LUNG CANCER TREATMENTS

UPDATED MAY 2021


What you need to know about...

biomarker testing






LUNGEVITY

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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introduction

Lung cancer treatment options now include a number of targeted therapies aimed at particular driver mutations and immunotherapies aimed at a person's own immune system. Each of these treatments can provide substantial benefits—but not to all patients. For doctors to know whether to prescribe any of these treatments to a lung cancer patient requires a type of testing known as biomarker testing.

Biomarker testing is used among diagnosed lung cancer patients to determine the presence of particular mutations, the presence of a particular protein, how aggressive the cancer is, and how well a patient is likely to respond to a particular treatment. It is the first step in precision medicine—ensuring that a patient gets matched to the right treatment at the right time, based on the patient's biomarker profile.

This booklet will help you:

- Understand what a biomarker is
- Learn how biomarkers are used to make lung cancer treatment decisions
- Understand how biomarker testing is done
- Consider whether you should have biomarker testing

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 understanding biomarkers

What is a biomarker?

A **biomarker** is any **molecule** that can be measured in blood, other bodily fluids, or tissues. The presence of a biomarker may be a sign of an abnormal bodily process or a condition or disease.

Your doctors may also use the terms molecular marker, genotype, or signature molecule.

Biomarkers can be used to:

- Determine whether a disease or condition is present
- Tell you how aggressive the disease is
- Predict how well the body will respond to a treatment for a disease or condition

What is biomarker testing? Why is it important?

Biomarker testing (also known as mutation, genomic, or molecular testing) is a way for your doctors to gather as much information as possible about your unique **lung cancer,** ideally before treatment begins. Your doctors may suggest biomarker testing to determine whether any of a number of **targeted therapies** or **immunotherapies** are right for you as part of your treatment plan. Biomarker testing is most often used to plan these treatments for **advanced-stage lung cancers**, but it may also be useful for certain **early-stage lung cancers.**

What types of biomarkers are used to determine the best treatment for lung cancer patients?

Two types of biomarkers currently have **U.S. Food and Drug Administration (FDA)**-approved drug therapies to help doctors optimize a lung cancer patient's treatment plan:

- **Driver mutations** within the cancer cells' **DNA**, to determine whether a targeted therapy is appropriate
- The level of expression of the **programmed death-ligand 1 (PD-L1) protein** in the patient's **tumor** to determine whether an immunotherapy drug is appropriate

Driver mutations

All the organs and tissues in our bodies are composed of cells, and each of these cells contains thousands of **genes**. Genes are in turn made up of DNA, material that carries a specific code that is used to ultimately make **proteins** that have specific functions for the cell. 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.

When a gene has an error in its DNA, it is said to be mutated, or changed. **Mutations** can be:

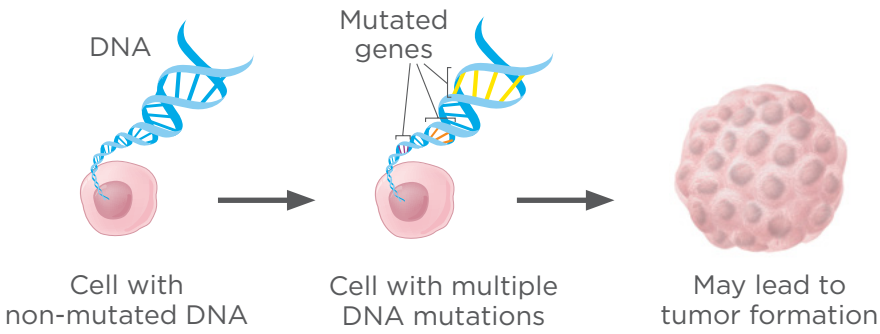
- **Acquired (or somatic):** Present only in the tumor and not passed on to children
- **Inherited (or germline):** Present in all cells of the body and passed on to children

Virtually all of the biomarkers that are helpful in making treatment decisions in lung cancer are acquired. Inherited biomarkers are still being researched.

In this booklet, we are discussing only acquired mutations.

Mutations occur often, and normally the body can correct them. However, depending on where in a gene the change occurs, the small change may go undetected by the body and become part of the cell's blueprint. Over time, an accumulation of mutations can result in the formation of a tumor. Mutations that cause cancer are called driver mutations.

DRIVER MUTATION



Targeted therapies are the drugs used to treat patients with driver mutations. Targeted therapies identify and attack specific parts of cancer cells and the signals that proteins send to cancer cells that cause them to grow and divide uncontrollably. All of the approved targeted therapies are kinase inhibitors, which block the cancer cells' ability to grow and spread.

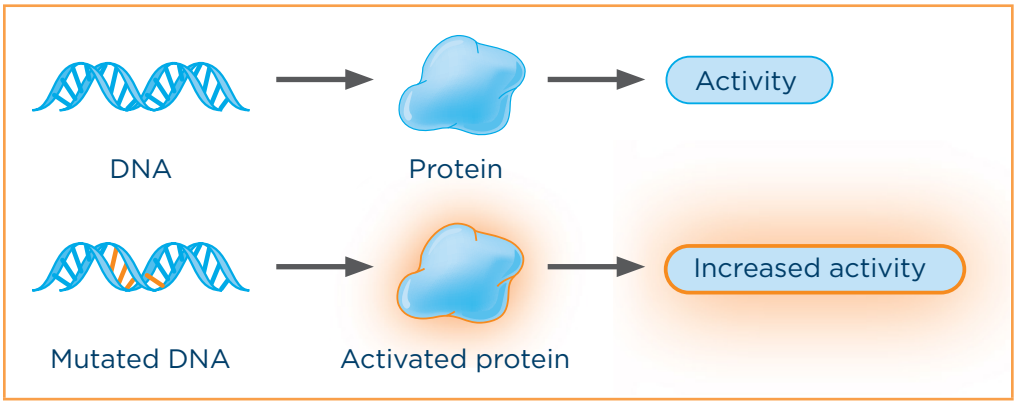
Targeted therapies are precise; they work to control a specific driver mutation. A patient may only be treated with a specific targeted therapy if they have the driver mutation for which the targeted therapy is intended. Not all driver mutations currently have targeted therapies to treat them.

Types of driver mutations

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 the protein is always active, leading to uncontrolled cell growth.

