



What you need to know about...

targeted therapy



foreword

About LUNgevity

LUNgevity is the nation's premier lung cancer-focused nonprofit, changing outcomes for people with lung cancer through research, education, and support.

About the LUNgevity PATIENT EDUCATION SERIES

LUNgevity has developed a comprehensive series of materials for lung cancer patients and their caregivers, focused on understanding how lung cancer develops, how it can be diagnosed, and treatment options. Whether you or someone you care about has been diagnosed with lung cancer, or is concerned about lung cancer 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 LUNgevity patient education series, additional information and resources can be found on LUNgevity's website at www.LUNgevity.org.

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table of contents

01 Driver Mutations	5
What is a driver mutation?	5
What are the different types of driver mutations?	7
Driver mutations seen in lung cancers.....	11
02 Targeted Therapy.....	15
What is targeted therapy?.....	15
Kinase inhibitors	16
Where do targeted therapies fit into a treatment plan?.....	17
Driver mutations and their FDA-approved targeted therapies.....	17
ALK.....	18
BRAF V600E.....	20
EGFR.....	21
MET	23
NTRK	24
RET	25
ROS1.....	26
Management of targeted therapy side effects	28
Resistance to tyrosine kinase inhibitors (TKIs)	28
Which driver mutations identified in lung cancer are being studied in clinical trials?	29
Finding a clinical trial that might be right for you	31
Questions to ask your healthcare team about targeted therapy	33
03 Biomarker Testing.....	34
How is biomarker testing performed?	35
Who should have their tumor tested, and when?	37
Questions to ask your healthcare team about biomarker testing.....	39
04 Glossary	40
05 Notes	47

introduction

Targeted therapy is a type of treatment that uses drugs to attack cancer cells, including the cells of 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 them. These drugs target specific parts of cells and the signals that proteins send to cells that cause them to grow and divide uncontrollably.

This booklet will help you:

- Learn about the mutations that can cause lung cancer
- Find out how lung cancer is tested for mutations
- 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.

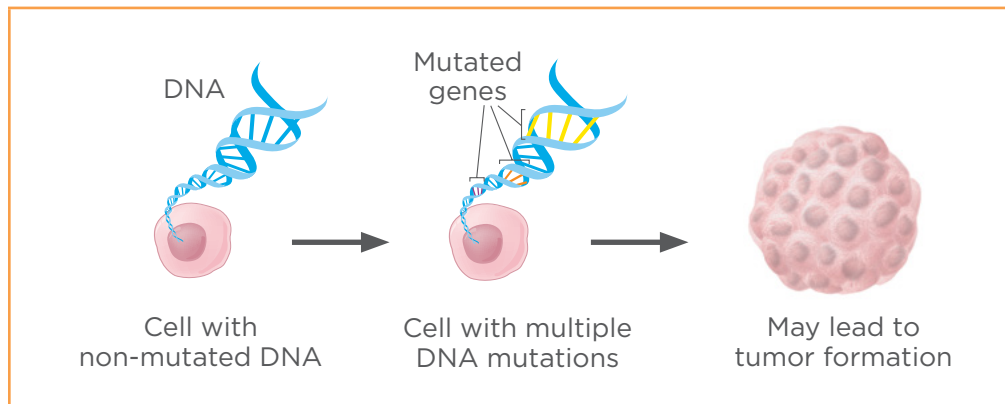
01 driver mutations

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**, material that carries a specific code that is used ultimately to 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 the mutation occurs in a gene, 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 discussing **targeted therapies** for acquired mutations.

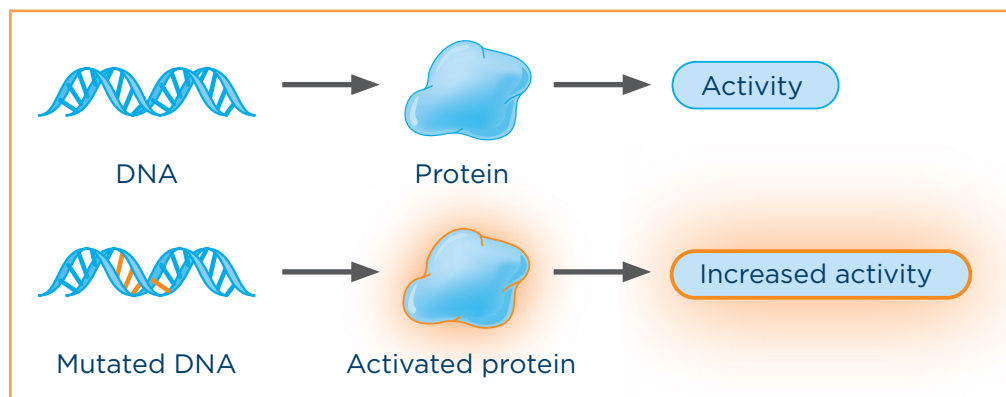
What are the different types of driver mutations?

