What's on the Horizon:

Clinical Trials in EGFR+ NSCLC

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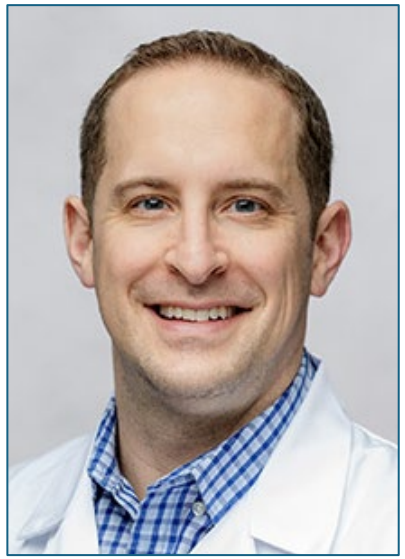
Session Speakers



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Session Objectives

1. Explain how clinical trials work, how to find them, and what factors determine whether a trial may be an option.

2. Share information about ongoing clinical trials, and upcoming *EGFR*-positive clinical trials that have the potential to influence future treatment options.

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Using 1 word, what has this Summit meant to you?

Tell us here!

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Please Send in Your Questions!

This QR code will be live throughout the session

Download the Slides Here

For Easier Viewing in PDF on Your Device

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Our plan for the next 70 minutes

The goal: leave informed, not buried under alphabet soup.

1. **Where we are now**
   Why EGFR+ lung cancer care is changing so quickly
2. **What is coming**
   The big categories: ADCs, bispecifics, 4th-gen TKIs, exon 20, resistance pathways
3. **What may change care soon**
   Late-phase trials patients may hear about next year
4. **Clinical trials 101**
   How to ask, enroll, and protect your own goals

Speaker promise: fewer acronyms, more ‘what does this mean for me?’

The one-slide big picture

Clinical trials are the reason EGFR lung cancer care has changed this much — and why there is **real hope.**

Clinical trials are not "extra."

They are how tomorrow's standard treatment **becomes real.**

Access

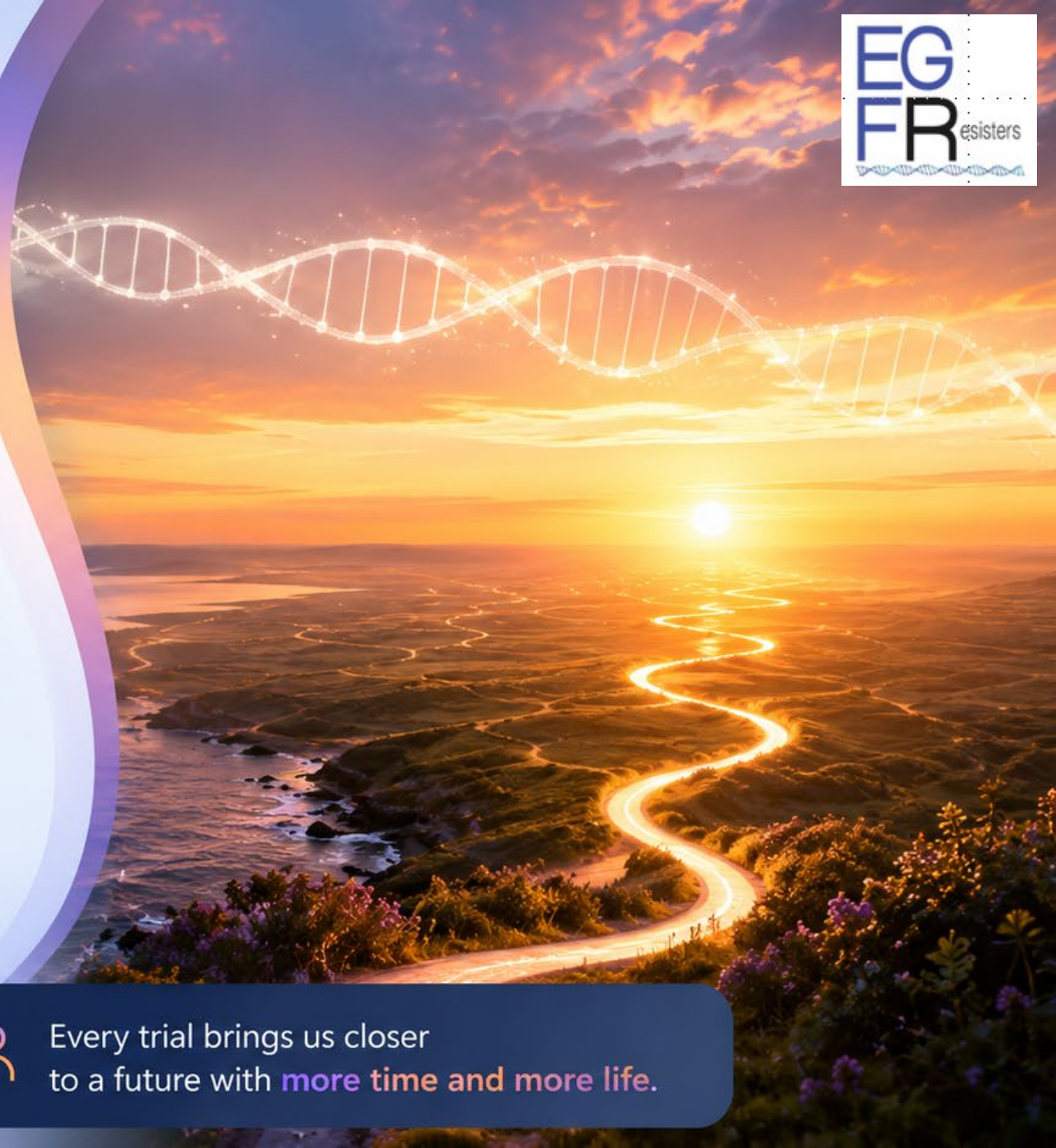
Often the **best way** to access a promising approach

Safety & Learning

The **safest way** to learn what works and what does not

Impact

A way patients **help the next patient** — and sometimes themselves



Hope is not passive.

*It's powered by research. It's built by **you**.*

Every trial brings us closer to a future with **more time and more life.**

General Overview of Clinical Trials

Principles and Definitions

Tools for management of lung cancer

Over the last decade, management of lung cancer, has been revolutionized.

But, how do we test the safety and efficacy of novel treatments?

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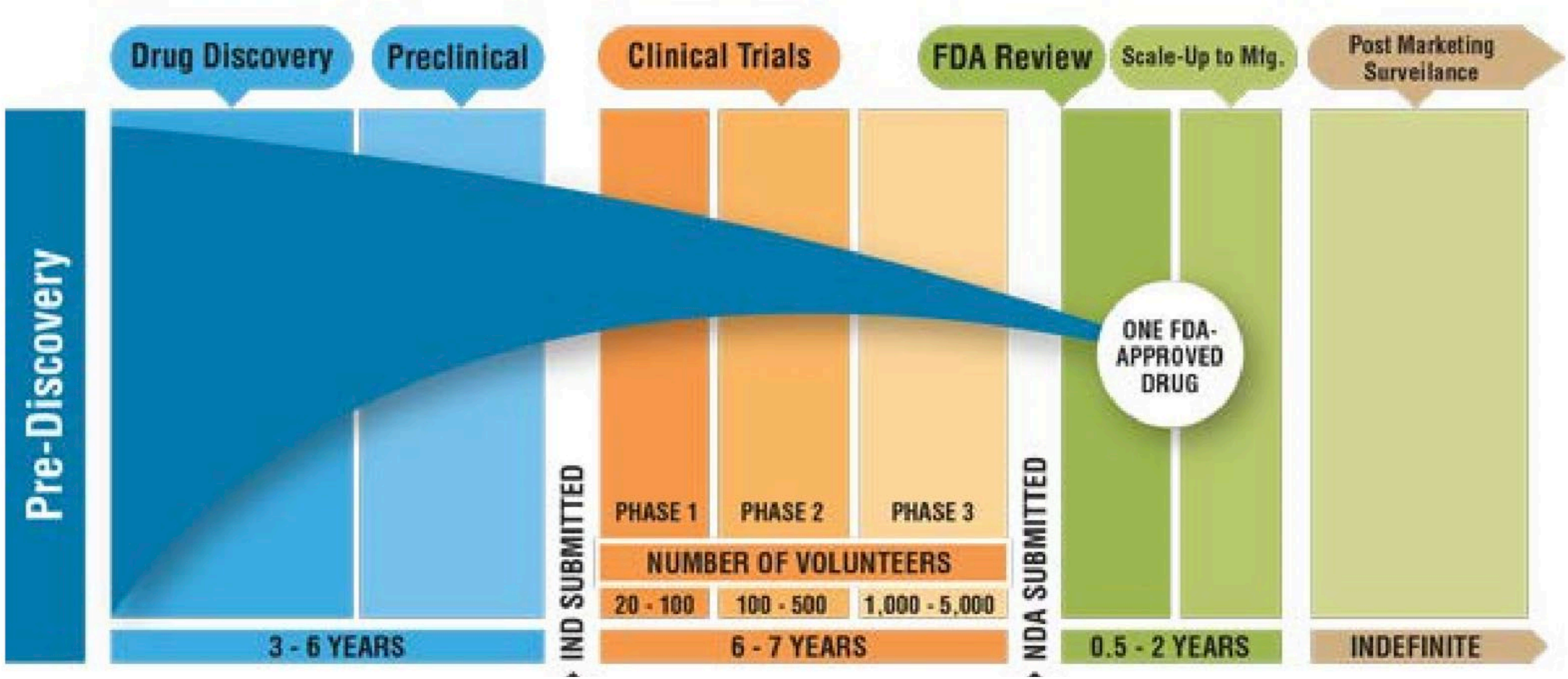