ACTIVATING MUTATION

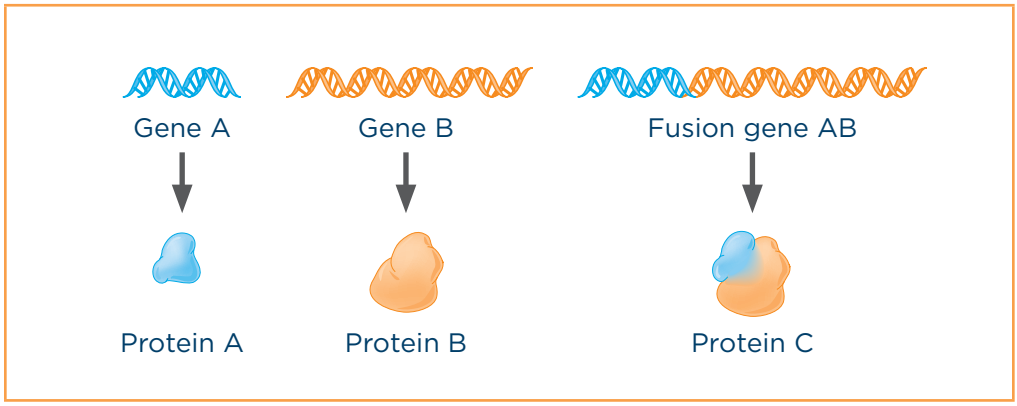


An example of an activating mutation in **lung adenocarcinoma**, a type of **non-small cell lung cancer (NSCLC)**, is BRAF V600E.

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

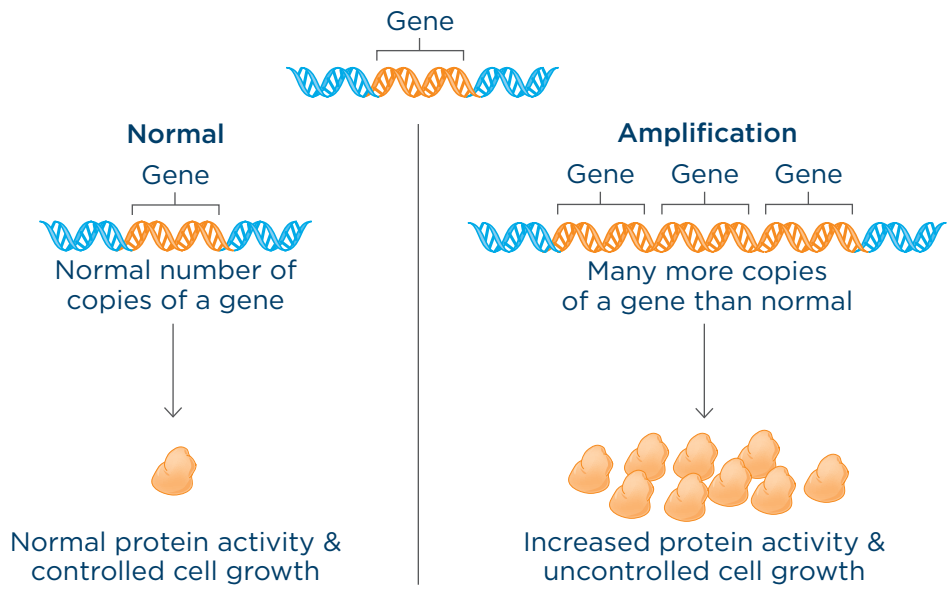


Examples of fusion genes in lung adenocarcinoma include EML4-ALK and CD74-ROS1.

Amplification

Amplification means 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

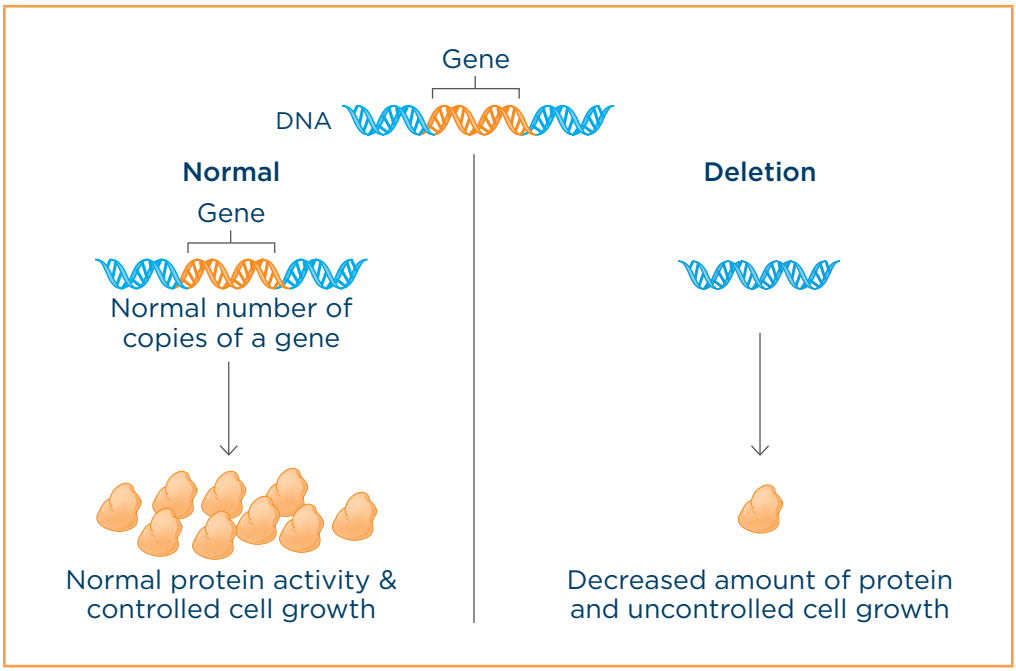


Examples of amplified genes in lung adenocarcinoma include HER2 (ERBB2) and mesenchymal-epithelial transition (MET).

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.

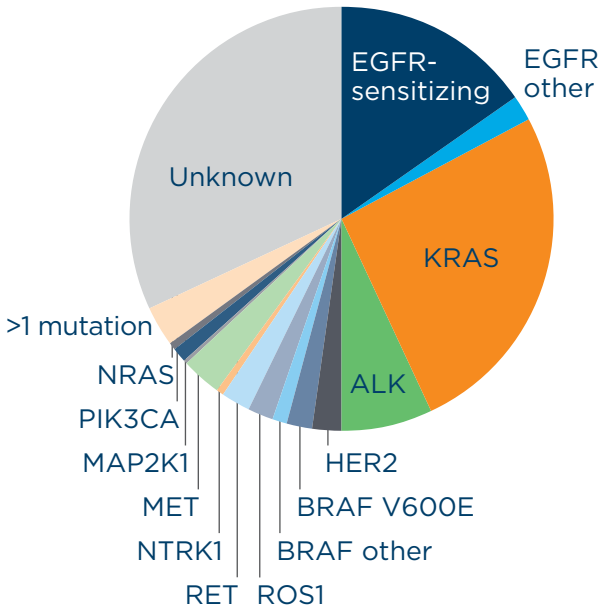
Driver mutations seen in lung cancers

A person's lung cancer may or may not have one of the many known driver mutations. So far, more than 20 different driver mutations sometimes found in NSCLC and SCLC have been identified, and the search for more continues.

These driver mutations are biomarkers that are used in biomarker testing in lung cancer; their presence may determine whether a patient will be prescribed one of the approved targeted therapies or be potentially eligible for a **clinical trial**.

