

Non-Small Cell Lung Cancer Metastatic

Presented with support from:  NATIONAL COMPREHENSIVE CANCER NETWORK®
FOUNDATION
Guiding Treatment. Changing Lives.





**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



NCCN Guidelines for Patients® are developed by the National Comprehensive Cancer Network® (NCCN®)



NCCN

- ✓ An alliance of leading cancer centers across the United States devoted to patient care, research, and education

Cancer centers that are part of NCCN:
[NCCN.org/cancercenters](https://www.nccn.org/cancercenters)



NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

- ✓ Developed by experts from NCCN cancer centers using the latest research and years of experience
- ✓ For providers of cancer care all over the world
- ✓ Expert recommendations for cancer screening, diagnosis, and treatment

Free online at
[NCCN.org/guidelines](https://www.nccn.org/guidelines)



NCCN Guidelines for Patients

- ✓ Present information from the NCCN Guidelines in an easy-to-learn format
- ✓ For people with cancer and those who support them
- ✓ Explain the cancer care options likely to have the best results

Free online at
[NCCN.org/patientguidelines](https://www.nccn.org/patientguidelines)

These NCCN Guidelines for Patients are based on the NCCN Guidelines® for Non-Small Cell Lung Cancer, Version 3.2022 – March 16, 2022.

© 2022 National Comprehensive Cancer Network, Inc. All rights reserved. NCCN Guidelines for Patients and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. No one, including doctors or patients, may use the NCCN Guidelines for Patients for any commercial purpose and may not claim, represent, or imply that the NCCN Guidelines for Patients that have been modified in any manner are derived from, based on, related to, or arise out of the NCCN Guidelines for Patients. The NCCN Guidelines are a work in progress that may be redefined as often as new significant data become available. NCCN makes no warranties of any kind whatsoever regarding its content, use, or application and disclaims any responsibility for its application or use in any way.

NCCN Foundation seeks to support the millions of patients and their families affected by a cancer diagnosis by funding and distributing NCCN Guidelines for Patients. NCCN Foundation is also committed to advancing cancer treatment by funding the nation's promising doctors at the center of innovation in cancer research. For more details and the full library of patient and caregiver resources, visit [NCCN.org/patients](https://www.nccn.org/patients).

National Comprehensive Cancer Network (NCCN) / NCCN Foundation
3025 Chemical Road, Suite 100
Plymouth Meeting, PA 19462
215.690.0300



NCCN Guidelines for Patients are supported by funding from the NCCN Foundation®

To make a gift or learn more, please visit NCCNFoundation.org/donate
or e-mail PatientGuidelines@NCCN.org.



Contents

- 6 Lung cancer basics
- 12 Tests for metastatic lung cancer
- 22 Treatment of driver mutations
- 33 Treatment by PD-L1 level
- 40 Treatment by cell type
- 51 Making treatment decisions
- 59 Words to know
- 63 NCCN Contributors
- 64 NCCN Cancer Centers
- 66 Index

1

Lung cancer basics

- 7 What is lung cancer?
- 8 What are the stages of lung cancer?
- 9 What stage is metastatic lung cancer?
- 9 What are the symptoms of metastatic lung cancer?
- 10 Can metastatic lung cancer be treated?
- 11 Key points



Lung cancer starts in the cells of the lungs. Non-small cell lung cancer is the most common type of lung cancer. This chapter answers some common questions about this cancer when it has spread far within the body.

What is lung cancer?

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

The lungs are the main organs of the respiratory system. They deliver oxygen to the blood and remove carbon dioxide from the blood.

Lung cancer often forms from cells that line the airways

Almost all lung cancers are carcinomas. 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 main groups based on how the cells look.

- ▶ Small cell lung cancer (SCLC) is a cancer of neuroendocrine cells. The NCCN Guidelines for Patients® on SCLC can be found at [NCCN.org/patientguidelines](https://www.nccn.org/patientguidelines).



- ▶ Non-small cell lung cancer (NSCLC) is much more common than SCLC.

Airways of the lungs

The air you breathe moves through a series of airways. It travels down your throat and through your 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.



There are several types of NSCLC

Each type of NSCLC forms from a particular kind of cell. Below are common types of NSCLC:

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

What are the stages of lung cancer?

The stage of lung cancer describes the extent of the cancer in the body. It is used to assess the outlook of the cancer called the prognosis. It is used to plan treatment. It is also used for research.

For some people, cancer staging is done twice. The stage assigned before any tissue (biopsy) testing is called the clinical stage. The second stage 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 is based on the AJCC 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.

What is cancer?

Cancer is a disease that affects cell growth. When cells become cancerous, they don't behave like normal cells. They break the rules of normal cell growth.

- Lung cancer cells make many new cancer cells. They also do not die when they should. This overgrowth of cancer cells becomes a mass of tissue called a tumor.
- Lung cancer cells don't stay in place. They can grow through the airway and into the lung tissue. They can grow through the lung wall and invade other body parts.
- Lung cancer cells can break away from a tumor and spread. They can enter the bloodstream or a fluid called lymph and spread to other places.

This out-of-control cell growth can harm the body. Cancer cells crowd out and overpower normal cells. Without enough normal cells, cancer cells can cause organs to stop working.

Scientists have learned a great deal about cancer. As a result, today's treatments work better than treatments in the past. Also, many people with cancer have more than one treatment option.

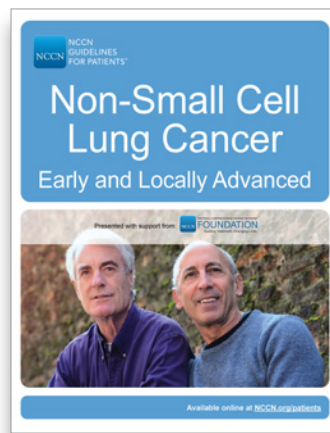
Stage 0 cancer is only in the airway

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.

Stage 1 through 3 cancers haven't spread far at the time of diagnosis

Stage 1, stage 2, and stage 3 cancers have grown into lung tissue. Some have spread to nearby disease-fighting tissue called lymph nodes.

Learn more about stage 1 through 3 lung cancers that have not spread far in *NCCN Guidelines for Patients: Early and Locally Advanced Non-Small Cell Lung Cancer*, available at [NCCN.org/patientguidelines](https://www.nccn.org/patientguidelines).

**Stage 4 cancer has spread far**

To be stage 4, lung cancer must have already spread far by the time of diagnosis. Most lung cancers are stage 4 at diagnosis. Lung cancer tends to spread to these body parts:

- Brain, liver, bone, and adrenal glands
- From one lung to the other lung

What stage is metastatic lung cancer?

Stage 4 lung cancer is metastatic cancer, but other stages may become metastatic cancer as well. Metastatic lung cancer is cancer that has spread far from the first lung tumor.

- After treatment of stage 1, stage 2, and stage 3 lung cancer, the cancer may appear in distant body parts. If this happens, the cancer is not staged again. Instead, it is referred to as metastatic lung cancer.
- Stage 4 lung cancer is metastatic lung cancer at diagnosis.

What are the symptoms of metastatic lung cancer?

Symptoms caused by metastatic NSCLC depend on where the cancer is. Examples of its signs and symptoms 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

Can metastatic lung cancer be treated?

Yes! 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. At this time, metastatic lung cancer is unlikely to be cured.

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 that has 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 and is the focus of this book. Systemic therapy affects all cancer in the body. It can treat widespread metastases. Medical oncologists are cancer doctors trained to use systemic therapy.