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What is a clinical trial?

- **A clinical trial is a carefully designed study that tests new cancer treatments in people to make sure they are safe, effective, and better than what we already use**
- **Bridge between laboratory discoveries and real treatments that improve patients' lives**

  → Scientific rationale

  → Participation is completely voluntary and withdrawal can occur at any time

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Phase 1 clinical trials: *is the treatment safe?*

- A phase 1 clinical trial is done with a small group of people (usually less than 100)
- The focus is to find the "right" dose and make sure it is safe, as the doctors carefully watch for side effects.

- **Example: phase 1 AURA trial results were so compelling that it directly led to the phase 3 FLAURA trial with osimertinib vs. earlier generation TKIs.**

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Ramalingam, JCO, 2018

Phase 2 clinical trials: *does the treatment work?*

- Compare new medication to a “control”
- Can answer questions such as:

  - **Does the cancer shrink/disappear?**
  - **There’s a longer period of time where the cancer doesn’t get any bigger.**
  - **There’s a longer time before the cancer comes back.**
  - **People who get the new treatment live longer and have better quality of life.**

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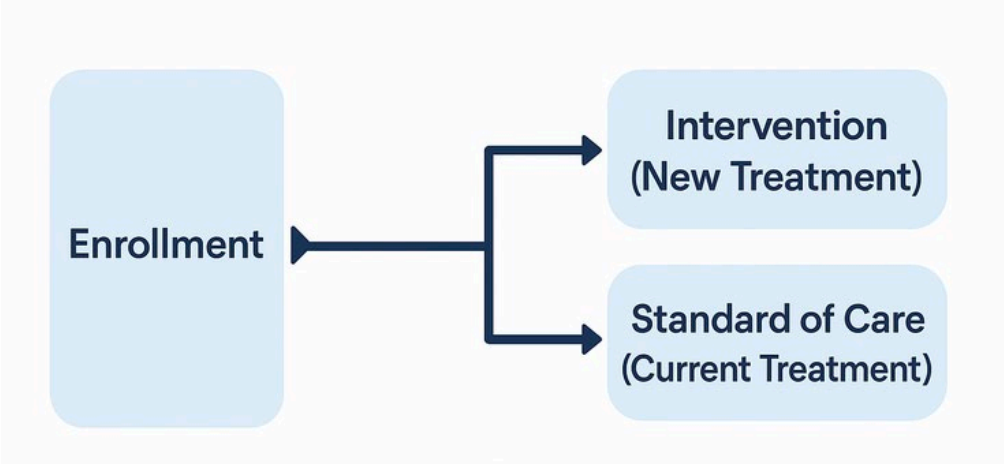
Phase 3 Clinical Trials: *is the new treatment better than the standard of care?*

- → Compare the safety and effectiveness of new treatment to standard of care
- → Often randomized
- → *Blinded*
- → Several hundreds-thousands of patients across many different locations



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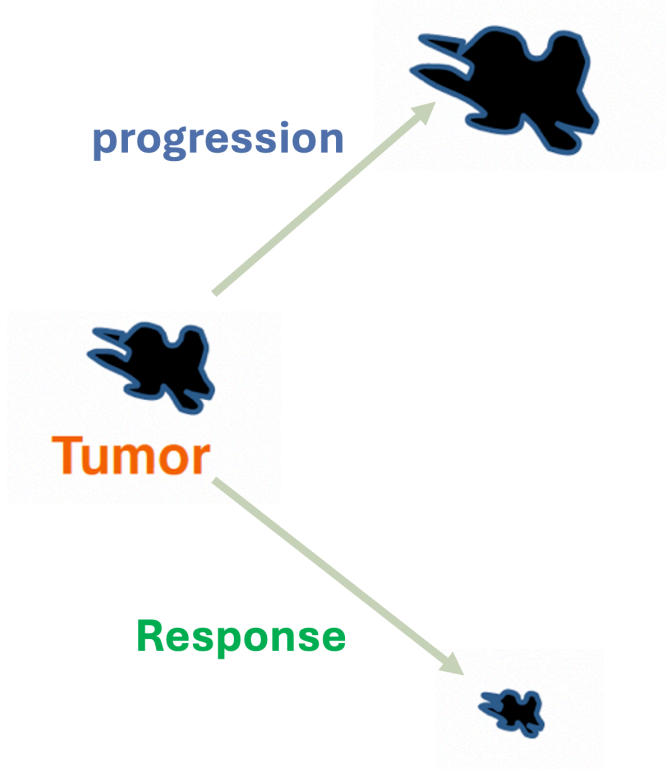
Endpoint	What It Means	Why It Matters
Objective Response Rate (ORR)	The percentage of patients whose tumors shrink or disappear after treatment.	Shows how well a treatment can make the cancer smaller or go away.
Progression-Free Survival (PFS)	The amount of time a person lives without the cancer growing or spreading.	Measures how long treatment can keep the cancer under control.
Overall Survival (OS)	The total length of time a person stays alive after starting treatment.	The most important measure of how much a treatment can help people live longer.
Disease-Free Survival (DFS)	The length of time after treatment (like surgery) that a person has no signs of cancer.	Shows how well treatment can prevent the cancer from coming back.



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Quick Word on Inclusion and Exclusion Criteria

- *Rules* in place by investigator that decide who can or cannot join the clinical trial to make sure study is safe, fair, and focused on the right population.
- Inclusion criteria (who is allowed): type and stage of the cancer, age and performance status, specific labs
- Exclusion criteria (who is not allowed): other medical issues, prior treatments, certain medication use/allergies

Safety, fairness and scientific accuracy

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What questions should I ask my team after diagnosis of lung cancer?

- **What kind of cancer?**
- **What is the stage of the cancer?**
- **What are the "biomarkers" of the cancer?**
- **What are treatment options and goals of treatment?**

- **Am I a candidate for clinical trials?**

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Considerations for participation in clinical trials

- Is there randomization?
- Risks vs benefits?
- How is the withdrawal process?
- How is my safety ensured?
- How is my data protected?

