Awoke Derbie , Daniel Mekonnen , Eyaya Misgan, Melanie Maier, Yimtubezinash Woldeamanuel, Tamrat Abebe, *Ethiop Med J, 2022, Vol. 60, No. 2*

LITERATURE REVIEW

ADVANCES IN CANCER IMMUNOTHERAPY: A REVIEW OF THE LITERATURE

Awoke Derbie[1, 2, 3*], Daniel Mekonnen[1, 3], Eyaya Misgan[4], Melanie Maier[5], Yimtubezinash Woldeamanuel[2, 6], Tamrat Abebe[6]

ABSTRACT

Background*: Conventional cancer treatment includes surgery, radiation, hormonal and chemotherapy, sometimes a combination of these. Each of these has limitations and serious side effects, which led to a search for new treatment options. Understanding tumor immunobiology and the complex interactions between immune cells and cancer pave the way for the introduction of a novel treatment approach called immunotherapy, which is a method that utilizes the body's immune system to fight cancer. As the subject is emerging, the review aimed to describe the present developments in the field of cancer immunotherapy.*

Methods*: Literature published in English were non-systematically retrieved from PubMed/Medline, SCOPUS, Google Scholar, and the Google database using relevant searching terms. Articles were prioritized and considered based on their originality and possible clinical applicability.*

Results*: Big interest in the field of cancer immunotherapy was inspired by the success of the most important products that achieved durable responses in patients with lethal stages of cancer. Two of these approaches were; a) immune checkpoint inhibitors that target the PD-1/CTLA-4 axes in advanced melanoma, lung, and renal cell carcinomas and b) adoptive cell therapy with chimeric antigen receptor (CAR) T-cells to treat leukemia and lymphomas. Immunotherapy either stimulates/boosts the activities of specific components of the immune system or counteracts signals produced by cancer cells that suppress immune responses. It can eliminate large tumor masses in advanced-stage cancer and elicit immunological memory that can lead to prolonged protection. Generally, cancer immunotherapy strategies currently being used in clinical settings and that are under different levels of trial include; monoclonal antibodies, adoptive transfer of ex-vivo activated T-cells, cancer vaccines, oncolytic viruses, cytokines, and use of recombinant proteins or antibodies that either stimulate the immune system or block the system inhibitory pathways.*

Conclusion*: The concept of cancer immunotherapy provides a new perspective in oncology as it artificially boosts the immune system and is not associated with many of the drawbacks of conventional cancer therapies. However, suboptimal vaccine design, an immunosuppressive cancer microenvironment, and better delivery strategies to improve the effectiveness of immunotherapy need further research.*

Keywords*: Cancer, tumor, immunotherapy*

BACKGROUND

Cancer is a generic term for more than two hundred large groups of diseases (1) that can affect any part of the body. It is characterized by the uncontrolled growth and spread of abnormal cells (2-4) that grow beyond their natural limits, and which can then invade the nearby parts of the body and could spread to other organs, the process called metastasis, which is a major cause of death from cancer (5).

In the past few decades, big steps have been made in elucidating the molecular mechanisms involved in the development of cancer. It is now clear that the transformation process involves somatic mutations that lead to activation of genes that are usually involved in the regulation of cell division and programmed cell death, as well as the inactivation of genes involved in the protection against DNA damage or driving apoptosis (6). Cancer cells are constantly formed in the body, which the immune system is continually destroying (7). However, cancer cells most often use different strategies to evade the immune system (8, 9).

There were an estimated 19.3 million new cases and 10.0 million cancer deaths globally in 2020. By the year 2030, the worldwide cancer burden is predicted to intensify to 21.7 million new cases and 13 million deaths annually (10).

There are varieties of treatment options depending on the type of cancer and how far it grows and spreads (11). The most common forms are surgery, radiation, transplantation, hormonal and chemotherapy. However, most cancer patients need a combination of these (9, 11). Each of these options have their own benefits but also limitations and paramount side effects, which led to a search for new treatment modalities. Immunotherapy, in which the immune system is targeted to launch anti-cancer activity, is a rapidly evolving novel treatment alternative in the fight against cancer (12).

Advances in the knowledge of immunology led to an improved understanding of the interactions

[1]Department of Medical Microbiology, College of Medicine and Health Sciences, Bahir Dar University, Ethiopia; [2]Centre for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa), Addis Ababa University, Ethiopia; [3]Department of Health Biotechnology, Biotechnology Research Institute, Bahir Dar University, Ethiopia; [4]Department of Gynecology and Obstetrics, College of Medicine and Health Sciences, Bahir Dar University, Ethiopia; [5]Department of Diagnostics, Institute of Virology, Leipzig University Hospital, Leipzig, Germany; [6]Department of Medical Microbiology, Immunology and Parasitology, College of Health Sciences, Addis Ababa University, Ethiopia

* Corresponding Author: E-mail: awoke.derbie@bdu.edu.et.

between the immune system and cancer cells, creating new interest in approaches that aim to treat cancer using this system (12). Immunotherapies either stimulate/boost the activities of specific components of the immune system or counteract signals produced by cancer cells that suppress immune responses (9). Strategies for generating a therapeutic immune response include the use of specific or monoclonal antibodies, adoptive T-cells transfer, immune checkpoint blockades, therapeutic vaccines, and other non-specific agents like cytokines. Approaches to unleash T-cells against tumors are particularly substantial, as the activities of T-cells present important features, which include specificity, memory, & diversity that are valued over other cancer therapies (6).

The field of cancer immunotherapy is flourishing and research findings are coming every day. With this context, the review aimed to describe the current developments on the principles of cancer immunotherapy and presently available cancer immunotherapeutic approaches. Professionals, especially those working in the field of oncology, could benefit from it both for their clinical and research practices.

METHOD

In this review of literature, we considered articles published in English on the subject of cancer immunotherapy. We conducted nonsystematic retrieval of papers from PubMed/Medline, SCOPUS, Google Scholar, and the Google database using relevant searching terms. Articles were prioritized and considered based on their originality and potential clinical relevance. Various algorithms including the following terms were used while searching literature: cancer, neoplasm, immunotherapy, cancer immunotherapy, types of cancer immunotherapy, checkpoint blockade, and cancer vaccines. The citations in this document were managed using EndNote X9.

RESULTS

Basics on tumor immunology

Cancer cells originate from several genetic and epigenetic events that deregulate homeostatic mechanisms controlling normal cell growth. However, the immune system, devoted to patrolling the organism against pathogenic events, can identify distorted cells, and in several cases cause their removal. It is however clear that several mechanisms encompassing both central and peripheral tolerance limit antitumor immunity, often resulting into progressive diseases. The acquired wing of the immune system is most relevant in managing the immune system, addressing intracellular infections (like viruses), and has evolved to be the most important part of the system in terms of controlling and exterminating cancer cells (1, 13, 14, 15).

Tumor immunology deals with the interaction between immune cells with cancer cells. Understanding this interaction is a milestone for the development of new approaches for cancer treatment (16). Long time evidence, first from animal models and later from studies in cancer patients, revealed that the immune system can recognize and reject transformed cells. Cancer immunology has been aimed at understanding the components of the immune system that are important for tumor immunosurveillance and tumor rejection to understand how, when, and why they fail in cases of clinical disease (1).

