ISSN Print: 2394-7500
ISSN Online: 2394-5869
Impact Factor: 8.4
IJAR 2023; SP4: 125-132

Harsha Chopra
DPG Degree College, Gurugram, Haryana, India

Khyati Bhargava
DPG Degree College, Gurugram, Haryana, India

Swati Sharma
DPG Degree College, Gurugram, Haryana, India

Correspondence
Swati Sharma
DPG Degree College, Gurugram, Haryana, India

(*Special Issue*)
"National Conference on Multidisciplinary research for sustainable development"

Cancer immunotherapy: A review

Harsha Chopra, Khyati Bhargava and Swati Sharma

Abstract
Cancer malignancies are one of the prime causes of death in the industrialized nations hence, the need to diagnose, treat and therefore prevent its spread and reoccurrence is of utmost importance to medical professionals and other individuals. In most cases, primary tumors are treated effectively by single or combination of traditional therapy methods; however, the prevention of metastasis and spread to various distant sites is ineffective. Therefore, the main objective of ongoing cancer researches is to eradicate the formation of distant metastases born through disseminated tumor cells which are present along with the circulations of blood and lymph fluids and in other organs. Latest study is always exploring for better and much more precise approaches to cure and manage malignancy. Cancer immunotherapy, which aims to reawaken the body's immunological responses to cancer, is exhibiting promising results in various kinds of tumors and cancers, including lung and bronchus cancers, kidney cancers, neck and head cancers, melanoma and also Hodgkin's lymphoma. The initial article talks about the disease of cancer along with the traditional treatment strategies. The later part mentions the recent advancements in cancer therapies which is basically an immunotherapy and its types.

Keywords: Cancer, immunotherapy, checkpoint inhibitors, CAR T-cells, targeted antibodies, monoclonal antibodies, oncolytic virus therapy, Cancer vaccine

Introduction
Cancer is a disease which is among the most common causes of death in humans in both the developed and developing countries. It is a disease characterized by uncontrolled growth of cells and their unregulated proliferation. Cancer or tumor cells are said to have certain distinguishing features which contribute to the disease's initiation and further progression. These factors that determine the growth of cells and the disease are termed as 'Cancer Hallmarks'. One of it is the avoidance of the destruction of the immune system which is generally a result of the poor regulation. Almost half of the cases reported yearly result in complications and eventually death. But, owing to the improved medical facilities, diagnosis and treatment regime and also the efforts put in cancer research and studies, cancer survival has approximately doubled in the past 4 decades. This has been made possible with efforts in prevention, early diagnosis and effective treatment.

Data suggests that annually out of the total cancer cases reported, around 1% of the diagnosed individuals die [1]. The data of 2008-14 regarding the 5-year survival rate suggests and ranges between 60-80% for colon and rectum, bladder and cervix cancers and between 20-40% for patients diagnosed with oesophagus, lungs and bronchus, stomach and various brain and nervous tissue cancers. It is above 90% for breast and prostate cancers whereas below 10% for cancer of the testes. Exact data for various types of cancers is depicted graphically in Figure 1. (Data from www.cancer.org)

Cancer malignancies are one of the prime causes of death in the industrialized nations hence, the need to diagnose, treat and therefore prevent its spread and reoccurrence is of utmost importance to medical professionals and other individuals. In most cases, primary tumors are treated effectively by single or combination of traditional therapy methods; however the prevention of metastasis and spread to various distant sites is ineffective.