Shared decision making; involve family and friends-

Can withdraw from participation anytime

Gather information, ask questions, study the consent form (translations available)

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Shared-decision making

- If interested or have questions, the research/care team will assess your candidacy for a clinical trial
- Another way to gain information on any open clinical trial:

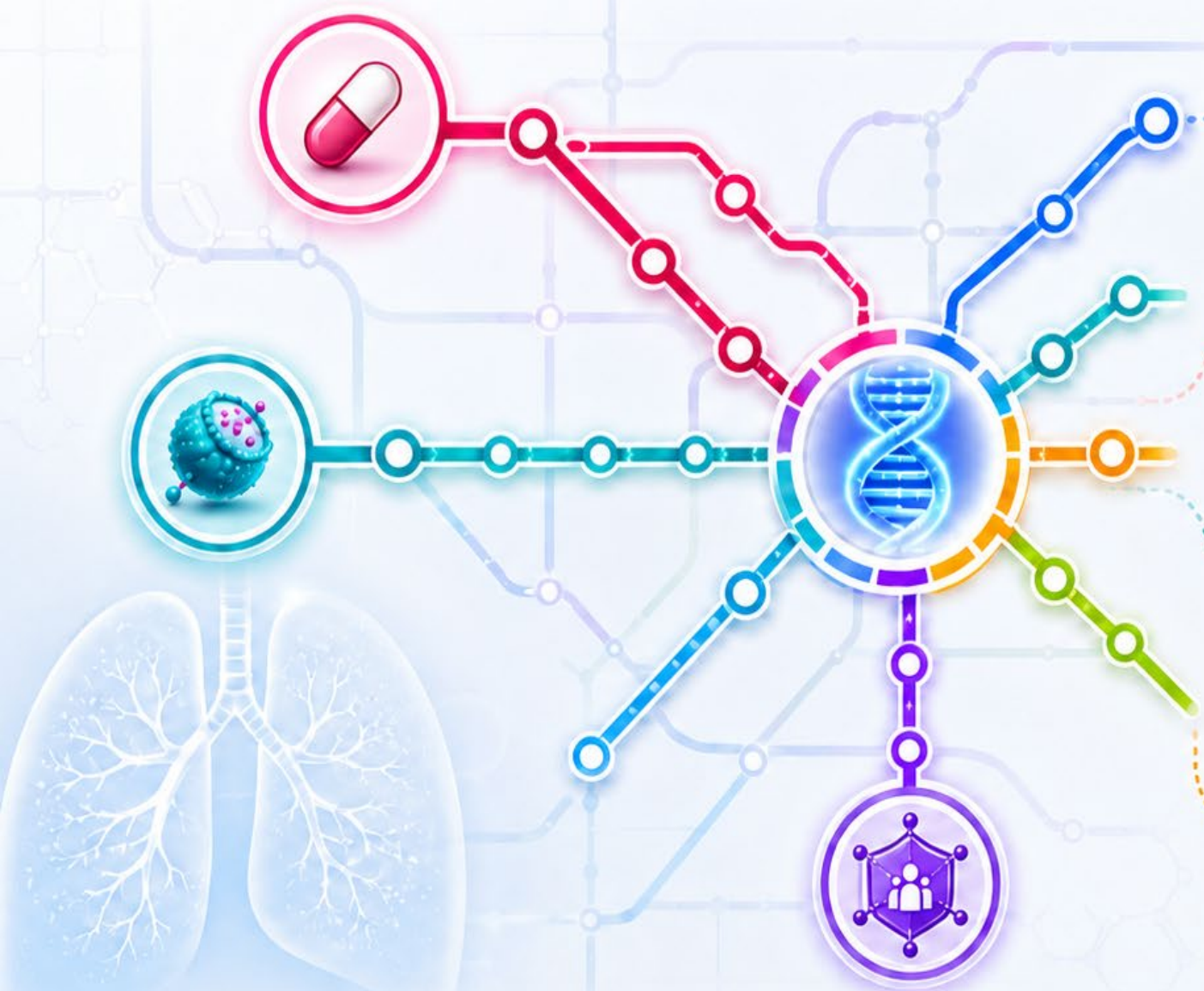
https://clinicaltrials.gov/

Clinical Trials in *EGFR*+ Lung Cancer – Part 1:

The Trials Most Likely to Change Practice

A practical “horizon” map

Think of the field as roads that are trying to answer different patient questions



Frontline intensification

Can we delay resistance further?

Post-TKI strategies

What is the best next step after osimertinib?

Resistance-targeted

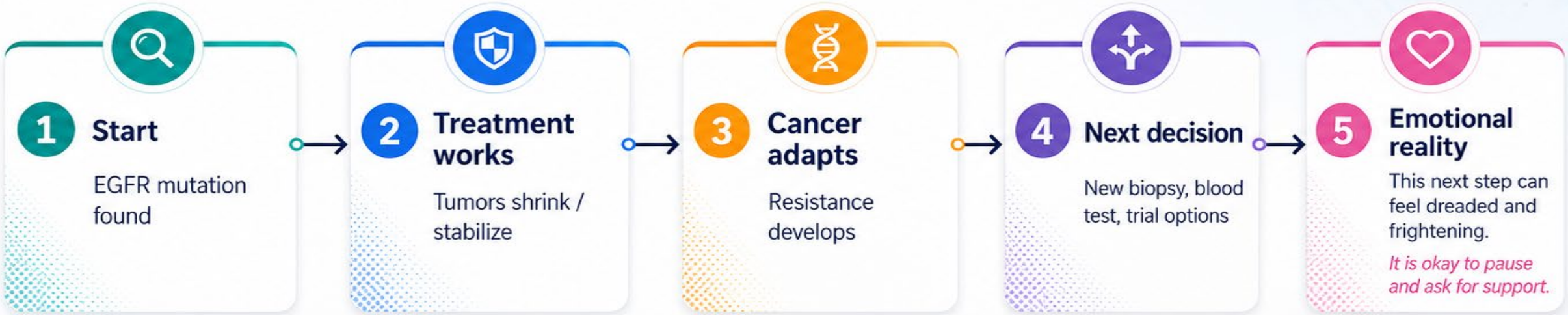
Can we match the treatment to the reason cancer changed?

Patient access

How do we make trials part of routine care?

Why are there so many trials?

Because EGFR+ cancer is treatable — but it is also very good at finding detours.



Clinical trials ask: what is the best next move when the cancer takes a detour?

Not all resistance is the same — and that is why one 'next treatment' will not fit every person.

Late-phase “landmark” trials to watch

These are the studies most likely to influence practice if positive.

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WHY THIS MATTERS NOW:

These late-phase trials are already showing **strong results** and could **become standard of care** in the next **1–3 years** — these are the studies that **matter most right now.**

1–3 YEARS
TO POTENTIAL STANDARD OF CARE

Study / Strategy	Patient setting	Plain-language question
MARIPOSA program	Newly diagnosed common EGFR	Is starting with EGFR+MET dual targeting better than osimertinib alone?
TROPION-Lung14	First-line osimertinib ± Dato-DXd	Does adding an ADC up front delay resistance?
TROPION-Lung15	After EGFR TKI progression	Can Dato-DXd ± osimertinib beat platinum chemo?
IZABRIGHT-Lung01	After 3rd-gen EGFR TKI	Can an EGFR×HER3 ADC replace standard chemo?
AndroMETas-Lung trials	1L or post-TKI MET strategy	Can a MET ADC prevent or treat MET-driven resistance?

Key message: some trials are trying to improve the first treatment; others are trying to improve the next treatment.

First-line treatment is changing

The ‘front door’ of EGFR+ care is no longer one-size-fits-all.

