



What you need to know about...

targeted therapy



foreword

About LUNGeivity

LUNGeivity is the largest national lung cancer-focused nonprofit, changing outcomes for people with lung cancer through research, education, and support.

About the LUNGeivity PATIENT EDUCATION SERIES

LUNGeivity has developed a comprehensive series of materials for patients/survivors and their caregivers, focused on understanding how lung cancer develops, how it can be diagnosed, and treatment options. Whether you have recently been diagnosed with lung cancer, someone you care about has been diagnosed, or you are concerned about your risk, we have resources to help you.

The medical experts and lung cancer survivors who provided their valuable expertise and experience in developing these materials all share the belief that well-informed patients make their own best advocates.

In addition to this and other booklets in the LUNGeivity patient education series, additional information and resources can be found on LUNGeivity's website, www.LUNGeivity.org, under "For Patients & Caregivers" and "For Supporters & Advocates."

This patient education booklet has been
produced through charitable donations from:



Boehringer
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NOVARTIS

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introduction

Targeted therapy is a type of treatment that uses drugs or other substances to attack specific cancer cells, including some kinds of lung cancers. As scientists have learned about driver mutations in cells that cause cancer, they have been able to develop drugs that directly target some of these mutations. These drugs target specific parts of cells and the signals that proteins send to cells that cause them to grow and divide uncontrollably. Targeted therapies are sometimes also called “biomarker-driven therapies,” “precision medicines,” “molecularly targeted drugs,” or “molecularly targeted therapies.”

This booklet will help you:

- Learn about the mutations that can cause lung cancer
- Find out about getting your tumor tested for mutations and how to go about doing so
- Learn which targeted therapy options are currently available for those with a mutation
- Understand whether targeted therapy might be a good treatment option for you

YOU’LL FIND A GLOSSARY TOWARD THE END OF THIS BOOKLET.

Words included in the glossary appear **blue** the first time that they are used in the text.

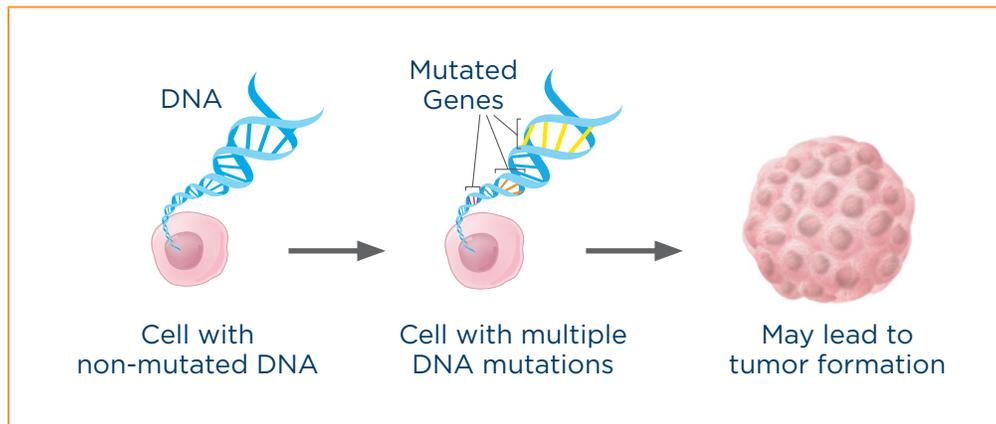
01 driver mutations

All organs and tissues in our body are made up of cells, and each of these cells contains thousands of **genes**. Genes are made up of **DNA**, which is a specific code that is used to ultimately make **proteins** that have specific functions in cells. It is essential for each gene to have the correct DNA code, or instructions, for making its protein. When the DNA is correct, the protein is able to perform the correct function.

What is a driver mutation?

When a gene has an error in its DNA code, it is said to be mutated. **Mutations** occur often, and normally the body can correct them. However, depending on where in a gene the mutation occurred, the mutation may become part of the cell's blueprint. Over time, an accumulation of many mutations in different genes can result in the formation of a **tumor**. Mutations that cause cancer are called driver mutations.

MUTATION



Mutations can be:

- **Acquired (also called somatic):** Present only in the tumor and not passed on to children
- **Inherited (also called germline):** Present in all cells of the body and passed on to children

Virtually all of the mutations that occur and inform treatment decisions in **lung cancer** are acquired. Inherited mutations are still being researched in lung cancer.

In this booklet, we are only talking about **targeted therapies** for acquired mutations.

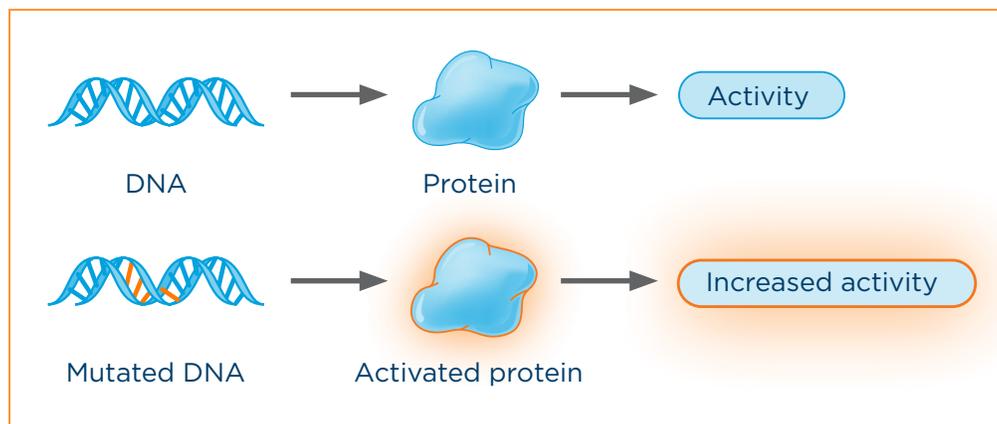
What are the different types of driver mutations that are known to cause cancer?

Several types of driver mutations cause cancer. Some of these include:

Activating mutation

An **activating mutation** is a change in the DNA sequence that can cause changes in the protein made by the gene so that it is always active. This may lead to uncontrolled cell growth.

