

## LUNG CANCER STAGING



What you need to know about...

# stage IV non-small cell lung cancer



# foreword

## About LUNGevity

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

## About the LUNGevity PATIENT EDUCATION SERIES

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

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

In addition to this and other booklets in the LUNGevity patient education series, information and resources can be found on LUNGevity's website at [www.LUNGevity.org](http://www.LUNGevity.org), under "For Patients and Caregivers" and "For Supporters and Advocates."

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# introduction

Lung cancer staging is a way of describing where the cancer is located, if and where it has spread, and whether it is affecting other parts of the body. Various tests are used to determine the lung cancer's stage. Knowing the stage helps your healthcare team recommend the best treatment plan for you. Lung cancer is treatable at all stages, including stage IV, which is the focus of this booklet.

This booklet will help you:

- Understand what lung cancer staging is
- Find out how lung cancer stages are determined
- Learn what stage IV non-small cell lung cancer is
- Find out what the treatment options are for stage IV non-small cell lung cancer

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

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

# 01 lung cancer staging

## What is lung cancer staging, and why is it important?

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Staging is a way of describing where the **lung cancer** is located, if or where it has spread, and whether it is affecting other parts of the body. Treatment options are available for all **stages** of lung cancer, and knowing the stage helps your healthcare team:

- Understand how advanced your lung cancer is
- Recommend those treatment options that are likely to be most effective for you
- Evaluate your response to treatment

## When is lung cancer staged?

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Lung cancer may be staged once or twice. The first staging, which all patients should undergo, is carried out when a patient is initially diagnosed, and should be completed before treatment begins. This type of staging is called clinical staging. Clinical staging is based on the results of various tests, discussed in more detail later in this chapter, including imaging tests and **biopsies**. The clinical stage is not only the basis for deciding on a patient's treatment plan, but is also the basis for comparison when checking into the patient's response to treatment. The second staging, called pathologic or surgical staging, adds what is learned about the patient's cancer from surgical treatment to the determination of staging. If the pathologic stage differs from the clinical stage (which it may, for example, if it is evident that the lung cancer has spread more than initially estimated), then the healthcare team can adjust the treatment more precisely.

## The TNM lung cancer staging system

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The staging system described in this booklet, the TNM staging system, is the system used for **non-small cell lung cancer (NSCLC)**, including lung adenocarcinoma, squamous cell lung cancer, and large cell lung cancer. Stage classifications are based on the 8<sup>th</sup> edition American Joint Committee on Cancer lung cancer stage classifications.

The TNM staging system can also be used for **small cell lung cancer**, although another staging system for small cell lung cancer that has only two stages, **limited-stage** and **extensive-stage**, is more often used.

TNM stages are based on the values assigned to a patient's lung cancer in three categories—T (**tumor**), N (**node**), and M (**metastasis**):

- **T:** The size of the **primary tumor** and if it has grown into adjacent structures. The primary tumor is the original, or first, tumor.
- **N:** Whether and how **regional lymph nodes** are affected by the cancer. **Lymph nodes** are small bean-shaped structures that are part of the body's circulatory and **immune systems**; regional lymph nodes are those that are in the region around a tumor.
- **M:** Whether there is **distant metastasis**. Distant metastasis is the spread of cancer cells from the place where they first formed to distant organs, such as the **adrenal gland**, bones, brain, or other lung, or to distant lymph nodes.

The particular combination of TNM values assigned to a patient's lung cancer determines its stage.

Stages using TNM classifications are designated by a number, zero (0) through four. For one through four, the Roman numerals I through IV are used. The lower the stage number, the less advanced the cancer is and the better the outcome is likely to be; the higher the stage number, the more advanced the cancer is. Stages I–IV are further divided into substages. Briefly, the TNM stages of lung cancer are:

- **Stage 0:** This is called "*in situ*" disease, meaning that the lung cancer is "in place" and has not spread from where it first developed.
- **Stage I:** Stage I lung cancer tumors are small tumors that are only in one lung and have not spread to any lymph nodes or metastasized.
- **Stage II:** Stage II lung cancer tumors are also in one lung, are larger than stage I tumors, may or may not have grown into nearby areas or spread to lymph nodes, and have not metastasized.
- **Stage III:** Stage III lung cancer tumors are also in one lung, are larger than stage II tumors, may or may not have grown into other areas or spread to nearby lymph nodes, and have not metastasized.
- **Stage IV:** Stage IV lung cancer primary tumors are of any size, may or may not have spread to any lymph nodes, and have metastasized.

Recurrent lung cancer is lung cancer that has come back after treatment. If there is a recurrence, then the cancer may need to be staged again (“restaged”), using the same TNM system.

## Tests to help determine the lung cancer stage

There are a number of tests that can be used to determine the lung cancer stage. Your healthcare team and you will determine which are appropriate for you. These tests include:

### Imaging tests

Imaging tests create pictures of the inside of the body. Examples include:

- **Computed tomography (CT or CAT scan):** This test uses a computer linked to an **X-ray** machine to make detailed pictures of the inside of the body. Unlike a conventional X-ray, which takes one picture, a CT scanner takes multiple pictures as it rotates around the patient in order to get images from different angles. Three-dimensional (3D) views of the organs and tissues can be created. A CT scan can provide specific information about the size, shape, and position of tumors in the lungs. It also can help find enlarged lymph nodes or masses in other organs that might be caused by the spread of lung cancer. CT scans usually only take a few minutes to complete.
- **Magnetic resonance imaging (MRI):** This test is used to find out whether the lung cancer has spread to the brain, spinal cord, liver, or other parts of the body. MRI scans provide detailed pictures of areas inside the body by using radio waves and strong magnets in a pattern that a computer translates into images. It is particularly good for images of the brain and nervous tissue. The patient may need to lie in a scanner for up to an hour or more.



