Non-Small Cell Lung Cancer Metastatic

Available online at NCCN.org/patients
It's easy to get lost in the cancer world

Let NCCN Guidelines for Patients® be your guide

✓ Step-by-step guides to the cancer care options likely to have the best results
✓ Based on treatment guidelines used by health care providers worldwide
✓ Designed to help you discuss cancer treatment with your doctors
Endorsed by

American Lung Association
The American Lung Association strongly supports efforts to help ensure all patients facing lung cancer get the highest standard of treatment and care. Helping patients understand treatment guidelines is one important step in empowering them to get the care they want and need. That is why we are pleased to endorse NCCN’s efforts to provide accessible treatment guidelines and information to patients through the NCCN Guidelines for Patients. lung.org

American Lung Cancer Screening Initiative
The American Lung Cancer Screening Initiative strongly advocates spreading awareness about the importance of lung cancer screening for high-risk individuals. It is critical to help patients and healthcare providers understand that increasing early detection of lung cancer through low-dose CT screening has been proven to be one of the easiest ways to combat lung cancer. We are determined to empower high-risk individuals, especially those from disadvantaged backgrounds, and provide them with accessible screening and treatment options. Thus, we are proud to collaborate with the NCCN and endorse their Guidelines for Patients. alcsi.org

Caring Ambassadors
The Caring Ambassadors Lung Cancer Program is pleased to endorse these NCCN Guidelines for Patients: Lung Cancer. Patients and their loved ones need reliable resources to achieve the best possible outcomes for their disease. lungcancercap.org

Clifton F. Mountain Foundation for Education and Research in Lung Cancer
The Clifton F. Mountain Foundation for Education and Research in Lung Cancer was created approximately 30 years ago by Clifton F. Mountain, MD, who developed the International System for the Staging of Lung Cancer while at M.D. Anderson Cancer Center in Houston, Texas. The Foundation’s primary function has been to educate physicians about application of the Staging System to lung cancer patients, and to emphasize that early detection of lung cancer is key to the best outcomes possible. The Foundation has created and distributed (worldwide) handbooks for physicians’ pockets, as a practical aid to proper staging. The Foundation has a current interest in educating primary care providers to keep lung cancer in their differential diagnoses. As President, Merel Mountain Nissenberg participates as the Advocate for the M.D. Anderson Lung Cancer SPORE; serves on the Lung Cancer Collaborative Group of the Early Detection Network of NCI; and is a participant in LungCAN.

Free ME From Lung Cancer
As a lung cancer survivor and Vice President and CEO of Free ME From Lung Cancer, I am pleased to endorse this vitally important resource so that lung cancer patients can have the information needed to make informed decisions about their treatment. freemefromlungcancer.org

GO2 Foundation for Lung Cancer
Founded by patients and survivors, GO2 Foundation for Lung Cancer, transforms survivorship as the world’s leading organization dedicated to saving, extending, and improving the lives of those vulnerable, at risk, and diagnosed with lung cancer. We work to change the reality of living with lung cancer by ending stigma, increasing public and private research funding, and ensuring access to care. go2foundation.org

Lung Cancer Research Foundation
As a non-profit organization focused on supporting lung cancer research, the Lung Cancer Research Foundation is proud to endorse the NCCN Guidelines for Patients. These guidelines play an important role in providing lung cancer patients with up to date information and empowering them to make informed decisions about their care. lcrf.org

With generous support from

- David Ettinger, MD, FACP, FCCP in honor of Joan McClure
- Kyle Hermann in honor of Don and Jeanne Cromwell
- Michael Winkel
- Miranda Hughes
- Peng Liang
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To make a gift or learn more, please visit NCCNFoundation.org/donate or e-mail PatientGuidelines@nccn.org.

NCCN Guidelines for Patients®: Metastatic Non-Small Cell Lung Cancer, 2021

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1 Lung cancer basics

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Lung cancer starts in the cells of the lungs. Non-small cell lung cancer is the more common type of lung cancer. Read this chapter to learn more about lung cancer, including metastatic lung cancer.

Types of lung cancer

The lungs are the main organs of the respiratory system. They deliver oxygen to the blood and remove carbon dioxide from the blood. The transfer of these gases in and out of the body is called respiration.

Lung cancer is a cancer of lung cells. Other cancers that have spread to the lung are not lung cancers. For example, breast cancer that has spread to the lungs is still breast cancer.

Lung carcinomas

Almost all lung cancers are carcinomas. Carcinomas are cancers of cells that line the inner or outer surfaces of the body. Lung carcinomas form from cells that line the airways of the lungs. The airways of the lungs are called the bronchus, bronchioli, and alveoli. Lung carcinomas are divided into 2 groups based on how the cells look.

- Small cell lung cancer (SCLC)
- Non-small cell lung cancer (NSCLC)

Airways of the lungs

Air moves through your body in a series of airways. It travels down your throat and through the windpipe (trachea). The windpipe splits into 2 airways called bronchi. Inside the lung, each bronchus branches off into the parts of the lung, called lobes. The right lung has 3 lobes, and the left lung has 2 lobes. The bronchi divide into smaller airways called the bronchioli. At the end of the bronchioli are sacs called alveoli. Oxygen is transferred from air into the blood in the alveoli.
Non-small cell lung cancer
NSCLC is much more common than SCLC. There are 3 main types of NSCLC.

- Adenocarcinoma
- Squamous cell carcinoma
- Large cell carcinoma

Adenocarcinoma is the most common lung cancer. It often forms from cells that line the alveoli and make mucus. Squamous cells line the bronchi. Large cell carcinoma forms from any of the large cells that are throughout the airways.

Lung cancer stages
The stage of the cancer describes the extent of the cancer in the body. Doctors use it for many things. It is used to assess the outlook of your cancer called the prognosis. It is used to plan the right treatment. It is also used for research.

For some people, cancer staging is done twice. The staging assigned before any tissue (biopsy) testing is called the clinical stage. The second staging is called the pathologic stage and is based on tissue tests. Cancer that is outside of the lungs may not be found until after surgery.

Staging system
The American Joint Committee on Cancer (AJCC) staging manual is used to stage lung cancer. The stages of NSCLC range from stage 0 to stage 4. Often, the stages are written with Roman numerals—stages 0, I, II, III, and IV. Occult carcinoma is a rare finding of cancer cells in mucus and no detection of a lung tumor.

Stage 0
Stage 0 is rare. Abnormal or cancer cells have formed in the airways but haven’t grown into the lung tissue. Stage 0 is also called carcinoma in situ.

Stages 1 through 3
Stage 1, stage 2, and stage 3 cancers have grown into lung tissue. Some have spread to nearby disease-fighting tissue called lymph nodes. These cancers have not spread to body parts far from the lung tumor.

Stage 4
To be stage 4, lung cancer must have already spread far by the time of diagnosis. Lung cancer tends to travel to the brain and adrenal gland and from one lung to the other lung. Most lung cancers are stage 4.

Metastatic lung cancer
The spread of cancer is called metastasis. When lung cancer has spread far from the first lung tumor, it is called metastatic lung cancer.

After diagnosis, stage 1, stage 2, or stage 3 lung cancer may metastasize to body parts far from the lung tumor. Stage 4 lung cancer is metastatic lung cancer at diagnosis. This book discusses treatment for metastatic lung cancers.

Learn more about stage 1 through 3 lung cancers that have not spread far in NCCN Guidelines for Patients: Early and Locally
Lung cancer basics

Advanced Non-Small Cell Lung Cancer, available at NCCN.org/patientguidelines.

Metastatic lung cancer

Lung cancer that has spread far from the main lung tumor is called metastatic lung cancer. All lung cancers that have spread outside the chest are metastatic lung cancers. Within the chest, distant sites include the tissue lining or fluid around a lung or heart. Lung cancer that has spread from one lung to the other lung is also metastatic lung cancer.

Symptoms

Symptoms caused by metastatic NSCLC depend on where it is. Some signs and symptoms of metastatic lung cancer are:

- Trouble breathing, chronic cough, and chest pain
- Pain in bone or spine
- Yellowing of the skin or eyes called jaundice
- Constant feeling of a full stomach
- Headaches, dizziness, or seizures
- Weakness or numbness of arms or legs
- Fatigue and unexplained weight loss
**Treatment**
Metastatic lung cancer is not often treated with local treatment. Local treatment includes surgery, radiation therapy, and chemoradiation. It may be an option if metastases are limited. An example is cancer spread to only the brain or adrenal gland. Local treatments may also be used to reduce (palliate) symptoms caused by a metastasis.

Most often, systemic therapy is used to treat metastatic lung cancer. Systemic therapy affects all cancer in the body. It can treat widespread metastases. Medical oncologists are cancer doctors trained to use systemic therapy. The focus of this book is systemic therapy for metastatic lung cancer.

At this time, metastatic lung cancer is unlikely to be cured. The aim of treatment is to reduce symptoms, control the cancer, and extend life. Newer treatments are better at controlling the cancer and improving quality of life. Your doctor will tailor treatment to you based on tests described in Chapter 2.

