Immunotherapy for the Treatment of Lung Cancer

A guide for patients and caregivers

LUNG CANCER RESEARCH FOUNDATION®

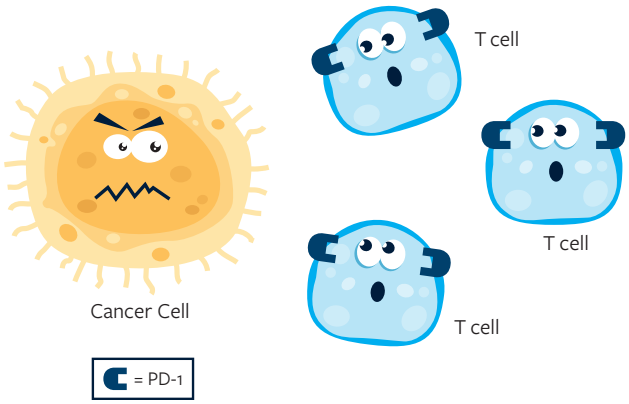


Figure 1: T cells recognize the cancer cell as something that is not supposed to be there.

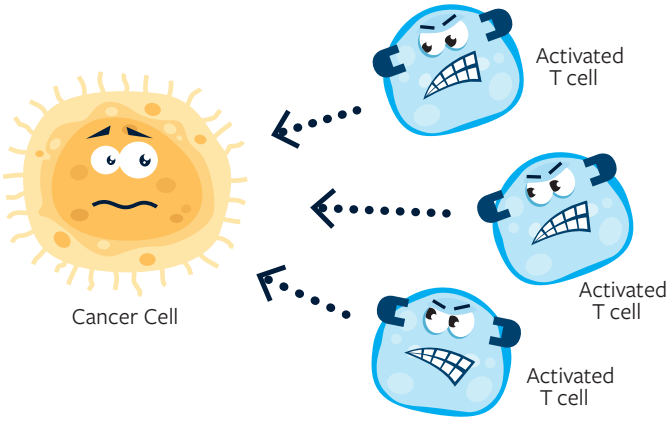


Figure 2: T cells then become activated to help destroy the cancer cell.

Protection central: The immune system

The immune system is the body's main defense against many diseases. It can identify and destroy not only bacteria and viruses, but also cancer cells. The immune system includes cells, tissues, and organs that work together to protect your body.

White blood cells are important components of the immune system which can recognize and attack germs or abnormal cells. There are many different types of white blood cells which fight different infections in different ways. T cells are a type of white blood cells called lymphocytes. When T cells recognize something as abnormal or foreign to the body, they activate other white blood cells in the immune system. It may be helpful to think of T cells as generals on the frontline of battle, the other types of white blood cells as the soldiers, and the abnormal cells and infections as invaders. The T cells identify an invader and call up the well-armed troops of other white blood cells to launch the attack.

But what protects healthy cells from being attacked by the immune system?

There's an important step that needs to occur before the T cells, or generals, can call up their troops, or other types of white blood cells. The T cells need to be activated. Activation takes place when the T cells recognize abnormal proteins that are present on the surface of the intruders, such as cancer cells, but not on normal cells. They wake up (become activated) only in a time of need, which is when there is an infection or development of cancer. If the T cells were active all the time, they would constantly be calling up other white blood cells to attack—regardless of whether it's invaders or normal cells.

This stop signal comes from **checkpoint proteins**, which are usually present on white blood cells, particularly on the T cells. Research is still underway to understand what these checkpoints are and how the body knows when and how to turn them on and off. The most studied checkpoint proteins in lung cancer are PD-1, PD-L1, and CTLA4, although there are many more.