Treatment takes team work

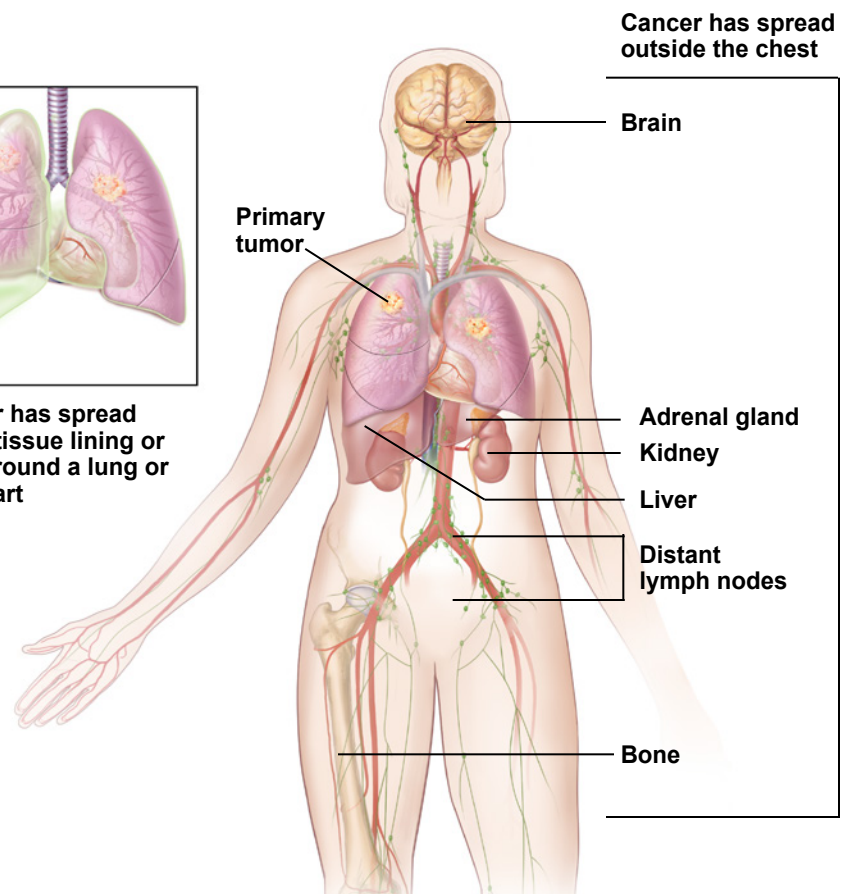
A team of health care providers is involved in diagnosing and treating lung cancers. Your primary doctor may be the first to suspect you have lung cancer and refer you to specialists. The diagnostic, treatment, and supportive care experts are explained throughout this book. These experts are supported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

Metastatic lung cancer

Lung cancer that has spread far from the main lung tumor is called metastatic lung cancer. It includes lung cancers that have spread outside the chest. 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.



Cancer has spread to the tissue lining or fluid around a lung or the heart



Key points

- Lung cancer is a cancer of lung cells. Other cancers that spread to the lungs are not lung cancer.
- Lung cancer often starts in the cells that line the airways. These cancers are called carcinomas. Non-small cell lung cancer (NSCLC) is a group of carcinomas.
- Common types of NSCLC are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.
- 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.
- Symptoms of metastatic lung cancer depend on where the cancer is in the body.
- There are newer treatments for metastatic lung cancer that better control the cancer and improve quality of life.
- Most often, systemic therapy is used to treat metastatic lung cancer. Systemic therapy affects all cancer in the body.
- A team of experts will work together with you to diagnose and treat the cancer as well as support you.



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](https://www.nccn.org/patients/response)

2

Tests for metastatic lung cancer

13 Goals of testing

14 Health history and exam

15 Blood tests

16 Imaging

17 Cancer tests

18 Biomarker tests

20 Breathing tests

20 Services after diagnosis

21 Key points



Not all metastatic lung cancers are the same. It is important to get the right tests to learn about the cancer you have and your overall health.

Goals of testing

When lung cancer is suspected, you will need to have several tests. These tests are needed to:

- Diagnose—identify the illness, and if there is cancer, identify the cell type
- Stage the cancer by testing areas to which the cancer may have spread
- Profile the cancer by testing for defining features called biomarkers
- Assess your general health and well-being

This chapter explains the tests that you may get, so your cancer care team can do a complete workup. Your team will review the test results and determine your treatment options. Talk with your team about your options and decide together what treatment plan is best for you.

This chapter also explains some specialized services that you'll receive. It's important to start these services right after a lung cancer diagnosis. They can improve your quality of life and may also help you live longer.

Tips for testing

Results from blood tests, imaging, and biopsies will be used to decide your treatment plan. It's important you understand what these tests mean. Ask questions and keep copies of your test results. Online patient portals are a handy way to access your test results.

Remember these tips for testing:

- Bring someone with you to doctor visits, if possible.
- Write down questions and take notes during appointments. Don't be afraid to ask your care team questions. Get to know your care team and help them get to know you.
- Get copies of blood tests, imaging results, and reports about the specific type of cancer you have.
- Organize your papers. Create files for insurance forms, medical records, and test results. You can do the same on your computer.
- Keep a list of contact information for everyone on your care team. Add it to your phone. Hang the list on your refrigerator or keep it in a place where someone can access it in an emergency. Keep your primary care provider informed of any changes.

Health history and exam

A standard part of a cancer evaluation is a health history and exam. It is typically the first step of the evaluation. [See Guide 1](#) for a list of all tests used to assess metastatic lung cancer.

Medical history

Expect your doctor to review your health in detail. This is known as taking a medical history. Your doctor will want to know a lot

about your past and current health. You will likely be asked about:

- Illnesses and injuries
- Symptoms like unexplained weight loss, trouble breathing, chest pain, and cough
- Prescribed and over-the-counter medications, herbals, and supplements

It may be helpful to bring a list of your medications, herbals, and supplements to appointments.

Guide 1

Health tests and services for metastatic lung cancer

Health history and exam	<ul style="list-style-type: none"> • Medical history including weight loss and smoking history • Physical exam and performance status
Blood tests	<ul style="list-style-type: none"> • CBC with differential • Chemistry profile
Imaging	<ul style="list-style-type: none"> • Diagnostic CT of the chest and upper abdomen • FDG PET/CT • Brain MRI
Cancer tests	<ul style="list-style-type: none"> • Biopsy or surgery to remove tissue sample • Pathology review to assess for cancer and learn cancer cell type
Biomarker tests	<ul style="list-style-type: none"> • Molecular tests for driver mutations • PD-L1 test
Breathing tests	<ul style="list-style-type: none"> • Spirometry • Gas diffusion test • Body plethysmograph
Services	<ul style="list-style-type: none"> • Smoking treatment • Supportive care

Smoking history

You can get lung cancer even if you never smoked. If you have lungs, you can get lung cancer. But, smoking does increase your chance of getting lung cancer.

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.

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

Your doctor will also perform a thorough physical exam of your body. This exam may include:

- ▶ Checking your vital signs—blood pressure, heart rate, breathing rate, and body temperature—and assessing your overall appearance
- ▶ Feeling and listening to organs, including your spleen and liver
- ▶ Feeling for enlarged lymph nodes, which are small clusters of disease-fighting tissue
- ▶ Assessing your level of pain, if any, when you are touched

Physical ability

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 can measure blood cells, proteins, and chemicals in the bloodstream. They are commonly used to screen for disease. They are also used to assess if cancer is affecting organs.

Samples of your blood will be removed with a needle that is inserted into a vein. This is called a blood draw. 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 the most common types of white blood cells—basophils, neutrophils, eosinophils, monocytes, and lymphocytes. It also checks if the cell counts are in balance with each other.

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.

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.

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 3D image.

A diagnostic CT involves a higher dose of radiation and contrast. Contrast is a substance that is often injected into the bloodstream. Blood vessels, organs, and other tissues are more clearly seen. 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 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.

Imaging

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.



Cancer tests

To diagnose lung cancer, bits of tissue need to be removed for testing. Often, tissue from the metastasis is removed rather than from the lung tumor.

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.

Tissue removal by biopsy or surgery

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 a tube 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.

The removed tissue must be large enough for testing

A doctor called a pathologist will assess the tissue. Pathologists are experts in tissue and cells and diagnosing cancer.

The tissue must be large enough to run several special lab tests. At some cancer centers, the pathologist checks the tissue size right after removal. This method is called rapid



Your diagnostic team

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
- 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.

on-site evaluation (ROSE). It helps to prevent having the same procedure a second time.

A pathologist will assess for cancer

A pathologist will look at the tissue with a microscope and classify the disease. This is called histologic typing. If cancer is found, the pathologist will also assess for the type of cancer. Cell (histologic) types of lung cancer include:

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

Your pathology report

Lab results used for diagnosis are put into a pathology report. This report will be sent to your doctor. It's used to plan your treatment.