- **Positron emission tomography (PET):** This type of scan is used to help determine whether the lung cancer has spread to lymph nodes, bones, or other organs in the body. (It is less useful in checking for cancer that has spread to the brain.) The patient is injected with a radioactive sugar. Because cancer cells grow rapidly, they absorb more of the radioactive sugar than do most healthy cells. About an hour after the injection, the patient is placed on a table in the PET scanner for approximately 30 minutes while a special camera creates a picture of the areas in the body that absorbed the radioactive sugar. (PET scans are usually used in place of a bone scan in lung cancer.)
- **PET/CT scan:** A combined PET/CT scan can be performed using a machine that does both simultaneously, allowing the comparison of areas of radioactivity as shown on the PET scan with the detailed view of that area as shown on the CT scan.

## Biopsies

Biopsies are procedures in which small amounts of tissue are removed for examination. Depending on which method is used, your healthcare team can determine whether the cancer has spread to lymph nodes or other organs. Examples of biopsy procedures used to help in lung cancer staging include:

- **Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA):** EBUS-TBNA is used to access **mediastinal** lymph nodes. A flexible **bronchoscope** fitted with an ultrasound device is guided in the **trachea** (windpipe). Once the bronchoscope is in place, a needle is inserted through the **bronchus** and into a lymph node to obtain a sample.

- **Endoscopic esophageal ultrasound:** This test uses an **endoscope** to access the esophagus. The esophagus is behind the trachea in near proximity to lymph nodes in the chest. The device can be aimed in different directions to observe the lymph nodes and other structures inside the chest to which the lung cancer may have spread. A needle can be inserted through the endoscope to obtain a sample.
- **Mediastinoscopy:** This procedure is used to acquire tissue samples from the **mediastinum**, which is the area between the lungs. A thin tube through which tissue samples from the nearby lymph nodes along the trachea can be taken is used; the tube is inserted through a small incision in the front of the neck.
- **Mediastinotomy:** This procedure allows access to lymph nodes that are not reachable by mediastinoscopy. The incision is larger and is made between the second and third ribs next to the breast bone. This is sometimes used to biopsy lymph nodes from tumors on the left side.
- **Thoracoscopy:** For staging, this procedure is used to sample tumors and lymph nodes on the outer parts of the lungs, check whether lung cancer has spread to the spaces between the lungs and chest wall, and check whether the tumor has spread to nearby lymph nodes and organs. This is a more invasive procedure than the others, and so usually is not the first to be used. (This procedure is also referred to as video-assisted thoracoscopic surgery [VATS].)

More details on lung biopsies can be found in LUNGeVity’s “What you need to know about biomarker testing” booklet, which can be downloaded at <https://lungevity.org/for-patients-caregivers/get-educational-materials> or <https://lungevity.org/for-patients-caregivers/lung-cancer-101/diagnosing-lung-cancer/biomarker-tests>.

## Deciding on a treatment plan

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There are a number of treatment options for each stage of lung cancer. Your healthcare team will recommend a treatment plan based on your stage as well as other factors about you and your cancer, including your overall health and information on how well the organs of your body are functioning.

You may have one or more kinds of laboratory tests to assess these factors, including:

- A **complete blood count (CBC)** to check for:
  - **Anemia:** a low number of red blood cells
  - **Thrombocytopenia:** a low number of platelets, which can cause bleeding
  - **Neutropenia:** a low number of white blood cells (WBCs), which can put a patient at increased risk for infection
- **Blood chemistry tests** to check whether your liver or kidneys are working well. The results from these blood tests help your healthcare team decide if you are able to undergo surgery or receive another type of lung cancer treatment.
- **Heart and lung function tests** to check if these organs are working well. Results of these tests will help your healthcare team decide whether you are eligible for surgery.

You may be as involved in the treatment plan decision as you want to be. Discuss all of the options, understand what the goal of each option is (for example, cure vs. control), consider the benefits and risks of each, check about likely side effects, understand how your everyday life might be affected, find out what the treatment will mean to you financially, and do not hesitate to get a second opinion if you have unaddressed concerns.

It is always a good idea to take someone with you to your appointment to help with questions and take notes.

## 02 stage IV non-small cell lung cancer

### What is stage IV non-small cell lung cancer (NSCLC)?

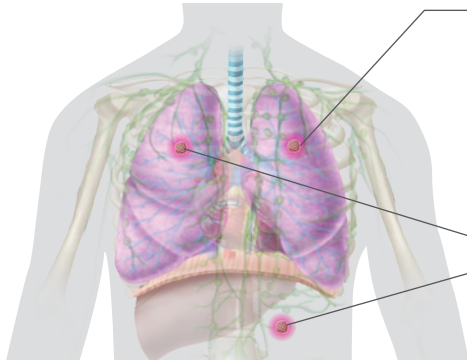
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Unlike the earlier stages of lung cancer, stage IV lung cancer has metastasized to distant parts of the body. The tumors may be of any size and may or may not have spread to lymph nodes.

Stage IV lung cancer is divided into two substages: stage IVA and stage IVB.

Stage IVA tumors have metastasized, either from one lung into the other lung, into the lung's lining (and have formed secondary nodules), into the heart's lining (and have formed secondary nodules), or into the fluid around the lungs or the heart; and/or tumors have spread to one site outside the chest area (e.g., adrenal gland or bones).

## LUNG CANCER: STAGE IVA



Any size tumor

**AND**

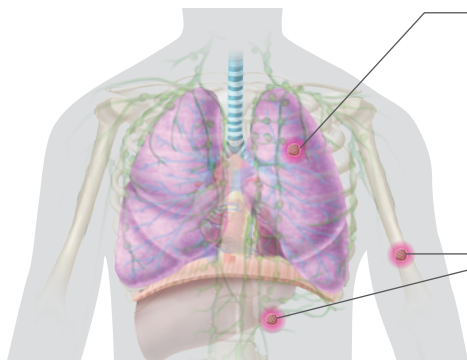
Cancer **may or may not have spread** to any lymph nodes

**AND**

Tumors have spread from one lung into the other lung (shown); into the lung's lining and have formed secondary nodules; into the heart's lining and have formed secondary nodules; or into the fluid around the lungs or the heart; and/or cancer has spread to one site outside the chest area (e.g., adrenal gland [shown])

Stage IVB tumors have metastasized to multiple sites outside the chest area (e.g., adrenal gland and bones).

