LUNG CANCER TREATMENTS

UPDATED DECEMBER 2016


What you need to know about...

immunotherapy






LUNGEVITY

foreword

About LUNGevity

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

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 brochures in the LUNGevity patient education series, information and resources can be found on LUNGevity's website at www.LUNGevity.org, under "About Lung Cancer" and "Support & Survivorship."

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introduction

Immunotherapy is a type of biological therapy that harnesses and increases the natural ability of the patient's immune system to fight cancer. Instead of trying to stop or kill the person's cancer cells directly, as most other cancer treatments do, immunotherapy trains the person's own natural immune system to recognize cancer cells and selectively target and kill them.

This brochure will help you:

- Learn how the immune system works
- Understand how immunotherapy may boost the immune system to help fight lung cancer
- Understand whether immunotherapy might be a good treatment option for you
- Consider if participating in a clinical research study using immunotherapy might be a good treatment option for you

YOU'LL FIND A GLOSSARY TOWARD THE END OF THIS BROCHURE.
Words included in the glossary appear **blue** the first time that they are used in the text.

01 immune system

What is the immune system?

The **immune system** is a network of cells, tissues, and organs that work together to protect the body from **foreign** invaders, such as **bacteria** or **viruses**.

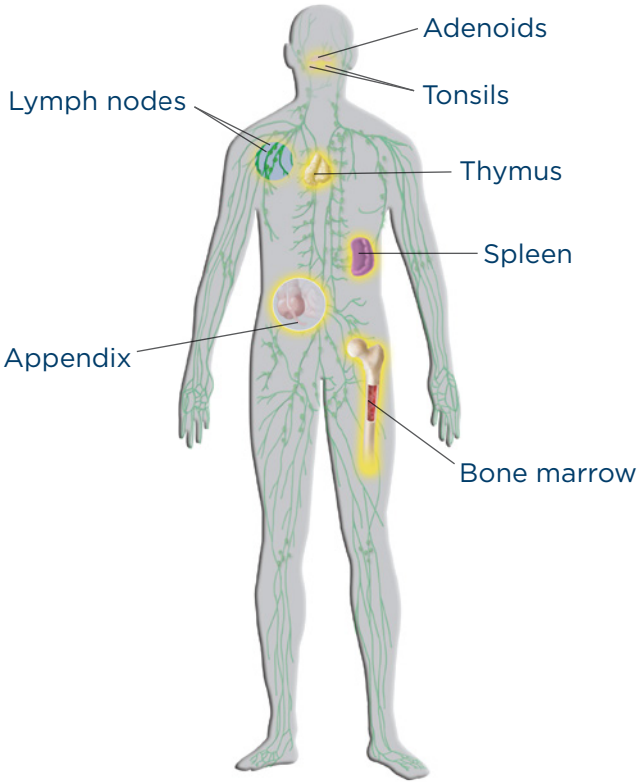
The key players in defending the body are a specific type of **white blood cell (WBC)** called **lymphocytes**. There are three major types of lymphocytes:

- **Natural killer (NK) cells**
- **B cells**
- **T cells**

Lymphocytes grow and develop in the **bone marrow**, **thymus**, and **spleen**. They can also be found in clumps throughout the body, primarily as **lymph nodes**. Lymph nodes in the neck are called **cervical lymph nodes**, and those between the lungs in the middle of the chest are known as **mediastinal** lymph nodes. Clumps of

lymphoid tissue are also found in the appendix, tonsils, and **adenoids**. Lymphocytes circulate through the body between the organs and nodes via **lymphatic vessels** and blood vessels. In this way, the immune system works in a coordinated way to monitor the body for germs and other abnormal cells.

ORGANS OF THE IMMUNE SYSTEM



How does the immune system work?

A key feature of the immune system is its ability to tell the difference between the body's own normal cells, or "self," and cells and other substances that are foreign to the body, or "non-self." Every cell in the body carries a set of distinctive **proteins** on its surface. These identifying surface proteins let the immune system know that they are cells that belong to the body.

Healthy cells display normal proteins on their surface. The immune system has learned to ignore normal proteins. If the surface proteins are abnormal, such as when a virus infects cells, or when cells become cancerous, they can be recognized by the immune system. Proteins recognized by the immune system are called **antigens**.

If a foreign substance—such as a bacteria, virus, or **tumor** cell—is recognized, the immune system kicks in to try to deal with it. It is the "non-self" antigens on the surface of these cells that the immune system identifies as abnormal. The immune system is great at recognizing bacteria and virus cells, because they look very different from healthy cells. On the other hand, tumor cells started as healthy cells and can look a lot like healthy cells. This makes it hard for the immune system to deal with tumor cells. As a result, the body may have a harder time recognizing tumor cells as foreign.

In other instances, the immune system may recognize a tumor antigen but may be unable to mount a response strong enough to destroy the tumor. As cancers grow, they can evolve ways to escape from attack by the immune system. For these reasons, many people with healthy immune systems still develop cancer and cancer still progresses. In many people with cancer, the cancer cells co-exist with immune cells capable of killing the cancer, but the cancer cells hold the immune cells back from working the way they should.

What is the role of the immune system in cancer?

The immune system has two responses that work together to detect and destroy cancer cells:

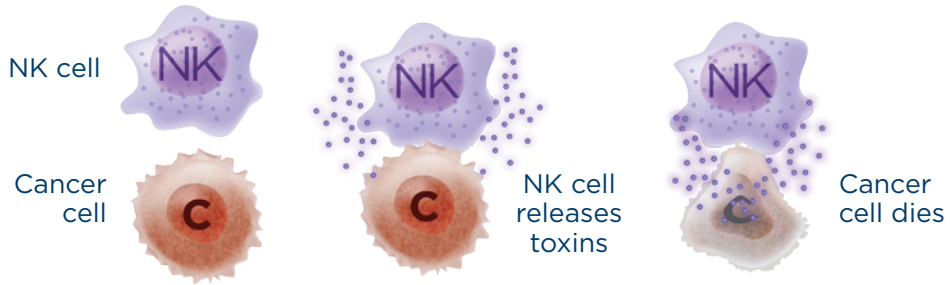
- **Innate immune response**
- **Adaptive immune response**

Innate immune response

Natural killer (NK) cells

The innate immune response is the first line of defense. The innate immune system's normal function is to protect the body from initial invasion by bacteria and viruses, such as when bacteria invade broken skin or viruses land in the throat. The system includes natural killer (NK) cells, a type of lymphocyte that patrols the body and is on constant alert, looking for foreign invaders and abnormal cells. If cells from the innate immune system recognize a cancer cell as abnormal, they can attach to it and immediately release toxic chemicals that kill it. NK cells and other cells of the innate immune system do not need to recognize a specific abnormality on a cell to be able to do their job.

