IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

Immuno-oncology agents for cancertherapy

Shubham .S .Sanap, SUMEDH S. SHIVGAN, Santosh B. gavhane, Nehal A.Thakare, puja G.Vyawhare ,Ashwini R.Bharati.,Yogita M.Vispute

Abstract:

Until recently, cancer therapy comprised of four main types of treatment: surgery, radiotherapy, chemotherapy, and targeted therapy. Over the past decade, immuno-oncology (IO) has emerged as a novel and important approach to cancer treatment through the stimulation of the body's own immune system to kill cancer cells. This newly recognised method of treating cancer is rapidly developing, with many accelerated approvals by the US Food and Drug Administration and European Medicines Agency in 2019.[8]

Several therapeutic classes have emerged within IO and are the focus of this review article. In particular, the immune checkpoint inhibitors have had remarkable success across multiple malignancies and are the most well- established therapeutic class of IO agents to date. Biomarker testing for the programmed death-ligand 1 (PD-L1) checkpoint target has been developed and is now obligatory before treatment with pembrolizumab (Keytruda, Merck) when used for non-small-cell lung carcinoma, gastric cancer, head and neck squamous cell carcinoma and cervical cancer, as well as before treatment with atezolizumab (Tecentriq, Roche) when used for urothelial carcinoma. However, ambiguity remains as to the relevance of PD-L1 expression for checkpoint inhibition therapy for other tumour types. More recently, combining IO agents with conventional therapies has been evaluated with some significant improvements in patient outcomes.[8]

[8]

Introduction:

Immunotherapy is a type of cancer treatment. It uses substances made by the body or in a laboratory to boost the immune system and help the bodyfind and destroy cancer cells. [1]

Immunotherapy can treat many different types of cancer. It can be used alone or in combination with chemotherapy and/or other cancer treatments.
[2]

Immunotherapy can:

- Educate the immune system to recognize and attack specific cancercells
- Boost immune cells to help them eliminate cancer
- Provide the body with additional components to enhance the immuneresponse [1]

Cancer is a disease of the genome, and it is characterized by a genomic instability in which numerous point mutations accumulate and structural alterations occur in the process of tumor progression. Such genomic variations could give rise to tumor antigens, which could be recognized by the immune system as nonself and elicit cellular immune responses. The immune system plays an essential role in immunosurveillance, as immune cells of the adaptive and innate immune systems infiltrate into the tumor microenvironment (TME) and contribute to the modulation of tumor progression. Innate immune cells, composed of natural killer (NK) cells, eosinophils, basophils, and phagocytic cells, including mast cells, neutrophils, monocytes, macrophages, and dendritic cells (DCs), participate in tumor suppression either by directly killing tumor cells or by triggering adaptive immune responses. The adaptive immune system functions with lymphocytes, including B cells and T cells, among which B cells play a major role in humoral immune responses, whereas T cells areinvolved in cell-mediated immune responses. [3]

Effective immune responses could either eradicate malignant cells or impair their phenotypes and functions. However, cancer cells have evolved multiple mechanisms, such as defects in antigen presentation machinery, the upregulation of negative regulatory pathways, and the recruitment of immunosuppressive cell populations, to escape immune surveillance, resulting in the impeded effector function of immune cells and the abrogation of antitumor immune responses. [3]

Immunotherapy, aiming to boost natural defences to eliminate malignant cells, is a monumental breakthrough for cancer treatment and has revolutionized the field of oncology. Although the idea of unleashing the host immune system to eradicate cancer could trace back to a century ago, significant advances have been achieved in recent basic and clinical investigations. Multiple cancer types have shown sustained clinical responses to immunotherapy, albeit with limited response rates and unclear underlying mechanisms. Immune cells are the cellular underpinnings of immunotherapy; thus, understanding the immune infiltrates in the TME is the key to improving responsive rates and developing new therapeutic strategies for cancer treatment with immunotherapy. Although the tumor–immune ecosystem is highly complex and comprises a heterogeneous collection of cells, single-cell technologies have emerged as powerful tools for the dissection of the TME. Although tremendous efforts have been devoted to T-cell characterizations, other immune cells of the innate and adaptive immune systems, including DCs, macrophages, NK cells, and B cells, have also been shown to contribute to tumor progression and immunotherapy responses. [3]

