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CANCER IMMUNOTHERAPY- REVIEW ARTICLE

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ABSTRACT

Background: Cancer is the second leading cause of. In many developing countries, the incidence of cancer appears to be much lower. Most patients are treated with a combination of surgery-radiology and/ Or chemotherapy, while in most cases the primary tumor is effectively treated with a combination of these standard treatments. Cancer immunotherapy is the use of the immune system to treat cancer. Immunotherapy is often divided into active, inactive or compound immunotherapy. This treatment highlights the fact that cancer cells often have slightly different molecules on their surface than normal cells that can be detected by the immune system. The aim of this research is to make a narrative revision on the topic of cancer immunotherapy from its beginnings to even its development with its various types and categories. **Materials and Methods:** Many articles and scientific researches dealing with the topic of cancer immunotherapy have been referenced. New ideas in those researches have been approached and the ideas that support the importance of immunotherapy have been arranged, as well as the challenges facing the application of this type of treatment in the treatment of cancer. **Discussion:** These immune cells can be reactivated and stimulated by inhibiting PD-1/PD-L1 resulting in the recognition and killing of cancer cells. However, not all cancers present appropriate immune antigens that can be effectively recognized by autologous T cells. Synthetic immune responses are the result of treatments that artificially link T cells to cancer cells that do not normally do so based on the T cell's binding to the histocompatibility complex. **Conclusion:** Immunotherapy is a long way of hope for the ability to treat different types of cancer, and this is still subject to continued researches in this field.

KEYWORDS: Cancer, Immunotherapy.

INTRODUCTION

Cancer is the second leading cause of death in industrialized countries such as the United States, in many developing countries the incidence of cancer appears to be much lower[1], likely due to the high rates of death due to infectious diseases, most patients are treated with a combination of surgery-radiology and/or treatment Chemotherapy, while in most cases the primary tumor is effectively treated with a combination of these standard treatments.[2] Preventing the spread of metastases from the cancerous tumor is often ineffective.[3] More than a third of cancer deaths worldwide (about 80-75% of cancers in the United States) are caused by modifiable risk factors.[4] Cancer treatments include surgery, radiotherapy, chemotherapy, targeted therapies, immunotherapy, hormonal therapy, angiogenesis inhibitors, symptom control, and complementary and alternative therapies.[5]

The immune system has evolved to distinguish the body's own components from the strange ones. Multicellular organisms face the problem of destructive infectious invading agents (microbes) or dysregulation (tumors).[6] Protection from infection and disease is provided by the cooperative efforts of the innate and adaptive immune systems. In contrast to adaptive immunity, the innate immune response is present prior to infection and is not enhanced by repeated infections, and is not antigen-specific.[7] Adaptive immunity is stimulated by signals from the innate response when the innate processes are unable to cope with the infection.[8] This immunity is specific to a specific antigen, dependent on exposure to that antigen, and can have a

very high affinity and gradually become dominant over time, and its cellular components include B and T lymphocytes.[9] The principle of immunotherapy is to use the body's immune system to fight disease. The immune system is the natural line of defense against any foreign body that enters the body, such as viruses or foreign bodies. When this device recognizes any foreign body in the body, it sets off an alarm bell to launch an attack, which is known as an immune reaction.[10] Immunotherapy is used to activate immune cells to help the body have a more severe reaction. It can also reduce a known reaction to the body's natural defenses, known as immunosuppressive therapy. The principle of immunotherapy depends on rehabilitating the natural immune system to combat cancer cells.[11] This technique is considered the latest method for treating tumors, especially those located in the lung, head and neck.[12] Cancer cells have the ability to disguise themselves as normal cells, although they differ from them to appear as normal cells that the immune system does not recognize.[13]