## LUNG CANCER: STAGE IVB



Any size tumor

**AND**

Cancer **may or may not have spread** to any lymph nodes

**AND**

Tumors have spread to multiple sites outside the chest area (e.g., adrenal gland and bones [shown])

## Signs and symptoms of stage IV NSCLC

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Symptoms of lung cancer are likely to be evident among stage IV NSCLC patients. Which symptoms are evident, and their severity, are different for each patient.

The following are signs and symptoms of lung cancer that may appear at stage IV. These signs and symptoms may also be caused by other conditions and are not specific to lung cancer. Speak with your healthcare team if you have any of the following:

- Coughing symptoms
  - A cough that gets worse or does not go away
  - Coughing up blood
- Chest symptoms
  - Breathing trouble, such as shortness of breath
  - New wheezing when you breathe
  - Ache or pain in your chest, upper back, or shoulder that doesn't go away and may get worse with deep breathing
  - A hoarse voice
  - Frequent respiratory tract infections, such as pneumonia or bronchitis
- General physical symptoms
  - Feeling unusually tired all the time
  - Weight loss with no known cause and loss of appetite
  - Trouble swallowing
  - Swelling in the face and/or veins in the neck

Lung cancer that spreads may cause other symptoms, like pain in the back or other bones or weakness in the arms or legs. If it spreads to the brain, it may cause headaches, seizures, nausea/throwing up, dizziness, or vision or other neurological changes.

## Treatment options for stage IV NSCLC

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Your healthcare team and you will determine the best treatment plan for you.

Treatment options for patients with stage IV NSCLC, which is metastatic and has spread beyond the lungs, depend in large part on your general health and on the presence of particular **biomarkers** that indicate that you may be eligible for a **targeted therapy** or an **immunotherapy** drug as part of your treatment plan. **Chemotherapy**, **radiotherapy**, and palliative, or supportive, care can also be a part of a stage IV treatment plan.

### General information about stage IV NSCLC treatment options

#### *Performance status*

Your healthcare team will use one of several scales, such as the Eastern Cooperative Oncology Group (ECOG) Performance Scale, to measure your general health to help determine treatments that may be the best for you. The ECOG scale scores a patient according to how a disease affects the patient's ability to care for himself or herself and do other activities. The ECOG scores used for treatment decisions range from 0 to 4, where:

- A score of 0 means that the patient is fully active and able to carry on all pre-disease performance without restriction
- A score of 1 means that the patient is restricted in physically strenuous activity but **ambulatory** and able to carry out work of a light or sedentary nature (e.g., light housework or office work)
- A score of 2 means that the patient is ambulatory and capable of all self-care but unable to carry out any work activities; the patient is up and about more than 50% of waking hours

- A score of 3 means that the patient is capable of only limited self-care. The patient is confined to bed or chair more than 50% of waking hours
- A score of 4 means that the patient is completely disabled, cannot carry on any self-care, and is totally confined to bed or chair

Some patients' performance scores improve after treatment, making them eligible for additional treatments.

### *Chemotherapy*

When chemotherapy is a treatment option, commonly used chemotherapy drugs used to treat stage IV NSCLC include:

Generic (chemical) name	Brand name (sold as)
Carboplatin	Paraplatin®
Cisplatin	Platinol-AQ®
Docetaxel	Taxotere®
Etoposide	Etopophos®
Gemcitabine	Gemzar®
Paclitaxel	Taxol®, Onxol®
Paclitaxel (albumin-bound)	Abraxane®
Pemetrexed	Alimta®
Vinorelbine	Navelbine®

Your healthcare team will select the appropriate chemotherapy drug(s).

### *Immunotherapy*

Immunotherapy is a treatment that enhances the ability of the body's immune system to kill lung cancer cells. There are currently three immunotherapy drugs that are U.S. Food and Drug Administration (FDA)-approved to treat stage IV NSCLC:

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



Each is used depending on a patient’s particular condition, including progression on platinum-based chemotherapy and, in certain situations with pembrolizumab (Keytruda®), the amount of **programmed death ligand 1 (PD-L1) protein** expressed by the tumor when biopsied. Your healthcare team will determine if you are a good candidate for immunotherapy.

### Targeted Therapies

An error in a gene’s DNA code, or a mutation, can lead to cells growing and dividing uncontrollably, causing the formation of a cancerous tumor. These mutations are known as **driver mutations**. Targeted therapies are a type of treatment that attacks the signals that cause the cancerous cells to grow and divide uncontrollably. These therapies are specific to a particular mutation. There are currently FDA-approved targeted therapies for five of the driver mutations: **epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS1, BRAF V600E, and NTRK.**

Generic (chemical) name	Brand name (sold as)	Mutation
Afatinib	Gilotrif®	EGFR
Dacomitinib	Vizimpro®	EGFR
Erlotinib	Tarceva®	EGFR
Gefitinib	Iressa®	EGFR
Osimertinib	Tagrisso®	EGFR
Crizotinib	Xalkori®	ALK and ROS1
Ceritinib	Zykadia®	ALK
Alectinib	Alecensa®	ALK
Brigatinib	Alunbrig®	ALK
Lorlatinib	Lorbrena®	ALK
Dabrafenib in combination with trametinib	Tafinlar® in combination with Mekinist®	BRAF V600E
Larotrectinib	Vitrakvi®	NTRK