**Treatment team**
A team of health care providers is involved in diagnosing and treating lung cancers. Your primary doctor may be the first to suspect you have lung cancer and refer you to specialists. The diagnostic, treatment, and supportive care experts are explained throughout this book. These experts are supported by nurses, technicians, and assistants, who are often on the frontline of cancer care. Patient navigators can help you through the maze of cancer care.

**Review**
- The lungs help the body get the air it needs to live.
- The lungs are made of many small airways and sacs.
- Lung cancer often starts in the cells that line the airways. These cancers are called carcinomas.
- Lung cancer more often affects the larger cells of the lungs. These cancers are called non-small cell lung cancer (NSCLC).
- The cancer stage is a rating of the extent of the cancer. Stages of lung cancer range from stage 0 to stage 4.
- Metastatic lung cancer has spread far from where it started. It includes stage 1 through 3 lung cancers that have spread far after diagnosis. It also includes all stage 4 lung cancers.
- Most often, systemic therapy is used to treat metastatic lung cancer. Systemic therapy affects all cancer in the body.
- There are newer treatments for metastatic lung cancer that better control the cancer and improve quality of life.
- A team of experts will work together with you to diagnose and treat the cancer as well as support you.
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Tests for metastatic lung cancer

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Metastatic Non-Small Cell Lung Cancer, 2021
Not all metastatic lung cancers are the same. It is important to get the right tests to learn about the cancer and your health. Read this chapter to learn what tests and other health care are needed before treatment.

### Health history and exam

Your cancer doctors need to have all of your health information. A complete report of your health is called a medical history. Your doctor will also perform a physical exam of your body. An exam is done to find signs of disease and decide which treatments may be options. See Guide 1 for a list of tests used for metastatic lung cancer.

#### Guide 1

#### Health tests and services for metastatic lung cancer

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Medical history
Your doctor will ask about any health problems and treatments during your lifetime. When you meet with your cancer doctors, be ready to talk about:

- Illnesses
- Injuries
- Health conditions
- Symptoms
- Medications

Your doctor will ask about symptoms that may be related to lung cancer. Such symptoms include cough, trouble breathing, chest pain, and weight loss. Early stages of lung cancer may not cause symptoms. Symptoms in late stages depend where the cancer is.

Smoking
You can get lung cancer even if you never smoked. If you have lungs, you can get lung cancer. Your doctors will ask about current and past smoking to plan treatment.

Tell your doctors if you smoke or have smoked in the past. Smoking is often measured by packs per day and the number of years that you have smoked.

If you do smoke, it is important to quit. Smoking can limit how well cancer treatment works. Nicotine addiction is one of the hardest addictions to stop. The stress of having cancer may make it harder to quit. There is help. Ask your health care providers about counseling and drugs to help you quit.

Family history
Be prepared to discuss the health problems of your close blood relatives. Such family members include brothers, sisters, parents, and grandparents. Some cancers and other health conditions can run in families.

Physical exam
Cancer can spread to lymph nodes and cause them to swell. Your doctor will gently press on your body to assess their size. There are lymph nodes all over your body. Lung cancer often spreads to nodes in the chest and neck.

During this exam, also expect the following to be checked:

- Your body temperature
- Your blood pressure
- Your pulse and breathing rate
- Your weight
- How your lungs, heart, and gut sound
- How your eyes, skin, nose, ears, and mouth look
- The size of your organs
- Level of pain when you are touched

Performance status
Based on your history and exam, your doctor will rate your performance status. Performance status is your ability to do day-to-day activities. Doctors use it to assess if you can undergo certain treatments.
Blood tests

Blood tests measure blood cells, proteins, and chemicals in the bloodstream. A blood draw removes a sample of blood for testing. It is done with a needle inserted into a vein. You may need to fast from food and most liquids for hours before the draw.

**CBC with differential**
If not done recently, a complete blood count (CBC) with differential is needed. A CBC measures parts of the blood including counts of white blood cells, red blood cells, and platelets. A differential measures the counts of each type of white blood cell and checks the balance of the counts. Cancer and other health problems can cause low or high blood counts.

**Chemistry profile**
Chemicals in your blood come from your liver, bone, and other organs. A chemistry profile assesses if the chemicals in your blood are too low or high. Abnormal levels can be caused by spread of cancer or by other health problems.

Imaging

Imaging makes pictures of the insides of your body. It can show cancer in deep tissue, lymph nodes, or distant body parts. A radiologist is a doctor who’s an expert in reading images. This doctor will convey the test results to your other doctors.

Your doctors will use imaging results to plan where to biopsy and which treatment is best. Scans that were done more than 60 days ago should not be used to decide your treatment.

Pictures of the insides of your body can be made with imaging. During the scan, you will lie on a table that will move into the tunnel of the machine. The pictures will be viewed by a doctor who will look for signs of cancer.
Diagnostic CT
Computed tomography (CT) makes a more detailed image than a plain x-ray. It takes many pictures of your body from different angles using x-rays. A computer then combines the pictures to make a 3-D image.

A diagnostic CT involves a higher dose of radiation and contrast. Contrast is a substance that is often injected into the bloodstream. It makes the images easier to read. For cancer staging, images of your chest and upper abdomen are needed.

FDG PET/CT
You will also need a PET/CT scan. PET is short for positron emission tomography. A PET/CT scan may detect cancer that was not found by CT alone.

PET detects cancer with a radioactive sugar and special camera. The radioactive sugar, called fluorodeoxyglucose (FDG), will be injected into your vein.

Cancer quickly uses sugar so it appears “hot” in images. Other health problems can also cause hot spots, too. Cancer detected by PET/CT often needs to be confirmed with biopsy or other imaging.

Brain MRI
Magnetic resonance imaging (MRI) uses a magnetic field and radio waves to make pictures. Contrast should be used. If you have or may have metastatic lung cancer, brain MRI is very important. It will show if the cancer has spread to your brain.

Biopsy vs. surgery
To diagnose lung cancer, a biopsy or surgery is used to remove bits of tissue for testing. Often, tissue from the metastasis is removed rather than from the lung tumor. The tissue must be large enough to run several special lab tests.

Your doctor may try to diagnose and stage the cancer at the same time. The body part that likely has cancer and is farthest from the lung tumor will be sampled and tested. By doing this, you'll have fewer procedures.

Your doctor will use imaging results to select the biopsy site. This site is often the adrenal gland, liver, or bone. The type of biopsy that will be done depends on the site.

- **External needle biopsies** involve guiding a thin needle through your skin and into the tumor. These biopsies include transthoracic needle aspiration (TTNA), core needle biopsies, pericardiocentesis, and thoracentesis.

- **Down-the-throat biopsies** involve guiding tools down your throat into your windpipe or esophagus. These biopsies include radial endobronchial ultrasound (EBUS) bronchoscopy and endoscopic ultrasound (EUS)-guided biopsies.

- **Portal surgeries** involve making small openings (ports) into your chest. Small tools are inserted through the ports to remove tissue. These surgeries include thoracoscopy.

- **Open surgery** involves making a larger cut through your chest wall to remove tissue. You may have open surgery when other methods won't work or a larger piece of tissue is needed.
Cancer cell tests

Tissue removed during biopsy or surgery is sent to a doctor called a pathologist. Pathologists are experts in tissue and cells and diagnosing cancer. In a lab, a pathologist will look at the tissue with a microscope. If lung cancer is found, more tests will be done because not all lung cancers are alike. Lung cancer differs by cell type and how the cells are abnormal.

Lab results used for diagnosis are included in a pathology report. This report will be sent to your cancer doctor. Ask for a copy. It is used to plan your treatment. Your doctor will review the results with you. Take notes and ask questions.

The pathologist will study the tumor to classify the disease. This is called histologic typing. The pathology report will state if the cancer started in the lung or elsewhere. If the cancer started in the lung, the report will also list the type of lung cancer. Cell (histologic) types of lung cancer include:

- Adenocarcinoma
- Large-cell lung carcinoma
- Squamous cell carcinoma
- Small cell carcinoma
- Mixed and rare types

Diagnosis

It takes a team to decide the best steps to diagnose lung cancer. Removing tissue for cancer testing is not always easy. Your team may include the following experts:

- Thoracic radiologist
- Interventional radiologist
- Thoracic surgeon
- Interventional pulmonologist

When planning, doctors think about the size and location of tumors, your health history, and their experience. They rely on the results of the physical exam and imaging.

Test results will determine your treatment plan. Ask questions about and keep copies of all your test results.
Biomarker tests

Lung cancer differs between people by cell type but also by abnormal cell changes. Changes in cancer cells affect treatment options and are called biomarkers. Because of biomarkers, a treatment that helps one person might not help you. See Guide 2 for a list of biomarkers and which cancers should be tested for them.

For lung cancer, there are 2 groups of biomarkers.

- Driver mutations
- PD-L1

Driver mutations are also called driver oncogenes. They cause normal cells to become cancer cells and support cancer growth. Typically, cancer cells do not have more than one driver mutation.