ACTIVATING MUTATION

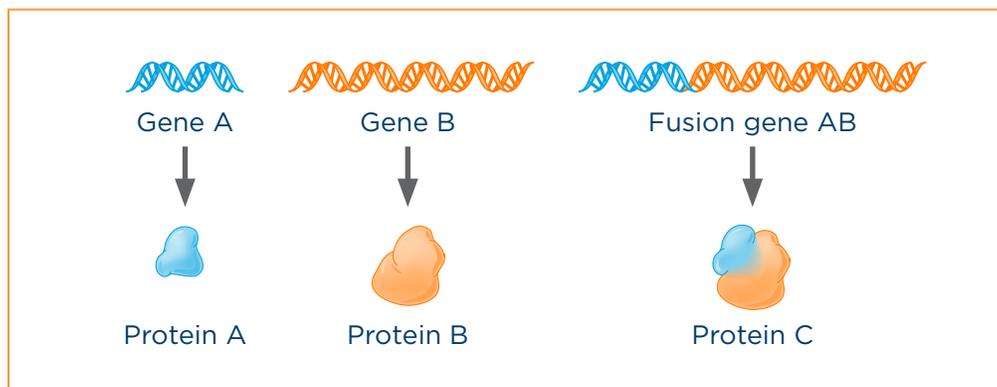


Examples of activating mutations in lung **adenocarcinoma** are an L858R substitution mutation or exon 19 **deletion** in the epidermal growth factor receptor (EGFR) gene and the V600E mutation in the BRAF gene.

Fusion

Fusion, or rearrangement, occurs when a part of one gene fuses with, or attaches to, a part of another gene. The fused gene then produces a unique protein that promotes abnormal, unchecked cell growth.

FUSION

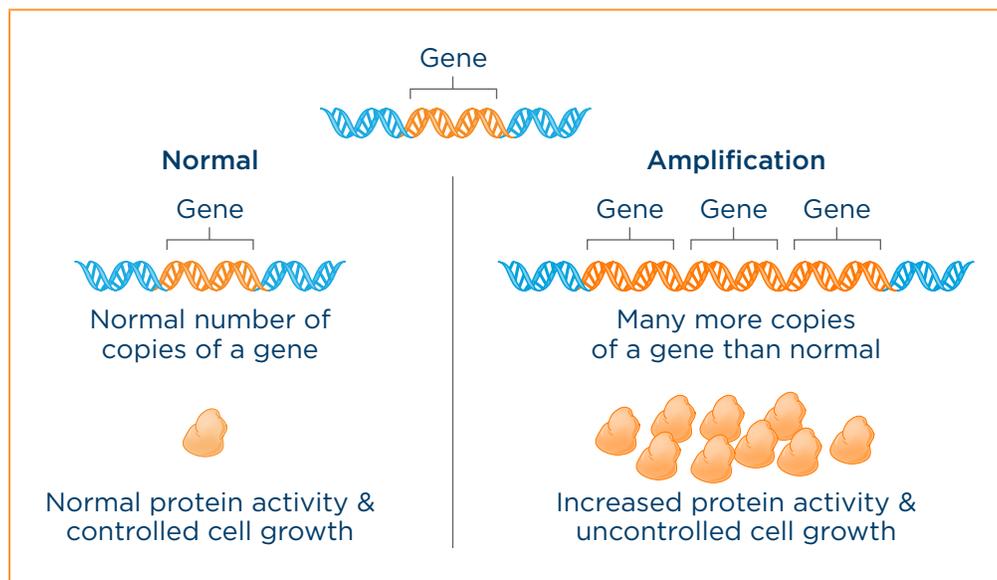


Examples of fusion genes in lung adenocarcinoma include the ALK-EML4 and the CD74-ROS1 fusion genes.

Amplification

Amplification means that there are many more copies of a gene than normal. The **overexpression** then leads to increased protein activity and uncontrolled cell growth.

AMPLIFICATION

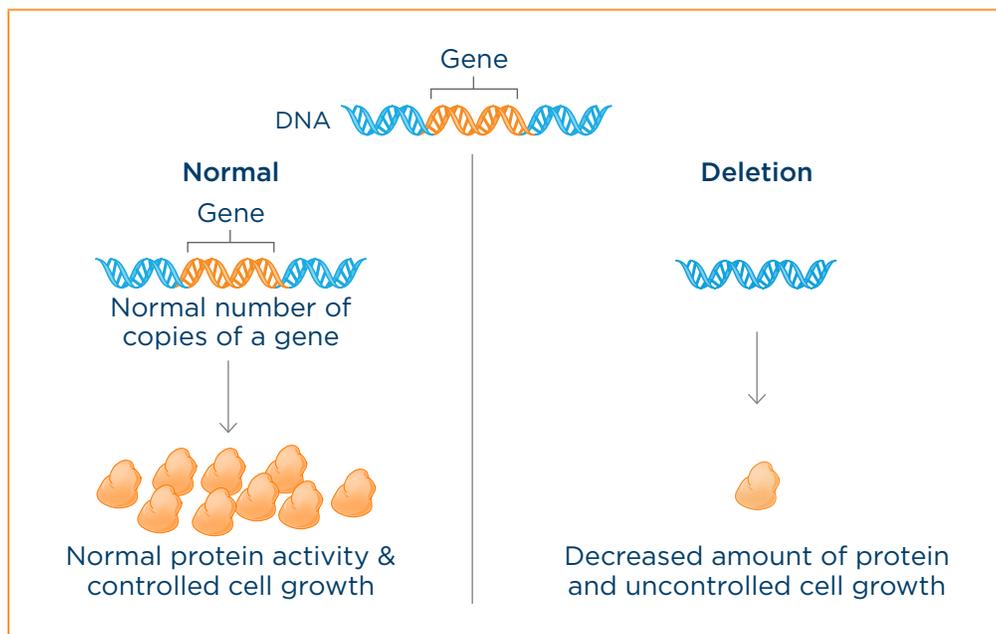


Examples of genes that can be amplified in lung adenocarcinoma include the HER2 and MET genes.

Deletion

Deletion means part of or the entire gene is missing in the cancer cells. The deletion then leads to reduced levels of protein being produced by the cancer cell.

DELETION



Examples of deleted genes in **small cell lung cancer (SCLC)** include the TP53 and the RB genes.