60%

alive at 36 months with amivantamab + lazertinib in

MARIPOSA

51%

alive at 36 months with osimertinib alone in

MARIPOSA

63%

alive at 36 months with osimertinib + chemotherapy in

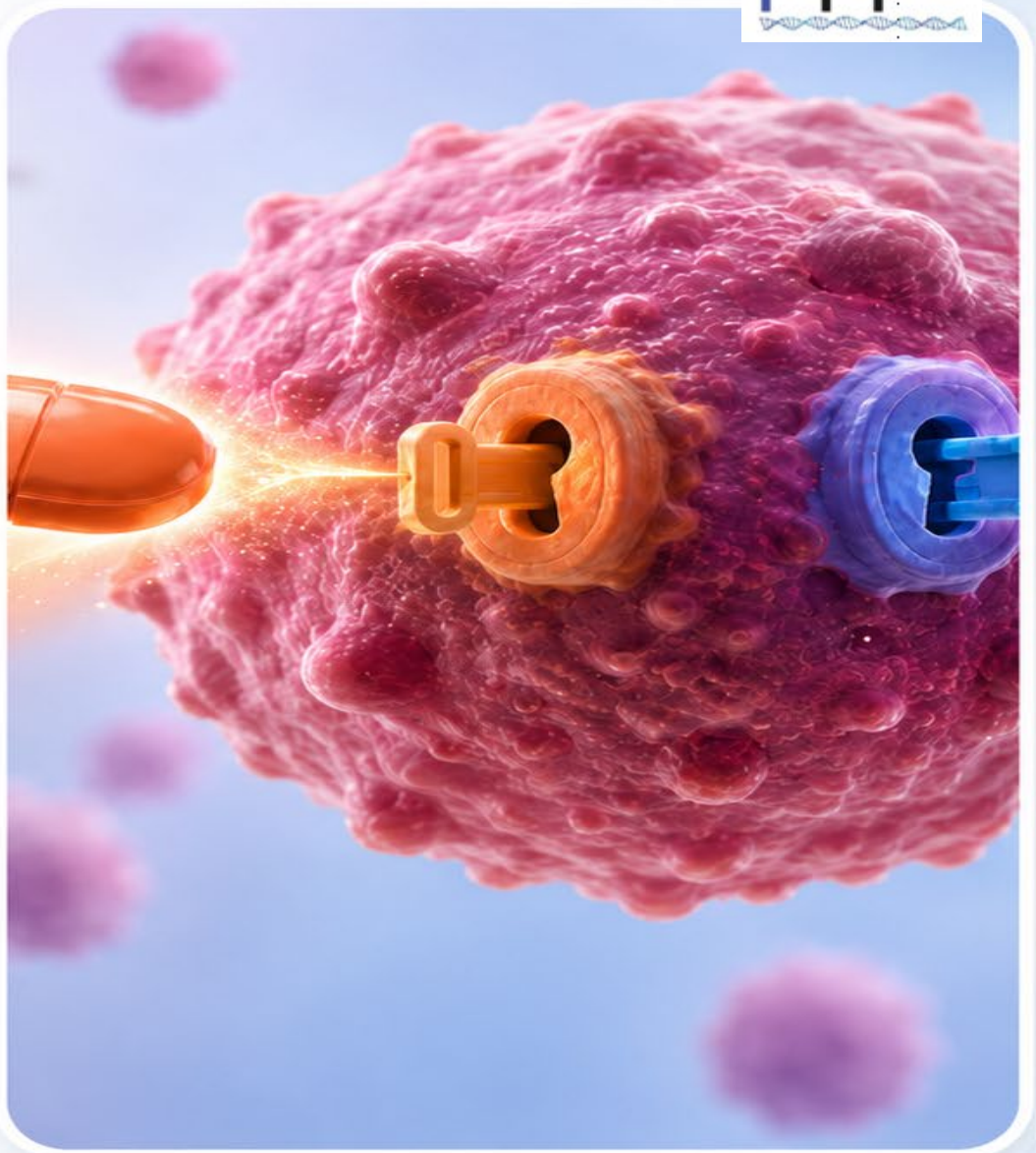
FLAURA2

Important: These results come from different studies and should not be directly compared.
They do **NOT** prove that FLAURA2 is the best first-line treatment.
Cross-trial comparisons can be misleading because the studies included different patients and used different designs.

Different studies; not a head-to-head comparison.

What this means for patients

There may be more than one strong first-treatment option. The best choice depends on the person, the cancer, side effects, and treatment goals.



The frontline “addition” question

Can we add something to osimertinib early enough to delay resistance?

ADC + EGFR pill

Datopotamab deruxtecan + osimertinib

TROPION-Lung14
NCT06350097

Could delay progression; side effects of both matter

MET ADC + EGFR pill

Telisotuzumab adizutecan + osimertinib

AndroMETa-Lung frontline
NCT07005102

Targets MET biology that can drive resistance

EGFR/MET antibody + EGFR pill

Amivantamab + lazertinib

MARIPOSA / COPERNICUS
NCT06667076

Already changing first-line conversations

Patient translation: “Do we hit harder earlier, and can we do it safely?”

After osimertinib: the key crossroads

Most patients eventually need a next plan. Clinical trials are trying to make that plan smarter.

1 Test again

Tissue biopsy and/or blood test

What changed?

2 Match biology

EGFR / MET / HER3 / TROP2 / other

Is there a target?

3 Choose strategy

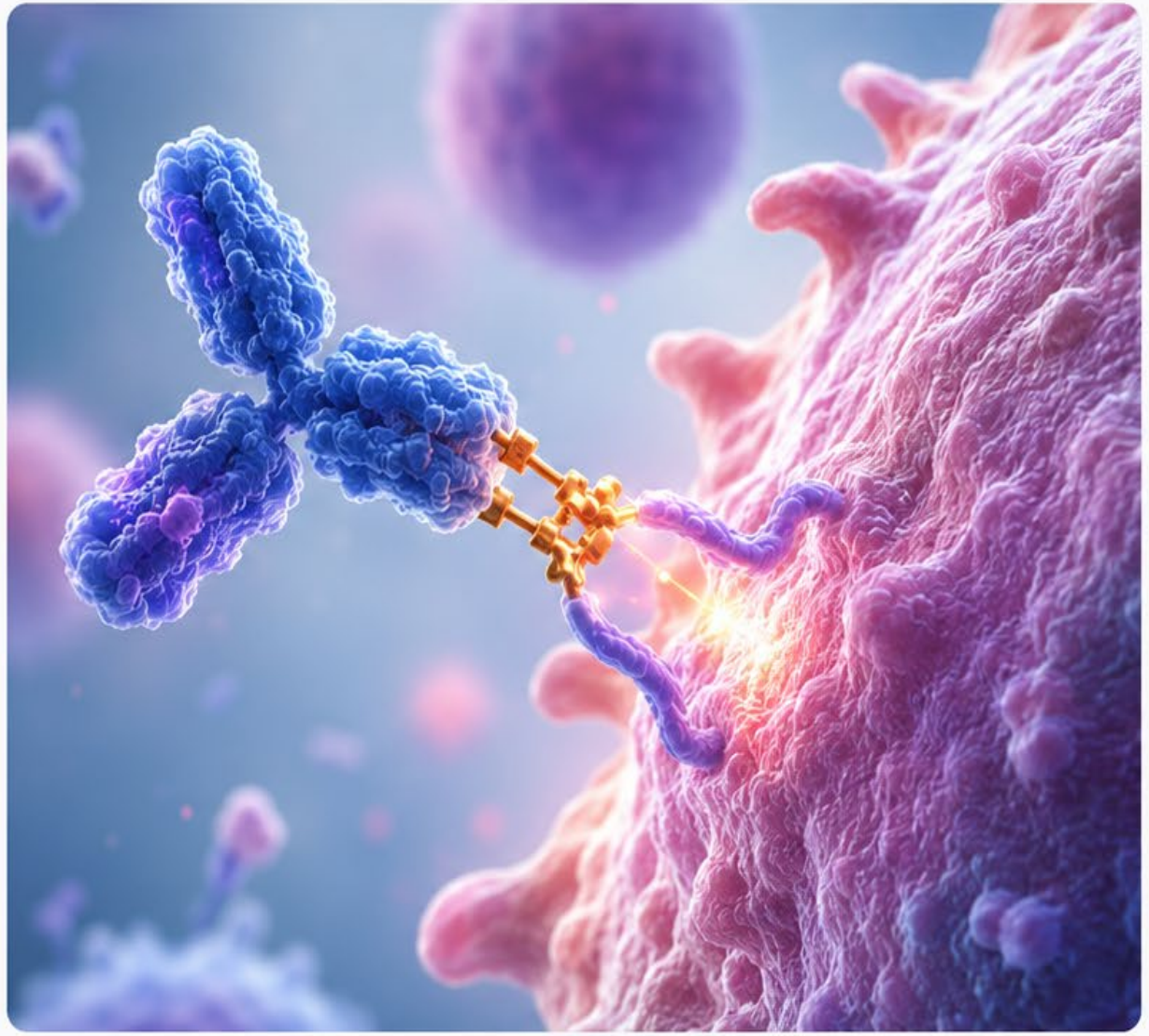
Chemo, ADC, antibody, TKI, trial

What fits goals?

The research direction: fewer “default” choices, more biology-guided choices.

ADC 101: a “guided missile” approach

Antibody–drug conjugates try to deliver chemotherapy more directly to cancer cells.