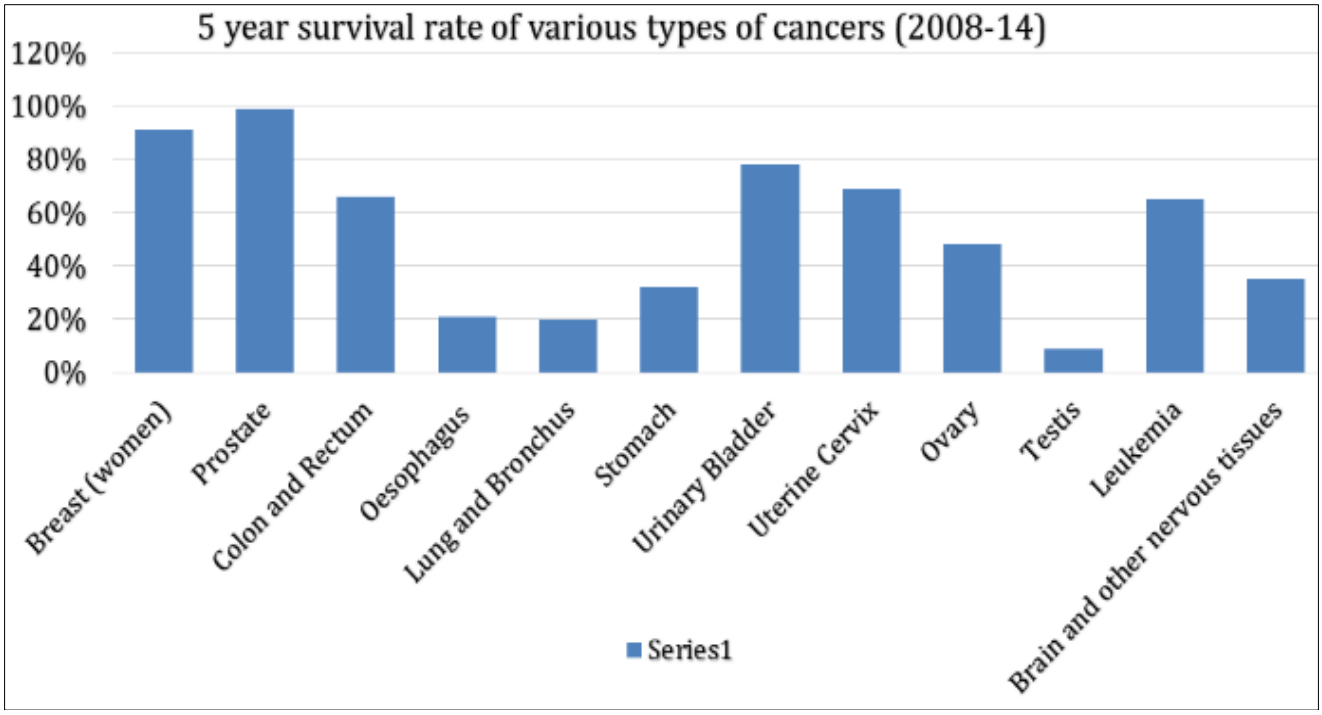

Fig 1: Graphical representation for percentages of 5 year survival rate of various types of cancers for the period 2008-14 (data through www.cancer.org)

Therefore, the main objective of ongoing cancer researches is to eradicate the formation of distant metastases born through disseminated tumor cells which are present along with the circulations of blood and lymph fluids and in other organs. Currently used and established cancer therapies include chemotherapy, radiation therapy, surgery or a combination of two or more of these. Remarkable breakthroughs in cancer monitoring and therapy have resulted in considerable reductions in cancer suffering and fatality. These, on the other hand, are frequently linked to undesirable side effects like vomiting, exhaustion, and baldness. Latest study is always exploring for better and much more precise approaches to cure and manage malignancy.

Cancer immunotherapy [2], which aims to reawaken the body's immunological responses to cancer, is exhibiting promising results in various kinds of tumors and cancers, including lung and bronchus cancers, kidney cancers, neck and head cancers, melanoma [1] and also Hodgkin's lymphoma [2]. The immune system is widely recognized for safeguarding us against a variety of illnesses, but it is now proven to have a role in cancer detection and destruction. Preliminary researches showed that activating the immune system could aid in the fight against cancer; we presently understand for sure that the immune system performs a critical function in recognising and destroying cancer cells. Immuno-surveillance is the process of the immune system continually searching for alterations and abnormalities in tissues that might contribute to disease. Cancer can arise when immuno-surveillance falters. The production of altered versions of host proteins termed as cancer antigens or tumor associated antigens (TAAs) is one of the modifications that transform a normal cell into a cancerous one. These help the immune system identify diseased tissues by distinguishing cancerous cells from healthy, normal cells. Cancerous cells, on the other hand, are genetically unstable and develop variations with features that allow them to conceal from the immune system, such as inhibiting TAA expression or sequestering immunosuppressive chemicals. The specialised cells of the immune system act by killing majority of the tumor or cancerous cells, but the cells which have been mutated to form variants often hide from the immune system and thus, they are left behind unharmed and continue to grow and proliferation resulting in a mass of tumors and eventually cancer. These cells or mass develop resistance against the immune system and evade immunity. The main focus of recent cancer researches is to bypass this evasion in order to achieve novel therapeutic advancements in cancer therapy.

Cancer Immunotherapy

Immune system, that is our body's natural defence against foreign pathogens or anything which doesn't belong to the body, is proven to protect us from various types of including the detection and eventual destruction of cancer cells [3, 4]. However, these cancerous cells develop resistance against the immune system or in other words simply disguise themselves in the face of normal cells to prevent their destruction by the cells of our immune system. This way they try to evade immunity in order to carry on with the progression of the disease. Immunotherapies are a novel group of cancer treatments that act by strengthening or manipulating the immune function to re-establish a targeted removal of tumor cells.

Immuno-surveillance is a notion that envisions the premature killing of aberrant cells by the host's individual immune systems to avoid the emergence of malignancies. As a result, an absence of or avoidance from immune-surveillance serves as an important function in cell proliferation and subsequently formation of tumors and cancer. This might be linked to tumor cells eluding immuno-surveillance, which in particularly appears to be an avoidance from specialized T cell-mediated immunity [5].