Cancer immunotherapy is the use of the immune system to treat cancer.[14] Immunotherapy is often divided into active, inactive or compound (active with inactive). This treatment highlights the fact that cancer cells often have slightly different molecules on their surface than normal cells that can be detected by the immune system. These molecules are known as cancer antigens. Most of them are proteins or large molecules.[15] Active (active) immunotherapy induces the immune system to attack cancer cells by targeting cancer-related antigens. Passive immunotherapy is basically the use of substances prepared outside the body, such as monoclonal antibodies, lymphocytes, and cytokines, which the body does not produce but is injected with. The antibodies are considered the most successful to date, and are used to treat different types of cancer.[16] Antibodies are proteins produced by the immune system that bind to a target antigen on the surface of cells. The most important proteins targeted by antibodies are cell surface receptors. CD20, CD274, CD279.[17]

When the antibody binds to the target antigen, it stimulates cell mediated cytotoxicity and either stimulates the complement system or prevents the receptor from interacting with its ligand. It is difficult for the immune system to immediately recognize cancer cells because they start out as normal cells, which gives them time to multiply and spread.[18] Cancer cells can also secrete a substance that prevents the immune system from recognizing it. The use of immunotherapy has led to a complete revolution compared to the usual cancer treatments that were used in the past. Traditional chemotherapy targets cancer cells to eliminate them and slow their reproduction, while immunotherapy relies on activating the body’s immune system to enhance its ability to target and eliminate cancer cells. Although it is not suitable for all types of cancer, it is effective in treating some.[19]

Elimination of circulating tumor cells present in the circulation and micro-metastases present in distant organs is another promising approach in cancer immunotherapy. The main strategies of cancer immunotherapy aim to exploit the therapeutic potential of anti-tumor antibodies and cellular immune response mechanisms. Whereas passive antibody therapy relies on the repeated application of large amounts of tumor antigen-specific antibodies. Active immunotherapy aims to generate a tumor-specific immune response that combines both humoral and cellular immunity to cytotoxic T cells by the host immune system after vaccination.[20]

Nano medicated immunotherapy targets the bone marrow to activate a process called "trained immunity". This process reprograms bone marrow progenitor cells; to produce 'trained' immune cells that can stop the growth of a cancerous tumor.[21] The term "trained immunity" was first coined in 2011 by three Dutch scientists who discovered that it was possible to develop the innate immune system - the body's primary immune system - and modify it to create an immune memory, so that the immune system quickly recognized the causing pathogens that attack the body.[22] The use of modern immunotherapy began more than 10 years ago, and has witnessed a lot of development since that time, and it has changed the directions of care for cancer patients, especially with the increase in the number of cancers that can be fought by these therapies.[23]

Immunotherapy has proven to be effective in treating different types of cancer, especially hard-to-treat types such as skin and lung cancers.

Types of immunotherapy

The term “trained immunity” was first coined in 2011 by three Dutch scientists. Who discovered that it is possible to develop the innate immune system - a basic immune system in the body - and modify it to form an immune memory, so that the immune system quickly recognizes pathogens that attack the body, the use of modern immunotherapy began more than 10 years ago, and many of the The development since that time, and changed the directions of care for patients with cancer, especially with the increase in the number of cancers that can be fought by these treatments. Immunotherapy has proven to be effective in treating different types of cancer, especially hard-to-treat types such as skin and lung cancers.[24]

Immunotherapy can be classified into active, passive, or hybrid (active and passive simultaneously). Active immunotherapy directs the immune system to attack tumor cells by targeting tumor antigens. Passive immune therapies improve pre-existing antitumor responses in the body, and include the use of monoclonal antibodies, lymphocytes and cytokines.[25]

A wide range of cancers can be treated with various immunotherapy drugs approved by many health authorities around the world. Passive immunotherapy usually involves targeting receptors on the surface of cells, and these include antibodies directed against CD20, CD274 and CD279.[26]