1 Antibody
finds a target on cancer cells

2 Linker
connects antibody to payload

3 Payload
cell-killing medicine released nearby

Plain English: not a magic bullet — but a more aimed delivery system.

ADCs patients may hear about

Same family idea, different targets, different side effects, different evidence maturity.

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ADC	Target / idea	Why it is exciting
Dato-DXd	TROP2-directed ADC	Already approved after EGFR TKI + platinum; now being tested earlier to see if it can help patients sooner.
Iza-bren / BL-B01D1	EGFR x HER3 bispecific ADC	Targets EGFR and HER3 at the same time — a promising idea for patients whose cancer has outsmarted an EGFR pill.
HER3-DXd / Patritumab	HER3-directed ADC	Has shown encouraging activity after EGFR pill resistance and may offer another option beyond chemotherapy.
Teliso-A / Teliso-V	MET-directed ADCs	May help patients whose cancer is using MET as a resistance pathway — a common detour after EGFR treatment.
AZD9592	EGFR/cMET ADC	An early EGFR/cMET ADC that aims to match treatment more closely to the biology driving resistance.

Patient ask: "What target does this trial require, and do I need a biopsy to know?"

MET-driven resistance:
Important, but often challenging

When cancer grows despite treatment, the MET pathway can be one reason why. It can happen in different ways—and knowing which one it is matters because treatment options can be different.

MET-driven resistance can happen 3 different ways

1. Changes in the cancer's DNA

The MET gene becomes altered (amplified or mutated).

2. More MET protein made

The cancer makes extra MET protein without a DNA change (overexpression).

3. MET pathway turned on by other signals

Other changes in the cancer activate the MET pathway.

Why distinguishing which one matters

The cause of MET-driven resistance can guide the best treatment choice.

Testing can be challenging

MET changes don't always show up on standard tests. More advanced testing or a new biopsy may be needed.

Questions to ask your care team

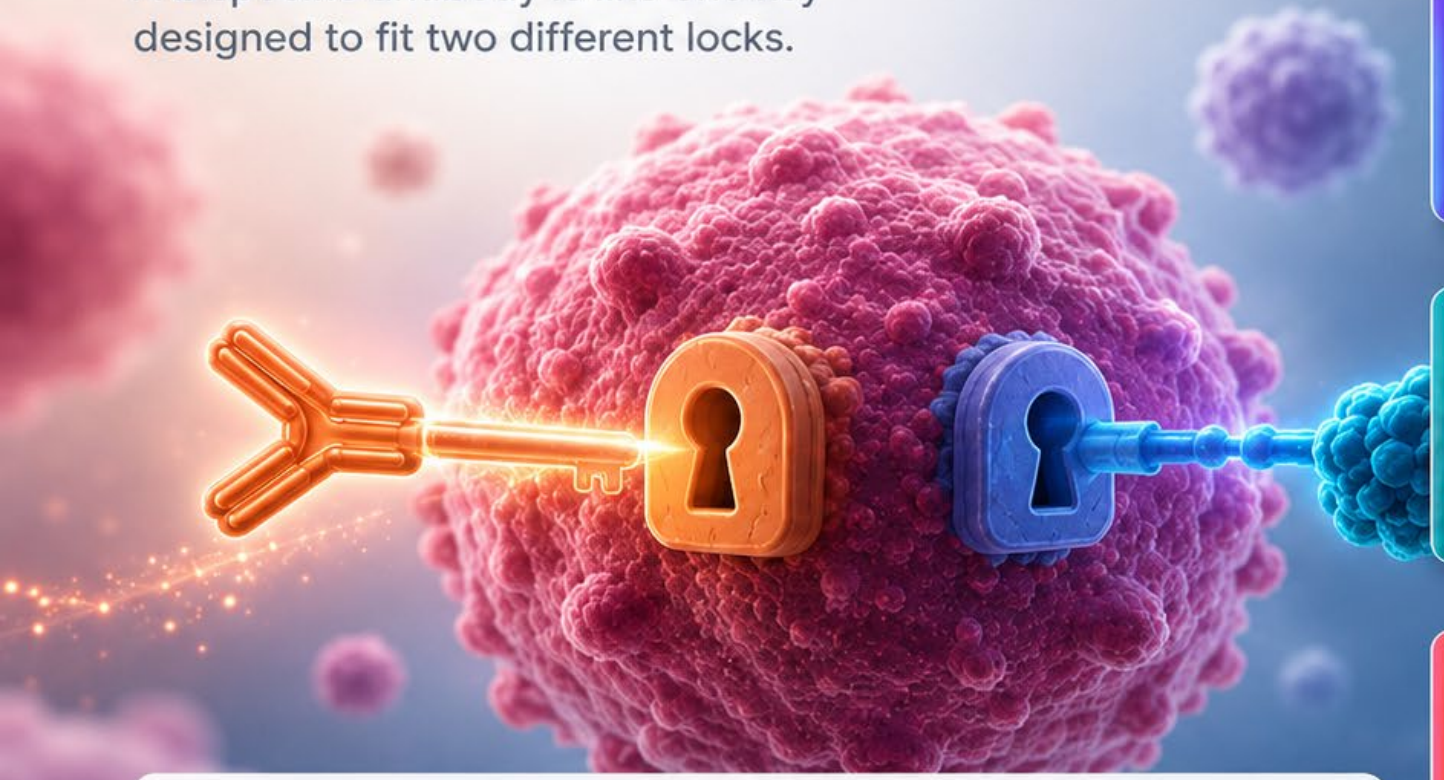
- Could MET be a reason my cancer is growing?
- What type of testing have we done—or should we do—to look at MET?
- Do we know which type of MET change I have (if any)?
- How could this result change my treatment options?
- Are there clinical trials for MET-driven resistance that might be right for me?

Clinical Trials in *EGFR*+ Lung Cancer – Part 2:

Other Major "Horizon" Strategies

Bispecific antibodies: one key, two locks

A bispecific antibody is like one key designed to fit two different locks.



Amivantamab — Targets EGFR + MET

Now central in EGFR+ treatment discussions

Ivonescimab — Targets PD-1 + VEGF

Immunotherapy-style strategy with anti-angiogenic biology

Ubamatamab — MUC16 × CD3

T-cell engager being explored in advanced NSCLC

One drug | Two different locks | Can connect targets or cells

Amivantamab combinations: why patients hear about them

Amivantamab targets EGFR and MET — a two-target approach already affecting care.

First line

Amivantamab + lazertinib showed an overall survival advantage vs osimertinib in MARIPOSA.

Practice-changing discussion

After progression

Combinations with chemotherapy and supportive-care strategies are being tested.

COPERNICUS / PALOMA

How given

Subcutaneous formulations aim to make treatment less cumbersome.

Less chair time?

Ivonescimab: a reminder that old rules can change

EGFR+ lung cancers often respond less well to immunotherapy alone — but combinations may matter.

