JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

Review On: Immuno-oncology Agents for Cancer Therapy

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Abstract : Until lately, cancer treatment involved four primary kinds of treatment: surgery, radiotherapy, chemotherapy and targeted therapy. Over the earlier decade, immuno-oncology (IO) has emerged as a novel and critical method for managing cancer therapy through the stimulation of the body's own immune system to kill cancer cells. This recently recognised technique of treating cancer is quickly developing, with many accelerated endorsement by the US Food and Drug Administration and European Medicines Agency in 2019. Immune checkpoint inhibitors, in particular, have had exceptional effectiveness across a wide range of cancers and are the most well-established therapeutic class of IO drugs to date. Biomarker testing for the programmed death-ligand 1 (PD-L1) checkpoint target has been created and is currently mandatory before therapy with pembrolizumab (Keytruda, Merck) when used for non-small-cell lung carcinoma, gastric cancer, head and neck squamous cell carcinoma and cervical cancer, just as before treatment with atezolizumab (Tecentriq, Roche) when used for urothelial carcinoma. However, the significance of PD-L1 expression for checkpoint inhibition therapy in other tumour types remains unclear. Combining IO drugs with conventional therapy has recently been studied, and patient outcomes have shown to be significantly improved. While IO agents are fast transforming the standard of treatment for cancer patients, there are still numerous obstacles to overcome in terms of managing their side effects and ensuring that healthcare systems, such as the NHS, can finance these expensive therapies. In addition to cancer vaccines and chimeric antigen receptor T-cell treatments, the IO pipeline contains chimeric antigen receptor T-cell therapies, both of which have their own set of toxicity and cost-effectiveness concerns.

IndexTerms **-** cancer, tumours, immuno-oncology, immunotherapy, anti-tumour, immunosuppression, immunosurveillance

I. INTRODUCTION

Cancer is a condition in which some of the body's cells divide abnormally, allowing them to invade neighbouring cells and tissues, as well as spread to other parts of the body via the blood and lymphatic systems [1]. Cancer is a genetic disease, means it is caused by mutations in genes that control how our cells work, particularly how they divide and grow. Cancer-causing genetic alterations can occur as a result of:

1. cell division abnormalities.
2. of DNA damage caused by toxic compounds in the environment, such as tobacco smoke chemicals and UV radiation from the sun.
3. they were passed down to us from our parents.

The genetic changes that contribute to cancer tend to affect three main types of genes- proto-oncogenes, tumour suppressor genes and DNA repair genes. These changes are called as "drivers" of cancer [2]. Cells with damaged DNA are generally eliminated by the body before they become malignant. However, as we get old, our bodies' ability to do so decreases. This is one of the reasons why people are more likely to

develop cancer later in life. Each person's cancer is comprised of a unique set of genetic alterations. Additional alterations will occur as the malignancy progresses.

Different cells within the same tumour may have different genetic alterations. Cancer develops when normal cells are transformed into tumour cells in a multi-stage process that usually evolves from a pre-cancerous lesion to a malignant tumour. These changes are the after effect of an individual's heredity factors interacting with three types of external agents:

- physical cancer causing agents, such as ultraviolet and ionising radiation;
- chemical cancer causing agents, such as asbestos, tobacco smoke components, aflatoxin (a food contaminant), and arsenic (a drinking water impurity); and
- biological cancer causing agents, such as infections from specific viruses, bacteria, or parasites.

Types of Cancer:

Cancers are normally named after the organs or tissues where the cancer cell arises, such as lung cancer or brain cancer, but they can also be classified according to the type of cells that produce them, such as epithelial or squamous cell cancer [3].

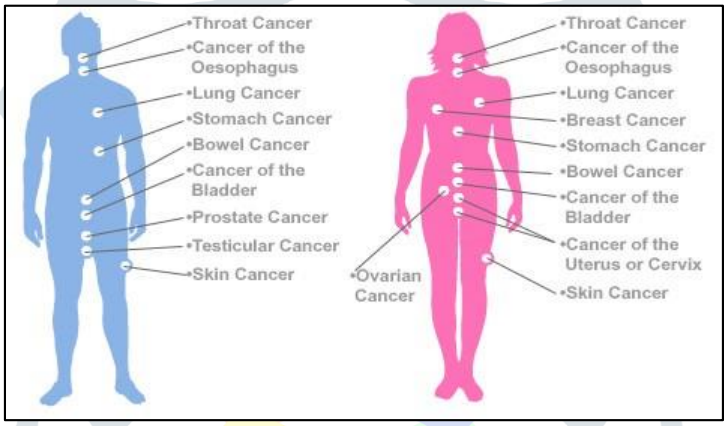

Figure 1: Different types of cancer in men and women

Types of cancer described by the type of cells that forms cancer.

Types of Cancer	Meaning
Carcinoma	Cancer of skin or tissue.
Sarcoma	Cancer of bones, soft tissues (muscle, fat, blood vessels, lymph vessels and fibrous tissue such as tendons and ligaments).
Leukaemia	Cancer of blood forming tissues of the bone marrow.
Lymphoma	Cancer of lymphocytes (T-cells and B-cells).
Multiple Myeloma	Cancer of the plasma cells.
Melanoma	Malignant cancer cells formed in melanocytes.
Brain and Spinal cord tumour	Tumours forms in brain and spinal cord.

Types of Cancer Treatment:

There are many types of cancer treatment. The types of treatment that you receive will depend on the type of cancer you have and how advanced it is [3].