PD-L1 is a protein on the surface of cells. PD-L1 on cancer cells stops T cells from killing them. The cancer cells survive and make more cancer cells.

Most lung cancers do not have a known biomarker for which there is treatment. Treatment options for these cancers are based on the lung cell type. Very few squamous cell carcinomas have a driver mutation. Biomarker testing may be done if you’ve never smoked or the cancer is a mix of cell types. All lung cancers should be tested for PD-L1.

Most often, biomarker testing is performed on tissue from the tumor. It is not the same as

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Guide 2
Biomarker testing

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● Testing is recommended ● Testing if needed

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genetic testing, which assesses what a person inherited from their parents.

A second biopsy may be needed if the first tissue sample is too small. Sometimes, a sample of blood may be used for biomarker testing. A blood sample is referred to as a “liquid biopsy.”

Broad molecular profiling of all biomarkers is advised. There are other known biomarkers linked with lung cancer. However, they are rare and related treatments are still being tested in clinical trials.

Lung function tests

Surgery or radiation therapy may be treatment options for some metastatic cancers. First, your doctors will need to know how well your lungs work. There are 3 pulmonary tests that may be used to assess your lungs:

- Spirometry involves blowing into a tube to measure how much air and how fast you breathe.
- A gas diffusion test involves breathing in a harmless gas and measuring how much you breathe out. It tells how much oxygen travels from your lungs into your blood.
- Body plethysmograph involves sitting in a small room and breathing into a tube. This test measures how much air your lungs can hold and how much air is left in your lungs after you exhale.

Supportive care

Supportive care aims to improve your quality of life. It is also sometimes called palliative care. Supportive care is important for everyone, not just people at the end of life. In fact, it has been shown to extend and enhance life for people with metastatic lung cancer.

Supportive care can address many needs. It includes care for health problems caused by cancer or cancer treatment. You can get help with making treatment decisions. You can get help with coordination of care between health providers.

Your palliative care doctor will work with your oncologists to provide you the best care. Other specialists who may be involved in your care include:

- Respiratory therapists
- Rehabilitation specialists
- Registered dieticians
- Social workers
Review

- To plan treatment, your doctors need to learn about the cancer and your health.
- Be ready to tell your doctors about any health problems and treatments you’ve had in your lifetime.
- Ask your doctor for help to quit smoking. Quitting may improve treatment results.
- Your doctors will examine your body for signs of disease. The exam will include touching parts of your body to see if anything feels abnormal.
- Your doctors will rate your ability to do day-to-day activities in order to decide your treatment options.
- Your doctors will order blood tests. Blood tests are used to look for signs of cancer.
- Diagnostic CT can help show where the cancer has spread. PET/CT may detect cancer that CT did not. MRI is used to see if the cancer has spread to your brain.
- A biopsy is needed to confirm that there is cancer. Doctors use imaging to decide what tissue should be removed and how best to remove it. Often, samples from the adrenal gland, liver, or bone are removed.
- A pathologist will study your tissue samples with a microscope. If there is cancer, the pathologist will identify the type of cell from which the cancer formed.
- Metastatic lung cancer should be tested for biomarkers to identify what is the best treatment for you. A treatment that helps one person might not help you. Most lung cancers do not have a known biomarker.
- Pulmonary function tests are needed if surgery or radiation therapy will be used for treatment.
- Start supportive care early. It has been shown to extend and enhance life for people with metastatic lung cancer.
3

Treatment of driver mutations

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Driver mutations promote the growth of cancer. They are most often found in adenocarcinomas and mixed cell types of lung cancer. Targeted therapy of lung cancer stops the effects of driver mutations.

**Driver mutations**

Genetic information tells your cells what to do. It is located in the nucleus of a cell and stored in 46 long strands of DNA. A gene is a small segment of DNA. DNA strands are carried and protected in 23 chromosomes.

Abnormal changes in genetic information often occur in cancer cells. The DNA can be broken, missing, rearranged, or have extra parts. Abnormal changes in genes are called mutations.

A driver mutation causes normal cells to become cancer cells. It enables the cancer cells to quickly duplicate, survive, and spread in the body. There are different types of driver mutations. Driver mutations are detected by biomarker testing of cancer cells and not genetic testing, which assesses inherited changes from parent to child.

In lung cancer, a common driver mutation is a gene rearrangement. A gene rearrangement is also called a gene fusion. This term refers to one part of a gene switching places (fusing) with a part from another gene. The gene fusion produces an abnormal protein that promotes cancer growth.

**Genetic information**

The nucleus is the control center or “brain” of cells. Within the nucleus is genetic information that tells the cells what to do. The information is stored in DNA. DNA looks like a twisted ladder when uncoiled from a chromosome. Genes are segments of DNA that contain “instructions” for the cell. Abnormal changes in genes that promote cancer growth are called driver mutations.
Targeted therapy

Targeted therapy is used to treat driver mutations of lung cancer. It treats cancer by stopping the specific ways by which cancer cells live, survive, and die. It harms fewer types of normal cells than chemotherapy, which destroys any type of fast-growing cell.

Kinase inhibitors

The most common type of targeted therapy for lung cancer is kinase inhibitors. They are pills that can be taken at home.

Kinases are a type of cell protein. They are part of many chemical pathways, some of which start cell growth. They are often part of a structure called a surface receptor. Surface receptors are on the outer membrane of a cell. They start changes within the cell when turned on.

Kinases change the action of other proteins by attaching phosphates to them. Kinase inhibitors stop cell growth signals by blocking the transfer of phosphates. This lowers the number of new cancer cells being made.

VEGF antibodies

Cancer cells need blood to grow, so they release a protein called VEGF. VEGF triggers endothelial cells to form new blood vessels on tumors. VEGF antibodies stop VEGF, and the cancer cells die from a lack of blood. You will need to go to a health care center to receive VEGF antibodies through a slow drip (infusion).

Switching to targeted therapy

You may have started a treatment different than targeted therapy before getting biomarker test results. If a driver mutation is found, you have two options:

- You may stop your current treatment early and start targeted therapy.
- The other option is to finish your current treatment (including the last phase called maintenance treatment), and then start targeted therapy.

Sensitizing EGFR mutations

A surface receptor called EGFR can be overactive causing lung cells to quickly grow. Mutations in the gene that controls EGFR are common. Sensitizing mutations are the ones that cause overactive EGFR. First-line treatment options for sensitizing EGFR mutations are listed in Guide 3.

Guide 3

First-line treatment of sensitizing EGFR mutations

Preferred options
- Osimertinib

Other options
- Erlotinib
- Afatinib
- Gefitinib
- Dacomitinib
- Erlotinib and ramucirumab
- Erlotinib and bevacizumab
First-line treatment

Erlotinib (Tarceva®) and gefitinib (Iressa®) were the first EGFR inhibitors used to treat lung cancer. The second group of EGFR inhibitors to be developed were afatinib (Gilotrif®) and dacomitinib (Vizimpro®). The newest EGFR inhibitor is osimertinib (Tagrisso®).

All EGFR inhibitors have been found to work well in well-designed clinical trials. Osimertinib is preferred because it stops cancer growth for a longer period of time. If your first treatment was immunotherapy, a short delay in starting osimertinib may be needed to prevent health problems.

Erlotinib is sometimes combined with a VEGF antibody. VEGF antibodies include bevacizumab (Avastin®) and ramucirumab (Cyramza®). It is not safe to receive bevacizumab if you are coughing up blood (hemoptysis).

After first-line treatment

Within a few years on first-line treatment, lung cancer starts to grow again in most people. You may get a biopsy:

- If the cancer grows while on erlotinib, afatinib, gefitinib, or dacomitinib, testing for a T790M mutation is advised. The T790M mutation in the EGFR gene often occurs after taking these drugs. It stops the cancer drugs from working. A liquid biopsy should be tried before a tumor biopsy is done.
- To rule out transformation to small cell lung cancer, you may get a biopsy.

Treatment options depend on how the cancer worsens. Your doctor will check for symptoms and if the cancer has spread to more places. Options are listed in Guide 4.

Guide 4
Options after first-line treatment for sensitizing EGFR mutations

Local treatment of limited tumors may be helpful for some people

Stay on first-line treatment if it has some benefit

- Stay on erlotinib, afatinib, gefitinib, or osimertinib unless the cancer is widespread
- Stay on dacomitinib unless the cancer is in the brain or widespread

Switch to a different targeted therapy

- Switch to osimertinib if the lung cancer cells have a T790M mutation
- Switch to afatinib with cetuximab if cancer worsens while taking osimertinib

Start treatment for cell type as listed in Chapter 5
If the cancer is not widespread, your doctor may recommend local treatment. It is used to treat cancer in a specific place like the brain or adrenal gland. In addition, EGFR inhibitors will be used to control cancer growth. The type of local treatment received differs between people:

- Stereotactic radiosurgery (SRS) for brain tumors
- Surgery
- Stereotactic ablative radiotherapy (SABR)
- Image-guided thermal ablation therapy if radiation therapy is not safe

Despite the cancer worsening, first-line treatment may be slowing down cancer growth. If this treatment is stopped, the cancer may worsen quicker. Staying on first-line treatment may be an option if the cancer isn’t widespread. Your doctor may not keep you on dacomitinib if the cancer has spread to your brain. There is no research on dacomitinib for brain metastases.