What it is

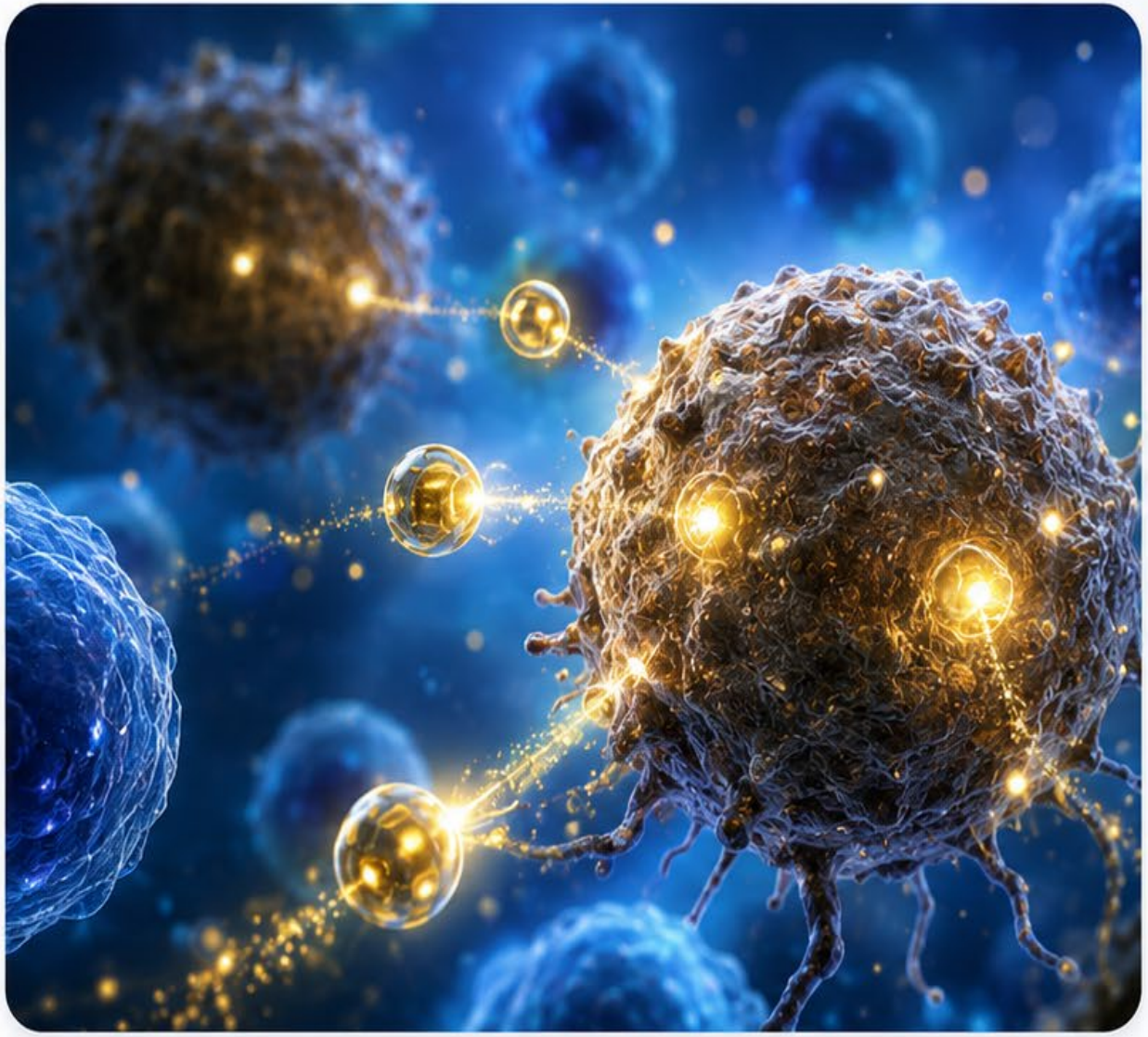
PD-1 + VEGF bispecific antibody

Why interesting

Reported PFS and OS benefit with chemotherapy after EGFR TKI in HARMONi-A

Big caveat

Not a US-approved EGFR+ standard yet; trial population and regulatory context matter



Next-generation EGFR TKIs: chasing the next mutation

The hope: keep the pill strategy alive even after osimertinib resistance.

Drug / trial	Idea	Patient-friendly takeaway
BH-30643	EGFR/HER2 mutant-selective TKI	Early phase, broad EGFR/HER2 mutation strategy
DZD6008	Oral EGFR inhibitor; C797X focus in development	Designed for on-target osimertinib resistance
STX-241	4th-gen EGFR TKI; C797S focus	Aims at one of the best-known resistance mutations
BAY2927088	EGFR/HER2 inhibitor	More developed in HER2; may inform EGFR/HER2 biology
NXP900 + osimertinib	SRC/YES1 inhibitor combo	Targets a bypass pathway, not EGFR itself

How to think about 4th-generation EGFR drugs

A simple lock-and-key analogy.

EGFR mutation

Original lock

The first key works.

Osimertinib resistance

The lock changes

C797S is one example.

Next-gen TKI

New key design

Try to fit the changed lock.

Translation: the biopsy/blood test helps tell us which "lock" we are trying to open.

Rare EGFR mutations: exon 20 and beyond

If your biomarker testing showed an exon 20 insertion or another uncommon EGFR mutation, this slide is for you.

Exon 20 insertions

This is a distinct EGFR group, so the treatment playbook is different from the more common exon 19 / L858R cancers.

Trials often focus on brain-penetrant drugs, bispecific antibodies, and smart combinations.

Patients may hear about horizon studies such as ORIC-114 + subcutaneous amivantamab.

Example: ORIC-114 + SC amivantamab

Other rare EGFR mutations

This includes uncommon EGFR mutations such as G719X, S768I, L861Q, and some compound mutations.

There have not been many dedicated trials in the past — but that is starting to change.

Examples patients may hear about include FURMO-006 and REZILIENT4, reflecting growing attention to rare EGFR subtypes.

Hopeful note: rare EGFR mutations are finally getting more study-specific attention.

Bottom line: the rarer the mutation, the more important it is to ask whether there is a trial designed for your specific biology.

Beyond the usual suspects: new angles, new hope

Cancer is complex. Researchers are looking beyond genomic drivers to find new ways **to stop it, control it, and improve outcomes.**

Pathway modulation

Targeting alternative signaling pathways cancer cells rely on.

Tumor biology & microenvironment

Changing the environment around the tumor and the way cancer cells interact, survive, and grow.

Innovative therapies

Delivering treatment in smarter, more targeted ways.

Immune & cell-based approaches

Harnessing the immune system and other cells to recognize and eliminate cancer.

Why this is hopeful

By looking beyond genomic drivers, researchers are uncovering **new vulnerabilities** cancer relies on to survive and adapt. This opens the door to **more durable responses** and **better outcomes** — not just kicking the can down the road.

Research is moving fast. More options. More answers. **More reasons for hope.**

Clinical Trials in *EGFR*+ Lung Cancer – Part 3:

Making Trial Information Useful at the Clinic Visit

A patient-friendly way to sort trials

Every trial can be understood by three questions.

1

Who is this for?

New diagnosis? After osimertinib? Exon 20? Brain mets?

2

What is the “new thing”?

Pill, antibody, ADC, immunotherapy combo, gene therapy, radiation delivery

3

What is the comparison?

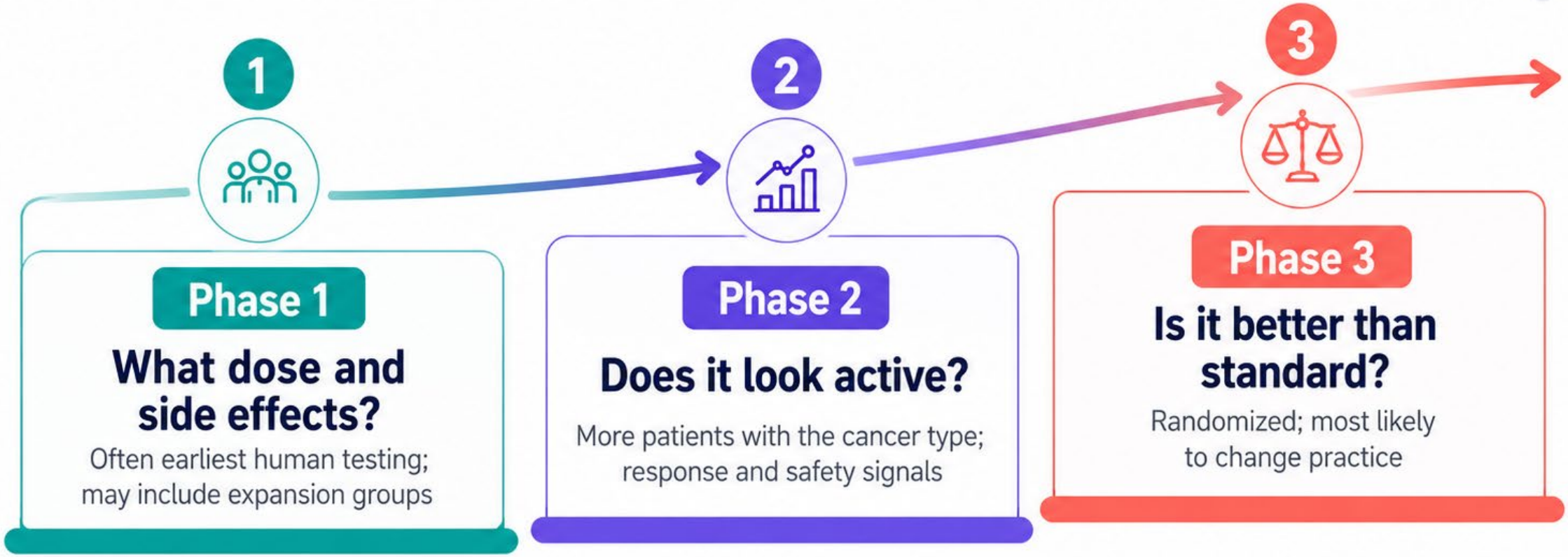
Standard treatment, another dose, or no randomization in early phase

Bonus question: “What would I give up by joining — and what could I gain?”