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

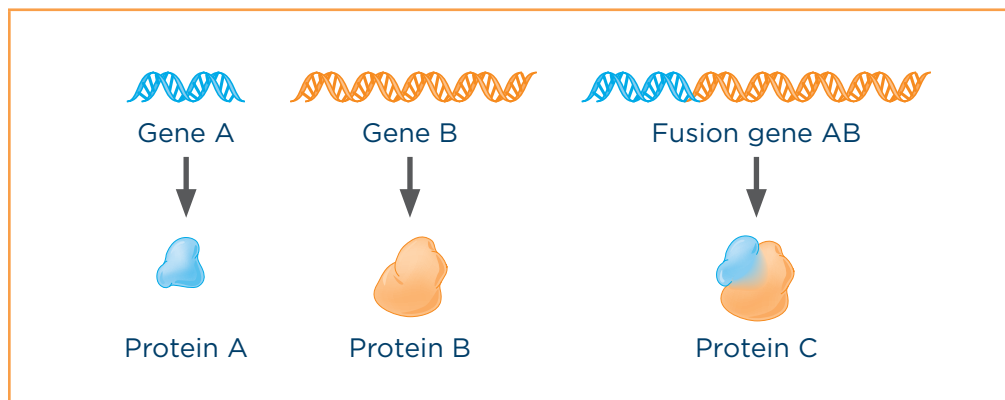


An example of an activating mutation in **lung adenocarcinoma**, a type of **non-small cell lung cancer (NSCLC)**, is the V600E mutation in the BRAF gene.

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. The gene rearrangement may also be referred to as a translocation.

FUSION PROTEIN

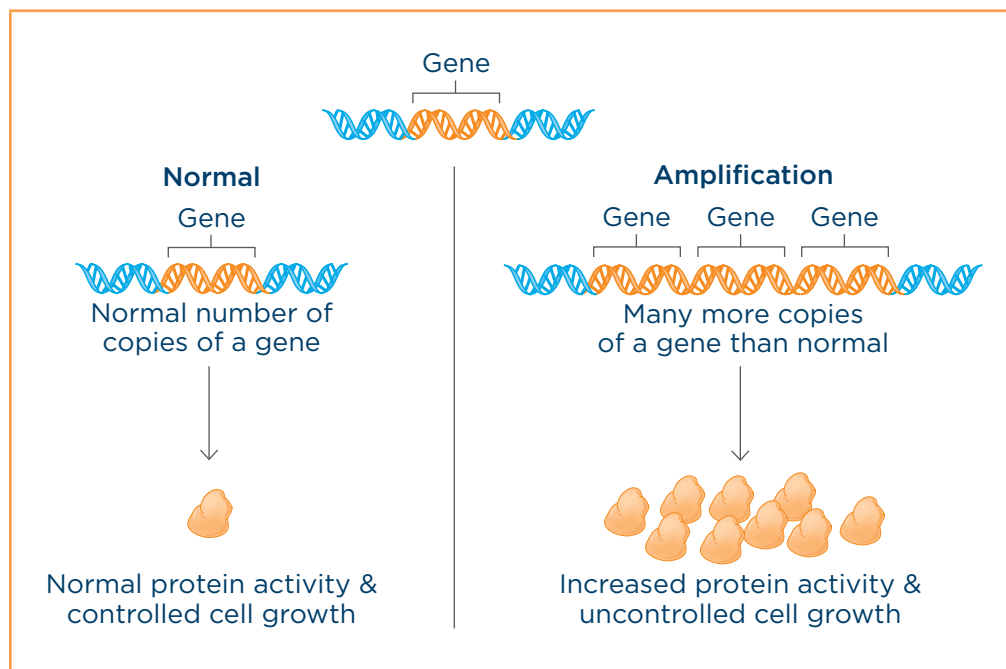


Examples of fusion genes in lung adenocarcinoma include EML4-ALK and CD74-ROS1.

Amplification

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

AMPLIFICATION

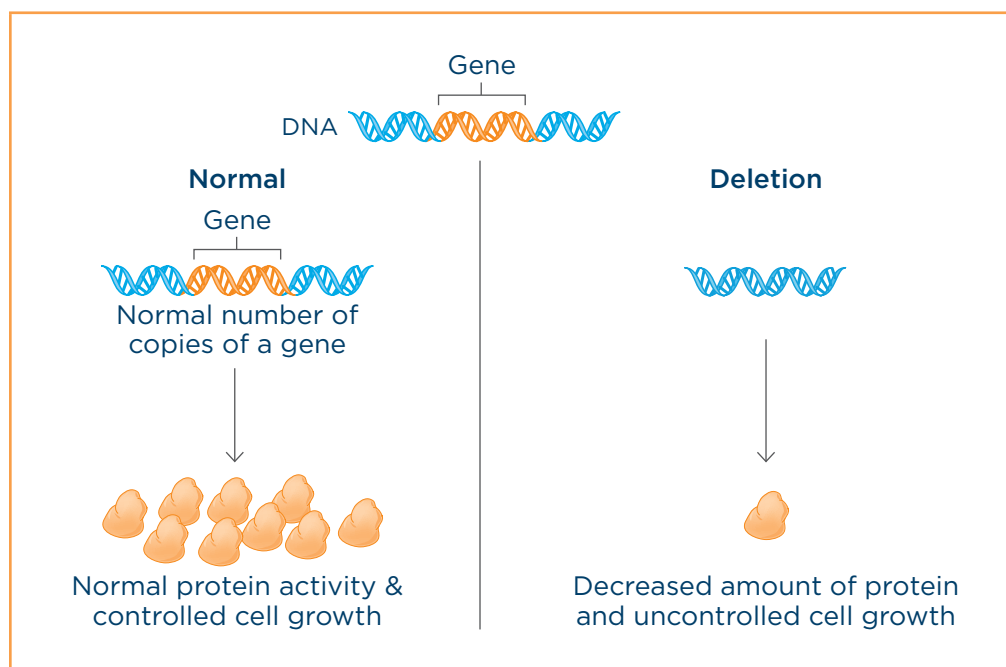


Examples of genes that can be amplified in lung adenocarcinoma include HER2 (ERBB2) and MET.