NK CELL RELEASING TOXINS TO CANCER CELL



If bacteria, viruses, or cancer cells evade the innate response, then the adaptive immune response becomes active.

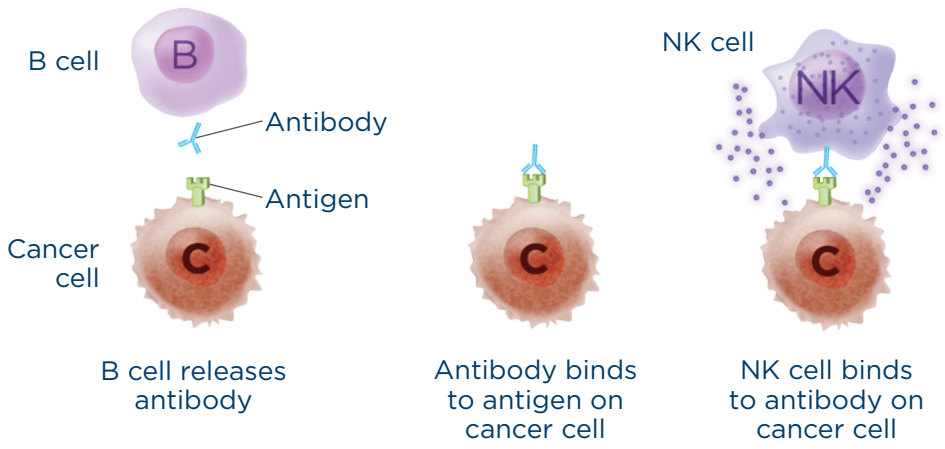
Adaptive immune response

The adaptive immune response recognizes specific abnormalities on cancer cells that make them different from the cells that are naturally found in the body. Though it is more effective than the innate immune response, the adaptive immune response takes longer to become activated. The cells of the adaptive immune response include the other two types of lymphocytes: B cells and T cells.

B cells

B cells are like the body's military intelligence system, seeking out their targets and sending defenses to lock onto them. They react to "non-self" antigens by making proteins called **antibodies**. Antibodies are proteins that can attach to foreign and abnormal cells and let the body know that they are dangerous. Antibodies can kill cancer cells in several ways, including binding natural killer cells to the cancer.

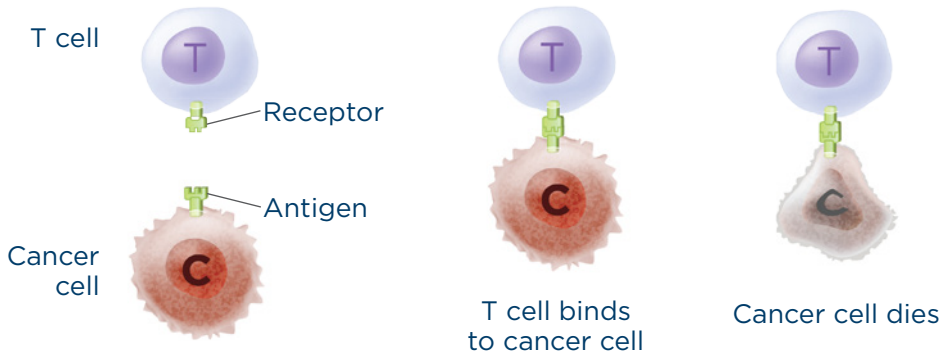
B CELL RELEASING ANTIBODY



T cells

T cells are the major cells the body uses to recognize and destroy abnormal cells. Once a foreign antigen or abnormal cancer protein has been recognized by T cells, the T cells rapidly increase in number. An army of T cells can be formed; these T cells are specifically designed to attack and kill cells that have foreign antigens. The T cells are like soldiers, destroying the invaders. They are responsible for coordinating the entire **immune response** and destroying infected cells and cancer cells.

T CELL ATTACKING CANCER CELL



T cells also develop “memory” after an initial response to an antigen. This memory is meant to ensure that the attack on cancer cells can persist long-term, for months or longer. The memory also allows for future responses against the specific abnormal antigen on cancer cells, if and when the cancer comes back.

How do cancer cells grow despite the innate and adaptive immune responses?

If the immune system recognizes the lung tumor cells and can destroy them, why are lung tumors able to grow?

- Research has shown that tumors enable their own growth by turning off the immune response
- An immune response beyond what is normal or necessary can be toxic, so T cells have many normal methods to dampen themselves down and essentially turn themselves off. This may allow the growth and development of tumor cells despite the presence of T cells with the potential to kill cancer cells

Researchers are working hard to understand exactly how this happens and how to best turn the immune T cells back on.

02 immunotherapy

Immunotherapy is a type of **biological therapy.** It aims to enhance the body's immune response and stop lung cancers from escaping from the immune system. Biological therapies use substances made from living organisms to treat disease.

What is immunotherapy?

Immunotherapy is a treatment that strengthens the natural ability of the patient's immune system to fight cancer. Instead of targeting the person's cancer cells directly, immunotherapy trains a person's natural immune system to recognize cancer cells and selectively target and kill them.

Immunotherapies do this in one of two ways:

- By enabling the immune system to mount or maintain a response
- By suppressing factors that prevent the immune response

There are many different types of immunotherapy. Three main types are currently being studied in people with **non-small cell lung cancer (NSCLC)**:

- **Immune checkpoint inhibitors**
- **Therapeutic cancer vaccines**
- **Adoptive T cell transfer**

Immune checkpoint inhibitors have made the most progress at this time, and the first FDA-approved immunotherapy drugs for lung cancer belong to this group. Immunotherapy is also being studied in **small cell lung cancer (SCLC)**.

Immune checkpoint inhibitors

Many lung cancers co-exist with T cells capable of killing the cancer cells. However, the immune system has many normal mechanisms for dampening itself down. The immune system has fail-safe mechanisms that are designed to suppress the immune response at appropriate times to minimize damage to healthy tissue. These mechanisms are called immune checkpoint pathways. They are essentially the brakes on the system that can prevent T cells from killing lung cancer cells.

The challenge is that cancers are able to use these immune checkpoint pathways to lessen the immune response at the wrong times. This may allow cancer cells to thrive.

How do immune checkpoint inhibitors work?

Immune checkpoint inhibitors work by targeting and blocking the fail-safe mechanisms of the immune system. Their goal is to block the immune system from limiting itself, so the original anti-cancer response works better.

What immune checkpoint inhibitors are currently available?