- **Chemotherapy** is a type of cancer treatment that uses drugs to kill cancer cells.
  - Intravenous (IV) chemotherapy.
  - Oral chemotherapy.
  - Injected chemotherapy.
  - Chemotherapy into an artery.
  - Chemotherapy into the peritoneum or abdomen.
  - Topical chemotherapy.
- **Hormone Therapy** is a treatment that slows or stops the growth of tumours that utilise hormones to proliferate, such as breast and prostate cancers.
- **Hyperthermia** is a method of treatment in which bodily tissue is heated to temperatures as high as 113 degrees Fahrenheit in order to destroy and kill cancer cells while causing little or no injury to healthy tissue.
- **Photodynamic Therapy** kills cancer and other defective cells by activating a medication with light.
- **Radiation Therapy** is a cancer treatment in which strong doses of radiation are used to kill cancer cells and shrink tumours.
- **Stem cell transplant** is a method that allows persons who have had their stem cells damaged by severe doses of chemotherapy or radiation therapy to have their stem cells grow back into blood cells.
- **Targeted Therapy** is a type of cancer treatment that focuses on the changes that help cancer cells grow, divide, and spread.
- **Surgery:** Surgical removal of cancer from the body is performed by a surgeon.
- **Immunotherapy** is a cancer treatment that boosts your immune system's ability to fight cancer.

Immuno-oncology:

Immuno-oncology is a type of immunotherapy in which the immune system of the body is targeted specifically to combat cancer. It works by encouraging our immune system to fight back when it otherwise wouldn't [5]. The purpose of I-O therapy is to help patients with advanced cancer achieve long-term survival [4]. The immune system, not the tumour, is the target of I-O treatments. They allow the immune system to recognise and kill tumour cells selectively. They provide the immune system with long-term memory, allowing it to adjust to the malignancy over time and achieve a durable, long-term response[6].

Mobilizing the body's own immune system:

Immuno-oncology therapies can be targeted directly against the tumour or have an untargeted effect. The immune system is often activated in non-specific immunotherapy to operate more effectively against foreign bodies, infections, and degenerated cells[14]. Checkpoint inhibition is also a type of non-specific immuno-oncology. It inhibits cancer cells from passing themselves off as healthy tissue and evading detection. Specific proteins on the surface of T cells (checkpoints) are inhibited for this aim. If these proteins didn't connect to tumour cells, they'd be classified as innocuous. Immune checkpoints, on the other hand, are employed to recognise the body's own structures. When immunological checkpoints are altered, the immune system may no longer tolerate healthy cells and may begin to remove them.which may lead to autoimmune side effects[15].

History of Immuno-oncology:

The idea was first proposed by William Coley (Father of Immunotherapy) in 1893, when he observed the decrease in or disappearance of signs and symptoms of cancer in patients who had contracted acute bacterial infections[7]; the followed by Paul Ehrlich in 1909, when he suggested that the immune system must have some role in preventing an outbreak of cancer in the body[8]. A later improvement included the Bacillus Calmette-Guerin (BCG) vaccine, initially created in the mid-1900s for use against tuberculosis (TB), and first utilized remedially for TB in the 1920s. Nonetheless, its job in disease treatment traces all the way back

to 1929at the point when a diminished frequency of disease among patients with TB was seen at autopsy. I-O therapy takes a different approach than traditional chemotherapy, which targets all cells – malignant and normal – in an indiscriminate, static, and toxic direct attack in the goal of hurting cancer cells more than host cells.

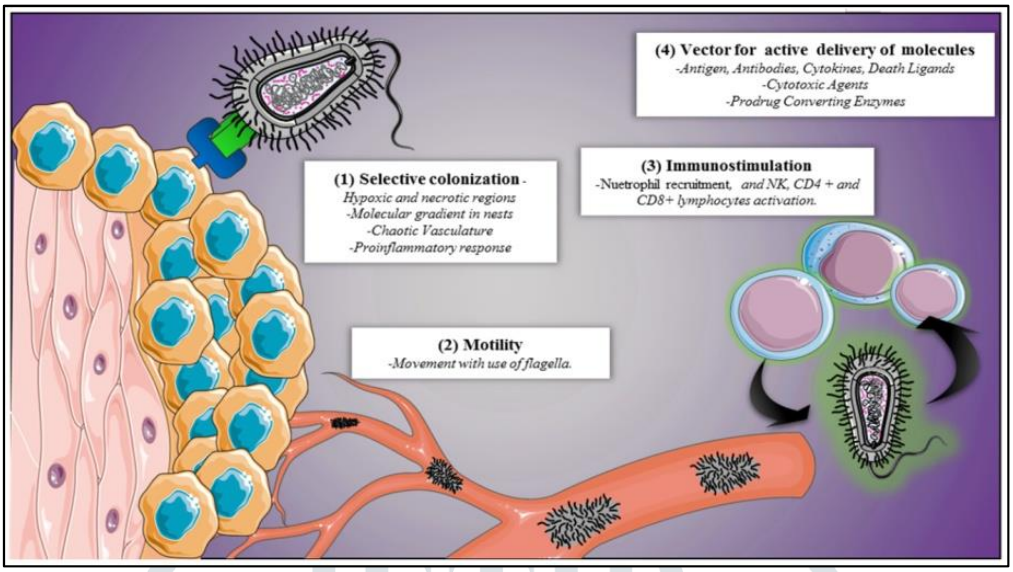

Figure 2: Use of bacteria in cancer immunotherapy

According to recent research, cytotoxic chemotherapy and targeted therapy may also target stromal and immunological cells in the tumour microenvironment. These findings point to the possibility of combining chemotherapy and IO drugs with the goal of optimising immune clearance rather than killing as many tumour cells as possible, thereby allowing for lower chemotherapy dose. Because cancer immunotherapy is primarily based on an indirect approach rather than a direct attack on cancer cells, the kinetics of response to I-O therapies can be delayed, and the tumour may appear to be growing in the short term when, in fact, the observed increase in volume is due to an inflammatory immune response that is working to eliminate the cancer.