History:

The earliest case of cancer immunotherapy can be traced back to 1891, when William

Coley, the father of immunotherapy, first attempted to leverage the immune system to treat cancer after noticing that mixtures of live and inactivated Streptococcus pyogenes and Serratia
marcescens could cause tumor regression in sarcoma patients. [3]

He discovered that infecting cancer patients with certain bacteria sometimes resulted in tumor regression and even some complete remissions. Advances in cancer immunology since Coley's time have revealed that, in patients that responded to his treatment, his bacterial toxintherapy stimulated their immune systems to attack the tumors. [1]

While Coley's approach was largely dismissed during his lifetime, his daughter, Helen Coley Nauts, discovered his old notebooks and founded the Cancer Research Institute in 1953 to support research into his theory. In 1990, the FDA approved the first cancer immunotherapy, a bacteria- based tuberculosis vaccine called Bacillus Calmette-Guerin (BCG), whichwas shown to be effective for patients with bladder cancer. [1]

What is immune:

Our immune system is a complex network of organs, cells and molecules that protects us from foreign substances such as bacteria, fungi and viruses that can cause infection. In addition to finding and destroying foreign substances, the immune system can also locate and attackabnormal cells.

There are two main parts of the immune system:

- **Innate immunity,** a defence system we are born with, is the ability of the body to immediately protect itself against foreign organisms and toxins.
- **Adaptive immunity** is a learned defence system that develops in response to exposure to a specific foreign substance. The adaptiveimmune system works in one of two ways:
  - Humoral, also called antibody-mediated, in which B-cells (a type of white blood cell called a lymphocyte) make antibodies (specific blood proteins) that identify and destroy foreign substances.
  - Cell-mediated, in which T-cells (another type of white blood cell or lymphocyte) identify and destroy abnormal cells, including those that are cancerous.

Unleashing the power of the immune system is a smart way to fightcancer:

1. The immune system is precise, so it is possible for it to target cancer cells exclusively while sparing healthy cells.

2. The immune system can adapt continuously and dynamically, just like cancer does, so if a tumor manages to escape detection, the immune system can re-evaluate and launch a new attack.

3. The immune system's "memory" allows it to remember what cancer cells look like, so it can target and eliminate the cancer if it returns. [1]

How the Immune System Works

Organs, tissues, and glands around your body coordinate the creation, education, and storage of key elements in your immune systems.

APPENDIX

Thin tube about 4 to 6 inches long in the lower right abdomen. The exact function is unknown; one theory is that it acts as a storage site for "good" digestive bacteria

BONE MARROW

Soft, sponge-like material found inside bones. Contains immature cells that divide to form more blood-forming stem cells, or mature into red blood cells, white blood cells (B cells and T cells), and platelets

GUT

Cells lining this set of organs and glands, as well as the bacteria throughout it, influence the balance of the immune system.

LYMPH NODES

Small glands located throughout the body that filter bacteria, viruses, and cancer cells, which are then destroyed by special white blood cells. Also the site where T cells are "educated" to destroy harmful invaders in your body

NOSE

This organ's receptors detect bacteria and viruses. Nasal mucus catches these pathogens so the immune system can learn to defend against them.

SKIN

This organ is not only a physical barrier against infection, but also contains dendritic cells for teaching the rest of the body about new threats. The skin microbiome is also an important influence the balance of the immune system.

SPLEEN

Organ located to the left of the stomach. Filters blood and provides storage for platelets and white blood cells. Also serves as a site where key immune cells (B cells) multiply in order to fight harmful invaders

TONSILS

A set of organs that can stop germs entering the body through the mouth or the nose. They also contain a lot of white blood cells.