If first-line treatment stops working, switching to a different targeted therapy may be an option. Your doctor may switch your treatment to osimertinib if the lung cancer cells have a T790M mutation.

Your doctor may switch treatment to afatinib and cetuximab if you were taking osimertinib. Cetuximab stops growth signals from EGFR by attaching to EGFR on the outside of cells. It is received by infusion.

If targeted therapy is not likely to help, your doctor may recommend other treatment. Treatment used for cell type may be an option. See Chapter 5.

**ALK rearrangement**

A surface receptor called ALK can be overactive causing lung cells to quickly grow. The cause of ALK overactivity is a rearrangement of the **ALK** gene. First-line treatment options for ALK rearrangements are listed in Guide 5.

There are 5 ALK inhibitors used to treat lung cancer. Crizotinib (Xalkori®) was the first ALK inhibitor used to treat lung cancer. The second group of ALK inhibitors to be developed were ceritinib (Zykadia®), alectinib (Alecensa®), and brigatinib (Alunbrig®). The newest ALK inhibitor is lorlatinib (Lorbrena®).

**After first-line treatment**

Within a few years of starting first-line treatment, lung cancer starts to grow again in most people. Treatment options depend on how the cancer worsens. Your doctor will

### Guide 5

**First-line treatment of ALK rearrangement**

**Preferred options**
- Alectinib
- Brigatinib
- Lorlatinib

**Other options**
- Ceritinib

**Sometimes useful**
- Crizotinib
check for symptoms and order tests to see if the cancer has spread to more places. Treatment options are listed in Guide 6.

If the cancer is not widespread, your doctor may recommend local treatment. Local treatment is used to treat cancer in a specific place like the brain or adrenal gland. In addition, ALK inhibitors will be used to control cancer growth. The type of local treatment received differs between people:

- SRS for brain tumors
- surgery
- SABR
- image-guided thermal ablation therapy if radiation therapy is not safe

Despite the cancer worsening, first-line treatment may be slowing down cancer growth. If this treatment is stopped, the cancer may worsen quicker. Staying on first-line treatment may be an option if the cancer isn’t widespread. Crizotinib doesn’t work if the cancer has spread to your brain. The other ALK inhibitors work better in the brain.

If first-line treatment stops working, your treatment may be switched to a newer ALK inhibitor. Treatment may be switched to lorlatinib if you’re on alectinib, brigatinib, or ceritinib. If on crizotinib, treatment may be switched to alectinib, brigatinib, ceritinib, or lorlatinib.

If ALK inhibitors are not likely to help, your doctor may advise other treatment. Treatment used for cell type may be an option. See Chapter 5.

Guide 6
Options after first-line treatment of ALK rearrangement

Local treatment of limited tumors may be helpful for some people

- Stay on first-line treatment if it has some benefit
  - Stay on alectinib, brigatinib, ceritinib, or lorlatinib unless the cancer is widespread
  - Stay on crizotinib unless the cancer is in the brain or widespread

- Switch to a newer ALK inhibitor
  - Switch to lorlatinib if on alectinib, brigatinib, or ceritinib
  - Switch to alectinib, brigatinib, ceritinib, or lorlatinib if on crizotinib

- Start treatment for cell type as listed in Chapter 5
**ROS1 rearrangement**

A surface receptor called ROS can be overactive causing lung cells to quickly grow. The cause of the overactivity is a gene rearrangement. Treatment options for ROS1 rearrangements are listed in Guide 7.

Entrecitinib (Rozlytrek®) and crizotinib (Xalkori®) are preferred options. Entrecitinib may work better for lung cancer in the brain. The other option is ceritinib (Zykadia®).

In time, the cancer will worsen after first-line treatment. Lorlatinib (Lorbrena®) may be an option after first-line treatment. Entrecitinib may be an option after crizotinib if the cancer has spread to the spinal cord or brain. Treatment used for cell type may be an option. See Chapter 5.

---

**BRAF V600E mutation**

A signaling protein inside of cells called BRAF can be overactive causing lung cells to quickly grow. It is overactive due to a BRAF V600E mutation. Treatment options for BRAF V600E mutation are listed in Guide 8.

Preferred treatment is dabrafenib plus trametinib. Dabrafenib (Tafinlar®) stops growth signals from BRAF. MEK is a protein within the same signaling pathway as BRAF. Trametinib (Mekinist®) stops growth signals from MEK.

If dabrafenib plus trametinib makes you too sick, you may receive vemurafenib (Zelboraf®). Vemurafenib also stops growth signals from BRAF. If not received before, treatment used for cell type may be an option. See Chapter 5.

In time, the cancer will worsen after first-line treatment. After targeted therapy, treatment used for cell type may be used to treat lung cancer. If not used before, dabrafenib plus trametinib may be started if the cancer worsens on first-line treatment.

---

### Guide 7

**Treatment of ROS1 rearrangement**

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<tr>
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<td>• Crizotinib</td>
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<tr>
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<table>
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<tr>
<th>Options after first-line treatment</th>
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<td>• Lorlatinib</td>
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<tr>
<td>• Entrecitinib</td>
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<tr>
<td>• Treatment for cell type as listed in Chapter 5</td>
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</tbody>
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### Guide 8

**Treatment of BRAF V600E mutation**

<table>
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<th>Preferred options</th>
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<tbody>
<tr>
<td>• Dabrafenib plus trametinib</td>
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<tr>
<th>Sometimes useful</th>
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</thead>
<tbody>
<tr>
<td>• Vemurafenib</td>
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<tr>
<td>• Treatment for cell type as listed in Chapter 5</td>
</tr>
</tbody>
</table>
**NTRK gene fusion**

Lung cells have a family of 3 surface receptors called TRK. *NTRK* genes contain instructions for making TRK. Some lung cancers have too much TRK, which causes fast cell growth. The cause of excess TRK is a joining (fusion) of *NTRK* with another gene. Treatment options for *NTRK* gene fusion are listed in Guide 9.

TRK inhibitors are preferred for first-line treatment of people with an *NTRK* mutation. These treatments include larotrectinib (Vitrakvi®) and entrectinib (Rozlytrek®). These treatments have not been compared in research, but entrectinib may work better for lung cancer in the brain. If not received before, treatment used for cell type may be an option. See Chapter 5.

In time, the cancer will worsen after first-line treatment. After targeted therapy, treatment used for cell type may be used to treat lung cancer. If not used before, a TRK inhibitor may be started if the cancer worsens on first-line treatment.

**Guide 9**

**Treatment of *NTRK* gene fusion**

**Preferred options**
- Larotrectinib
- Entrectinib

**Sometimes useful**
- Treatment for cell type as listed in Chapter 5

---

**MET exon 14 skipping**

Some lung cancers have too much of a surface receptor called MET. Too much MET causes fast cell growth. The cause of excess MET is a deleted (skipped) part of the *MET* gene called exon 14. Treatment options for *MET* exon 14 skipping are listed in Guide 10.

MET inhibitors are preferred for first-line treatment. These treatments include capmatinib (Tabrecta™) and tepotinib (Tepmetko®). Crizotinib (Xalkori®) is useful for some people. It inhibits MET and other kinases. If not received before, treatment used for cell type may be an option. Treatment regimens are listed in Chapter 5.

In time, the cancer will worsen after first-line treatment. After targeted therapy, treatment for cell type may be used to treat lung cancer. If not used before, targeted therapy may be started if the cancer worsens on first-line treatment.

**Guide 10**

**Treatment of *MET* exon 14 skipping**

**Preferred options**
- Capmatinib
- Tepotinib

**Sometimes useful**
- Crizotinib
- Treatment for cell type as listed in Chapter 5
RET rearrangement

A surface receptor called RET can be overactive causing lung cells to quickly grow. The cause of the overactivity is a gene rearrangement. Treatment options for RET rearrangements are listed in Guide 11.

RET inhibitors are preferred for first-line treatment. These treatments include selpercatinib (Retevmo™) and pralsetinib (Gavreto™). Cabozantinib (Cometriq®, Cabometyx®) and vandetanib (Caprelsa®) are useful for some people. They inhibit RET and other kinases but don’t work as well as preferred treatments. If not received before, treatment used for cell type is another option. See Chapter 5.

In time, the cancer will worsen after first-line treatment. After targeted therapy, treatment used for cell type may be an option. If not used before, targeted therapy may be started if the cancer worsens on first-line treatment.

Guide 11
Treatment of RET rearrangement

Prefered options
- Selpercatinib
- Pralsetinib

Sometimes useful
- Cabozantinib
- Vandetanib

Other
- Treatment for cell type as listed in Chapter 5

Side effects

All cancer treatments can cause unwanted health issues. Such health issues are called side effects. Some side effects may be harmful to your health. Others may just be unpleasant.