Effective cellular therapies usually remove tumor cells from the blood or from a solid tumor. Alternatively, immune cells can be genetically engineered to express a tumor-specific receptor, cultured in cell cultures, and then returned to the patient's body. Cells that can be genetically engineered in this way include natural killer (NK) cells, lymphokine-activated killer (KAL) cells, killer T cells, and dendritic cells (antigen-presenting cells).[27]

Cytokines regulate both the innate immune cells and the acquired immune system.
cytokines IL2 & IFN-a2b are approved by the FDA to treat a variety of signs and symptoms of cancer[28]:

- IL2 is used to treat renal cell carcinoma, leukemia, and lymphoma. IFN is approved for the treatment of Kaposi's sarcoma and various types of cancer.
- Interferons (IFNs) are a type of small signaling protein of many types produced by T lymphocytes, macrophages, and cancer cells. Interferons belong to a large class of proteins known as cytokines, which are molecules used for communication between cells to stimulate the protective defenses of the immune system that help eliminate pathogens. There are three types of them named according to the initial letters of the Greek alphabet, interferon alpha beta gamma and interferon alpha is the most used in cancer treatment, one of the most important properties of the group of interferon in affecting cancer cells:

✓ It directly affects the tumor cells, as it interferes with the processes of their cell division.
✓ It interferes with the processes of forming and building blood vessels and the growth of new capillaries that tumors need to continue to grow.
✓ Supports immune cells and increases their ability to kill tumor cells.

Passive cancer immunotherapy[29,30]
Passive (inactive) immunotherapy establishes the link between tumor-associated TAAs antigens and the individual's native immune system, by supplementing with tumor-specific antigen Ig, the FC segment that interacts with the host's immune system. The biological effects of passive antibody administration are manifold, and include agglutination, neutralization of signaling proteins or inactivation of receptor binding sites. Passive immunotherapy for cancer in any case requires large amounts of specific antibodies to the tumor antigen, and unlike effective immunotherapy, it is for a limited period.

The table includes passive immune therapies approved for use.

Antibody	Quality	UseQuality
Rituximab	**CD20**	**NHL**
Gemtuzumab Ozogamicin	**CD33**	**AML**
Alemtuzumab	**CD52**	**CLL**
Ibritumomab Tiuxetan	**CD20**	**NHL**
Tositumomab	**CD20**	**NHL**
Trastuzumab	**HER2\neu**	**Breast cancer**
Cetuximab	**EGFR**	**CRC**
Bevacizumab	**VEGF**	**CRC**

Cellular Immunotherapy[31,32,33]
T cells express clonally distributed antigen receptors that are present in the context of MHC proteins and can recognize either a unique oncogene that evolves from mutations or self-antigens derived from overexpression of the proteins. Efforts have focused on identifying tumor antigens and providing antigens in immune modulators to induce responses, as well as manipulating T-cell responses to increase the number of reactive cells and increase response functions.

Humoral Immunotherapy[34,35,36]
The activation of B cells occurs by the production of antibodies that can bind to proteins on the surface of immune cells on the tumor cell. This initiates complement mediated cell lysis, bridges natural killer cells or phagocytes to the tumor by blocking or preventing their survival, inducing programmed cell death signals, or increasing immunity by facilitating the capture and presentation of tumor antigens by APCs thus enhancing the response of B cells in vivo.

Adaptive Immunotherapy
That immunotherapy has the potential to treat patients with specific types of cancer, this hope was recently revised with some data supporting one type of immunotherapy (adaptive cell transfer, ACT through adaptive cancer immunotherapy and harnessing the T-cell response.

Monoclonal Antibodies
It is a special type of protein molecule produced in the laboratory. There are types of monoclonal antigen, which are naturally produced by the immune systems of humans and animals. The natural antibodies in the blood are a mixture of several antibodies, which interact with many antigens; Thus they act as the body's front line of defense against disease. A monoclonal antigen solution acts against a specific antigen and can be made in large quantities. As of 2017, the FDA has approved 31 monoclonal antibodies for use in cancer patients directed at 19 different targets.