In order to determine whether a targeted therapy should be used, a patient’s tumor must be tested for biomarkers, which will indicate whether a targetable driver mutation is present. It is commonly recommended that all stage IV adenocarcinoma patients’ tumors be biomarker-tested to determine whether a targeted therapy or immunotherapy drug may be of benefit or if there is an available **clinical trial**. Stage IV squamous cell lung cancer patients’ tumors may also be recommended for testing. Specifically:

Type of Lung Cancer	Recommendations for Biomarker Testing Among Stage IV NSCLC Patients
<p><b>Stage IV adenocarcinoma, or adenocarcinoma that has recurred or progressed after an initial diagnosis of stage I, II, or III lung cancer in patients who were not previously tested</b></p>	<p>Tumors should be tested for EGFR, ALK, KRAS, ROS1, BRAF V600E, and NTRK mutations at the time of diagnosis. Testing for other biomarkers may be helpful in deciding eligibility for clinical trials. Broad biomarker testing using a next generation sequencing (NGS) panel is recommended.</p> <p>PD-L1 immunohistochemistry is recommended to determine whether you will benefit from single-agent immunotherapy in the first-line setting.</p>
<p><b>Stage IV squamous cell lung cancer</b></p>	<p>PD-L1 immunohistochemistry is recommended to determine whether you will benefit from single-agent immunotherapy in the first-line setting.</p> <p>Testing for EGFR and ALK mutations is recommended ONLY if your healthcare team suspects that the tumor has adenocarcinoma cells (this type of lung cancer is referred to as mixed lung cancer with an adenocarcinoma component).</p> <p>Currently, comprehensive biomarker testing is performed primarily for clinical trials. Broad NGS may be recommended to help identify potential rare mutations, which may have clinical trial options, particularly in never-smokers or patients with limited smoking history or where there is concern for adenocarcinoma cells, as described above.</p>

### *Palliative care*

Palliative care does not treat the lung cancer directly. The goal of palliative care is to prevent or treat the symptoms and side effects of the disease and its treatment. At the same time, it addresses the emotional, social, practical, and spiritual problems that a patient faces. Palliative care improves a patient's quality of life while he or she is receiving standard medical care by anticipating, preventing, and treating suffering. Palliative care can be provided from the time of diagnosis, throughout treatment, and at the end of life. There is evidence to show that palliative care can extend life. The American Society of Clinical Oncology (ASCO) recommends that all patients with advanced cancer receive palliative care early on and concurrent with cancer treatment.

### **Specific stage IV NSCLC treatment options**

The treatment options outlined here are based primarily on 2018 recommendations by the National Comprehensive Cancer Network. Your healthcare team may suggest other treatment options, including a clinical trial. Your healthcare team will take into account several factors such as your medical history, your performance status, and your biomarker profile.

Your healthcare team may discuss your care at a cooperative tumor board at which multiple specialists meet to coordinate the best personalized care for you.

*Treatment options for patients with stage IV adenocarcinoma, large cell, or unknown types of lung cancer where there are no or unknown biomarkers present may include:*

- For these patients, first-line (initial) treatments depend largely on the patient's performance status.
- For those patients with the best performance scores, 0 or 1, platinum-based chemotherapy alone (e.g., cisplatin or carboplatin); chemotherapy in combination with bevacizumab (Avastin®), an anti-angiogenic treatment; pembrolizumab (Keytruda®), an immunotherapy drug, in combination with chemotherapy; or atezolizumab (Tecentriq®), an immunotherapy drug, in combination with chemotherapy and bevacizumab (Avastin®), may be recommended.
- For those patients with a performance score of 2, chemotherapy may be recommended.
- For those patients with a performance score of 3 or 4, palliative care may be recommended.

Depending on your health and response, your healthcare team will make recommendations for **maintenance therapy, second-line therapy**, or further treatment. Maintenance therapy may include the same or other chemotherapies or simply a “watch and wait” approach. Second-line or further treatments may include immunotherapy drugs and other chemotherapies (including a combination of ramucirumab [Cyramza®], a **vascular endothelial growth factor receptor 2 [VEGFR2]** inhibitor with docetaxel [Taxotere®]) for patients with performance scores of 2 or lower, and palliative care for patients with performance scores of 3 or 4.

*Treatment options for patients with stage IV adenocarcinoma with an EGFR mutation may include:*

- For these patients, the options are recommended irrespective of performance status.
- For these patients, first-line treatment may include one of the five FDA-approved targeted therapies for EGFR: afatinib (Gilotrif®), dacomitinib (Vizimpro®), erlotinib (Tarceva®), gefitinib (Iressa®), or osimertinib (Tagrisso®).

If the cancer progresses, your healthcare team will make recommendations for second- and further-line treatment:

- For those whose first-line treatment was afatinib (Gilotrif®), erlotinib (Tarceva®), or gefitinib (Iressa®), these treatments may include staying on the first-line treatment but starting or stopping a local treatment (e.g., radiation to treat the metastasis if it is in a confined area); switching to osimertinib (Tagrisso®) if the T790M EGFR mutation is present; or treating with chemotherapy.
- For those whose first-line treatment was osimertinib (Tagrisso®) or dacomitinib (Vizimpro®), these treatments may include staying on it but starting or stopping a local treatment; or treating with immunotherapy drugs and/or other chemotherapies (as is done for first-line treatment for non-EGFR-mutated cancer) for patients with performance scores of 2 or lower, and palliative care for patients with performance scores of 3 or 4.

*Treatment options for patients with stage IV adenocarcinoma with an ALK gene rearrangement may include:*

- For these patients, the options are recommended irrespective of performance status.
- First-line treatment may include one of these three FDA-approved targeted therapies for ALK: alectinib (Alecensa®), crizotinib (Xalkori®), or ceritinib (Zykadia®).