Ask for a copy of the report. Ask your doctor to review your results with you. Take notes and ask questions.

Biomarker tests

Lung cancer differs between people by cell type but also by abnormal cell changes. These abnormal cell changes are types of biomarkers. Because of biomarkers, a treatment that helps one person might not help you.

Lung cancer biomarkers

Most often, biomarker testing is performed on tissue from the tumor. It is not the same as genetic testing that assesses what a person inherited from their parents. See [Guide 2](#) for a list of biomarkers and which cancers should be tested for them.

Driver mutations are also called driver oncogenes. They cause normal cells to become cancer cells and support cancer growth. A driver mutation is found in at least 1 in 3 people with metastatic lung cancer. It is very rare for cancers to have more than one driver mutation.

Molecular tests are biomarker tests that assess for mutations. Very few squamous cell carcinomas have a driver mutation, so molecular testing is decided on a person-by-person basis.

NCCN experts strongly advise broad molecular profiling of all mutations listed in [Guide 2](#). There are other known mutations linked with lung cancer that may be tested, too. This testing will help many people get the best treatment for their cancer.

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. All lung cancers should

be tested for PD-L1. A lab method called immunohistochemistry (IHC) detects PD-L1.

What if there's not enough tissue for testing? If not enough tissue was collected, a second biopsy may be scheduled. Sometimes, a blood sample may be drawn, and the plasma in the sample tested for biomarkers.

What if the cancer has no biomarkers?

Some 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 as discussed in Chapter 5.

Guide 2 Biomarker tests

	Adenocarcinoma, large cell, and rare lung cancers	Squamous cell lung cancer
Driver mutation		
<i>EGFR</i> exon 19 deletion or L858R mutation	●	●
<i>EGFR</i> S768I, L861Q, or G719X mutation	●	●
<i>EGFR</i> exon 20 insertion	●	●
<i>ALK</i> rearrangement	●	●
<i>ROS1</i> rearrangement	●	●
<i>BRAF</i> V600E mutation	●	●
<i>NTRK</i> gene fusion	●	●
<i>MET</i> exon 14 skipping	●	●
<i>RET</i> rearrangement	●	●
<i>KRAS</i> G12C mutation	●	●
Cell protein		
PD-L1	●	●

● Testing is recommended for everyone ● Testing is a person-by-person decision

Breathing tests

Surgery or radiation therapy may be part of treatment for some metastatic cancers. First, your doctors will need to know how well your lungs work. There are 3 pulmonary function tests to assess how well you breathe:

- Spirometry involves blowing into a tube to measure how much air and how well 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 plethysmography 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.



A common myth is that palliative care is only for terminally ill patients. It is so much more! It is worth reaching out to palliative care in your hospital or clinic. They treat the whole patient, not just cancer.”

– Robert

Cancer survivor

Services after diagnosis

Start supportive care early

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 with the best care. Other specialists who may be involved in your care include:

- Respiratory therapists
- Rehabilitation specialists
- Registered dietitians
- Social and mental health workers

It's never too late to quit smoking

If you 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.

If you tried to quit before, try again. Most people slip or relapse before quitting for good.

Key points

- 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.
- 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 sampled.
- 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 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.
- Ask your doctor for help to quit smoking. Quitting may improve treatment results.



DO NOT be afraid to ask your medical team ANY questions at any time!!! Your questions will help you and them. No question is stupid.”

– Steve
Cancer survivor

3

Treatment of driver mutations

23 What are driver mutations?

24 Targeted therapy

25 *EGFR* mutations

28 *ALK* rearrangement

30 *ROS1* rearrangement

30 *BRAF* V600E mutation

31 *NTRK* gene fusion

31 *MET* exon 14 skipping

32 *RET* rearrangement

32 *KRAS* G12C mutation

32 Key points



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.

What are driver mutations?

A driver mutation is an abnormal gene that supports the growth of cancer cells. It enables cancer cells to quickly duplicate, survive, and spread in the body.

Several driver mutations of lung cancer have been found

A gene is a small segment of DNA. There are tens of thousands of genes in a cell.

Most of them contain instructions for making proteins that control how the cell works.

An abnormal change in a gene is called a mutation. All cancer cells have mutations, but not all mutations promote cancer. Only mutations that support cancer growth are called driver mutations.

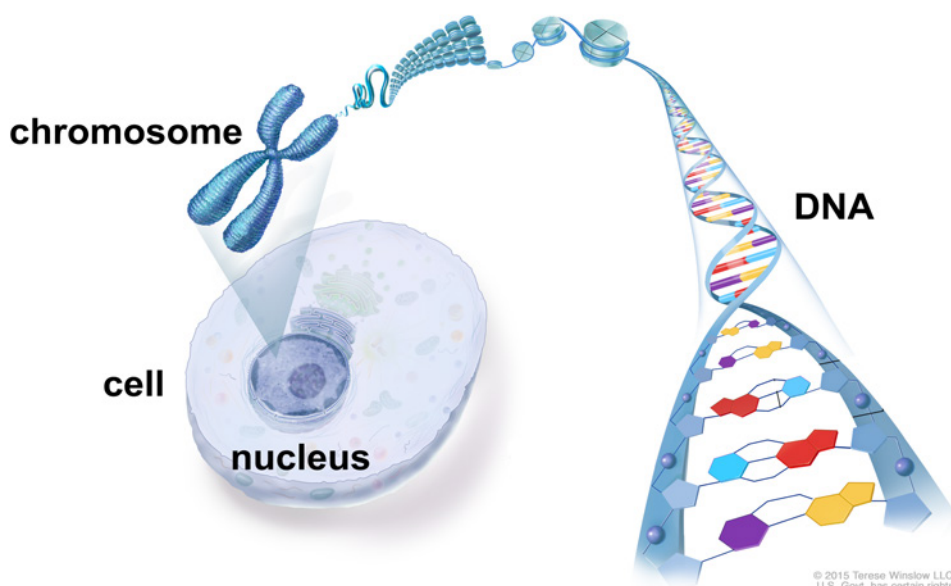
At this time, several driver mutations in lung cancer are known. They can be detected by molecular testing. Ongoing research is looking for more driver mutations.

Treating mutations is more precise

Chemotherapy destroys fast-growing cells whether or not they're cancer cells. It was once the only treatment for metastatic lung cancer. Newer treatments target the effects of driver mutations and harm fewer normal cells.

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, which looks like a twisted ladder. Genes are parts of DNA that contain “instructions” for the cell. At times, strands of DNA tightly coil and form into chromosomes.



© 2015 Terese Winslow LLC
U.S. Govt. has certain rights

Targeted therapy

Driver mutations create abnormal cell proteins that help cancer cells grow. Targeted therapy works by stopping these proteins.

Kinase inhibitors

Kinases are a type of cell protein. They are part of many chemical pathways, some of which start cell growth. Kinase inhibitors stop the activity of kinases and, in turn, lower the number of new cancer cells being made. They are pills that can be taken at home.

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).

New targeted therapy for lung cancer

Other types of targeted therapy are being studied in clinical trials. Clinical trials are a type of medical research. Ask your treatment team if there is an open clinical trial that's a good fit for you.

What if I already started a different type of treatment? If a driver mutation is found after starting treatment, 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 therapy), and then start targeted therapy.

Treatment side effects

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

Not everyone has the same side effects. Some people have none. Side effects depend on many factors. These factors include treatment type, length or dose of treatment, and the person.

Discuss with your cancer doctor which treatments in this book are options for you. If you have more than one option, comparing the possible side effects of each treatment may help you make your choice.

Before starting treatment, ask your treatment team for a complete list of side effects of your treatment. Each treatment has common and rare side effects. It can be helpful to know what to expect.

Tell your treatment team about any new or worse symptoms you get. There may be ways to help you feel better.

EGFR mutations

Lung cancer cells have a receptor on their surface called EGFR. Cell receptors receive and send signals like antennas. Certain mutations in the gene that makes EGFR causes the receptor to be overactive. EGFR overactivity makes the cancer cells quickly grow.

Starting EGFR-targeted therapy

Targeted therapy of EGFR-mutated lung cancer is based on the type of mutation. See [Guide 3](#) for treatment options.