Dinutuximab is a murine human chimeric monoclonal antibody that binds to GD2 that is expressed on the surface of neuroblastoma cells.[37]

Rituximab is a chimeric mouse anti-human CD20 monoclonal antibody and that has demonstrated efficacy in patients with various lymphoid malignancies.[38]

Tocilizumab is a monoclonal recombinant against the IL6 receptor that prevents IL6 from binding to its soluble and membrane-bound receptor. It is FDA approved for the treatment of juvenile idiopathic arthritis and adult rheumatoid arthritis.[39]

Catumaxomab is a family of trifunctional monoclonal antibodies and the first bispecific antibody to be approved for production and treatment. This drug is a bi-specific anti-CD3 cell adhesion molecule (EPCAM). Catumaxomab binds to epithelial tumor cells with different levels of EPCAM.[40]

Blinatumomab is a fusion of bispecific CD3 T-cell and CD19-directed antibodies that has been approved for treatment type II for Philadelphia chromosome-negative or refractory ALL.[41]

Olaratumab is a human monoclonal antibody, immunoglobulin G subclass (IgG) that binds to the platelet-derived growth factor receptor PDGFR. This is the third type of receptor tyrosine kinase expressed in many types of tumors that is involved in the growth, differentiation, and angiogenesis of stem cells. PDGF and its associated receptors are involved in the regulation of the tumor microenvironment and the ability of metastases to spread in many types of tumors.[42]

Daratumumab is a human IgG1 monoclonal antibody that targets CD32 which is a transmembrane glycoprotein highly expressed in myeloma and other hematopoietic cell tumor types. This drug induces apoptosis with CDC and ADCC and immune functions that deplete CD38-positive immunosuppressive regulator cells.[43]

Immune checkpoint inhibitors[44,45,46,47]

Cancer immune modulation is the process by which various components of the immune system protect the host from initial tumor development or promote tumor escape, or both, either by tumor scraping or attenuating antitumor immune responses. The process is tightly regulated by immune checkpoints[66], which are immune cell surface receptors that control the activation or inhibition of immune responses. The activation of the immune system, on the one hand, is the desired outcome for achieving tumor control, but on the other hand it is responsible for autoimmunity. The discovery and development of monoclonal antibodies against the inhibitory immune checkpoints CTLA-4 and PD-1 resulted in good antitumor responses by regulating immune activation at different stages of the immune cycle. The checkpoints are not equal in their potential. Blocking immune checkpoints enhances antitumor T-cell activity and shifts the balance from immune resistance to tumor immune expression. Several classes of checkpoint inhibitors (mab) have been developed:

Anti-CTLA-4

Negative immune receptor expressed on the surface of T cells. Antibody therapies targeting CTLA-4 have been used and tested in a number of cancers, most notably metastatic or melanoma and large cell lung cancer.

Anti-PD-1

Anti-PD-L1

PD-1 is an inhibitory receptor involved in immune checkpoint signaling and is highly expressed on the surface of tumor infiltrating lymphocytes (TILs), including cytotoxic T cells, B cells, and macrophages. The ligands of the PD-1 receptor, PD-L1 and PD-L2, are expressed on malignant tumor cells and antigen-presenting cells.

Ipilimumab: The first therapeutic antibody targeting humans approved for the treatment of patients with undetectable disease or metastatic melanoma is a fully human IgG1 class antibody consisting of four polypeptide chains.[48]

Tremelimumab is a human monoclonal antibody. This drug is intended to stimulate the immune system's attack on tumors. Cytotoxic T cells (CTls) can recognize and destroy cancer cells. However, there is also an inhibitory mechanism that interrupts this destruction.[49]