THYMUS GLAND

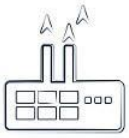
Small gland situated in the upper chest beneath the breastbone. Functions as the site where key immune cells (T cells) mature into cells that can fight infection and cancer

Boosting the Body's Immune System to Fight Cancer

Immunotherapy treatment harnesses the body's natural strength to fight cancer—empowering the immune system to conquer more types of cancer and save more lives.

ANTIBODIES

bind to antigens on threats in the body (e.g., bacteria, viruses, cancer cells) and mark cells for attack and destruction by other immune cells



B CELLS

release antibodies to defend against threats in the body

CD4+ HELPER T CELLS

send "help" signals to the other immune cells (e.g., B cells and CD8+ killer T cells) to make them more efficient at destroying harmful invaders

CD8+ KILLER T CELLS

destroy thousands of virus-infected cells each day, and are also able to seek out and destroy cancer cells

CYTOKINES

help immune cells communicate with each other to coordinate the right immune response

DENDRITIC CELLS

digest foreign and cancerous cells and present their proteins to immune cells that can destroy them

MACROPHAGES

engulf and destroy bacteria, virus-infected cells, and cancer as well as present antigens to other immune cells

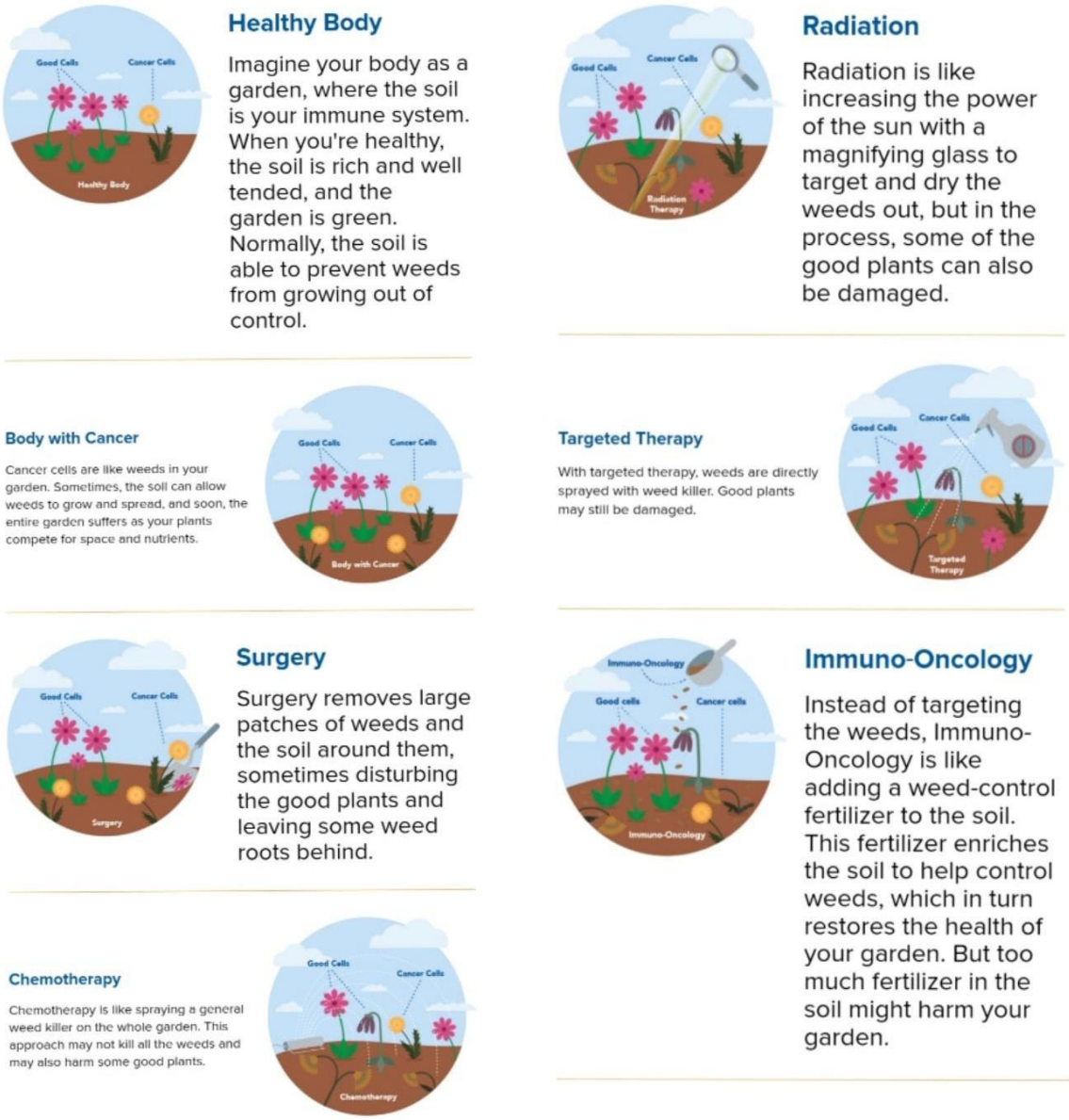
NATURAL KILLER CELLS

recognize and destroy virus-infected and tumor cells quickly without the help of antibodies and "remember" these threats

REGULATORY T CELLS

provide the checks and balances to ensure that the immune system does not overreact

Different types of therapies for cancer treatment:



[4]

Major categories of immunotherapies:

Different types of immunotherapy work in different ways. Some immunotherapy treatments help the immune system stop or slow the growth of cancer cells. Others help the immune system destroy cancercells or stop the cancer from spreading to other parts of the body. [2]

The different types of immunotherapies include:

- Monoclonal antibodies and immune checkpoint inhibitors
- Non-specific immunotherapies
- Oncolytic virus therapy
- T-cell therapy
- Cancer vaccines [2]