If the cancer progresses, your healthcare team will make recommendations for second- and further-line treatment. These treatments may include staying on the first-line treatment but starting or stopping a local treatment (e.g., radiation to treat the metastasis if it is in a confined area); switching from crizotinib (Xalkori®) to ceritinib (Zykadia®), alectinib (Alecensa®), or brigatinib (Alunbrig®), switching from crizotinib® and at least one other ALK inhibitor to lorlatinib (Lorbrena®), switching from alectinib (Alecensa®) or ceritinib (Zykadia®) to lorlatinib (Lorbrena®) and starting or stopping a local treatment; or treating with immunotherapy drugs and other chemotherapies for patients with performance scores of 2 or lower, and palliative care for patients with performance scores of 3 or 4.

*Treatment options for patients with stage IV adenocarcinoma with a ROS1 gene rearrangement may include:*

- First-line treatment for these patients may include the targeted therapies crizotinib (Xalkori®) and ceritinib (Zykadia®).

If the cancer progresses, your healthcare team will make recommendations for second- and further-line treatment. These may include treating with immunotherapy drugs and other chemotherapies for patients with performance scores of 2 or lower, and palliative care for patients with performance scores of 3 or 4.

*Treatment options for patients with stage IV adenocarcinoma with a BRAF V600E mutation may include:*

- For these patients, first-line treatment may include the combination of dabrafenib (Tafinlar®) and trametinib (Mekinist®). However, these treatments have the potential to make the patient sick and may be discontinued. There are other options, including platinum-based chemotherapy.

*Treatment options for patients with stage IV adenocarcinoma with an NTRK mutation may include:*

- Larotrectinib (Vitrakvi®) may be prescribed for those patients without a known acquired resistance mutation who have no satisfactory treatments or have progressed following treatment.

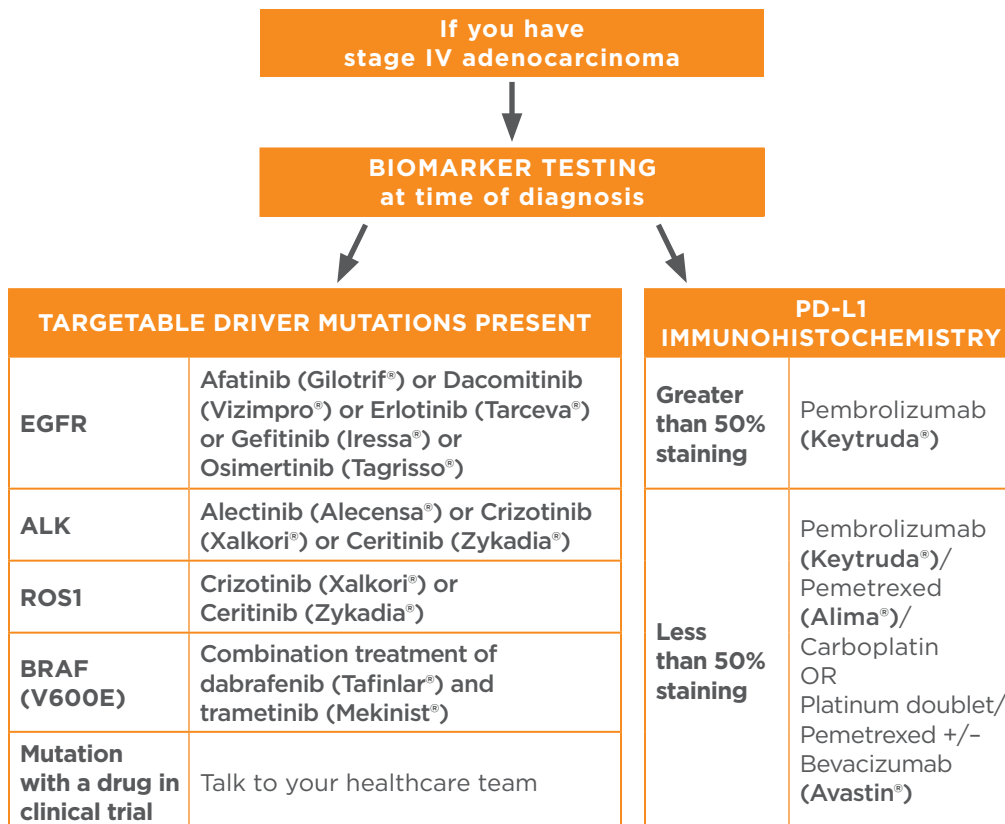
*Treatment options for patients with stage IV adenocarcinoma whose tumors have high PD-L1 expression (tumor proportion score [TPS] ≥ 50%) with no EGFR or ALK mutations may include:*

- For these patients, the immunotherapy drug pembrolizumab (Keytruda®) is an option for first-line treatment. For patients who cannot receive pembrolizumab, platinum-based chemotherapy may be an alternative.

*Treatment options for patients with stage IV adenocarcinoma whose tumors have low PD-L1 expression (TPS < 50%) with no EGFR or ALK mutation may include:*

- For these patients, the immunotherapy drug pembrolizumab (Keytruda®) along with the chemotherapy drug, pemetrexed (Alimta®) may be considered as an option for first-line treatment.

The following chart summarizes first-line treatment options for stage IV adenocarcinoma for patients who have had biomarker testing at the time of diagnosis.