Side effects depend on many factors. These factors include the treatment type, length or dose of treatment, and the person.

Many effects of treatment quickly resolve after treatment ends. Long-term effects start during treatment and persist after treatment is done. Less often, effects start long after treatment has ended.

Ask your treatment team for a complete list of side effects of your treatments. Also, tell your treatment team about any new or worse symptoms you get. There may be ways to help you feel better. There are also ways to prevent some side effects.

NCCN has a patient guide on late and long-term effects of cancer and treatment. Such effects include fatigue, poor sleep, and heart disease.

Read about common effects in NCCN Guidelines for Patients: Survivorship Care for Cancer-Related Late and Long-Term Effects, available at NCCN.org/patientguidelines.
Review

- A driver mutation causes normal cells to become cancer cells. It enables the cancer cells to quickly duplicate, survive, and spread in the body.

- Targeted therapy is used to treat driver mutations of lung cancer. Kinase inhibitors are the most common type of targeted therapy of lung cancer.

- Some people start treatment before getting the results of biomarker testing. You could stay on your current treatment then take targeted therapy. A second option is to switch from your current treatment to targeted therapy.

- For each type of driver mutation there is at least one preferred targeted therapy and often other regimens.

- When targeted therapy is not likely to help, you may start treatment for cell type.

- Ask your treatment team for a complete list of side effects of your treatments. Also, tell your treatment team about any new or worse symptoms you get.

We want your feedback!

Our goal is to provide helpful and easy-to-understand information on cancer.

Take our survey to let us know what we got right and what we could do better:

NCCN.org/patients/feedback
4

Treatment by PD-L1 level

- Immune checkpoints
- Immunotherapy
- Treatment options
- Side effects
- Review
Some people have lung cancer cells that evade death by T cells. Read this chapter to learn more about this survival skill of cancer cells. Immunotherapy restores the killing ability of T cells.

**Immune checkpoints**

The body’s defense against disease is called the immune system. T cells are a key part of this system. T cells that kill infected and cancer cells are called cytotoxic or killer T cells.

The immune system has “brakes” that prevent or slow down an immune response. The brakes are called immune checkpoints. They protect the body’s healthy cells. Proteins called CTLA-4 and PD-1 are two types of brake pedals on T cells.

In people with lung cancer, the brake pedals on T cells may be overused. CTLA-4 is activated when attached to B7 on immune cells called dendritic cells. PD-1 is activated when attached to PD-L1 on lung cancer cells. With the brakes on, T cells are not able to kill cancer cells.

**Immunotherapy**

Immunotherapy is a treatment that uses the immune system to kill cancer cells. Immune checkpoint inhibitors are a type of immunotherapy. They work by releasing the brake pedals on T cells.

Immunotherapy

Some lung cancers consist of cells that have PD-L1 on their surface. PD-L1 can attach to PD-1 on T cells and stop T cells from killing cancer cells. Immunotherapy stops PD-L1 from attaching. As a result, T cells are able to attack cancer cells. There are two types of immunotherapy. PD-1 inhibitors attach to T cells. PD-L1 inhibitors attach to cancer cells.
There are 5 checkpoint inhibitors used to treat metastatic lung cancer:

- Pembrolizumab (Keytruda®)
- Nivolumab (Opdivo®)
- Cemiplimab (Libtayo®)
- Atezolizumab (Tecentriq®)
- Ipilimumab (Yervoy®)

These checkpoint inhibitors block proteins to keep the immune checkpoint turned off. Pembrolizumab, nivolumab, and cemiplimab are PD-1 inhibitors. They attach to PD-1 on T cells and block PD-L1. Atezolizumab is a PD-L1 inhibitor. It attaches to PD-L1 on cancer cells so PD-L1 can’t attach to T cells. Ipilimumab is a CTLA-4 inhibitor. It attaches to CTLA-4 on T cells and blocks attachment to B7.

Checkpoint inhibitors are slowly injected into a vein (infusion). It may take 30 or 60 minutes to get the full dose. Infusions are received every few weeks. The number of weeks between treatments depends on the inhibitor used. Often, people get infusions until they stop working and the cancer worsens.

Not all lung cancers should be treated with immunotherapy. Immunotherapy should not be the first treatment if the cancer cells have cancer-promoting (driver) mutations. Cancers with driver mutations should first be treated with targeted therapy as described in Chapter 3. First-line targeted therapy has better results and causes less serious health problems.

Immunotherapy may also not be given if it may be unsafe. Some people may be too sick to take it. For some people, immunotherapy may impair their immune system. Tell your doctor if you have an autoimmune disease, such as Crohn’s disease, ulcerative colitis, or lupus. Bring a list of your medications to your health care appointments.

### Treatment options

Immunotherapy options are partly based on PD-L1. A pathologist will assess the percentage of cancer cells with PD-L1. A sample of a lung tumor is needed for testing.

- High PD-L1 means that at least half of the cancer cells have PD-L1 (50% or more)
- Low PD-L1 means that less than half of cancer cells have PD-L1 (1% to 49%)
- No PD-L1 means that fewer than 1 out of 100 cells have PD-L1 (less than 1%)

For lung cancer with PD-L1, see Guide 12 for a list of treatment options for adenocarcinoma, large cell, and rare lung cancer. Treatment options for squamous cell lung cancer are listed in Guide 13. Treatment of lung cancer with no PD-L1 is discussed in Chapter 5.

### First-line treatment

Used alone, PD-1 inhibitors have good results for lung cancer with high PD-L1. Combining PD-1 or PD-L1 inhibitors with chemotherapy also has good results. It is standard treatment when PD-L1 is high or low.

Platinum-doublet chemotherapy is used with checkpoint inhibitors. It consists of cisplatin or carboplatin—drugs made with platinum—and another type of chemotherapy. Choice of
Guide 12
First-line treatment options by PD-L1 level
Adenocarcinoma, large cell, and rare types of lung cancer

<table>
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<th>Preferred regimens</th>
<th>Low PD-L1</th>
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<tr>
<td>Cemiplimab</td>
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<tr>
<td>Pembrolizumab, carboplatin, and pemetrexed</td>
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</tr>
<tr>
<td>Pembrolizumab, cisplatin, and pemetrexed</td>
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Other regimens

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<tbody>
<tr>
<td>Pembrolizumab, carboplatin, and paclitaxel</td>
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<tr>
<td>Pembrolizumab, carboplatin, and albumin-bound paclitaxel</td>
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Sometimes useful

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<th>Preferred regimens</th>
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<td>Pembrolizumab</td>
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Guide 13
First-line treatment options by PD-L1 level
Squamous cell lung cancer

<table>
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<th>Preferred regimens</th>
<th>Low PD-L1</th>
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Other regimens

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<tbody>
<tr>
<td>Nivolumab, ipilimumab, carboplatin, and paclitaxel</td>
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Sometimes useful

<table>
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<tr>
<th>Preferred regimens</th>
<th>Low PD-L1</th>
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<tbody>
<tr>
<td>Nivolumab with ipilimumab</td>
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<td>●</td>
</tr>
<tr>
<td>Pembrolizumab</td>
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</table>
chemotherapy partly depends on the type of cancer cell. Platinum-doublet chemotherapy can cause health problems called side effects. You must be healthy enough to get this chemotherapy.

Two checkpoint inhibitors, nivolumab and ipilimumab, are used together to treat lung cancer. They are given with platinum-doublet chemotherapy.

Atezolizumab with platinum-doublet chemotherapy is an option for non-squamous cell cancers. Bevacizumab is a part of one atezolizumab regimen. It is a targeted therapy called a VEGF antibody. It stops the growth of blood vessels on tumors. Without blood, cancer cells die.

**Maintenance treatment**

If treatment results are good, you may shift to maintenance treatment, which includes some of your first-line treatments. This is called continuation maintenance. The goal of maintenance treatment is to prolong the time until the cancer worsens. Options for maintenance treatment are listed in Guide 14.

Within a few years on first-line treatment, lung cancer starts to grow again in most people. Options after first-line treatment are listed in Chapter 5.

---

### Guide 14

**Maintenance treatment options by PD-L1 level**

<table>
<thead>
<tr>
<th>Adenocarcinoma, large cell, and rare lung cancers</th>
<th>Low PD-L1</th>
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<tr>
<td>Cemiplimab</td>
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**Squamous cell lung cancer**

| Pembrolizumab                                                   | ●         | ●          |
| Nivolumab and ipilimumab                                         | ●         | ●          |
| Atezolizumab                                                    | ●         | ●          |
| Cemiplimab                                                      | ●         | ●          |
Side effects

Immunotherapy can cause your immune cells to attack healthy cells in your body. This results in health problems called side effects. Immune-related side effects range from mild to life-threatening. They can occur during or after treatment. Some side effects may worsen over the course of treatment, with each treatment dose. Most side effects can be managed if found and treated early.