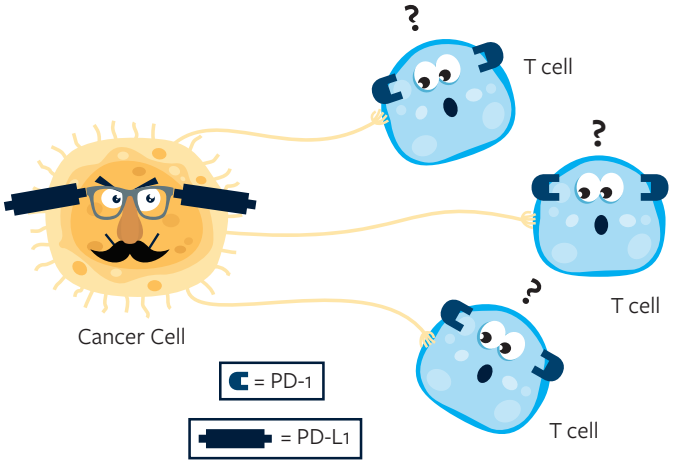


Figure 3: When cancer cells make their own PD-L1, T cells don't "see" the cancer cells.

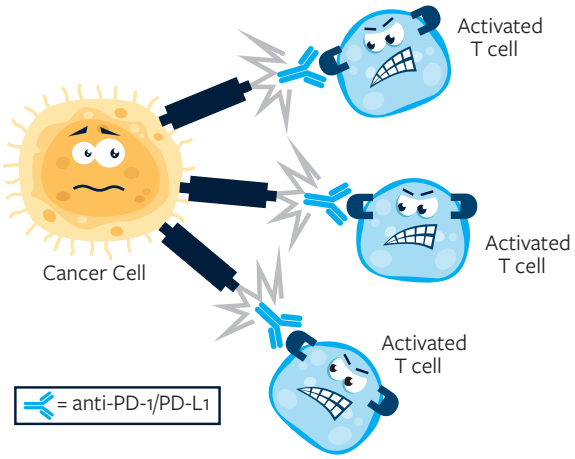


Figure 4: Other immunotherapies bind to PD-1 or PD-L1 and stop PD-L1 from binding to PD-1. The end result is that T cells can recognize and destroy the cancer cell.

These images are provided as an example. PD-L1 is not the only way cancer cells 'trick' the immune cells.

How does cancer escape the immune system?

Checkpoint proteins have the important task of keeping the checks and balances in place for T cell activation. One way cancer cells mislead the immune system is by taking advantage of this delicate balance. They do this by making their own checkpoint proteins, called PD-L1. Checkpoint proteins on T cells, such as PD-1, attach to the PD-L1 on the cancer cells and prevent activation of the T cells. If there are no activated T cells, there are no generals to call up troops, and the invaders (cancer cells) can pass right along their desired path.

Thanks to research, scientists have recently found ways to block the checkpoint proteins PD-1, PD-L1, and CTLA4. These are called **checkpoint inhibitors**. These drugs remove the blocking effect that the checkpoint proteins have on the immune cells. One way to understand this is by imagining the checkpoint proteins as a foot on the brakes, and the checkpoint inhibitors as something that takes the foot off the brakes of the immune system, allowing T cells to recognize the cancer cells, get activated, and call in the troops.

What's the difference between PD-1 and PD-L1 inhibitors?

Since immune checkpoints, PD-1 and PD-L1, work by attaching to each other, PD-1 and PD-L1 inhibitors are very similar in the way they work and in their side effects. The main difference between the two is their **targets**. PD-1 inhibitors target PD-1, which is usually present on T cells, while PD-L1 inhibitors target PD-L1, which is usually present on cancer cells.

Informing the treatment plan

There are some tests that predict how the cancer responds to checkpoint inhibitors. A common test is the PD-L1 expression test, which looks at the percentages of cancer cells that have these proteins (also called protein expression). Since PD-L1 is present on tumor cells, while PD-1 is present on activated T cells, PD-L1 is the biomarker that is usually tested. This test is done on a sample of the cancer, which is typically obtained through a biopsy. If these tests reveal a high amount of a checkpoint protein in the tumor, checkpoint inhibitors are likely to be an effective treatment option. However, this is not a perfect test, because some tumors that don't have PD-L1 expression can still respond to the treatment.

