

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



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Sponsored through an independent educational event from Bioclinical Therapeutics.

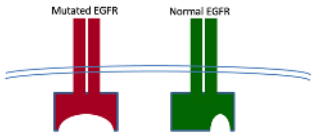
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There are so many ways to talk about mutations that are not that common — **uncommon, rare, non-classical, acquired, atypical** — how do we best explain to patients that these all mean the same things and guide them to the questions they need to ask their doctors?

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How do EGFR-targeted treatments work?



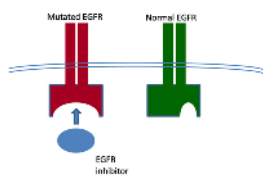
- The *EGFR* gene tells the cell how to make the EGFR protein
- The EGFR protein sits on the cell surface and helps cells to grow and survive when it is on
- Normal EGFR should turn on and off, depending on whether normal cell growth is needed
- Mutations in the *EGFR* gene lead to an abnormal EGFR protein which stays “On” too much

American Cancer Society, 2022. <https://www.cancer.org/cancer/types/lung-cancer/treating/non-small-cell/targeted-therapies.html>

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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;10:1867-1872.

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Types of EGFR Mutations at Lung Cancer Diagnosis “Driver Mutations”

EGFR Exon 19 Deletions

EGFR L858R

Non-Classical EGFR Mutations

EGFR Exon 20 Insertions

“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”**

“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.)

➔

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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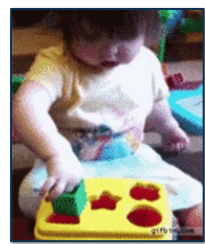
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Is there targeted therapy for people with uncommon mutations?

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Matching Mutation to Drug:
 Sometimes it's hard to fit a square into a round hole.

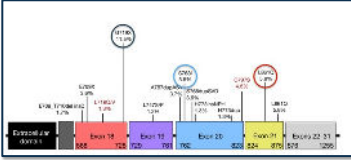
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Treating Uncommon EGFR Mutations

Percentage of Patients with NSCLC Containing Classical and Uncommon EGFR Mutations

There are many different uncommon EGFR mutations—making establishing a best first-treatment strategy difficult as each individual mutation is rare.

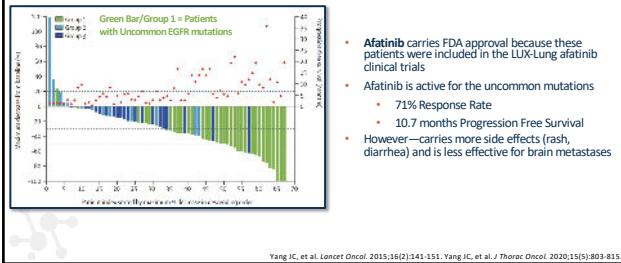
G719X, *S768I*, and *L861Q* are the most common of the uncommon EGFR mutations so we have more data for them



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



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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)
<i>G719X</i>	16	53% (30-75)	8.6 months (6.9-NA)
<i>L861Q</i>	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

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

- 7% - 12.5% of acquired resistance

Residue C797 is the site of osimertinib covalent binding

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

- EGFRm + EGFR C797X “Double Mutant”**
 - Acquired resistance to first-line osimertinib
 - Reported sensitivity to 1st generation EGFR TKIs (gefitinib, erlotinib)
- 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)