Driver mutations seen in lung cancers

Lung cancer describes many different types of cancer that start in the lung or related structures. There are two different ways of describing what kind of lung cancer a person has:

- **Biomarker profile** (also called **molecular profile**, genomic profile, or signature profile)—the genomic characteristics, as well as any other unique biomarkers, found in a person’s cancer
- **Histology**—what the cells look like under a microscope; histological types include SCLC and **non-small cell lung cancer (NSCLC)**. Subtypes of NSCLC include adenocarcinoma, **squamous cell lung cancer**, **large cell lung cancer**, and some rarer types

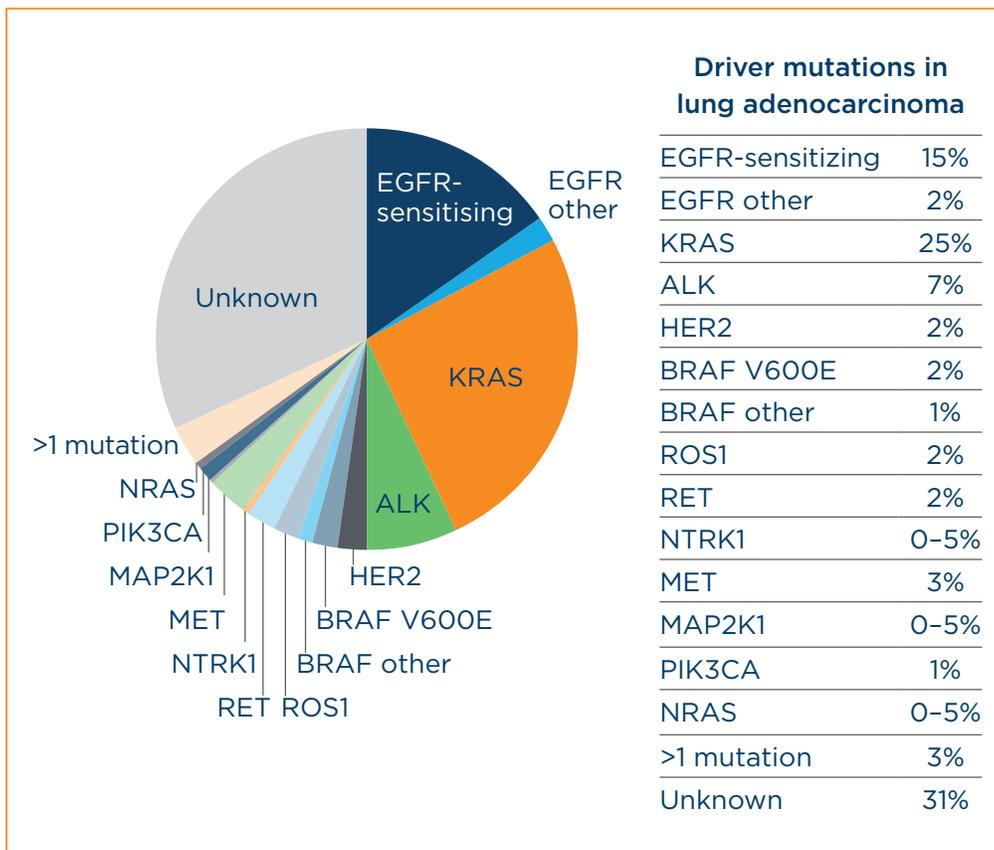
A person’s lung cancer may or may not have one of the many known driver mutations. So far, scientists have identified more than 20 different driver mutations that can be found in NSCLC and SCLC, and they are continuing to look for more.

These driver mutations are biomarkers that can be identified through molecular (or genomic) testing of a lung cancer. This testing is typically performed on a piece of tumor taken from a **biopsy** or, in some cases, through a blood test. Their presence may determine whether a patient will be prescribed one of the targeted therapies approved by the U.S. Food and Drug Administration (FDA) or be potentially eligible for a **clinical trial**.

Right now, scientists have the most information about driver mutations in the histological subtype of NSCLC called adenocarcinoma.

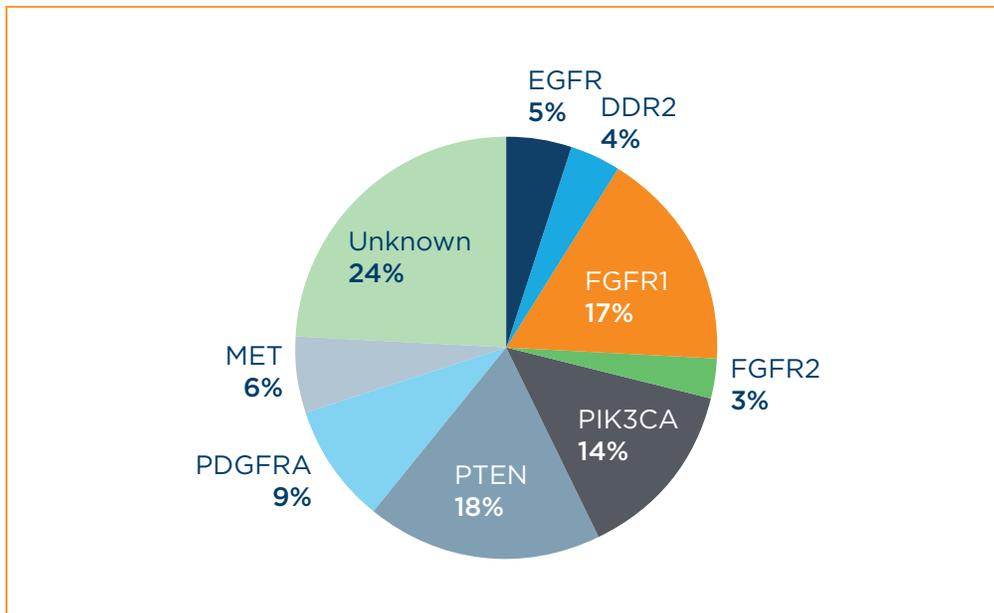
The driver mutations that currently have targeted therapies approved by the FDA include anaplastic lymphoma kinase (ALK), EGFR, ROS1, and BRAF V600E.

DRIVER MUTATIONS IN LUNG ADENOCARCINOMA



Scientists are also making progress in understanding mutations in squamous cell lung cancer.

DRIVER MUTATIONS IN SQUAMOUS CELL LUNG CANCER



Driver mutations in SCLC and other types of lung cancer are also being studied. However, there are as yet no targeted therapy drugs that are FDA-approved for them. This may change, so check with your doctors.

02 targeted therapy

What are targeted therapies?

Targeted therapies are a type of treatment that targets specific parts of cancer cells and the signals that proteins send to cancer cells that cause them to grow and divide uncontrollably. These drugs are often grouped by how they work or what part of the cell they target.

Targeted therapies are sometimes also called:

- Biomarker-driven therapies
- Precision medicines
- Molecularly targeted drugs
- Molecularly targeted therapies

Tyrosine kinase inhibitors (TKIs)

All of the targeted therapy drugs that have already been FDA-approved for lung cancer belong to a class of drugs called **tyrosine kinase inhibitors (TKIs)**.