[1] A type of skin cancer
[2] A type of lymphoma (cancer of lymphatic system)

Mutations in genes encoding proteins involved in directing biochemical events that affect cell proliferation are frequently linked to tumorigenesis [3]. Malignant tumor cells, as a result, have an uncontrollable and disorganised growth pattern. Specific metastatic cells have the potential to infect adjoining normal tissue as the tumor grows, resulting towards the spread of the disease spread. Moreover, cancerous cells can also split free from a malignant tumor mass and migrate to other regions of the body. Tumor cells frequently express unusual proteins called tumor-associated antigens (TAAs), that have no or extremely restricted expression in healthy cells owing to their genetic instabilities. TAAs like this reveal distinct, presumably immunological epitopes that the host's immune cells can detect. Surprisingly, the tumor is only marginally affected by the natural immune system response targeting such epitopes. For instance, endogenous tumor antigen specific antibodies have been found in a small percentage of individuals with CRC [4], but only in weak and insufficient, as estimated through titers. The cytotoxic immune reaction at the target tissue has been observed to be suppressed as tumorigenesis progresses, and invading T cells and antigen-presenting cells (APCs) frequently seem to be non-functional. Immuno-suppressed individuals with autoimmune disorders or who have undergone organ transplantation have been shown to have a connection among poor immuno-surveillance and the spontaneous onset of lymphoma or skin cancers. Furthermore, tumors have indeed been demonstrated to impair immuno-surveillance by secreting and sequestering certain kinds immunosuppressive substances such as transforming growth factor-β and interleukin IL-10 [6].

Cancer immunotherapy aims to reactivate the immune function of the patient to fight cancer. Coley, a surgeon based in New York who medicated patients with sarcoma [5] using Coley's toxin. It was a combination of bacteria like attenuated staphylococcus and streptococcus. He pioneered immunotherapy more than a century ago. Identical results have been observed following tuberculosis vaccination with attenuated or weakened form (Bacille Calmette Guerin, BCG) of bacteria closely related to *Mycobacterium tuberculosis* that is *Mycobacterium bovis*. Bladder cancer has been treated with the unspecific immunological activation that comes with BCG boosting. During the later parts of the twentieth century, modern cancer immunotherapy received a significant boost.

Firstly, Koehler and Milstein's discoveries of 'Hybridoma Fusion' technology established the opportunities for better, target-specific agents that could even be loaded with a cytotoxic substance. Secondly, the research and application of molecular genetics enabled the dissection of signalling pathways implicated in the development of cancer, such as epidermal growth factor signalling in breast cancer. Finally, the discovery of cytokines contributed to the array of cancer-fighting tools. Cancer immunotherapy, as an innovative therapeutic approach, has advanced dramatically in recent years and now delivers the clinical inventory. Immunotherapy, unlike other treatment interventions, focuses on preventing the disease from spreading to other parts of the body and improving the standard of living of those who are suffering. Immunotherapy strategies use a variety of compounds to compliment or activate the immune system, including vaccinations, *in vitro*-stimulated immune effector cells, lymphokines and antibodies.

These therapies offer the opportunity to produce long-term and effective eradication with reduced adverse effects in comparison to standard chemotherapy drugs or surgical procedures since they operate by activating a patient's natural immune response. Altogether, such drugs have the ability to address and perhaps even eliminate a few of humanity's most serious medical problems, such as cancer, by changing the activity of personal immune systems. Immunotherapy studies, from scientific knowledge to clinical testing, requires continuous and expanded funding to uncover the optimal cancer targets, processes, and therapeutic modalities.

Types of Cancer Immunotherapies

When an individual is undergoing treatment for cancer, they may want to know about the therapy they would be administered with. Moreover, if the doctor has recommended immunotherapy, either individually or with a combination of other traditional therapies, knowing the exact type of immunotherapy given becomes crucial. A few of the approaches involved in cancer immunotherapy are mentioned in this section (Fig 2) and how that is their plan of action. These are not all the immunotherapies available presently but are the ones that have earlier given promising effects and results and have had all the levels of clinical trials and approved by the FDA [6].

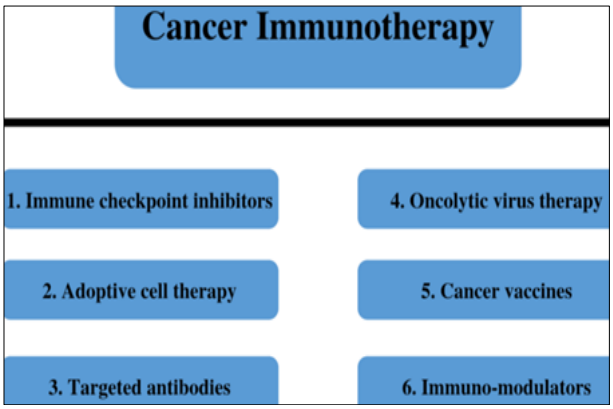

Fig 2: Types of cancer immunotherapy

Immune Checkpoint Inhibitors

Stop signalling or brakes, are integrated into the immune system. Whenever the immune system fights pathogens, it employs a system of "checkpoints" to prevent it from targeting their personal normal cells. These help to stop an immune reaction and avoid the immune system from destroying normal tissue in healthy people [7]. Several cancerous cells activate or deactivate these checkpoints in order to conceal. They take advantage of these stop signals (also known as immune checkpoints) to halt the immune reaction prematurely.