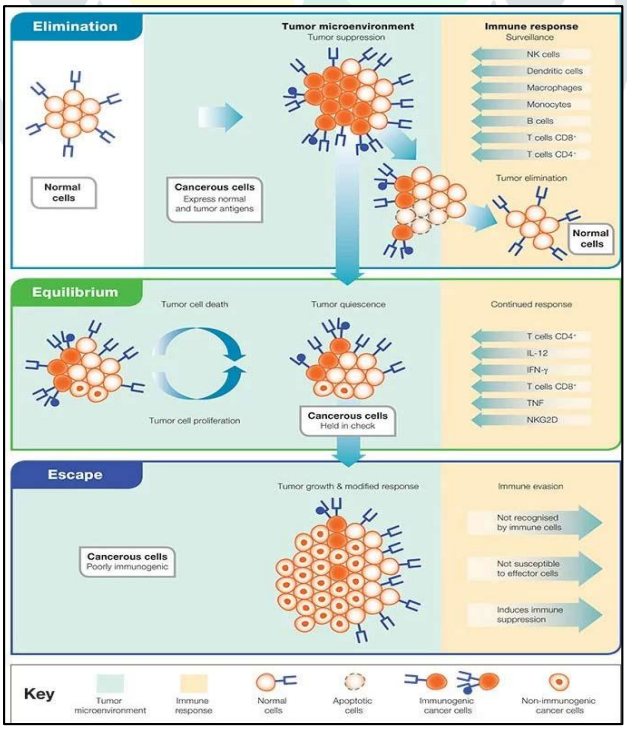

Figure 3: The three Es of Cancer Immunoediting

Interaction between Immune system and Cancer:

Our immune system is a complex network of organs, cells, and molecules that protects us from bacteria, fungi, and viruses, as well as other foreign substances that can cause infection. The immune system can seek and target aberrant cells in addition to detecting and killing invading substances. The immune system is divided into two parts:

• **Innate immunity,** a defence system we are born with, is the ability of the body to immediately protect itself against cancer, foreign organisms and toxins.

• **Adaptive immunity** is a learned defence system that develops in response to exposure to a specific foreign substance. There are two ways in which the adaptive immune system functions:

1. **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 body.
2. **Cell-mediated,** in which T-cells (another type of white blood cell) identify and destroy abnormal cells, including cancer cells. An immune system that is both hyperactive and underactive might be destructive. Immunotherapies have been developed as a therapy method for many types of cancer as our understanding of the health advantages of a healthy immune system has grown.

Since the middle of the past century, there has been mounting evidence that the immune system can recognise and reject tumours, first in animal models and then in human trials. Tumour immunology's goal has been to better understand the immune system components that are critical for tumour immunosurveillance and tumour rejection, as well as how, when, and why they fail in clinical illness. Immunotherapy, which involves boosting a cancer patient's immune system's ability to recognise tumours or replacing a lost immune effect or function, is one treatment option that has the potential to provide a long-term cure[10].

Immune checkpoint proteins are proteins present on the surface of T-cells that operate as immune system regulators. They are essential for self-tolerance because they prevent the immune system from indiscriminately attacking the body's own cells, allowing a differentiation to be made between 'self' and 'non-self'[12]. Immune checkpoints are also important in preventing uncontrolled immune responses by limiting the duration and amplitude of a physiological immune response, preventing collateral harm, which is why the word 'off switch' is occasionally used to characterise their function. It is well known that tumours use immunological checkpoint pathways to avoid being attacked by the immune system. Some tumour cell types, for example, produce these proteins on their surfaces to pass as ‘self,' allowing them to avoid detection by the immune system and boosting tumour spread[13]. Currently, 11 immune checkpoint inhibitors (Table 2) and 2 chimeric antigen receptor T cell (CAR-T) products have been approved in treating 16 types of malignant diseases and 1 tissue-agnostic indication[11].

Although immunotherapies are expensive, it is crucial to remember that the expense of longer, less effective chemotherapy treatments may be outweighed by the cost of a longer, less effective response. Targeting biomarkers to isolate select patient populations that have a better likelihood of seeing more benefits from these treatments and resulting in a lower total economic burden is one method currently being studied. Personalized combinatory immunotherapies will face a number of hurdles in the future. The standard of care for oncologic therapy is fast evolving, and immunotherapy is quickly becoming one of the most important treatments in modern medicine [12].

Classification of Immunotherapy:

Monoclonal antibodies (MABs):

MABs are a type of immunotherapy. They function by activating the immune system and assisting it in the fight against cancer. Some MABs are more targeted than others. They can, for example, stop cancer cells from dividing by blocking signals. Antibodies are proteins found in our blood that aid in the fight against illness. Monoclonal just means all one type. As a result, each MAB is a large number of copies of a single antibody. A MAB works by recognizing and finding specific proteins on cells. Some work on cancer cells, while others target proteins in immune system cells. Each MAB recognizes one particular protein. Depending on the protein they're targeting, they act in different ways. Depending on the protein they're

targeting, they act in different ways. MABs function as immunotherapy in a variety of ways. Some MABs have many functions. They can:

- trigger the immune system to attack and kill cancer cells
- act on cells to help the immune system attack cancer cells

Cancer cells are aberrant, but they originate from normal cells, making them difficult to detect by the immune system. Some MABs attach themselves to cancer cells, making it easier for immune system cells to locate them. This process is called antibody-dependent cell-mediated cytotoxicity or ADCC. Other MABs work by acting on cells of the immune system. Checkpoint inhibitors, for example, are a kind of immunotherapy. Checkpoint inhibitors work by preventing proteins from preventing the immune system from attacking cancer cells [16].