Deletion

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

DELETION



Examples of deleted genes in **small cell lung cancer (SCLC)** include TP53 and RB1.

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 NSCLC and SCLC. Subtypes of NSCLC include lung adenocarcinoma, **squamous cell lung cancer**, **large cell lung cancer**, and some rarer types.

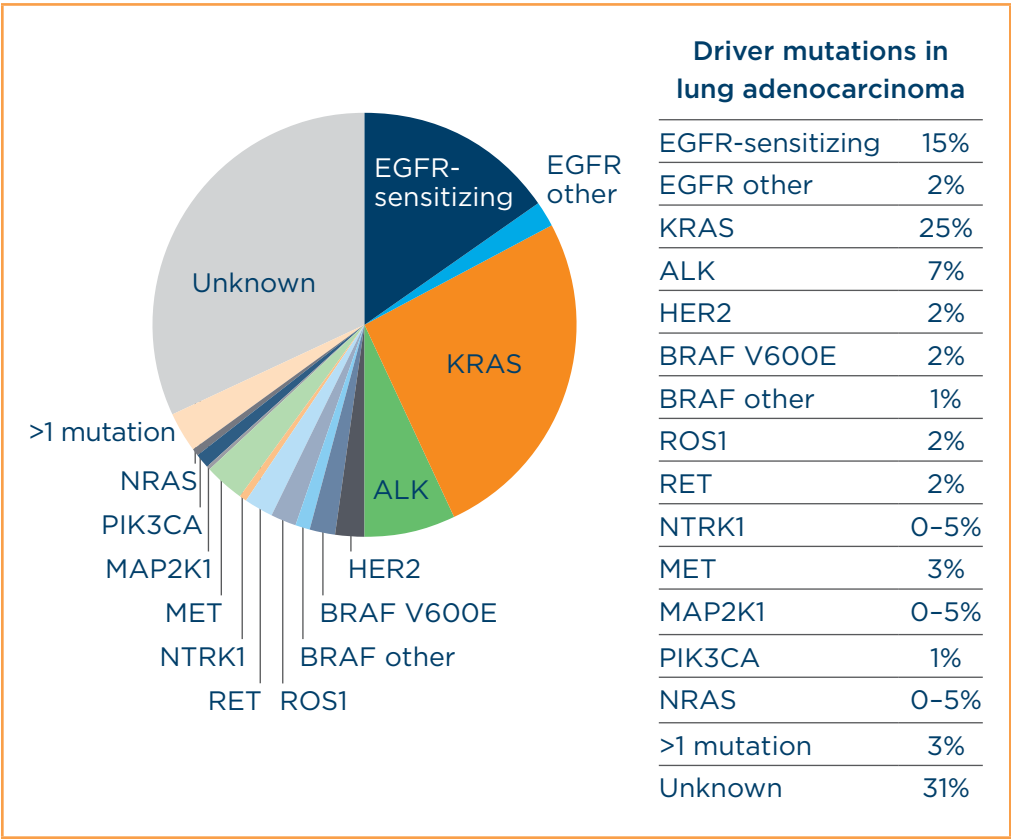
A person's lung cancer may or may not have one of the many known driver mutations. So far, scientists have identified more than 20 different driver mutations that can be found in NSCLC and SCLC, and they are continuing to look for more.

These driver mutations can be identified through **biomarker testing**. This testing is typically performed on a piece of tumor tissue taken during a **biopsy**, but, in some cases, on a blood sample. The presence of a driver mutation may determine whether a patient can be prescribed one of the targeted therapies approved by the **U.S. Food and Drug Administration (FDA)** and/or is potentially eligible for a **clinical trial**. Biomarker testing is discussed in more detail in a later chapter of this booklet.

Right now, scientists have the most information about the driver mutations in lung adenocarcinoma.

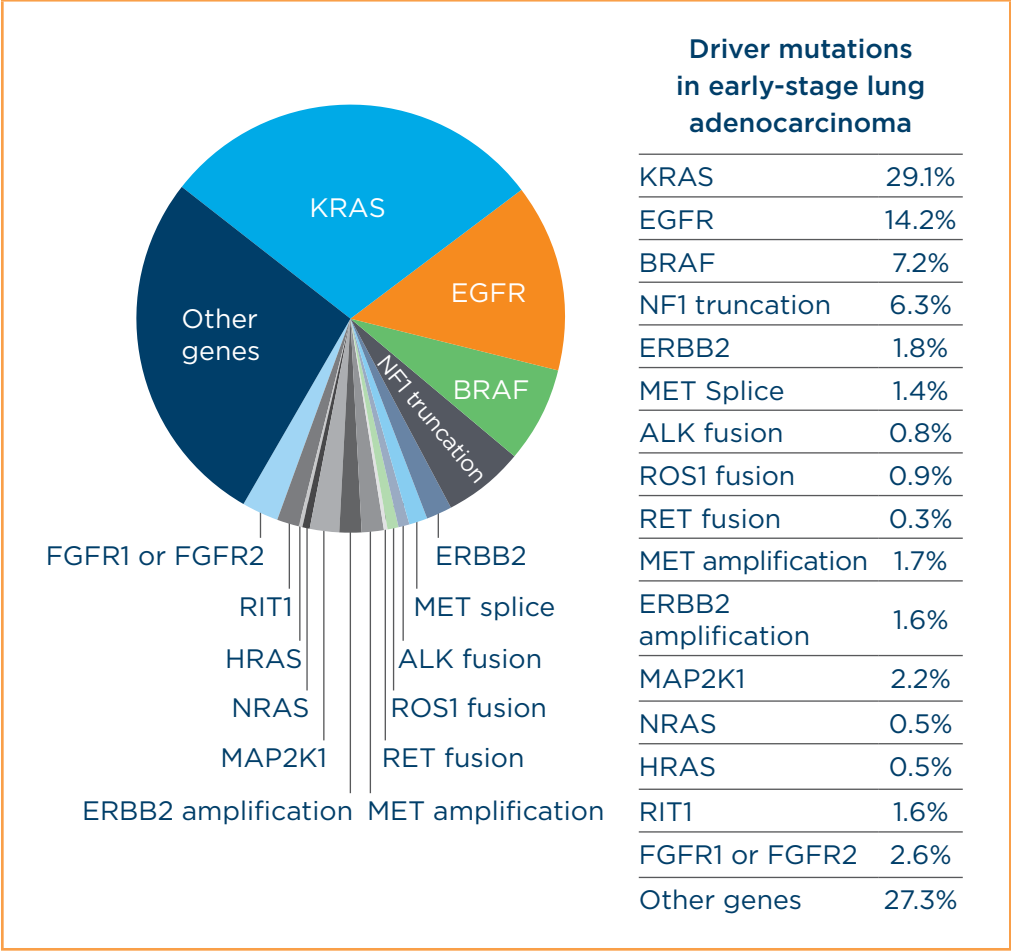
In patients with **metastatic** lung adenocarcinoma, the driver mutations that currently have targeted therapies approved by the FDA include ALK, BRAF V600E, EGFR, MET exon 14 skipping, NTRK, RET, and ROS1.