Tyrosine kinases are specific proteins that act as **enzymes** that may signal cancer cells to grow. The proteins encoded by the ALK, EGFR, ROS1, and BRAF genes are all examples of tyrosine kinases. TKIs are targeted therapies that block these cell signals. By blocking the signals, they keep the cancer from growing and spreading. TKIs are named based on the enzyme, or protein, that they block. The driver mutations for which there are FDA-approved drugs on the market are:

- ALK
- EGFR **non-resistant** (sensitizing) **mutations**
- ROS1
- BRAF V600E

In addition, clinical trials are currently studying promising drugs to target other driver mutations.

Anaplastic lymphoma kinase (ALK) inhibitors

An anaplastic lymphoma kinase (ALK) rearrangement is a fusion between two genes: ALK and, most commonly, **echinoderm microtubule-associated protein-like 4 (EML4)**. (Note that the ALK gene can rarely be fused to other genes.) The fusion of these two genes produces an abnormal ALK protein that causes cancer cells to grow and spread.

About 7% of patients with lung adenocarcinoma in the U.S. have tumors with an ALK mutation. A similar frequency has been reported in Asian populations. The fusion between ALK and EML4 is more common among younger patients (median age at diagnosis is 52 years), nonsmokers or light smokers, and those with adenocarcinomas. It has rarely been found in patients with squamous cell lung cancer.

There are currently four approved ALK inhibitors, which are also known as **anaplastic lymphoma kinase tyrosine kinase inhibitors (ALK TKIs)**:

- **Crizotinib (Xalkori®)**: Approved for patients with **metastatic** NSCLC who are ALK-positive, as detected by an FDA-approved test
- **Ceritinib (Zykadia®)**: Approved for patients with metastatic NSCLC who are ALK-positive, as detected by an FDA-approved test
- **Alectinib (Alecensa®)**: Approved for patients with metastatic NSCLC who are ALK-positive, as detected by an FDA-approved test
- **Brigatinib (Alunbrig®)**: Approved for patients with metastatic ALK-positive NSCLC who have progressed on or are intolerant to crizotinib

In addition, other ALK inhibitors are currently being studied in clinical trials.

How do ALK inhibitors work?

ALK inhibitors work by blocking the signals that the abnormal ALK proteins send to cells to grow and divide uncontrollably. This stops the growth and spread of the cancer cells.

How are ALK inhibitors administered?

- Crizotinib (Xalkori®) is given as a pill 2 times a day, with or without food.
- Ceritinib (Zykadia®) is given as a pill once a day and must be taken at least 1 hour before a meal or at least 2 hours after a meal.
- Alectinib (Alecensa®) is given as a pill 2 times a day, with food.
- Brigatinib (Alunbrig®) is given as a pill once a day, with or without food.

What are the side effects of ALK inhibitors?

The side effects of the ALK inhibitors differ by drug and by patient.

Some common side effects of ALK inhibitors as a group include:

- Nausea
- Vomiting
- Fatigue
- Diarrhea
- Constipation

Some of these side effects can be improved by reducing the dosage of ALK inhibitors.

Some serious but rare side effects of ALK inhibitors as a group include:

- Liver problems
- Breathing problems (**pneumonitis**)
- Abnormal heartbeats

Overall, these drugs are well tolerated.

In addition, crizotinib (Xalkori®) has unique vision-specific side effects. These include:

- Trouble looking at light
- Blurred vision
- Double vision
- Seeing flashes of light
- New or increased **floaters**

Low testosterone is one source of fatigue in patients being treated with crizotinib (Xalkori®). This can also lead to sexual dysfunction and depression. Scientists have found that hormone replacement therapy is an effective method of managing these side effects.

When you start a new ALK inhibitor, you should discuss with your doctor:

- Which potential side effects to expect
- What can be done to manage them
- Which side effects are serious and need to be reported immediately

Where do ALK inhibitors fit in the lung cancer treatment plan?

Sometimes, treatment with an ALK inhibitor will be the only treatment a patient receives. However, in most cases, ALK inhibitors are used before, together with, or after other treatments, which can include **chemotherapy**, surgery, and/or **radiation therapy**.

Epidermal growth factor receptor (EGFR) inhibitors

Epidermal growth factor receptor (EGFR) is a protein found in abnormally high levels on the surface of some cancer cells. Driver mutations involving EGFR can lead to uncontrolled cancer cell growth and survival.

Approximately 10% of patients with NSCLC in the U.S. and 35% in East Asia have tumors with an EGFR driver mutation. Regardless of the patient's ethnicity, EGFR driver mutations are more often found in tumors of female nonsmokers. Most commonly, these patients have adenocarcinoma.

There are currently four FDA-approved EGFR inhibitors, which are also known as **epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs)**.

All of these are approved for **first-line treatment**; erlotinib (Tarceva®) and osimertinib (Tagrisso®) are also approved for additional treatments:

- **Afatinib (Gilotrif®)**: Approved for first-line treatment of patients with metastatic NSCLC whose tumors have EGFR non-resistant mutations, as detected by an FDA-approved test. The most common of these are the exon 19 deletions and the exon 21 (L858R) substitution mutations. The more rare mutations are S768I, L861Q, and G719X.
- **Erlotinib (Tarceva®)**: Approved for the treatment of patients with EGFR-positive metastatic NSCLC. This includes patients whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, as detected by an FDA-approved test, who are receiving first-line or **maintenance treatment**, or second- or greater-line treatment after progression following at least one prior chemotherapy regimen.
- **Gefitinib (Iressa®)**: Approved for the first-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, as detected by an FDA-approved test.
- **Osimertinib (Tagrisso®)**: Approved for first-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) mutations, as detected by an FDA-approved test. It is also approved for second-line treatment of patients with metastatic NSCLC whose tumors are (EGFR) T790M-positive, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy.

How do EGFR inhibitors work?

EGFR inhibitors work by blocking the signals that activate the EGFR protein, resulting in decreased tumor growth and survival.

How are EGFR inhibitors administered?

- Afatinib (Gilotrif®) is given as a pill once a day, 1 hour before or 2 hours after a meal.
- Erlotinib (Tarceva®) is given as a pill once a day on an empty stomach.
- Gefitinib (Iressa®) is given as a pill once a day, with or without food.
- Osimertinib (Tagrisso®) is given as a pill once a day, with or without food.

What are the side effects of EGFR inhibitors?

A very common side effect of EGFR inhibitors is an acne-like rash on the scalp, face, neck, chest, and upper back. This occurs because normal skin cells have a lot of EGFR, and they must grow quickly to maintain the skin's surface layer. Drugs that target EGFR also turn off the signal for skin cells to grow normally, and make it harder for them to retain moisture.

