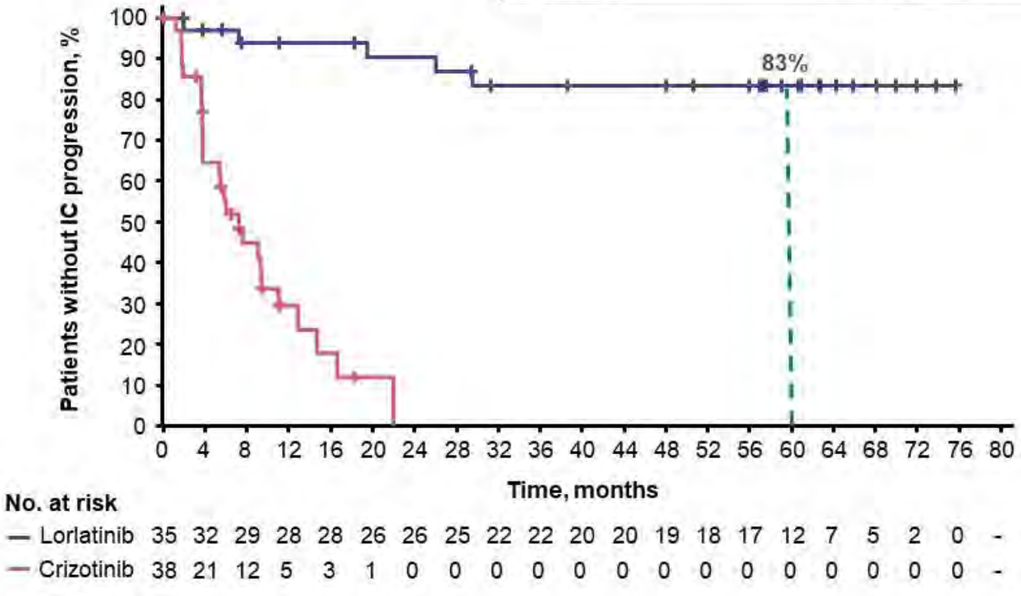
Strickland et al., *Cancer Discov*, 2022

There is an urgent need to identify therapeutic targets in brain metastases to improve outcomes in this challenging patient population

Lorlatinib have significant CNS activity in the first line setting

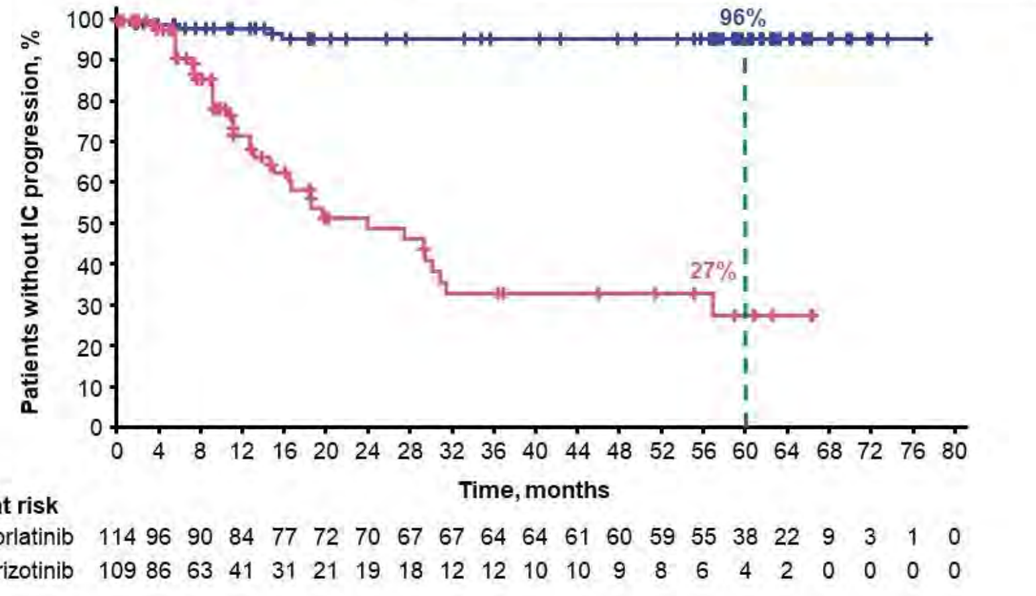
With Baseline Brain Metastases

	Lorlatinib (n=35)	Crizotinib (n=38)
Events, n	5	26
Time to IC progression, median (95% CI), months	NR (NR-NR)	7.2 (3.7-11.0)
HR (95% CI)	**0.03 (0.01-0.13)**	



Without Baseline Brain Metastases

	Lorlatinib (n=114)	Crizotinib (n=109)
Events, n	4	39
Time to IC progression, median (95% CI), months	NR (NR-NR)	23.9 (16.4-30.8)
HR (95% CI)	**0.05 (0.02-0.13)**	

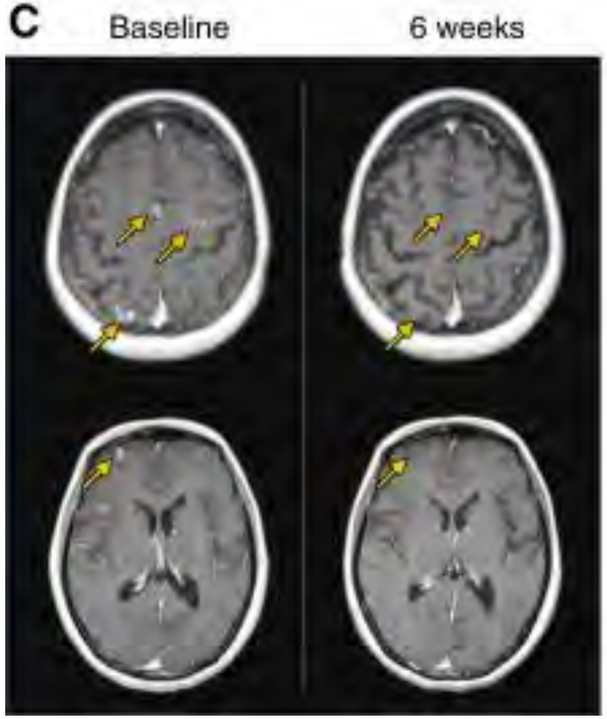


- **5-year PFS rate of 53% vs. 0 % in patients with baseline BM.**
- **Confirmed icORR 92% vs. 33% for patients with measurable baseline brain metastases,**

Mok et al. Annals of Oncology, 2020; Solomon et al. ASCO 2024; Solomon et al. JCO, 2024

What to do at time of progression on lorlatinib? NVL-655 (Neladalkib)

After progression on lorlatinib

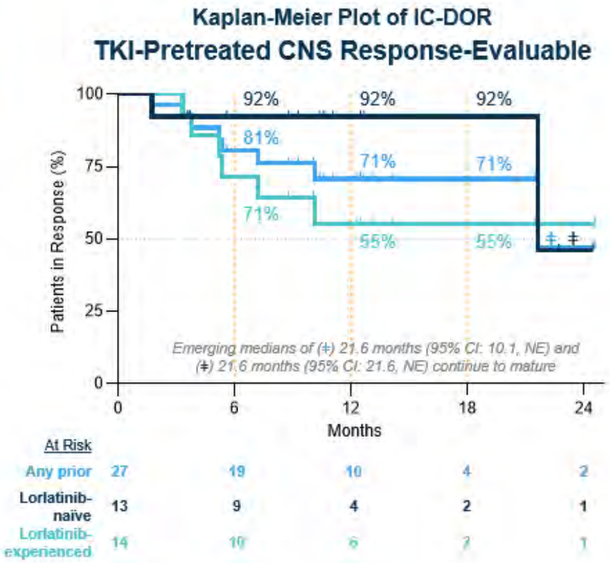


ALKOVE-1: CNS Activity

TKI-Pretreated CNS Response-Evaluable [a] RECIST 1.1, BICR [95% CI]	Any prior ALK TKI ± chemotherapy N = 92	Lorlatinib-naive ± chemotherapy N = 24	Lorlatinib-experienced ± chemotherapy N = 68
IC-ORR, % (n/N)	**32%** (29/92) [b] [22, 42]	**63%** (15/24) [b] [41, 81]	**21%** (14/68) [12, 32]
IC-CR, % (n/N)	13% (12/92) [c]	21% (5/24) [c]	10% (7/68)
IC-DOR ≥ 6 months [d]	**81%** [59, 91]	**92%** [57, 99]	**71%** [41, 88]
IC-DOR ≥ 12 months [d]	**71%** [48, 85]	**92%** [57, 99]	**55%** [26, 77]
IC-DOR ≥ 18 months [d]	**71%** [48, 85]	**92%** [57, 99]	**55%** [26, 77]

[a] Includes patients with measurable (≥5mm) CNS lesions by BICR at baseline and no brain radiation within 2 months before first dose of neladalkib. [b] Includes 2 single-timepoint IC-PR pending confirmation in ongoing patients. [c] Includes 1 single-timepoint IC-CR pending confirmation in ongoing patient with prior confirmed IC-PR. [d] Analyses of DOR based on Kaplan-Meier estimates.