The type of immunotherapy, dose, and treatment schedule your doctor recommends will depend on many factors. These can include the type of cancer, size, location, and where it has spread. Your age, general
health, body weight, and the possible side effects are also important. Talk with your doctor about why a specific immunotherapy plan is being recommended for you. [2]

Monoclonal antibodies and immune checkpoint inhibitors:

When the immune system detects something harmful, it makes antibodies. Antibodies are proteins that fight infection by attaching to antigens.
Antigens are molecules that start the immune response in your body. [2]

Monoclonal antibodies are made in a laboratory to boost the body's natural antibodies or act as antibodies themselves. Monoclonal antibodies can help fight cancer in different ways. For example, they can be used to block the activity of abnormal proteins in cancer cells. This is also considered a type of targeted therapy, which is a cancer treatment using medication that targets a cancer's specific genes, proteins, or the tissue environment that helps the tumor grow and survive. [2]
Other types of monoclonal antibodies boost your immune system by inhibiting or stopping immune checkpoints. Immune checkpoints are used by the body to naturally stop an immune system response and prevent the immune system from attacking healthy cells. Cancer cells can find ways to hide from the immune system by activating these checkpoints. [2]

Checkpoint inhibitors prevent cancer cells from blocking the immune system. Common checkpoints that these inhibitors affect are the PD-1/PD-L1 and CTLA-4 pathways. [2]

Examples of immune checkpoint inhibitors include:

- Atezolizumab (Tecentriq)
- Avelumab (Bavencio)

- Dostarlizumab (Jemperli)
- Durvalumab (Imfinzi)
- Ipilimumab (Yervoy)
- Nivolumab (Opdivo)
- Pembrolizumab (Keytruda) [2]

Many checkpoint inhibitors are approved by the U.S. Food and Drug Administration (FDA) for specific cancers. There are also 2 checkpoint inhibitors that are used to treat tumors anywhere in the body if they have specific genetic changes. This kind of approach is called a "tumor-agnostictreatment." [2]