Among *EGFR* mutations, **EGFR exon 19 deletions and L858R mutations** are the most

common. NCCN experts recommend a kinase inhibitor for the first treatment. The same inhibitors also treat the less common **EGFR S768I, L861Q, or G719X mutations**.

Among the EGFR inhibitors, erlotinib (Tarceva) and gefitinib (Iressa) were the first of their kind. The second group of EGFR inhibitors to be developed were afatinib (Gilotrif) and dacomitinib (Vizimpro).

The newest EGFR inhibitor is osimertinib (Tagrisso). If your first treatment was immunotherapy, a short delay in starting osimertinib may be needed to prevent health problems.

Guide 3 Options when starting EGFR-targeted therapy

Mutation	Preferred options	Other options
EGFR exon 19 deletion or EGFR L858R mutation	<ul style="list-style-type: none"> • Osimertinib 	<ul style="list-style-type: none"> • Erlotinib • Afatinib • Gefitinib • Dacomitinib • Erlotinib and ramucirumab • Erlotinib and bevacizumab
EGFR S768I, L861Q, or G719X mutation	<ul style="list-style-type: none"> • Afatinib • Osimertinib 	<ul style="list-style-type: none"> • Erlotinib • Gefitinib • Dacomitinib
EGFR exon 20 insertion	<p>Targeted therapy is started if the cancer worsens after chemotherapy. More research is needed to know if there is a preferred treatment.</p> <ul style="list-style-type: none"> • Amivantamab-vmjw • Mobocertinib 	

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).

Recent studies found that targeted therapy also treats lung cancers with **EGFR exon 20 insertion**. These cancers are first treated with chemotherapy that is discussed in Chapter 5. If the cancer worsens, there are two options for targeted therapy:

- Mobocertinib (Exkivity) is a kinase inhibitor
- Amivantamab-vmjw (Rybrevant) is a newer option and is an EGFR antibody that is given by infusion

Options when the cancer worsens

Within a few years of starting targeted therapy, lung cancer starts to grow again in most people. You may get a biopsy to test for:

- Mutations that stop targeted therapy from working—a T790M mutation is common after taking erlotinib, afatinib, gefitinib, or dacomitinib
- A change in the type of cancer from an adenocarcinoma to small cell lung cancer

Treatment options depend on features of the cancer growth. Your doctor will check for symptoms and where the cancer has spread. Options are listed in [Guide 4](#).

Local treatment. If the cancer did not spread to many more places, your doctor may recommend local treatment. It is used to treat cancer in a specific place like the brain or

Guide 4

Options after the cancer worsens during EGFR-targeted therapy

Local treatment of limited tumors and targeted therapy

Stay on the first targeted therapy if it has some benefit

- Stay on osimertinib if the cancer didn't spread to many more places
- Stay on erlotinib, afatinib, gefitinib, or dacomitinib if there is no T790M mutation and no widespread cancer

Switch to a different targeted therapy

- Switch to osimertinib if there is a T790M mutation after erlotinib, afatinib, gefitinib, or dacomitinib
- Switch to afatinib with cetuximab (an EGFR antibody) if cancer worsens while taking osimertinib
- Switch to the other targeted therapy for *EGFR* exon 20 insertion that you haven't received

Start treatment for cell type as listed in Chapter 5

adrenal gland. In addition, targeted therapy will be used to control cancer growth.

The type of local treatment received differs between people. Options for local treatment include:

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

Staying on current targeted therapy. If the cancer is growing, it may get worse if targeted therapy is stopped. The treatment may be slowing down the cancer growth. Your doctor may keep you on your current treatment. There is no research on dacomitinib for brain metastases.

Switching targeted therapy. If the cancer grew, switching to a different targeted therapy may be an option. A different targeted therapy may help, especially if there are new mutations.

Treatment by cancer cell type. If targeted therapy is not likely to help, your doctor may recommend other treatment. See Chapter 5 for options.



share with us.

Take our [survey](#)

And help make the
NCCN Guidelines for Patients
better for everyone!

[NCCN.org/patients/comments](https://www.nccn.org/patients/comments)

ALK rearrangement

For some lung cancers, the ALK surface receptor is overactive causing lung cells to quickly grow. The overactivity is caused by parts of two genes switching places with each other—a gene rearrangement. First-line therapy options for ALK rearrangements are listed in [Guide 5](#).

Starting targeted therapy

There are 5 ALK inhibitors used to treat lung cancer. Crizotinib (Xalkori) was the first ALK inhibitor to be used. The second group of ALK inhibitors to be developed were ceritinib

(Zykadia), alectinib (Alecensa), and brigatinib (Alunbrig). The newest ALK inhibitor is lorlatinib (Lorbrena).

Options when cancer worsens

Within a few years of starting targeted therapy, lung cancer starts to grow again in most people. You may get a biopsy to test for new mutations that limit how well targeted therapy works.

Treatment options depend on features of the cancer growth. Your doctor will check for symptoms and where the cancer has spread. Treatment options are listed in [Guide 6](#).



When you are deciding on your treatment options remember that even though some decisions need to be made fast, don't rush. Think through your options and get second, or even third opinions. Have people you can trust to talk through your options so you feel comfortable in your decisions."

– Cari
Cancer survivor

Guide 5

Options when starting ALK-targeted therapy

Preferred options

- Alectinib
- Brigatinib
- Lorlatinib

Other options

- Ceritinib

Sometimes useful

- Crizotinib

Local treatment. If the cancer did not spread to many more places, 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, targeted therapy will be used to control cancer growth.

The type of local treatment received differs between people. Options for local treatment include:

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

Staying on current targeted therapy. If the cancer is growing, it may get worse if targeted therapy is stopped. The treatment may be slowing down the cancer growth. Your doctor may keep you on your current treatment.

Switching targeted therapy. If the cancer grew, switching to a different targeted therapy may be an option. A different targeted therapy may help, especially if there are new mutations.

Treatment by cancer cell type. If targeted therapy is not likely to help, your doctor may recommend other treatment. See Chapter 5 for options.

Guide 6

Options after the cancer worsens on ALK-targeted therapy

Local treatment of limited tumors may be helpful for some people

Stay on first-line therapy if it has some benefit

- Stay on alectinib, brigatinib, ceritinib, or lorlatinib if the cancer didn't spread to many more places
- Stay on crizotinib if the cancer didn't spread to the brain or many more places

Switch to a newer ALK inhibitor

- Switch to lorlatinib if there's a *KRAS* G1202R mutation after taking 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 overactivity is caused by parts of two genes switching places with each other—a gene rearrangement. Treatment options are listed in [Guide 7](#).

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

In time, the cancer will worsen on targeted therapy. If the cancer didn't spread to many more places, your doctor may recommend local treatment. You may also stay on your current treatment if there is some benefit.

A different targeted therapy may be used. If the lung cancer is in the brain, you may be switched to entrectinib. If the cancer has

spread to many more places, you may be switched to lorlatinib (Lorbrena).

If targeted therapy is not likely to help, your doctor may recommend other treatment. See Chapter 5 for options.

BRAF V600E mutation

A signaling protein inside of cells called BRAF can be overactive causing lung cells to quickly grow. Its overactivity is caused by a *BRAF* V600E mutation. Treatment options are listed in [Guide 8](#).

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

If dabrafenib plus trametinib makes you too sick, you may receive dabrafenib alone or vemurafenib (Zelboraf). Vemurafenib also stops growth signals from BRAF. Sometimes, treatment based on cancer cell type is useful as the first treatment (see Chapter 5).

Guide 7 Treatment of *ROS1* rearrangement

First targeted therapy

Preferred options

- Entrectinib
- Crizotinib

Other options

- Ceritinib

Options if cancer worsens on targeted therapy

- Local treatment
- Stay on entrectinib, crizotinib, or ceritinib
- Switch to entrectinib or lorlatinib
- Treatment for cell type as listed in Chapter 5

Guide 8 Treatment of *BRAF* V600E mutation

Preferred options

- Dabrafenib plus trametinib

Sometimes useful

- Vemurafenib or dabrafenib
- Treatment for cell type as listed in Chapter 5

In time, the cancer will worsen on targeted therapy. After targeted therapy, treatment based on cell type may be received. If not used before, dabrafenib plus trametinib may be started if the cancer worsens on another type of treatment.