DRIVER MUTATIONS IN LUNG ADENOCARCINOMA



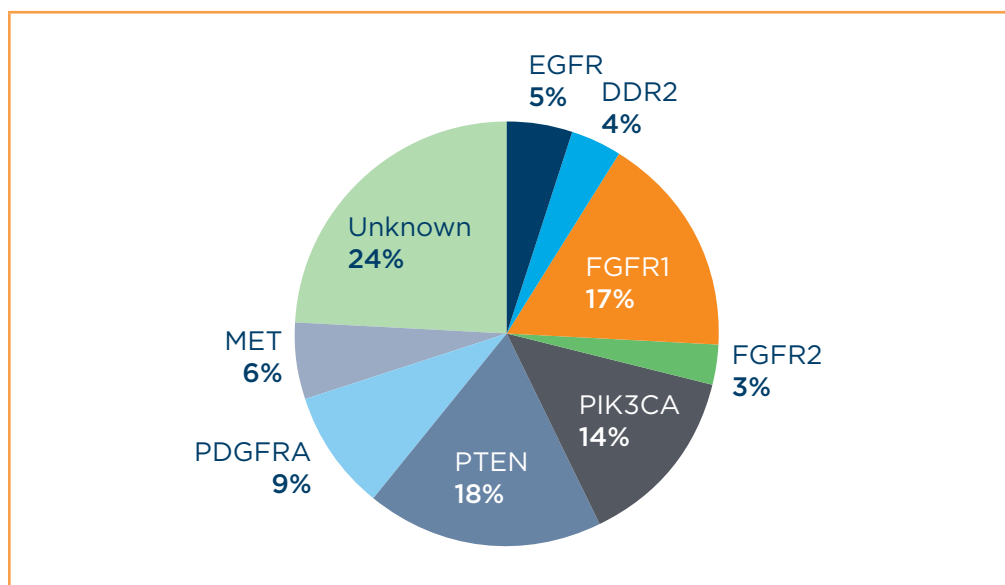
As science progresses, we are also learning about mutations in early-stage lung adenocarcinoma.

DRIVER MUTATIONS IN EARLY-STAGE LUNG ADENOCARCINOMA



Scientists are also making progress in understanding and targeting mutations in squamous cell lung cancer. Driver mutations unique to squamous cell lung cancer have not yet been identified; those that more commonly occur in lung adenocarcinoma, such as EGFR mutations or MET exon 14 skipping mutations, may also occur 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 of yet no targeted therapy drugs that are FDA-approved for them. This may change, so check with your doctors.

02 targeted therapy

What is targeted therapy?

Targeted therapy is a type of cancer treatment that identifies and attacks specific parts of cancer cells and the signals that proteins send to cancer cells that cause them to grow and divide uncontrollably. Targeted therapies are precise; they prevent the growth and spread of the cancer cells only. They do no harm to the body's normal, healthy cells.

Because each targeted therapy works to control a specific driver mutation, a patient may be treated with that targeted therapy only if they have the driver mutation for which the targeted therapy is intended.

Targeted therapies are approved primarily for patients whose lung cancer is metastatic; that is, the cancer has spread from its original site to other places in the body.

Targeted therapies are sometimes also called:

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

Targeted therapies work differently from the other three types of lung cancer drug treatments. To summarize the differences:

- **Targeted therapy:** Blocks the cancer cells' growth and division; leaves healthy cells alone
- **Standard chemotherapy:** Attacks the cancer cells directly, but also attacks healthy cells
- **Immunotherapy:** Stimulates the body's immune system to attack the cancer cells
- **Angiogenesis inhibitor:** Stops the formation of new blood vessels to cut off the tumor's blood supply

In addition, targeted therapies are administered orally (typically by pill once or twice daily), while other drug treatments are most likely to be administered **intravenously**.

A targeted therapy is given to a patient until **disease progression**—the lung cancer continues to grow and spread—or the side effects of the drug become intolerable.