Monoclonal antibodies

Checkpoint inhibitors are a type of monoclonal antibody. Monoclonal antibodies (also called moAbs or mAbs) are proteins that have been designed in laboratories to act like the proteins called antibodies we have in our bodies. Antibodies are made by our immune system to seek out the antigens (foreign materials), attach to them, and destroy them. Checkpoint inhibitors are called monoclonal antibodies because they are made in the lab, they all bind to checkpoint proteins.

An antigen is a substance that causes an immune response against it.

At the time of this publication, a number of immunotherapy agents have been approved to treat lung cancer. By the time you read this, it is possible that many more may have been approved.

Checkpoint Inhibitors

Generic Name	Brand Name
NIVOLUMAB	OPDIVO®
PEMBROLIZUMAB	KEYTRUDA®
ATEZOLIZUMAB	TECENTRIQ®
DURVALUMAB	IMFINZI®
CEMIPLIMAB-RWLC	LIBTAYO®
TREMELIMUMAB	IMJUDO®
IPILIMUMAB	YERVOY®

When you see "mab" at the end of the generic drug name, it stands for monoclonal antibody.

“I do have side effects but the quality of my life the last 10 months exceeded my expectations. I have not missed out on anything I wanted to participate in. Most importantly being there actively for my six grandchildren all five years old and under.”

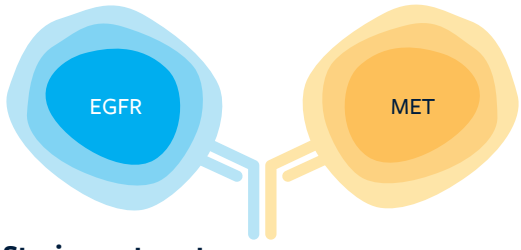
- Lori, Immunotherapy Patient

Not all monoclonal antibodies are checkpoint inhibitors

There are other types of monoclonal antibodies that are not checkpoint inhibitors as they do not block checkpoint proteins. Instead, they work by attaching to other antigens on the surfaces of a cell.

For example, bevacizumab and ramucirumab (Cyramza®) are monoclonal antibodies that bind to proteins called VEGF and VEGFR-2.

Bevacizumab and ramucirumab block the proteins from promoting growth of the new blood vessels that supply oxygen and nutrients to the tumors.



Staying on target:
Unlike monoclonal antibodies, these bispecific antibodies, feature two halves that can bind to two different targets.

Bispecific antibodies

Unlike bevacizumab and ramucirumab mentioned above which bind to only one antigen, **bispecific antibodies (bsAbs)** are designed to bind to two different antigens at the same time. Amivantamab (Rybrevant®) is a drug that binds to two antigens, namely *EGFR* and *MET*, which are two genes often mutated in lung cancer. Amivantamab is currently approved for patients whose tumors have a special kind of *EGFR* mutation called exon 20 insertion mutations.

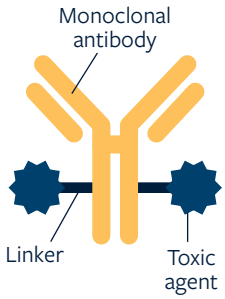
At the time of publication, there is one available treatment using bispecific antibodies for a specific type of lung cancer.

Generic Name	Brand Name
AMIVANTAMAB-VMJW	RYBREVANT®

Antibody–drug conjugates (ADCs)

An ADC consists of an antibody linked to a toxic agent, such as chemotherapy. The antibody binds to a specific "target" (antigen) on a cancer cell, and then the toxic agent gets delivered into the cancer cell and kills it.

One ADC that is approved for lung cancers that have a specific type of mutation called HER 2 exon 20 insertion mutation is trastuzumab deruxtecan (Enhertu®), or T-Dxd for short. The antibody portion of T-Dxd binds to the mutated gene on a cancer called *HER2*. It is linked to a chemotherapy drug called MMAE, which is released only when this ADC binds to its target and gets absorbed into the cell.