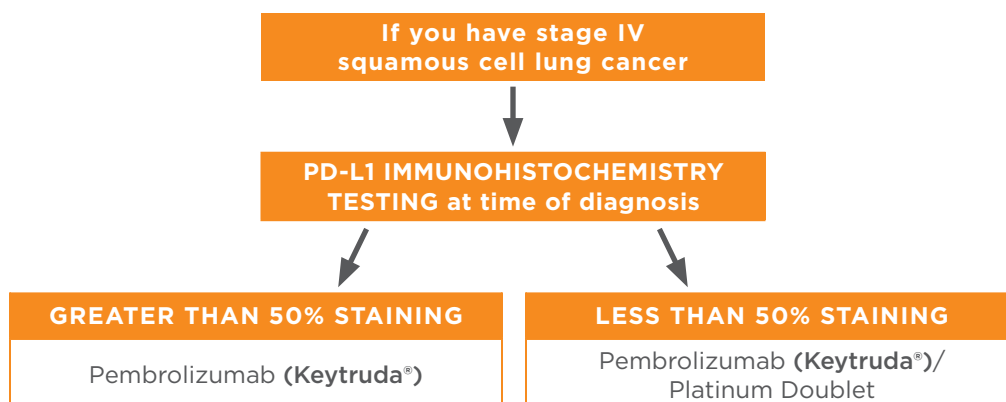




*Treatment options for patients with stage IV squamous cell lung cancer may include:*

- For these patients, performance status may determine treatment options
- For patients whose performance score is 0 or 1, platinum-based chemotherapy is an option
- For patients whose performance score is 2 or less, combined chemotherapy and immunotherapy is a first-line treatment option
- For patients whose performance score is 2, chemotherapy is an option
- For patients whose performance score is 3 or 4, palliative care is an option
- For maintenance therapy, chemotherapy is an option, as is a “watch and wait” approach

The following chart summarizes first-line treatment options for stage IV squamous cell lung cancer for patients who have had biomarker testing at the time of diagnosis.



If the cancer has progressed on first-line treatment, then second- or further-line treatments may include:

- For patients whose performance score is 2 or less, any of the three immunotherapy drugs nivolumab (Opdivo®), pembrolizumab (Keytruda®), or atezolizumab (Tecentriq®) (preferred if the patient has not had them previously and is a candidate), chemotherapy, or a combination of ramucirumab (Cyramza®) with docetaxel (Taxotere®) are all options.
- For patients whose performance score is 3 or 4, palliative care is an option.

*Other treatment options for patients with stage IV NSCLC may include:*

- Treatments specific to bone and brain metastasis, such as **bisphosphonates** (for bone metastasis) or brain radiation or surgery (for brain metastasis), may also be given.

Recommendations for the best option may change over time, so your healthcare team may recommend options that are not outlined here. In addition, there are new treatments for stage IV NSCLC that are available now only through clinical trials that may be a preferred option for you. Discuss clinical trial options with your healthcare team.

## Side effects of stage IV NSCLC treatment and how to manage them

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Side effects from lung cancer treatment are common, but just because a side effect is common does not mean that you will have it. Before you begin your treatment for stage IV NSCLC, discuss with your healthcare team what side effects you might expect and how to prevent or ease them. Speak with your healthcare team if and when new side effects begin, as treating them early on is often more effective than trying to treat them once they have already become severe. Although most side effects go away when treatment is over, some can last a long time.

The management techniques outlined below are not all-inclusive; your healthcare team will have a more extensive set of recommendations.

### Common side effects of chemotherapy

- **Fatigue:** Fatigue can be treated by relieving conditions related to it, such as anemia and depression. If a patient is depressed, antidepressant medications may be prescribed.
- **Nausea, vomiting:** There are multiple medications available to prevent and treat nausea and vomiting. If one anti-nausea medication doesn't work, then a different one or an additional one can be prescribed. Techniques such as distraction, relaxation, and positive imagery can help change the expectation and fear of nausea and vomiting.
- **Hair loss:** Some chemotherapy drugs may cause hair loss from all over the body. Not all chemotherapy drugs cause hair loss. Certain medications and cold cap therapy may prevent hair loss during chemotherapy.

- **Loss of appetite:** Appetite stimulants and nutritional supplements can be given to improve appetite and reduce weight loss.
- **Diarrhea:** Antidiarrheal medications may be prescribed as needed.
- **Constipation:** Stool softeners and laxatives can be used.
- **Peripheral neuropathy:** Sometimes physical therapy and complementary therapies, such as massage and acupuncture, can help. The most common medications to treat neuropathic pain are anticonvulsants and antidepressants. Over-the-counter pain medications may be recommended for mild pain, or prescription non-steroidal anti-inflammatory drugs or analgesics may be prescribed for severe symptoms.

Sometimes, the doses of the chemotherapy drugs may need to be lowered or treatment may need to be delayed to prevent the side effects from getting worse.

## Common side effects of radiation therapy

- **Fatigue:** Fatigue can be treated by relieving conditions related to it, such as anemia and depression. If a patient is depressed, antidepressant medications may help.
- **Sunburn-like skin changes, such as dryness, itching, or peeling:** Moisturizing creams, showering and bathing with warm water rather than hot, and antihistamines may help.
- **Hair loss:** Hair is lost only in the area being treated. In most cases, hair will grow back.
- **Cough, difficulty breathing, and shortness of breath:** These symptoms can develop as “radiation pneumonitis” up to months after therapy and may require anti-inflammatory medication.

- **Sore throat and trouble swallowing:** Pain and anti-inflammatory medications and speech pathology to learn different ways to swallow may help.
- **Loss of appetite:** Appetite stimulants and nutritional supplements can be given to improve appetite and reduce weight loss.
- **Nausea, vomiting (when the treated area is near the stomach):** There are multiple medications available to prevent and treat nausea and vomiting. If one anti-nausea medication doesn't work, a different one or an additional one can be prescribed. Techniques such as distraction, relaxation, and positive imagery can help change the expectation and fear of nausea and vomiting.