The immune checkpoints are found on the surface of either T-cells or tumor cells and functions to prevent T cells from becoming overactive. Under normal circumstances, these inhibitory checkpoint proteins are present to avoid damage caused by auto-immune diseases but upon encountering a tumor, it prevents T-cells from attacking the tumor,

[3] Formation of tumor mass
[4] Colorectal cancer
[5] Cancer that begins in the bone or soft tissues
[6] US Food and Drug Administration

decreasing the immune system's potential to recognise and eliminate tumor cells. The immunological response of T cells can be considerably activated and the anti-tumor immune response can be re-established by utilising ICIs [8]. Immunosuppressive checkpoints have been employed in a vast series of researches, and the amount of efficient immune checkpoints offered for immunotherapy is tremendous, but more specific sites are still being explored. The efficacy of ICIs is linked to the expression of biomarkers such PD-L1 activity, TMB [7] and MSI [8].

Immune checkpoint inhibitors are medications that allow the immune system to function normally. This form of immunotherapy, known as Keytruda and Yervoy, was recently licenced for treatment in melanoma[9] and is currently being studied in a variety of other cancers. Seven of such medications have been licensed for cancer treatment (Table 1). To allow immune cells to aggressively target cancerous proliferation, they inhibit the proteins PD-1 [10], PD-L1 [11], and CTLA-4 [12] on their surfaces [9].

Adoptive Cell Therapy

Adoptive cell therapy, also known as cellular immunotherapy, is a form of cancer immunotherapy in which the defense system's cells are used to fight cancer. Some of these treatments involve isolating and basically multiplying the number of our own immune cells, whereas others involve genetically manipulating our immune cells (through gene therapy) to strengthen their cancer-fighting abilities [13].

Our immune system is capable of identifying and destroying diseased or damaged cells as well as tumor cells. Because of their propensity to connect to markers called as antigens on the surface of cancerous cells, immune cells called as killer T-cells are extremely effective against malignancy. Cellular immunotherapies make use of this inherent potential and can be used in a variety of ways, as shown in table 2.

Targeted Antibodies

Targeted antibodies are a type of cancer immunotherapy that works by disrupting cancerous cell's function and alerting the immune system to track and destroy tumor cells.

Antibodies are proteins produced naturally by B cells, a type of defensive immune cell that protects individuals from a number of dangers including microbes, pathogens, and cancerous cells. Antibodies accomplish this by accurately targeting and attaching to antigens, which are cell surface markers [14]. They next enlist the help of other elements of the defence system to eliminate the malignancy. Our natural defence system has the potential to produce billions of distinct antibodies by itself. Experts can now create and customise antibodies targeting specific cancer antigens in the laboratory to strengthen our immune response. Because of their similar structure, these antibodies are commonly referred to as monoclonal antibodies. These monoclonal antibodies work in various ways as depicted in table 3.

The majority of targeted antibodies are classified as "passive" immunotherapies since they attack cancer cells directly instead of attacking our body's natural defensive cells. However, new and recent advancements have resulted in targeted antibodies that are classified as "active" immunotherapies since they also attack natural defensive cells (as in case of bispecific antibodies). Several distinct targeted antibodies are now being studied in drug development for a range of cancer varieties, both independently and in conjunction with other therapies, due to its cancer-targeting capabilities.

Oncolytic Virus Therapy

Viruses are the organisms that act by infecting or entering our cells and subsequently exploit the host's genetic machinery in an attempt to replicate itself and migrate to non-infected, healthy cells in the nearby area. Infections by specific viruses have been linked to the formation of tumors. For example, HBV [13] and HPV [14] have shown to cause liver cancers and cervical cancers respectively. Viruses have lately been employed for targeting and destroying cancers that have previously grown [16].

Oncolytic viruses are viruses that have been engineered in some way, although not all of them. They are a type of immunotherapy that involves infecting and destroying cancerous cells with viruses. They are a hopeful cancer treatment option for various reasons:

- These naturally occurring viruses can be modified to have beneficial qualities, such as reducing their propensity to invade normal cells and allowing them to carry therapeutic loads to cancer cells while also producing immune-boosting substances after they attack cancer cells.
- These oncolytic viruses can induce cancerous cells to "rupture," destroying them and revealing cancer antigens upon infection. These antigens can then trigger immune function that search for and destroy those residual cancer cells in the area, as well as elsewhere in the body.
- Antiviral defences in cancer cells are frequently compromised, making them vulnerable to infections.