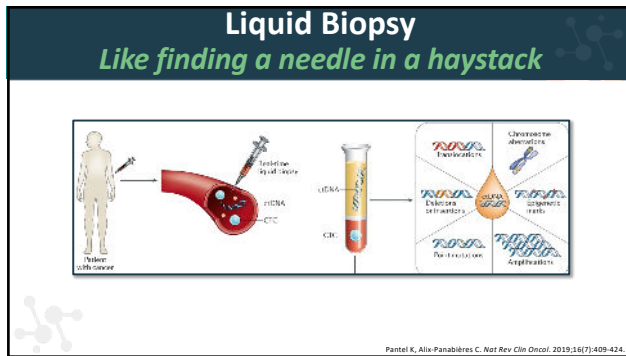
*Uncommon: e.g., L747P, L728Q

Predicted Not Active
Predicted Active
No available data

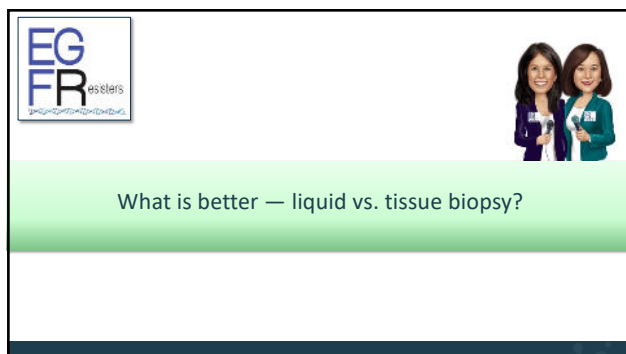
Shum E, et al. Cancer Res. 2022; 82(12) Supplement; CT184 Tavera-Mendoza LE, et al. AACR NCI EORTC. 2022. Abstract No. 177. Lucas M, et al. ENA. 2022. Abstract No. 64. Spira A, et al. AACR NCI EORTC. 2023. Poster No. C222. Zhang S, et al. AACR NCI EORTC. 2022. Poster No. 236. Siegel F, et al. ENA. 2022. 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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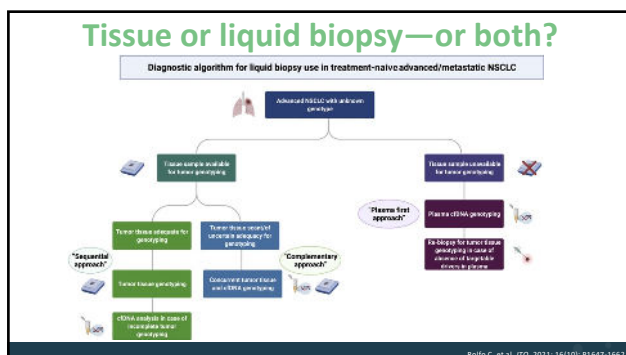
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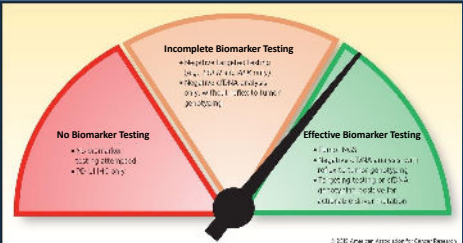
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How can I make sure my doctor gives me all the information about the subtype of my EGFR mutation?

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Advocate for Effective Biomarker Testing



NGS, next generation sequencing; cDNA, circulating free DNA; ctDNA, circulating tumor DNA. Adapted from: Meador CB and Oxnard GR. Clin Cancer Res. 2019; 25(13): 4589–4595.

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Biomarker testing in the guidelines



Biomarker testing in real life



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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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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?

Different Strategies

- Using Existing Drugs in New Ways
- Adding to Standard Treatments
- Replacing Standard Treatments

Multiple ways a clinical trial might evaluate a potential new treatment

Different Phases of Drug Development

Phase 1 → Phase 2 → Phase 3

Understanding side effects → Understanding anti-cancer activity

Different Timing

'1st Line' → '2nd Line' → Any # of Prior Treatments

As a first treatment after diagnosis → After many prior types of treatment

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What is it like to participate in a clinical trial?

Evaluation with Study Site
Discuss Clinical Trial Options

Written Consent Process

Formal Eligibility Evaluation
"Screening"

Treatment on Study
"Study Protocol"



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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

- Gather details about your cancer**
 - NCI Cancer details checklist:
<https://www.cancer.gov/research/participate/clinical-trials-search/steps/detailschecklist.pdf>
- 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)
- What trials interest you?**
 - Things to consider: trial objective, eligibility, location, length
- 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
- 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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Downloadable Fact Sheets on EGFR Resisters Website
Also located on the patient portal for this webinar

<https://egfrcancer.org/ask-the-egfr-experts/egfr/>

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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

Amrinda Delgado, Achala Kumar Gaddati

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 investigators to help guide clinical decision making. While overall survival (OS) has frequently been regarded as the “gold standard” primary clinical endpoint, its 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, and point

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

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