Right now, there is the most information about driver mutations in the lung adenocarcinoma subtype of NSCLC. In patients with **metastatic** lung adenocarcinoma, the driver mutations that currently have FDA-approved targeted therapy drugs available are ALK, BRAF V600E, EGFR, MET exon 14 skipping, NTRK, RET, and ROS1.

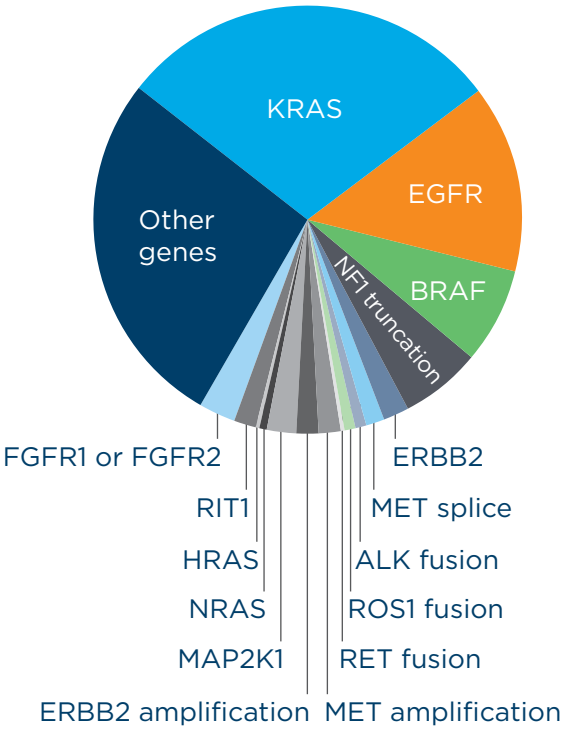
DRIVER MUTATIONS IN LUNG ADENOCARCINOMA



Driver mutations in lung adenocarcinoma	
EGFR-sensitizing	15%
EGFR other	2%
KRAS	25%
ALK	7%
HER2	2%
BRAF V600E	2%
BRAF other	1%
ROS1	2%
RET	2%
NTRK1	0–5%
MET	3%
MAP2K1	0–5%
PIK3CA	1%
NRAS	0–5%
>1 mutation	3%
Unknown	31%

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

DRIVER MUTATIONS IN EARLY-STAGE LUNG ADENOCARCINOMA

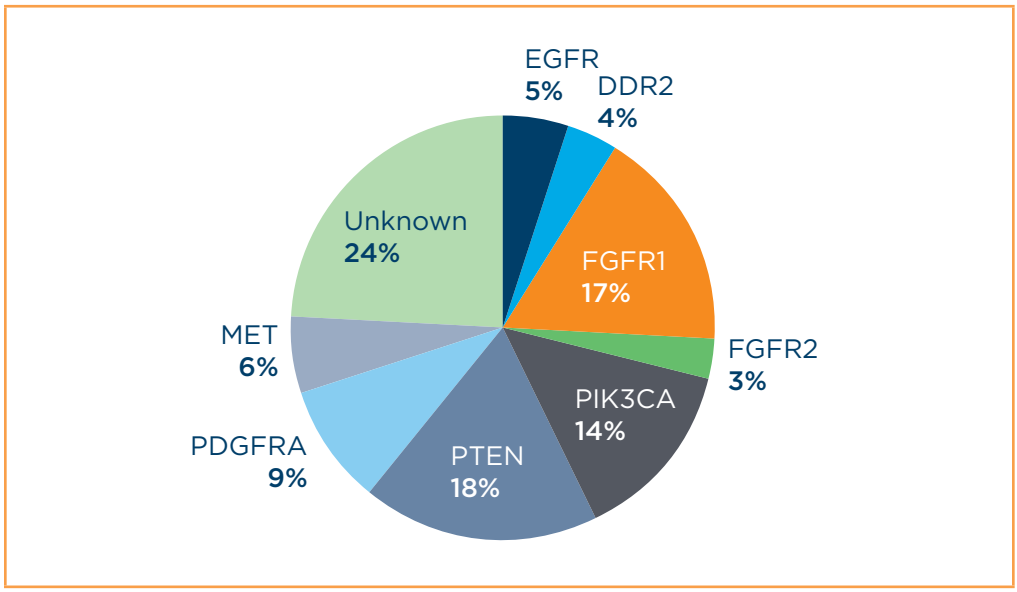


Driver mutations in early-stage lung adenocarcinoma

KRAS	29.1%
EGFR	14.2%
BRAF	7.2%
NF1 truncation	6.3%
ERBB2	1.8%
MET Splice	1.4%
ALK fusion	0.8%
ROS1 fusion	0.9%
RET fusion	0.3%
MET amplification	1.7%
ERBB2 amplification	1.6%
MAP2K1	2.2%
NRAS	0.5%
HRAS	0.5%
RIT1	1.6%
FGFR1 or FGFR2	2.6%
Other genes	27.3%

Scientists are also making progress in understanding and targeting mutations in **squamous cell lung cancer**. While driver mutations unique to squamous cell lung cancer have not yet been identified, driver mutations that more commonly occur in lung adenocarcinoma can also occur in squamous cell lung cancer. These include EGFR mutations and MET exon 14 skipping mutations.

DRIVER MUTATIONS IN SQUAMOUS CELL LUNG CANCER



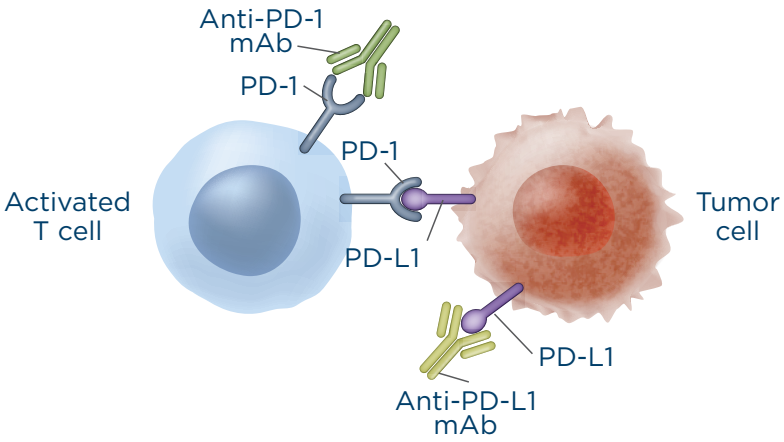
Driver mutations in SCLC and other types of lung cancer are also being studied. However, there are as of yet no targeted therapy drugs that are FDA-approved for them. This may change, so check with your doctors.