Cancer cells are identified and recognized by components of the immune system and their development can be stopped or controlled long-term through a process known as immunosurveillance by which altered cells with a potential to abnormally proliferating could be identified and eliminated. For this to function, cancer cells must display some new discriminating surface structure/antigen that can be recognized by the immune system (1, 17-20). These antigens could be recognized in two ways as non-self: by reacting against tumor-specific antigens or against tumor-associated antigens (fragments that are expressed by cancer cells and normal cells). Identification of tumor antigens recognized by T-cells is important for the forthcoming vaccine synthesis that marks tumors (1, 18, 21, 22).

Tumors are essentially invisible to T-cells until they are activated by antigen-presenting cells and because of cross priming by dendritic cells (DCs) that present tumor antigens. Recognition of tumor antigen and the costimulatory ligands by T-cells concurrently initiate a complex set of genetic programs that result in cytokine production, cell-cycle progression, and production of anti-apoptotic factors that result in proliferation and functional differentiation of T-cells. Consistent with the role of both antigen receptor and costimulatory signals in starting anti-tumor response, many vaccines identified for treatment nowadays integrate both antigen and DCs or agents that augment costimulatory signaling (6, 17). Once the cancer cells are recognized and the effecter cells are activated through cascaded of cytokines activations, the Cytotoxic T-lymphocytes (CTL) use different tools to eradicate tumor cells including exocytosis of granules containing the cytotoxic effector molecules perforin and granzyme and secretion of tumor necrosis

factor (TNF) and interferon-gamma (IFNg) that also have a tumoricidal effect (19).

The innate arm of the immune system has also a significant role in the fight against cancer. Macrophages, which often infiltrate a tumor mass, can destroy tumor cells in tissue culture through the copious production of reactive oxygen intermediates and TNF. Similarly, natural killer (NK) cells subserve a function as the earliest cellular effector mechanism against the dissemination of lymph and blood-borne metastases (19).

In general, understanding the basic principles that govern controlling immunity provided the rationale for the development of approaches to actively involve the immune system for cancer treatment. Approaches to unleash T-cells against tumors are particularly substantial, as the activity of these cells presents important features, which include specificity, memory, and diversity/adaptability that are advantageous over other cancer therapies (6).

Mechanism of evading the immune response

Tumors can occur among people who are not immunosuppressed. The findings from immunological studies, murine tumor models, and patients with cancer evidently showed that tumors have a number of mechanisms to escape the immune reaction (21, 23, 24) which is actually a major limiting factor in designing effective anticancer therapy (24).

During the early stages of tumor development, transformed cells can be poor stimulators, present poor targets, while at later stages; increasingly mounting tumors harm the acquired immune response by blocking the maturation and function of antigen-presenting cells (APCs) and causing changes in T-cell signal transduction and function. There is a correlation between some of these changes and an increased metastatic potential of a tumor, a diminished response to immunotherapy, and poor prognosis (23). Further, the majority of escape mechanisms from the routine surveillance are attributed to changes in the tumor cells themselves (loss of tumor antigens, loss of human leukocyte antigen molecules, loss of sensitivity to complement, or T cell or NK cell lysis), making them a poor target of an immune attack (1).

Tumor cells have also an intrinsic flaw in antigen processing or presentation as they lack co-stimulatory molecules such as the B7 (CD80 and CD86) molecules (19). There are reports indicating that CD80 is spontaneously expressed at low levels in tumor cells.

T-cell anergy occurs following antigen– major histocompatibility complex (MHC) recognition in the absence of co-stimulation. Furthermore, many tumors express reduced or absent levels of class-I MHC, which imparts resistance to Tc although presumably increasing susceptibility to NK cells. On top of these, tumors themselves may release various immunosuppressive factors such as transforming growth factor-b(TGFb), which is a potent immunosuppressive cytokine having effects on many mediators of the immune response including a potent inhibitory effect on differentiation of CTL [19]. Another immune evasion tactic is immune editing; one of the key features why tumors evade surveillance causing the tumors to lie latent in patients for years (24).

It is also stated that the incessant loading of vascular endothelial growth factor (VEGF), a factor produced by most solid tumors, inhibits the functional maturation of DCs, significantly decreases T-cell to B-cell ratios in the peripheral lymphoid organs, and causes rapid thymic atrophy among animals with tumor (21).
In general, mechanisms by which tumors evade the immune system include down-modulation of components of antigen processing and presentation machinery; employment of suppressor immune cells, such as regulatory T cells, myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages; production of soluble factors associated with immunosuppression, such as TGF-β and IL-10; and upregulation of ligands for co-inhibitory receptors such as programmed death ligand-1 (PD-L1) (1, 25).

Understanding the mechanisms used by tumor cells to evade immune system could result in new therapeutic approaches for preventing and/or reversing these immune alterations and could have the possibility of cultivating the present results of immunotherapy studies (23).

Immune function in cancer patients

In several cases, malignant progression is accompanied by profound immune suppression that interferes with effective antitumor activity and tumor elimination (1). It is often noted that there is a degree of systemic immune suppression among cancer patients (21). Approximately 60% to 70% of patients with some type of cancer can, in fact, be shown to have generalized systemic immunosuppression. While multiple factors such as stress and chemotherapeutic factors contribute to a reduced immune function, it is clear that tumor cells also directly induce suppression of immune responses by a number of strategies as stated above. These include secretion of cytokines,

which suppress or disrupt the robust antitumor effector responses, and mechanisms that make use of tumor cell surface receptors to modulate the function or kill immune cells. An additional means of immune suppression is when the tumor derives from the hematopoietic tissues and disrupts normal bone marrow function, resulting in reduced immune function (1, 25-27).

Cancer immunotherapy

General overview

Spontaneous tumor regression may occur following bacterial, fungal, viral, and protozoal infections. This achievement inspired the development of a number of initial cancer immunotherapies, with a history spanning thousands of years. William Coley, a US bone surgeon and cancer investigator, pioneer of cancer immunotherapy, took advantage of this natural phenomenon, developing a killed bacterial vaccine for cancer in the late 1800s. He observed that inducing a fever/ and inflammation was crucial for tumor regression (25, 28).

Conventional treatments for cancer include surgery, radiation, transplantation, hormonal and chemotherapy, and sometimes combination of these, which all have limitations and detrimental side effects. However, an increasing number of clinical trials are underway to stimulate the immune system to combat cancer (24, 29-31). The first checkpoint-inhibitor, which takes the molecular brakes off T-cells to unleash them on tumors was approved by the US FDA in 2011. In 2017, the FDA also approved two chimeric antigen receptor (CAR) T-cell treatments, in which a person's immune cells are re-engineered to attack cancers (7). The notion of cancer immunotherapy offers a renewed standpoint as it is not associated with many of the drawbacks of conventional therapies. When fully activated, the immune system has immense potential as is evident from mismatched transplanted organs undergoing rapid immunological attack and rejection (31).