Kinase inhibitors

Kinases are specific proteins that act as **enzymes** to control cell functions, including **cell signaling**, growth, and division. There are different types of kinases. The proteins encoded by the ALK, EGFR, MET, NTRK, RET, and ROS1 genes are all examples of a type of kinase called a **tyrosine kinase**. The BRAF gene encodes a different type of kinase, serine/threonine. If a gene has a driver mutation, the kinases can signal the cancer cell to grow and divide.

The targeted therapy drugs that have been approved so far by the FDA for the treatment of driver mutations in NSCLC are all kinase inhibitors, which block the cell functions and keep the cancer from growing and dividing. Except for the BRAF V600E combination treatment, all of the inhibitors are **tyrosine kinase inhibitors (TKIs)**.

Where do targeted therapies fit into a treatment plan?

Sometimes, treatment with a targeted therapy will be the only treatment a patient receives. However, a targeted therapy may also be used before, together with, or after other treatments; treatment will depend on when the driver mutation was discovered, the patient's response to treatment, and other individual factors that the doctors consider. The other treatments are most likely to include another targeted therapy, chemotherapy, chemotherapy-immunotherapy, an angiogenesis inhibitor, and/or **radiation therapy**. In addition, in those cases where a targeted therapy is appropriate and there is more than one approved therapy for a particular driver mutation, doctors again consider factors specific to the patient before prescribing a particular treatment.

Driver mutations and their FDA-approved targeted therapies

Genes with driver mutations in NSCLC for which there are currently FDA-approved targeted therapies are:

- ALK
- BRAF V600E
- EGFR
- MET exon 14 skipping
- NTRK
- RET
- ROS1

There are as of yet no approved targeted therapies for SCLC.

In addition, clinical trials are currently studying promising drugs to target these and other driver mutations; read more about these in a later section in this chapter.

ALK

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

About 5% of patients with NSCLC in Western populations have tumors with an ALK mutation. A similar frequency has been reported in Asian populations. An ALK fusion is more common among younger patients (median age at diagnosis is 52 years), nonsmokers or light smokers, and those with lung adenocarcinomas. It has rarely been found in patients with squamous cell lung cancer.

What are the approved ALK TKIs?

There are currently five FDA-approved ALK TKIs:

- Alectinib (Alecensa®): Approved for patients with metastatic ALK-positive NSCLC, as detected by an FDA-approved test
- Brigatinib (Alunbrig®): Approved for patients with metastatic ALK-positive NSCLC, as detected by an FDA-approved test
- Ceritinib (Zykadia®): Approved for patients with metastatic ALK-positive NSCLC, as detected by an FDA-approved test
- Crizotinib (Xalkori®): Approved for patients with metastatic ALK-positive NSCLC, as detected by an FDA-approved test
- Lorlatinib (Lorbrena®): Approved for patients with metastatic ALK-positive NSCLC, as detected by an FDA-approved test

What are the side effects of ALK TKIs?

Side effects of the ALK TKIs vary by drug and by patient.

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

- Nausea
- Vomiting
- Fatigue
- Muscle aches
- Diarrhea
- Constipation
- Swelling of the hands or feet

Among the more serious but less common side effects of ALK TKIs as a group are:

- Liver problems
- **Pneumonitis**
- Abnormal heartbeats

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.

BRAF V600E

Mutations in the BRAF V600E gene occur in 1%–3% of lung adenocarcinoma patients. Most of these patients are current or former smokers.

What is the approved BRAF V600E combination inhibitor?

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 kinase inhibitor, dabrafenib (Tafinlar®), with a MEK kinase inhibitor, trametinib (Mekinist®).

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

Side effects of the BRAF V600E combination inhibitor vary by patient.

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

- Fever
- Fatigue
- Nausea
- Vomiting
- Diarrhea
- Dry skin
- Decreased appetite
- Swelling of the hands or feet
- Rash
- Bleeding
- Cough
- Difficulty breathing
- Chills

Among the more serious but less common side effects of the BRAF V600E combination inhibitor are:

- Vision toxicities
- Pneumonitis
- **Cardiomyopathy**
- **Hyperglycemia**

EGFR

Approximately 15% of patients with NSCLC in the U.S. and 35% of patients from East Asia have tumors with an EGFR (epidermal growth factor receptor) driver mutation. Regardless of the patient's ethnicity, EGFR driver mutations are more often found in tumors of females and nonsmokers. Most commonly, these patients have lung adenocarcinomas.

What are the approved EGFR TKIs?

There are currently five FDA-approved EGFR TKIs:

- 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 rarer mutations are S768I, L861Q, and G719X.)
- Dacomitinib (Vizimpro®): Approved for 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
- 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. Erlotinib (Tarceva®) is also approved in combination with ramucirumab (Cyramza®), an angiogenesis inhibitor, for the first-line treatment of metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

- 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) substitution 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, and whose disease has progressed on or after EGFR TKI therapy.

Note: The U.S. FDA granted approval for the use of osimertinib as **adjuvant therapy** after surgical removal of a tumor in adult patients with **stage** IB to IIIA NSCLC whose tumors are mostly nonsquamous and have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, as detected by an FDA-approved test.

What are the side effects of the EGFR TKIs?

Side effects of the EGFR TKIs vary by drug and by patient.