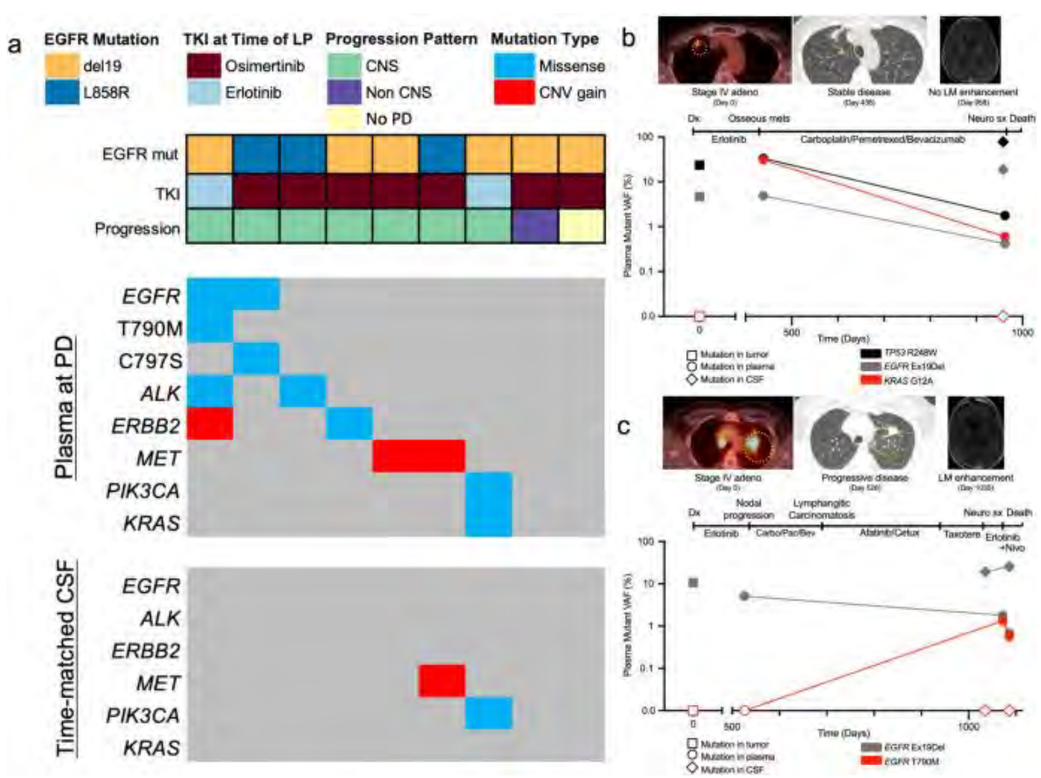
- **CNS response-evaluable after prior alectinib only ± chemotherapy:** IC-ORR = **60%** (9/15; 1 IC-uPR); no intracranial progressors among confirmed intracranial responders.
- **CNS response-evaluable after ≥ 2 prior ALK TKIs ± chemotherapy:** IC-ORR = **25%** (19/75; 1 IC-uPR); IC-DOR at 6 months = **78%** (95% CI: 51, 91) and at 12 and 18 months = **66%** (95% CI: 39, 83).

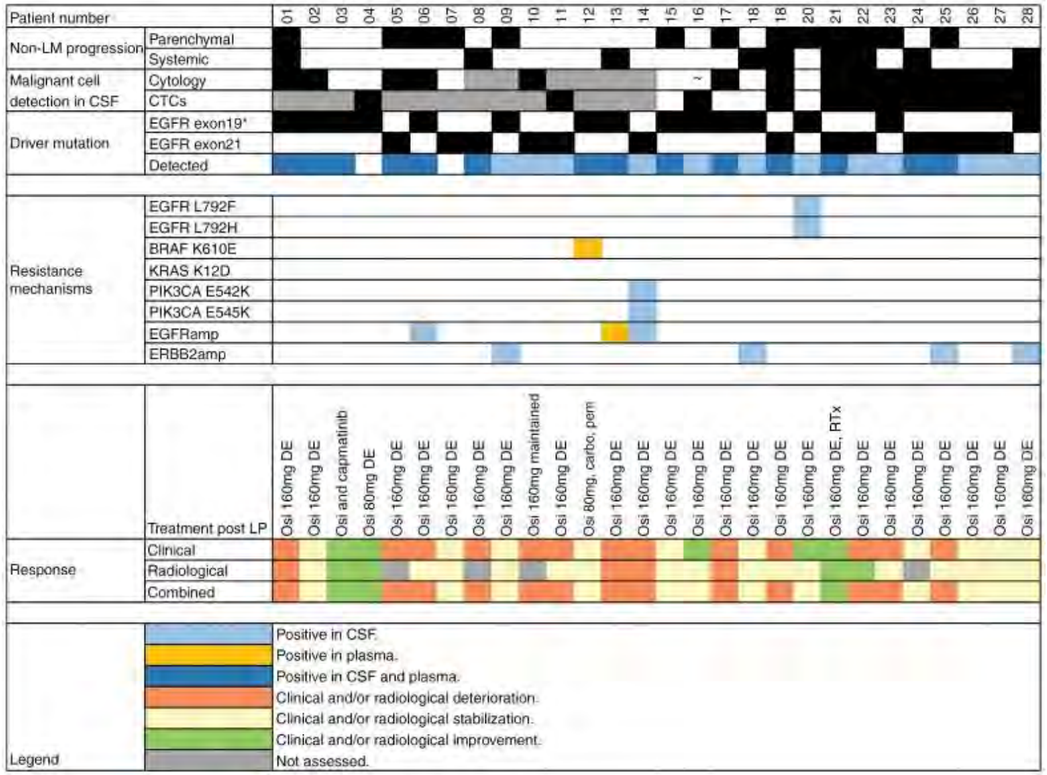


Are we reaching the limits of on-target inhibitors to treat brain metastases?

Drilon et al. ESMO 2024, Lin et al. Cancer Discov. 2024, Lin et al. ASCO 2026

Can we use CSF to find TKI resistance mechanisms?



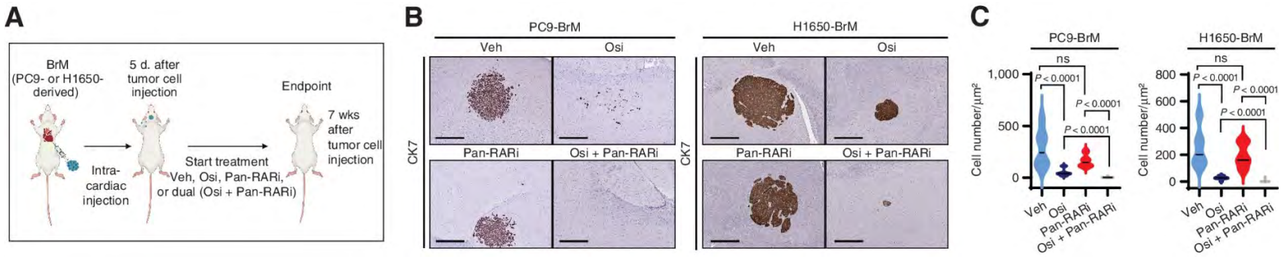


Azad TD et al. NPJ Precis Oncol. 2024.van der Wel JWT, et al. Neuro Oncol. 2024

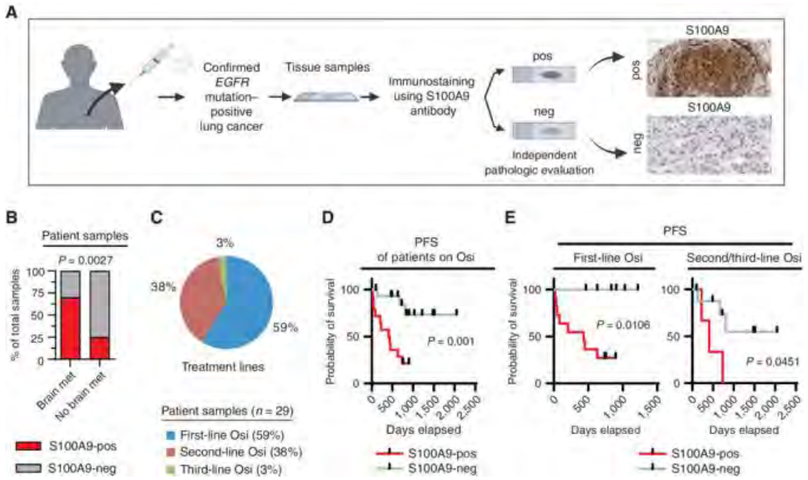
- Shared resistance mechanisms in the CSF can be detected but frequently the observed extracranial resistance mechanisms are absent.
- Is this a limitation of the assay (BM was not sequenced since LMD)?
- Is the performance better in brain metastases patients without LMD or are resistance mechanism unique for brain metastases as well?