Immunotherapy biomarkers

Programmed death–ligand 1 (PD-L1) protein

T cells are the major immune cells the body uses to recognize and destroy abnormal cells. However, the **immune system** has fail-safe mechanisms that are designed to control the immune response at appropriate times in order to reduce damage to healthy tissue. These mechanisms are called immune checkpoint pathways. They are essentially the brakes on the immune system. The PD1/PD-L1 proteins are an example of an immune checkpoint pathway. The PD-1 protein is found on T cells and acts as the brakes that keep the T cells from attacking healthy cells. PD-L1 is a protein that is overexpressed on cancer cells. When the PD-1 on T cells attaches to the PD-L1 on cancer cells, the T cells know not to attack the cancer cells. Cancer cells can thus evade detection by T cells, with the result that the T cells' immune response is lessened at a time when it should be active.

PD-1/PD-L1 IMMUNE CHECKPOINT PATHWAY



Instead of attacking a patient's cancer cells directly, as targeted therapies do, immunotherapy drugs strengthen the natural ability of the patient's immune system to fight cancer. The type of immunotherapy known as **immune checkpoint inhibitors** works by targeting and blocking the PD-L1 fail-safe mechanism of the immune system, allowing the immune system to work better.

Patients who have a high level of PD-L1 expression are more likely to respond to immune checkpoint inhibitors. However, even those with tumors that express a low level or do not express PD-L1 may respond to these treatments.

Other immunotherapy biomarkers

There are other types of immunotherapy biomarkers currently being studied, including:

- Tumor mutational burden (TMB): The number of mutations found in a patient's cancer cells
- CTLA-4: A protein that, when blocked, enhances the immune system's ability to kill cancer cells
- Microsatellite instability (MSI): A number of mutations in the microsatellites, which are short, repeated sequences of DNA

02 biomarker testing in lung cancer

Is biomarker testing appropriate for you?

Biomarker testing may be appropriate:

- If your doctors suspect lung cancer and have recommended a **biopsy**
- If you are already diagnosed with lung cancer
- If your lung cancer recurs (comes back) after treatment

If you have a diagnosis of lung cancer, you should discuss biomarker testing with your doctors.

To find out whether a targeted therapy or immunotherapy may be a good therapeutic option for a patient who has been diagnosed with lung cancer, that patient's tumor tissue or blood can be tested for the presence of driver mutations. The tumor tissue can also be tested for the PD-L1 protein.

Biomarker testing should be an ongoing part of the discussion 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.

For which biomarkers should you be tested?

Guidelines commonly recommend that all patients diagnosed with advanced-stage lung adenocarcinoma be tested for the ALK, BRAF V600E, EGFR, KRAS, MET exon 14 skipping, NTRK, RET, and ROS1 mutations and the PD-L1 protein. Patients with stage IB–IIIA NSCLC may consider testing for mutations in the EGFR gene after their tumor has been surgically removed.

When discussing biomarker testing with your doctors, you may also want to consider that driver mutations other than ALK, BRAF V600E, EGFR, KRAS, MET exon 14 skipping, NTRK, RET, and ROS1 have been found in both lung adenocarcinoma and squamous cell lung cancers. Drugs that target many of those mutations are being tested through clinical trials, so it is important for patients with NSCLC to consider comprehensive biomarker testing that includes many mutations, rather than just the eight mutations listed above. You may also ask about being tested for PD-L1 expression.

Note: Currently, no drug targeting the KRAS mutation is FDA-approved. This is likely to change soon with several promising drugs targeting KRAS mutations in clinical trials. Also, KRAS testing can be informative because cancers with KRAS mutations are very unlikely to have other driver mutations. KRAS mutations are associated with resistance to EGFR targeted therapy. Finding a KRAS mutation can help you and your doctors decide whether testing for very rare mutations makes sense.

If you have SCLC, your doctors may test for the expression of PD-L1 and small cell-specific biomarkers, such as DLL3, to determine if you are eligible for certain clinical trials.

The tables below display common recommendations for biomarker testing. Again, any decision about biomarker testing should be made together by you and your doctors.

Lung adenocarcinoma

COMMON RECOMMENDATIONS FOR BIOMARKER TESTING

Stage of lung cancer	Recommendations for biomarker testing
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 and PD-L1 protein levels at the time of diagnosis and surgical resection is not always recommended but may be considered. The decision should be made on an individual basis with your doctors.
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 of other biomarkers such as MET amplifications and HER2 (ERBB2) mutations may be helpful in deciding eligibility for clinical trials. PD-L1 **immunohistochemistry** is recommended to determine whether you might benefit from immunotherapy in the **first-line** setting.

Squamous cell lung cancer

COMMON RECOMMENDATIONS FOR BIOMARKER TESTING

Stage of lung cancer	Recommendations for biomarker testing
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 such as MET amplifications and HER2 (ERBB2) mutations may be helpful in deciding eligibility for clinical trials. PD-L1 immunohistochemistry is recommended to determine whether you might benefit from immunotherapy in the first-line setting.

Small cell lung cancer (SCLC)

COMMON RECOMMENDATIONS FOR BIOMARKER TESTING

Stage of lung cancer	Recommendations for biomarker testing
All stages	Currently, biomarker testing is performed only for clinical trials.

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, under certain circumstances, your doctors may also make use of **liquid biopsies**, tests done on a sample of blood.

Tissue biopsies

Biomarker testing based on a tissue biopsy requires a sample of the tumor. Your doctors will suggest the best approach for acquiring this sample, as well as discuss the risks and benefits of each approach.

Be sure to confirm with your doctors that enough tissue will be gathered so that all necessary biomarkers tests can be performed.

Biomarker testing can be done on both **primary tumors** and metastatic tumors. If the tumor sample is too small to run through multiple tests, priority should be given to testing for mutations that are the most likely to be present, have an FDA-approved drug treatment, or otherwise help with treatment decisions. Therefore, at this time, if there is only a limited amount of tumor sample, tumors should be tested for the ALK, BRAF V600E, EGFR, KRAS, MET exon 14 skipping, NTRK, RET, and ROS1 mutations.

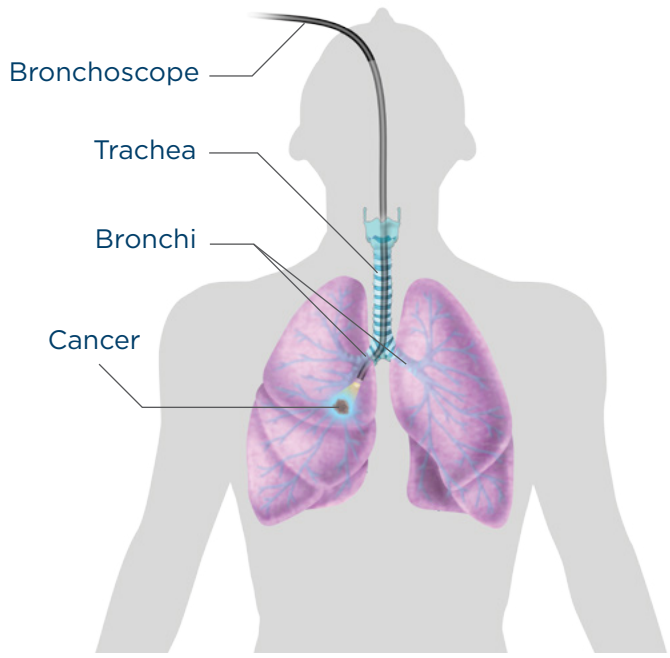
Tissue biopsy collection techniques

Tissue collection techniques include:

Bronchoscopy

During a **bronchoscopy**, doctors will insert a bronchoscope (a thin, flexible tube) into the patient's mouth or nose, down the trachea, and into the lungs. A light and a camera at the end of the tube allow the doctors to look for abnormal areas. Tiny tools can be passed down through the bronchoscope to take samples of tissue, which are checked under a microscope for signs of cancer. Prior to a bronchoscopy, a numbing medicine is sprayed in the mouth and throat. Sometimes the patient may also be given sedation through an intravenous (IV) line to help them relax or to prevent pain.