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 are listed in [Guide 9](#).

Preferred treatment is TRK inhibitors. These treatments include larotrectinib (Vitrakvi) and entrectinib (Rozlytrek). They have not been compared in research, but entrectinib may work better for lung cancer in the brain. Sometimes, treatment based on cancer cell type is useful as the first treatment (see Chapter 5).

In time, the cancer will worsen on targeted therapy. Your next treatment may be based on

cell type. If not used before, a TRK inhibitor may be started if the cancer worsens on another type of treatment.

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 are listed in [Guide 10](#).

Preferred treatment is MET inhibitors. These treatments include capmatinib (Tabrecta) and tepotinib (Tepmetko). Crizotinib (Xalkori) is useful for some people. It inhibits MET and other kinases. Sometimes, treatment based on the cancer cell type is useful as the first treatment (see Chapter 5).

In time, the cancer will worsen after targeted therapy. Your next treatment may be based on cell type. If not used before, a MET inhibitor may be started if the cancer worsens on other types of treatment.

Guide 9 Treatment of *NTRK* gene fusion

Preferred options

- Larotrectinib
- Entrectinib

Sometimes useful

- Treatment for cell type as listed in Chapter 5

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 overactivity is caused by parts of genes switching places with each other—a gene rearrangement. Treatment options are listed in [Guide 11](#).

Preferred treatment is RET inhibitors. These treatments include selpercatinib (Retevmo) and pralsetinib (Gavreto). Cabozantinib (Cometriq, Cabometyx) is useful for some people. It inhibits RET and other kinases but doesn't work as well as preferred treatments. Sometimes, treatment used for cancer cell type is used as the first treatment. See Chapter 5.

In time, the cancer will worsen on targeted therapy. After targeted therapy, treatment used for cell type may be an option. If not used before, a RET inhibitor may be started if the cancer worsens on other types of treatment.

Guide 11 Treatment of *RET* rearrangement

Preferred options

- Selpercatinib
- Pralsetinib

Sometimes useful

- Cabozantinib

Other

- Treatment for cell type as listed in Chapter 5

KRAS G12C mutation

A signaling protein inside of lung cells called KRAS can be overactive causing the cells to quickly grow. Its overactivity is caused by a mutation in the *KRAS* G12C gene.

Lung cancers with *KRAS* G12C mutation are first treated by cancer cell type. See Chapter 5 for treatment options. If the cancer worsens, sotorasib (Lumakras) may be helpful. It is a KRAS inhibitor. Treatment options after sotorasib are again based on cancer cell type.

Key points

- 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.
- 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.
- 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.
- For almost all the driver mutations, 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.

4

Treatment by PD-L1 level

34 Immune checkpoints

34 Immunotherapy

36 Treatment options

38 Key points



Some people have lung cancer cells that evade death by T cells of the immune system. 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.

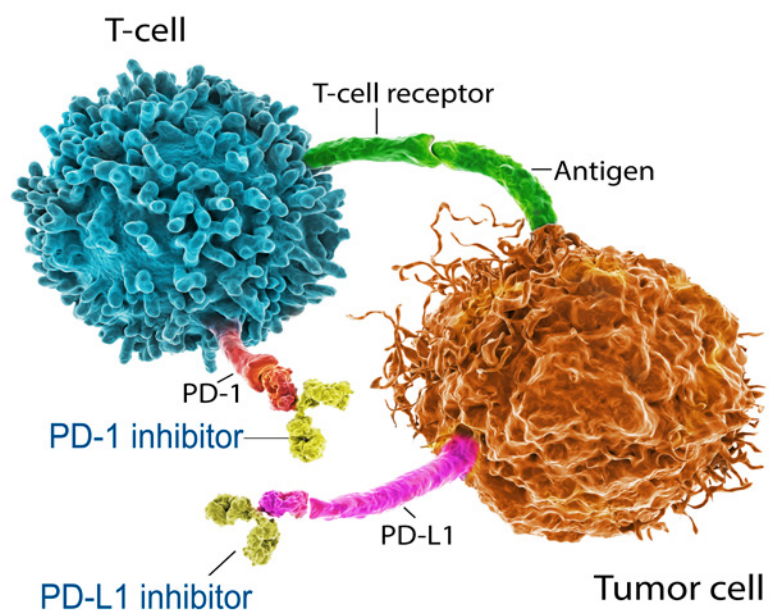
In people with lung cancer, the brake pedals on T cells may be overused. CTLA-4 is activated when attached to B7 on immune cells called dendritic cells. PD-1 is activated when attached to PD-L1 on lung cancer cells. With the brakes on, T cells are not able to kill cancer cells.

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.

PD-1 and PD-L1 inhibitors

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. There are two types of immunotherapy used to stop PD-L1 on cancer cells. PD-L1 inhibitors attach to cancer cells, and PD-1 inhibitors attach to T cells. When either inhibitor is attached, T cells are able to attack cancer cells.



There are 5 checkpoint inhibitors discussed in this chapter. These checkpoint inhibitors block proteins to keep the immune checkpoint turned off.

- Pembrolizumab (Keytruda), nivolumab (Opdivo), and cemiplimab (Libtayo) are PD-1 inhibitors. They attach to PD-1 on T cells and block PD-L1.
- Atezolizumab (Tecentriq) is a PD-L1 inhibitor. It attaches to PD-L1 on cancer cells so PD-L1 can't attach to T cells.
- Ipilimumab (Yervoy) 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.

When not to take immunotherapy

Not all lung cancers should be treated with immunotherapy:

- 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. That's why it's important to tell your doctors about all your medical conditions and medications.

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 or heart inflammation
- Joint and muscle pain
- Dry eyes

Read about managing side effects in *NCCN Guidelines for Patients: Immunotherapy Side Effects, Immune Checkpoint Inhibitors*, available at [NCCN.org/patientguidelines](https://www.nccn.org/patientguidelines).



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 therapy

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.

Guide 12

First-line therapy options by PD-L1 level

Adenocarcinoma, large cell, and rare types of lung cancer

Preferred regimens	Low PD-L1	High PD-L1
Pembrolizumab		●
Atezolizumab		●
Cemiplimab		●
Pembrolizumab, carboplatin, and pemetrexed	●	●
Pembrolizumab, cisplatin, and pemetrexed	●	●
Other regimens		
Nivolumab, ipilimumab, carboplatin, and pemetrexed	●	●
Nivolumab, ipilimumab, cisplatin, and pemetrexed	●	●
Atezolizumab, carboplatin, paclitaxel, and bevacizumab	●	●
Atezolizumab, carboplatin, and albumin-bound paclitaxel	●	●
Sometimes useful		
Nivolumab with ipilimumab	●	●
Pembrolizumab	●	

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 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 therapy

If treatment results are good, you may shift to maintenance therapy, which includes some of your first-line therapy. This is called continuation maintenance. The goal

Guide 13 First-line therapy options by PD-L1 level Squamous cell lung cancer

Preferred regimens	Low PD-L1	High PD-L1
Pembrolizumab		●
Atezolizumab		●
Cemiplimab		●
Pembrolizumab, carboplatin, and paclitaxel	●	●
Pembrolizumab, carboplatin, and albumin-bound paclitaxel	●	●
Other regimens		
Nivolumab, ipilimumab, carboplatin, and paclitaxel	●	●
Sometimes useful		
Nivolumab with ipilimumab	●	●
Pembrolizumab	●	

of maintenance therapy is to prolong the time until the cancer worsens. Options for maintenance therapy are listed in [Guide 14](#).

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

Key points

- 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 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.
- 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.

Guide 14

Maintenance therapy options by PD-L1 level

Adenocarcinoma, large cell, and rare lung cancers	Low PD-L1	High PD-L1
Pembrolizumab	●	●
Nivolumab and ipilimumab	●	●
Atezolizumab	●	●
Pembrolizumab and pemetrexed	●	●
Atezolizumab and bevacizumab	●	●
Cemiplimab		●
Squamous cell lung cancer		
Pembrolizumab	●	●
Nivolumab and ipilimumab	●	●
Atezolizumab		●
Cemiplimab		●

- 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 therapy.