There are currently three immune checkpoint inhibitors available outside clinical trials for use in people with lung cancer:

- Nivolumab (Opdivo®): Approved for the treatment of patients with **metastatic** non-small cell lung cancer with **disease progression** on or after platinum-based **chemotherapy**

Note: Platinum-based chemotherapies include carboplatin and cisplatin.

- Pembrolizumab (Keytruda®): Approved for patients with metastatic NSCLC in the following situations:
  - As first-line treatment for patients whose tumors have high PD-L1 expression (Tumor Proportion Score [TPS] greater than or equal to 50%) with no EGFR or ALK mutation and no prior systemic chemotherapy treatment for metastatic NSCLC. Approximately 30% of patients with newly diagnosed metastatic NSCLC will have tumors with this high level of PD-L1 expression
  - For patients whose tumor expresses PD-L1 (TPS greater than or equal to 1%) with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK mutations should have disease progression on FDA-approved therapy for these mutations before receiving pembrolizumab

Note: The Tumor Proportion Score (TPS) is 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.

- Atezolizumab (Tecentriq®): Approved for patients with metastatic NSCLC in the following situations:
  - For patients whose lung cancer has progressed during or after being treated with platinum-containing chemotherapy
  - For patients with ALK-positive or EGFR-positive NSCLC, their lung cancer should have progressed on an approved ALK or EGFR inhibitor before they are treated with Tecentriq

In addition, these and other immune checkpoint inhibitors are being studied for use in lung cancer as **monotherapy** or in combination with other treatments. They are being studied in **phase 1**, **phase 2**, and **phase 3 research studies**, and in people with all different **stages** of the disease. The results in lung cancer with antibodies that block the **Programmed Death 1 (PD-1)** or **Programmed Death Ligand 1 (PD-L1)** pathway are so promising that many pharmaceutical companies are working to develop drugs focused on PD-1 or PD-L1. They are also making major investments in developing other types of immunotherapy to be used in combination with drugs focused on PD-1. Numerous other immune checkpoint inhibitor drugs are being developed.

IMMUNE CHECKPOINT INHIBITORS BEING DEVELOPED

Generic Name	Brand Name (in US)	Types of lung cancer being studied
Ipilimumab	Yervoy	NSCLC, SCLC
Durvalumab (MEDI4736)	To be determined	NSCLC
Avelumab (MSB0010718C)	To be determined	NSCLC
PDR001	To be determined	NSCLC
REGN2810	To be determined	NSCLC
Tremelimumab	To be determined	NSCLC

How are immune checkpoint inhibitors administered?

Infusion time and schedules may vary depending on the drug.

Immune checkpoint inhibitors are given **intravenously** over 30 to 90 minutes. They are given every 2 to 4 weeks until disease progression.

How well do anti-PD-1/anti-PD-L1 drugs work?

In research studies of non-small cell lung cancer patients that have been published to date, approximately 15%–20% have responded to immune checkpoint inhibitors. This includes patients who tested negative for PD-1 and PD-L1, as well as those who tested positive. In **clinical trials**, people who tested negative, as well as those who tested positive, have responded to immune checkpoint inhibitors. The response may continue after treatment is stopped. Some of the responses to date have been long-term. There are many reasons to think that the results will improve as researchers learn how best to use these drugs.

Researchers are looking for ways to increase the number of people who respond to this treatment. In clinical trials, they are combining treatments, boosting the immune system, and using other strategies.

Note: Patients whose tumors have high levels of PD-L1 expression are more likely to respond to PD-1/PD-L1 therapies. However, even those with tumors that do not express PD-L1 may respond to these treatments.

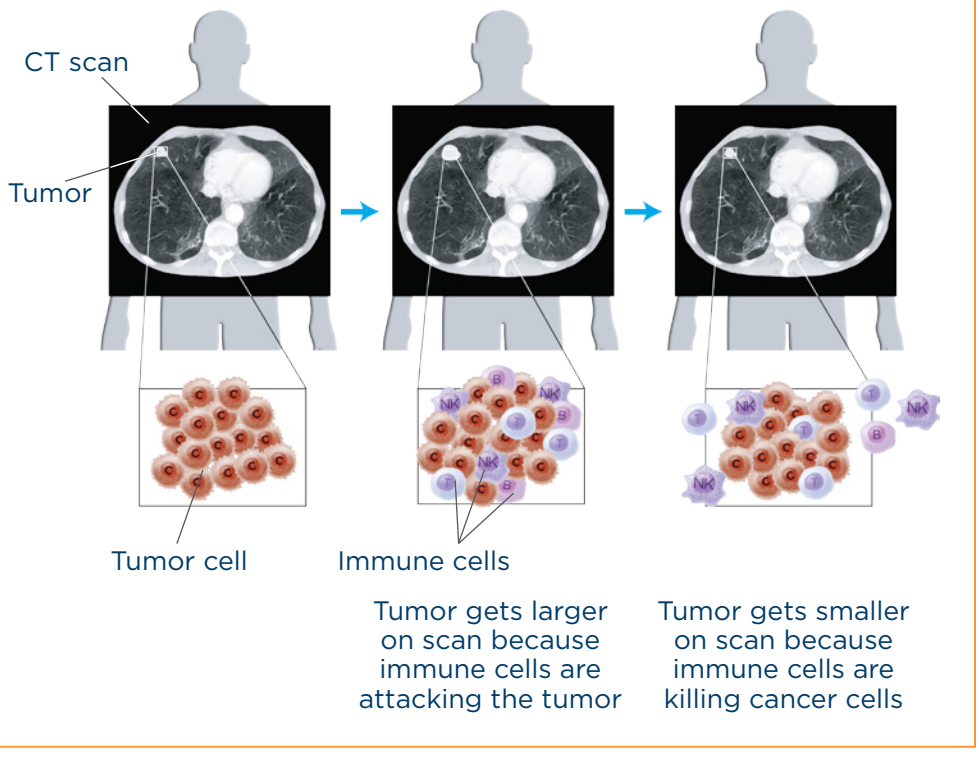
How long does it take to see results from therapy with immune checkpoint inhibitors?

Of the patients in clinical trials with immune checkpoint inhibitors who have responded, about half have seen their tumors respond in 6 to 8 weeks. However, another half of the patients may take a much longer time to produce a response, possibly as long as 6 months.