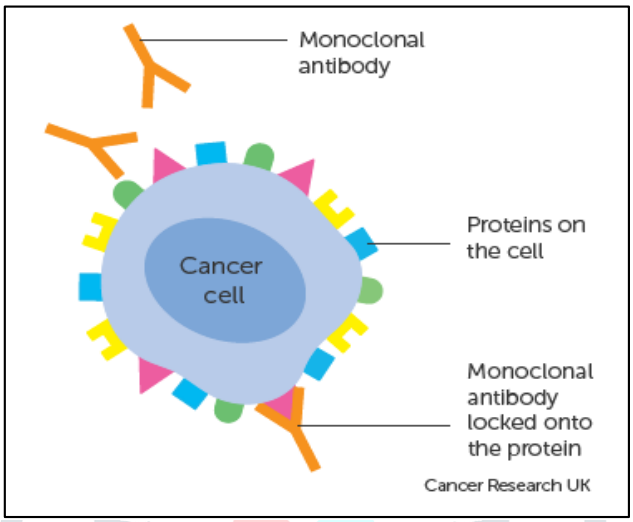

Figure 4: Monoclonal antibody attached to cancer cell.

Side effects:

It may include;

- skin changes such as red and sore skin or an itchy rash
- diarrhea
- tiredness
- flu-like symptoms such as chills, fever, dizziness
- feeling or being sick

Checkpoint Inhibitors:

Checkpoint inhibitors are a type of immunotherapy. They prevent the immune system from attacking cancer cells by blocking proteins that prevent the immune system from attacking cancer cells. A type of monoclonal antibody or targeted medicine, checkpoint inhibitors are also known as. Some checkpoint proteins aid in the activation of T lymphocytes, such as when an infection is present. T cells, on the other hand, can start to kill healthy cells and tissues if they remain active for too long or react to things they shouldn't. As a result, other checkpoints assist in instructing T cells to turn off. Protein levels are elevated in some cancer cells. These can turn off T lymphocytes, which are supposed to be fighting cancer cells. As a result, cancer cells are putting the immune system on hold. And the T cells can no longer recognize and kill cancer cells.Drugs that block checkpoint proteins are called checkpoint inhibitors. They prevent cancer cells' proteins from pressing the stop button. This reactivates the immune system, allowing T cells to locate and kill cancer cells.

Types:

These drugs block different checkpoint proteins including:

- CTLA-4 (cytotoxic T lymphocyte associated protein 4)
- PD-1 (programmed cell death protein 1)
- PD-L1 (programmed cell death ligand 1)

CTLA-4 and PD-1 are found on T cells. PD-L1 are on cancer cells.

1. **PD-1:**
   Checkpoint inhibitors that block PD-1 include:
   - nivolumab (Opdivo)
   - pembrolizumab (Keytruda)

2. **CTLA-4:**
   Ipilimumab (Yervoy) is a CTLA-4-blocking checkpoint inhibitor. It is used to treat advanced melanoma and renal cell carcinoma.

3. **PD-L1:**
   Checkpoint inhibitors that block PD-L1 include:
   - atezolizumab
   - avelumab
   - durvalumab

Avelumab is a treatment for Merkel cell carcinoma (MCC), a kind of skin cancer that has migrated to other regions of the body. It's also used to treat some malignancies of the urinary system (urothelial cancers). Durvalumab is a non-small cell lung cancer therapy (NSCLC) [17].

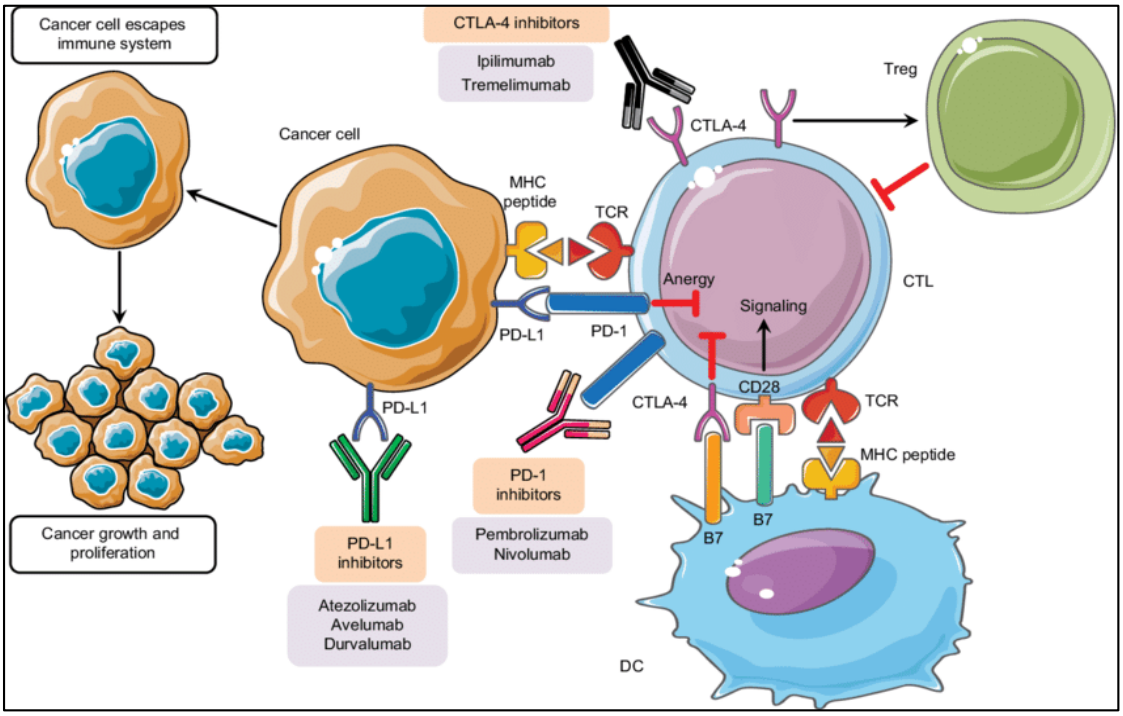

Figure 5: Immune checkpoint inhibitors in cancer therapy

Side effects:

These medications enhance all immune cells, not only cancer-fighting ones. As a result, hyperactive T cells may have unintended consequences. These might include:

- tiredness (fatigue)
- feeling or being sick
- dry, itchy skin, skin rash
- loss of appetite
- diarrhea
- breathlessness and a dry cough, caused by inflammation of the lungs