Working principle of immunotherapy

Instead of targeting tumors directly, the principle of cancer immunotherapy relies on the control of cancer cells through activating or reactivating the immune system (14, 29, 32, 33). Hence, the principal goal of immunotherapy is a resurrection of the patient's inefficient or suppressed immune system which would ideally result in total and permanent eradication of cancer (34). Immunotherapy works in different ways; some boost the body's immune system while others help train it to attack cancer cells (11). This approach emphasizes dual aspects; to eliminate immune-suppressing factors, and 2) to enhance tumor-killing activities (24).

In general, the goal of most approaches to cancer immunotherapy is to activate a population of effector T-cells, which can then traffic to evolving tumors and mediate the specific lysis of cancer cells (35-41).

Types of cancer immunotherapy

As it is briefly described above, over the years, researchers around the world have tried many different approaches to turn the immune system against cancer, such as cutting the brakes on immune cells, flagging cancer cells for recognition and destruction, or genetically engineering a patient's immune cells to directly target and eventually eliminate cancer cells (42). Cancer immunotherapy encompasses a variety of approaches, including the marvelous specificity of adaptive immunity as well as the diverse and potent cytotoxic arsenal of both adaptive and innate immunity (36). Cancer immunotherapy sometimes can be categorized by whether it *actively* stimulate the immune system, or *passively* alter immune system signaling or cell populations, and, the treatment is targeted at a specific, known antigenic target, or is non-specifically stimulating the entire immune system (14). The most common immunotherapeutic approaches are summarized in (Table

Table 1: Common cancer immunotherapeutic approaches currently being used in medical settings and under

Types	Working principle
Monoclonal antibodies	Target specific antigen of cancer cell
Immune checkpoint blockades	Take the 'brakes off' the immune system (unleash anti-cancer activity of T-cells) to eliminate cancer
Adoptive cell transfer	Transfusion of adoptive allogeneic or autologous T-cells into patients, tolerance to tumor antigens will be lost so that a large amount of high avidity effector T-cells will act on cancer.
Cancer vaccines	Stimulate the host immune system
Cytokines **(IL-2, IFN-α)***	Stimulate the host immune system
Oncolytic viruses	Acute tumor exposure owing to tumor cell infection and lysis and induction of systemic antitumor immunity
Combination therapy	Improves anti-cancer activity of products

*IL: Interleukin-2, IFN: Interferon-alpha

Monoclonal antibodies (mAb)

Monoclonal antibodies are used to treat different kinds of diseases, including some types of malignancies. To make a monoclonal antibody, investigators first have to identify the correct antigen to attack. For cancer, this is not constantly easy, as these cells are *self-modified* cells, and so far mAbs have proven to be more useful against some cancers than others (11). By directly targeting specific antigens expressed by cancer cells, mAbs are well-established classes of immunotherapeutic agents (1). The three most common anticancer drugs (ie, rituximab, trastuzumab, and bevacizumab) are certainly mAbs. Therapeutic levels of mAbs allow more extensive lymphocyte trafficking and activation and lysis of cancer cells (14).

Immune checkpoint inhibitors/ immune-modulating antibodies

The activity of the immune system is modulated and controlled by co-stimulatory molecules, called immune checkpoints, which are crucial for self-tolerance. The immune checkpoint pathways are normal immune signals capable of ending an immune reaction. They involve inhibitory receptors and their ligands; one is expressed by a putative target cell and the other is expressed by effector cells, like T-cells (40). When antigen recognition occurs, other molecules interact on the surface of the immune cell and the target cell to govern the balance of the interaction. If the signals are largely positive, immune cells activate and are primed to attack the antigen presented by the target cell. However, if the balance of signals is negative, then the immune cell can become deactivated, sometimes permanently, and the antigen is accepted as a self-antigen (14). Overexpression of immune checkpoint molecules by tumor cells profoundly affects tumor-specific T-cell immunity in the cancer microenvironment. This efficiently marks tumor cells as not for elimination, and can therefore reform tumor progression and eventually metastasis. Since most tumor immune escape mechanisms that use immune checkpoints block effector cell functions, antitumor immunity may be *restored by antibodies that block the inhibitory receptor-ligand interaction and thus inactivate the immune checkpoints* (40). On the basis of this immunology knowledge, antibodies capable of disrupting the ligand-receptor association for immune checkpoints and/or its functional consequences were developed. These drugs essentially take the *'brakes off'* the immune system, which benefits it recognizing and eliminating tumors (40).
Immune checkpoint treatment has led to important medical advances and provided a new firearm against cancer. This therapy has caused durable clinical responses and, in a segment of patients, long-term remissions where patients showed no clinical signs of cancer for many years (43).

Interactions between molecules on the surfaces of T cells and antigen-presenting cells (APCs) at the immune checkpoint can lead to the induction of immune tolerance. The most clinically relevant of these interactions are those between 1) Cytotoxic T lymphocyte-associated protein-4 (CTLA-4) on T cells and its ligands B7 on APC and 2) PD-1 on T cells and its main ligand PD-L1 on APC or tumor cells (44).
Immune checkpoint inhibitors that interfere either of the above interactions could lead to the activation and expansion of existing tumor-specific immune cells that are otherwise suppressed in the tumor microenvironment (TME) (22).

Ipilimumab (Yervoy), a monoclonal antibody targeting CTLA-4

In the late 1980s, French scientists who were not considering cancer at all identified a new protein on the surface of T-cells, called CTLA-4(45) also known as CD-152. It is an immune checkpoint protein receptor (46) that is expressed exclusively on T-cells, and is a critical *negative regulator* of the antitumor T-cell response (40, 47). James Allison, at the University of Texas, reported that CTLA-4 makes the *brakes on* T-cells, stopping them from launching full-out immune responses. He speculated whether blocking the blocker, i.e., the CTLA-4 molecule would make the immune system *free to eliminate cancer*. In 1996, Allison and his colleagues published a paper in *Science* showing that antibodies against CTLA-4 removed tumors in mice. In 2010, a US-based company called Bristol-Myers Squibb described patients with metastatic melanoma lived an average of ten months on the antibody, compared with six months without it. It was the first time any treatment had prolonged life in advanced melanoma in a randomized clinical trial. Nearly a quarter of participants survived at least 2 years (45).

Similarly, according to Sharma P study, tumor regression was observed in phase I/II trials using CTLA-4 antibodies in patients with a variety of tumor types, including melanoma, renal cell carcinoma, prostate cancer, urothelial carcinoma, and ovarian cancer (6, 40). In 2011, the US FDA approved Bristol-Myers Squibb's *anti–CTLA-4 antibodies*, called *Ipilimumab*, for metastatic melanoma, which marked the beginning of a new era for cancer immunotherapy (6, 25, 45, 48). The clinical achievement of anti-CTLA-4 paved a new arena termed *immune checkpoint therapy* as additional T-cell intrinsic pathways were identified and target-

for clinical development (6).