The good news is that today the medical industry has made great advances in treating cancer. They create a custom designed treatment specifically for you.”

– Steve
Cancer survivor

5

Treatment by cell type

- 41 How treatment is planned
- 43 Types of treatment used
- 44 Treatment options
- 48 Clinical trials
- 50 Key points



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.

How treatment is planned

Most non-small cell lung cancers (NSCLC) do not have a known biomarker for which there is treatment. When there is no such biomarker, treatment is based on other factors, such as:

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

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.

Guide 15

Performance status and treatment of NSCLC without biomarkers

Score	Abilities	Treatment
0	You are fully active.	Systemic therapy based on cell type
1	You are able to do self-care activities but unable to do hard physical work.	Systemic therapy based on cell type
2	You are able to do self-care activities and spend most of waking time out of bed. You are unable to do any work.	Systemic therapy based on cell type
3	You are unable to do self-care activities and any work. You spend most of waking time in bed.	Supportive care
4	You are fully disabled.	Supportive care

Systemic therapy 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.

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.

Cell types of NSCLC

There are many regimens of systemic therapy that are used to treat lung cancer. Which ones are options for you partly depends on the cancer cell type.

There are 3 main types of NSCLC. 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).”

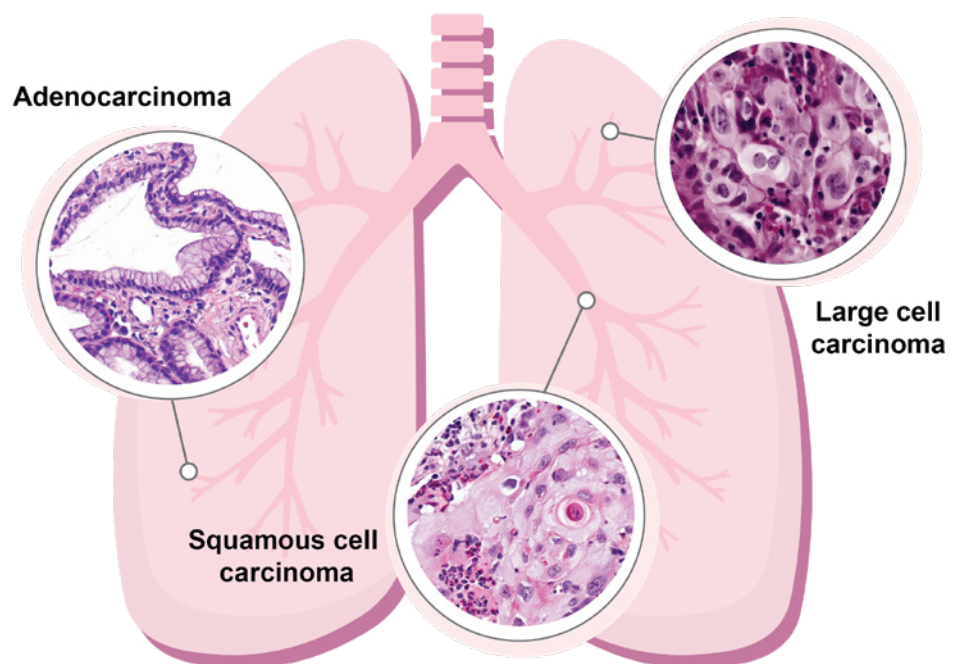
Types of non-small cell lung cancer

There are 3 main types of non-small cell 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: https://commons.wikimedia.org/wiki/File:Mucinous_lung_adenocarcinoma_-_high_mag.jpg

https://commons.wikimedia.org/wiki/File:Large_cell_carcinoma_of_the_lung.jpg

https://commons.wikimedia.org/wiki/File:Lung_squamous_carcinoma_-_high_mag.jpg



Types of treatment used

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.

Immunotherapy is very often used with chemotherapy. It is a treatment that uses the immune system to kill cancer cells. There are 4 immunotherapies, called immune checkpoint inhibitors, that are used to treat lung cancer based on cell type:

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

Targeted therapy is sometimes used with chemotherapy. It stops the specific ways by which cancer cells live, survive, and die. For treatment by cell type, a type of targeted therapy called VEGF inhibitors is used. It stops the growth of blood vessels on tumors. Without blood, cancer cells die.

Side effects

All cancer treatments cause health problems called side effects. Side effects differ between people. They depend on treatment type, length or dose of treatment, and the person.

Here are a few examples of side effects by treatment type:

- Side effects from chemotherapy are caused by the death of fast-growing normal cells. You may feel nauseated during treatment. You may lose your hair.

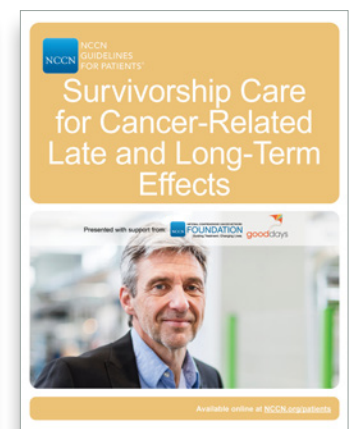
- Immune checkpoint inhibitors can cause your immune cells to attack healthy cells in your body. They can cause problems with your skin, digestive tract, eyes, heart, or lungs. You may have fatigue.
- VEGF inhibitors can cause high blood pressure, bleeding, and headaches. Wounds may be slow to heal. Tears in the digestive tract may happen.

Ask your treatment team for a list of all the 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 other patient guides that focus on side effects of treatment:

- Read about immune-related side effects in *NCCN Guidelines for Patients: Immunotherapy Side Effects, Immune Checkpoint Inhibitors*.
- Fatigue, pain, and other side effects are 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](https://www.nccn.org/patientguidelines).



Treatment options

Medical oncologists are doctors trained to prescribe systemic therapy. Your oncologist may prescribe more than one “line” of treatment for you. A line of treatment is a newly prescribed regimen numbered in the order received. Examples include:

- The first treatment given is referred to as first-line therapy.
- If the cancer worsens, you may receive another treatment called second-line therapy because it’s the second treatment to be tried.

If a line of treatment works, you may receive maintenance therapy after the regimen is finished. The goal of maintenance therapy is to increase the time until the cancer worsens.

First-line therapy

First-line therapy for lung cancer without biomarkers is listed in [Guide 16](#) and [Guide 17](#).

For performance scores of 0 or 1, chemotherapy with immunotherapy is standard treatment:

- Platinum-doublet chemotherapy is used. It consists of cisplatin or carboplatin—drugs made with platinum—and another type of chemotherapy.
- The type of immunotherapy used is called immune checkpoint inhibitors. Checkpoint inhibitors treat lung cancer with PD-L1 but also extend life when lung cancer does not have PD-L1.

Some people are not able to receive immune checkpoint inhibitors. Checkpoint inhibitors may not be an option because of an autoimmune disease, organ transplant, certain medicines, or worse performance scores. In these cases, there are several options:

- Platinum-doublet chemotherapy is most often used for treatment. A VEGF antibody called bevacizumab is a part of some regimens.
- Gemcitabine with either docetaxel or vinorelbine
- Single-agent chemotherapy

For single-agent chemotherapy, there are several drugs that may be used:

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

Monitoring and maintenance

Systemic therapy is given in cycles of treatment days followed by days of rest. One cycle typically lasts for 3 to 4 weeks. 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.

After two 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.