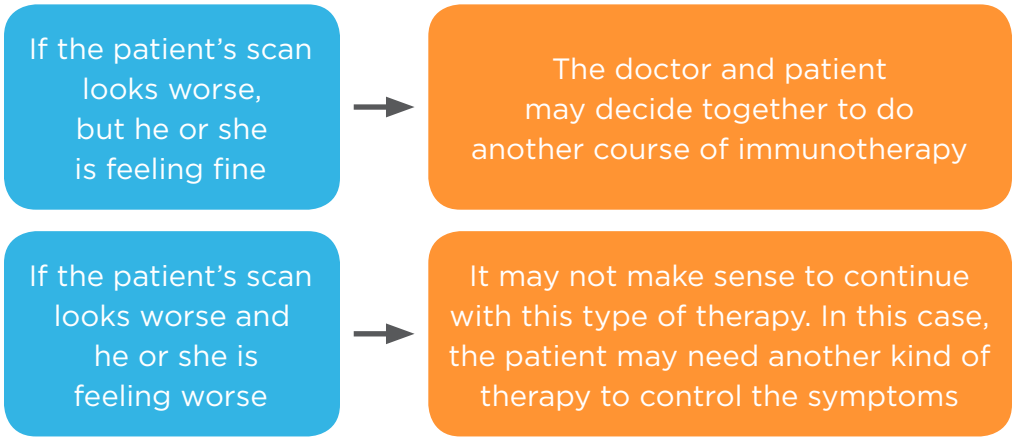
In the nivolumab clinical trials that led to the first FDA approval of a checkpoint inhibitor, the median time to onset of response was 3.3 months.

In a small subset of patients, the tumor on a **CT scan** may seem to get worse at first and then get better, or there may be new areas of tumor. Doctors have coined the term **pseudoprogression** to describe this situation. One theory of why this happens is that, as the lymphocytes come in to attack a tumor, the tumor gets larger, and then, as they kill cancer cells, the tumor gets smaller again. The current scientific thinking is that the tumors get larger because a large number of the patient's T cells move into the tumor to clean it up. Therefore, some tumors that look larger on scans are larger because the immune system is attacking the cancer, not because the cancer cells are growing.

PSEUDOPROGRESSION



In cases like this, the best course of action will likely be based on a number of factors:



What side effects have been reported in clinical studies of immune checkpoint inhibitors?

The most common side effects reported from immune checkpoint inhibitors as a group include:

- Diarrhea
- Fatigue
- Rash
- Pruritus, or itching of the skin

Treatment with immune checkpoint inhibitors may also cause an **infusion site reaction**, as is also the case with chemotherapy. In addition, a side effect seen with certain immune checkpoint inhibitors in lung cancer is **pneumonitis**, which is inflammation of the lung tissue that may lead to difficulty breathing if not treated early and correctly.

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, 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.

Note: It's important to let your doctor(s) know if you are experiencing any problems while on treatment, so they can sort out if the side effects are related to the treatment. It is especially important to be very clear with your doctor about the side effects that you are experiencing, because this may impact future treatment plans.

Some patients experience side effects that are severe enough that they need to stop taking the immunotherapy treatment. In general, based on what has been seen with patients in clinical research studies to date, these kinds of treatments are well tolerated by most patients.

Because these drugs have only been studied in patients for a few years, we do not know for certain what the long-term side effects are in patients with profound responses, including remission of cancer.

However, doctors have some ideas about what they may be:

- One potential long-term side effect of immunotherapy may be that, if it affects the endocrine gland, a patient may need thyroid hormone supplementation for the rest of his or her life
- Some patients develop diabetes and need to be on medication

Note: It's important to tell your doctor(s) if you were ever treated with immunotherapy, even a long time ago, because side effects can show up after long periods of time.

RESOURCES FOR MANAGING TREATMENT SIDE EFFECTS:

– LUNGevity Survivor Resource Center
www.LUNGevity.org

Where do immune checkpoint inhibitors fit into the treatment plan for lung cancer?

The three FDA-approved drugs in this class, nivolumab (Opdivo®), pembrolizumab (Keytruda®), and atezolizumab (Tecentriq®), are currently approved for treating patients with metastatic non-small cell lung cancer who have been or are being treated with platinum-based chemotherapy. Pembrolizumab is also approved as first-line treatment for patients whose tumors have high expression of PD-L1.

In addition, these and other immune checkpoint inhibitors are being studied in patients with **stage IB**, **stage II**, **stage III**, **stage IV**, or **recurrent** non-small cell lung cancer in clinical trials. The inhibitors are being studied in the non-small cell lung cancer types

adenocarcinoma and squamous cell lung cancer. There are also clinical trials looking at these agents for small cell lung cancer.

To be eligible for immunotherapy in some clinical research studies, patients must have been previously treated with surgery, **radiation therapy**, and/or chemotherapy. Several studies using immune checkpoint inhibitors as **first-line treatment** in certain patients with non-small cell lung cancer are also planned or underway.

Immune checkpoint inhibitors are being used alone and in combination with other therapies, including:

- Chemotherapy
- **Targeted therapy**
- Radiation therapy
- Other checkpoint antibodies
- Other immunotherapies

The first thing you need to do is ask your **oncologist** what clinical research studies are available locally and what research studies he or she recommends for you. If your doctor doesn't have a clinical trial available, he or she may be able to help you find another place that is enrolling patients in a trial.

A patient may have to travel to get to a clinical trial if the immunotherapy is being given by someone other than their primary oncologist.

Can immune checkpoint inhibitors be used in someone with a pre-existing autoimmune disorder?

Autoimmune disorders are diseases in which the immune system is very active, but is attacking the patient's normal cells. Prior to commencing immunotherapy, it is important to inform your oncologist if you think you may have an autoimmune disorder. Patients with an existing autoimmune disorder, such as **systemic lupus erythematosus (SLE)**, rheumatoid arthritis, ulcerative colitis, or Crohn's disease, usually have not been included in the clinical trials due to worries about causing serious side effects. However, it is possible that anti-PD-1 inhibitors will eventually be tested in those patients, as well.

Can I be treated with immune checkpoint inhibitors if I'm immunocompromised?

Whether immunotherapy is right for patients who think they may be **immunocompromised** may depend on several things. Every research study investigating immune checkpoint inhibitors has unique requirements for who can participate; however, some possible requirements include the following:

- A certain level of white blood cell count
- A certain level of lymphocyte count. This treatment is trying to make a person's lymphocytes more active. Therefore, an extremely low lymphocyte count may mean the immune checkpoint inhibitor would not work, but scientists are still learning about that

What are other considerations related to eligibility requirements for treatment with immune checkpoint inhibitors?

Patients who already take daily steroids, like prednisone or dexamethasone, are usually not eligible to participate in immune checkpoint inhibitor clinical research studies. People may be on that type of medication to keep another disease under control, like emphysema or chronic obstructive pulmonary disease (COPD), or to try to control swelling from brain metastasis. However, some studies do allow steroid use if it is taken at a very low and stable dose.

Depending on the specific clinical trial, being on this kind of immunotherapy may prevent you from participating in additional immunotherapy trials. If you are doing well afterwards, you should be able to participate in other clinical trials. Talk to your doctor(s) about this before beginning any new clinical research study.