As described above, CTLA-4 mainly regulates the amplitude of early-stage T-cell activation. One of its mechanisms of action encompasses antagonism of B7-CD28–mediated co-stimulatory signals, which occur because CTLA-4 has a *much higher affinity* for B7 than CD28 does: binding of CTLA-4 to CD80/86 is 500 to 2,500 times more than that of the CD28. Signaling through CD28 promotes mRNA expression of the cytokine IL-2 and entry into the cell cycle, T-cell survival, Th-cell differentiation, and immunoglobulin isotype switching. Thus, signaling through CTLA-4 inhibits IL-2 mRNA production and inhibits cell cycle progression (40).

Anti-Programmed Death-1 (PD-1) (Nivolumab) and anti–PD-L1 antibodies

The other T-cell-intrinsic inhibitory-pathway recognized after CTLA-4 was mediated by PD-1 (***P***rogrammed ***D***eath 1) and its ligand PD-L1. PD-1 function as an immune checkpoint was not well-known until 2000 upon identification of its ligands even though it was initially cloned in 1992 in a study of molecules involved in negative selection of T-cells by programed cell death in the thymus. PD-L1 was then revealed to protect tumor cells by inducing T-cell apoptosis. Later, studies in animals assessed anti-PD-1 and anti-PD-L1 antibodies as immune checkpoint agents to treat tumors (6). Much like CTLA-4, PD-1 is expressed only in activated T-cells. However, unlike CTLA-4, PD-1 inhibits T-cell responses by interfering with T-cell receptor signaling in contrary to outcompeting CD28 for binding to B7(6, 33, 45).

PD-1 receptor is an inhibitory receptor expressed by antigen-stimulated T-cells. Interactions between PD-1 and its ligand, PD-L1, expressed in many tumors activate signaling pathways that inhibit T-cell activity and thus block the antitumor response. However, antibodies targeting PD-1 or PD-L1 block the PD-1 pathway and reactivate T-cell activity (28). As far as the past viewpoint of this drug is concerned, it was in the early 1990s that a biologist in Japan revealed a molecule expressed in dying T-cells, which he named *programmed death* 1 (PD-1) and which he recognized as the other *brake* on T cells. The first clinical trial, involving 39 participants and five different cancers, began in the year 2006. After two years, by 2008, medics were jolted by what they saw: in five of the volunteers, all of them with refractory disease, tumors were shrinking (33, 45).
According to Weinstock M *et al*. review article antibodies that block the PD-1 immune checkpoint pathway have shown encouraging antitumor activity against metastatic renal cell carcinoma in phase I and phase II trials. They have also suggested that combination approaches would be essential to enhance their efficacy (44). Similarly, according to the Carosella E *et al*. report, antibodies blocking immune check-points offer interesting and long-lasting response rates in heavily pretreated patients with advanced urologic cancers. More promising results are currently provided by - PD-1/PD-L1 inhibitors in renal cancer (40) and lung cancer (46). Nivolumab was FDA approved for patients with metastatic melanoma in 2014. Besides, nivolumab was FDA approved in 2015 for patients with previously treated advanced or metastatic non-small-cell lung cancer based on a phase III clinical trial, which reported an improvement in overall survival for patients treated with nivolumab as compared to patients treated with chemotherapy (6).

Like other cancer therapies, immune checkpoint therapies may lead to side effects and toxicities (6, 47, 49)**.** Briefly, these effects involve immune-related adverse reactions that are defined by inflammatory conditions, like dermatitis, colitis, hepatitis, pancreatitis, and pneumonitis. These side effects can be managed and usually involve administration of immunosuppressive agents such as corticosteroids, which do not appear to interfere with clinical benefit that is derived from the immune checkpoint agents. The profile of side effects that occur with both anti-CTLA-4 and anti-PD-1/PD-L1 antibodies is similar. However, the side effects appear to occur more frequently in the setting of anti-CTLA-4 therapy as compared to anti-PD-1 and anti-PD-L1 therapies (6). The future for this group of anti-cancer agents lies on a closer understanding of our immune responses in the tumor microenvironment. This will provide valuable information regarding the dynamic nature of the immune response and regulation of additional pathways that will need to be targeted through combination therapies to provide survival benefit for greater numbers of patients (43).

Adoptive cell transfer

Adoptive cellular therapy with various lymphocytes is the other groundbreaking innovation in the pillar of cancer immunotherapy, which depends on the tumor-specific T-cell (18, 50). The transfusion of adoptive allogeneic or autologous T-cells into patients is effective management for regression of cancer (51). The two main approaches in adoptive T-cell transfer in cancer immunotherapy are; 1) infusion of *ex-vivo* expanded tumor-infiltrating lymphocytes (TILs) and 2) infusion of engineered T-cells (which includes CAR-T cells and TCR-engineered T cells). So far, genetic engineering of T-cells seems a powerful tool for shaping tumor

T-cells seems a powerful tool for shaping tumor immunity (13). The approach has made a significant development on utilizing T-cells, especially in hematologic malignancies (52). Lymphocytes are firstly isolated from patients' blood, tumor-draining lymph nodes, or tumor tissue, expanded ex-vivo, and reinfused back into the patient. This strategy would, in theory, avoid the baffling duty of breaking tolerance to tumor antigens and produce a large amount of high avidity effector T cells (22, 28).

Initial tests in mice revealed that T-cells that had been cultured with leukemia cells could eliminate an established leukemia in-vivo. In patients who receive an allogeneic hematopoietic stem-cell transplant, mature T-cells in the graft mount a potent anti-leukemia response. Several groups have pursued this approach in patients with solid tumors by infusing autologous T-cells with specificity for a tumor antigen (18). According to Zhang *et al.* report, in-vitro induction and proliferation of expanded activated autologous lymphocytes is biologically safe even though it demands logistical and technical complexities (50).

In 2010, researchers published findings from chimeric antigen receptor (CAR) therapy, personalized management that involves genetically altering a patient's T-cells to make them target transformed cells. A research team in 2013 also reported that the T-cell therapy in their studies put 45 of 75 adults and children with leukemia into complete remission (33, 45). The FDA approved two CAR T-cell treatments in the year 2017. It is well described that CAR therapy and immune checkpoint inhibitors are generally different but complementary agents. In the former, patients' immune cells are genetically engineered to acquire new tumor-targeting specificity and potency while the latter leads to the activation and expansion of existing tumor-specific immune cells that are otherwise suppressed in the tumor microenvironment (22).

Cancer vaccines

Preventive vaccination against infectious diseases is considered one of the most successful health measures of all times. In addition to the successful use of preventative vaccines used in the defense against cancer causing infectious diseases like hepatitis B virus and human papillomavirus, the evidence that patients can harbor CD8+ and CD4+ T-cells capable of recognizing tumor expressed antigens hinted at the possibility of developing cancer vaccines (28). Generally, cancer vaccines activate the adaptive antitumor response largely by increased tumor antigen presentation. With the US FDA approval of the therapeutic vaccine Sipulencel-T (Provenge), cancer vaccine development is gaining huge ground. Approval of these vaccines has encouraged the concept of cancer treatment through cellular immunotherapy (53).