Guide 16**First-line systemic therapy of adenocarcinoma, large cell, and rare types of lung cancer by performance status (PS)**

Chemotherapy with immunotherapy	PS 0 or 1	PS 2
(Carboplatin or cisplatin), pemetrexed, and pembrolizumab (preferred)	●	
Carboplatin, paclitaxel, bevacizumab, and atezolizumab	●	
Carboplatin, albumin-bound paclitaxel, and atezolizumab	●	
Nivolumab and ipilimumab	●	
(Carboplatin or cisplatin), pemetrexed, nivolumab, and ipilimumab	●	
Chemotherapy without immunotherapy		
Carboplatin, paclitaxel, and bevacizumab	●	
(Carboplatin or cisplatin), pemetrexed, and bevacizumab	●	
Cisplatin and another chemotherapy	●	
Carboplatin and another chemotherapy	●	●
Gemcitabine and (docetaxel or vinorelbine)	●	●
Single-agent chemotherapy		●

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

Chemotherapy with immunotherapy	PS 0 or 1	PS 2
Carboplatin, paclitaxel, and pembrolizumab (preferred)	●	
Carboplatin, albumin-bound paclitaxel, and pembrolizumab (preferred)	●	
Nivolumab and ipilimumab	●	
Carboplatin, paclitaxel, nivolumab, and ipilimumab	●	
Chemotherapy without immunotherapy		
Cisplatin and another chemotherapy	●	
Carboplatin and another chemotherapy	●	●
Gemcitabine and (docetaxel or vinorelbine)	●	●
Single-agent chemotherapy		●

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 therapy. This is called switch maintenance. Options for maintenance therapy are listed in [Guide 18](#).

You may stay on maintenance therapy for 2 years if your first-line therapy included immunotherapy. If immunotherapy was part of second-line therapy, stay on maintenance therapy until the cancer worsens.

Options after first-line therapy

In time, lung cancer often starts to grow again after first-line therapy. Options after first-line therapy are listed in [Guide 19](#).

- 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.
- Other options include docetaxel with ramucirumab. Ramucirumab is 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.



People will ask how they can help. Be specific. For example, you could say, 'You can cook for me. Please pack meals in 4-ounce containers because that is all I can handle at any one time.'

– Diane
Cancer survivor



During chemo, listen to music. I prefer relaxing and calming music. I listen deeply. Lose yourself.

– Steve
Cancer survivor

Guide 18**Maintenance therapy 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

- Pemetrexed

Squamous cell lung cancer**Continuation maintenance**

- Nivolumab and ipilimumab
- Gemcitabine
- Pembrolizumab

Guide 19**Options after you've had chemotherapy with or without immunotherapy****Preferred options when you haven't had immunotherapy before**

- Nivolumab
- Pembrolizumab
- Atezolizumab

Other options whether you've had immunotherapy or not

- Docetaxel
- Gemcitabine
- Ramucirumab and docetaxel
- Albumin-bound paclitaxel
- Pemetrexed (non-squamous lung cancers 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, safety, and side effects of a drug or treatment approach. They also look for early signs that the drug or approach is helpful.
- **Phase II trials** study how well the drug or approach works against a 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.



Finding a clinical trial

In the United States

NCCN Cancer Centers
[NCCN.org/cancercenters](https://www.nccn.org/cancercenters)

The National Cancer Institute (NCI)
[cancer.gov/about-cancer/treatment/clinical-trials/search](https://www.cancer.gov/about-cancer/treatment/clinical-trials/search)

Worldwide

The U.S. National Library of Medicine (NLM)
clinicaltrials.gov

**Need help finding a clinical trial?
NCI's Cancer Information Service (CIS)**
1.800.4.CANCER (1.800.422.6237)
[cancer.gov/contact](https://www.cancer.gov/contact)

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 it with family, friends, or others whom 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. If you have already started standard treatment you may not be eligible for certain clinical trials. 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.

Will I get a placebo?

Placebos (inactive versions of real medicines) are almost never used alone in cancer clinical trials. It is common to receive either a placebo with a standard treatment or a new drug with a standard treatment. You will be informed, verbally and in writing, if a placebo is part of a clinical trial before you enroll.

Are clinical trials free?

There is no fee to enroll in a clinical trial. The study sponsor pays for research-related costs, including the study drug. You may, however, have costs indirectly related to the trial, such as the cost of transportation or child care due to extra appointments. During the trial, you will continue to receive standard cancer care. This care is billed to—and often covered by—insurance. You are responsible for copays and any costs for this care that are not covered by your insurance.

Key points

- ▶ Treatment of lung cancer without treatable biomarkers is partly based on performance status and 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 of 3 and 4.
 - ▶ Systemic therapy differs by cancer cell type. Regimens for squamous cell carcinoma differ from those used to treat adenocarcinoma, large cell, and rare types of lung cancer.
 - ▶ Learn about the side effects of your treatments. Let your treatment team know about any new or worsening symptoms.
 - ▶ Chemotherapy with immunotherapy is standard treatment for fairly healthy people. Other options are chemotherapy by itself or chemotherapy with bevacizumab.
 - ▶ Your doctor will monitor the results of treatment. You may receive between 4 and 6 cycles of treatment.
 - ▶ Maintenance therapy 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

52 It's your choice

52 Questions to ask

57 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 treatment team.

It's your choice

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

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 *Resources* section in this chapter.

Questions to ask

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 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 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 about what to expect

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/lung-health-diseases/lung-disease-lookup/lung-cancer

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



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.

immunohistochemistry (IHC)

A special lab test done on a tissue sample.

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 therapy

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.

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.

rapid on-site evaluation (ROSE)

A size assessment of removed tissue during a medical procedure.

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.

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 ablative radiotherapy (SABR)

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

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.

transthoracic 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.



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](https://www.nccn.org/patients/feedback)

NCCN Contributors

This patient guide is based on the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer, Version 3.2022. It was adapted, reviewed, and published with help from the following people:

Dorothy A. Shead, MS
Senior Director
Patient Information Operations

Laura J. Hanisch, PsyD
Patient Information Program Manager

Susan Kidney
Senior Graphic Design Specialist

The NCCN Guidelines® for Non-Small Cell Lung Cancer, Version 3.2022 were developed by the following NCCN Panel Members:

David S. Ettinger, MD/Chair
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

Douglas E. Wood, MD/Vice Chair
Fred Hutchinson Cancer Research Center/
Seattle Cancer Care Alliance

Dara L. Aisner, MD, PhD
University of Colorado Cancer Center

Wallace Akerley, MD
Huntsman Cancer Institute
at the University of Utah

Jessica R. Bauman, MD
Fox Chase Cancer Center

Ankit Bharat, MD
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

Debora S. Bruno, MD, MS
Case Comprehensive Cancer Center/
University Hospitals Seidman Cancer Center
and Cleveland Clinic Taussig Cancer Institute

Joe Y. Chang, MD, PhD
The University of Texas
MD Anderson Cancer Center

Lucian R. Chirieac, MD
Dana-Farber/Brigham and Women's
Cancer Center

Thomas A. D'Amico, MD
Duke Cancer Institute

Malcolm DeCamp, MD
University of Wisconsin Carbone
Cancer Center

Thomas J. Dilling, MD, MS
Moffitt Cancer Center

Jonathan Dowell, MD
UT Southwestern Simmons
Comprehensive Cancer Center

Scott Gettinger, MD
Yale Cancer Center/Smilow Cancer Hospital

Travis E. Grotz, MD
Mayo Clinic Cancer Center

Matthew A. Gubens, MD, MS
UCSF Helen Diller Family
Comprehensive Cancer Center

Aparna Hegde, MD
O'Neal Comprehensive
Cancer Center at UAB

Rudy P. Lackner, MD
Fred & Pamela Buffett Cancer Center

Michael Lanuti, MD
Massachusetts General
Hospital Cancer Center

Jules Lin, MD
University of Michigan Rogel Cancer Center

Billy W. Loo, Jr., MD, PhD
Stanford Cancer Institute

Christine M. Lovly, MD, PhD
Vanderbilt-Ingram Cancer Center

Fabien Maldonado, MD
Vanderbilt-Ingram Cancer Center

Erminia Massarelli, MD, PhD, MS
City of Hope National Medical Center

Daniel Morgensztern, MD
Siteman Cancer Center at Barnes-
Jewish Hospital and Washington
University School of Medicine

Thomas Ng, MD
The University of Tennessee
Health Science Center

*Gregory A. Otterson, MD
The Ohio State University Comprehensive
Cancer Center - James Cancer Hospital
and Solove Research Institute

Jose M. Pacheco, MD
University of Colorado Cancer Center

*Sandip P. Patel, MD
UC San Diego Moores Cancer Center

Gregory J. Riely, MD, PhD
Memorial Sloan Kettering Cancer Center

Jonathan Riess, MD
UC Davis Comprehensive Cancer Center

Steven E. Schild, MD
Mayo Clinic Cancer Center

*Theresa A. Shapiro, MD, PhD
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

Aditi P. Singh, MD
Abramson Cancer Center at the
University of Pennsylvania

James Stevenson, MD
Case Comprehensive Cancer Center/
University Hospitals Seidman Cancer Center
and Cleveland Clinic Taussig Cancer Institute

Alda Tam, MD
The University of Texas
MD Anderson Cancer Center

Tawee Tanvetyanon, MD, MPH
Moffitt Cancer Center

Jane Yanagawa, MD
UCLA Jonsson Comprehensive Cancer
Center

Stephen C. Yang, MD
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

Edwin Yau, MD, PhD
Roswell Park Comprehensive Cancer Center

NCCN Staff

Kristina Gregory, RN, MSN, OCN
Vice President, Clinical Information Programs

Miranda Hughes, PhD
Oncology Scientist/Senior Medical Writer

* Reviewed this patient guide. For disclosures, visit [NCCN.org/disclosures](https://www.nccn.org/disclosures).