Table-2: Immune checkpoint inhibitors and their US FDA/EMA/China NPMA approved applications [11]

Immune checkpoint inhibitor	Targets	US FDA/EMA Approved Indications.	China NPMA approved indications.
Pembrolizumab	PD-1	Melanoma, non-small cell lung cancer, head and neck cancer, Hodgkin's lymphoma, urothelial carcinoma, MSI-H/dMMR colorectal cancer, MSI-H/dMMR cancers, gastric cancer, cervical cancer, hepatocellular carcinoma, Merkel cell carcinoma, renal cell carcinoma, small cell lung cancer, oesophageal carcinoma, endometrial cancer	Melanoma, non-small cell lung cancer
Nivolumab	PD-1	Melanoma, non-small cell lung cancer, renal cell carcinoma, Hodgkin's lymphoma, head and neck cancer, urothelial carcinoma, MSI-H/dMMR colorectal cancer, hepatocellular carcinoma, small cell lung cancer	Non-small cell lung cancer
Atezolizumab	PD-L1	Urothelial cancer, non-small cell lung cancer, breast cancer, small cell lung cancer	Non-small cell lung cancer
Durvalumab	PD-L1	Urothelial carcinoma, non-small cell lung cancer	-
Avelumab	PD-L1	Merkel cell carcinoma, urothelial carcinoma, renal cell carcinoma	-
Cemiplimab	PD-1	Cutaneous squamous cell carcinoma	-
Ipilimumab	CTLA4	Melanoma, metastatic, renal cell carcinoma, MSI-H/dMMR colorectal cancer	-
Toripalimab	PD-1	-	Melanoma
Sintilimab	PD-1	-	Hodgkin's lymphoma
Camrelizumab	PD-1	-	Hodgkin's lymphoma
Tislelizumab	PD-1	-	Hodgkin's lymphoma

Cytokines Therapy:

Cytokines are a type of protein found in the body that aids in the immune system's function. The body produces cytokines such as interferon and interleukin. To treat cancer, scientists have created man-made replicas of these. The man-made version of interleukin is called aldesleukin. Interferon and aldesleukin work in several ways, including:

- interfering with cancer cells' ability to grow and multiply
- activating the immune system and encouraging killer T cells and other cells to attack cancer cells.
- encouraging cancer cells to generate substances that attract immune system cells to them

1. **Interferon:**

   Interferon is also known as Intron A or interferon alpha. Interferons are no longer often utilized. Instead, the usage of newer types of immunotherapy medications has risen. However, interferon can be used to treat a variety of cancers, including:

   - kidney cancer (renal cell cancer)
   - some types of leukemia
   - skin (cutaneous) lymphoma

2. **Aldesleukin:**

   Interleukin 2, or Proleukin, is another name for Aldesleukin. It is most commonly used in the treatment of kidney cancer. It's also utilised in clinical trials for a variety of different cancers. It is administered subcutaneously.

Side effects:

The side effects of interferon and aldesleukin include:

- a drop in blood cells causing an increased risk of infection, bleeding problems, tiredness and breathlessness
- flu-like symptoms
- diarrhea
- tiredness and weakness (fatigue)
- feeling sick
- loss of appetite

Aldesleukin can also cause low blood pressure [18].

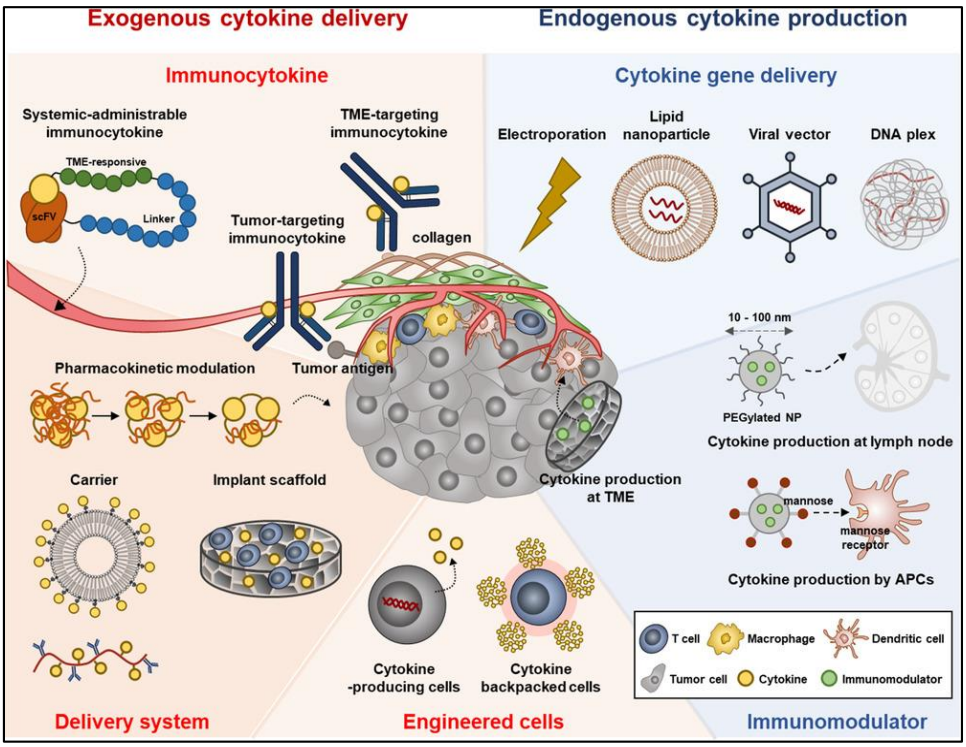

Figure 6: Cytokines in cancer therapy

Vaccine Therapy:

Cancer therapy vaccinations, unlike vaccines that protect us from disease, are for patients who have already been diagnosed with cancer. Cancer vaccinations assist your immune system in identifying and attacking cancer cells. Vaccines are designed to detect proteins found on certain cancer cells. Antigens are substances that cause the immune system to react to them. Antigens on the surface of a virus, for example, cause the immune system to attack it. Antigens are found on both body cells and cancer cells. Antigens detected in cancer cells are known as tumour associated antigens. Normal cells either don't carry these antigens or have a very minimal amount of them. Vaccines for cancer treatment assist your immune system recognize these antigens and attack and destroy them.