Age-old interest in cancer vaccines comes from the wonderful successes of prophylactic vaccines for infectious diseases. Historically, the primary approach to specifically activate host T-cells against tumor antigens (ie, active immunotherapy) has been therapeutic cancer vaccination (14). Active immunotherapy products are agents proposed to stimulate an immune response to destruct or reduce the progression of disease in patients where cancer has been diagnosed (54). However, despite impressive clinical outcomes achieved with immune checkpoint blockade and CAR therapies, the overall results of therapeutic vaccination against established tumors remain sub-optimal, as a clinical benefit for patients with cancer was largely noted as prolonged survival (25).

There are different vaccination strategies for cancer that either target the immune system in a general way (like Bacillus Calmette-Guerin (BCG)) or that directed to immune cells specifically to the cancer tissue (9). Generally, common cancer vaccination strategies include; 1)Viral vaccines; in which weakened version of herpes simplex virus (HSV) modified to produce an immune stimulating factor is being developed for melanoma and head and neck cancer. 2) Patient own tumor cells; that are extracted from the patient, irradiated to stop spreading, and engineered to produce activating growth factors. When these cells are injected back to the patient, the growth factors alert the immune system to the cancer. 3) APC like, DCs based vaccine - immature DC cells are taken from the patient, matured outside the body, loaded with tumor antigen then introduced back to the patient. Eventually the antigens will stimulate the immune cells to fight the cancer (6, 55).

Immunostimulatory cytokines

Research on the use of cytokine is currently at the front line in cancer therapy (30). Cytokines that are released in response to infection, inflammation, and immunity can function to inhibit tumor development and progression (56, 57). Immune therapy based on the use of cytokine has historically been the mainstay of immunotherapy in cancers such as melanoma and kidney cancer (52). Cytokines are groups of relatively small proteins that play a critical role in cell signaling, allowing immune cells to communicate and respond in an organized manner. They play important roles in the body's normal immune responses and in the fight against cancer. (14, 18).

As different cytokines that present in the tumor microenvironment shapes the host immune response, therapeutic manipulation of the cytokine environment constitutes one approach to stimulate protective immune responses. Indeed, William Coley's pioneering work at the end of the 19th century, in which bacterial extracts *(Streptococcus pyogenes* and *Serratia marcesens)* were administered as cancer immunotherapy (Coley's toxins) which resulted in marked alterations in cytokine levels and tumor clearance in some of the treated patients (56).

Proinflammatory cytokines can promote effector T-cell proliferation and activation. It is a promising line in cancer immunotherapy. In addition, the manipulation of cytokines can directly disrupt tumor cells, leading to apoptosis and inhibition of proliferation (18). Interferons (IFNs) and interleukins (ILs) are the common types of cytokines used in cancer immunotherapy. *IFN-α* (that enhances tumor antigen presentation and cytotoxicity) and *IL-2* (enhances NK cell and CD8+ T-cell function and increases vascular permeability) (56) were previously mainstays of treatment of metastatic renal cell carcinoma and melanoma. IFN-α was used as adjuvant therapy in resected high-risk melanoma, though the survival advantage was debatable (18). IL-2 was approved for the treatment of metastatic renal cell carcinoma and melanoma and is still used in some countries in limited highly restricted patients. Treatment requires admission in the intensive care unit because of severe systemic inflammatory responses and hypotension. A proportion of patients who took IL-2 have experienced long-term remission of their cancer (14, 18). Several additional cytokines are currently in clinical development pipeline (18).

Oncolytic viruses (OV)

OV encompasses a broad diversity of DNA and RNA viruses that are emerging as important immunotherapy to activate and redirect functional innate and adaptive immune responses towards the tumor (26, 58). They are naturally cancer-selective or can be genetically engineered (53) for optimization of tumor selectivity and enhanced immune stimulation (59) with minimal toxicity to normal tissues. They provide a diverse platform; they act as in-situ vaccines and can be armed with immune-modulatory transgenes or combined with other immunotherapies (26, 58).

Their induction of immunogenic tumor cell death and association with pro-inflammatory signals make OV promising anticancer agents. These viruses are believed to promote antitumor responses mainly through two distinct mechanisms of action: 1) acute tumor exposure owing to tumor cell infection and 2) lysis and induction of systemic antitumor immunity (22, 26). OVs selectively replicate in and kill cancer cells, and spread within the tumor. In addition to this direct oncolytic activity, they are also very effective at inducing immune responses to themselves and to the infected tumor cells (59).

The viral genome can be modified to augment anti-tumor activity and attenuate pathogenicity. Some of the abundant modifications that have been made and verified include the insertion of promoters that limit the expression of disease-causing genes to tumor cells or the deletion of pathogenic genes to limit the growth and the killing action of viruses to cancers. Additionally, oncolytic viruses can be engineered to express specific cytokines that favor immune cell recruitment and activation or to produce T-cell co-stimulatory molecules on infected tumor cells, thus facilitating the generation of T-cell activating signals (22).

Numerous viruses were tested as vectors for OV immunotherapy. Some of them are naturally non-pathogenic to humans, such as the Newcastle disease virus, a naturally oncolytic RNA virus, reovirus, and Seneca Valley virus. Others, including herpes simplex virus, measles virus, vaccinia virus, are genetically manipulated to become non-pathogenic (53, 58, 60). In 2005, an oncolytic adenovirus called H101 was approved to treat head-and-neck cancer, after evidence showed that the treatment could shrink tumors (53).

In 2015, the US FDA approved the genetically engineered oncolytic simplex virus type 1– derived **t**alimogene laherparep**vec** (T-VEC) in advanced melanoma. It becomes the first oncolytic immunotherapy against melanoma in a phase III clinical trial and is of its kind to demonstrate therapeutic benefit approved for use in Europe and the US (15, 53, 59). T-VEC is designed in such a way to selectively multiply within tumors and produce granulocyte-macrophage colony-stimulating factor (GM-CSF) to augment systemic antitumor reaction (15, 53, 58, 60).

The host anti-viral immune response is considered a major problem in achieving maximal antitumor effect by OVs. In other words, an initial host response to the virus may result in the rapid clearance of the virus before it manages to replicate and infect tumor cells at a magnitude that will ensure the initiation of an efficient vaccination response (60). Circumvention of this initial response is an active area of research (22).

Cancer vaccines

Preventive vaccination against infectious diseases is considered one of the most successful health measures of all times. In addition to the successful use of preventative vaccines used in the defense against cancer causing infectious diseases like hepatitis B virus and human papillomavirus, the evidence that patients can harbor CD8+ and CD4+ T-cells capable of recognizing tumor expressed antigens hinted at the possibility of developing cancer vaccines (28). Generally, cancer vaccines activate the adaptive antitumor response largely by increased tumor antigen presentation. With the US FDA approval of the therapeutic vaccine Sipulencel -T (Provenge), cancer vaccine development is gaining huge ground. Approval of these vaccines has encouraged the concept of cancer treatment through cellular immunotherapy (53).

Age-old interest in cancer vaccines comes from the wonderful successes of prophylactic vaccines for infectious diseases. Historically, the primary approach to specifically activate host T-cells against tumor antigens (ie, active immunotherapy) has been therapeutic cancer vaccination (14). Active immunotherapy products are agents proposed to stimulate an immune response to destruct or reduce the progression of disease in patients where cancer has been diagnosed (54). However, despite impressive clinical outcomes achieved with immune checkpoint blockade and CAR therapies, the overall results of therapeutic vaccination against established tumors remain sub-optimal, as a clinical benefit for patients with cancer was largely noted as prolonged survival (25).