BRONCHOSCOPY



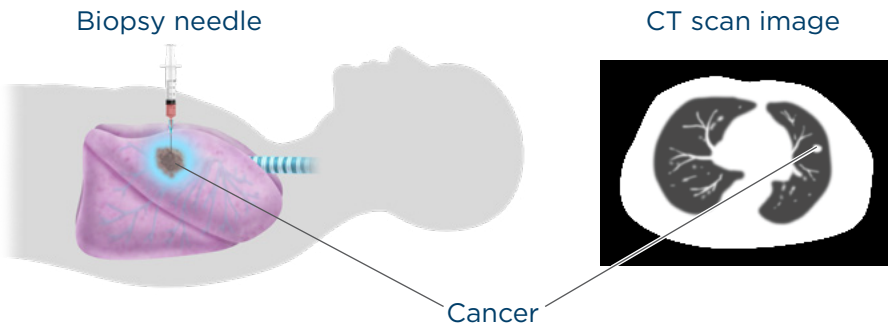
Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA)

Doctors may use endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TNA) to access mediastinal **lymph nodes**. A flexible bronchoscope fitted with an **ultrasound** device will be guided down the trachea (windpipe). Once the bronchoscope is in place, a needle will be inserted through the bronchus and into a lymph node to obtain a sample. EBUS-TBNA requires local anesthesia.

Transthoracic needle biopsy

If a suspicious mass is found in the edges of the lungs, a needle can be passed through the chest wall with **computed tomography (CT)** or ultrasound guidance to biopsy tissue or remove suspicious fluid. When a small needle is inserted through the skin of the chest wall, it is called a **fine needle aspiration (FNA)** or transthoracic needle aspiration. If a larger sample is needed, a core biopsy is done with a larger needle. The only difference between an FNA and a core biopsy is in the diameter of the needle used.

FINE NEEDLE ASPIRATION (FNA) BIOPSY OF THE LUNG



For a transthoracic needle biopsy, the patient's skin will be numbed, and the doctor will insert a needle through the chest wall. A chest CT scan or a special X-ray machine called a fluoroscope is used to help the doctors guide the needle toward the suspicious area. A sample of the mass is then aspirated, or sucked out, and sent to the lab to check for cancer cells.

An advantage of this type of biopsy is that it does not require a surgical incision, and usually local numbing medicine is all a patient needs. The disadvantages of a transthoracic needle biopsy are that

sometimes it can miss small **nodules** or might not provide enough of a sample to make a diagnosis and perform biomarker testing.

There is also a risk that air may leak out of the lung at the biopsy site and into the space between the lung and the chest wall. This complication, called a **pneumothorax**, can lead to trouble breathing and may cause part of the lung to collapse. A chest tube can be inserted to treat the pneumothorax, or the air may be sucked out of the space with a needle.

Thoracoscopy

A thoracoscopy is a surgical procedure performed in the operating room under general anesthesia. A surgeon will make a small incision in the skin of the chest wall and insert a special instrument with a small video camera on the end to examine the lungs and inside of the chest. Samples of tissue are removed for a **pathologist** to look at under the microscope. This procedure is also referred to as video-assisted thoracoscopic surgery (VATS).

A thoracoscopy can be used for multiple reasons:

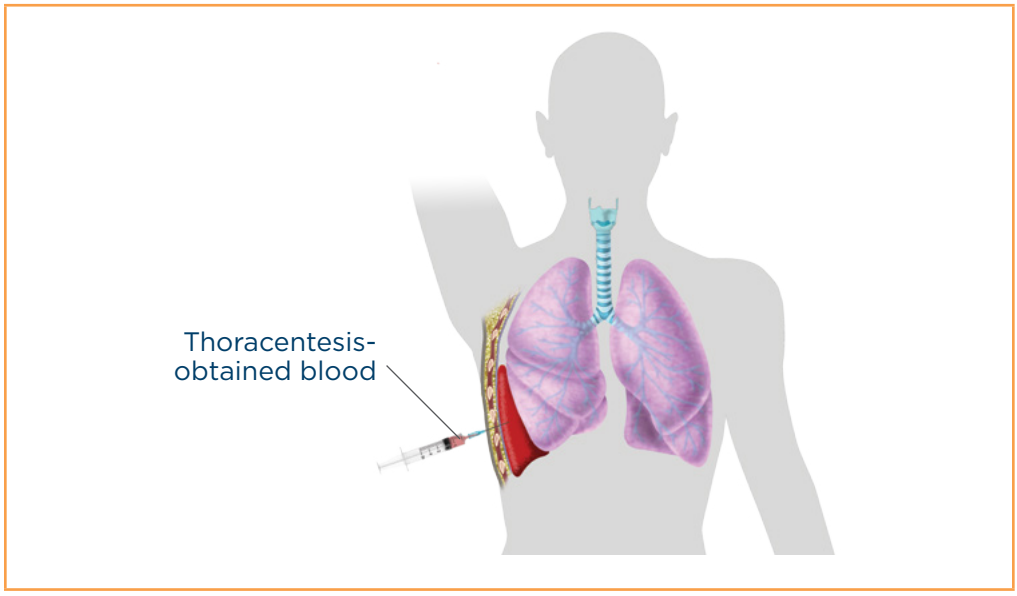
- To sample tumors and lymph nodes on the outer parts of the lungs
- To see if lung cancer has spread to the spaces between the lungs and the chest wall
- To check if the tumor has spread to nearby lymph nodes and organs
- As part of the treatment to remove part of a lung in some early-stage lung cancers

Because thoracoscopy is more invasive and requires general anesthesia, it is not usually the first procedure used to get tissue to diagnose lung cancer if a less invasive procedure can be used. Thoracoscopy is sometimes used for diagnosis if tests, such as transthoracic needle biopsies, are unsuccessful in getting enough tissue for diagnosis.

Thoracentesis

If a patient has a **pleural effusion**, doctors can perform a thoracentesis to see if it was caused by cancer that spread to the linings of the lungs. In this procedure, a doctor numbs the skin and then inserts a hollow needle between the ribs to drain the fluid. The fluid is sent to a laboratory to be checked for cancer cells.