NCCN has a two-part book series on immunotherapy side effects. One book focuses on side effects of immune checkpoint inhibitors. It includes care options for many side effects, such as:

- Rash, itching, or blisters
- Fatigue
- Diarrhea
- Low or high hormone levels
- Lung inflammation
- Joint and muscle pain
- Heart inflammation
- Dry eyes

Read about managing side effects in NCCN Guidelines for Patients: Immunotherapy Side Effects, Immune Checkpoint Inhibitors, available at NCCN.org/patientguidelines.

“Learning to manage side effects is well worth the effort!”

– Jon
Lung cancer survivor
Review

- The body’s defense against disease is called the immune system. T cells are part of this system. They kill cancer cells.
- Immune checkpoints keep immune responses in check. PD-1 and CTLA-4 are two types of immune checkpoints on T cells.
- In people with lung cancer, PD-1 and CTLA-4 are often activated and stop T cells from killing cancer cells.
- Immune checkpoint inhibitors are a type of immunotherapy. They prevent PD-1 and CTLA-4 from being activated.
- Immunotherapy options for lung cancer are based on the level of PD-L1. PD-L1 is a protein on lung cancer cells that turns on PD-1. When PD-1 is activated, T cells do not kill cancer cells.
- When PD-L1 is high, immunotherapy by itself can be used for treatment. Immunotherapy combined with chemotherapy is also standard treatment for low and high PD-L1.
- If treatment results are good, you may stay on some of them to increase the time until the cancer worsens. This is called maintenance treatment.
- Immunotherapy can cause your immune cells to attack healthy cells in the body. The immune-related health problems range from mild to life-threatening. Most of these health problems can be managed if found and treated early.

Let us know what you think!

Please take a moment to complete an online survey about the NCCN Guidelines for Patients.

NCCN.org/patients/response
5

Treatment by cell type

- 38  Cell type
- 39  Performance status
- 40  Systemic therapy
- 44  Clinical trials
- 45  Review
Lung cancer differs between people based on the type of cell affected. Read this chapter to learn the best treatment options based on cell type. Treatment can be further improved with clinical trials.

**Cell type**

Most lung cancers do not have a known biomarker for which there is treatment. When there is no biomarker, treatment is based on other factors, such as:

- Type of cancer cell
- Performance status
- Health conditions and medications

There are 3 main types of lung cancer. They are named after the normal cell from which the cancer formed:

- Lung adenocarcinoma
- Large cell carcinoma
- Squamous cell carcinoma

Rare types of lung cancer are sometimes described as “not otherwise specified (NOS).”

**Types of non-small cell lung cancer**

There are 3 main types of lung cancer. Adenocarcinoma is the most common type. It is a cancer of mucus-making cells. Large cell carcinoma starts in large cells of the lung. Squamous cell carcinoma starts in squamous cells.

[Credit images: https://commons.wikimedia.org/wiki/File:Mucinous_lung_adenocarcinoma_-_high_mag.jpg](https://commons.wikimedia.org/wiki/File:Mucinous_lung_adenocarcinoma_-_high_mag.jpg)
[Credit images: https://commons.wikimedia.org/wiki/File:Lung_squamous_carcinoma_-_high_mag.jpg](https://commons.wikimedia.org/wiki/File:Lung_squamous_carcinoma_-_high_mag.jpg)
Performance status

Performance status is your ability to do day-to-day activities. Disease can limit what you can do. Your doctors will use your performance status to decide what treatments are options for you.

The Eastern Cooperative Oncology Group (ECOG) Performance Status is a common scoring system. It consists of five scores ranging from 0 to 4. Lower scores represent a better ability to do self-care. See Guide 15 for treatment based on performance scores.

Performance scores of 0 to 2 mean that you are fairly healthy. NCCN experts advise receiving systemic therapy. Systemic therapy is a term for cancer drugs that travel in the bloodstream to the cancer. It can treat cancer that is in many places and in hard-to-reach places. It is given in cycles of treatment days followed by days of rest. The cycles vary in length depending on which drugs are used.

A performance score of 3 or 4 suggests that cancer drugs will be too harmful. NCCN experts advise receiving supportive care if the cancer does not have a driver mutation. Treatment of driver mutations is discussed in Chapter 3.

Supportive care aims to improve your quality of life. It is sometimes called palliative care. One of its aims is to treat the symptoms caused by the cancer. Talk with your doctor about supportive care to get the best care plan for you.

Guide 15
Performance status and treatment

<table>
<thead>
<tr>
<th>Score</th>
<th>Abilities</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>0</td>
<td>You are fully active.</td>
<td>Systemic therapy</td>
</tr>
<tr>
<td>1</td>
<td>You are able to do self-care activities but unable to do hard physical work.</td>
<td>Systemic therapy</td>
</tr>
<tr>
<td>2</td>
<td>You are able to do self-care activities and spend most of waking time out of bed. You are unable to do any work.</td>
<td>Systemic therapy</td>
</tr>
<tr>
<td>3</td>
<td>You are unable to do self-care activities and any work. You spend most of waking time in bed.</td>
<td>Supportive care if there is no driver mutation</td>
</tr>
<tr>
<td>4</td>
<td>You are fully disabled.</td>
<td>Supportive care if there is no driver mutation</td>
</tr>
</tbody>
</table>
Systemic therapy

The classic treatment of widespread metastatic lung cancer is chemotherapy. Chemotherapy is a term for drugs that kill rapidly dividing cells. Newer treatments are sometimes used with chemotherapy to improve control of the cancer. Treatment options for lung cancer without biomarkers are listed in Guide 16 and Guide 17.

First-line treatments
For performance scores of 0 or 1, chemotherapy with immunotherapy is standard treatment. The type of immunotherapy used is called immune checkpoint inhibitors. Checkpoint inhibitors are used to treat lung cancer with PD-L1 as discussed in Chapter 4. They also extend life when lung cancer does not have PD-L1. There are 4 inhibitors used to treat lung cancer based on cell type:

- Pembrolizumab (Keytruda®)
- Nivolumab (Opdivo®)
- Atezolizumab (Tecentriq®)
- Ipilimumab (Yervoy®)

Platinum-doublet chemotherapy is used with checkpoint inhibitors for treatment. It consists of cisplatin or carboplatin—drugs made with platinum—and another type of chemotherapy. Choice of chemotherapy partly depends on the type of cancer cell.

Some people are not able to receive immune checkpoint inhibitors. Checkpoint inhibitors may not be an option because of an autoimmune disease, certain medicines, or higher performance scores. In these cases, platinum-doublet chemotherapy is most often used for treatment. Another option is gemcitabine with either docetaxel or vinorelbine.

Bevacizumab is a part of some systemic regimens. It is a targeted therapy called a VEGF antibody. It stops the growth of blood vessels on tumors. Without blood, cancer cells die.

Sometimes, regimens with 2 chemotherapy drugs are not options. Instead, a single-agent chemotherapy may be given. There are several drugs that may be used:

- Albumin-bound paclitaxel
- Docetaxel
- Gemcitabine
- Paclitaxel
- Pemetrexed (only for non-squamous cell types)

Side effects
All cancer treatments cause health problems called side effects. Side effects from chemotherapy are caused by the death of fast-growing normal cells. Immune checkpoint inhibitors can cause your immune cells to attack healthy cells in your body.

Ask your treatment team for a complete list of side effects of your treatments. Also, tell your treatment team about any new or worse symptoms you get. There may be ways to help you feel better. There are also ways to prevent some side effects.

Read about immune-related side effects in NCCN Guidelines for Patients: Immunotherapy Side Effects, Immune Checkpoint Inhibitors. Fatigue, pain, and other side effects are
### Guide 16
**First-line systemic therapy by performance status (PS)**
**Adenocarcinoma, large cell, and rare types of lung cancer**

<table>
<thead>
<tr>
<th>Chemotherapy with immunotherapy</th>
<th>PS 0 or 1</th>
<th>PS 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Carboplatin or cisplatin), pemetrexed, and pembrolizumab (preferred)</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Carboplatin, paclitaxel, bevacizumab, and atezolizumab</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Carboplatin, albumin-bound paclitaxel, and atezolizumab</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Nivolumab and ipilimumab</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>(Carboplatin or cisplatin), pemetrexed, nivolumab, and ipilimumab</td>
<td>●</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chemotherapy without immunotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin, paclitaxel, and bevacizumab</td>
</tr>
<tr>
<td>(Carboplatin or cisplatin), pemetrexed, and bevacizumab</td>
</tr>
<tr>
<td>Cisplatin and another chemotherapy</td>
</tr>
<tr>
<td>Carboplatin and another chemotherapy</td>
</tr>
<tr>
<td>Gemcitabine and (docetaxel or vinorelbine)</td>
</tr>
<tr>
<td>Single-agent chemotherapy</td>
</tr>
</tbody>
</table>

### Guide 17
**First-line systemic therapy by performance status (PS)**
**Squamous cell lung cancer**

<table>
<thead>
<tr>
<th>Chemotherapy with immunotherapy</th>
<th>PS 0 or 1</th>
<th>PS 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin, paclitaxel, and pembrolizumab (preferred)</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Carboplatin, albumin-bound paclitaxel, and pembrolizumab (preferred)</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Nivolumab and ipilimumab</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Carboplatin, paclitaxel, nivolumab, and ipilimumab</td>
<td>●</td>
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<td>Cisplatin and another chemotherapy</td>
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<tr>
<td>Gemcitabine and (docetaxel or vinorelbine)</td>
</tr>
<tr>
<td>Single-agent chemotherapy</td>
</tr>
</tbody>
</table>
addressed in *NCCN Guidelines for Patients: Survivorship Care for Cancer-Related Late and Long-Term Effects*. Both patient guides are available at [NCCN.org/patientguidelines](http://NCCN.org/patientguidelines).