Therapeutic cancer vaccines

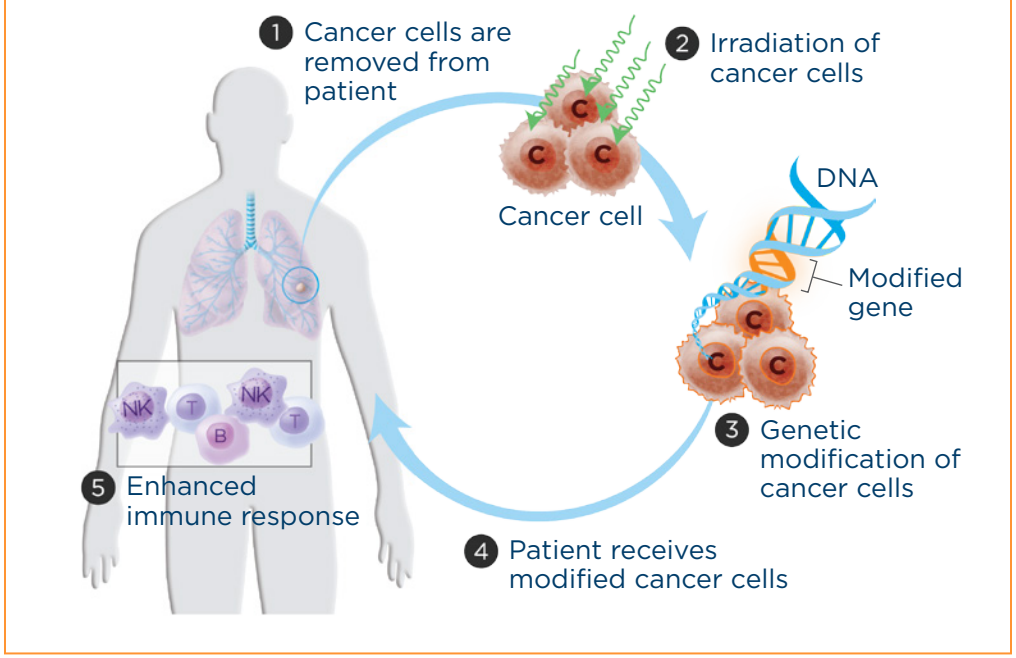
When most people think of a vaccine, they think of a traditional vaccine given to prevent an infectious disease, such as measles or polio. In addition to traditional vaccines, there are two types of cancer vaccines:

- A preventive cancer vaccine is given to prevent cancer from developing in healthy people. For example, the hepatitis B vaccine is given to children to protect against a hepatitis B viral infection, which can lead to liver cancer
- A therapeutic cancer vaccine is given to treat an existing cancer by causing a stronger and faster response from the immune system. Most commonly, this type of vaccine is used in patients in remission in an attempt to prevent likely **relapse**, or the cancer from returning

How do therapeutic cancer vaccines work?

A therapeutic cancer vaccine is made from a patient's own tumor cells or from substances taken from the tumor cells. They are designed to work by activating the cells of the immune system to recognize and act against the specific antigen on the tumor cell. Because the immune system has special cells for memory, the hope is that the vaccines will also help keep the lung cancer from coming back.

THERAPEUTIC CANCER VACCINE



A number of different therapeutic vaccines are being studied in lung cancer.

THERAPEUTIC CANCER VACCINES BEING DEVELOPED FOR LUNG CANCER

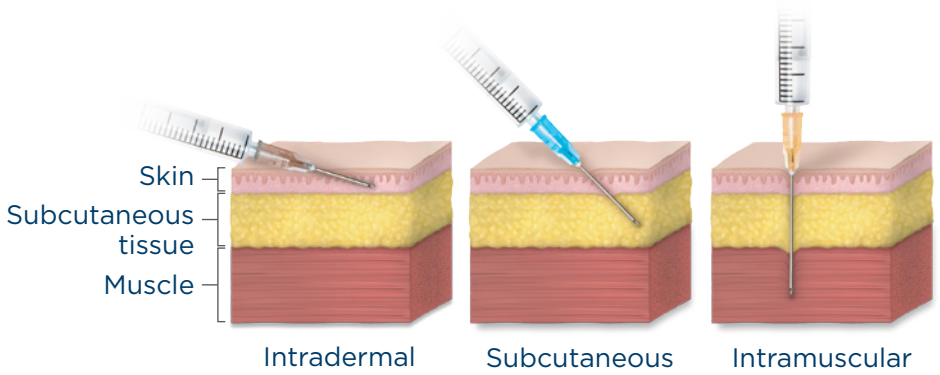
Generic Name	Brand Name (in US)	Types of lung cancer being studied
GV1001	To be determined	NSCLC
Tergenpumatucel-L	HyperAcute	NSCLC
TG4010	To be determined	NSCLC
Dribbles (DPV-001)	To be determined	NSCLC
CV9202	RNActive	NSCLC
INGN	To be determined	SCLC

How is a therapeutic cancer vaccine administered?

Therapeutic cancer vaccines are given as an injection either:

- Right below the skin's top layer (**intradermally**)
- Beneath the skin (**subcutaneously**)
- Into the muscle (**intramuscularly**)

TYPES OF INJECTIONS



Early on in the study, the vaccines are given from 1 to 3 times a week. The doses are then spread out to every other week, and eventually, to every other month. The studies range from 1 year to 3 years.

Results of therapeutic cancer vaccine administration

Several studies have suggested that therapeutic cancer vaccines may be most effective when given in combination with other forms of cancer therapy. In addition, they may even increase the effectiveness of the other treatments. There is also evidence that when patients have a large amount of disease, the immune system may become overwhelmed. Therefore, surgical removal of the tumor before administration of a cancer vaccine may make it easier for the immune system to develop an effective response.

A major question going forward is whether vaccines will make anti-PD-1 immune checkpoint inhibitors more effective.

Where do therapeutic cancer vaccines fit in a lung cancer treatment plan?

Presently, therapeutic cancer vaccines are being studied for both small cell and non-small cell lung cancer. They are being investigated as first-line therapy, **second-line therapy**, and **maintenance therapy**. They are being tested alone and in combination with chemotherapy and radiation therapy.

What side effects of therapeutic cancer vaccines have been seen in clinical studies?