Brain metastasis specific resistance mechanisms (Bypass pathways) exist

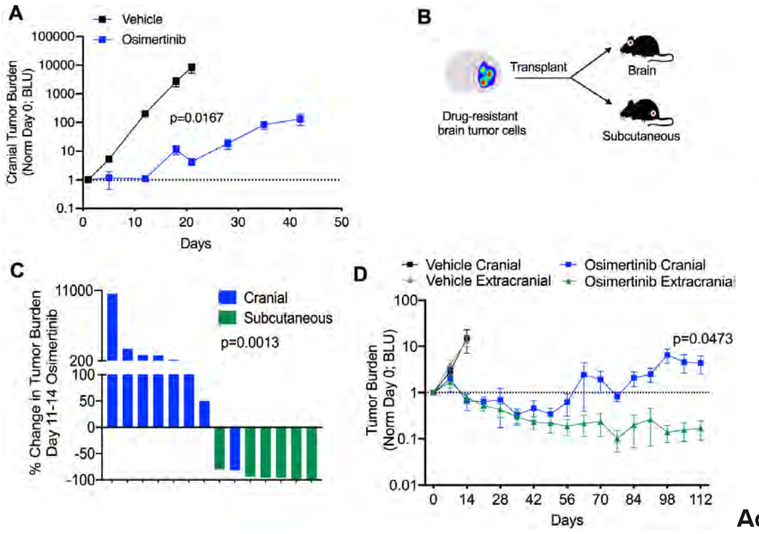
The S100A9–ALDH1A1–Retinoic Acid Signaling causes resistance to Osimertinib in the Brain

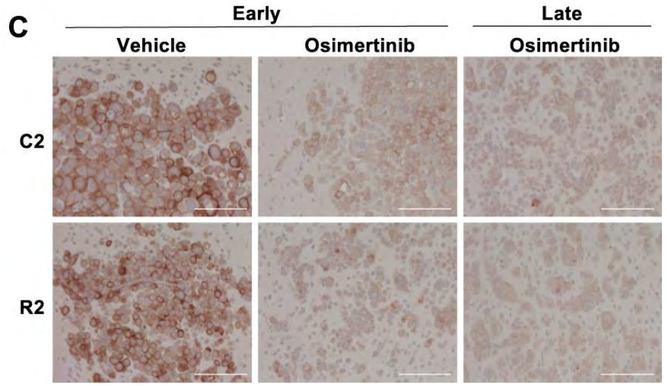


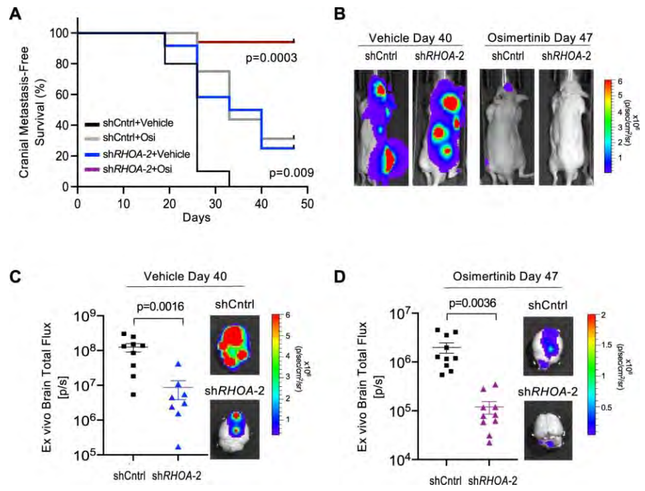
Biswas et al., Cancer Discov. 2022;12(4):1002-1021.



Exposure to the brain TME promotes osimertinib persistence and resistance through RhoA signaling



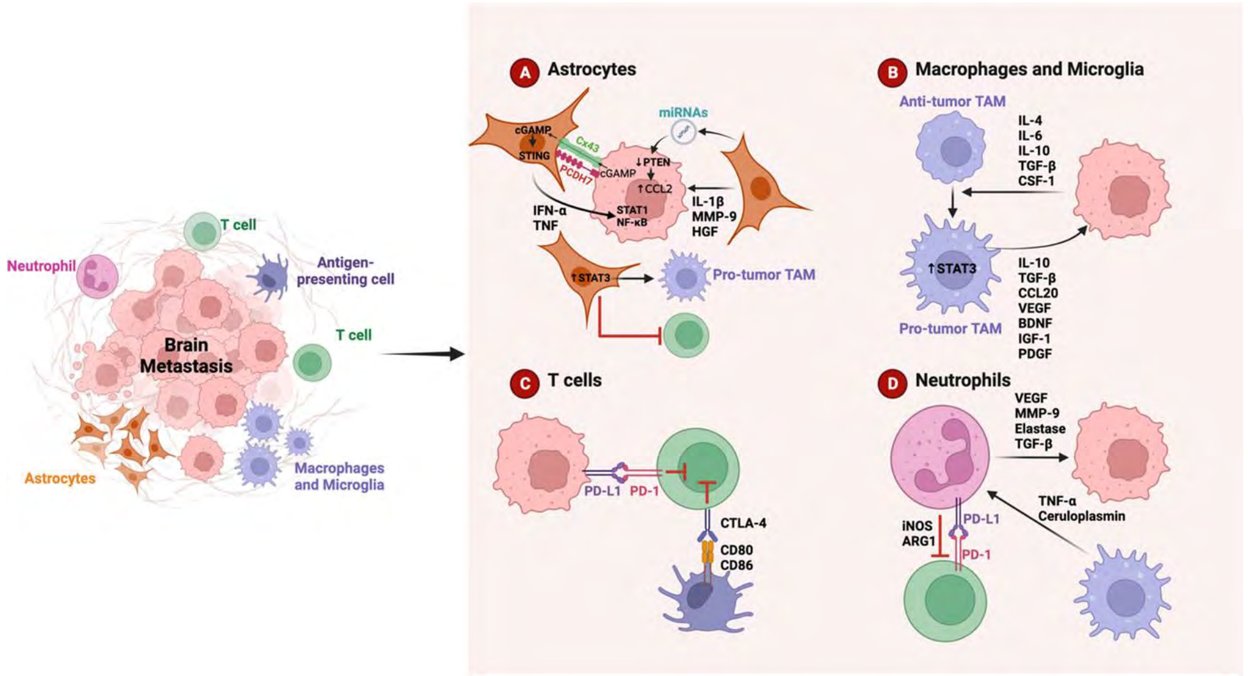




Adua, S.J., et al. Nat Commun 13, 7690 (2022).

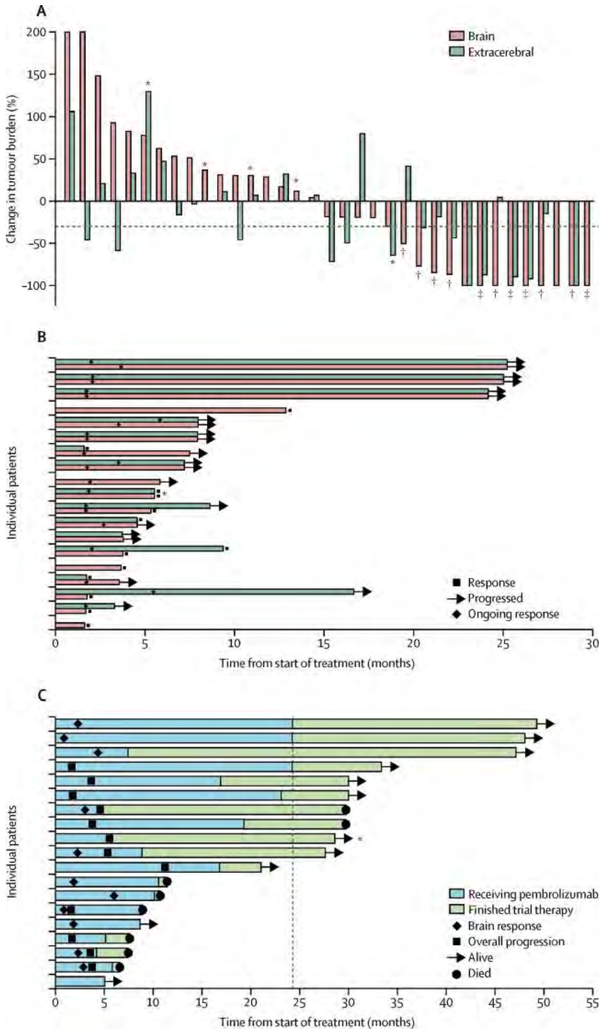
How do we identify brain specific resistance mechanism in patients?

The brain metastasis tumor immune microenvironment plays a key role in brain metastases and resistance



icORR 29·7%
PD-L1 ≥ 1%

mOS 9.8 months
2 year survival rate: 34%
PD-L1 ≥ 1%



Wu, Stabile and Burns. Clin Lung Cancer. 2024 Sep;25(6):483-501.

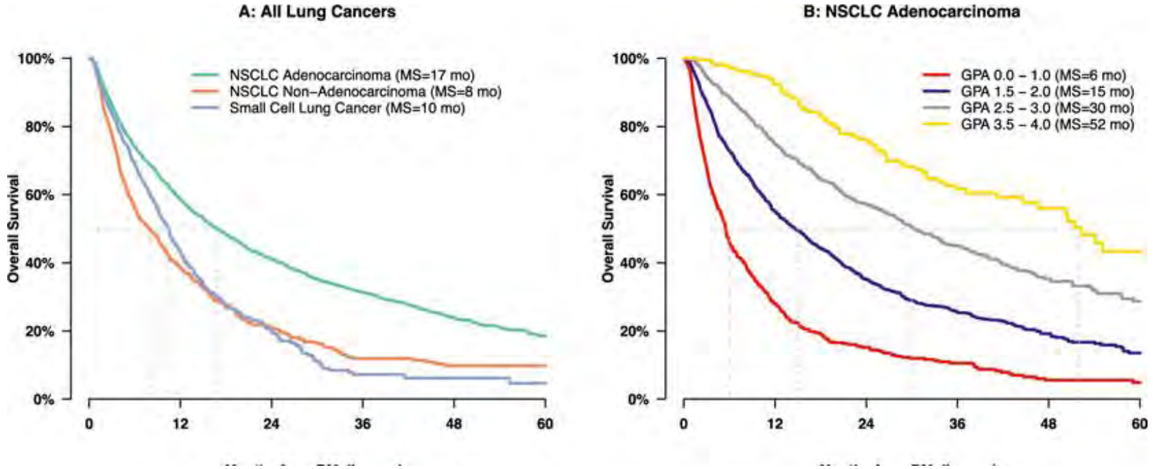
Goldberg et al. Lancet Oncol . 2020 May;21(5):655-663.

So how do we find resistance mechanism in the brain metastases if they are mostly brain specific?