NCCN Cancer Centers

Abramson Cancer Center
at the University of Pennsylvania
Philadelphia, Pennsylvania
800.789.7366 • penmedicine.org/cancer

Case Comprehensive Cancer Center/
University Hospitals Seidman Cancer
Center and Cleveland Clinic Taussig
Cancer Institute
Cleveland, Ohio
800.641.2422 • UH Seidman Cancer Center
uhhospitals.org/services/cancer-services
866.223.8100 • CC Taussig Cancer Institute
my.clevelandclinic.org/departments/cancer
216.844.8797 • Case CCC
case.edu/cancer

City of Hope National Medical Center
Duarte, California
800.826.4673 • cityofhope.org

Dana-Farber/Brigham and Women's
Cancer Center | Massachusetts General
Hospital Cancer Center
Boston, Massachusetts
617.732.5500 • youhaveus.org
617.726.5130
massgeneral.org/cancer-center

Duke Cancer Institute
Durham, North Carolina
888.275.3853 • dukecancerinstitute.org

Fox Chase Cancer Center
Philadelphia, Pennsylvania
888.369.2427 • foxchase.org

Fred & Pamela Buffett Cancer Center
Omaha, Nebraska
402.559.5600 • unmc.edu/cancercenter

Fred Hutchinson Cancer
Research Center/Seattle
Cancer Care Alliance
Seattle, Washington
206.606.7222 • seattlecca.org
206.667.5000 • fredhutch.org

Huntsman Cancer Institute
at the University of Utah
Salt Lake City, Utah
800.824.2073 • huntsmancancer.org

Indiana University
Melvin and Bren Simon
Comprehensive Cancer Center
Indianapolis, Indiana
888.600.4822 • www.cancer.iu.edu

Mayo Clinic Cancer Center
Phoenix/Scottsdale, Arizona
Jacksonville, Florida
Rochester, Minnesota
480.301.8000 • Arizona
904.953.0853 • Florida
507.538.3270 • Minnesota
mayoclinic.org/cancercenter

Memorial Sloan Kettering
Cancer Center
New York, New York
800.525.2225 • mskcc.org

Moffitt Cancer Center
Tampa, Florida
888.663.3488 • moffitt.org

O'Neal Comprehensive
Cancer Center at UAB
Birmingham, Alabama
800.822.0933 • uab.edu/onealcancercenter

Robert H. Lurie Comprehensive Cancer
Center of Northwestern University
Chicago, Illinois
866.587.4322 • cancer.northwestern.edu

Roswell Park Comprehensive
Cancer Center
Buffalo, New York
877.275.7724 • roswellpark.org

Siteman Cancer Center at Barnes-
Jewish Hospital and Washington
University School of Medicine
St. Louis, Missouri
800.600.3606 • siteman.wustl.edu

St. Jude Children's
Research Hospital/
The University of Tennessee
Health Science Center
Memphis, Tennessee
866.278.5833 • stjude.org
901.448.5500 • uthsc.edu

Stanford Cancer Institute
Stanford, California
877.668.7535 • cancer.stanford.edu

The Ohio State University
Comprehensive Cancer Center -
James Cancer Hospital and
Solove Research Institute
Columbus, Ohio
800.293.5066 • cancer.osu.edu

The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins
Baltimore, Maryland
410.955.8964
www.hopkinskimmellcancercenter.org

The University of Texas
MD Anderson Cancer Center
Houston, Texas
844.269.5922 • mdanderson.org

UC Davis
Comprehensive Cancer Center
Sacramento, California
916.734.5959 • 800.770.9261
health.ucdavis.edu/cancer

UC San Diego Moores Cancer Center
La Jolla, California
858.822.6100 • cancer.ucsd.edu

UCLA Jonsson
Comprehensive Cancer Center
Los Angeles, California
310.825.5268 • cancer.ucla.edu

UCSF Helen Diller Family
Comprehensive Cancer Center
San Francisco, California
800.689.8273 • cancer.ucsf.edu

University of Colorado Cancer Center
Aurora, Colorado
720.848.0300 • coloradocancercenter.org

University of Michigan
Rogel Cancer Center
Ann Arbor, Michigan
800.865.1125 • rogelcancercenter.org

University of Wisconsin
Carbone Cancer Center
Madison, Wisconsin
608.265.1700 • uwhealth.org/cancer

UT Southwestern Simmons
Comprehensive Cancer Center
Dallas, Texas
214.648.3111 • utsouthwestern.edu/simmons

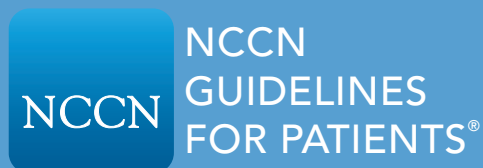
Vanderbilt-Ingram Cancer Center
Nashville, Tennessee
877.936.8422 • vicc.org

Yale Cancer Center/
Smilow Cancer Hospital
New Haven, Connecticut
855.4.SMILOW • yalecancercenter.org

Index

- ablation** 27, 29
- biomarker** 18–19, 21, 32, 41, 53, 59
- biopsy** 8, 16–17, 19, 21, 26, 28, 53, 59–60
- cancer stage** 11, 59
- chemoradiation** 10, 59
- chemotherapy** 25–26, 36–37, 39, 43–47, 50, 52, 59, 61
- clinical trial** 24, 48–50, 55, 59
- driver mutation** 18, 23–24, 32
- imaging** 13, 16–17, 21, 60, 62
- immunotherapy** 25, 34–35, 39, 44–47, 50, 60
- medical history** 14, 60
- NCCN Cancer Centers** 5, 48, 64
- NCCN Contributors** 5, 63
- pathology report** 18, 53
- performance status** 14–15, 41, 45, 50, 61
- physical exam** 15, 17, 61
- radiation therapy** 10, 20, 21, 27, 29, 61
- second opinion** 52
- side effect** 56, 61
- smoking** 14–15, 20–21
- stereotactic ablative radiotherapy** 27, 29
- stereotactic radiosurgery** 27, 29
- supportive care** 10, 20–21, 42, 54, 61
- surgery** 8, 10, 14, 17, 21, 52, 61
- targeted therapy** 24–32, 35, 37, 43, 62





Non-Small Cell Lung Cancer Metastatic 2022

NCCN Foundation gratefully acknowledges the following corporate supporters for helping to make available these NCCN Guidelines for Patients: Bristol Myers Squibb; Janssen Biotech, Inc.; Novartis Pharmaceuticals Corporation; and Pfizer Inc. NCCN independently adapts, updates, and hosts the NCCN Guidelines for Patients. Our corporate supporters do not participate in the development of the NCCN Guidelines for Patients and are not responsible for the content and recommendations contained therein.

To support the NCCN Guidelines for Patients

[DONATE NOW](#)

Visit [NCCNFoundation.org/Donate](https://www.nccn.org/Donate)



National Comprehensive
Cancer Network®

3025 Chemical Road, Suite 100
Plymouth Meeting, PA 19462
215.690.0300

[NCCN.org/patients](https://www.nccn.org/patients) – For Patients | [NCCN.org](https://www.nccn.org) – For Clinicians