THORACENTESIS



What happens after the tumor tissue is collected?

Once the tumor tissue is collected, it is sent to a laboratory for testing. What is sometimes called comprehensive biomarker testing will ideally be done. In comprehensive biomarker testing, driver mutations in multiple genes are tested for at the same time, rather than sequentially, including 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. An advantage of comprehensive biomarker testing is that when a new mutation 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.

Biomarker testing results are analyzed by a pathologist. All laboratory results are recorded in a **pathology report**. It is a good idea to get a copy of your pathology report for your own information and to have it available to show other doctors, if necessary. The test results can take up to two or so weeks to be received by your doctor.

Liquid biopsies

Currently, tissue biopsies are the only way to confirm a diagnosis of lung cancer. However, your doctors may also use a liquid biopsy instead of a tissue biopsy to decide if certain targeted therapies are right for you.

Liquid biopsies for the detection of driver mutations in lung cancer currently work in this way:

- When cancer cells die, they release DNA. The DNA then enters the bloodstream in the liquid part of the blood (plasma). This is called circulating tumor DNA, or ctDNA.

- A blood sample is drawn from a vein
- The blood sample is then sent to the laboratory to check for the presence of driver mutations

Liquid biopsy test results typically come back sooner than tissue biopsy test results. In addition, the same type of comprehensive biomarker 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.

Will you need multiple biopsies?

Sometimes, doctors may recommend an additional biopsy. This could happen when:

- Not enough tissue was obtained during the initial diagnostic biopsy
- A targeted therapy that worked well against the cancer has stopped working, and the cancer has recurred. Testing the resistant cancer for additional mutations that may have evolved or rare changes in **histology** is indicated to help guide your doctors toward the next, best treatment.
- New drugs are approved for the treatment of lung cancer from which you might possibly benefit. The new drug or treatment might require biomarker testing.

Therefore, doctors may recommend additional biopsies (either tissue or liquid) and biomarker testing at several points in your treatment process.

The ultimate decision to have another biopsy should be jointly made by you and your doctors.

03 how biomarker testing impacts treatment

What do the results of your biomarker test(s) mean?

The results of your test(s) will reveal if your lung cancer has a driver mutation that makes it likely that you will benefit from an FDA-approved targeted therapy or if your PD-L1 protein level is high enough that you are likely to benefit from FDA-approved immunotherapy drugs.

The drugs listed in the following sections are the ones that are currently FDA-approved, **but check with your doctors because new drugs may be available at the time of your treatment**.

Targeted therapy treatments

The targeted therapies currently approved for the treatment of patients with each of the targetable driver mutations are:

ALK:

- **Alectinib (Alecensa®)**, **brigatinib (Alunbrig®)**, **ceritinib (Zykadia®)**, **crizotinib (Xalkori®)**, and **lorlatinib (Lorbrena®):** Approved as first- and **subsequent-line treatments** for patients with metastatic ALK-positive NSCLC

BRAF V600E:

- Combination treatment of **dabrafenib (Tafinlar®)** with trametinib **(Mekinist®):** Approved as first- and subsequent-line treatment for patients with metastatic BRAF V600E-positive NSCLC

EGFR:

- **Afatinib (Gilotrif®)**, **dacomitinib (Vizimpro®)**, or **gefitinib (Iressa®):** Approved as first-line treatment for patients with metastatic EGFR-positive NSCLC
- **Erlotinib (Tarceva®)** and **osimertinib (Tagrisso®):** Approved as first- or subsequent-line treatment for patients with metastatic EGFR-positive NSCLC

Note: The U.S. FDA granted approval for the use of osimertinib (Tagrisso®) 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.

MET exon 14 skipping:

- **Capmatinib (Tabrecta™):** Approved as first- and subsequent-line treatment of adult patients with metastatic NSCLC whose tumors have a mutation that leads to MET exon 14 skipping
- **Tepotinib (Tepmetko®):** Approved as first- and subsequent-line treatment of adult patients with metastatic NSCLC harboring MET exon 14 skipping alterations

NTRK:

- **Entrectinib (Rozlytrek®)** and larotrectinib **(Vitrakvi®):** Approved as first- and subsequent-line treatment of NTRK-positive patients

RET:

- **Pralsetinib (Gavreto™)** and **selpercatinib (Retevmo™):** Approved as first- and subsequent-line treatment of metastatic RET-positive patients

ROS1:

- **Crizotinib (Xalkori®)** and **entrectinib (Rozlytrek®):** Approved for the first- and subsequent-line treatment of metastatic ROS1-positive patients

Immunotherapy treatments

The immunotherapy treatments currently approved are:

- **Atezolizumab (Tecentriq®):** Approved for patients in the following settings:
  - As first-line treatment for patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 stained ≥50% of tumor cells or PD-L1 stained tumor-infiltrating immune cells covering ≥10% of the tumor area), as determined by an FDA-approved test, with no EGFR or ALK mutations, or
  - As first-line treatment in combination with bevacizumab, paclitaxel, and carboplatin for patients with metastatic nonsquamous NSCLC with no EGFR or ALK mutations, or
  - As first-line treatment in combination with paclitaxel protein-bound and carboplatin for patients with metastatic nonsquamous NSCLC with no EGFR or ALK mutations, or
  - As **second-line** or subsequent-line treatment for patients with metastatic NSCLC whose disease has progressed during or following platinum-containing chemotherapy. Patients with EGFR or ALK mutations should first have disease progression on FDA-approved therapy for these mutations, or
  - As first-line treatment in combination with carboplatin and etoposide for patients with extensive-stage SCLC
- **Cemiplimab (Libtayo®):** As first-line treatment of patients with NSCLC whose tumors have high PD-L1 expression (tumor proportion score [TPS] ≥50%) as determined by an FDA-approved test, with no EGFR, ALK, or ROS1 mutation, and are:
  - Locally advanced where patients are not candidates for surgical resection or **definitive** chemoradiation, or
  - Metastatic