Staying on target:
A key feature of the ADC, the linker, is the stable connection between the antibody and the cancer-killing drug. Once the ADC binds to certain proteins on the cancer cell, it is absorbed and can release the medicine it has carried.

A few other ADCs have been granted "breakthrough therapy designation" by the FDA, which allows the pharmaceutical company to speed up the development process.

Many more ADCs are sure to follow. Scientists are actively designing ADCs that bind to different targets, or link to more potent types of chemotherapy, or link better so that the chemotherapy can get into the cancer cell easier.

Other novel therapies, such as chimeric antigen receptor (CAR-T) cell therapy and vaccines are in early-stage investigation in clinical trials.

At the time of publication, there is one ADC approved for the treatment of a specific type of lung cancer.

Generic Name	Brand Name
TRASTUZUMAB DERUXTECAN (T-DXD)	ENHERTU®

CAR-T

Successes in blood cancer research are helping scientists advance treatment for solid tumors. CAR-T therapy is a process where T cells are removed from a patient's blood and re-engineered in a lab to become stronger and fight specific cancer cells before being transfused back into the body. CAR-T treatment for both non-small cell lung cancer and small cell lung cancer are still in clinical trials.

Vaccines

Vaccines are medicines that train the immune system to find and destroy harmful germs and cells. Cancer vaccines give the body the type of information the cells need to identify the cancer-specific antigens—before large quantities of the antigen arrive. It is a way of activating the immune system *now*, should it be needed in the future. Research is currently underway to develop a vaccine for lung cancers.

How do you check if immunotherapy is working?

Your doctor will likely recommend scans to see how your tumor is responding to the immunotherapy.

Immunotherapies work differently from chemotherapy. When a patient is treated with chemotherapy, changes in the size of a tumor can be measured soon after starting treatment, usually within a few weeks, by CT scan. With immunotherapy, the benefits can take much longer to appear. This is because the immune response can take a while to get activated. Sometimes, during immunotherapy, T cells and other immune cells may gather around the tumor, causing it to appear larger before it eventually starts to shrink. This phenomenon is known as pseudoprogression.

Your doctor will work with you to determine how to best monitor your progress while you are on an immunotherapy.

Treatment comparison quick overview

Type of therapy	Chemotherapy	Immunotherapy	Targeted therapy
How it fights cancer	Uses medicine to kill cancer cells directly, but can also destroy healthy cells in the process	Uses the body's own immune system to fight cancer	Is a type of treatment that targets specific mutations that are linked to cancer growth

Healthy cells may be affected by all three processes, but in different ways.

Side effects

Because chemotherapy, immunotherapy, and targeted therapy all work in different ways, they also have completely different side effects. For example, immunotherapy side effects can impact any part of the whole body. Because immunotherapies work by enhancing or turning on the immune system, they can sometimes cause your immune system to become overactive and attack normal tissues or organs. The most common side effects patients experience with immunotherapies are mild and can include fatigue, itching, skin rashes, muscle, joint or bone pain, and nausea. Another common side effect is hypothyroidism, which means the immune system causes your thyroid to not put out as much thyroid hormone. Fortunately, hypothyroidism can be readily treated with thyroid supplements.

In rare cases, the "revved up" immune system can cause serious side effects if it attacks normal organs. This is most commonly seen in the lungs, liver, intestines, kidney, or hormone glands. When this happens, conditions can occur, such as pneumonitis, a lung problem with symptoms of cough, chest pain, shortness of breath, or colitis, an intestinal problem that can result in diarrhea or tears or holes in the intestine. These side effects need urgent attention.

Fortunately, however, serious side effects are rare. Be sure you talk to your doctor about any concerns or side effects you experience during your treatment.