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

- | | | |
|------------|--------------------|-----------------------------|
| • Rash | • Mouth sores | • Inflammation around nails |
| • Itching | • Loss of appetite | • Cough |
| • Diarrhea | • Weakness | |

Among the more serious but less common side effects of EGFR TKIs as a group are:

- | | |
|------------------------------------|------------------|
| • Interstitial lung disease | • Cardiomyopathy |
| • Vision toxicities | • Liver issues |
| • Severe skin lesions | |

MET

Approximately 3%–4% of NSCLC patients have a mutation that leads to MET (mesenchymal-epithelial transition) exon 14 skipping. There are several types of MET exon 14 skipping mutations, all of which have the same effect—the production of a MET protein that can cause cancer cells to grow and divide. Patients with MET-positive lung cancers are most likely to have a smoking history; a minority are never-smokers.

What are the approved MET TKIs?

There are currently two FDA-approved MET TKIs:

- Capmatinib (Tabrecta™): Approved for the treatment of adult patients with metastatic NSCLC whose tumors have a mutation that leads to MET exon 14 skipping, as detected by an FDA approved test
- Tepotinib (Tepmetko®): Approved for the treatment of adult patients with metastatic NSCLC whose tumors have a mutation that leads to MET exon 14 skipping

What are the side effects of the MET TKIs?

Side effects of the MET TKIs vary by drug and by patient.

Some common side effects of the MET TKIs as a group include:

- | | | |
|---------------------------------|------------------------|------------------------|
| • Swelling of the hands or feet | • Musculoskeletal pain | • Fatigue and weakness |
| • Vomiting | • Shortness of breath | • Loss of appetite |
| • Nausea | | |

Among the more serious but less common side effects of the MET TKIs as a group are:

- Pneumonitis
- Liver damage

NTRK

About 1%–4% of NSCLC patients have an NTRK (neurotrophic receptor kinase) gene fusion. NTRK fusions are more likely to be seen in patients who are light or never-smokers.

What are the approved NTRK TKIs?

There are currently two FDA-approved NTRK TKIs:

- Entrectinib (Rozlytrek®): Approved for the treatment of adult and pediatric patients 12 years of age and older with **solid tumors** that:
 - Have an NTRK gene fusion without a known **acquired resistance** mutation,
 - Are metastatic or where surgical resection (removal) is likely to result in severe **morbidity**, *and*
 - Have progressed following treatment or have no satisfactory alternative therapy
- Larotrectinib (Vitrakvi®): Approved for the treatment of patients with NTRK solid tumors that:
 - Have an NTRK gene fusion without a known acquired resistance mutation,
 - Are metastatic or where surgical resection is likely to result in severe morbidity, *and*
 - Have progressed following treatment or have no satisfactory alternative therapy

What are the side effects of the NTRK TKIs?

Side effects of the NTRK TKIs vary by drug and by patient.

Some common side effects of NTRK TKIs as a group include:

- Fatigue
- Vomiting
- Diarrhea
- Nausea
- Cough
- Dizziness
- Constipation
- High AST (aspartate aminotransferase) levels, indicating liver issues
- High ALT (alanine aminotransferase) levels, indicating liver issues

Among the more serious but less common side effects of the NTRK TKIs as a group are:

- Congestive heart failure
- Central nervous system effects
- Skeletal fractures
- Vision disorders

RET

Approximately 1% of NSCLC patients have a RET (rearranged during transfection) fusion. RET patients have been seen to be more likely to have lung adenocarcinoma and be non-smokers.

What are the approved RET TKIs?

There are currently two FDA-approved RET TKIs:

- Pralsetinib (Gavreto™): Approved for the treatment of adult patients with metastatic RET fusion-positive NSCLC, as detected by an FDA-approved test
- Selpercatinib (Retevmo®): Approved for the treatment of adult patients with metastatic RET fusion-positive NSCLC

What are the side effects of the RET TKIs?

Side effects of RET TKIs vary by drug and by patient.

Some common side effects of RET TKIs as a group include:

- High blood pressure
- Musculoskeletal pain
- Swelling of the hands or feet
- Fatigue
- Dry mouth
- Rash
- Constipation
- Diarrhea
- High AST (aspartate aminotransferase) levels, indicating liver issues
- High ALT (alanine aminotransferase) levels, indicating liver issues
- Other laboratory test abnormalities (e.g., increased glucose and decreased calcium)

Among the more serious but less common side effects of RET TKIs as a group are:

- Bleeding
- Pneumonitis

ROS1

A ROS1 (receptor tyrosine kinase) 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 NSCLC in the U.S. and 2%–3% in East Asia have tumors with a ROS1 mutation. ROS1 tumors are more commonly found among younger patients (median age at diagnosis is 50 years), females, never-smokers, and patients with lung adenocarcinomas.

What are the approved ROS1 TKIs?

There are currently two FDA-approved ROS1 TKIs:

- Crizotinib (Xalkori®): Approved for patients with metastatic NSCLC whose tumors are ROS1-positive, as detected by an FDA-approved test
- Entrectinib (Rozlytrek®): Approved for adult patients with metastatic NSCLC whose tumors are ROS1-positive

What are the side effects of the ROS1 TKIs?

Side effects of ROS1 TKIs vary by drug and by patient.

Some common side effects of ROS1 TKIs as a group include:

- Nausea
- Diarrhea
- Vomiting
- Constipation
- Fatigue
- Muscle aches

Among the more serious but less common side effects of the ROS1 TKIs as a group are:

- Vision disorders
- Skeletal fractures
- Low testosterone
- Central nervous system effects

Crizotinib (Xalkori®) is also approved for the treatment of metastatic ALK-positive NSCLC; see the earlier section about ALK TKIs for more detail on the rarer eye and testosterone side effects of this drug.