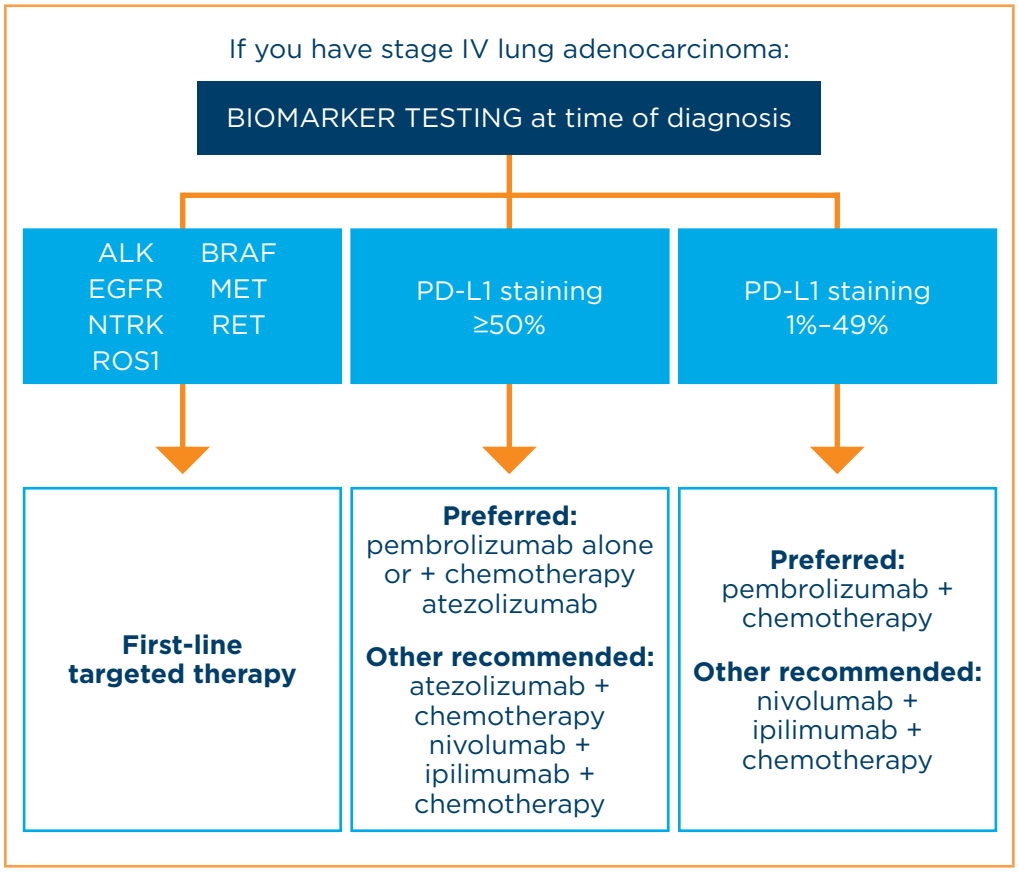
- **Durvalumab (Imfinzi®):** Approved for patients in the following settings:
  - As second- and subsequent-line treatment for patients with **unresectable** stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy, or
  - As first-line treatment in combination with etoposide and either carboplatin or cisplatin for patients with extensive-stage SCLC
- **Nivolumab (Opdivo®):** Approved for patients in the following settings:
  - As first-line treatment in combination with ipilimumab for patients with metastatic NSCLC whose tumors express PD-L1 (≥1%), as determined by an FDA-approved test, with no EGFR or ALK mutations, or
  - As first-line treatment in combination with ipilimumab and two cycles of platinum-doublet chemotherapy for patients with metastatic or recurrent NSCLC, with no EGFR or ALK mutations, or
  - As subsequent-line treatment for patients with metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK mutations should first have disease progression on FDA-approved therapy for these mutations.

- **Pembrolizumab (Keytruda®):** Approved for patients in the following settings:
  - As first-line treatment in combination with pemetrexed and platinum chemotherapy for patients with metastatic nonsquamous NSCLC, with no EGFR or ALK mutations, or
  - As first-line treatment in combination with carboplatin and either paclitaxel or paclitaxel protein-bound for patients with metastatic squamous cell lung cancer, or
  - As first-line treatment for patients with NSCLC expressing PD-L1 with a tumor proportion score ≥1%, as determined by an FDA-approved test, with no EGFR or ALK mutations, and is either:
    - Stage III where patients are not candidates for surgical resection or definitive chemoradiation, *or*
    - Metastatic, or
  - As subsequent-line treatment for patients with metastatic NSCLC whose tumors express PD-L1 with a tumor proportion score ≥1%, as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK mutations should first have disease progression on FDA-approved therapy for those mutations.

Approaches to first-line treatment following biomarker testing

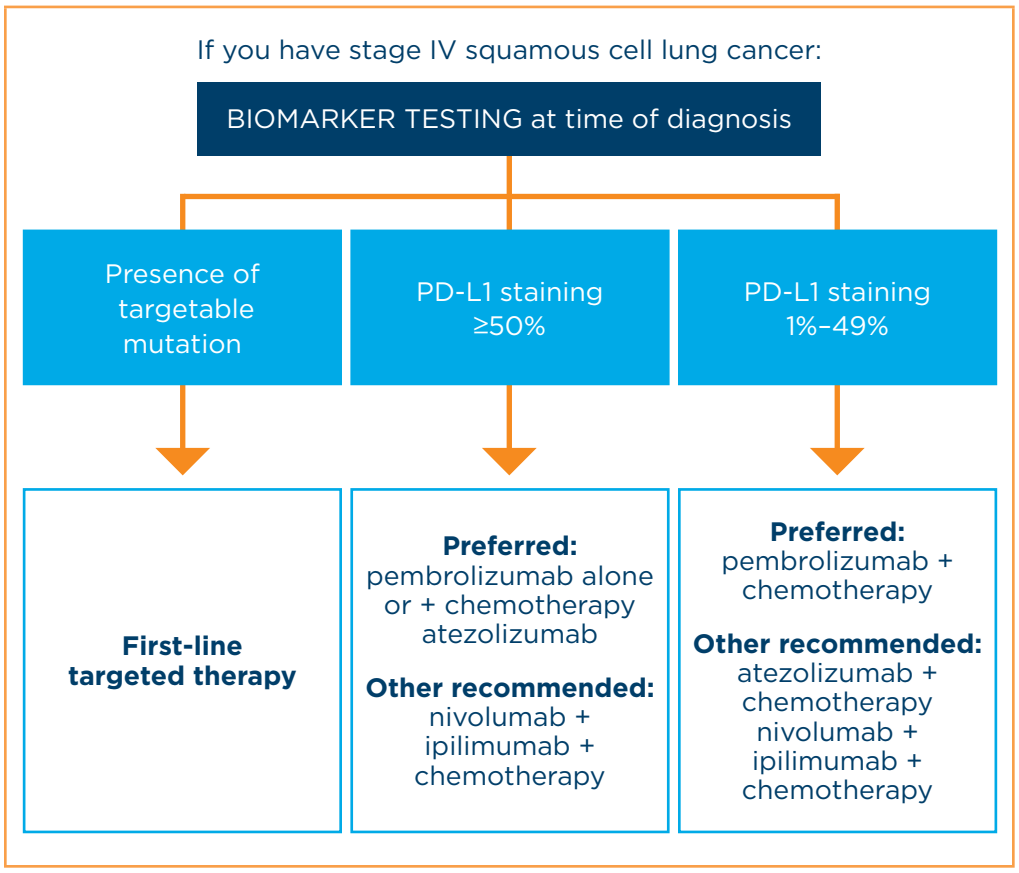
The following chart summarizes the first-line treatment approaches for stage IV lung adenocarcinoma, following biomarker testing.