Types of Cancer Vaccines:

1. Protein or peptide vaccines: These vaccines are made from special proteins in cancer cells. Or from small pieces of protein (peptides). They try to boost your immune system's ability to fight cancer. Many cancer cell proteins' genetic codes have been deciphered, allowing scientists to mass-produce them in the lab.

2. DNA and RNA vaccines: These vaccines are made with bits of DNA or RNA that are usually found in cancer cells. They can be injected into the body to improve the immune system's ability to recognize and destroy cancer cells.
3. Whole cell vaccines: A whole cell vaccine uses the whole cancer cell, not just a specific cell antigen, to make the vaccine. In the lab, cancer cells are modified to make them easier to detect by the immune system.
4. Dendritic cell vaccines: Dendritic cells help the immune system recognize and attack abnormal cells, such as cancer cells. Dendritic cells are grown alongside cancer cells in the lab to create the vaccine. Your immune system is thus stimulated to attack the cancer as a result of the vaccine.
5. Virus vaccines: Viruses are used as a type of carrier to deliver cancer antigens into your body. They alter the viruses so that they are no longer capable of causing significant sickness. The modified virus is referred to as a viral vector.

To deliver cancer antigens into your body, some vaccinations use a viral vector. The viral vector elicits a response from your immune system. And this then helps your immune system to recognize and respond to the cancer antigen.A treatment called T-VEC (talimogene laherparepvec), also known as Imlygic, is similar to virus vaccines. It makes use of a cold sore viral strain (herpes simplex virus). The virus has been altered by changing the genes that control how it behaves. It instructs the virus to target cancer cells while ignoring healthy cells. This procedure also appears to assist the immune system in locating and eliminating other cancer cells[19].

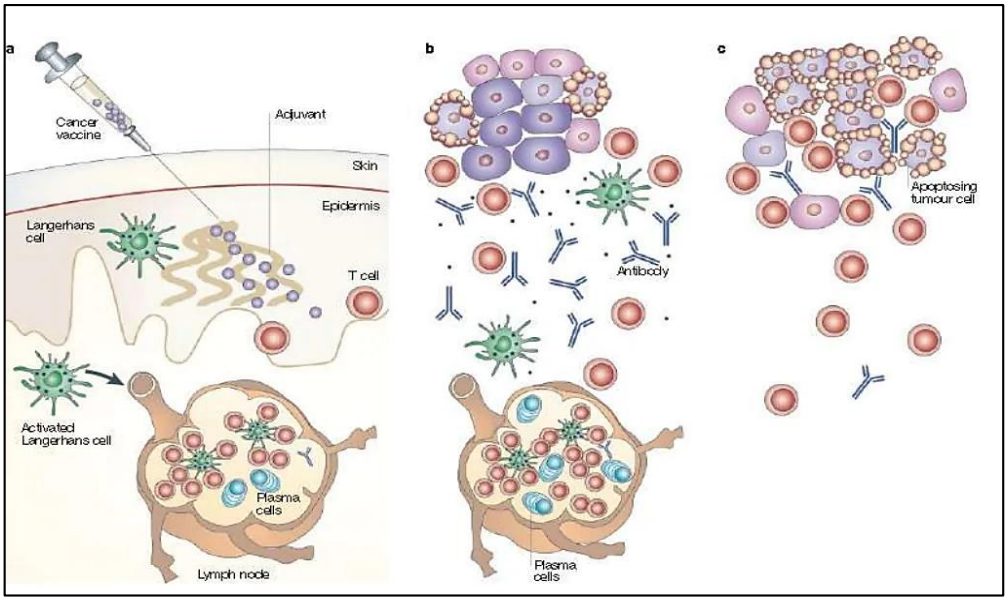

Figure 7: Vaccines for cancer immunotherapy

Side effects:

- redness, swelling, mild pain or itching where you have the injection
- Flu like symptoms such as feeling unwell or a high temperature (fever) for a few days.

CAR T-cell therapy:

Chimeric Antigen Receptor T-cell therapy is a difficult and specialised procedure. A expert harvests and modifies your T cells as part of this treatment. After a few weeks, you'll receive a drip that will reintroduce these cells into your bloodstream. The CAR T-cells then recognise the cancer cells and attack them. CAR T-cells have been engineered to recognise and attack a specific protein on cancer cells[20].

T cells are extracted from the patient's blood and genetically modified in the lab by adding a gene for a man-made receptor (called a chimeric antigen receptor or CAR). This aids in the identification of specific cancer cell antigens. After that, the CAR T cells are returned to the patient. Because various tumours have distinct antigens, each CAR is tailored to the antigen of a given tumour. The cancer cells in certain types of leukaemia and lymphoma, for example, have an antigen called CD19. CAR T-cell treatments for certain tumours are designed to connect to the CD19 antigen and will not work if the CD19 antigen is missing[31].

Side effects:

- Allergic reaction
- Cytokine-release syndrome
- Changes in the brain (neurological side effects)
- Increased risk of infection
- High uric acid levels in the blood, due to cancer cells breaking down quickly (tumour lysis).