For instance, pembrolizumab (Keytruda) is approved to treat any tumors that have spread to distant parts of the body if they have a specific molecular change called microsatellite instability-high (MSI-H) or DNA mismatch repair deficiency (dMMR). Another example is that dostarlimab (Jemperli) can be used for advanced cancer or cancer that has come backif it has dMMR. Learn more about tumor-agnostic treatments. [2]
The side effects of monoclonal antibody treatment depend on the drug's purpose. For example, the side effects of monoclonal antibodies used for targeted therapy are not like those used for immunotherapy. The side effects of immune checkpoint inhibitors may include side effects similar toan allergic reaction. [2]

Non-specific immunotherapies:

Non-specific immunotherapies, also called non-specific immunomodulating agents, help your immune system destroy cancer cells. There are several kinds of non-specific immunotherapies that work in different ways. [2]

Cytokines. Cytokines are a part of the immune system. They are proteins that send messages between cells to activate the immune system. [2]

There are two types of cytokines that are used to treat cancer:

- **Interferons:** These proteins are produced by your immune system to alert your body that there is a pathogen, typically a virus, in your body. Interferons can be made in a laboratory to help your immune system fight cancer. They can also slow thegrowth of cancer cells. [2]
The most common type of interferon used in cancer treatment is called interferon alpha (Roferon-A [2a], Intron A [2b], Alferon [2a]). Interferon can be used to several many different types of cancer. Side effects of interferon treatment may include flu-like symptoms, an increased risk of infection, skin rashes, and hairthinning. [2]

- **Interleukins:** Interleukins are proteins that pass messages between cells. They also start an immune response. For example, the lab-made interleukin-2 (IL-2) or aldesleukin (Proleukin) can treat kidney cancer and melanoma. Common side effects of IL-2 treatment include weight gain and low blood pressure. Some people also experience flu-like

symptoms. [2]

Bacillus Calmette-Guerin (BCG): This type of immunotherapy is similar to the bacteria that causes tuberculosis. It is used to treat bladder cancer.
BCG is placed directly into the bladder through a catheter. It attaches to the inside lining of the bladder and activates the immune system to destroy tumor cells. BCG can cause flu-like symptoms. [2]

Oncolytic virus therapy:

Oncolytic virus therapy, sometimes just called virus therapy, uses viruses that have been changed in a laboratory to destroy cancer cells. A genetically modified version of the virus is injected into the tumor. When the virus enters the cancer cells, it makes a copy of itself. As a result, the cancer cells burst and die. As the cells die, they release proteins that trigger your immune system to target any cancer cells in your body that have the same proteins as the dead cancer cells. The virus does not enter healthy cells. [2]

Currently, one type of oncolytic virus therapy is approved in the United States to treat cancer:

Talimogene laherparepvec (Imlygic) or T-VEC. This oncolytic virus therapy is approved to treat advanced melanoma that cannot be treated with surgery. It is used most often for people who cannot or choose not to receive any other recommended treatments. T-VEC is a modified version of the herpes simplex virus, which causes cold sores. It is injected directly into 1 or more melanoma tumors. Side effects of oncolytic virus therapy include flu-like symptoms and pain at the injection site. [2]
Clinical trials are testing other oncolytic viruses for different cancers. They are also testing how the viruses work with other cancer treatments, such aschemotherapy. [2]