There are different vaccination strategies for cancer that either target the immune system in a general way (like Bacillus Calmette-Guerin (BCG)) or that directed to immune cells specifically to the cancer tissue (9). Generally, common cancer vaccination strategies include; 1)Viral vaccines; in which weakened version of herpes simplex virus (HSV) modified to produce an immune stimulating factor is being developed for melanoma and head and neck cancer. 2) Patient own tumor cells; that are extracted from the patient, irradiated to stop spreading, and engineered to produce activating growth factors. When these cells are injected back to the patient, the growth factors alert the immune system to the cancer. 3) APC like, DCs based vaccine - immature DC cells are taken from the patient, matured outside the body, loaded with tumor antigen then introduced back to the patient. Eventually the antigens will stimulate the immune cells to fight the cancer (6, 55).

Immunostimulatory cytokines

Research on the use of cytokine is currently at the front line in cancer therapy (30). Cytokines that are released in response to infection, inflammation, and immunity can function to inhibit tumor development and progression (56, 57). Immune therapy based on the use of cytokine has historically been the mainstay of immunotherapy in cancers such as melanoma and kidney cancer (52). Cytokines are groups of relatively small proteins that play a critical role in cell signaling, allowing immune cells to communicate and respond in an organized manner. They play important roles in the body's normal immune responses and in the fight against cancer. (14, 18).

As different cytokines that present in the tumor microenvironment shapes the host immune response, therapeutic manipulation of the cytokine environment constitutes one approach to stimulate protective immune responses. Indeed, William Coley's pioneering work at the end of the 19th century, in which bacterial extracts *(Streptococcus pyogenes* and *Serratia marcesens)* were administered as cancer immunotherapy (Coley's toxins) which resulted in marked alterations in cytokine levels and tumor clearance in some of the treated patients (56).

Proinflammatory cytokines can promote effector T -cell proliferation and activation. It is a promising line in cancer immunotherapy. In addition, the manipulation of cytokines can directly disrupt tumor cells, leading to apoptosis and inhibition of proliferation (18). Interferons (IFNs) and interleukins (ILs) are the common types of cytokines used in cancer immunotherapy. *IFN-α* (that enhances tumor antigen presentation and cytotoxicity) and *IL-2* (enhances NK cell and CD8+ T-cell function and increases vascular permeability) (56) were previously mainstays of treatment of metastatic renal cell carcinoma and melanoma. IFN-α was used as adjuvant therapy in resected high-risk melanoma, though the survival advantage was debatable (18). IL-2 was approved for the treatment of metastatic renal cell carcinoma and melanoma and is still used in some countries in limited highly restricted patients. Treatment requires admission in the intensive care unit because of severe systemic inflammatory responses and hypotension. A proportion of patients who took IL-2 have experienced long-term remission of their cancer (14, 18). Several additional cytokines are currently in clinical development pipeline (18).

Oncolytic viruses (OV)

OV encompasses a broad diversity of DNA and RNA viruses that are emerging as important immunotherapy to activate and redirect functional innate and adaptive immune responses towards the tumor (26, 58). They are naturally cancer-selective or can be genetically engineered (53) for optimization of tumor selectivity and enhanced immune stimulation (59) with minimal toxicity to normal tissues. They provide a diverse platform; they act as in-situ vaccines and can be armed with immune-modulatory transgenes or combined with other immunotherapies (26, 58).

Their induction of immunogenic tumor cell death and association with pro-inflammatory signals make OV promising anticancer agents. These viruses are believed to promote antitumor responses mainly through two distinct mechanisms of action: 1) acute tumor exposure owing to tumor cell infection and 2) lysis and induction of systemic antitumor immunity (22, 26). OVs selectively replicate in and kill cancer cells, and spread within the tumor. In addition to this direct oncolytic activity, they are also very effective at inducing immune responses to themselves and to the infected tumor cells (59).

The viral genome can be modified to augment antitumor activity and attenuate pathogenicity. Some of the abundant modifications that have been made and verified include the insertion of promoters that limit the expression of disease-causing genes to tumor cells or the deletion of pathogenic genes to limit the growth and the killing action of viruses to cancers. Additionally, oncolytic viruses can be engineered to express specific cytokines that favor immune cell recruitment and activation or to produce T-cell co-stimulatory molecules on infected tumor cells, thus facilitating the generation of T-cell activating signals (22).

Numerous viruses were tested as vectors for OV immunotherapy. Some of them are naturally non-pathogenic to humans, such as the Newcastle disease virus, a naturally oncolytic RNA virus, reovirus, and Seneca Valley virus. Others, including herpes simplex virus, measles virus, vaccinia virus, are genetically manipulated to become non-pathogenic (53, 58, 60). In 2005, an oncolytic adenovirus called H101 was approved to treat head-and-neck cancer, after evidence showed that the treatment could shrink tumors (53).

In 2015, the US FDA approved the genetically engineered oncolytic simplex virus type 1– derived **t**alimogene laherparep**vec** (T-VEC) in advanced melanoma. It becomes the first oncolytic immunotherapy against melanoma in a phase III clinical trial and is of its kind to demonstrate therapeutic benefit approved for use in Europe and the US (15, 53, 59). T-VEC is designed in such a way to selectively multiply within tumors and produce granulocyte -macrophage colony-stimulating factor (GM-CSF) to augment systemic antitumor reaction (15, 53, 58, 60).

The host anti-viral immune response is considered a major problem in achieving maximal antitumor effect by OVs. In other words, an initial host response to the virus may result in the rapid clearance of the virus before it manages to replicate and infect tumor cells at a magnitude that will ensure the initiation of an efficient vaccination response (60). Circumvention of this initial response is an active area of research (22).

Combination therapy

Cancer immunotherapy could be combined with conventional therapies to achieve maximal patient benefit. Fortunately, many conventional treatments for prostate and other cancers have beneficial immunological effects, making combinatorial trials an attractive area (12). Combining immune-based treatments, or pairing them with other anticancer agents like radiation or chemotherapy, scientists in the field anticipate increasing and broadening the benefits to patients (7).

In 2017, according to a report in Nature magazine, a 69 years old patient in California started to take an experimental combination of immunotherapy drugs for melanoma. The patient had a tumor growth bulging under his armpit. It was difficult to operate the tumor, and his doctor suspected that it might be spread to the patient's lungs. However, the combination of the antibodies nivolumab and ipilimumab had a remarkable outcome in which the tumor was shown destroyed (7).

Similarly, according to Antonia et al, the majority of patients with some form of cancer, like lung cancer, treated with single-agent anti–PD-1/PD-L1 do not benefit much. They stated that combination therapy with multiple immunotherapeutics was necessary to improve clinical efficacy (46). For example, because CTLA-4 and PD-1 regulate different inhibitory pathways on T-cells, combination therapy with antibodies targeting both molecules was tested and found to improve anti-tumor responses in a preclinical murine model. A phase I clinical trial with anti-CTLA-4 in combination with anti-PD-1 also demonstrated tumor regression in about 50% of treated patients with advanced melanoma, in most cases with tumor regression of 80% or higher that highlight this combination as an effective immunotherapy strategy for cancer patients (6).