Cancer Vaccines

Vaccines have been shown to be beneficial in avoiding viral and bacterial illnesses. Vaccines have avoided a few of the worst infections of the 20th century and aided protect hundreds and thousands of individuals around the world after they were initially introduced over 200 years back. Vaccines operate by individual exposure to an attenuated or inactivated variant of the danger in the instance of bacteria (tetanus, diphtheria, TB) or viruses (polio, measles, smallpox). This allows the body's natural defence system to recognise such dangers based on its unique markers, or "antigens," and develop a defence against such pathogens [12].

Cancer vaccines are a type of immunotherapy that trains the immune system how to recognise and remove cancerous cells by teaching it what they "look like". These vaccinations operate optimally in a preventive environment, meaning that they are administered to a person prior to the event of them getting the bacterial or viral infection. Unfortunately, in the context of cancer, the picture is highly complex considering a multitude of factors, making the development of vaccines to avoid or cure cancer extremely challenging. Cancerous cells, for instance, mimic our

[7] Tumor mutation burden
[8] Microsatellite instability
[9] Serious type of skin cancer when melanocytes become cancerous; malignant
[10] Programmed cell death protein 1
[11] Programmed death ligand 1
[12] Cytotoxic T-lymphocyte associated antigen-4
[13] Hepatitis B virus
[14] Human papilloma virus

typical, normal cells almost exactly as opposed to viruses and bacteria that are perceived by our immune system as strange and something that doesn't belong to our body. Additionally, every person's tumors are distinct in certain way and it has its own set of antigens. As an outcome, increasingly advanced methodologies to designing efficient cancer vaccines are required.

Preventive Cancer Vaccines

Several malignancies are caused by viral infections, and preventative vaccinations play a significant function in lowering the likelihood of development of the disease. For example, HPV and HBV are the causative organisms for certain types of cancers (as mentioned in section 3.4) Numerous vaccines have already been produced to safeguard against HBV and HPV infections and, as a consequence, the development of HBV and HPV-related tumors. FDA has approved four of such preventive cancer vaccines (Table 5).

Therapeutic Cancer Vaccines

Every person's tumor is distinct in a certain way and it has its own set of antigens. As an outcome, increasingly advanced methodologies to designing efficient cancer vaccines are required. Luckily, doctors now can detect targets on patients' tumor which can aid in the differentiation of cancerous cells from healthy cells. Normal proteins secreted at unusually elevated amounts by cancer cells are often used as targets, such as overexpression of PAP[15] by prostate cancer cells. With that knowledge, several vaccines have been approved by FDA (Table 5). Virus-derived molecules generated by virus-infected cancerous cells are also a prospective source of indicators that could be targeted by vaccinations.

Personalized Neo-antigen Vaccines

Tumors have specific targets that originate as a genetic marker, unlike normal-yet-overexpressed proteins like PAP. These are known as neo-antigens ("new antigens"), and they are only expressed by cancer cells and not by normal cells in an individual. As a result of neo-antigen vaccines, immunological reactions could be aimed accurately towards individuals' cancer cells while protecting other normal cells from immunological invasion, perhaps avoiding negative impacts. Various kinds of neo-antigen vaccines are presently being tested in clinical research in a range of cancer subtypes, either independently and in conjunction with other therapies.

2.6 Immune System Modulators (Immuno-Modulators)

Researchers have been able to design therapeutics to increase the immune system's potential to fight and remove malignancies because they have discovered much more regarding the brakes and gas pedals of the natural defence system. Immuno-modulators are substances that work on the immune system's activity-regulating pathways. These could be split into four distinct groups.

Checkpoint inhibitors

These are probably the most well-known and extensively used immuno-modulators ever created. Checkpoint inhibitors function by preventing tumors from manipulating immune checkpoints, often known as the immune system's "brakes," to block the immune reactions and help safeguard themselves. As a way, checkpoint inhibitors can both trigger newer immune reactions towards cancer and boost current ones, allowing cancerous cells to be eliminated.

The PD-1/PD-L1 immune checkpoint pathway, for instance, can inhibit cancer-targeting T cells. Checkpoint inhibitors, on the other hand, can help T cells kill cancerous cells by blocking the PD-1/PD-L1 pathway. Seven such checkpoint inhibitors have been approved by FDA (Table 1).

Cytokines

Cytokines are signalling proteins that control the development, proliferation, and response of immune cells. They include interleukins and interferons. There exists four FDA-approved cytokine immunotherapies (Table 6).

Agonists

Agonists stimulate the action of innate immunity like dendritic cells, which help to stimulate killer T-cells that also target cancerous cells actively, or assist to trigger killer T-cells, that further assists to synchronise general immune reactions against cancer by displaying disease markers and boosting T-cell function.