Some common side effects of EGFR inhibitors as a group include:

- Rash
- Itching (**pruritus**)
- Diarrhea
- Mouth sores (**stomatitis**)
- Loss of appetite
- Weakness
- Cough

Serious but rare side effects that have been seen with one or more of the EGFR inhibitors are:

- Breathing problems because of **interstitial lung disease**
- Liver and kidney damage
- Eye inflammation
- Severe skin lesions
- Bleeding problems
- Heart issues

Where do EGFR inhibitors fit in the lung cancer treatment plan?

Sometimes, treatment with an EGFR inhibitor will be the only treatment a patient receives. However, in most cases, EGFR inhibitors are used before, together with, or after other treatments, which can include chemotherapy, surgery, and/or radiation therapy.

When you start a new EGFR inhibitor, you should discuss with your doctor:

- Which potential side effects to expect
- What can be done to manage them
- Which side effects are serious and need to be reported immediately

ROS1 inhibitor

A ROS1 rearrangement is a fusion between two genes, ROS1 and another gene. As with ALK, the fusion of the two genes produces an abnormal protein that causes cancer cells to grow and spread.

About 1%–2% of patients with lung adenocarcinoma in the U.S. and 2%–3% in East Asia have tumors with a ROS1 mutation. ROS1 fusions are more commonly found among younger patients (median age at diagnosis is 50 years), females, never-smokers, and patients with adenocarcinoma.

There is currently one tyrosine kinase inhibitor that has been FDA-approved for patients with metastatic NSCLC whose tumors are ROS1-positive, as detected by an FDA-approved test. This is crizotinib (Xalkori®), a TKI that is also used for patients with ALK-positive tumors.

Other ROS1 inhibitors are currently being studied in clinical trials.

How does the ROS1 inhibitor work?

Crizotinib (Xalkori®) works by blocking the signals that the abnormal ROS1 proteins send to cells to grow and divide uncontrollably. This stops the growth and spread of the cancer cells.

How is it administered?

Crizotinib (Xalkori®) is given as a pill 2 times a day, with or without food.

What are the side effects of the ROS1 inhibitor?

The side effects of crizotinib (Xalkori®) on patients who are ROS1-positive are in general the same as those of patients who are ALK-positive. The most common side effects are:

- Visual problems
- Diarrhea
- Nausea
- Swelling of the hands and feet
- Constipation
- Vomiting
- Liver damage (as shown by abnormal blood tests related to liver function)
- Feeling tired
- Changes in taste
- Dizziness

Most of these side effects are mild and not permanent.

When you start on crizotinib, you should discuss with your doctor:

- Which potential side effects to expect
- What can be done to manage them
- Which side effects are serious and need to be reported immediately

Where does the ROS1 inhibitor fit in the lung cancer treatment plan?

Sometimes, treatment with crizotinib (Xalkori®) will be the only treatment a ROS1-positive patient receives. However, in most cases, crizotinib (Xalkori®) is used before, together with, or after other treatments, which can include chemotherapy, surgery, and/or radiation therapy.

BRAF V600E combination inhibitor

Mutations in the BRAF gene occur in 1%–3% of lung adenocarcinoma patients. Unlike other driver mutations in lung cancer, BRAF mutations are commonly seen in lung cancer patients who are current or former smokers. The V600E mutation is the most common mutation in the BRAF gene, but other mutations (called non-V600E mutations) can also occur.

There is currently one FDA-approved targeted treatment for patients with metastatic NSCLC with a BRAF V600E mutation, as detected by an FDA-approved test. This is a combination treatment of a BRAF tyrosine kinase inhibitor, dabrafenib (Tafinlar®), with a MEK kinase inhibitor, trametinib (Mekinist®). These and other targeted therapies are also being tested for patients with non-V600E BRAF mutations in clinical trials.

How does the BRAF V600E TKI combination inhibitor work?

The combination inhibitor works by blocking the signals that the abnormal BRAF proteins send to cells to grow and divide uncontrollably. This stops the growth and spread of the cancer cells.

How is it administered?

Dabrafenib (Tafinlar®) is given as a pill 2 times a day approximately 12 hours apart and at least 1 hour before or at least 2 hours after eating. Trametinib (Mekinist®) is also given as a pill, but just once a day, at least 1 hour before or at least 2 hours after eating.

What are the side effects of the BRAF V600E combination inhibitor?

Like other targeted therapies, the combination of medications used to target BRAF V600E has a unique side-effect profile.

Some common side effects of the BRAF V600E combination treatment include:

- Fever
- Fatigue
- Nausea
- Vomiting
- Diarrhea
- Dry skin
- Decreased appetite
- Edema
- Rash
- Chills
- Hemorrhage (bleeding)
- Cough
- Dyspnea

There are a number of more rare and serious side effects of the BRAF V600E combination treatment that may occur. Some of these include:

- **Hyponatremia**
- **Lymphopenia**
- **Anemia**
- **Hyperglycemia**

When you start on the combination therapy, you should discuss with your doctor:

- Which potential side effects to expect
- What can be done to manage them
- Which side effects are serious and need to be reported immediately

Which driver mutations identified in lung cancer are being studied in clinical trials?

Currently, clinical trials are open for many drugs that inhibit the effect of mutations seen in NSCLC and SCLC. The targeted treatments are being studied alone as well as in combination with other targeted therapies, **immunotherapy**, chemotherapy, and radiation therapy. As the number of known driver mutations in lung cancer tumors increases, so does the number of drugs being developed to target them. Discuss with your doctor whether participating in a clinical trial might be a good option for you. Drugs that are currently being studied are intended to act against the driver mutations in the table on the next page.

DRIVER MUTATIONS WITH DRUGS IN CLINICAL TRIALS

Driver Mutation	Lung Adenocarcinoma	Squamous Cell Lung Cancer	Small Cell Lung Cancer
TP53	X	X	X
EGFR	X		
KRAS	X		
MEK1 (MAP2K1)	X	X	
RB1	X	X	X
ALK (fusion)	X		
MYC	X	Rare	X
FGFR1 (amp)	X	X	X
RET	X		
MET			
<i>Amplification (de novo)</i>	X		
<i>Amplification (EGFR TKI-resistant)</i>	X		
<i>Exon 14 skipping</i>	X	X	
PTEN	X	X	X
PIK3CA			
<i>Mutation</i>	X	X	
<i>Amplification</i>	X	X	X
BRAF	X		
ROS1	X		
NTRK1	X		
HER2			
<i>Mutation</i>	X		
<i>Amplification</i>	X		
IGR1			X
PARP1		X	X
Notch Signaling			X

Resistance to TKIs

The biggest challenge of TKIs is that a majority of those lung cancer patients who initially benefit from them eventually develop resistance. **Acquired resistance** is defined as **disease progression*** in a patient after:

- a complete or partial response following treatment with a targeted therapy, OR
- more than 6 months of **stable disease** following treatment with a targeted therapy

Cancer cells are clever enough to bypass roadblocks to their survival and often further mutate to overcome the effects of targeted drugs.