Moreover, combinations of cancer vaccines with blocking monoclonal antibodies against immune checkpoint receptors such as CTLA-4 and PD-1 demonstrate dramatic synergy in murine tumor models (14). Other reports also showed that combining ipilimumab and anti–PD-1 led to tumor regression in almost a third of melanoma patients (33, 45).

Currently, there are hundreds of clinical trials on cancer combination therapies as pieces of evidence showed that two- and three-drug regimens lead to clinical benefits though do have added expenses and side effects (7, 28). Nevertheless, cancer combination therapies that include immune-based elements face specific challenges, both clinical and monetary. Some immunotherapies trigger dangerous autoimmune reactions that combination treatments can exacerbate. Besides, the cost of the drugs is much greater than that of conventional cancer treatments (7).

CONCLUSIONS

A great deal has been studied about the potential of the immune system to fight and control cancer and the range of ways that immunotherapy can improve the potential of the immune system. This knowledge has stimulated the discovery of a number of novel therapeutic options including antibodies, cell-based treatments, and cancer vaccines, which are currently being used in clinical settings, either alone or in various combinations. The clinical success by immune checkpoint therapy, using blocking antibodies to CTLA-4 and PD-1, and by CAR- T cells represents the result of efforts to harness the immune system in the eradication of cancer cells. Yet, not all patients benefited from the immunotherapeutic discovery. Efforts should now onwards focus on improving the efficacy of immunotherapy through the use of numerous combination approaches and predictive biomarkers of treatment outcome. Among possible reasons for lack of cancer eradication, suboptimal vaccine design and the presence of an immunosuppressive tumor microenvironment take the front line. Hence, unraveling the mechanisms by which cancer cells evade the immune system and developing new agents to target the relevant pathways represent the next steps in this approach for cancer treatment.

List of abbreviations

APC	Antigen-presenting cell
CAR	Chimeric antigen receptor
CD	Cluster of differentiation
CTL	Cytotoxic T-lymphocytes
CTLA-4	Cytotoxic T lymphocyte antigen 4
DC	Dendritic cells
FDA	Food and drug administration (US)
GM-CSF	Granulocyte acrophage colony-stimulating factor
HSV	Herpes simplex virus
ICAM-1	Intercellular adhesion molecule-1
IL	Interleukin
LFA-3	Lymphocyte function-associated antigen-3
mAb	monoclonal antibody
MHC	major histocompatibility complex
NK cells	Natural killer cells
OV	Oncolytic virus
PD-1	Programmed cell death 1
PD-1L	Programmed cell death 1 ligand
TME	Tumor microenvironment
TNF	tumor necrosis factor
T_{reg}	Regulatory T cells
T-VEC	Talimogene laherparepvec
WHO	World health organization

Declarations

Ethical Approval and Consent to participate: Not applicable in this section

Consent for publication: Not applicable in this section

Availability of data and material*:* All the generated data are included in the manuscript.

Competing interests*:* Authors declare that they have no competing interests.

Funding*:* We received no funds for this particular review.

Authors' contributions: AD and TA conceived the review topic and objectives. AD, DM and EM participated in the write-up. MM, YW and TA reviewed the manuscript critically for its scientific content. All authors reviewed and approved the manuscript.

Acknowledgments: We would like to thank Bahir Dar and Addis Ababa Universities and CDT-Africa for the provided opportunity to undertake this review.

REFERENCE

1. Finn OJ. Immuno-oncology: understanding the function and dysfunction of the immune system in cancer. *Annals of Oncology*. 2012, 23(suppl_8):p.viii6-9.
2. Global Cancer Facts & Figures 3rd.ed Available at: [https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/global-cancer-facts-and-figures/global-cancer-facts-and-figures-3rd-edition.pdf]. Accessed on 28 February 2022.
3. American Cancer Society. What Is Cancer? Available at: [https://www.cancer.org/cancer/cancer-basics/what-is-cancer.html]. Accessed on 28 February 2022.
4. Cancer.net. What is Cancer? Available at: [https://www.cancer.net/navigating-cancer-care/cancer-basics/what-cancer]. Accessed on 1 February 2022.
5. World Health Organization. Cancer. Available at: [http://www.who.int/mediacentre/factsheets/fs297/en/]. Accessed on Decmber 2021.
6. Padmanee S, James A. Immune Checkpoint Targeting in Cancer Therapy: Toward Combination Strategies with Curative Potential. Cell. 2015, 161:10.
7. Bender E. Cancer immunotherapy. *Nature. 2017,* **552***, S61.* doi: *https://doi.org/10.1038/d41586-017-08699-z*
8. Velcheti V, Schalper K. Basic Overview of Current Immunotherapy Approaches in Cancer. *Am Soc Clin Oncol Educ Book* 2016, 35:298-308.
9. National Institute of Health. Immunotherapy: Using the Immune System to Treat Cancer. Available at: [https://www.cancer.gov/research/areas/treatment/immunotherapy-using-immune-system]. Accessed on October 2021.
10. Sung, H, Ferlay J, Siejel RL et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*, 2021. 71(3): p. 209-249.
11. Whiteside TL. The tumor microenvironment and its role in promoting tumor growth. *Oncogene* 2008, 27:5904.
12. Drake CG. Prostate cancer as a model for tumour immunotherapy. *Nat Rev Immunol* 2010, 10 (8):580-593.
13. Bonini C, Mondino A. Adoptive T-cell therapy for cancer: The era of engineered T cells. *Eur J Immunol* 2015, 45(9):2457-2469.
14. Topalian SL, Weiner GJ, Pardoll DM. Cancer Immunotherapy Comes of Age. *Journal of Clinical Oncology* 2011, 29(36):4828-4836.
15. Andtbacka RH, Kaufman HL, Collichio F et al. Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma. *Journal of Clinical Oncology* 2015, 33(25):2780-2788.
16. Heinberg A and Granot Z. Tumour immunology. *Nature Cancer* 3, 136-137. Available at: [https://www.nature.com/subjects/tumour-immunology]. Accessed on December 21.
17. Palucka AK, Coussens Lisa M. The Basis of Oncoimmunology. *Cell*, 164(6):1233-1247.
18. Finn OJ. Cancer immunology. *N Engl J Med* 2008, 358(25):2704-2715.
19. Rabson A, Delves PJ. Really Essential Medical Immunology, 2nd edn: Blackwell Publishing Ltd; 2005.
20. Fuchs EJ, Matzinger P. Is cancer dangerous to the immune system? In: *Seminars in immunology: 1996*: Elsevier; 1996: 271-280.
21. Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiol Biomarkers Prev* 2010, 19(8):1893-1907.
22. Lohmueller J, Finn OJ. Current modalities in cancer immunotherapy: Immunomodulatory antibodies, CARs and vaccines. *Pharmacol Ther* 2017, 178:31-47.
23. Rodriguez PC, Zea AH, Ochoa AC. Mechanisms of tumor evasion from the immune response. *Cancer Chemother Biol Response Modif* 2003, 21:351-364.
24. Vinay DS, Ryan EP, Pawelec G et al. Immune evasion in cancer: Mechanistic basis and therapeutic strategies. *Semin Cancer Biol* 2015, 35(10):25.
25. Yang Y. Cancer immunotherapy: harnessing the immune system to battle cancer. *J Clin Invest* 2015, 125(9):3335-3337.
26. de Gruijl TD, Janssen AB, van Beusechem VW. Arming oncolytic viruses to leverage antitumor immunity. *Expert Opin Biol Ther* 2015, 15(7):959-971.
27. Disis ML. Mechanism of action of immunotherapy. *Semin Oncol* 2014, 41(5):6.
28. Farkona S, Diamandis EP, Blasutig IM. Cancer immunotherapy: the beginning of the end of cancer? *BMC Medicine* 2016, 14:73.