Adjuvants

Adjuvants enhance generalized immune reactions and, in turn, enhance adaptive immunity by activating innate immune response pathways. One such immunotherapy is FDA-approved (Table 6).

Conclusion

Since it is incredibly specialized and targets just the cells it needs to, the immune system is excellent at safeguarding us against infection. Cancer immunotherapy offers a comparable benefit in that it is extremely specific for cancerous cells and could be adjusted to the patient's specific cancer, making it a type of personalized treatment. They have fewer side effects as compared to traditional therapy methods like radiation and chemotherapy. It moreover increases the chances of long-term cancer relapse and lowers the chances of recurring by triggering a long-lasting immune response towards cancer. In the mainstream, cancer immunotherapy is presented as offering prospects for the long-awaited "cancer cure." But, because it is a new science, there are still a multitude of obstacles to address until cancer immunotherapy's true promise can be achieved. Immunotherapy for cancer is not really a "one-size-fits-all" approach. That is, while one therapy may be effective for one individual, that might not be effective for the other. The destiny of cancer therapy is anticipated to include a variety of individual immunotherapies, most likely in conjunction with traditional procedures and with the possibility for long-term or even life-long administration.

In conclusion, with the emergence of cancer immunotherapy and subsequent breakthroughs in the field, people with cancer appear to have a realistic chance of being cured. Cancer therapies have been changed by the advent of cancer vaccines, CAR-T cells, and checkpoint inhibitors. Combination therapy could be an effective cancer treatment technique in the long term. The ability to recognise and control the side effects of cancer immunotherapy would likewise be critical towards therapeutic efficacy. The most successful cancer therapy tactics will be personalised combined treatments that use innovative methods to target individual patient's disease genetics.

[15] Prostatic acid phosphatase

Table 1: Summary of Immune Checkpoint Inhibitors (ICIs) approved by FDA [10, 11, 12].

Immune Checkpoint Inhibitors (ICIs)	Expression site	Generic name	Trade name	Type of tumor being treated by the inhibitor	Adverse effects
PD-1 inhibitors	Tumor cells, dendritic cells, natural killer (NK) cells, monocytes, T-cell, B-cell	Pembrolizumab	Keytruda	Melanoma, NSCLC [16], classical Hodgkin's lymphoma, advanced stomach cancer, etc.	Vision problem, neck stiffness, blood in stools, bruising or bleeding, etc.
		Nivolumab	Opdivo	Metastatic melanoma, metastatic NSCLC, breast cancer, advanced renal cancer, etc.	Itching, fatigue, diarrhea, etc.
		Cemiplimab	Libtayo	Breast cancer, metastatic melanoma, CSCC [17], etc.	Breathing problem, swelling, increased or decreased urination, blood in urine, severe weakness, etc.
PD-L1 inhibitors	Tumor cells, dendritic cells, macrophages	Atzeolizumab	Tecentriq	Urothelial carcinoma, NSCLC, SCLC [18], TNBC [19]	Pneumonitis [20], hepatitis [21], swelling of face and lips, etc.
		Avelumab	Bavencio	MCC [22], RCC [23], urothelial carcinoma	muscle or bone pain, UTI [24], hypertension, hypothyroidism, jaundice, etc.
		Durvalumab	Imfinzi	Stage 3 NSCLC, SCLC, metastatic urothelial carcinoma	Swollen legs or arms, upper respiratory infection, allergic reactions, etc.
CTLA-4 inhibitor	Natural killer (NK) cells, activated T-cells	Ipilimumab	Yervoy	Metastatic melanoma, kidney cancer, colorectal cancer, pleural mesothelioma	Decreased appetite, muscle, bone or joint pain, hormonal problems, etc.

Table 2: Types of Cellular Immunotherapy [13]

Type of therapy	Features	Course of action	FDA approved therapy	Types of cancers treated by the therapy
Tumor-Infilterating Lymphocyte (TIL) Therapy	Utilises the property of immune cells, particularly T-Cells. These are powerful WBCs that are effectively able to fight infections; harvests naturally occuring T-cells that have already started to infiltrate the tumor mass	Removal of T-cells that have begun to fight and attack the tumor → growth of such cells in large batches (known as TILs) → activated fighters returned to the body of the diseases individual. [Isolation → activation → expansion → Re-infusion]	LN-145	Ovarian cancer, advanced cervical cancer, osteosarcoma, anaplastic thyroid cancer, soft tissue sarcomas
			ITIL-168	Melanoma,
Engineered T-Cell Receptor (TCR) Therapy	Employed in the case of patients whose T-cells have not been able to recognise the tumor mass; inactivated T-cells	Removal of T-cells from blood → T-cells reprogrammed (equipped with new T-cell receptor) in a laboratory, enabling them to find malignancies more conveniently by targeting specific cancer antigen. [Isolation → Equip new TCR → activation → expansion → re-infusion]	TCR therapy have yet to be approved by the FDA.	Individuals with particular forms of sarcoma and late-stage melanoma are being evaluated for this therapy.
Chimeric Antigen Receptor (CAR) T-Cell Therapy	Overcame the limitations shown by TIL and engineered TCR therapy (tumor cells are their only targets and are the ones that present antigen upon their surface via MHC are eliminated); CAR has the ability to bind to cancerous cells even in the absence of surface antigens via MHC.	Removal of T-cells → T-cells of the patient equipped with a synthetic receptor called CAR (Chimeric Antigen Receptor) [Isolation → Introduction OF CAR → RE-Infusion]	Generic Name: Tisagenlecleucel Trade Name: Kymriah (CD-19 targeting CAR T-cell therapy)	Large B-cell lymphoma, ALL [25]
			Generic Name: Axicabtagene ciloleucel Trade Name: Yescarta (CD-19 targeting	non-Hodgkin's lymphoma