Immunotherapy toxicity

Cutaneous toxicity is the most common immunological event (irAE) seen in patients treated with CTLA4, PD-1, or Pdl-4 blockers. All reported dermatological toxicities occurred in 30-40% of patients treated with these blockers and 50% for patients treated with ipilimumab. Vitiligo has been reported only in melanoma patients and was observed in 7.5% of patients treated with nivolumab and 8.3% of patients treated with pembrolizumab. An analysis of 137 studies that included patients with advanced melanoma who received several different types of immunotherapy, including 28 ICI studies, found development of vitiligo associated with no progression and improved survival. Manifestations are varied and include maculopapular or pustular rash, skin hypersensitivity reaction, dermatomyositis, Sweet's syndrome, pyoderma necrosis (gangrenous), exanthematous exanthematous pustules, acneiform rash, and photosensitivity reactions. The most commonly reported dermatological toxicities are maculopapular rash, pruritus, and vitiligo.[50,51]

Pulmonary toxicity: Pneumonia is the most common pulmonary toxicity with ICI therapy.[34] Although the incidence of pneumonia is low, it is potentially life-threatening. It should be taken into account in any patient

who develops new respiratory symptoms. The symptom of pneumonia varies in both severity. Patients may develop coughing, chest pain, wheezing, shortness of breath, hypoxia or fatigue.[52]

Thyroid toxicity: Hypothyroidism is more common with ICI treatment than hyperthyroidism. The total incidence of hypothyroidism is 6.6%, with the lowest incidence of 3.8% reported in patients treated with ipilimumab and the highest incidence of 13.2% in patients treated with combination therapy. Hyperthyroidism is less common than hypothyroidism with total involvement of 2.9%, the lowest incidence is 0.6% with PDL-1 inhibitors, and the highest incidence is 8% with the combination therapy.[53]

Strategies to Increase T-cell Tumor Antigen Frequency

- **Cancer Vaccines**: Totally cell-based vaccines represented the first approved strategy. These applications do not take advantage of the opportunity to focus more on antigen-specific, and it is not clear if whole-cell use is desirable. Platforms are based on multiple or single tumor-specific (known) antigens in recombinant viral or bacterial vectors, peptides or proteins prepared in a variety of immunomodulatory adjuvants, and specific antigens or encoded sequences of DNA or RNA loaded onto autoantigen-presenting cells (eg PC) that It is given back to the patient.[54]
- **Adaptive cell therapy**: is a promising form of immunotherapy that exploits the anti-lymphoma properties to eliminate primary and metastatic neoplastic cells. Lymphocytes were first isolated from patients' peripheral blood, neoplastic lymph nodes or tumor tissue, or ex vivo and reinfused into the patient. This strategy would theoretically circumvent the puzzling task of breaking down tumor antigen tolerance and producing a large amount of highly efficient T cells. This approach attempts to reverse tumor-specific intra-tumour-specific T-cell dysfunction caused by the tumor-suppressive microenvironment, by growing them prior to re-infusion in a mixture of diverse cytokines.[55]

Immunotherapy in combination with chemotherapy

Combinational strategies against cancer can include either the simultaneous application of a different immunotherapy approach or a combination of standard chemotherapy or radiotherapy. Some chemotherapeutic agents have shown the ability to regulate the expression of tumor-associated antigens or reduce the resistance of cancer cells to cytotoxic T lymphocytes. Although lymphocytopenia frequently occurs after chemotherapy with subsequent influence on the immune system[63], some of these combinations have been found to generate synergistic rather than additive effects.[56]

Some Challenges Facing Cancer Immunotherapy

Developing models for pre-clinical trials that simulate human immunity

Cancer drug discovery relies on preclinical models to prioritize drug targets, study mechanisms, treatment approach, and treatment dose. However, the immunobiology of human cancer is not always well reflected in the models used, as key differences typically include the composition of immune cells in the microenvironment, tumor antigens, and the complexity of immune cell suppression that results from recognition and chronic immune exposure.[57]