The prognosis of oncogene driver negative NSCLC brain metastases remains poor

2015-2020

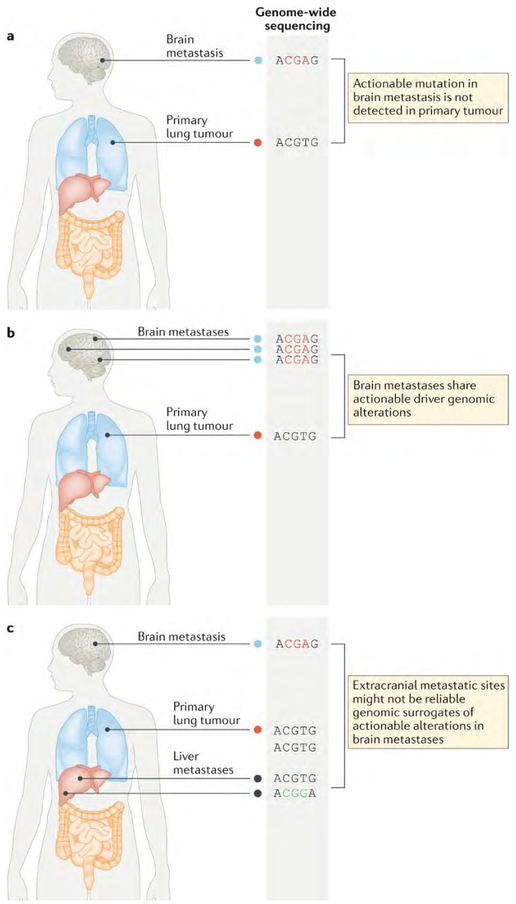
NSCLC adenocarcinoma	Prognostic factor	0	0.5	1.0	1.5	2.0	Patient score	Total score	Median survival (IQR)
	KPS at BM dx	≤70	80	90–100	NA	NA		0.0–1.0	6 (2, 13)
	Age at BM dx	≥70	<70	NA	NA	NA		1.5–2.0	15 (5, 38)
	Number BM	≥5	1–4	NA	NA	NA		2.5–3.0	30 (12, NR)
	ECM at BM dx	Present	NA	Absent	NA	NA		3.5–4.0	52 (25, 69)
	EGFR and ALK	Both negative or unknown	EGFR or ALK NA positive	NA	NA	NA			
	PD-L1	Negative or unknown	Positive	NA	NA	NA			
						Sum =			

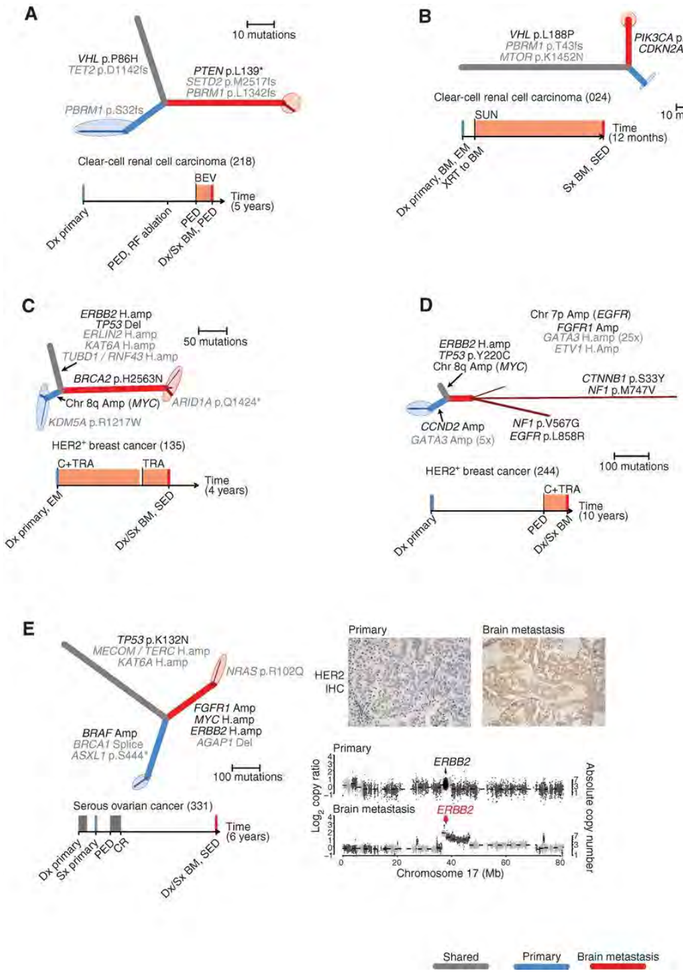


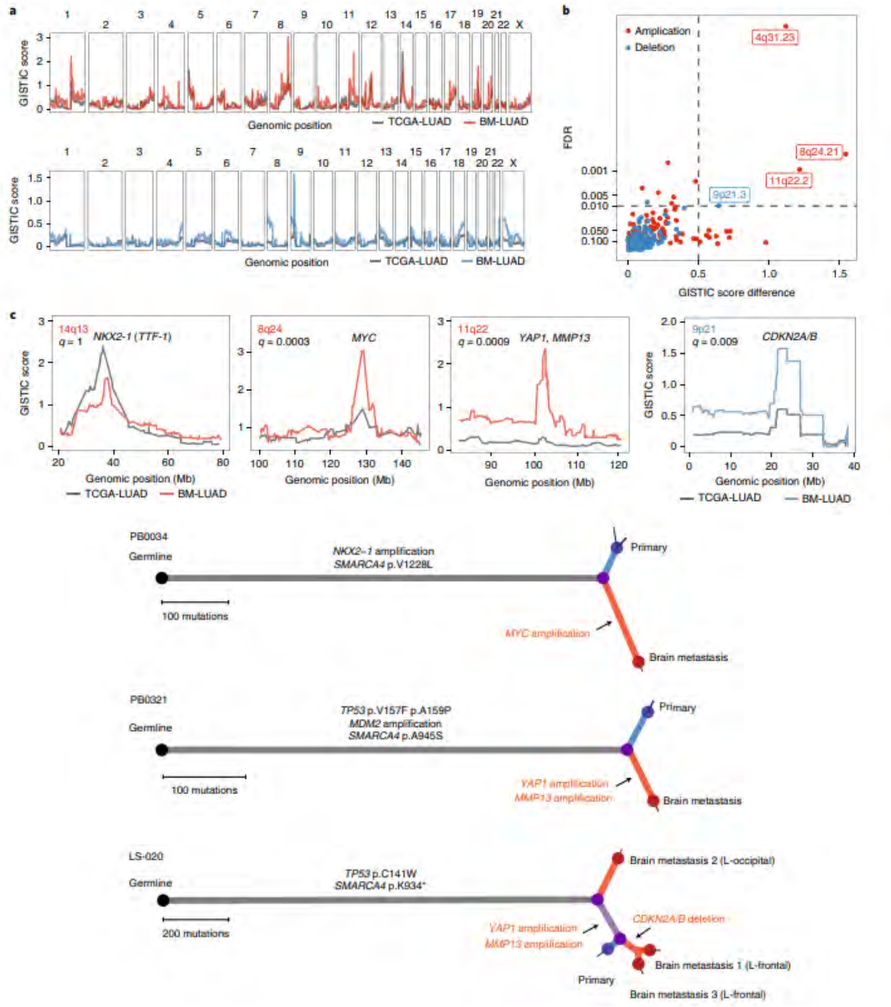
Can we improve outcomes for patients without known oncogenic drivers?

Sperduto et al. JAMA Oncol. 2017;3(6):827-831.Sperduto et al. Int J Radiat Oncol Biol Phys. 2022 Sep 1; 114(1): 60–74.