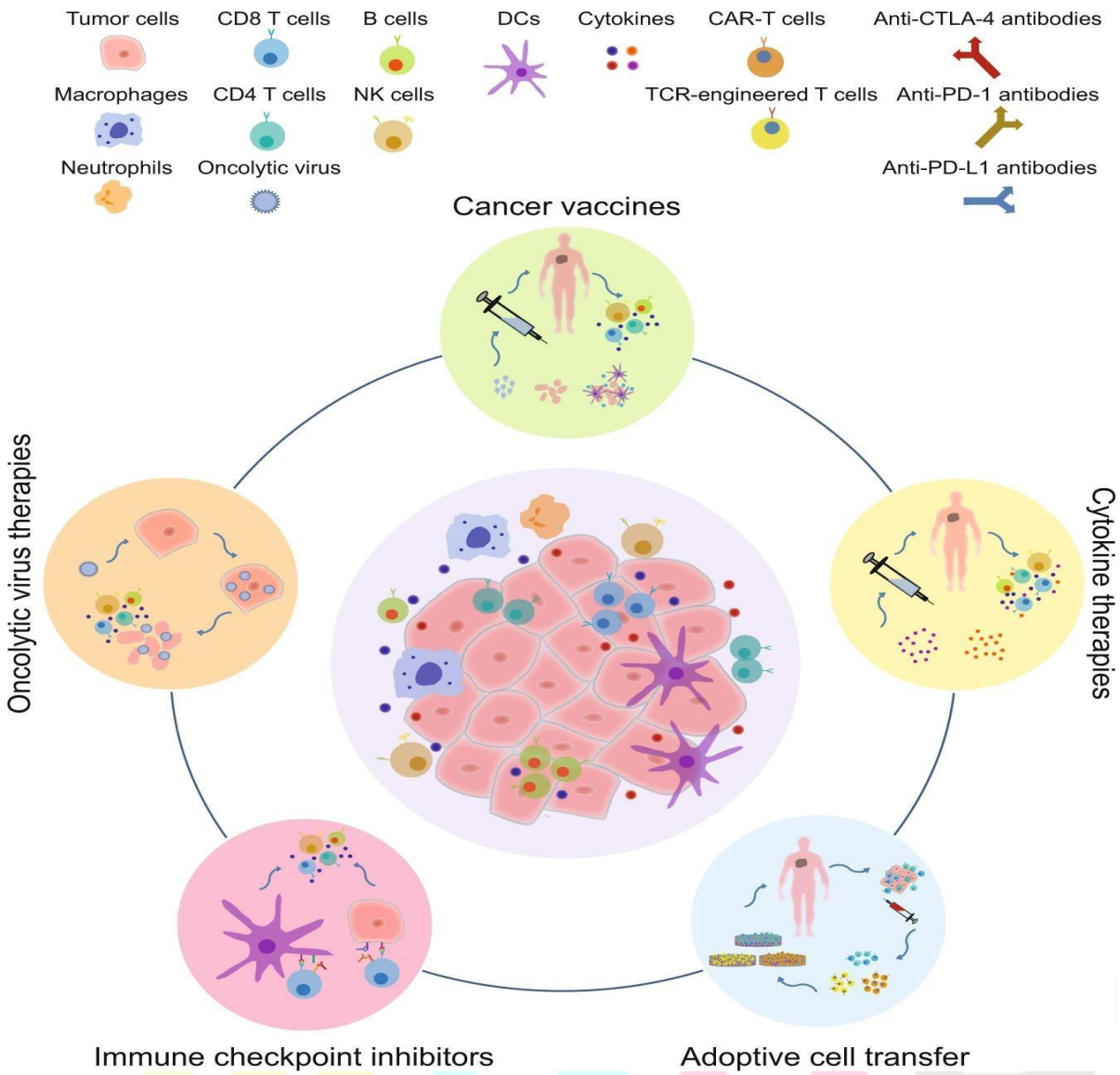
T-cell therapy:

T cells are immune cells that fight infection. In T-cell therapy, the doctor removes T cells from the blood. Then, a laboratory adds specific proteins called receptors to the cells. The receptor allows those T cells to recognize cancer cells. The changed T cells are put back into the body. Once there, they find and destroy cancer cells. This type of therapy is known as chimeric antigen receptor (CAR) T-cell therapy. Side effects include fevers, confusion, low blood pressure, and, in rare occasions, seizures. [2]
CAR T-cell therapy is used to treat certain blood cancers. Researchers are still studying this type of therapy and other ways of changing T cells to treatcancer. [2]

Cancer vaccines:

A cancer vaccine can also help your body fight disease. A vaccine exposes your immune system to a foreign protein, called an antigen. This triggers the immune system to recognize and destroy that antigen or related substances. There are 2 types of cancer vaccine: prevention vaccines andtreatment vaccines. [2]