Clarify the benefits of autoimmunity versus artificial immunity

The development of PD-1/PD-L1 inhibitors has enabled a highly effective anticancer autoimmune response to eliminate cancer cells in many patients. This autoimmune response is largely dependent on CD8+ T cells that recognize cancer cells in particular. These immune cells can be reactivated and stimulated by inhibiting PD-1/PD-L1 resulting in the recognition and killing of cancer cells.[58]

However, not all cancers present appropriate immune antigens that can be effectively recognized by autologous T cells. Additionally, some cancers use mechanisms to lose or reduce the MHC to avoid immune destruction. Synthetic immune responses are the result of treatments that artificially link T cells to cancer cells that do not normally do so based on the T cell's binding to the histocompatibility complex. The idea here is that in contrast to adaptive or autoimmune immunity, artificial immunity enhances the proliferation of T cells or stimulates them to become more resistant to tumors.

REFERENCE

1. Bray, Freddie, et al. "Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries." *CA: a cancer journal for clinicians*, 2018; 68.6: 394-424.
2. Bilynskyj, B. T. "The breast cancer treatment as a marker of progress in oncology." *Experimental oncology*, 2010; 32.3: 190-194.
3. Schuster, Manfred, Andreas Nechansky, and Ralf Kircheis. "Cancer immunotherapy." *Biotechnology Journal: Healthcare Nutrition Technology*, 2006; 1.2: 138-147.
4. Bonita, Ruth, Robert Beaglehole, and Tord Kjellström. *Basic epidemiology*. World Health Organization, 2006.
5. A Baudino, Troy. "Targeted cancer therapy: the next generation of cancer treatment." *Current drug discovery technologies*, 2015; 12.1: 3-20.
6. Bagasra, Omar, and Donald Gene Pace. *Immunology and the Quest for an HIV Vaccine: A New Perspective*. Author House, 2012.
7. Lu, Lenette L., et al. "Beyond binding: antibody effector functions in infectious diseases." *Nature Reviews Immunology*, 2018; 18.1: 46-61.