[16] Non-small cell lung cancer
[17] Cutaneous squamous cell carcinoma
[18] Small cell lung cancer
[19] Triple negative breast cancer
[20] Inflammation of lung tissues
[21] Inflammation of liver cells/tissues
[22] Merkel cell carcinoma (rare and aggressive skin cancer)
[23] Renal cell carcinoma
[24] Urinary tract infection
[25] Acute lymphoblastic leukemia

			CAR T-cell therapy)	
Natural Killer (NK) Cell Therapy	Utilise the property of attacking foreign invaders of natural killer (NK) cells; employed with other cellular immunotherapies/ adoptive cell therapy.	Combining cancer targeting CARs with NK cells for more effective treatment	NKX019	Relapsed/refractory B Cell malignancies
			CYNK-001	GBM (Glioblastoma)

Table 3. Types of targeted antibodies [15]

Type of antibody	Features	FDA approved antibodies	Types of tumor treated by the antibody
Naked monoclonal antibodies (mAbs)	Called naked since they are not attached to any other thing; produced by B-cells; often works by binding to the cancer cell (target) via the variable region thereby causing disruption of the pathways that aid in the cell's uncontrolled proliferation; the constant region may bind to other immune cells or send signals for the recruitment of certain cells to destroy the cancer like macrophages.	Generic Name: Rituximab Trade Name: Rituxan (Targets CD-20 pathway)	Lymphoma, leukemia
		Generic Name: Trastuzumab Trade Name: Herceptin (Targets HER2 [26] pathway)	Breast cancer, stomach cancer, oesophageal cancer
Antibody-Drug Conjugates (ADCs)	Antibodies equipped with radioactive particles/ anti-cancer drugs/ chemotherapeutic drugs in order to deliver a toxic drug to destroy the cancer cell when the antibody attaches to it; reduces side effects; aids in improved effects of radiation and chemotherapy.	Generic Name: Belantamab mafodotin-blmf Trade Name: Blenrep (Targets BCMA [27] pathway)	Advanced multiple myeloma
		Generic Name: Enfortumab vedotin Trade Name: Padcev (Targets Nectin-4 pathway)	Advanced bladder cancer
Bispecific antibodies	Made by a combination of the variable ends of two different antibodies so as to enable them to bind to 2 different targets. BiTEs: target both cancer and immune cells (T-cells); bring both the cells in close proximity so that T-cells can destroy the cancer cells	Generic Name: Blinatumomab Trade Name: Blincyto (Targets CD-3 on T-cells and CD-19 on cancer cells)	Leukemia
		Generic Name: Amivantamab Trade Name: Rybrevant (Targets MET [28] and EGRF [29] receptors on cancer cells)	Lung cancer

Table 4: Summary of oncolytic virus therapy

Type of immunotherapy	Course of action	FDA approved oncolytic virus		Features of the approved virus	Type of cancer treated by the therapy
		Generic Name	Trade Name		
Oncolytic Virus Therapy	Infecting viruses engineered and modified to lessen their viral infective effect → infection to the host enabling it to produce necessary immunological response to fight the viral pathogen → cancer destruction	Talimogene laherparepvec	T-VEC, Imlygic	Engineered and modified HSV; target gene: GM-CSF [30], producing immune stimulating protein	Metastatic melanoma

Table 5: Cancer vaccine treatment options [13]