Targetable Alterations may be Brain Metastasis Specific



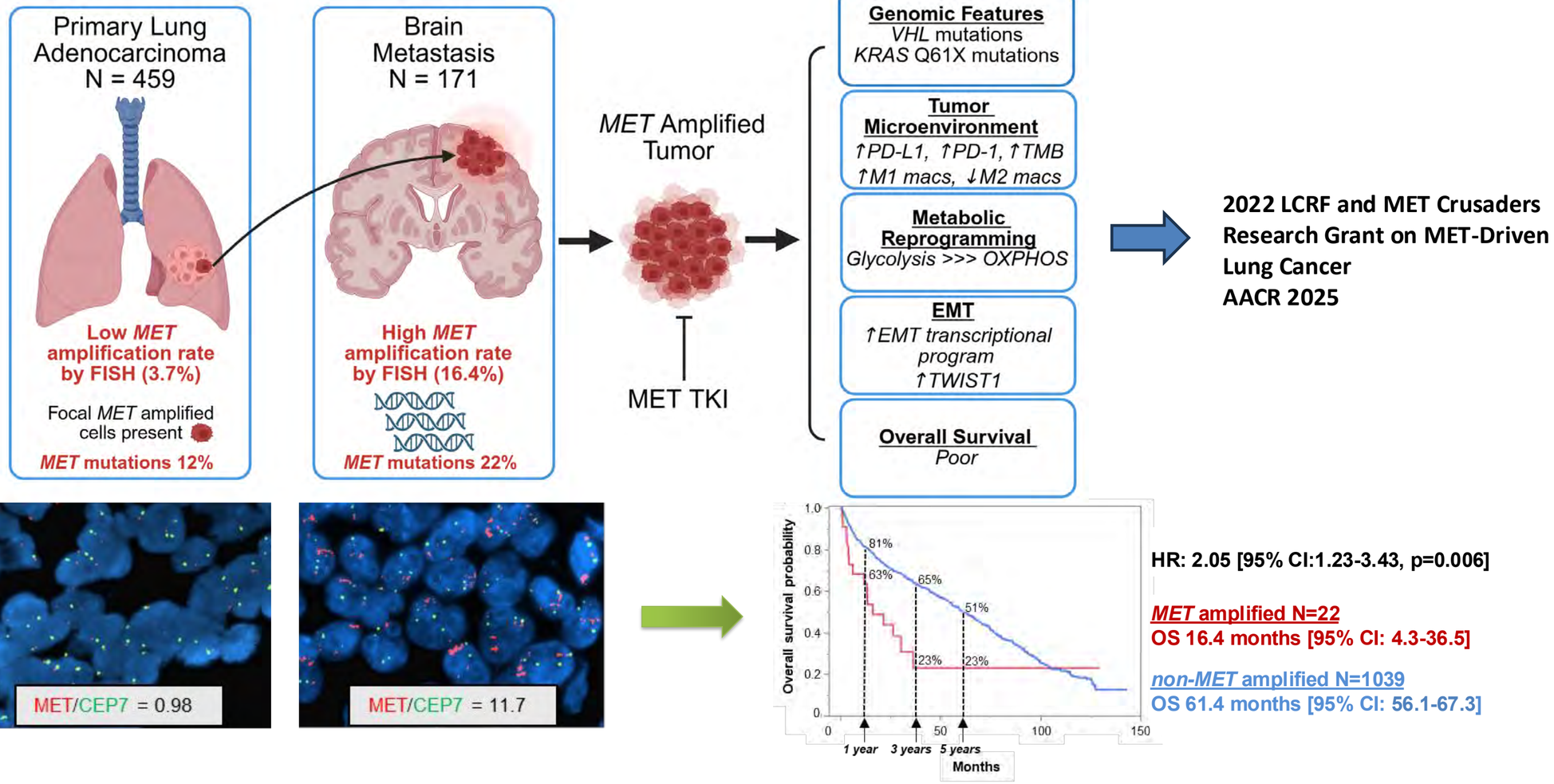




Suh, *et al.* Current approaches to the management of brain metastases. *Nat Rev Clin Oncol* 17, 279–299 (2020); Brastianos et al. Cancer Discov. 2015; Shi et al. Nat Genet. 2020 Apr; 52(4): 371–377.

MET amplification is a common, targetable alteration in lung adenocarcinoma brain metastases

All MET amplifications were identified in EGFR and ALK wild type patients. No patient with a MET amp positive BM had received prior targeted therapy

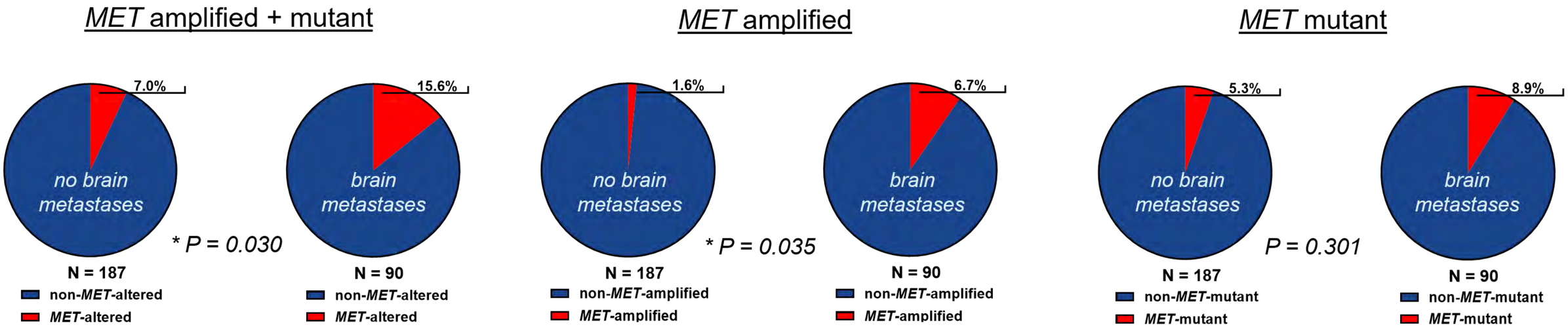


There is an unmet clinical need for non-invasive methods to detect brain-specific MET amplification to identify patients who will benefit from MET TKIs

Burns *et al.* JCI 2026

MET alterations detected in ctDNA are found more often in patients with brain metastases: *retrospective data*

277 patients with metastatic NSCLC → SOC ctDNA testing with Guardant360 CDx platform → Evaluate presence of BMs on brain MRI scans

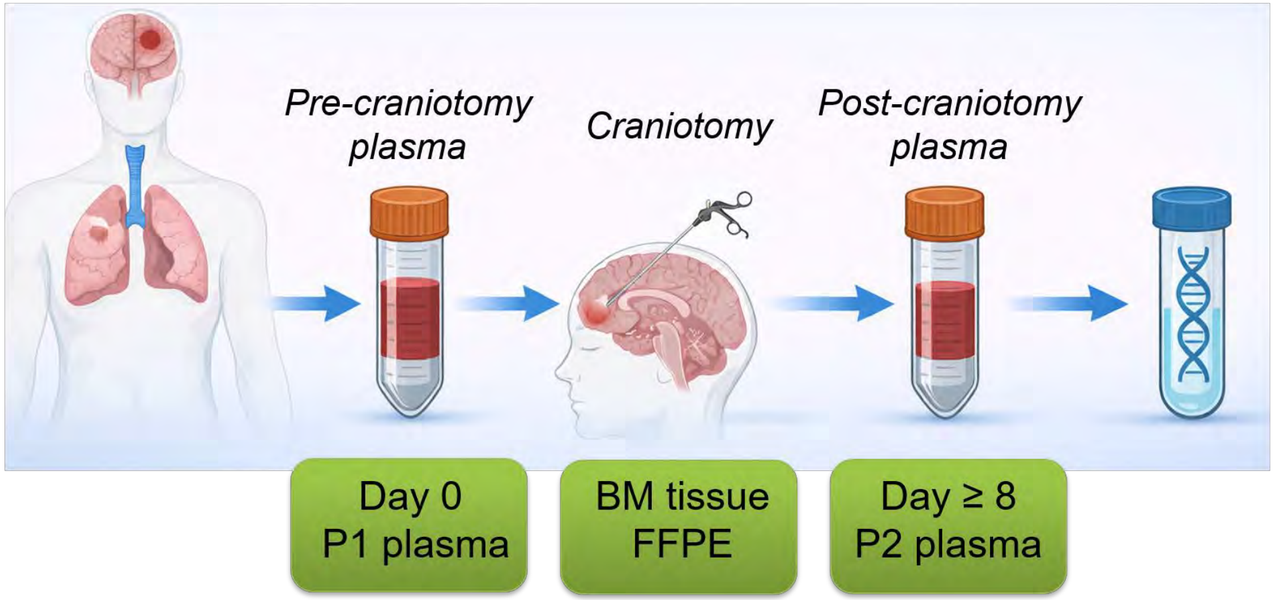


This supports the potential of ctDNA as a non-invasive method for detecting brain metastasis-specific MET amplification

Burns *et al.* JCI 2026

Detection of *MET* alterations in NSCLC patients with brain metastases using PredicineCare™ assay: ***prospective***

Patients with metastatic NSCLC undergoing surgery for symptomatic brain lesions (N = 28)



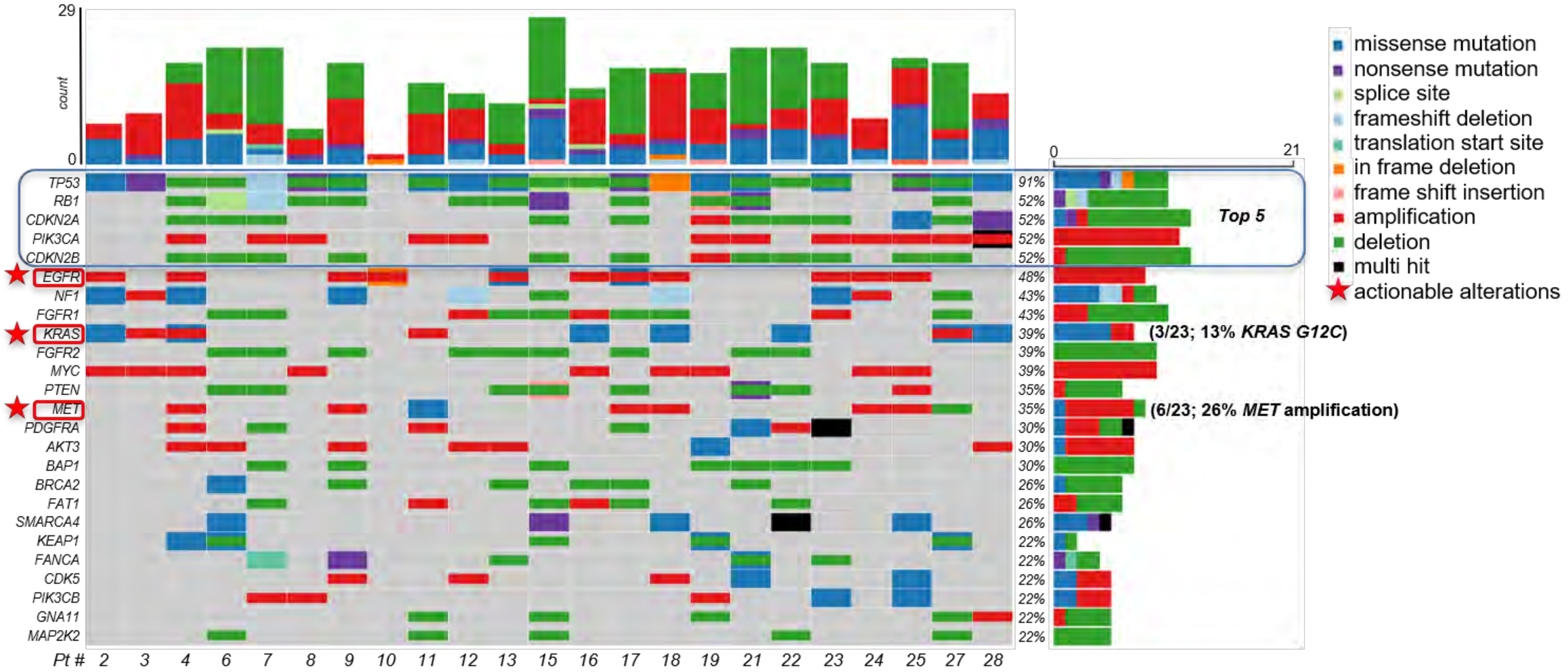
PredicineCare™ 200-gene NGS assay + DeepSea bioinformatics pipeline