For example, the most common way adenocarcinomas become resistant to EGFR inhibitors is by mutating to a drug-resistant state that stops the drugs from working. Another way a tumor can become resistant to EGFR inhibitors is by activating a different **signaling pathway** in the cell to bypass the pathway that the drug uses to kill the cells. In a small number of cases, the adenocarcinoma may transform into SCLC.

Similarly, lung cancers with an ALK or a ROS1 rearrangement normally have good responses to ALK or ROS1 inhibitors. However, the majority of patients also eventually become resistant to the effects of the drugs. In many cases, resistance arises because of further mutations.

Doctors and scientists are working to overcome resistance in tumors and to keep TKIs effective against cancer for longer periods of time.

*According to Response Evaluation Criteria in Solid Tumors (RECIST) or **World Health Organization (WHO) criteria**

Their approaches include:

- Simultaneously prescribing multiple **enzyme inhibitors**, in case a different driver mutation in the cell has been activated
- Developing the next generation of enzyme inhibitors that will inhibit not only the activity of the mutated gene but also the mutant form into which it could change

If a patient's cancer has grown after treatment with a targeted therapy, a decision needs to be made about the next treatment option. Your doctor may recommend that a biopsy be done of one of the tumors that is growing to determine whether there is a new mutation. For example, for EGFR patients, if the (EGFR) T790M mutation is present (it is found in about two-thirds of patients who have this biopsy), your doctor may recommend the next-generation EGFR inhibitor, osimertinib (Tagrisso®), or a clinical trial.

In addition to osimertinib (Tagrisso®) for EGFR patients, several other next-generation inhibitors have already been approved, including ceritinib (Zykadia®), alectinib (Alecensa®), and brigatinib (Alunbrig®) for ALK-positive NSCLC patients. Scientists are researching approaches to overcome resistance to crizotinib (Xalkori®) in ROS1-positive lung cancer and learning about acquired resistance in BRAF-positive lung cancers.

How does targeted therapy differ from chemotherapy and radiation therapy?

Targeted therapies are aimed at specific pathways that tumor cells use to thrive, blocking them in the same way that blocking a car's fuel line would keep it from running properly. The advantage of such precise treatments is that they can target the root cause of why a tumor is growing, which may make them more effective.



QUESTIONS TO ASK YOUR HEALTHCARE TEAM ABOUT TARGETED THERAPY:

- Why do you recommend a targeted therapy for me?
- What mutation do I have?
- What kind of targeted therapy will I get?
- Will targeted therapy be my only treatment or will it be combined with another treatment?
- How often will I take this therapy and for how long?
- How and when will I know if the treatment is working?
- How often do I need to be seen between treatments for a physical exam and/or lab work?
- Are there any tests or procedures I will need during the treatment?
- What side effects can I expect?
- What can I do to manage these side effects?
- How will this treatment affect my daily life? Will I be able to work, exercise, and perform my usual activities?
- What tests will I need after treatment is completed?
- Are there any long-term health issues I should expect from treatment with targeted therapy?
- How much will my treatment cost?

Finding a clinical trial that might be right for you

If you are considering participating in a clinical trial, start by asking your healthcare team whether there is one that might be a good match for you in your geographic area. In addition, there are several resources to help you find one that may be a good match.



RESOURCES TO HELP YOU NAVIGATE YOUR CLINICAL TRIALS SEARCH:

- **LUNgevity Clinical Trial Finder:** <https://clinicaltrials.lungevity.org/>
 - Find available clinical trials by type of lung cancer and geographic location
 - Also find information and links to the medical centers at which these clinical trials are taking place
- **EmergingMed:** <https://app.emergingmed.com/lcctal/home>
 - LUNgevity partners with this free clinical trials matching service to help you with the decision of whether to participate in a clinical trial; EmergingMed helps you identify lung cancer clinical trials for which you may be eligible
 - Clinical trial navigators are available Monday through Friday from 9:00am to 5:00pm ET at 877-769-4834
- **National Cancer Institute (NCI):** www.clinicaltrials.gov
- **My Cancer Genome:** www.mycancergenome.org/
 - My Cancer Genome gives up-to-date information on what mutations make cancers grow and related treatment options, including available clinical trials

(CONTINUED)



RESOURCES TO HELP YOU NAVIGATE YOUR CLINICAL TRIALS SEARCH (CONTINUED):

- **Lung Cancer Mutation Consortium (LCMC):**
www.golcmc.com/
 - Composed of 16 leading cancer centers across the country, LCMC's goal is to examine the tumors of patients who have **advanced stage non-small cell lung cancer adenocarcinoma (advanced stage NSCLC)** (stage IIIB or IV), and match those patients to the best possible therapies, including clinical trials
- **Lung Cancer Master Protocol (LUNG-MAP):**
www.lung-map.org/
 - For patients with squamous cell lung cancer, LUNG-MAP is a collaboration of many research sites across the country. They use a unique approach to match patients to one of several drugs being developed

In addition, if you are interested in a specific drug or other treatment that is being developed, you can often find information about studies for that drug on the website of the company developing it.

03 biomarker testing

To find out whether targeted therapy is appropriate for a person who has been diagnosed with lung cancer, that person's tumor tissue will be tested for the presence of driver mutations. Patients who have a mutation that a specific FDA-approved targeted therapy targets are candidates for that treatment. The process of testing for a mutation in a tumor is called **biomarker testing** (also known as mutation, genomic, or molecular testing).

Note: At this time, tissue biopsies are the only way to confirm a diagnosis of lung cancer and to detect driver mutations. However, liquid biopsies that make use of blood can sometimes be used to look for resistance mutations like EGFR T790M, and are being studied in other contexts.

Biomarker testing should be an ongoing part of the discussions with your doctors. Any decision to test for biomarkers should be made together, and will depend on a number of factors, including your type and **stage** of lung cancer, your current treatment plan, your overall health, and your preferences.

Note that biomarker testing may also be used to determine whether an immunotherapy drug is appropriate; in this booklet, we are only discussing biomarker testing that will help doctors determine whether a targeted therapy is an appropriate treatment.

How is biomarker testing performed?

