# EGFR Resisters “Ask the Experts”: Clinical Trials within Uncommon EGFR Alterations in NSCLC


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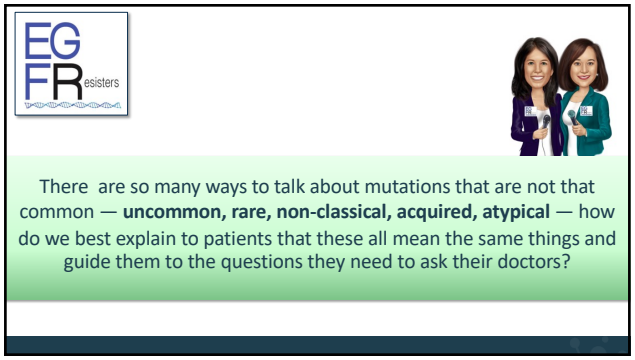


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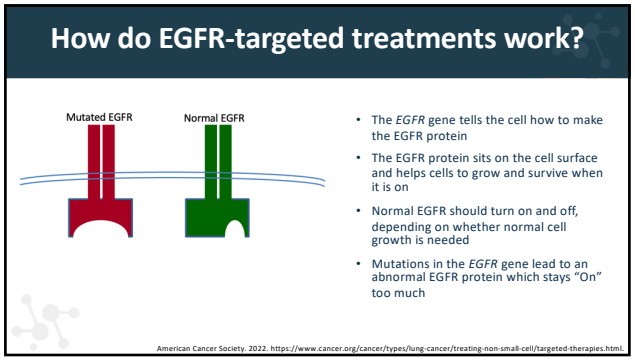


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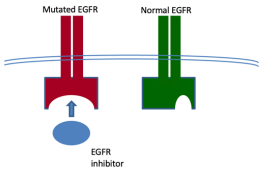
## How do EGFR-targeted treatments work?




- We currently treat lung cancer with the most common EGFR mutations with EGFR-targeted therapy called osimertinib
- This drug is able to ***bind to the abnormal mutated EGFR and turn it off***
- It is more potent/selective for mutated EGFR than 1st generation (erlotinib/gefitinib) and 2nd generation (afatinib/dacomitinib) EGFR inhibitors. It works longer on average with fewer side effects than the older drugs.

American Cancer Society. 2022. https://www.cancer.org/cancer/types/lung-cancer/treating-non-small-cell/targeted-therapies.html.
Zhang H. *Drug Des Devel Ther.* 2016;10:3867-3872.

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## Types of EGFR Mutations at Lung Cancer Diagnosis "Driver Mutations"

**EGFR Exon 19 Deletions**
**EGFR L858R**

***"Common"*** EGFR Mutations
- Make up ~85% of newly diagnosed EGFR-mutated lung cancer
- Produce an EGFR protein which is overly active, causing too much tumor cell growth and survival
- Other names include: ***"Classical"***

**Non-Classical EGFR Mutations**
**EGFR Exon 20 Insertions**

***"Uncommon"*** EGFR Mutations
- Each make up ~5-10% of EGFR mutated lung cancer
- Unique considerations when selecting treatment
- Other names include: ***"Less common," "Atypical," "Rare"***

Batra U, et al. *BMJ Open Respiratory Research.* 2023;10:e001492.

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## What about "Acquired" or "Resistance" EGFR mutations?

**Uncommon mutations do not always exist at initial diagnosis—these mutations can also be acquired following EGFR TKI therapy**

**Driver EGFR Mutation**
- Classical (Common) Mutations (L858R, Exon 19 deletions)
- Uncommon Mutations (G719X, L861Q, etc.)

**Selective Pressure During EGFR TKI Therapy**

**Acquired Resistance Mutations**
- Acquired EGFR resistance mutations (*EGFR C797S, Other*)
- Bypass pathway alterations

TKI, tyrosine kinase inhibitor.

Leonetti A, et al. *Br J Cancer.* 2019; 121:725–737.