Phase 1, 2, 3 — without the intimidation factor

Phase does not mean "how sick you are." It means what question the study is designed to answer.

EGFR sisters



Friendly reminder: "Phase 3" does not mean the drug is automatically best — it means the study is finally asking the big question.

Randomization is not abandonment

A clinical trial should never mean ‘we stop taking care of you.’

What randomization means

A fair way to compare two options when we genuinely do not know which is better.

Most randomized cancer trials include a standard-of-care option — not ‘nothing.’

What to ask

- What are the arms?
- Can I cross over?
- What happens if it is not working?
- Who do I call after hours?

The clinical team should still be your team.

Clinical trial side effects: ask specifically

"What are the side effects?" is good. "Which side effects matter most for this drug?" is better.

Treatment type	Side effects to discuss
EGFR TKIs	rash, diarrhea, nail/skin changes, lung inflammation, heart/QT monitoring
Antibodies / bispecifics	infusion reactions, rash, swelling, clots, eye/skin effects depending on drug
ADCs	blood counts, nausea, mouth sores, fatigue, eye/lung inflammation depending on ADC
Immunotherapy combinations	immune inflammation, thyroid/liver/lung/colon effects, steroid management
Radiopharmaceuticals	blood counts, kidney/salivary exposure, scan-based eligibility, radiation precautions

Report side effects early.

- Speaking up usually does **NOT** get you taken off a trial.
- Most side effects can be managed, and dose reductions are common and okay.
- Patients are usually taken off study only if side effects become serious or unsafe.

Patient translation: the 'type' of drug helps predict what the team will watch.

The most useful trial questions at each disease moment

Timing matters. It is easier to look before the next decision is urgent.

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1 At diagnosis

What is my EGFR subtype?
Are there frontline trials?

2 Before each scan

If things change,
what testing will we do?

3 At progression

Can we biopsy?
Do I have a trial match?

4 Before starting next treatment

Would joining now
close or open later options?

Put this in your phone:

‘Ask about trials before we need the next treatment.’

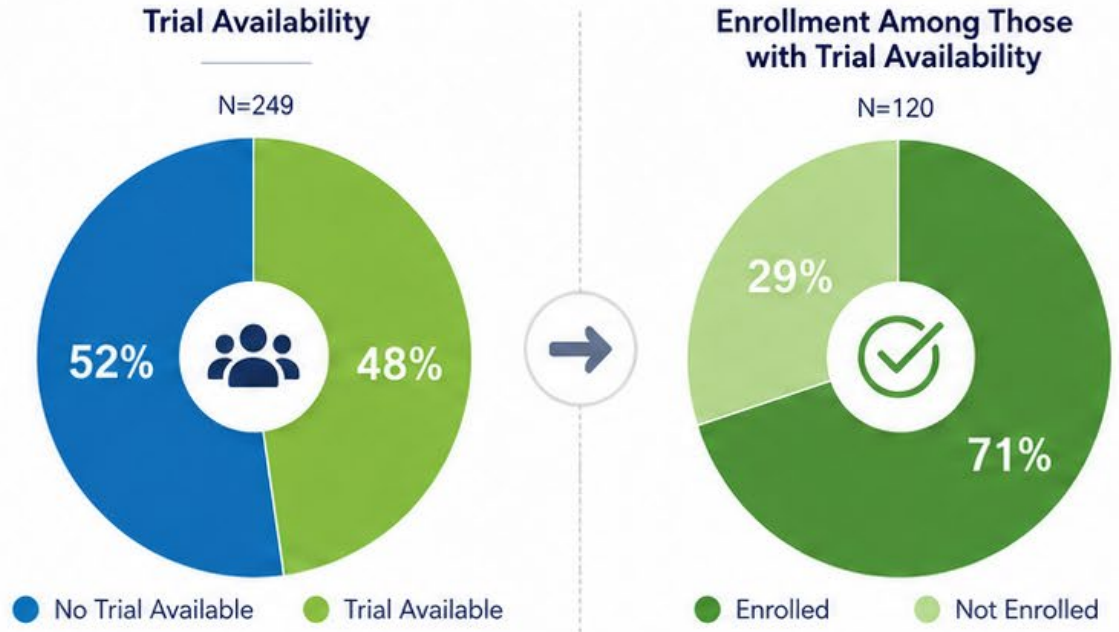
Clinical Trials in *EGFR*+ Lung Cancer – Part 4:

Trial Access is Part of Cancer Care

What we learned at UI Health

Trial enrollment can be high in a safety-net setting when access is built into care.

Percentage of Patients



249
patients with lung cancer reviewed

48%
had a therapeutic clinical trial available

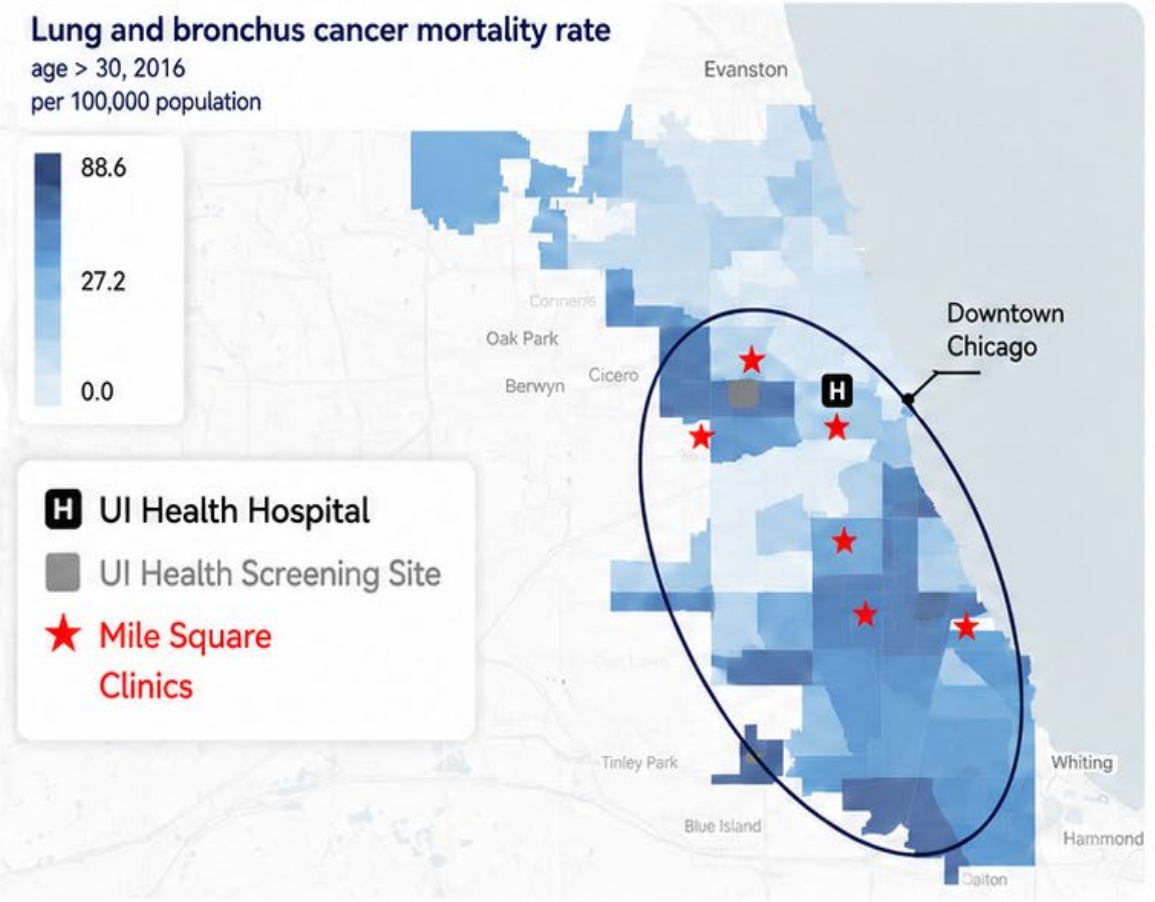
71%
enrolled/consented among those with availability in figure cohort