FIRST-LINE TREATMENT APPROACHES FOR STAGE IV LUNG ADENOCARCINOMA



The following chart summarizes the first-line treatment approaches for stage IV squamous cell lung cancer, following biomarker testing.

FIRST-LINE TREATMENT APPROACHES FOR STAGE IV SQUAMOUS CELL LUNG CANCER



For second-line (and further) treatment options, check with your doctors whether biomarker testing may be needed before deciding on the treatment plan.

How does biomarker testing help you enroll in clinical trials?

Whether your cancer tests positive for a driver mutation that already has targeted therapies or for a driver mutation that does not, you may want to speak with your doctor about participating in clinical trials for new drugs or combination treatments targeting your cancer's driver mutation.

Stages I, II, and IIIA lung cancer: If your stage I, II, or IIIA NSCLC tests positive for a driver mutation for which an FDA-approved therapy exists, you may be eligible to enroll for a trial with specific targeted therapies.

Stage IIIB/Stage IV lung cancer or extensive-stage disease SCLC: If you have stage IIIB/IV advanced-stage NSCLC or extensive-stage disease SCLC, you may want to consider clinical trials that are open for patients with a variety of driver mutations. These targeted treatments are being studied alone and in combination with other targeted drugs, immunotherapy, chemotherapy, and radiation therapy.

In addition, several clinical trials using immunotherapies also require biomarker testing.

The driver mutations on the following page are currently being studied in lung cancer for the development of targeted therapies.

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			
Amplification (de novo)	X		
Amplification (EGFR TKI-resistant)	X		
Exon 14 skipping	X	X	
PTEN	X	X	X
PIK3CA			
Mutation	X	X	
Amplification	X	X	X
BRAF	X		
ROS1	X		
NTRK1	X		
HER2 (ERBB2)			
Mutation	X		
Amplification	X		
IGR1			X
PARP1		X	X
Notch Signaling			X

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

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

Adjuvant therapy—An 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

Advanced-stage lung cancer—A lung cancer that has spread either locally or to distant parts of the body

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

Biomarker—A biological molecule found in blood, other bodily fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease

Biomarker testing (mutation, genomic, or molecular 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 them under a microscope or perform other tests on them

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

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

Computed tomography (CT) scan—A procedure that uses a computer linked to an X-ray machine to make a series of detailed pictures of areas inside the body. The pictures are taken from different angles and are used to create 3-dimensional (3D) views of tissues and organs. A dye may be injected into a vein or swallowed to help the tissues and organs show up more clearly. Also called CAT scan and computed tomography scan

Definitive treatment—The treatment plan for a disease or disorder that has been chosen as the best one for a patient after all other choices have been considered

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

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

Driver mutation—A change in the gene sequence of a cell that leads to the development or progression of a tumor

Early-stage lung cancer—Refers to cancer that is early in its growth and may not have spread to other parts of the body

Fine needle aspiration (FNA)—The removal of tissue or fluid with a thin needle for examination under a microscope, usually to determine if cancer is present or what the cancer cell type is

First-line treatment or therapy—The first treatment 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 treatments may be added or used instead

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

Gene—The 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; also used to indicate what the cells look like

Immune checkpoint inhibitors—The agents that target the pathways that tumor cells use to evade recognition and destruction by the immune system

Immune system—A complex network of cells, tissues, organs, and the substances they make that help the body fight infections and other diseases. The immune system includes white blood cells and organs and tissues of the lymph system, such as the thymus, spleen, tonsils, lymph nodes, lymph vessels, and bone marrow

Immunohistochemistry—A lab test that uses antibodies to test for certain antigens (markers) in a sample of tissue. The antibodies are usually linked to an enzyme or a fluorescent dye. When the antibodies bind to the antigen in the tissue sample, the enzyme

or dye is activated, and the antigen can then be seen under a microscope. Immunohistochemistry is used to help diagnose diseases such as cancer. It may also be used to help tell the difference between different types of cancer

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

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 or to find out how well treatment is working or if 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—A 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

Lymph node (lymph gland)—A rounded mass of lymphatic tissue that is surrounded by a capsule of connective tissue. Lymph nodes filter lymph (lymphatic fluid), and they store lymphocytes (white blood cells [WBCs]). They are located along lymphatic vessels

Metastatic—Relating to the spread of cancer from the primary site, or place where it started, to other places in the body

Molecule—The smallest particle of a substance that has all of the physical and chemical properties of that substance. Molecules are made up of one or more atoms. If they contain more than one atom, the atoms can be the same (an oxygen molecule has two oxygen atoms) or different (a water molecule has two hydrogen atoms and one oxygen atom). Biological molecules, such as proteins and DNA, can be made up of many thousands of atoms

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

Nodule—A growth or lump that may be malignant (cancerous) or benign (noncancerous)

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. The overexpression of certain proteins or other substances may play a role in cancer development

Pathologist—A doctor who identifies diseases by studying cells and tissues under a microscope or with other equipment

Pathology report—The description of cells and tissues made by a pathologist based on what is seen under a microscope. This is sometimes used to make a diagnosis of lung cancer or another disease. It may also be referred to in short form as “path report” or even “the path”

PD-L1—See programmed death-ligand 1 (PD-L1) protein

Pleural effusion—An abnormal amount of fluid between the tissue lining the lungs and the wall of the chest cavity

Pneumothorax—A condition in which air or other gas is present in the pleural cavity, the space enclosed by the pleura, which is a thin layer of tissue that covers the lungs and lines the interior wall of the chest cavity

Precision medicine—A form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease. In cancer, precision medicine uses specific information about a person's tumor to help diagnose, plan treatment, find out how well treatment is working, or make a prognosis. Examples of precision medicine include using targeted therapies to treat specific types of cancer cells, such as ALK-positive lung cancer cells, or using biomarker testing to help diagnose cancer. Also called personalized medicine

Primary tumor—The original, or first, tumor in the body

Programmed death-ligand 1 (PD-L1) protein—The part of the immune system mechanism that keeps T cells from functioning

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

SCLC—See small cell lung cancer

Second-line treatment or therapy—A treatment that is started after the first set of treatments doesn't work, has stopped working, or has side effects that are not tolerated

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 (NSCLC) that usually starts near a central bronchus. It begins in squamous cells, which are thin, flat cells that look like fish scales

Stage—The extent of a cancer in the body. In non-small cell lung cancer (NSCLC), stages range in severity from 0 to IV. In small cell lung cancer (SCLC), stages are usually described as limited-stage disease and extensive-stage disease

Subsequent-line treatment or therapy—A type of treatment that is started after an earlier treatment or treatments have not worked, have stopped working, or have side effects that are not tolerated

Targeted therapy—A type of treatment that uses drugs to 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

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

Ultrasound—A procedure that uses high-energy sound waves to look at tissues and organs inside the body

Unresectable—Unable to be removed with surgery

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 are safe

05 notes

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