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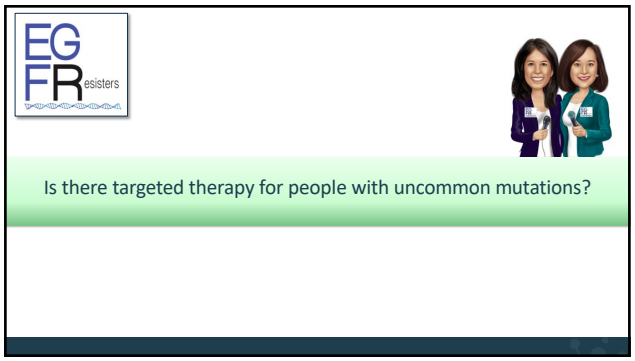


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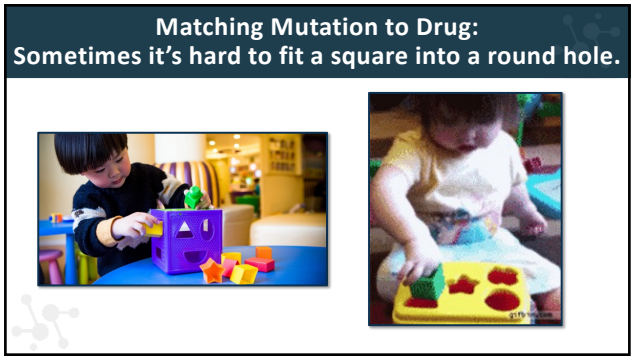


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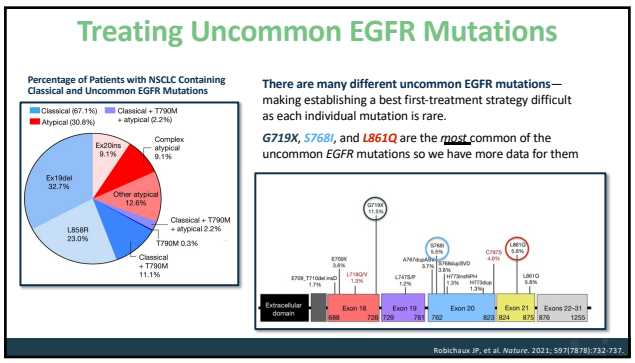


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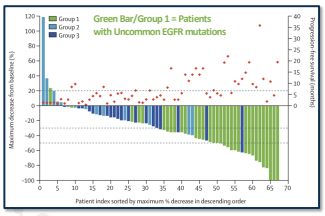
## What is FDA-Approved for *S786I*, *L861Q*, *G719X*?




- **Afatinib** carries FDA approval because these patients were included in the LUX-Lung afatinib clinical trials
- Afatinib is active for the uncommon mutations
  - 71% Response Rate
  - 10.7 months Progression Free Survival
- However—carries more side effects (rash, diarrhea) and is less effective for brain metastases

Yang JC, et al. *Lancet Oncol.* 2015;16(2):141-151. Yang JC, et al. *J Thorac Oncol.* 2020;15(5):803-815.

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## Can you use osimertinib for the uncommon EGFR mutations? *Maybe*

**The use of osimertinib to treat uncommon EGFR mutations is off-label, but may be preferred in selected uncommon mutations (e.g., L861Q) or if needed to treat brain metastases**

- The UNICORN study evaluated osimertinib for uncommon mutations
- Response rate/progress free survival were not the same across all mutations
- Novel agents are being evaluated in clinical trials for the uncommon EGFR mutations

| Patient Subgroup | Number of patients | Response Rate (95% CI) | Progression-free Survival (95% CI) |
|---|---|---|---|
| All Uncommon | 44 | 60% (45–74) | 8.6 months (7.3–13.5) |
| *G719X* | 16 | 53% (30–75) | 8.6 months (6.9–NA) |
| *L861Q* | 11 | 78% (45–94) | 15.7 months (8.9–18.8) |

Bar J, et al. *J Thorac Oncol.* 2023;18(2):169-180.

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Are there mutations that don't currently have a treatment but are being studied for treatment right now?