The most common side effect of therapeutic cancer vaccines is inflammation at the site of the injection, including:

- Redness
- Pain
- Swelling
- Warming of the skin
- Itchiness
- Rash (occasional)

Flu-like symptoms have also been reported after administration of a therapeutic cancer vaccine, including:

- Fever
- Chills
- Weakness
- Dizziness
- Nausea or vomiting
- Muscle ache
- Fatigue
- Headache
- Occasional breathing difficulties

More serious health problems have been reported in a smaller number of people after receiving a therapeutic cancer vaccine, but these may not have been caused by the vaccine. These include:

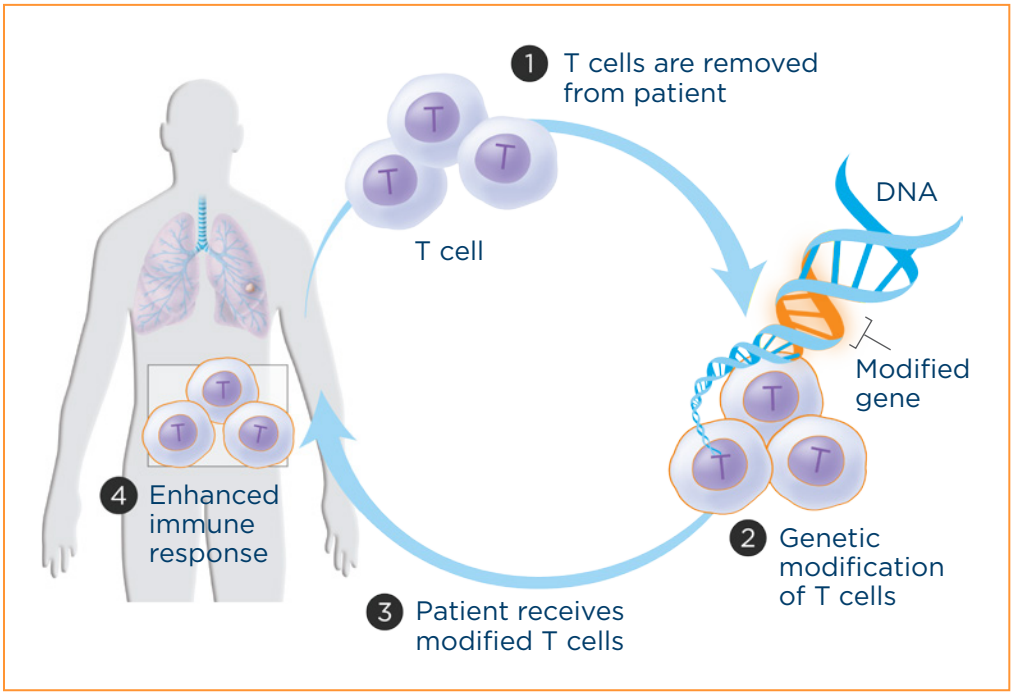
- Asthma
- Appendicitis
- **Pelvic inflammatory disease**
- Certain autoimmune disorders, including arthritis and systemic lupus erythematosus (SLE)

Rarely, severe allergic reactions to specific vaccine ingredients have been seen following vaccination.

Adoptive T cell transfer

Adoptive T cell transfer is being developed as a new approach to cancer treatment. The goal is to improve the ability of a person's own T cells to fight cancer. A sample of T cells is removed from the patient and then genetically changed in order to make the T cells more active against specific cancer cells. Scientists can change what is on the surface of the T cells. For example, they can add a receptor to the surface of the T cell that will target a specific antigen on a cancer cell. The receptors work like very specific Velcro that allows T cells to stick to cancer cells and kill the cells. The T cells are then returned to the patient, and the altered T cells quickly home in on their targets.

ADOPTIVE T CELL TRANSFER



How does adoptive T cell transfer work?

Typically, during an immune response, T cells multiply. After the initial response, most of the newly made T cells are eliminated. This keeps the total T cell number in the body at a normal level. The normal level of T cells is usually not high enough to sustain a response strong enough to effectively fight cancer.

However, there is evidence that T cells have the ability to multiply in abundance when given to someone whose immune system has been weakened. Therefore, in an adoptive T cell transfer, patients are given chemotherapy prior to the adoptive T cell transfer in order to suppress their immune system. Once the chemotherapy is completed and the immune system is weakened, billions of modified T cells are then reintroduced into the patient.

The goal of the T cell transfer is to enable the immune system to attack the tumors in a large number that is otherwise impossible and in a way that it is incapable of doing on its own.

How is adoptive T cell transfer administered?

How are T cells removed from a patient?

The three ways of performing adoptive T cell transfer include:

- Collecting a sample from the tumor and multiplying the T cells in a laboratory
- Taking T cells from the bloodstream, through a procedure called **leukapheresis**, and genetically altering them to attack cancer cells that have specific antigens
- Taking T cells from the bloodstream and putting special receptors, called chimeric antigen receptors (CARs), on them. CARs recognize specific proteins found on the surface of cancer cells. The CAR T cells then bind to the cancer cells that have those proteins and destroy them

How are T cells returned to the patient?

After the T cells are removed from a patient by any of these ways, the T cells are returned to the patient through an infusion.

Results of clinical trials involving adoptive T cell transfer

Small clinical trials using adoptive T cell transfer have generated some remarkable responses in patients with blood cancers, such as acute lymphocytic leukemia and lymphoma. Most patients' cancers disappeared entirely, and several of these patients have remained cancer-free for extended periods. Whether T cell therapy will eventually prove to be as effective in lung cancer is unknown, but some patients are likely to benefit.

Where does adoptive T cell transfer fit into the treatment plan for non-small cell lung cancer?

Adoptive T cell transfer can only be considered in patients whose tumor expresses one of the antigens being studied. Currently, this treatment is being studied by itself, in combination with chemotherapy, and with concurrent administration of interleukin-2. These studies are being conducted with patients whose tumors have not responded to prior therapies and for whom no alternative treatments are available.

What side effects have been seen in clinical studies involving adoptive T cell transfer?

The most common side effects of adoptive T cell transfer include:

- Pain, swelling, soreness, redness, itchiness, and rash at the site of infusion
- Flu-like symptoms, for example:
  - Fever
  - Chills
  - Weakness
  - Dizziness
  - Nausea or vomiting
  - Muscle or joint aches
  - Fatigue
  - Headache
  - Occasional breathing difficulties
  - Change in blood pressure

In addition to the more common side effects, lowered blood counts can also occur. This leads to a risk of severe or even fatal allergic reaction to T cell transfer.

A very serious side effect of adoptive T cell transfer is cytokine-release syndrome, a rapid and large-scale release of **cytokines** into the bloodstream. Cytokines are chemical messengers that help the T cells carry out their duties. Too many cytokines can lead to dangerously high fevers and quick drops in blood pressure.

For most patients on clinical trials, side effects have been mild enough to be managed with standard supportive treatments, including steroids. Patients with more severe reactions have been successfully treated with anti-inflammatory drugs, such as etanercept (Enbrel®) and tocilizumab (Actemra®).