29. Gulley JL, Madan RA, Heery CR. Therapeutic vaccines and immunotherapy in castration-resistant prostate cancer: current progress and clinical applications. *Am Soc Clin Oncol Educ Book* 2013, 10 (33).
30. Gasparri ML, Attar R, Palaia I, et al. Tumor infiltrating lymphocytes in ovarian cancer. *Asian Pac J Cancer Prev* 2015, 16(9):3635-3638.
31. Chaudhuri D, Suriano R, Mittelman A, Tiwari RK. Targeting the immune system in cancer. *Curr Pharm Biotechnol* 2009, 10(2):166-184.
32. Wang RF, Wang HY. Immune targets and neoantigens for cancer immunotherapy and precision medicine. *Cell Res* 2017, 27(1):11-37.
33. Wang M, Zhao J, Zhang L et al. Role of tumor microenvironment in tumorigenesis: J Cancer. 2017;8 (5):761-73. doi:10.7150/jca.17648.
34. Klener P, Otahal P, Lateckova L, Klener P. Immunotherapy Approaches in Cancer Treatment. *Curr Pharm Biotechnol* 2015, 16(9):771-781.
35. Butterfield LH, Kaufman HL, Marincola FM. Cancer Immunotherapy Principles and Practice: Springer Publishing Company; 2017.
36. Bellmunt J, Powles T, Vogelzang NJ. A review on the evolution of PD-1/PD-L1 immunotherapy for bladder cancer: The future is now. *Cancer Treat Rev* 2017, 54:58-67.
37. Ledford H. Cancer-fighting viruses win approval: Nature. 2015 Oct 29;526(7575):622-3. doi: 10.1038/526622a.
38. Couzin-Frankel J. Breakthrough of the year 2013. Cancer immunotherapy: Science. 2013 Dec 20;342 (6165):1432-3. doi: 10.1126/science.342.6165.1432.
39. Gulley JL, Madan RA, Pachynski R et al. Role of Antigen Spread and Distinctive Characteristics of Immunotherapy in Cancer Treatment. *J Natl Cancer Inst* 2017, 109(4).
40. Carosella ED, Ploussard G, LeMaoult J, Desgrandchamps F. A Systematic Review of Immunotherapy in Urologic Cancer: Evolving Roles for Targeting of CTLA-4, PD-1/PD-L1, and HLA-G. *Eur Urol* 2015, 68(2):267-279.
41. Yang JC, Rosenberg SA. Adoptive T-Cell Therapy for Cancer. *Adv Immunol* 2016, 130:279-294.
42. Cancer Research UK. The immune system and cancer. Available at: [http:// www.cancerresearchuk.org/about-cancer/what-is-cancer/body-systems-and-cancer/the-immune-system-and-cancer]. Accessed on January 2021.
43. Sharma P, Allison JP. The future of immune checkpoint therapy. *Science* 2015, 348(6230):56-61.
44. Weinstock M, McDermott DF. Emerging role for novel immunotherapy agents in metastatic renal cell carcinoma: from bench to bedside. *Am Soc Clin Oncol Educ Book* 2015, 7(10).
45. Couzin-Frankel J. Cancer Immunotherapy. *Science* 2013, 342(6165):1432.
46. Antonia SJ, Vansteenkiste JF, Moon E. Immunotherapy: Beyond Anti-PD-1 and Anti-PD-L1 Therapies. *Am Soc Clin Oncol Educ Book* 2016, 35(8).
47. Tarhini A, Lo E, Minor DR. Releasing the Brake on the Immune System: Ipilimumab in Melanoma and Other Tumors: Cancer Biother Radiopharm. 2010 Dec;25(6):601-13. doi:10.1089/ cbr.2010.0865.
48. Weber JS: Current perspectives on immunotherapy. *Semin Oncol* 2014, 41(5):8.
49. YERVOY® (ipilimumab) is the 1st FDA-approved immune checkpoint inhibitor. Available at: [http://www.hcp.yervoy.com/metastatic-melanoma/mechanism-of-action]. Accessed on February 2021.
50. Zhang GQ, Li F, Sun SJ et al. Adoptive immunotherapy for small cell lung cancer by expanded activated autologous lymphocytes: a retrospective clinical analysis. *Asian Pac J Cancer Prev* 2015, 16 (4):1487-1494.
51. Yang F, Jin H, Wang J et al. Adoptive Cellular Therapy (ACT) for Cancer Treatment. *Adv Exp Med Biol* 2016, 909:169-239.
52. Subramaniam DS, Liu SV, Giaccone G. Novel approaches in cancer immunotherapy. *Discov Med* 2016, 21(116):267-274.
53. Banday AH, Jeelani S, Hruby VJ. Cancer vaccine adjuvants--recent clinical progress and future perspectives. *Immunopharmacol Immunotoxicol* 2015, 37(1):1-11.
54. Camarero J, Ruiz S. Cancer immunotherapy products: regulatory aspects in the European Union. *Hum Vaccin Immunother* 2012, 8(9):1354-1359.
55. Shang N, Figini M, Shangguan J et al. Dendritic cells based immunotherapy. *Am J Cancer Res* 2017, 7(10):2091-2102.
56. Dranoff G. Cytokines in cancer pathogenesis and cancer therapy. *Nat Rev Cancer* 2004, 4(1):11-22.
57. Kim-Schulze S, Taback B, Kaufman HL. Cytokine therapy for cancer. *Surg Oncol Clin N Am* 2007, 16(4):793-818.

58. Chiocca EA, Rabkin SD: Oncolytic viruses and their application to cancer immunotherapy. *Cancer Immunol Res* 2014, 2(4):295-300.
59. Yamaguchi Y, Yamaue H, Okusaka T et al. Guidance for peptide vaccines for the treatment of cancer: Cancer Sci. 2014 Jul;105(7):924-31. Epub 2014 Jul 14 doi:10.1111/cas.12443.
60. Schirrmacher V: Oncolytic Newcastle disease virus as a prospective anti-cancer therapy. A biologic agent with potential to break therapy resistance. *Expert Opin Biol Ther* 2015, 15(12):1757-1771