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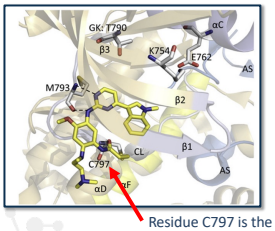
## Acquired EGFR Mutations at Osimertinib Resistance: *C797S*




Residue C797 is the site of osimertinib covalent binding

***C797S* is the most common second-site *EGFR* mutation at osimertinib resistance**

- 7% - 12.5% of acquired resistance

Ramalingam SS, et al. *J Thorac Oncol*. 2022. 17(9):567-68. Roskoski R Jr. *Pharmacol Res*. 2019;144:19-50.

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## Double Mutant vs. Triple Mutant Acquired EGFR Mutations

*What we know about treatment*

1. **EGFRm + EGFR C797X "Double Mutant"**
   - Acquired resistance to first-line osimertinib
   - Reported sensitivity to 1st generation EGFR TKIs (gefitinib, erlotinib)
2. **EGFRm + EGFR T790M + EGFR C797X "Triple Mutant" *in trans***
   - Acquired resistance to sequential 1st and 3rd generation *EGFR* tyrosine kinase inhibitors
   - Resistant to all approved EGFR tyrosine kinase inhibitors if in same *EGFR* protein
   - *4th Generation EGFR tyrosine kinase inhibitors in clinical trials*

*In trans*=EGFR T790M + EGFR C797X mutations occur on separate alleles.

Leonetti A, et al. *Br J Cancer*. 2019;121(9):725-737.

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## *C797S*-Active Compounds in Development

*Preclinical Data*

| Compound | Del19 | L858R | Del19/ T790M | L858R/ T790M | Del19/ C797S | L858R/ C797S | Triple Mutant | Other | CNS? | Status |
|---|---|---|---|---|---|---|---|---|---|---|
| BLU-945 | - | X | X | X | ? | X | X | | - | Phase 1/2 (NCT04862780) |
| BLU-525 | X | X | - | - | X | X | X | | X | Preclinical |
| BDTX-1535 | X | X | - | - | X | X | X | *Uncommon | X | Phase 1 (NCT05256290) |
| THE-349 | X | X | X | X | X | X | X | | X | Preclinical |
| H002 | X | X | X | X | X | X | X | | X | Phase 1/2 (NCT05552781) |
| BAY 2927088 | X | X | | | X | X | | Ex20ins | | Phase 1 (NCT05099172) |
| JIN-A02 | X | X | X | X | X | | X | | X | Phase 1/2 (NCT05394831) |
| BBT-176 | X | X | X | | X | X | X | | X | Phase 1/2 (NCT04820023) |

*Uncommon: e.g., *L747P*, *L718Q*

Predicted Not Active | Predicted Active | No available data

Shum E, et al. *Cancer Res*; 2022; 82 (12_Supplement): CT184. Tavera-Mendoza LE, et al. *AACR-NCI-EORTC*; 2022. Abstract No. 177. Lucas M, et al. *ENA*; 2022. Abstract No. 64. Spira A, et al. *AACR-NCI-EORTC*; 2023. Poster No. C022. Zhang S, et al. *AACR-NCI-EORTC*; 2022. Poster No. 236. Siegel F, er al. *ENA*; 2022. Abstract No. 17. Lim SM, et al. *IASLC WCLC*; 2022. Abstract No. MA07.08. Lim SM, et al. *Clin Cancer Res*. 2023;29(16):3004-3016.

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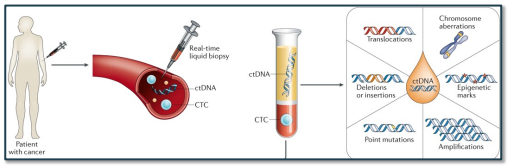
## Liquid Biopsy
*Like finding a needle in a haystack*




Pantel K, Alix-Panabières C. *Nat Rev Clin Oncol*. 2019;16(7):409-424.

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What is better — liquid vs. tissue biopsy?