### Monitoring and maintenance

Systemic therapy is given in cycles of treatment days followed by days of rest. After 2 cycles, your doctor will assess the results. The extent of the cancer can be seen on computed tomography (CT) scans. Contrast may be used. CT will be repeated after another 2 to 4 cycles. In general, systemic therapy is given for 4 cycles. If treatment isn't making you too sick, a total of 6 cycles may be completed.

If results are good at the end of treatment, you may stay on at least one of the medicines. This is called continuation maintenance. Another option is changing to a medicine that you didn't take as a first-line treatment. This is called switch maintenance. Options for maintenance treatment are listed in Guide 18.

The goal of maintenance treatment is to increase the time until the cancer worsens. You may stay on maintenance treatment for 2 years if your first-line treatment included immunotherapy. If immunotherapy was part of second-line treatment, stay on maintenance treatment until the cancer worsens.

### Options after first-line treatment

In time, lung cancer often starts to grow again after first-line treatment. Preferred treatments include immune checkpoint inhibitors if not received before. If the cancer worsened while taking a checkpoint inhibitor, switching to another checkpoint inhibitor is not advised. Options after first-line treatment are listed in Guide 19.

Other options include docetaxel with ramucirumab. Ramucirumab is a targeted therapy called a VEGF antibody. Single-agent chemotherapy is another option.

Your doctor will monitor treatment results. You will get a CT scan every 6 to 12 weeks. Contrast may be used.
### Guide 18
**Maintenance treatment by lung cell type**

#### Adenocarcinoma, large cell, and rare types of lung cancer

**Continuation maintenance**
- Bevacizumab
- Pemetrexed
- Bevacizumab and pemetrexed
- Pembrolizumab and pemetrexed
- Atezolizumab and bevacizumab
- Atezolizumab
- Nivolumab and ipilimumab
- Gemcitabine

**Switch maintenance**
- Docetaxel

#### Squamous cell lung cancer

**Continuation maintenance**
- Nivolumab and ipilimumab
- Gemcitabine
- Pembrolizumab

**Switch maintenance**
- Pemetrexed

### Guide 19
**Options after you’ve had chemotherapy with or without immunotherapy**

#### Preferred options
- Nivolumab
- Pembrolizumab
- Atezolizumab

#### Other options
- Docetaxel
- Gemcitabine
- Ramucirumab and docetaxel
- Pemetrexed (non-squamous only)
Clinical trials

Despite advances in treatment, more research is needed. There still is no cure for metastatic lung cancer. Improving treatment is made possible with clinical trials.

A clinical trial is a type of medical research study. After being developed and tested in a laboratory, potential new ways of fighting cancer need to be studied in people. If found to be safe and effective in a clinical trial, a drug, device, or treatment approach may be approved by the U.S. Food and Drug Administration (FDA).

Everyone with cancer should carefully consider all of the treatment options available for their cancer type, including standard treatments and clinical trials. Talk to your doctor about whether a clinical trial may make sense for you.

Phases
Most cancer clinical trials focus on treatment. Treatment trials are done in phases.

- **Phase I trials** study the dose and safety of an investigational drug or treatment approach.
- **Phase II trials** study how well the drug or approach works against a specific type of cancer.
- **Phase III trials** test the drug or approach against a standard treatment. If the results are good, it may be approved by the FDA.
- **Phase IV trials** study the long-term safety and benefit of an FDA-approved treatment.

Who can enroll?
Every clinical trial has rules for joining, called eligibility criteria. The rules may be about age, cancer type and stage, treatment history, or general health. These requirements ensure that participants are alike in specific ways and that the trial is as safe as possible for the participants.

Informed consent
Clinical trials are managed by a group of experts called a research team. The research team will review the study with you in detail, including its purpose and the risks and benefits of joining. All of this information is also provided in an informed consent form. Read the form carefully and ask questions before signing it. Take time to discuss with family, friends, or others you trust. Keep in mind that you can leave and seek treatment outside of the clinical trial at any time.

Start the conversation
Don’t wait for your doctor to bring up clinical trials. Start the conversation and learn about all of your treatment options. If you find a study that you may be eligible for, ask your treatment team if you meet the requirements. Try not to be discouraged if you cannot join. New clinical trials are always becoming available.

Frequently asked questions
There are many myths and misconceptions surrounding clinical trials. The possible benefits and risks are not well understood by many with cancer.

What if I get the placebo?
A placebo is an inactive version of a real medicine. Placebos are almost never used alone in cancer clinical trials. All participants
receive cancer treatment. You may receive a commonly used treatment, the investigational drug(s), or both.

Do I have to pay to be in a clinical trial? Rarely. It depends on the study, your health insurance, and the state in which you live. Your treatment team and the research team can help determine if you are responsible for any costs.

Review

- Treatment for lung cancer without biomarkers is partly based on the cell type.
- Performance status is your ability to do day-to-day activities. Doctors use this status to decide which treatments are safe options.
- Systemic therapy consists of cancer drugs. It is recommended for a performance score of 0 through 2. Supportive care is recommended for scores 3 and 4.
- Chemotherapy with immunotherapy is standard treatment for fairly healthy people. Other options are chemotherapy by itself or chemotherapy with bevacizumab. The cancer drugs selected for treatment are based on the cell type.
- Learn about the side effects of your treatments. Let your treatment team know about any new or worsening symptoms.
- Your doctor will monitor the results of treatment. You may receive between 4 and 6 cycles of treatment.
- Maintenance treatment slows down the growth of the cancer. It consists of one or more drugs from your first treatment.
- The next treatment options for lung cancer are immunotherapy if not received before, chemotherapy with ramucirumab, and single-agent chemotherapy.
- Clinical trials are a type of research. New ways of fighting cancer are studied among people in clinical trials. A clinical trial may be an option in addition to standard treatment.
6
Making treatment decisions

47 It’s your choice
47 Questions to ask your doctors
52 Resources
It’s important to be comfortable with the cancer treatment you choose. This choice starts with having an open and honest conversation with your doctors.

**It’s your choice**

In shared decision-making, you and your doctors share information, discuss the options, and agree on a treatment plan. It starts with an open and honest conversation between you and your doctor.

Treatment decisions are very personal. What is important to you may not be important to someone else. Some things that may play a role in your decision-making:

- What you want and how that might differ from what others want
- Your religious and spiritual beliefs
- Your feelings about certain treatments like surgery or chemotherapy
- Your feelings about pain or side effects such as nausea and vomiting
- Cost of treatment, travel to treatment centers, and time away from work
- Quality of life and length of life
- How active you are and the activities that are important to you

Think about what you want from treatment. Discuss openly the risks and benefits of specific treatments and procedures. Weigh options and share concerns with your doctor. If you take the time to build a relationship with your doctor, it will help you feel supported when considering options and making treatment decisions.

**Second opinion**

It is normal to want to start treatment as soon as possible. While cancer can’t be ignored, there is time to have another doctor review your test results and suggest a treatment plan. This is called getting a second opinion, and it’s a normal part of cancer care. Even doctors get second opinions!

Things you can do to prepare:

- Check with your insurance company about its rules on second opinions. There may be out-of-pocket costs to see doctors who are not part of your insurance plan.
- Make plans to have copies of all your records sent to the doctor you will see for your second opinion.

**Support groups**

Many people diagnosed with cancer find support groups to be helpful. Support groups often include people at different stages of treatment. Some people may be newly diagnosed, while others may be finished with treatment. If your hospital or community doesn’t have support groups for people with cancer, check out the websites listed on page 52.

**Questions to ask your doctors**

Possible questions to ask your doctors are listed on the following pages. Feel free to use these questions or come up with your own. Be clear about your goals for treatment and find out what to expect from treatment.
Questions to ask about testing and staging

1. What tests will I have? Is biomarker testing needed?

2. Do I need a biopsy? What kind of biopsy do I need? Will enough tissue be removed for biomarker testing? What are the risks?

3. How do I prepare for testing?

4. What if I am pregnant?

5. Where do I go to get tested? How long will the tests take and will any test hurt?

6. Should I bring someone with me? Should I bring a list of my medications?

7. How soon will I know the results and who will explain them to me?

8. Would you give me a copy of the pathology report and other test results?

9. What type of lung cancer do I have? What is the stage? Has the cancer spread far?

10. Can this cancer be cured? If not, how well can treatment stop the cancer from growing?

11. Who will talk with me about the next steps? When?
Questions to ask about treatment options

1. What are my treatment options? Are you suggesting options other than what NCCN recommends? If yes, why?

2. Do your suggested options include clinical trials? Please explain why.

3. What will happen if I do nothing?

4. How do my age, overall health, and other factors affect my options? What if I am pregnant or planning to get pregnant?