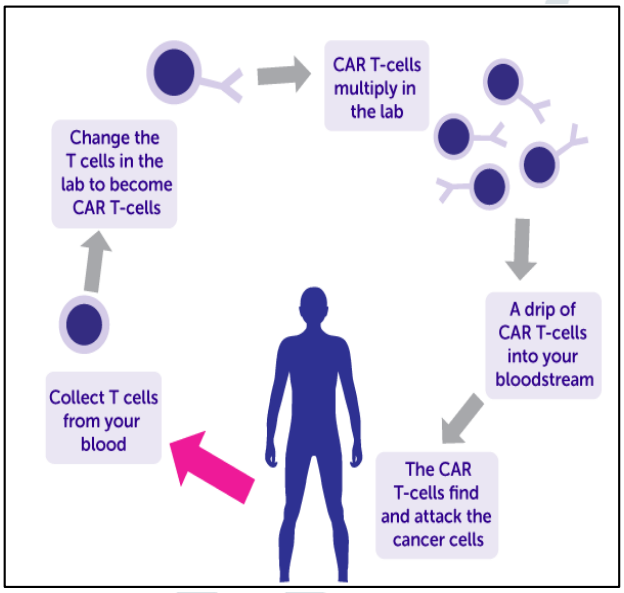

Figure 8: CAR T-cell therapy

Increasing the responsiveness of tumours to the immune system:

Tumour immunogenicity varies a lot between cancers of the same type in different people, as well as between different cancers. Some cancers, such as pancreatic ductal adeno-carcinoma are considered to be non-immunogenic (i.e., lacking the ability to induce an immune response) [21]. Common features of non-immunogenic tumours include a lack of tumour-infiltrating lymphocytes (TILs) and a lower response to immunotherapy [21,22]. An elevated neutrophil/lymphocyte ratio (from baseline) has been correlated with poor patient outcomes following immunotherapy across multiple cancer types [23]. A promising related treatment strategy has emerged basedon categorising tumours as ‘hot’ or ‘cold’ from an immunological perspective. For example, if the tumour microenvironment contains antigen-specific CD8 TILs, it is considered 'hot,' since lymphocyte infiltration corresponds with inflammation, and this has the effect of increasing inflammation potential to act as a biomarker to determine whether a tumour will respond to IO therapy. The aim is to transform ‘cold’ tumours into ‘hot’ tumours, thus increasing their responsiveness to IO agents and to prevent these tumoursfrom ‘cooling off’ and becoming unresponsive to therapy.

An oncolytic virus, which promotes a robust anti-viral immune response, has also been proposed as a way to boost the immunogenicity of tumours[24]. The resulting cytokine production (e.g., type-1 interferons) can directly promote the expression of PD-L1, while chemokines (e.g., CCL3 and CCL4) can attract PD-1/CTLA-4-expressing immune cells. This increased expression of cell-surface targets and infiltration of immune cells can facilitate the binding of ICPis and facilitate their effects. A small phaseIb trial has demonstrated that intra-lesional injection of herpes simplex virus (i.e., talimogene laherparepvec) in combination with systemic anti-PD-1 treatment results in a 62% ORR (and 33% complete response rate) in patients with metastatic melanoma. Although chemotherapy and radiotherapy are generally regarded as immunosuppressive, it is now accepted that they can work synergistically with IO-based therapies to achieve additive clinical benefit[25]. The mechanism is thought to involve induction of immunogenic cell death by chemotherapy that causes the release of damage-associated molecular patterns — host bio-molecules with the ability to initiate an inflammatory immune response that can increase the responsiveness to IO agents.

Future of Immunotherapy:

Instead of focusing on the pathways implicated and the expression of certain biomarkers in tumours, regardless of their origin or location (i.e., ‘tissue agnostic' therapies), IO medicines are currently rarely licence for a single kind of cancer [26]. The FDA's first tumour-agnostic approval of Keytruda in 2017 for patients with unresectable or metastatic solid tumours based on their MSI-high and dMMR status, rather than the location or origin of the tumour, demonstrates this pan-cancer strategy. Merck, which developed Keytruda, is now seeking a second pan-cancer indication for the TMB biomarker in order to broaden patient access even more [27]. There has been a similar trend towards a tumour agnostic approach in the small-molecule oncology area; forexample, in the past two years, the kinase inhibitors Larotrectinib and entrectinib have been granted accelerated approval by the FDA for use in patients with any solid tumour-type that has theNTRK fusion mutation[28]. To date, two comprehensive studies of the global IO landscape have been conducted[29,30]. Over a one-year period, between 2017 and 2018, it was establishedthat the global IO pipeline had increased by 67%, with cell therapy showing the most significant increase of 113% in the numberof active agents, followed by other immunomodulatory (e.g.,aldesleukin and interferons; 79%) and T-cell-targeted immunomodulatory therapies (76%). Importantly, the number of IO targets increased by 50% from 2017 to 2018, indicating that the IO landscape may be significantly expanded in the future. It's worth noting that within the same time span, the number of agents being developed against non-tumour-specific antigens actually declined, implying that IO is becoming excessively focused on a few select targets. In both the pharmaceutical business and academics, however, there is growing interest and enthusiasm for the IO field. In addition, clinical data suggest that IO agents havesignificant potential for the future and may lead to several breakthrough treatments that could improve the standard of care inmany different cancer types.

Conclusion:

IO is a fundamentally different approach to cancer therapy and is redefining the way that both solid and haematological tumours are treated. However, this new treatment pattern is still in its infancy, and there is still much work to be done in terms of optimising the use of these novel medicines, reducing their side effects, and learning how to integrate them into the present standard of care. Furthermore, given their high cost, integrating them into healthcare systems in an economically sustainable manner while boosting patient availability will be difficult. ICPs have been at the centre of the recent IO revolution, with two key antibodies (pembrolizumab and ipilimumab, respectively) getting multiple approvals for PD-1/PD-L1 and CTLA-4 inhibition. Because of their success, there has been a lot of talk about combining IO medicines with traditional therapy. Despite their potential clinical usefulness, the ICPis cause substantial side effects in some patients. These side effects are common, although they differ from those encountered with traditional cancer treatments. As a result, clinical research is increasingly focusing on managing and anticipating these side effects, as well as tracking long-term outcomes. This should lead to guidelines on how to manage these new therapies and encourage practitioners to include them into treatment pathways as soon as possible.