8. Palm, Noah W., and Ruslan Medzhitov. "Pattern recognition receptors and control of adaptive immunity." *Immunological reviews*, 2009; 227.1: 221-233.
9. Gajewski, Thomas F., Hans Schreiber, and Yang-Xin Fu. "Innate and adaptive immune cells in the tumor microenvironment." *Nature immunology*, 2013; 14.10: 1014-1022.
10. Eppler, Haleigh B., and Christopher M. Jewell. "Biomaterials as tools to decode immunity." *Advanced Materials*, 2020; 32.13: 1903367.
11. Chang, Mengyu, et al. "Recent Advances in Hyperthermia Therapy-Based Synergistic Immunotherapy." *Advanced Materials*, 2021; 33.4: 2004788.
12. León, Xavier, et al. "Second neoplasm in patients with head and neck cancer." *Head & Neck: Journal for the Sciences and Specialties of the Head and Neck*, 1999; 21.3: 204-210.
13. Kosaka, Nobuyoshi, et al. "Competitive interactions of cancer cells and normal cells via secretory microRNAs." *Journal of Biological Chemistry*, 2012; 287.2: 1397-1405.
14. …
15. Shields IV, C. Wyatt, et al. "Materials for immunotherapy." *Advanced Materials*, 2020; 32.13: 1901633.
16. Chodon, Thinle, Richard C. Koya, and Kunle Odunsi. "Active immunotherapy of cancer." *Immunological investigations*, 2015; 44.8: 817-836.
17. Weidle, Ulrich H., Roland E. Kontermann, and Ulrich Brinkmann. "Tumor-antigen–binding bispecific antibodies for cancer treatment." *Seminars in oncology*, 2014; 41(5). WB Saunders.
18. Pandya, Pankita H., et al. "The immune system in cancer pathogenesis: potential therapeutic approaches." *Journal of immunology research*, 2016.
19. Ng, Chee Wee, Jingchao Li, and Kanyi Pu. "Recent progresses in phototherapy-synergized cancer immunotherapy." *Advanced Functional Materials*, 2018; 28.46: 1804688.
20. Yang, Isaac, Seunggu Han, and Andrew T. Parsa. "Heat-shock protein vaccines as active immunotherapy against human gliomas." *Expert review of anticancer therapy*, 2009; 9.11: 1577-1582.
21. Mi, Yu, et al. "Emerging nano-/microapproaches for cancer immunotherapy." *Advanced Science*, 2019; 6.6: 1801847.
22. Netea, Mihai G., Jessica Quintin, and Jos WM Van Der Meer. "Trained immunity: a memory for innate host defense." *Cell host & microbe*, 2011; 9.5: 355-361.
23. Finn, Olivera J. "A believer's overview of cancer immunosurveillance and immunotherapy." *The Journal of Immunology*, 2018; 200.2: 385-391.
24. Muenst, S., et al. "The immune system and cancer evasion strategies: therapeutic concepts." *Journal of internal medicine*, 2016; 279.6: 541-562.
25. Galluzzi, Lorenzo, et al. "Classification of current anticancer immunotherapies." *Oncotarget*, 2014; 5.24: 12472.
26. Feigal, Ellen G., et al. "At the end of the beginning: immunotherapies as living drugs." 2019; 955-962.
27. Kloesel, Benjamin. *Cytotoxic drugs sensitize tumor cells to immune cell-mediated killing by interleukin-2 activated peripheral blood leukocytes*. Diss. University of Toledo, 2007.
28. Liu, Qin, et al. "Superior Antitumor Efficacy of IFN-α2b-Incorporated Photo-Cross-Linked Hydrogels Combined with T Cell Transfer and Low-Dose Irradiation Against Gastric Cancer." *International journal of nanomedicine*, 2020; 15: 3669.
29. Sato, Nagato, et al. "Wnt inhibitor Dickkopf-1 as a target for passive cancer immunotherapy." *Cancer research*, 2010; 70.13: 5326-5336.
30. Madsen, Caroline B., Hans H. Wandall, and Anders Elm Pedersen. "Potential for novel MUC1 glycopeptide-specific antibody in passive cancer immunotherapy." *Immunopharmacology and immunotoxicology*, 2013; 35.6: 649-652.
31. Ribas, Antoni, et al. "Current developments in cancer vaccines and cellular immunotherapy." *Journal of clinical oncology*, 2003; 21.12: 2415-2432.
32. Armstrong, Anne C., David Eaton, and Joanne C. Ewing. "Cellular immunotherapy for cancer." *Bmj*, 2001; 323.7324: 1289-1293.
33. Xie, Guozhu, et al. "CAR-NK cells: A promising cellular immunotherapy for cancer." *EBioMedicine*, 2020; 59: 102975.
34. Fonsatti, E., et al. "Emerging role of protectin (CD59) in humoral immunotherapy of solid malignancies." *La Clinica terapeutica*, 2000; 151.3: 187-193.
35. Silina, Karina, et al. "Sperm-associated antigens as targets for cancer immunotherapy: expression pattern and humoral immune response in cancer patients." *Journal of immunotherapy*, 2011; 34.1: 28-44.
36. Chu, Yaya, et al. "Advances in cellular and humoral immunotherapy–implications for the treatment of poor risk childhood, adolescent, and young adult B-cell non-Hodgkin lymphoma." *British journal of haematology*, 2019; 185.6: 1055-1070.
37. Dhillon, Sohita. "Dinutuximab: first global approval." *Drugs*, 2015; 75.8: 923-927.
38. Keating, Gillian M. "Rituximab." *Drugs*, 2010; 70.11: 1445-1476.
39. Oldfield, Vicki, Sohita Dhillon, and Greg L. Plosker. "Tocilizumab." *Drugs*, 2009; 69.5: 609-632.
40. Seimetz, Diane, Horst Lindhofer, and Carsten Bokemeyer. "Development and approval of the trifunctional antibody catumaxomab (anti-EpCAM× anti-CD3) as a targeted cancer