One example of a cancer prevention vaccine is Gardasil, the vaccine to protect against the human papillomavirus (HPV), a virus that can cause specific types of cancer. An example of a treatment vaccine
includes spuleucel-T (Provenge), which treats advanced prostate cancer that does not respond to hormone therapy. T-VEC (see above) is also considered a cancer treatment vaccine. Side effects for both of these cancer vaccines are flu-like symptoms. [2]



[3]

Side effect:

Immunotherapy can cause side effects, many of which happen when the immune system that has been revved-up to act against the cancer also acts against healthy cells and tissues in the body. Different people have dif- ferent side effects. The ones you have and how they make you feel will de- pend on how healthy you are before treatment, your type of cancer, how advanced it is, the type of immunotherapy you are getting, and the dose. [5]

You might be on immunotherapy for a long time, and side effects can occur at any point during and after treatment. Doctors and nurses cannot know for certain when or if side effects will occur or how serious they will be. So, it is important to know what signs to look for and what to do if you start to have problems. [5]

Some side effects are common with all types of immunotherapies. For in- stance, you might have skin reactions at the needle site, which include:

- pain
- swelling
- soreness
- redness
- itchiness
- rash [5]

You may have flu-like symptoms, which include:

- fever
- chills
- weakness
- dizziness
- nausea or vomiting
- muscle or joint aches
- fatigue
- headache
- trouble breathing

- low or high blood pressure [5]

Other side effects might include:

- swelling and weight gain from retaining fluid
- heart palpitations
- sinus congestion
- diarrhoea
- infection
- organ inflammation [5]

Some types of immunotherapies may cause severe or even fatal allergic and inflammation-related reactions. However, these reactions are rare. [5]

Certain side effects might happen depending on the type of immunotherapyyou receive. [5]

Immunotherapy may be accompanied by side effects that differ from those associated with conventional cancer treatments, and side effects may vary depending on the specific immunotherapy used. In most cases, potential immunotherapy-related side effects can be managed safely as long as the potential side effects are recognized and addressed early. [1]

- Cancer immunotherapy treats the patient—by empowering their immune system—rather than the disease itself like chemotherapy and radiation. Patients may be tested for biomarkers that may indicate whether cancer immunotherapy would be an effective treatment.

- Side effects of immunotherapy may result from stimulation of the immune system and may range from minor inflammation and flu-like symptoms, to major, potentially life-threatening conditions similar to autoimmune disorders.

- Common side effects may include but are not limited to skin reactions, mouth sores, fatigue, nausea, body aches, headaches, andchanges in blood pressure. [1]

Conventional cancer treatments also have a range of side effects with a wide range of severity.

- Chemotherapy is intended to target fast-growing cancer cells, so it may damage other fast-growing normal cells in your body. Common side effects may include but are not limited to hair loss, nausea, diarrhoea, skin rash, and fatigue.

- Radiation uses radioactive particles to destroy cancer cells in a localized area, so it may damage other healthy cells in that area. Side effects may be associated with the area of treatment, such as difficulty breathing when aimed at the chest, or nausea when aimed at the stomach. Skin problems and fatigue are common.

• The goal of surgery is to remove the cancerous tumor or tissue and varies according to the type of surgery performed. Common side effects may include but are not limited to pain, fatigue, swelling, numbness, and risk of infection. [1]

Advantages:

• The treatment effect of "immunoinflammatory" tumor is good, and the long-term survival rate is significantly improved.
• High accuracy, specificity and targeting of immunotherapy.
• Immunotherapy is effective for a long time.
• Wide adaptability. The treatment can control and kill multiple types oftumours.
• Be persistent. The treatment initiates the body's immune system to restore immune function and kill tumor cells for a long time.
• Be comprehensive. It can restore and improve the body's immune function, fully identify, search, and kill tumour cells, and effectivelyprevent tumor recurrence and metastasis.
• With thoroughness. It can thoroughly remove residual tumor cells and microscopic lesions from the body.
• The side effects are less than the traditional. treatment. [6]

Disadvantages:

• There are limitations in the treatment objects and high selectivity for the users. When the type of tumor is "immune suppression type" and "immune exclusion type", the effect of immunotherapy is poor.
• The use of immune checkpoint inhibitors can produce negative regulation, leading to autoimmune diseases and even death.
• A variety of non-specific toxic and side effects may occur after use in some patients, and even hyper progressive disease may occur, accelerating the death of patients.
• The effect of immunotherapy is affected by many factors. The survival rate and prognosis of patients are uncertain.
• Treatment costs are high. [6]

List of antibodies that are approved:

Antibody	Brandname	Type	Target	Approval date	Approved treatment(s)
Alemtuzumab	Campath	humanized	CD52	2001	B-cell chronic lymphocytic leukemia (CLL)[34]
Atezolizumab	Tecentriq	humanized	PD-L1	2016	bladder cancer[35]
Avelumab	Bavencio	human	PD-L1	2017	metastatic Merkel cell carcinoma[36]
Ipilimumab	Yervoy	human	CTLA4	2011	metastatic melanoma[37]
Elotuzumab	Empliciti	humanized	SLAMF7	2015	Multiple myeloma[38]
Ofatumumab	Arzerra	human	CD20	2009	refractory CLL[39]
Nivolumab	Opdivo	human	PD-1	2014	unresectable or metastatic melanoma squamous non-small cell lung cancer Renal cell carcinoma, colorectal cancer hepatocellular carcinoma, classica hodgkin lymphoma[40][41]
Pembrolizumab	Keytruda	humanized	PD-1	2014	unresectable or metastatic melanoma squamous non-small cell lung cance (NSCLC),[42] Hodgkin's lymphoma,[43 Merkel-cell carcinoma (MCC),[44 primary mediastinal B-cell lymphoma (PMBCL),[45] stomach cancer, cervical cancer[46]
Rituximab	Rituxan, Mabthera	chimeric	CD20	1997	non-Hodgkin lymphoma[47]
Durvalumab	Imfinzi	human	PD-L1	2017	bladder cancer[48] non-small cell lung cancer[49]

[7]

References

[1] E. Cohen, "What Is Cancer Immunotherapy?," October 2020. [Online]. Available: https://www.cancerresearch.org/en-us/immunotherapy/what-is-immunotherapy. [Accessed 25 October 2022].

[2] "What Is Immunotherapy?," May 2022. [Online]. Available: https://www.cancer.net/navigating- cancer-care/how cancer-treated/immunotherapy-and-vaccines/what-immunotherapy. [Accessed25 October 2022].

[3] Y. Zhang and . Z. Zhang, "The history and advances in cancer immunotherapy: understanding the characteristics o tumor-infiltrating immune cells and their therapeutic implications," 1 July 2020. [Online]. Available https://www.nature.com/articles/s41423-020-0488-6. [Accessed 25 October 2022].

[4] "Immuno-Oncology Is a Different Type of Cancer Treatment Approach," Bristol Mayers Squibb, 2021. [Online] Available: https://www.immunooncology.com/about/io-different-approach. [Accessed 25 October 2022].

[5] "Immunotherapy Side Effects," 24 September 2019. [Online]. Available: https://www.cancer.gov/about cancer/treatment/types/immunotherapy/side-effects. [Accessed 25 October 2022].

[6] S. Tan, D. Li and X. Zhu, "Cancer immunotherapy: Pros, cons and beyond," Elsevier Masson SAS, April 2020. [Online] Available: https://www.sciencedirect.com/science/article/pii/S0753332220300111. [Accessed 25 October 2022].

[7] "Cancer immunotherapy," 16 October 2022. [Online]. Available https://en.wikipedia.org/wiki/Cancer_immunotherapy#FDA-approved_antibodies. [Accessed 25 October 2022].

[8] S. Carter and D. E. Thurston, "Immuno-oncology agents for cancer therapy," 07 May 2020. [Online]. Available https://pharmaceutical-journal.com/article/research/immuno-oncology-agents-for-cancer-therapy. [Accessed 25 October 2022].