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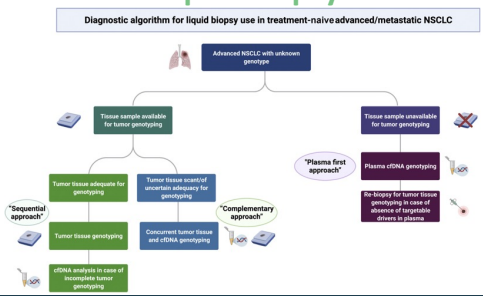
## Tissue or liquid biopsy—or both?




Rolfo C, et al. *JTO*. 2021; 16(10): P1647-1662.

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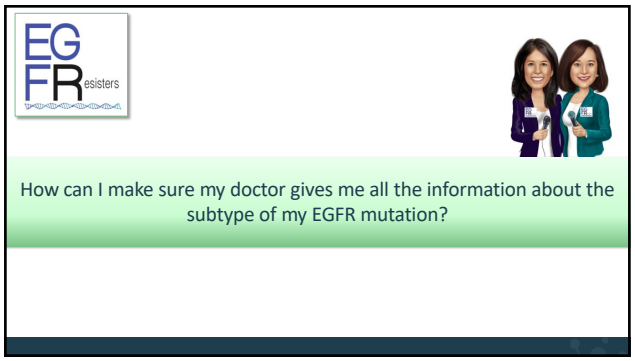


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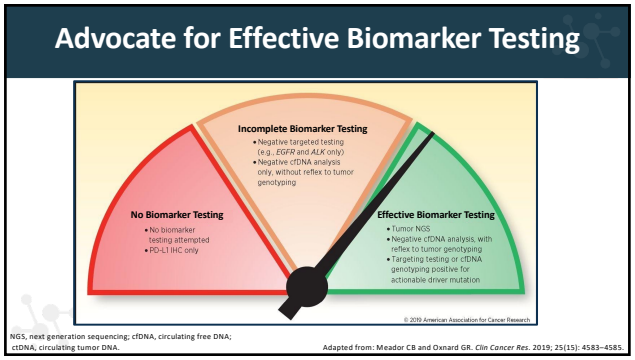


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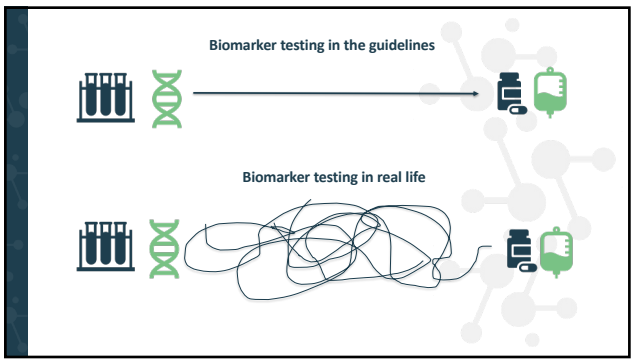


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## We NGS—Leave No Gene Stranded!

NGS, next generation sequencing.

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## Biomarker testing—takes a relay team!

- Tissue biopsy
  - Bronchoscopy
  - CT-guided needle biopsy
- Pathology
- Molecular lab
- Oncology

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Clinical trials targeting uncommon and acquired EGFR alterations—What are my options?

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# EGFR Resisters "Ask the Experts": Clinical Trials within Uncommon EGFR Alterations in NSCLC

## When is the right time to consider clinical trial enrollment?

**How can I find out about possible clinical trials?**

- Through your treating oncologist
- Patient advocacy groups
- Clinicaltrials.gov
- Evaluation at an academic center

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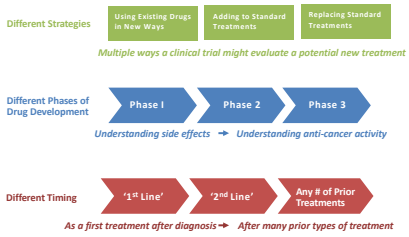
## What are the different types of clinical trials?