QUESTIONS TO ASK YOUR HEALTHCARE TEAM ABOUT IMMUNOTHERAPY AS A TREATMENT OPTION:

- Why do you recommend immunotherapy for me?
- Will immunotherapy be my only treatment or will it be combined with another treatment?
- Where do I go to get my immunotherapy?
- How will it be administered?
- How often will I get my treatment? How long will it last?
- How often do I need to be seen in-between treatments for a physical exam and/or lab work?
- What side effects can I expect?
- How will this treatment affect my daily life? Will I be able to work, exercise, and perform my usual activities?
- Are there any tests or procedures I will need to undergo during the treatment?
- When will you know whether or not the immunotherapy worked?
- What tests will I need after treatment is completed?
- Are there any long-term health issues I should expect from treatment with immunotherapy?
- How much will my treatment cost?

What clinical trial options are available?

Many clinical trials are ongoing to study these different types of immunotherapy and answer key questions, including:

- Whether one of the immunotherapies works better alone or in combination with other treatments
- Whether immunotherapies should be given before or after another treatment
- When in the treatment of NSCLC immunotherapies should be used

There are many phase 1, phase 2, and phase 3 research studies currently underway that will add to our understanding of immunotherapies.

If you are considering whether to participate in a clinical trial, start by asking your doctor whether there is one for which you might qualify in your area. There are several other questions that you should consider asking your doctor about participating in a clinical trial.

QUESTIONS TO ASK YOUR HEALTHCARE TEAM IF YOU ARE CONSIDERING PARTICIPATING IN AN IMMUNOTHERAPY CLINICAL TRIAL:

About your treatment history:

- What type(s) of treatment(s) for lung cancer have I had so far?
- What line of therapy am I looking for?
  - If you have never been treated before, you are looking for a **first-line clinical trial**
  - If you have had a prior chemotherapy for metastatic disease, you may be looking for a **second-line clinical trial**
  - If you have had multiple lines of therapy, you want a clinical trial that allows for several previous treatments

About immunotherapy clinical trials:

- What are the benefits and risks of participating in an immunotherapy clinical trial?
- How will I be monitored while participating in a clinical trial?
- What are my responsibilities during the clinical trial?
- Are there any costs associated with my participation in a clinical trial?
- Where can I learn more about clinical trials?
- Who can I talk to if I have questions during the clinical trial?
- What happens if I decide I do not want to participate in the clinical trial at some point?

In addition, there are several resources that may help you find a clinical trial that may be a good match for you.

RESOURCES TO HELP YOU NAVIGATE YOUR CLINICAL TRIALS SEARCH:

- **LUNGevity Clinical Trial Finder:** https://clinicaltrials.lungevity.org/index.html
  - The LUNGevity Clinical Trial Finder helps you connect with lung cancer trials
  - The screening process locates nearby clinical trials as well as provides information and links to centers performing these studies
- **EmergingMed:** www.emergingmed.com/networks/LUNGevity
  - LUNGevity partners with this **free** clinical trials matching service to help you with the decision of whether to participate in a clinical trial
  - EmergingMed helps you identify lung cancer clinical trials for which you may be eligible
  - Clinical trial navigators are available Monday through Friday from 8:30am to 6:30pm ET at 800-698-0931
- **U.S. National Institutes of Health:** www.clinicaltrials.gov
- **National Cancer Institute (NCI):** www.cancer.gov/clinicaltrials/search
- **Coalition of Cancer Cooperative Groups:** www.cancertrialshelp.org/cancer-trial-search

03 glossary

Adaptive immune response—Specific response of the immune system; creates T cells to respond to a specific antigen on a cancer cell

Adenocarcinoma—A type of non-small cell lung cancer that usually develops in the cells lining the lungs. It is the most common type of lung cancer seen in non-smokers

Adenoids—A mass of lymphatic tissue located where the nose blends into the throat

Adoptive T cell therapy or transfer—Therapy that involves removing some of a patient's own immune system cells—often altering and increasing their ability to recognize and kill cancer cells—growing billions of them in the laboratory, and infusing the cultured cells into the patient. The idea is to provide an invading force of immune cells that can attack tumors at a level that the immune system is not capable of doing on its own

Antibody—A protein made by B cells in response to an antigen. Each antibody can bind to only one specific antigen. The purpose of this binding is to help destroy the antigen. Some antibodies destroy antigens directly. Others make it easier for white blood cells to destroy the antigen

Antigen—A protein on the surface of a cell that causes the body to make a specific immune response

Arthritis—A disease that causes inflammation and pain in the joints

Autoimmune disorder—A condition in which the body recognizes its own tissues as foreign and directs an immune response against them

Bacteria—A large group of single-cell microorganisms. Some cause infections and disease in animals and humans

B cell—A type of white blood cell that circulates in the blood and lymph, seeking out foreign invaders. Upon meeting a "non-self" antigen, it makes proteins called antibodies, which detect and destroy the antigens. Also called B lymphocyte

Biological therapy—A type of treatment that uses substances made from living organisms to treat disease. These substances may occur naturally in the body or may be made in the laboratory. Some biological therapies stimulate or suppress the immune system to help the body fight cancer, infection, and other diseases. Other biological therapies attack specific cancer cells, which may help keep them from growing or kill them

Bone marrow—The soft, sponge-like tissue in the center of most bones. It produces white blood cells, red blood cells, and platelets

Cervical lymph nodes—Lymph nodes found in the neck

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

Colitis—An illness that causes pain and swelling in the colon

CT scan—A procedure that uses a computer linked to an X-ray machine to make a series of detailed pictures of areas inside the body. The pictures are taken from different angles and are used to create 3-dimensional (3-D) 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

Cytokine—A type of protein that is made by certain immune and non-immune cells and has an effect on the immune system. Some cytokines stimulate the immune system, while others slow it down

Disease progression—Cancer that continues to grow or spread

Dyspnea—Difficult, painful breathing or shortness of breath

Endocrine gland—A gland (for example, the thyroid or the pituitary) that produces an endocrine secretion

First-line clinical trial—A clinical trial for a patient who has never been treated before

First-line treatment or therapy—The first treatment given for a disease. It is often part of a standard set of treatments, such as surgery followed by chemotherapy and radiation. When used by itself, first-line therapy is the one accepted as the best treatment. If it doesn't cure the disease, or it causes severe side effects, other treatments may be added or used instead

Foreign—In medicine, this term describes something that comes from outside the body. A foreign substance in the body's tissues, such as a bacterium or virus, may be recognized by the immune system as not belonging to the body. This causes an immune response. Other foreign substances in the body, such as artificial joints, are designed to not cause an immune response