Type of Cancer Vaccine	FDA approved vaccines		Features of approved vaccine	Type of cancer treated by the vaccine
	Generic Name	Trade Name		
Preventive Vaccine		Cervarix	Against HPV types 16 and 18 infections that causes most cervical cancers	HPV related penile, vulvar, vaginal, cervical, anal and head and neck cancers
		Gardasil	Against HPV types 6, 11, 16 and 18 infections	HPV related penile, vulvar, vaginal, cervical, anal and head and neck cancers
		Gardasil-9	Against HPV types 16, 18, 31, 33, 45, 52, and 58 infections and genital warts caused by HPV types 6 or 11	HPV related penile, vulvar, vaginal, cervical, anal, head and neck and throat cancers
	Hepatitis B vaccine	HEPLISAV-B	Against HBV infections	HBV related liver cancers
Therapeutic Vaccine	Bacillus Calmette-Guérin	BCG	Weakened *Mycobacterium bovis* used	Early stage bladder cancer
	Sipuleucel-T	Provenge	Individual's stimulated dendritic cells used for vaccine	Advanced Prostate Cancer

[26] Human Epidermal Growth Factor Receptor 2
[27] B-cell maturation antigen
[28] Also called Hepatocyte growth factor receptor (HGRF)
[29] Epidermal growth factor receptor
[30] Granulocyte-macrophage colony stimulating factor

Table 6: Immuno-modulators treatment options under different types

Type of immuno-modulator		FDA approved immunotherapy		Target site	Types of cancers treated by the therapy
		Generic Name	Trade Name		
Cytokines	Interleukins	Aldesleukin	Proleukin	IL-2/IL-2R pathway	Melanoma, kidney cancer
	Interferons	Interferon alfa-2a	Zavinex	IFNAR1/2 pathway	Leukemia, sarcoma
		Interferon alfa-2b	Intron A	IFNAR1/2 pathway	Leukemia, sarcoma, melanoma, lymphoma
	Immunomodulatory	GM-CSF	Sargramostim	-	Neuroblastoma
Adjuvants		Poly ICLC	Hiltonol	TLR-3 pathway	Squamous cell carcinoma
Small molecules		Pexidartinib	Turalio	CSF1R, FLT3 and KIT pathways	Tenosynovial giant cell tumor

References

1. Vanaudenaerde J. Towards a personalised cancer vaccine: optimisation of Indel detection in a Neoantigen prediction pipeline (Doctoral dissertation, Ghent University); c2020.
2. Topalian SL, Weiner GJ, Pardoll DM. Cancer immunotherapy comes of age. Journal of Clinical Oncology. 2011;29(36):4828.
3. Dillman RO. Cancer immunotherapy. Cancer biotherapy & radiopharmaceuticals. 2011;26(1):1-64.
4. Tan S, Li D, Zhu X. Cancer immunotherapy: Pros, cons and beyond. Biomedicine & Pharmacotherapy. 2020;124:109821.
5. Drake CG. Combination immunotherapy approaches. Annals of oncology: official journal of the European Society for Medical Oncology. 2012;23(8):viii41–viii46.
6. Maecker B, von Bergwelt-Baildon MS, Anderson KS, Vonderheide RH, Anderson KC, Nadler LM, *et al*. Rare naturally occurring immune responses to three epitopes from the widely expressed tumour antigens hTERT and CYP1B1 in multiple myeloma patients. Clinical & Experimental Immunology. 2005;141(3):558-562.
7. Ward RL, Hawkins NJ, Coomber D, Disis ML. Antibody immunity to the HER-2/neu oncogenic protein in patients with colorectal cancer. Human immunology. 1999;60(6):510-515.
8. Guilloux Y, Viret C, Gervois N, Dréan EL, Pandolfino MC, Diez E, *et al*. Defective lymphokine production by most CD8+ and CD4+ tumor-specific T cell clones derived from human melanoma-infiltrating lymphocytes in response to autologous tumor cells *in vitro*. European journal of immunology. 1994;24(9):1966-1973.
9. Radoja S, Frey AB. Cancer-induced defective cytotoxic T lymphocyte effector function: another mechanism how antigenic tumors escape immune-mediated killing. Molecular medicine. 2000;6(6):465-479.
10. Zeier Martin, *et al*. Malignancy after renal transplantation. American Journal of Kidney Diseases. 2002;39(1):e5-1.
11. Kiessling Rolf, *et al*. Tumor-induced immune dysfunction. Cancer immunology, immunotherapy. 1999;48(7):353-362.
12. Salih HR, Nüssler V. Commentary: Immune escape versus tumor tolerance: how do tumors evade immune surveillance?. European journal of medical research. 2001;6(8):323-332.
13. Coley WB. The classic: The treatment of malignant tumors by repeated inoculations of erysipelas: With a report of ten original cases. Clinical Orthopaedics and Related Research®.1991;262:3-11.
14. Perabo FG, Willert PL, Wirger A, Schmidt DH, Von Ruecker A, Mueller SC. Superantigen-activated mononuclear cells induce apoptosis in transitional cell carcinoma. Anticancer research. 2005;25(5):3565-3573.
15. Köhler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. Nature. 1975;256(5517):495-497.
16. Liu L, Xie Y, Lou L. PI3K is required for insulin-stimulated but not EGF-stimulated ERK1/2 activation. European journal of cell biology. 2006;85(5):367-374.