## Common side effects of immunotherapy drugs

- **Fatigue:** Fatigue can be treated by relieving conditions related to it, such as anemia and depression. If a patient is depressed, antidepressant medications may help.
- **Pneumonitis and other inflammatory conditions:** Symptoms of pneumonitis, such as cough, difficulty breathing, and shortness of breath, can develop up to months after therapy and may require anti-inflammatory medication. Pneumonitis and some of the other side effects seen with immune checkpoint inhibitors are related to “turning on” the immune system, which then may also attack some healthy cells and cause inflammation. Other examples of this include:
  - Arthritis
  - Colitis
  - Hepatitis
  - Inflammation of the endocrine glands, like the thyroid
  - Nephritis and renal dysfunction

Inflammation of the thyroid can cause either high or low thyroid hormone levels (**hyperthyroidism** or **hypothyroidism**, respectively). Inflammation of the liver can also occur, and so liver function tests may be run periodically to check for that. About half of patients develop some inflammation-related side effects. These are usually easy to manage, but sometimes patients may need to take additional medications, including corticosteroids or thyroid hormone replacement.

- **Upper respiratory tract infection:** Signs and symptoms may include fever, cough, frequent urination, pain when urinating, and flu-like symptoms. Antibiotics may be used for treatment.
- **Rash:** Depending on the severity of the rash, symptoms can be managed with cream corticosteroids, oral corticosteroids, cream antibiotics, or oral antibiotics.
- Rare autoimmune side effects are possible as well and may occur weeks or months after the therapy starts, including but not limited to a risk of hypothyroidism, cardiac or kidney damage, or changes in hormone secretion. Tell your doctor about any new or unusual symptoms if you develop them after starting immunotherapy.

## Common side effects of targeted therapies

### *EGFR drugs*

- **Skin problems, including an acne-like rash:** Depending on the severity of the rash, symptoms can be managed with cream antibiotics or oral antibiotics.
- **Diarrhea:** Antidiarrheal medications can be prescribed as needed.
- **Mouth sores:** Have a dental check-up before treatment; if sores develop, coating medications that form a film to protect the sores and minimize pain or topical painkillers can be used.
- **Loss of appetite:** Appetite stimulants and nutritional supplements can be given to improve appetite and reduce weight loss.

### *ALK drugs and ROS1 drugs*

- **Nausea, vomiting:** There are multiple medications available to prevent and treat nausea and vomiting. If one anti-nausea medication doesn't work, a different one or an additional one can be prescribed. Techniques such as distraction, relaxation, and positive imagery can help change the expectation and fear of nausea and vomiting.
- **Diarrhea:** Antidiarrheal medications may be prescribed as needed.
- **Constipation:** Stool softeners and laxatives can be used.
- **Fatigue:** Fatigue can be treated by relieving conditions related to it. If a patient is depressed, antidepressant medications may help. Low testosterone is one source of fatigue in patients being treated with crizotinib (Xalkori®). This can also lead to sexual dysfunction and depression. Researchers have found that hormone replacement therapy is an effective method to manage these side effects.
- **Changes in vision:** Schedule regular exams with an eye doctor throughout treatment (it is good to establish baseline before treatment); wearing corrective lenses, using artificial tears to keep eyes moist, and applying a warm washcloth to eyelids can help.

### *BRAF V600E drug combination*

- **Fatigue:** Fatigue can be treated by relieving conditions related to it, such as anemia and depression. If a patient is depressed, antidepressant medications may help.
- **Nausea, vomiting:** There are multiple medications available to prevent and treat nausea and vomiting. If one anti-nausea medication doesn't work, a different one or an additional one can be prescribed. Techniques such as distraction, relaxation, and positive imagery can help change the expectation and fear of nausea and vomiting.
- **Diarrhea:** Antidiarrheal medications can be prescribed as needed.
- **Decreased appetite:** Appetite stimulants and nutritional supplements can be given to improve appetite and reduce weight loss.
- **If you experience the following side effects, report them to your healthcare team immediately:**
  - Dry skin and rash
  - Swelling of the face, arms, and legs
  - Fever and/or chills
  - Bleeding
  - Cough or shortness of breath
- **Increased risk of skin cancer:** Patients on this combination of drugs should be followed by a dermatologist as well because their risk of new skin cancers increases.



### *NTRK drug*

- **Fatigue:** Fatigue can be treated by relieving conditions related to it. If a patient is depressed, antidepressant medications may be prescribed.
- **Nausea, vomiting:** There are multiple medications available to prevent and treat nausea and vomiting. If one anti-nausea medication doesn't work, then a different one or an additional one can be prescribed. Techniques such as distraction, relaxation, and positive imagery can help change the expectation and fear of nausea and vomiting.
- **Diarrhea:** Antidiarrheal medications may be prescribed as needed.
- **Constipation:** Stool softeners and laxatives can be used.
- **Dizziness:** The anti-emetic drugs prescribed for nausea and vomiting, drinking plenty of fluids, and changing position and moving around slowly and carefully may help.

## Outlook for stage IV NSCLC patients

There have been many developments in the treatment of stage IV NSCLC in the last several years, and there are more new treatment options in development. There are a number of factors that determine the outlook for any individual stage IV NSCLC patient, including the type of NSCLC, the patient's health in general, and the responsiveness of the patient's NSCLC to treatment. Individual patient outlook can vary a great deal depending on the biomarkers present. Discuss your outlook with your healthcare team.

## Finding a clinical trial that might be right for you

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If you are considering participating in a clinical trial, start by asking your healthcare team whether there is one that might be a good match for you in your geographic area. Note that if your stage IV NSCLC tests positive for a driver mutation for which a U.S. Food and Drug Administration (FDA)-approved therapy exists, you may be eligible to enroll in a trial with specific targeted therapies.

Below are several resources in addition to your healthcare team to help you find a clinical trial that may be a good match.