Lungs

Possible side effects:

Inflammation of the lungs (pneumonitis)

What you may experience:

- Shortness of breath
- Cough
- Chest pain

Kidney

Possible side effects:

Inflammation of the kidney (nephritis)

What you may experience:

- Change in the amount or color of your urine

Infusion reactions

Possible side effects:

Side effects related to IV administration

What you may experience:

- Chills
- Fever
- Rash or itching

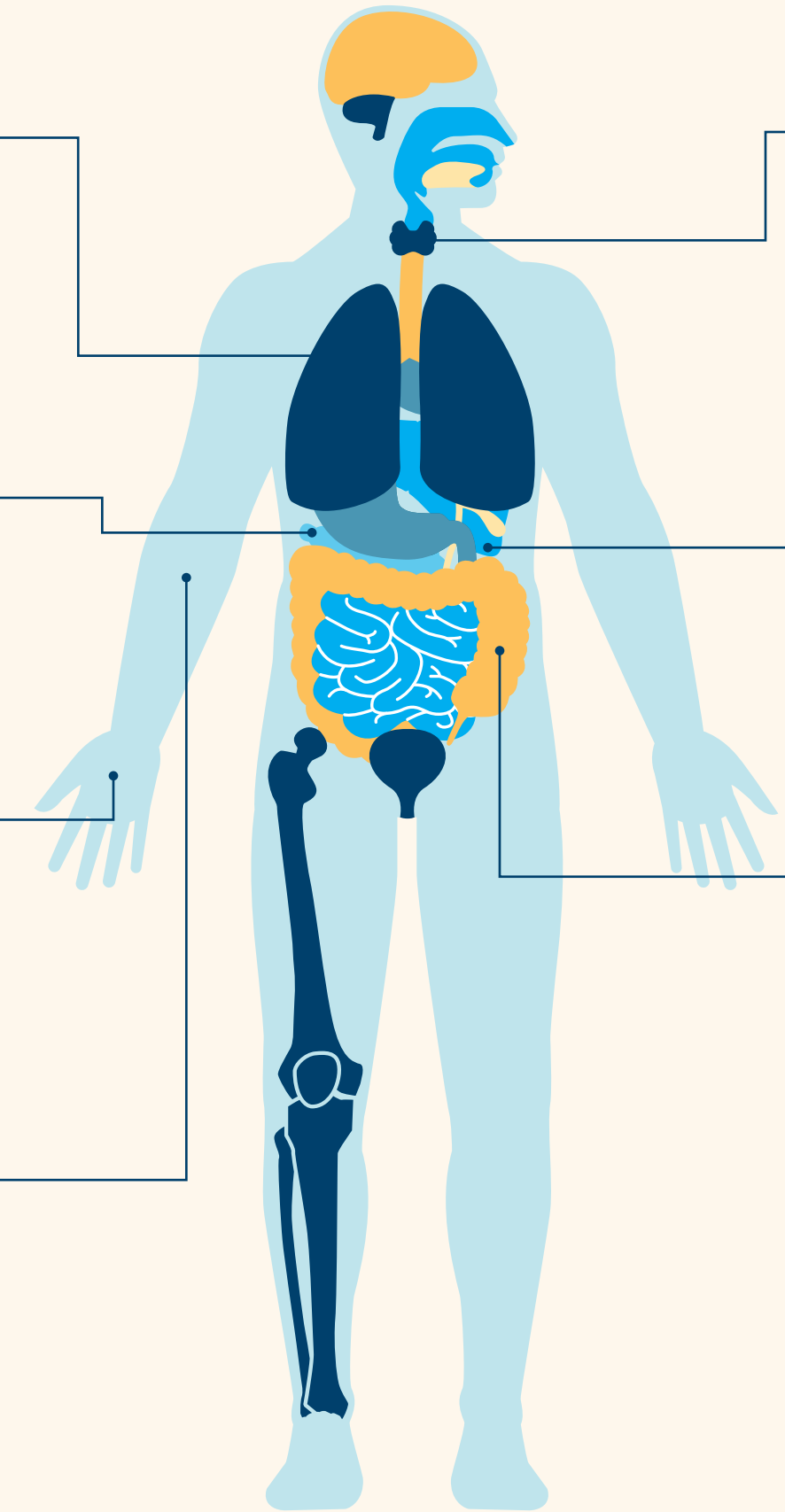
Skin or other organs

Possible side effects:

Rash, eye problems, or muscle problems

What you may experience:

- Rash
- Changes in eyesight
- Muscle pain or weakness



Thyroids or other hormone glands

Possible side effects:

Thyroid problems, such as underactive thyroid (hypothyroidism)

What you may experience:

- Feeling cold
- Headaches
- Weight loss or gain

Liver

Possible side effects:

Inflammation of the liver (hepatitis)

What you may experience:

- Dark urine
- Feeling less hungry

Intestine

Possible side effects:

Inflammation of the colon (colitis)

What you may experience:

- Diarrhea
- Abdominal pain

If something not listed here occurs, it's still recommended to contact your care team. Any symptom that is new is important to report.

Checkpoint inhibitors currently used for lung cancer treatment

Type of Treatment	Drug	PD-L1 Status
Metastatic NSCLC: First Treatment		
Immunotherapy	Pembrolizumab	1% or more
	Atezolizumab	50% or more
	Cemiplimab	50% or more
	Nivolumab + Ipilimumab	1% or more
Immunotherapy with Chemotherapy	Pembrolizumab	Any
	Atezolizumab with or without Bevacizumab	Any
	Cemiplimab	Any
	Nivolumab + Ipilimumab	Any
	Durvalumab + Tremelimumab	Any
Stage 3 NSCLC		
Immunotherapy After Chemotherapy and Radiation	Durvalumab	Any
Early-Stage NSCLC: Adjuvant		
Immunotherapy After Surgery and Chemotherapy	Atezolizumab	1% or more
	Pembrolizumab	Any
Early-Stage NSCLC: Neoadjuvant		
Immunotherapy and Chemotherapy Before Surgery	Nivolumab	Any
Extensive Stage SCLC		
Immunotherapy with Chemotherapy	Atezolizumab	Any
	Durvalumab	Any

At the time of this publication, these immunotherapies are approved to treat lung cancer.

Questions to ask your doctor about immunotherapy

- Is immunotherapy a good treatment option for me?
- What type of immunotherapy do you recommend and why?
- Has my tumor been tested for biomarkers, such as PD-L1, that can help provide information about whether I would benefit from checkpoint inhibitors? If not, why not? If it has been tested, what is my percentage of PD-L1?
- Will I need other testing or imaging while on this type of treatment?
- How will we know if this immunotherapy is working?
- What are possible side effects of immunotherapy? How severe are they, and how often are they likely to occur?
- What are possible short- and long-term side effects of this immunotherapy? How can these be managed?
- How often will I get immunotherapy and how long does the infusion last? For how long am I likely to receive it?
- Could the dose or duration of my immunotherapy change over time?
- I keep hearing about combination therapies. What are they?
- What immunotherapy clinical trials are open to me, and should I consider them as part of my treatment plan?
- How often and where will I receive my treatment? In a hospital? In a doctor's office or clinic?
- Will immunotherapy be my only treatment, or will other treatments be explored at the same time?
- How will this treatment affect my daily life?
- Will I be able to work, exercise, and perform my usual activities?
- What supportive care (or palliative) treatments are available to me?
- If I'm worried about managing the costs of cancer care, who can help me?
- If I have a question or problem, whom should I call?

Notes

This free resource provided with support from AbbVie, Bristol-Myers Squibb, Eisai Inc., Eli Lilly and Company, Foundation Medicine Inc., Genentech - a member of the Roche Group, Jazz Pharmaceuticals, Merck, Mirati Therapeutics Inc., Novartis, Sanofi, Takeda Pharmaceuticals U.S.A. Inc., and generous donations.

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