immunotherapy." *Cancer treatment reviews*, 2010; 36.6: 458-467.
41. Przepiorka, Donna, et al. "FDA approval: blinatumomab." *Clinical Cancer Research*, 2015; 21.18: 4035-4039.
42. Shirley, Matt. "Olaratumab: first global approval." *Drugs*, 2017; 77.1: 107-112.
43. McKeage, Kate. "Daratumumab: first global approval." *Drugs*, 2016; 76.2: 275-281.
44. Jenkins, Russell W., David A. Barbie, and Keith T. Flaherty. "Mechanisms of resistance to immune checkpoint inhibitors." *British journal of cancer*, 2018; 118.1: 9-16.
45. Spain, Lavinia, Stefan Diem, and James Larkin. "Management of toxicities of immune checkpoint inhibitors." *Cancer treatment reviews*, 2016; 44: 51-60.
46. Darvin, Pramod, et al. "Immune checkpoint inhibitors: recent progress and potential biomarkers." *Experimental & molecular medicine*, 2018; 50.12: 1-11.
47. Hargadon, Kristian M., Coleman E. Johnson, and Corey J. Williams. "Immune checkpoint blockade therapy for cancer: an overview of FDA-approved immune checkpoint inhibitors." *International immunopharmacology*, 2018; 62: 29-39.
48. Cameron, Fiona, Glenn Whiteside, and Caroline Perry. "Ipilimumab." *Drugs*, 2011; 71.8: 1093-1104.
49. Ribas, Antoni. "Clinical development of the anti–CTLA-4 antibody tremelimumab." *Seminars in oncology*. Vol. 37. No. 5. WB Saunders, 2010.
50. Kennedy, Lucy Boyce, and April KS Salama. "A review of cancer immunotherapy toxicity." *CA: a cancer journal for clinicians*, 2020; 70.2: 86-104.
51. Thompson, John A. "New NCCN guidelines: recognition and management of immunotherapy-related toxicity." *Journal of the National Comprehensive Cancer Network*, 2018; 16.5S: 594-596.
52. Rashdan, Sawsan, John D. Minna, and David E. Gerber. "Diagnosis and management of pulmonary toxicity associated with cancer immunotherapy." *The Lancet Respiratory Medicine*, 2018; 6.6: 472-478.
53. Chang, Lee-Shing, et al. "Endocrine toxicity of cancer immunotherapy targeting immune checkpoints." *Endocrine reviews*, 2019; 40.1: 17-65.
54. Melief, Cornelis JM, et al. "Therapeutic cancer vaccines." *The Journal of clinical investigation*, 2015; 125.9: 3401-3412.
55. Protti, M. P., L. D. Monte, and G. D. Lullo. "Tumor antigen-specific CD4+ T cells in cancer immunity: from antigen identification to tumor prognosis and development of therapeutic strategies." *Tissue Antigens*, 2014; 83.4: 237-246.
56. Yu, Wei-Di, et al. "Mechanisms and therapeutic potentials of cancer immunotherapy in combination with radiotherapy and/or chemotherapy." *Cancer letters*, 2019; 452: 66-70.
57. HogenEsch, Harm, and Alexander Yu Nikitin. "Challenges in pre-clinical testing of anti-cancer drugs in cell culture and in animal models." *Journal of controlled release*, 2012; 164.2: 183-186.
58. Kumar, Prabhakaran, Palash Bhattacharya, and Bellur S. Prabhakar. "A comprehensive review on the role of co-signaling receptors and Treg homeostasis in autoimmunity and tumor immunity." *Journal of autoimmunity*, 2018; 95: 77-99.