### **RESOURCES TO HELP YOU NAVIGATE YOUR CLINICAL TRIALS SEARCH:**

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

**(CONTINUED)**



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

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

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



### QUESTIONS TO ASK YOUR HEALTHCARE TEAM ABOUT LUNG CANCER STAGING:

- What kind of lung cancer do I have?
- What is the stage of my lung cancer?
- Has the cancer spread to the lymph nodes?
- Has the cancer spread to other parts of my body? If so, where?
- Do I need any other tests before treatment can start? If so, why, and what are they?
- May I have a copy of the pathology reports (that show the results of diagnostic tests and/or surgery)?
- May I have a copy of the imaging and radiology reports?
- What are my near-term and long-term outlooks given the stage of my lung cancer?
- What are the survival statistics for this stage? How do these statistics relate to me?
- What are my treatment options? What is the intent of each of the treatment options?
- What can I expect after we start treatment? How long will I need to have treatment?
- If my cancer spreads, will my stage change? How will this impact my treatment options?
- Will my cancer be tested for biomarkers?
- Are there clinical trials for new treatment options for my stage of lung cancer?

## 03 glossary

**Adrenal gland**—A small gland that makes hormones that help control heart rate, blood pressure, and other important body functions. There is an adrenal gland on top of each kidney

**ALK**—See anaplastic lymphoma kinase

**Ambulatory**—Able to walk about and not bedridden

**Anaplastic lymphoma kinase (ALK)**—A gene that the body normally produces but, when it fuses with another gene, produces an abnormal protein that leads to cancer cell growth

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

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

**Bisphosphonate**—A drug or substance used to treat hypercalcemia (abnormally high blood calcium) and bone pain caused by some types of cancer

**Blood chemistry tests**—A common panel of blood tests that measures the amount of electrolytes and other chemicals made in the body. It provides information on how the body’s organs, such as kidneys, liver, and heart, are functioning

**BRAF V600E**—A mutation in the BRAF gene, which makes a protein that is involved in sending signals in cells and in cell growth. It may increase the growth and spread of cancer cells in non-small cell lung cancer

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

**Bronchus**—A large airway that leads from the trachea (windpipe) to a lung

**Chemotherapy**—Treatment with drugs that kill cancer cells

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

**Complete blood count (CBC)**—A measure of the number of red blood cells, white blood cells (WBCs), and platelets in the blood. A CBC is used to help diagnose and monitor many conditions. Also called blood cell count

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

**Distant metastasis**—Refers to cancer that has spread from the primary (original) tumor to distant organs or distant lymph nodes

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

**EGFR**—See epidermal growth factor receptor

**Endoscope**—A thin, tube-like instrument used to look at tissues inside the body. An endoscope has a light and a lens for viewing and may have a tool to remove tissue

**Epidermal growth factor receptor (EGFR)**—The protein found on the surface of some cells and to which epidermal growth factor binds, causing the cells to divide. It is found at abnormally high levels on the surface of many types of cancer cells, so these cells may divide excessively in the presence of epidermal growth factor

**Extensive-stage small cell lung cancer**—Small cell lung cancer that has spread outside the lung in which it began or to other parts of the body

**Hyperthyroidism**—Too much thyroid hormone. Symptoms include weight loss, chest pain, cramps, diarrhea, and nervousness. Also called overactive thyroid

**Hypothyroidism**—Too little thyroid hormone. Symptoms include weight gain, constipation, dry skin, and sensitivity to the cold. Also called underactive thyroid

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



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

**Limited-stage small cell lung cancer**—Small cell lung cancer found in one lung, the tissues between the lungs, and nearby lymph nodes only

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

**Lymph node**—A bean-shaped structure that is part of the body's immune system. Lymph nodes filter lymph (lymphatic fluid) and store lymphocytes (white blood cells [WBCs]). They are located along lymphatic vessels

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

**Mediastinal**—Of the mediastinum

**Mediastinum**—The area between the lungs. The organs in this area include the heart and its large blood vessels, the trachea, the esophagus, the thymus, and lymph nodes but not the lungs

**Metastasis**—The spread of cancer from the primary site, or place where it started, to other places in the body

**Neurotrophic receptor tyrosine kinase (NTRK)**—A gene that the body normally produces but, when it fuses with another gene, produces an abnormal protein that leads to cancer cell growth

**Node**—See lymph node

**Nodule**—A growth or lump that may be malignant (cancerous) or benign (non-cancerous)

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

**NTRK**—Neurotrophic receptor tyrosine kinase

**PD-L1 (programmed death ligand 1) protein**—Part of the immune system mechanism that keeps T cells from functioning

**Peripheral neuropathy**—A nerve problem that causes pain, numbness, tingling, swelling, or muscle weakness in different parts of the body

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

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

**Regional lymph node**—A lymph node that drains lymph from the region around a tumor

**ROS1**—A gene that makes a protein called ROS1, which is involved in sending signals in cells and in cell growth. Mutated forms of the ROS1 gene have been found in non-small cell lung cancer

**Second-line therapy**—Treatment that is given when first-line therapy (initial treatment) doesn't work or stops working

**Small cell lung cancer**—An aggressive (fast-growing) cancer that forms in tissues of the lung and can spread to other parts of the body. The cancer cells look small and oval-shaped when looked at under a microscope

**Stage**—The extent of a cancer in the body. In non-small cell lung cancer (NSCLC), lung cancer stages go from stage 0 to stage IV. The higher the stage, the more advanced the cancer is. In small cell lung cancer, the stages used most often are limited-stage disease and extensive-stage disease

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

**Trachea**—The airway that leads from the larynx (voice box) to the bronchi (large airways that lead to the lungs). Also called windpipe

**Tumor**—An abnormal mass of tissue that results when cells divide more than they should or do not die when they should. Tumors may be benign (not cancerous) or malignant (cancerous). Also called neoplasm

**Tumor proportion score (TPS)**—The percentage of cancer cells that produce the PD-L1 proteins. The lung cancer tissue is stained with special dyes that mark PD-L1 positive tumor cells. A pathologist counts the number of cells that stain positive and determines the TPS

**Vascular endothelial growth factor receptor 2 (VEGFR2)**—  
A substance made by cells that stimulates new blood vessel formation









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