Exclusions
insufficient viable tumor
low tumor fraction <0.005
failed QC

Analyzed
13 complete sets (P1, BM, P2)
3 partial sets (BM and P1)
7 BM only (total 23 BM samples)

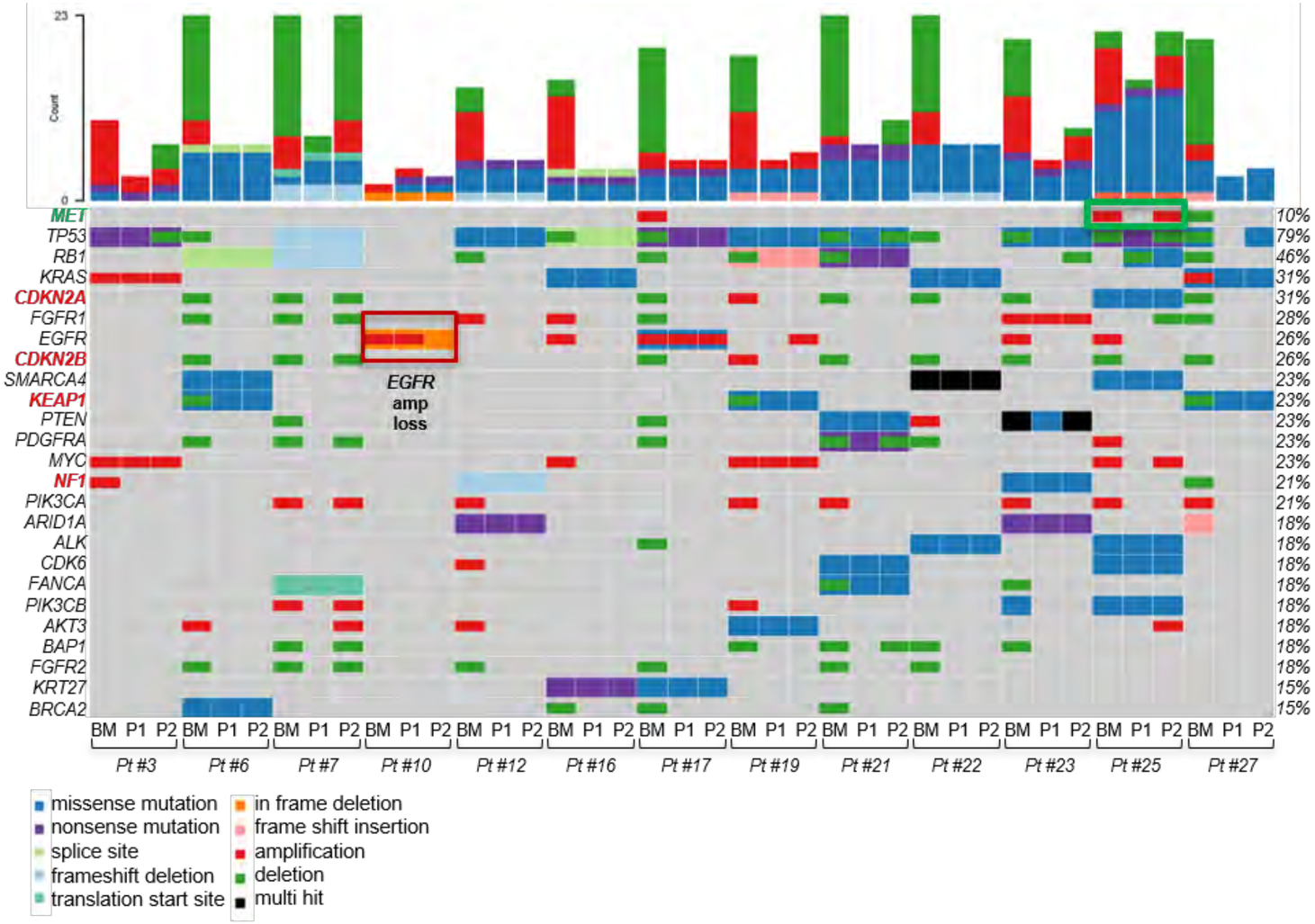
Are alterations detected in ctDNA at baseline absent or reduced in post-craniotomy ctDNA?
Can BM-specific alterations found in the tumor tissue also be detected in ctDNA?

Molecular landscape of lung cancer brain metastases in our cohort



Stabile.....Burns et al. AACR 2026

Detection of BM-specific alterations in plasma is feasible but lacks necessary sensitivity



complete sets N = 13

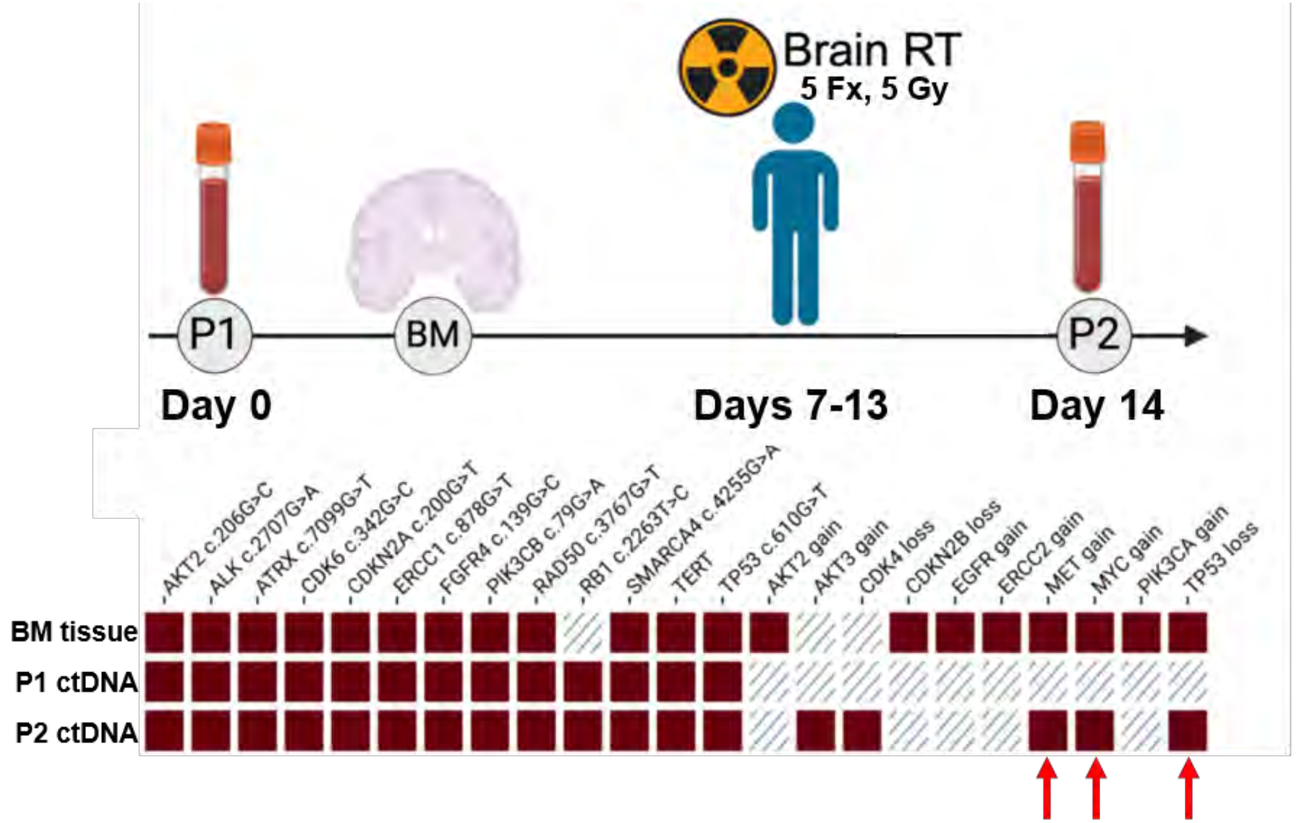
Complete loss of an alteration in P2 plasma that was detected in both P1 plasma and the BM was infrequent (***1/13*** patients; *EGFR* amp).