Once the decision has been made to do biomarker testing, a surgeon will remove either the entire tumor (surgery) or part of the tumor (biopsy). **Be sure to confirm with your doctor that adequate tissue will be gathered so that all necessary biomarkers tests can be performed.**

There are a number of tissue collection techniques, including **bronchoscopy**, **endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA)**, **transthoracic needle biopsy (TTNB)**, **thoracoscopy**, and **thoracentesis**. Tumor tissue is then sent to a laboratory that can test it for driver mutations. Test results are generally available within 10 to 14 days. Biomarker testing can be done on both **primary tumors** and **metastatic tumors**.

Multiplex testing—testing for multiple gene mutations at the same time from the same sample of tumor tissue—is currently used in some laboratories. This allows more testing to be done on a small tumor sample. An example of multiplex testing is next-generation sequencing, or NGS.

Who should have their tumor tested, and when?

Again, the decision to have your tumor tested and when to test it depends on a number of factors. Below are common recommendations for biomarker testing for driver mutations.

ADENOCARCINOMA

Stage of Lung Cancer	Recommendations for Biomarker Testing for Driver Mutations
Stage I, II, and III	Testing for the ALK, EGFR, KRAS, ROS1, and BRAF V600E mutations at the time of diagnosis can be considered.
Stage IV adenocarcinoma or adenocarcinoma that has recurred or progressed after an initial diagnosis of stage I, II, or III lung cancer in patients who were not previously tested	<p>Tumors should be tested for ALK, EGFR, KRAS, ROS1, and BRAF V600E mutations at the time of diagnosis. Testing for other biomarkers may be helpful in deciding eligibility for clinical trials.</p> <p>While there is no approved targeted therapy for the KRAS driver mutation, testing for it can be informative because cancers with KRAS mutations are very unlikely to have other driver mutations. Targeted therapies for KRAS-positive cancers are being developed in clinical trials. Additionally, KRAS mutations can also be associated with resistance to EGFR targeted therapy.</p>

SQUAMOUS CELL LUNG CANCER

Stage of Lung Cancer	Recommendations for Biomarker Testing for Driver Mutations
Stage I, II, and III	Currently, biomarker testing is performed only for clinical trials.
Stage IV	If your doctors suspect that the tumor may have adenocarcinoma cells (this type of lung cancer is referred to as mixed lung cancer with an adenocarcinoma component), testing for ALK and EGFR mutations is recommended. Otherwise, biomarker testing is currently only performed for clinical trials.

SMALL CELL LUNG CANCER

Stage of Lung Cancer	Recommendations for Biomarker Testing for Driver Mutations
All stages	Currently, biomarker testing is performed only for clinical trials.

Testing to identify other possible driver mutations in the tumor may help you find clinical trials. These trials are testing new treatments for mutations in other types of lung cancer. Therefore, you should consider biomarker testing for other mutations if tests for ALK, EGFR, ROS1, or BRAF mutations are negative.



QUESTIONS TO ASK YOUR HEALTHCARE TEAM ABOUT BIOMARKER TESTING:

Before getting biomarker testing:

- What are you trying to find with biomarker tests?
- Have I already had any biomarker tests? Which ones?
- Who performs these tests?
- How are the tests performed?
- Are there any complications from these tests?
- How long will it take to get the test results?
- Where can I get more information about biomarker testing?
- Are there any limitations of biomarker testing?
- Will insurance pay for these tests?

After getting biomarker testing:

- What tests were done?
- What are the results of these tests?
- How will the results affect my treatment?
- The test results are negative: should I be retested?
- The test results are not clear: should I be retested?
- Are there any medications that target my type of lung cancer?
- Will I need these tests again? If so, why? When?
- Are there any clinical trials open to me based on these results?
- How can I get a copy of my pathology report?

04 glossary

Acquired resistance—Disease progression after a complete or partial response to treatment, or disease progression after 6 months or more of stable disease, after treatment with a targeted therapy

Activating mutation—A mutation that causes increased protein activity. This overly active protein may lead to uncontrolled cell growth

Adenocarcinoma—One type of non-small cell lung cancer that usually develops in the cells lining the lungs. It has an increased incidence in smokers and is the most common type of lung cancer seen in nonsmokers

Advanced stage non-small cell lung cancer (advanced stage NSCLC)—Refers to NSCLC that has spread either locally or to distant parts of the body

ALK TKI—See anaplastic lymphoma kinase tyrosine kinase inhibitor

Amplification—A usually massive replication of genetic material and especially of a gene or DNA sequence

Anaplastic lymphoma kinase tyrosine kinase inhibitor (ALK TKI)—

Drug that blocks the activity of a protein called anaplastic lymphoma kinase (ALK). Blocking ALK may stop the growth and spread of cancer cells

Anemia—A condition in which the number of red blood cells is below normal

Biomarker profile—The genomic characteristics, as well as any other unique biomarkers, found in a person’s cancer. The information is used to identify and create targeted therapies that are designed to work for a specific cancer tumor profile

Biomarker testing—Analyzing DNA to look for a gene mutation that may indicate an increased risk for developing a specific disease or disorder

Biopsy—The removal of cells or tissues for examination by a pathologist. The pathologist may study the tissue under a microscope or perform other tests on the cells or tissue

Bronchoscopy—A procedure that uses a bronchoscope to examine the inside of the trachea, bronchi, and lungs. A bronchoscope is a thin, tube-like instrument with a light and a lens for viewing. It may also have a tool to remove tissue; this tissue can then be checked under a microscope for signs of disease. The bronchoscope is inserted through the nose or mouth

Chemotherapy—Treatment that uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing

Clinical trial—A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. Also called clinical research trial or study

Deletion—The absence of a section or all of a gene. Deletion results in reduced protein levels being produced by the cell

Disease progression—Cancer that continues to grow or spread

DNA—The molecules inside cells that carry genetic information and pass it from one generation to the next. Also called deoxyribonucleic acid

EBUS-TBNA—See endobronchial ultrasound-guided transbronchial needle aspiration

Echinoderm microtubule-associated protein like-4 (EML4)—A gene that when combined with the anaplastic lymphoma kinase (ALK) gene, produces an abnormal protein that leads to cancer cell growth

EGFR TKI—See epidermal growth factor receptor tyrosine kinase inhibitor

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA)—Endobronchial ultrasound bronchoscopy (EBUS) is a type of bronchoscopy that uses a flexible bronchoscope fitted with an ultrasound device. Ultrasound uses high-frequency sound waves to make pictures of the insides of the body. The flexible tube is moved around to get a clear picture of the lung tissue. The picture is viewed on a computer screen to decide the optimal position for a biopsy