5. Does any option offer a cure or long-term cancer control? Are my chances any better for one option than another? Less time-consuming? Less expensive?

6. How do you know if treatment is working? How will I know if treatment is working?

7. What are my options if treatment stops working?

8. What are the possible complications? What are the short- and long-term side effects of treatment?

9. What can be done to prevent or relieve the side effects of treatment?

10. What supportive care services are available to me during and after treatment?

11. Can I stop treatment at any time? What will happen if I stop treatment?
Questions to ask about clinical trials

1. Are there clinical trials for my type of cancer?
2. What are the treatments used in the clinical trial?
3. What does the treatment do?
4. Has the treatment been used before? Has it been used for other types of cancer?
5. What are the risks and benefits of this treatment?
6. What side effects should I expect? How will the side effects be controlled?
7. How long will I be in the clinical trial?
8. Will I be able to get other treatment if this doesn’t work?
9. How will you know the treatment is working?
10. Will the clinical trial cost me anything? If so, how much?
Questions to ask about getting treated

1. Will I have to go to the hospital or elsewhere? How often? How long is each visit?

2. What do I need to think about if I will travel for treatment?

3. Do I have a choice of when to begin treatment? Can I choose the days and times of treatment?

4. How do I prepare for treatment? Do I have to stop taking any of my medicines? Are there foods I will have to avoid?

5. Should I bring someone with me when I get treated?

6. Will the treatment hurt?

7. What should I do if a side effect gets bad when my cancer center is closed?

8. How much will the treatment cost me? What does my insurance cover?

9. Will I miss work or school? Will I be able to drive?

10. Is home care after treatment needed? If yes, what type?

11. How soon will I be able to manage my own health?

12. When will I be able to return to my normal activities?
Resources

American Cancer Society
cancer.org/cancer/lung-cancer.html

American Lung Association
lung.org

American Lung Cancer Screening Initiative
alcsi.org

Caring Ambassadors Program, Inc.
lungcancercap.org

Free ME from Lung Cancer
freeMEfromLungCancer.org

GO2 Foundation for Lung Cancer
go2foundation.org

Lung Cancer Alliance
lungcanceralliance.org

Lung Cancer Research Foundation
lcrf.org

LUNGevity Foundation
LUNGevity.org

National Cancer Institute (NCI)
cancer.gov/types/lung

National Coalition for Cancer Survivorship
canceradvocacy.org/toolbox

NCCN Patient Resources
NCCN.org/patients

share with us.

Take our survey
And help make the NCCN Guidelines for Patients better for everyone!

NCCN.org/patients/comments
Words to know

**adenocarcinoma**
A cancer of cells that line organs and make fluids or hormones.

**adrenal gland**
A small organ on top of each kidney that makes hormones.

**AJCC**
American Joint Committee on Cancer

**alveoli**
The tiny sacs in the lungs where gases are transferred in and out of the blood.

**anaplastic lymphoma kinase (ALK)**
A type of protein on the edge of a cell that sends signals for cell growth.

**biomarker**
Any molecule in your body that can be measured to assess your health.

**biomarker testing**
Tests of any molecule in your body that can be measured to assess your health. Also called molecular testing.

**biopsy**
A procedure that removes fluid or tissue samples to be tested for a disease.

**board certified**
A status for doctors who finished training in a specialized field of medicine.

**body plethysmograph**
A test of how much air is in your lungs after inhaling or exhaling.

**bronchi**
The two airways extending from the windpipe into the lungs.

**bronchioli**
Small airways within the lungs.

**bronchus**
One of the two main airways that extends into the lungs.

**cancer stage**
A rating of the outlook of a cancer based on its growth and spread.

**carcinoma**
A cancer of cells that line the inner or outer surfaces of the body.

**chemoradiation**
A cancer treatment with both cell-killing drugs and high-energy rays.

**chemistry profile**
A lab test of the amount of 8 chemicals in a sample of blood. Also called metabolic panel.

**chemotherapy**
Cancer drugs that stop the cell life cycle so cells don’t increase in number.

**clinical stage**
The rating of the extent of cancer before treatment is started.

**clinical trial**
A type of research that assesses how well health tests or treatments work in people.

**complete blood count (CBC)**
A lab test that measures the parts of the blood.

**computed tomography (CT)**
A test that uses x-rays from many angles to make a picture of the insides of the body.

**continuation maintenance**
A treatment phase using one or more first-line drugs to prolong good treatment results.

**contrast**
A dye put into your body to make clearer pictures during imaging.
core needle biopsy
A procedure that removes tissue samples with a hollow needle. Also called core biopsy.

diagnosis
An identification of an illness based on tests.

DNA
deoxyribonucleic acid

ECOG
Eastern Cooperative Oncology Group

endobronchial ultrasound–guided transbronchial needle aspiration (EBUS-TBNA)
A procedure that removes lung tissue with a needle on an imaging device guided down the windpipe.

epidermal growth factor receptor (EGFR)
A protein on the edge of a cell that sends signals to the cell to grow.

FDG
fluorodeoxyglucose

gas diffusion
A test that uses harmless gas to measure how much you can breathe out.

gene
Coded instructions in cells for making new cells and controlling how cells behave.

gene rearrangement
A coded instruction within a cell that is made from parts of other coded instructions.

immunotherapy
A treatment with drugs that help the body find and destroy cancer cells.

large-cell lung carcinoma
A cancer of lung cells that lack features to classify as another type of lung cancer.

lobe
A clearly seen division in an organ.

lymph node
A small, bean-shaped, disease-fighting structure.

magnetic resonance imaging (MRI)
A test that uses radio waves and powerful magnets to make pictures of the insides of the body.

maintenance treatment
A treatment phase that is given to prolong good treatment results.

medical history
A report of all your health events and medications.

metastasis
The spread of cancer from the first tumor to a new site.

mutation
Abnormal changes in coded instructions within cells (genes).

NCCN
National Comprehensive Cancer Network

non-small cell lung cancer (NSCLC)
A cancer that starts in lung cells that are not small.

NOS
Not otherwise specified

pathologic stage
A rating of the extent of cancer based on tests given after treatment.

pathologist
A doctor who’s an expert in testing cells and tissue to find disease.

performance status
A rating of one’s ability to do daily activities.

pericardiocentesis
A procedure that removes fluid from around the heart with a needle.
Words to know

**physical exam**
A review of the body by a health expert for signs of disease.

**platinum-doublet chemotherapy**
A treatment with two cell-killing drugs, one of which contains the chemical platinum.

**positron emission tomography (PET)**
A test that uses radioactive material to see the shape and function of body parts.

**positron emission tomography/computed tomography (PET/CT)**
A test that uses two picture-making methods to show the shape and function of tissue.

**prognosis**
The likely course and outcome of a disease based on tests.

**pulmonary function tests**
A set of breathing tests to test the strength of the lungs.

**radiation oncologist**
A doctor who’s an expert in treating cancer with radiation.

**radiation therapy**
A treatment that uses intense energy to kill cancer cells.

**respiratory system**
The group of organs that transfers gases in and out of the body.

**ROS1**
A type of protein on the edge of a cell that sends signals for cell growth.

**stereotactic ablative radiotherapy (SABR)**
Treatment with high-dose radiation within one or a few sessions. Also called stereotactic body radiation therapy (SBRT).

**side effect**
An unhealthy or unpleasant physical or emotional response to treatment.

**small cell lung cancer (SCLC)**
A cancer of small, round lung cells.

**spirometry**
A test that uses a tube to measure how fast you breathe.

**squamous cell carcinoma**
A type of cancer of thin and flat cells that line the surface of organs.

**stereotactic radiosurgery (SRS)**
Treatment of a brain tumor with high-dose radiation within one or a few sessions.

**supportive care**
Health care that includes symptom relief but not cancer treatment. Also sometimes called palliative care.

**surgery**
An operation to remove or repair a part of the body.

**switch maintenance**
A treatment phase with a new drug that is given to prolong good treatment results.

**targeted therapy**
A drug treatment that impedes the growth process specific to cancer cells.

**thoracic radiologist**
A doctor who’s an expert in reading imaging tests of the chest.

**thoracoscopy**
A procedure to do work in the chest with a device passed through a small cut in the skin. Also called VATS.

**trachea**
The airway between the throat and airway into the lungs. Also called the windpipe.
**Words to know**

**transsthoracic needle aspiration (TTNA)**
A procedure that removes tissue samples with a thin needle guided through the ribs.

**ultrasound**
A test that uses sound waves to take pictures of the inside of the body.

**vascular endothelial growth factor (VEGF)**
A molecule that triggers the growth of blood vessels.
This patient guide is based on the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer, Version 4.2021. It was adapted, reviewed, and published with help from the following people:

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* Reviewed this patient guide. For disclosures, visit NCCN.org/about/disclosure.aspx.

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