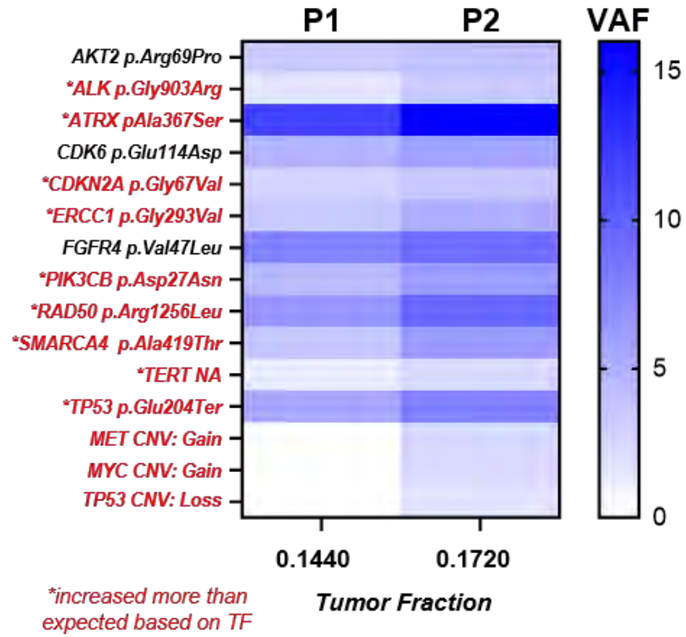
A decrease of > 50% VAF was seen for multiple variants in an additional ***2/13*** patients despite similar % tumor fractions, suggesting that detecting ctDNA shed from BM is possible.

CDKN2A/B, KEAP1, NF1 amplifications or deletions were only detected in the BM and only ***1/2*** ***MET*** amplifications were detected in the plasma in complete sets and ***1/6*** when including all patients (partial BM/P1).

Stabile……Burns et al. AACR 2026

ctDNA variants including MET amplification are found in plasma after brain radiation therapy



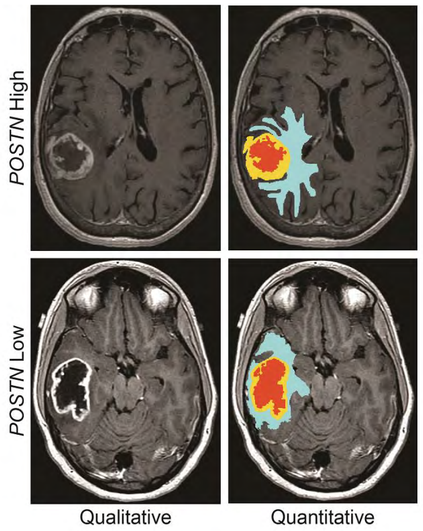


Stabile.....Burns et al. AACR 2026

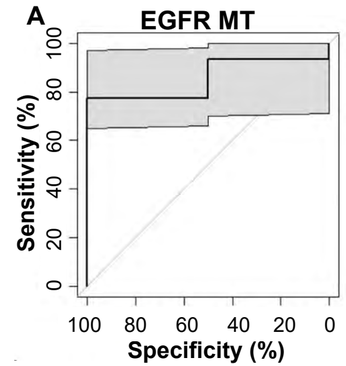
Radiation therapy may enhance tumor DNA shedding

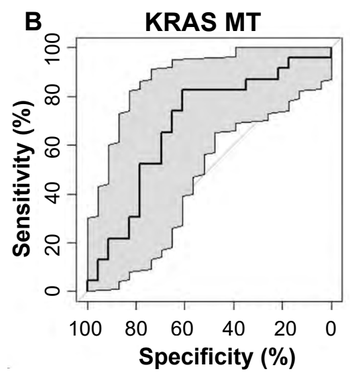
- Can we see demonstrated a consistent increase in shed and detection of BM-specific alterations after post-op radiation?
- What about for intact lesions after SRS?

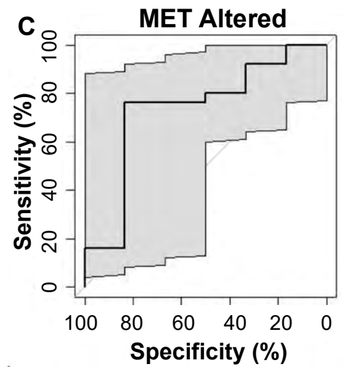
Can we detect oncogenic driver mutations in brain metastases with imaging?



Zinn PO et al. CCR 2018





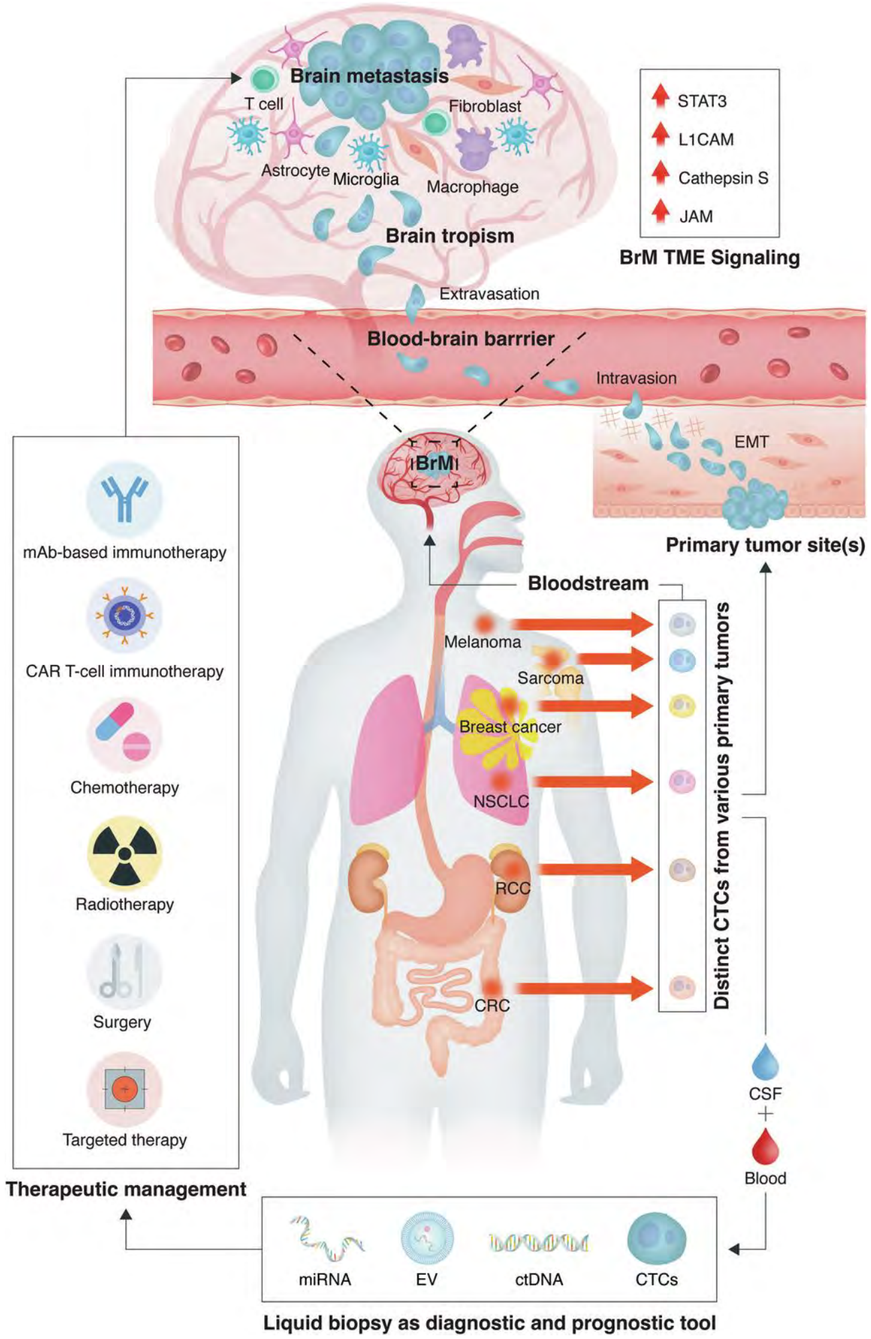


Patient group	Accuracy	Sensitivity	Specificity	AUC	p-value
KRAS MT	0.72	0.83	0.61	0.68	0.0023
EGFR MT	0.78	0.78	1.0	0.85	0.99
MET Altered	0.78	0.76	0.83	0.73	0.76

Rivka Colen, MD

Summary

- Molecular divergence between primary lung tumors and BMs highlights the need for non-invasive detection of BM-specific genomic alterations.
- Testing is required in the acquired resistance setting to targeted therapy and in patients with oncogene driver negative extracranial disease.
- BM-specific alterations can be detected in plasma ctDNA, but *sensitivity remains a major limitation*, especially for copy number alterations.
- Improved detection will require assays with greater sensitivity, and optimized sample collection timing (e.g., post-radiation therapy).
- Ongoing work includes refining sampling windows and assay sensitivity in both plasma and CSF, and integrating with radiogenomic modeling.
- Detection of resistance mechanisms due to the brain metastases TME as well as upregulation of key signaling pathways will require additional innovations in detection strategies (RNAseq, scRNAseq, immunoprofiling, proteomics).



Patel, L. *npj Precis. Onc.* 9, 31 (2025).