Management of targeted therapy side effects

As seen above, TKIs can cause side effects. However, just because a side effect is possible does not mean that a patient will experience it. Before beginning treatment with a targeted therapy, the patient should discuss with the healthcare team what side effects, both common and rare, might occur and how to prevent or ease them. The patient should speak with the healthcare team if and when new side effects begin, as treating them early on is often more effective than trying to treat them once they have already become severe. In addition, it needs to be determined whether the symptoms are related to treatment or not. What side effects are being experienced may impact future treatment plans. Although most side effects go away when treatment is over, some can last a long time.

Resistance to tyrosine kinase inhibitors (TKIs)

The biggest challenge of TKI targeted therapies is that a majority of patients with lung cancer who initially benefit from them eventually develop resistance. Acquired resistance can be defined as disease progression in a patient after initial benefit from a TKI.

Cancer cells are adept enough to bypass roadblocks to their survival and often further mutate to overcome the effects of TKIs. Another way a tumor can become resistant to TKIs is by activating a different signaling pathway in the cell to bypass the pathway that the TKI uses to kill the cells. In a small number of cases among EGFR patients, the lung adenocarcinoma may even transform into other histologies, such as SCLC.

Research is underway to overcome resistance in tumors and to keep the TKIs effective against cancer for longer periods of time.

Approaches include:

- Simultaneously prescribing multiple TKIs, in case a different mutation in the cell has been activated
- Developing the next generation of inhibitors that will inhibit not only the activity of the mutated gene, but also the mutant form it could change into
- Prescribing other combination treatments (e.g., a TKI in combination with chemotherapy, immunotherapy, or radiation therapy)

In the meantime, if a patient's cancer has progressed after treatment with a TKI, a decision needs to be made about the next treatment option. A patient's doctor may recommend that a biopsy be done on one of the tumors that is growing to determine whether there is a new mutation, but will consider all of the treatment options mentioned earlier and make a determination based on the patient's particular situation.

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 doctors whether participating in a clinical trial might be a good option for you. Read more about resources to help you locate clinical trials in the next section in this chapter.

Targeted therapy drugs that are currently being studied are intended to act against the driver mutations in the table below.

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 (ERBB2)			
<i>Mutation</i>	X		
<i>Amplification</i>	X		
IGR1			X
PARP1		X	X
Notch Signaling			X

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 in your geographic area. In addition, there are several resources to help you find one that may be a good match.

People are often surprised that a clinical trial is not the last option one turns to when standard treatments have failed. Today, clinical trials may present the FIRST line of treatment.



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

(CONTINUED)



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

- **National Cancer Institute (NCI):** www.clinicaltrials.gov
- **My Cancer Genome:**
www.mycancergenome.org/content/clinical_trials/
 - My Cancer Genome gives up-to-date information on what mutations make cancers grow and related treatment options, including available clinical trials
- **Lung Cancer Master Protocol (Lung-MAP):**
www.lung-map.org/
 - For patients with NSCLC, Lung-MAP is a collaboration of many research sites across the country. Lung-MAP uses a unique approach to match patients to one of several drugs being developed.



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?

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 or blood will be tested for the presence of driver mutations. Patients who have a mutation that a specific FDA-approved 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).

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.

While biomarker testing may also be used to determine whether an immunotherapy drug is an appropriate treatment, in this booklet, biomarker testing is discussed only in the context of whether a targeted therapy is an appropriate treatment.

For a more comprehensive look at biomarker testing, download LUNgevity's Biomarker Testing booklet at www.LUNgevity.org.

How is biomarker testing performed?

Currently, tissue biopsies are the only way to confirm a diagnosis of lung cancer; they are also the standard way to detect driver mutations. However, your doctors may also make use under certain circumstances of **liquid biopsies**, a test done on a sample of blood, to detect driver mutations.

Tissue biopsies

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**. Regardless of how the tissue is collected, a patient should confirm with the doctors before the tissue is removed that, if possible, enough tissue will be collected so that all necessary biomarker tests can be performed.

After the tumor tissue is collected, it is sent to a laboratory for testing. Ideally, what is sometimes called comprehensive biomarker testing will be done. In comprehensive biomarker testing, driver mutations in multiple genes are tested for at the same time, rather than sequentially. These may include not only the ones with approved treatments, but also other known driver mutations. For patients with a driver mutation with a targeted therapy, this means that treatment may start sooner. In addition, some of the driver mutations currently without approved treatments may have treatments being tested now or in the near future in clinical trials to which a patient could be matched. An advantage of comprehensive biomarker testing is that when a new mutation target is discovered, it can easily be added to the set of mutations being tested for. Comprehensive biomarker testing can be done via a process known as next-generation sequencing, or NGS.

Liquid biopsies

Liquid biopsies have the advantage of requiring only a simple blood sample (which contains DNA from the tumor) drawn from a vein rather than a sampling of tissue, which comes with some discomfort and risk. Test results come back sooner as well, and the same type of testing for multiple driver mutations done on tissue samples can be done on the blood samples. In several studies, it has been shown that liquid biopsies can be very effective in detecting the driver mutations that have targeted therapies to treat them.

At this time, liquid biopsies may help a patient's doctors:

- Determine if a targetable mutation is present at the time of diagnosis and decide if targeted therapies are appropriate
- Check if the patient's cancer has become resistant to a targeted therapy and decide the next treatment option
- Follow the patient's response to a particular targeted therapy

If a liquid biopsy test is negative, results from the tissue biopsy are used to make treatment decisions at diagnosis. If a liquid biopsy is negative as the cancer spreads or comes back, a tissue biopsy may be recommended. It is important to note that not all cancer cells shed DNA, so not all patients can be successfully tested via liquid biopsy.