Hepatitis—Disease of the liver causing inflammation

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

Immune response—The activity of the immune system against foreign substances (antigens)

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

Immunocompromised—Having a weakened immune system caused by certain diseases or treatments

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

Infusion—A method of putting fluids, including drugs, into the bloodstream. Also called intravenous infusion

Infusion site reaction—Skin reaction at the place where an intravenous catheter enters the skin; symptoms may include redness, itching, and pain

Innate immune response—Immune response to a pathogen that involves the pre-existing defenses of the body; such a response is not specific to a pathogen

Intradermal—Within the skin. Also called intracutaneous

Intramuscular (IM)—Within a muscle

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

Irradiate—To treat with radiation

Leukapheresis—Removal of the blood to collect specific blood cells. The remaining blood is returned to the body

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

Lymphatic vessels—Thin-walled tubular structures that collect and filter lymph fluid before transporting it back to the blood circulation. Also called lymph vessels

Lymphocyte—A type of white blood cell that is made in the bone marrow and is found in the blood and in lymph tissue. The main types of lymphocytes are B cells, T cells, and NK cells

Maintenance therapy—Treatment that is given to help keep cancer from growing after it has shrunk or stabilized following 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 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

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

Monotherapy—The use of a single drug to treat a particular disorder or disease

Natural killer (NK) cell—A type of white blood cell that patrols the body and is on constant alert, seeking foreign invaders. Once NK cells recognize a cell as abnormal, they release granules (small particles) with enzymes that can kill tumor cells or cells infected with a virus

Nephritis—Acute or chronic inflammation of the kidney caused by infection, degenerative processes, or vascular disease

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 non-small cell lung cancer are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma. Non-small cell lung cancer is the most common kind of lung cancer

Oncologist—A doctor who specializes in treating cancer. Some oncologists specialize in a particular type of cancer or cancer treatment. For example, a thoracic oncologist specializes in treating lung, esophageal, pleural, mediastinal, and chest wall tumors. A medical oncologist specializes in treating cancer with chemotherapy. A radiation oncologist specializes in treating cancer with radiation

Pelvic inflammatory disease—A condition in which the female reproductive organs are inflamed. It may affect the uterus, Fallopian tubes, ovaries, and certain ligaments. Pelvic inflammatory disease is usually caused by a bacterial infection. It may cause infertility and an increased risk of an ectopic pregnancy (pregnancy in the Fallopian tubes). Also called PID

Phase 1 research study—Researchers test a new drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects

Phase 2 research study—The drug or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety

Phase 3 research study—The drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely. Once phase 3 is completed, the drug or treatment can be submitted to the U.S. Food and Drug Administration (FDA) for approval

Pneumonitis—Inflammation of the lungs that may be caused by disease, infection, radiation therapy or other therapies, allergy, or irritation of lung tissue by inhaled substance

Programmed Death 1/Programmed Death Ligand 1 (PD-1/PD-L1)—Part of the immune system mechanism that keeps T cells from functioning

Protein—A molecule, made up of amino acids, that is needed for the body to function properly. Proteins are the basis of body structures, such as skin and hair, and of other substances, such as enzymes, cytokines, and antibodies

Pruritus—Itching of the skin

Pseudoprogression—Growth in tumor size that is due to response to treatment and not to growth of cancer cells

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). Also called irradiation and radiotherapy

Renal dysfunction—Reduced ability of the kidneys to filter blood and remove waste products and excess fluid from the body

Recurrent lung cancer—Lung cancer that has come back after a period of time during which the cancer could not be detected. The lung cancer may come back in the lung near the original tumor, in lymph nodes, or in a distant organ

Relapse—The return of a disease or the signs and symptoms of a disease after a period of improvement

Second-line clinical trial—Clinical trial for patients who have had a prior chemotherapy for metastatic disease

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

Small cell lung cancer (SCLC)—A fast-growing cancer that forms in tissues of the lung and can spread to other parts of the body. Named "small" for how the cancer cells look under a microscope

Spleen—An organ that is part of the lymphatic system. The spleen makes lymphocytes, filters the blood, stores blood cells, and destroys old blood cells. It is located on the left side of the abdomen near the stomach

Stage—The extent of a cancer in the body

Stage 0 lung cancer in situ—Abnormal cells found in the lining of the airways. These abnormal cells may become cancer and spread into nearby normal tissue

Stage I lung cancer—The lung tumor has grown through the innermost lining of the lung into deeper lung tissue. The tumor is no more than 5 centimeters across. Cancer cells have not spread to nearby tissues or lymph nodes

Stage II lung cancer—The lung tumor is smaller than 7 centimeters across, and cancer cells have spread to lymph nodes on the same side as the tumor. Or, the lung tumor is more than 5 centimeters across and the cancer did not spread to the lymph nodes, but it did invade nearby tissues, such as the chest wall, diaphragm, pleura, main bronchus, or tissue that surrounds the heart. More than one tumor may be found within the same lobe of the lung

Stage III lung cancer—The lung tumor can be any size and more than one tumor may be within the same lung. Cancer cells may have spread to lymph nodes on either side of the chest or the neck. The tumor may have invaded nearby organs, such as the heart, esophagus, or trachea

Stage IV lung cancer—Lung tumors are found in both lungs. Or, the lung cancer has spread to other parts of the body, such as the brain, bones, liver, or adrenal glands

Subcutaneous—Beneath the skin

Systemic lupus erythematosus (SLE)—A chronic, inflammatory connective tissue disease that can affect the joints and many organs, including the skin, heart, lungs, kidneys, and nervous system. It can cause many different symptoms; however, not everyone with systemic lupus erythematosus has all of the symptoms. Also called lupus

Targeted cancer 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

T cell—A type of white blood cell. T cells are part of the immune system and develop from stem cells in the bone marrow. They help protect the body from infection and may help fight cancer. Also called T lymphocyte

Therapeutic cancer vaccine—A type of treatment using a vaccine that is usually made from a patient's own tumor cells or from substances taken from tumor cells. A cancer vaccine may help the immune system kill cancer cells

Thymus—An organ that is part of the lymphatic system, in which T lymphocytes grow and multiply. The thymus is in the chest behind the breastbone

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

Virus—A very simple microorganism that infects cells and may cause disease

White blood cell (WBC)—A type of blood cell that is made in the bone marrow and found in the blood and lymph tissue. White blood cells are part of the body's immune system. They help the body fight infection and other diseases. Types of white blood cells are granulocytes (neutrophils, eosinophils, and basophils), monocytes, and lymphocytes (NK cells, T cells, and B cells)

04 notes

LUNGEVITY

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