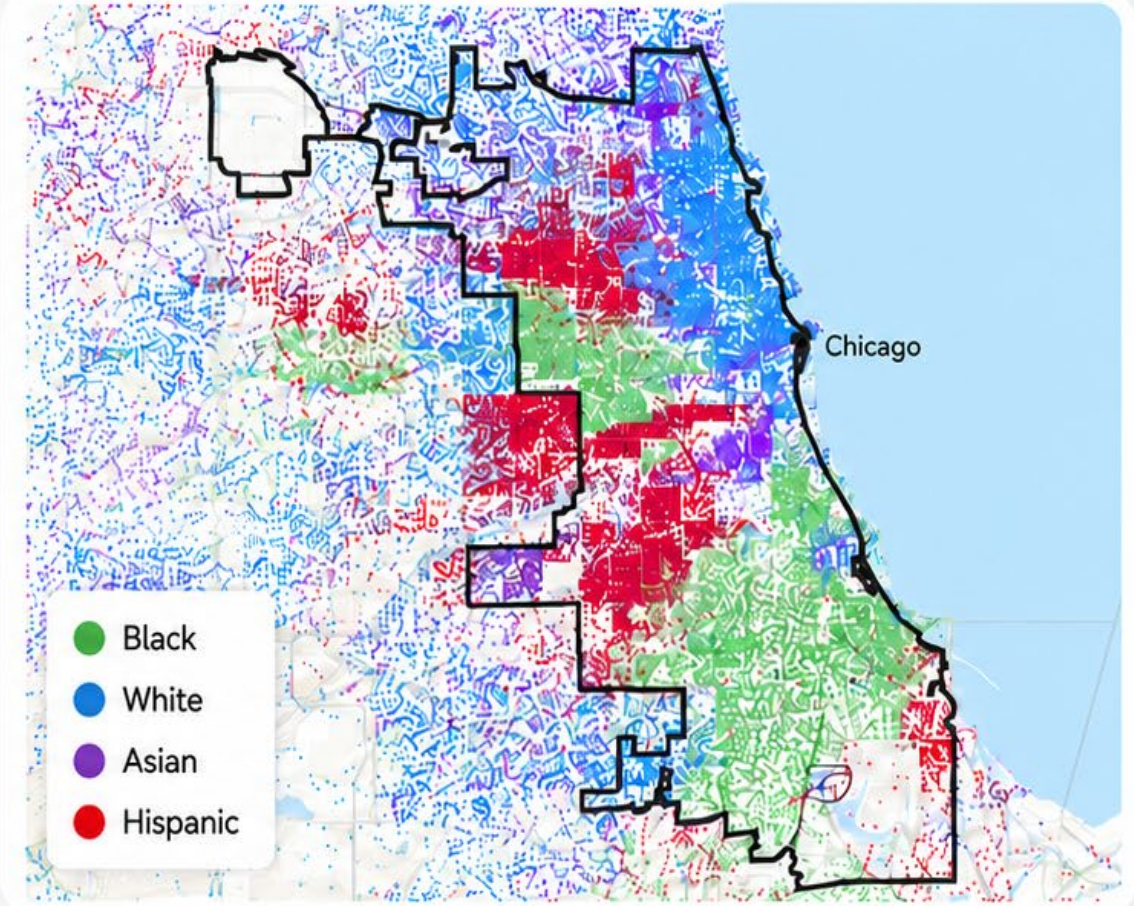
Key idea: patients will enroll when trials are offered, explained, and logistically supported.

UI Health—retrospective lung cancer trial enrollment analysis, 2021–2023; Figure 1 and Figure for slide ideas provided by RW Team.

Access is geographic, social, and clinical

Our patients come from communities where lung cancer burden and structural barriers intersect.





Clinical trial enrollees are not 'just referrals' — they are our community.

Why patients say yes

The reason is often not ‘I love research paperwork.’

1. **Trust**
   Trust in physician and care team was a major theme

2. **Family/community**
   Many patients want to contribute to medical research for others

3. **Access**
   Some see trials as access to the latest scientific advances

4. **Hope**
   Not hype — a structured option when choices matter

Patients often say yes because of trust, access, and hope.

Why patients say no

Declining a trial is a decision — and often a reasonable one if concerns are not addressed.

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58% — Concern about side effects

31% — Not wanting to feel experimented on

19% — Logistics too difficult

8% — Distrust in the medical system

Translation: better enrollment starts with better listening.

How to lower the “trial burden”

Sometimes the medicine is not the barrier — the parking garage is.

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Time

Can visits/labs align with regular care?

Travel

Is gas/parking/ride-share support available?

Cost

What is billed to insurance vs study sponsor?

Communication

Who is the single person to call?

Caregiver load

Can schedules protect family/work responsibilities?

Language/trust

Is consent explained in plain language?

A good trial program treats access as a design feature, not a favor.

The “trial-ready” checklist

Patients and caregivers can keep this ready before the next decision point.

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- Exact EGFR alteration and prior mutations
- Most recent scans and date of progression
- Prior treatments and side effects
- Brain metastasis history and radiation history
- Biopsy/ctDNA results, including MET/HER2/HER3/TROP2 if available
- **Goals: tumor control, symptom relief, travel limits, quality of life**

Clinical trial matching is faster when the cancer story is organized.

What caregivers can do

Caregivers are often the clinical-trial search engine, calendar app, and reality check.

1. Ask: “Is there a trial now or soon?”
2. Track scan dates and treatment start deadlines
3. Write down side-effect questions before consent
4. Help compare logistics honestly
5. Protect the patient’s goals — not just the trial’s goals

Helpful trial-finding resources:

- Your oncology team
- EGFR Resisters Living Spreadsheet
- ClinicalTrials.gov
- Your cancer center trial office

Green flags and red flags when reviewing a trial

This is not about being difficult. This is about being informed.

Green flags

- Clear explanation of options
- A written plan for side effects
- Costs and visits explained up front
- Your goals are part of the conversation

Red flags

- You feel rushed to sign
- No one can explain the alternatives
- Side effects are minimized
- Logistics are vague

Red flags are not automatic reasons to say no — they are reasons to ask more questions.

A good team will answer them clearly.

What may change clinic conversations soon

A realistic, hopeful shortlist.

EGFR esisters

1. **First-line choices may broaden**
   Amivantamab/lazertinib and ADC combinations could make initial treatment more personalized.

2. **Post-TKI could become less "chemo by default"**
   Dato-DXd, EGFR × HER3 ADCs, HER3/MET ADCs and other strategies may add options.

3. **Biopsies may matter more**
   Some trials need MET expression, resistance mutation status, or other markers.

4. **Clinical trial literacy will matter**
   Knowing how to ask may be as important as knowing the drug name.

More choices
Emerging combinations could match treatments more closely to each patient's cancer.

More options
New agents and strategies could expand what's possible after TKI treatment.

More information
Biomarkers and molecular data may help guide which trials are the best fit.

More empowerment
A better understanding of trials helps patients take an active role in their care decisions.

More access for some
If no trial fits or you are not eligible, ask whether expanded access / compassionate use is an option.

Names will change. The decision framework will stay useful.

Take-home messages

High-level, patient-centered, and hopefully less alphabet soup-y.

1

Ask early, not late.

Bring up trials before the next decision point — not after options are running out.

2

Ask what may be changing.

First-line choices and post-TKI options may keep evolving — ask what matters for you now.

3

Keep your biology handy.

Know your EGFR mutation, recent biopsy/blood-test results, and scan timeline.

4

Make the next visit count.

Write down 3 questions:

- Is there a trial now or soon?
- What tests matter?
- What are my real options?

Tangible takeaway: at your next visit, ask about trials early, know your mutation, and leave with a clear next-step plan.

Interactive Q&A