Who should have their tumor tested, and when?

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

LUNG ADENOCARCINOMA

Stage of lung cancer	Recommendations for biomarker testing for driver mutations
Stages I, II, and III	• Testing for mutations in the EGFR gene should be conducted • Testing for the ALK, BRAF V600E, KRAS, MET exon 14 skipping, NTRK, RET, and ROS1 mutations at the time of diagnosis and surgical resection is not recommended but can be considered. The decision should be made on an individual basis with the doctor.
Stage IV lung adenocarcinoma or lung 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	Tumors should be tested for ALK, BRAF V600E, EGFR, KRAS, MET exon 14 skipping, NTRK, RET, and ROS1 at the time of diagnosis. Testing for other biomarkers, such as the HER2 (ERBB2) mutation may be helpful in deciding eligibility for clinical trials. While there is no approved targeted therapy for the KRAS driver mutation, it is likely that one will be approved soon. In addition, testing for it can be informative because cancers with KRAS mutations are very unlikely to have other driver mutations. Additionally, KRAS mutations can also be associated with resistance to EGFR targeted therapy.

SQUAMOUS CELL LUNG CANCER

Stage of lung cancer	Recommendations for biomarker testing for driver mutations
Stages I, II, and III	Currently, biomarker testing is performed only for clinical trials.
Stage IV	Consider testing for ALK, BRAF V600E, EGFR, KRAS, MET exon 14 skipping, NTRK, RET, and ROS1 at the time of diagnosis. Testing for other biomarkers may be helpful in deciding eligibility 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, BRAF V600E, EGFR, KRAS, MET exon 14 skipping, NTRK, RET, and ROS1 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—A disease progression after a complete or partial response to treatment, or disease progression after six 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

Adjuvant therapy—The additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy

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

Angiogenesis inhibitor—A drug or substance that keeps new blood vessels from forming. In cancer treatment, angiogenesis inhibitors may prevent the growth of new blood vessels that tumors need to grow

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. Also called molecular profile, genomic profile, or signature profile

Biomarker testing—A way to look for genes, proteins, and other substances that can provide information to help determine a treatment plan

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

Cardiomyopathy—A disease of the heart muscle that makes it more difficult for the heart to pump blood to the rest of the body

Cell signaling—The process by which a cell responds to substances outside the cell through signaling molecules found on the surface of and inside the cell. Most molecules that lead to cell signaling are chemical substances, such as hormones, neurotransmitters, and growth factors, that bind to a specific protein receptor (signaling molecule) on or in a cell. The signals are then passed from one molecule to another inside the cell, which results in a specific cell response, such as cell division or cell death. Cell signaling is important for cells to grow and work normally. Cells that have abnormal signaling molecules may become cancer cells

Chemotherapy—A 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—The continuation in the growth or spread of cancer

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

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA)—A type of bronchoscopy that uses a flexible bronchoscope fitted with an ultrasound device. The 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

First-line treatment or therapy—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. Also called induction therapy, primary therapy, and primary treatment

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—The coded instructions within a cell that control how the cell grows in a systematic and precise way

Genomic—Relating to a body's genes

Histology—The study of tissues and cells under a microscope; also used to indicate what the cells look like

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

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 immunotherapies 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 cause scarring of the lungs, which eventually affects the body's ability to get enough oxygen into the bloodstream and to breathe

Intravenous—Into or within a vein. Intravenous usually refers to a way of giving a drug or other substance through a needle or tube inserted into a vein. Also called IV

Large cell lung cancer—A type of non-small cell lung cancer (NSCLC) in which the cells are large and look abnormal when viewed under a microscope

Liquid biopsy—A test done on a sample of blood to look for cancer cells from a tumor that are circulating in the blood or for pieces of DNA from tumor cells that are in the blood. A liquid biopsy may be used to help find cancer at an early stage. It may also be used to help plan treatment, find out how well treatment is working, or if the cancer has come back. Being able to take multiple samples of blood over time may also help doctors understand what kind of molecular changes are taking place in a tumor

Lung adenocarcinoma—One type of non-small cell lung cancer (NSCLC) that usually develops in the cells lining the lungs. It is the most common type of lung cancer seen in nonsmokers

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

Maintenance treatment—A 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

Morbidity—The medical problems caused by a treatment

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-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 subtypes of NSCLC are lung adenocarcinoma, squamous cell lung cancer, and large cell lung cancer. 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—An inflammation of the lungs that may be caused by disease, infection, radiation therapy, allergy, or irritation of lung tissue by inhaled substance

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

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 inside the body near cancer cells (internal radiation therapy). Also called irradiation and radiotherapy

SCLC—See small cell lung cancer

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

Solid tumor—An abnormal mass of tissue that usually does not contain cysts or liquid areas. Solid tumors may be benign (noncancerous) or malignant (cancerous). Solid tumors include lung cancer tumors

Squamous cell lung cancer—A type of non-small cell lung cancer (NSCLC) 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

Stage—The extent of a cancer in the body

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. The fluid is checked for cancer cells

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. Tumors may be benign (noncancerous) or malignant (cancerous). Also called neoplasm

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

U.S. Food and Drug Administration (FDA)—The agency in the U.S. federal government whose mission is to protect public health by making sure that food, cosmetics, and nutritional supplements are safe to use and truthfully labeled. The FDA also makes sure that drugs, medical devices, and equipment are safe and effective and that blood for transfusions and transplant tissue is safe

05 notes

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