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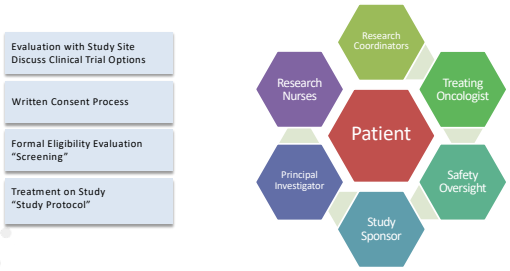
## What is it like to participate in a clinical trial?

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There are so many clinical trials — how do patients and clinicians find the right trial for the uncommon mutations?

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## Steps to Find a Clinical Trial

1. **Gather details about your cancer**
   - NCI Cancer details checklist:
     https://www.cancer.gov/research/participate/clinical-trials-search/steps/detailschecklist.pdf
2. **Find clinical trials**
   - Trials are sponsored in many different ways and there are many places to look. No one list will contain every trial. Places to check:
     - NCI-supported trials, clinicaltrials.gov, cancer centers/clinics, drug and biotechnology companies, cancer advocacy groups (i.e., EGFR Resisters)
3. **What trials interest you?**
   - Things to consider: trial objective, eligibility, location, length
4. **Contact the team running the trial**
   - There are a few ways to do this: directly through the “principal investigator” contact information or ask your doctor to contact for you
5. **Ask questions**
   - Questions to ask before joining a treatment clinical trial:
     https://www.cancer.gov/research/participate/clinical-trials/why-participate
   - Connect with patient advocacy and support groups to ask about their clinical trial experiences

https://www.cancer.gov/research/participate/clinical-trials-search/steps

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Where should I go for more information about treating uncommon mutations? Resources?

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# EGFR Resisters "Ask the Experts": Clinical Trials within Uncommon EGFR Alterations in NSCLC

## Downloadable Fact Sheets on EGFR Resisters Website

*Also located on the patient portal for this webinar*


EGFR Resisters

egfrcancer.org

https://egfrcancer.org/ask-the-egfr-experts/#pdf.

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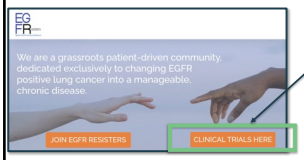
## Finding Clinical Trials




***Spreadsheet compiled by EGFR Resisters*:***
This spreadsheet is to help you find clinical trials that may be appropriate for you after progression on osimertinib.

***Disclaimer: This spreadsheet serves only to help you find a clinical trial and is NOT intended as medical advice. Please feel free to share this spreadsheet with your oncologist for discussion.**

https://egfrcancer.org

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## Understanding Clinical Trial Jargon

*Review Article*

**Clinical endpoints in oncology - a primer**

Amanda Delgado, Achuta Kumar Guddati

*Division of Hematology/Oncology, Georgia Cancer Center, Augusta University, GA 30912, Augusta*

Received January 27, 2021; Accepted February 17, 2021; Epub April 15, 2021; Published April 30, 2021

**Abstract:** Clinical endpoints are essential for assessing the safety and efficacy of new cancer therapies. They are used by oncologists to help guide clinical decision making. While overall survival (OS) has frequently been regarded as the "gold standard" primary clinical endpoint, it's utility is constrained by several disadvantages. The time-consuming nature of trials using OS has led to a recent push to explore surrogate clinical endpoints and their potential to serve as primary clinical endpoints in lieu of OS. Additionally, it is becoming evident that other endpoints add valuable information about quality of life and treatment failure as their use is becoming increasingly prevalent in oncology clinical trials. Without a doubt, the use of clinical endpoints will continue to expand and evolve as new cancer therapies are developed and novel treatments, including immunotherapy, draw interest. This review explores the roles of primary and surrogate clinical endpoints as well as the benefits and drawbacks of each specific endpoint. In addition, it directly compares the unique features of each suggesting some of the specific uses each one fulfills.

**Keywords:** Progression, treatment failure, overall survival, end point

Delgado A, Guddati AK. *Am J Cancer Res.* 2021;11(4):1121-1131.

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