REFERENCES

1. https://www.cancer.gov/about-cancer/understanding/what-is-cancer (accessed Dec 2021).
2. https://www.cancer.gov/about-cancer/understanding/what-is-cancer#genes-causing-cancer(accessed Dec 2021).
3. https://www.cancer.gov/about-cancer/understanding/what-is-cancer#types(accessed Dec 2021).
4. https://www.immunooncology.com/about-io (accessed Dec 2021)
5. https://www.proclinical.com/blogs/2017-9/uncovering-the-futureofimmunooncology-cancer-therapies (accessed Dec 2021).
6. https://www.healthpolicypartnership.com/app/uploads/What-is-immuno-oncology.pdf (accessed Dec 2021).
7. Coley WB, The treatment of malignant tumours by repeated inoculations of erysipelas: with a report of the original cases. *Am J Med Sci* (1893) 105:487-511. doi:10.1097/00000441-189305000-000017
8. Ichim CV. Revisiting immunosurveillance and immunostimulation: implications for cancer immunotherapy. *J Transl Med* (2005) 3(1):8 doi:10.1186/1479-5876-3-8
9. https://www.bio-rad-antibodies.com/immuno-oncology-minireview.html (accessedDec2021).
10. Finn OJ. Cancer immunology. N Engl J Med 2008; 358: 2704–2715.
11. Chongxian Pan, Hongtao Liu, Elizabeth Robins, Wenru Song, Delong Liu, Zihai Li and Lei Zheng. Next-generation immuno-oncology agents: current momentum shifts in cancer immunotherapy. *Pan et al. Journal of Haematology& Oncology* (2020) 13:29.
12. Cody Barbari, Tyler Fontaine, Priyanka Parajuli, Narottam Lamichhane, Silvia Jakubski, Purushottam Lamichhane and Rahul R. Deshmukh," Immunotherapies and Combination Strategies for Immuno-Oncology", *International Journal of Molecular Sciences*,21, 5009, **2020**
13. Carter Sophie, Thurston David E." Immuno-oncology agents for cancer therapy". *The Pharmaceutical Journal. VOL 304 NO 7937 2020*.
14. Monjazeb, Arta M., et al. "The role of antigen-specific and non-specific immunotherapy in the treatment of cancer." Journal of immunotoxicology 9.3 (2012): 248-258.
15. Thallinger, Christiane, et al. "Review of cancer treatment with immune checkpoint inhibitors." Wiener Klinische Wochenschrift 130.3-4 (2018): 85-91.
16. https://www.cancerresearchuk.org/aboutcancer/cancergeneral/treatment/immunotherapy/types/monoclonal-antibodies (accessed Dec 2021).
17. https://www.cancerresearchuk.org/aboutcancer/canceringeneral/treatment/immunotherapy/types/checkpoint-inhibitors (accessed Dec 2021).
18. https://www.cancerresearchuk.org/aboutcancer/canceringeneral/treatment/immunotherapy/types/cytokines (accessed Dec 2021).
19. https://www.cancerresearchuk.org/aboutcancer/canceringeneral/treatment/immunotherapy/types/vaccines-to-treat-cancer (accessed Dec 2021).
20. https://www.cancerresearchuk.org/aboutcancer/canceringeneral/treatment/immunotherapy/types/CAR-T-cell-therapy(accessed Dec 2021).
21. Lutz ER, Wu AA, Bigelow E et al. Immunotherapy converts non-immunogenicpancreatic tumours into immunogenic foci of immune regulation. Cancer Immunol Res 2014;2(7):616–631. doi: 10.1158/2326-6066.CIR-14-0027
22. Blank CU, Haanen JB, Ribas A & Schumacher TN. The "cancer immunogram".Science 2016;658–660. doi: 10.1126/science. aaf2834
23. Cassidy MR, Wolchok RE, Zheng J et al. Neutrophil to lymphocyte ratiois associated with outcome during ipilimumab treatment. EBioMedicine 2017; 18:56–61. doi:10.1016/j.ebiom.2017.03.029
24. Gujar S, Pol JG & Kroemer G. Heating it up: oncolytic viruses make tumourshot and suitable for checkpoint blockade immunotherpies. Oncoimmunology2018;7(8): e1442169. doi: 10.1080/2162402X.2018.1442169
25. Kershaw MH, Devaud C, John LB et al. Enhancing immunotherapy usingchemotherapy and radiation to modify the tumour microenvironment. Oncoimmunology 201;2(9): e25962. doi: 10.4161/onci.25962
26. Flaherty KT, Le DT & Lemery S. Tissue-agnostic drug development. Am SocClin Oncol Educ Book 2017; 37:222–230. doi: 10.1200/EDBK_173855
27. Ray T. Merck bid for second pan-cancer Keytruda indication would raisetumour mutation burden to CDx status. 2020. Available from: https://www.genomeweb.com/molecular-diagnostics/merck-bid-second-pan-cancer-keytruda-indication-would-raise-tumour-mutation (accessed Dec 2021)

28. Gray A. Going against type: the new class of cancer therapies targetingmutations rather than tissues. Pharm J 2020;304(7935):164–166. doi: 10.1211/PJ.2020.20207799
29. Tang J, Shalabi A & Hubbard-Lucey VM. Comprehensive analysis of the clinical immuno-oncology landscape. Ann Oncol 2018;29(1):84–91. doi: 10.1093/annonc/mdx755
30. Tang J, Pearce L, O'Donnell-Tormey J et al. Trends in the globalimmuno-oncology landscape. Nat Rev Drug Discov 2018;17(11):783–784.doi: 10.1038/nrd.2018.167
31. https://www.cancer.org/treatment/treatmentsandsideeffects/treatmenttypes/immunotherapy/car-t-cell1.html (accessed Dec 2021)