Enzyme—A special protein that the body produces to control its cells and carry out chemical reactions quickly. Sometimes enzymes signal cancer cells to grow

Enzyme inhibitor—A type of targeted therapy that works by blocking the signals an enzyme sends cancer cells to grow

Epidermal growth factor receptor tyrosine kinase inhibitor

(EGFR TKI)—Drug that blocks the activity of a protein called epidermal growth factor receptor (EGFR). Blocking EGFR may keep cancer cells from growing. Also called EGFR inhibitor and epidermal growth factor receptor inhibitor

First-line treatment—The first therapy given for a disease. It is often part of a standard set of treatments, such as surgery followed by chemotherapy and radiation. When used by itself, first-line therapy is the one accepted as the best treatment. If it doesn't cure the disease or it causes severe side effects, other treatment may be added or used instead

Floater—A bit of optical debris (as a dead cell or cell fragment) in the vitreous body (clear gel that fills the space between the lens and the retina of the eyeball) or lens that may be perceived as a spot before the eye

Fusion—A gene made by joining parts of two different genes. Once fused together, they produce an abnormal protein that promotes abnormal, unchecked cell growth

Gene—Coded instructions within a cell that control how the cell grows in a systematic and precise way

Histology—The study of tissues and cells under a microscope

Hyperglycemia—Higher-than-normal amount of glucose (a type of sugar) in the blood. Also called high blood sugar

Hyponatremia—Lower-than-normal amount of sodium in the blood

Immunotherapy—A type of cancer therapy that uses substances to stimulate or suppress the immune system to help the body fight cancer, infection, and other diseases. Some types of immunotherapy only target certain cells of the immune system. Others affect the immune system in a general way

Interstitial lung disease—A group of disorders that causes scarring of the lungs, which eventually affects the body’s ability to get enough oxygen into the bloodstream and to breathe

Large cell lung cancer—Lung cancer in which the cells are large and look abnormal when viewed under a microscope

Lung cancer—Cancer that begins in tissues of the lung, usually in the cells lining air passages

Lymphopenia—A condition in which there is a lower-than-normal number of lymphocytes (a type of white blood cell) in the blood. Also called lymphocytic leukopenia and lymphocytopenia

Maintenance treatment—Therapy that is given to help keep cancer from coming back after it has disappeared following the initial therapy. It may include treatment with drugs, vaccines, or antibodies that kill cancer cells, and it may be given for a long time

Metastatic—Having to do with metastasis, which is the spread of cancer from the primary site, or place where it started, to other places in the body

Metastatic tumor—A tumor that has metastasized, or spread from the primary site, or place where it started, to other places in the body

Molecular profile—See biomarker profile

Multiplex testing—The testing for multiple mutations at one time

Mutation—Any change in the gene sequence of a cell. Mutations may be caused by mistakes during cell division, or they may be caused by exposure to gene-damaging agents in the environment. Certain mutations may lead to cancer or other diseases

Non-resistant mutation—Mutation in a gene that responds to tyrosine kinase inhibitors (TKIs)

Non-small cell lung cancer (NSCLC)—A group of lung cancers that are named for the kinds of cells found in the cancer and how the cells look under a microscope. The three main types of NSCLC are squamous cell lung cancer, large cell lung cancer, and adenocarcinoma. NSCLC is the most common kind of lung cancer

NSCLC—See non-small cell lung cancer

Overexpression—The expression of too many copies of a protein or other substance. Overexpression of certain proteins or other substances may play a role in cancer development

Pneumonitis—Inflammation of the lungs that may be caused by disease, infection, radiation therapy, allergy, or irritation of lung tissue by inhaled substance

Primary tumor—A term used to describe the original, or first, tumor in the body

Protein—A molecule made up of amino acids that is needed for the body to function properly. Proteins are the basis of body structures, such as skin and hair, and of other substances, such as enzymes, cytokines, and antibodies

Pruritus—Itching of the skin

Radiation therapy—The use of high-energy radiation from X-rays, gamma rays, neutrons, protons, and other sources to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external-beam radiation therapy) or it may come from radioactive material placed in the body near cancer cells (internal radiation therapy). Also called irradiation and radiotherapy

Sensitizing mutation—See non-resistant mutation

Signaling pathway—Describes a group of molecules in a cell that work together to control one or more cell functions, such as cell division or cell death. After the first molecule in a pathway receives a signal, it activates another molecule. This process is repeated until the last molecule is activated and the cell function is carried out. Abnormal activation of signaling pathways can lead to cancer, and drugs are being developed to block these pathways. These drugs may help block cancer cell growth and kill cancer cells

Small cell lung cancer (SCLC)—A fast-growing cancer that forms in tissues of the lung and can spread to other parts of the body. Named small for how the cancer cells look under a microscope

Squamous cell lung cancer—A type of non-small cell lung cancer that usually starts near a central bronchus. It begins in squamous cells, which are thin, flat cells that look like fish scales. Also called squamous cell carcinoma

Stable disease—Cancer that is neither decreasing nor increasing in extent or severity

Stage—The extent of a cancer in the body

Stomatitis—Inflammation or irritation of the mucous membranes in the mouth

Targeted therapy—A type of treatment that uses drugs to identify and attack specific types of cancer cells with less harm to normal cells. Some targeted therapies block the action of certain enzymes, proteins, or other molecules involved in the growth and spread of cancer cells

Thoracentesis—A procedure that removes fluid that may build up around your lung. A needle is inserted through the skin into the lung and fluid is removed

Thoracoscopy—The examination of the inside of the chest, using a thoracoscope. A thoracoscope is a thin, tube-like instrument with a light and a lens for viewing. It may also have a tool to remove tissue to be checked under a microscope for signs of disease

TKI—See tyrosine kinase inhibitor

Transthoracic needle biopsy (TTNB)—A technique to biopsy certain lung nodules and also some lymph nodes. Sometimes referred to as transthoracic needle aspiration (TTNA) or percutaneous needle biopsy. A very thin needle is inserted through the chest wall to get a tissue sample

Tumor—An abnormal mass of tissue that results when cells divide more than they should or do not die when they should

Tyrosine kinase—A specific enzyme produced by the body to control cell functions, including cell signaling, growth, and division. These enzymes may be too active or found at high levels in some types of cancer cells

Tyrosine kinase inhibitor (TKI)—A type of targeted therapy that blocks the action of enzymes called tyrosine kinases in order to keep cancer cells from growing

World Health Organization (WHO) criteria—Tumor response criteria, mainly for use in clinical trials, where tumor response is the primary endpoint. Response to therapy is evaluated by the change from baseline while on treatment



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