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Lung Cancer Research Foundation and MET Crusaders
We Wish Foundation

Brain Metastases are common and targetable in Oncogene Driven NSCLC

Oncogenic driver	Frequency of oncogenic driver alterations in patients with NSCLC, % (n/N)[a]	Reference	Proportion of patients with oncogene-addicted NSCLC who have CNS metastases, % (n/N)[a,b]	Reference
ALK	**2.6–7.2** 7.2 (531/7,395)[c] 6.7 (5/75)[e] 4.8 (388/8,134)[f] 2.6 (8/305)[e]	Si *et al.* 2021 [214] Soda *et al.* 2007 [216] Barlesi *et al.* 2016 [218] Koivunen *et al.* 2008 [219]	**23.8–73** 73 (-)[g] 58.4 (-)[f,g] 39.1 (-)[h] 33.9 (39/115)[i] 25.3 (22/87)[i] 23.8 (5/21)[i,j]	Gainor *et al.* 2017 [215] Rangachari *et al.* 2015 [217] Gainor *et al.* 2017 [215] Patil *et al.* 2018 [220] Digumarthy *et al.* 2020 [221] Rangachari *et al.* 2015 [217]
BRAF	**1.9–4.1** 4.1 (36/883)[k] 4.0 (298/7,395)[l] 3.5 (37/1,046)[k] 1.9 (262/13,906)[k]	Cardarella *et al.* 2013 [222] Si *et al.* 2021 [214] Marchetti *et al.* 2011 [223] Barlesi *et al.* 2016 [218]	**18.8** 18.8 (3/16)[l]	Patil *et al.* 2018 [220]
EGFR	**11.0–51.7** 51.7 (3,821/7,395)[m] 32.3 (-)[m,c] 26.3 (30,466/115,815)[m] 11.0 (1,947/17,706)[m]	Si *et al.* 2021 [214] Zhang *et al.* 2016 [224] Zhang *et al.* 2016 [224] Barlesi *et al.* 2016 [218]	**24.4–52.9** 52.9 (-)[m,n] 47.0 (94/200)[m] 27.6 (53/192)[i] 24.4 (19/78)[i,m]	Rangachari *et al.* 2015 [217] Offin *et al.* 2019 [225] Patil *et al.* 2018 [220] Rangachari *et al.* 2015 [217]
HER2	**0.8–7.0** 7.0 (517/7,395)[o] 1.7 (65/3,800)[o] 0.8 (98/11,723)[o]	Si *et al.* 2021 [214] Mazières *et al.* 2013 [226] Barlesi *et al.* 2016 [218]	**46.9** 46.9 (46/98)[o]	Offin *et al.* 2019 [225]
KRAS[r]	**13.1–28.8** 28.8 (4,894/17,001) 21.4 (1,004/4,686) 13.1 (966/7,395)	Barlesi *et al.* 2016 [218] Araujo *et al.* 2021 [228] Si *et al.* 2021 [214]	**28.4–40.1** 40.1 (150/374) 35.2 (316/899)[s] 33 (-) 32.0 (64/200) 28.4 (29/102)[i]	Sabari *et al.* 2022 [227] Lamberti *et al.* 2023 [229] Cui *et al.* 2020 [230] Offin *et al.* 2019 [225] Patil *et al.* 2018 [220]
KRAS^{G12C}	**7.4–15.4** 15.4 (160/1,039) 13.8 (1,443/10,444) 7.4 (346/4,686)	Sebastian *et al.* 2021 [231] Nassar *et al.* 2021 [233] Araujo *et al.* 2021 [228]	**23.4–41.7** 41.7 (20/48)[t] 40.3 (60/149) 40 (-) 37.2 (146/392)[s] 26.9 (43/160)[u] 23.4 (174/743)[i]	Wu *et al.* 2021 [232] Sabari *et al.* 2022 [227] Cui *et al.* 2020 [230] Lamberti *et al.* 2023 [229] Sebastian *et al.* 2021 [231] Spira *et al.* 2021 [234]
MET	**1.3–5.6** 5.6 (414/7,395)[v] 2.7 (298/11,205)[v] 2.6 (18/687)[v] 1.3 (23/1,770)[v]	Si *et al.* 2021 [214] Schrock *et al.* 2016 [236] Tong *et al.* 2016 [237] Zheng *et al.* 2016 [238]	**16.9–36.1** 36.1 (30/83)[w,x] 16.9 (14/83)[h,w]	Offin *et al.* 2020 [235] Offin *et al.* 2020 [235]
NTRK	**<1.0%** 0.6 (44/7,395)[z] 0.2 (11/4,872)[a2] 0.2 (-)[a2] 0.2 (6/3,658)[a2] 0.1 (4/4,073)[a2]	Si *et al.* 2021 [214] Farago *et al.* 2018 [239] Forsythe *et al.* 2020 [240] Rosen *et al.* 2020 [241] Gatalica *et al.* 2019 [242]	**36.4 (low n)** 36.4 (4/11)[a2]	Farago *et al.* 2018 [239]
RET	**1.4** 1.4 (13/936)[a2] 1.4 (25/1,746)[c2] 1.4 (103/7,395)[c2]	Wang *et al.* 2012 [243] Wu *et al.* 2023 [245] Si *et al.* 2021 [214]	**24.8–46.5** 46.5 (33/71)[c2,d2] 31.8 (7/22)[i] 24.8 (33/133)[i,c2]	Drilon *et al.* 2018 [244] Digumarthy *et al.* 2020 [221] Drilon *et al.* 2018 [244]
ROS1	**0.7–5.9** 0.7–5.9[e2,f2] 0.9 (67/7,395)[e2]	Gainor *et al.* 2013 [246] Si *et al.* 2021 [214]	**10.2–36.4** 36.4 (12/33)[i] 34 (-)[g] 19.4 (-)[h] 10.2 (5/49)[i]	Patil *et al.* 2018 [220] Gainor *et al.* 2017 [215] Gainor *et al.* 2017 [215] Digumarthy *et al.* 2020 [221]

- **Frequency of brain metastases varies across molecular subtype from 20%->60% in some studies.**
- **Intracranial Response Rate varies by molecular subtype and drug.**

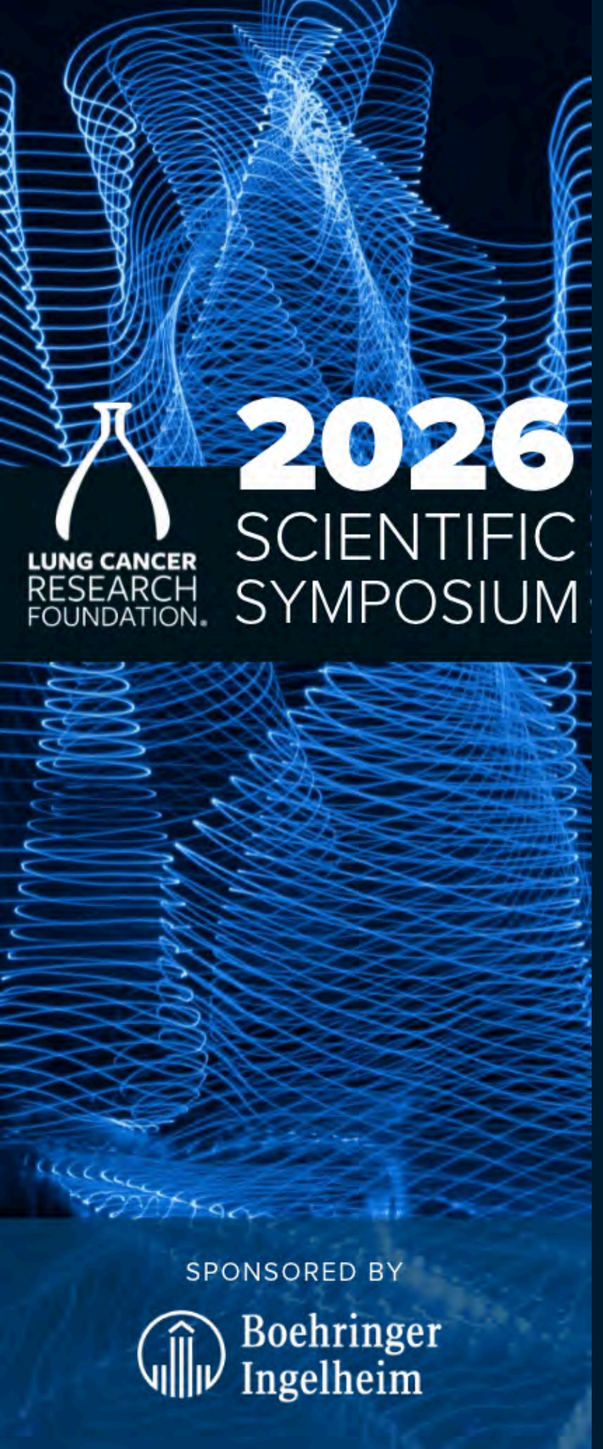
Table 2. Intracranial response rates of precision agents in NSCLC brain metastases.

Oncogenic Driver	Brain Metastasis Rates	Precision Agent	Intracranial Response Rates
EGFR	20–30% [45–48]	Osimertinib	66% [60]
RET	* 50% [54]	Selpercatinib (LOXO-292)	85% [61]
ALK	23–34% [49–52,57,62]	Brigatinib Alectinib Lorlatinib	78% [63] 81% [64,65] 82% [66]
ROS1	19% [53]	Lorlatinib, Entrectinib Repotrectinib	64% [67] 79% [68] 100% [69]
KRAS	29% [55]	Sotorasib Adagrasib	88% [70] 42% [71]
MET	11–23% [58]	Capmatinib Tepotinib	50% [72] 71% [73]
HER2	47% [59]	Poziotinib	89% [74]

* lifetime prevalence. *anaplastic lymphoma kinase (ALK), epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), Kristen rat sarcoma viral oncogene homolog (KRAS), mesenchymal–epithelial transition factor (MET), rearranged during transfection (RET), c-ros oncogene 1 (ROS1).*

Weller et al. Cancer Treatment Reviews, Volume 130,2024,102807; Boldig et al. Int. J. Mol. Sci. 2024, 25, 6961.


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